Application of hydroformylation for the stereoselective synthesis of piperidine alkaloids

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**NANYANG
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APPLICATION OF HYDROFORMYLATION FOR THE
STEREOSELECTIVE SYNTHESIS OF PIPERIDINE
ALKALOIDS

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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STEREOSELECTIVE SYNTHESIS OF PIPERIDINE
ALKALOIDS

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TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS	I
TABLE OF CONTENTS	II
ABSTRACT	IV
LIST OF ABBREVIATIONS.....	V
 CHAPTER 1 – HYDROFORMYLATION IN NATURAL PRODUCT SYNTHESIS	
1.1 Introduction.....	1
1.2 Synthesis of Aldehydes as Intermediates for Natural Product Synthesis.	1
1.2.1 Applications of Diastereoselective Hydroformylation.....	3
1.2.2 Asymmetric Hydroformylation using Ligand Controls.....	9
1.2.3 Hydroformylation of Dienes.....	12
1.3 Tetrahydropyran Synthesis.....	16
1.4 Tetrahydrofuran Synthesis.....	20
1.5 Alkaloid Synthesis Using Hydroformylation.....	23
1.6 Tandem Hydroformylation Processes for Alkaloid Synthesis.....	29
1.6.1 Nitrogen Nucleophiles.....	30
1.6.2 Carbon Nucleophiles	40
1.7 Summary, Conclusions, Outlook.....	45
1.8 References	45
 CHAPTER 2 - PSEUDOCONHYRINE	
2.1 Introduction.....	52
2.2 Review of Pseudoconhydrine.....	52
2.3 Results and Discussion	83
2.4 Conclusion	106
2.5 Experimental.....	107
2.6 Reference	115
 CHAPTER 3 – AZIMIC ACID	
3.1 Introduction.....	122
3.2 Review of Previous Syntheses of Azimic Acid	124
3.3 Results and Discussion	142
3.4 Conclusion.....	167
3.5 Experimental.....	167

3.6	Reference	177
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CHAPTER 4 – FLOW CHEMISTRY

4.1	Introduction to Flow Chemistry.....	182
4.1.1	Components in a Typical Flow Setup for Gas/Liquid Phase Reactions (One-Loop System).....	183
4.1.2	Tube-in-Tube Reactor	185
4.2	Review of Reactions in Flow Utilizing Tube-in-Tube Reactors.....	187
4.2.1	Heck Reactions with Ethylene Gas	187
4.2.2	Carboxylation	191
4.2.3	Carbonylations	195
4.2.4	Hydrogenation	199
4.3	Results and Discussion	204
4.4	Conclusion	227
4.5	Experimental	227
4.6	Reference	233

CHAPTER 5 – 1,2-ALKYL MIGRATION

5.1	Introduction	240
5.2	Results and Discussion	242
5.3	Conclusion	264
5.4	Experimental	264
5.5	Reference	269

APPENDIX

A	Chapter 2 Supporting Information	S1
B	Chapter 3 Supporting Information	S36
C	Chapter 4 Supporting Information	S51
D	Chapter 5 Supporting Information	S67

ABSTRACT

This thesis describes the advantages of hydroformylation, when incorporated into natural product synthesis as well as, flow chemistry.

The first chapter gives a brief overview of application of hydroformylation in natural product synthesis. It highlights the importance of hydroformylation as a tool for formation of a new carbon-carbon bond and its capability of introducing reactive aldehyde functional groups.

The second and third chapters describe the synthesis of pseudoconhydrine and azimic acid using a common methodology that incorporates hydroformylation, for a simple yet efficient stereoselective synthesis of these types of piperidine alkaloids.

The fourth chapter explores the advantages of application of hydroformylation in flow chemistry. It discusses the improvement in the safety profile, the simplification in the experimental procedures and the efficient synthesis of styrenes as compared to batch chemistry.

The fifth chapter explores the possibilities of inducing a 1,2-alkyl shift in 2,3,6-trisubstituted piperidines.

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
aq	aqueous
BDP	bisdiazaphospholane
BINAPHOS	2-diphenylphosphino-1,1'-binaphthalene-2,2'-diylphosphite
BIPHEPHOS	6,6'-[(3,3'-Di- <i>tert</i> -butyl-5,5'-dimethoxy-1,1'-biphenyl- 2,2'-diyl) bis(oxy)]bis(dibenzo[<i>d,f</i>][1,3,2]dioxaphosphepin)
B:L	branched : linear ratio
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BPR	Back Pressure Regulator
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
CAN	Cerium (IV) Ammonium Nitrate
Cbz	benzyloxycarbonyl
CDG	catalyst directing group
cod	cyclooctadiene
conv	conversion
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCC	N,N-dicyclohexylcarbodiimide
DIBALH	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DCM	dichloromethane
DMSO	dimethyl sulfoxide
DMTMM	4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium

<i>o</i> -DPPB	ortho-diphenylphosphanylbenzoyl
dr	diastereomer ratio
DuPHOS	1,2-bis[2,5-di- <i>iso</i> -propylphospholano]benzene
d	doublet
ee	enantiomer excess
<i>gem</i>	germinal
GPR	Gas Pressure Regulator
<i>n</i> -hept	<i>n</i> -heptyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
h	hour(s)
IBX	2-iodoxybenzoic acid
Ipc	isopinocampheyl
<i>J</i>	coupling constant
LiHMDS	lithium bis(trimethylsilyl)amide
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
m	multiplet
mol	mole(s)
NMO	N-methylmorpholine-N-oxide
Nu	nucleophile
Pd-TMM	Pd-trimethylenemethane
PDC	pyridinium dichromate
PDMS	polydimethylsiloxane
PFL	<i>Pseudomonas fluorescens</i> lipase
Ph	phenyl
PMP	<i>p</i> -methoxyphenyl
PMBS	<i>p</i> -methoxybenzenesulfonyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl

i-Pr	isopropyl
pTSA	<i>p</i> -toluenesulfonic acid
PTFE	Poly tetra fluoro ethylene
Pv	pivaloyl
py	pyridine
q	quartet
rt	room temperature
SEM	$\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si}(\text{CH}_3)_3$
s	singlet
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
Temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THP	tetrahydropyran-2-yl or tetrahydropyran
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethyl- 1,2-ethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl (trityl)
Ts	tosyl, 4-toluenesulfonyl
XANTPHOS	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

CHAPTER 1

Hydroformylation

in

Natural Product Synthesis

1.1. Introduction

As with alkene metathesis, hydroformylation was serendipitously discovered in industry. The original conditions employed for bulk chemical manufacture would be considered to be “brutal” by organic chemists. This may be the reason that, historically, uses of hydroformylation for the synthesis of natural products and complex natural product like molecules are scarce in the literature. With the development of much milder conditions and greater appreciation of stereochemical control issues, this situation is starting to change. Hydroformylation allows the formation of a carbon-carbon bond, often highly chemoselectively, under neutral conditions. Application of this reaction to the synthesis of complex molecules is increasing.

1.2. Synthesis of Aldehydes as Intermediates for Natural Product Synthesis.

Aldehydes have always played a prominent role in organic synthesis, both as targets in themselves, mostly as intermediates. This is particularly for subsequent carbon-carbon or carbon-nitrogen bond formation. While there are various methods available for the introduction of aldehydes, the most common is, undoubtedly, the oxidation of alcohols. Hydroformylation offers an alternative. Not only is the reaction atom efficient, but occurs under neutral conditions and tolerates a wide range of functional groups. Hydroformylation, thus, offers a route to aldehydes that can be significantly more efficient than the alternatives. The starting materials for hydroformylation, alkenes, may also be introduced by a number of methods, with asymmetric allylation becoming of greater and greater importance. The alkene functional group may also be carried through many standard synthetic steps without any need for protection.

Dolabelide B **1**, isolated from the sea hare *Dolabella auricularia*, has been shown to exhibit cytotoxicity.¹ Keck and McLaws required aldehyde **2** as an intermediate in a synthesis of the C₁-C₁₃ segment (Scheme 1).²

Scheme 1. Dolabelide Retrosynthesis.

Aldehyde **2** was initially synthesized *via* crotylstannylation chemistry through a sequence of seven steps (Scheme 2). Alkene **4** was prepared from the aldehyde **3** using asymmetric crotylation to introduce the additional stereocentres and establish the *syn-anti* stereochemistry. Alkene **4** could then be converted to aldehyde **2** in 46% yield by a five step sequence involving ozonolysis of the alkene, Wittig olefination, selective alkene reduction, which required the use of samarium(II) iodide, and then a reduction-oxidation pair. It was recognised that out of these seven steps, a five step sequence was equivalent to hydroformylation of alkene **4**. Indeed, hydroformylation of alkene **4** gave aldehydes **2** and **2a** with a linear to branched ratio of 96:4 respectively and an isolated yield of 82% (Scheme 2), easily replacing the original more cumbersome and lengthy approach.

Scheme 2. Synthesis of the Dolabelide C₁-C₇ fragment.

1.2.1 Applications of Diastereoselective Hydroformylation.

While hydroformylation of a monosubstituted alkene simply yields an aldehyde, hydroformylation of a *gem*-disubstituted alkene also generates a new stereogenic centre. Further, hydroformylation of a 1,2-disubstituted alkene can yield either or both of two regioisomers, as well as a new stereogenic centre (Scheme 3). For hydroformylation of these kinds to be useful, the new stereocentre must be controlled. One way to achieve this goal is to employ a directing group within the substrate. As most functional groups in organic synthesis are poor ligands for rhodium, a temporarily attached group, sometimes called a catalyst directing group or CDG, can be used.

Scheme 3. Alkene hydroformylation: stereo- and regiochemical issues.

Burke *et al.*³ worked on the total synthesis of (+)-phyllanthocin **8** which is a methanolysis product of the bisabolane glycoside phyllanthoside obtained from the root extract of the Central American plant *P. accuminatus* Vahl.⁴ They had multiple concerns in mind when synthesising this molecule and one of the major concern was to avoid complications in accommodating the C3 carbo-methoxy group until a late stage of the synthesis (Scheme 4). These concerns proved to be valid, as, despite subjecting substrate **6a** to hydrozirconation⁵ or hydroboration or oxymercuration/demercuration based methodologies, only limited success was achieved. It was suggested that the lack of reactivity could be due to other Lewis basic sites in **6a**, or to unfavourable steric and electronic factors reducing the reactivity of the allylic ether. It was found to be possible to introduce the carbomethoxy

group via a multistep sequence involving the Corey-Tius procedure⁶ to afford descinnamoylphyllanthocin **7** and its C3 epimer. Although this formally completed a synthetic route to (+)-phyllanthocin **8**, this method for C3 functionalization was deemed to be unreliable and tedious.

Scheme 4. Phyllanthocin synthesis.

Hence, Burke *et al.* turned to hydroformylation (Scheme 5). Their initial attempt only produced partially satisfying results, whereby the C3- α - and C3- β -formyl products **9a** and **9b** were isolated in 21% and 20% yield respectively together with the C4-formyl product **10** that was isolated in 12% yield. Luckily, both the C3 epimers could be used for the synthesis of (+)-phyllanthocin due to the fact that the undesired epimer **9a** could be equilibrated with NaOMe/MeOH at 25°C to give a 2.3:1 mixture favouring the desired epimer **9b** in 80% yield.

Scheme 5. Hydroformylation in Phyllanthocin synthesis.

In efforts to improve the hydroformylation reaction, Burke *et al.* ventured into intramolecular phosphine-directed hydroformylation (Scheme 6). Burke subjected substrate **11** (made from coupling *m*-(diphenylphosphino)benzoic acid to the alcohol **6b**) to hydro-

formylation conditions which led to a mixture of aldehydes **13a-d** in a ratio of 7.7:1:1:0.3 via the intermediate **12**. The combined yield of the desired C3-formyl isomers **13a** and **13d** was achieved in 72% isolated yield.

Scheme 6. Directed Hydroformylation in Phyllanthocin synthesis.

Taking advantage of the equilibration reaction with aqueous NaOH/MeOH, the phosphine oxide⁷ of the major C3-formyl isomer **14a** was converted to the desired epimeric aldehyde **14d** in 73% yield, with an 18% recovery of **14a** (Scheme 7). The aldehyde **14d** was then submitted to a series of steps to obtain (+)-phyllanthocin **8** in 82% yield.

Scheme 7. Completion of Phyllanthocin synthesis.

Breit and Zahn developed methodology utilizing hydroformylation to generate stereotriads,⁸ which are short subunits of polypropionate chains consisting of an alternating methyl-hydroxyl-methyl array.⁹ From the four different stereotriads differentiated by Breit and Zahn (**A** – **D**, Scheme 8), stereotriads **A** and **B** were synthesized in excellent yield and diastereoselectivities¹⁰ using diastereoselective hydroformylation of methallyl alcohol derivatives **15** and **17** which each carry a catalyst directing group (CDG).¹¹

Scheme 8. Access to stereotriads by directed Hydroformylation. Adapted with permission from Breit, B.; Zahn, S. K. J. Org. Chem. 2001, 66, 4870-4877. Copyright (2001) American Chemical Society.

This strategy was employed in a synthesis of (*R, R, R*)- α -Tocopherol **21** (Scheme 9)¹², which is the most prominent and biologically most active naturally occurring member of the compounds covered by the term vitamin E.¹³ Aldehyde **20** was obtained when alkene **19** was subjected to *o*-DPPB-directed rhodium-catalyzed hydroformylation. The reaction proceeded with good diastereoselectivity (dr = 91:9) in 81% yield. The stereogenic centre

generated by this reaction then became the C8 stereogenic centre of α -tocopherol **21**, while the phosphinobenzoate ester was lost in an S_N' cuprate displacement.

Scheme 9. α -Tocopherol synthesis.

However, using the CDG-controlled hydroformylation of methallyl alcohol derivatives with *o*-diphenylphosphanyl benzoate (*o*-DPPB), only *syn*- products can be obtained. Alternatively, the inherent conformation of the substrate can be used to influence the formation of the new stereogenic centre. Thus, Breit and Zahn devised a new model taking advantage of *syn*-pentane interactions to achieve *anti*-selective hydroformylation. The model was tested by subjecting benzylidene acetals **22a**, **22b** and **24** to hydroformylation conditions (Scheme 10). The aldehydes **23a** and **23b** (stereotriad **D**) were obtained in good yield and excellent diastereoselectivity (*anti*:*syn* ≥ 99 :1) but the reaction of the *syn*-acetal **24** proceeded slowly to give, in low yield, a mixture of *anti*-**25** and *syn*-**25** with reversed diastereoselectivity.

Scheme 10. Access to stereotriads by conformational control.

Therefore, to achieve the *anti*-selective hydroformylation for the construction of stereotriad **C**, a longer sequence had to be adopted (Scheme 11). This alternative involves hydroformylation of benzyloxy-substituted acetal **26** and converting the reactive aldehyde **27** via Wittig olefination to alkene **28**. Regioselective benzylidene ring opening with DIBAL and reductive removal of the alcohol function gave the desired *syn-anti* stereotriad building block **31** in diastereomerically pure form.

Scheme 11. Access to stereotriads C.

Directed hydroformylation was employed in a synthesis of neopeltolide **32**. This 12-membered macrolide marine natural product is a potent inhibitor of tumour proliferation and has attracted extensive interest from synthetic organic chemists.¹⁴ Directed hydroformylation was employed in one synthesis to establish the C7 stereogenic centre (Scheme 12).¹⁵ The diol derivative **34** was prepared by diastereoselective methallylation of aldehyde **33**. After installation of the catalyst directing group, hydroformylation gave the desired aldehyde **36** with 5:1 diastereoselectivity.

Scheme 12. Directed Hydroformylation in Neopeltolide synthesis.

1.2.2. Asymmetric Hydroformylation using Ligand Controls.

The new stereogenic centre may also be controlled by the use of chiral ligands. Numerous ligands have been proposed for asymmetric hydroformylation, and this chemistry offers

good prospects for the asymmetric synthesis of natural products. Burke reported a very short, novel and high yielding synthesis of (+)-Patulolide C **39** via asymmetric hydroformylation.¹⁶ (+)-Patulolides A, B and C **37** - **39** were discovered by Yamada in 1985 from the culture filtrate of *Penicillium urticae* S11R59 mutant. They exhibit both antifungal and antibacterial activities (Scheme 13).¹⁷

Scheme 13. The Patulolides.

The Landis group developed the (*S, S, S*)-bis(diazaphospholane) [(*S, S, S*)-BDP] ligand **40**, and its enantiomer, which display high activity with very high enantio- and regioselectivity for a variety of olefins.¹⁸ Vinyl acetate **41** is one such example where it reacts exceptionally well favouring the branched aldehyde **42**, with high enantioselectivity, over the linear aldehyde **43** (Scheme 14), giving access to lactaldehyde derivatives.¹⁹

Scheme 14. Asymmetric hydroformylation of vinyl acetate.

Rhodium catalysed hydroacetoxylation of alkyne **44** in the presence of pyridyl phosphine ligand **45** afforded enol acetate **46** in 82% yield and > 95% regio- and stereoselectivity.²⁰ Enol acetate **46** was then subjected to asymmetric hydroformylation conditions using Rh(acac)(CO)₂ catalyst with the (S, S, S)-BDP ligand **40** to afford the α-acetoxyaldehyde **47** with complete regiocontrol and high diastereoselectivity as only one aldehyde was observed by ¹H NMR. Aldehyde **47** was substantially pure and, thus, treated directly with Bestmann ylide **48**²¹ leading to the formation of 12-membered lactone **49** in 62% yield with complete *E*-selectivity. Acetate **49** was then deacetylated under neutral conditions using *Pseudomonas fluorescens* lipase²² (PFL) to afford (+)-Patulolide C **39** in 49% overall yield (Scheme 15).

Scheme 15. Patulolide C synthesis.

The (BDP) ligands have also been used for the synthesis of both enantiomers of Garner's aldehyde **50**²³ by asymmetric hydroformylation of the achiral alkene **50**.²⁴ Garner's aldehyde has typically been available as only one enantiomer, starting from serine. Using hydroformylation, both enantiomers could be prepared in moderate yield but with excellent regio- and enantioselectivity. (Scheme 16)

Scheme 16. Synthesis of Garner's aldehydes.

1.2.3 Hydroformylation of Dienes.

Hydroformylation of dienes has long been problematic, often giving mixtures of isomers (Scheme 17). If mono-hydroformylation is considered (and alkene regiochemistry is disregarded), then three products may be predicted: the linear and branched products, plus the alkene isomerisation product of the latter. Nozaki *et al.* were able to address this long standing problem, favouring the branched isomer with suppression of isomerisation, and

controlling stereochemistry, by the use of BINAPHOS **52** as the ligand.²⁵ The favouring of the branched isomer was attributed to the participation of η^3 -allyl complexes of rhodium.

Scheme 17. Diene Hydroformylation.

Jacobsen²⁶ reported the total synthesis of a novel antifungal agent called Ambruticin **53** that was isolated from fermentation extracts of the myxobacterium *Polyangium cellulosum* by Warner-Lambert scientists in 1977.²⁷ They planned the synthesis *via* Kocienski-Julia olefination²⁸ of sulfone **54** (Scheme 18). This sulfone would arise from aldehyde **55**.

Scheme 18. Ambruticin retrosynthesis.

The key reaction in this synthesis involves the installation of the C15 stereocentre of fragment **55** by asymmetric hydroformylation reaction of a diene precursor **56**. The required diene **56** was prepared from α,β -unsaturated ketone **57**, and subjected to Nozaki's hydroformylation conditions. Aldehyde **55** was obtained with high regio- and diastereoselectivity, which was then further reacted to give (+)-ambruticin **53** (Scheme 19).

Scheme 19. Ambruticin synthesis.

Smith *et al.*²⁹ synthesized the C1-C12 fragment **59** of the marine natural product Tedanolide C **58**, which was isolated from a species of *Ircina* sponge from the waters near Papua New Guinea.³⁰ (Scheme 20)

Scheme 20. Tedanolide retrosynthesis.

Due to stereochemical ambiguity at C10, synthetic flexibility was required, by establishing this stereocenter at a late stage with as many common intermediates as possible. Following the example set by Jacobsen in the synthesis of Ambruticin by way of an asymmetric diene hydroformylation, a model diene **61** was prepared (Scheme 21). The rhodium-catalyzed hydroformylation with a variety of ligands was investigated (Table 1). Nozaki's original conditions were found to be the best of those tested as (*R*, *S*)-BINAPHOS **52** (entry 6) led to a 93:7 ratio of C10 epimers **62a** and **62b**, accompanied by a small amount of the linear isomer **63**.

Scheme 21. Hydroformylation studies for Tedanolide synthesis.

Entry	Ligand	Temp/ °C	Time/hr	Branched: linear ratio	R/S
1	PPh ₃	35	24	86:14	48:52
2	(<i>R,R</i>)-Chiraphite	35	72	100:0	57:43
3	(<i>R,R</i>)-Kelliphite	35	24	95:5	59:41
4	(<i>R,R</i>)-Ph-Bpe	35	24	-	-
5	(<i>R,R</i>)-Ph-Bpe	80	18	96:4	52:48
6	(<i>R,S</i>)-BINAPHOS	35	113	96:4	93:7
7	(<i>S,R</i>)- BINAPHOS	35	113	92:8	6:94

Table 1. Hydroformylation in Tedanolide synthesis.

Application of these conditions to the actual intermediate **64** proceeded smoothly and with > 95:5 diastereoselectivity. Although aldehyde **65** could be isolated, it was directly methylated and the resulting secondary alcohol was oxidised to provide methyl ketone **59** as a single stereoisomer (Scheme 22). Use of (*S*, *R*)-BINAPHOS as the ligand gave the other diastereoisomer with the same efficiency.

Scheme 22. Hydroformylation in Tedanolide synthesis.

1.3 Tetrahydropyran Synthesis.

An aspect of aldehyde synthesis of particular usefulness is in the hydroformylation of homoallylic alcohols. This is because a hemiacetal will be formed directly. These are useful precursors of oxonium ions, allowing formation of a 2,6-disubstituted tetrahydropyran in a short sequence (Scheme 23). The final nucleophilic addition is typically under stereo-electronic control, leading to the *trans* product.

Scheme 23. Hydroformylation in THP synthesis.

In the total synthesis of Leucascandrolide A **72**, Leighton *et al.* introduced a THP ring into their molecule *via* a tandem hydroformylation / acetalization of the alkene **68** to give a ~1:1 anomeric mixture of hemiacetals **69** in 89% yield (Scheme 24).³¹ After conversion to the corresponding anomeric acetates **70**, allylation proceeded with better than 10:1 diastereoselectivity selectivity.

Scheme 24. Hydroformylation in Leucascandrolide synthesis according to Leighton.

A related strategy for the formation of this tetrahydropyran ring was developed by Floreancig (Scheme 25).³² The homoallylic alcohol **73**, available by asymmetric crotylation, was subjected to hydroformylation under conditions developed by Breit using the phosphinopyridone ligand **74**,³³ to give hemiacetal **75**. This is notable as one of the few examples of hydroformylation being carried out at atmospheric pressure, with the two gases being delivered by balloons. The hydroxy group was then replaced by an axial allyl group

under stereoelectronic control, with concomitant removal of the silyl ether, to give tetrahydropyran **76**. While the now free alcohol was extended using oxidation and Mukaiyama aldol chemistry, the allyl group was subsequently employed in cross metathesis.

Scheme 25. Hydroformylation in Leucascandrolide synthesis according to Floreancig.

A closely related series of transformations was employed to make polyketide-like compounds, such as tetrahydropyran **78** (Scheme 26).³⁴

Scheme 26. Synthesis polyketide-like compounds.

Similarly, in a formal synthesis of Carbomycin B **82**, Wuts *et al.* employed tetrahydropyran intermediates, although this ring is not present in the final molecule (Scheme 27). The THP was generated by a tandem regioselective hydroformylation / acetalization of the alkene **79** to give the alcohol **80**, which was then further converted to the formal synthesis product **81** through a series of steps.³⁵

Scheme 27. Hydroformylation in Carbomycin B synthesis.

Zincophorin **87** is an ionophore product with a particular affinity for both zinc and magnesium cations, isolated from *Streptomyces griseus*.³⁶ Leighton proposed to construct the tetrahydropyran ring by the combination of hydroformylation and alkylation (Scheme 28).³⁷ The required homoallylic alcohol **84** was prepared by the addition of a Batey crotyl trifluoroborate³⁸ to aldehyde **83** under substrate control. Hydroformylation gave a lactol, which was converted into the corresponding acetate **85**. Successful use of acetate **85** in the subsequent alkylation process depended on both the expected axial attack by the nucleophile, which was obtained, and the facial selectivity on the nucleophile to control the stereochemistry α to the eventual carboxylic acid. Ultimately, this aspect was controlled by the use of a chiral auxiliary. The auxiliary was then removed by methanolysis, allowing the remainder of the molecule to be built up through the agency of the benzyl ether.

Scheme 28. Hydroformylation in Zincophorin synthesis.

1.4 Tetrahydrofuran Synthesis.

Just as tetrahydropyrans are available by hydroformylation of homoallylic alcohols, tetrahydrofurans, as well as related structures such as butyrolactones, must be available by the hydroformylation of allylic alcohols.

Spirocyclic γ -butyrolactones play a key role as synthetic intermediates³⁹ for many natural products.⁴⁰ Schmidt introduced a novel approach to spirocyclic γ -butyrolactones, by combining ruthenium catalysed ring-closing metathesis with rhodium-catalysed hydroformylation-acetalation sequence (Scheme 29).⁴¹ The utility of their approach was demonstrated by the synthesis of various substituted di- or tetrahydropyrans linked to lactones in a spirocyclic fashion. They also showed the advantage of utilizing the

BIPHEPHOS ligand system⁴², as it allows the differentiation between exocyclic and endocyclic C-C double bonds under hydroformylation conditions.

Scheme 29. Hydroformylation in spirocyclic butyrolactone synthesis.

Terpestacin **100**, a fungal sesquiterpene natural product, has been found to inhibit the formation of syncytia, multinucleated cells involved in HIV,⁴³ and to inhibit angiogenesis.⁴⁴ Jamison reported an efficient synthesis of this compound (Scheme 30), starting with the hydroformylation of methallyl alcohol **94** in a reaction that could be carried out on a mole scale.⁴⁵ After dehydration of the resulting lactol **95**, the resulting dihydrofuran could be subjected to kinetic resolution under Brown's conditions to give the key building block **96** in >95% ee.⁴⁶

Scheme 30. Hydroformylation in terpestacin synthesis.

An interesting aspect of this synthesis is that the five membered ring formed by hydroformylation is not actually present in the final product. The ring serves to ensure that the Pauson-Khand reaction with dicobalt complex **98**, which establishes the cyclopentenone, proceeds with high stereoselectivity, due to the methyl substituent on dihydrofuran **96**. The ether ring present in bicycle **99**, created by hydroformylation, also serves to protect the C24 hydroxy group. Indeed, the protecting C-O bond is only cleaved in the final step of the synthesis.

Alkynes may also be used as the substrate in place of alkenes. Under the correct conditions, they appear to undergo reduction prior to hydroformylation. This reaction was exploited to convert ethisterone **101** to spironolactone **104**, a diuretic and an aldosterone antagonist (Scheme 31). Protection of the ketone as a dioxolane was required for successful hydroformylation, otherwise the 4,5-alkene was affected.

Scheme 31. Hydroformylation in spironolactone synthesis.

1.5 Alkaloid Synthesis Using Hydroformylation.

Breit *et al.*⁴⁷ have shown that homoallylic azides can undergo hydroformylation without affecting the azide function. In this way, a reactive nitrogen atom may be carried through a synthesis without the need for extensive protecting group strategies. Phosphites have been found to be the most appropriate ligands for this reaction as they do not undergo the Staudinger reaction with the azide under the reaction conditions. Phosphines, on the other hand, react readily with azides. Hence, Breit's ligand of choice was BIPHEPHOS, a sterically hindered bis-phosphite ligand that greatly favours the linear/branched ratio with a high turnover frequency.⁴⁸ With these practical concepts in place, a variety of alkaloids have become easily accessible (Scheme 32).

Scheme 32. Piperidine and pyrrolidine alkaloids synthesised using Hydroformylation.

Firstly, the well-known alkaloid (±)-sedamine **105**^{49,50} was synthesized in 3 steps starting from the homoallylic azide **109**. Hydroformylation of the homoallylic azide **109** gave the aldehyde **110** which was reduced to the primary amine with Pearlman's catalyst in the presence of aqueous formaldehyde to give the cyclized methylated amine **111** that was deprotected to provide (±)-sedamine **105**. (Scheme 33)

Scheme 33. Hydroformylation in sedamine synthesis.

Secondly 2,6-disubstituted piperidine **106** was obtained in a one-pot fashion, by hydroformylation/Wittig olefination/Staudinger/Michael addition reaction with an overall yield of 60% (Scheme 34).

Scheme 34. One-pot Hydroformylation-Wittig reaction-aza-Michael addition.

Finally, the chiral pyridinyl-homoallylazide **113** was utilized in the synthesis of two major alkaloids from *Nicotiana tabacum*, (*S*)-anabasine **107** and (*S*)-nicotine **108** (Scheme 35).

After hydroformylation of azido-alkene **113**, replacement of the *syngas* by hydrogen allowed reductive amination in the presence of Pearlman's catalyst to give (*S*)-anabasine in 81% yield and 94% ee. Alternatively, after hydroformylation of azido-alkene **113** and removal of *syngas*, addition of trifluoroacetic acid resulted in an intramolecular Schmidt rearrangement⁵¹ to give *N*-formyl pyrrolidine **114**. Tandem deformylation and Eschweiler-Clarke reaction provided (*S*)-nicotine **108** in 80% yield and 94% ee.

Scheme 35. Hydroformylation in pyridyl alkaloid synthesis.

This strategy has been extended to encompass double hydroformylation with the syntheses of two naturally occurring quinolizidine alkaloids, (+)-lupinine **115** and (+)-epiquinamide **116** (Scheme 36).⁵²

Scheme 36. Quinolizidine retrosynthesis.

Hydroformylation of the intermediate homoallylic azide **118**, obtained in 5 steps from ox-azolidinone **117**, gave the desired bis-aldehyde **119**. Tandem azide reduction-double reductive amination using Pearlman's catalyst gave the desired quinolizidine core **120** in 87% yield. De-protection with TBAF then gave (+)-lupinine **115** with an overall yield of 15% (Scheme 37).

Scheme 37. Hydroformylation in lupinine synthesis.

Similarly, hydroformylation of the bis-homoallylic azide **121**, obtained in 9 steps from Cbz-L-methionine, and further reduction of azide **122** using Pearlman's catalyst gave (+)-epiquinamide **116** with an overall yield of 29% (Scheme 38).

Scheme 38. Hydroformylation in epiquinamide synthesis.

Catalyst directing groups have also been employed in the area of alkaloid synthesis. Breit has achieved stereoselective total syntheses of three Lycopodium alkaloids: (+)-clavolonine **123**, (-)-deacetylfawcettiine **124** and (+)-acetylfawcettiine **125** (Scheme 39).⁵³

Scheme 39. Selected lycopodium alkaloids.

In the synthesis of (+)-clavolonine **123**, two hydroformylation reactions were employed, using the *o*-DPPB directing group (Scheme 40).

Scheme 40. Clavolonine retrosynthesis.

o-DPPB ester **128** was synthesized in 9 steps from 4-chlorobutanol. Hydroformylation of this ester was chemo-, regio- and diastereoselective giving the *syn*-aldehyde **129** in excellent yield (dr = 97:3, 89%) with no reaction at the tri-substituted alkene (scheme 41).⁵⁴ Following an intramolecular ene-reaction to form cyclohexanol **127**, the second directed

hydroformylation step was attempted, but the diastereoselectivity was not as high as expected (dr = 71:29). The alcohol was, therefore, protected as a bulky TIPS ether⁵⁵ to create a greater conformational bias. Hydroformylation of TIPS ether **130a** then proceeded to give aldehyde **126** with much higher stereoselectivity (dr = 95:5) at C6. Aldehyde **126** could then be taken through to the three natural products. A transition state **131** has been proposed to explain the high diastereoselectivity.

Scheme 41. Hydroformylation in clavolonine synthesis.

To prove that the participation of the catalyst-directing group *o*-DPPB was essential in achieving both chemo- and diastereo-selectivity of this second hydroformylation step, control experiments were carried out by subjecting the analogous benzyl ether **130b** and

the benzoate **130c** to the same hydroformylation conditions. No product formation was observed in either case. This is due to the low reactivity of simple 1,1-disubstituted alkenes in hydroformylation due to steric hinderance (Scheme 42).

Scheme 42. Control experiments in the clavolonine synthesis.

1.6 Tandem Hydroformylation Processes for Alkaloid Synthesis.

While azides are unaffected by the hydroformylation process, many other nitrogen functional groups will condense with the aldehyde that is formed (Scheme 43).⁵⁶ While there are exceptions, in general, a primary amine will condense to give an enamine which will be further reduced in a tandem process. This process may be either inter- or intramolecular. On the other hand, amides and sulfonamides will add to the aldehyde. In some cases, elimination to the *N*-acyl or *N*-sulfonyl enamine is observed. Typically, the alkene is not further reduced nor further hydroformylated. In alcohol solvents, an *N,O*-acetal is often formed. These processes are intramolecular, forming either five or six membered rings.

Scheme 43. Tandem Hydroformylation-addition/condensation for alkaloid synthesis.

1.6.1 Nitrogen Nucleophiles.

Desmethylveramiline **132**, a steroidal alkaloid, was desired in order to study its ability to inhibit the Sonic Hedgehog signaling pathway.⁵⁷ The Fernholtz acid **133** was selected as a suitable starting material (Scheme 44). The carboxylic group could be converted to an aldehyde **134** in a routine way. Subjection of aldehyde **134** to an aza-Sakurai-Hosomi process proceeded with excellent diastereoselectivity to give a homoallylic amine derivative **135**. Hydroformylation using BIPHEPHOS as the ligand in the presence of some acid to promote dehydration yielded the protected enamine **136**, which was reduced and deprotected in one pot to give the piperidine **132**. Neither transition metal catalysed process affected the hindered 5,6-alkene.

Scheme 44. Hydroformylation in Desmethylveramiline synthesis.

Robinson *et al.* carried out hydrogenation of the dienamides **137a** and **137b** in the presence of both Rh-DuPHOS and either Rh-BIPHEPHOS or Rh-PPh₃ catalysts (Scheme 45).

After completion of low pressure hydrogenation, the gas was vented and replaced by 1:1 CO/H₂ gas mixture and the temperature raised to 80°C. Good to very good yields of the heterocycles **140** and **141** with excellent enantioselectivity (> 95% ee) was observed. It was also shown that Rh-DuPHOS itself can be used as an efficient catalyst for one-pot tandem hydrogenation-hydroformylation reactions although it needed slightly more harsh conditions than Rh-BIPHEPHOS and Rh-PPh₃.⁵⁸

Scheme 45. Hydrogenation-Hydroformylation reactions.

Mann *et al.* reported the use of the aza-Sakurai-Hosomi three-component reaction to generate *anti*-allylamines, which were used for the syntheses of piperidine alkaloids from the sedamine and lobeline families (Scheme 46).⁵⁹

Scheme 46. A synthetic strategy for piperidine alkaloids.

(±)-allo-Sedamine **142** was synthesized starting from aldehyde **144** that was converted to the homoallylamine **145**.⁶⁰ The homoallylamine **145** was then hydroformylated to give the *N*-acyl enamine **146**. Reduction in the presence of Pearlman's catalyst and formaldehyde resulted in tandem deprotection-methylation to furnish (±)-allo-sedamine **142** after cleavage of the TBS protecting group (Scheme 47).⁶¹

Scheme 47. Hydroformylation in allo-sedamine synthesis.

Similarly, in the synthesis of ($\pm$)-allo-lobeline **143**, the protected homoallylamine **149** was subjected to a one-pot hydroformylation-Wittig olefination, a sequence initially described by Breit *et al.*,⁶² to give the enone **151** in 77% isolated yield, as a mixture of *E*- and *Z*-isomers.⁶³ Treatment of the enone **151** under acidic conditions allowed *N*-Boc deprotection followed by an aza-Michael reaction and desilylation to afford ($\pm$)-allo-lobeline **143** in 72% yield. (Scheme 48)

Scheme 48. Hydroformylation in allo-lobeline synthesis.

The versatility of the aza-Sakurai-Hosomi hydroformylation strategy was further demonstrated by the syntheses of piperidines such as (±)-coniine **154** (64% overall yield for three steps), (±)-anabasine **107** (34% overall yield for three steps), (±)-dihydropinidine **156** (34% overall yield over four steps), (±)-9-*epi*-Alkaloid 195C **158a** (27% overall yield over five steps) and other quinolizidines **157a**, **157b** and **158b** (Scheme 49).⁶⁴

Scheme 49. Hydroformylation in piperidine alkaloid synthesis.

Highly functionalized piperidine alkaloids are widespread in nature, such as (+)-prosopinine **159** and (-)-prosophylline **160** which were isolated from the leaves of *Prosopis africana* Taub and exhibit biological activity of medicinal interest (Scheme 50).⁶⁵ Similarly, their reduced analogues (+)-deoxoprosopinine **161**⁶⁶ and (-)-deoxoprosophylline **162**⁶⁷ also exhibit similar biological properties. Ojima *et al.* utilized

their previously developed methodology⁶⁸ of rhodium-catalyzed hydroformylation of functionalized homoallylic amine intermediates in the synthesis of these alkaloids.

Scheme 50. Trisubstituted piperidine alkaloids.

The synthesis of (+)-Prosopinine **159** started with (*R*)-serine **163**, thus securing the *R* absolute configuration (Scheme 51). Serine was carried through to homoallylic amine derivative **167a**, which was subjected to hydroformylation in ethanol to give piperidine **169a**. Alternatively, hydroformylation of substrate **167a** in an aprotic solvent led to the formation of the enamine **168**. Both of these key intermediates were converted to the final natural product (+)-Prosopinine **159** in good yields using different methods for attachment of the remaining side chain.

Scheme 51. Hydroformylation in Prosopinine synthesis.

(-)-Deoxoprosophylline **162** was synthesised in a similar way, except TIPS protecting groups were used and a Sakurai reaction was employed to introduce the final side chain (Scheme 52).

Scheme 52. Hydroformylation in Deoxoprosophylline synthesis.

Recently, Bates and Kasinathan showed that incorporation of hydroformylation into organic synthesis could lead to an efficient and concise synthesis of natural products such as pseudoconhydrine **177**, isolated from *Conium maculatum*⁶⁹ and azimic acid **180**, isolated from *azima tetracantha L.*⁷⁰ The tosyl-protected amine **174** obtained by the Vilaivan procedure⁷¹ was subjected to hydroformylation to obtain the key enamine intermediates **175** and **178**. In the case of pseudoconhydrine synthesis ($R = n\text{-Pr}$), dihydroxylation under Upjohn conditions gave the all-*cis* diol **176**. This could be converted to either the natural product **177** or the diastereoisomer. In the case of azimic acid **180**, double hydroformylation of sulfonamide **174** ($R = \text{pentenyl}$) occurred to give the aldehyde **178**. Once again using dihydroxylation, this could be taken through to the natural product **180** (Scheme 53).⁷²

Scheme 53. Hydroformylation in hydroxypiperidine alkaloid synthesis.

Helmchen *et al.* combined iridium-catalyzed⁷³ enantioselective allylic substitution with tandem hydroformylation-condensation in order to synthesise pyrrolidine alkaloids. They discovered that the outcome of the hydroformylation reaction was controlled by the substituent at nitrogen, and not by the substituent at carbon. This chemistry was used to achieve very short syntheses of (*S*)-nicotine **108** and the alkaloid 225C **187**. They showed that, in the case of hydroformylation of *N*-sulfonyl- and *N*-acyl-allylamines **181** under basic conditions, the hemiaminals **182** produced after cyclization of the intermediary aldehydes,⁷⁴ did not dehydrate to form enamines and could be isolated in good to excellent yields (Scheme 54). The hydroxy group could be subsequently removed under Kursanov-Parnes conditions.

Scheme 54. Hydroformylation in pyrrolidine synthesis.

On the other hand, hydroformylation of *N*-alkylallylamine **184** resulted *in situ* reduction to give (*S*)-nicotine **108**⁷⁵ in 61% yield and 99% ee without racemization (Scheme 55).

Scheme 55. Hydroformylation in nicotine synthesis.

Further, hydroformylation of *N*-unprotected primary allylamine **185** produced cyclic imine **186**. Addition of an organolithium reagent to imine **186** gave alkaloid 225C **187**,⁷⁶ a constituent of the venom of the fire-ant *Solenopsis fugax* (Scheme 56).

