Towards The Synthesis Of Hyacinthacines

A Thesis Submitted to the College of

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By

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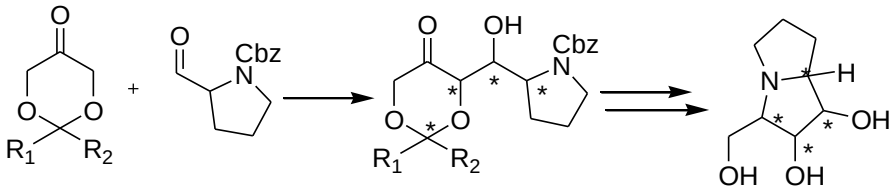
ABSTRACT

The organocatalytic aldol reaction of tropinone with benzaldehyde using *(S)*-5-pyrrolidin-2-yl-1H-tetrazole as organocatalyst is described and it results in the formation of the dehydrated aldol adduct in moderate selectivity. The organocatalytic aldol reaction of C_S and C_{2V}-symmetrical dioxanones is also demonstrated and in most cases C_S-symmetrical dioxanones offer a better stereoselectivity.

A new approach towards synthesis of hyacinthacine alkaloids: 2-epihyacinthacine A_2, 3-epihyacinthacine A_2 and their enantiomers is illustrated. The key step involves an organocatalytic aldol reaction of dioxanones where proline is used both as the catalyst and as the precursor for the aldehyde building block (scheme 1.0)



Scheme 1.0

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Finally and most importantly, I thank God, the most merciful and the most gracious for giving me the courage to write this thesis and for giving me the chance to have known so many nice people.

DEDICATION

Dedicated to my Parents

Rehena and Reshard Delawarally

To my sister

Wazeela Ahsun

And most importantly to my beloved wife and best friend

Adilah Allibacus

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

α	observed optical rotation in degrees
[α]	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are understood)
Ac	acetyl (ethanoyl)
Ac_2O	acetic anhydride
AcOH	acetic acid
AO	atomic orbital
aq	aqueous
Ar	aryl
Bn	benzyl
t-Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
Br	broad (spectral)
t-Bu	*tert*-butyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
Chx	cyclohexyl,
CI	chemical ionization
CSA	camphorsulfonic acid
COSY	correlation spectroscopy
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
DCC	1,3-dicyclohexylcarbodiimide
DHAP	1,3-dihydroxyacetone phosphate
DIBAL-H	diisobutylaluminum hydride
DIPEA or DIEA	*N*,*N*,-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide

2,2-DMP	2,2-dimethoxypropane
DMP	Dess-Martin periodinane
DMSO	dimethyl sulphoxide
DCM	dichloromethane
de	diastereomeric excess
DDO	dimethyldioxirane
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomers ratio
DRIFT	diffuse reflectance Fourier transform infrared
ee	enantiomeric excess, for a mixture of two enantiomers *R* and *S*, ee is calculated from equation : ee=([*R*]-[*S*])/([*R*]+[*S*]) x 100%
EI	electron impact ionization
EPC	enantiomerically pure compound
er	enantiomeric ratio
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
EtOAc	ethyl acetate
FCC	flash column chromatography
FT	Fourier transform
H-bonding	hydrogen bonding
HMBC	heteronuclear multiple bond correlation (2 and 3 bond *J*CH correlation with inverse detection)
HMQC HMQC	heteronuclear multiple quantum coherence (1 bond *J*CH correlation with inverse detection)
^{1}H NMR	proton nuclear magnetic resonance
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
i-Bu	isobutyl (2-methylpropyl)

i-Pr	isopropyl
IR	infrared
LA	Lewis acid
LB	Lewis base
LDA	lithium diisopropylamide
LHMDS (LiHMDS)	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide
LiCl	lithium chloride
J	coupling constant (in NMR spectrometry)
LRMS	low resolution mass spectrometry
m-CPBA	3-chloroperoxybenzoic acid
m	multiplet (spectral); meter(s); milli
M^+	parent molecular ion
max	maximum
Me	methyl
MeCN	acetonitrile
MeLi	methyllithium
MeOH	methanol
mp	melting point
MS	mass spectrometry
MW	molecular weight
m/*z*	mass-to-charge ratio
MS 4A	molecular sieves 4Å
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl

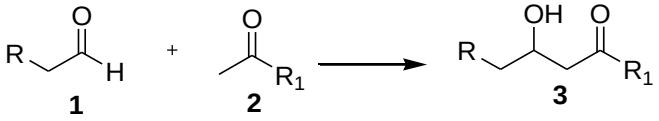
*i*Pr	isopropyl
PTLC	preparative thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid (4-methylbenzenesulfonic acid)
Py	pyridine
Ra/Ni	Raney-nickel
Rf	retention factor (in chromatography)
Rt	room temperature, usually 22-25 °C
s	singlet (spectral)
sat.	saturated; as in a saturated aqueous solution
t	triplet (spectral)
TBAF	tetra-*n*butylammonium fluoride
TBDMS or TBS	*tert*--butyldimethylsilyl
TBDMSCl or TBSCl	*tert*-butyldimethylsilyl chloride
temp	temperature
TFA	trifluoroacetic acid
TFAE	2,2,2-trifluoro-1-(9-anthryl)ethanol
t-Bu	*tert*-butyl (1,1-dimethylethyl)
t-BuLi	*tert*-butyllithium
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
TMSCl	trimethylsilyl chloride(chlorotrimethylsilane)
TMSOTf	trimethylsilyl trifluoromethanesulfonate
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
w/w	weight per unit weight (weight-to-weight ratio)
Y	yield

CHAPTER 1

1. Introduction

1.1 Aldol reaction

The aldol reaction is known to be a cornerstone in the field of organic synthesis as it is a powerful means of forming carbon-carbon bonds.[1] In simplistic terms, an aldol reaction usually involves the reaction of two carbonyl compounds (e.g an aldehyde and a ketone) to form a β-hydroxy carbonyl compound (scheme 1.1).

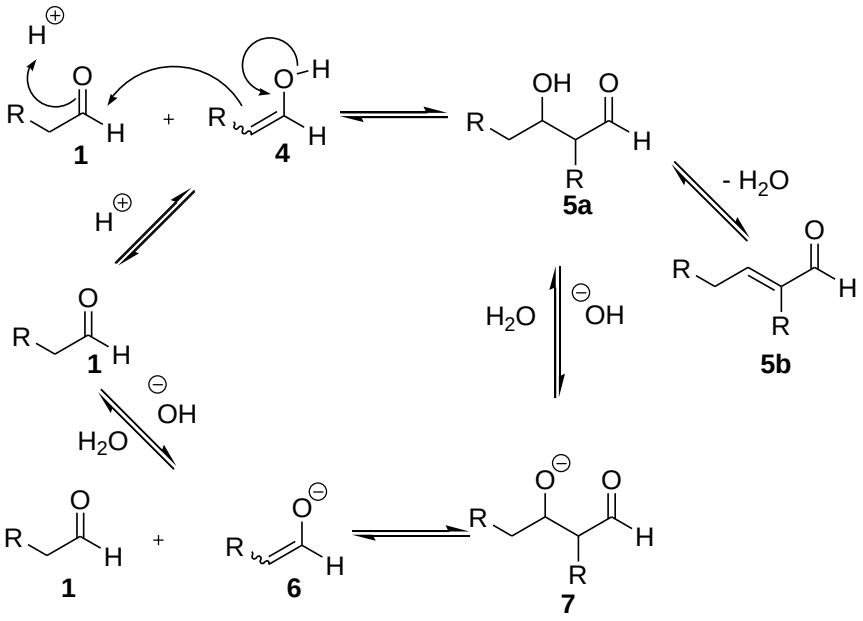


Scheme 1.1

Since the discovery of the aldol reaction by Charles-Adolphe Wurtz in 1872,[2] several modifications have been developed to maximize the yield of the reaction as well as to control the stereochemical outcome.[1] As it is impossible to illustrate all the developments in this thesis, I will only give a brief overview of the aldol reaction. In the first part of the introduction, I will describe the concepts of the aldol reaction with some emphasis on the methods of stereocontrol. In the second part, the organocatalytic aldol reaction will be briefly described.

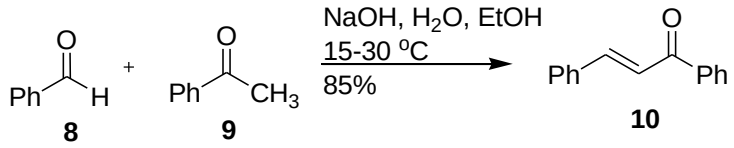
1.2 Traditional aldol

The traditional aldol reaction was usually carried out in a protic solvent either under acid or base catalysis (scheme 1.2).[1]



Scheme 1.2

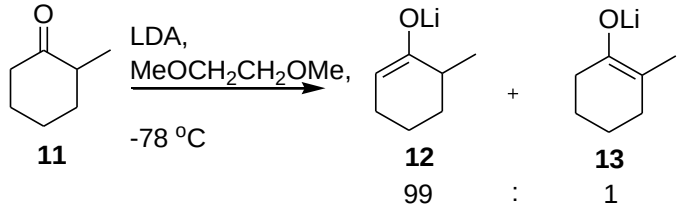
Under these conditions, the reaction is reversible and often results in poor selectivity.[3] A major problem involves running a crossed aldol reaction, i.e. the reaction in which the nucleophile and the electrophile are different carbonyl compounds. An efficient way to overcome this problem is to use a combination of an enolizable ketone with an unenolizable aldehyde so that the self-condensation of the aldehyde cannot happen. Moreover, the self-aldolization of ketones is an endothermic process and therefore does not occur to a significant extent. The product of this type of reaction is usually the condensed (i.e dehydrated) aldol adduct. An example of such combination is shown in the following scheme 1.3.[4]



Scheme 1.3[4]

1.3 Modern aldol and the 'Lithium diisopropylamide (LDA) era'

In the 1970's, the use of lithium bases such as LDA to generate enolates from carbonyl compounds such as aldehydes, ketones, esters, amides and carboxylic acids became the method of choice.[5] Lithium amide bases allowed the kinetically controlled deprotonation of carbonyl compounds often with excellent regioselectivity. An example was the deprotonation of 2-methyl cyclohexane **11** with LDA to form the kinetically favored intermediate **12** as the major enolate (scheme 1.4).[6]



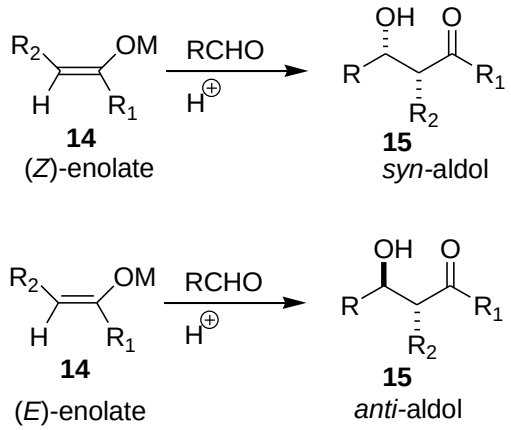
Scheme 1.4[6]

1.4 Methods of stereocontrol

As I have previously stated, the traditional aldol reaction suffered from a lack of stereocontrol. With the advent of preformed lithium enolates as well as other metals enolates, the problem of stereocontrol was successfully addressed.[1]

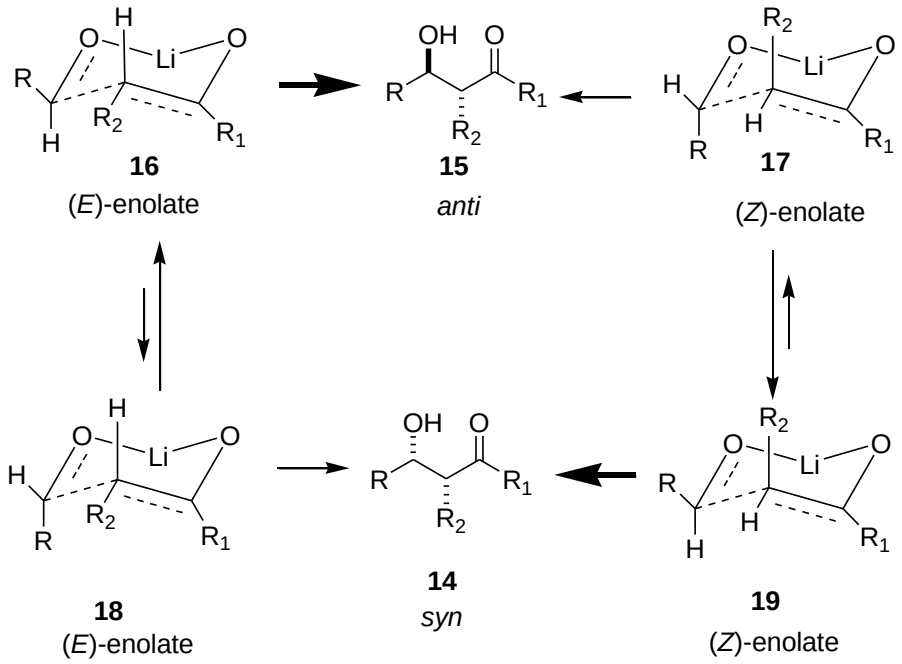
Studies carried out by several groups[7-8] showed that in many kinetically controlled aldol reactions, the outcomes were often dictated by the geometry of the enolates. For instance, in most cases the (*Z*)-enolate would result in a *syn* aldol adduct while the (*E*)-enolate

would result in an *anti* aldol adduct as the major product (scheme 1.5).



Scheme 1.5

The Zimmerman-Traxler transition state model is often used as a plausible explanation to account for these observations (scheme 1.6).[9]



Scheme 1.6

As shown in the above scheme, when an (*E*)-enolate reacts with an aldehyde, there can exist predominantly 2 transition states. If transition state **16** predominates, it will result in an *anti* aldol adduct while if transition state **18** predominates, it will result in a *syn* aldol

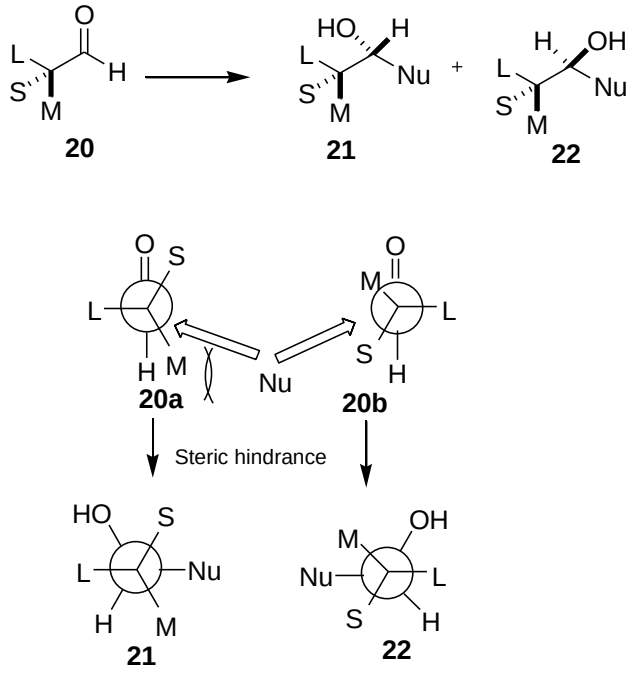
adduct. However due to steric hindrance between the R group of the aldehyde and the R_1 group of the ketone in **18**, transition state **16** is favored and therefore the *anti* aldol adduct will be the major product. Similarly, for (*Z*)-enolates, **19** is favored resulting in the major product being the *syn* aldol adduct.

The Zimmerman-Traxler model was first developed to explain the stereochemical outcome of reactions of magnesium enolates[9] and later it was successfully applied to enolates of other metals such as lithium, titanium and boron.[1] However, it is noteworthy that this model is not absolute and there are a number of exceptions that can be explained by other transition state models such as the open-chain transition state model.[10]

Synthesis of enantiomerically pure aldol adducts is of great interest. As was previously shown, the configuration of the enolate generally determines the relative stereochemical outcome. In the following section, we will look at some of the ways to control the absolute stereochemical outcome of the aldol reaction.

1.5 Reaction of achiral enolates with aldehydes containing an α stereogenic center

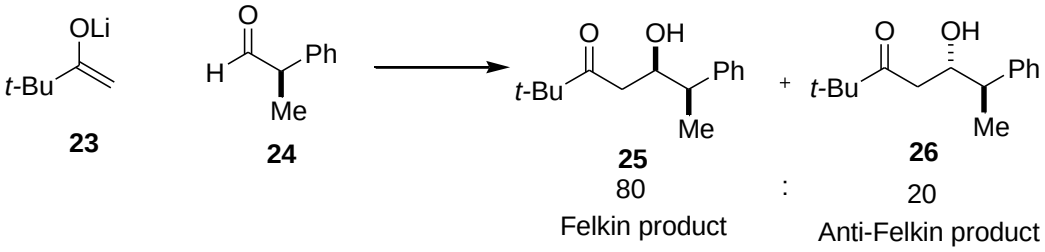
The addition of enolates to chiral aldehydes having a stereogenic center at the α-carbon often leads to the formation of one stereoisomer as the major product. This can be explained by several transition state models which deal with the addition of a nucleophile to the C=O bond. One such model is the Felkin-Anh model.[11] In the Felkin-Anh model, three groups are defined on the stereogenic centre; large (L), medium (M) and small (S). The large group has to be orthogonal to the C=O to minimize non-bonded interaction and the nucleophile (the enolate in the case of the aldol reaction) will approach at an angle of approximately 109° known as the Burgi-Dunitz angle.[12] Out of the two possible pathways, the least hindered pathway is favored (scheme 1.7).



Scheme 1.7

Based on the Felkin-Anh model, the nucleophile can approach the aldehyde in two different ways (scheme 1.7). However, in **20a** the proximity of the medium group to the nucleophile exerts a greater steric hindrance compared to the proximity of the small group to the nucleophile as in the case of **20b**. As a result, conformer **20b** reacts predominantly leading to **22** to be formed as the major product.

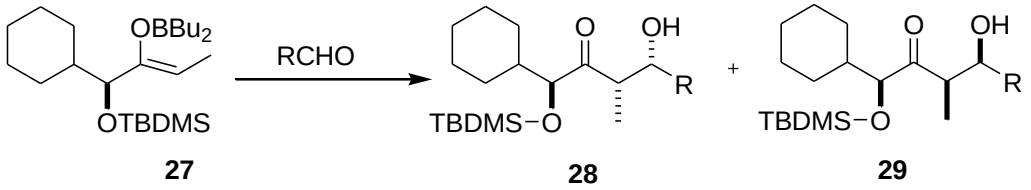
An example of such diastereofacial selectivity reported by Heathcock *et al* leading to the Felkin product is shown below (scheme 1.8). [13]



Scheme 1.8

1.6 Reactions of chiral enolates with achiral aldehydes (facial selectivity of chiral enolates)

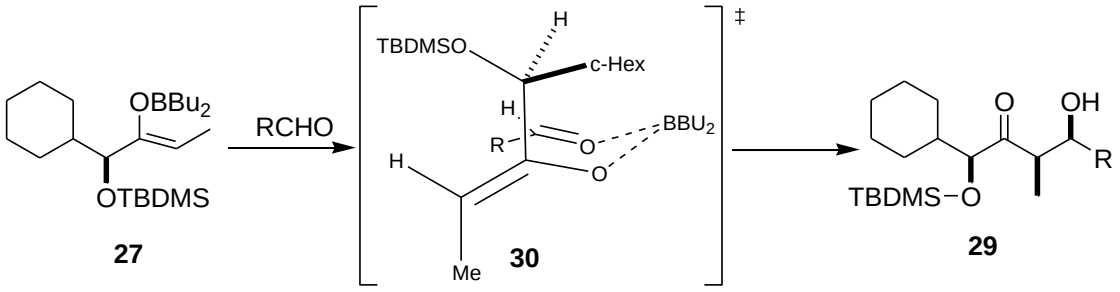
The reactions of chiral enolates with achiral aldehydes can also lead to the formation of enantiomerically enriched aldol adducts. The scheme below shows an example described by Masamune *et al*. [14]



R	28	29
Ph	2.5	97.5
i-Pr	1	99
Et	2	98

Scheme 1.9

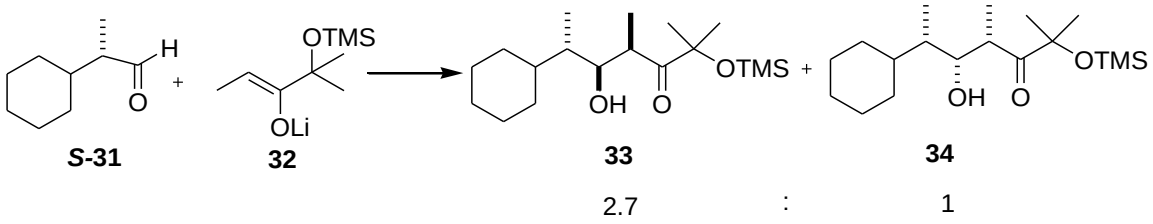
The reactions of the boron enolate **27** with different aldehydes lead to the selective formation of compound **29** as the major product. This could be explained by the transition state **30** (scheme 1.10) which shows that the bottom face of the boron enolate is less hindered leading to **29** as major aldol adducts.



Scheme 1.10

1.7 Double stereodifferentiation

Double stereodifferentiation arises when two chiral substrates react with each other. The diastereoselectivity of the reaction will greatly depend on the diastereofacial selectivity of each reactant.[14] In other words; one has to determine the facial reactivity of the chiral aldehyde with achiral enolates similar to the chiral enolate and vice-versa. An illustrative example is shown in the following schemes.[14]

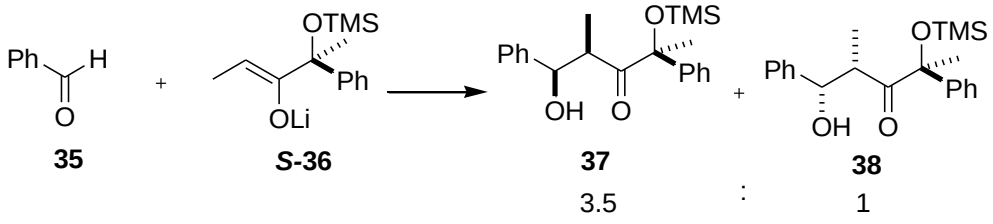


***S*-31** **32** **33** **34**

2.7 : 1

Scheme 1.11

In the above reaction, the chiral aldehyde favors the formation of the aldol adduct **33** and therefore it is said that the aldehyde is biased towards the Re face of the enolate. Next the facial bias of the chiral enolate is investigated with achiral aldehyde (scheme 1.12).



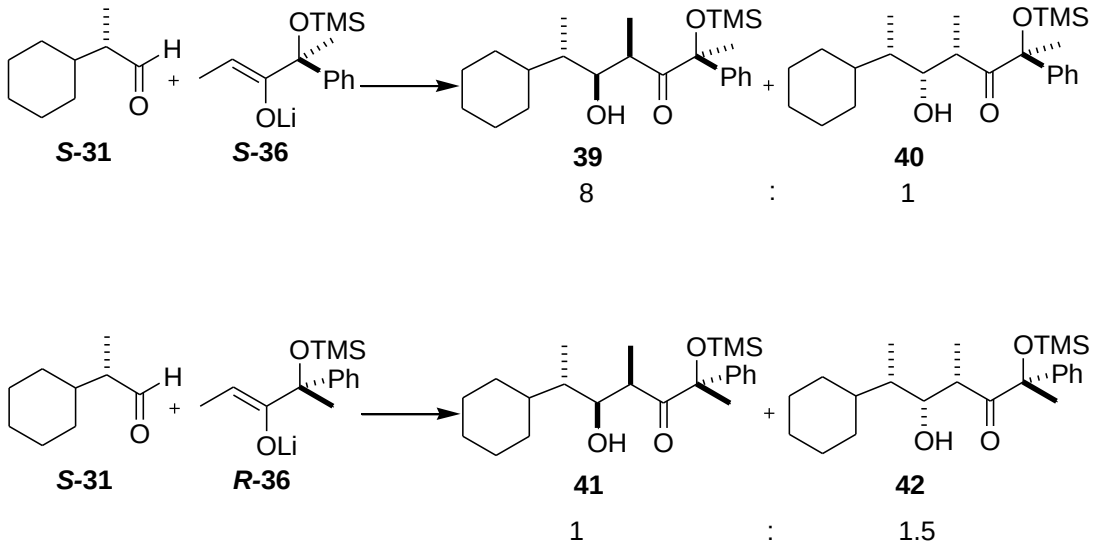
35 ***S*-36** **37** **38**

3.5 : 1

Scheme 1.12

Since the chiral enolate favors the formation of aldol adduct **37**, it is said that the enolate is biased towards the Re face of the aldehyde. This implies that the reaction of the aldehyde ***S*-31** with enolate ***S*-36** will occur in high selectivity because they both favor Re face attack. However, if the enantiomer of the aldehyde or enolate is used, the reaction

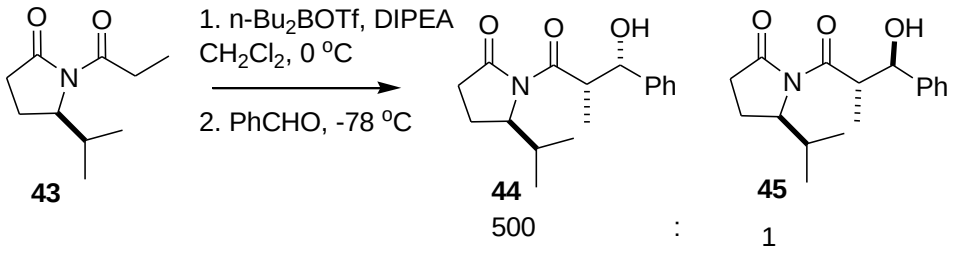
will occur with low selectivity (scheme 1.13). When the reaction occurs in high selectivity, it is termed as a matched pair while the reaction with lower selectivity is termed as a mismatched pair.



Scheme 1.13

1.8 Chiral auxiliaries

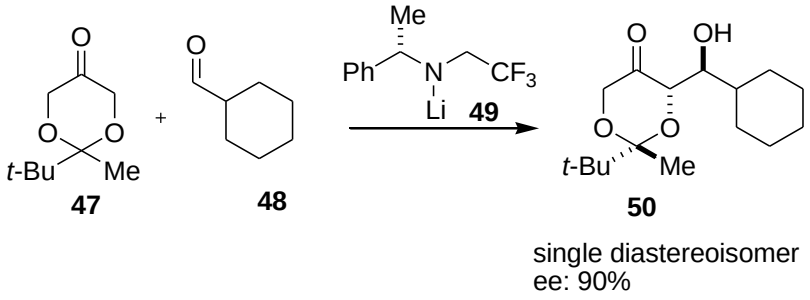
In order to induce stereoselectivity in aldol reactions of achiral compounds, researchers have made use of several techniques and one of them involves using a chiral auxiliary. As its name suggests, a chiral auxiliary is a chiral fragment which is temporarily attached to one of the reactants. The chiral auxiliary through steric hindrance will favor the formation of one stereoisomer and can then be removed to give the enantiomerically enriched compound. An example described by Evans and coworkers is shown below (scheme 1.14).[15]



Scheme 1.14

1.9 Chiral lithium amides

Chiral lithium amides have also been used to yield non racemic aldol adducts from achiral starting materials. The complexation of the enolates with the chiral lithium amides would form chiral complexes which are responsible for the observed stereoselectivity. An example reported by our group is shown below.[16]



Scheme 1.15

1.10 Organocatalysis

Organocatalysis is defined as a process whereby a compound of small molecular weight (< 1000 g/mol) usually consisting of carbon, hydrogen, sulfur and other nonmetal elements catalyzes a chemical reaction. The term "organic catalysts" was first introduced by Ostwald in 1900, in order to distinguish small organic molecules as catalytic principles from enzymes or inorganic catalysts.[17] Following the rediscovery of proline-catalyzed transformations in 2000 by List, Barbas III and MacMillan, the term

"organocatalysis" was proposed as the name for this field of research and it has been used in the literature since then.[18] The area of organocatalysis has been growing rapidly over the past decade as illustrated in the following chart.

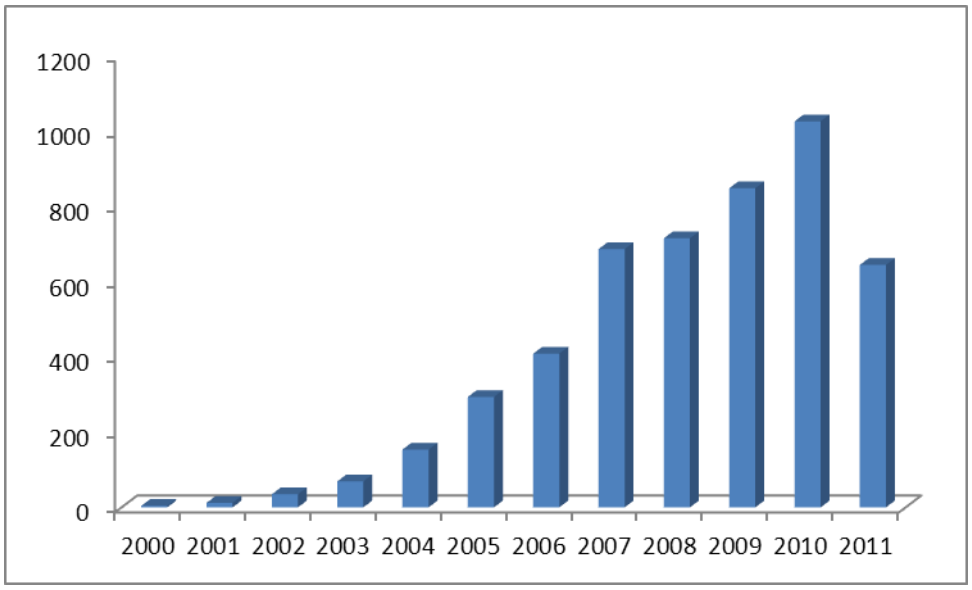
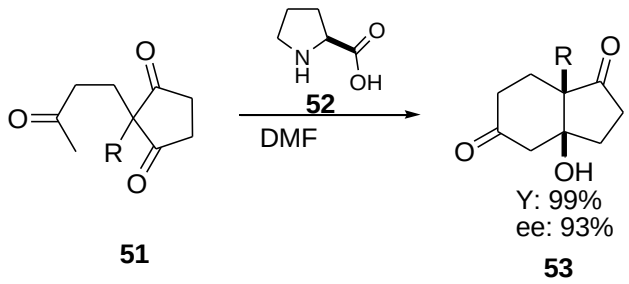


Figure 1.1: SciFinder hits on organocatalysis (August 2011)

Even though there had been some precedents in the literature concerning the use of organic catalysts in enantioselective chemical transformations, the (*S*)-proline catalyzed Robinson annulation, independently discovered by two groups at Hoffmann-La Roche[19] and at Schering[20], commonly called the Hajos-Parrish-Eder-Sauer-Wiechert reaction, is viewed as the first efficient organocatalyzed asymmetric transformation (scheme 1.16).



Scheme 1.16

1.12 Organocatalytic aldol reaction

(*S*)-Proline, known as "non-demanding reaction conditions catalyst" formed a foundation in the field of organocatalytic aldol reaction.[21] This nonmetallic, small-molecule is nontoxic, commercially available in both enantiomeric forms, and relatively cheap compared to metal based catalysts. Moreover, the reactions catalyzed by proline do not usually require anhydrous or oxygen-free conditions and can be run at room temperature.[23] Also prior modification of the carbonyl substrates such as deprotonation or silylation is not necessary. Proline stability (in comparison to metal based catalysts), easy access and properties allowing for possibility of removal from the reaction mixture by a simple aqueous extraction are only a few advantages responsible for the fact that this amino acid has been used as a catalyst in a wide range of asymmetric transformations with excellent results.

