Metal catalysed reductions: Application and development of new synthetic strategies

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A Thesis submitted for the degree of Doctor of Philosophy

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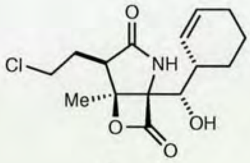
March 2010

Contents

Abstract

Development of reductive aldol cyclisation methodologies in the Lam group led to the point where it was possible to initiate a total synthesis using this highly valuable transformation. Upon analysis of possible synthetic targets a salinosporamide A (**1**) was chosen. This molecule was recently isolated from marine micro-organisms and attracted a lot of attention in scientific community because of its highly bioactive properties.



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Scheme 1: Structure of salinosporamide A

Application of a reductive aldol cyclisation in the formal synthesis of salinosporamide A led to a concise synthetic pathway. A nickel-catalysed reductive aldol cyclisation with a sequential lactonisation step was employed in the construction of the γ-lactam core of **1**. In the key step of synthesis we installed the C2 side-chain of the γ-lactam core, the C5 oxygen was protected for later modification and a ready to reduce γ-lactone ring was prepared for a reduction in a late stage of formal synthesis.

Upon completion of salinospormaide A (formal synthesis) a new methodology was devised. A copper-catalysed asymmetric reduction of 2-alkenylheteroarenes was based on published procedures for enantioselective reduction of alkenes activated with strong electron-withdrawing substituents. We questioned whether a much less electron withdrawing groups could be used in a similar fashion. A selection of nitrogen based heterocycles have been successfully employed for activation of alkenes. Extensive screening of reaction conditions afforded a high yielding and selective catalyst system for the asymmetric reduction of conjugated 2-alkenylheteroarenes.

Acknowledgments

I would like to thank Dr Hon Wai Lam for the opportunity to work in his group. Patience and encouragement I received allowed successfully completion of this work. Thanks to Isabel Villanueva salinosporamide A synthesis was synthesised in less then infinite time. Thanks also to Aakarsh Saxena for his help during my second project.

Finally, a very big thank you to all of you who I had fun with during my studies, your contribution will never be forgotten: Florian Achrainer, Beatriz Ballesteros, Sarah Boys, Brat, Samantha Brogan, Armando Carlone, Serghei Chercheja, Max Von Delius, Philip Dorgan, Alba Dornadair, Charlene Fallan, Euan Fordyce, Edzard Geertsema, Emiliano Gemma, Araceli Gonzalez-Campana, Benoit Gourdet, Philipp M. E. Gramlich, Kevin Haenni, Mary Ieva, Pekka Joensuu, Marius Kroll, Felicia Landi, Bartek Lewandowski, Ula Lewandowska, Ania Loksztejn, Darryl Low, Ralph Lumby, Monika Machulska, Paul McGonigal, Monika Mruczek, Gordon Murray, Gordon Nimmo-Smith, Claire Oswald, Graham Pattison, Zbyszek Pianowski, Oscar Prieto, Mairi Rudkin, Aakarsh Saxena, Myriam Scansetti, Christina Simpson, Siostra, Donna Smith, Isabel Villanueva, Yi Wang, Jhenyi Wu, David Yeaman.

Abbreviations

°C	degrees celsius
Ac	acetyl
acac	acetyl acetonate
AIBN	2,2-azobis(isobutyronitrile)
Aq	aqueous
Ar	aromatic group
Atm	atmosphere(s)
ATP	adenosine 5'-triphosphate
BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2-bis(diphenylphosphino)-1,1-binaphthyl
MeO-BIPHEP	(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine))
Bn	benzyl
Boc	tert-butoxycarbonyl
BOPCl	N,N-bis(2-oxo-3-oxazolidinyl)-phosphinic chloride
BOX	2,2-isopropylidenebis-2-oxazoline
Bu	butyl
Cald	Calculated
CAN	Cerium(IV) ammonium nitrate
Cat	catalytic; catalyst
COD	cyclooctadiene
Cp	cyclopentadiene
CSA	camphor sulfonic acid
cy	cyclohexyl
d	doublet
DCM	dichloromethane
DMA	dimethylacetamide
DCC	N,N-dicyclohexylcarbodiimide

dd	doublet of doublets
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride
DIC	N,N-diisopropylcarbodiimide
DIMCARB	dimethylamine carbon dioxide complex
DMAP	4-dimethylaminopyridine
DME	dimethylether
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DPPB	1,2-bis(diphenyl-phosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1 -bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
(S,S)-Et-DuPhos	(+)-1,2-bis((2S,5S)-2,5-diethylphospholano)benzene
EDC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron ionization
EtOAc	ethyl acetate
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
FAB	fast atom bombardment
g	gram
h	hour
HMPA	hexametylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	Hertz
*i*Pr	iso-propyl
IR	infra red spectroscopy
J	coupling constant
KHMDS	potassium bis-(trimethylsilyl)amide
L	litre
LDA	lithium diisopropylamide
LHMDS	lithium bis-(trimethylsilyl)amide
LRMS	low resolution mass spectrometry
MAO	methylaluminoxane
M	Molar
m.p.	melting point
MeOH	methanol
Me	methyl
MeCN	acetonitrile
Me-DuPhos	1,2-Bis(2,5-dimethylphospholano)benzene
mg	milligram
min	Minute
mL	millilitre
mmol	millimole
mol	mole
MsCl	methanesulfonyl chloride
NaHMDS	sodium bis-(trimethylsilyl)amide
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	p-methoxybenzyl

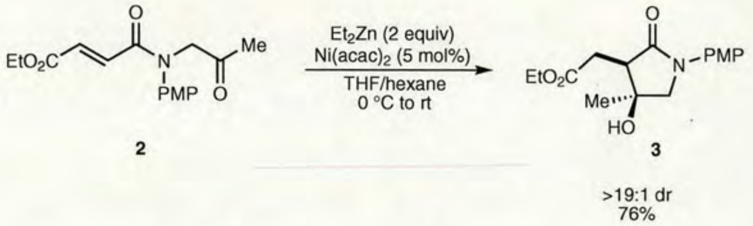
PMHS	polymethylhydrosiloxane
ppm	parts per million
Pr	propyl
p-TsOH	p-toluenesulfonic acid
pybox	2,6-bis(oxazolinyl)pyridine
q	quartet
rac-BINAP	racemic 2,2 -bis(diphenylphosphino)-1,1 -binaphthyl
rt	room temperature
sal	salicylaldehydate
SEGPHOS	(S)-(4,4-bi-1,3-benzodioxole)-5,5-diylbis(diphenylphosphine)
t	triplet
TBS	tert-butyldimethylsilyl
t-BuOH	tert-butanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
Thr	threonine
TLC	thin layer chromatography
TBAF	tetrabutylammonium fluoride
TMDS	1,1,3,3-tetramethylhydrosiloxane
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

Chapter 1

Formal Synthesis of Salinosporamide A

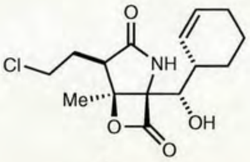
The synthesis of naturally occurring compounds has been the foundation of organic chemistry. The first synthesis of this kind was the synthesis of urea [$CO(NH_2)_2$] by Woehler in 1828.[1] It was followed by the synthesis of acetic acid[2] (Kolbe, 1845), glucose[3] (Fischer, 1890), camphor (Komppa, 1903) and many others. Modern chemists consider these compounds as building blocks (because of their simplicity) and not synthetic targets. Several generations of chemists have provided us with the tools and skills that allow the synthesis of almost any desired molecule. However, despite this long history and over 20 Nobel Prizes awarded for related fields organic synthesis is still full of challenges.

Advances in transition metal-catalysed cyclisation reactions have provided the means to access increasingly diverse carbocyclic and heterocyclic compounds from relatively simple starting materials, often with impressive levels of diastereo- and enantioselectivity.[4–16] Reductive cyclisations, where the reaction is promoted by stoichiometric reductants such as molecular hydrogen, silanes, formic acid, stannanes, borohydrides or main group organometallic reagents, represent an important class of these transformations.[10–16] Many of these reactions have been developed to a level of utility that enable their application in natural product synthesis.[17–25]



Scheme 1.1: Example of reductive aldol cyclisation

Previous research in the Lam group has led to the development of a series of metal-catalysed reductive aldol cyclisation reactions that form β-hydroxylactones and β-hydroxylactams in a highly diastereoselective fashion.[26–29] A notable result is the cyclisation of **2** using $Ni(acac)_2$ as the precatalyst and Et_2Zn as the stoichiometric reductant, which provided β-hydroxy-γ-lactam **3** as a single diastereomer.[29,30] This outcome was of interest to us because examination of the structure of **3** revealed similarities with the core of salinosporamide A (**1**) (Scheme 1.2), a secondary metabolite isolated by Fenical.[31] A full discussion of nickel catalysed reductive aldol reactions will be provided in section 1.3.



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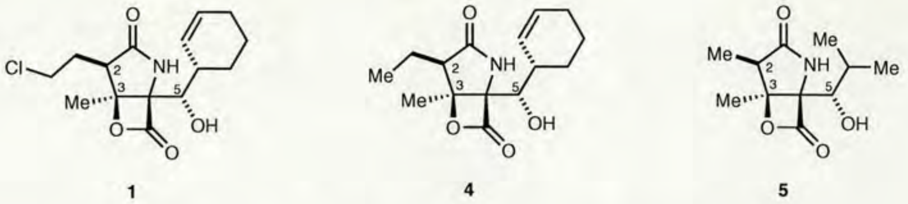
Scheme 1.2: Structure of Salinosporamide A

1.1 Biological background

Salinosporamide A (**1**) is structurally related to omuralide **5** (isolated in 1991 by Omura[32,33]) Omuralide was one of the first 20S proteasome inhibitors. This complex regulates protein degradation and can be an important target for anti-cancer drugs.



Scheme 1.3: Analogues of Salinosporamide A

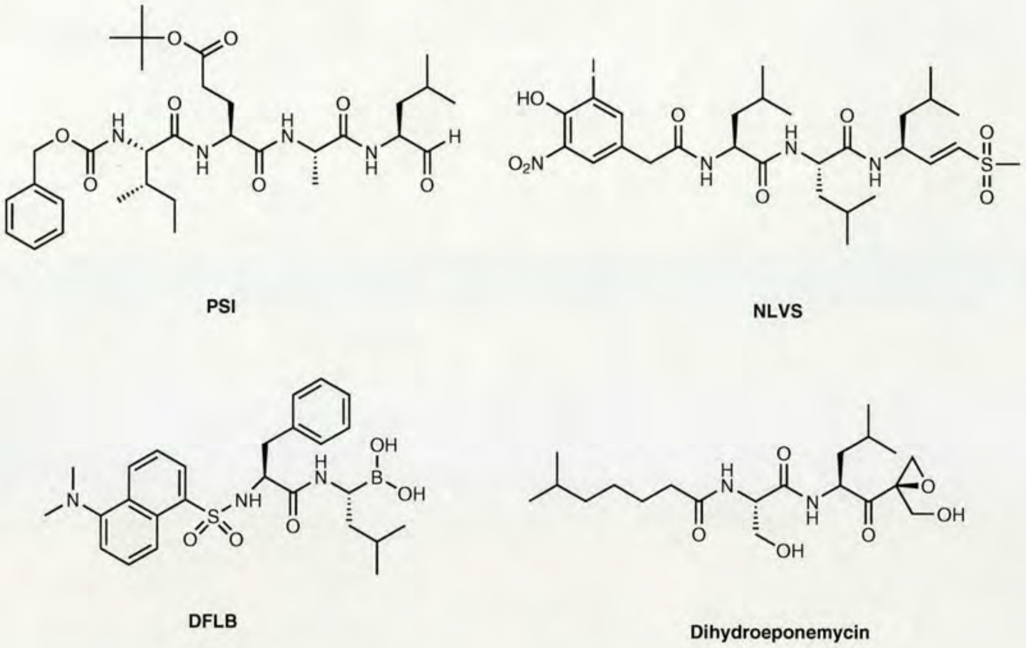
Ubiquitin-mediated proteolysis

A large part of protein degradation is mediated through the ubiquitin pathway. Ubiquitin is a highly conserved 76 amino acid protein capable of being covalently linked to lysine residues in protein targets. A cascade of enzymatic events that covalently tag substrates with polyubiquitin chains most commonly trigger regulated intracellular protein degradation by a multisubunit protease known as the proteasome.

Protein degradation is a commonly employed mechanism for the control of protein abundance. It is a particularly effective method for promoting unidirectional cell cycle transitions because of its rapidity and irreversibility. Major cell cycle transitions require the degradation of specific proteins via the ubiquitin-26S proteasome pathway. The formation of ubiquitin-protein conjugates involves three components that participate in a cascade of ubiquitin transfer reactions. Ubiquitin is activated as a thiol-ester on E1 in an ATP dependent reaction, transferred to an E2 as a thiol ester and, in conjunction with an E3, which functions in substrate recognition and also serves as a thiol-ubiquitin carrier. Together, these enzymes polyubiquitinate lysine residues in target proteins through formation of isopeptide bonds with ubiquitin, leading to recognition by the 26S proteasome and protein destruction.

20S Proteasome inhibition

The 26S proteasome (a 2 MDa complex) is made up of two subcomplexes: the 20S proteasome and the regulatory complex. The former is a 700 kDa cylindrical protease complex consisting of four stacks of heptameric rings with 28 subunits with molecular masses of about 20–35 kDa, whereas the latter is a 700–1000 kDa complex consisting of at least 18 subunits with molecular masses of 28–110 kDa.