Scheme 56. Hydroformylation in alkaloid 225C synthesis.

Condensation of the aldehyde generated by hydroformylation with two nitrogen nucleophiles was used in a synthesis of tetraopnerine T-3 **190**.^{77,78} Starting with the commercial-

ly available enantiomerically pure form of homopipericolic alcohol **188**, allylamine **189** was generated in seven steps. Hydroformylation of this compound under microwave conditions using an ionic liquid co-solvent gave (+)-Tetraponerine T-3 **190** directly (Scheme 57).

Scheme 57. Hydroformylation in tetraponerine synthesis.

If systems with greater unsaturation are used, then aromatic nitrogen heterocycles may be formed. Campi *et al.* showed that rhodium catalysed hydroformylation of readily available β -alkynylamines **191** gives 3-substituted or 2,4-disubstituted pyrroles **193** in good yields (Scheme 58).⁷⁹

Scheme 58. Hydroformylation in pyrrole synthesis.

1.6.2 Carbon Nucleophiles.

Lazzaroni *et al.* reported the first example of the one-pot synthesis of 5,6-dihydroindolizine **197** via rhodium-catalysed hydroformylation of 1-allylpyrrole **194** (Scheme 59).⁸⁰ 5,6-Dihydroindolizine **197** constitutes the basic skeleton of many natural alkaloids.⁸¹ On hydroformylation of 1-allylpyrrole **194**, both the linear **195a** and the

branched **195b** aldehydes were formed. The branched to linear aldehyde ratio ranged from 80:20 at 20°C to 59:38 at 100°C; only the linear regioisomer underwent intramolecular electrophilic aromatic substitution to give the intermediate alcohol **196**, which underwent dehydration to yield the 5,6-dihydroindolizine **197**. Interestingly, no extra ligands were added for these hydroformylation reactions. The reaction proved to be quite general, tolerating a wide range of substitution patterns.⁸²

Scheme 59. Hydroformylation in indolizine synthesis.

This process was subsequently used as a key reaction in a synthesis of Indolizidine 167B **202** (Scheme 60).⁸³ Pyrrole **198** was synthesized from the amino acid D-norvaline⁸⁴ and subjected to hydroformylation to give an aldehyde **199** which underwent *in situ* intramolecular electrophilic substitution-dehydration to provide dihydroindolizine **200**. Replacement of the hydroformylation *syngas* with hydrogen resulted in conversion of dihydroin-

dolizine **200** to 5,6,7,8-tetrahydroindolizine **201** without reduction of the pyrrole nucleus. On the other hand, use of Rh on carbon as a catalyst, resulted in complete reduction to (-)-indolizidine 167B **202**. The latter conditions could also be used on dihydroindolizine **201**, converting it directly to the natural product, indolizidine 167B **202**.

Scheme 60. Hydroformylation in indolizidine synthesis.

Other electron rich arenes may also be used to intercept the aldehyde formed by hydroformylation. Chiou *et al.* reported the hydroformylation of *N*-allylic amide of phenylacetic acid **203** to yield aldehyde **204**.⁸⁵ The aldehyde formed first condenses with the amide nitrogen to give an *N*-acyl iminium ion **206**. This condensation is followed by the second cyclization with the electron-rich arene to afford bicyclization product **207** (Scheme 61). This chemistry was used for the rapid construction of crispine A **208**,⁸⁶ isolated from *Carduus crispus*, which is a potent antitumor agent. Use of an indole as the electron rich aromatic nucleophile resulted in a synthesis of the β -carboline alkaloid har-

micine **211**,⁸⁷ isolated from *Kopsia griffithii*, which possesses strong antileishmania activity (Scheme 62).

Scheme 61. Hydroformylation in crispine synthesis.

Scheme 62. Hydroformylation in harmicine synthesis.

An alkyne-mediated tandem Rh-catalyzed hydroformylation /double cyclization, for ready construction of indolizidine derivatives has been devised as an extension of this concept.⁸⁸ The bicyclization process is initiated by Rh-catalysed hydroformylation of amide **212** using a suitable ligand⁸⁹ to give the linear aldehyde **213** as the major isomer. The resulting aldehyde **213** undergoes spontaneous intramolecular cyclization to give hemi-amidal **214**, which in the presence of an acid, dehydrates to yield *N*-acyliminium ion

215.⁹⁰ *N*-Acyliminium ion **215** then undergoes a subsequent intramolecular cyclization with the alkyne moiety as a π carbon nucleophile leading to the formation of the cation intermediate **216**, followed by solvent addition to give final bicyclic product **217** (Scheme 63).

Scheme 63. Hydroformylation with interception by an alkyne.

Electron donating groups on the phenyl moiety enhance the nucleophilicity of the triple bond moiety. Thus, a *p*-methoxyphenyl substituted alkyne **212a** was used in the synthesis of the naturally occurring indolizidine alkaloid ($\pm$)-tashiromine **221**, isolated from an Asian deciduous shrub *Maackia tashiroi*.⁹¹ (Scheme 64)

Scheme 64. Hydroformylation in tashiromine synthesis.

1.7 Summary, Conclusions, Outlook

Hydroformylation is becoming increasingly accepted as a tool for the formation of a new carbon-carbon bond, and the introduction of the reactive aldehyde functional group. The use of specialised ligands, both to improve efficiency and control stereochemistry, the development of directed hydroformylation, and the possibilities opened up by tandem reactions are making this old reaction into a valuable new method.

1.8 References

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CHAPTER 2

A Synthesis of Pseudoconhydrine & its Epimer via Hydroformylation & Dihydroxylation

2.1. Introduction

Piperidine alkaloids are widespread in nature, and most of them exhibit biologically interesting properties. Pseudoconhydrine is one of those alkaloids, a 2,5-disubstituted piperidine which can be found in a plant more commonly known as Poison Hemlock, *Conium Maculatum*. As early as 399 BC in ancient Greece, hemlock plant was made infamous by the philosopher Socrates. He was given a potent infusion of the hemlock plant after being sentence to death for impiety.

Pseudoconhydrine with its simplistic structure and attractive stereochemistry lured many chemists to exhibit their methodology towards synthesis of the general piperidine alkaloids. We too, became interested in employing the tandem hydroformylation-condensation chemistry, combined with oxidation of the resulting enamine derivative, to synthesize pseudoconhydrine.

2.2. Review of Pseudoconhydrine

Although their synthetic scheme totally lacks of stereochemical control, Marion and Cockburn conjured a short synthetic route towards pseudoconhydrine (Scheme 1).¹ Their initial starting material **1** was obtained in 54% yield by sulfonation of α -picoline according to the procedure reported in an earlier paper.² It can be noted that they did not mention their yield in generating the 5-hydroxy-2-methylpyridine **2**.

Scheme 1 (a) excess potassium hydroxide, iron filings (process known as potashfusion) (b) ethereal diazomethane, aq. methanol (40%) (c) ethyl chloride, potassamide (22%) (d) 48% hydrobromic acid in glacial acetic acid, reflux (66%) (e) 50 lb. pressure, Adams catalyst (96%).

It was impressive for them to have synthesized the racemic version of pseudoconhydrine, because at that point of time the stereochemistry of the compound was unknown. They only knew what the structure was following the findings of Spath *et al.*³ who based their studies upon the empirical formula that Ladenburg⁴ proposed after being the first to isolate pseudoconhydrine.

Sasaki *et al.*⁵ designed a novel and flexible synthetic strategy in which they claim to be able to produce each of the four possible diastereoisomers of 2,5-disubstituted piperidines in a straight forward manner and in optically pure form (Scheme 2).

Scheme 2 (a) 2 equiv *n*-BuLi, -78°C, THF (b) HCl, MeOH, rt (90% over two steps) (c) 6% Na-Hg, MeOH, 0°C (93%) (d) MsCl, pyridine, -40°C → -15°C (71%) (e) TBDMSIM, 0.5 equiv. PPTS, CH₂Cl₂, r.t. (81%) (f) NaH, HMPA, r.t. (89%) (g) H₂, Pd/C, MeOH, r.t. (97%) (h) PDC, CH₂Cl₂, r.t. (i) EtPPh₃Br, *n*-BuLi, THF, -78°C → r.t. (24% yield over two steps) (j) H₂, Pd/C, MeOH, r.t. (89%) (k) HCl, MeOH, r.t. (99%).

Treatment of 2,3-O-isopropylideneglycerol triflate (*R*)-**8** with 1.1 equiv. of dilithiated chiral building block (*S*)-**7** prepared from L-serine,⁶ provided compound **9**. The product **9** was directly hydrolysed in the presence of a catalytic amount of HCl in MeOH to afford diol **10** in 90% yield (over two steps). They had to remove the sulfonyl group with 6% sodium amalgam in the presence of 3 equiv. of Na₂HPO₄ in MeOH at 0°C to give **11** in 93% yield, to avoid complication in the NMR spectra of the molecules later in the synthesis. Prior to the removal of the sulfonyl group they had to purify the diol **10** to remove the unreacted starting material (*S*)-**7** by chromatography. It is notable at this point that the sulfonyl group is made redundant after it serves its purpose in making the starting material, which does not reflect well in the atom economy of this synthetic route and also

they did not mention how much unreacted (*S*)-**7** recovered or efficiency of the step towards generating compound **9**. They then subjected the crude diol **11** to selective mesylation in pyridine to afford monomesylate **12** in 71% yield. They also made an important observation in that the dimesylated product was enhanced when the concentration of diol **11** in pyridine exceeded 0.05 M. It is peculiar that they isolated the purified diol **11** in 93% yield, but yet they used the crude diol **11** to proceed on the synthesis with claims that it has rather high solubility in water. They then protected the monomesylate **12** with 1-(TBDMS)imidazole prior to cyclization with NaH in HMPA to obtain the 2,5-disubstituted piperidine compound **14** in 72% yield (over two steps).

The 2,5-disubstituted piperidine compound **14** was then hydrogenated to give the alcohol **15** in 97% yield. The 5-substituted pipercolinol **15** was then oxidised using PDC to give the crude aldehyde **16** that was subjected directly, without purification, to a Wittig reaction to afford **17** in 24% yield (over two steps). There was neither a mention of the yield of the oxidation step nor the stability of the aldehyde **16**. Hence, it is ambiguous as to where the cause for the low yield lies. Sasaki *et al.* also attempted the Swern oxidation but it proceeded more sluggishly. They attributed this to the steric effect of the Boc group. In our opinion, it could be the HCl that is generated during the Swern oxidation process causing the cleavage of the Boc group which contributes to the low yield. The alkene **17** was then hydrogenated and acidified with HCl to provide (+)-pseudoconhydrine hydrochloride in 88% yield. Overall, it could be said that their synthetic route is lengthy, involving a number of protection and de-protection steps.

Again, starting off the synthesis with an amino acid derivative (*R*)-phenylglycinol **19**, Agami *et al.*⁷ synthesized their key intermediate N-Boc 2-acyloxazolidine **22** in 4 steps. They then reduced their intermediate N-Boc 2-acyloxazolidine **22** using NaBH₄ with the addition of CeCl₃·7H₂O, to give the diastereomer **23** (de = 70%). They reported to have

achieved opposite selectivity as compared to diastereomer **23a** with the addition of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Scheme 3), and provided a good explanation stating “the chelate structure **B** compels the nucleophile to add to the least hindered *Re* diastereoface, whereas a Felkin-Ahn model **A** orientates the hydride attack onto the *Si* diastereoface” (Figure 1) with literature precedents from Scolastico⁸ and Hoppe⁹ for nucleophilic attacks onto N-tosyl-2-acyloxazolidines. Although the explanation matches their experimental observations, there are some ambiguities that could have been addressed such as, (i) would they have achieved the stereochemical outcome without the N-Boc group, (ii) whether the H_2O present in the reaction have any influences in the observed selectivity and (iii) would a different metal produce similar or better result. Moving forward, they protected the resulting alcohol **23** with a benzyl group, transformed it into an aldehyde **25** followed by Grignard addition to install the propyl group and further oxidation of the resulting alcohol to give the ketone **27**. From this ketone **27**, aminonitrile **28** was obtained as a single stereoisomer, which was treated with NaBH_4 to achieve reductive decyanation to give compound **29**. There was no mention of why such a stereochemistry was observed in the formation of aminonitrile **28**. It could be suggested that the formation of the iminium ion during the cyclization step after deprotection of the N-Boc group, be responsible for the reported stereoselectivity. They ended their synthesis displaying an efficient use of Pearlman’s catalyst. Hydrogenation of the bicyclic compound **29**, led to (i) reduction of the oxazolidine moiety, (ii) N-debenzylation and (iii) O-debenzylation, giving (+)-pseudoconhydrine hydrochloride in 85% yield (Scheme 4).

Figure 1 shows the intermediates leading towards the formation of the diastereoisomers 23a and 23.

Scheme 3 (e) NaBH_4 , EtOH, -78°C , (84%) (b) NaBH_4 , $\text{CeCl}_3 \cdot 7(\text{H}_2\text{O})$, EtOH, -78°C , (63%).

Scheme 4 (a) OHCCO_2Et , toluene, reflux $-\text{H}_2\text{O}$, then $(\text{Boc})_2\text{O}$; (b) LiOH , EtOH/THF/ H_2O , rt (c) *N*-methyl morpholine, *i*- BuCO_2Cl , -40°C , then $\text{NH}(\text{OMe})\text{Me} \cdot \text{HCl}$, $(\text{Et})_3\text{N}$, (78% over three steps) (d) 4-butenylmagnesium bromide, Et_2O , rt, (quant.) (e) NaBH_4 , $\text{CeCl}_3 \cdot 7(\text{H}_2\text{O})$, EtOH, -78°C , (63%) (f) NaH , BnBr , $\text{N}(\text{Bu})_4\text{I}$, DMF, rt (88%) (g) OsO_4 (cat.), NaIO_4 , THF/water, (80%) (h) PrMgBr , Et_2O , rt, (78%) (i) PDC , CH_2Cl_2 , rt (70%) (j) CF_3COOH , 1,2-dichloroethane, rt then aqueous KCN (92%) (k) NaBH_4 , EtOH, reflux (80%) (l) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOH/ HCl (50:1), (85%).

Starting the synthesis with yet another amino acid L-norvaline, Momose *et al.*¹⁰ synthesized (+)-pseudoconhydrine **6** in what appears to be as a short number of steps. In the reaction scheme 5 it was shown that it took 3 steps to achieve pseudoconhydrine **6** and its epimer **6a**, and not taking into consideration the four steps needed to make the alkene **30** from L-Norvaline. There was no mention of the overall yield in which they obtained their alkene **30** but instead they quoted two literature reports^{11,12} containing the known procedure which did not start the synthesis with L-Norvaline. They obtained pseudoconhydrine **6** and its epimer **6a** from alkene **30** with just dihydroxylation, mesylation and a deprotection step. Although, the synthetic route is straight forward, the stereochemical outcome of the asymmetric dihydroxylation step was not so impressive with a ratio of 4:1 of isomers as determined in the later part of the synthesis. It is noteworthy that alkenes of the type are known to be poor substrates for Sharpless AD.¹³ The ratios were based on the isolated yields of the final products pseudoconhydrine **6** and its epimer **6a**. This might not have been the best way to express the diastereoselectivity (enantioselectivity) of dihydroxylation, as loss of yield during work-up and isolation should be taken into consideration. There was also no mention of whether the stereoisomers of the obtained diol **31** were separable or why the selectivity could not be measured upon getting diol **31** (Scheme 5).

Scheme 5 (a) AD-mix- α (84%) (b) MsCl/pyridine (quant.) (c) (i) $\text{H}_2/\text{Pd}(\text{OH})_2$ (ii) K_2CO_3 .

Starting from enantiopure azidolactone **33**, synthesized from L-glutamic acid in a four-step reaction¹⁴ sequence, Herdeis *et al.*¹⁵ achieved the synthesis of *epi*-pseudoconhydrine hydrochloride **6** in 11 steps. The azidolactone **33** was reduced at low temperature with diisobutylaluminium hydride to give a disatereomeric mixture of acetals **34**. The mixture of acetals **34** were put through a ring enlargement reaction via tandem Wittig 1,3-dipolar cycloaddition reaction¹⁶⁻²² to give triazolines **37** and the diazomines **36** in a ratio about 8:2. These compounds were found to equilibrate easily in the presence of base. It was also observed that there was no significant stereoselectivity in the 1,3-dipolar cycloaddition [(3*S*,6*R*)-**37**/(3*S*,6*S*)-**37** $\approx$ 1:1.2]. The products **37** and **36** were then heated in toluene at 90-100°C, to give vinylogous urethane **38** as a sole product after elimination of nitrogen with concomitant 1,2-H shift. The alcohol **38** was then put through a standard set of reactions namely protection, reduction, oxidation and Wittig olefination. Finally, acidification in methanol gave *epi*-pseudoconhydrine hydrochloride **6** in 12% overall yield from L-glutamic acid (Scheme 6). Although, their synthetic route is simple and straight forward, their ring enlargement key reaction involving the tandem Wittig 1,3-dipolar cycloaddition lacks stereochemical control.

Scheme 6 (a) DIBAL-H, -60°C (83%); (b) $\text{Ph}_3\text{P}=\text{CH}-\text{CO}_2\text{Et}$, toluene, 20°C , 36h (87%); (c) toluene, 100°C , 14 h (79%); (d) $\text{Bu}^t\text{Me}_2\text{SiCl}$, imidazole, (87%); (e) Pd/C, H_2 ; (f) Boc_2O , Et_3N ; (92% over two steps) (g) LiAlH_4 , Et_2O , (78%); (h) DMSO, oxalyl chloride, Et_3N (87%); (i) $\text{Ph}_3\text{P}^+-\text{HBr}^-$, BuLi or $(\text{Me}_3\text{Si})\text{N}^-\text{Na}^+$, (91%); (j) Pd/C, H_2 , (98%); (k) MeOH, HCl (99%).

Utilizing a [3+3] cycloaddition reaction Harrity *et al.*²³ introduced another strategy to synthesize functionalized piperidines. Employing the commercially available reagent 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate **44**, Pd-trimethylenemethane (Pd-TMM)

complex was generated *in situ* using $\text{Pd}(\text{OAc})_2$ and $\text{P}(\text{OiPr})_3$ in a 1:6 ratio with *n*-BuLi as reductant and reacted with the aziridine **45** to provide the desired piperidine **46** smoothly with 63% yield. The piperidine **46** was then subjected to ozonolysis followed by reduction with L-selectride to provide alcohol **47** as a single diastereoisomer. Finally, removal of the *p*-methoxybenzenesulfonyl (PMBS) group gave pseudoconhydrine in an overall yield of 38% from aziridine **45**. They deduced the stereochemistry for the reduction step by studying the X-ray crystal structure of piperidine **46** which showed the expected 2-axial alkyl conformation.^{24,25} On the assumption that there was no change in the stereochemistry after ozonolysis, they utilized a bulky reducing agent to attack the less hindered face of the carbonyl moiety **A** to achieve the desired stereochemistry in the alcohol **47** (Scheme 7). This methodology provides a short and beautiful synthetic route towards pseudoconhydrine and other related piperidines, but it has its limitation, for example the use of carbamates (Boc, Cbz) and diphenylphosphinoyl moieties fails to provide the corresponding piperidines. It is also noteworthy the enantiomerically pure aziridine was not obtained readily but instead prepared in 3 steps from the appropriate amino acid via the method of Craig.²⁶

Scheme 7 (a) 10 mol % Pd(OAc)₂, 60 mol % P(Oi-Pr)₃, 20 mol % *n*-BuLi, (82%); (b) O₃, DMS (c) L-Selectride (77% yield over two steps) (d) Na-Naphthalenide (79%).

Hirai *et al.*²⁷ showcased the application of their palladium(II)-catalyzed intramolecular N $\rightarrow$ π cyclization by stereo-controlled construction of 2-functionalised 5-hydroxypiperidines such as pseudoconhydrine. They started the synthesis of pseudoconhydrine with (*R*)-O-*t*-butylsilyl glycidol **48** to generate their key substrate **54** for the palladium(II)-catalyzed cyclization. Their first step towards the synthesis of the key substrate **54** is important as it generates the desired chiral regioisomer **49** whose chirality carries forward till the final product.²⁸ It can be noted that they obtained the desired chiral regioisomer **49** in 45% yield which is quite low, especially at the start of a synthesis. Their key cyclization reaction with the substrate **54** was very stereoselective to give a product consisting predominantly of the piperidine **55a** and its stereoisomer **55b** in a ratio of 8:1. They explained their stereoselectivity towards one isomer over the other using non-bonding interaction between the carbamate moiety and π -allyl-oxy palladium complex (Figure 2). The isomers **55a** and **55b**, which had no mention of whether they were separable, was converted to piperidines **56a** and **56b** over three steps with yields of 42% and 6% respectively. It is noteworthy that, in their report, the individual yields for

the three steps towards the synthesis of **56a** and **56b** adds up to 30% overall yield. The major isomer **56a** was then carried forward to (-)-epi-pseudoconhydrine **6c** via a simple deprotection step. It was also used to generate (-)-pseudoconhydrine **6d** with the aid of a Mitsunobu reaction to invert the alcohol's stereochemistry. The minor isomer **56b**, which was obtained in a low yield of 6%, was carried forward to (+)-pseudoconhydrine **6** via a simple deprotection step as well. The display of the efficient 1,4-asymmetric induction in palladium-catalyzed intramolecular N-alkylation reaction in their synthetic scheme is impressive, although it could be critiqued that they could have carried the synthesis forward to the final product from alcohol **53** via iminium ion²⁹⁻³¹ chemistry (Scheme 8). The overall yields in generating (-)-epi-pseudoconhydrine, (-)-pseudoconhydrine and (+)-pseudoconhydrine are 1.4% , 0.3% and 0.2% respectively.

Figure 2 Shows why their cyclization reaction is more selective for the isomer **55a** than isomer **55b**.

Scheme 8 (a) NaN₃, NH₄Cl, DMF (45%); (b) BnBr, NaH, BuNI, THF (94%); (c) LiAlH₄, Et₂O (76%); (d) (Boc)₂O, Et₃N, CH₂Cl₂ (70%); (e) (COCl)₂, DMSO, Et₃N, CH₂Cl₂ (84%); (f) Ph₃P=CHCO₂Me, CH₂Cl₂ (68%); (g) H₂/Pd-C, AcOEt (97%); (h) DIBAL, THF, -78°C (79%); (i) (COCl)₂, DMSO, Et₃N, CH₂Cl₂ (98%); (j) Ph₃P=CHCO₂Me, benzene, reflux (91%); (k) DIBAL, THF, -78°C (95%); (l) 30 mol%-PdCl₂(CH₃CN)₂, THF (81%, **9a:9b**=8:1). (m) O₃ and then Me₂S, CH₂Cl₂ (85%); (n) Ph₃P⁺CH₂CH₃Br⁻, *n*-BuLi, THF (61%); (o) H₂, Pd-C, MeOH (58%); (p) CF₃CO₂H, CH₂Cl₂ (80%); (q) DEAD, PhCO₂H, Ph₃P, benzene (52%); (r) K₂CO₃, MeOH (40%); (s) CF₃CO₂H, CH₂Cl₂ (90%); (t) CF₃CO₂H, CH₂Cl₂ (95%).

Backvall *et al.*³² previously established a synthetic route in generating amidoalkenols of *anti* **61** and *syn* **71** stereochemistry starting from either *cis* or *trans*-1-benzyloxy-2,3-epoxybutan-4-ol (**58** or **68**) respectively.^{33,34} In this report they demonstrate the versatility

of the intermediates **61** and **71** by generating (+)-pseudoconhydrine **6** and (±)-*epi*-pseudoconhydrine **6ac** respectively. Pd(0)-catalyzed ring opening of vinyl epoxides **60** and **70** by NaNHTs, are emphasised as key steps in their synthesis to generate the intermediates **61** and **71** as these steps define the regio- and stereo-selectivity of the final products **6**.^{35,36} In this reaction the TsNH⁻ does an external attack on the intermediate (π-allyl) palladium complex.^{33,35,37-47} By subjecting the key intermediate **61** to a series of standard reactions, (+)-pseudoconhydrine was achieved in 14% overall yield from **58**. Although it was shown that *cis*-epoxyalcohol **68** led to the formation of (±)-*epi*-pseudoconhydrine there was no mention of the yields (Scheme 9 and 10). It is surprising that with the same procedure used in the preparation of enantiopure (+)-pseudoconhydrine, they chose to report the generation of the racemate (±)-*epi*-pseudoconhydrine instead of the enantiopure version. They too had introduced an easy access to the epoxides stating it as essential for efficient synthesis of the target molecule. Reduction⁴⁸ of the alkyne moiety in **78** with LiAlH₄ gave (*E*)-2-butene-1,4-diol **79** followed by monobenzoylation⁴⁹ and Sharpless epoxidation^{50,51} under standard conditions gave the *trans*-epoxyalcohol **58** in an overall yield of 64% and 93% ee (Scheme 11). There was neither a mention of how they obtained the (*Z*)-2-butene-1,4-diol nor the yield of *cis*-epoxyalcohol. Although they did mention that monobenzoylation of the (*Z*)-2-butene-1,4-diol under standard conditions (1 equiv. NaH, BnBr, THF) gave the monoether in 70% yield. It is noteworthy that both the (*E*) and the (*Z*)-2-butene-1,4-diols are commercially available. From an overall view of starting the synthesis with 2-butene-1,4-diols, it is lengthy, but their key palladium catalysed reaction is impressive as it delivers highly regio- and stereo-selective products with good yields.

Scheme 9 (a) TPAP, NMO, CH₂Cl₂, mol sieves 4 Å, (65%); (b) *n*-C₄H₉-(PPh₃)Br, KO^tBu, (67%); (c) NH₂Ts, NaNHTs, Pd(PPh₃)₄, CH₃CN, (81%); (d) TBDMSCl, imidazole, (91%); (e) PtO₂, EtOH, H₂, (97%); (f) Pd/C, MeOH, H₂, (93%); (g) MsCl, Et₃N, THF (h) K₂CO₃, MeOH, (81% over two steps); (i) Na(Hg), Na₂HPO₄, MeOH (85%) (j) HCl, EtOH, (98%).

Scheme 10 (a) TPAP, NMO, CH₂Cl₂, mol sieves 4 Å, (76%); (b) *n*-C₄H₉-(PPh₃)Br, KO^tBu, (51%); (c) NH₂Ts, NaNHTs, Pd(PPh₃)₄, CH₃CN, (67%); (d) TBDMSCl, imidazole; (e) PtO₂, EtOH, H₂; (f) Pd/C, MeOH, H₂; (g) MsCl, Et₃N, THF (h) K₂CO₃, MeOH; (i) Na(Hg), Na₂HPO₄, MeOH; (j) HCl, EtOH.

Scheme 11 (a) LiAlH_4 , THF, (87%); (b) Ag_2O , BnBr, CH_2Cl_2 , (84%); (c) (-)-DET (7%), $\text{Ti}(i\text{-PrO})_4$ (6%), $t\text{-BuOOH}$, CH_2Cl_2 , (87%, 93% ee).

The key intermediate **85** in this report was synthesized from 4-bromobutene over 4 steps with 41% overall yield. Harding *et al.*⁵² utilized this key intermediate **85** to demonstrate the synthetic utility of their intramolecular amidomercuration reaction by completing a stereoselective synthesis of racemic pseudoconhydrine **6**. The intermediate **85** was subjected to mercuric acetate in tetrahydrofuran to give the organomercury intermediate **86**, via a chair like transition state **A** with the *n*-propyl group in the equatorial position.⁵³ The organomercury intermediate **86** was further treated with KI and then I_2 ⁵⁴⁻⁵⁶ to give the iodo compound **87** in 78% yield. The iodo compound **87** was subjected to hydrogen bromide to cleave the carbamate group and treated with sodium carbonate to form the aziridine **88**. Slow addition of 1 equivalent of trifluoroacetic acid and allowing time for equilibration for a period of 12-16 h at room temperature led to the formation of the thermodynamically favoured piperidine structure **89** as the major product. Thereafter, hydrolysis of the trifluoroacetyl group of **89** and purification by distillation and sublimation gave the pure racemic pseudoconhydrine **6** (Scheme 12). It can be noted that the overall yield from intermediate **85** to pure crystalline ($\pm$)-pseudoconhydrine is 30%. This is a good methodology demonstrating the stereoselective conversion of δ -alkenyl carbamates into 5-substituted piperidine derivatives, but they only dealt with relative stereochemistry. It can be speculated that application of this methodology to more functionalised and complex molecules might prove to be challenging due to the hindrance to form the chair like transition state **A**.

Scheme 12 (a) butyraldehyde, Et₂O, (66%); (b) PCC, celite, CH₂Cl₂, (68%); (c) NH₂OH·HCl, Na₂CO₃, MeOH, (96%); (d) (i) LiAlH₄, Et₂O (ii) benzyl chloroformate, (95%); (e) mercuric acetate, THF; (f) KI, acetone; (g) I₂, CH₂Cl₂, (78% over three steps); (h) HBr, AcOH, (84%); (i) Na₂CO₃, H₂O; (j) TFA, hexane; (k) K₂CO₃, MeOH, (50% over two steps).

Similar to the ring expansion idea mentioned in the report of Harding *et al.*⁵² but using a different approach and conditions, Cossy *et al.*⁵⁷ achieved the synthesis of (-)-pseudoconhydrine to demonstrate their methodology. They introduced a beautiful method which allows ring expansion of optically active N-alkylated prolinol and their derivatives with primary, secondary and tertiary alcohols to 3-hydroxypiperidines with good yields and in high enantiomeric excess (Figure 3).⁵⁸⁻⁶⁰

Figure 3 shows the mechanism of the ring expansion of the optically active N-alkylated prolinol.

Starting from the commercially available L-proline, they synthesized the pyrrolidine intermediate **94** over five steps in 62% overall yield. Subjecting the intermediate **94** to their key ring expansion reaction conditions gave in 57% yield the piperidin-3-ol (-)-**96** via a 1-azabicyclo[3.1.0]hexane intermediate **95** through S_Ni solvolysis of the primary alcohol of the pyrrolidine **94**. The piperidin-3-ol **96** was then debenzylated via hydrogenolysis in the presence of Pd(OH)₂ to give (-)-pseudoconhydrine **6d** in 60% yield (Scheme 13). Hence, the total synthesis of (-)-pseudoconhydrine was achieved in 21% overall yield from L-proline **90**.

Scheme 13 (a) PhCOCl , NaOH (b) MeI , K_2CO_3 , (88% over two steps); (c) $-2e^-$ (anodic oxidation⁶¹), MeOH , Et_4NTs , (95%); (d) $n\text{-PrMgBr}$, $\text{CuBr}\cdot\text{Me}_2\text{S}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, (86%); (e) LiAlH_4 , THF , (86%); (f) (i) $(\text{CF}_3\text{CO})_2\text{O}$, (ii) Et_3N ; (g) NaOH , (57% over two steps); (h) H_2 , $\text{Pd}(\text{OH})_2$, MeOH (60%).

(-)-*epi*-Pseudoconhydrine is one of the natural product synthesized by Huang *et al.*⁶² to demonstrate their *cis*-diastereoselective α -amidoalkylation with 1,4-asymmetric induction methodology. Sodium borohydride reduction⁶³ of the amido-ester **97** followed by chemoselective oxidation of the primary hydroxyl group via Bandgar's conditions⁶⁴ gave a 1:1 diastereomeric mixture of tautomer **99**, which was further acetylated to give a 2-piperidinone N, O-acetal **100** in 45% yield over the three steps. Subjecting the N, O-acetal **100** to their key α -amidoalkylation^{65,66} reaction provided the desired product **101** in 70% isolated yield. Further reduction with lithium aluminium hydride followed by simultaneous hydrogenation and N-deprotection in the presence of $\text{Pd}(\text{OH})_2$ gave (-)-*epi*-pseudoconhydrine **6c**, which was isolated as its hydrochloride salt in 16% overall yield from amido-ester **97** (Scheme 14).

Scheme 14 (a) NaBH_4 , MeOH , $0^\circ\text{C} \rightarrow \text{r.t.}$, (89%); (b) NaNO_2 , Ac_2O , (70%); (c) Ac_2O , DMAP, TEA, CH_2Cl_2 , r.t. , (73%); (d) allyltrimethylsilane, TMSOTf, CH_2Cl_2 , -78°C , (70%); (e) LiAlH_4 , THF, reflux, (66%); (f) (i) H_2 , 20% $\text{Pd}(\text{OH})_2$, EtOH , r.t. ; AcCl , MeOH ; (ii) AcCl , MeOH , (74%).

They speculated that the stereochemical outcome of the α -amidoalkylation might be due to two reasons. Firstly, the rigidity of the piperidine-2-one ring system which hinders the formation of the bicyclic oxonium intermediate.⁶⁷ Secondly, the formation of the favourable half-chair conformer **B** over conformer **A**, which proceeds with allylation under stereoelectronic control⁶⁸ to give the more favourable chair conformation **D** over twist-boat **C** (Figure 4).

Figure 4 shows the pathway towards the more favourable chair conformation **D**.

It should be noted that the starting material amido-ester **97**, was synthesized from (S)-glutamic acid in three steps (Scheme 15).

Scheme 15 (a) H_2SO_4 , NaNO_2 ; (b) SOCl_2 , 60°C ; (c) PMB-NH_2 , CH_2Cl_2 , rt, (70% over two steps).

Utilizing sodium borohydride for reduction of pyridine **105** to give the 1-carbamate ester of 1,2-dihydropyridine **106** is a well-established reaction (Scheme 16).^{69,70}

Scheme 16 (a) NaBH_4 , ClCO_2CH_3 , CH_3OH , -70°C .

By slight modification of this reduction reaction using 3-hydroxypyridine **107** instead of pyridine and in the presence of benzyl chloroformate, Ogasawara *et al.*⁷¹ found a novel synthetic route towards 1-benzyloxycarbonyl-5-hydroxy-2-piperidine **112** in good yield (Scheme 17). They speculated that the 3-hydroxyl group on the pyridine **107** forms the oxygen-boron complex **109** that directs the regiospecific reduction to give 1,2-dihydropyridine **110**. This intermediate **110** then undergoes isomerization to ketone **111** and further reduction to provide the alcohol **112**, which they proved to be a useful intermediate via synthesis of (+)-Pseudoconhydrine and its derivatives (Scheme 17).

Scheme 17 (a) ClCO_2Bn (1.5 equiv), NaBH_4 (2.2 equiv), NaHCO_3 (2.0 equiv), MeOH , -80°C , 1.5h, (69%).

Scheme 18 (a) conc. HCl-MeOH (0.5%), rt, (66%); (b) Ac₂O, Et₃N, 4-(N,N-dimethylamino)pyridine (DMAP) (cat.), CH₂Cl₂, rt, (99%); (c) allyltrimethylsilane, ZnCl₂, rt, 3 d, (87%) (1 : 10); (d) Lipase PS, phosphate buffer-acetone (9:1), rt, 99 h, (-)-**119** (35%) and (+)-**120** (39%); (e) H₂ (1 atm), Pd(OH)₂, MeOH, (91%); (f) K₂CO₃, MeOH, (92%); (g) H₂ (1 atm), Pd(OH)₂, MeOH, (90%); (h) LiAlH₄, THF, reflux, (95%); (i) H₂ (1 atm), PtO₂, CH₂Cl₂, (90%).

The alcohol **112** was alkoxylated and acetylated to give a 1:1 diastereoisomeric mixture of compound **114**, which was further reacted with allyltrimethylsilane⁷² in the presence of zinc chloride,⁷³ to give a separable 1:10 diastereoisomeric mixture of *cis*-**118** and *trans*-**117** respectively in 57% yield (over 3 steps). They speculated that the anchimeric assistance⁶⁸ of the acetate group of **114** caused the rather unexpected low *cis*-selective addition, because this effect converted the initially generated acyliminium intermediate **116** into the bicyclic oxonium intermediate **115** facilitating the *anti*-addition more than the stereoelectronically favoured *syn* addition⁶⁸ (Scheme 18).

Comparing the transition states **115** and **116** of Ogasawara *et al.*⁷¹ (Scheme 18) with the transition state **B** of Huang *et al.*⁶² (Figure 4), the key difference resulting from the presence and absence of a carbonyl functional group α to the nitrogen can be clearly understood. Hence, it could be said that the presence of a ketone α to the piperidine ring contributes a fair amount of rigidity to the system, hindering the formation of the bicyclic intermediate.

Under hydrolytic conditions using Lipase PS (*Pseudomonas cepacia*, Amano) in a phosphate buffer-acetone mixture (9:1),^{74,75} the diastereoisomeric mixture of **117** and **118** was resolved to give the (-)-*trans*-alcohol **119** and the (+)-*trans*-acetate **120** in 35% and 39% yields respectively (Scheme 18). The reaction also gave small amounts of *cis*-**118** (6% yield) and trace amounts of *cis*-**119** (<1%) of which the absolute configurations were not determined. Simultaneous hydrogenation and decarbamylation of the (-)-*trans*-alcohol **119** in the presence of palladium hydroxide in methanol gave the saturated secondary amine **6d** in 91% yield. It also confirmed the absolute stereochemistry to be that of the unnatural (-)-pseudoconhydrine thus, unquestionably proving that the (-)-alcohol **119** and the (+)-acetate **120** had *trans*-2*R*,5*S* and 2*S*,5*R* configuration respectively. Hence, having determined the stereochemistry, they deacetylated and

hydrogenated the (+)-*trans*-acetate **120** to obtain the natural (+)-pseudoconhydrine **6** in 83% yield (over two steps). Additionally, the (+)-*trans*-acetate **120** was also reduced with lithium aluminium hydride and hydrogenated over Adams catalyst to give the natural (+)-N-methylpseudoconhydrine **6e** in 86% yield (over two steps) (Scheme 18).

It can be noted that there is no control of the stereochemical outcome in their initial key reduction reaction (Scheme 17). Hence, they made up for it in the later stage of the synthesis by using enzyme chemistry to resolve the diastereoisomeric mixture to achieve optically pure compounds leading to low yields of the individual chiral compounds. Although, their synthetic route is impressive, it will not be practical in a large scale production, if the synthesis is directed towards a specific stereoisomer.

Contemplating the possibilities of hydroboration to introduce hydroxyl group into the β -position of the enecarbamates as shown in earlier reports,⁷⁶ Hootele *et al.*^{77,78} introduced hydroboration of enecarbamates as their key step for the stereoselective synthesis of both *cis* and *trans* β -hydroxypiperidine derivatives, two of which being ($\pm$)-pseudoconhydrine **6** and its derivative ($\pm$)-N-methylpseudoconhydrine **6e** (Scheme 19).

Scheme 19 (a) *p*-toluenesulfonic acid (10% w/w), benzene, rt, (90-95%); (b) (i) $\text{BH}_3 \cdot \text{SMe}_2$, THF; (ii) H_2O_2 , NaOH (c) TMSI, CH_2Cl_2 , (89%); (d) LiAlH_4 , THF, reflux, (80%).

Their starting material α -methoxy carbamate **123**, can easily be prepared in high yields via anodic methoxylation using well established procedures.⁷⁹⁻⁸² Subjecting the α -methoxy carbamate **123** to acidic conditions at room temperature gave the enecarbamate **124** in high yields (90-95%). The enecarbamate **124** was then put through hydroboration-oxidation sequence to provide 71% yield of the separable diastereomeric alcohols **125** and **126** in 1:6 ratios respectively. The major diastereoisomer **126** was then deprotected with TMSI in dichloromethane to give ($\pm$)-pseudoconhydrine **6** in 89% yield or reduced with LiAlH_4 to give ($\pm$)- N -methylpseudoconhydrine **6e** in 80% yield. In this report, Hootele *et al.* showed that during hydroboration process the borane complex prefers to attack from the less hindered side of the molecule to give *trans* as the major product. They also highlighted that, at low temperatures, the selectivity for the *trans* isomer is higher, indicating it is a kinetic product. This is a short and impressive synthetic route exploiting hydroboration reaction to achieve the synthesis of β -hydroxypiperidine derivatives.

After the publication of Hootele *et al.*⁷⁷ in 1993, Oppolzer *et al.*⁸³ published a report in which he synthesized ($\pm$)-pseudoconhydrine **6** utilizing the hydroboration-oxidation

sequence as their key step as well. They went on to synthesize ($\pm$)-pesudoconhydrine **6** in 27% yield from N-hydroxylamine **127**. It can be noted that, there was no mention of the synthesis of the N-hydroxylamine **127** (Scheme 20).

Scheme 20 (a) (i) NaH, toluene, reflux; (ii) C₆H₅COCl, pyridine, 110°C→rt, (55%) (b) (i) BH₃·SMe₂, THF; (ii) H₂O₂, NaOH, (98%, 9:1 *trans* : *cis* ratio respectively) (c) Pd(OH)₂/C, H₂, MeOH, (56%).