Since the use of this molecule in 2000,[18] numerous organocatalytic systems were developed, widening the scope of substrates and applications in target-oriented syntheses. In order to increase the level of efficiency, it is imperative to have a good understanding of the mechanism involved. A lot of research has been done in this field and although there are still a few uncertainties, the mechanism proposed by List is generally well accepted.[21,22]

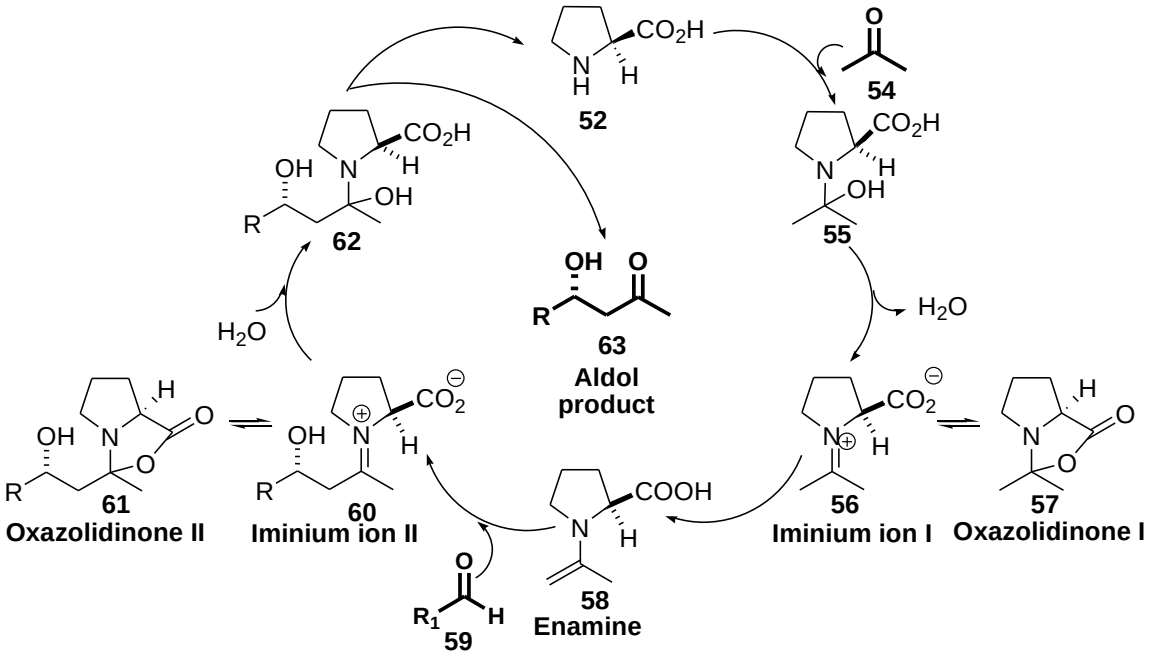


Figure 1.2: Catalytic cycle in (S)-proline catalyzed aldol reactions

In the catalytic cycle, the proline molecule is presented as a "micro-aldolase" that provides both the nucleophilic amino group and an acid/base co-catalyst in the form of the carboxylate. Proline **52** forms an iminium ion **56** with the ketone **54** which can equilibrate via an imine–enamine tautomerism to the corresponding nucleophilic enamine species **58**. Reaction of the enamine with the electrophile (in the scheme aldehyde **59**) will yield the corresponding iminium ion **60** which can hydrolyze to release the aldol adduct **63** and the catalyst **52** back in the cycle. The co-catalyst (carboxylate) is believed to facilitate each individual step of the mechanism, including the nucleophilic attack of the amino group, the dehydration of the hemiaminal intermediate **55**, the deprotonation of the iminium species (**56 → 58)**, the carbon-carbon bond forming step, and both steps of the hydrolysis of the iminium-aldol intermediate.

1.12 Organocatalytic aldol reaction in water

In general, organocatalytic processes have been carried out by stirring the reactants in organic solvents such as DMSO, DMF or chloroform.[23] The use of water as a substitute for these conventional organic solvents appeared as the ideal solution due to the low cost, safety and the 'green' nature of water.[27]

However, unlike biochemical processes involving aldolases, the majority of the organocatalytic aldol reactions resulted in poor yield and stereoselectivity if carried out in aqueous conditions.[24] It was suggested that water interferes with the organocatalysts and disrupts the polar interactions such as hydrogen bonds between the catalysts and the reactants.[25] For the past decade several groups have tried to overcome the limitations imposed by the use of water.[25c,26-29,30-32] Some of the advances in this area are described below.

1.12.1 Use of siloxyproline as organocatalyst in water

In 2006 the Hayashi group developed a new strategy for the organocatalytic aldol reaction under aqueous condition.[26] The key catalyst in this reaction was 4-*tert*-butyldimethylsiloxyproline **64a** which was prepared from the commercially available *trans* 4-hydroxyproline.

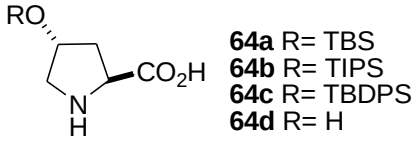
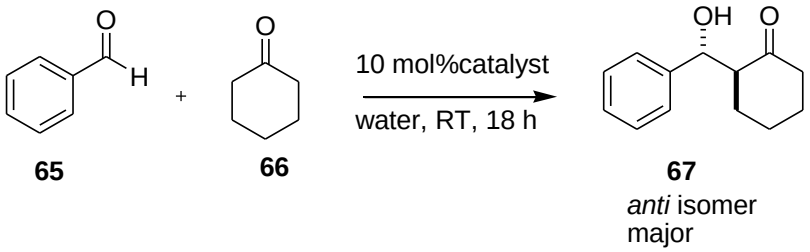


Figure 1.3: Catalysts used by Hyashi's group

Using this catalyst, the aldol reaction of cyclohexanone with benzaldehyde proceeded with high diastereo- and enantioselectivity in water. It was found that TBDPS **64c** and TIPS **64b** protected hydroxy proline could also be used as an efficient catalyst for this reaction (table 1.1). When the reaction was carried out in an organic solvent such as DMSO or without any solvent, it resulted in poor selectivity (entry 5).



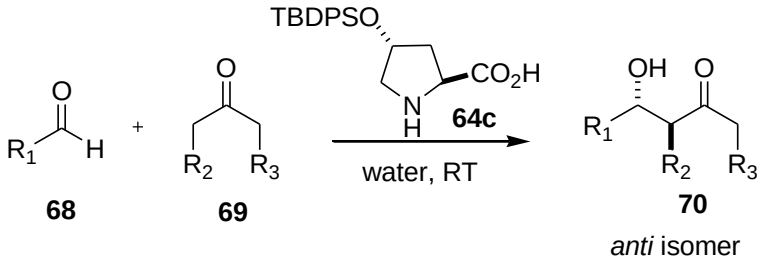
Scheme 1.17

Table 1.1: The effect of catalyst on reaction yield and selectivity.[a] [ref. 26]

Entry	Catalyst	Yield [%][b]	*anti:syn*[c]	ee [%][d]
1	**64a**	61	19:1	>99
2[e]	**64a**	66	20:1	>99
3[f]	**64a**	69	20:1	>99
4[g]	**64a**	61	1.8:1	89
5[h]	**64a**	65	1:1	80
6	**64b**	71	14:1	>99
7	**64c**	78	13:1	>99
8	**64d**	<5	-	-

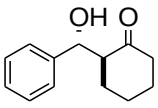
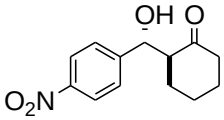
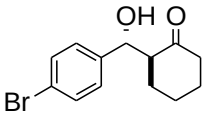
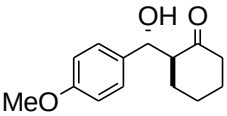
[a] Reaction was performed with benzaldehyde (0.4 mmol), cyclohexanone (207 µL, 2.0 mmol), catalyst (0.04 mmol) and H_2O (0.13 mL).
[b] Yield refers to the combined yield of isolated diastereoisomers.
[c] Diastereoselectivity was determined by ^1H NMR analysis of the reaction mixture
[d] ee was measured on the anti isomer and was determined by HPLC on Chiralcel OD-H.
[e] 72µL of H_2O was used.
[f] 36µL of H_2O was used.
[g] No solvent was used.
[h] 0.4 mL of DMSO was used as solvent.

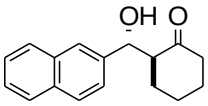
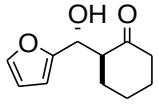
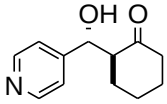
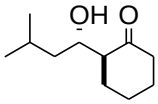
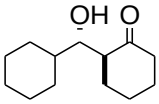
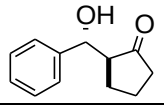
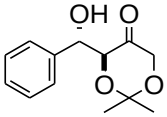
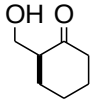
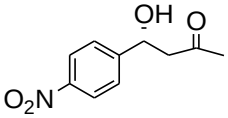
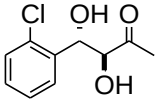
The general scope of the reaction was also tested using various ketones and aldehydes (scheme 1.18, table 1.2) and it was found that a wide range of aldehydes could be used although an electron rich aldehyde afforded a low yield. However, under Hayashi's conditions, aldol reaction with ketones such as acetone and hydroxy acetone afforded only moderate selectivity. It was also demonstrated that the catalytic loading could be reduced to 1 mol % of organocatalyst with low loss in yield and selectivity. To conclude, these siloxy catalysts were among the first organocatalysts employed in the organocatalytic aldol reactions in aqueous media to afford the aldol adducts with high diastereo and enantioselectivities.



Scheme 1.18

Table 1.2: Catalytic aldol reaction in water catalyzed by **64c**[a] [ref. 26]

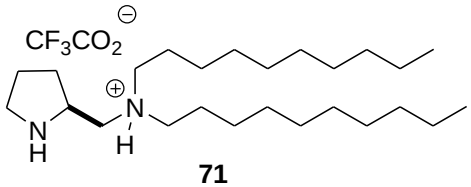
Entry	Product	Time [h]	Yield [%][b]	*anti:syn*[c]	ee[%][d]
1		18	78	13:1	>99
2		5	86	20:1	>99
3		28	80	20:1	97
4		50	21	5:1	96

5		40	89	19:1	97
6[e]		28	79	4.7:1	97
7		2.5	92	12:1	95
8		20	54	>20:1	>99
9		24	76	>20:1	>99
10		18	74	9:1	>99
11		18	48	25:1	95
12[f]		90	37	-	96
13[g]		18	63	-	67
14		72	61	1:1	64,61[h]

[a] Reaction was performed with 0.4 mmol aldehyde, 2 mmol ketone 0.04 mmol catalyst and 0.13 mL water.
[b] Yield refers to the combined yield of isolated diastereoisomers.
[c] Determined by ^{1}H NMR of reaction mixture.
[d] ee was measured on the anti isomer and was determined by HPLC.
[e] Catalyst 15a instead of 15c was used.
[f] Aqueous formalin and NaCl were employed.
[g] Acetone was employed.
[h] ee of *syn* isomer

1.12.2 Organocatalytic aldol reaction in water with Barbas diamine

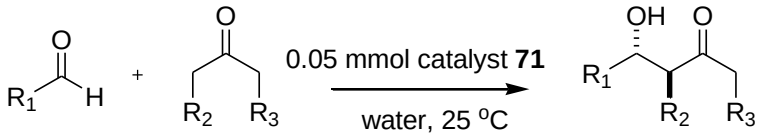
At almost the same time as the Hayashi group, the Barbas group also reported a novel strategy for the organocatalytic aldol reaction in water.[27] They used diamine **71** to catalyze the aldol reaction of cyclohexanone with p-nitrobenzaldehyde in water using TFA as the additive. The resulting aldol adduct was obtained with high diastereo- and enantioselectivity.



71

Figure 1.4: Barbas catalyst

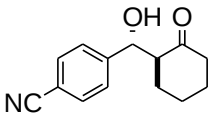
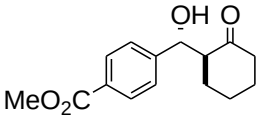
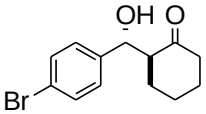
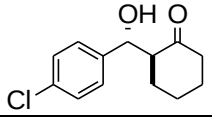
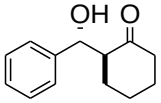
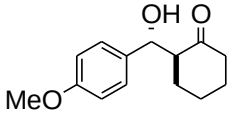
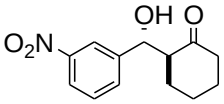
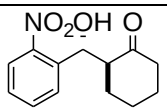
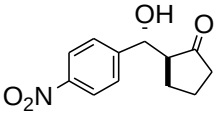
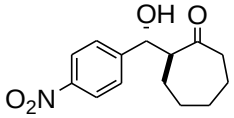
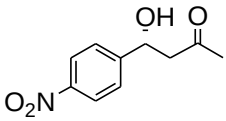
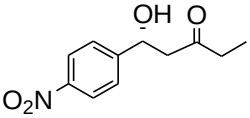
It should be noted that a stoichiometric amount of cyclohexanone was enough for the reaction to proceed (scheme 1.19). This differs from previous approaches which in general used an excess of cyclohexanone or other low molecular weight ketones, thereby making the reaction more economical.[25c,27] The general applicability of this reaction was also investigated and in most cases good diastereo- and enantioselectivities were observed (table 1.3). To summarize, it was found that diamine **71** in the presence of TFA could catalyze the organocatalytic aldol reaction in high selectivities.



68 **69** **70**
anti isomer

Scheme 1.19

Table 1.3: Catalytic aldol reaction in water catalyzed by **71** and TFA [ref. 27]

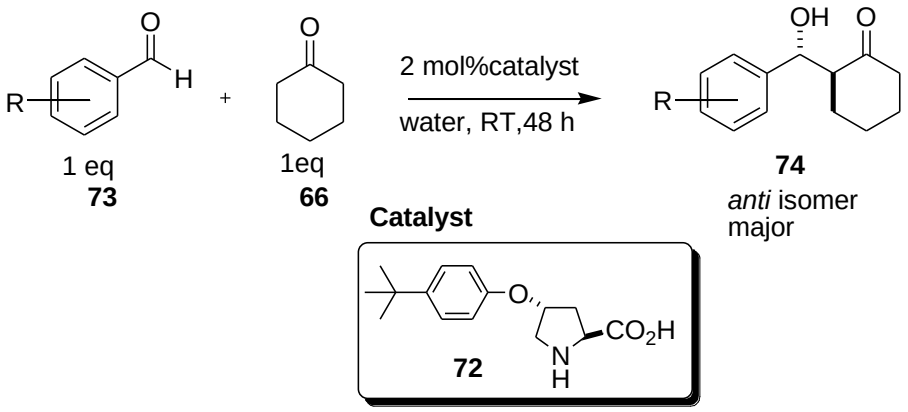
Entry	Product	Reaction Time	Yield [%]	*anti*:*syn*[a]	ee [%][b]
1		48	99	86:14	87
2		48	89	90:10	91
3		72	43	91:9	97
4		72	74	88:12	90
5		72	46	90:10	99
6		72	5	86:14	96
7		24	99	90:10	99
8		24	98	89:11	98
9		24	98	61:39	87
10[c]		72	40	46:54	99(*syn*)
11[c]		72	82	-	55
12[c]		72	49	-	54

[a] Determined by ^{1}H NMR of reaction mixture.
[b] ee was measured on the anti isomer and was determined by HPLC.
[c] 0.3 eq catalyst was used.

1.12.3 Organocatalytic aldol reaction in water/cyclodextrine

A highly efficient asymmetric aldol reaction was also developed by Armstrong *et al*.[28] The researchers used *tert*-butyl phenoxy proline **72** in the presence of cyclodextrine. It was believed that the sulfated β-CD would form a hydrophobic pocket in water increasing the concentration of the catalyst and the reactants while at the same time decreasing the contacts between water (solvent) and the reactants. This would in turn prevent water from interfering with the hydrogen bonds between the catalyst and the reactants.

Organocatalytic aldol reaction of cyclohexanone with various aryl aldehydes was investigated using this system. Quantitative yields and high diastereo- and enantioselectivity were observed (scheme 1.20, table 1.4)



Scheme 1.20

Table 1.4: Catalytic aldol reaction in water catalyzed by **72** [ref. 28].

Entry	Aryl Aldehyde	Yield [%][a]	*anti:syn*[b]	ee [%][b]
1	benzaldehyde	78	90:10	96
2	2-nitrobenzaldehyde	97	>99:1	>99
3[c]	2-nitrobenzaldehyde	0	-	-
4	3-nitrobenzaldehyde	97	96:4	>99
5	4-nitrobenzaldehyde	100	96:4	>99
6	4-chlorobenzaldehyde	80	95:5	99
7	4-bromobenzaldehyde	92	93:7	99
8	4-trifluoromethylbenzaldehyde	100	94:6	>99
9	4-methylbenzaldehyde	65	88:12	98
10	4-methylbenzaldehyde	62	92:8	96
11	2-furaldehyde	71	84:16	98

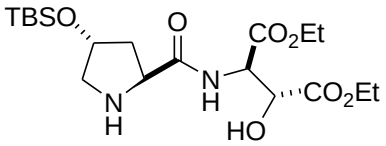
[a] Yield refers to the combined yield of isolated diastereoisomers.
[b] Determined by ^{1}H NMR and HPLC on a chiral stationary phase.
[c] Without catalyst.

In summary *tert*-butyl phenoxy proline **72** in the presence of cyclodextrine was successfully employed in the organocatalytic aldol reactions of cyclohexanone with strong electron-withdrawing aromatic aldehydes in aqueous media. In most cases, high enantioselectivities often ≥ 99% ee were obtained.

1.12.4 Using L-proline amides as catalyst

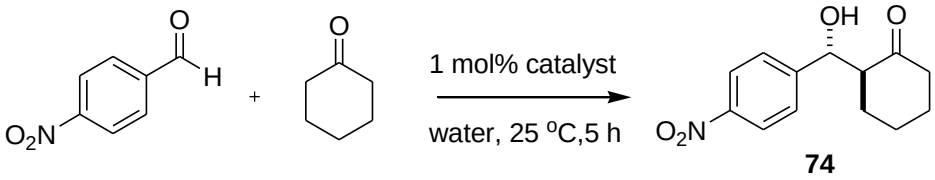
Another example of successful organocatalytic reaction in water includes the work of Gong and co-workers.[29] After investigating and optimizing the organocatalytic aldol

reaction of cyclohexanone with *p*-nitro-benzaldehyde in water with several L-proline amides as catalyst, they found that catalyst **75** offers the best selectivity and yield (scheme 1.21). It was proposed that one of the requirements for a good organocatalyst to function efficiently in water involves a good balance between its hydrophilicity and hydrophobicity. The authors suggested that while the two electron-withdrawing esters increased the hydrophilicity of the catalyst, the siloxy group increases the hydrophobicity, thus maintaining the hydrophobicity-hydrophilicity balance.



75

Figure 1.5: Catalyst used by Gong *et al*.[29]



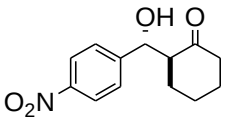
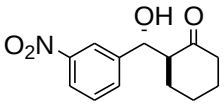
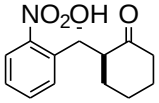
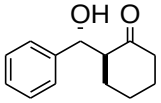
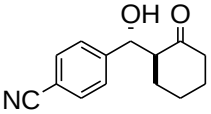
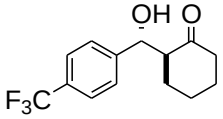
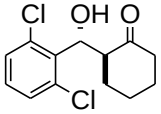
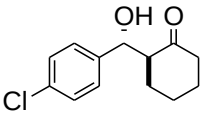
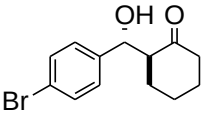
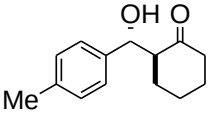
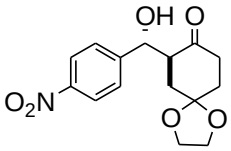
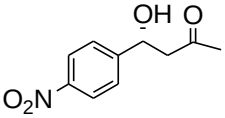
76 **66** **74**
anti isomer
major

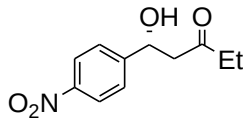
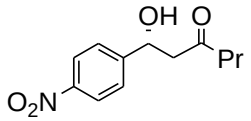
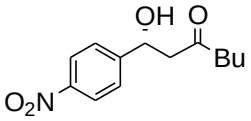
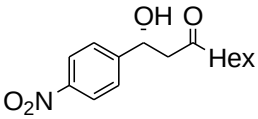
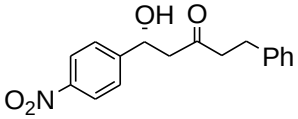
Scheme 1.21

Under the optimal conditions, the scope of the reaction was investigated with several aryl aldehydes and ketones. The results showed that organocatalyst **75** was indeed highly efficient in catalyzing the direct aldol reaction of cyclohexanone with both electron rich and electron deficient aryl aldehydes.

To conclude, by fine tuning the hydrophilicity and hydrophobicity of proline amide derivatives, Gong and co-workers were able to develop a highly efficient organocatalyst.

Table 1.5: Catalytic aldol reaction in water catalyzed by **75** [ref. 29]

Entry	Product	Time (h)	Yield [%][a]	*anti:syn*[b]	ee [%][c]
1		5	99	>99:1	94
2		8	95	98:2	92
3		10	85	>99:1	95
4		24	75	>99:1	92
5		24	90	96:4	92
6		10	93	>99:1	95
7		5	95	>99:1	98
8		24	80	>99:1	93
9		24	94	>99:1	93
10		24	50	>99:1	92
11		70	75	90:10	95
12		14	85	-	71

13		12	30	-	78
14		35	75	-	85
15		24	62	-	84
16		24	80	-	85
17		70	88	-	89

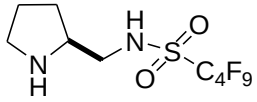
[a] Isolated yield
[b] Determined by ^{1}H NMR of crude product.
[c] ee was measured on the anti isomer and was determined by HPLC

1.13 Reusable organocatalysts

With the advance of organocatalytic aldol reaction, many new organocatalysts have been developed to fine tune the selectivity.[23-25] However, in most conventional organocatalytic reactions, the organocatalyst is often discarded at the end of the reaction. Since these catalysts are often expensive, the ability to recover and recycle them is desirable. The use of fluorous chemistry as a means to overcome this limitation has been recently envisioned. It was first developed by Horvat and Rábai in the mid 1990's[30] and Curran *et al.* elaborated on the use of flourous solid-phase extraction for the separation of reaction mixtures.[31] In the following part, some recent advances on fluorous organocatalysts applied in asymmetric aldol reactions in water are discussed.

1.13.1 Organocatalytic aldol reaction catalyzed by recyclable fluorous pyrrolidine sulfonamide

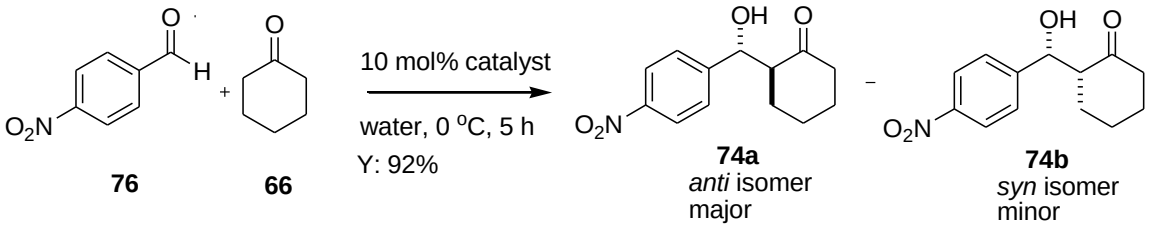
In 2008 Wang and co-workers were among the first ones to successfully develop a water compatible and recyclable fluorous organocatalyst for the organocatalytic aldol reaction.[32]



78

Figure 1.6: Organocatalyst used by Wang *et al*.

They had previously applied their catalyst in the enantioselective Michael addition of various ketones and aldehydes with nitroolefins.[32] An aqueous solution of cyclohexanone and p-nitro benzaldehyde was used as the model study. The reaction was optimized using different ratios of the donor and the acceptor as well as varying the temperature. It was found that the reaction proceeded best when the ratio of 66/76 was 10:1 and at 0 °C (scheme 1.22).



Scheme 1.22

Having optimized the reaction conditions, the authors then investigated the recycling capability of the catalyst **78** using the fluorous silica gel based solid-liquid extraction to recover the catalyst.

Table 1.6: Reuse of catalyst in the aldol reaction of cyclohexanone with p-nitro benzaldehyde [ref. 32].

Cycle	Time (h)	Yield [%][a]	*anti:syn*[b]	ee [%][c]
1	6	90	5:1	90
2	7	92	5:1	90
3	12	90	5:1	90
4	13	90	5:1	90
5	19	91	5:1	89
6	24	92	5:1	87
7	40	88	5:1	87

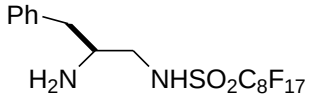
[a] Isolated yield
[b] Determined by ^{1}H NMR of crude product.
[c] ee was measured on the anti isomer and was determined by HPLC

For each cycle, the catalyst can be easily recovered (>90%) and was used without purification in the next cycle. The results showed that the catalyst was effective even after seven cycles. However as shown in table 1.6 the reaction time increased from 6 to 40 hours while the enantioselectivity started to decrease after the fourth cycle.

Finally the authors also evaluated the scope of **78** in catalyzing the aldol reactions of various ketones with different aryl aldehydes. It was found that both electron rich and electron deficient aromatic aldehydes gave excellent enantioselectivity.

1.13.2 Organocatalytic aldol reaction in brine using recyclable fluorous β-aminosulfoamide as organocatalyst

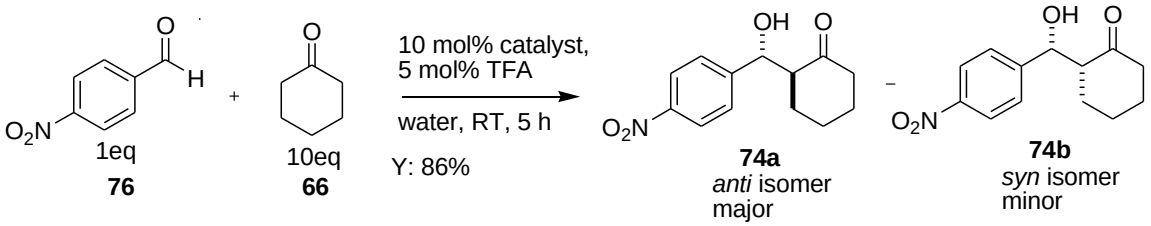
A more recent approach on the asymmetric aldol reaction with recyclable fluorous organocatalyst has been developed by Miura *et al*.[33] It makes use of the fluorous sulfonamide which was prepared from phenylalaninol (fig 1.7)



79

Figure 1.7: Catalyst used by Miura *et al*.

Optimization of the reaction was done in brine using p-nitrobenzaldehyde and cyclohexanone. It was found that better selectivity was observed when TFA was used as an additive. Although the reaction gave the best result at 0 °C, the longer reaction time prompted the authors to carry out the reaction at room temperature instead (scheme 1.23).



Scheme 1.23

Next, the recycling capability and reusability of the catalyst were evaluated using the reaction of cyclohexanone with p-nitrobenzaldehyde as model (table 1.7).

Table 1.7: Reuse of catalyst **79** in the aldol reaction of cyclohexanone with p-nitro benzaldehyde [ref. 33].

Cycle	Time [h]	Yield [%][a]	*anti*:*syn*[b]	ee [%][c]	Catalyst recovery
1	5	89	83:17	85	100
2	5	86	84:16	91	89
3	6	78	85:15	90	94
4	6	65	83:17	87	92
5	9	75	85:15	90	91
6	12	75	84:16	86	90

[a] Isolated yield
[b] Determined by ^{1}H NMR of crude product.
[c] ee was measured on the anti isomer and was determined by HPLC

The results showed that catalyst **79** could be efficiently recycled using fluorous silica gel based solid-liquid extraction with a high percentage recovery. The catalyst **79** also maintained its diastereo- and enantioselectivity after repeated usage. However, the reaction time increased from 5 h to 12 h while the yield decreased from 89 % to 75 % after repeated usage of the catalyst without purification.

In summary, both the catalysts developed by Wang and Miura could be easily recycled and reused in the organocatalytic aldol reaction. However, the selectivities of the catalysts were found to be moderate with diastereoselectivities not exceeding 6 : 1 (*anti* : *syn*).

1.15 Conclusions

In this chapter, I have reviewed some of the major concepts of the aldol reaction. Some, but not all, of the methods for inducing stereoselectivity in the aldol reaction were briefly described.

In the second part of the introduction, I focused on the organocatalytic aldol reaction. Being a vast topic in itself, it was impossible to write a comprehensive review in this thesis. Instead, some selected recent advances in the organocatalytic aldol reactions in water as well as the use of reusable fluorous organocatalysts were reviewed.

Interestingly, some authors observed that most organocatalysts that were highly active in aqueous media were made up of a hydrophilic part as well as a hydrophobic part. It was suggested that these types of catalysts would mimic aldolases better in the sense that the hydrophobic part of the catalysts could reduce contacts between the reactants and water.[25, 29]

This brief introduction was intended to help the reader to relate to the next chapter which elaborated on the efforts of using the aldol reaction towards the synthesis of alkaloids.

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CHAPTER 2

2. Results and discussion

This thesis deals with the chemistry of tropinone and dioxanones with main emphasis on organocatalytic aldol reactions of these compounds. As I have previously described in Chapter 1, organocatalysts were employed in a number of reactions. Below the objectives of my research are briefly described. The objective of the tropinone project was to repeat the synthesis of some tropane alkaloids using methodologies previously described by Majewski's group followed by a brief investigation of the use of organocatalysis to functionalize tropinone. The second part of the thesis deals with a methodological study of the proline-catalyzed aldol reaction of different dioxanones. Finally, some applications of the dioxanone methodology in the synthesis of hyacinthacines are described.

2.1 Tropane alkaloids

Tropane alkaloids containing the 8-azabicyclo[3.2.1]-octane skeleton, are usually found in plants belonging to families *Solanaceae, Erythroxylaceae* and *Convolvulaceae.* Due to the unique biological properties of this constrained nitrogen heterocycle, tropane derivatives have found widespread uses as therapeutics.[1] Consequently, an efficient synthesis of enantiomerically pure tropane alkaloids is of great importance.