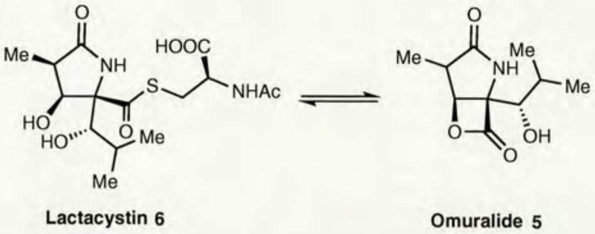
PSI **NLVS**

DFLB **Dihydroeponemycin**

Scheme 1.4: Examples of proteasome inhibitors

Enzyme-specific inhibitors of proteases are usually short peptides linked to a pharmacophore (Scheme 1.4). The pharmacophore interacts with a catalytic residue resulting in the formation of a reversible or an irreversible covalent adduct, while the peptide portion specifically associates with the enzyme substrate binding pocket at the active site. Although the proteasome has multiple active sites, inhibition of all of them is not required to significantly reduce protein breakdown.[34–36]

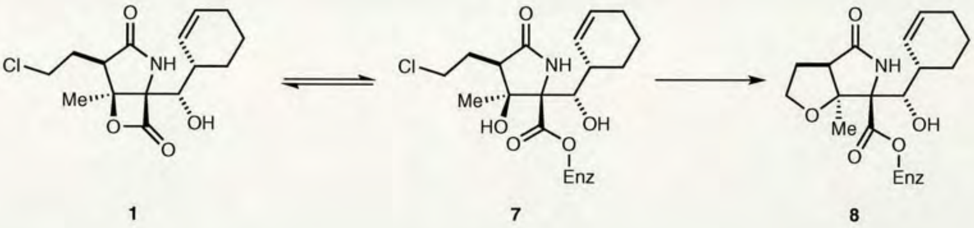
Examples of non-peptide inhibitors are lactacystin and omuralide. Lactacystin **6** is a *Streptomyces* metabolite, which was discovered by Omura and was later synthesised by Corey and co-workers.[37] Subsequent studies demonstrated that **6** itself is not active against proteasomes *in vitro* but, undergoes spontaneous transition to *clasto*-lactacystin-β-lactone,[38] for which the name "omuralide" (**5** was suggested (Scheme 1.5).[37] Kinetic analysis demonstrated that this β-lactone, but not lactacystin, reacts with the proteasome's active site threonines,[38] resulting in the opening of the β-lactone ring and acylation of the proteasome's catalytic hydroxyl. The structure of the lactacystin-proteasome complex was determined by X-ray diffraction, and provided strong evidence that an acyl enzyme conjugate is indeed an intermediate in catalysis by the proteasome.[39]



Scheme 1.5: New class of proteasome inhibitors

Discovery of salinosporamide A

In 2003, Fenical and co-workers isolated salinosporamide A (Scheme 1.2) from marine actinomycete bacteria of Salinospora strain CNB-392.[31] This compound has attracted significant attention because of its impressive biological activity.[31] Salinosporamide A (**1**) inhibits proteasomal proteolytic activity with an IC_{50} value of 1.3 nM. In a parallel assay, the IC_{50} of **5** was 49 nM. Structurally, **1** shares its fused γ-lactam-β-lactone bicyclic core with omuralide (**5**), Although omuralide (**5**) is also an effective 20S proteasome inhibitor, differences between **1** and **5** at C2, C3 and C5 render **1** approximately 35 times more potent than **5**.[31] Moreover, **1** has potent *in vitro* cytotoxicity (LC_{50} 10 nM), and it also exhibits promising potential as an anti-cancer therapeutic agent. Indeed, **1** is currently in clinical trials for this purpose.[40–42] X-ray crystallographic studies revealed that **1** binds to the same threonine residue of the proteasome that is acylated by **6**.[43] Higher activity of **1** compared to **6** is attributed to irreversible proteasome inhibition by **1** (Scheme 1.6).



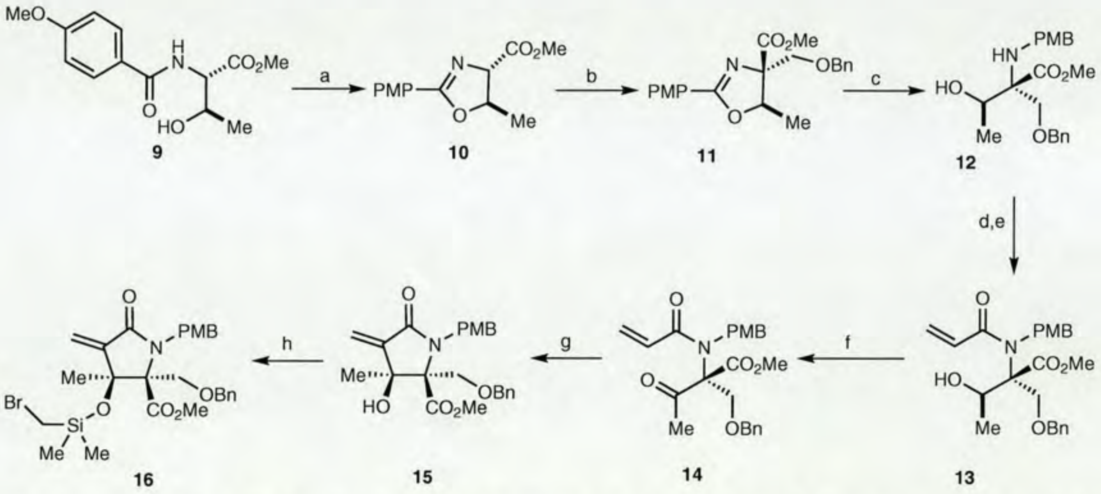
Scheme 1.6: Irreversible binding of Salinosporamide A to proteasome

1.2 Previous syntheses of salinosporamide A

Salinosporamide A (**1**) has elicited significant interest from a synthetic perspective, with a number of total and partial syntheses having been reported.[44–53] However, this molecule is only a single member of a large family of highly potent drug candidates possessing a densely functionalised γ-lactam-β-lactone fused ring system. Total synthesis of these compounds is needed to fully understand structure-activity relationships and further improve anti-cancer potency.

1.2.1 Corey's synthesis

Corey and co-workers were the first group to accomplish an enantioselective total synthesis of salinosporamide A in 2004.[45] Their synthesis was based on previous work by Corey on lactacystine and omuralide several years before.[54–57]



Conditions: (a) p-TsOH, toluene, reflux, 12 h, 80%; (b) LDA, THF-HMPA, 78 °C then $ClCH_2OBn$, 4 h, 69%; (c) $NaCNBH_3$, AcOH, 40 °C, 12 h, 90%; (d) TMSCl, Et_2O, 23 °C, 12 h; (e) Acryloyl Chloride, $i$$Pr_2NEt$, CH_2Cl_2, 1 h, 0 °C then H^+, Et_2O, 23 °C, 1 h, 96%; (f) Dess-Martin periodinane, 23 °C, 1 h, 96%; (g) Quinuclidine, DME, 0 °C, 7 d, 90%; (h) $BrCH_2Si(CH_3)_2Cl$, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min, 95%;

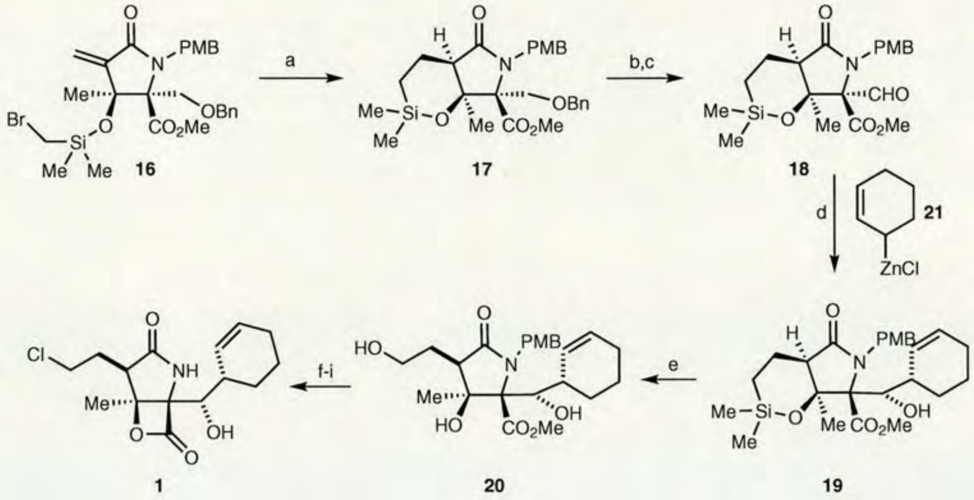
Scheme 1.7: Corey's synthesis

N-Acylation of (S)-Threonine methyl ester with 4-methoxybenzoyl chloride in DCM at 23 °C produced **9** (71%). Cyclisation of **9** to oxazoline **10** (80%) was achieved by refluxing in toluene with p-TsOH. Oxazoline **10** was deprotonated with lithium diisopropylamide in a mixture of THF and HMPA at -78 °C and the resultant anion was reacted with chloromethyl benzyl ether to selectively form the required quaternary stereocentre of **11** in 69% yield. The selective reduction of **11** with $NaBH_3CN$ gave the N-protected amino alcohol **12** (90%). The successful acylation of secondary amine **12** required a sequence of protection and deprotection steps. Reaction of **12** with TMSCl and Et_3N gave the TMS ether, that was acylated with acryloyl chloride at 0 °C, and a subsequent work up with HCl_{aq} removed the TMS protection to give **13** in 96% overall yield. Alcohol **13** was oxidised with Dess-Martin periodinane[58,59] to produce the keto amide ester **14** in 96% yield.

The key transformation of Corey's synthesis of salinosporamide A was intramolecular Baylis–Hillman-aldol[60–64] reaction of **14** using quinuclidine as a catalyst in dimethoxyethane at 0 °C for 7 d. The γ-lactam **15** was obtained in 90% yield and 9:1 diastereoselectivity, it was demonstrated that this reaction can proceed much faster at 20 °C (only 9 h as compared to 7 days). However, the ratio of diastereomers at the higher temperature was reduced to 4:1. Silylation of **15** with bromomethyldimethylsilyl chloride afforded **16** in 95% yield. At this stage the diastereoisomers produced in the Baylis–Hillman cyclisation were easily separated by silica gel column chromatography.

Reaction of **16** with tri-n-butyltin hydride and catalytic AIBN in refluxing benzene allowed the formation of the required stereocenters at C2 and C3 through radical-chain cyclisation to give **17** in 89% yield. Removal of the benzyl ether and subsequent oxidation with Dess-Martin periodinane provided **18** in 90%. Alkylation of the aldehyde **18** with **21** established the last two remaining stereocenters of **19** in 88% yield and with an impressive 20:1 diastereomeric ratio. The 2-cyclohexenylzinc chloride (**21**) reagent can be easily obtained from 1,2-cyclohexadiene by palladium catalysed 1,2-addition of tributyltin hydride and then transmetallation with n-butyllithium and zinc chloride.

Tamao-Fleming oxidation[65–67] of **19** produced triol **20** in 92% yield. Compound **20** was transformed in four steps to salinosporamide A (**1**). Firstly the PMB and methyl ester protecting groups were removed using Ce(IV)-driven oxidative cleavage (83%) and lithium hydroxide catalysed ester hydrolysis to give the corresponding γ-lactam-

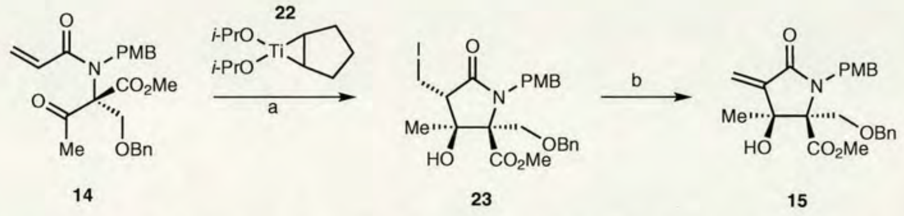


Conditions: (a) Bu_3SnH, AIBN, Benzene, reflux, 8 h, 89%; (b) Pd-C, EtOH, H_2 (1 atm), 18 h, 95%; (c) Dess-Martin periodinane, 23 °C, 1 h, 95%; (d) **21**, THF, 78 °C, 5 h, 88%; (e) KF, $KHCO_3$, H_2O_2, THF-MeOH (1:1), 23 °C, 18 h, 92%; (f) CAN, $MeCN-H_2O$; (3:1), 0 °C, 1 h, 83%; (g) 3N LiOH-THF (3:1), 5 °C, 4 d; (h) BOPCl, pyridine, DCM, 23 °C, 1 h; (i) Ph_3PCl_2, MeCN, pyridine, 23 °C, 1 h, 65% (over 3 steps).

Scheme 1.8: Corey's synthesis

carboxylic acid. The crude product was converted to β-lactone-γ-lactam with BOPCl and chlorination of the primary alcohol afforded salinosporamide A (**1**) in 65% yield over three steps.