In the hydroboration-oxidation step, Oppolzer *et al.* tried to reproduce the results of Hootele *et al.*⁷⁷ but obtained only a 3:1 mixture of *trans*- and *cis*- hydroxypiperidines **125** and **126** respectively (Scheme 21). Interestingly, they went on to comment on the work of Hootele *et al.*⁷⁷ stating “their modest diastereomer ratio does not match the ratio 6:1, previously claimed to result from similar reaction conditions”. Not long after this comment was made, Hootele *et al.* published another report⁷⁸ stating “although, the last ratio was recently questioned,⁸³ it appears reproducible in our hands”. Hence, it is ambiguous as to what is the actual ratio that could be obtained from the hydroboration-oxidation sequence of the enecarbamate **124**.

Scheme 21 (a) (i) NaH, toluene, reflux; (ii) C₆H₅COCl, pyridine, 110°C→rt, (capricious, 10-34%) (b) (i) BH₃·SMe₂, THF; (ii) H₂O₂, NaOH, (68%, 3:1 *trans* : *cis* ratio respectively).

Pursuing their previous work,⁸⁴ the addition of a range of organolithium and Grignard reagents to *O*-(1-phenylethyl) aldoximes in the presence of boron trifluoride etherate achieving good yields with moderate diastereoselectivity, Moody *et al.*⁸⁵ focused their interest to improve the levels of 1,4-induction in such additions by developing (*R*)- and (*S*)-*O*-(1-phenylbutyl)hydroxylamines (ROPHy and SOPHy) for synthesis of a range of oxime ethers.

The ROPHy oxime **133** of butyraldehyde was prepared from the commercially available 1-phenylbutanol **131** via Mitsunobu reaction with *N*-hydroxyphthalimide followed by cleavage of the phthaloyl unit with hydrazine hydrate. The ROPHy oxime **133** was then subjected to their key reaction involving the pentenyl Grignard reagent to give the hydroxylamine **134**. They then cleaved the N-O bond using the zinc/acetic acid/ultrasound method,⁸⁶ and protected the resulting amine *in situ* to give benzyl carbamate **135**. Subjecting carbamate **135** to Lemieux-Johnson oxidation⁸⁷ followed by hydroboration reaction using the conditions reported by Oppolzer *et al.*⁸³ gave hydroxypiperidine **137** with a 2:1 *trans* to *cis* ratio in 58% yield from (*S*)-enecarbamate **136**. It is noteworthy that this *trans* to *cis* ratio of hydroxypiperidine **137** is even worse than what was achieved by Oppolzer.⁸³ The benzyloxycarbonyl group was then cleaved via hydrogenolysis to give (+)-pseudoconhydrine **6** in 88% yield. It should be noted that

there was no mention of the yields and selectivities of the intermediates involved in the synthesis towards (*S*)-enecarbamate **136** (Scheme 22).

Scheme 22 (a) *N*-hydroxyphthalimide, Ph_3P , DEAD; (b) (i) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH (ii) PrCHO ; (c) $\text{BF}_3 \cdot \text{OEt}_2$, Toluene, pentenyl Grignard reagent; (d) (i) Zn, AcOH, ultrasound (ii) CbzCl ; (e) OsO_4 , NaIO_4 ; (f) $\text{BH}_3 \cdot \text{SMe}_2$, Me_3NO , (58%); (g) H_2 , Pd/C, (86%).

Moody *et al.*⁸⁵ have shown an impressively high yielding methodology with excellent control of the stereochemical outcome to achieve the enecarbamate **136**, but its conversion to (+)-pseudoconhydrine was not as impressive due to the poor ratio of the *cis* and *trans* isomers obtained during hydroboration reaction.

Das *et al.*⁸⁸ began their synthesis towards (+)-pseudoconhydrine by mono-protecting the butane-1,4-diol **138** with a TBS group and subjecting it oxidation using PCC followed by Maruoka allylation^{89,90} with allyltributylstannane in the presence of the (*S*)-Binol complex (*S,S*)-**I** (Figure 5) to obtain the chiral homoallylic alcohol **140**. They then induced a $\text{S}_{\text{N}}2$ nucleophilic displacement with allylamine via mesylation of the chiral homoallylic alcohol **140** to obtain amine **141**. The secondary amine in compound **141** was then protected with a Boc group followed by de-protection of the TBS group to give compound **143** prior to ring-closing metathesis (RCM)^{91,92} using Grubbs' second

generation catalyst (Figure 5) to obtain the cyclic tetrahydropyridine derivative **144**. The compound **144** was then converted to the corresponding iodide derivative, which was further reduced with Zn/AcOH⁹³ to produce (+)-pseudoconhydrine derivative **145**. The compound **145** was then put through a hydroboration-oxidation sequence under similar condition to that reported by Hootle *et al.*⁷⁷ to give (+)-pseudoconhydrine and its diastereomer in 9:1 ratio, which is higher than the ratio obtained by Hootle.⁷⁷ They then isolated (+)-pseudoconhydrine in its salt form with 25% overall yield starting from butane-1,4-diol **138** (Scheme 23).

Scheme 23 (a) TBSCl, imidazole, CH₂Cl₂, 0°C to rt, 0.5 h, (90%); (b) (i) PCC, CH₂Cl₂, 0°C→rt, 0.5 h, (90%); (ii) (S,S)-**I** (fig. 5), CH₂=CHCH₂SnBu₃, CH₂Cl₂, -15→0°C, 72 h, (85%); (c) (i) MsCl, Et₃N, DMAP, CH₂Cl₂, 0°C to rt, 1 h; (ii) allylamine, DMF, H₂O, 50°C, 30 h, (78% over two steps); (d) (Boc)₂O, Et₃N, CH₂Cl₂, rt, 3 h, (92%); (e) pTSA, THF/H₂O (3:1), rt, 0.5 h, (89%); (f) Grubbs' II catalyst (10 mol%), CH₂Cl₂, reflux at 50°C, 4 h, (90%); (g)(i) I₂, TPP, imidazole, CH₃CN/ether (1:3), 0°C to rt, 15 min; (ii) Zn, CH₂Cl₂, rt, 30 min, then AcOH, 0°C→rt, 0.5 h, (80% over two steps); (h) BH₃.SMe₂, THF, -78°C→rt, 20 h, then H₂O, 20% NaOH, 30% H₂O₂, rt, 2 h, (90%); (i) 5 N HCl, THF, rt, 0.5 h, (87%).

(S, S)-I

Grubbs' II generation catalyst

Figure 5 shows the structure of (S)-Binol complex and Grubbs' second generation catalyst.

Although, they had showed impressive control of the stereochemical outcome, their synthesis is not straight forward and non-atom economic as they incorporated many protection and deprotection steps together non-atom economic reactions such as nucleophilic displacement by mesylation.

There was much controversy about hydroboration oxidation of enamines between a few groups, thus a summary of results obtained by the different groups are as shown in Table 1.

Groups	Method utilized	Hydroboration-Oxidation Substrate	Product Ratio
Hootele ⁷⁷	Hootele ⁷⁷		 1 6
Oppolzer ⁸³	Hootele ⁷⁷		 1 3

Table 1 shows a summary of hydroboration-oxidation reactions done by different research groups.

Various different types of synthetic strategies were reviewed but it is unfortunate that none of them incorporated hydroformylation in their synthesis. As mentioned earlier in chapter 1, hydroformylation which has a good tolerance of many functional groups and an atom economic reaction, is being under-utilized in academic laboratories.

2.3. Results and Discussion

A simple retrosynthetic analysis led to homoallylic amine derivative **148** (Scheme 24). A tosyl group was chosen for N-protection in part due to the clarity of NMR spectra compared to carbamates at the piperidine stage but also due to the robustness of this protecting group under many conditions.⁹⁴ Hydroformylation⁹⁵ was suggested to generate the enamine **147**, setting it up for stereoselective dihydroxylation and subsequent removal of the hydroxyl group α to the nitrogen leading to the formation of pseudoconhydrine **6d**.

Scheme 24 shows the retro-synthetic analysis of pseudoconhydrine

The Vilaivan imine asymmetric allylation was chosen for the preparation of **148** on the grounds of requiring readily available starting material, and simple operation.⁹⁶

The unstable imine **149** of butyraldehyde and (*S*)-phenylglycinol was prepared and treated with allyl bromide and indium (Scheme 25).

Scheme 25 (a) Butyraldehyde, CH_2Cl_2 , MgSO_4 , r.t.; (b) allylzinc bromide, THF, -20°C (c) $\text{Pb}(\text{OAc})_4$, $\text{NH}_2\text{OH}\cdot\text{HCl}$, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1) (d) CH_2Cl_2 , Et_3N , TsCl , overnight, r.t.

Unfortunately in our hands, using the conditions of Vilaivan *et al.*⁹⁶ the same result was not reproducible. Although the yield of the reaction was good, the diastereoselectivity was bad, giving us almost zero selectivity. We postulated that there might be heat generated *in situ*, causing the diastereoselectivity to plunge. Therefore, we lowered the reaction temperature to 0°C and added indium portionwise to a solution of imine **149** and allyl bromide in methanol. As anticipated, we obtained 9:1 diastereoselectivity with the desired product being the major isomer. To our delight, when we lowered reaction temperature even further to -10°C , it gave the allylation product **150** in 80% yield and

good diastereoselectivity. Hence, it was concluded that the control of temperature during addition of indium is essential for obtaining a high degree of selectivity (Scheme 25).

Indium metal is expensive, and Valivan's procedure⁹⁶ requires 2 equivalents of the indium metal. Valivan attributed the stereoselectivity to delivery of the allylating reagent through indium-oxygen coordination. Therefore, we replaced the indium metal (5 grams costs 133.00 SGD) with a cheaper alternative, zinc (500 grams costs 84.40 SGD), which will also coordinate effectively to oxygen. Interestingly, treatment of the imine with allylzinc bromide,⁹⁷⁻⁹⁹ prepared by the method of Knochel,¹⁰⁰ yielded the same allylation product **150** in slightly higher diastereoselectivity (> 98%) with a yield of 80% (Scheme 25).

The phenylethanol moiety was cleaved according to the method of Vilaivan, and the free amine was tosylated. The ee of the sulfonamide **148** resulting from the zinc procedure, determined by chiral HPLC, was found to be 90%. The indium procedure gave at best, an ee of 88% but was capricious (Scheme 25).

Hydroformylation of alkene **148** (Scheme 26) was carried out using dirhodium tetraacetate (1 mol%) in THF under a mixture of CO and H₂ (30 psi of each gas).

Scheme 26 (a) Rh₂(OAc)₄ 1 mol %, THF, CO (30 psi), H₂ (30 psi), 65°C, phosphorus ligand (Table 1).

With triphenyl phosphite as the ligand, the product of linear hydroformylation, ene-sulfonamide **147**, with tandem cyclo-dehydration was obtained in 56-82% yield (Table 2).

Entry	Ligand, Loading (mol %)	Enamine 147 , yield (%)	Acetal 152 , Yield (%)	Alkene 151 Yield (%)
1	(PhO) ₃ P, 2	56	10	15
2	(PhO) ₃ P, 6	67	20	4
3	(PhO) ₃ P, 12	78	Trace	8
4	(PhO) ₃ P, 18	82	0	15
5	(PhO) ₃ P, 26	79	0	12
6	(PhO) ₃ P, 50	80	0	17
7	BIPHEPHOS, 2	quant	0	0

Table 2 Hydroformylation conditions as in Scheme 3: Rh₂(OAc)₄ 1 mol %, Ligand, THF, CO (30 psi), H₂ (30 psi) at 65°C.

A small amount of the products of branched hydroformylation-cyclization were always obtained. While the linear product was always obtained in its dehydrated form as a cyclic ene-sulfonamide, the branched product was usually obtained as a mixture of dehydrated form **151** and the cyclic N,O-acetal **152**, itself, a complex mixture of stereoisomers. Interestingly, increasing the loading of the phosphite ligand resulted, at first, in an increased yield of the desired ene-sulfonamide **147**. This increase levelled off at about 12 mol % (P:Rh ratio = 6:1). Further increases in the phosphite loading, up to 50 mol%, did not result in any noticeable inhibition of the reaction but it did cause an increase in the yield of the five-membered ring ene-carbamate **151** at the expense of the N,O-acetal mixture **152**. The optimum conditions for the formation of the desired six-membered ring ene-carbamate appears to be with 18 mol % of the phosphite. On the other hand, the use of bulky bisphosphite BIPHEPHOS¹⁰¹ resulted in complete selectivity for the linear isomer **147**. We confirmed the formation of ene-sulfonamide **147** and branched isomer **151** via spectroscopic analysis.

For ene-sulfonamide **147**, the carbon spectrum showed thirteen carbons which are consistent with the number of carbons on the molecule. The presence of two sp² carbon peaks at δ 123.8 and 109.6 suggest the presence of a double bond on the molecule. A peak

at 1643 cm^{-1} in the infra-red spectrum also indicates that there are alkenes present in the molecule. Looking at the ^1H NMR spectrum (Figure 6), it can be seen there are three significant protons H_x , H_y , H_z present at δ 6.58, 5.02 and 3.91 respectively. The coupling constant for H_x δ 6.58 (d, $J=8.2\text{ Hz}$, 1H) could suggest the presence of a *cis* J^3 alkene coupling. The signal peak for H_y and H_z appears broad hence it was difficult to confirm the relationship between these protons with coupling constants, hence turning our attention towards the COSY spectrum. We were then able to establish their connections clearly (Figure 7). It can be seen from the COSY that protons H_x and H_y are related to each other but not H_z . This tells us that H_x and H_y are related to each other through bond but not H_z as it is too far away. Together with the fact, that the protons H_x and H_y are more deshielded than H_z , it suggests that these protons are on the sp^2 carbon while H_z is the proton α' to the nitrogen. As for H_x , which is the most deshielded proton, it is only related to H_y suggesting it as proton α to the nitrogen. Finally, together with the mass-spectroscopy data MS (ESI+) m/z 280 ($\text{M}^+ + 1$, 100) which indicates the side product has a molecular weight of 279, the structure could be confirmed to be that of the ene-sulfonamide **147**.

Figure 6 shows the ^1H NMR spectrum of the ene-sulfonamide **147**.

Figure 7 shows the cosy spectrum of the ene-sulfonamide **147**.

For the branched product **151**, the carbon spectrum showed thirteen carbons which are consistent with the number of carbons in the molecule. The presence of two sp^2 carbon peaks at δ 124.6 and 123.6 suggest the presence of a double bond in the molecule. A peak at 1598 cm^{-1} in the infra-red spectrum also indicates that there are alkenes present in the molecule. Looking at the ^1H NMR spectrum (Figure 8), it can be seen there are two significant protons H_x , H_y present at δ 5.98, 3.67 respectively. The proton H_x appears as a singlet, which suggests that it is not coupling to any protons, we confirmed this by observing the COSY spectrum (Figure 9). It can be seen from the COSY that protons H_x and H_y are not related to each other and that only H_y has a strong correlation to the hydrocarbon protons and not H_x (the correlation that can be seen between H_x and the hydrocarbons might be due to the presence of the alkene causing long range coupling). Together with the fact that proton H_x is more deshielded than H_y suggests it is more likely to be on an sp^2 carbon. Finally, together with the mass-spectroscopy data MS (ESI+) m/z 280 ($M^+ + 1$, 100) which indicates the side product has a molecular weight of 279, the structure could be confirmed to be that of the branched product **151**.

Figure 8 shows the ^1H NMR spectrum of the branched product **151**.

Figure 9 shows the cosy spectrum of the branched product **151**.

With the ene-sulfonamide **147** at hand, we needed *trans*-selective dihydroxylation to occur. Six-membered ring ene-carbamates have been shown to undergo hydroboration-oxidation¹⁰²⁻¹⁰⁴ and epoxidation¹⁰⁵ with *trans* selectivity. As substituents α to the ring nitrogen of N-acyl and N-sulfonyl piperidines are known to occupy axial positions,¹⁰⁶ this corresponds to the reagent approaching from the less hindered face.

Dihydroxylation of ene-sulfonamide **147** under Upjohn condition¹⁰⁷ gave a 7:1 ratio of an inseparable mixture of isomers in 90% yield (Scheme 27). At this point, it could not be confirmed whether the *cis* or *trans* isomer is the major product because the ¹H NMR spectrum signal peaks of the diol appeared broad making it difficult to calculate the coupling constants (Figure 10). Even so, any interpretation of coupling constants relies on the assumption of a chair conformation which may not be valid.

Scheme 27 (a) K₂OsO₄, NMO, MeSO₂NH₂, THF/H₂O (9:1), r.t.

Figure 10 shows the ^1H NMR spectrum of the crude sample of the dihydroxylation reaction.

A quick literature search revealed that Harrity *et al.*¹⁰⁸ had reported that with a similar molecule and conditions, they obtained their major product with the all *cis* stereochemistry (Scheme 28). But they did not mention why they observed such selectivity nor did they provide sufficient evidence to support their claims.

Scheme 28 (a) (i) cat. OsO_4 , NMO; (ii) Ac_2O , Et_3N , cat. DMAP.

Hence, we wanted to prove that we had obtained the all *cis* isomer **153** as the major product. Bernd F. Straub from university of Heidelberg preformed a DFT calculation on the transition state of this dihydroxylation reaction. He revealed that the calculation predicted *cis/trans* ratio of 6:1 at room temperature, which is in good agreement with the experimentally obtained 7:1 ratio. He also proposed a transition state as shown in Figure 11 in which he claimed that the tosyl orientation originates from the electrostatic attraction between the partially positive tolyl group and the negatively polarized oxygen atoms on osmium, and an electrostatic repulsion of the latter with the negatively polarized sulfonyl fragment. There is also a lipophilic attraction between the pseudo-axial orientated n-propyl group and the tolyl group. Therefore, the DFT calculation revealed findings which support Harrity's results of the all-*cis* isomer being the major product, strongly suggesting that we obtained the all-*cis* isomer as the major product as well.

Figure 11 shows Bernd F. Straub's the proposed transition state of the dihydroxylation reaction.

While the DFT calculation for the molecule was on going, we wanted to obtain evidential proof such as a crystal structure of the major diol **153** from the mixture of isomers to confirm our findings.

The problem was that the crude diol was an inseparable mixture of isomers that was present as a yellowish oil. Hence, we decided to convert the crude inseparable mixture of

diol to a bis (3,5-dinitrobenzoyl) derivative to increase the molecular weight of the compound thus forcing it to become a solid. The bis(3,5-dinitrobenzoyl) derivative could also possibly have some π π stacking interactions which might aid the product to be present as a solid (Scheme 29).

Scheme 29 (a) DMAP, Et₃N, 3,5-dinitrobenzoyl chloride, CH₂Cl₂, r.t., overnight.

To our delight, the bis(3,5-dinitrobenzoyl) derivative turned out to be solid in nature. Just when we thought we could finally lay this problem to rest, disaster struck. Both the isomers were solid and were still inseparable, hence even if we were to send the crystallized derivative **154** for X-ray we would not know whether the *cis* or the *trans* is the major product.

When all hope seemed lost, serendipity happened when we were transferring the bis(3,5-dinitrobenzoyl) derivative from one flask to the other, we noticed that one isomer was more soluble in ethyl acetate than the other isomer. At that point we did not know which was the more soluble isomer, but we knew that if we were able to separate them, we would be able to identify exactly the major isomer from the minor isomer and confirm our findings. Hence, following the traditional purification technique known as trituration, we began separating our isomers. After multiple rounds of trituration using ethyl acetate we

ended up with tiny amounts of solid in the flask. We then took the tiny solids and recrystallized them from a solvent combination of dichloromethane and tiny amounts of ethyl acetate. Since initially we started off with small amounts of solid, we had very little amount of the recrystallized product hence we sent it directly for X-ray analysis. To our delight, recrystallized product turned out to be the major isomer (Figure 12). Now, it can be clearly seen that the two substituents α to the nitrogen are in the axial position. Although it could be speculated that the $-OR$ group α to the nitrogen could be anomeric, our observations are consistent with that of Yongna¹⁰⁶ and earlier workers.¹⁰⁹

Figure 12 shows the crystal structure of the all-*cis* major isomer.

We made sure the crystal that was analysed was the major isomer, by recording the ¹H NMR of the sample that was submitted for the X-ray analysis. Hence, just by comparing the ¹H NMR spectra of the crude inseparable mixture of bis(3,5-dinitrobenzoyl) derivative (Figure 13) and the X-ray analysis sample of bis(3,5-dinitrobenzoyl) derivative (Figure 14) it is very clear that we isolated our major isomer which is the all *cis* product **154**.

Figure 13 shows the ^1H NMR spectrum of the crude inseparable mixture of the bis(3,5-dinitrobenzoyl) derivative.

Figure 14 shows the ^1H NMR spectrum of the x-ray analysis sample of the bis(3,5-dinitrobenzoyl) derivative.

As the saying goes “the proof of the pudding is in the eating”, while both the DFT calculations and efforts to isolate and crystalize the major isomer was still on going, we decided to proceed on with our synthesis to prove the stereochemistry by synthesis of the natural product pseudoconhydrine or its diastereoisomer.

When attempting Kursanov-Parnes reduction¹¹⁰ to carry out an exchange of the hydroxyl group α to the nitrogen, we obtained a mystery product **156** (Scheme 30). It is noteworthy, that attempts towards purification of diol **153** via silica gel column chromatography led to the formation of ketopiperidine **156**.

Scheme 30 shows the formation of the unexpected ketopiperidine under Kursanov-Parnes reduction conditions.

Mechanistically we knew that it could be a facile rearrangement involving 1,2-hydride shift to give the ketopiperidine **156** in good yield (Scheme 31). There are also a few reports of general routes to such potentially versatile building blocks.¹¹¹⁻¹¹⁴

Scheme 31 shows the facile rearrangement involving 1,2-hydride shift to give the ketopiperidine.

To confirm our postulate, we turned to spectral analysis of this mystery molecule. The carbon spectrum showed thirteen carbons which are consistent with the number of carbons on the molecule. There is also peak at δ 206.7 suggesting the presence of a ketone (C=O) carbon. A peak at 1730 cm^{-1} in the infra-red spectrum strongly suggests that there is a ketone functional group present in the molecule. From ^1H NMR (Figure 15) it can be seen that there are two doublets H_x and H_y with similar coupling constants at δ 4.16 (d, $J=18.5\text{ Hz}$, 1H) and 3.64 (d, $J=18.5\text{ Hz}$, 1H) which strongly suggest they are geminal protons interacting with each other. There is also a peak at δ 4.01 which represents proton H_k that appears like a quintet (Figure 16). It could have been a tdd with similar coupling constant ($H_{eq}-H_{ax} \approx H_{eq}-H_{eq}$), that agrees with the proton α' to the nitrogen being in an equatorial position on the basis that the *n*-propyl side chain would adopt an axial position.¹⁰⁶ Finally, together with the mass-spectroscopy data MS (ESI+) m/z 296 ($M^+ + 1$, 100) which indicates the side product has a molecular weight of 295, the structure could be confirmed to be that of the ketopiperidine **156**.

Not taken back by the sudden unexpected occurrence, we improvised and carried on the synthesis towards pseudoconhydrine. On the basis that the *n*-propyl side chain would

adopt an axial position,¹⁰⁶ the ketone was reduced with K-selectride.¹¹⁵ It is because bulky reagents are known to approach from the equatorial position giving the expected single *trans* isomer **157**, in 95% yield (Scheme 32 and Figure 17).¹²⁴

Scheme 32 (a) K-selectride, THF, 0°C → r.t.

Figure 17 shows the mechanism of reduction of scheme 32.

This isomer was then deprotected in 70% yield under Carpino's conditions¹¹⁶ with the modification of using ultrasound. The isolation of pseudoconhydrine was made simple due to the presence of the secondary amine group. Hence, by performing acid base extraction and further acidification, pseudoconhydrine **6d** was obtained as its hydrochloride, with spectroscopic data, optical rotation ($[\alpha]^{22.7}_D = -10.4$ (c = 0.11, EtOH)) and melting point (185 – 185.5 °C) in excellent agreement with that reported (Scheme 33).¹¹⁷

Scheme 33 (a) Mg, MeOH, (((

On the other hand, reduction with sodium borohydride gave a separable 3:1 mixture of alcohols. This is because the small hydride is known to approach from the axial position giving the expected *cis* isomer **158** as the major product (Scheme 34 and Figure 18).¹²⁴

Scheme 34 (a) NaBH₄, MeOH, r.t.

Figure 18 shows the mechanism of reduction of scheme 34.

Deprotection of the major alcohol **158** yielded, after acidification, provided *epi*-pseudoconhydrine **6c** (Scheme 35) as its hydrochloride salt with spectroscopic data, optical rotation ($[\alpha]^{22.7}_D = -8.1$ ($c = 0.2$, EtOH)) and melting point (120 – 121 °C) in excellent agreement with that reported.¹¹⁸

Scheme 35 (a) Mg, MeOH, (((

Although we managed to synthesize pseudoconhydrine from the unexpected the ketopiperidine **156**, the stereochemical information was lost in the process. We postulated that this pinacol like reaction occurs because the hydroxyl groups are electron rich and they tend to share their electrons providing a push factor for the hydride shift to occur satisfying the electron craving of the iminium ion which can be seen as the pull factor (Scheme 31). Therefore, to rectify this problem, we decided to acetylate the hydroxyl groups making them less electron rich (Scheme 36).

Scheme 36 (a) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , r.t.

To our delight, acetylated derivative **159** was not prone to the pinacol like reaction. We could purify the acetylated compound via silica gel column chromatography, to obtain a clean sample of the product but unfortunately still as an inseparable mixture of diastereoisomers.

The ^1H NMR spectra of the acetylated product showed nice coupling patterns of the protons, hence using it to our advantage we wanted to further support our claims that the major product is the all-*cis* diastereoisomer. Firstly, we confirmed the chemical shift of the proton of interest H_y with the aid of a COSY spectra (Figure 19). It is known that the most deshielded proton would be H_x as it is α to the nitrogen and the acetate group, and is related to proton H_y , hence confirming the position of H_y in the spectrum. Thereafter, calculating its coupling constants from its ^1H NMR led us to believe there were two H_{eq} -

H_{ax} (4.12 Hz) and one H_{ax} - H_{ax} coupling (11.7 Hz) present, which clearly supports our claims assuming a chair conformation (Figure 20).

Figure 19 shows the COSY spectrum of the acetylated derivative 159.

Figure 20 shows the coupling pattern of the proton H_y of the acetylated derivative.

Back tracking, it can be seen that the bis (3,5-dinitrobenzoyl) derivative **154** and the acetylated product **159** has the same coupling pattern for that particular H_y proton, suggesting their substituents are all-*cis* orientated (Figure 21).

Figure 21 shows the coupling pattern of the acetylated product **159** and the bis (3,5-dinitrobenzoyl) derivative **154**.

Kursanov-Parnes¹¹⁰ reduction of diacetate **159** with triethylsilane and trifluoroacetic acid selectively removed the acetoxy group α to nitrogen (Scheme 37).

Scheme 37 (a) Trifluoroacetic acid, Et₃SiH, CH₂Cl₂, r.t.

Methanolysis of the remaining acetate group gave hydroxypiperidine **158** as a single diastereoisomer after chromatography, identical to the major isomer from sodium borohydride reduction of ketopiperidine **156**.

While the synthesis towards pseudoconhydrine was ongoing, we wanted to know whether it would be possible to control stereoselectivity of the dihydroxylation reaction with the aid of Sharpless¹¹⁹ ligands (DHQD or DHQ). Although these ligands were used with the mnemonic device¹²⁰ (Figure 22) to predict the outcome of mainly tri-substituted alkenes, we thought it might have some influence over our di-substituted alkene as well.

Figure 22 Rationalization for enantiofacial selectivity in the Sharpless dihydroxylation reaction.²⁶

The addition of either (DHQ)₂PHAL or (DHQD)PHAL to the reaction mixture under Upjohn condition¹⁰⁷ resulted in a stereoselectivity of 4.7:1 and 3.6:1 respectively.^{119,121} They were both selective towards the *cis*-isomer, which was odd, as we expected opposite selectivity between the two ligands (Scheme 38, Table 3). It should be noted that the stereoselectivity was much lower in the presence of the Sharpless ligands than in the absence of these ligands.

Scheme 38 (a) K_2OsO_4 , Ligand (refer to Table 3), NMO, MeSO_2NH_2 , THF/ H_2O (9:1), r.t.

Ligand	Product 153	Product 153a
	Ratio	
(DHQ) ₂ PHAL	4.7	1
(DHQD)PHAL	3.6	1

Table 3 shows the ratio of the isomers obtained with the use of Sharpless ligands.

2.4. Conclusion

While hydroformylation of homoallylic amine derivatives provides a facile route to six-membered ring ene-carbamates, dihydroxylation subsequently gives access to the *cis*-hydroxy piperidines. Facile rearrangement of the diol to the ketopiperidine, on the other hand, provides access to both stereochemical series. Pseudoconhydrine and its epimer are obtained in 37% and 30% yields, respectively from butyraldehyde.

2.5. Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane and acetonitrile were dried by distillation from CaH₂ immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh. ¹H NMR spectra were recorded at 300, 400 or 500 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz. Optical rotations are given with units of 10⁻¹ deg cm² g⁻¹. Rotations were measured at a wavelength of 589 nm. Enantiomeric excess was determined by chiral HPLC analysis, using a Diacel OJ-H column, eluting with IPA/hexane.

150

(S)-2-((R)-Hept-1-en-4-ylamino)-2-phenylethanol (150). (a) Indium powder (240 mg, 2.09 mmol) was added portionwise to a solution of imine **149** (200 mg, 1.05 mmol) and allyl bromide (0.27 mL, 3.14 mmol) in methanol (10 mL) at -10 °C. The resulting mixture was stirred at -10 °C for 6 h. The reaction mixture was diluted with 10% aqueous NaHCO₃, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and evaporated. The residue was purified by silica gel flash column chromatography to give 195 mg (80% yield) of the allylation product **150** as a colorless oil.

(b) 1,2-Dibromoethane (0.01 mL, 0.12 mmol) was added to a suspension of zinc dust (226 mg, 3.45 mmol) in THF (20 mL). The mixture was heated gently until ebullition of the solvent and stirred for 5 min. After the heating and stirring process was repeated three times, chlorotrimethylsilane (0.02 mL, 0.136 mmol) was added and the mixture was stirred for another 15 min. Allyl bromide (0.1 mL, 1.15 mmol) was added dropwise and stirring was continued for 1 h. The mixture was added via cannula to a solution of imine **149** (200 mg, 1.05 mmol) in THF (10 mL) at -20 °C and stirred for 6 h. The reaction mixture was then poured into a water and ethyl acetate mixture and stirred vigorously. The mixture was then filtered, and the water layer was extracted with ethyl acetate, dried over magnesium sulfate, and evaporated. The product was then purified by silica gel flash column chromatography to give 195 mg (80% yield) of the allylation product **150** as a colorless oil: ^1H NMR(400 MHz, CDCl_3) δ 0.79 (t, 3H, J = 6.8 Hz), 1.41-1.14 (m, 4H), 2.10-2.28 (m, 2H), 2.48-2.60 (m, 1H), 3.47 (dd, 1H, J = 10.5, 8.7 Hz), 3.66 (dd, 1H, J = 10.5, 4.6 Hz), 3.88 (dd, 1H, J = 8.7, 4.6 Hz), 5.04-5.14 (m, 2H), 5.74-5.86 (m, 1H), 7.24-7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.3, 19.2, 37.2, 38.1, 53.7, 61.7, 67.0, 117.4, 127.4, 127.7, 128.8, 135.5, 141.5; MS (ESI+) m/z 234 ($[\text{M}^+ + 1]$, 100).

148

(R)-N-Tosylhept-1-en-4-amine (148). Lead tetraacetate (456 mg, 1.03 mmol) was added to a solution of amino alcohol **150** (200 mg, 0.857 mmol) in dry $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1) at 0 °C and stirred (30 min) until confirmed complete by TLC. Hydroxylamine hydrochloride (596 mg, 8.57 mmol) was added to the resulting mixture and stirred for another 30 min. The residue remaining after removal of the solvents was washed with hexane and suspended in CH_2Cl_2 followed by filtration of the lead precipitates. The organic solvent

was evaporated and the residue was dried in vacuo. The residue was taken up in dry CH_2Cl_2 (10 mL), and Et_3N (0.25 mL, 1.77 mmol) and TsCl (168 mg, 0.883 mmol) were added and stirred overnight. The reaction mixture was then diluted with sat. aq ammonium chloride, extracted with ethyl acetate, dried over magnesium sulfate, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give 179 mg (78% yield) of the sulfonamide product **148** as a colorless solid: FTIR (neat, cm^{-1}): ν_{max} 1359, 1165; ^1H NMR (400 MHz, CDCl_3) δ 0.80 (t, 3H, $J = 7.3$ Hz), 1.09-1.44 (m, 4H), 2.09 (approx t, 2H, $J = 6.9$ Hz), 2.42 (s, 3H), 3.20-3.34 (m, 1H), 4.32-4.44 (m, 1H), 4.88-5.06 (m, 2H), 5.48-5.62 (m, 1H), 7.29 (d, 2H, $J = 8.2$ Hz), 7.74 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 13.9, 18.8, 21.7, 36.9, 39.2, 53.2, 119.1, 127.3, 129.8, 133.5, 138.4, 143.4; MS (ESI+) m/z 268 ($[\text{M}^+ + 1]$, 100); HRMS Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$) 268.1371, found 268.1366; $[\alpha]^{22.3}_{\text{D}} = 19.1$ ($c = 2$, CHCl_3).

147

(R)-1,2,3,4-Tetrahydro-2-propyl-1-tosylpyridine (147). Amine **148** (100 mg, 0.375 mmol), $\text{Rh}_2(\text{OAc})_4$ (1.8 mg, 3.75×10^{-3} mmol), and $\text{P}(\text{OPh})_3$ ¹²² (20 μL , 0.075 mmol) were dissolved in THF (3 mL) in a Fisher-Porter tube. The Fisher-Porter tube was purged (three times) with H_2/CO (1:1) and finally charged with H_2 (30 psi)/ CO (30 psi). The reaction mixture was stirred vigorously at 65 °C for 18 h. The solvent was removed under reduced pressure and the residue was purified by silica gel flash column chromatography to give 83 mg (80% yield) of the ene-sulfonamide **147** as a colorless oil: FTIR (neat, cm^{-1}): ν_{max} 1359, 1165, 1645; ^1H NMR (400 MHz, CDCl_3) δ 0.81-0.99 (m, 1H), 0.93 (t, 3H, $J = 7.32$), 1.22-1.99 (m, 8H), 2.41 (s, 3H), 3.91 (br s, 1H), 5.02 (t, 6.4 Hz), 6.58 (d, 1H, $J =$

8.2 Hz), 7.28 (d, 2H, $J = 8.2$ Hz), 7.66 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 17.5, 19.3, 21.8, 23.0, 33.9, 53.0, 109.6, 123.8, 127.2, 129.8, 136.4, 143.4; MS (ESI+) m/z 280 ($[\text{M}^+ + 1]$, 100); HRMS Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2\text{S}$ ($\text{M}^+ + \text{H}$) 280.1371, found 280.1376; $[\alpha]^{22.5}_{\text{D}} = -311.6$ ($c = 1$, CHCl_3).

153

(2S,3S,6R)-6-Propyl-1-tosylpiperidine-2,3-diol (153). MeSO_2NH_2 (120 mg, 1.25 mmol) was added to a solution of ene-sulfonamide **147** (350 mg, 1.25 mmol) in THF (4 mL), and the mixture was stirred until it was completely dissolved. To the resulting solution were added NMO (0.77 mL, 3.76 mmol), H_2O (0.44 mL), and K_2OsO_4 (46 mg, 0.125 mmol), and the mixture was stirred overnight. The reaction mixture was quenched with sat. aq $\text{Na}_2\text{S}_2\text{O}_3$, washed with water and brine, dried over MgSO_4 , filtered, and evaporated to give 353 mg (90% yield) of the diol **153** as a yellowish oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 1329, 1161, 3503; ^1H NMR (400 MHz, CDCl_3) δ 0.92 (t, 3H, $J = 7.3$ Hz), 1.20-2.00 (m, 6H), 2.21 (t, 1H, $J = 7.8$ Hz), 2.42 (s, 3H), 3.00-3.12 (m, 1H), 3.22-3.36 (m, 1H), 3.82-3.92 (m, 1H), 5.37 (t, 1H, $J = 3.2$ Hz), 7.29 (d, 2H, $J = 8.2$ Hz), 7.69 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 20.8, 21.7, 22.6, 26.5, 36.7, 52.5, 69.4, 78.4, 127.0, 130.0, 138.3, 143.7; MS (ESI+) m/z 314 ($\text{M}^+ + 1$, 9), 296 ($\text{M}^+ - \text{OH}$, 100); HRMS Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_4\text{S}$ ($\text{M}^+ + \text{H}$) 314.1426, found 314.1436.

159

(2*S*,3*S*,6*R*)-6-Propyl-1-tosylpiperidine-2,3-diacetate (159). Acetic anhydride (0.07 mL, 0.702 mmol), triethylamine (0.11 mL, 0.798 mmol), and DMAP (4 mg, 0.032 mmol) were added to a solution of diol **153** (100mg, 0.320 mmol) in CH₂Cl₂ (5 mL). The mixture was stirred for 3 h. The reaction mixture was diluted with sat. aq NH₄Cl, extracted with CH₂Cl₂, washed with water, dried over MgSO₄, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give a quantitative yield of the diacetate **159** as a colorless oil and as an inseparable mixture of diastereoisomers:¹²³ FTIR (neat, cm⁻¹): $\nu_{\max}$ 1738, 1732, 1339, 1163; ¹H NMR (400 MHz, CDCl₃) δ 0.91 (t, 3H, J = 7.32Hz), 1.18-1.40 (m, 2H), 1.47-1.81 (m, 6H), 1.97 (s, 3H), 2.03 (s, 3H), 2.42 (s, 3H), 3.95 (approx q, 1H, J = 6.4 Hz), 4.61 (approx dt, 1H, J = 11.9, 4.1 Hz), 6.79 (d, 1H, J = 3.7 Hz), 7.30 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.2Hz); ¹³C NMR (100 MHz,CDCl₃) δ 14.2, 19.4, 20.5, 21.0, 21.2, 21.8, 26.4, 35.5, 52.6, 69.9, 76.1, 127.3, 130.0, 137.9, 144.0, 169.3, 170.1; MS (ESI+) m/z 314 (M^+ - OAc, 100), 296 (M^+ - C₃H₆, 14); HRMS Calcd for C₁₉H₂₇NO₆SN_a (M^+ + Na) 420.1457, found 420.1461.

156

(*R*)-6-Propyl-1-tosylpiperidin-3-one (156). Trifluoroacetic acid (10 μ L, 0.128 mmol) was added to a solution of diol **153** (100 mg, 0.320 mmol) in CH₂Cl₂ (3 mL), and the mixture was stirred for 2 h. The reaction mixture was evaporated, taken up in CH₂Cl₂, washed with water and brine, dried over MgSO₄, filtered, and evaporated. The crude product was purified by silica gel flash column chromatography to give quantitative yield

of the ketone **156** as a colorless oil: FTIR (neat, cm^{-1}): ν_{max} 1730, 1342, 1160; ^1H NMR (400 MHz, CDCl_3) δ 0.94 (t, 3H, $J = 7.1$ Hz), 1.30-1.76 (m, 6H), 1.94-2.06 (m, 1H), 2.14-2.26 (m, 1H), 2.41 (s, 3H), 3.64 (d, 1H, $J = 18.8$ Hz), 4.01 (approx quin, 1H, $J = 14.2, 7.3$ Hz), 4.16 (d, 1H, $J = 18.3$ Hz), 7.76 (d, 2H, $J = 7.8$ Hz), 7.65 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 19.2, 21.7, 26.1, 35.6, 36.1, 51.1, 52.9, 127.2, 130.2, 136.7, 144.0, 206.7; MS (ESI+) m/z 296 ($\text{M}^+ + 1$, 100); HRMS Calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$) 296.1320, found 296.1320; $[\alpha]^{22.3}_{\text{D}} = 71.3$ ($c = 0.5$, CHCl_3).

(3S,6R)-6-Propyl-1-tosylpiperidin-3-ol (158). NaBH_4 (0.02 mg, 0.51 mmol) was added to a solution of ketone **156** (100 mg, 0.339 mmol) in MeOH and the mixture was stirred at room temperature for 2 h. The reaction mixture was evaporated, taken up in CH_2Cl_2 , washed with water and brine, dried over MgSO_4 , filtered, and evaporated to give 93 mg (93% yield) of the hydroxypiperidine **158** as a yellowish oil and as a 3:1 mixture of diastereoisomers.