In the past, our group used chiral lithium amides and LiCl as additive for the enantioselective deprotonation of tropinone (**1**). Through this methodology, several tropane alkaloids and analogs were synthesized in enantiomerically enriched form (up to 98% ee, fig 2.1).[2,3]

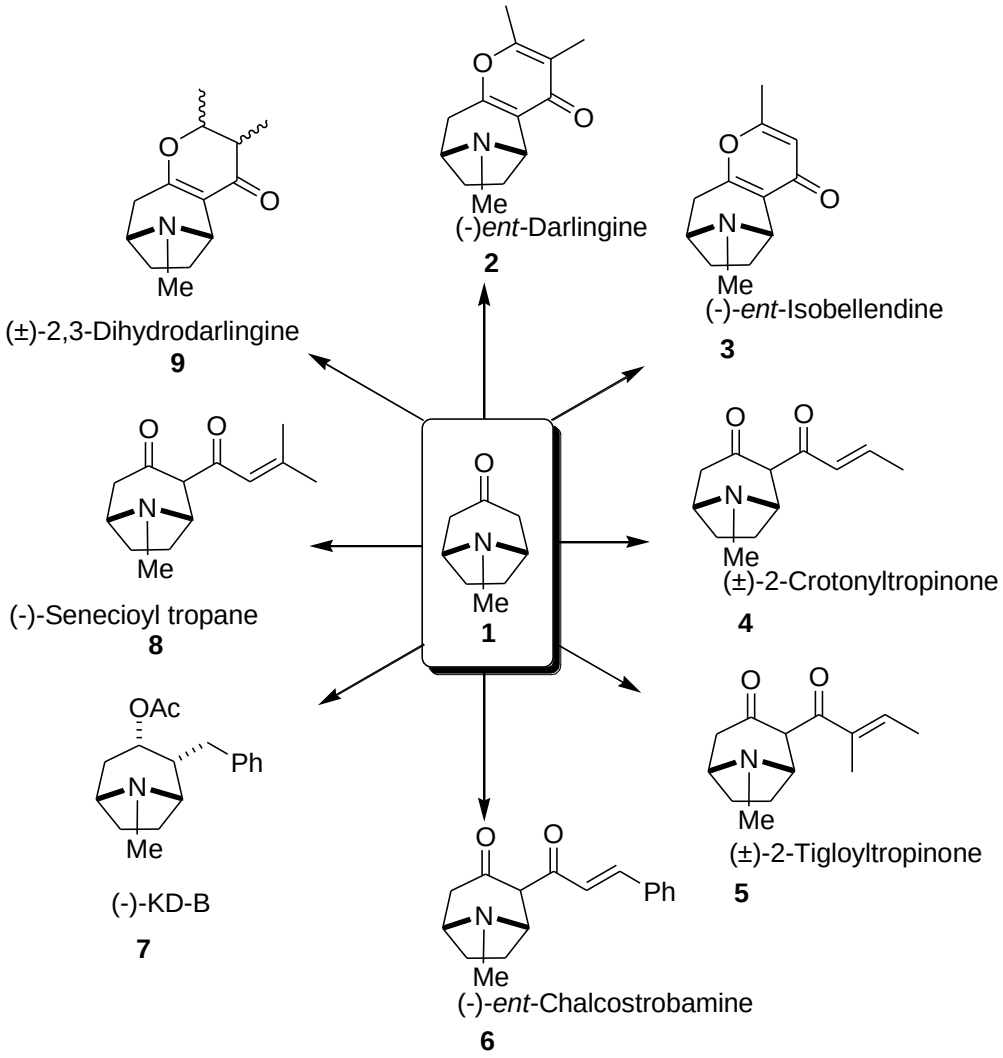


Figure 2.1: Examples of tropane alkaloids synthesized by Majewski's group

The re-emergence of organocatalysis in the early 2000's, made it possible to catalyze a wide array of chemical reactions with moderate to high diastereo- and enantioselectivities. Often-used catalysts include proline and its derivatives. Their availability, efficiency and easy removal by aqueous work-up have made them very attractive to use. However, the organocatalytic aldol reaction on tropinone has not yet been reported, thus inviting more research.

2.1.2 Research Objectives

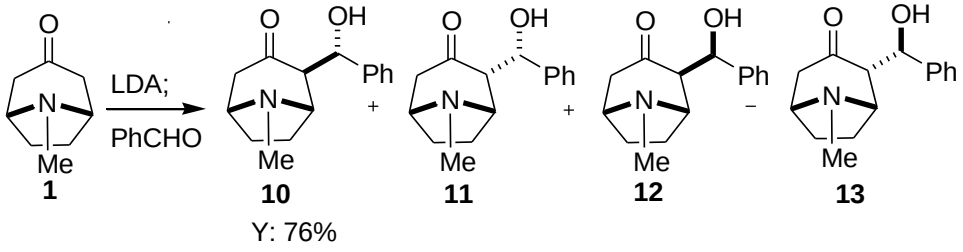
The goal of the tropinone project can be subdivided into two main parts:

- To repeat the synthesis of some tropane alkaloids through enantioselective deprotonation of tropinone using chiral lithium amide.
- To investigate the enantioselective deprotonation of tropinone using organocatalysis.

2.1.3 Deprotonation of tropinone using LDA

In order to determine the enantiomeric excess of any compound, it is often useful to have its racemic form. It was decided to first investigate the formation of the racemic tropinone enolate and to subsequently apply it in the synthesis of racemic tropane alkaloids.

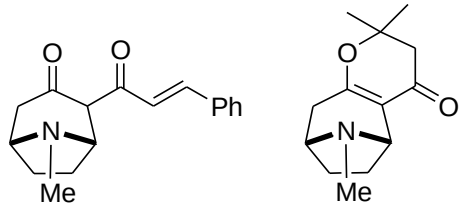
The aldol reaction between tropinone and benzaldehyde was chosen as the model study. At first the reaction was carried out using LDA as the base. In principle, the treatment of the lithium enolate with benzaldehyde could yield four different diastereoisomers (scheme 2.1).



Scheme 2.1

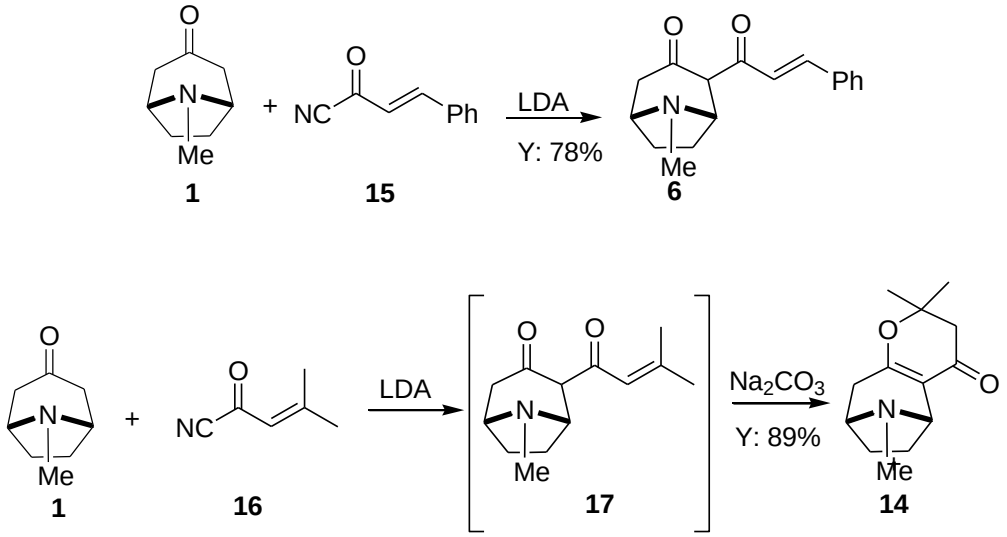
As it has been previously reported,[3] the reaction was very diastereoselective and diastereoisomer **10** was formed selectively (dr: 20 : 1). Next, we decided to synthesize

some racemic tropane alkaloids and analogs namely; (-)-*ent*-Chalcostrobamine (**6**) and (-)-11,11-Dimethyl-10,11-dihydropyranotropane-3-one (**14**).



6 **14**

Reaction of racemic tropinone enolate with cinnamoyl cyanide **15** gave racemic chalcostrobamine **6** in 78% yield while the reaction with senecioyl cyanide **16** followed by an *in situ* cyclization with anhydrous sodium carbonate gave the racemic compound **14** in 89 % yield (Scheme 2.2).



1 **15** **6**

1 **16** **17** **14**

Scheme 2.2

2.1.4 Enantioselective deprotonation of tropinone

Having synthesized the aldol adduct **10** and the two compounds **6** & **14** in the racemic form, the next step was to attempt the EPC synthesis through the enantioselective deprotonation of tropinone. Previous studies by Zheng and Lazny identified several

promising chiral amines (fig 2.2) as sources of chiral lithium amides that react with high enantioselectivity. [2, 3]

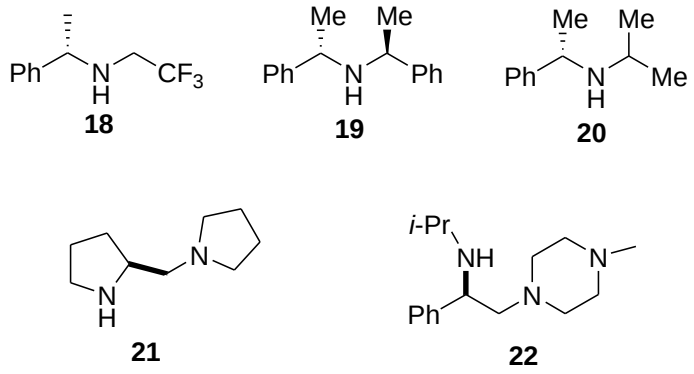
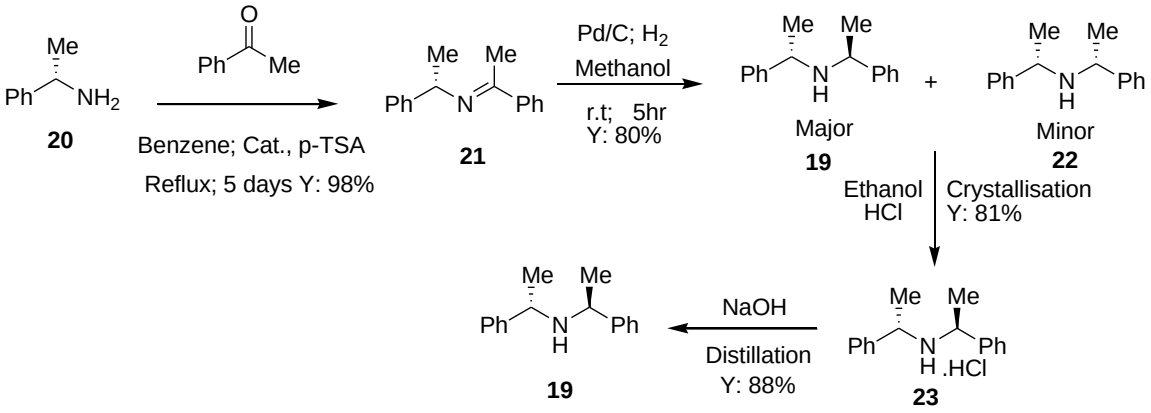


Figure 2.2: Examples of chiral amines precursors to chiral Li amides

Of these, the chiral amine **19** was chosen since it can be prepared on a large scale and the starting material is relatively cheap (scheme 2.3). Moreover, enantioselective deprotonation involving the Li amide of this amine is also well established.[2,3]



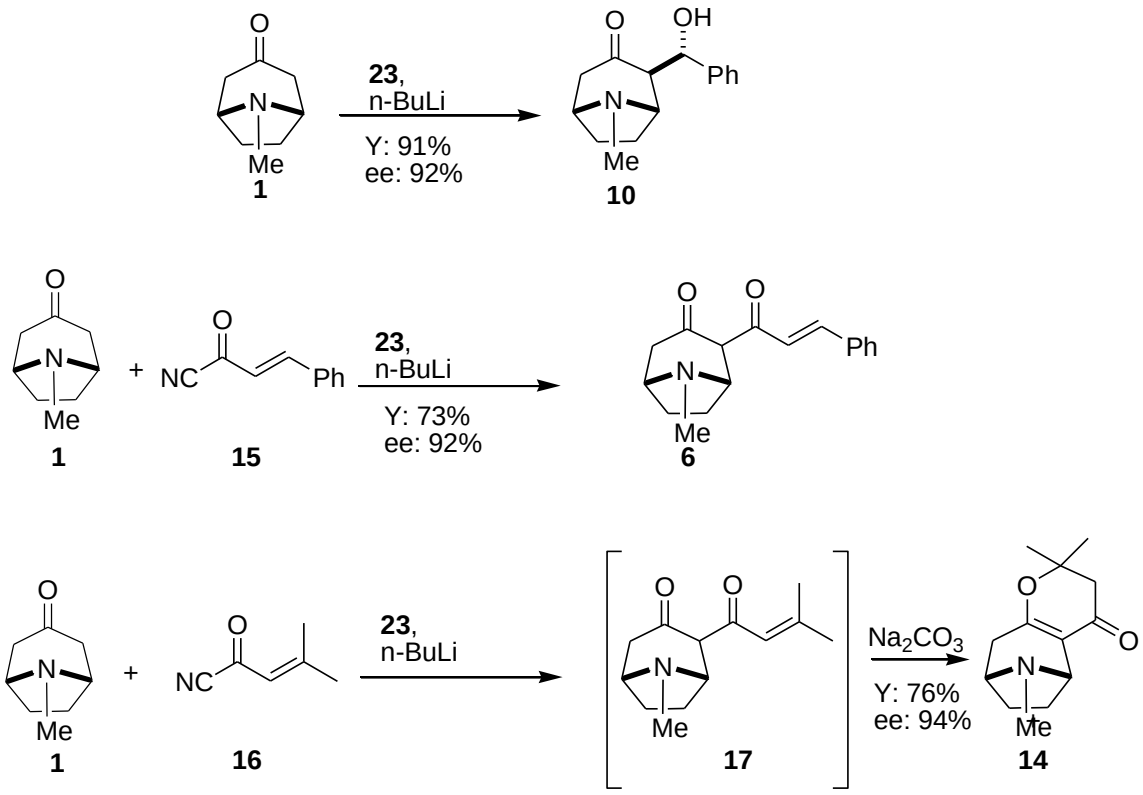
Scheme 2.3

The synthesis of the amide was done as described in literature.[3] (*S*)-(-)-α-Methylbenzylamine **20** was refluxed with acetophenone in the presence of p-TsOH to give the enamine **21** in 98 % yield. Reduction of **21** with palladium on carbon gave a mixture of the amine 1**9** and its meso diastereoisomer **22.** Purification by crystallization gave the hydrochloride salt **23** which could be converted back to the free base **19** by

treating it with sodium hydroxide and purifying the product through vacuum distillation. Instead of using the amine **19** for lithium amide formation, its hydrochloride salt **23** could also be used. Moreover, this provides certain advantages:

- Lithium chloride which is an important additive in the enantioselective deprotonation of tropinone will be generated *in situ* and will therefore be moisture free.
- It requires one less step to prepare the base for the enantioselective deprotonation of tropinone.
- The hydrochloride salt **23** has a longer shelf life than the amine **19**

The aldol reaction of tropinone with benzaldehyde using **23**/*n*-BuLi as the base proceeded in high yield. However, the enantioselectivity of the reaction was lower (50% ee) than the expected value (93 % ee).[2] Low enantiomeric excess was also observed for the synthesis of the tropane alkaloids **6** and **14** (42 & 52 % ee respectively).This was mainly due to the presence of impurities such as LiOH in *n*-BuLi and the minor isomer **22** in the crystallization step. The reactions were repeated using a fresh bottle of *n*-BuLi and recrystallized amine hydrochloride **23** and afforded **6**, **10** and **14** in high enantiomeric excess (scheme 2.4).



Scheme 2.4

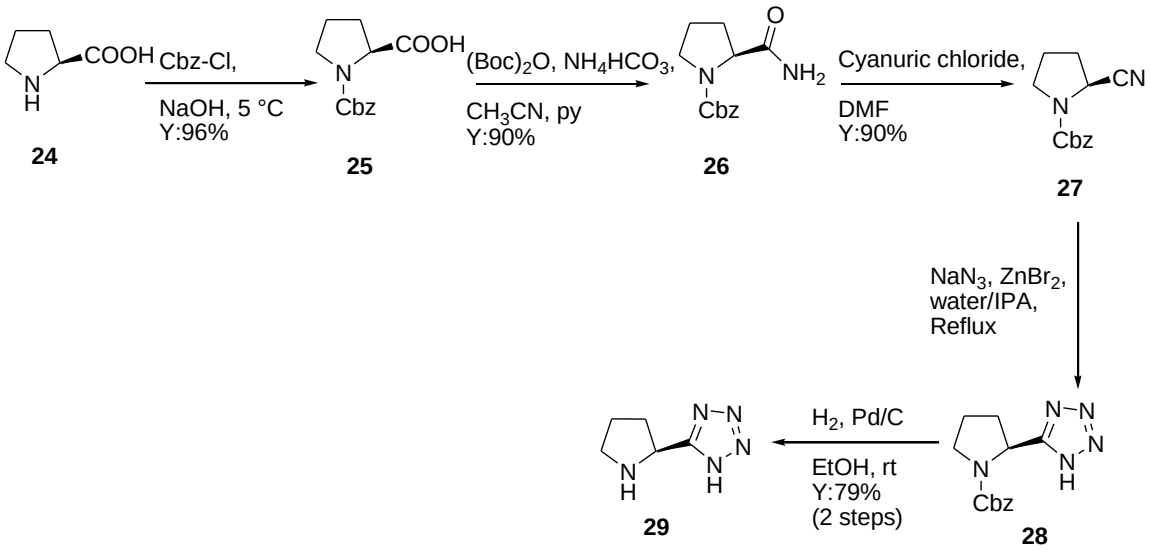
Finally, the reactions were repeated with the free amine **19**. The yields and the enantioselectivities of the reactions were in accordance to the reported values[2]; aldol adduct **10** in 86% yield and 90% ee, (-)-*ent*-Chalcostrobamine **6** in 78% yield and 88% ee and (-)-11,11-dimethyl-10,11-dihydropyranotropane-3-one **14** in 90% yield and 92% ee. This short study illustrated the importance of carefully controlling reaction conditions in order to obtain high selectivity.

2.1.5 Organocatalytic aldol reaction of tropinone

In our lab the organocatalytic aldol reaction on tropinone was briefly investigated by Laura Sikorska.[4] She found that the use of proline as the catalyst was not promising and in most cases a mixture of four aldol adducts was obtained in almost equal ratios.

Attempts to optimize the reaction conditions using additives (water, LiCl, PPTS) were not successful as they provided no increase in the selectivity or yield.

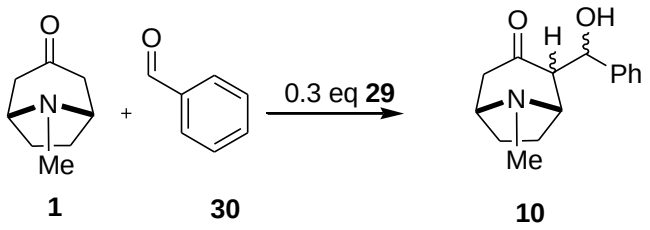
In recent years, the tetrazole derivative of proline **29** has been used as the catalyst alternative to proline. In some cases, it was found that the tetrazole derivative offered better catalytic activity and higher selectivity.[5] Consequently, I decided to investigate using this compound as the catalyst for the aldol reaction of tropinone with different aldehydes. *(S)*-5-Pyrrolidin-2-yl-1H-tetrazole was synthesized according to the literature procedure (scheme 2.5). [6]



24 **25** **26** **27** **28** **29**

Scheme 2.5

Having synthesized the (*S*)-proline tetrazole catalyst, the next goal was to optimize the set of conditions for the organocatalytic aldol reaction of tropinone with different aldehydes. The aldol reaction of tropinone with benzaldehyde was again used as the model reaction (Scheme 2.6).



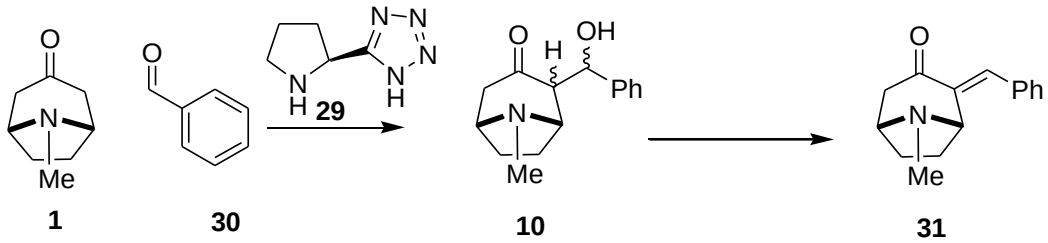
Scheme 2.6

First, the reaction temperature was varied. Acetonitrile was used as the solvent and water as the additive due to literature precedence. (Table 2.1).[5]

Table 2.1: Organocatalytic reaction of tropinone with benzaldehyde at different temperatures

Entry	Temp	Reaction time	Conversion
1	5°C	3days	<1%
2	rt	10 days	<5%
3	40°C	4 days	>99%

Interestingly, TLC of the reaction mixture from the experiment at 40 °C (entry 3) showed the formation of two new compounds. NMR analysis of the crude mixture showed a mixture of the aldol **10** and the dehydrated aldol adduct **31** (Scheme 2.7). However, upon purification through FCC, only the unsaturated ketone **31** was isolated. Based on previous reports[2] compound **31** was assigned as the (*E*)-isomer.



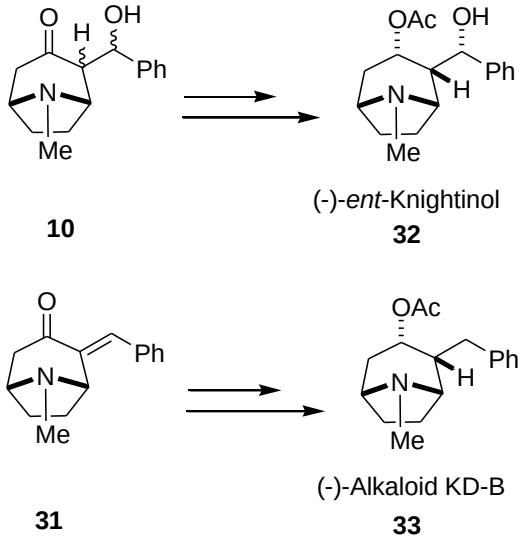
Scheme 2.7

The reaction conditions were further optimized using different solvents and additives as shown in the following table

Table 2.2: Reaction of tropinone with benzaldehyde catalyzed by (*S*)-proline tetrazole .

Entry	Solvent	Additive (1eq)	Ratio of product (10:31)
1	MeCN	LiCl	2:1
2	MeCN	H_2O	1:1.4
3	MeCN	-	1:6.8
4	DMSO	LiCl	1:3.7
5	DMSO	H_2O	1:7.2
6	DMSO	-	1:9.6

In the absence of additives, the dehydrated product was favored, while the addition of either lithium chloride or water tended to prevent the dehydration of the aldol product to some extent. It should be noted that both the aldol and the dehydrated aldol adduct could be useful compounds as they both can be used in the synthesis of tropane alkaloids (Scheme 2.8).[2]



Scheme 2.8

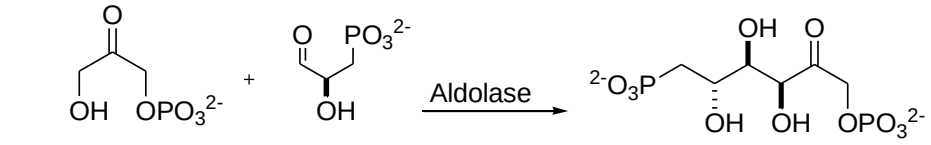
However, for some unknown reasons, purification of the crude product led to a dramatic decrease in the yield and only the dehydrated product was isolated (usually in yields lower than 10%). This observation was similar to what other group members have reported for the organocatalytic aldol with proline as the catalyst.[4]

2.1.6 Conclusions

The syntheses of two tropane alkaloids were successfully repeated. Organocatalytic aldol reaction of tropinone with benzaldehyde using (*S*)-5-pyrrolidin-2-yl-1H-tetrazole was successfully carried out to give the dehydrated aldol adduct as the major product. To the best of my knowledge, this is the first example where an organocatalytic aldol reaction on tropinone showed moderate selectivity and a pure product was actually isolated.

2.2 Exploring the chemistry of dioxanones

Dihydroxy acetone (DHA), a simple triose carbohydrate, is a very important building block in the biosynthesis of sugars. In the process of photosynthesis, plants produce D-fructose from the aldol reaction of dihydroxyacetone phosphate (DHAP, donor component) with D-glyceraldehyde-3-phosphate (acceptor component, scheme 2.9).[7]



(DHAP) dihydroxyacetone phosphate

34 **35** **36**

D-fructose-1,6-diphosphate

Scheme 2.9

For years, researchers have been trying to find synthetic equivalents for DHAP and to use them in target oriented synthesis. In the 1990's our group became interested in the ketal

and acetal protected form of DHA i.e 2,2-disubstituted 1,3 dioxanones (**37**). Synthetic studies carried out by Pawel Nowak resulted in the first application of dioxanones in the synthesis of a natural compound namely, (+)-frontalin.[8] The potential of dioxanones as a synthetic scaffold was also extensively studied by several other groups.[9] More than 25 natural products and/ or their derivatives have been synthesized from dioxanones to date. Some of these are illustrated in figure 2.3.[8,9,10]

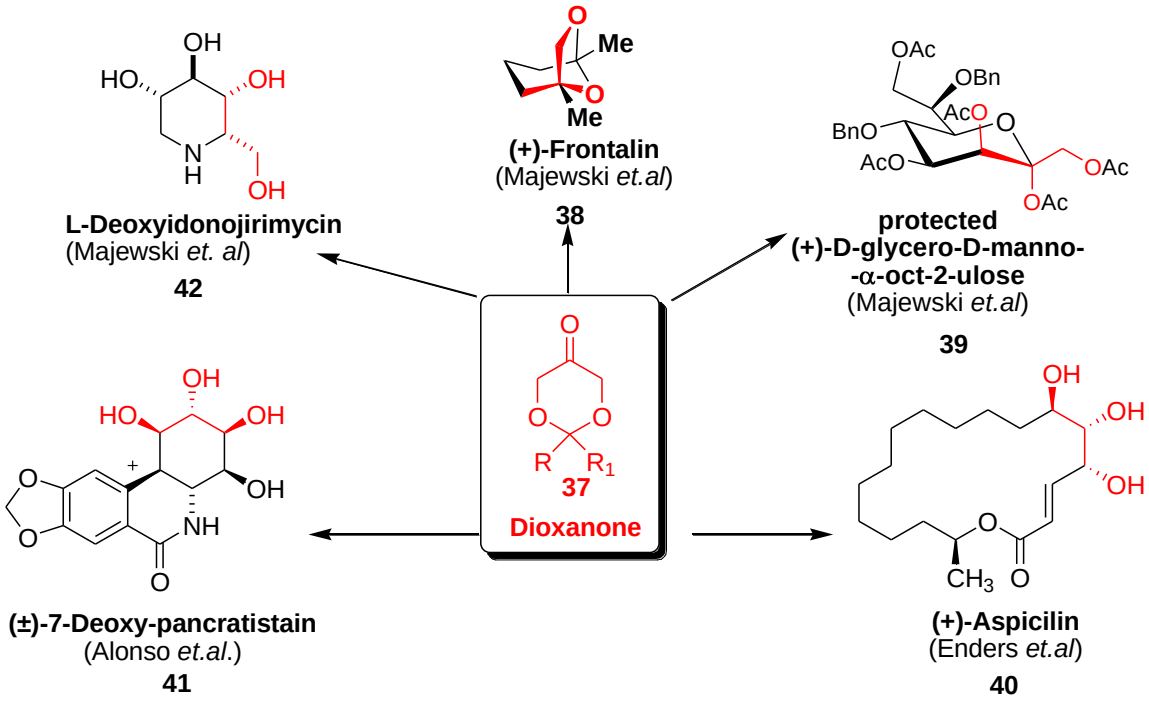


Figure 2.3: Examples of natural products synthesized from dioxanone scaffold

2.2.1 Research objectives

From the initial studies started around 20 years ago, the chemistry of dioxanones has greatly evolved. We can now control several aspects of dioxanone chemistry:

- Enantioselective deprotonation of dioxanones through chiral lithium amides.[10]
- Organocatalytic aldol, Michael and Mannich reactions.[11]
- The second aldol at the α' position, through lithium and boron enolate chemistry.[12]

However, there are still some limitations, since both the alkylation and the acylation of dioxanones through lithium enolate or under organocatalytic conditions proved elusive. Moreover, we do not have full control of stereochemistry of the aldol reaction. Accordingly, I have defined my research objectives as:

- Expanding the methodology of organocatalytic aldol on dioxanones and analyzing the effect of different substituents on dioxanones.
- Increasing the stereoselectivity control in the first aldol reaction on dioxanones.
- Demonstrating and applying the dioxanone methodology in the synthesis of polyoxygenated compounds.

The following chart gives a broader overview of the project

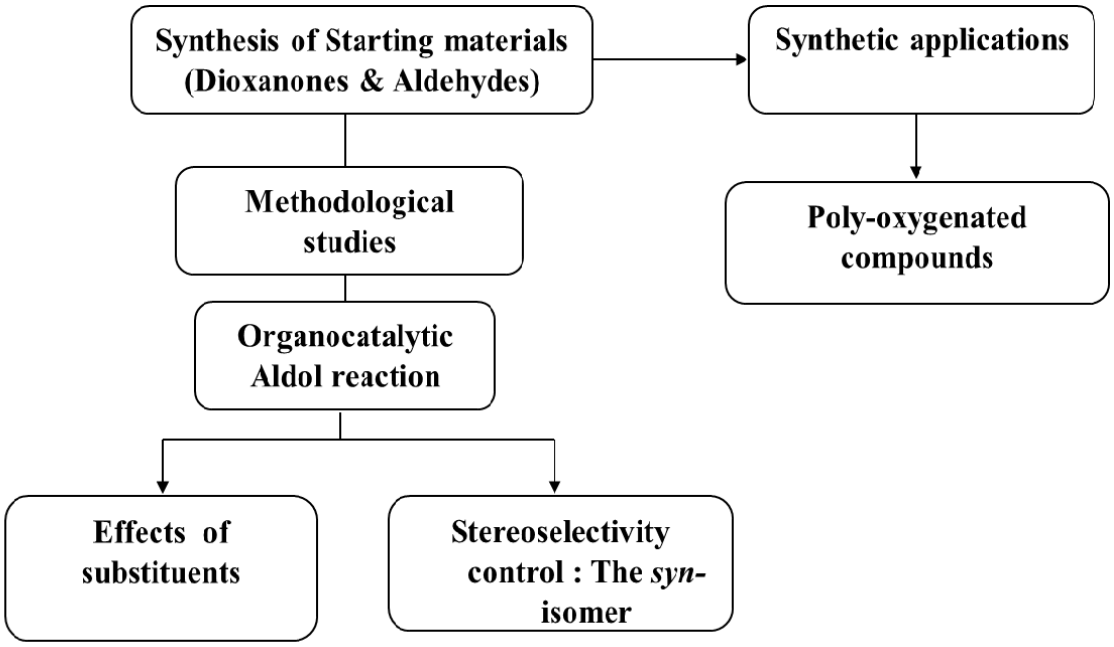
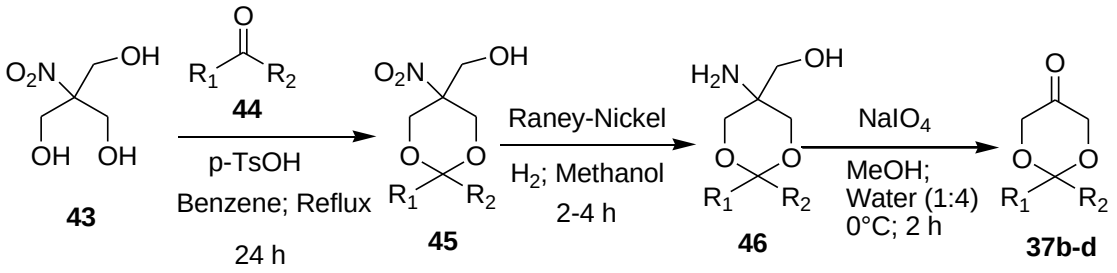


Figure 2.4: Conceptual outline of the dioxanone project

2.2.2 Synthesis of dioxanones

As I have previously stated, the first part of the dioxanone project was about the study of how different substituents at the C-2 position on the dioxanone ring can alter the reactivity. In order to do so, it was imperative to have a reliable protocol to synthesize several dioxanones with different alkyl groups at C-2. In our lab, a general synthetic protocol was developed by Gleave and later refined by Nowak and Palyam (scheme 2.10).[10,13,14]



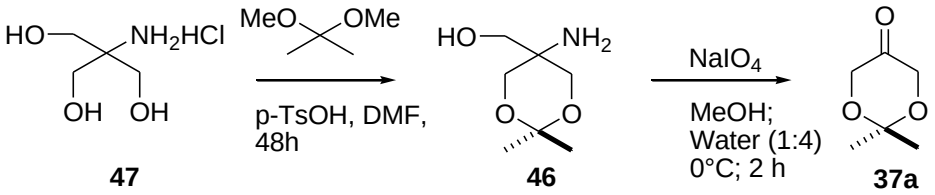
Scheme 2.10

Standard acetalization/ketalization of tris(hydroxymethyl)nitromethane **43** with the desired aldehyde/ketone resulted in the nitro compound **45** which could be reduced at 85 °C and 1400 psi using Raney-Nickel catalyst to give the corresponding amine **46**. Palyam further optimized the reductive step and found that the reaction could be carried out at room temperature and at much lower pressure of 50 psi.[14] Finally, oxidative cleavage of the amine using sodium periodate afforded the desired dioxanones. Unfortunately, I found that ketones with electron withdrawing groups did not undergo ketalization (entry 5). This was most probably due to the strong inductive effect of CCl_3 group. The yields of the reaction are summarized in the following table.