Modifications



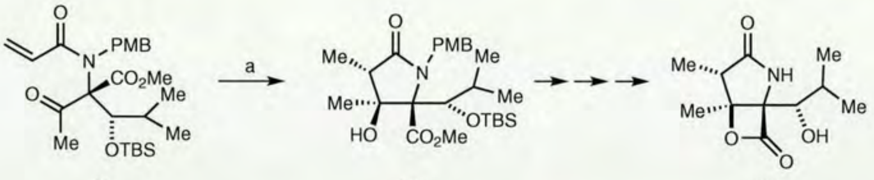
Conditions: (a) $Ti(Oi\text{-}Pr)_4$ (4 equiv), $c\text{-}C_5H_9MgCl$ (7 equiv), t-BuOMe, 40 °C, 30 min, I_2 (5 equiv), -40 °C, 2 h then 0 °C, 2 h; (b) Et_3N, DCM, 30 min, 83%.

Scheme 1.9: Corey's synthesis

The same group reported improved conditions for the cyclisation of **14** in the following year. This time compound **14** was treated with Kulinkovich reagent (**22**)[68,69] formed from $Ti(Oi\text{-}Pr)_4$ and a large excess of cyclopentylmagnesium chloride, to produce **23** after quenching with iodine α-iodomethyl-γ-lactam, that was transformed into

15 by addition of triethylamine in 83% yield. The new conditions provided **15** with complete diastereoselectivity (>99:1).[46,53]

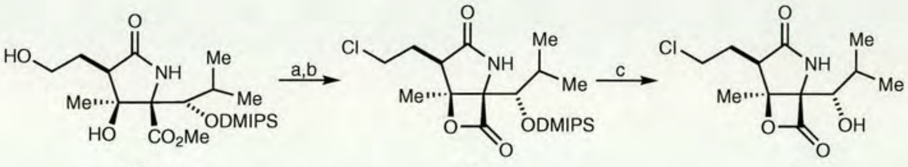
Alongside the new methodology Corey published a synthesis of 3-methyl-2-epi-omuralide[70] (Scheme 1.10 **26**). The cyclisation precursor **24** was treated with Kulinkovich reagent to give a titanium intermediate that was hydrolysed with 1 M HCl to produce γ-lactam **25** in 95% yield.


24 **25** **26**

Conditions: (a) $Ti(Oi\text{-}Pr)_4$ (4 equiv), $c\text{-}C_5H_9MgCl$ (7 equiv), t-BuOMe, -40 °C, 30 min, then 1 M *aq* HCl 95%.

Scheme 1.10: Corey's synthesis

To further improve his approach, an innovative methodology was published by Corey that facilitated methyl ester cleavage, β-lactone formation, and primary alcohol chlorination procedure in one pot.[46,53] Hydrolysis of the methyl ester was particularly difficult as **27** can go through a series of undesired reactions including retroaldol cleavage. Steric hindrance of this methyl ester makes it difficult to find a strong and yet selective agent for hydrolysis. To overcome these issues a new tellurium based reagent was developed $(Me_2TeAlMe)_2$. It can be easily formed by warming tellurium powder and trimethylaluminum in toluene for 6 h.[71] This reagent can accomplish methyl ester hydrolysis under mild conditions by selectively attacking the methyl substituent of the methyl ester rather then the carbonyl center.


27 **28** **29**

Conditions: (a) $[Me_2TeAlMe]_2$ Toluene, 23 °C, 12 h; (b) PPh_3Cl_2, DCM, pyridine, 12 h, 89%; (c) Et_3NHF, THF, 23 °C, 4 h, 92%.

Scheme 1.11: Corey's synthesis

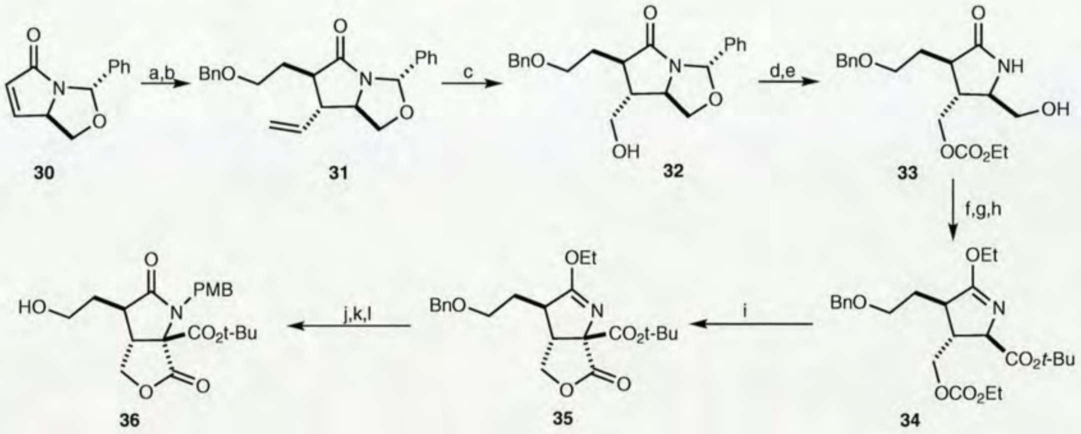
The carboxylic acid obtained after tellurium-induced hydrolysis was, without added purification, reacted with Ph_3PCl_2 in a 1:1 mixture of dry MeCN-pyridine to directly deliver **28** in 89% yield. This valuable operation allowed the new method of β-lactone formation and the side chain chlorination procedure to take place in one-pot. Subsequently, desilylation of **28** gave the salinosporamide-omuralide hybrid **29** in 92% yield.

In his approach to salinosporamide A, Corey took advantage of the fact that the target molecule has five continuous stereocentres. He started with the formation of the synthetically most difficult tetrasubstituted stereocentre (at C4) that was neatly formed with assistance of the oxazoline ring derived from threonine. This chirality was then used to control the construction of neighbouring stereocentres in almost text-book fashion. The Baylis-Hillman cyclisation (later Kulinkovich) did deliver the required configuration at C3 in the γ-lactam ring with a high diastereomeric ratio. However, it took Corey and co-workers several steps including a tin hydride-mediated radical cyclisation to transform the exomethylene group of **15** into the chloroethyl functionality with the appropriate configuration at C2. It seems more than likely that initialy Corey envisaged a different approach involving Michael type addition to the α-β-unsaturated amide **15** that proved to be unsuccessful and so an alternative route involving a radical cyclisation was devised. It is worth mentioning that the procedure for the β-lactone formation and chlorination of primary alcohol developed in this study have been applied by several different groups in their total synthesis of **1**.

Salinosporamide A was synthesised by Corey in 18 steps and 8.7% overall yield through Baylis-Hillman cyclisation, which was later increased to 9.1% yield using Kulinkovich reagent.

1.2.2 Danishefsky's synthesis

Danishefsky and co-workers reported the second approach to salinosporamide A in 2005.[47] Their synthesis started with a known procedure to convert L-glutamic acid to pyroglutamate **30**.[72–74] This compound possesses a substantial facial bias of bicyclo[3.3.0] ring system, that was used to facilitate the formation of the C3 stereocentre. Addition of vinylmagnesium bromide in the presence of CuI gave the product of α-face attack of the vinyl cuprate in 75% yield as a single diastereomer. Deprotonation of this intermediate with LDA and addition of β-benzyloxy iodoethane, that mostly attacked the preformed enolate from the β-face, yielded **31** as a 14:1 mixture of diastereomers (77%).



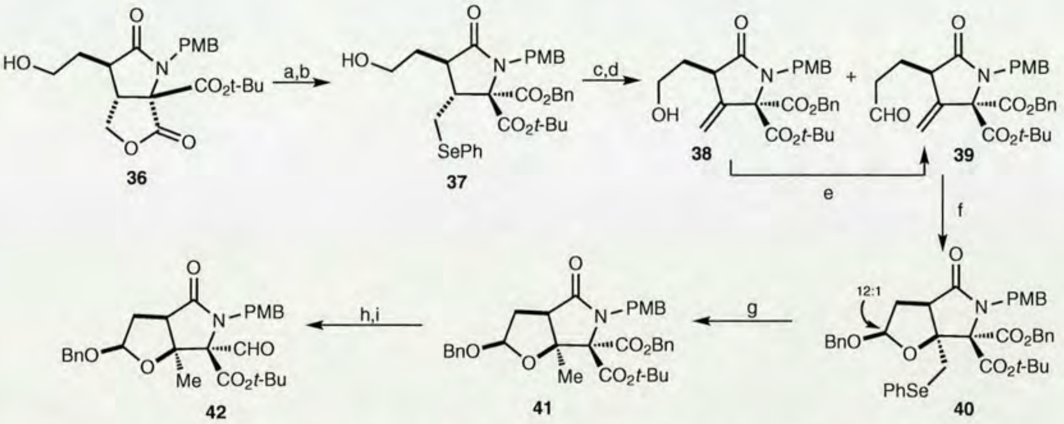
Conditions: (a) vinylmagnesium bromide, TMSCl, CuI, 78 °C, 75%; (b) [(2-iodoethoxy)methyl]benzene, LDA, THF, rt, 77%, *dr* = 14:1; (c) O_3, DCM-MeOH (3:1), -78 °C then $NaBH_4$, 0 °C, 86%; (d) $ClCO_2Et$, pyridine, rt, 96%; (e) TfOH, THF-H_2O (9:1), rt, 100%; (f) Jones reagent, acetone, rt; (g) $Me_2NCH(Ot\text{-}Bu)_2$, toluene, reflux, 72% over 2 steps; (h) Et_3OBF_4, K_2CO_3, DCM, rt, 88%; (i) LHMDS, THF, -20 °C, 82%; (j) 1 M HCl *aq*, THF, 0 °C, 90%; (k) PMBCl, NaH, DMF, rt, 61%; (l) $Pd(OH)_2$ on carbon, H_2, EtOH, rt, 100%

Scheme 1.12: Danishefsky's synthesis

The terminal olefin present in **31** was converted to the primary alcohol **32** in 86% yield by first ozonolysis and reductive quenching with sodium borohydride. The alcohol **32** was reacted with ethyl chloroformate in pyridine to form a mono-ethyl carbonate (96%) and this intermediate was treated with triflic acid to produce the amino alcohol **33** in 100% yield. The primary hydroxyl group in **33** was converted to a carboxylic acid with Jones reagent and then directly esterified with $Me_2NCH(Ot\text{-}Bu)_2$ (72% over two steps). The use of Et_3OBF_4 (Meerwein's reagent) afforded the imidate product **34** in 88% yield.

The imidate **34** concealed γ-lactam character and facilitated acylation at C4. Deprotonation of **34** with LHMDS and intramolecular trapping of the enolate by the carbonate substituent gave **35** in 82% yield as a single diastereoisomer. At this stage

Danishefsky shuffles protecting groups. Firstly the γ-lactam was unmasked using *aq* 1 M HCl (90%) and then PMB protection was introduced on to nitrogen with NaH and PMBCl (61%). Cleavage of the benzyl ether protection from the primary hydroxyl group was achieved by palladium-catalysed hydrogenation to give **36** in quantitative yield.



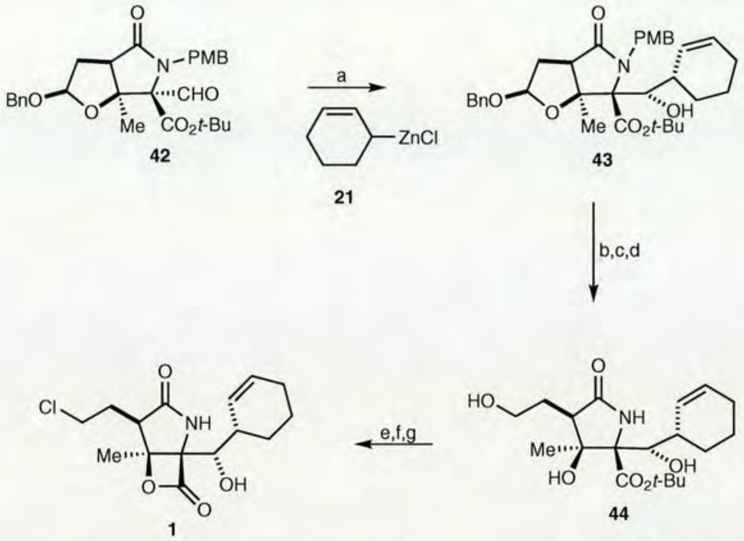
Conditions: (a) PhSeSePh, NaBH4, EtOH, 60 °C; (b) BnBr, K_2CO_3, DMF, rt, 72% over 2 steps; (c) 30% H_2O_2 *aq*, THF, rt; (d) toluene, 100 °C, 72% + 22% over 2 steps; (e) Dess-Martin periodinane, DCM, rt, 92% (f) PhSeBr, $AgBF_4$, BnOH, DCM, 20 to 0 °C, 74% (12:1); (g) AIBN, nBu_3SnH, toluene, 100 °C, 98%; (h) $NaBH_4$, THF-EtOH (3:1), rt, 85%; (i) Dess-Martin periodinane, DCM, rt, 95%;

Scheme 1.13: Danishefsky's synthesis

The γ-lactone ring of **36** was then opened by a nucleophilic attack of a phenylselenium anion (pregenerated from $(PhSe)_2$ and $NaBH_4$) and subsequent esterification with benzyl bromide afforded **37** in 72% yield over two steps. Oxidation of the phenyl selenium substituent of **37** produced the corresponding selenoxide that was eliminated at 100 °C in toluene to give alcohol **38** (72%) as the major product together with the unexpected aldehyde **39** (22%) which was a one-step advancement in the synthetic route. The alcohol **38** was oxidized to aldehyde **39** with Dess-Martin periodinane to produce aldehyde **39** in 89% yield (over three steps)

The formation of acetal **40** was facilitated by the addition of phenylselenium bromide and $AgBF_4$ to aldehyde **39** in the presence of benzyl alcohol. This transformation set up the required stereocentres at C2 and C3 positions. The phenylselenium substitution of **40** was removed under radical conditions to give compound **41** in 98%

yield. The benzyl ester of **41** was selectively cleaved in the presence of *tert*-butyl ester with sodium borohydride in a mixture of THF and ethanol. Oxidation of the resultant alcohol gave the desired aldehyde **42** in 95% yield.