Trifluoroacetic acid (19 μL , 0.252 mmol) was added to a solution of the diacetate **159** (100 mg, 0.252 mmol) and Et_3SiH (0.40 mL, 2.52 mmol) in CH_2Cl_2 . The resulting mixture was stirred (3 h) at room temperature until confirmed complete by TLC. The reaction mixture was diluted with water, extracted with CH_2Cl_2 , dried over MgSO_4 , filtered, and evaporated. The residue was taken up in MeOH (3 mL). K_2CO_3 (52 mg, 0.378 mmol) was added, and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated, taken up in CH_2Cl_2 , washed with water and brine, dried over MgSO_4 , filtered, evaporated, and purified by silica gel flash column chromatography

to give 57 mg (76% yield) of the piperidinol **158** as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 0.87 (t, 3H, $J = 7.3$ Hz), 1.15-1.83 (m, 8H), 2.42 (s, 3H), 2.71 (dd, 1H, $J = 13.3$, 11.0 Hz), 3.37-3.50 (m, 1H), 3.85 (ddd, 1H, $J = 13.3$, 5.0, 1 Hz), 3.92-4.01 (m, 1H), 7.28 (d, 2H, $J = 7.8$ Hz), 7.70 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 19.9, 21.7, 26.7, 28.4, 31.4, 46.4, 51.9, 66.3, 127.1, 129.9, 138.5, 143.3; MS (GC) m/z 254 ($\text{M}^+ - \text{C}_3\text{H}_7$, 100), 155 ($\text{M}^+ - \text{C}_8\text{H}_{16}\text{NO}$, 24); HRMS Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$) 298.1477, found 298.1483; $[\alpha]^{21.9}_{\text{D}} = -2.2$ ($c = 1$, CHCl_3).

157

(3R,6R)-6-Propyl-1-tosylpiperidin-3-ol (157). K-Selectride (0.37mL of a 1 M solution in THF, 0.37 mmol) was added to a solution of ketopiperidine **156** (100 mg, 0.339 mmol) in THF (3 mL) at 0 °C, and the mixture was stirred and allowed to warm slowly to room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2 , dried over MgSO_4 , filtered, evaporated, and purified by silica gel flash column chromatography to give 95 mg (95% yield) of the *trans* isomer **157** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.84 (t, 3H, $J = 7.3$ Hz), 1.11-1.29 (m, 2H), 1.32-1.48 (m, 3H), 1.60-1.76 (m, 2H), 1.82-2.06 (m, 1H), 2.40 (s, 3H), 3.11 (dd, 1H, $J = 14.6$, 1.8 Hz), 3.69 (d, 1H, $J = 14.7$ Hz), 3.82 (br. s, 1H), 3.98-4.07 (m, 1H), 7.27 (d, 2H, $J = 7.8$ Hz), 7.73 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 19.9, 21.7, 21.9, 25.4, 30.9, 46.1, 52.6, 63.8, 127.4, 129.7, 138.0, 143.3; MS (GC) m/z 254 ($\text{M}^+ - \text{C}_3\text{H}_7$, 100), 155 ($\text{M}^+ - \text{C}_8\text{H}_{16}\text{NO}$, 24); HRMS Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_3\text{S}$ ($\text{M}^+ + \text{H}$) 298.1477, found 298.1478. ^1H and ^{13}C NMR spectroscopic data were in agreement with literature values.¹¹⁷

General Procedure for Detosylation. Mg turnings (163 mg, 6.72 mmol) were added to a solution of tosylpiperidinol (100 mg, 0.336 mmol) in MeOH (3 mL) portionwise over 3 h as the reaction mixture was being sonicated (ultrasonic cleaning bath) or until confirmed to be complete by TLC. The reaction mixture was acidified with 2 M HCl, washed with CH₂Cl₂, neutralized with 2 M NaOH, and extracted with CH₂Cl₂. The organic layer was reacidified with 2 M HCl, and the aqueous layer was evaporated to give 42 mg (70% yield) of the piperidinol salt as a brownish solid.

(3*R*,6*R*)-6-Propylpiperidin-3-ol Hydrochloride (6d). ¹H NMR (400 MHz, D₂O) δ 0.90 (t, 3H, *J* = 7.4 Hz), 1.28-1.80 (m, 6H), 2.00-2.20 (m, 2H), 2.77 (app. t, 1H, *J* = 11.5 Hz), 3.04-3.20 (m, 1H), 3.41 (ddd, 1H, *J* = 12.6, 3.9, 1.8 Hz), 3.84-4.00 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 12.9, 18.1, 25.9, 30.1, 34.1, 48.1, 55.8, 63.8; MS (ESI+) *m/z* 144 (*M*⁺+1, 100); HRMS Calcd. for C₈H₁₇NO (*M*⁺+H) 144.1388, found 144.1389; [*α*]_D^{22.7} = -10.4 (*c* = 0.11, EtOH); mp 185 - 185.5 °C [lit.¹ mp 214 - 215 °C]. ¹H and ¹³C NMR spectroscopic data were in agreement with literature values.¹¹⁷

(3*S*,6*R*)-6-Propylpiperidin-3-ol Hydrochloride (6c). ¹H NMR (400 MHz, D₂O) δ 0.78 (t, 3H, *J* = 7.32 Hz), 1.20-1.90 (m, 8H), 2.90-3.20 (m, 3H), 4.08 (s, 1H); ¹³C NMR (100 MHz, D₂O) δ 12.9, 17.8, 22.7, 27.6, 35.1, 49.1, 56.6, 61.5; MS (ESI+) *m/z* 144 (*M*⁺ + 1,

100); HRMS Calcd for C₈H₁₇NO (M⁺ + H) 144.1388, found 144.1385; [α]^{22.7}_D = -8.1 (c = 0.2, EtOH) {lit.¹¹⁷ [α]²⁰_D = -10.2 (c = 1.0, EtOH)}; mp 120-121 °C [lit.¹¹⁷ mp 148 °C].

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CHAPTER 3

Synthesis of Azimic Acid using Hydroformylation

3.1. Introduction

Azima tetracantha L., also known as needle bush, bee sting bush or fire thorn comes from the Salvadoraceae family.¹ This plant can be found in many places such as Peninsular India, West Bengal, Orissa, African countries and tropical Asia. It is reported to have various biological activities such as wound-healing, anti-inflammatory, diuretic and analgesic activities. It is also claimed to have been administered with food as a remedy and used to treat rheumatism, chronic diarrhoea and many other conditions.²

Carica papaya L., or also known by its common name the papaya tree comes from the Caricaceae family.³ This plant grows mainly in the tropical and sub-tropical zone. There are many traditional medical uses for this plant. For example the fruit pulp as well as the extract of the green leaves were reported to have antisickling properties.⁴ There are also many claims of the leaf extract having antiseptic properties, promoting digestion and aiding in treatment of ailments such as chronic indigestion and obesity.⁵

The common link between these two plants, *Azima tetracantha* L. and *Carica papaya* L. is the presence of the macrocyclic dilactones, azimine and carpaine, which could be isolated from the two plant species respectively. The only difference between them lies in the carbon chain length (Figure 1).

Figure 1 shows the structures of (+)-azimine, (+)-carpaine, (+)-azimic acid and (+)-carpamic acid.

These macrocyclic dilactones are hydrolysed to 2,6-disubstituted 3-piperidinols i.e. azimic and carpamic acid (Figure 1). Piperidine alkaloids are abundant in nature and make up a large group of natural alkaloids which exhibits important biological activities. These trisubstituted piperidines, have a common structure with all the substituents on the same face of the ring. Thus, the challenge of installation of the three stereocentres of the piperidine ring *cis* to each other around the ring sparked interest in many groups towards the syntheses of this molecule including us.

3.2. Review of Previous Syntheses of Azimic Acid

Huang *et al.*⁶ started the enantioselective synthesis of (+)-azimic acid **9** from *cis*-6-methyl-5-benzyloxy-2-piperidinone derivative **2**, which was synthesized from the protected (*S*)-3-hydroxyglutarimide **1** (overall yield: 74%; dr = 80:20) as described in a previous report.⁷ Employing Savoia's method,⁸ the C-6 substituent (numbered based on **9**), was installed *via* a stepwise regioselective reductive alkylation of imide **4** in 85 % yield. Huang *et al.* achieved the enantioselective synthesis of (+)-azimic acid **9** in six steps with 26% overall yield starting from the piperidinone **2** (Scheme 1). The blatant claims of Huang *et al.* in this paper, stating the completion of (+)-Azimic acid in six steps is misleading as they expended a lot of effort in the synthesis (over multiple steps with moderate dr ratio and yield) of the starting material *cis*-6-methyl-5-benzyloxy-2-piperidinone derivative **2**.⁷ The crucial information that is not mentioned is that the protected (*S*)-3-hydroxyglutarimide **1** which was used as the starting material, is not commercially available and has to be synthesized over five steps (with one of the step requiring 7 days of stirring) from D-glutamic acid according to the procedures in one of their previous reports.⁹ Thus, taking into account the effort and steps needed for making their starting material **2**, it can be said that their synthetic route towards the synthesis of (+)-Azimic acid is much more complicated than shown in Scheme 1.

Scheme 1 (a) CAN, CH₃CN/H₂O, rt, 30 min (56%); (b) Boc₂O, Et₃N, DMAP, CH₂Cl₂, rt (91%); (c) TBSO(CH₂)₆MgBr, THF, -78°C, 3h (85% based on 17% of recovered SM); (d) BF₃·OEt₂, CH₂Cl₂, 0°C – rt, 1 h (90%); (e) RuCl₃, NaIO₄, CCl₄, CH₃CN, H₂O, 0°C, 1 h (89%); (f) TFA, rt, 1 h; (g) Pd/C, H₂, EtOH, rt, 14 h (76% over two steps).

Based on the concept of “chiral templates” which was introduced by Hanessian¹⁰, Frenette *et al.*¹¹ synthesized (+)-azimic acid **9** starting with the unsaturated derivative **11** which was derived from methyl α-D-glucopyranoside **10** in high overall yield by known procedures.¹² The C-6 substituent (numbered based on **9**) was installed *via* Grignard addition to aldehyde **17**, hence there is the flexibility to generate both azimic and carpamic acid by varying the Grignard reagent. Further, oxidation of alcohol **18** followed by a domino hydrogenation, condensation and hydrogenation reaction gave the chiral cyclic amine **20**. Frenette *et al.* attributed the high degree of stereocontrol in generating the chiral cyclic amine **20** to the selective hydrogenation of the intermediate piperidine derivative from the α-face of the molecule (Scheme 2). They did not state the chemical reason as to why this occurs but instead based it upon experimental observation of Hill *et al.*¹³ who achieved similar high degree of stereocontrol utilizing the hydrogenation method. It can be understood that this reaction proceeded to give the desired

stereochemical outcome due to hydrogenation on the less hindered side, the α -face of the molecule. As is commonly the case when starting from a sugar, this synthesis proved to be long and tedious as the starting material is more complex than the product.

Scheme 2 (a) 5% Pd/C, H₂, MeOH (quant.); (b) NBS/CCl₄, reflux, 30 min. (95%); (c) NaOMe, MeOH; (d) LAH, THF, 25°C; (e) BnBr, NaH, DMF (86% overall); (f) EtSH, HCl (71%); (g) TsCl, pyridine (98%); (h) NaN₃, DMF, 80°C, overnight (98%); (i) Br₂, ether, H₂O (63%); (j) BrMg(CH₂)₇CH₂OTHP, THF, -50°C, 30 min, (48-53%); (k) pyridinium chlorochromate NaOAc, CH₂Cl₂, overnight, (83%); (l) Pd/C, H₂, EtOAc, (85%); (m) CbzCl, aq. Acetone (88%); (n) CrO₃, aq. H₂SO₄, acetone, (57%); (o) 10% Pd/C, H₂, MeOH, 8 h (83%).

Kumar and Datta¹⁴ constructed a functionalized *syn*-1,2-amino alcohol fragment **24** with the required stereochemistry *via* chelation controlled addition of a suitable Grignard reagent to *N*-Boc-alaninal. Similar to the work of Frenette *et al.*¹¹ by varying the Grignard reagents, Kumar and Datta could generate caripamic acid and other related compounds *via* the same route. They too obtained the stereochemistry at the C-6 position (numbered based on **9**) based on a similar assumption that hydrogenation of the imine **33** will occur from the less hindered α -face of the molecule (Scheme 3).

Scheme 3 (a) LiAlH_4 , THF then Boc_2O (70%); (b) Swern oxidation then $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_2\text{MgBr}$ (54%); (c) $\text{Me}_2\text{C}(\text{OMe})_2$, PPTS (81%); (d) OsO_4 , NMO then NaIO_4 (impregnated on silica gel) (93%); (e) $\text{BrMg}(\text{CH}_2)_6\text{OTHP}$ (79%); (f) 2-iodoxybenzoic acid (88%); (g) PTSA, EtOH (80%); (h) $\text{RuCl}_3 \cdot \text{H}_2\text{O}$, NaIO_4 then CH_2N_2 , Et_2O (78%); (i) 80% AcOH - H_2O (84%); (j) Ac_2O , DMAP (92%); (k) HCO_2H , CH_2Cl_2 (72%); (l) Pd/C , H_2 (77%); (m) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, MeOH (68%).

Zhou *et al.*¹⁵ started the synthesis of (+)-azimic acid **9** from (2*S*,6*S*)-6-hydroxy-2-methyl-N-tosyl-Δ-piperidone-3 **36**, which was synthesized from (*S*)-α-furfuryl amide **35** utilizing the aza-Achmatowicz reaction, in high yield as described in a previous report.¹⁶ Referring to his previous report, the (*S*)-α-furfuryl amide **35** was synthesized from the racemic α-furfuryl amide *via* modified Sharpless asymmetric epoxidation and the racemic α-furfuryl amide was initially synthesized by another procedure by Albrecht *et al.*¹⁷ starting with *N*-furfuryl-*p*-toluene-sulfonylimine. Thus again, there are a lot of unmentioned steps prior to the start of this synthesis that need to be taken in account. The piperidone **36** was converted stereoselectively into alcohol **39** in three steps with a high overall yield.¹⁸ The hydroxyl group at C3 in alcohol **38** was corrected to the desired stereochemistry *via* a Mitsunobu reaction.¹⁹ The C6 substituent was then installed with the right configuration *via* Sakurai reaction as the steric bulk associated with the tosyl group directs the attack of the allylsilane on the iminium ion to the side of the C2-methyl group. Instead of carrying on the synthesis with an ozonolysis and a Wittig sequence to achieve their desired side chain, they could have nowadays shortened their route by a simple cross-metathesis reaction (Scheme 4). It can be noted that in this synthesis of (+)-Azimic acid¹⁵ Zhou *et al.* did not report any information about the stereochemistry of the hydroxyl group on piperidone **36** after aza-Achmatowicz reaction. In fact in their previous paper¹⁶ they left the stereochemistry of the hydroxyl unknown. Although, normally we would expect the stereochemistry of the hydroxyl group of piperidone **36** to be *cis* to the methyl group as the substituents should be pseudoaxially oriented to avoid steric strain from the tosyl group. They also went on to claim that reduction using NaBH₄ in methanol gave solely the C₃-β-hydroxyl compound **38**, which is the opposite stereoselectivity of what we would expect, because of the steric hindrance between, the pseudoaxially oriented bulky 2,6-substituents and an axial approaching hydride reagent (Figure 2).

Figure 2 shows our predicted outcome of the product's stereochemistry if NaBH₄ was used as for reduction.

All these ambiguities were clarified by Zhou in a later paper²⁰ when he reported that a (2*R*)-dihydropyridone prepared by similar oxidative cyclization has the *cis*-configuration as confirmed by X-ray analysis and also by indicating that by addition of CeCl₃ in the NaBH₄ reaction, the expected all *cis*-stereochemistry was obtained. It is noteworthy that Zhou did not mention why he got such a stereochemical result from the reduction reaction. Thus, it is unknown why addition of CeCl₃ would change the stereochemistry of the product. Finally, it can be noted that during NaBH₄ reduction in the synthesis of (+)-Azimic acid¹⁵ Zhou did not mention any problem associated with 1,2 or 1,4 addition, as it is well known for α,β-unsaturated carbonyl substrates to have such complications.²¹

Scheme 4 (a) $\text{HC}(\text{OEt})_3$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (b) NaBH_4 , MeOH ; (c) $\text{H}_2\text{C}=\text{CHCH}_2\text{SiMe}_3$, TiCl_4 (66% over three steps); (d) DEAD , Ph_3P , benzoic acid, THF (88%); (e) 3N NaOH in EtOH (98%); (f) $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$, NaH , Bu_4NI , THF (quant.); (g) O_3 , $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (9:1) (90%); (h) $\text{Ph}_3\text{As}=\text{CHCH}=\text{CHCO}_2\text{Et}$, $\text{THF}:\text{Et}_2\text{O}:\text{H}_2\text{O}$ (4:5:1) (83%); (i) 10% Pd/C , EtOH , H_2 (1 atm) (quant.); (j) 1N NaOH , EtOH (98%); (k) Na/naphthalene , DME (85%).

Similar to the work of Zhou *et al.*,^{15, 18} starting with furyl sulfonamide **48**, utilizing the aza-Achmatowicz oxidation conditions reported by Ciufolini²² as the key reaction followed by methoxylation of **48a**, reduction of dihydropyridone **49** and stereoselective addition of the C-6 side chain to *N*-sulfonyliminium ion, Padwa and Cassidy²³ developed a synthetic route towards several *cis*-2,3,6-trisubstituted piperidines, one of which is azimic acid **9**. They methoxylated their hemiaminal **48a** to form *N*-tosyl-*O*-methyaminal **49** because they claimed that the hemiaminal **48a** was unstable and difficult to purify. Strangely Zhou *et al.* did not report any difficulties that they faced with the stability or purification of this compound. The exclusive *cis*-orientation of the substituent groups on

the aminal **49** was rationalized based on the assumption that the A²⁴-strain of the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation. They produced alcohol **50** stereoselectively by reduction of the ketone **49** under Luche conditions²⁵ (sodium borohydride in the presence of CeCl₃·7H₂O) so as to prevent 1,4 addition from occurring. Unlike in the case of Zhou *et al.*¹⁵ who used a standard reduction conditions without any modification (sodium borohydride in methanol) to reduce their ketone **37** to the alcohol **38**, they did not mention any problem regarding the competition between the 1,4-addition and 1,2-addition product. Padwa and Cassidy introduced the substituent at C-6 (numbered based on **9**), selectively *cis* to the rest of the substituents *via* a Sakurai reaction, based on the previous work of others,²⁶ with the assumption that the steric bulk associated with the tosyl group directs the attack of the silyl reagent on the iminium ion to the side of the C2-methyl group. It can be noted that unlike Zhou *et al.*,¹⁵ Padwa and Cassidy installed the side chain at C-6 as a complete unit, and not adding it on as an allyl group and then building it up, therefore making their synthesis more convergent (Scheme 5).

Scheme 5 (a) HC(OMe)_3 , $\text{BF}_3 \cdot \text{OEt}$ (85%); (b) NaBH_4 , CeCl_3 , MeOH , -40°C (60%); (c) TBSCl , imidazole, DMAP , CH_2Cl_2 , 25°C (82%); (d) methyl 3-(trimethylsilyl)-4-pentenoate, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , -78°C ; (e) H_2 , PtO_2 , MeOH (57% over two steps); (f) LiAlH_4 , THF , 0°C (95%); (g) MsCl , Et_3N , CH_2Cl_2 , 0°C ; (h) NaCN , DMF , 50°C ; (i) NaOH , MeOH , 70°C (89% over three steps); (j) Li , NH_3 , THF , -78°C (70%).

Brown and Dhal²⁷ synthesized ($\pm$)-azimic acid by hydrolysis of the di-ester **59** which was prepared in quantitative yield by alkylating ethyl β -oxo-ester **58** with 5-bromopentanoate **57** and submitting the resulting crystalline acid **60** to ozonolysis to generate the aldehyde **70**, which was condensed with nitroethane to give the β -nitro-alcohol **71** in high yield. Unfortunately, there was no control over the stereochemical outcome of this Henry reaction. Finally, β -nitro-alcohol **71** was subjected to catalytic hydrogenation (5% Pd-C) to give a mixture of 5'-epi-Azimic acid **72** and ($\pm$)-Azimic acid **9** with isolated yields of 35% and 45% respectively (Scheme 6). Although, this synthetic scheme is straight forward and short, it lacks stereochemical control.

Scheme 6 shows Brown and Dhal's synthesis of (±)-azimic acid.

Natsume and Ogawa²⁸ started their synthesis with 1-Benzyloxycarbonyl-2-methyl-1,2-dihydropyridine **73** which was prepared from pyridine, benzyl chloroformate, and methylmagnesium iodide in 97% yield. The dihydropyridine **73** was then further put through sensitized photooxygenation, which is a short and efficient way to obtain a highly functionalized piperidine, to give the endoperoxide **74**. After which, the acetal **75**, was formed by condensation of the endoperoxide 2-methyl derivative **74** with ethyl vinyl ether in the presence of SnCl_2 , followed by the addition of EtOH.²⁹ The SnCl_2 in this case plays a unique role and acts as both a reducing agent for the peroxide and as a Lewis acid. The alcohol **75** was then oxidised and reduced with sodium borohydride to give a mixture of 1,2- and 1,4 addition products **78** and **77** respectively. It is noteworthy that they could have used Luche reduction instead, to avoid getting a mixture and forming only the 1,2 addition product. The aldehyde prepared from compound **77** was condensed with the

Wittig reagent **80** and the reaction product was isolated as ester acetate **81**, which was further hydrolysed with Ba(OH)₂ and hydrogenated over Pd-C to afford (±)-Azimic acid **9** in 58% yield (Scheme 7). In this report, Natsume and Ogawa, did not mention why they chose compound **77** over compound **78** to continue their synthesis towards (±)-Azimic acid **9**. It appears odd as it seems like both molecules **77** and **78** could be carried forward to produce (±)-Azimic acid **9**. Their synthetic route is relatively short but with very low overall yield of the final product. They also only deal with the relative stereochemistry in their synthetic route as the outcome of their initial step, which is the preparation of compound **73**, lacks stereochemical control.

Scheme 7 shows Natsume and Ogawa's synthesis of (±)-azimic acid.

Naito *et al.*³⁰ reported a synthetic scheme towards (+)-Azimic acid **9** via a combination of 1,3-dipolar cycloaddition³¹ to a chiral dipolarophile and subsequent ring transformation reactions. Cycloaddition of Z-nitrone **82** to the free allyl alcohol **83** in toluene at reflux gave a mixture of three adducts **84**, **85** and **86** in 35%, 37% and 11% yield respectively. From the three adducts **84-86**, only the *cis*-threo **84** and the *trans*-erythro **86** were employed for the synthesis of (+)-azimic acid **9**. Further, protection, deprotection, mesylation and hydrogenation of adducts **84-86** gave a crude mixture of the ring-transformed piperidinols **93-95** and the acyclic mesylates **90-92**. The incomplete cyclization products **90-92** were then pushed to completion to form piperidinols **93-95** by subjecting them to mildly basic conditions. Deoxygenation of the piperidinols **93** and **95** via Barton's ester³² gave the identical piperidine **96** in 93% yield from **93** and 81% yield from **95**, respectively. Finally, deprotection of the MEM group with TiCl₄ and hydrolysis of the ester group with KOH-MeOH gave the chiral natural product **9** (Scheme 8). The initial part of their synthesis is quite inefficient as the yields of the starting materials **84-86** are quite low and out of these low yielding products only two of the products **84** and **86** are fully utilized to generate the final natural product **9**. It is also notable that they did not mention the isolated percentage yield of the (+)-Azimic Acid.

Scheme 8 (a) toluene, reflux (83%); (b) MEMCl, (*i*-Pr)₂NEt, CH₂Cl₂, reflux; (c) (*n*-Bu)₄NF, THF, reflux (54%-76% yield over two steps); (d) MsCl, Pyridine, 0°C; (e) 20% Pd(OH)₂-C, MeOH, H₂; (f) NaHCO₃, H₂O-MeOH (62-93% yield over three steps); (g) Im₂CS, THF; (h) Bu₃SnH, toluene, reflux; (i) TiCl₄, CH₂Cl₂, 0°C (81%); (j) MeOH, KOH.

Kibayashi *et al.*³³ developed a synthetic route towards the total synthesis of (+)-Azimine and (+)-Carpaine which involves stereoselective intramolecular hetero-Diels-Alder reaction of an acylnitroso compound. They began the synthesis with (*S*)-1,2,4-butanetriol as a single source of chirality, which makes up the C-3 stereocenter in (+)-Azimic acid **9**. Upon making the hydroxamic acid **103** it was oxidised with NaIO₄ in an aqueous medium³⁴ at 0°C, to generate acylnitroso compound **104** *in situ* that would undergo intramolecular Diels-Alder reaction to afford a 6.4:1 mixture of the *trans* and *cis* adducts in 69% total yield. The major isomer **105** was further reacted to give compound **107** which was treated with methylmagnesium bromide to give the enamine **108**, which was immediately reduced with NaBH₃CN in an acidic medium to the desired (*8S*)-methylated single stereoisomer **110** in 76% overall yield from compound **107**. The exclusive selectivity for this reaction can be accounted for by considering the iminium intermediate **109** which adopts the required conformation for stereoelectronic controlled axial addition of hydride from the less hindered β-face. Subsequent N-O bond cleavage of (*8S*)-methylated product **110**, followed by a series of reactions and finally hydrogenolytic removal of the Cbz group from **116** provided the natural product (+)-azimic acid **9** (Scheme 9). Although in their synthetic scheme they had good control of the stereochemical outcome (*e.g.* stereoselective intramolecular hetero-Diels-Alder reaction of an acylnitroso compound), it is rather long-winded and requires a lot of protecting groups. Thus, it is not a very atom economical pathway.

Scheme 9 (a) (i) PhCHO, TsOH (ii) Swern oxidation; (b) Br⁻ Ph₃P⁺CH₂=CHCH₂CH₂CH₂OH, LiHMDS, THF-HMPA (2:1), rt, 66%; (c) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, 60°C, 93%; (d) DIBAL-H, CH₂Cl₂, 0°C, 84%; (e) TsCl, Et₃N, DMAP, CH₂Cl₂, rt, 91%; (f) *hν*, I₂, benzene, 94%; (g) NaCN, DMSO, 50°C, 95%; (h) NaOH, MeOH-H₂O, reflux; (i) CH₂N₂, Et₂O, 0°C, 94% over two steps; (j) NH₂OH.HCl, KOH, MeOH, 0°C, 88%; (k) NaIO₄, H₂O-DMF (50:1), 0°C, 69%; (l) H₂, Pd/C, THF, 97%; (m) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF, -78°C, 99%; (n) TBDPSCl, imidazole, DMF, rt, 73%; (o) MeMgBr, THF, 0°C; (p) NaBH₃CN, AcOH, THF, 0°C, 76% over two steps; (q) Zn, 90% AcOH, 60°C, 93%; (r) H₂, Pd(OH)₂, MeOH; (s) CbzCl, Na₂CO₃; (t) 1 M NaOH, MeOH, rt, 45% over three steps; (u) CS₂, NaH, imidazole, THF, reflux, then MeI, reflux, 93%; (v) Bu₃SnH, AIBN, benzene, reflux, 99%; (w) PPTS, *t*-BuOH, reflux, 73%; (x) PDC, MS 4Å, DMF, rt; (y) Bu₄NF, THF, rt, 82% over two steps; (z) H₂, Pd/C, MeOH, 99%.

Utilizing the Baeyer-Villiger oxidation³⁵ as their key step in the final stage of their synthetic route, Ma *et al.*³⁶ synthesised Azimic acid in 12 steps starting with α - β -unsaturated ester **117**. It should be noted that the author did not mention anything about the synthesis of their starting material **117**, but a quick literature search revealed that it could be synthesized in three steps starting from the commercially available 1,7-heptanediol.³⁷ Thus, it can be said that their synthesis is not as short as it seemed in their paper. The C6 stereochemistry was installed using the method of Davies,³⁸ *via* diastereoselective Michael addition of lithium (*S*)-*N*-benzyl- α -methylbenzylamide to the ester **117** to give the β -amino ester **118**. Thereafter, both the C2 and C3 stereochemistry was introduced simultaneously *via* regioselective addition of hydrogen on the less hindered face of the piperidine **121**, which was obtained with Michael's chemistry³⁹ from compound **120**. Ma *et al.* used their key step in their final step subjecting compound **123** to Baeyer-Villiger Oxidation followed by deprotection to give (+)-azimic acid **9** (Scheme 10).

Scheme 10 shows Ma. *et al.* Synthesis of Azimic Acid.

Gerlach and Hasseberg⁴⁰ started the synthesis of ($\pm$) Azimic acid by replacing the bromine atom on the SEM ether **124** with lithium to give compound **125** and further reacting it with methyl iodide to give exclusively the key compound **126**. The key compound **126** was then subjected to Kumada coupling with Grignard reagent **127** in the presence of dpppNiCl_2 ⁴¹ catalyst to give compound **128**. Subsequent, methanolysis, hydrolysis and hydrogenation gave racemic natural product **9** (Scheme 11). They introduced a very short, simple and straight forward synthetic scheme, but it totally lacks control of the stereochemical outcome. The only control over stereochemistry was in the last hydrogenation step, where all the hydrogens adds simultaneously to one face of the

molecule **130** either the α or the β face, giving rise to all *cis* stereochemistry of the side chains hence generating ($\pm$) Azimic acid **9**.

Scheme 11

3.3. Results and Discussion

It has been shown that dihydroxylation of six membered ring ene-sulfonamides shows good selectivity for the isomer in which the diol is *cis* to an α' -substituent (Scheme 12).⁴² This selectivity, which has been attributed to a combination of lipophilic and electrostatic effects, delivers the correct stereochemistry of the 3 and 6 substituents. We anticipated that replacement of the 2- hydroxy group of the diol **133a** with a methyl group via an iminium ion⁴³ would deliver the desired stereochemistry under stereoelectronic control.^{15, 18, 44} The required ene-sulfonamide **133b**⁴⁵ would, in turn, be available by tandem hydroformylation-condensation,⁴⁶ as in our recent synthesis of pseudoconhydrine,⁴² building on the work of Ojima.^{46b, 47} Given that the long side chain of azimic acid terminates with a carboxylic acid, we planned to employ a double hydroformylation of diene **133**.⁴⁸

Scheme 12 shows the retrosynthetic scheme of azimic acid.

The method of Vilaivan *et al.*⁴⁹ was employed to generate the desired tosyl protected diene **133** for the initial part of our synthesis (Scheme 13).^{24c}

Scheme 13 shows Vilaivan's methodology leading towards the formation of the desired diene **133**.

Hence, (*S*)-phenylglycinol **129** was condensed with hex-5-enal **128** obtained from oxidising the commercially available alcohol 5-hexene-1-ol with IBX, expecting to obtain the imine **130** as indicated by Vilaivan *et al.* but suprisingly, there was no presence of imine observed through spectroscopic analysis.

We first tried to rule out the presence of the imine **130** with the aid of spectroscopic data obtained from the unknown condensed product. Thus, referring to the ^{13}C NMR spectra (Figure 3), there was no imine carbon peak seen in the region δ 150 – 160 ppm, which suggests the absence of imine **130**. But from the ^1H NMR spectra, the presence of imine peak in the region δ 7 – 8 ppm, cannot be ruled out as it might be lost within the phenyl ring signals which also appear around the same region.

Figure 3 shows the ^{13}C NMR spectrum of the crude product from the imine formation reaction.

Looking closely at the ^{13}C NMR spectra (Figure 3) of the unknown compound it can be suggested that a pair of diastereomers is present due to the close relationship of the chemical shifts of the carbons of the two different compounds. The possible explanation to support this observation would be that the alcohol which is supposedly present in the imine **130** that was predicted to be formed underwent an intra-molecular addition reaction with the imine **130** to give oxazolidine **134** (Figure 4), as a mixture of diastereomers. Evidently, analysing the ^1H NMR spectra (Figure 5), showed that there are two sets of signal for the four significant protons H_1 , H_2 , H_3 , and H_4 present in oxazolidine **134** suggesting the presence of two different diastereomers possibly differentiated by the proton H_1 as shown in Figure 4.

134

Figure 4 shows the structure of the oxazolidine 134.

Thus, from the ^1H NMR spectrum (Figure 5), it can be seen that the H_1 signal for both the diastereomers overlaps each other hence it appears as a multiplet in the region δ 4.60 – 4.54 ppm. As for the H_2 , H_3 and H_4 protons, two sets of signals of these protons coupling with one another were evident from COSY (Figure 6). One set of signal appeared at δ 4.51 (app. t, $J=7.0$ Hz, 0.5H), δ 4.29 (app. t, $J=7.9$ Hz, 0.5H), δ 3.60 (dd, $J=8.2$, 6.6 Hz, 0.5H) and the other set of signal appeared at δ 4.38 (app. t, $J=7.5$ Hz, 0.5H), δ 4.12 (app. t, $J=7.7$ Hz, 0.5H), δ 3.68 (app. t, $J=7.6$ Hz, 0.5H).

Figure 5 shows the 4.60 ppm to 3.55 ppm region of the ^1H NMR spectrum of the oxazolidine 134.

Figure 6 shows the 4.60 ppm to 3.55 ppm region of the COSY spectrum of the oxazolidine **134**.

With this substantial information, it could be suggested that unknown compound that is being formed by condensing (*S*)-phenylglycinol **129** with hex-5-enal **128** is indeed the oxazolidine. But the fact that it reacts under the allylation condition in the next step to generate product **131** suggests that it is in equilibrium with the imine form **130**. Hence, in conclusion it can be said they are present in equilibrium with each other but largely on the side of the oxazolidine **134**.

Initially, Knochel's⁵⁰ method using allylzinc bromide from our previous synthesis of pseudoconhydrine⁴² was utilized to generate the allylation product, but this time the reaction did not proceed as well as before, due to formation of complex side products, giving low yields but with high diastereoselectivity. Thus, we re-directed our efforts towards the original procedure of Vilaivan *et al.*,⁴⁹ the oxazolidine **134** was reacted with

allyl bromide under Barbier conditions using indium to give amino alcohol **131** with a low yield and about a 1:1 ratio of diastereomers.

The low yield of the amino alcohol **131** was due to the formation of a side product, which was thought to be an allylation product from a 2:1 condensation of the aldehyde **128** with the (*S*)-phenylglycinol **129**. The ^{13}C NMR spectra of the side product showed the presence of twelve carbons in the downfield region 110-145 ppm which was consistent with the presence of a benzene ring and three allyl groups. There was also a peak at 65.8 ppm which could represent a CH_2 carbon on an oxazolidine ring. The ^1H NMR spectra (Figure 7) showed three protons H_x , H_y and H_z which are suggestive of being the ring protons of the oxazolidine and their relation to each other was confirmed by computing and comparing their coupling constants δ 3.77 (dd, $J=6.8, 4.7$ Hz, 1H), 3.69 (dd, $J=10.5, 4.6$ Hz, 1H), 3.49 (dd, $J=10.5, 6.9$ Hz, 1H) respectively. The multiplet proton peaks present at the regions δ 5.90-5.59 (m, 3H) and 5.12-4.84 (m, 6H) suggests the presence of three allyl groups. A peak at 1639 cm^{-1} in the infra-red spectrum also indicates that there are alkenes present in the molecule. Finally, together with the mass-spectroscopy data MS (ESI+) m/z 340 ($\text{M}^+ + 1, 100$) which indicates the side product has a molecular weight of 339, the structure of the side product could be confirmed to be that of compound **135**.

Figure 7 shows the selected regions of the ^1H NMR spectrum of the side product **135**.

We proposed the formation of the side product **135**, could have occurred through the mechanism as shown in Scheme 14.

Scheme 14 shows the proposed mechanism towards the formation of the side product **135**.

Interestingly, the ^1H NMR of the side product **135**, suggested that it is a single diastereoisomer. Hence, we proposed hydrolysing the oxazolidine using an acid to

determine the stereochemistry of the allylation by comparing the hydrolysed product with the substrate from the work of Vilaivan⁴⁹ (Scheme 15).

Scheme 15 shows the hydrolysis of side product **135** via addition of an acid.

Unfortunately, efforts to determine the stereochemistry at the allylation site *via* acid hydrolysis using both *p*-toluenesulfonic acid (PTSA) and 2 M HCl failed. No reaction occurred and the unreacted side product **135** was recovered in both cases.

The low yield, due to the formation of the side product **135** was eventually resolved by employing a precisely measured quantity of the freshly distilled aldehyde to achieve a satisfactory Barbier allylation, as the use of an excess of undistilled aldehyde resulted in the formation of the side product **135**.

After the yield of the allylation step was improved, the diastereoselectivity was still almost zero. Initially, following procedures of Vilaivan *et al.*,⁴⁹ allyl bromide was added to a mixture of imine and indium powder in absolute methanol at room temperature. It was speculated that the heat generated during reaction *in situ* affects the diastereoselectivity of the product. Thus, to test this speculation, the temperature of the reaction mixture was lowered to 0°C, prior to addition of the allyl bromide and allowed to stir till room temperature overnight. The diastereoselectivity of the ratio of desired:undesired isomer improved from almost zero to 5:1. Further, reduction in temperature to -10°C, made only a slight change to the ratio from 5:1 to 6:1.

It was then suggested that the heat generated during reaction *in situ* can be controlled by slow addition of the allyl bromide at low temperature. Thus, the temperature of the reaction mixture containing the imine and indium in methanol was lowered to -10°C, and allyl bromide was added slowly *via* syringe pump overnight, while stirring the reaction mixture at -10°C. To our delight, the crude ¹H NMR spectrum showed >98% selectivity for the desired isomer.

Hence, overall in making minor adjustments to the original Vilaivan⁴⁹ procedure as described previously, we were able to achieve high diastereoselectivity (>98%) of the amino alcohol **131** in good yield. Following through with the procedures of Vilaivan *et al.* the amino alcohol **131** was converted to the diene **133** after cleavage of the chiral auxiliary, *N*-sulfonylation and chromatographic purification in 42% yield (from hex-5-enal) and >98% ee (enantiomeric excess was determined by chiral HPLC analysis, using a Diacel IC column, eluting with IPA/hexane), setting it up for double hydroformylation.

The double hydroformylation of the sulfonamide **133** was achieved using triphenylphosphine or BIPHEPHOS with the same conditions established previously in the synthesis of pseudoconhydrine⁴² to give the ene-sulfonamide **138**, with the tandem condensation occurring exclusively at the nearer of the two aldehydes (Scheme 16). Although it is possible for the formation of four different types of isomers **137**, **138**, **137a** and **138a** from this reaction, only two of the isomers **137** and **138** were identified from the crude mixture after isolation *via* column chromatography using silica gel. The ¹H NMR spectra of the rest of the side products obtained from the crude mixture was too complicated to clearly identify their structure.

Scheme 16 shows the four different types of products that can be formed by hydroformylation of diene **133**.

Compound	Ligand	Branched (137) (% yield)	Linear (138) (% yield)
133	BIPHEPHOS (2 mol%)	0	74
133	$\text{P}(\text{OPh})_3$ (25 mol%)	10	60

Table 1 shows the two different ligands tried with hydroformylation reaction in Scheme 16.

As mentioned before in the chapter of pseudoconhydrin, the capability of BIPHEPHOS to produce exclusively the linear isomer proved to be true again in this case of dihydroformylation. Triphenylphosphite gave a mixture of linear isomer **138** and the branched isomer **137**, with a yield of 10% and 60% respectively (Table 1). Since triphenylphosphite is cheap and is a very common chemical in the lab, it was chosen as the ligand of choice during our synthesis as it also gave moderate yields of the desired linear isomer. Clean isolation of these branched **137** and the linear **138** isomers proved to be challenging because their retention factors (R_f) on thin layer chromatography plates are very close, that is 0.33 and 0.30 respectively using an eluant system of 25% ethyl acetate and 75% hexane. Initially we knew that we obtained both isomers of the cyclic enamines, because they both contain 3 significant protons H_x , H_y and H_z which approximately fall in the regions δ 6.50, 5.00 and 3.9 respectively. They have very similar ^1H NMR chemical shift compared to the enamine **137b** from our previous work⁴² in the synthesis of

pseudoconhydrine because the chemical environment is not much different for all these molecules (Figure 8).

Figure 8 Shows specific regions of ^1H NMR of the three compounds indicating the presence of the three significant protons.