Table 2.3: Synthesis of 2,2-dialkyl substituted dioxanones (scheme 2.10, 2.11)

Entry	**Dioxanone**	**R_1**	**R_2**	**Dioxanone Overall yield (%)**
1	**37a**	Me	Me	66
2	**37b**	*t*-Bu	Me	72
3	**37c**	*i*-Bu	*i*-Bu	60
4	**37d**	*t*-Bu	H	66
5	**37e**	CCl_3	CCl_3	no reaction

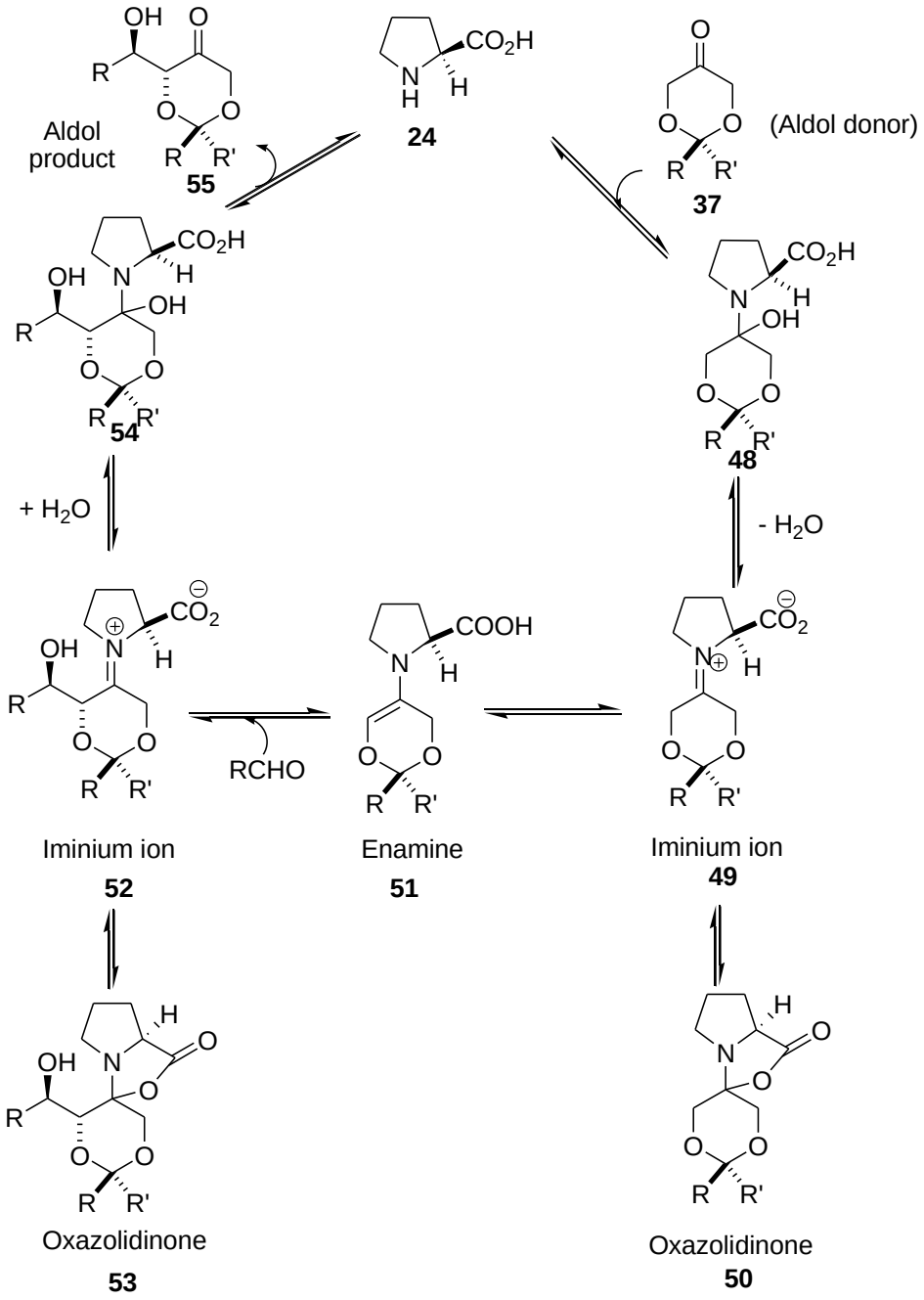
It should be noted that the synthesis of dioxanone **37a** was achieved through Niewczas, modified protocol (Scheme 2.11).[12] This pathway provides a better yield and requires only two steps.



Scheme 2.11

2.2.3 Organocatalytic aldol reaction of dioxanones

Among all the dioxanone reactions that have been studied, the organocatalytic aldol reaction is definitely the one that has received the most attention. The organocatalytic cycle describing this reaction is illustrated in scheme 2.12.

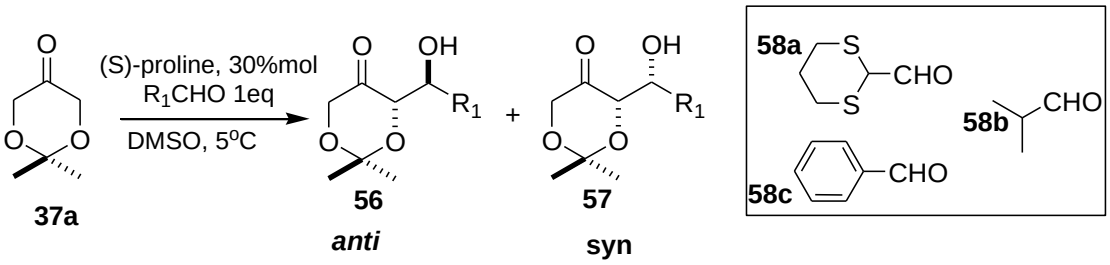


Scheme 2.12

The description of the cycle is based on the well accepted theory[15] but it should be noted that there is no actual evidence for the steps. In the organocatalytic cycle, reaction of the dioxanone with (*S*)-proline leads to the hemiaminal moiety **48** which then forms the

corresponding iminium ion intermediate **49**. The latter can then form either the corresponding enamine **51** or the oxazolidinone **50**. The formation of the oxazolidinone will lead to a decrease in the turnover of the catalyst.[15] Reaction of the enamine **51** with the electrophile (aldehyde) results in the formation of a new iminium ion **52** which can either form the oxazolidinone **53** or hydrolyze to give the aldol product **55** and releases (*S*)-proline back to the catalytic cycle.

The organocatalytic aldol reactions of dioxanones with various aldehydes were successfully developed in the Majewski's lab (Scheme 2.13, Table 2.4) and by others.[16] However, it was found that the enantioselectivities of the reactions were often low which made them synthetically unappealing. During the optimization of the reactions, Niewczas found that the use of additives such as lithium chloride (LiCl, weak Lewis acid) and pyridinium-*p*-toluenesulfonate (PPTS, Bronsted acid) enhanced the stereoselectivities of the reactions (from ee of 66% up to 93% depending on the substrate).[12] This was explained by the hypothesis that the use of additives such as LiCl prevented the formation of the oxazolidinone intermediates.[15a]



Scheme 2.13

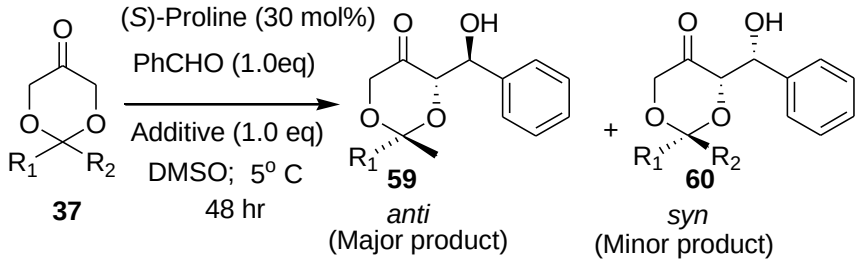
Table 2.4: (*S*)-Proline-catalyzed aldol reaction of dioxanone **37a** in the presence of additives [ref 15a]

Entry	R_1CHO	Additive (eq)	Time (days)	Isolated yield [%]	dr[a] (syn/anti)	ee[b] (anti)[%]
1	58a	-	3	78	> 99	66
2	58a	PPTS (1)	3	83	> 99	93
3	58a	LiCl (1.5)	3	85	> 99	90
4	58c	-	4	54	36 : 64	68
5	58c	LiCl (1.5)	4	85	29 : 71	86
6	58c	PPTS (1)	4	61	18 : 82	86
7	58b	-	3	80	> 99	86
8	58b	LiCl (1)	3	74	> 99	92
9	58b	PPTS (1)	3	70	> 99	96

[a] dr was measured by ^{1}H NMR on the crude reaction mixture,
[b] ee was measured by ^{1}H NMR on pure (anti) isomer with $Eu(tfc)_3$ or (S)-(+)-TFAE as shift reagents.

2.2.4 Modulating dioxanone reactivity and selectivity by changing the alkyl substituents

Further optimization of the organocatalytic aldol reaction by Palyam showed that replacing one of the methyl groups on 2,2-dimethyl-1,3-dioxan-5-one with a bulkier group such as *tert*-butyl greatly increased diastereoselectivity of the reaction (Scheme 2.14, Table 2.5).[14]



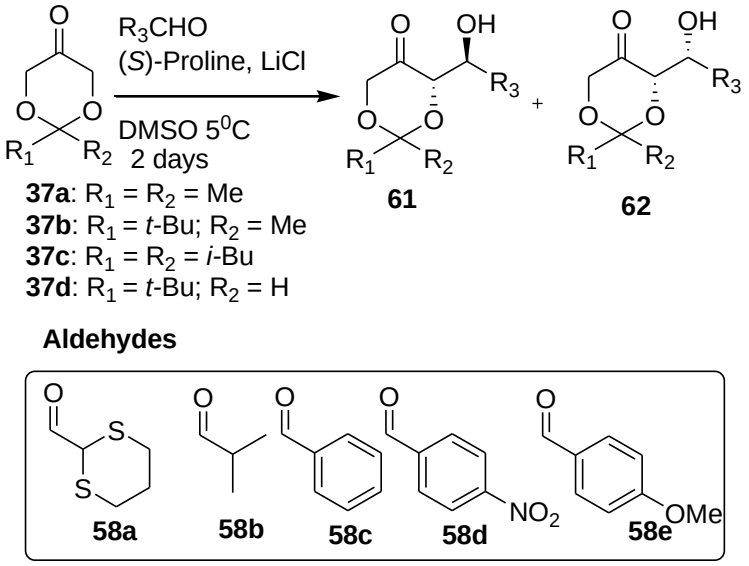
Scheme 2.14

Table 2.5: (*S*)-Proline-catalyzed aldol reaction of dioxanones with benzaldehyde [ref. 14]

Entry	Dioxanone (1eq)		Additive (1eq)	Yield (%)	dr [a] (*anti*:*syn*)	er [b] (*anti*)
	R_1	R_2				
1	Me	Me	-	54	67:33	84:16
2	*t*-Bu	Me	-	63	94:06	80:20
3	*t*-Bu	Me	LiCl	72	98:02	84:16
4	*t*-Bu	Me	PPTS(0.3eq)	71	95:05	92:08

[a] dr was measured by ^{1}H NMR on the crude reaction mixture
[b] Determined by HPLC on Chiralpack AD column

Following these observations, the effects of substitution on the dioxanone ring were further investigated by a joint study involving Nagarjuna Palyam, Izabella Niewczas and myself. Table 2.6 summarizes the results that have been obtained.



Scheme 2.15

Table 2.6: Effect of substitution on dioxanone ring on selectivity in aldol reaction catalyzed by (*S*)-proline

Entry	Dioxanone (1eq)		Aldehyde	Yield (%)	dr [a] (*anti*:*syn*)	ee [d] (%)
	R_1	R_2				
1[b]	Me	Me	58a	85	98:02	90
2[c]	*t*-Bu	Me	58a	85	98:02	96
3	*i*-Bu	*i*-Bu	58a	70	95:05	92
4[b]	Me	Me	58b	66	96:04	92
5[c]	*t*-Bu	Me	58b	80	95:05	92
6	*i*-Bu	*i*-Bu	58b	68	95:05	90
7[b]	Me	Me	58c	85	71:29	86
8[c]	*t*-Bu	Me	58c	72	98:02	68
9	*i*-Bu	*i*-Bu	58c	60	80:20	62

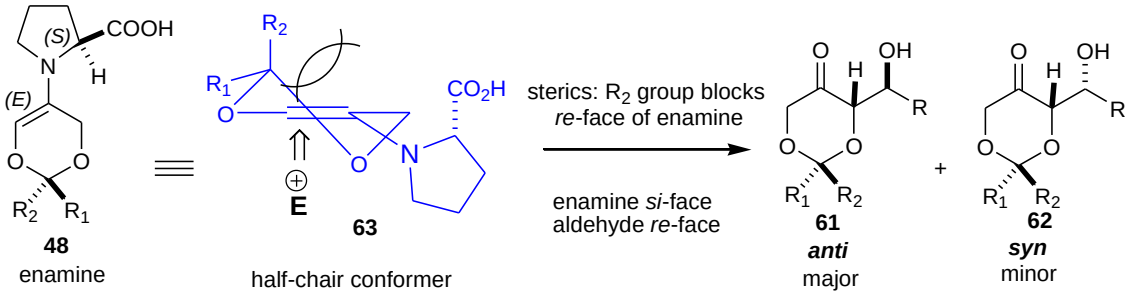
10	*t*-Bu	H	58c	47	76:24	-
11[c]	*t*-Bu	Me	58d	61	98:02	-
12	*i*-Bu	*i*-Bu	58d	66	89:11	68
13[c]	*t*-Bu	Me	58e	53	98:02	-
14	*i*-Bu	*i*-Bu	58e	35	80:20	-

[a] dr was measured by ^{1}H NMR on the crude reaction mixture
[b] Reactions were carried out by Niewzcas and/or Palyam
[c] Reactions were carried out by Palyam and Delawarally
[d] ee was measured by ^{1}H NMR on *anti*-isomer with Eu(tfc)$_3$ or (S)-(+)-TFAE as shift reagents and/or HPLC on Chiralpack AD column

In the search for the best dioxanone substrate for the proline-catalyzed aldol reaction, it was found that 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one (**37b**) which belongs to the C_s symmetry point group generally shows a better selectivity than dioxanone **37a** and **37c** which belong to C_{2v} point group symmetry. It was also observed that dioxanone **37d** was the least selective.

2.2.4.1 Rationalizing the effect of substitution on selectivity

The intermediate formed between proline and dioxanone is believed to control the stereochemical outcome of the aldol reaction. The stereogenic center on proline moiety controls the enantioselectivity while the enamine moiety controls the diastereoselctivity of the reaction.[12,14,16] In general, for dioxanone chemistry, aldehydes add to dioxanones enolates and dioxanones enamines via an equatorial attack to lead to the *anti* aldol adduct as the major product (scheme 2.16).[8b,12,14] This is contrary to Evan's model of similar transformations on enolates of cyclic ketones such as cyclohexanone.[29] The reason for this anomaly of equatorial addition of electrophiles (aldehydes in the case of aldol reaction) to the reactive dioxanone enamine or enolate intermediate is still unclear.[8b]

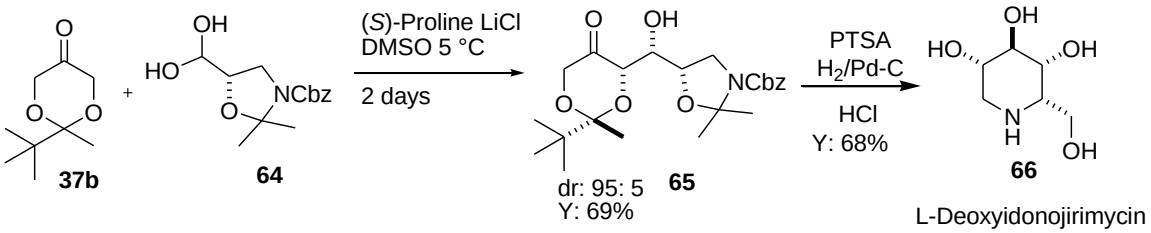


Scheme 2.16

As shown in scheme 2.16, the enamine most probably exists predominantly as the half chair conformer. In dioxanones which have different substituents at the C-2 position, the conformer with the bulkier group at the equatorial position predominates. It maybe hypothesized that bulkier R_2 group (scheme 2.16) will have a higher chance of blocking the re-face of the enamine leading to higher diastereoselectivity as observed in the case of dioxanone **1b** while in the case of dioxanone **1d** the R_2 group being hydrogen offers little steric hindrance accounting for the low diastereoselectivity.[14]

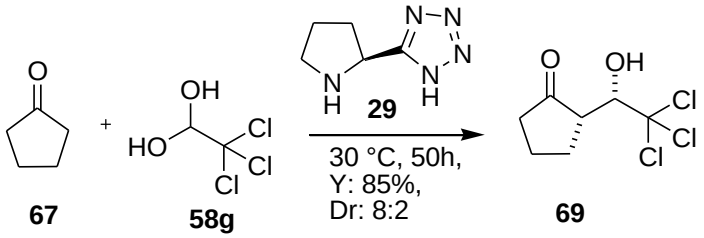
2.2.5 Stereoselectivity control: The *syn* aldol isomer

In most cases, the organocatalytic aldol reactions of dioxanones with various aldehydes gave the *anti* aldol adducts as the major products.[12,14,16] On the one hand the diastereoselectivity is desirable, on the other hand having access to only one diastereoisomer limits the scope of the reaction during the synthesis of a particular target. Recently, in the two-step synthesis of L-deoxyidonojirimycin from dioxanone **37b**, Palyam found that using the hydrate of the aldehyde, gave the *syn* aldol adduct in a high selectivity (scheme 2.17).[9a]



Scheme 2.17

A similar observation was observed by Saito and Yamamoto on the organocatalytic aldol reaction of cyclopentanone with chloral hydrate (Scheme 2.18).[5, 17]

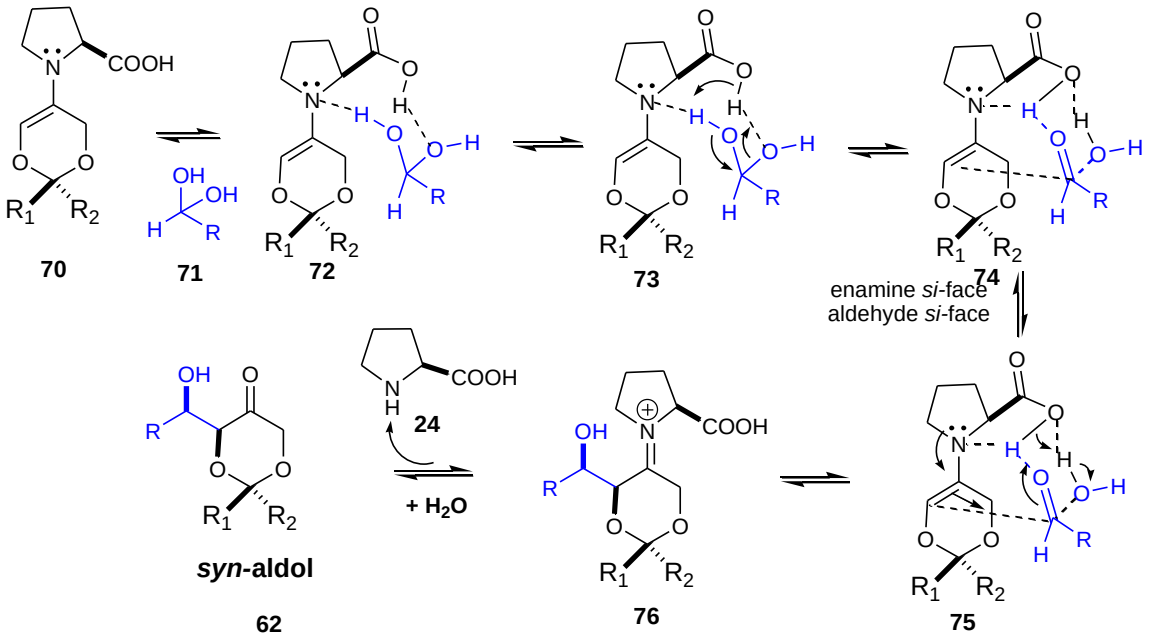


Scheme 2.18

2.2.5.1 Rationalizing the reversal of selectivity

Saito and Yamamoto rationalized the reversal of selectivity in the organocatalytic aldol reaction of cyclopentanone with the hydrated form of the aldehyde by a hypothesis of a hydrogen-bond networking in the transition state.[17]

I believe that a similar mechanism is operating in the case of proline-catalyzed aldol reaction between dioxanone and other aldehyde hydrates (scheme 2.19).

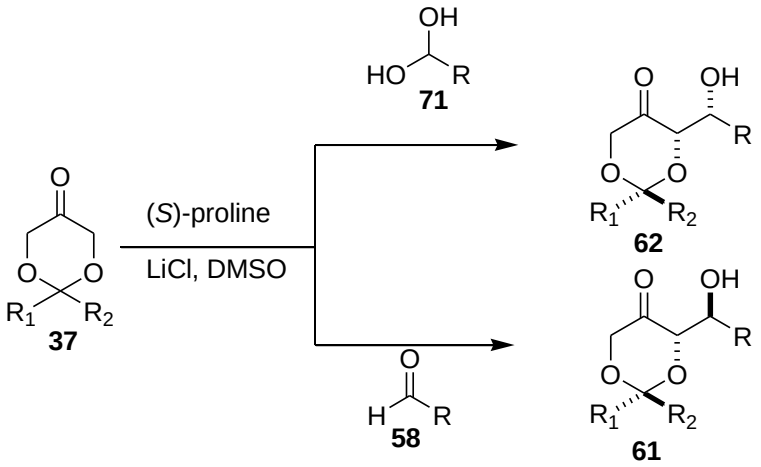


Scheme 2.19

The enamine formed between dioxanone and proline might form a network of hydrogen bonds with the hydrated aldehyde **71**. When this hydrate reacts to give the corresponding aldehyde and water, the si-face of the aldehyde is in such a position that it faces the si-face of the enamine. Subsequent reaction between the enamine and the aldehyde will result in the observed *syn* selectivity.

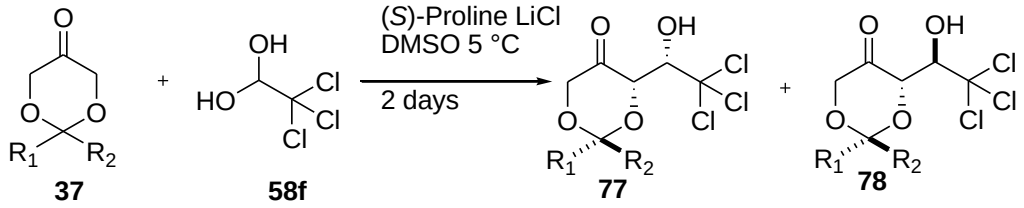
2.2.5.2 Organocatalytic aldol reaction of dioxanone with an aldehyde and the corresponding hydrate

Based on these observations, I decided to further investigate the general applicability of this reaction using different hydrates. An interesting question would be if an aldehyde and its hydrate would give products with opposite diastereoselectivity (scheme 2.20). To be able to answer this question, it is important to have access to both the aldehyde and the hydrate.



Scheme 2.20

Reaction of dioxanones **37b** and **37c** with chloral hydrate were highly selective and gave one major compound. The relative configuration of the major aldol adduct was assigned based on the J-coupling constant between the two adjacent CH(O) protons.[9a, 12, 14] In both cases small coupling constants were observed suggesting that the newly formed bond was indeed *syn* configuration.



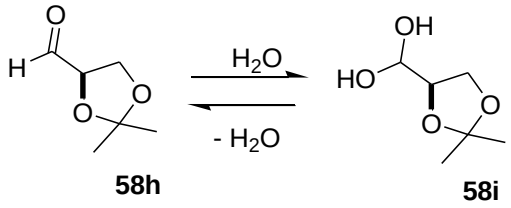
37b: R_1 = Me, R_2 = *t*-Bu, Y= 61%, dr; 9:1
37c: R_1 = R_2 = *i*-Bu, Y= 56%, dr: 20:1

Scheme 2.21

Next, the reaction between anhydrous chloral aldehyde and dioxanone was investigated. However, no appreciable reaction was observed.

2.2.5.3 Reaction of dioxanone with (*R*)-2,3-O-isopropylideneglyceraldehyde

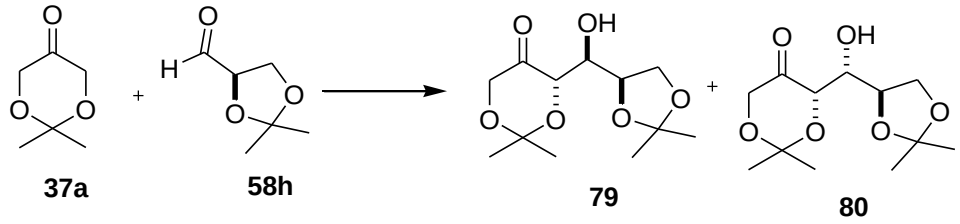
(*R*)-2,3-O-Isopropylideneglyceraldehyde (**58h**) is an important building block in the synthesis of natural products such as carbohydrates. [18] It was found that the aldehyde dissolves readily in H_2O and equilibrates to the corresponding hydrate (scheme 2.22). This was confirmed through both proton and carbon NMR study of **58h** in D_2O.



58h **58i**

Scheme 2.22

Reactions of **58h/58i** with dioxanone under different conditions were then carried out (scheme 2.23) and table 4 summarizes the results obtained.



37a **58h** **79** **80**

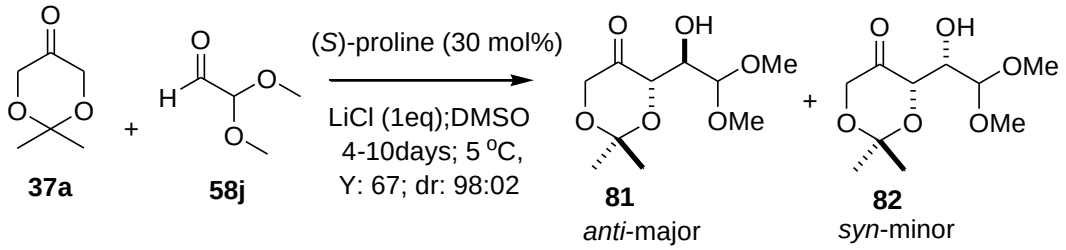
Scheme 2.23

Table 2.4: Organocatalytic aldol reaction between dioxanone and protected glyceraldehyde

Entry	Catalyst	Additive	Water	Solvent	Temp	Reaction time	Conversion	Ratio (79:80)
1	(*S*)-proline	LiCl	-	DMSO	5°C	4 days	>99%	20:1
2	(*S*)-proline	LiCl	0.1ml	DMSO	rt	10 days	>99%	20:1
3	(*S*)-proline-tetrazole	-	0.1ml	DMSO	rt	10 days	>99%	20:1
4	(*S*)-proline-tetrazole	-	0.1ml	MeCN	rt	10 days	>99%	20:1

Both the hydrated and the anhydrous forms **58h/58i** reacted with the dioxanone to give the *anti* aldol adduct as the major product

A similar observation was previously made with dimethoxyacetaldehyde **58j**. Dimethoxyacetaldehyde is usually available commercially as a 60 % solution in water [19] and in this solution exists predominantly as the hydrate. The organocatalytic aldol reaction between **58j** and dioxanones (scheme 2.24) has been reported a number of times in the literature.[12,14,16] In all cases, the *anti* aldol adduct was the major product.



Scheme 2.24

It should be noted that in both cases, i.e the hydrates of **58h** and **58j** in equilibrium with the parent aldehyde, the reaction time was usually longer (4 - 10 days, while the reaction time for most aldehydes was usually 2 days).

Based on the rate of the reactions I believe that in both cases, the reactive species are the aldehydes and that the hydrates do not participate in the reaction. Since under aqueous conditions, the hydrates form of the aldehydes predominate, the low concentration of the aldehyde could lead to a longer reaction time.

2.2.6 Summary

The syntheses of several dioxanones were carried out and the effect of substitution on the dioxanone ring on the selectivity of proline catalyzed aldol reactions was investigated. It was found that substitution at the C-2 position of the dioxanone ring exerts a major effect on the selectivity of the aldol reaction.

The use of hydrates in proline-catalyzed aldol reaction on dioxanones was also investigated. It was found that some, but not all, hydrates gave the *syn* aldol adducts as the major products. Seemingly, the network of hydrogen bonds postulated by Yamamoto[5,17] was the controlling factor in some cases, while in other cases a different mechanism operates. The reasons for this are not clear at this time.