Conditions: (a) cyclohexenyl zinc chloride **21**, THF, 78 °C; (b) CAN, DCM-H_2O, 0 °C, 90%; (c) Na, *liq* NH_3, 78 °C; (d) $NaBH_4$, THF-H_2O (2:1), rt, 97% over two steps; (e) BCl_3, DCM, 0 °C; (f) BOPCl, Et_3N, DCM, rt; (g) PPh_3Cl_2, pyridine, DCM, rt, 51% over 3 steps.

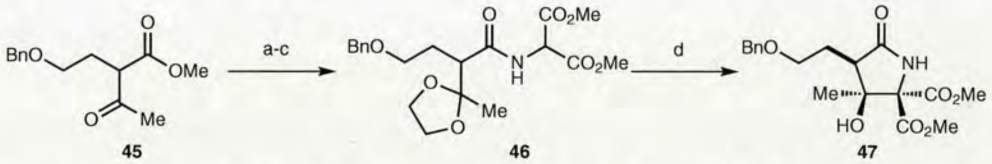
Scheme 1.14: Danishefsky's synthesis

Danishefsky and co-workers employed Corey's procedure for the introduction of the last two remaining stereocentres.[45] Addition of cyclohexenyl zinc chloride reagent **21** to the aldehyde **42** afforded **43** with 88% yield and excellent diastereoselectivity. The same procedure was also attempted on an aldehyde derived from compound **35** but this yielded only 78% of 4:3 mixture of diastereoisomers. It was speculated that PMB protection of the γ-lactam ring plays a crucial role in controlling the diastereoselectivity of this transformation. After the successful addition of cyclohexenyl zinc chloride, the PMB protection of **43** was removed with CAN. The benzyl glycoside moiety of the corresponding intermediate was reduced with sodium and sodium borohydride in liquid ammonia to give the triol **44** (97% over two steps). Hydrolysis of *tert*-butyl ester was performed using BCl_3 and the crude acid was transformed to salinosporamide A using Corey's lactonisation-chlorination procedure.

The total synthesis of salinosporamide A by Danishefsky and co-workers was achieved in 28 steps and 1.8% overall yield. In his synthesis Danishefsky is almost constantly changing protecting groups, oxidation steps and configuration of stereocenteres. For these reasons this is the longest approach to salinosporamide A and it is also difficult to point out a key transformation. However, formation of the C4 stereocentre by intramolecular cyclisation of an enolate onto the mono-ethyl substituent is an important point in the synthesis. Surprisingly Danishefsky does not use this stereocentre to control the configuration at the C3 position. Instead, the stereocentre at C2, constructed very early in synthesis, is employed to control the substituents around C3.

1.2.3 Pattenden racemic synthesis

A short approach to racemic salinosporamide A was published by Pattenden in 2006[48] (Scheme 1.15). Starting from compound **45** (synthesis of which was previously reported[75] a high yielding synthesis was obtained. Firstly, the ketone group in **45** was protected using ethylene glycol in the presence of a catalytic amount of *p*-TsOH to give an acetal derivative that was subsequently treated with a solution of NaOH to hydrolyse the methyl ester. The resultant acid was coupled to dimethyl 2-aminomalonate under conventional peptide coupling conditions to produce amide **46**.

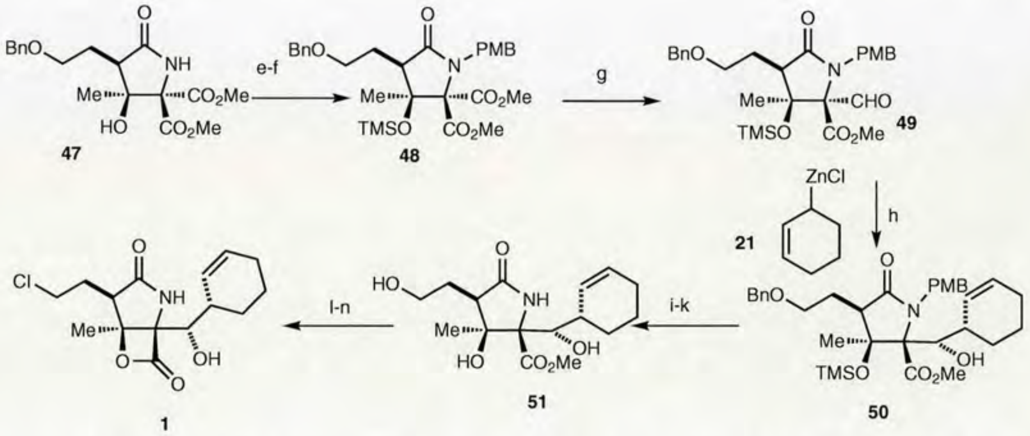


Conditions: (a) ethylene glycol, *p*-TsOH, benzene, 110 °C, 14 h; (b) 2M NaOH, EtOH, 70 °C, 3 h; (c) dimethyl aminomalonate, HOBt, EDCI, DCM, NMM, 0 °C to rt (82% over 3 steps); (d) 4:1 AcOH-H_2O, 65 °C, 4 d (71%);

Scheme 1.15: Pattenden synthesis

Compound **46** was then treated with diluted acetic acid at 65 °C for 4 days to give the γ-lactam **47** in 71% by initial hydrolysis of the acetal followed by a highly diastereoselective intramolecular cyclisation. This transformation was a key step in Pattenden synthesis, it delivered a single diastereomer of the desired product in good yield. Intermediate **47** possesses a γ-lactam backbone with the desired functionality in place making it relatively straight forward to transform it to salinosporamide A.

Protection of the hydroxyl group in **47** with a silyl ether and the lactam nitrogen using a *p*-methoxybenzyl group afforded **48** in 75% yield over two steps. Selective reduction of one of the methyl esters (positioned *anti* to the silyl ether) with $LiEt_3BH$ gave the aldehyde **49** in 78% yield. Addition of cyclohexenyl zinc (**21**) to aldehyde **49** was done following Corey's protocol.[45] Compound **50** was formed in 78% yield with very high levels of diastereoselectivity and this intermediate posseses all stereocentres in place.



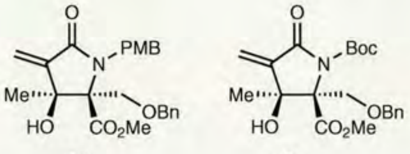
Conditions: (e) TMSOTf, 2,6-lutidine, DCM, 78 °C to 0 °C, then 1 M HCl (91%); (f) PMBBr, NaH, DMF, 0 °C to rt, 14 h (82%); (g) $LiEt_3BH$ (1.0 M in THF), DCM, 78 °C, (78%); (h) 2-cyclohexenylzinc chloride **21**, THF, 78 °C (87%); (i) Me_2SBCl3, DCM, 24 h, 0 °C to rt; (j) 48% HF in H_2O-MeCN (1:9), rt, 22 h; (k) CAN, MeCN, H_2O (3:1), 0 °C, 1 h (87% over 3 steps); (l) $[MeTeAlMe_2]_2$, toluene, rt, 24 h; (m) BOPCl, DCM, pyridine, rt, 3 h; (n) PPh_3Cl_2, MeCN, pyridine, rt, 4 h (45% over 3 steps).

Scheme 1.16: Pattenden synthesis

Subsequent deprotection of the benzyl ether with BCl_3, TMS ether with HF and *p*-methoxybenzyl with CAN produced Corey's intermediate **51**[45] in 87% over three steps. The triol **51** was transformed according to previously reported procedures[46,53,71] to salinosporamide A (**1**). The total synthesis of racemic salinosporamide A was achieved in 14 steps and an impressive 11.5 % overall yield.

1.2.4 Langlois's formal synthesis

Langlois and co-workers published two separate approaches to salinosporamide A.[49,50] The first report described a racemic synthesis of **52** which is a derivative of Corey's key intermediate **15** (Scheme 1.17). In their approach a highly stereoselective nitrone cycloaddition was applied.



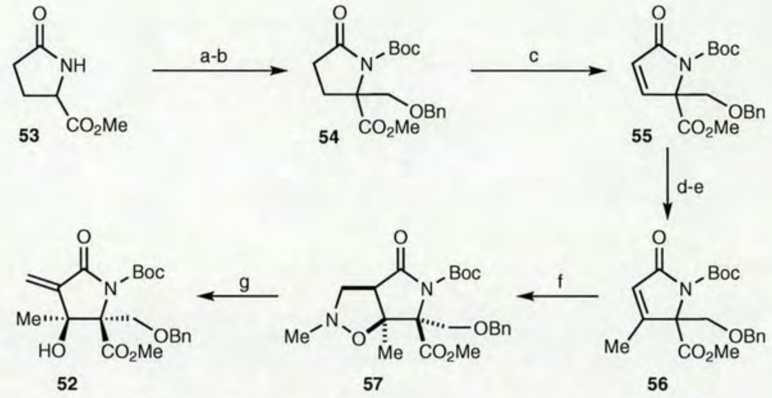
15 **52**

Scheme 1.17: Langlois's synthesis

Deprotonation of γ-lactam **53** with LHMDS followed by addition of chloromethylbenzylether gave the alkylated intermediate in 53% yield, which was later BOC protected on nitrogen to give **54** (quantitative yield). The BOC protection in **54** allowed the deprotonation at the α-carbon (to the lactam carbonyl) and the formation of a selenium intermediate that was subsequently reacted with H_2O_2 in the presence of pyridine to give the α,β-unsaturated lactam **55**. Addition of methylcuprate to **55** gave an alkylated product that was once more subjected to the previous condition to reform the carbon-carbon double bond in compound **56**.

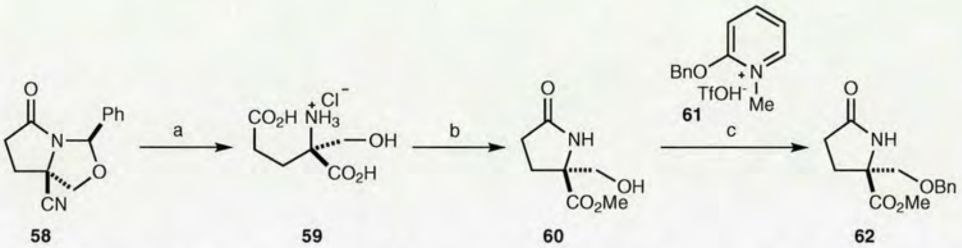
A key step in the Langlois synthesis was a 1,3-dipolar cycloaddition. Treatment of **55** with N-methylnitrone in refluxing toluene gave **56** in 57% yield. This highly regio- and stereoselective reaction installed the relative configuration at the C3 carbon. In this step Langlois used Pearlman's catalyst to selectively break the nitrogen-oxygen bond (through hydrogenolysis, 72% yield) without deprotection of the benzyl ether. Addition of excess iodomethane and triethylamine gave the methylation product **52** in 65% yield.

In Langlois's second report an enantioselective version of the previous approach to salinosporamide A (**1**) is described. An enantiopure bicyclic nitrile **58**[76,77] was hydrolysed in the presence of 6 M HCl to give **59** in 98% yield. Treatment of this intermediate with diazomethane in ether afforded γ-lactam **60** in 67%, which was selectively benzylated using 2-benzyloxy-1-methylpyridinium triflate **61** to produce **62** in 75% yield. Using **62** as a chiral precursor and Langlois previously reported synthesis, compound **52** was made without lost of enantioenrichment from **62**.



Conditions: (a) LHMDS, THF, $BnOCH_2Cl$ (53%); (b) $(Boc)_2O$, DMAP, MeCN (100%); (c) LHMDS, THF, PhSeCl; H_2O_2, DCM, pyridine (89%); (d) Me_2CuLi, THF, TMSCl (83%); (e) LHMDS, THF, PhSeCl; H_2O_2, DCM, pyridine (75%); (f) N-methylnitrone, toluene, reflux (57%); (g) H_2, $Pd(OH)_2$, EtOAc-MeOH (72%); MeI, THF, Et_3N (65%).