Although, it is difficult to differentiate the branched **137** from the linear **138** isomer by infrared spectroscopy (both isomers have similar functional groups), mass spectrometry (both isomers have similar molecular weight) and ^{13}C NMR (difficult to identify a slight change in carbon chemical shift), they could easily be identified by the presence and absence of a methyl group in the region between $\delta 1.00$ to 2.00 from ^1H NMR (Figure 9).

Figure 9 shows the difference of the branched **137** and linear isomer **138** via their ^1H NMR spectrum.

Following through the standard transformation steps as established before in our previous work⁴² the ene-sulfonamide **138** was converted to the methyl ester **140** with high overall yield in just two steps. Dihydroxylation of the alkene following the Upjohn procedure with the addition of methane sulfonamide proceeded in 87% yield and gave an inseparable 5.8:1 mixture of diols **141**. Again based upon our previous work⁴² and that of Harrity,⁵¹ the major diol was assigned the all-*cis* stereochemistry (Scheme 17).

Scheme 17

It is important to point that the methods used to generate the ester **140**, over two steps from aldehyde **138** were carefully chosen to be non-acidic because of the presence of ene-

sulfonamide. Under acidic condition the ene-sulfonamide might hydrolyse as shown in Scheme 18.

Scheme 18 shows the hydrolysis of the ene-sulfonamides under acidic conditions.

Similar to the diols in the synthesis of pseudoconhydrine, the mixture of diols **141** are also as unstable in the presence of acid and will undergo a pinacol type reaction to give the ketone **143**, even in the slightest acidic condition (*e.g.* on silica-gel during column chromatography) (Scheme 19).

Scheme 19 shows the mechanism of the degradation of diol **141** to ketone **143** under acidic condition.

Therefore, to prevent the pinacol type reaction from occurring the diols were acetylated for the reasons mentioned in our previous work⁴² to give the diacetates **144** in 97% yield as a 5.8:1 mixture, but still inseparable (Scheme 20).

Scheme 20

Comparing the ^1H NMR spectrum of the diacetate **144** with the ^1H NMR spectrum of the diacetate **144a** obtained during the synthesis of pseudoconhydrine⁴², it can be realised that their three significant protons are very similar in chemical shift as well as their coupling constants, hence strongly suggesting the major isomer is the one with the all-*cis* stereochemistry (Figure 10). This is because these molecules are only differentiated by their C-6 side chain, and the side chain functional group of the diacetate **144** is too far away to have any significant electronic effect on the three protons under discussion.

Figure 10 compares the ^1H NMR spectra of the diacetylated compounds of pseudoconhydrine and azimic acid.

To methylate regio- and stereo- selectively on C-2 of the piperidine derivative **144**, we suggested generating an iminium ion which would be intercepted stereospecifically under

stereoelectronic control by a nucleophilic methyl group *via* a chair transition state to provide the desired *cis*-selective product (Scheme 21).⁵²

Scheme 21 shows the two possible pathways leading towards the formation of *cis* and *trans* isomers via the iminium ion intermediate **145**.

Hence, initial attempts of adding trifluoroacetic acid (TFA) as a source of acid and $\text{BF}_3 \cdot \text{OEt}_2$ as a Lewis acid to the cyclic amide **144** to generate the iminium ion **145** on two separate attempts, prior to addition of MeMgBr as a source of methyl nucleophile to intercept the iminium ion failed. In both experiments, it can be seen from the crude ^1H NMR spectra that the acetate group was cleaved to give many other side products which could not be identified.

Hence, re-thinking the approach towards the generating and intercepting the iminium ion with a carbon nucleophile, we arrived at a reagent which preforms both tasks. Treatment of the diacetates **144** with trimethylaluminium, which serves as both a methyl source and as a Lewis acid, gave what we assumed to be the all *cis* methylated product **146** in 73% yield and the minor product **147** in 5% isolated yield (Scheme 22).

Scheme 22

To justify our assumption, we turned our attention towards spectroscopic analysis of the major product **146**. We thought that the coupling constant of the two protons H_x and H_y could potentially aid us with resolving the molecule's stereochemistry. To our misfortune, analysis of ^1H NMR (Figure 11) revealed that the two protons H_x and H_y were overlapping each other, as deduced by analysis of the COSY spectrum (Figure 12).

Figure 11 shows the ^1H NMR spectrum of the methylated product **146**.

Figure 12 shows the COSY spectrum of the methylated product **146**.

The COSY spectrum (Figure 12) above clearly shows that the H_x (which has correlation with the methyl group protons) and H_y (which has correlation with the cyclic carbon protons) protons are overlapping each other, hindering the calculation of the coupling constants.

As hopes to identify the stereochemistry of the acetylated molecule were diminishing, serendipity happened, when the minor product **147** that was separated by column chromatography, solidified. Hence, using it to our advantage we confirmed the actual configuration of the minor acetylated isomer by X-ray crystallography, which showed the 2- and 6- substituents being *cis* diaxial (Figure 13). Although it is intriguing to see how all three carbon substituents prefer to be in the axial position due to steric strains caused by the tosyl protecting group (Scheme 23), we were not surprised as this phenomenon was reported before by our laboratory.^{53, 52b, c}

Figure 13 shows the crystal structure of the minor product **147**.

Scheme 23 shows why all three carbon substituents prefer to be in the axial position.

Backed with findings from the X-ray crystallography data of the minor acetylated isomer, we postulated that the stereochemistry of both products is consistent with axial attack by a methyl nucleophile on the corresponding iminium ions **145a** and **148a** (Scheme 24).⁵⁵

Scheme 24 shows the axial attack of the methyl nucleophile on the respective iminium ions.

With the methylated product **146** at hand, we tried to cleave the tosyl group prior to hydrolysis as we thought isolation of the products would be easier if done in this sequence. Thus, magnesium in methanol⁵⁴ under sonication as in our previous work⁴² was utilized for cleavage of the tosyl group.

Unfortunately, the de-tosylation did not proceed as smoothly as expected, as the acetate group and the ester group were affected under the same reaction conditions. Therefore providing multiple products and giving low yields of the desired de-tosylated product **149** (Scheme 25).

Scheme 25

It was not known which functional group was affected first by the reaction condition, hence losing control of the outcome, causing this reaction to be capricious. It was also understood that the desired product **149** might have been affected during the acid base extraction, instead of the original reaction condition as the ester and the acetate protecting group are prone to hydrolysis. Thus, making the isolation *via* acid base extraction difficult, which is necessary to separate the metal salts and other organic impurities from the desired product **149**.

To resolve this problem, we decided to reverse the order of the final two steps, hydrolysing the methylated product **146** prior to de-tosylation to obtain (+)-Azimic acid. Initially, hydrolysis of the methylated product **146** was carried out using 2 M sodium hydroxide in methanol, but surprisingly, only the acetate group was cleaved giving the ester **152** (Scheme 26).

We then decided to change to a more polar solvent system from methanol to dimethyl sulfoxide. Hence, employing 2 M sodium hydroxide in dimethyl sulfoxide, the methylated product **146** was properly hydrolysed to the carboxylic acid **151**. Although the reaction went to completion, isolation of the product **151** from the solvent dimethyl sulfoxide was difficult. Thus, we thought of using a stronger base, 2 M potassium hydroxide instead of 2 M sodium hydroxide in methanol. To our delight, the reaction went to completion although it took a longer period of time (24 h) the isolation of the product was made easy (Scheme 26).

Scheme 26

From the ^1H NMR spectra of compound **151** it could be seen that the proton H_y alpha to the oxygen has a beautiful doublets of doublets of doublets (ddd) coupling pattern. Therefore, we intended to use it to our advantage to help support our postulation of the major product having an all *cis* stereochemistry. We first utilized the COSY spectra to confirm the chemical shift of the proton H_y alpha to the oxygen (Figure 15). Thereafter, calculating its coupling constants lead us to believe there were two $\text{H}_{\text{eq}}\text{-H}_{\text{ax}}$ (6.9 Hz and 4.4 Hz) and one $\text{H}_{\text{ax}}\text{-H}_{\text{ax}}$ coupling (11.7 Hz) present, which clearly supports our claims (Figure 14).

Figure 14 shows the coupling pattern of the Hy proton of compound **151**.

Figure 15 shows the COSY spectrum of the compound **151**.

We then proceeded with reductive detosylation of the known⁴⁴ sulfonamide **151** using magnesium in methanol,⁵⁴ promoted by ultrasound, to obtain (+)-Azimic acid. The reaction went to completion as judged by the disappearance of the starting material, as the

product (+)-Azimic acid could not be seen clearly on thin layer chromatography plate. Although the reaction went to completion the isolation of the product was very tricky. In hopes of getting an idea on how to isolate (+)-Azimic acid, we did a literature search looking for other groups who ended their synthesis in a similar manner to us. To our surprise, the procedures were complex and in some cases they did not make much practical sense.

Zhou *et al.*¹⁵ utilized sodium naphthalenide to cleave off their tosyl group in their final step towards (+)-Azimic Acid. In their procedure they used methanol to separate the inorganic salts (NH₄Cl, NaCl) which existed in the aqueous layer. Other groups such as Padwa *et al.*,⁴⁴ Naito *et al.*,^{30b} Huang *et al.*⁶ used the same method as well to separate the inorganic salts from the organic product. But when we tried the same method used by all these groups to get rid of the inorganic salts, it was not possible. The inorganic salts were very much soluble in methanol hence, making it hard for clean isolation of the compound. Although (+)-Azimic acid does not have any chromophore in the molecule, and that it is also hard to be visualised in thin layer chromatography, Zhou *et al.*¹⁵ went ahead and purified it using preparative thin layer chromatography with a very polar solvent combination of n-BuOH:EtOH:AcOH:H₂O, 4:2:2:1 as eluant to give (+)-Azmic acid in 85% yield. Also Data *et al.*¹⁴ isolated (+)-Azmic acid in 68% yield with a simple silica gel column chromatography using a solvent combination of methanol:ethyl acetate, 1:24 as eluant. It can be noted that both Zhou *et al.* and Data *et al.* did not mention the R_f of the product and also that Zhou *et al.* did not mention as to what type of material they used for their preparative thin layer chromatography (*e.g.* silica gel or alumina) or how the problem of lack of chromophore was addressed.

Since we found it difficult to visualise (+)-Azmic acid on thin layer chromatography, we thought of an alternative route and proceeded cautiously making sense out of each step to isolate our desired compound. Hence, after the reaction, taking advantage of the fact that

the magnesium salts are almost insoluble in water, we quenched the reaction mixture with water and evaporated it to dryness. Taking it up in water again will ensure almost all magnesium salt that was produced during the reaction can be removed by filtration. To remove any organic impurities, the resulting aqueous layer was acidified with 2 M hydrochloric acid, so that the product will remain in the water layer and washed with dichloromethane. Even after the organic wash, there were some side products which appeared to be sulfonyl salts and other inorganic salts present in the product mixture. Thus, we suggested utilizing the power of ion exchange chromatography, to obtain the product, by washing off the impurities prior to releasing the product.

We chose to use amberlite® CG-50-type 1 which is a crosslinked methacrylic type of weakly acidic cation exchange resin powder. The resins were thoroughly washed with water to remove any impurities, and suspending in a column with water. The product mixture which, after an acidic organic wash, was evaporated to dryness, taken up in small amount of water and added to the resins suspended in water. The rather labile H^+ ions present in the molecule will exchange with the positively charged product allowing it to be held onto to column while the salts and other impurities are washed down with water. Unfortunately the unknown sulfonyl side product was still present in the column even after multiple water washes. Thus, we proceeded on eluting the column with 0.5% aq ammonium hydroxide collecting the eluant in fractions. The individual fractions were then analysed by liquid chromatography-mass spectrometry, to locate and isolate the (+)-Azimic acid fraction according to its mass. The natural product **9** was finally isolated in 59% yield from the ion exchange chromatography. The 1H NMR⁴⁴ and ^{13}C NMR^{40, 44} spectroscopic data and chiroptical data^{6, 11, 14-15, 30b, 36} were in good agreement with those reported for the natural product.

The groups who ended their synthesis with a de-tosylation step did not publish their spectra online, except for Padwa *et al.*,⁴⁴ thus comparing his 1H NMR spectrum (Figure

16) to our ^1H NMR spectrum (Figure 17) it can be said that our isolation technique works well.

Figure 16 shows the ^1H NMR spectrum of azimic acid isolated by Padwa *et al.*

Figure 17 shows the ^1H NMR spectrum of azimic acid isolated by us.

3.4. Conclusion

We have demonstrated the use of the hydroformylation-dihydroxylation sequence for the stereoselective synthesis of 2,3,6-trisubstituted piperidines. The synthesis of (+)-Azimic acid has been achieved in a 10-step sequence from phenylglycinol with 8 % overall yield, employing the less common strategy of installing the majority of the substituents after ring formation. The synthesis further illustrates the utility of hydroformylation as a tool for C–C bond formation in organic synthesis, and the value of ene-sulfonamides as synthetic intermediates.^{24c}

3.5. Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane and acetonitrile were dried by distillation from CaH₂ immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh. ¹H NMR spectra were recorded at 300, 400 or 500 MHz in CDCl₃ solutions. ¹³C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz. Chemical shifts are recorded in parts per million and coupling constants are recorded in hertz. Optical rotations are given with units of 10⁻¹ deg cm² g⁻¹. Rotations were measured at a wavelength of 589 nm. Enantiomeric excess was determined by chiral HPLC analysis, using a Diacel IC column, eluting with IPA/hexane.

134

(4S)-2-(Pent-4-en-1-yl)-4-phenyloxazolidine (134). Hex-5-enal (0.16 g, 1.60 mmol) was added to a mixture of (S)-phenylglycinol (0.2 g, 1.46 mmol) and MgSO_4 (1.75 g, 14.60 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight, filtered, evaporated to give the crude oxazolidine **134** (0.32 g, quant.) as a 1:1 mixture of diastereoisomers and as a yellowish oil. ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.20 (m, 5H), 5.88-5.76 (m, 1H), 5.03 (d, $J=17.4$ Hz, 1H), 4.97 (d, $J=10.1$ Hz, 1H), 4.60-4.54 (m, 1H), 4.51 (app. t, $J=7.0$ Hz, 0.5H), 4.38 (app. t, $J=7.5$ Hz, 0.5H), 4.29 (app. t, $J=7.9$ Hz, 0.5H), 4.12 (app. t, $J=7.7$ Hz, 0.5H), 3.68 (app. t, $J=7.6$ Hz, 0.5H), 3.60 (dd, $J=8.2, 6.6$ Hz, 0.5H), 2.21-2.04 (m, 2H), 1.95-1.45 (m, 4H).

131

(S)-2-((R)-Nona-1,8-dien-4-ylamino)-2-phenylethanol (131). Allyl bromide (0.53 mL, 6.07 mmol) was added slowly via syringe pump over 3 h to a mixture of indium powder (465 mg, 4.05 mmol) and crude oxazolidine **134** (440 mg, 2.02 mmol) in methanol (10 mL) at -10 °C and the mixture was stirred for another 6 h. The mixture was diluted with 10% aqueous NaHCO_3 (10 mL), extracted with ethyl acetate (15 mL x 3), dried (MgSO_4), filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give homoallylic amine **131** (350 mg, 66%) as a yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 3326, 1639; ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.22 (m, 5H), 5.88-5.62 (m, 2H), 5.14-5.03 (m, 2H), 4.98-4.86 (m, 2H),

3.88 (dd, $J=8.6, 4.6$ Hz, 1H), 3.66 (dd, $J=10.6, 4.5$ Hz, 1H), 3.47 (dd, $J=10.6, 8.7$ Hz, 1H), 2.60-2.47 (m, 1H), 2.26-2.12 (m, 2H), 1.96-1.84 (m, 2H), 1.45-1.20 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 141.2, 138.7, 135.1, 128.6, 127.6, 127.4, 117.4, 114.6, 66.9, 61.7, 53.6, 37.6, 34.2, 33.7, 25.1; MS (ESI+) m/z 259 ($[\text{M}+\text{H}]^+$, 100); HRMS calcd for $\text{C}_{17}\text{H}_{25}\text{NO}$ ($[\text{M}+\text{H}]^+$) 260.2014, found 260.2025; $[\alpha]_{\text{D}}^{21} +82.3$ (c 1.1, CHCl_3).

133

(R)-N-Tosylnona-1,8-dienyl-4-amine (133). Lead tetraacetate (1.46 g, 3.29 mmol) was added to a solution of aminoalcohol **131** (711 mg, 2.74 mmol) in dry $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1, 20 mL) at 0 °C and the mixture was stirred until confirmed complete by TLC (30 min). Hydroxylamine hydrochloride (1.90 g, 27.4 mmol) was added to the mixture and it was stirred for another 30 min at 0 °C. The solvents were evaporated under reduced pressure. The residue was washed with hexane (15 mL x 3), then suspended in CH_2Cl_2 (20 mL) and filtered. The filtrate was concentrated in vacuo. The residue was taken up in dry CH_2Cl_2 (20 mL), Et_3N (0.76 mL, 5.48 mmol), TsCl (575 mg, 3.02 mmol) and DMAP (33 mg, 0.274 mmol) were added and the mixture was stirred overnight. The reaction mixture was then diluted with sat. aq ammonium chloride (20 mL), extracted with ethyl acetate (20 mL x 3), dried over MgSO_4 , filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexane to give sulfonamide **133** (510 mg, 64% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 3279, 1641, 1322, 1156; ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, $J=8.1$ Hz, 2H), 7.29 (d, $J=8.1$ Hz, 2H), 5.68 (ddt, $J=16.1, 11.1, 6.7$ Hz, 1H), 5.55 (ddt, $J=17.3, 10.1, 7.3$ Hz, 1H), 5.16-

4.79 (m, 4H), 4.32 (d, $J=7.9$ Hz, 1H), 3.33-3.24 (m, 1H), 2.43 (s, 3H), 2.10 (app. t, $J=6.4$ Hz, 2H), 1.93 (app. q, $J=6.9$ Hz, 2H), 1.52-1.17 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.3, 138.3, 138.3, 133.4, 129.7, 127.2, 118.9, 114.8, 53.3, 39.2, 34.0, 33.3, 24.7, 21.6; MS (ESI+) m/z 293 ($[\text{M}+\text{H}]^+$, 100), 316 ($[\text{M}^++\text{Na}]$, 71); HRMS Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 294.1528, found 294.1537; $[\alpha]_D^{22} +3.0$ (c 1.35, CHCl_3).

138

6-((R)-1,2,3,4-Tetrahydro-1-tosylpyridin-2-yl)hexanal (138). Sulfonamide **133** (440 mg, 1.50 mmol), $\text{Rh}_2(\text{OAc})_4$ (7 mg, 15.0×10^{-3} mmol) and $\text{P}(\text{OPh})_3$ (98 mL, 0.375 mmol) were dissolved in THF (15 mL) in a Fisher-Porter tube. The Fisher-Porter tube was purged (three times) with H_2/CO (1:1) and finally charged with H_2 (30 psi)/ CO (30 psi). The reaction mixture was stirred vigorously at 65°C for 18 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 2% ethyl acetate/hexane to give ene-sulfonamide **138** (300 mg, 60% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 1721, 1645, 1339, 1164; ^1H NMR (400 MHz, CDCl_3) δ 9.77 (t, $J=1.6$ Hz, 1H), 7.66 (d, $J=8.1$ Hz, 2H), 7.29 (d, $J=8.1$ Hz, 4H), 6.57 (d, $J=8.3$ Hz, 1H), 5.09-4.97 (m, 1H), 3.89 (br s, 1H), 2.48-2.38 (m, 2H), 2.41 (s, 3H), 2.01-1.07 (m, 10H), 1.02-0.71 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.0, 143.4, 136.1, 129.7, 127.0, 123.5, 109.7, 52.8, 43.8, 31.3, 28.9, 25.6, 23.0, 22.0, 21.6, 17.3; MS (ESI+) m/z 336 ($[\text{M}+\text{H}]^+$, 100); HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 336.1633, found 336.1634; $[\alpha]_D^{22} -265.8$ (c 1.0, CHCl_3).

139

6-((*R*)-1,2,3,4-Tetrahydro-1-tosylpyridin-2-yl)hexanoic acid (139). NaOH (137 mg, 3.43 mmol) was added to a suspension of Ag₂O (175 mg, 0.754 mmol) in H₂O (5 mL). Aldehyde **138** (230 mg, 0.686 mmol) dissolved in diethyl ether (3 mL) was added and the mixture was stirred overnight. The reaction mixture was acidified with 2M HCl (15 mL), extracted with Et₂O (20 mL x 3), washed with water (20 mL) and brine (20 mL), and dried (MgSO₄), filtered and evaporated to give carboxylic acid **139** (228 mg, 95% yield) as a pale yellowish oil: FTIR (neat, cm⁻¹): $\nu_{\max}$ 2930, 1705, 1646, 1339, 1163; ¹H NMR (400 MHz, CDCl₃) δ 7.66 (d, *J*=8.1 Hz, 2H), 7.29 (d, *J*=8.1 Hz, 2H), 6.58 (d, *J*=8.2 Hz, 1H), 5.08-4.98 (m, 1H), 3.89 (br s, 1H), 2.41 (s, 3H), 2.36 (t, *J*=7.4 Hz, 2H), 1.99-1.16 (m, 11H), 0.97-0.77 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 180.1, 143.4, 136.1, 129.7, 127.0, 123.6, 109.7, 52.9, 34.1, 31.3, 28.9, 25.5, 24.6, 23.0, 21.6, 17.3; MS (ESI+) *m/z* 352 ([M+H]⁺, 100); HRMS calcd for C₁₈H₂₅NO₄S ([M+H]⁺) 352.1583, found 352.1583; $[\alpha]_D^{23}$ -260.2 (c 0.25, CHCl₃).

140

Methyl 6-((*R*)-1,2,3,4-tetrahydro-1-tosylpyridin-2-yl)-hexanoate (140). Methyl iodide (78 mL, 1.25 mmol) dissolved in toluene (10 mL) was added to a solution of carboxylic acid **139** (200 mg, 0.569 mmol) and DBU (0.10 mL, 0.683 mmol) in toluene. The mixture was heated at reflux with vigorous stirring for 3 h. The mixture was filtered, washing with Et₂O (20 mL). The organic layer was washed with water (10 mL), 2 M HCl (10 mL), sat. aq NaHCO₃ (10 mL), water (10 mL) and brine (10 mL), and dried (MgSO₄), filtered and

evaporated. The crude product was purified by flash chromatography on silica gel eluting with 20% ethyl acetate/hexane to give ene-sulfonamide **140** (189 mg, 91% yield) as a colourless oil: FTIR (neat, cm^{-1}): ν_{max} 1734, 1645, 1340, 1163; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J=8.3$ Hz, 2H), 7.28 (d, $J=8.3$ Hz, 2H), 6.57 (dd, $J=8.2, 0.8$ Hz, 1H), 5.06-4.98 (m, 1H), 3.89 (br s, 1H), 3.67 (s, 3H), 2.41 (s, 3H), 2.31 (t, $J=7.5$ Hz, 2H), 1.98-1.21 (m, 11H), 0.96-0.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 143.4, 136.3, 129.8, 127.1, 123.7, 109.7, 53.0, 51.6, 34.2, 31.4, 29.1, 25.6, 25.0, 23.1, 21.7, 17.4; MS (ESI+) m/z 366 ($[\text{M}+\text{H}]^+$, 100), 388 ($[\text{M}+\text{Na}]^+$, 15); HRMS calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 366.1739, found 366.1735; $[\alpha]_{\text{D}}^{23}$ -173.4 (c 0.4, CHCl_3).

141

Methyl 6-((2R,5S,6S)-5,6-dihydroxy-1-tosylpiperidin-2-yl)- hexanoate (141).

Methane-sulfonamide (62 mg, 0.657 mmol) was added to a solution of ene-sulfonamide **140** (240 mg, 0.657 mmol) in THF (4.50 mL), and the mixture was stirred until it was completely dissolved. NMO (50% w/w) (0.40 mL, 1.97 mmol), H_2O (0.50 mL) and K_2OsO_4 (24 mg, 65.7×10^{-3} mmol) were added to the solution, and the mixture was stirred overnight. The mixture was quenched with sat. aq $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL), washed with water (10 mL), brine (10 mL), dried (MgSO_4), filtered and evaporated to give diols **141** (228 mg, 87% yield) as a yellowish oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 3475, 1734, 1327, 1159; ^1H NMR (400 MHz, CDCl_3 , major diastereoisomer) δ 7.69 (d, $J=8.2$ Hz, 2H), 7.29 (d, $J=8.2$ Hz, 2H), 5.40 (app. t, $J=3.1$ Hz, 1H), 3.92-3.77 (m, 1H), 3.67 (s, 3H), 3.51 (d, $J=2.8$ Hz, 1H), 3.34-3.21 (m, 1H), 2.42 (s, 3H), 2.31 (t, $J=7.5$ Hz, 2H), 1.97-1.19 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , major diastereoisomer) δ 174.5, 143.6, 138.3, 129.9, 126.9, 78.4, 69.3, 52.5, 51.7, 34.1, 34.1,

29.0, 27.0, 26.6, 24.9, 22.5, 21.6; MS (ESI+) m/z 382 ($[M^+ - OH]$, 100), 422 ($[M+Na]^+$, 40); HRMS calcd for $C_{19}H_{29}NO_6S$ ($[M+H]^+$) 400.1794 found 400.1803.

144

Methyl 6-((2*R*,5*S*,6*S*)-5,6-diacetoxy-1-tosylpiperidin-2-yl)-hexanoate (144). Acetic anhydride (0.25 mL, 2.64 mmol), triethylamine (0.42 mL, 3.00 mmol) and DMAP (7 mg, 6.01 x 10⁻² mmol) were added to a solution of diols **141** (240 mg, 0.601 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 3 h. The reaction mixture was diluted with sat. aq NH_4Cl (20 mL), extracted with CH_2Cl_2 (15 mL x 3), washed with water (20 mL) dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 25% ethyl acetate/hexane to give diacetates **144** (280 mg, 97% yield) as a colourless oil and as an inseparable mixture of diastereoisomers: FTIR (neat, cm^{-1}): ν_{max} 1738, 1346, 1240, 1162; 1H NMR (400 MHz, $CDCl_3$, major diastereoisomer) δ 7.71 (d, $J=8.3$ Hz, 1H), 7.29 (d, $J=8.3$ Hz, 1H), 6.78 (d, $J=3.8$ Hz, 1H), 4.59 (dt, $J=12.1$, 4.2 Hz, 1H), 3.96-3.87 (m, 1H), 3.66 (s, 3H), 2.41 (s, 3H), 2.29 (t, $J=7.5$ Hz, 2H), 2.02 (s, 3H), 1.96 (s, 3H), 1.80-1.13 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereoisomer) δ 174.2, 170.0, 169.2, 143.9, 137.8, 129.9, 127.2, 76.0, 69.7, 52.6, 51.6, 34.1, 33.2, 29.1, 26.9, 26.4, 24.9, 21.7, 21.1, 20.9, 19.3. MS (ESI+) m/z 424 ($[M^+ - OAc]$, 100), 506 ($[M+Na]^+$, 54); HRMS calcd for $C_{23}H_{33}NO_8S$ ($[M+Na]^+$) 506.1825 found 506.1824.

146

Methyl 6-((2*R*,5*S*,6*S*)-5-acetoxy-6-methyl-1-tosylpiperidin-2-yl) hexanoate (146).

Trimethylaluminium (0.22 mL of a 2 M solution in toluene, 0.447 mmol) was added dropwise to a solution of diacetates **144** (180 mg, 0.372 mmol) in CH₂Cl₂ (5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 1 h. The reaction was quenched with water (10 mL), extracted with CH₂Cl₂ (15 mL x 3), washed with water (20 mL), dried over MgSO₄, filtered and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/hexane to give acetate **146** (120 mg, 73% yield) as a pale yellowish oil: FTIR (neat, cm⁻¹): $\nu_{\max}$ 1736, 1337, 1238, 1164; ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, *J*=8.2 Hz, 2H), 7.28 (d, *J*=8.2 Hz, 2H), 4.44-4.24 (m, 2H), 3.91 (app. q, *J*=6.8 Hz, 1H), 3.66 (s, 3H), 2.40 (s, 3H), 2.31 (t, *J*=7.5 Hz, 2H), 2.00 (s, 3H), 1.81-1.30 (m, 12H), 1.25 (d, *J*=6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 170.2, 143.2, 138.7, 129.9, 126.8, 70.8, 52.1, 51.6, 49.6, 35.1, 34.1, 29.1, 27.0, 26.9, 24.9, 21.7, 21.2, 19.6, 15.8; MS (ESI+) *m/z* 440 ([M⁺+H], 100), 462 ([M⁺+Na], 13); HRMS calcd for C₁₈H₂₅NO₄S ([M+H]⁺) 440.2107, found 440.2109; [α]_D²³ +16.7 (c 0.3, CHCl₃).

147

Methyl 6-((2*R*,5*R*,6*S*)-5-acetoxy-6-methyl-1-tosylpiperidin-2-yl) hexanoate (147).

Colourless crystalline solid: FTIR (neat, cm⁻¹): $\nu_{\max}$ 1733, 1329, 1243, 1159; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J*=7.8 Hz, 2H), 7.26 (d, *J*=7.8 Hz, 2H), 4.63 (s, 1H), 4.13-3.88 (m, 2H), 3.67 (s, 3H), 2.39 (s, 3H), 2.31 (t, *J*=7.7 Hz, 2H), 1.98-1.12 (m, 18H). ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 170.2, 142.7, 139.1, 129.5, 127.2, 70.5, 52.6, 51.9, 51.6, 35.6, 34.1, 29.1, 27.1, 24.9, 21.5, 21.3, 21.0, 20.9, 18.7; MS (ESI+) *m/z* 440

($[M+H]^+$, 100), 462 ($[M+Na]^+$, 13); HRMS Calcd for $C_{18}H_{25}NO_4S$ ($[M+H]^+$) 440.2107, found 440.2101; mp 96-99 °C; $[\alpha]_D^{24} +7.4$ (c 0.79, $CHCl_3$).

151

6-((2R,5S,6S)-5-Hydroxy-6-methyl-1-tosylpiperidin-2-yl)-hexanoic acid (151).⁴⁴

Potassium hydroxide (3 mL of a 2 M aqueous solution, 6 mmol) solution was added to a solution of acetate **146** (0.1 g, 0.227 mmol) in MeOH (1 mL). The mixture was stirred at room temperature for 24 h. The volatiles were evaporated. The remaining aqueous layer was washed with CH_2Cl_2 (10 mL), acidified with 2 M HCl (10 mL) and extracted with CH_2Cl_2 (15 mL x 3). The combined organic layers were washed with brine (20 mL), and dried ($MgSO_4$), filtered and evaporated to give carboxylic acid **151** (84 mg, 97% yield) as a colourless oil: 1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, $J=8.2$ Hz, 2H), 7.26 (d, $J=8.2$ Hz, 2H), 4.17 (app. quin., $J=6.9$ Hz, 1H), 3.98-3.88 (m, 1H), 3.36 (ddd, $J=11.7, 6.9, 4.4$ Hz, 1H), 2.41 (s, 3H), 2.35 (t, $J=7.3$ Hz, 2H), 1.75-1.30 (m, 12H), 1.24 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.6, 22.9, 24.7, 27.1, 27.3, 29.0, 34.0, 34.9, 51.9, 52.3, 69.0, 126.8, 129.8, 138.8, 143.1, 179.5. MS (ESI+) m/z 384 ($[M+H]^+$, 100); HRMS calcd for $C_{19}H_{29}NO_5S$ ($[M+H]^+$) 384.1845, found 384.1836; $[\alpha]_D^{23} -5.13$ (c 0.23, EtOAc).

9

Azimic acid (9). Mg turnings (13 mg, 0.52 mmol) were added to a solution of tosylpiperidinol **151** (20 mg, 0.052 mmol) in MeOH (3 mL) as the reaction mixture was

sonicated (ultrasonic cleaning bath). The addition of Mg turnings was repeated till complete consumption of the starting material as judged by TLC. The reaction mixture was quenched with water (10 mL), evaporated to remove methanol, taken up in water (10 mL) again and filtered to remove the insoluble magnesium salts. The resulting aqueous layer was acidified with 2 M HCl washed with CH₂Cl₂ (10 mL x 3), evaporated till dryness. The crude product was taken up in water and loaded onto a column of water washed amberlite[®] CG-50-type 1 ion exchange resin (4 g) suspended in water, and further washed with water (100 mL). The resin column was eluted with 0.5% aq NH₄OH collecting the fractions containing azimic acid as identified by LCMS, to give azimic acid 1 (7 mg, 59% yield) as a yellowish solid: ¹H NMR (400 MHz, MeOD) δ 3.83 (br s, 1H), 3.23 (br q, *J*=6.9 Hz, 1H), 3.10-3.00 (m, 1H), 2.17 (t, *J*=7.2 Hz, 1H), 2.00-1.90 (m, 1H), 1.85-1.34 (m, 11H), 1.33 (d, *J*=6.5 Hz, 3H). ¹³C NMR (100 MHz, MeOD) δ 15.9, 23.7, 25.8, 27.0, 30.0, 31.0, 34.5, 38.6, 57.4, 58.5, 65.9, 182.5; MS(ESI+) *m/z* 230 ([M+H]⁺, 100); HRMS calcd for C₁₂H₂₃NO₃ ([M+H]⁺) 230.1756, found 230.1758; mp 216-219 °C [lit. 214-215 °C,¹¹ 210-214 °C,¹⁵ 217 °C,^{30b} 209-211 °C,¹⁴ 212-214 °C⁶]; [α]_D²³ +7.7 (c 0.37, MeOH) [lit. +8 (MeOH),¹¹ +7.6 (c 1.1, MeOH),⁹ +7.9 (c 1, MeOH),^{14,15} +7.4 (c 0.52, MeOH),^{30b} +7.7 (c 0.5, MeOH)⁶].

135

(4S)-3-(Nona-1,8-dien-4-yl)-2-(pent-4-en-1-yl)-4-phenyloxazolidine (135). Pale yellow oil: FTIR (neat, cm⁻¹): ν_{max} 2920, 2851, 1639, 908; ¹H NMR (400MHz, CDCl₃) δ 7.35-7.23 (m, 5H), 5.91-5.61 (m, 3H), 5.28 (t, *J*=7.2 Hz, 1H), 5.13-4.83 (m, 6H), 3.77 (dd, *J*=6.8, 4.7 Hz, 1H), 3.69 (dd, *J*=10.5, 4.6 Hz, 1H), 3.49 (dd, *J*=10.5, 6.9 Hz, 1H), 3.08 (t,

$J=6.4$ Hz, 1H), 2.25 (t, $J=6.5$ Hz, 2H), 2.14-1.77 (m, 10H), 1.50-1.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 141.8, 139.9, 138.9, 138.7, 135.8, 128.6, 127.8, 127.6, 127.3, 117.0, 114.7, 114.6, 65.7, 61.5, 61.4, 38.9, 33.7, 33.6, 29.2, 28.0, 27.2; MS (ESI+) m/z 340 ($[\text{M}+\text{H}]^+$, 100).

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CHAPTER 4

Syngas-Mediated C-C Bond Formation in Flow: Selective Rhodium-Catalysed Hydroformylation of Styrenes

4.1. Introduction to Flow Chemistry

Flow chemistry and related continuous processing techniques have become more widespread, thus having an increasingly significant impact on how chemistry is carried out in a typical laboratory setting.¹⁻¹⁰ Being referred to as the new paradigm of chemical synthesis,¹¹⁻¹³ flow chemistry stands out, not only as providing clear advantages compared to batch chemistry,^{1,3-9,14-20} but also offering solutions to problems associated with batch processes.²¹⁻²⁵ This technology also gives rise to the possibility of using inline purification techniques such as scavenging²⁶ and phase-switching¹⁰ that can potentially eliminate labour intensive and repetitive operations.²⁷⁻³²

One advantage of flow chemistry is that at any point of time, only small volumes of reactive materials (reagents and reactants) are being processed through a small reaction zone. This mitigates the impact of any hazard that could be caused by harsh reaction conditions (e.g. high pressure or temperature) and also provides an advantage towards processes which are dependent on interfacial phenomena (e.g. heat transfer and mixing). In addition, since the flow process is also continuous, accumulation of any explosive or toxic intermediates can be avoided. It should also be noted that the high surface-area /volume ratio (attained due to small dimensions of the reaction zone) makes handling of the interfacial phenomena more precise and reliable. All of these factors greatly enhance the overall safety profile of this technique.^{11-13,33,34}

Scaling up reactions in batch processes may compromise the safety such as Mechanical failure and unexpected venting of toxic and/or flammable gases. These issues can be avoided by switching to flow chemistry. Unlike batch process chemistry, the scale up in flow is greatly simplified due to the fixed morphology and dimensions of the reaction zone.^{12,33} This can be achieved either by parallelization of the reaction through multiple

identical paths or by increasing the run-time of the reaction. By doing so, it suppresses the damages that could be caused by hazards occurring during scale up.

4.1.1. Components in a Typical Flow Setup for a Gas/Liquid Phase Reactions (One-Loop System)

Gas-liquid phase reactions are made possible in flow by incorporating a tube-in-tube reactor in the system. A flow system can be erected according to the needs of the reaction of interest. A simple one-loop system incorporating a tube-in-tube reactor is as shown below in Figure 1.

Figure 1 shows the set-up of an One-Loop-System.

Section **A** of Figure 1 represents the pumping mechanism which is used to pump the desired solvent across the whole flow system. This pump controls the overall flowrate of the whole system.

Section **B** of Figure 1 represents the sample loop. The length of the sample loop can be varied to accommodate the volume of reactants that is required for the reaction. PEEK

(Poly-Ether-Ether-Ketone) tubing is typically used for sample loops as it is a chemically inert and a mechanically strong polymer, but downside of it is its opacity. Alternatively, PTFE (Poly-Tetra-Fluoro-Ethylene) tubing can be used as it is translucent.

Section **C** of Figure 1 represents the gas tank of the gas which is required for the reaction of interest. The pressure of the gas at any point of time present in the tube-in-tube reactor is controlled here.

Section **D** of Figure 1 represents the tube-in-tube reactor (Figure 4), where the gas phase comes into contact with liquid phase.

Section **E** of Figure 1 represents the additional residence loop. This loop can be made of stainless steel, PEEK (Poly-Ether-Ether-Ketone) or PTFE tubing. Increasing the length of the residence loop increases the reaction time of the reaction and vice-versa. If necessary, the residence loop can be raised to the desired temperature.

Section **F** of Figure 1 represents a back pressure regulator (BPR). The back pressure regulator (BPR) is usually placed at the end of a stream. It is essential as it creates a pressure difference that helps to keep the gas dissolved in the carrier liquid stream, hence this prevents outgassing that results in the formation of segmented flow (Figure 2), maintaining a homogenous solution which leads to a predictable and consistent relationship between the dissolved gas concentration and the flow parameters (e.g. flowrate and pressure).

Figure 2 shows a segmented flow in a tube.

4.1.2. Tube-in-Tube Reactor

The reactions between a gas phase and a liquid phase has gone through a number of milestones. Many researchers focused on segmented flow where the separate gas and liquid streams are mixed to form isolated plugs of liquid and gas.³⁵⁻⁵¹ For segmented flow, the extent of reaction and its reproducibility are dependent on the linear relationship between the flow rate and morphology of the interface. Hence, there was a struggle to achieve accurate and dependable control of the interfacial processes deterring the progress of research in this area.¹¹ Recently, to improve the mechanical mixing of this dual phase reaction, researchers turned to engineering solutions to achieve greater interfacial surface areas.^{35-42,44-48,52-57} However, most of these solutions require fabrication techniques that surpass the capability of most synthesis laboratories as they often turn out to be technically quite complex.¹¹

To overcome the above mentioned issues and in the hopes of providing a more controlled, accessible and consistent solution towards gas liquid contact, Ley *et al.*^{11-13,33,34,58-60} suggested the use of a gas-permeable polymer membrane (AF-2400) to generate homogenous gas solutions in flow synthesis. Teflon AF-2400 is an extensively microporous and amorphous membrane that is a co-polymer of Tetrafluoroethylene (TFE) and 2,2-bis(trifluoromethyl)-4,5-difluoro-1,3-dioxole (Figure 3). It exhibits not only a broad chemical resistance associated with PTFE (polytetrafluoroethylene) but also has very high gas permeability to a wide range of gases and it is practically impermeable to liquids.^{61 62}

Figure 3 shows the structure of AF-2400.

By placing Teflon AF-2400 tubing concentrically with another outer pressure-containing tube such as PTFE (Poly-Tetra-Fluoro-Ethylene), *Ley et al.* constructed compact tube-in-tube reactors (Figure 4). This design efficiently reduces the volume of pressurised gas required at any point of time enhancing its safety profile. The gas can be in the inner tube (Teflon AF-2400) with the liquid in the outer tube (PTFE), or vice-versa.