2.3 Application of dioxanone methodology in the synthesis of hyacinthacines

2.3.1 Introduction

Polyhydroxylated pyrrolizidine alkaloids with a hydroxyl substituent at C-3 have been isolated from flowering and leguminous plants and they are relatively rare in Nature.[20] Alexine and Australine were the first ones to be isolated in the late 1980's by Nash and co-workers[21] and Molyneux and co-workers[22] from *Alexia leiopetala* and seeds of *Castanospermum austral* respectively. More recently, Asano and co-workers reported the isolation of more hyacinthacines such as hyacinthacines A_1, A_2, A_3 from bluebells (*Hyaxinthoides non-scripta)* and grape hyacinths (*Muscari armeniacum)*. [23] It has been shown that several of these alkaloids exhibit interesting biological properties. For example hyacinthacine A_1 and A_2 act as glycosidase inhibitors[22] while alexine has been shown to display antiviral and anti-HIV activity.[24]

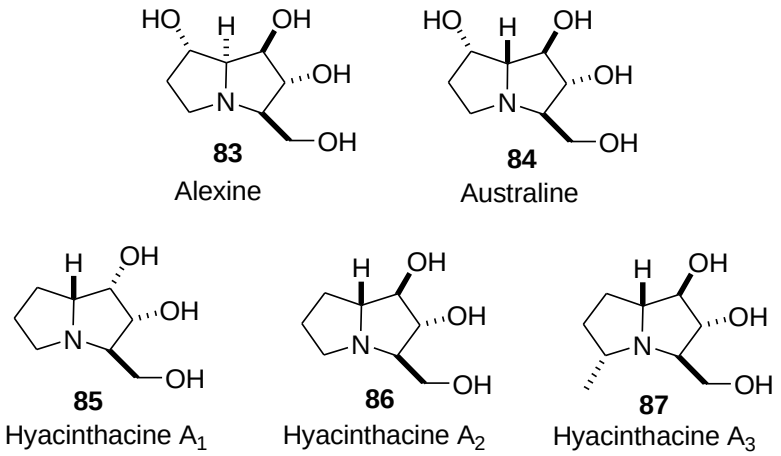
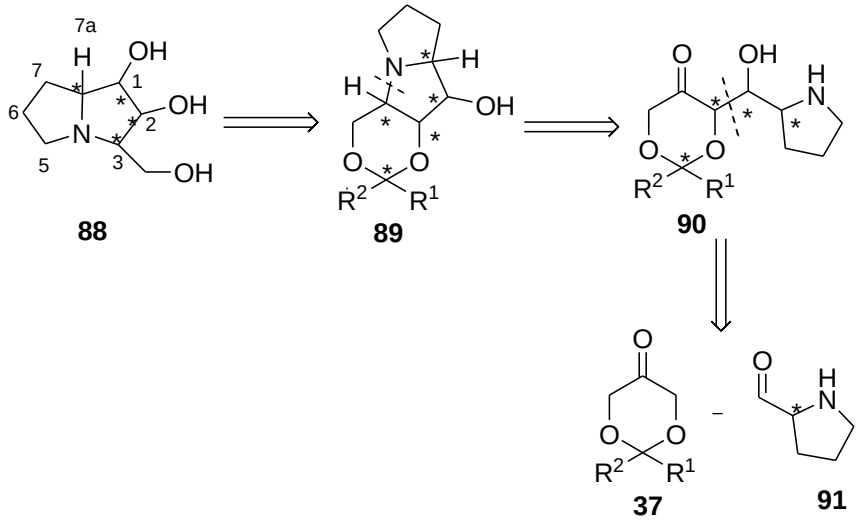


Figure 2.5: Examples of hyacinthacines

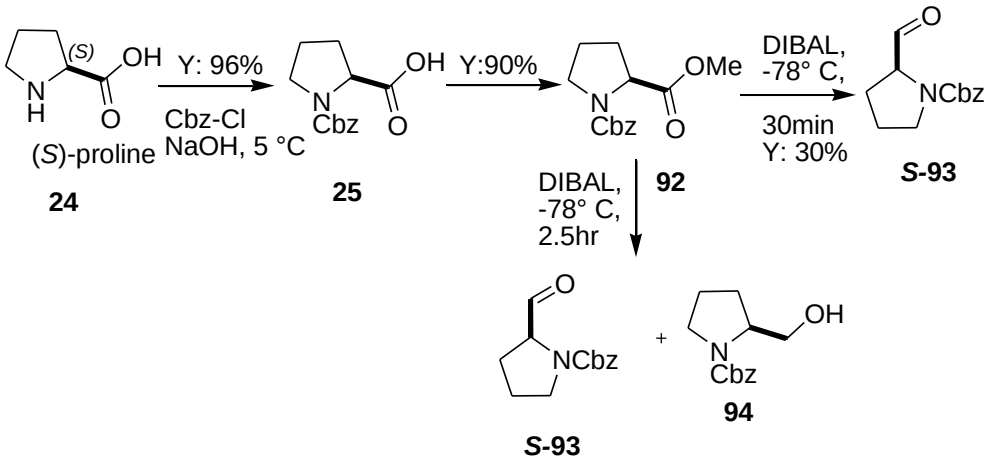
Since the initial isolation of these compounds, numerous syntheses of hyacinthacines A_1 and A_2 have been developed. [25] However, these syntheses usually involved a number of steps and the overall yields and selectivities were often poor. It should be noted that the stereochemistry of these compounds has an important role in their biological activity.[23b] Therefore, it is essential to develop routes to easily access different stereoisomers and analogs of these alkaloids. We envisaged that dioxanones can be used as the scaffold in the synthesis of several stereisomers of hyacinthacine A_1 and A_2. The retrosynthetic analysis (scheme 2.25) shows that the hyacinthacine A_1 and A_2 skeleton can be reduced to simple starting materials such as dioxanone and *N*-Cbz-prolinal. The configuration at C-7a is controlled by the choice of the aldehyde, while the configuration at C-1 and C-2 can be controlled by the aldol reaction. Finally, selective hydrogenation should direct the stereochemical outcome at C-3.



Scheme 2.25

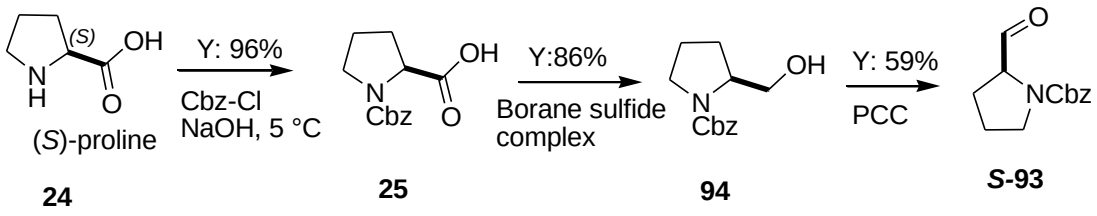
2.3.2 Synthesis of N-Cbz-prolinal aldehyde

The forward pathway begins with the synthesis of (*S*)-N-Cbz-prolinal aldehyde which was carried out according to the literature procedure.[26] However, under the reported conditions; the reduction of the ester **92** gave a 1:1 mixture of the aldehyde product and the starting material. Allowing the reaction to proceed for a longer time (2.5 hours) resulted in a mixture of the corresponding alcohol **94** as well as the desired aldehyde product and the starting ester **92** (scheme 2.26).



Scheme 2.26

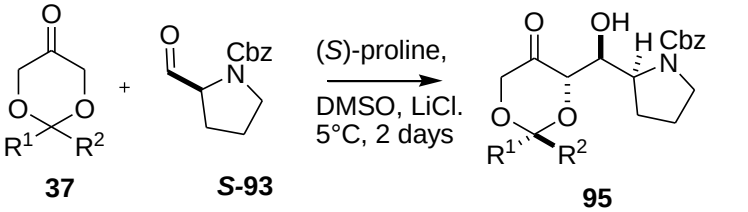
Consequently, another approach was used to synthesize the aldehyde.[27] Protected (*S*)-N-Cbz-proline **27** was first reduced to the corresponding alcohol **94** and then oxidized with PCC to give the (*S*)-N-Cbz-prolinal ***S*-93** in 59% yield (scheme 2.27). The (*R*)-N-Cbz-prolinal ***R*-93** was synthesized via the same route to give the aldehyde in 56% overall yield.



Scheme 2.27

2.3.3 Organocatalytic aldol reaction of (*S*)-N-Cbz-prolinal with dioxanones

Having synthesized the aldehyde, the stage was set for the key aldol reaction. First, (*S*)-N-Cbz-prolinal ***S*-93** was reacted with different dioxanones using (*S*)-proline as the catalyst and lithium chloride (Lewis acid) as an additive. In both cases, only one isomer was isolated (scheme 2.28)



37a: $R^1 = R^2$ = Me
37b: R^1 = *t*-Bu, R^2 = Me

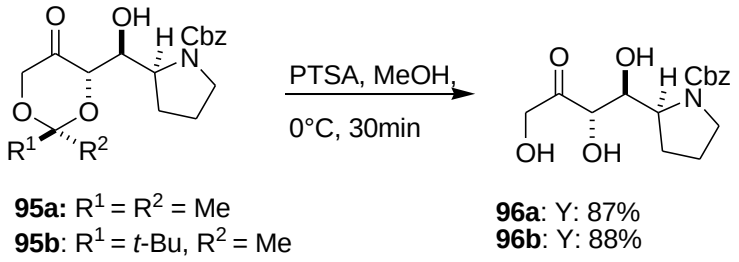
95a: Y: 58%; dr: 20:1
95b: Y: 56%; dr: 20:1

Scheme 2.28

Due to the presence of the carbamate group, it was difficult to accurately characterize the proton NMR of the aldol adduct and the relative configuration of the product was assigned based on previous studies from our group.[12, 14]

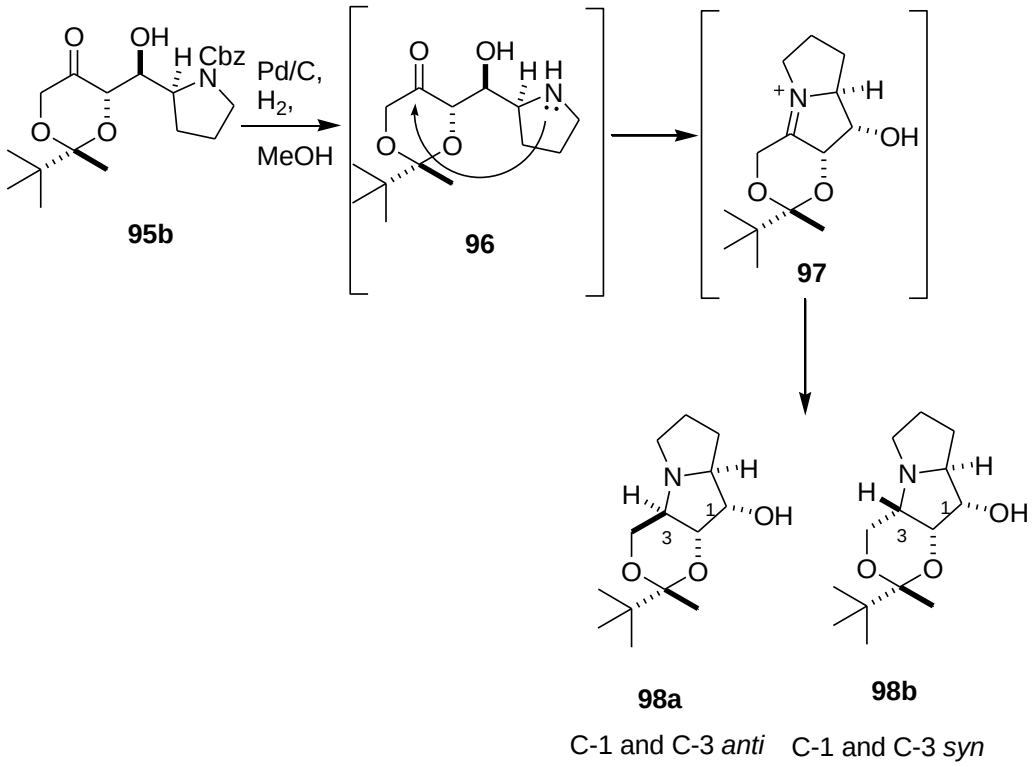
Fortunately, I was pleased to observe that when the ketal group of **95a** and **95b** were hydrolyzed in methanol with a catalytic amount of PTSA (scheme 2.29), the resulting products had a well-defined proton NMR spectra. The coupling constant between protons

connected to the newly formed carbon-carbon bond was 8.7 Hz suggesting *anti* the configuration.[8]



Scheme 2.29

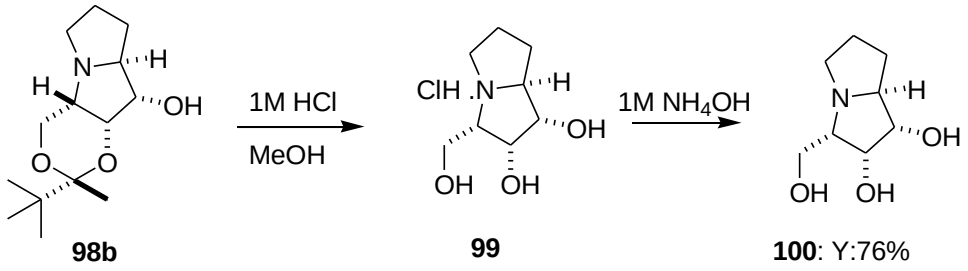
Removal of the Cbz group via hydrogenation followed by an *in situ* cyclization and reductive amination could give two possible products (Scheme 2.30).



Scheme 2.30

Fortunately, only one product was formed. According to a literature precedent, hydrogenation occurs in such a way that the hydrogens at C-1 and C-3 should be in the

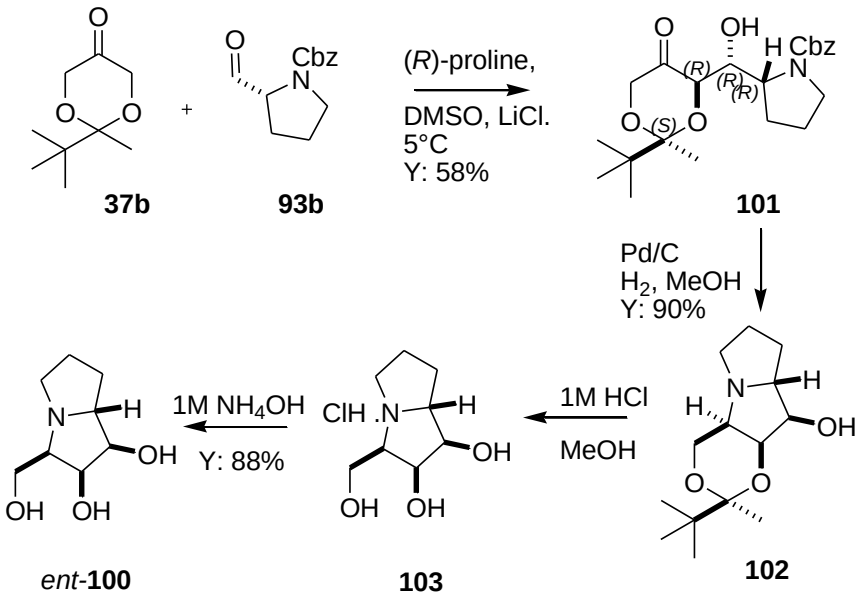
syn orientation.[25l, 28] Moreover, the coupling constants for C-3 H were small (J_1 2.0 Hz, J_2 2.2 Hz) implying that the C-3 hydrogen was in the equatorial position. Acid hydrolysis of the ketal group gave the hydrochloride salt **99** that was passed through a column containing a layer of basic Dowex with 1M NH_4OH as the eluent to give e*nt*-2-epihyacinthacine A_2 **100** (scheme 2.31).



98b **99** **100**: Y:76%

Scheme 2.31

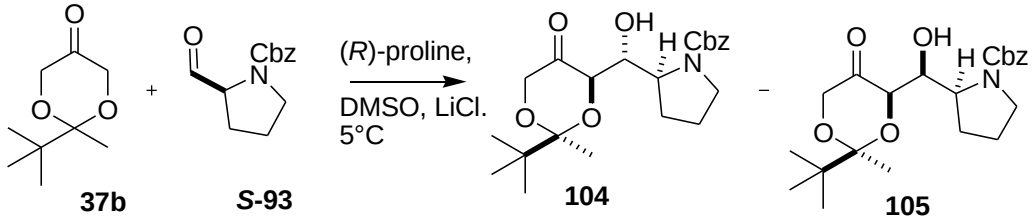
Synthesis of the enantiomer of **100** was carried out using the same protocol. Aldol reaction of (*R*)-Cbz-prolinal and dioxanone using (*R*)-proline as the catalyst gave the adol adduct **101**, which, upon deprotection and reductive amination gave the protected hyacinthacine **102.** Acid hydrolysis followed by treatment with excess NH_4OH gave 2-epihyacinthacine A_2 (*ent*-**100**, **s**cheme 2.32). Identical NMR data and opposite signs of the optical rotation confirmed that compounds **100** and *ent*-**100** were indeed enantiomers.



Scheme 2.32

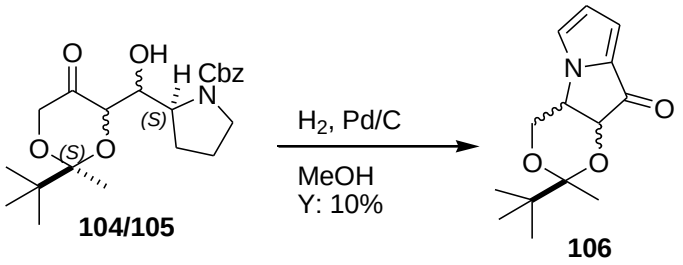
2.3.4 Aldol reaction with a mismatched pair

The aldol reaction of aldehyde ***S*-93** with dioxanone **37b** was repeated but this time (*R*)-proline instead of (*S*)-proline was used as the catalyst (scheme 2.33). This resulted in the formation of two new diastereoisomeric aldol products (**104** and **105**). Due to the presence of rotamers, it was difficult to accurately measure the ratio of the diastereoisomers. The formation of two aldol adducts instead of one suggested that that the aldehyde's facial bias did not complement the facial bias of the enamine (mismatched pair).



Scheme 2.33

The two diastereoisomers, could not be separated through FCC and the mixture was submitted to Cbz deprotection and reductive amination (scheme 2.34). ^{1}H NMR of the crude product showed a mixture of compounds and, after purification through PTLC, only one unknown compound was isolated.

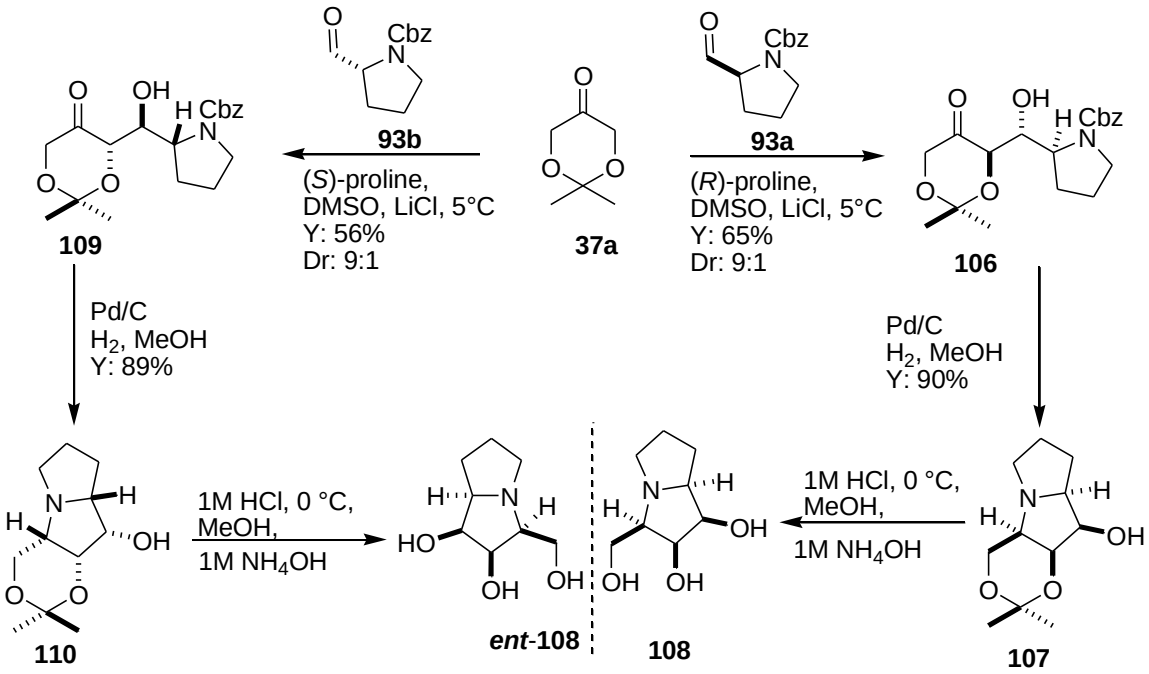


Scheme 2.34

After careful analysis, the compound was assigned to be the aromatized product **106**.

Next, the proline catalyzed aldol reaction with dioxanone **37a** was carried out. Upon purification, only one compound was isolated. The relative and absolute configuration of the compound was assigned based on the previous studies from the Majewski's group.[12,14]

Removal of the protecting group followed by an *in situ* cyclization gave compound **107** which was hydrolyzed with 1M HCl to give the hydrochloride salt. The hyancinthacine was obtained by passing the hydrochloride salt through a column containing a layer of basic dowex using NH_4OH as eluent. The enantiomer was synthesized via the same pathway but using the opposite enantiomer of the pyrrolidine substrate (scheme 2.35).


93b
(S)-proline,
DMSO, LiCl, 5°C
Y: 56%
Dr: 9:1
37a
93a
(R)-proline,
DMSO, LiCl, 5°C
Y: 65%
Dr: 9:1
109
106
Pd/C
H2, MeOH
Y: 89%
Pd/C
H2, MeOH
Y: 90%
1M HCl, 0 °C,
MeOH,
1M NH4OH
1M HCl, 0 °C,
MeOH,
1M NH4OH
110
ent-108
108
107

Scheme 2.35

2.4 Conclusions

The main objective of expanding the organocatalytic aldol reaction on tropinone and dioxanone was successfully carried out.

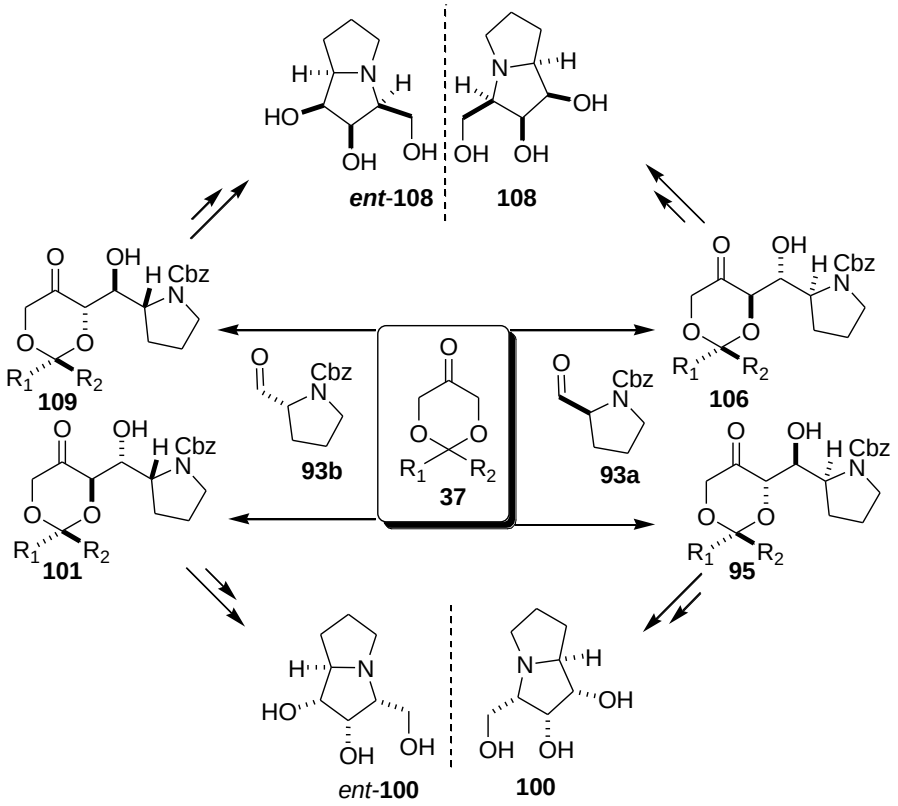
- Organocatalytic aldol of tropinone with benzaldehyde was successfully carried out to yield the condensed (dehydrated) aldol adduct as the major product. Based on our observations, there are still some major limitations and the use of chiral lithium amides for enantioselective deprotonation of tropinone remains a better option.

- The methological studies on dioxanone iniated by Niewczas and Palyam in our group were further pursued.[12,14] In screening for the best dioxanone, it was found that substitution at the C-2 position of the dioxanone ring plays a major role in the diastereoselectivity of the reaction. 2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (**37b**) which belongs to the C_s symmetry point group usually offers a better diastereoselectivity than its C_2 symmetrical dioxanone.

- Use of hydrates in proline catalyzed aldol reaction on dioxanones was also investigated. The results showed that some, but not all hydrates gave the *syn* aldol adducts as the major products. It was suggested that while the network of hydrogen bonds postulated by Yamamoto[5,17] was the controlling factor in some cases, in other cases a different mechanism, which is still unclear at this time, operates.

- Application of the dioxanone methodology in the synthesis of 4 stereoisomers of hyacinthacine A_1/A_2 was successfully demonstrated. The key step of the synthesis

involved the organocatalytic aldol reaction of dioxanone with protected prolinal (scheme 2.36). It should be noted that the target compounds can be synthesized in 2 steps from commercially available dioxanone and only one purification through flash column chromatography is required making this an attractive synthetic approach to hyacinthacines.



Scheme 2.36

2.5 References

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CHAPTER 3

3. Experimental

3.1 General Methods

All experiments involving air- and/or moisture-sensitive compounds were conducted in oven dried round-bottom flasks (or vials) capped with rubber septa, and attached via a needle and to a nitrogen manifold.

All solvents were distilled prior to use by standard procedures.[1, 2] Anhydrous solvents were distilled under nitrogen atmosphere as follows: tetrahydrofuran (THF), diethyl ether (Et_2O) and benzene (PhH) from benzophenone sodium ketyl; dichloromethane (CH_2Cl_2) and toluene ($PhCH_3$) from calcium hydride (CaH_2), diisopropylamine (DIA), triethylamine (TEA), diisopropylethylamine (DIPEA) and pyridine were distilled from calcium hydride (CaH_2) under nitrogen and stored over pre-dried 4Å molecular sieves. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were dried with (CaH_2) according to known procedures.[3]

Low temperature baths were ice/water (0 °C), ice/NaCl/MeOH (-20 °C), and CO_2(s)/acetone (-78 °C).[4] Reaction temperatures refer to the bath temperature. All liquid aldehydes and acetic anhydride (Ac_2O) were distilled and stored under nitrogen at - 20 °C. *n*-BuLi was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator.[5] LiCl was dried at 130-150 °C under vacuum overnight, and it was kept under nitrogen. All other commercially available reagents were used as received without further purification, unless stated otherwise. Concentrated phosphate buffer, used to quench

reactions, was prepared by dissolving Na_2HPO_4 (47.0 g) and NaH_2PO_4 (32.0 g) in H_2O (500 mL).[6]

Preparative TLC (PTLC) and TLC were carried out on glass plates (20 x 20 cm) precoated (0.25 mm) with silica gel 60 F254. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of:

1) Potassium permanganate (1.50 g) in water (200 mL) containing K_2CO_3 (10.0 g) and NaOH (1.25 mL, 10%), or a solution of

2) Phosphomolybdic acid hydrate (40.0 g), cerium(IV) sulfate (10.0 g) and concentrated sulfuric acid (50.0 g) in distilled water (1000 mL) followed by charring on a hot plate.

As the visualization of some of the oxygenated compounds was not possible by using solutions described above, other stains were considered:

3) *p*-Anisaldehyde (1.00 mL), concentrated sulfuric acid (9.50 mL), concentrated acetic acid (2.70 mL,) disolved in EtOH (250 mL)

4) Vanillin (1.5 g) dissolved in EtOH (100 mL) containing concentrated sulfuric acid (1.0 mL).

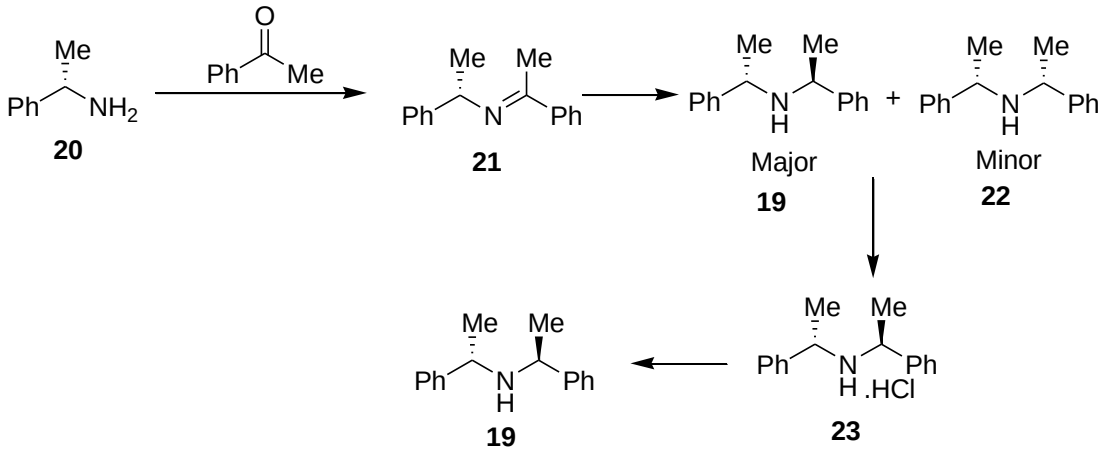
Flash column chromatography (FCC) was performed according to Still *et al.* [7] with Merck Silica Gel 60 (40-63 μm). Dry flash column chromatography (DFC) was performed according to Harwood.[8] Melting points and boiling points are uncorrected. Melting points were measured on a Gallenkamp melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter (1 dm, 1 mL cell). All concentrations for optical rotation are quoted in grams per 100 mL. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT)

and only diagnostic peaks are reported. Nuclear magnetic resonance (NMR) spectra were recorded on Bruker at 500 MHz for ^{1}H and 125 MHz for ^{13}C in the deuterated solvents stated. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.26 δH, 77.23 δC); CD_3OD (3.31 δH, 49.15 δC); C_6D_6 (7.16 δH, 128.39 δC); D_2O (4.80 δ_H).[9] The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), dd (doublets of doublets), ddd (doublet of doublets of doublets), dddd (doublet of doublets of doublets of doublets), t (triplet), m (multiplet), br (broad). Coupling constants (*J*) are reported to the nearest 0.5 Hz. The ^{1}H NMR assignments were made based on chemical shifts and multiplicities. Where necessary, 2D gradient COSY, and homonuclear decoupling experiments were used to aid assignment of assigning ^{1}H NMR spectra. The ^{13}C NMR assignments were made on the basis of chemical shifts and were confirmed, where necessary, by two dimensional $^{1}H/^{13}C$ correlation experiments (HSQC and/or HMBC).[10] HRMS and LRMS were obtained on an API QSTAR® Pulsar Hybrid LC/MS/MS system and/or a VG 70E double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI at 50 eV with ammonia as the reagent gas; only partial data are reported. The relative configuration of aldol products (*syn* or *anti*) were assigned based on ^{1}H NMR coupling constant (*syn* J = 2 – 6 Hz, *anti* J = 7 – 10 Hz) of the vicinal C(O)-C<u>H</u>-C<u>H</u>-OH. [11]

HPLC analysis was performed with Gilson 715 Series HPLC utilizing Chiralpack AD or Chiralpack IB columns (Daicel Chemical Industries) or a ChiraDex 250-4 column (Merck) with visualization at 254 nm.

3.2 Synthesis of the chiral amine for Li-amide

(-)-Bis((*S*)-1-phenylethyl)amine (19) [12, 13]



This compound was synthesized according to the known procedure.[12]

(*S*)-(-)-α-Methylbenzylamine (9.23 g, 76.0 mmol), acetophenone (12.1 g, 101 mmol), and p-TsOH (0.190 g, 1.00 mmol) were refluxed in dry benzene (160 mL) for 5 days using a Soxhlet apparatus containing 4Å molecular sieves. The reaction mixture was cooled to room temperature, then it was further cooled in ice, washed with aqueous K_2CO_3 and dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product **3** (16.9 g, 98%) which was used directly in the following step.

$[\alpha]^{25}_{D}$ + 50 (c 1.5, MeOH), **lit. $[\alpha]^{25}_{D}$** + 48.8 (c 1.50, MeOH) [12]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92-7.85 (m, 2H), 7.57-7.23 (m, 8H), 4.92 (q, J = 6.5 Hz, 1H), 2.33 (s, 3H), 1.65 (d, J = 6.5 Hz, 3H)

A solution of imine **3** (16.9 g, 74.5 mmol) in THF (70 mL) was hydrogenated on 30% Pd/C catalyst (ca 0.400 g) in a Parr apparatus at 50 psi overnight. The catalyst was filtered off via a Celite pad and the solvent was removed under reduced pressure to afford the crude product as viscous oil. The latter was vacuum distilled (bp 112-115 °C/ 0.2 mmHg), diluted with ethanol (20mL), and poured into a mixture of warm water (60mL), ethanol (40 mL) and hydrochloric acid (7 mL) at 60 °C. The solution was allowed to slowly cool down to room temperature and was then set aside for slow crystallization (1-2 weeks) to yield the amine hydrochloride **23** which could directly be used in the asymmetric formation of the tropinone enolate. Treatment of **23** with aqueous NaOH followed by extraction with ethyl acetate (3 x 100 mL) and vacuum distillation afforded the pure amine **19** (12.0 g, 88 %).