Scheme 1.18: Langlois's synthesis

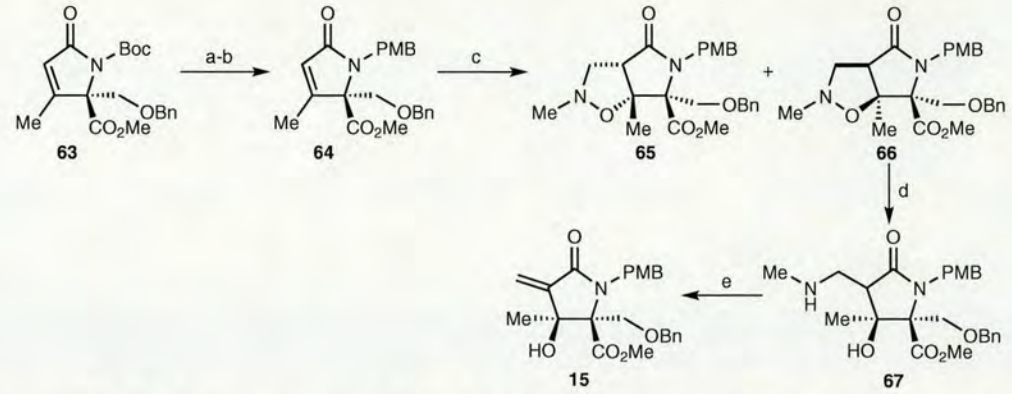


Conditions: (a) 6M HCl, reflux (98%); (b) diazomethane, Et2O (67%); (c) **61**, MgO, $PhCF_3$, reflux (75%).

Scheme 1.19: Langlois's synthesis

Synthesis of Corey's intermediate **15** was achieved through the initial substitution of N-BOC protection in **52** to PMB in **64** (two steps, 57% yield). However, 1,3-dipolar cycloaddition of N-methylnitrone to compound **64** gave lower than expected stereoselectivity (4:1) and product **66** was isolated in 54% yield. Cleavage of the nitrogen-oxygen bond with hydrogenolysis and formation of the exo-methylene group proceeded as previously giving α-methylenelactam **15**.

The formal synthesis of salinosporamide A was achieved in 18 steps (from **60**) in 4% overall yield.

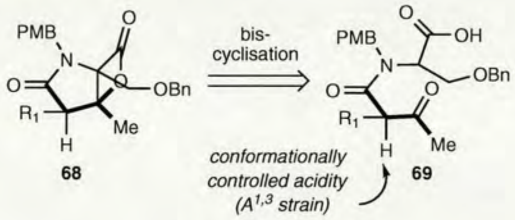


Conditions: (a) CF_3CO_2H, DCM (100%); (b) Cs_2CO_3, PMBBr, DMF (57%); (c) N-methylnitrone, toluene, reflux (14% for **65**, 54% for **66**); (d) H_2, $Pd(OH)_2$, EtOAc-MeOH (64%); (e) MeI, MeOH; Na_2CO_3, DCM (90%).

Scheme 1.20: Langlois's synthesis

1.2.5 Romo's racemic synthesis

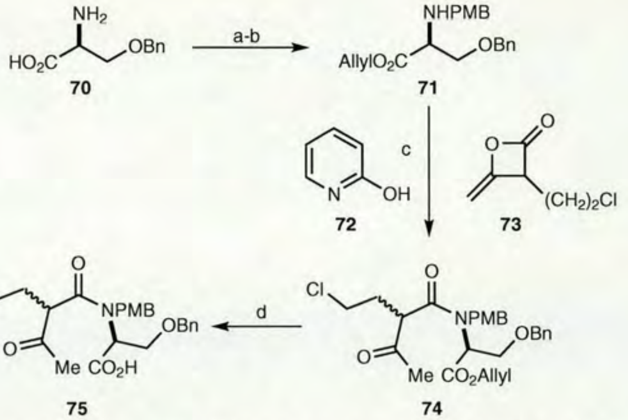
Romo and co-workers reported a racemic synthesis of salinosporamide A using a novel methodology to form the β-lactone ring.[51] Sequential formation of the carbon-carbon and carbon-oxygen bonds during intramolecular cyclisation (Scheme 1.21) allowed efficient synthesis of the γ-lactone-β-lactam ring system and a very short synthesis of racemic **1** (9 steps). Romo observed that $A_{1,3}$ strain[78] present in **69** allowed the stereoselective formation of **68** without a the risk that the highly acidic β-ketoamide hydrogen could effect a racemisation at C2 carbon upon deprotonation.



Scheme 1.21: Romo's synthesis

A benzyl ether serine derivative **70** was functionalised with p-methoxybenzyl and allyl protecting groups to give **71** in 74% over two steps. Addition of **73** to **71** provided the intermediate **74** in 80% yield. Deprotection of the allyl ester with tetrakis(triphenylphosphine)palladium and morpholine afforded the acid **75** (75% yield).

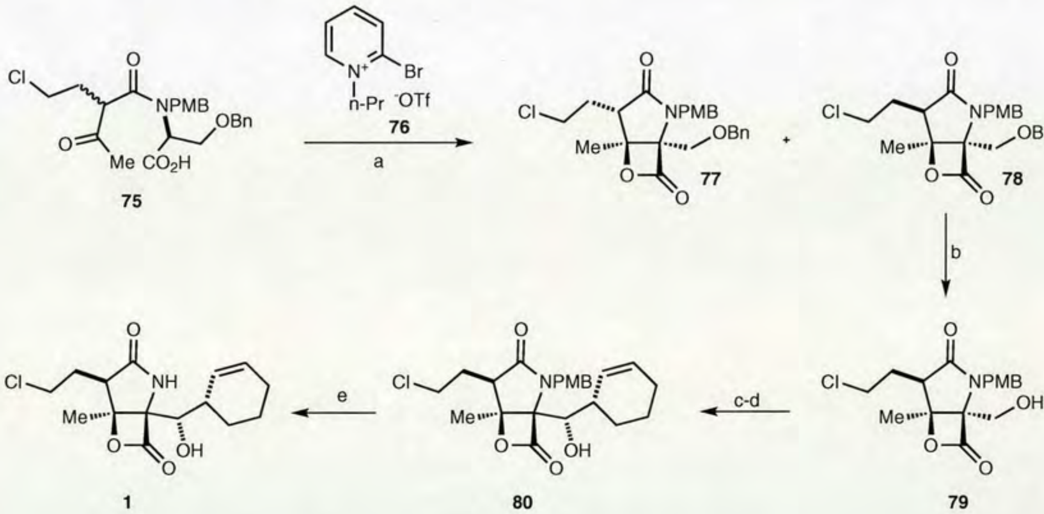
A key step in Romo's synthesis was the cyclisation of **75** to form epimers of γ-



Conditions: (a) *p*-anisaldehyde, MeOH, $NaBH_4$; (b) *p*-TsOH, allyl alcohol (74%, 2 steps); (c) THF, 60 °C, 36 h (80%); (d) $Pd(PPh_3)_4$, morpholine (75%)

Scheme 1.22: Romo's synthesis

lactone-β-lactam (**77** and **78**) in 25-35% yield. The major product (*dr* 2-3:1) contained the appropriate configuration of stereocentres required for the synthesis of salinosporamide A. However, a much higher total yield was expected based on previous experiments. These results were explained by significant steric hindrance caused by substituents at the C4 carbon that were not present in model studies.



Conditions: (a) DIPEA, PPY, DCM, 10 °C, 6 h (25-35 %, dr 2-3:1); (b) H_2, Pd/C, THF, 25 °C (98%); (c) EDCI, DMSO, $Cl_2CHCOOH$; (d) 2-cyclohexenylzinc chloride 24, THF, 78 °C(33%, 2 steps, dr 3.5:1); (e) CAN, $MeCN/H_2O$ (49%, major diast.).

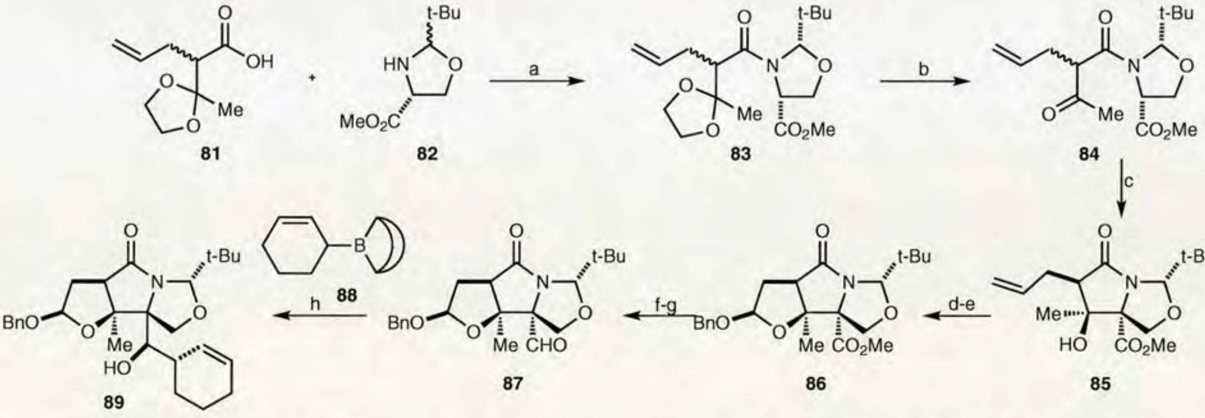
Scheme 1.23: Romo's synthesis

Hydrogenation of **78** mediated by Pd/C afforded debenzylated intermediate **79** in quantitative yield. Alcohol **78** was oxidized using Moffat[79] protocol and the aldehyde product was reacted with cyclohexenyl zinc chloride to give **80** in 33% as a 3.5:1 mixture of diastereoisomers. Removal of the PMB protective group in **80** with CAN furnished salinosporamide A (**1**) in 49% yield.

The total synthesis of racemic salinosporamide A was achieved in only 9 steps with 1.2% overall yield.

1.2.6 Macherela's total synthesis

Macherela and co-workers reported the enantioselective total synthesis of salinosporamide A in 2007.[52] Formation of an amide bond between **81** and **82** using MsCl and triethylamine gave amide **83**. Cleavage of acetal protection in **83** gave the *β*-ketoamide **84** as a mixture of diastereoisomers. A key step in Macharela's synthesis was a novel intramolecular aldol cyclisation, treatment of **84** with *t*-BuOK produced **85** in 64% yield and 70% de. This new transformation allowed the self-regeneration of stereocentres[80] to subsequently form the desired configurations around C2 and C3.



Conditions: (a) MsCl, Et_3N, DCM, 0 °C to rt, o/n (66%); (b) $CeCl_3$, NaI, MeCN, 60 °C, 4 h (84%); (c) *t*-BuOK, THF, rt, 15 min (64%, 70% de); (d) OsO_4, NMO, H_2O/THF, 3 h then $NaIO_4$, 2 h, (99%); (e) BnBr, *t*-BuOK, THF, 6 h, 76%; (f) $LiBH_4$, THF, 24 h (94%); (g) TPAP (cat.), NMO, DCM, 18 h (79%); (h) THF, 78 °C to rt, 11.5 h (80%)

Scheme 1.24: Macherela's synthesis

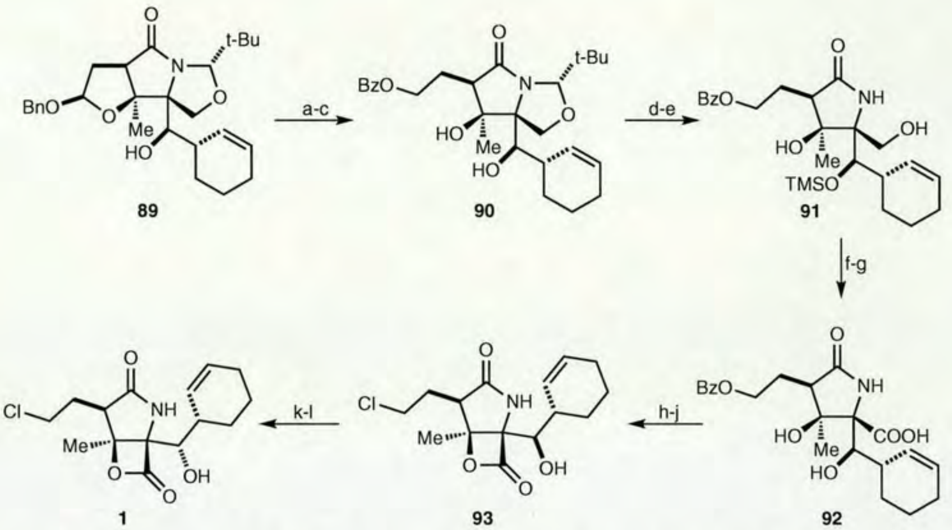
The obtained mixture of diastereoisomers of **85** was reacted with OsO_4/NMO and followed by addition of $NaIO_4$ and then BnBr to give **86**. This methyl ester was then reduced with $LiBH_4$ and subsequently oxidised to aldehyde **87**. The cyclohexenyl moiety was introduced via the addition of B-2-cyclohexen-1-yl-9-BBN (**88**) to aldehyde **87** which gave **89** in 80% yield. As predicted, a *syn* addition product **89** was obtained that contained the required configuration at C6. However, the orientation of the hydroxyl group at C5 was incorrect for the final product and would have to be reversed at a later stage in the synthesis.

The ring opening of benzyl acetal moiety in **89** was achieved by acid hydrolysis followed by reduction with $NaBH_4$. Benzoyl protection of the obtained intermediate gave **90** in 70% yield over three steps. This protection step allowed the use of relatively harsh conditions for the hydrolysis of oxazoline. Treatment of **90** with 1,3-propanedithiol, HCl and trifluoro-ethanol afforded the desired product that was subsequently protected with TMS ether at the C5 hydroxyl to give intermediate **91**. The primary hydroxyl group in **91** was then oxidized to a carboxylic acid by a two-step procedure giving **92** in 63% yield overall. Hydrolysis of the benzoyl protective group of **92** was followed with a BOPCl-mediated β-lactone formation. A subsequent chlorination of the primary alcohol using Ph_3PCl_2 gave **93** that is a C5 epimer of salinosporamide A. In an attempt to obtain the desired configuration at C5, the secondary hydroxyl group in **93** was oxidized using Dess–Martin periodinane[81,82] and the resulting ketone was selectively reduced with ketoreductase enzyme to produce salinosporamide A **1**.