Figure 4 shows the tube-in-tube reactor in detail.

It should be noted that there is a cheaper and more widely available elastomeric polymer, PDMS (polydimethylsiloxane) that is also permeable to several gases and has been

successfully applied in preparative gas-liquid flow chemistry.⁶³⁻⁶⁶ While PDMS (polydimethylsiloxane) has its advantages, it also has its drawbacks such as lack of chemical resistance, mechanical strength and swelling severely in multiple organic solvents, hence limiting the number of reaction cycles through which they can operate. On the other hand, Teflon AF-2400 tubing can be used in tube-in-tube reactors for several hundred runs without being significantly affected physically and also without affecting the reaction conversion and yield.^{11-13,33,34,58-60}

4.2. Review of Reactions in Flow Utilizing Tube-in-Tube Reactors

4.2.1. Heck Reactions with Ethylene Gas

Styrenes are known to be useful intermediates in synthesis.⁶⁷⁻⁷¹ However, due to a general reluctance of research laboratories to use reactive gases, the development of a practical ethylene Heck process^{72,73} has been hampered (Scheme 1).

Scheme 1 shows a general ethylene Heck process

Ley *et al.*⁷⁴ showed that by carrying out the Heck reaction as a flow process, the safety issues regarding the use of pressurised ethylene gas can be mitigated (Figure 5).

Figure 5 shows a typical ethylene Heck flow process.

After a thorough screening of the Heck-type reaction in their flow system using 3-iodoanisole **1a** as the substrate, they achieved the optimum reaction conditions for their system (Table 1, entry 9). They went on to evaluate the scope of this process by screening substrates with hydroxyl, electron withdrawing and electron donating substituents (Table 2).

Entry	Ligand (mol%)	Additive (equiv)	Conv. (%)
1^a	XantPhos (6)	-	36
2^a	JohnPhos (12)	-	46
3^a	SPhos (12)	-	5
4^a	XPhos (12)	-	10
5^a	<i>t</i> -Bu ₃ P (15)	-	25
6^{a,c}	Ph ₃ P (15)	-	-
7^{a,d}	JohnPhos (12)	-	54
8^{a,d}	JohnPhos (12)	<i>n</i> -Bu ₄ NOAc (1)	60
9^{a,d}	JohnPhos (12)	<i>n</i> -Bu ₄ NI (1)	96

Table 1 Optimisation of the Reaction : ^a Et₃N (2 equiv), Pd(OAc)₂ (5 mol%), dioxane (0.1 M), 120°C, 50 min, ethylene (15 bar); ^b Conversions determined by ¹H NMR analysis; ^c No reactions was observed; ^d DMF in dioxane (1:4) was used as solvent.

Entry	Substrate	Product	Yield ^a (conv.)
1	1a		80% (94%)
2			83% (99%)
3			71% (82%)
4			73% (87%)
5			85% (98%)
6			43% (60%)
7			78% (88%)
8			76% (94%)
9			75% (92%)
10			81% (95%)

Table 2 Reaction conditions: Aryl iodide (0.5 mmol), Et₃N (2 equiv), Pd(OAc)₂ (5 mol%), JohnPhos (12 mol%), TBAI (1 equiv), DMF in toluene (1:4), 120°C, 20 min, 1 mL/min, ethylene (15 bar), AF-2400 (0.7 m). ^b Isolated yield after distillation

Following this success, they took it a step further by telescoping the first Heck process to a second Heck reaction (Figure 6). Reinvestigating the Heck reaction with *t*-Bu₃P as the ligand, they found that in the presence of TBAI and Cy₂NMe, the reaction gave similar or even better conversions than JhonPhos without the formation of Pd black. Hence with the newly found conditions, they used *t*-Bu₃P as the ligand to perform their initial Heck reaction. Following this, they degassed the product stream of the initial Heck reaction with excess argon gas and merged it with another stream of Ar²I (1 equiv) before passing it through a second heated reaction coil to effect a second Heck cross-coupling reaction (Table 3).

Figure 6 shows the flow step for two consecutive Heck reactions.

Entry	Substrate	Product	Yield ^a (conv.)
1			72% (92%)
2			73% (81%)
3			68% (92%)
4			(25%) ^b

Table 3 ^aIsolated yield after distillation. ^b 99% conversion into 4-vinyl styrene; however, poor olefin reactivity gave low stilbene conversion.

Ley *et al.*⁷⁴ managed to design an efficient ethylene Heck and double ethylene heck flow process towards generating functionalised styrenes and unsymmetrical stilbenes respectively. Another advantage of flow chemistry, is that reactions can easily be telescoped with other reactions, like for example this ethylene Heck reaction was telescoped with hydroformylation in flow chemistry to generate branched aldehydes.⁷⁵ This process not only minimizes exposure of harmful gases but also mitigates safety issues regarding the use of pressurised gases as the volume of gas occupying the reactor at any given instance does not exceed 1-2 mL.

4.2.2. Carboxylation

Using a commercially available Vapourtec R2+ unit⁷⁶ to control the flowrate of the reagent, Ley *et al.*⁵⁹ carried out carboxylation, efficiently converting the Grignard reagents to the corresponding carboxylic acids. They optimized the reaction parameters

by studying the conversion of substrate **2a** to 3,5-dimethoxybenzoic acid **2b** (Figure 7). Hence, they achieved high conversions with a flowrate of $400\ \mu\text{L min}^{-1}$, a CO_2 pressure of 4 bar with a short residence time of 42 seconds.

Figure 7 shows the carboxylation flow set-up.

They further studied the carboxylation of various Grignard reagents using their optimal conditions with the flow setup as shown in Figure 8.

Figure 8 shows the carboxylation flow step-up incorporating in-line purification *via* the “catch and release” protocol.

The output stream containing the magnesium salt of carboxylic acid was directed through a glass cartridge⁷⁷ loaded with polymer supported sulfonic acid to convert it the corresponding acid form via removal of the magnesium salts. The product was further purified using a “catch and release” protocol. The carboxylic acid was trapped using a polymer-supported ammonium hydroxide (A-900) and released by washing with a solution of formic acid/THF (1:9), after washing off unwanted impurities using THF (Table 4).

Entry	Substrate	Product	Yield
1			93%
2			87%
3			86%
4			100%
5			98%
6			86%
7			100% 98% ^b
8			95%
9			75%
10			100%

Table 4 Carboxylic acids^a prepared under continuous-flow conditions with CO₂: ^a 1 mmol scale, yields of isolated, analytically pure products are reported. ^b yield of isolated product at 20 mmol scale.

It is noteworthy that, the volume of gas occupying the reactor at any given instance does not exceed 1-2 mL. Thus, eliminating the risks and hazards associated with exposure to large amounts of CO₂.

4.2.3. Carbonylations

There are many safety issues regarding the use of carbon monoxide given the toxicity and flammability of this reactive gas. It is also made worse by its odourless and tasteless nature. However, utilization of this gas in flow processes alleviates these safety issues as only 1.2 mL of gas will be present per meter of tubing. Ley *et al.*¹³ went on to prove the capability of the tube-in-tube reactor by performing the transition metal-mediated insertion of carbon monoxide (Figure 9) in flow (Figure 10).

Figure 9 shows the general reaction of transition metal-mediated insertion of carbon monoxide.

Figure 10 shows the flow setup for transition metal-mediated insertion of carbon monoxide.

The combined reagent stream pumped at a rate of 0.1 mL min^{-1} was merged with a third CO enriched stream from the tube-in-tube reactor. The overall combined stream was directed into the heating coils followed by a polymer supported thiourea (QP-TU) cartridge to scavenge the palladium from the product stream. Although they managed to obtain the optimum reaction conditions (entry 6, Table 5) by evaluating the methoxycarbonylation of *m*-iodotoluene (entry 1, Table 6), they decided to carry out further methoxycarbonylation on various other substrates (Table 6) to test the scope of the process with a lower CO pressure that gave a slightly lower conversion (entry 4, Table 5). This is because the tube-in-tube reactor was a prototype and it was not fully tested for safety at that time. When they were confident about the robustness of their tube-in-tube prototype later on, they used CO pressures of up to 15 bar for some of the reactions in Table 6 (entries 6, 8, 11, 12, 14, 15, Table 2) but with the added precaution of only charging the tube-in-tube reactor with CO periodically as it was adequate to maintain constant pressure for several hours.

Entry	Pd(II)/L (mol %)	CO (bar)	Pump a = b (mL min ⁻¹)	Pump c (mL min ⁻¹)	Coils d total (mL)	Coils d (°C)	Conv. (%)
1	2.5/5	7	0.1	0.1	20	100	18
2	2.5/5	7	0.1	0.6	20	100	73
3	2.5/5	7	0.1	0.6	30	100	86
4	2.5/3.0	7	0.1	0.6	30	100	86
5	2.5/3.0	7	0.1	0.6	30	70	80
6	2.5/3.0	10	0.1	0.6	30	100	90

Table 5

Entry	Substrate (a)	Product (b)	Solvent ^a	Yield ^b (Conv. ^c)
1			A	70 (85)
2			A	63 (78)
3			A	81 (95)
4			A	88 (95) ^d
5			A	(11) ^e
6			A B	38 (95) ^f 83 (100) ^{g, h}
7			A	93 (95)

8			B	69 (77)
9			A	72 (90)
10			A	71 (85)
11			A B	43 (60) ^e 65 (73) ^{h, j}
12			B	62 (88) ^{h, j}
13			B	62 (100) ^j
14			B	81 (100) ^{i, k}
15			B	72 (94) ^{h, i, j, l} 77 (90) ^{h, i, j}

Table 6 ^a A = PhMe : MeOH : DMF 45 : 45 : 10, B = dioxane : MeOH 1 : 1. ^b isolated yield after column chromatography on silica gel. ^c conversion based on signals from product and starting material in ¹H NMR spectrum of crude product material (no reference compound was added). ^d Substrate and base were introduced in DMF. ^e Rapid Pd(0) precipitation observed. ^f Reaction performed at 50°C, side products observed. ^g Reaction performed at 25°C, 15 bar CO, no xantphos, 5 mol% Pd(OAc)₂. ^h No thiourea cartridge used. ⁱ 5 mol% Pd(OAc)₂/6 mol% xantphos used. ^j 15 bar CO used and 30 mol% hydrazine (from 1.0 M THF solution) added. ^k reaction performed at 25 °C, 15 bar CO. ^l reaction performed at 120 °C.

In addition, they studied the absorption of CO gas into the liquid stream using an in-line IR measurement device. They quantified the gas concentration of CO via the intensity of

the peak at 2133 cm^{-1} . By fixing the flowrate at 0.6 mL min^{-1} and increasing the pressure they found that the relative peak intensity at 2133 cm^{-1} also increases, indicating that the CO gas concentration increases with increasing pressure of CO gas. However, it starts to reach saturation point at about 9 bar of CO gas pressure.

When the CO gas pressure was fixed at 7 bar, they found that the concentration of CO gas in the solvent stream is independent of flowrates below 1.0 mL min^{-1} .

4.2.4. Hydrogenation

Reduction reactions are very widely used by synthetic organic chemist, in industries and in academic research laboratories. One of the important reagents used in this reaction is hydrogen gas. As much as it is an important reagent, it is also as dangerous due to its highly flammable nature (especially in the presence of the catalyst), not to mention the explosive mixtures it forms with oxygen. Standard batch chemistry would require using hydrogen in large quantity and in high pressures, but in flow chemistry these threats can be mitigated.

Initially, Ley *et al.*⁶⁰ utilized Crabtree's catalyst **4** and ethyl cinnamate **3a** as the substrate to evaluate homogenous catalysis in flow chemistry.⁷⁸ Having a setup as shown in Figure 11 below, they were able to easily vary the amount of substrates and catalyst introduced into the system as well as to vary the reaction time by varying the length of the additional residence loop.

Figure 11 shows the flow setup for homogenous hydrogenation.

They found that the conversion was strongly dependent on the volume of the additional residence loop indicating that longer reaction time leads to higher conversion. The conversion will eventually plateau at about 70% at higher volumes (residence time of more than 150 seconds). They also found that the conversion rate was highly pressure dependant, as the reaction achieved complete conversion at 30 bar of hydrogen.

Coming to a compromise with their findings on the reaction parameters, they carried out hydrogenation on a series of other alkenes using hydrogen pressure of 25 bar and with a combined flowrate of 1.4 mL min^{-1} and 0.002 equiv. of catalyst (Table 7).

Entry	Substrate	Product	Yield ^a (conv.) ^b
1			Quant. (100)
2			Quant. (100)
3			Quant. (100)
4			Quant. (100)
5			Quant. (100)
6			Quant. (100)
7			Quant. (100)
8			Quant. (100)

Table 7 ^a Isolated yield after removal of solvent. ^b Conversion to product based on ¹H NMR.

Ley *et al.*⁶⁰ also proved the capability of this system to run heterogenous catalytic hydrogenation by using a similar setup but with an omnifit glass column (packed with 250 mg of 10% palladium on carbon catalyst, 7.7 mol % wrt substrate) installed between the tube-in-tube reactor and the back-pressure regulator (BPR). Similarly, they found that the conversion rate varied linearly with hydrogen pressure, hence an increase in pressure will lead to an increase in percentage conversion.

Due to the fact that the reactor being used was a prototype and not fully tested, they avoided utilizing high pressures to attain complete conversions but instead they recycled the product stream back into the system by placing the pump inlet in the product collection flask (Figure 12).

Figure 12 shows the recycling flow setup for heterogeneous hydrogenation.

Utilizing this recycling configuration, a series of alkenes were reduced on a 5 mmol scale under 15 bar of hydrogen gas pressure with a larger cartridge of catalyst (750 mg, 0.71 mmol Pd, 14% wrt substrate) (Table 8).

Entry	Substrate	Product	Yield ^a (Time) ^b
1			Quant. (125) Quant. (360) ^c
2			Quant. (130)
3			Quant. (120)
4			Quant. (115)
5			Quant. (120)
6			Quant. (250)
7			Quant. (108)
8			Quant. (110)

Table 8 ^a Isolated yield after removal of solvent. ^b Time (in minutes) for complete conversion as monitored by return of outgassing and/or TLC/NMR analysis, reactions performed on 5 mmol unless otherwise stated. ^c Reaction performed on a 60 mmol scale (10.49g).

Overall, the safety profile of homogenous hydrogenation reaction is improved as the volume of gas occupying the tube-in-tube reactor at any given instance is much lower than a traditional batch process. Heterogeneous hydrogenation in flow required high pressures to possibly attain complete conversion. Due to the tube-in-tube reactor still

being in testing stage, increment of pressure was not advisable; hence an alternative solution of recycling the product stream was introduced. Although, this method gave complete conversions, it required a longer period of time as well as monitoring of the reaction process by TLC and ^1H NMR analysis.

4.3. Results & Discussion

So far, we have discussed about single gas reactions such as Heck reaction (ethylene gas), carboxylation (carbon dioxide), carbonylation (carbon monoxide), hydrogenation (hydrogen). Hence, in efforts to look into dual gas reactions, we decided to introduce hydroformylation in flow which requires the use of both carbon monoxide and hydrogen gas.

In efforts to actualize hydroformylation in flow, a simple one loop system incorporating a tube-in-tube reactor was assembled for initial optimisation studies using styrene as the substrate. A *syngas* cyclinder ($\text{H}_2\text{:CO}$, 1:1) was used instead of two separate cylinders for each gas because the tube-in-tube reactor was designed with only one gas inlet (Figure 13). It should be noted that during experiments, no difference in conversion for the same reaction was observed as the pressure of the *syngas* in the cylinder decreased. It should also be noted that the ratio of hydrogen and carbon monoxide in the cylinder was not monitored.

Figure 13 shows a general flow setup for hydroformylation.

Styrene will be added to a pre-mixed solution of rhodium pre-catalyst and ligand in anhydrous solvent and loaded onto the PTFE sample loop. A commercially available flow system will then be used to pump the reaction mixture from the sample loop to the tube-in-tube reactor where it will be saturated with *syngas*. The saturated stream will be pumped through the stainless steel reaction coil at a certain temperature. The exiting stream from the stainless steel coil, passing through the back-pressure-regulator will be expected to contain the desired products. The residence time of the reaction mixture in the reaction coil will be determined by the flow rate of the system. As mentioned previously, the back-pressure-regulator is essential to avoid segmented flow by preventing outgassing of the dissolved CO/H₂ from the solvent mixture. It should be noted that pressure of the system (liquid stream) must always be higher than the pressure of the *syngas* in gas-flow reactor to prevent damage to the AF-2400 tubing in the reactor.

Before proceeding on with the optimisation studies, it is important to first understand the mechanism of hydroformylation and the reaction parameters which are capable of altering its pathway. The key factors that influence hydroformylation are temperature, partial pressure (CO and H₂), substrate, ligand and rhodium pre-catalyst.

The widely accepted dissociative mechanism^{79,80,81} proposed by Breslow and Heck still holds true for rhodium catalysed hydroformylation till this day (Figure 14).⁸²

Figure 14 shows the hydroformylation reaction cycle, leading to the formation of the branched and the linear isomer.

The reaction parameters play an essential role in altering the catalytic pathway due to the difference in behaviour between the linear **B** and the branched **C** alkyl-rhodium intermediates. While the branched alkyl-rhodium intermediate predominantly undergoes β -hydride elimination to generate the π -complex **A** and only partial carbonylation, the linear alkyl-rhodium intermediate is more prone to undergo carbonylation followed by oxidative addition and reductive elimination to give the linear aldehyde. It should be

noted that the η^2 -complex **A** gives rise to both the linear and the branched alkyl-rhodium intermediates.

Increasing the temperature causes an increase in the β -hydride elimination process giving rise to the formation of the linear alkyl-rhodium complex which leads to the formation of the linear aldehyde. At low temperatures of 20°C or under mild conditions it has been proven via deuterioformylation experiments that β -hydride elimination process would not occur and formation of the alkyl-rhodium intermediates is irreversible.⁸³ It is noteworthy that in the case of styrene, Lazzaroni *et al.* observed a significant increase in the formation of the linear isomer with increasing temperature.⁸⁴

Increasing or decreasing the partial pressure of carbon monoxide or hydrogen gas affects the branched to linear isomer ratio, and the changes are more significant at higher temperatures. At low pressures the β -hydride elimination process of the branched alkyl-rhodium intermediate becomes competitive with the acylation process and since the branched alkyl-rhodium species is more prone to β -hydride elimination, there would eventually be an increase in the formation of the linear isomer. This is unlike at higher pressure, the alkyl intermediates have lesser chance of undergoing β -hydride elimination process.⁸³

The type of substrate used is important as it has a significant influence over the ratio of isomers and also the reactivity of the reaction. For example, in the case of styrene, the partial negative charge on the carbon atom is better delocalized on the branched alkyl-rhodium species **D** than on the linear alkyl-rhodium species **E** by the polarizable $-\text{C}_6\text{H}_5$ group due to inductive effect (Figure 15). Therefore, it is more selective towards the formation of the branched isomer.^{84,85}

Figure 15 shows the influence of styrene over the ratio of isomers and also the reactivity in hydroformylation.

Phosphines and Phosphites are the two most commonly used ligands in hydroformylation, their steric factors and electronic effects play a crucial role in this reaction. Steric factors usually depend on the type of ligand and the substrate of interest but in light of electronic effect, there is a significant difference between these two ligands. The phosphite ligands are generally stronger π -acceptors and weaker σ -donors than phosphines, hence they increase the reaction rate of hydroformylation. This is because electron-withdrawing effect of phosphites affects the p-back bonding which contributes significantly to the strength of metal-to-ligand bond, thus resulting in more facile CO dissociation and stronger alkene association.^{86,87} There are also other advantages in using phosphites as ligands as they can be easily prepared as compared to phosphines and also they are less sensitive to sulphur compounds and oxidizing agents, but there are also disadvantages like they being more sensitive to side reactions such as alcoholysis, hydrolysis and Arbuzov reaction.

As a starting point, hydroformylation conditions established by Bates *et al.*⁸⁸ were used in the flow system as shown earlier in Figure 13 with styrene as the substrate (Figure 16, Table 9). To our surprise, the conversion of styrene to aldehyde was very low. Although the conversion was low the substrate effect of styrene could still be observed as there were more branched than linear isomer present in the product mixture. Increasing the ligand loading did not make any significant changes to the percentage conversion.

Figure 16 shows the general hydroformylation reaction of styrene.

Entry	Styrene (mmol)	P(Ph) ₃ (mol%)	Rh ₂ (OAc) ₄ (mol%)	Reaction Time (flowrate)	Styrene (%)	Conv. (%)	B : L
1	1	2	1	100 (0.2)	97	3	3:1
2	1	4	1	100 (0.2)	96	4	3:1
3	1	6	1	100 (0.2)	94	6	2:1
4	1	8	1	100 (0.2)	92	8	2:1
5	1	10	1	100 (0.2)	94	6	3:1
6	1	12	1	100 (0.2)	96	4	2:1
7	1	20	1	100 (0.2)	97	3	3:1
8	1	16	2	100 (0.2)	94	6	3:1
9	1	8	1	333 (0.06)	94	6	2:1

Table 9 2 mL loop, 20 mL heating coil, 0.5M substrate concentration, B – branched isomer, L – linear isomer, flowrate in mL/min and reaction time in min, 60°C, 10 bar, eluant – toluene, CO:H₂ (1:1).

It can be seen that the highest conversion of 8 % was obtained with 8 mol % of ligand loading (Entry 4, Table 9). At this point, it was speculated that maybe the reaction time was not sufficient hence the flow rate was decreased to increase the residence time of the reaction mixture in the system (Entry 9, Table 9). Again, to our surprise, the conversion dropped to 6 % instead of the expected increase.

From the poor conversion results (Table 9), we were convinced that triphenylphosphite was not an appropriate ligand for this system. Hence, swapping the ligand to triphenylphosphine and using it with the same rhodium pre-catalyst (Rh₂[OAc]₄), it was noticed that there was a significant increase in the percentage conversion (Figure 16, Table 10).

Entry	Styrene (mmol)	PPh ₃ (mol%)	Rh ₂ (OAc) ₄ (mol%)	Reaction Time (flowrate)	Styrene (%)	Conv. (%)	B : L	Solvent used for Catalyst preparation	Solvation method	Molarity
1	0.35	4	1	100 (0.2)	100	0	-	Toluene (5mL) THF (5 mL)	(((	0.04
2	0.35	4	1	100 (0.2)	76	24	3:1	Toluene (5mL) THF (5mL)	Shaker	0.04
3	0.35	4	1	100 (0.2)	92	8	4:1	Toluene (10mL)	Shaker	0.04
4	0.35	4	1	100 (0.2)	86	14	3:1	THF (10mL)	Shaker	0.04
5	0.18	8	2	100 (0.2)	51	49	4:1	Toluene (5mL) THF (5mL)	Shaker	0.02

Table 10 5 mL loop, 20 mL heating coil, B- branched isomer, L – linear isomer, flow rate in mL/min, reaction time in min, 60°C, 10 bar, eluant – toluene, CO:H₂ (1:1).

There was a major problem faced at this point. The active catalyst that is formed by mixing rhodium(II)acetate and triphenylphosphine was not soluble in the current solvent system. When the sonicator was used as the technique for solubilisation, all of the active catalyst precipitated out giving 0 % conversion (Entry 1, Table 10). When a shaker was used instead, partial solubilisation was attained and the reaction gave promising conversion results (Entry 2-5, Table 10). It was noticed that the solvent used for catalyst preparation significantly affected the conversion (Entry 2-4, Table 10). The molarity of the reaction mixture also plays an essential role in the conversion. When the molarity of the solution was reduced by a factor of half, a conversion of 49 % was achieved (Entry 5, Table 10).

Curious of whether triphenylphosphite would have given a better result with similar conditions, the experiment was repeated with triphenylphosphite as the ligand (Figure 16, Table 11). A better conversion was observed but this could be attributed to the drop in molarity as compared to the previous runs where 0.5 M reaction mixtures were used (Table 9). Thus, when the molarity of the reaction mixture was increased to 0.2 M (Entry 2, Table 11) it can be seen that the conversion dropped dramatically to 4 %.

Entry	Styrene (mmol)	PPh ₃ (mol%)	Rh ₂ (OAc) ₄ (mol%)	Reaction Time (flowrate)	Styrene (%)	Conv. (%)	B : L	Solvent used for Catalyst preparation	Solvation method (Loop)	Molarity
1	0.35	8	1	100 (0.2)	83	17	3:1	Toluene(5mL) THF (5mL)	Shaker (5mL)	0.04
2	0.35	8	1	100 (0.2)	96	4	4:1	Toluene (1mL) THF (1mL)	Shaker (5mL)	0.2

Table 11 20 mL heating coil, B – branched isomer, L – linear isomer, flow rate in mL/min, reaction time in min, 60°C, 10 bar, eluant – toluene, CO:H₂ (1:1).

Although a better conversion was observed with triphenylphosphite (Entry 1, Table 11) using a reaction mixture of lower molarity it was still not as good as with triphenylphosphine as the ligand (Entry 2, Table 10). It should be noted that the branched to linear ratio was not affected significantly throughout the experiments shown on Tables 10 and 11.

Although, triphenylphosphine showed huge potential as the ligand and gave promising conversion results, it could not be completely solubilized, causing blockages in the flow system. It also raised the ambiguity of how much active catalyst is actually involved in the reaction. This would potentially cause inconsistent results, as each time the amount of active catalyst generated *in situ* cannot be quantified.

Hydroformylation was also attempted with Wilkinson's catalyst (Figure 16, Table 12) but to our disappointment, only very low percentage conversions were observed. Similarly, other ligands such as Tri(o-tolyl)phosphine (Figure 16, Table 13) and tri(2-furyl)phosphine (Figure 16, Table 14) did not give impressive results as well. It should be noted, that an unexpected behaviour was observed while using tri(2-furyl)phosphine as the ligand; when the reaction time was increased by decreasing the flow rate the percentage conversion plunged instead of rising (Entry 3, Table 14).

Entry	RhCl(PPh ₃) ₃ (mol %)	Eluant	Molarity (M)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	3	DCM	0.25	98	< 2	0	< 2
2	3	Toluene	0.25	98	< 2	0	< 2
3	3	Toluene	0.1	98	< 2	0	< 2

Table 12 1 mL loop, 20 mL heating coil, flowrate – 0.2 mL/min, reaction time – 100 min, catalyst solution prepared using DCM, 60°C, 10 bar, CO:H₂ (1:1).

Entry	Rh ₂ (OAc) ₄ (mol %)	P(o-tol) ₃ (mol %)	Molarity (M)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	3	12	0.25	100	0	0	0
2	3	6	0.25	100	0	0	0

Table 13 1 mL loop, 20 mL heating coil, flowrate – 0.2 mL/min, reaction time – 100 min, catalyst solution prepared using THF, 60°C, 10 bar, eluant – toluene, CO:H₂ (1:1).

Entry	Rh ₂ (OAc) ₄ (mol %)	Tri(2-furyl) phosphine (mol %)	Eluant	Molarity (M)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	1	2	Toluene	0.25	94	5	1	6
2	1	2	DCM	0.25	93	5	2	7
3 ^x	1	2	DCM	0.25	97	2	1	3
4	3	6	Toluene	0.25	91	7	2	9
5	3	6	Toluene	0.125	86	11	3	14
6	3	6	Toluene	0.0625	86	11	3	14
7	3	6	Toluene	0.03125	88	9	3	12

Table 14 1 mL loop, 20 mL heating coil, flow rate – 0.2 mL/min, reaction time – 100 min, catalyst solution prepared using DCM, 60°C, 10 bar, CO:H₂ (1:1), x: flow rate - 0.08 mL/min, reaction time – 250 min.

Reverting back to using triphenylphosphine as the ligand, a search was carried out for a rhodium pre-catalyst that would eliminate the solubilization problem and give good conversions. To our delight rhodium(III)acetylacetonate gave very promising results (Figure 16, Table 15). Using 0.1 M reaction mixture, a promising conversion of 23% was obtained (Entry 1 of Table 15). It should also be noted that an increase in the molarity of the reaction mixture, there is a decrease in the percentage conversion.

Entry	Molarity (M)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol %)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	0.1	3	6	77	19	4	23
2	0.2	3	6	87	10	3	13
3	0.3	3	6	91	8	1	9
4	0.4	3	6	92	7	1	8
5	0.5	3	6	92	7	1	8

Table 15 1 mL loop, 20 mL heating coil, flow rate – 0.2 mL/min, reaction time – 100 min, 60°C, 10 bar, eluant – toluene, CO:H₂ (1:1).

When the same experiments in Table 15 were run at a higher pressure of 20 bar the conversions significantly increased (Figure 16, Table 16). Utilizing the best result (Entry 1 of Table 16) the mol percentage of the ligand (Figure 16 and Table 17), temperature (Figure 16 and Table 18) and flow rate (Figure 16 and Table 19) were varied.

Entry	Molarity (M)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol %)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	0.1	3	6	64	32	4	36
2	0.2	3	6	76	22	2	24
3	0.3	3	6	80	17	3	20
4	0.4	3	6	89	10	1	11
5	0.5	3	6	89	10	1	11

Table 16 1 mL loop, 20 mL heating coil, flow rate – 0.2 mL/min, reaction time – 100 min, 60°C, 20 bar, eluant – toluene, CO:H₂ (1:1).

Entry	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol %)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	3	6	58	36	6	42
2	3	12	57	38	5	43
3	3	18	57	38	5	43
4	3	24	58	38	4	42
5	3	30	57	40	3	43

Table 17 1 mL loop, 20 mL heating coil, flow rate – 0.2 mL/min, reaction time – 100 min, molarity – 0.1 M, 60°C, 20 bar, eluant – toluene, CO:H₂ (1:1).

Entry	Temp. (°C)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol %)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	rt	3	30	96	4	0	4
2	40	3	30	76	24	0	24
3	50	3	30	64	36	0	36
4	60	3	30	57	40	3	43
5	80	3	30	54	35	11	46
6	100	3	30	63	18	19	37

Table 18 1 mL loop, 20 mL heating coil, flow rate – 0.2 mL/min, reaction time – 100 min, molarity – 0.1 M, 20 bar, eluant – toluene, CO:H₂ (1:1).

Entry	Flowrate (mL/min)	Reaction Time (mins)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (Mol %)	PPh ₃ (mol%)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	0.1	200	3	24	76	21	3	24
2	0.2	100	3	24	58	38	4	42
3	0.3	67	3	24	49	45	6	51
4	0.5	40	3	24	47	48	5	53
5	0.75	27	3	24	46	49	5	54
6	1	20	3	24	63	34	3	37

Table 19 1 mL loop, 20 mL heating coil, molarity – 0.1 M, eluant – toluene, 60°C, 20 bar, CO:H₂ (1:1).

Surprisingly, the ligand loading under these fixed conditions (Figure 16, Table 17) had no significant effect on the conversion rate but it did affect the branched to linear ratio. It can be seen that with an increase in the ligand loading, led to an increase in the branched to linear ratio.

As for temperature, the percentage conversion increased significantly with increasing temperature (Figure 16, Table 18). However, the branched to linear ratio was compromised at higher temperatures. For example, at 100°C, the branched to linear ratio was almost 1:1 (Entry 6, Table 18).

It can also be seen that the flow rate significantly affected the percentage conversion rates (Figure 16, Table 19). If the flow rate is slow (Entry 1, Table 19) or fast (Entry 6, Table 19) the conversion drops. Hence, keeping the flowrate in a moderate range gives the best percentage conversion (Entry 4 & 5, Table 19).

Based on the conclusions of the earlier experiments (Table 10, 11 and 14), it was known that the solvent system could also have a significant effect on the percentage conversion. The one-loop system under optimal condition obtained previously was screened with different solvents for both catalyst preparation and elution of the system (Figure 16, Table 20). It turns out that using toluene as the solvent for catalyst preparation and also as the eluant gave a good percentage conversion with the best branched to linear isomer ratio (Entry 7, Table 20).

Entry	Rh(CO) ₂ (C ₅ H ₄ O ₂) (Mol %)	PPh ₃ (mol%)	Solvent used for Catalyst Prep.	Eluant	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	3	24	Toluene	THF	66	31	3	34
2	3	24	DCM	THF	51	45	4	49
3	3	24	THF	THF	59	38	3	41
4	3	24	Toluene	DCM	58	40	2	42
5	3	24	DCM	DCM	52	45	3	48
6	3	24	THF	DCM	44	51	5	56
7	3	24	Toluene	Toluene	46	50	4	54
8	3	24	DCM	Toluene	79	20	1	21
9	3	24	THF	Toluene	42	52	6	58

Table 20 1 mL loop, 20 mL heating coil, flow rate – 0.7 mL/min, reaction time – 29 min, molarity – 0.1 M, 60°C, 20 bar, CO:H₂ (1:1).

The pressure could be increased at this point, to improve the percentage conversion further but it would be strenuous on the AF-2400 tubing. Therefore, the length of the AF-2400 tubing in the tube-in-tube reactor was extended from 1 meter to 2 meters instead. This would increase the duration of exposure of the reaction mixture to the *syngas* (Figure 13).

To understand the new system with the 2 meter long AF-2400 tubing a number of reactions were carried out (Figure 16, Table 21). As expected, changing the pressure from 10 bar (Entry 1, Table 21) to 20 bar (Entry 2, Table 21) improved the percentage conversion. Increasing the temperature from 60°C (Entry 6, Table 21) to 80°C (Entry 7,

Table 21) improved the percentage conversion as well, but jeopardized the branched to linear ratio. Surprisingly, changing the ligand loading from 18 mol % (Entry 5, Table 21) to 12 mol % (Entry 6, Table 21) caused a dramatic change in the percentage conversion generating ambiguity in the relationship between ligand loading and the other parameters (e.g. flowrate, pressure, percentage conversion). It should be noted that in all cases, increasing the length of the AF-2400 tubing from 1 meter to 2 meter increased the percentage conversion.

Entry	Flowrate (mL/min)	Reaction Time (mins)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol%)	Styrene (%)	Branched (%)	Linear (%)	Conv. (%)
1	0.2	100	3	18	76	21	3	24 ^X
2	0.2	100	3	18	55	40	5	45
3	0.5	40	3	18	40	54	6	60
4	0.7	29	3	18	39	55	6	61
5	1	20	3	18	51	44	5	49
6	1	20	3	12	40	54	6	60
7	1	20	3	12	35	47	18	65 ^Y
8	1.5	13	3	12	56	40	4	44

Table 21 1 mL loop, 20 mL heating coil, flow rate – 0.7 mL/min, reaction time – 29 min, molarity – 0.1 M, 60°C, 20 bar, CO:H₂ (1:1), AF-2400 – 2 m, X : reaction was performed at 10 bar, Y : reaction was performed at 80°C.

To address this ambiguity, a series of experiments were carried out at pressure of 5 bar (Figure 16, Table 22, Chart 1) and 10 bar (Figure 16, Table 23, Chart 2) with varying flow rate and ligand loading to understand the systems behaviour towards the percentage conversion.

Entry	Flowrate (mL/min)	Reaction Time (mins)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (Mol %)	PPh ₃ (Mol %)	Conv. (%)	Branched : Linear
1	0.2	100	3	6	17	3 : 1
2	0.2	100	3	12	15	4 : 1
3	0.2	100	3	18	17	5 : 1
4	0.2	100	3	24	13	7 : 1
5	0.4	50	3	6	16	3 : 1
6	0.4	50	3	12	19	3 : 1
7	0.4	50	3	18	18	4 : 1
8	0.4	50	3	24	19	5 : 1
9	0.6	33	3	6	20	3 : 1
10	0.6	33	3	12	19	4 : 1
11	0.6	33	3	18	22	5 : 1
12	0.6	33	3	24	19	6 : 1
13	0.8	25	3	6	20	2 : 1
14	0.8	25	3	12	16	5 : 1
15	0.8	25	3	18	16	6 : 1
16	0.8	25	3	24	14	8 : 1
17	1	20	3	6	17	2 : 1
18	1	20	3	12	13	6 : 1
19	1	20	3	18	13	7 : 1
20	1	20	3	24	10	9 : 1

Table 22 1 mL loop, 20 mL heating coil, catalyst solution prepared using THF, eluant – toluene, 60°C, 5 bar, 0.1 M, CO:H₂ (1:1), AF-2400 – 2 m.

Chart 1 showing the conversion vs flowrate results from Table 22

Entry	Flowrate (mL/min)	Reaction Time (mins)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (Mol %)	PPh ₃ (Mol %)	Conv. (%)	Branched : Linear
1	0.2	100	3	6	23	4 : 1
2	0.2	100	3	12	26	5 : 1
3	0.2	100	3	18	24	6 : 1
4	0.2	100	3	24	23	6 : 1
5	0.4	50	3	6	24	3 : 1
6	0.4	50	3	12	31	5 : 1
7	0.4	50	3	18	30	6 : 1
8	0.4	50	3	24	31	7 : 1
9	0.6	33	3	6	34	5 : 1
10	0.6	33	3	12	34	5 : 1
11	0.6	33	3	18	39	6 : 1
12	0.6	33	3	24	33	7 : 1
13	0.8	25	3	6	34	4 : 1
14	0.8	25	3	12	34	5 : 1
15	0.8	25	3	18	36	6 : 1
16	0.8	25	3	24	32	7 : 1
17	1	20	3	6	32	4 : 1
18	1	20	3	12	33	5 : 1
19	1	20	3	18	32	8 : 1
20	1	20	3	24	27	8 : 1

Table 23 1 mL loop, 20 mL heating coil, catalyst solution prepared using THF, eluant – toluene, 60°C, 10 bar, 0.1 M, CO:H₂ (1:1), AF-2400 – 2 m.

Chart 2 showing the conversion vs flowrate results from Table 23

Although there are a lot of fluctuation in the results (Chart 1 and 2) a general trend can be seen. For 5 bar system from lower flow rates (0.2 mL/min, Table 22) to higher flow rates (1 mL/min, Table 22) the ligand ratio affects the percentage conversion. At moderate flow rates the system achieves higher percentage conversions. For 10 bar system, a similar trend can be observed. It should be noted that in all cases the ligand loading affected the branched to linear ratio, with higher ligand loading there was an increase in the amount of branched isomer produced.

At 5 bar of pressure the highest conversion was observed at the flow rate of 0.6 mL/min with 18 mol % ligand loading (Entry 11, Table 22) and at 10 bar of pressure, the highest conversion was also observed at the same point (Entry 11 of Table 23). Thus, to get a better picture of the trend, a table consisting of the percentage conversion and selectivity of styrene hydroformylation at varying pressure and ligand loading at a constant flow rate (0.6 mL/min) of interest was created (Figure 16, Table 24).

Entry	Pressure (bar)	Rh(CO) ₂ (C ₅ H ₄ O ₂) (mol %)	PPh ₃ (mol%)	Branched (%)	Linear (%)	Conv. (%)	B : L
1	5	3	6	15.24	5.24	20	3 : 1
2	5	3	12	15.42	3.79	19	4 : 1
3	5	3	18	18.59	3.65	22	5 : 1
4	5	3	24	15.93	2.85	19	6 : 1
5	10	3	6	28.18	5.84	34	5 : 1
6	10	3	12	28.37	5.74	34	5 : 1
7	10	3	18	33.21	5.63	39	6 : 1
8	10	3	24	29.06	4.20	33	7 : 1
9	15	3	6	40.84	5.08	46	8 : 1
10	15	3	12	40.29	4.76	45	8 : 1
11	15	3	18	40.47	4.27	45	9 : 1
12	15	3	24	40.77	4.29	45	10 : 1

Table 24 1 mL loop, 20 mL heating coil, catalyst solution prepared using THF, eluant – toluene, 60°C, 10 bar, 0.1 M, CO:H₂ (1:1), AF-2400 – 2 m, flow rate – 0.6 mL/min, reaction time – 33 min, B – branched isomer, L – linear isomer, CO:H₂ (1:1).

In all cases when different pressures were applied, at higher ligand (PPh_3) to rhodium ratio, the regioselectivity was shifted to the branched isomer, while percentage conversion had no change (Table 24).

Having a brief understanding of the behaviour of the system at lower pressures, a more careful analysis was carried out, studying the temperature, flow rate, ligand loading effect on percentage conversion and selectivity by selective accumulation of previous results at 20 bar.

Starting with the influence of temperature, the reaction temperature was varied from 25°C to 100°C . Higher conversions were generally achieved at higher reaction temperatures but the regioselectivity decreased. Thus, 65°C was chosen as an optimum reaction temperature for achieving higher conversion without higher loss of selectivity (Figure 16, Table 25, Chart 3).