Data for amine **19**

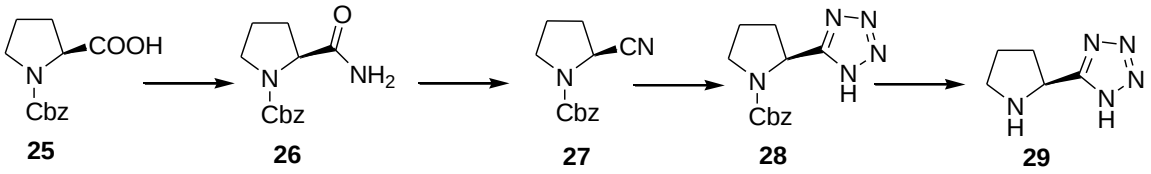
$[\alpha]^{25}_{D}$ - 156 (c 1.0, MeOH), **lit. $[\alpha]^{25}_{D}$** -165 (c 1.03, MeOH) [12]

^{1}H NMR (500 MHz, CDCl3) δ: 7.45-7.24 (m, 10H), 3.59 (q, J = 6.5 Hz, 2H), 1.53 (br, 1H), 1.37 (d, J = 6.5 Hz, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 145.9, 128.6, 126.9, 126.6, 55.2, 25.1

3.3 Synthesis of the organocatalyst

(*S*)-5-Pyrrolidin-2-yl-1H-tetrazole (29) [17]



This compound was synthesized according to the known procedure.[17]

To a 400 mL of acetonitrile was added Cbz-(*S*)-proline **25** (20.0 g, 80.2 mmol, 1.00 eq) di-*tert*-butyl dicarbonate (22.7 g, 104 mmol, 1.30 eq) and ammonium bicarbonate (7.60 g, 96.2 mmol, 1.20 eq) under nitrogen atmosphere. The resulting mixture was stirred briefly and pyridine (3.89 mL, 48.1 mmol, 0.6 eq) was added via a syringe and stirring was continued for 5 h at room temperature. The reaction was monitored by TLC and after complete consumption of the starting material the resulting mixture was concentrated under reduced pressure until approximately 100 mL of the solvent remained. Ethyl acetate (200 mL) and water (200 mL) were then added and the mixture was extracted with ethyl acetate (2 × 200 mL). The organic phases were combined, washed with brine (200 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a white solid. The latter was recrystallized from ethyl acetate to give (*S*)-2-amido-pyrrolidine-1-carboxylic acid benzyl ester **26** as white crystals (18.0 g, 90%).

Melting point: 91-93 °C; **lit** 91-93 °C [17]

$[\alpha]^{25}_{D}$ -101 (c 0.6, $CHCl_3$); **lit. $[\alpha]^{25}_{D}$** -100.6 (c 0.51, $CHCl_3$) [17]

^{1}H NMR (500 MHz, $CDCl_3$): 7.22-7.41 (m, 5 H), 6.72 (s, 1H), 6.13 (s, 1H), and 5.98 (s, 2 H), 5.08-5.18 (m, 2 H), 4.27-4.32 (m, 1 H), 3.43-3.51 (m, 2 H), 2.28 (s, 1H), and 2.14 (s, 2 H), 1.87-2.03 (m, 2 H)

(*S*)-2-Amido-pyrrolidine-1-carboxylic acid benzyl ester **26** (17.8 g, 71.7 mmol) and *N*,*N*-dimethylformamide (220 mL) were added to a 1 L round-bottomed flask under inert atmosphere. The resulting solution was cooled to 0 °C and cyanuric chloride (8.59 g, 46.6 mmol, 0.65 equiv) was then added. The reaction mixture was stirred at 5 °C for 1 h, allowed to warm to room temperature over 45 min and then stirred for an additional 2.5 h. After TLC shows complete consumption of the starting material, the mixture was cooled back to 5 °C and distilled water (200 mL) was slowly added. The mixture was then transferred to a separatory funnel and extracted with ethyl acetate (3 × 250 mL). The organic phases were combined, washed with a lithium chloride solution (10 wt % in distilled water, 3 × 200 mL), dried with anhydrous $MgSO_4$ concentrated under reduced pressure and filtered through a pad of silica to give (*S*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester **27** as a colorless, viscous oil (15.0 g, 90%).

$[\alpha]_D^{25}$ -90 (c 1.0, $CHCl_3$); **lit. $[\alpha]^{25}_D$** −91.6 (c 0.995, $CHCl_3$) [17]

^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.31-7.42 (m, 5 H), 5.13-5.22 (m, 2 H), 4.61 (dd, J_1 = 7.4 Hz, J_2 = 2.3 Hz, 1H) and 4.53 (dd, J_1 = 7.6 Hz, J_2 = 2.4 Hz, 1 H), 3.54-3.61 (m, 1 H), 3.36-3.52 (m, 1 H), 1.98-2.28 (m, 4 H)

(*S*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester **27** (15.3 g, 66.4 mmol, 1.00 eq), sodium azide (5.61 g, 86.3 mmol, 1.3 equiv), triethylamine hydrochloride (11.9 g, 86.3 mmol, 1.30 equiv) and toluene (65 mL) were added to a 250 mL round-bottomed flask, and refluxed at 95 °C for 24 h under a nitrogen atmosphere. The reaction was monitored by TLC and after complete consumption of the starting material, water (100 mL) was added and the mixture was transferred to a 250 mL separatory funnel and extracted with deionized water (2 x 25 mL). The aqueous extracts were combined, cooled to 0 °C and sodium nitrite solution (20 wt % aqueous, 21 mL, 61 mmol) was added followed by dropwise addition of sulfuric acid (20 wt % aqueous, 20 mL, 72 mmol). The solution was stirred until no more gas was evolved. The mixture was extracted with ethyl acetate (3 x 100 mL). Next the organic phases were combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford (*S*)-2-(1*H*-tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester **28** as an orange foam (15.3 g) which was then used directly in the next step.

$[\alpha]^{25}_{D}$ −88 (c 1.0, $CHCl_3$); **lit $[\alpha]^{25}_{D}$** −90.7 (c 1.29, $CHCl_3$) [17]

^{1}H NMR (500 MHz, $CDCl_3$) (mixture of rotamers) δ: 7.31-7.35 (m, 3H), 7.24 (s, 1H), 7.02 (s, 1H), 5.40-5.42 (m, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.10-5.14 (m, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 3.60-3.63 (m, 1H), 3.51-3.57 (m, 1H), 2.65-2.69 (m, 1H), 2.20-2.43 (m, 1H), 2.06-2.12 (m, 1H), and 1.86-2.01 (m, 1H)

(*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidin-1-carboxylic acid benzyl ester **28** (15.3 g, 56.1 mmol), ethanol (255 mL) and 10 % Pd/C (ca 1.50 g) were added to a 500 mL round bottom flask under nitrogen atmosphere. The flask was purged with hydrogen gas and the

reaction mixture was then stirred under a hydrogen atmosphere (hydrogen balloon) at room temperature overnight. The reaction was monitored by TLC and after complete consumption of the starting material, the catalyst was removed by filtration through a Celite pad and washed with ethanol (30 mL), acetic acid (10 mL) and water (50 mL), and then again with ethanol (30 mL), acetic acid (10 mL) and water (50 mL). Concentration of the filtrate under reduced pressure followed by further drying under vacuum (0.1 mmHg) overnight afforded crude **29** as a pale brown solid. Recrystallization in ethanol afforded *(S)*-5- pyrrolidin-2-yl-1H-tetrazole **29** (6.10 g, 79%) as a white solid.

Melting point = 269 - 271 °C

$\mathbf{[\alpha]_D^{25}}$ = - 9.0 (c 1.0, MeOH)

^{1}H NMR (500 MHz, DMSO) δ: 9.39 (br, 1H), 4.77 (t, J = 7.5 Hz, 1H), 3.30 (m, 2H), 2.32 (m, 1H), 2.12 (m, 1H), 2.01 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.2, 54.6, 44.8, 30.3, 23.3

IR (KBr): 2966, 2165 cm^{-1}

3.4 General procedure for formation of tropinone lithium enolate[12]

Method A: Using chiral amine hydrochloride 23

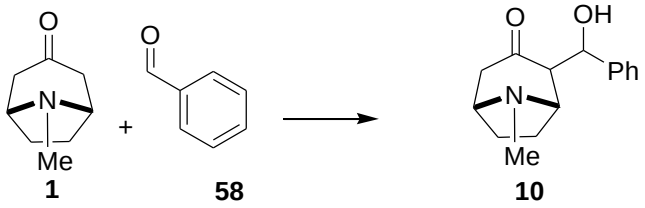
(*S*,*S*)-(-)-N,N-Bis(1-phenylethyl)amine hydrochloride (0.288g, 1.10 mmol, 1.10 eq) was dissolved in dry THF (10 mL) and the mixture was cooled to 0 °C. *n*-BuLi (2.5 M, 0.90 mL, 2.2 eq) was then slowly added and the mixture was stirred for another 45 min. It was then cooled to -78 °C and tropinone (0.139g, 1.00 mmol, 1.00 eq) in THF was added dropwise (over 30-45 min) and stirring was continued for another 120 min.

Method B: Using chiral amine 19

To a solution of (*S*,*S*)-(-)-N,N-bis(1-phenylethyl)amine (0.247 g, 1.10 mmol, 1.10 eq) in THF (5.00 mL) at 0 °C was added *n*-BuLi (2.50 M, 0.450 mL, 1.10 eq) and the mixture was stirred for 45 min. Lithium chloride in THF (0.50 M, 1.10 mL, 0.550 eq) was then added and the resulting mixture was stirred for 15 min. The solution was then cooled to – 78 °C and tropinone (0.139g, 1.00 mmol) in THF (1.00 mL) was added dropwise and stirring was continued for another 165 min.

3.5 Synthesis of tropane alkaloids

(+)-(1*S*,2*R*,5*R*)-2-(Hydroxy(phenyl)methyl)-8-methyl-8-aza-bicyclo[3.2.1]octan-3-one (10) [12]



This compound was synthesized according to the known procedure. [12]

Benzaldehyde (0.130 mL, 0.136 g, 1.28 mmol) was added via syringe to a tropinone enolate solution (method A, 1.00 eq) and the mixture was stirred for another 15 min at -78 °C. Aqueous NH_4Cl (4 mL) was then added to quench the reaction and the resulting mixture was allowed to warm up to room temperature. The reaction mixture was transferred to a separatory funnel and extracted with ether (4 x 10 mL). The organic phases were combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield a yellow solid as crude product. The product was recrystallized from DCM and hexane to yield **10** as a pale yellow solid (0.223 g, 91 % yield).

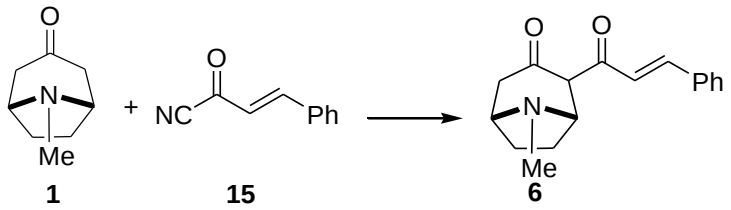
Melting point = 129-131 °C; **lit.** 128-130 °C [12]

$[\alpha]^{24}_D$ + 29 (c 0.6, $CHCl_3$), **lit. $[\alpha]^{25}_D$** +30 (c 0.50, $CHCl_3$) [12]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44-7.721 (m, 5H), 5.26 (d, J = 3.0 Hz, 1H), 3.62 (d, J = 6.5 Hz, 1H), 3.63-3.47 (m, 1H), 2.86 (ddd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, J_3 = 15.3 Hz, 1H), 2.49 (s, 3H), 2.45 (m, 1H), 2.32 (ddd, J_1 = 1.5 Hz, J_2 = 4.2 Hz, J_3 = 15.5 Hz, 1H), 2.20 (m, 2H), 1.72- 1.65 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 208.0, 141.7, 128.0, 127.3, 125.2, 76.5, 67.1, 63.8, 61.5, 51.6, 40.5, 26.3, 26.1

(-)-*ent*-Chalcostrobamine (6) [12]



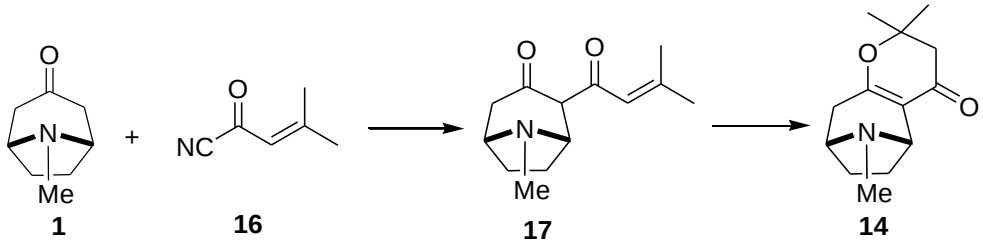
This compound was synthesized according to the known procedure. [12]

Cinnamoyl cyanide (0.772 g, 1.10 mmol) in THF (1.50 mL) was added via syringe a tropinone enolate solution (method A, 1.00 eq) and the mixture was stirred for another 30 min at -78 °C. A solution of 40 % K_2CO_3 (4mL) was then added to quench the reaction and the resulting mixture was allowed to warm up to room temperature. The reaction mixture was transferred to a separatory funnel and extracted with chloroform (3 x 10mL). The organic phases were combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product. The product was purified via FCC on deactivated silica gel (ethyl acetate: hexane 1:1 followed by MeOH:DCM 1:9) to give (-)-*ent*-Chalcostrobamine **6** as a yellowish oil (0.200 g, 73%)

$[\alpha]^{24}_D$ - 180 (c 1.0, $CHCl_3$), **lit. $[\alpha]^{25}_D$** -179 (c 1.04, $CHCl_3$) [12]

^{1}H NMR (500 MHz, CDCl3) δ: 7.67 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 6.5 Hz, 1H), 7.37 (m, 2H), 6.82 (d, J = 15.6 Hz, 1H), 4.05 (d, J = 5.2 Hz, 1H), 3.42 (t, J = 5.2 Hz, 1H), 2.86 (dd, J = 19 Hz, J = 3.1 Hz, 1H), 2.43 (s, 3H), 2.29 (m, 2H), 2.14 (d, J = 19 Hz, 1H), 1.79 (m, 1H), 1.63 (m, 1H)

(-)-11, 11-Dimethyl-10, 11-dihydropyranotropane-3-one (14) [12]



This compound was synthesized according to the known procedure. [12]

Senecioyl cyanide (0.200 mL, 0.280 g, 2.60 mmol) was added a tropinone enolate solution (method A, 1.00 eq) and the mixture was stirred for another 30 min at -78 °C. A solution of 40 % K_2CO_3 (4mL) was then added to quench the reaction and the resulting mixture was allowed to warm up to room temperature. The reaction mixture was transferred to a separatory funnel and extracted with ether (3 x 10 mL). The organic phases were combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product **17**. Anhydrous sodium carbonate was added to **17** and the mixture was refluxed for 1 h in ethanol (3mL). Removal of the solvent under reduced pressure and the sodium carbonate through filtration with ether followed by purification via FCC on deactivated silica gel (ethyl acetate: hexane 1:1 followed by MeOH:DCM 1:9) afforded (-)-11, 11-dimethyl-10, 11-dihydropyranotropane-3-one **14** as a yellowish oil in 76% yield (0.437 g).

$[\alpha]^{24}_D$ - 39 (c 1.0, MeOH), **lit. $[\alpha]^{25}_D$** -35.1 (c 1.02, MeOH) [12]

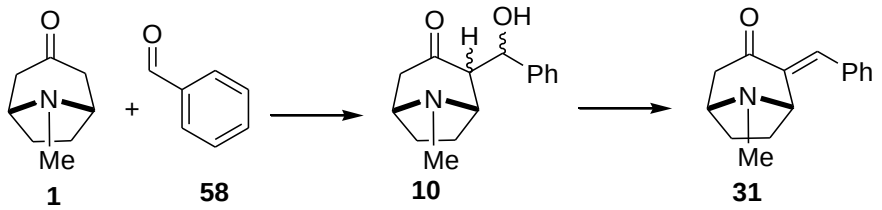
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.05 (d, J = 5.0 Hz, 1H), 3.39 (t, J = 5.1 Hz, 1H), 2.74 (dd, J_1 = 5.2 Hz, J_2 = 12.0 Hz, 1H), 2.53 (q, J = 18.5 Hz, 2H), 2.34 (s, 3H), 2.23-2.18 (m,

2H), 1.88 (d, J = 18.5 Hz, 1H), 1.79-1.73 (m, 1H), 1.59-1.54 (m, 1H), 1.44 (s, 3H), 1.41(s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 190.1, 166.9, 114.1, 80.5, 57.5, 54.9, 47.1, 36.7, 34.7, 33.0, 28.7, 27.0, 25.2

IR (KBr): 1662, 1610 cm^{-1}

(-)-*trans*-2-Benzylidentropinone (31) [12]



Dry DMSO or MeCN (0.5 mL), tropinone (**10**,1.0 eq, 0.50 mmol), benzaldehyde (1.0 eq, 0.50 mmol), *(S)*-5-pyrrolidin-2-yl-1H-tetrazole (0.30 eq, 0.15 mmol) and an additive (1.0 eq, 0.50 mmol) were added to a glass vial. The resulting mixture was stirred at 40 °C for 4 days. The reaction was monitored by TLC. Upon consumption of the starting material, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic phases were combined, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product **31.** Purification via FCC on deactivated silica gel (ethyl acetate: hexane 1:1 followed by MeOH:DCM 1:9) afforded **31** as a gummy yellowish solid.

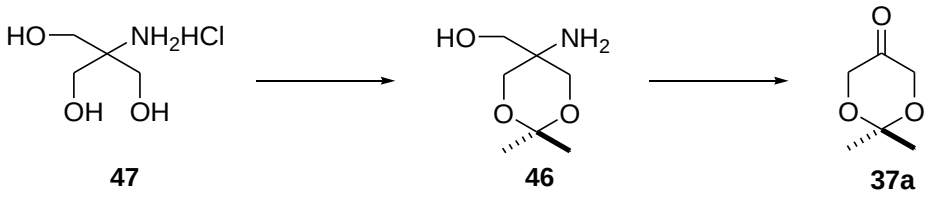
$[\alpha]^{20}_D$ - 363 (c 1.0, MeOH), **lit. $[\alpha]^{25}_D$** -390 (c 1.03, MeOH) [12]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.62 (s, 1H), 7.47-7.33 (m, 5H), 4.45 (d, J = 7.1 Hz, 1H), 3.65 (t, J = 6.1 Hz, 1H), 2.95 (ddd, J_1 = 1.9 Hz, J_2 = 5.5 Hz, J_3 = 18.5 Hz, 1H), 2.48 (s, 3H), 2.63-2.35 (m, 3H), 2.09-1.98 (m, 1H), 1.89-1.76 (m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 140.5, 134.5, 130.8, 128.8, 128.0, 60.9, 59.0, 44.7, 37.3, 30.4, 28.9

3.6 Synthesis of dioxanones

1, 3-Dioxan-5-one (37a) [6, 14, 18]



This compound was synthesized according to the known procedure. [6, 14, 18]

To a mixture of tris(hydroxymethyl) aminomethane hydrochloride (17.4 g, 110 mmol) and *p*-TsOH H_2O (0.960 g, 5.00 mmol) in dry DMF (90 mL) were added 2,2-dimethoxypropane (14.8 mL, 120 mmol) and the resulting mixture was stirred at room temperature for 2 days (48 h). Triethylamine (5.00 mL) was then added and the solvent was removed under reduced pressure. The viscous residue was suspended in ethyl acetate (200 mL) and triethylamine (25.0 mL) was added and stirred for 20 min. The white precipitate was filtered off and the solvent was evaporated to give (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (12.5 g, 77.3 mmol, 70 %) as a white solid. No further purification was needed and the crude product was directly used in the next step.

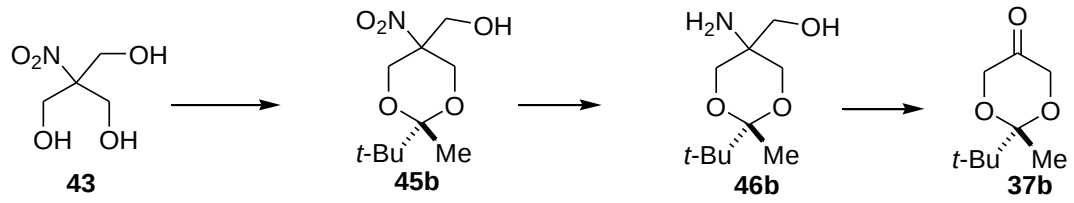
To a solution of the α-amino alcohol (12.3 g, 76.5 mmol) dissolved in H_2O/MeOH (4 : 1; 125 mL) at 0 °C was added a cold (0-5 °C) solution of sodium periodate (21.2 g, 99.0 mmol, 1.30 eq) in H_2O (250 mL) over 70 min. The mixture was stirred at 0 °C for 1.5 h. The white suspension was then filtered off and the resulting solution was extracted with CH_2Cl_2 (5 x 100 mL). The organic layers were combined and washed with a sodium bicarbonate solution (5 %), brine and dried with anhydrous magnesium sulphate. Removal of the solvent under low pressure and room temperature followed by vacuum

distillation of the crude product gave the pure 2, 2-dimethyl-1, 3-dioxan-5-one **37a** (9.20 g, 121 mmol, 93 % yield) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.15 (s, 4H), 1.46 (s, 6H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 208.1, 100.3, 67.2, 23.9

2-*tert*-Butyl-2-methyl-1,3-dioxan-5-one (37b) [14, 19]



This compound was synthesized according to the known procedure.[14, 19]

To a mixture of tris(hydroxymethyl)nitromethane (20.0 g, 132 mmol, 1.00 eq.) and *p*-TsOH.H_2O (254 mg, 1.32 mmol, 0.1 eq.) in dry benzene (400 mL) was added pinacolone (19.8 mL, 159 mmol, 1.20 eq.) and the resulting mixture was refluxed using Soxhlet apparatus with 4Å molecular sieves for 24 hr. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (300 mL). The organic layer was washed with saturated solution of sodium bicarbonate (300 mL), saturated brine solution (300 mL) and dried over anhydrous magnesium sulphate and the solvent was removed under reduced pressure to yield the crude product as a mixture of *cis*/*trans* isomers in a ratio of 1: 1.1 as a pale yellow solid in 89 % yield (13.7 g, 58.9 mmol). No effort was made to separate the *cis* and *trans* isomers.

A solution of crude mixture (2-*tert*-butyl-2-methyl-5-nitro-1,3-dioxan-5-yl)methanol **45b** (13.6 g, 58.4 mmol) was dissolved in methanol (100 mL). Raney nickel (0.200 g) was added and the solution was stirred for 5 min, filtered, and a fresh portion of Raney nickel was added (2.00 g). Reaction mixture was hydrogenated overnight (50 psi, room temperature). The reaction was monitored by TLC and upon consumption of the starting material; the mixture was filtered through a Celite bed to remove the catalyst. Then the

filter bed was washed with methanol (50.0 mL) and the solvent was removed under reduced pressure to provide the crude product as a mixture of *cis*/*trans* isomers (1 : 1) as a white solid (11.4 g, 56.0 mmol) in 96 % yield. No efforts were made to assign the *cis*/*trans* configuration.

An ice cold (0-5 °C) solution of sodium periodate (17.4 g, 81.3 mmol, 1.50 eq) in H_2O (40 mL) was added over 10 min. at 0 °C to the α-amino alcohol (11.0 g, 54.2 mmol, 1.00 eq) dissolved in H_2O-MeOH (1 : 3; 100 mL). The mixture was stirred at this temperature for 4 h. Next, the white suspension was filtered off and the solution was thoroughly extracted with CH_2Cl_2 (4 x 75 mL). The combined organic layers were washed with a saturated sodium bicarbonate solution (50 mL), dried with anhydrous Na_2SO_4 and evaporated on a rotovap (temp < 30 °C). The crude product was purified by passing through a silica column (hexane : ethyl acetate, 98 : 2) to give pure 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one **37b** (8.25 g, 47.9 mmol, 88 %) as a colorless viscous product which crystallized upon storing in refrigerator.

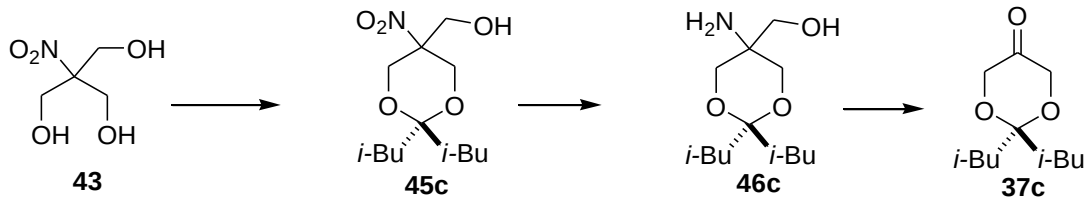
Melting point: 47-49 °C; l**it**. 47-48 °C [19]

^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.30 (d, 1H, *J* = 18.2 Hz), 4.23 (d, 1H, *J* = 18.2 Hz), 1.36 (s, 3H), 1.02 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 207.9, 103.5, 68.7, 40.4, 25.3, 15.8.

IR (KBr): 2890 , 1735, 1140 cm^{-1}.

2,2-Diisobutyl-1,3-dioxan-5-one (37c)



A similar three step procedure to that described for compound **37b** produced dioxanone **37c** as a colorless liquid in 60% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.08 (s, 4H), 1.73 (m, 2H), 1.63 (d, J = 6.6 Hz, 4H), 0.96 (d, J = 6.6 Hz, 12H)

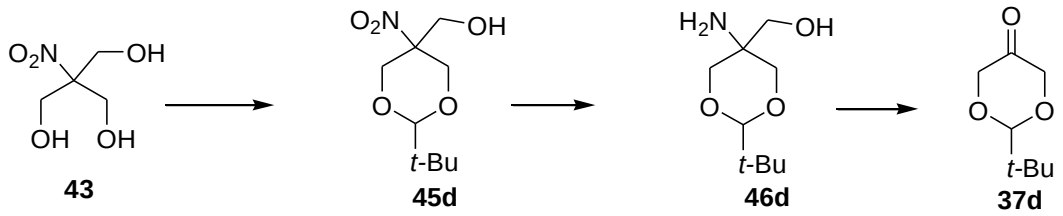
^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.6, 100.1, 66.3, 41.6, 24.4, 24.0

HRMS (CI, NH_3) exact mass calcd for $(C_{12}H_{23}O_3 + H)^+$ 215.1647 found m/z 215.1654

LRMS (CI, NH_3): m/z (relative intensity %): 215 (M + 1, 100), 157 (56)

IR (KBr): 1730, 1220 cm^{-1}

2-*tert*-Butyl-1,3-dioxan-5-one (37d) [20]



A similar three step procedure to that described for compound **37b** produced dioxanone **37d** as a white solid in 66% yield.

Melting point: 40-42 °C

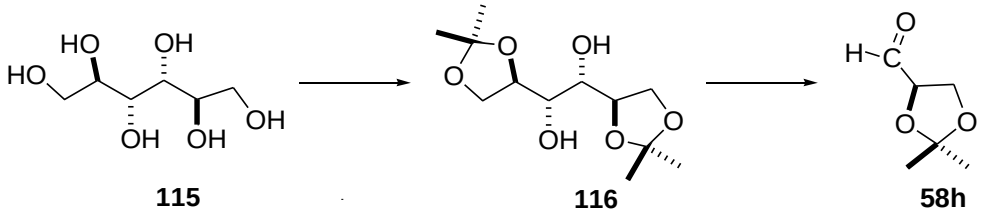
^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.46 (d, J = 18.0 Hz, 2H), 4.43 (s, 1H), 4.27 (d, J = 18.0 Hz, 2H), 1.01 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 205.2, 105.6, 73.2, 35.1, 24.4

IR (KBr): 1730, 1110 cm^{-1}

3.7 Synthesis of aldehydes

(*R*)-2,3-O-Isopropylideneglyceraldehyde (58h) [21]



115 **116** **58h**

This compound was synthesized according to the known procedure. [21]

To a freshly distilled 1,2-dimethoxyethane (25 mL) were added D-mannitol (5.12 g, 28.1 mmol) followed by stannous chloride dihydrate (100 mg, 0.440 mmol) and 2,2-dimethoxypropane (8.00 mL, 65.0 mmol). The mixture was stirred and heated under reflux for about 2.5 h, until it became clear. The resulting clear solution was allowed to cool down to room temperature and pyridine (20 μL) was added. The solvent was then removed under vacuum to provide crude 1,2 : 5,6-diisopropylidene-D-mannitol as a semi-solid which was used in the next step without further purification.

To CH_2Cl_2 (50.0 mL) were added the crude protected D-mannitol **116** (5.25 g, 20.0 mmol) and the mixture was refluxed with vigorous stirring. After 30 min, Celite (500 mg) was added and the slurry was allowed to cool down to room temperature. The solid was filtered off and washed with CH_2Cl_2 (30 mL). Saturated sodium bicarbonate (3.20 mL) was added to the filtrate. Next, sodium periodate (6.57 g, 30.8 mmol) was added over 5 min and the resulting mixture was stirred for another 2 h. To the slurry was added

anhydrous magnesium sulphate (3.50 g) and the mixture was stirred for another 20 min. The solid was then filtered off and the filtrate was concentrated to give the crude aldehyde which was purified by vacuum distillation to yield the pure (*R*)-2,3-O-isopropylideneglyceraldehyde **58h** in 37 % yield.

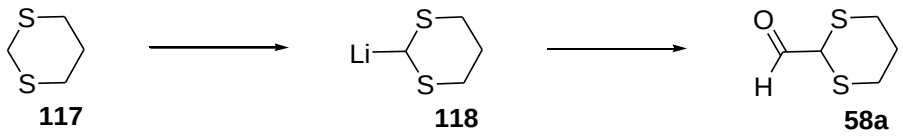
$[\alpha]^{24}_{D}$ +49.1 (c 1.0, benzene), **lit. $[\alpha]^{25}_{D}$** +54.3 (c 1.4, benzene) [21];

$[\alpha]^{25}_{D}$ +43.1 (c 1.1, benzene) [9]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.72 (d, J=1.5 Hz, 1H), 4.39 (ddd, J_1=1.5 Hz, J_2=4.7 Hz, J_3=7.6 Hz, 1H), 4.19 (dd, J_1=7.6 Hz, J_2=8.8 Hz, 1H), 4.09 (dd, J_1=4.7 Hz, J_2=8.8 Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.2, 111.9, 80.1, 65.3, 26.1, 25.4

1,3-Dithiane-2-carbaldehyde (58a) [6, 22]



This compound was synthesized according to the known procedure. [6, 22]

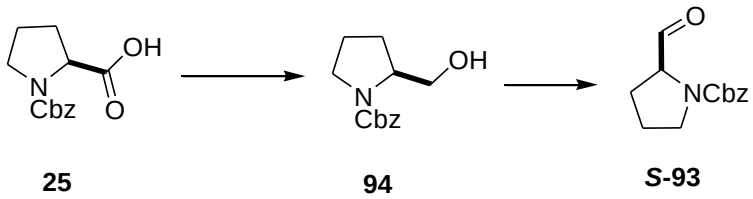
1,3-Dithiane **(**5.29 g, 44.0 mmol**)** was dissolved in a a solution of THF (100 mL) and the solution was cooled at -30 °C. Next, *n*-BuLi (22.0 mL, 44.0 mmol, 2.00 M in hexane) was added drop wise and the reaction mixture was stirred for 1 h then was transferred by a cannula to a round bottom flask containing cold DMF (14.0 mL, 1.32 g, 180 mmol,-10.0 °C). The resulting mixture was stirred for 2 h at -10 °C, stored overnight at 0 °C and then poured into ice water (100 mL). The mixture was then transferred to a separatory funnel and extracted with hexane (3 x 25 mL). The aqueous layer was acidified with hydrochloric acid (1 M) until pH 4 and then extracted with ether (3 x 50 mL). The ethereal extracts were combined, washed with saturated sodium bicarbonate, dried with anhydrous magnesium sulphate and concentrated under reduced pressure to give the crude aldehyde that was distilled under reduced pressure to give the pure 1,3-dithiane-2-carbaldehyde **58a** as a colorless oil in 85 % yield.

b.p. 84-87 °C/ 0.1 mm Hg **(lit.** 99-100 °C/2.3 mm Hg [6], 85 °C/0.5 mm Hg) [22]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 4.11 (s,1H), 3.06-3.01 (m, 2H), 2.59-2.54 (m, 2H), 2.12-1.97 (m, 2H), 1.54 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 188.6, 47.7, 25.8, 25.2

(*S*)-N-Cbz-prolinal (*S*-93) [24]



25 **94** ***S*-93**

This compound was synthesized according to the known procedure.[17]

To a solution of (*S*)-N-Cbz-proline **25** (8.00 g, 32.0 mmol, 1.00 eq) in 50 mL THF at 0 °C, borane methyl sulfide complex was slowly added under a nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 3 h and then at room temperature for 22 h. The solution was then cooled to 0 °C and the reaction was quenched by the slow addition of 40 mL ice cold water. The mixture was allowed to stir for another 30 min, then transferred to a separatory funnel and extracted with ethyl acetate (3 x 150 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude **94** in 86 – 90 % yields. The crude compounds were used in the next step.