Although Macherela managed to successfully apply an enantioselective intramolecular aldol cyclisation, a lot of synthetic steps were needed for protecting group manipulations. Salinosporamide A was synthesised in 24 steps with 0.2% overall yield.

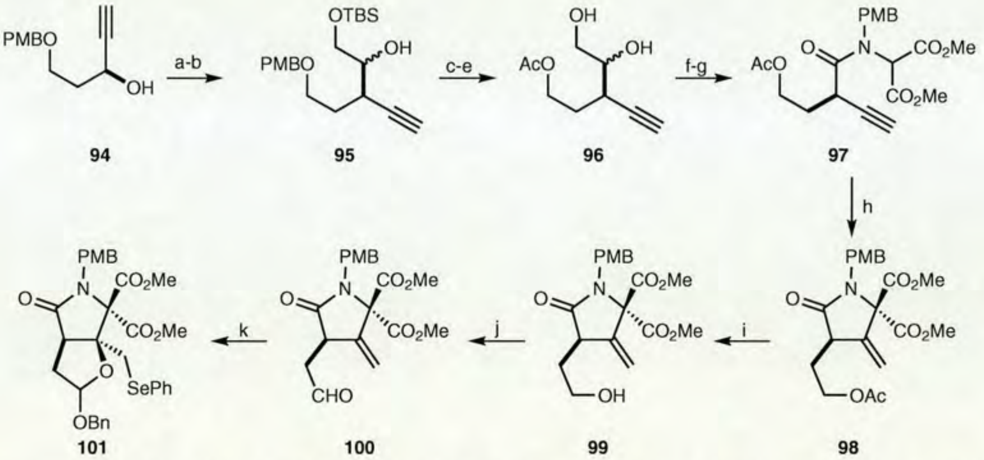
1.2.7 Hatakeyama's total synthesis

In 2008 Hatakeyama and co-workers applied their indium-catalysed conia-ene reaction in the total synthesis of salinsoporamide A (Scheme 1.26).[83] The synthesis began with the stereoselective preparation of **97** that was a precursor for a key $In(OTf)_3$-catalysed cyclisation. A chiral propargyl alcohol **94** was converted to the mesylate derivative and then treated with (*tert*-butyldimethylsilyloxy)acetaldehyde via the allenylzinc species to afford **95** as a 90:10 mixture of epimers. Removal of the PMB and silyl protecting groups and a selective acylation of one of the hydroxyls gave **96**. Treatment with CrO_3



Conditions: (a) HCl, THF, 60 °C, 10 h; (b) $NaBH_4$, THF/H_2O, 30 min (81%, 2 steps); (c) BzCl, Et_3N, DCM, 10 h (87%); (d) 1,3-propanedithiol, HCl, CF_3CH_2OH, 60 °C, 4 h (94%); (e) TMSCl, Et_3N, DCM, 12 h (53%); (f) Dess-Martin periodinane, DCM, 2 h; (g) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, t-BuOH/H_2O, 0 °C, 1.5 h (63%, 2 steps); (h) K_2CO_3, MeOH, 15 h; (i) BOPCl, pyridine, MeCN, 2 h (60%, 2 steps); (j) Ph_3PCl_2, pyridine, MeCN, 18 h (57%); (k) Dess-Martin periodinane, DCM, 2 h (60%); (l) KRED-EXP-B1Y, NAD+, GDH-103, glucose, pH 6.9, 37-39 °C, 40 min (56%).

Scheme 1.25: Macherela's synthesis

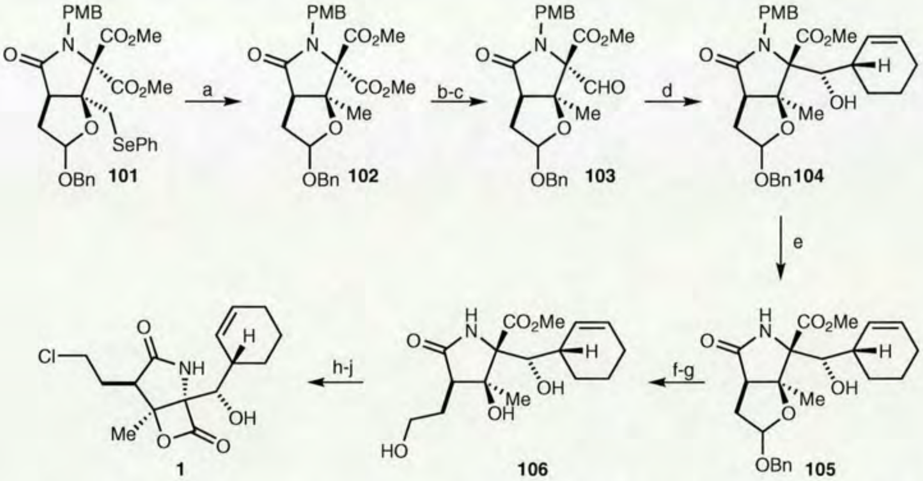


Conditions: (a) MsCl, Et_3N, DMAP, DCM, 0 °C, 95%; (b) $Pd(OAc)_2$, PPh_3, Et_2Zn; then $TBSOCH_2CHO$, THF, -78 to -20 °C, 63%; (c) DDQ, DCM / H_2O (10:1), 0 °C, 87%; (d) AcCl, 2,4,6-collidine, DCM, -78 °C, quant.; (e) TBAF, THF, 0 °C, 92%; (f) CrO_3, HIO_4, acetone, H_2O, 0 °C; (g) $(COCl)_2$, DMF, DMF, 0 °C; then $PMBNHCH(CO_2Me)_2$, toluene, 75%; (h) $In(OTf)_3$ (5 mol%), toluene, 110 °C, 96%; (i) Lipase PS, phosphate buffer, acetone, 35 °C, 89%; (j) Dess-Martin periodinane, DCM, 88%; (k) PhSeBr, $AgBF_4$, $PhCH_2OH$, DCM, -20 to 0 °C, 85%;

Scheme 1.26: Hatakeyama's formal synthesis

and HIO_4 in a mixture of acetone and water afforded the corresponding carboxylic acid. Condensation with dimethyl 2-(4-methoxybenzylamino)malonate gave **97**. Upon purification by column chromatography, **97** spontaneously cyclised to give a mixture of

97 and **98**. This mixture was reacted with catalytic amount of $In(OTf)_3$ in refluxing toluene and gave complete conversion to **98**. A very mild hydrolysis of the acetoxy group using a lipase-catalysed reaction afforded **99**. Oxidation of **99** with Dess-Martin periodinane provided the aldehyde **100**. The quaternary centre have been assembled using Danishefsky's acetal-mediated cationic cyclisation.[47] Treatment of **100** with phenylselenyl bromide, $AgBF_4$ and benzyl alcohol afforded **101** with 93:7 dr at C3.



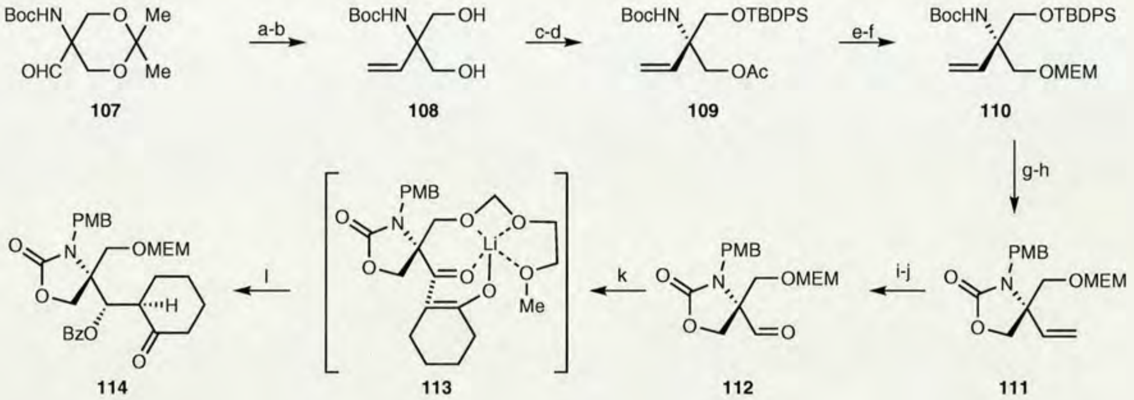
Conditions: (a) AIBN, *n*-Bu_3SnH, toluene, 100 °C, 83%; (b) $NaBH_4$, THF / EtOH, 88%; (c) Dess-Martin periodinane, DCM, 94%; (d) cyclohex-2-enylzinc chloride, THF, -78 °C, 88%; (e) CAN, aq MeCN, 0 °C, 83%; (f) Na, liq. NH_3, THF, -78 °C; (g) $NaBH_4$, *aq* THF, 71% (over 2 steps); (h) $(Me_2AlTeMe)_2$, toluene; (i) BOP-Cl, pyridine, DCM, 54% (over 2 steps); (j) Ph_3PCl_2, pyridine, 77%.

Scheme 1.27: Hatakeyama's formal synthesis

Removal of phenylselenium with tin hydride under radical conditions produced **102** (Scheme 1.27). Selective reduction of one of the methyl esters with $NaBH_4$ and subsequent reoxidation with Dess-Martin periodinane gave aldehyde **103**. Using Corey's procedure, addition of cyclohex2-enylzinc chloride to aldehyde **103** produced **104** as a single stereoisomer. The PMB group of **104** was removed with CAN to yield **105**. Using sodium in liquid ammonia and $NaBH_4$ in THF a reductive opening of the cyclic acetal gave intermediate **106**. A cleavage of the methyl ester with $(Me_2AlTeMe)_2$, β-lactonisation with BOP-Cl in pyridine and a final chlorination completed the synthesis of salinosporamide A **1**.

1.2.8 Omura's formal synthesis

A lengthy total synthesis of salinospormiade A was published by Omura and co-workers in 2008.[84] Several aspects of this synthesis were particularly interesting. A lipase-catalysed desymmetrisation of the diol **108** afforded an optically active acetate that was protected with TBDPS to give **109** in 97% *ee* (Scheme 1.28). This stereocentre is then gradually converted into the quaternary chiral centre of salinosporamide A.



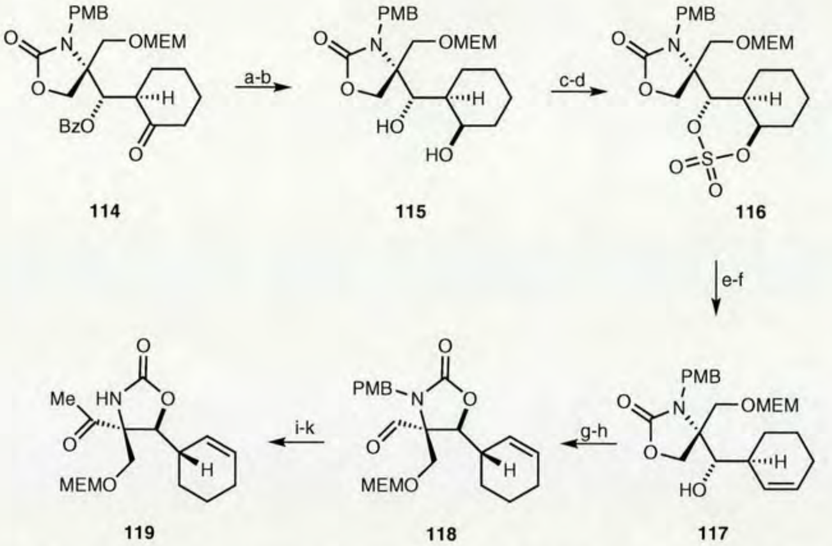
Conditions: (a) $Ph_3{}^+CH_3Br^-$, NaHMDS, THF, rt, 97%; (b) *p*-TsOH, MeOH, rt, 82%; (c) Lipase, vinyl acetate, *i*-Pr_2O, rt; (d) TBDPSCl, imidazole, DMF, rt, 94%, 97% *ee* (over 2 steps); (e) K_2CO_3, MeOH, rt; (f) MEMCl, *i*-Pr_2NEt, DCM, rt, 94% (over 2 steps); (g) TBAF, THF, rt; (h) NaH, THF / DMF, then PMBCl, rt, 97% (over 2 steps); (i) OsO_4, NMO, acetone / H_2O, rt; (j) $NaIO_4$, MeOH / H_2O, rt, 92% (over 2 steps); (k) LDA, cyclohexanone, THF, -78 °C; (l) BzCl, 79%

Scheme 1.28: Omura's formal synthesis

Installation of the C5 and C6 stereocentres using Corey's protocol of stereoselective addition of cyclohexenylzinc chloride only gave limited selectivity when aldehyde **112** was used. Instead Omura optimised conditions for a chelation-controlled aldol addition of cyclohexanon that upon quenching with BzCl, afforded the desired product **114** in 79% yield and 20:1 *dr*.