Entry	Temp. ($^\circ\text{C}$)	Branched (%)	Linear (%)	Conv. (%)	Branched : Linear	Selectivity
1	rt	3.76	0.00	4	>99	>99
2	40	24.00	0.00	24	>99	>99
3	50	35.79	0.00	36	>99	>99
4	60	39.72	3.93	42	10:1	91:9
5	80	34.73	11.44	46	3:1	75:25
6	100	18.29	18.94	37	1:1	50:50

Table 25 AF-2400 - 1m, eluant - toluene, 0.1 M, $\text{Rh}(\text{CO})_2(\text{C}_5\text{H}_7\text{O}_2)$ (3 mol%), PPh_3 (30 mol%), (catalyst prepared using Toluene), 1mL loop, pressure: 20 bar, flow rate: 0.2 mL/min, 20 mL heating coil, reac. time: 100 min, $\text{CO}:\text{H}_2$ (1:1).

Chart 3 showing the conversion and selectivity versus temperature results from Table 25

To observe the influence of flowrate (reaction time) on the system, the flowrates was varied between from 0.1 mL/min to 1.0 mL/min. The reaction conditions were also modified according to our previous observation considering pressure and ligand to metal ratio influence. It was found that between 0.5-0.7 mL/min the conversion to aldehyde reached its optimum level. At higher flowrate of 1 mL/min the conversion dropped down, plausibly because of the shorter reaction time. The lower conversion at low flowrates was probably caused by an inefficient mixing of gas to solvent in the tube-in-tube reactor (Figure 16, Table 26, Chart 4).

Entry	Flowrate (mL/min)	Reaction time (mins)	Branched (%)	Linear (%)	Conv. (%)	Branched : Linear	Selectivity
1	0.1	200	21.31	2.77	24	8:1	88:12
2	0.2	100	38.00	3.93	42	10:1	91:9
3	0.3	67	45.20	5.83	51	8:1	89:11
4	0.5	40	48.66	4.69	53	10:1	91:9
5	0.75	27	49.00	5.47	54	9:1	90:10
6	1	20	34.27	3.08	37	11:1	92:8

Table 26 AF-2400 1m, eluant - toluene, 0.1 M, Rh(CO)₂(acac) (3 mol%), PPh₃ (24 mol%), (catalyst prepared using toluene), 1mL loop, pressure: 20 bar, 20 mL heating coil, 60°C, CO:H₂ (1:1).

Chart 4 showing the conversion and selectivity versus flow rate results from Table 26

As for the influence of ligand loading, the trend as observed from the previous study done at different pressures (Table 24) still upholds for 20 bar pressure. Higher amounts of ligand (PPh₃) to rhodium shifts the regioselectivity towards the branched isomer, while conversion remains unchanged (Table 27, Chart 5).

Entry	PPh ₃ (mol%)	Branched (%)	Linear (%)	Conv. (%)	Branched : Linear	Selectivity
1	6	35.52	6.04	42	6:1	85:15
2	12	38.25	5.25	43	7:1	88:12
3	18	38.34	4.59	43	8:1	89:11
4	24	38.00	3.93	42	10:1	91:9
5	30	39.72	3.22	43	12:1	92:8

Table 27 AF-2400 1m, eluant - toluene, 0.1 M, Rh(CO)₂(C₅H₄O₂) (3 mol%), catalyst prepared using Toluene, 1mL loop, pressure: 20 bar, Flow rate: 0.2 mL/min, 20 mL heating coil, reac. time: 100 min., 60°C, CO:H₂ (1:1).

Chart 5 showing the conversion and selectivity versus PPh₃ results from Table 27

As for the pressure of *syngas*, it had a huge impact on both conversion and regioselectivity of hydroformylation. Hence, a proper pressure screening was done using optimal conditions regarding previous results. At lower pressures only modest yields and good regioselectivities were obtained, while at 25 bar of *syngas* pressure the conversion of styrene reached 57% with high regioselectivity (Table 28, Chart 6).

Entry	Pressure (bar)	Branched (%)	Linear (%)	Conv. (%)	Branched : Linear	Selectivity
1	5	18.59	3.65	22	5:1	84:16
2	10	33.21	5.63	39	6:1	85:15
3	15	40.47	4.27	45	9:1	90:10
4	20	45.21	4.29	50	10:1	91:9
5	25	53.50	3.86	57	14:1	93:7

Table 28 AF-2400 2m, eluant - toluene, 0.1 M, Rh(CO)₂(C₅H₄O₂) (3 mol%), PPh₃ (18 mol%), catalyst prepared using Toluene, 1mL loop, pressure: 20 bar, Flow rate: 0.6 mL/min, 20 mL heating coil, reac. time: 33 min., 60°C, CO:H₂ (1:1).

Chart 6 showing the conversion and selectivity versus pressure results from Table 28

Revisiting the solvent influence on the system, it was expected that a more polar solvent would give higher concentrations of the *syngas* in the tube-in-tube reactor. Several solvents for catalyst premixing as well as solvents for reaction have been tried using optimal reaction conditions. A dramatic increase in conversion and regioselectivity was seen when methanol was used as the solvent. Methanol is not traditionally used in

hydroformylations because it may react with aldehyde products to form acetals.⁸⁹

However in our system, the aldehyde regioisomers were the only products (Table 29, 30).

Entry	Solvent used for Catalyst Preparation	Eluant	Branched (%)	Linear (%)	Conv. (%)	Branched : Linear	Selectivity
1	Toluene	THF	31.38	3.50	34	9:1	90:10
2	DCM	THF	45.00	4.44	49	10:1	91:9
3	THF	THF	38.22	3.22	41	12:1	92:8
4	Toluene	DCM	39.55	2.41	42	16:1	94:6
5	DCM	DCM	44.98	3.52	48	13:1	93:7
6	THF	DCM	50.84	5.49	56	9:1	90:10
7	Toluene	Toluene	49.38	4.15	54	12:1	92:8
8	DCM	Toluene	19.93	1.43	21	14:1	93:7
9	THF	Toluene	52.09	5.42	58	10:1	91:9

Table 29 AF-2400 2m, 0.1 M, Rh(CO)₂(C₅H₄O₂) (3 mol%), PPh₃ (24 mol%), 1 mL loop, Flow rate: 0.7 mL/min, 20 mL heating coil, reac. time: 29 min., 60°C, 20 bar, CO:H₂ (1:1).

Entry	Solvent used for Catalyst Preparation	Eluant	Pressure (Bar)	Heating Coil (mL)	B (%)	L (%)	Conv. (%)	B : L	Selectivity
1	Toluene	Toluene	20	30	65.52	3.97	69	16:1	94:6
2	Toluene	MeOH	20	30	75.51	3.92	79	19:1	95:5
3	Toluene	MeOH	25	30	85.40	5.75	91	15:1	93:7
4	Toluene	MeOH	25	35	83.89	5.65	90	15:1	93:7
5	MeOH/ Toluene	MeOH	25	35	87.38	5.16	93	17:1	94:6

Table 30 AF-2400 2m, 0.1 M, Rh(CO)₂(C₅H₄O₂) (3 mol%), PPh₃ (18 mol%), 1 mL loop, Flow rate: 0.6 mL/min, 60°C, CO:H₂ (1:1).

After comprehensive screening of reaction parameters, the optimal conditions employing PPh₃ (18 mol%) as a ligand, Rh(CO)₂(acac) (3 mol%) as a metal, 25 bar of *syngas*, MeOH as a solvent was chosen. Several styrene derivatives were then tested by employing these conditions to show the feasibility of this process (Figure 17, Table 31).

Figure 17 shows the general scheme of hydroformylation of aryl compounds.

Entry	Substrate (a)	Conv. (%) ^a	B:L ^a	Yield B (%) ^b
1		90	13:1	71
2		89	12:1	82
3		95	16:1	86
4		97	31:1	94
5		81	9:1	75
6		93	13:1	85
7		92	10:1	80
8		96	18:1	70
9		90	6:1	69
10		86	11:1	69
11		-	-	- ^c
12		95	23:1	81

Table 31 1 mmol of substrate, 3 mol% Rh(CO)₂(acac), 18 mol% PPh₃, 25 bar CO:H₂ (1:1), substrate dissolved in 10 mL PhCH₃, eluant - MeOH 0.6 mL/min, reaction time 1 hour, CO:H₂ (1:1). See Experimental for more details. ^aDetermined by GC. ^bIsolated yield of the branched regioisomer after purification by flash chromatography on silica gel. ^{a,b}Values corresponds to two runs of each substrate. ^cSignificant amount of the 2-ethylpyridine was observed.

It can be seen from the results (Table 30) that the electronic properties of the aryl substituents on the styrene compounds affected the reaction conversions and selectivities.⁹⁰ It can also be observed that styrene substrates with electron withdrawing substituents gave the desired aldehydes with better regioselectivities and higher conversions than those having electron-donating substituents. It should be noted that all the reactions were highly reproducible in terms of conversions as well as regioselectivity.

4.4. Conclusion

A highly regioselective and high yielding continuous flow hydroformylation process using the tube-in-tube gas-liquid reactor was developed. It was also shown that rapid optimization can easily be facilitated in this semi-permeable polymer Teflon AF-2400 based system, as homogeneous solutions of gas in liquid can be generated in a reliable and controllable manner.

4.5. Experimental

Methanol was freshly distilled under argon from powdered CaH_2 prior to use. Toluene was freshly distilled under argon from powdered CaH_2 prior to use. Flash chromatography was performed using silica gel 60Å (230-400 mesh). Analytical TLC was carried out utilizing 0.25 mm plates precoated with silica gel 60 UV_{254} and spots were visualized by the use of UV light. For NMR spectroscopy, samples were dissolved in CDCl_3 and analyzed at room temp ^1H (400 MHz), ^{13}C (100 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts for protons are reported using the residual CHCl_3 as internal reference (d 7.26). Carbon signals are referenced to the shift from the ^{13}C signal of CDCl_3 (d 77.16). The chemical shifts for

fluorine are reported relative to external CFCl_3 . IR spectra were measured using FT-IR apparatus. Conversion were measured by GC-MS (G-TA, 5.0 psi, 0.4 mL/min); method 1: 40°C 5 min, 3 °C/min 120 °C, 20 °C/min 180 °C, 180 °C 5 min; method 2: 40°C 2 min, 40 °C/min 180 °C, 180 °C 6 min; method 3: 100°C 0 min, 2 °C/min 180 °C, 180 °C 5 min.

2-(2-Fluorophenyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.73 (d, $J = 0.7$ Hz, 1H), 7.35 – 7.23 (m, 1H), 7.21 – 7.04 (m, 3H), 3.90 (q, $J = 7.1$ Hz, 1H), 1.45 (d, $J = 7.2$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.2 (s), 161.0 (d, $J = 246.1$ Hz), 129.6 (d, $J = 4.4$ Hz), 129.4 (d, $J = 8.2$ Hz), 125.4 (d, $J = 15.3$ Hz), 124.8 (d, $J = 3.6$ Hz), 115.9 (d, $J = 22.0$ Hz), 46.6 (s), 13.8 (d, $J = 0.7$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -117.9; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_9\text{FO}$ ($\text{M}^+ + \text{Na}$) 175.0530, found 175.0529. The conversion was determined by GC, method 2: $t_{\text{R}}(2\text{-Fluorostyrene}) = 3.944$; $t_{\text{R}}(2\text{-(2-fluorophenyl)propanal}) = 5.099$; $t_{\text{R}}(2\text{-(2-fluorophenyl)propanal}) = 5.159$; $t_{\text{R}}(3\text{-(2-fluorophenyl)propanal}) = 5.325$.

2-Phenylpropanal: ^1H NMR (400 MHz, CDCl_3) δ 9.69 (d, $J = 1.4$ Hz, 1H), 7.44 – 7.18 (m, 5H), 3.64 (qd, $J = 7.1, 1.3$ Hz, 1H), 1.45 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 137.9, 129.2, 128.4, 127.6, 53.1, 14.7; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_{10}\text{O}$

($M^+ + Na$) 157.0624 found 157.0624. The conversion was determined by GC, method 1:

$t_{R(\text{styrene})} = 8.289$; $t_{R(2\text{-phenylpropanal})} = 23.873$; $t_{R(3\text{-phenylpropanal})} = 26.241$.

2-(4-Methoxyphenyl)propanal: 1H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, $J = 1.5$ Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 3.80 (s, 3H), 3.57 (qd, $J = 7.1, 1.3$ Hz, 1H), 1.41 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 159.1, 129.7, 129.4, 114.6, 55.4, 52.2, 14.7; HRMS (EI) m/z calcd. for $C_{10}H_{12}O_2$ ($M^+ + Na$) 187.0730, found 187.0727. The conversion was determined by GC, method 2: $t_{R(4\text{-vinylanisole})} = 5.102$; $t_{R(2\text{-(4-methoxyphenyl)propanal})} = 6.012$; $t_{R(3\text{-(4-methoxyphenyl)propanal})} = 6.336$.

2-(4-(Trifluoromethyl)phenyl)propanal: 1H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, $J = 1.1$ Hz, 1H), 7.63 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 3.71 (q, $J = 7.1$ Hz, 1H), 1.48 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2 (s), 142.0 (q, $J = 1.3$ Hz), 130.0 (q, $J = 32.6$ Hz), 128.8 (s), 126.1 (q, $J = 3.8$ Hz), 124.2 (q, $J = 272.0$ Hz), 52.9 (s), 14.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9; HRMS (EI) m/z calcd. for $C_{10}H_9F_3O$ ($M^+ + Na$) 225.0498, found 225.0495. The conversion was determined by GC, method 1: $t_{R(4\text{-(trifluoromethyl)styrene})} = 9.641$; $t_{R(2\text{-(4-(trifluoromethyl)phenyl)propanal})} = 24.437$; $t_{R(2\text{-(4-(trifluoromethyl)phenyl)propanal})} = 24.617$; $t_{R(3\text{-(4-(trifluoromethyl)phenyl)propanal})} = 29.395$.

2-(4-Fluorophenyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.65 (d, $J = 1.4$ Hz, 1H), 7.22 – 7.12 (m, 2H), 7.10 – 7.00 (m, 2H), 3.62 (qd, $J = 7.1, 1.2$ Hz, 1H), 1.43 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.8 (s), 162.3 (d, $J = 246.2$ Hz), 133.6 (d, $J = 3.2$ Hz), 129.9 (d, $J = 8.0$ Hz), 116.1 (d, $J = 21.4$ Hz), 52.3 (s), 14.8 (s); ^{19}F NMR (376 MHz, CDCl_3) δ -115.2; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_9\text{FO}$ ($\text{M}^+ + \text{Na}$) 175.0530, found 175.0528. The conversion was determined by GC, method **1**: $t_{\text{R}}(4\text{-fluorostyrene}) = 8.598$; $t_{\text{R}}(2\text{-(4-fluorophenyl)propanal}) = 23.714$; $t_{\text{R}}(3\text{-(4-fluorophenyl)propanal}) = 27.886$.

2-(p-Tolyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.67 (d, $J = 1.5$ Hz, 1H), 7.20 (d, $J = 7.8$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 3.61 (qd, $J = 7.0, 1.2$ Hz, 1H), 2.36 (s, 3H), 1.44 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 137.3, 134.7, 129.9, 128.3, 52.7, 21.1, 14.7; HRMS (EI) m/z calcd. for $\text{C}_{10}\text{H}_{12}\text{O}$ ($\text{M}^+ + \text{H}$) 149.0961 found 149.0962. The conversion was determined by GC, method **1**: $t_{\text{R}}(4\text{-methylstyrene}) = 12.845$; $t_{\text{R}}(2\text{-(p-tolyl)propanal}) = 25.594$; $t_{\text{R}}(2\text{-(p-tolyl)propanal}) = 26.117$; $t_{\text{R}}(3\text{-(p-tolyl)propanal}) = 29.275$.

2-(3-Methoxyphenyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.67 (d, $J = 1.4$ Hz, 1H), 7.29 (app. t, $J = 7.9$ Hz, 1H), 6.84 (ddd, $J = 8.3, 2.6, 0.8$ Hz, 1H), 6.80 (d, $J = 7.6$ Hz, 1H), 6.75 (app. t, $J = 2.1$ Hz, 1H), 3.80 (s, 3H), 3.59 (qd, $J = 7.0, 1.3$ Hz, 1H), 1.43 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.9, 160.2, 139.3, 130.1, 120.6, 114.2, 112.8, 55.3, 53.0, 14.5; HRMS (EI) m/z calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$ ($\text{M}^+ + \text{Na}$) 187.0730, found 187.0729. The conversion was determined by GC, method 2: $t_{\text{R}}(3\text{-vinylanisole}) = 5.108$; $t_{\text{R}}(2\text{-(3-methoxyphenyl)propanal}) = 5.922$; $t_{\text{R}}(3\text{-(3-methoxyphenyl)propanal}) = 6.286$.

2-(4-Chlorophenyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.66 (d, $J = 1.4$ Hz, 1H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 3.62 (qd, $J = 7.1, 1.2$ Hz, 1H), 1.44 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 200.5, 136.3, 133.6, 129.7, 129.3, 52.4, 14.7; HRMS (EI) m/z calcd. for $\text{C}_9\text{H}_9\text{ClO}$ ($\text{M}^+ + \text{H}$) 169.0415, found 169.0416. The conversion was determined by GC, method 2: $t_{\text{R}}(4\text{-chlorostyrene}) = 4.767$; $t_{\text{R}}(2\text{-(4-chlorophenyl)propanal}) = 5.793$; $t_{\text{R}}(3\text{-(4-chlorophenyl)propanal}) = 6.181$.

2-(*o*-Tolyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.67 (d, $J = 1.2$ Hz, 1H), 7.28 – 7.17 (m, 3H), 7.10 – 7.02 (m, 1H), 3.85 (qd, $J = 7.0, 1.2$ Hz, 1H), 2.37 (s, 3H), 1.42 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.2, 136.8, 136.5, 131.1, 127.7, 127.6, 126.8, 49.4, 19.7, 14.4; HRMS (EI) m/z calcd. for $\text{C}_{10}\text{H}_{12}\text{O}$ ($\text{M}^+ + \text{Na}$) 171.0779 found 171.0780. The conversion was determined by GC, method **3**: t_{R} (2-methylstyrene) = 2.342; t_{R} (2-(*o*-tolyl)propanal) = 6.599; t_{R} (2-(*o*-tolyl)propanal) = 6.702; t_{R} (3-(*o*-tolyl)propanal) = 8.689.

2-(3,4-Dimethoxyphenyl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.61 (d, $J = 1.5$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.73 (dd, $J = 8.2, 2.1$ Hz, 1H), 6.66 (d, $J = 2.1$ Hz, 1H), 3.84 (s, 3H), 3.84 (s, 3H), 3.54 (qd, $J = 7.0, 1.4$ Hz, 1H), 1.39 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.0, 149.5, 148.5, 130.1, 120.5, 111.7, 111.4, 55.9, 55.9, 52.5, 14.6; HRMS (EI) m/z calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_3$ ($\text{M}^+ + \text{Na}$) 217.0839, found 217.0835. The conversion was determined by GC, method **3**: t_{R} (3,4-dimethoxystyrene) = 11.814; t_{R} (2-(3,4-dimethoxyphenyl)propanal) = 21.700; t_{R} (3-(3,4-dimethoxyphenyl)propanal) = 26.368.

2-(4-Methylthiazol-5-yl)propanal: ^1H NMR (400 MHz, CDCl_3) δ 9.56 (d, $J = 1.5$ Hz, 1H), 8.65 (s, 1H), 3.91 (qd, $J = 7.2, 1.4$ Hz, 1H), 2.39 (s, 3H), 1.45 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 198.3, 151.1, 150.5, 127.9, 45.0, 16.0, 15.3; IR (neat): $\nu_{\text{max}} = 1725$ (s, CHO); $R_f = 0.3$ (50% ethyl acetate / pentane); HRMS (EI) m/z calcd. for $\text{C}_7\text{H}_9\text{NOS}$ ($\text{M}^+ + \text{H}$) 156.0479 found 156.0478. The conversion was determined by GC, method 3: $t_R(4\text{-methyl-5-vinylthiazole}) = 3.177$; $t_R(2\text{-(4-methylthiazol-5-yl)propanal}) = 10.999$; $t_R(3\text{-(4-methylthiazol-5-yl)propanal}) = 15.343$.

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CHAPTER 5

Inducing 1,2-Alkyl Migration in 2,3,6-Trisubstituted Piperidines

5.1 Introduction

Based on the work we carried out for the synthesis of pseudoconhydrine and azimic acid, it is known that the introduction of oxygenation at the β -position of piperidines can be easily achieved from enamine **1** (Figure 1).

Figure 1 General synthetic scheme of ketone formation from an enamine.

The mechanism by which ketone **4** was formed (Scheme 1), left us to ponder whether it would be possible to induce a 1,2-alkyl shift instead of a 1,2-proton shift (Scheme 2).

Scheme 1 Mechanism of 1,2-hydride shift.

Scheme 2 Mechanism of 1,2-alkyl shift.

From a stereochemical view point, and in contrast to the synthesis of azimic acid, this is advantageous because this method can be used to generate *trans*-selective methylation at the C-2 position with respect to the C-6 propyl group. In our original azimic acid synthesis, we only managed to generate the *cis*-methylated product *via* allylation of the iminium ion intermediate, but with this methodology, the *trans*-methylated product can also be generated. From Scheme 2, it can be seen that the R group is postulated to shift with retention of stereochemistry hence, generating the *trans*-alkylated product **7**.

This thought led to the need for generating C-C bonds at the β -position of the enamine **1**, to derive **8**-type compounds which can then undergo dihydroxylation. Acidification of diol **9** will induce the 1,2-alkyl migration to obtain the migratory ketone product **10** (Figure 2). Even if the 1,2-shift does not occur, introducing a carbon at the β -position would be useful.

Figure 2 General synthetic scheme to achieve the α -substituted ketone from an enamine.

5.2 Results and Discussion

A careful literature search revealed there were very few precedents on achieving this β -substituted piperidine from enamine **1** (Figure 2). For example, Harrity employed Furukawa modification of Simmons-Smith reaction,¹ Gillaizeau employed a palladium(II)-catalyzed reaction² and Sulikowski employed Sonogashira coupling reaction after halogenation³ (Scheme 3). There are also many other coupling reactions such as Stille coupling,⁴ Suzuki coupling,⁵ Kumada coupling,⁶ Negishi coupling⁷ and Hiyama coupling,⁸ that can be used to achieve the β -substituted piperidine but, to our knowledge, have not been employed.

Harrity *et al.*

Gillaizeau *et al.*

Sulikowski *et al.*

Scheme 3 Shows the methods employed by different groups in generating β -substituted piperidines.

We proposed to perform alkyl substitution on enamine **1** prior to dihydroxylation to attain diol **12**. Thus, there were two potential pathways that could be undertaken to achieve this β -substituted enamine **11**. One pathway being iodination of the enamine **1**, followed by a coupling reaction and the other pathway being cyclopropanation of the enamine **1**, followed by ring-opening of the cyclopropane (Scheme 4).

Scheme 4 General synthetic scheme of the two pathways that can be taken to achieve the precursor for the 1,2-alkyl shift reaction.

In order to generate enamine **1** in a fast and efficient manner, we turned our attention towards the Aza-Sakurai-Hosomi three-component reaction⁹ to produce the racemic allyl-amine **13** in just one step (Scheme 5). The allyl-amine **13** was then submitted to hydroformylation utilizing the established conditions from our previous work on pseudoconhydine to produce the racemic version of the enamine **14**.

Scheme 5 (a) $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 , 1 hr, 0°C ; (b) $\text{Rh}_2(\text{OAc})_4$, $\text{P}(\text{OPh})_3$, $\text{H}_2:\text{CO}$ (1:1), 65°C , 60 psi, 18 hr (c) I_2 , AgOAc , CH_2Cl_2 , room temperature, overnight (d) Trifluoroacetic acid, CH_2Cl_2 , room temperature.

The racemic enamine **14** produced *via* the Aza-Sakurai-Hosomi three-component reaction,⁹ followed by hydroformylation was iodinated, following the procedure of Mott.¹⁰ Unfortunately, only 28% yield of product **15** was obtained together with 63 % of the then unknown compound **16** (Scheme 5).

Thin layer chromatography (TLC) of the crude sample of the iodination reaction, showed the presence of two spots. The top spot, which was identified via spectroscopic analysis, to be the iodinated compound **15** had a R_f of 0.53 (eluant: 25 % ethyl acetate / hexane) which was the same R_f as the starting material **14** (Figure 3). The ^1H NMR spectrum of compound **15** clearly showed the presence of the two characteristic protons; the alkene proton H_a a singlet at about 7 ppm and the proton alpha to the nitrogen, H_b a multiplet at about 3.9 ppm (Figure 4).

Figure 3 ^1H NMR spectrum of the enamine **14**.

Figure 4 ^1H NMR spectrum of the iodinated enamine **15**.

Figure 5 ^1H NMR spectrum of the iodinated hydroxy-enamine **16**.

The bottom spot, which was the mystery compound, had an R_f of 0.43 (eluant: 25 % ethyl acetate / hexane) indicating it is a more polar molecule than the iodinated compound **15**. Further, infrared spectroscopy experiment of the mystery compound revealed a broad peak at 3476 cm^{-1} indicating the presence of a hydroxyl group. The ^1H NMR spectrum of compound **16** clearly showed the presence of the three characteristic protons; the alkene proton α to the nitrogen and the hydroxyl group, H_c , a broad singlet at about 5.4 ppm, the proton α to the nitrogen, H_e , a multiplet at about 3.9 ppm, and the proton α to the iodine, H_d a broad singlet, about 4.4 ppm (Figure 5). The combination of these analyses suggests that it might be a hydroxylated iodine compound **16** present as a mixture of isomers. Thus, to validate our speculation, trifluoroacetic acid was added to the crude product in dichloromethane to induce dehydration, and to our delight we obtained an 88% yield of the desired iodinated compound **15** (Scheme 5).

Hence, being able to generate the iodinated product **15** efficiently, we proceeded on towards the synthesis of β -substituted enamine **17**, *via* the Stille coupling reaction⁴ but to our disappointment, the coupling reaction did not proceed as planned. When the reaction mixture was heated at reflux in tetrahydrofuran, the reaction did not go to completion; hence, we tried changing the reaction solvents to ones with a higher boiling point in hopes of pushing the reaction to completion (Scheme 6, Table 1). It should be noted that in all cases the formation of enamine **14** was seen and all the three compounds; the iodinated product **15**, the β -substituted enamine **17** and the enamine **14** had the same R_f value of 0.53 (25% ethyl acetate / 75% hexane).

Scheme 6 (a) SnMe_4 , CuI , $(\text{Ph}_3\text{P})_2\text{PdCl}_2$, THF, reflux, 30h.

Entry	Solvent	Temperature (°C)	Compound 15	Compound 17	Compound 14
			Ratio		
1	THF	reflux	1	2	0.4
2	Dioxane	reflux	1	0.5	3
3	DMF	reflux	-	2	1
4*	THF	reflux	1	1	1

Table 1 Shows the table of different solvents tried with the reaction on Scheme 6. *Entry 4 Utilizes condition of Shaw *et al.*¹¹ $\text{Pd}_2(\text{dba})_3$, CuI , Me_4Sn , AsPh_3 , 36h.

While efforts to synthesize the β -substituted enamine **17** via Stille coupling was still ongoing, we turned towards the cyclopropanation pathway in hopes of achieving β -substituted enamine **17** (Scheme 3).

There are a number of different procedures available to generate cyclopropanes including effective enantioselective methods.¹² Their potential to provide a driving force for many ring-opening reactions¹³ due to their ring strain, makes cyclopropanation an attractive reaction. We were particularly interested in generation of cyclopropane **18** from enamine **1** (Figure 6).

Figure 6 General synthetic scheme of cyclopropanation of enamine.

Hence, a careful literature search led to the work of Harrity *et al.*¹ and Madsen *et al.*^{14,15} who worked on cyclopropanation of molecules similar to that of enamine **14**. Since, both of them utilized Furukawa modification of Simmons-Smith reaction,¹⁶ we followed on their footsteps to generate cyclopropane **19**. Indeed, Furukawa noted the superiority of his method over the traditional Simmons-Smith method when acid sensitive substrates, such as enol-ethers, are employed.

Following the procedure of Harrity *et al.*¹ it was made possible to attain cyclopropane **19** easily in high yields (Scheme 7) although a long reaction time is required. It should be noted that a single diastereoisomer was obtained, but not being able to identify as to which isomer, it was presumed to be *trans*, based on the work of Harrity.

Scheme 7 (a) Et_2Zn , CH_2I_2 , toluene, 60h, 0°C .

Figure 7 ^1H NMR spectrum of the cyclopropane **19**.

Figure 8 COSY spectrum of the cyclopropane **19**.

Looking at the ^1H spectrum of the product **19**, it could be clearly identified that the cyclopropane was present due to the presence of its characteristic proton shifts X_2 and X_3 at 0.53 ppm and -0.17 ppm respectively (Figure 7). Further analysing the COSY spectrum, the relationship between the protons could be clearly established confirming the formation of the cyclopropane product **19** (Figure 8). The proton, X_1 correlates with X_3 , X_2 , H_y and K ; X_2 correlates with X_3 , X_1 and H_y ; X_3 correlates with X_2 , X_1 and H_y .

Having easy access to cyclopropane **19**, we now wanted to find an efficient way to ring-open cyclopropane **19** to generate β -substituted enamine **17**. The first thought was to try acidification of cyclopropane **19** as the predictable mechanism leading towards the β -substituted enamine **17** seemed promising (Figure 9). There were also literature

precedents of ring-opening of cyclopropanes with alkoxy substituents, including cyclopropanated dihydropyrans with strong acids^{17,18,23}. Notably, Boeckmann has employed the acid catalysed opening of a cyclopropanated dihydropyran in a synthesis of Calcimycin.

Figure 9 Mechanism of ring-opening of cyclopropane under acidic condition.

To our disappointment, ring-opening under acidic condition did not occur. Initially, PTSA was used as the acid in polar solvents such as MeOH and DMSO under both refluxing and room temperature conditions, but no reaction was observed. Hence, a stronger acid, TFA, was tried in MeOH under both refluxing and room temperature conditions but still no reaction was observed. It should be noted that in all cases, the starting material was recovered.

Therefore, we referred back to Harrity¹ and Madsen^{14,15} looking for an alternative route as they worked on similar substrates. Harrity *et al.*¹ showed that the cyclopropane **22** could be opened up *via* halogenation, generating two chiral centers, which could be further manipulated to generate the allylated product **24** (Scheme 8). They also reported that the intermediate **23** is extremely sensitive to decomposition on silica gel, or by warming above ambient temperature.

Scheme 8 Cyclopropane formation and ring-opening scheme of Harrity *et al.*¹ (a) CH_2I_2 , Et_2Zn , toluene; (b) NIS, MeOH; (c) Bu_3SnH , AIBN, toluene; (d) **24a**, $\text{BF}_3 \cdot \text{OEt}_2$, CH_2Cl_2 .

On the other hand, based on the earlier work of Jennings and Olberg, Madsen *et al.*^{14,15} worked on transition metal-catalyzed ring-opening of cyclopropanes. They discovered that utilizing Zeise's dimer²¹ $[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$ in the presence or in the absence of alcohol leads to formation of different products. For example, in the absence of alcohol, compound **25** underwent ring opening to give the olefin **26** as the only product (Scheme 9).

Scheme 9 Shows Madsen *et al.*^{14,15} scheme of cyclopropane ring-opening with Zeise's salt in the absence of alcohol. (a) 5% $[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$, CH_2Cl_2 , rt.

When they carried out the same reaction on D-glucal derived cyclopropane **27**, in the presence of BnOH, the benzyl glycoside **28** was isolated as the major product and there was no *exo*-cyclic olefin observed (Scheme 10).

Scheme 10 Shows Madsen *et al.*^{14,15} scheme of cyclopropane ring-opening with Zeise's salt in the presence of alcohol. (a) 3.7% $[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$, BnOH, CH_2Cl_2 , rt.

From their discovery, they suggested that the mechanism could possibly proceed by the pathway as shown in Figure 10. It should be noted that the formation of platinacyclobutanes have been known since the early 1950s.²²

Figure 10 Shows Madsen's^{14,15} suggested cyclopropane ring-opening mechanism using Zeise's salt in the presence of alcohol.

The first step in their proposed mechanism is well documented, where the platinum inserts into the cyclopropane to give a platinacyclobutane.¹⁹ The electron donating ability of oxygen in compound **29**, contributes to the further polarization of the platinum (IV)-carbon σ bond causing it to have substantial oxocarbenium ion character. This effect makes compound **29** vulnerable to nucleophilic attack by the alcohol to give the compound **30** which can further undergo reductive elimination to give the product **31** and releasing the active catalyst Pt(II) back into the reaction cycle.

We were intrigued by the work of Madsen *et al.*^{14,15} with the utilization of transition metal-catalyzed ring-opening of cyclopropanes. Hence, a series of reactions were done utilizing transition metal catalysts with our substrate (Scheme 11, Table 2).

Scheme 11 (a) reaction conditions are shown in Table 2.

Entry	Catalyst	Mol (%)	Solvent	Temp.	Time (h)	Cmpd 19	Cmpd 32	Cmpd 17	Remarks
						Ratio			
1	[Pt(C ₂ H ₄)Cl ₂] ₂	10	DCM	r. t.	20	-	-	-	no reaction
2	[Pt(C ₂ H ₄)Cl ₂] ₂	10	toluene	r. t.	24	0.88	0.23	1	partial conversion
3	[Pt(C ₂ H ₄)Cl ₂] ₂	10	toluene	r. t.	48	0.35	0.22	1	partial conversion
4	[Pt(C ₂ H ₄)Cl ₂] ₂	10	toluene	reflux	12	-	1	0.24	complete conversion
5	[Pt(C ₂ H ₄)Cl ₂] ₂	10	m-xylene	reflux	12	-	1	0.18	complete conversion
6	[Pt(C ₂ H ₄)Cl ₂] ₂	10	toluene / methanol	r. t.	12	1	trace	trace	minimal conversion
7	[Pt(C ₂ H ₄)Cl ₂] ₂	10	toluene / methanol	reflux	12	-	0.06	1	complete conversion
8	[Pt(C ₂ H ₄)Cl ₂] ₂	10	methanol	reflux	12	-	-	1	complete conversion
9	(EtCN) ₄ Pt(OTf) ₂	10	toluene	r. t.	12	-	-	-	no reaction
10	(EtCN) ₄ Pt(OTf) ₂	10	toluene	reflux	12	-	-	1	complete conversion
11	Ph ₃ PAuCl, AgOTf	10	toluene	r. t.	12	1	trace	2	partial conversion
12	Ph ₃ PAuCl, AgOTf	30	toluene	reflux	12	-	-	1	complete conversion
13	Ph ₃ PAuCl, AgOTf	10	methanol	reflux	12	-	-	-	no reaction
14	AuCl ₃	10	toluene	r. t.	12	-	-	-	no reaction
15	AuCl ₃	10	toluene	reflux	12	-	-	-	no reaction

16	AuCl ₃	10	DCM/ MeCN	reflux	12	-	-	-	no reaction
17	AuCl ₃	10	MeCN/ toluene	reflux	12	-	-	-	no reaction
18	(MeCN) ₂ PdCl ₂	10	toluene	r. t.	12	-	-	-	no reaction
19	(MeCN) ₂ PdCl ₂	10	toluene	reflux	12	-	-	-	no reaction
20	Pd(OAc) ₂	10	toluene	r. t.	12	-	-	-	no reaction
21	Pd(OAc) ₂	10	toluene	reflux	12	-	-	-	no reaction
22	Pd(O ₂ CCF ₃) ₂	10	toluene	r. t.	12	-	-	-	no reaction
23	Pd(O ₂ CCF ₃) ₂	10	toluene	reflux	12	-	-	-	no reaction
24	PtI ₂	10	toluene	r. t.	12	-	-	-	no reaction
25	PtI ₂	10	toluene	reflux	12	-	-	-	no reaction

Table 2 shows the results of utilizing various transition metal catalyst in the ring opening of cyclopropane. *Isolated yields for Entries 8, 10 and 12 are 83%, 81% and 76% respectively.

The *endo*-alkene product **17** and *exo*-alkene product **32** can be easily differentiated from one another from their ¹H NMR spectrums (Figure 11 and 12). For the *endo*-alkene product **17**, a significant singlet peak of the proton H_g can be seen at 6.34 ppm (Figure 11). As for the *exo*-alkene product **32**, the alkene protons can be seen at 4.72 ppm and 4.62 ppm, appearing as a broad singlet due to the typical 0 Hz gem coupling and the diastereotopic ring protons can be seen at 4.21 ppm and 3.66 ppm, with a matching coupling constant of 15.3 Hz (Figure 12).

Figure 11 1H NMR spectrum of the *endo*-alkene product **17**.

Figure 12 1H NMR spectrum of the *exo*-alkene product **32**.

Taking into consideration the mechanism proposed by Madsen *et al.*^{14,15} (Figure 10), it could be suggested that Zeise's salt proceeds *via* the mechanism as shown in Figure 13.

Figure 13 Shows our proposed mechanism in the ring opening of cyclopropane using Zeise's salt.

Based upon the mechanism proposed by Madsen, it can be postulated that the PtCl_2 undergoes oxidative addition to one of the cyclopropane **33** C-C bonds to form a platinacyclobutane **34**. This undergoes ring opening to an iminium/ alkyl platinum (II) species **35**. β -hydride elimination could then give a η^2 -platinum complex **36**. B-hydride elimination is well known to be reversible and re-insertion with the opposite regiochemistry would give a *t*-alkyl platinum (II) complex **38**. This complex could undergo demetallation to give the *endo*-product **39**. Alternatively, after β -hydride

elimination the platinum might migrate from the *exo*-cyclo alkene **36** to the iminium ion **37**. Hydride delivery from platinum would then deliver the *exo*-cyclic alkene **40**.

The migration, re-insertion and the β -hydride elimination steps in Figure 13 could possibly be both reversible and strongly temperature dependant hence the difference in the product formation under reflux and room temperature conditions.

Looking at the results from entries 2 and 3 (Table 2), it could be seen that at room temperature with toluene as the solvent, compound **17** was present as the major product. From entry 4 (Table 2), it can be seen that under refluxing toluene conditions, compound **32** was present as the major product. This is initially surprising, as the *exo*-cyclic alkene is the higher energy product, yet it is favoured at higher temperature. On analysis of this difference in selectivity between entries 2, 3 and 4 (Table 2), it could be suggested that the pathway leading to the more stable *exo* alkene **32** has a higher energy barrier to overcome (Figure 14).

Figure 14 Shows the intermediates prior to formation of the *endo*- and *exo*- alkene products.

Looking at our suggested mechanism (Figure 13), what if the Pt catalyst was made to be positively charged, preventing it from being a hydride donor, would it block the hydride transfer pathway leading to the formation of solely the *endo* alkene **17**?

Therefore a positively charged catalyst (EtCN)₄Pt(OTf)₂ prepared using the procedures of Kukushkin²⁰ (Scheme 12), was used under refluxing condition in toluene (Entry 10, Table 2). To our delight, compound **17** was produced as the only product with complete conversion of the starting material. This is because the positively charged Pt catalyst is not a hydride donor, hence the proton transfer pathway is blocked, forcing the reaction to proceed down the re-insertion pathway leading to formation of only the *endo* alkene **17** (Figure 15).

Scheme 12 Synthetic scheme towards the positively charged Pt catalyst following the procedures of Kukushkin.

Figure 15 shows the mechanism of the positively charged Pt catalyst.

Again, looking at the suggested mechanism (Figure 13), we wanted to intercept the iminium ion so that we can employ it synthetically. Therefore the ring-opening reaction was carried out in methanol instead of toluene (entry 8, Table 2) so that it would give the methoxy compound, analogous to the benxyloxy compound obtained by Madsen (Scheme 10).

To our surprise, the ring-opening reaction (entry 8, Table 2) proceeded with complete conversion of the starting material, to give the *endo* alkene product **17** as the major or only product. Although, small amounts of side product which looks like the methoxylated product was isolated, it could not be clearly identified. The reason why there is no obvious formation of methoxylated product seen, might be due to its formation being reversible (Figure 16). A further question is the disfavouring of the *exo*-cyclic alkene **32**

in the presence of methanol. It may be suggested that the use of a more polar solvent stabilizes the more polar η^2 -complex **36**.

Figure 16 shows the reversible pathway of the methoxylated compound.