(*S*)-N-Cbz-prolinol **94** (5.04 g, 21.4 mmol, 1eq) was dissolved in 100 mL DCM at 0 °C in the presence of 4Å molecular sieves under nitrogen atmosphere. To this slurry was added PCC (6.4g, 30 mmol) and acetic acid (2 mL) and the mixture was allowed to stir at 0 °C for 15 min and at room temperature for 2 h. The reaction was monitored by TLC. Upon completion of the reaction, 7 g of Celite and 80 mL of ether were added to the mixture and the resulting slurry was filtered through a Celite/silica bed. The Celite was washed with ether (3 x 30 mL) and the filtrates were combined and evaporated under

reduced pressure to afford the crude aldehyde ***S*-93.** Purification via FCC (ether as solvent) afforded the pure aldehyde ***S*-93** in 59 % yield. The enantionmer of ***S*-93** was synthesized via the same protocol using the enantiomer of **7**.

$[\alpha]_D^{23}$ = - 83 (c 1.2, $CHCl_3$); **lit.** – 83.1 (c 1.0, $CHCl_3$)[17]

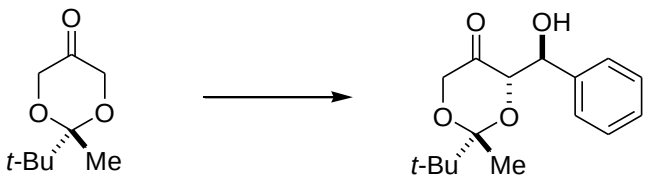
^{1}H NMR (500 MHz, CDCl3) δ: 9.55 (d, J = 20.1 Hz, 1H), 7.34 (m, 5H), 5.16 (br, 2H), 4.31 (m, 1H), 3.45 (m, 2H), 2.03 (m, 2H), 1.88 (m, 2H)

3.8 General procedure for (S)-proline catalyzed aldol reaction

Procedure P1: (*S*)-Proline-catalyzed aldol reaction with an additive [6, 19]

To a flame dried glass vial were added dry DMSO (0.5 mL), dioxanone (**37**,1 eq, 0.5 mmol), the aldehyde (1 eq, 0.5 mmol), (*S*)-proline (0.3 eq, 0.15 mmol) and the additive (0.3- 0.5 eq). The mixture stirred at room temperature for 5-15 min and stored in the refrigerator at 5 ^{o}C. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (x 3). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified using flash column chromatography (FCC) to yield the aldol product.

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(phenyl)methyl)-2-methyl-1,3-dioxan-5-one (120)[19]



37b **120**

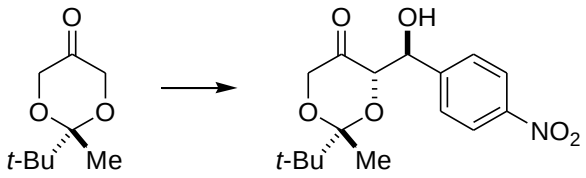
Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish gummy solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude product **120** was purified via FCC (hexane : ethyl acetate 8 : 2) to give the *anti* aldol adduct (0.097 g, 70 %) as a yellowish oil.

$[\alpha]^{25}_{D}$ = -32 (c 1.0, $CHCl_3$); **lit**. -34 (c 1.0, $CHCl_3$) [19]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39-7.30 (m, 5H), 5.03 (dd, J_1 = 2.5 Hz, J_2 = 6.3 Hz, 1H), 4.38 (d, J = 6.3 Hz, 1H), 4.26 (d, J = 18.5 Hz, 1H), 4.19 (d, J = 18.5 Hz, 1H), 3.49 (d, J = 2.5 Hz, 1H, OH), 1.27 (s, 3H), 0.99 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.6, 138.9, 128.0, 127.9, 127.1, 104.2, 78.7, 73.7, 69.7, 40.3, 25.1, 16.3

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(4-nitrophenyl)methyl)-2-methyl-1,3-dioxan-5-one (121)



37b **121**

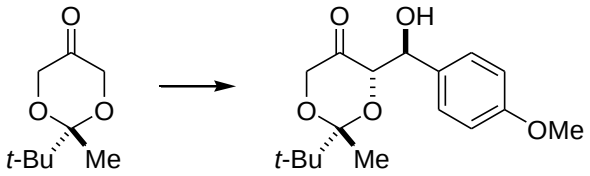
Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish gummy solid in a diastereomeric ratio of 9:1 (*anti: syn*). Crude **121** was purified by FCC (hexane: ethyl acetate 8 : 2) to give the *anti* aldol adduct (0.096 g, 60 %), as a yellow solid. Only the *anti* aldol adduct was isolated.

$[\alpha]^{25}_{D}$ = -26 (c 1.0, $CHCl_3$); **lit**. **$[\alpha]^{25}_{D}$** -24.7 (c 1.0, $CHCl_3$) [19]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 5.11 (dd, J_1 = 1.4 Hz, J_2 = 6.8 Hz, 1H), 4.33 (dd, J_1 = 1.7 Hz, J_2 = 18.4 Hz, 1H), 4.30 (d, J = 6.8 Hz, 1H), 4.24 (d, J = 18.4 Hz, 1H), 3.74 (br, 1H, OH), 1.24 (s, 3H), 0.93 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.3, 147.9, 146.3, 128.1, 123.3, 104.5, 78.4, 73.0, 69.8, 40.4, 25.3, 16.1.

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(4-methoxyphenyl)methyl)-2-methyl-1,3-dioxan-5-one (122) [19]



37b **122**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product **122** as a yellowish gummy solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **122** was purified via FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.077 g, 50 %) as a yellow gummy solid. Only the *anti* aldol adduct was isolated.

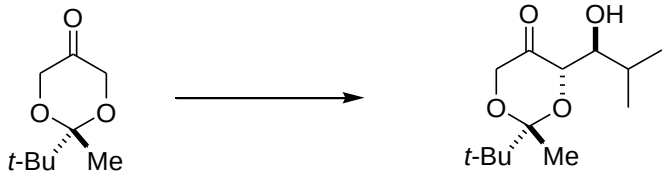
$[\alpha]^{25}_{D}$ = -29 (c 1.0, $CHCl_3$); **lit. $[\alpha]^{25}_{D}$** -32 (c 1.1, $CHCl_3$) [19]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.95 (d, J = 6.3 Hz, 1H), 4.33 (dd, J_1 = 1.2 Hz, J_2 = 6.3 Hz, 1H), 4.20 (dd, J_1 = 1.2 Hz, J_2 = 18.2 Hz, 1H), 4.13 (d, J = 18.2 Hz, 1H), 3.78 (s, 3H), 3.40 (br, 1H, OH), 1.26 (s, 3H), 0.94 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.8, 159.6, 131.3, 128.4, 113.6, 104.3, 78.9, 73.5, 69.9, 55.5, 40.5, 25.4, 16.4.

IR (KBr): 3491, 3048, 1736 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-1-hydroxy-2-methylpropyl)-2-methyl-1,3-dioxan-5-one (123) [19]



37b **123**

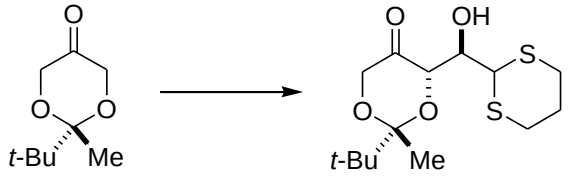
Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish oil in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **123** was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol adduct (0.097 g, 80 %) as a colorless oil.

$[\alpha]^{25}_{D}$ = -109 (c 1.2, $CHCl_3$); **lit. $[\alpha]^{25}_{D}$** -112 (c 1.1, $CHCl_3$) [19]

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.33 (dd, J_1 = 1.3 Hz, J_2 = 18.3 Hz, 1H), 4.20 (dd, J_1 = 1.3 Hz, J_2 = 6.3 Hz, 1H), 4.19 (d, J = 18.3 Hz, 1H), 3.70 (dd, J_1 = 5.6 Hz, J_2 = 6.3 Hz, 1H), 2.97 (br, 1H, OH), 1.98 (m, 1H), 1.39 (s, 3H), 1.02 (s, 9H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.0, 103.9, 76.8, 76.3, 69.9, 40.6, 29.1, 25.4, 19.3, 16.5, 16.2.

(2*R*,4*S*)-4-((*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-2-tert-butyl-2-methyl-1,3-dioxan-5-one (124) [19]



37b **124**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **124** was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol adduct (0.136 g, 85 %) as a white solid

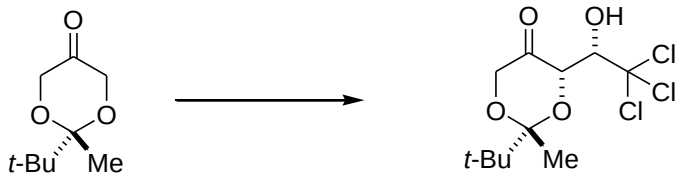
Melting point: 65-67 °C; **lit.** 67-68 °C [19]

$[\alpha]^{25}_{D}$ = -35 (c 1.0, $CHCl_3$); **lit. $[\alpha]^{25}_{D}$** = -34 (c 1.0, $CHCl_3$) [19]

^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.71(dd, J_1 = 2.2 Hz, J_2 = 9.1 Hz, 1H), 4.67 (d, J_1 = 2.2 Hz, 1H), 4.53 (d, J = 18 Hz, 1H), 4.22 (d, J = 18 Hz, 1H), 3.85 (d, J = 9.1 Hz, 1H), 3.04 (m, 2H), 2.96 (s, OH), 2.71 (t, J = 2.4 Hz, 1H), 2.56 (m, 1H), 2.41 (m, 1H), 2.05 (m, 2H), 1.4 (s, 3H), 1.04 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.4, 103.6, 77.5, 72.3, 69.2, 43.2, 40.4, 25.4, 25.35, 24.9, 24.5, 15.4.

(2*R*,4*S*)-2-*tert*-Butyl-4-((S)-2,2,2-trichloro-1-hydroxyethyl)-2-methyl-1,3-dioxan-5-one (125)



37b **125**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a white solid in a diastereomeric ratio of 9:1 (*anti: syn*). Crude **125** was purified by FCC (hexane: ethyl acetate 8 : 2) to give the *syn* aldol adduct (0.097 g, 61 %) as a white solid. Only the *syn* aldol adduct was isolated.

Melting point: 175-176 °C

$[\alpha]^{25}_{D}$ = -75 (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.05 (d, *J* = 2.0 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.27 (d, *J* = 12.1 Hz 1H), 3.61 (d, 1H, 10.9 Hz), 1.36 (s, 3H), 1.05 (s, 9H).

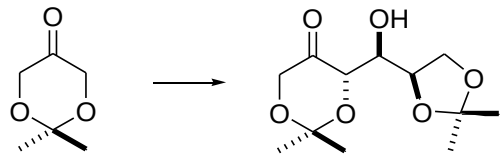
^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.1, 107.13, 78.8, 75.8, 67.2, 41.3, 31.1, 25.4, 17.4.

HRMS (CI, NH_3) exact mass calcd for $[M + H]^+$ ($C_{11}H_{17}Cl_3O_4 + H^+$) requires 319.0270 found m/z 319.0277

LRMS (CI, NH_3): m/z (relative intensity %): 319 ($[M + 1]^+$, 100), 215 (53), 160 (18), 157 (25), 122 (16)

IR (KBr): 3428, 2985, 1734 cm^{-1}

(-)-1,3 : 5,6-di-O-Isopropylidene-D-tagatose (126) [6, 14]



37a **126**

Procedure P1 (0.50 mmol scale) using water as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **126** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct in 50% yield as a white solid.

m.p. 102-104 °C**, lit.** 103-105 °C[6], 102-103 °C [14]

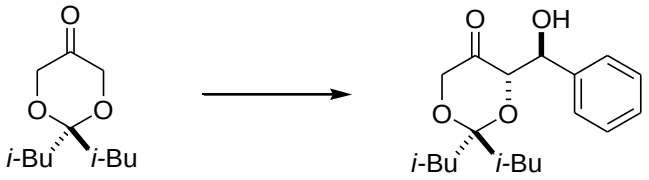
$[\alpha]^{25}_{D}$ -154 (c 1.0, CH_2Cl_2) **lit. $[\alpha]^{24}_{D}$** -148 (c 0.9, CH_2Cl_2)[6], **$[\alpha]^{25}_{D}$** -167 (c 1.1, CH_2Cl_2)[14]

^{1}H NMR (500 MHz, CDCl3) δ: 4.28-4.23 (m, 3H), 4.03 (d, J=17.5 Hz, 1H), 3.97 (dd, J_1=8.0 Hz, J_2=8.0 Hz, 1H), 3.87-3.81 (m, 2H), 3.14 (br, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.5, 109.4, 101.5, 75.4, 73.7, 70.3, 66.9, 65.8, 26.5, 25.8, 23.9, 23.7

.

(*S*)-4-((*S*)-Hydroxy(phenyl)methyl)-2,2-diisobutyl-1,3-dioxan-5-one (127)



37c **127**

Procedure P1 (0.50 mmol scale) using LiCl as additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 5:1 (*anti* : *syn*). Crude **127** was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol adduct (0.093 g, 58 %) as a viscous oil.

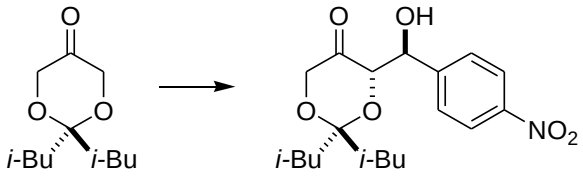
$[\alpha]^{25}_{D}$ = -82 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38-7.22 (m, 5H), 4.83 (dd, J_1 = 2.2 Hz, J_2 = 7.7 Hz, 1H), 4.26 (dd, J_1 = 1.4 Hz, J_2 = 7.8 Hz, 1H), 4.22 (d, J = 18.0 Hz, 1H), 3.98 (d, J = 18.0 Hz, 1H), 3.98 (d, J = 1H), 3.66 (s, 1H), 1.78 (m, 1H), 1.64 (m, 2H), 1.54 (d, J = 6.5 Hz, 2H), 1.48-1.44 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1, 146.8, 129.8, 124.8, 123.2, 105.1, 76.2, 73.1, 66.2, 41.8, 41.5, 24.5, 24.3, 24.2, 24.0, 23.1, 22.8

IR (KBr): 3443, 1731 cm^{-1}

(*S*)-4-((*S*)-Hydroxy(4-nitrophenyl)methyl)-2,2-diisobutyl-1,3-dioxan-5-one (128)



37c **128**

Procedure P1 (0.50 mmol scale) using LiCl as additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 9:1 (*anti* : *syn*). Crude **128** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.118 g, 65 %) as a yellowish oil.

$[\alpha]^{25}_{D}$ = -88 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (d, J = 8.34 Hz, 2H), 7.57 (d, J = 8.34 Hz, 2H), 4.96 (d, J= 8.3 Hz, 1H), 4.25 (d, J = 18.0 Hz, 1H), 4.22 (d, J = 8.35 Hz, 1H), 4.03 (d, J = 18.0 Hz, 1H), 3.82 (d, J = 2.2 Hz, 1H), 1.63 (m, 1H), 1.55 (d, J = 5.7 Hz, 2H), 1.47 (dd, J_1 = 4.8 Hz, J_2 = 14.0 Hz, 1H), 1.35 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.4 Hz, 3H), 0.38 (d, 6.6 Hz, 3H)

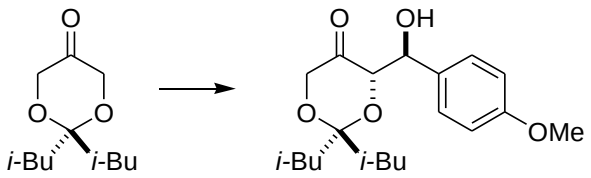
^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.1, 147.9, 146.6, 128.4, 123.3, 105.3, 76.0, 72.5, 66.1, 41.9, 41.6, 24.5, 24.3, 24.1, 24.0, 23.3, 23.0

HRMS (CI, NH_3) exact mass calcd for $[M + H]^+$ ($C_{19}H_{28}NO_6 + H^+$) requires 366.1916 found m/z 366.1912.

LRMS (CI, NH_3): m/z (relative intensity %): 366 ($[M + 1]^+$, 100), 307 (34), 215 (53), 160 (18), 157 (25), 122 (16)

IR (KBr): 3452, 1740 cm^{-1}

(*S*)-4-((*S*)-Hydroxy(4-methoxyphenyl)methyl)-2,2-diisobutyl-1,3-dioxan-5-one (129)



Procedure P1 (0.50 mmol scale) using LiCl as additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 4:1 (*anti* : *syn*). Crude **129** was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol adduct in 35 % yield.

$[\alpha]^{25}_{D}$ = - 54 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: δ: 7.92 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 4.86 (d, J= 8.5 Hz, 1H), 4.25 (d, J = 17.5 Hz, 1H), 4.22 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 17.5 Hz, 1H), 3.79 (s, 1H), 1.66 (m, 1H), 1.53 (d, J = 5.2 Hz, 2H), 1.47 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 1.35 (m, 2H), 0.91 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H), 0.76 (d, J = 6.0 Hz, 3H), 0.68 (d, 6.0 Hz, 3H)

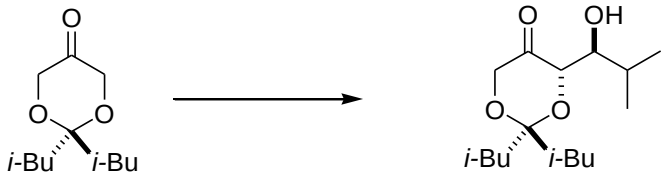
^{13}C NMR (125 MHz, $CDCl_3$) δ: 210.1, 147.9, 139.6, 129.4, 120.4, 104.3, 76.5, 73.4, 66.3, 42.3, 41.6, 24.5, 24.3, 24.2, 24.0, 23.5, 23.2

HRMS (CI, NH_3) exact mass calcd for $[M + H]^+$ ($C_{20}H_{30}O_5 + H^+$) requires 351.2171 found m/z 351.2187.

LRMS (CI, NH_3): m/z (relative intensity %): 351 ($[M + 1]^+$, 33), 334 (11), 304 (28), 215 (48), 136 (100).

IR (KBr): 3449, 1722 cm^{-1}

(*S*)-4-((*S*)-1-Hydroxy-2-methylpropyl)-2,2-diisobutyl-1,3-dioxan-5-one (130)



37c **130**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **130** was purified by FCC (hexane : ethyl acetate 9 : 1) to provide the *anti* aldol adduct (0.097 g, 68 %) as a colorless oil.

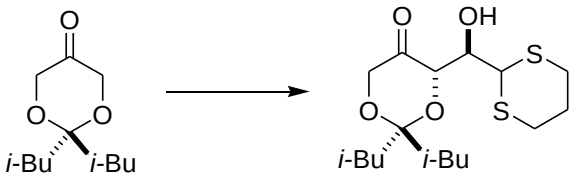
$[\alpha]^{25}_{D}$ = -126 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.21 (d, J = 17.5 Hz, 1H), 4.14 (d, J = 7.3 Hz, 1H), 3.95 (d, J = 17.5 Hz, 1H), 3.63 (m, 1H), 2.96 (d, J = 2.5 Hz, 1H), 1.99 (m, 1H), 1.76- 1.68 (m, 2H), 1.65 (d, J = 5.9 Hz, 2H), 1.62 (d, J = 6.8 Hz, 2H), 0.91 (m, 18H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.3, 104.5, 75.2, 73.8, 66.5, 42.4, 42.1, 28.7, 24.5, 24.4, 24.3, 24.2, 24.0, 23.8, 23.6

IR (KBr): 3399, 1723 cm^{-1}

(*S*)-4-((*R*)-(1,3-Dithian-2-yl)(hydroxy)methyl)-2,2-diisobutyl-1,3-dioxan-5-one (131)



37c **131**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **131** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.108 g, 60%) as a colorless oil.

$[\alpha]^{25}_{D}$ = -62 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.59 (d, J = 2.5 Hz, 1H), 4.53 (d, J = 8.5 Hz, 1H), 4.30 (d, J = 17.0 Hz, 1H), 3.89 (d, J = 17.0 Hz, 1H), 3.82 (d, J = 8.0 Hz, 1H), 2.98 (m, 1H), 2.78 (m, 1H), 2.56-2.42 (m, 2H), 2.07 (m, 1H), 1.96 (m, 1H), 1.72 (m, 2H), 1.69-1.65 (m, 3H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H)

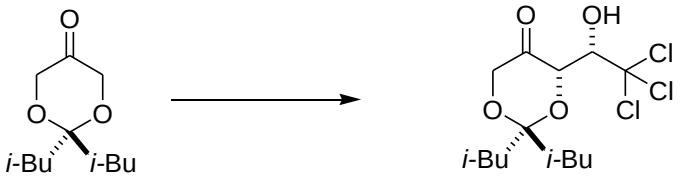
^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.2, 104.3, 75.6, 72.5, 66.9, 42.3, 41.8, 26.4, 25.4, 24.5, 24.2, 24.0, 23.9, 23.2, 23.0

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{17}H_{30}O_4S_2$) requires 362.1586, found m/z 362.1586.

LRMS ((EI+, 70 eV): m/z (%): 362 ($[M]^+$, 9), 220 (17), 201 (19), 157 (96), 85 (100), 69 (30), 57 (53)

IR (KBr): 3479, 1713 cm^{-1}

(*S*)-4-((*S*)-2,2,2-Trichloro-1-hydroxyethyl)-2,2-diisobutyl-1,3-dioxan-5-one (77c)



37c **77c**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish oil in a diastereomeric ratio of 20:1 (*anti* : *syn*). Crude **77c** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.101 g, 56 %) as a colorless oil.

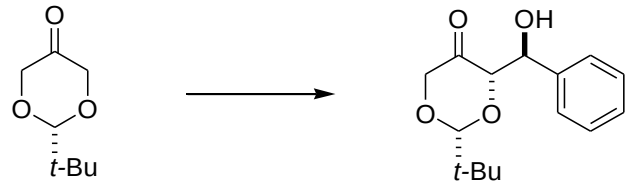
$[\alpha]^{25}_{D}$ = -106 (c 1.0, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.58 (d, J = 3.0 Hz, 1H), 4.56 (d, J = 10.3 Hz, 1H), 4.46 (dd, J_1 = 2.8 Hz, J_2 = 10.8 Hz, 1H), 3.83 (d, J = 17.3 Hz, 1H), 3.51 (d, J = 17.5 Hz, 1H), 1.66 (m, 1H), 1.58 (m, 2H), 1.49 (dd, J_1 = 4.9 Hz, J_2 = 14.0 Hz, 1H), 1.38 (m, 2H), 0.91 (m, 12H)

^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 204.1, 106.5, 83.1, 72.4, 66.5, 42.2, 41.1, 28.7, 24.4, 24.1, 24.2, 23.9, 23.7, 23.6

IR (KBr): 3429, 1743 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(phenyl)methyl)-1,3-dioxan-5-one (132)



37d **132**

Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 4:1 (*anti* : *syn*). Crude **132** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.020 g, 15 %) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.30 (m, 5H), 4.42 (d, J = 18.0 Hz, 1H), 4.27 (d, J = 8.1 Hz, 1H), 4.23 (d, J = 18.2 Hz, 1H), 3.50 (br, 1H), 0.85 (s, H)

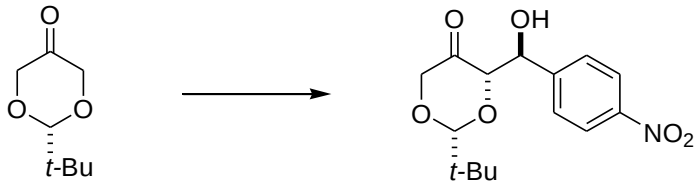
^{13}C NMR (125 MHz, $CDCl_3$) δ: 206.5, 137.8, 128.2, 127.8, 127.0, 104.6, 78.7, 73.3, 69.2, 40.7, 25.6

HRMS (CI, NH_3) exact mass calcd for for $[M + H]^+$ ($C_{15}H_{20}O_4 + H^+$) requires 265.0440 found m/z 265.0574.

LRMS (CI, NH_3): m/z (relative intensity %): 265 ($[M + 1]^+$, 4), 247 (40), 178 (12), 161 (16).

IR (KBr): 3381, 2960, 1726 cm^{-1}

(2*R*,4*S*)-2-*tert*-Butyl-4-((*S*)-hydroxy(4-nitrophenyl)methyl)-1,3-dioxan-5-one (134)



Procedure P1 (0.50 mmol scale) using LiCl as the additive afforded the crude product as a yellowish solid in a diastereomeric ratio of 4:1 (*anti* : *syn*). Crude **134** was purified by FCC (hexane : ethyl acetate 8 : 2) to provide the *anti* aldol adduct (0.038 g, 25 %) as a gummy yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 5.01 (d, J = 7.6 Hz, 1H), 4.78 (s, 1H), 4.45 (s, 1H), 4.30 (d, J = 7.4 Hz, 1H), 4.20 (d, J = 18.3 Hz, 1H), 4.09 (d, J = 18.0 Hz, 1H), 0.87 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.3, 147.2, 145.9, 127.3, 124.2, 104.1, 78.1, 74.3, 68.9, 41.4, 24.1

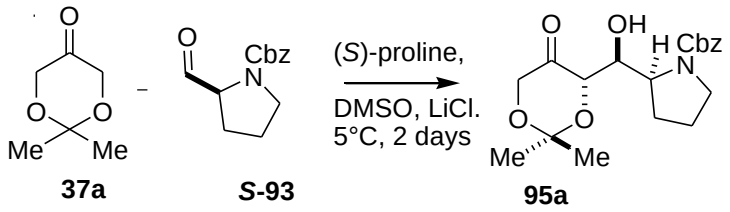
HRMS (CI, NH_3) exact mass calcd for $[M + NH_4]^+$ ($C_{15}H_{19}NO_6 + NH_4^+$) requires 327.1556 found m/z 327.1550

LRMS (CI, NH_3): m/z (relative intensity %): 327 ($[M + 18]^+$, 100), 312 (20), 308 (73), 290 (16), 101 (26).

IR (KBr): 3438, 1734 cm^{-1}

3.8 Synthesis of hyacinthacines

Compound 95a



To a flame dried glass vial were added dry DMSO (0.5 mL), dioxanone **37a** (0.065 g, 1.00 eq, 0.500 mmol), (*S*)-N-Cbz- prolinal ***S*-93** (0.116 g, 1.00 eq, 0.500 mmol), (*S*)-proline (0.017 g, 0.300 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 10 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified via FCC (hexane: ethyl acetate, 8: 2) to yield the aldol adduct **95a** (0.105 g, 58%) as a viscous colorless oil.

$[\alpha]_D^{24}$ = + 60 (c 1.1, CH_2Cl_2)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.29 (d, J = 6.9 Hz, 2H), 7.13 (dd, J_1 = 7.4 Hz, J_2 = 7.6 Hz, 2H), 7.05 (t, J = 7.6 Hz, 1H), 5.18 (m, 2H), 4.79 (br, 1H), 4.34 (br, 1H), 3.91 (br, 1H), 3.79 (br, 1H), 3.73 (d, J = 17.3 Hz, 1H), 3.59 (d, J = 17.2 Hz, 1H), 3.36 (br, 1H), 3.24 (br, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.41 (m, 1H), 1.31 (m, 1H), 1.12 (s, 3H), 1.09 (s, 3H)

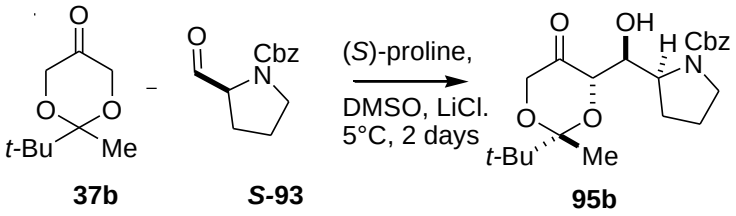
^{13}C NMR (125 MHz, C_6D_6) *δ:* 208.21, 167.42, 136.68, 128.64, 128.31, 128.25, 128.19, 101.45, 79.68, 76.75, 67.37, 64.43, 60.01, 48.73, 25.50, 20.49, 18.17

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_{19}H_{25}NO_6 + H^+$) requires 364.1760 found m/z 364.1752

LRMS (CI, NH_3): m/z (%): 364 ($[M + 1]^+$, 89), 346 (39), 234 (100), 204 (83), 190 (28), 160 (55), 131 (20), 108 (22), 91 (72)

IR (KBr): 3392, 2967, 1730, 1706, 1114 cm^{-1}

Compound 95b



To a flame dried glass vial were added dry DMSO (0.5 mL), dioxanone **37b** (0.0836 g, 1.00 eq, 0.500 mmol), (*S*)-N-Cbz- prolinal ***S*-93** (0.116g, 1.00 eq, 0.500 mmol), (*S*)-proline (0.017 g, 0.300 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 10 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified via FCC (hexane: ethyl acetate, 8: 2) to yield the aldol adduct **95b** (0.113 g, 56%) as a viscous colorless oil.