The conversion of the cyclohexanone group in **114** to the cyclohexene moiety in salinosporamide A appeared quite difficult (Scheme 1.29). Six synthetic steps were required involving a cyclic sulfate **116** as a key intermediate that upon exposure to DBU at 100 °C and subsequent treatment with TsOH produced **117**.

A γ-lactam ring was afforded by N-acylation of **119** and a subsequent intramolecular aldol reaction using LHMDS and chloroacetyl chloride. The desired compound **120** was produced as a single isomer. This procedure also constructed a C3 stereocentre.



Conditions: (a) $NaBH_4$, $CeCl_3$, MeOH, rt; (b) K_2CO_3, MeOH, rt, 95% (over 2 steps); (c) $SOCl_2$, pyridine, DCM, rt; (d) $RuCl_3$, $NaIO_4$, MeCN / CCl_4 / H_2O, rt, 94% (over 2 steps); (e) DBU, toluene, 100 °C; (f) TsOH, dioxane, rt, 97% (over 2 steps); (g) NaH, THF / EtOH, rt; (h) $(COCl)_2$, DMSO, Et_3N, DCM, -78 °C, 92% (over 2 steps); (i) MeMgBr, THF, -78 °C; (j) Dess-Martin periodinane, DCM, rt, 100% (over 2 steps); (k) CAN, MeCN / H_2O, 0 °C, 92%

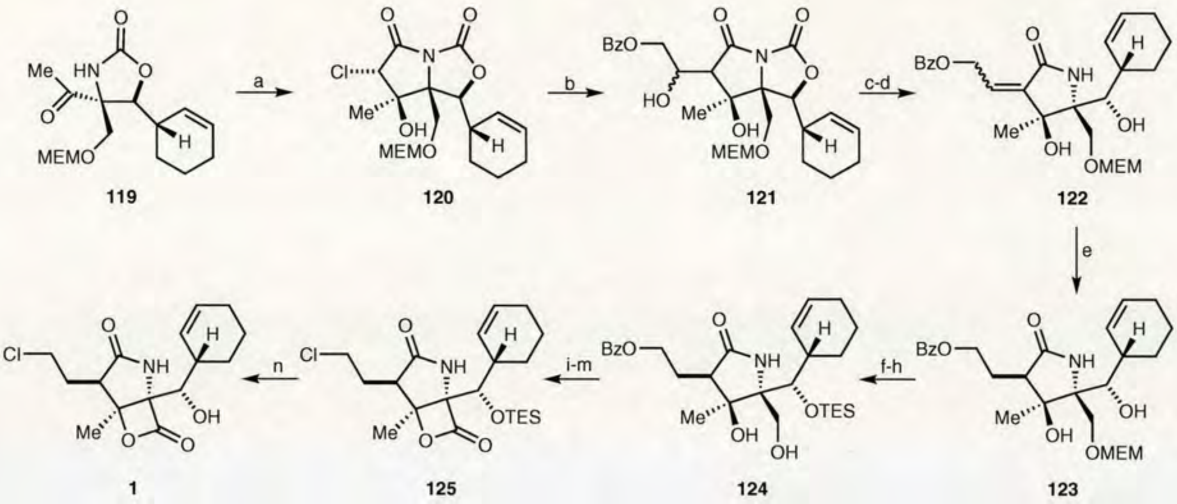
Scheme 1.29: Omura's formal synthesis

To install the C2 side chain a Reformatsky-type reaction of **120** with benzyloxy acetaldehyde gave **121** (Scheme 1.30). For a successful deoxygenation step, it was necessary to convert **121** into a mesylate derivative. Subsequent alkaline hydrolysis afforded **122** that was chemoselectively reduced with $LiEt_3BH$ to produce a 4.2:1 mixture of diastereoisomers of **123**.

After a shuffle of protecting groups, a sequence of 5 synthetic steps have been applied. Oxidation of the primary alcohol, deprotection of the benzyl group using a Birch reduction, BOP-Cl mediated β-lactonisation and chlorination with Ph_3PCl_2 afforded the γ-lactam-β-lactone **125**. Deprotection of the TES ether with HF-pyridine gave salinospormiade A (**1**) as the final product.

1.2.9 Bode's formal synthesis

A recent publication by Bode describes a formal synthesis of salinosporamide A.[85] A novel NHC-catalysed intramolecular lactonisation was developed and successfully



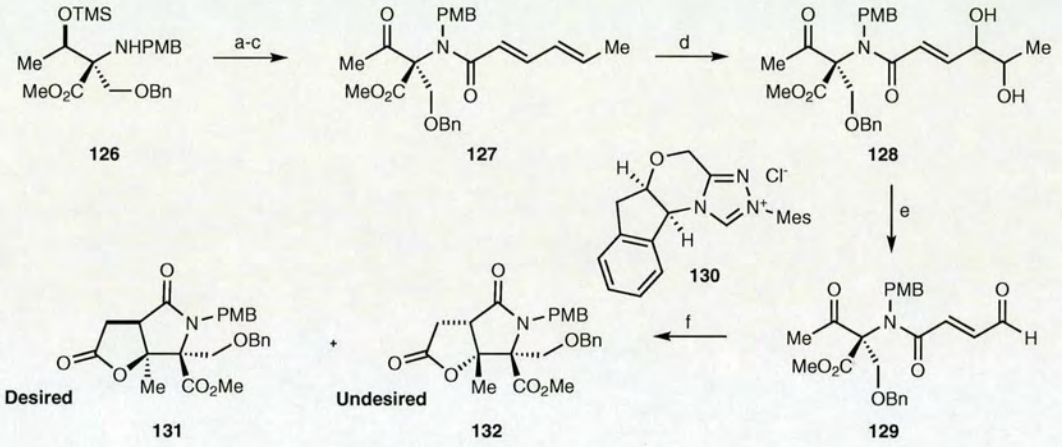
Conditions: (a) LHMDS, THF, -78 °C, chloroacetyl chloride, 63%; (b) SmI_2, LiCl, benzyloxyacetaledhyde, THF, -78 °C, 83%; (c) MsCl, Et_3N, Me_3NHCl, toluene, rt; (d) NaOH, MeOH / H_2O, 0 °C, 81% (over 2 steps); (e) $LiEt_3BH$, THF, 0 °C, 77%; (f) TESCl, NaI, MeCN, 0 °C, 100%; (g) TESOTf, 2,6-lutidine, DCM, -78 °C, 48%; (h) HF-pyridine, THF, 0 °C, 90%; (i) Dess-Martin periodinane, DCM, rt; (j) $NaClO_2$, 2-methyl-2-butene, Na_2HPO_4, *t*-BuOH / H_2O, rt; (k) Li, NH_3, *t*-BuOH, THF, -78 °C; (l) BOPCl, pyridine / DCM, rt; (m) PH_3PCl_2, pyridine / MeCN, rt, 48% (over 5 steps); (n) HF-pyridine, THF, rt, 84%

Scheme 1.30: Omura's formal synthesis

applied albeit with limited selectivity (Scheme 1.31). Compound **126** was prepared following Corey's procedure.[45] Although the initial plan to obtain **129** was a two step procedure involving acylation of **126** using an α,β-unsaturated acid containing an aldehyde functionality masked as an acetal and then an acid catalysed hydrolysis to reveal the aldehyde has failed (similar difficulties in acylation have been encountered in our formal synthesis of salinosporamide A), a longer route was developed.

N-Acylation of **126** with sorbyl chloride was followed by TMS ether deprotection and Dess-Martin oxidation to give **127**. A regioselective Sharpless dihydroxylation afforded **128** as a single diastereomer that was subsequently treated with sodium periodate to give the product of the diol cleavage **129**.

Cyclisation of **129** was achieved using N-heterocyclic carbene **130** as a catalyst. The products were obtained as a 1:1.1 mixture of diastereomers (in favour of the undesired isomer). Compound **131** was identical to the one obtained in this study.[86]



Conditions: (a) sorbyl chloride, DIPEA, DCM, 0 °C to rt, 28 h; (b) 6 N $HCl_{(aq)}$, rt, 1 h; (c) Dess-Martin periodinane, DCM, rt, 16 h, 60% over 3 steps; (d) AD-mix α, $(DHQ)_2PHAL$, OsO_4, $MeSO_2NH_2$, $NaHCO_3$, 3:2 H_2O:*t*-BuOH, rt, 24h, 40%; (e) $NaIO_4$, sat. $NaHCO_{3(aq)}$, DCM, rt, 20 h, quant. (f) **130** (15 mol%), DBU (10 mol%), 10:1 THF:*t*-BuOH (0.05M), 40 °C, 3 h, 88% (*dr* = 1:1.1)

Scheme 1.31: Bode's formal synthesis

1.3 Reductive aldol cyclisations in the Lam group

The synthesis of salinosporamide A was initiated in our group after an extensive development of reductive aldol cyclisation methodology. Our plan was to prove the applicability of our reductive aldol cyclisation methodology in a synthesis of a valuable natural product. Using experience gained during the development of our reductive aldol cyclisations we managed to apply this methodology as a key step in the formal synthesis of salinosporamide A. A short overview of the research leading to this project is presented below.

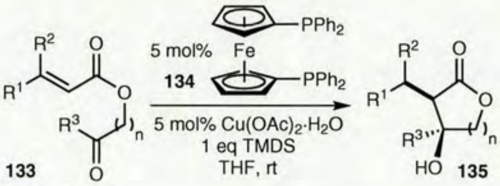
1.3.1 Copper-catalysed reductive aldol cyclisation

Our first target was a reductive aldol cyclisation of α,β-unsaturated esters containing ketone acceptors. In 2005 Lam and co-workers reported a highly stereoselective copper-catalysed process that allowed the formation of five- and six-membered β-hydroxylactones.[26] Similar reactions of this type had been carried out utilising Stryker's reagent with stoichiometric amounts of silanes.[87,88] Our initial study was to optimise reaction conditions with easier to handle sources of copper precatalyst. It was also crucial to fine tune the reactivity of copper hydride with phosphine ligands.

Initial screening of copper salts and bisphosphine ligands proved to be fruitful, and a highly reactive catalyst system consisting of $Cu(OAc)_2$, TMDS and either DPPF or *rac*-BINAP, in THF was found. These conditions allowed the formation of five- and six-membered lactones with good yields and exceptionally high diastereoselectivities (>20:1).

The application of enantiopure chiral ligands allowed the formation of products with good levels of enantioselectivity. It was observed that MeO-BIPHEP and SEGPHOS ligands delivered better selectivity in final product as compared to BINAP.

We have proposed a catalytic cycle for these reactions (Scheme 1.33). A copper(II) precatalyst is initially reduced to a copper(I) hydride species **143** with TMDS. A nucleophilic 1,4-conjugate addition of **143** to the starting material **144** forms a copper



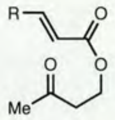
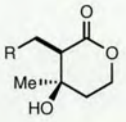
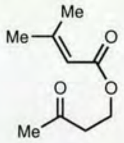
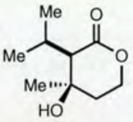
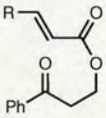
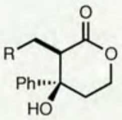
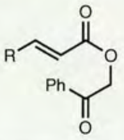
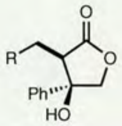
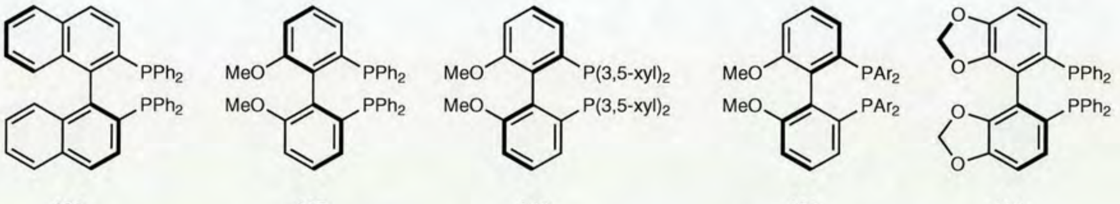
Entry	Substrate	R	Product	Yield
1		PMP		61
2		4-ClC$_6$H$_4$		65
3		2-furyl		63
4		*i*-Bu		73
5		PhCH$_2$CH$_2$		61
6				62
7		H		71
8		Me		50
9		Ph		47
10		H		69
11		Me		72
12		*i*-Bu		65
13		PhCH$_2$CH$_2$		60

Table 1.1: Copper-catalysed reductive aldol cyclisations


136
(*S*)-BINAP

137
(*S*)-Ph-MeO-BIPHEP

138
(*R*)-3,5-xyl-MeO-BIPHEP

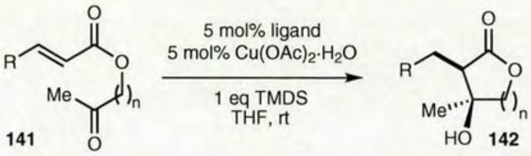
139
Ar = 3,5-di-*i*-PrPh
(*R*)-3,5-di-*i*-PrPh-MeO-BIPHEP

140
(*S*)-SEGPHOS

Scheme 1.32: Chiral bisphosphines for asymmetric cyclisations

enolate **145**. Enolate **145** undergoes an intramolecular aldol reaction to generate the copper alkoxide **146** that reacts with a molecule of TMDS (σ-bond metathesis) to regenerate the copper hydride and release silyl ether **147**. During acidic work-up, the silyl ether is hydrolysed and alcohol products are isolated.