Other transition metal catalysts such as Au and Pd were also tested with this reaction (Table 2). The transition metal Au was chosen because it is a π -acid and cyclopropane C-C bonds exhibits π character. The transition metal Pd was chosen because it is in the same group as Pt and is often more reactive. As can be seen from the results on Table 2, only Au(I) gave promising results even though it required high catalyst loading under refluxing conditions in toluene (Entry 12, Table 2). Surprisingly, for Au(I) catalyst in toluene, the migration step (Figure 13) did not occur, giving rise to only the formation of the *endo* alkene **17**. This might be because the Au(I) catalysts cannot undergo β -hydride

elimination,²⁴ hence the mechanism for Au(I) must be different to the mechanism with Pt, on the assumption that our proposed Pt mechanism (Figure 13) is correct. From further analysis of the results in Table 2, it can be seen that all of the Pd catalysts tried gave no reaction. This might be due to the Pd catalyst having greater difficulty in attaining the (IV) oxidation state.

With the *endo* alkene **17** at hand, we reverted back to our main interest, which is to investigate 1,2-alkyl migration (Scheme 2). Subjecting alkene **17** to Upjohn conditions easily gave a 1:2 ratio of diastereoisomers **48**, to which 20 mol% of trifluoroacetic acid was added in hopes of observing 1,2-alkyl shift product **49** (Scheme 13).

Scheme 13 (a) K_2OsO_4 , NMO, MeSO_2NH_2 , THF: H_2O (9:1), room temperature, overnight; (b) Trifluoroacetic acid, CH_2Cl_2 , room temperature 3 h.

To our disappointment, the migration of the alkyl group did not occur, but instead an unknown compound was obtained as a white solid. Even after analysis of the ^1H NMR spectrum and knowing this molecule has a molecular weight of 310.07 as indicated by mass spectrometry results the mystery compound could not be identified. The ^{13}C NMR of this mystery compound showed that it had 14 carbons present in the molecule. Being confused, as to what the mystery compound could be, we took advantage of the fact that the product was a white solid by recrystallizing it from dichloromethane and studying it *via* X-ray analysis. The X-ray results clearly revealed that the diol **48** dimerized to give the dimer **50** as the major product (Figure 17, Scheme 14). This result came as a surprise

as the M^+ as indicated by mass spectrometry only showed half of its molecular weight. Clearly, the molecule undergoes complete fragmentation under the mass spectrometry conditions and no molecular ion is observable.

Scheme 14 (a) Trifluoroacetic acid, room temperature, CH_2Cl_2 , overnight.

Figure 17 Crystal structure of dimer **50**.

In hopes of preventing this dimerization from occurring, the strong trifluoroacetic acid was replaced with a mild Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$. This Lewis acid was added to the solution of diol **48** in dichloromethane at -78°C allowing it to slowly warm up to 0°C . Again to our disappointment, the dimerized compound **50** was obtained as the major product.

Not giving up as yet, we approached this reaction in a different manner by slow addition of the diol **48** dissolved in dichloromethane *via* a syringe pump to a stirred solution of 20 mol % $\text{BF}_3\cdot\text{OEt}_2$ over a 6 hour period. This was done to disfavour dimerization by maintaining a low concentration. Nonetheless, dimerization still occurred to give compound **50** as the major product once again. Hence, further work towards achieving the 1,2-alkyl shift is still in progress.

5.3 Conclusion

Work is still in progress to achieve 1,2-alkyl migration, but the journey towards the synthesis of the precursor **48** lead to interesting new chemistry such as ring-opening reactions of cyclopropanes with transition metal catalysts. So far, gold and platinum catalyst showed large potential in cyclopropane ring-opening reaction hence, further investigation is needed to fully exploit their potential.

5.4 Experimental

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran was distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Flash chromatography was carried out on silica gel, 230-400 mesh. ^1H NMR spectra were recorded at 300, 400 or 500 MHz in CDCl_3 solutions. ^{13}C NMR spectra were recorded at the corresponding frequency on the same instruments at 75, 100 or 125 MHz.

Chemical shifts are recorded in parts per million and coupling constants are recorded in Hertz.

15

5-Iodo-2-propyl-1-tosyl-1,2,3,4-tetrahydropyridine (15): A mixture of iodine (100 mg, 0.39 mmol) and silver acetate (6 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) was stirred for 15 mins at room temperature under 1 atm of N_2 . A solution of enamine **14** (100 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) was added rapidly and the resulting mixture was left to stir overnight. The reaction mixture was filtered washing with CH_2Cl_2 . Trifluoroacetic acid (5 drops) was added to the filtrate and further stirred for another 3 h. The solution was evaporated till dryness and taken up in CH_2Cl_2 , washed with satd aq. sodium thiosulfate, water, brine, dried over MgSO_4 , filtered and evaporated to give compound **15** (118 mg, 81%) as a yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 2957, 2931, 2872, 1626, 1337, 1165; ^1H NMR (400 MHz, CDCl_3) δ 7.65 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.07 (s, 1H), 4.00 – 3.85 (brs, 1H), 2.43 (s, 3H), 2.39-2.25 (m, 1H), 2.23-2.11 (m, 1H), 1.68 – 1.19 (m, 5H), 1.13 – 0.99 (m, 1H), 0.93 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 144.0, 135.9, 130.1, 129.3, 127.2, 75.6, 52.0, 34.0, 30.9, 25.8, 21.8, 19.2, 14.0; MS (ESI+) m/z 406 ($[\text{M}+\text{H}]^+$, 100).

16

3-Iodo-6-propyl-1-tosylpiperidin-2-ol (16): Obtained as a mixture of isomers; FTIR (neat, cm^{-1}): ν_{max} 3476, 2957, 2931, 2871, 1326, 1161; ^1H NMR (400 MHz, CDCl_3)²⁵ δ

7.77 (d, $J = 8.2$ Hz, 2H), 7.28 (d, $J = 8.2$ Hz, 2H), 5.42 (s, 1H), 4.41 (s, 1H), 4.04 – 3.78 (m, 1H), 3.11 (d, $J = 2.8$ Hz, 1H), 2.40 (s, 3H), 2.34 – 1.01 (m, 8H), 0.92 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3)²⁵ δ 143.8, 136.8, 129.6, 128.0, 81.8, 53.2, 38.0, 28.9, 23.1, 22.9, 21.8, 20.9, 14.1; ; MS (ESI+) m/z 406 ($[\text{M}^+ - \text{OH}]$, 100).

5-Methyl-2-propyl-1-tosyl-1,2,3,4-tetrahydropyridine (17): A mixture of Cyclopropane **19** (100 mg, 0.34 mmol) and 10 mol % $(\text{EtCN})_4\text{Pt}(\text{OTf})_2$ (24 mg, 0.034 mmol) in dry toluene (3 mL) was heated to reflux overnight, filtered, evaporated. The residue was purified by flash chromatography on silica gel eluting with 15% ethyl acetate/hexane to give alkene **17** (81 mg, 81%) as a yellowish oil: FTIR (neat, cm^{-1}): ν_{max} 2959, 2930, 2873, 1668, 1344, 1162; ^1H NMR (400 MHz, CDCl_3) δ 7.63 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 6.35 (s, 1H), 4.02 – 3.72 (m, 1H), 2.40 (s, 3H), 1.96 – 1.75 (m, 1H), 1.64 (s, 3H), 1.62 – 1.17 (m, 5H), 0.91 (t, $J = 7.2$ Hz, 3H), 0.95-0.84 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.2, 136.5, 129.8, 127.2, 118.7, 118.1, 52.3, 33.9, 23.2, 23.0, 21.7, 21.1, 19.4, 14.1; MS (ESI+) m/z 294 ($[\text{M}+\text{H}]^+$, 100).

3-Propyl-2-tosyl-2-azabicyclo[4.1.0]heptane (19): Et_2Zn (1.47 mL, 2.15 mmol) and CH_2I_2 (0.35 mL, 4.29 mmol) was added to a solution of enamine **14** (100 mg, 0.36 mmol) in toluene (4 mL) at 0°C . The resulting solution was allowed to stir at 0°C for 60 hours.

The solution was diluted with satd aq. NH_4Cl (10 mL), extracted with EtOAc (10 mL x 3), washed with brine (20 mL) dried over MgSO_4 , filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexane to give cyclopropane **19** (87 mg, 82%) as a yellowish oil: : FTIR (neat, cm^{-1}): ν_{max} 3008, 2955, 2933, 2871; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 8.2$ Hz, 2H), 3.84 – 3.62 (m, 1H), 2.76 (ddd, $J = 9.6, 6.4, 3.6$ Hz, 1H), 2.40 (s, 3H), 1.85 – 1.71 (m, 1H), 1.69 – 1.55 (m, 1H), 1.54 – 1.09 (m, 7H), 1.07 – 0.80 (m, 5H), 0.92 (t, $J = 7.1$ Hz, 3H), 0.52 (ddd, $J = 9.6, 6.0$ Hz, 1H), -0.17 (ddd, $J = 6.0, 3.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 143.0, 138.4, 129.5, 127.5, 51.3, 34.2, 26.2, 24.1, 21.7, 19.8, 14.7, 14.2, 10.3, 8.7; MS (ESI+) m/z 294 ($[\text{M}+\text{H}]^+$, 100).

32

5-Methylene-2-propyl-1-tosylpiperidine (32): A mixture of Cyclopropane **19** (70 mg, 0.24 mmol) and 10 mol% Zeise's dimer $[\text{Pt}(\text{C}_2\text{H}_4)\text{Cl}_2]_2$ (14 mg, 0.024 mmol) in dry toluene (3 mL) was heated to reflux overnight, filtered, evaporated to give the crude alkene **32** (quant.) as a brownish oil in a 4:1 isomeric mixture of exo:endo respectively: ^1H NMR (400 MHz, CDCl_3)²⁵ δ 7.67 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.2$ Hz, 2H), 4.72 (brs, 1H), 4.62 (brs, 1H), 4.21 (d, $J = 15.3$ Hz, 1H), 3.98-3.80 (m, 1H), 3.65 (d, $J = 15.3$ Hz, 1H), 2.38 (s, 3H), 2.21 (m, 1H), 1.94 (m, 1H), 1.78 – 1.56 (m, 2H), 1.51 – 1.20 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3)²⁵ δ 143.0, 141.3, 138.4, 129.6, 127.5, 110.5, 52.7, 46.7, 32.4, 28.2, 27.4, 21.7, 19.7, 14.1.

48

3-Methyl-6-propyl-1-tosylpiperidine-2,3-diol (48): Methane-sulfonamide (32 mg, 0.34 mmol) was added to a solution of ene-sulfonamide **17** (100 mg, 0.34 mmol) in THF (4.50 mL), and the mixture was stirred until it was completely dissolved. NMO (50% w/w) (0.21 mL, 1.02 mmol), H₂O (0.50 mL) and K₂OsO₄ (13 mg, 34.1 x 10⁻³ mmol) were added to the solution, and the mixture was stirred overnight. The mixture was quenched with satd aq Na₂S₂O₃ (10 mL), washed with water (10 mL), brine (10 mL), dried (MgSO₄), filtered and evaporated to give crude diols **48** (quant.) as a yellowish oil and as an inseparable mixture of diastereoisomers: ¹H NMR (400 MHz, CDCl₃) δ 7.76 (d, *J* = 8.3 Hz, 0.7H), 7.72 (d, *J* = 8.3 Hz, 1.3H), 7.29 (d, *J* = 8.3 Hz, 2H), 4.94 (d, *J* = 2.8 Hz, 0.7H), 4.92 (d, *J* = 3.2 Hz, 0.3H), 3.97-3.85 (m, 1H), 3.02 (d, *J* = 2.8 Hz, 0.7H), 2.67 (d, *J* = 3.2 Hz, 0.3H), 2.48 (s, 0.7H), 2.42 (s, 2H), 2.41 (s, 1H), 2.17 (s, 0.3H), 2.03 – 1.50 (m, 4H), 1.45 – 1.14 (m, 5H), 0.99 – 0.85 (m, 5H).

50

4a,9a-Dimethyl-2,7-dipropyl-1,6-ditosyldodecahydro-[1,4]dioxino[2,3-b:5,6-b']dipyridine (50): Trifluoroacetic acid (5 drops) was added to a solution of Diols **48** (100 mg, 0.31 mmol) in CH₂Cl₂ (5 mL), and stirred overnight at room temperature. The solution was evaporated and the residue purified by flash chromatography on silica gel eluting with 10% ethyl acetate/hexane to give dimer **50** (81 mg, 43%) as a white solid and as a single diastereoisomer: FTIR (neat, cm⁻¹): ν_{max} 2963, 2935, 2872, 1326, 1167; ¹H NMR

(400 MHz, CDCl₃) δ 7.73 (d, J = 8.5 Hz, 4H), 7.25 (d, J = 8.5 Hz, 4H), 5.37 (s, 2H), 3.88 – 3.76 (m, 2H), 2.68 – 2.52 (m, 2H), 2.42 (s, 6H), 1.78-1.62 (m, 6H), 1.36 – 0.84 (m, 8H), 1.13 (s, 6H) 0.75 (t, J = 7.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 143.5, 138.7, 129.4, 127.8, 79.3, 74.2, 52.2, 34.1, 25.1, 23.9, 21.8, 21.6, 20.9, 14.0; MS (ESI+) m/z 310 ([M+H]⁺, 76).

5.5 Reference

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APPENDIX A

CHAPTER 2

SUPPORTING INFORMATION

A Synthesis of Pseudoconhydrine and its Epimer via Hydroformylation and Dihydroxylation

^1H and ^{13}C NMR spectra

<i>epi</i> -Pseudocinhydrine hydrochloride 6C	S2
Pseudoconhydrine hydrochloride 6D	S3
Ene-sulfonamide 147	S4
Sulfonamide 148	S5
Homoallylic amine 150	S6
Dihydropyrrole 151	S7
Diol 153	S8
Ketone 156	S9
Alcohol 157	S10
Alcohol 158	S11
Diacetate 159	S12
ORTEP structure of the bis(dinitrobenzoyl) derivative of diol 154	S13
Cartesian Coordinates and Energy Data for Computed Model Structures	S14

ORTEP structure: bis(dinitrobenzoyl) derivative of diol **154**

Cartesian Coordinates and Energy Data for Computed Model Structures

Level of theory: B3LYP/ LACV3P**// B3LYP/ LACV3P**

C₂H₄

atom	x	y	z
C1	0.0000000000	0.0000000000	0.6635583203
C2	0.0000000000	0.0000000000	-0.6635583203
H3	0.0000000000	0.9225655915	1.2347074734
H4	0.0000000000	0.9225655915	-1.2347074734
H5	0.0000000000	-0.9225655915	-1.2347074734
H6	0.0000000000	-0.9225655915	1.2347074734

SCF energy: DFT(b3lyp) -78.61389979275 hartrees

NIMAG 0

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 31.879 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
	-----	-----	-----	-----	-----	-----
trans.	0.889	2.981	35.927	1.481	-9.230	15.57911
rot.	0.889	2.981	15.849	0.889	-3.837	6.47558
vib.	0.131	2.134	0.534	0.131	-0.028	0.04703
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	1.909	8.096	52.310	2.501	-13.095	22.10172

Total internal energy, Utot (SCFE + ZPE + U): -78.560056 hartrees

Total enthalpy, Htot (Utot + pV): -78.559112 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -78.583966 hartrees

OsO₄

atom	x	y	z
O1	0.9962662077	-0.9962662077	0.9961530912
Os2	0.0000000000	0.0000000000	0.0000000000
O3	-0.9962662077	0.9962662077	0.9961530912
O4	0.9962662077	0.9962662077	-0.9961530912
O5	-0.9962662077	-0.9962662077	-0.9961530912

SCF energy: DFT(b3lyp) -392.01040948286 hartrees

NIMAG 0

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 7.852 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
	-----	-----	-----	-----	-----	-----
trans.	0.889	2.981	42.519	1.481	-11.196	18.89655
rot.	0.889	2.981	23.282	0.889	-6.053	10.21580
vib.	1.331	9.790	6.871	1.331	-0.718	1.21156
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	3.108	15.752	72.672	3.701	-17.966	30.32391

Total internal energy, Utot (SCFE + ZPE + U): -391.992943 hartrees

Total enthalpy, Htot (Utot + pV): -391.991999 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -392.026528 hartrees

atom	x	y	z
O1	1.3705353571	-1.1120311370	0.9539299203
Os2	0.4541961306	-0.0229455826	-0.0227212295
O3	-0.8476922826	-0.8648044448	-0.8844630524
O4	-0.6656554106	0.9411458987	0.9584518327
O5	1.3749844625	0.9734269468	-1.0899721571
C6	-2.6956678040	0.6199835174	0.6257610066
C7	-2.7928924815	-0.3429305824	-0.3556559328
H8	-2.8030587738	1.6680854337	0.3817454964
H9	-2.9781704064	-0.0645997010	-1.3841406103
H10	-2.9806511734	-1.3761096520	-0.0970485202
H11	-2.8060479486	0.3566093824	1.6688482741

SCF energy: DFT(b3lyp) -470.61686631534 hartrees

NIMAG 1: -328 cm⁻¹

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 41.577 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
trans.	0.889	2.981	42.829	1.481	-11.288	19.05244
rot.	0.889	2.981	28.445	0.889	-7.592	12.81424
vib.	2.943	20.268	16.687	2.943	-2.033	3.43051
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	4.720	26.229	87.962	5.313	-20.913	35.29719

Total internal energy, Utot (SCFE + ZPE + U): -470.543086 hartrees

Total enthalpy, Htot (Utot + pV): -470.542142 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -470.583936 hartrees

atom	x	y	z
O1	-0.7207872290	-1.3079245389	-1.1930252317
Os2	0.0000000000	0.0000000000	-0.3478896075
O3	-1.0676842668	0.6556974260	1.1047359341

O4	1.0676842668	-0.6556974260	1.1047359341
O5	0.7207872290	1.3079245389	-1.1930252317
C6	0.4653987317	-0.5937494641	2.4189574691
C7	-0.4653987317	0.5937494641	2.4189574691
H8	1.2813303359	-0.5087595541	3.1392997842
H9	0.0753430833	1.5300694478	2.5912504232
H10	-1.2813303359	0.5087595541	3.1392997842
H11	-0.0753430833	-1.5300694478	2.5912504232

SCF energy: DFT(b3lyp) -470.67565458709 hartrees

NIMAG 0

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 44.377 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
	-----	-----	-----	-----	-----	-----
trans.	0.889	2.981	42.829	1.481	-11.288	19.05244

rot.	0.889	2.981	26.816	0.889	-7.107	11.99442
vib.	2.651	18.624	14.905	2.651	-1.793	3.02557
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	4.429	24.586	84.551	5.021	-20.187	34.07243

Total internal energy, Utot (SCFE + ZPE + U): -470.597877 hartrees

Total enthalpy, Htot (Utot + pV): -470.596933 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -470.637106 hartrees

atom	x	y	z
C1	1.9459310270	-2.5003942289	0.3633775209
C2	1.8516676330	-1.4718908944	-0.5727663472
C3	1.8657969420	-1.7457089169	-1.9370197882
C4	1.9617767389	-3.0676182182	-2.3627917375
C5	2.0444471897	-4.1202082477	-1.4466568712
C6	2.0362068921	-3.8133950420	-0.0800750783
S7	1.7117955031	0.2310286199	-0.0098323697
O8	2.5367162059	0.3620274985	1.1855620056
C9	2.1786001735	-5.5479999854	-1.9134983315

N10	0.1155635898	0.4261169056	0.4921138300
C11	-0.2140434661	0.3268600595	1.8578920259
C12	-1.4081806295	0.6817308958	2.3418899986
C13	-2.4767249297	1.2970357460	1.4814522282
C14	-1.8749703124	1.7932063380	0.1601189365
C15	-0.9578063157	0.7377737050	-0.4843938374
H16	-0.4681702187	1.1897076514	-1.3481826054
O17	1.8937081129	1.0808689022	-1.1824390598
H18	0.5812172063	-0.0392648942	2.4909987496
H19	-1.5885124773	0.5496011498	3.4019158946
H20	-3.2883983290	0.5810369551	1.2942329981
H21	-2.9418695900	2.1369063731	2.0087035116
H22	-2.6584868450	2.0764176162	-0.5459411759
H23	-1.2737364582	2.6867549682	0.3497536491
C24	-1.6859883319	-0.5450475101	-0.9313357961
H25	1.8176737778	-0.9312850888	-2.6483865386
H26	1.9770411302	-3.2814552359	-3.4261801397
H27	2.1084620536	-4.6145939560	0.6477765645
H28	1.9653810201	-2.2753164611	1.4219391937
H29	1.6560596144	-6.2363310033	-1.2452210507
H30	1.7774145443	-5.6786273317	-2.9204337531
H31	3.2310170704	-5.8506526793	-1.9361413149
H32	-2.1571886854	-1.0215248310	-0.0650719005
C33	-2.7275614106	-0.3215217196	-2.0348858913
H34	-0.9356942390	-1.2533182517	-1.2955880725
C35	-3.3216899305	-1.6337398186	-2.5558930664
H36	-3.5382425621	0.3157823300	-1.6668558637
H37	-2.2633016489	0.2230332261	-2.8664876061

H38 -4.0633016477 -1.4514562812 -3.3382385673
H39 -2.5448562576 -2.2796950800 -2.9761790301
H40 -3.8151627948 -2.1903967590 -1.7532319520

SCF energy: DFT(b3lyp) -1187.79162395178 hartrees

NIMAG 0

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature
are kelvins, the units for U, H, and G are
kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 211.530 kcal/mol
is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
	-----	-----	-----	-----	-----	-----
trans.	0.889	2.981	42.778	1.481	-11.273	19.02664
rot.	0.889	2.981	33.851	0.889	-9.204	15.53434
vib.	10.376	67.170	72.477	10.376	-11.233	18.95963
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	12.153	73.131	149.106	12.746	-31.710	53.52061

Total internal energy, Utot (SCFE + ZPE + U): -1187.435163 hartrees

Total enthalpy, Htot (Utot + pV): -1187.434219 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1187.505064 hartrees

atom	x	y	z
C1	1.6093154977	-3.0976909627	-2.1989579598
C2	1.9745516996	-2.5850199870	-0.9554707959
C3	2.6241947982	-3.3752884877	-0.0090925559
C4	2.8843005936	-4.7083366193	-0.3106212115
C5	2.5116038403	-5.2581936979	-1.5407920806
C6	1.8820041351	-4.4293829246	-2.4784603206
S7	1.6513670904	-0.8662965985	-0.5743941024
O8	2.5010549271	-0.5038788450	0.5526280498
C9	2.7618752748	-6.7112222517	-1.8526191144
N10	0.0229022747	-0.8392662054	0.0347962901
C11	-0.2165757580	-1.2833357718	1.4418885733
C12	-1.6453998262	-1.8366881709	1.5468000937
C13	-2.6743279960	-0.8288535270	1.0281365981

C14	-2.3331287448	-0.4462875942	-0.3829048965
C15	-0.9873746779	-0.4117704433	-0.7868435700
C16	0.0778929680	-0.1343873477	2.4285170053
C17	0.1017983232	-0.5716548796	3.8986728489
C18	0.5183875301	0.5676515653	4.8341022507
O19	1.6234789658	-0.0856459699	-1.8008977708
O20	-3.2725934208	-2.0258225384	-1.1723751657
Os21	-2.5655401587	-2.9004020887	-2.5624823230
O22	-2.1369574421	-4.5290333477	-2.1599564702
O23	-1.1177306171	-1.8605434389	-2.5329553508
O24	-3.4925982786	-2.6654846395	-4.0023727672
H25	-0.6750844252	0.1558604497	-1.6473623269
H26	-3.0016550432	0.2146488157	-0.9176237582
H27	0.4840949134	-2.0989706125	1.6382952306
H28	-2.6948768419	0.0694602054	1.6572641191
H29	-3.6788965565	-1.2545157535	1.0571450032
H30	-1.8472119110	-2.0979703392	2.5867526363
H31	-1.7226530323	-2.7578751684	0.9640474815
H32	1.1114158673	-2.4679262713	-2.9224927498
H33	1.5973803331	-4.8338411680	-3.4434298202
H34	3.3925027184	-5.3266813271	0.4210321772
H35	2.9458309296	-2.9448262110	0.9301438307
H36	3.4913091849	-7.1489476962	-1.1689509728
H37	1.8346530187	-7.2871854686	-1.7659276366
H38	3.1287585186	-6.8395964555	-2.8738006696
H39	-0.6592853731	0.6639682702	2.2891170874
H40	1.0494081034	0.2893052720	2.1730551808
H41	-0.8802031062	-0.9457720695	4.2071957818

H42	0.8010879505	-1.4089284411	4.0136522372
H43	0.5361741026	0.2381618139	5.8760869006
H44	1.5159134445	0.9389228609	4.5826997692
H45	-0.1761489269	1.4104475601	4.7640465348

SCF energy: DFT(b3lyp) -1579.80001713296 hartrees

NIMAG 1: -273 cm⁻¹

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 220.368 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)

trans.	0.889	2.981	44.718	1.481	-11.851	20.00272
rot.	0.889	2.981	36.087	0.889	-9.871	16.65952
vib.	13.892	86.349	98.761	13.892	-15.554	26.25152
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	15.669	92.310	179.565	16.262	-37.275	62.91376

Total internal energy, Utot (SCFE + ZPE + U): -1579.423868 hartrees

Total enthalpy, Htot (Utot + pV): -1579.422924 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1579.508241 hartrees

atom	x	y	z
C1	2.0245546679	-3.3945268091	-2.0499818787
C2	2.5236682066	-2.7111592225	-0.9418016438
C3	3.3993417185	-3.3280027093	-0.0530132899
C4	3.7678945551	-4.6524227756	-0.2745417670
C5	3.2777037023	-5.3656038312	-1.3711793615
C6	2.4059967843	-4.7132238128	-2.2540727162
S7	2.0864210444	-0.9869419644	-0.6792817765
O8	2.9669266423	-0.4872887774	0.3703102781
C9	3.6636071572	-6.8053011194	-1.5997184791
N10	0.5065633378	-0.9708095685	-0.0328154674
C11	0.3031450453	-1.5040460365	1.3482319705
C12	-1.1146411967	-2.0886876274	1.4365194478
C13	-2.1721665914	-1.0474772401	1.0547312169

C14	-1.8998339238	-0.4121973451	-0.3234370507
C15	-0.5761091070	-0.8362067686	-0.9501645606
C16	0.5938418309	-0.4109625118	2.3951466258
C17	0.5761292424	-0.9052561227	3.8465445028
C18	0.9997841585	0.1863492523	4.8342494324
O19	1.9882547214	-0.3241491138	-1.9742525887
O20	-2.9252542788	-0.8014650126	-1.2710997165
Os21	-2.6074806163	-2.3616055411	-2.3437687967
O22	-3.4431772430	-3.7057258240	-1.6765432400
O23	-0.8514685912	-2.1257372720	-1.6203236976
O24	-2.6098014116	-2.0619733406	-4.0329047545
H25	-0.2788140713	-0.1505614970	-1.7419326246
H26	-1.9623753809	0.6760849030	-0.2779756741
H27	1.0137190149	-2.3242677059	1.4959852858
H28	-2.2112766527	-0.2588906199	1.8093361674
H29	-3.1664564456	-1.4987316733	1.0281543099
H30	-1.2910858988	-2.4432587275	2.4535190781
H31	-1.1823865993	-2.9601081304	0.7814820914
H32	1.3506684569	-2.9011443977	-2.7363463987
H33	2.0247237258	-5.2456813800	-3.1188957030
H34	4.4560907793	-5.1321940357	0.4127957182
H35	3.8044494154	-2.7677433747	0.7792870711
H36	4.5451604911	-7.0800893591	-1.0180328231
H37	2.8494372922	-7.4765140047	-1.3067889287
H38	3.8772904380	-6.9954882586	-2.6543595162
H39	-0.1213151847	0.4103341261	2.2734135295
H40	1.5772603314	0.0050375928	2.1727743831
H41	-0.4213559794	-1.2660005410	4.1205058878

H42	1.2509899859	-1.7647398927	3.9441949373
H43	0.9868753794	-0.1814785078	5.8634952702
H44	2.0110044574	0.5421145694	4.6175366280
H45	0.3278476043	1.0485695877	4.7810144795

SCF energy: DFT(b3lyp) -1579.84907404811 hartrees

NIMAG 0

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 222.730 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
	-----	-----	-----	-----	-----	-----
trans.	0.889	2.981	44.718	1.481	-11.851	20.00272
rot.	0.889	2.981	36.197	0.889	-9.903	16.71490
vib.	13.594	85.315	95.901	13.594	-14.999	25.31524
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	15.371	91.277	176.815	15.964	-36.754	62.03286

Total internal energy, Utot (SCFE + ZPE + U): -1579.469635 hartrees

Total enthalpy, Htot (Utot + pV): -1579.468690 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1579.552701 hartrees

atom	x	y	z
C1	1.0411605404	-2.1724535627	0.2264070620
C2	1.2082532992	-1.0884808219	-0.6336627661
C3	1.4858092430	-1.2700509804	-1.9863488204
C4	1.5863038660	-2.5656364819	-2.4831989720
C5	1.4098560145	-3.6753448584	-1.6513346589
C6	1.1403927564	-3.4558662788	-0.2937185288
S7	1.1150221511	0.5782559759	0.0109098328
O8	1.7965444996	0.6398063738	1.2952731329
C9	1.4827661208	-5.0760724079	-2.2036722233
N10	-0.5606123192	0.8339914735	0.3684847515
C11	-0.9650175748	0.8802534271	1.6731165289
C12	-2.2460969787	1.3266522779	2.0234476312
C13	-3.1056853790	2.0597053411	1.0196705880

C14	-2.3487141507	2.3434077078	-0.2858234836
C15	-1.5072711222	1.1391978034	-0.7388571274
H16	-0.8871973242	1.4547562760	-1.5791357228
O17	1.4305122266	1.4954147183	-1.0770606298
H18	-0.1839836484	0.7871705362	2.4089627213
H19	-2.3849492567	1.5526960955	3.0709950395
H20	-4.0128380743	1.4783833596	0.8305414600
H21	-3.4384959821	3.0026275616	1.4635117409
H22	-3.0467702676	2.6212590789	-1.0776171439
H23	-1.6690683064	3.1888549473	-0.1462155733
C24	-2.3148355538	-0.1055915184	-1.1489485891
H25	1.6353003897	-0.4120454821	-2.6274192386
H26	1.8110036826	-2.7134644594	-3.5342569522
H27	1.0045410496	-4.3042647232	0.3687200619
H28	0.8186810237	-2.0165002160	1.2730917009
H29	1.8737132792	-5.7760997014	-1.4627057115
H30	0.4865600218	-5.4280058924	-2.4917265883
H31	2.1179454764	-5.1240294537	-3.0904136120
H32	-2.9781591299	-0.4062708823	-0.3338478733
C33	-3.1359025121	0.0876848434	-2.4298553372
H34	-1.6154039240	-0.9335904919	-1.2978519263
C35	-3.8276025542	-1.2048055866	-2.8737963595
H36	-3.8928372025	0.8648818021	-2.2788351062
H37	-2.4810784161	0.4477249316	-3.2330160943
H38	-4.4243412028	-1.0449821821	-3.7757175563
H39	-3.0961319081	-1.9891198321	-3.0902577606
H40	-4.4930486447	-1.5838040637	-2.0927784840
O41	-1.1092440541	-1.2711742252	2.3997018700

O42	-3.4701112213	-0.2796989253	2.2564989870
Os43	-2.7715359549	-1.8919596204	2.5784050893
O44	-3.1328772433	-3.0093956972	1.3055620593
O45	-3.0878185065	-2.4136238817	4.1957077013

SCF energy: DFT(b3lyp) -1579.80128686007 hartrees

NIMAG 1: -254 cm⁻¹

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 220.286 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
trans.	0.889	2.981	44.718	1.481	-11.851	20.00272
rot.	0.889	2.981	35.904	0.889	-9.816	16.56734
vib.	13.995	86.495	99.877	13.995	-15.783	26.63826
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	15.773	92.456	180.498	16.365	-37.450	63.20832

Total internal energy, Utot (SCFE + ZPE + U): -1579.425103 hartrees

Total enthalpy, Htot (Utot + pV): -1579.424159 hartrees

Total Gibbs free energy, Gtot (Htot - T*S): -1579.509919 hartrees

atom	x	y	z
C1	0.9690409094	-2.6015663260	-0.2791914091
C2	1.2505415248	-1.4634536989	-1.0307847336
C3	1.6954306493	-1.5613378548	-2.3469254254
C4	1.8524163092	-2.8207997994	-2.9143653333
C5	1.5713248422	-3.9832593624	-2.1880567862
C6	1.1288376576	-3.8511401318	-0.8667688721
S7	1.0806236173	0.1665459939	-0.2936793479
O8	1.7544577596	0.1591274136	1.0003233952
C9	1.7584028499	-5.3417134068	-2.8157276758
N10	-0.5694964597	0.3923604093	0.0496308992
C11	-1.0351114207	0.1604310688	1.3751243087
C12	-2.1705422626	1.0763699037	1.8181249982
C13	-3.1905623795	1.3661550772	0.7191681103

C14	-2.4783389377	1.7800472096	-0.5717416029
C15	-1.5102565688	0.6920777555	-1.0641439045
H16	-0.8942407445	1.1315379443	-1.8502489809
O17	1.4206769394	1.1396338845	-1.3262089711
H18	-0.1905155426	0.2444701910	2.0578963717
H19	-1.7561650227	2.0061100990	2.2162590315
H20	-3.7991294587	0.4731468564	0.5477903130
H21	-3.8715714634	2.1482038090	1.0622465182
H22	-3.2109230996	1.9989579678	-1.3511482243
H23	-1.9066057221	2.6982556686	-0.4039869172
C24	-2.1869549006	-0.5736611607	-1.6277925077
H25	1.9181214065	-0.6620610128	-2.9060062967
H26	2.2005503138	-2.8997618907	-3.9389049095
H27	0.9047391762	-4.7397584615	-0.2870075463
H28	0.6125072235	-2.5162635257	0.7391530758
H29	1.3508432352	-6.1336181041	-2.1853682713
H30	1.2678886185	-5.3970562134	-3.7913792967
H31	2.8205002028	-5.5538497890	-2.9744406529
H32	-2.8324243594	-1.0309603610	-0.8720542894
C33	-2.9810068065	-0.3289404677	-2.9172651325
H34	-1.4036777413	-1.3087636112	-1.8328840094
C35	-3.4962283340	-1.6288825103	-3.5425616250
H36	-3.8311045762	0.3330499780	-2.7205128411
H37	-2.3446928462	0.1954768639	-3.6408319544
H38	-4.0622488795	-1.4320317432	-4.4567997202
H39	-2.6689271566	-2.2973417365	-3.7990054440
H40	-4.1540467277	-2.1662138539	-2.8528804810
O41	-1.5488097627	-1.2137523488	1.5175766429

O42	-2.8063775833	0.4200732197	2.9356430180
Os43	-2.8127271420	-1.5029171117	2.9304226931
O44	-4.3349378105	-2.0776393654	2.3801643345
O45	-2.0346446804	-2.2034599174	4.2894150966

SCF energy: DFT(b3lyp) -1579.85454310387 hartrees

NIMAG 1: -28 cm⁻¹

Thermodynamic properties calculated assuming an ideal gas

In the table below, the units for temperature

are kelvins, the units for U, H, and G are

kcal/mol and the units for Cv and S are cal/(mol K)

The zero point energy (ZPE): 222.729 kcal/mol

is not included in U, H, or G in the table below

T = 298.15 K

	U	Cv	S	H	G	ln(Q)
trans.	0.889	2.981	44.718	1.481	-11.851	20.00272
rot.	0.889	2.981	36.069	0.889	-9.865	16.65078
vib.	13.041	83.347	88.779	13.041	-13.429	22.66511
elec.	0.000	0.000	0.000	0.000	0.000	0.00000
total	14.818	89.308	169.566	15.411	-35.145	59.31862

Total internal energy, U_{tot} (SCFE + ZPE + U): -1579.475987 hartrees

Total enthalpy, H_{tot} (U_{tot} + pV): -1579.475043 hartrees

Total Gibbs free energy, G_{tot} (H_{tot} - T^*S): -1579.555609 hartrees

APPENDIX B

CHAPTER 3

SUPPORTING INFORMATION

A Synthesis of Azimic Acid Using Hydroformylation

^1H and ^{13}C NMR spectra

Oxazolidine 134	S37
Amino alcohol 131	S38
Diene 133	S39
Aldehyde 138	S40
Carboxylic acid 139	S41
Ester 140	S42
Diols 141	S43
Acetates 144	S44
Acetate 146	S45
Acetate 147	S46
ORTEP structure of the bis(dinitrobenzoyl) derivative of diol 147	S47
Alcohol 151	S48
Azimic acid 9	S49
Oxazolidine 135	S50

ORTEP diagram of acetate **147**

¹H NMR spectra of compound **151** ¹³C NMR spectra of compound **151**

APPENDIX C

CHAPTER 4

SUPPORTING INFORMATION

Syngas-Mediated C-C Bond Formation in Flow: Selective Rhodium-Catalysed Hydroformylation of Styrenes

^1H , ^{13}C and ^{19}F NMR spectra

2-(2-fluorophenyl)propanal S52

2-phenylpropanal S54

2-(4-methoxyphenyl)propanal S55

2-(4-(trifluoromethyl)phenyl)propanal S56

2-(4-fluorophenyl)propanal S58

2-(p-tolyl)propanal S60

2-(3-methoxyphenyl)propanal S61

2-(4-chlorophenyl)propanal S62

2-(o-tolyl)propanal S63

2-(3,4-dimethoxyphenyl)propanal S64

2-(4-methylthiazol-5-yl)propanal S65

Internal Standard Experiment S66

¹H NMR of 2-(2-fluorophenyl)propanal

¹³C NMR of 2-(2-fluorophenyl)propanal

^{19}F NMR of 2-(2-fluorophenyl)propanal

¹H NMR of 2-phenylpropanal

¹³C NMR of 2-phenylpropanal

¹H NMR of 2-(4-methoxyphenyl)propanal

¹³C NMR of 2-(4-methoxyphenyl)propanal

¹H NMR of 2-(4-(trifluoromethyl)phenyl)propanal

¹³C NMR of 2-(4-(trifluoromethyl)phenyl)propanal

^{19}F NMR of 2-(4-(trifluoromethyl)phenyl)propanal

¹H NMR of 2-(4-fluorophenyl)propanal

¹³C NMR of 2-(4-fluorophenyl)propanal

^{19}F NMR of 2-(4-fluorophenyl)propanal

¹H NMR of 2-(p-tolyl)propanal

¹³C NMR of 2-(p-tolyl)propanal

¹H NMR of 2-(3-methoxyphenyl)propanal

¹³C NMR of 2-(3-methoxyphenyl)propanal

¹H NMR of 2-(4-chlorophenyl)propanal

¹³C NMR of 2-(4-chlorophenyl)propanal

¹H NMR of 2-(o-tolyl)propanal

¹³C NMR of 2-(o-tolyl)propanal

¹H NMR of 2-(3,4-dimethoxyphenyl)propanal

¹³C NMR of 2-(3,4-dimethoxyphenyl)propanal

¹H NMR of 2-(4-methylthiazol-5-yl)propanal

¹³C NMR of 2-(4-methylthiazol-5-yl)propanal

Internal Standard Experiment

Method 3 (Shifts in minutes)

Styrene: 11.814

Branched aldehyde: 21.700

Linear aldehyde: 26.368

Decane: 1.832

Initial analysis of reaction mixture (Area)

Styrene: 233.7

Decane: 51.9

After reaction analysis of reaction mixture (Area)

Styrene: 4.9

Branch: 39.4

Linear: 4.9

Decane: 9.8

Calculation of conversion with internal standard

Relative Styrene: $4.9 / 9.8 = 0.5$

Relative Aldehyde: $(39.4 + 4.9) / 9.8 = 4.5$

Relative Conversion: $4.5 / (0.5 + 4.5) = 0.9$ (Hence, 90% conversion)

Calculation of the amount of styrene left

Initial = Styrene / Decane = $233.7 / 51.9 = 4.5$

Reaction = Styrene / Decane = $4.9 / 9.8 = 0.5$

Hence, amount of styrene left, $0.5 / 4.5 = 0.11$ (Thus, 11% left)

APPENDIX D

CHAPTER 5

SUPPORTING INFORMATION

1,2-Alkyl Shift

^1H and ^{13}C NMR spectra

Iodinated enamine 15	S68
Hydroxy piperidine 16	S69
Enamine 17	S70
Cyclopropane 19	S71
Exo-alkene 32	S72
Diol 48	S73
Dimer 50	S74
ORTEP structure of dimer 50	S75

ORTEP structure of dimer **50**