$[\alpha]_D^{20}$ = + 75 (c 1.0, CH_2Cl_2)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.22 (d, J_1 = 6.6 Hz, 2H), 7.12 (dd, J_1 = 7.3 Hz, J_2 = 7.5 Hz, 2H), 7.06 (br, 1H), 5.6 (br, 1H), 5.05 (m, 2H), 4.42 (br, 2H), 4.19 (m, 2H), 3.91 (d, *J* = 17.6 Hz, 1H), 3.18 (br, 1H), 2.97 (br, 1H), 1.67 (br, 1H), 1.37 (br, 1H), 1.24 (br, 2H), 1.17 (s, 3H), 1.11 (s, 9H)

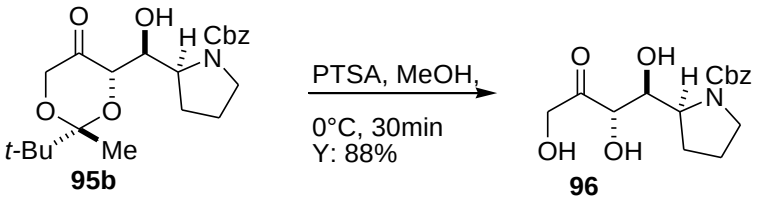
^{13}C NMR (125 MHz, $CDCl_3$) δ*:* 207.85, 155.28, 136.70, 128.53, 128.13, 128.01, 127.95, 105.31, 79.68, 70.26, 67.14, 66.94, 61.09, 47.08, 40.85, 25.39, 17.23

HRMS (CI, NH_3) exact mass calcd for $[M + H]^+$ ($C_{16}H_{21}NO_6 + H^+$) requires 406.2230 found m/z 406.2236

LRMS (CI, NH_3): m/z (%): 406 ($[M + 1]^+$, 30), 389 (25), 388 (99), 350 (10), 348 (19), 306 (12), 281 (17), 264 (48), 251 (46), 234 (94), 204 (100), 190 (15), 173 (25), 160 (49)

IR (KBr): 3422, 2976, 2876, 1740, 1698, 1414 cm^{-1}

(*S*)-Benzyl 2-((1*S*,2*S*)-1,2,4-trihydroxy-3-oxobutyl)pyrrolidine-1-carboxylate (96)



To a vial were added the adol adduct **95b** (0.041 g, 1.00 eq, 0.100 mmol), PTSA (0.002 g, 0.200 eq, 0.020 mmol), methanol (1.00 mL) and the mixture was stirred at 0 ^{o}C for 30 min. The reaction was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure and the residue was purified via FCC (ethyl acetate) to afford compound **96** (0.028 g, 88 %) as a colorless oil.

$[\alpha]_D^{24}$ = + 65 (c 1.0, CH_2Cl_2)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.80 (br, 1H), 5.17 (d, J = 12.3 Hz, 1H), 5.12 (d, J = 12.2 Hz, 1H), 4.68 (d, J = 20.7 Hz, 1H), 4.57 (d, J = 20.7 Hz, 1H), 4.26 (ddd, J_1 = 2.5 Hz, J_2 = 2.6 Hz, J_3 = 8.5 Hz, 1H), 3.98 (d, J_1 = 8.6 Hz, 1H), 3.72 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 3.59 (ddd, J_1 = 1.6 Hz, J_2 = 7.5 Hz, J_3 = 10.7 Hz), 3.43 (dd, J_1 = 4.7 Hz, J_2 = 8.4 Hz, 1H), 2.18 (m, 1H), 2.07 (ddd, J_1 = 8.4 Hz, J_2 = 12.2 Hz, J_3 = 16.9), 2.00 (m, 1H), 1.81 (m, 1H)

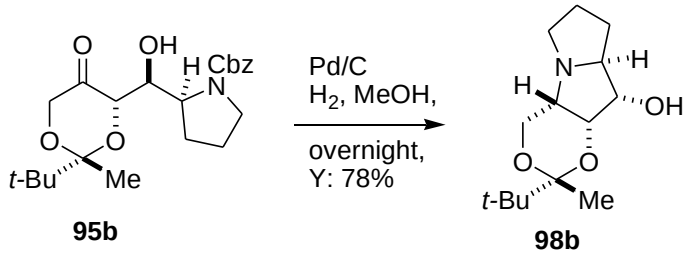
^{13}C NMR (125 MHz, $CDCl_3$) δ: 215.75, 158.08, 136.33, 128.78, 128.4, 128.0, 76.52, 75.59, 67.93, 67.30, 57.97, 48.20, 29.05, 24.51

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_{16}H_{21}NO_6 + H^+$) requires 324.1447 found m/z 324.1437

LRMS (CI, NH_3): m/z (%): 324 ($[M + 1]^+$, 94), 308 (14), 306 (24), 264 (19), 235 (11), 234 (75), 204 (62) 190 (11), 160 (40), 91 (100), 70 (18)

IR (KBr): 3440, 1736, 1708, cm^{-1}

(2*R*,4a*S*,8a*S*,9*S*,9a*R*)-2-*tert*-Butyl-octahydro-2-methyl-[1,3]dioxino[4,5-b]pyrrolizin-9-ol (98b)



95b **98b**

To a solution of **95b** (0.082 g**,** 1.00 eq, 0.200 mmol) in methanol (2.00 mL) was added 10 % Pd/C (0.005 g) and the resulting mixture was stirred at room temperature under H_2 atmosphere (a balloon containing hydrogen gas was attached to the flask) for 10-12 h. Upon completion of the reaction, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford **98b** (0.040 g, 78 %) as a pale yellow solid.

Melting point: 101-105 °C

$[\alpha]_D^{24}$ = + 56 (c 0.8, H_2O)

^{1}H NMR (500 MHz, D_2O) δ: 4.49 (dd, J_1 = 2.0 Hz, J_2 = 2.2Hz, 1H), 4.28 (dd, J_1 = 2.4 Hz, J_2 = 14.3 Hz, 1H), 4.12 (br, 2H), 3.96 (d, J_1 = 14.3, 1H), 3.41 (br, 1H), 3.36 (m, 1H), 3.33 (m, 1H), 2.01 (m, 4H), 1.35 (s, 3H), 0.88 (s, 9H)

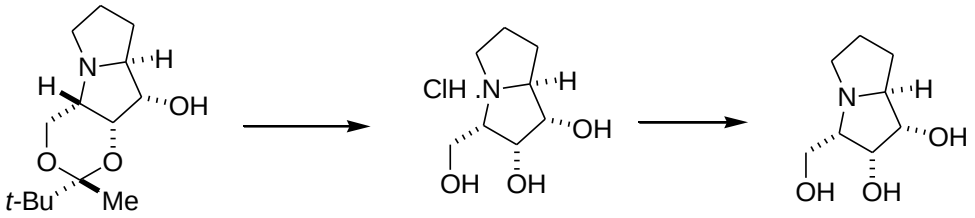
^{13}C NMR (125 MHz, D_2O) δ: 104.10, 75.93, 70.76, 70.18, 62.62, 57.32, 55.27, 39.23, 28.32, 24.16, 23.86, 12.09

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{11}H_{19}NO_3$) requires 255.1834, found m/z 255.1834

LRMS (EI+, 70 eV): m/z (%): 255 ($[M]^+$, 28), 240 (21), 224 (47), 198 (38), 141 (11), 125 (100), 108 (28), 96 (90), 70 (75)

IR (KBr): 3088, 2958, 2890, 2816, 1603, 1170 cm^{-1}

***ent*-2-Epihyacinthacine A_2 (*ent*-100)**



To a solution of **98b** (0.051 g, 1.00 eq, 0.200 mmol) in methanol (2.00 mL) at 0 ^{o}C was added HCl (1.00 mL, 10 % v/v) and the resulting mixture was stirred at 0 ^{o}C for 30 min. The reaction was monitored by TLC and upon completion the solvent was removed and the residue was passed through a column of basic Dowex using 1.00 M NH_4OH as the solvent. Removal of the solvent under reduced pressure afforded the hyancinthacine *ent*-**100** (0.026 g, 76 %) as a gummy brown solid.

$[\alpha]_D^{24}$ = + 22 (c 0.6, H_2O); [Lit enantiomer: **$[\alpha]_D^{20}$** = -34.0 (c 0.9, MeOH) [24]; **$[\alpha]_D^{22}$** = -26.5 (c 2, H_2O) [23]]

^{1}H NMR (500 MHz, D_2O) δ: 4.32 (dd, J_1 = 3.2 Hz, J_2 = 3.2 Hz, 1H), 4.14 (dd, J_1 = 3.6 Hz, J_2 = 8.9 Hz), 4.04 (ddd, J_1 = 3.6 Hz, J_2 = 7.6 Hz, J_3 = 8.8 Hz, 1H), 3.96 (m, 1H), 3.61 (ddd, J_1 = 2.9 Hz, J_2 = 5.26 Hz, J_3 = 7.9 Hz, 1H), 3.40 (m, 1H), 3.35 (m, 1H), 2.15 (m, 3H), 2.02 (m, 1H)

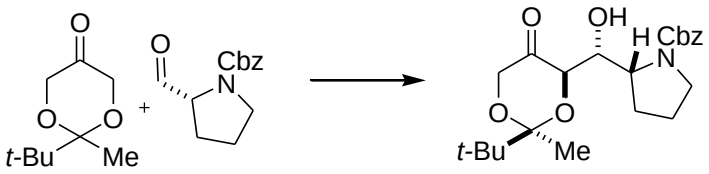
^{13}C NMR (125 MHz, D_2O) δ: 75.28, 72.69, 70.39, 69.76, 57.87, 55.35, 27.96, 24.47

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_8H_{15}NO_3 + H^+$) requires 174.1130 found m/z 174.1131

LRMS (CI, NH_3): m/z (%): 174 ($[M + 1]^+$, 100), 146 (10), 142 (16)

IR (KBr): 3368, 2856 cm^{-1}

Compund 101



37b ***R*-93** **101**

To a flame dried glass vial were added dry DMSO (0.500 mL), dioxanone **37b** (0.086 g, 1.00 eq, 0.500 mmol), (*R*)-N-Cbz- prolinal ***R*-93** (0.116 g, 1.00 eq, 0.500 mmol), (*S*)-proline (0.017 g. 0.300 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 10 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified via FCC (hexane: ethyl acetate, 8: 2) to yield the aldol adduct **101** (0.115 g, 58 %) as a colorless viscous oil.

$[\alpha]_D^{23}$ = - 70 (c 1.0, CH_2Cl_2)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.22 (d, J_1 = 6.6 Hz, 2H), 7.12 (dd, J_1 = 7.3 Hz, J_2 = 7.5 Hz, 2H), 7.06 (br, 1H), 5.6 (br, 1H), 5.05 (m, 2H), 4.42 (br, 2H), 4.19 (m, 2H), 3.91 (d, *J* = 17.6 Hz, 1H), 3.18 (br, 1H), 2.97 (br, 1H), 1.67 (br, 1H), 1.37 (br, 1H), 1.24 (br, 2H), 1.17 (s, 3H), 1.11 (s, 9H)

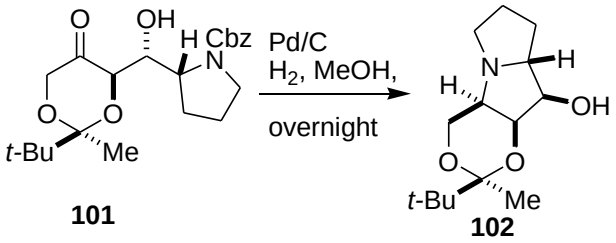
^{13}C NMR (125 MHz, $CDCl_3$) δ: 207.85, 155.28, 136.70, 128.53, 128.13, 128.01, 127.95, 105.31, 79.68, 70.26, 67.14, 66.94, 61.09, 47.08, 40.85, 25.39, 17.23

HRMS (CI, NH_3) exact mass calcd for $[M + 1]^+$ ($C_{16}H_{21}NO_6 + H^+$) requires 406.2230 found m/z 406.2236

LRMS (CI, NH_3): m/z (%): 406 ($[M + 1]^+$, 30), 389 (25), 388 (99), 350 (10), 348 (19), 306 (12), 281 (17), 264 (48), 251 (46), 234 (94), 204 (100), 190 (15), 173 (25), 160 (49)

IR (KBr): 3422, 2976, 2876, 1740, 1698, 1414 cm^{-1}

(2*S*,4a*R*,8a*R*,9*R*,9a*S*)-2-*tert*-Butyl-octahydro-2-methyl-[1,3]dioxino[4,5-b]pyrrolizin-9-ol (102)



101 **102**

To a solution of **101** (0.082 g, 1.00 eq, 0.200 mmol) in methanol (2.00 mL) was added 10 % Pd/C (0.005 g) and the resulting mixture was stirred at room temperature under H_2 atmosphere (a balloon containing hydrogen gas was attached to the flask) for 10-12 h. Upon completion of the reaction, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford **102** (0.045 g, 89 %) as a pale yellow solid.

Melting point = 102-103 °C

$[\alpha]_D^{25}$ = - 52 (c 0.8, MeOH)

^{1}H NMR (500 MHz, D_2O) δ: 4.49 (dd, J_1 = 2.0 Hz, J_2 = 2.2 Hz, 1H), 4.28 (dd, J_1 = 2.4 Hz, J_2 = 14.4 Hz, 1H), 4.12 (br, 2H), 3.96 (d, J_1 = 14.4, 1H), 3.41 (br, 1H), 3.36 (m, 1H), 3.33 (m, 1H), 2.01 (m, 4H), 1.35 (s, 3H), 0.88 (s, 9H)

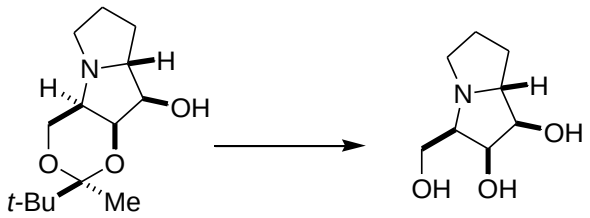
^{13}C NMR (125 MHz, D_2O) δ: 104.10, 75.93, 70.76, 70.18, 62.62, 57.32, 55.27, 39.23, 28.32, 24.16, 23.86, 12.09

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{11}H_{19}NO_3$) requires 255.1834, found m/z 255.1834

LRMS (EI+, 70 eV): m/z (%): 255 ($[M]^+$, 28), 240 (21), 224 (47), 198 (38), 141 (11), 125 (100), 108 (28), 96 (90), 70 (75)

IR (KBr): 3088, 2958, 2890, 2816, 1603, 1170 cm^{-1}

2-Epihyacinthacine A_2 (100)



102 **100**

To a solution of **102** (0.051 g, 1.00 eq, 0.200 mmol) in methanol (1.00 mL) at 0 ^{o}C was added HCl (1.00 mL, 10% v/v) and the resulting mixture was stirred at 0 ^{o}C for 30 min. The reaction was monitored by TLC and upon completion the solvent was removed and the residue was passed through basic Dowex using 1M NH_4OH as the solvent. Removal of the solvent under reduced pressure afforded the hyancinthacine **100** (0.027 g, 79 %) as a brown gummy solid.

$[\alpha]_D^{24}$ = - 29 (c 0.6, H_2O); (**Lit $[\alpha]_D^{20}$** = -34.0 (c 0.9, MeOH) [24]; **$[\alpha]_D^{22}$** = -26.5 (c 2, H_2O) [23]

^{1}H NMR (500 MHz, D_2O) δ: 4.32 (dd, J_1 = 3.2 Hz, J_2 = 3.2 Hz, 1H), 4.14 (dd, J_1 = 3.6 Hz, J_2 = 8.9 Hz), 4.04 (ddd, J_1 = 3.6 Hz, J_2 = 7.6 Hz, J_3 = 8.8 Hz, 1H), 3.96 (m, 1H), 3.61 (ddd, J_1 = 2.9 Hz, J_2 = 5.3 Hz, J_3 = 7.9 Hz, 1H), 3.40 (m, 1H), 3.35 (m, 1H), 2.15 (m, 3H), 2.02 (m, 1H)

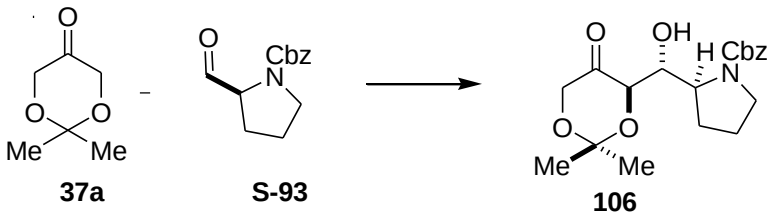
^{13}C NMR (125 MHz, D_2O) δ: 75.28, 72.69, 70.39, 69.76, 57.87, 55.35, 27.96, 24.47

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{18}H_{15}NO_3$) requires 173.1052, found m/z 173.1052

LRMS (EI+, 70 eV): m/z (%): 173 (3) $[M]^+$, 142 (100), 113 (14), 96 (52), 70 (38)

IR (KBr): 3368, 2856 cm^{-1}

Compound 106



To a flame dried glass vial were added dry DMSO (0.50 mL), dioxanone **37a** (0.065 g, 1.00 eq, 0.500 mmol), (*S*)-N-Cbz- prolinal ***S*-93** (0.116 g, 1.00 eq, 0.500 mmol), (*R*)-proline (0.017 g, 0.300 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 10 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified via FCC (hexane: ethyl acetate, 8: 2) to yield the aldol adduct 106 (0.117 g, 65 %), as a viscous colorless oil.

$[\alpha]_D^{24}$ = - 23 (c 1.0 CH_2Cl_2)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.33 (d, 1H, J = 7.4 Hz), 7.21 (dd, 1H, J_1 = 7.2, J_2 = 7.4 Hz), 7.15 (d, 1H, J = 7.3 Hz), 5.21 (d, 1H, J = 12.4 Hz), 5.16 (br, 1H), 5.09 (d, 1H, J = 12.3 Hz), 4.66 (br, 1H), 4.57 (br, 1H), 4.21 (br, 1H), 4.08 (d, 1H, J = 16.6 Hz), 3.78 (d, 1H, J = 16.6 Hz), 3.34 (br, 1H), 3.21 (br, 1H), 1.61 (m, 2H), 1.53 (s, 3H), 1.45 (br, 1H), 1.34 (s, 3H), 1.24 (m, 1H)

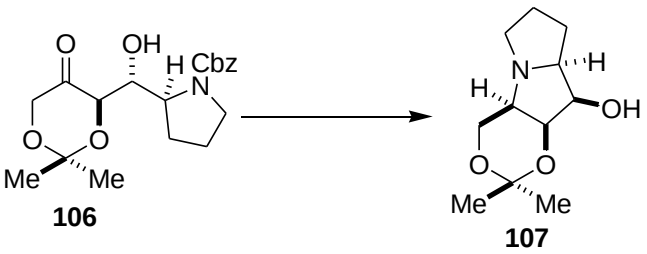
^{13}C NMR (125 MHz, C_6D_6) *δ:* 23.68, 24.22, 29.46, 47.37, 59.47, 66.93, 67.30, 75.61, 76.92, 100.95, 127.91, 128.12, 128.30, 128.62, 137.40, 157.42, 209.92

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_8H_{15}NO_3 + H^+$) requires 364.1760 found m/z 364.1753

LRMS (CI, NH_3): m/z (%): 364 ($[M + 1]^+$, 89), 346 (59), 204 (100), 160 (91), 91 (48)

IR (KBr): 3640, 2967, 1738, 1710, 1099 cm^{-1}

(4a*R*,8a*S*,9*R*,9a*S*)-Octahydro-2,2-dimethyl-[1,3]dioxino[4,5-b]pyrrolizin-9-ol (107)



To a solution of **106** (0.073 g, 1.00 eq, 0.200 mmol) in methanol (2.00 mL) was added 10 % Pd/C (0.005 g) and the resulting mixture was stirred at room temperature under H_2 atmosphere (a balloon containing hydrogen gas was attached to the flask) for 10-12 h. Upon completion of the reaction, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford **107** (0.038 g, 90 %) as a colorless oil.

$[\alpha]_D^{24}$ = -15 (c 1.0, MeOH)

^{1}H NMR (500 MHz, D_2O) δ: 4.43 (dd, J_1 = 4.8 Hz, J_2 = 8.2 Hz, 1H), 4.38 (dd, J_1 = 4.5 Hz, J_2 = 4.8 Hz, 1H), 4.33 (dd, J_1 = 3.4 Hz, J_2 = 13.8 Hz, 1H), 4.06 (d, J = 13.8 Hz, 1H), 3.56 (dd, J_1 = 7.9 Hz, J_2 = 12.8 Hz, 1H), 3.48 (m, 1H), 3.00 (m, 1H), 2.88 (br, 1H), 1.98 (m, 1H), 1.67 (m, 1H), 1.51 (s, 3H), 1.39 (s, 3H)

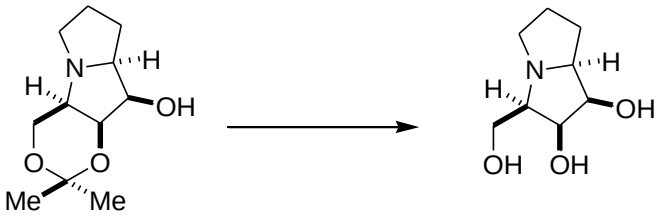
^{13}C NMR (125 MHz, D_2O) δ: 102.22, 73.25, 71.92, 71.62, 60.01, 57.06, 56.74, 55.05, 30.83, 28.71, 28.63, 21.79, 20.46, 17.68

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{11}H_{19}NO_3$) requires 213.65, found m/z 213.64

LRMS (EI+, 70 eV): m/z (%) = 213 (29) $[M]^+$, 198 (15), 154 (10), 141 (23), 125 (45), 108 (18), 96 (100), 70 (50)

IR (KBr): 3397, 2986 cm^{-1}

7-Deoxy-2-epialexine (108)



107 **108**

To a solution of **107** (0.036 g, 1.00 eq, 0.100 mmol) in methanol (1.00 mL) at 0 ^{o}C was added HCl (1.00 mL, 10 % v/v) and the resulting mixture was stirred at 0 ^{o}C for 30 min. The reaction was monitored by TLC and upon completion the solvent was removed and the residue was passed through basic Dowex using 1M NH_4OH as the solvent. Removal of the solvent under reduced pressure afforded the hyancinthacine **108** (0.013 g, 78 %).

$[\alpha]_D^{24}$ = -7 (c 0.9, MeOH); **Lit** -1.0 (0.6, MeOH) [23]

^{1}H NMR (500 MHz, D_2O) δ: 4.60 (dd, J_1 = 3.9 Hz, J_2 = 7.09 Hz, 1H), 4.46 (br, 1H), 4.43 (dd, J_1 = 6.6 Hz, J_2 = 14.0 Hz, 1H), 4.23 (br, 1H), 4.21 (br, 1H), 3.97 (m, 2H), 3.82 (d, J = 8.0 Hz, 2H), 2.72 (m 2H), 2.56 (m, 1H), 2.42 (m 1H)

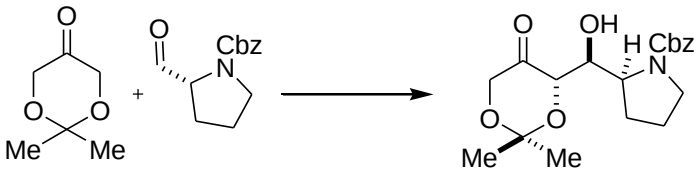
^{13}C NMR (125 MHz, D_2O) δ: 73.63, 71.62, 70.12, 66.64, 58.59, 53.65, 29.74, 29.34

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_8H_{15}NO_3$) requires 173.1052 found m/z 173.1052

LRMS (EI+, 70 eV): m/z (relative intensity %): 173 (3) $[M]^+$, 142 (100), 113 (15), 96 (56), 70 (38)

IR (KBr): 3256, 2864 cm^{-1}

Compound 109



To a flame dried glass vial were added dry DMSO (0.500 mL), dioxanone **37a** (0.065 g, 1.00 eq, 0.500 mmol), (*R*)-N-Cbz- prolinal ***R*-93** (0.116 g, 1.00 eq, 0.500 mmol), (*S*)-proline (0.017 g, 1.00 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 5-15 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure afforded the crude product which was then purified via FCC (hexane: ethyl acetate, 8: 2) to yield the aldol adduct **109** (0.103 g, 56 %) as a viscous oil.

$[\alpha]_D^{25}$ = +27 (c 1.0 CH_2Cl_2)

^{1}H NMR (500 MHz, C_6D_6) δ: 7.33 (d, 1H, J = 7.4 Hz), 7.21 (dd, 1H, J_1 = 7.2, J_2 = 7.4 Hz), 7.15 (d, 1H, J = 7.3 Hz), 5.21 (d, 1H, J = 12.3 Hz), 5.16 (br, 1H), 5.09 (d, 1H, J = 12.36 Hz), 4.66 (br, 1H), 4.57 (br, 1H), 4.21 (br, 1H), 4.08 (d, 1H, J = 16.6 Hz), 3.78 (d, 1H, J = 16.6 Hz), 3.34 (br, 1H), 3.21 (br, 1H), 1.61 (m, 2H), 1.53 (s, 3H), 1.45 (br, 1H), 1.34 (s, 3H), 1.24 (m, 1H)

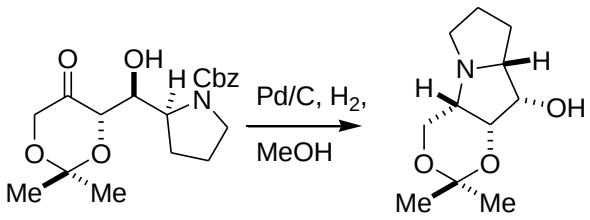
^{13}C NMR (125 MHz, $CDCl_3$) *δ:* 23.68, 24.22, 29.46, 47.37, 59.47, 66.93, 67.30, 75.61, 76.92, 100.95, 127.91, 128.12, 128.30, 128.62, 137.40, 157.42, 209.92

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_8H_{15}NO_3 + H^+$) requires 364.1760 found m/z 364.1753

LRMS (CI, NH_3): m/z (%): 364 ($[M + 1]^+$, 89), 346 (59), 204 (100), 160 (91), 91 (48)

IR (KBr): 3640, 2967, 1738, 1710, 1099 cm^{-1}

(4a*S*,8a*R*,9*S*,9a*R*)-Octahydro-2,2-dimethyl-[1,3]dioxino[4,5-b]pyrrolizin-9-ol (110)



109 **110**

To a solution of **109 (**0.073 g, 1.00 eq, 0.200 mmol) in methanol (2.00 mL) was added 10 % Pd/C (ca 0.005 g) and the resulting mixture was stirred at room temperature under H_2 atmosphere (a balloon containing hydrogen gas was attached to the flask) for 10-12 h. Upon completion of the reaction, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to afford **110** (0.035 g, 81 %) as a colorless oil.

$[\alpha]_D^{24}$ = +17 (c 1.0 MeOH)

^{1}H NMR (500 MHz, D_2O) δ: 4.43 (dd, J_1 = 4.8 Hz, J_2 = 8.2 Hz, 1H), 4.38 (dd, J_1 = 4.5 Hz, J_2 = 4.8 Hz, 1H), 4.33 (dd, J_1 = 3.4 Hz, J_2 = 13.8 Hz, 1H), 4.06 (d, J = 13.8 Hz, 1H), 3.56 (dd, J_1 = 7.9 Hz, J_2 = 12.8 Hz, 1H), 3.48 (m, 1H), 3.00 (m, 1H), 2.88 (br, 1H), 1.98 (m, 1H), 1.67 (m, 1H), 1.51 (s, 3H), 1.39 (s, 3H)

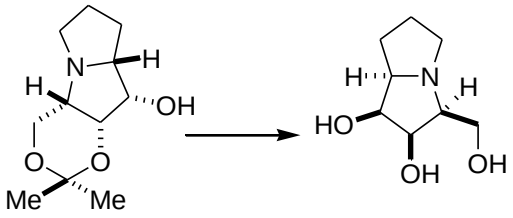
^{13}C NMR (125 MHz, D_2O) δ: 102.22, 73.25, 71.92, 71.62, 60.01, 57.06, 56.74, 55.05, 30.83, 28.71, 28.63, 21.79, 20.46, 17.68

HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_{11}H_{19}NO_3$) requires 213.65, found m/z 213.64

LRMS (EI+, 70 eV): m/z (%) = 213 (29) $[M]^+$, 198 (15), 154 (10), 141 (23), 125 (45), 108 (18), 96 (100), 70 (50)

IR (KBr): 3389, 2989 cm^{-1}

***ent*-7-Deoxy-2-epialexine (*ent*-108)**



110 ***ent*-108**

To a solution of **110** (0.036 g, 1.00 eq, 0.100 mmol) in methanol (1.00 mL) at 0 ^{o}C was added HCl (1.00 mL, 10 % v/v) and the resulting mixture was stirred at 0 ^{o}C for 30 min. The reaction was monitored by TLC and upon completion the solvent was removed and the residue was passed through basic Dowex using 1M NH_4OH as the solvent. Removal of the solvent under reduced pressure afforded the hyancinthacine *ent*-**108** (0.013 g, 78 %) as a gummy solid.

$[\alpha]_D^{24}$ = + 5 (c 0.6, MeOH); (Lit of enantiomer: **$[\alpha]_D^{20}$** = -1.0 (c 0.6, MeOH) [23]

^{1}H NMR (500 MHz, D_2O) δ: 4.60 (dd, J_1 = 3.9 Hz, J_2 = 7.1 Hz, 1H), 4.46 (br, 1H), 4.43 (dd, J_1 = 6.6 Hz, J_2 = 14.0 Hz, 1H), 4.23 (br, 1H), 4.21 (br, 1H), 3.97 (m, 2H), 3.82 (d, J = 8.0 Hz, 2H), 2.72 (m 2H), 2.56 (m, 1H), 2.42 (m 1H)

^{13}C NMR (125 MHz, D_2O) δ: 73.63, 71.62, 70.12 66.64, 58.59, 53.65, 29.74, 29.34

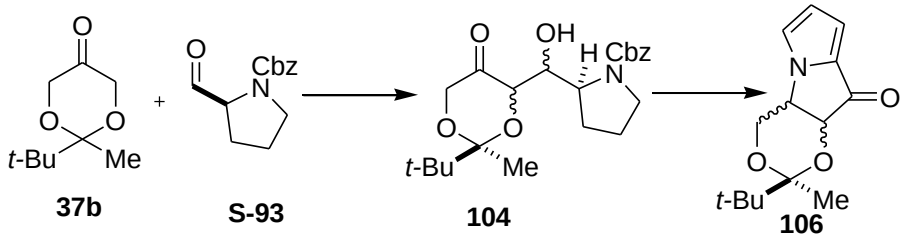
HRMS (EI+, 70 eV) exact mass calcd for $[M]^+$ ($C_8H_{15}NO_3$) requires 173.1052 found m/z 173.1052

LRMS (EI+, 70 eV): m/z (relative intensity %): 173 (3) $[M]^+$, 142 (100), 113 (15), 96 (56), 70 (38)

IR (KBr): 3236, 2852 cm^{-1}

1.9 Miscelleanous reactions

Compound 69



To a flame dried glass vial were added dry DMSO (0.50 mL), dioxanone **37b** (0.065 g, 1.00 eq, 0.500 mmol), (*S*)-N-Cbz- prolinal ***S*-93** (0.116 g, 1.00 eq, 0.500 mmol), (*R*)-proline (0.017 g, 0.300 eq, 0.150 mmol) and LiCl (0.021 g, 1.00 eq, 0.500 mmol). The mixture was stirred at room temperature for 10 min and stored in the refrigerator at 5 ^{o}C for 2 days. The reaction was monitored by TLC. Upon completion, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure to afford the crude product **104** which was dissolved in methanol (2.00 mL) and 10 % Pd/C (0.005 g) was added. The resulting mixture was stirred at room temperature under H_2 atmosphere (a balloon containing hydrogen gas was attached to the flask) for 24 h. Upon completion of the reaction, the mixture was filtered through a Celite pad and concentrated under reduced pressure to afford the crude product **106**. Purification via FCC on deactivated silica gel (Ethyl acetate: hexane 1:1) afforded **106** as a yellowish gummy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.98 (s, 1H), 6.87 (d, J = 4.0 Hz, 1H), 6.55 (dd, J_1 = 2.4 Hz, J_2 = 3.0 Hz, 1H), 4.77 (d, J = 6.1 Hz, 1H), 4.62 (m 1H), 4.24 (dd, J_1 = 8.7 Hz, J_2 = 11.2 Hz, 1H), 3.83 (dd, J_1 = 9.0 Hz, J_2 = 11.0 Hz, 1H), 1.43 (s, 3H), 0.99 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ: 185.1, 131.5, 122.3, 117.8, 110.3, 104.6, 74.1, 62.9, 52.6, 24.9, 17.8

HRMS (CI, NH_3) exact mass calcd for $[M]^+$ ($C_{14}H_{20}NO_3 + H^+$) requires 250.1443 found m/z 250.1437

LRMS (CI, NH_3): m/z (%): 250 ($[M + 1]^+$, 100), 192 (61), 120 (10), 102 (9)

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