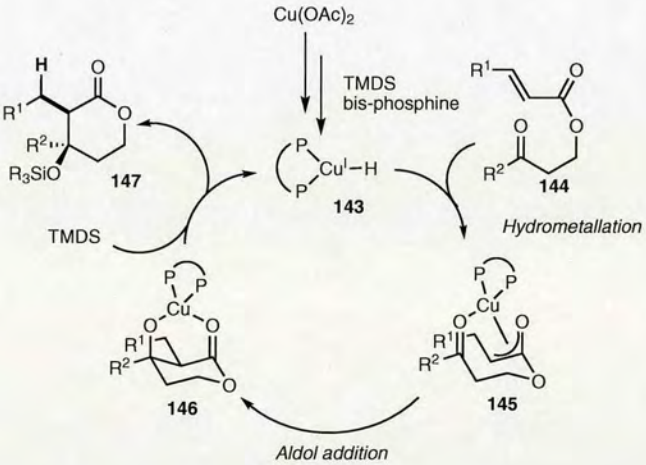
It was observed that α,β-unsaturated amides can also be used in this process giving 4-hydroxypiperidin-2-ones with high levels of diastereoselectivity. Once more a broad scope of ketone acceptors was tolerated. However, only acryloyl and crotonyl amide



Entry	R	Ligand	Yield	*ee*
1	Ph	**136**	72	62
2	Ph	**137**	73	73
3	Ph	**138**	69	70
4	Ph	**139**	64	77
5	Ph	**140**	62	74
6	4-ClPh	**136**	79	73
7	4-ClPh	**137**	71	76
8	4-ClPh	**138**	71	83
9	4-ClPh	**140**	73	82
10	$PhCH_2CH_2$	**136**	60	72
11	$PhCH_2CH_2$	**137**	60	72
12	$PhCH_2CH_2$	**138**	61	80
13	$PhCH_2CH_2$	**140**	68	80

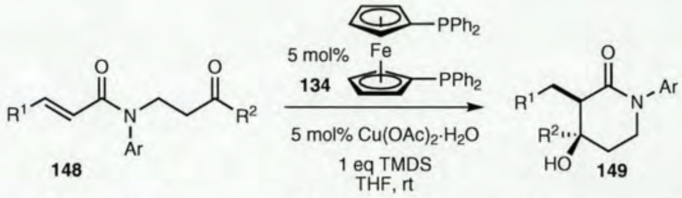
Table 1.2: Copper-catalysed asymmetric reductive aldol cyclisations

components were reactive enough to undergo the reaction under these conditions. In addition, it was not possible to form five-membered lactam rings.[27]



Scheme 1.33: Proposed catalytic cycle of the copper-catalysed reductive aldol cyclisation

The presence of a stereocentre at C5 or C6 delivered a strong 1,2- and 1,3-asymmetric induction and excellent levels of diastereoselectivities were observed in this class of starting materials (Table 1.4).



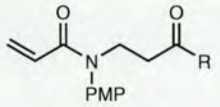
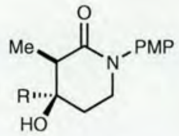
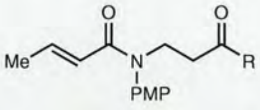
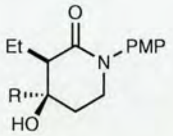
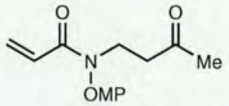
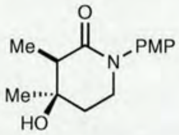
Entry	Substrate	R	Product	Time	Yield
1		Me		2.5	66
2		Et		5.5	61
3		*i*-Bu		24	64
4		Ph		21	69
5		4-MePh		24	64
6		2-furyl		24	53
7		Me		22	55
8		Et		24	52
9				4	70

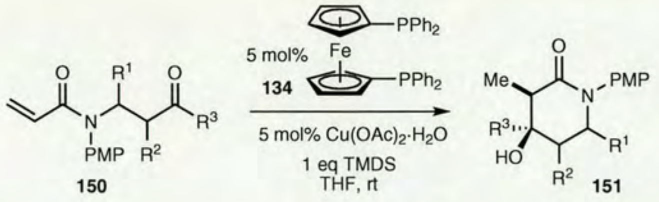
Table 1.3: Copper-catalysed reductive aldol cyclisation to form 4-hydroxypiperidin-2-ones

1.3.2 Cobalt-catalysed reductive aldol cyclisation

Although copper catalysis had proven to be highly successful in the formation of β-hydroxylactones, its efficiency in the formation of β-hydroxylactams was diminished by the low electrophilicity of α,β-unsaturated amides. To counter the limitations of the copper-catalysed reductive aldol cyclisation reaction a new catalytic system had to be invented.

The application of non-copper metal salts proved to be unsuccessful despite previous reports of similar processes involving Co(II) and silanes.[89–91] Inspired by several articles in which organometallic reagents were used in place of silanes[92–96] we became interested in applying similar conditions for reductive aldol cyclisations. When a Co(acac)$_2$ pre-catalyst was used together with Et$_2$Zn as the stoichiometric reductant a high yielding reaction was observed.[28]

Upon investigation of the reaction scope it was observed that this new catalyst system allowed a broad range of starting materials to undergo the reductive aldol cy-



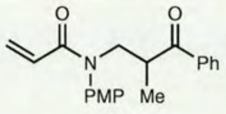
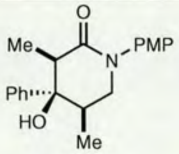
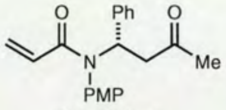
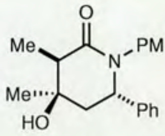
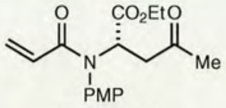
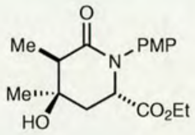
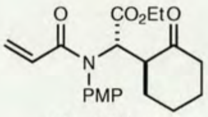
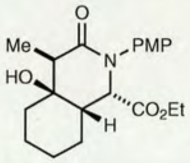
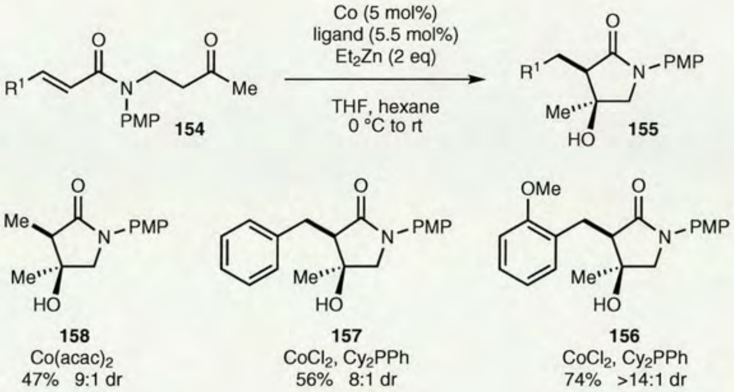
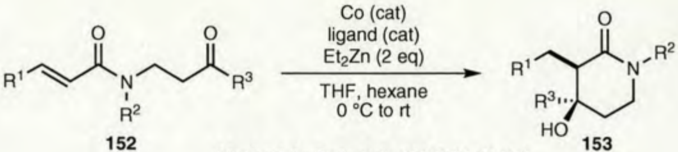
Entry	Substrate	Product	*dr*	Yield
1	 **3a**		8:1	78
2	 **3b** 85% ee		>19:1	65
3	 **3c** 96% ee		>19:1	68
4	 **3d** >99% ee		5:1	66

Table 1.4: Formation of C5- and C6-substituted 4-hydroxypiperidin-2-ones

clisation. It was possible to obtain five- and six-membered β-hydroxylactams containing a wide variety of substitutions that were previously unreactive under the copper-catalysed procedure. Although Co(acac)$_2$ was the most versatile precatalyst, CoCl$_2$ together with electron-rich ligand (Cy$_2$PPh) was used for some starting materials .



Scheme 1.34: Cobalt-catalysed reductive aldol cyclisations to form five-membered lactams



152 → **153**

Method A: $Co(acac)_2 \cdot 2H_2O$ (5 mol%)
Method B: $CoCl_2$ (5 mol%), Cy_2PPh (5.5 mol%)

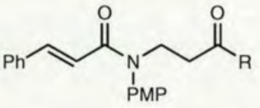
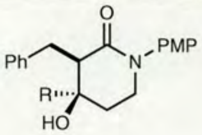
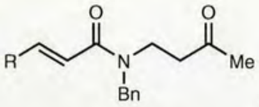
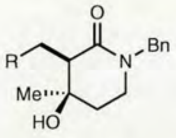
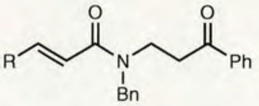
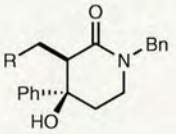
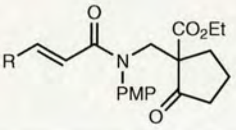
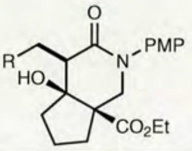
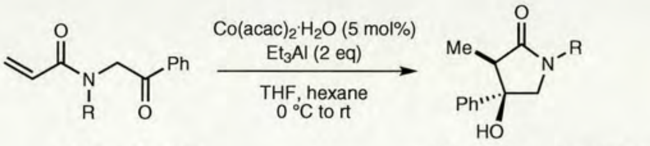
Entry	Substrate	R	Method	Product	*dr*	Yield
1		Me	A		12:1	89
2		Et	A		9:1	79
3		H	A		9:1	88
4		*i*-Pr	A		>19:1	>99
5		Ph	A		>19:1	97
6		2-furyl	A		>19:1	>99
7		Me	A		>19:1	94
8		*i*-Bu	A		>19:1	94
9		H	B		9:1	56
10		Me	B		>19:1	80
11		Ph	B		>19:1	88

Table 1.5: Cobalt-catalysed reductive aldol cyclisations

Although the formation of five-membered lactams was achieved with lower yields, these results were later to be of great importance in synthesis of salinosporamide A intermediates.

Cobalt-catalysed reductive aldol reactions with diethylzinc were underperforming when starting materials containing phenyl ketone were used (<20% yield). This limitation was partially overcome when Et_3Al was used instead of Et_2Zn. In this case β-hydroxy-β-phenyl-lactams were obtained in modest yields.



159 R = PMP
160 R = PMB

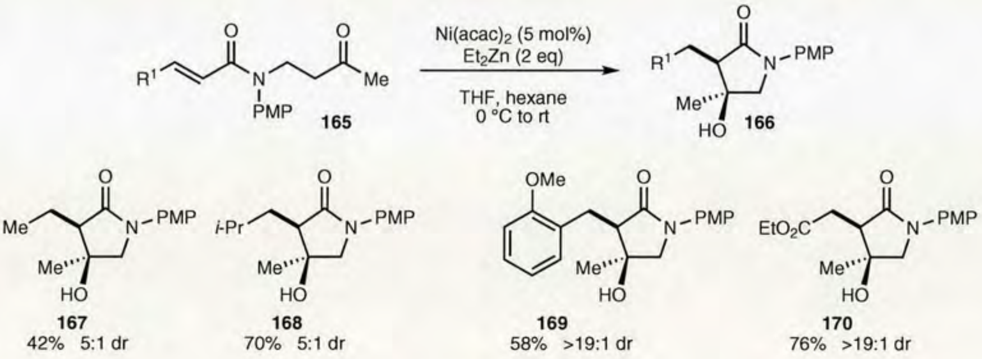
161 57 % yield, >19:1 dr
162 53 % yield, 8:1 dr

Scheme 1.35: Cyclisations to five-membered ring lactams using Et_3Al

1.3.3 Nickel-catalysed reductive aldol cyclisations

The improvements observed using the cobalt catalyst and diethylzinc inspired us to further extend the search for a catalyst for our reductive aldol reactions. At that time, nickel was rarely used as a catalyst for similar reactions, in one recent example Montgomery applied $Ni(COD)_2$ with Et_3B.[30] After thorough investigations it was demonstrated that $Ni(acac)_2$ in conjunction with Et_2Zn was a superb catalyst system for reductive aldol cyclisations. The reactivity of the nickel catalyst towards α,β-unsaturated amides not only improved previous results obtained with the cobalt catalyst but also allowed a much broader scope of starting materials then any other catalyst.[29]

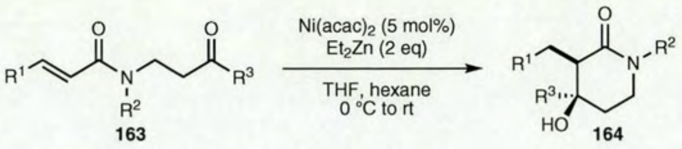
Interestingly, reactions of substrates with mono-ethyl esters of fumaric amides yielded bicyclic products in which the initial reductive aldol cyclisation to form the lactam ring was followed by a γ-lactone formation (Table 1.6 entries 14 and 15). Most importantly these conditions allowed the preparation of a wide variety of γ-lactams. These results initiated efforts in the total synthesis of salinosporamide A.



Scheme 1.36: Nickel-catalysed cyclisations to form γ-lactams

Reactions of α,β-unsaturated esters were also effective with the nickel catalyst. Upon comparison it was observed that many previously unreactive starting materials gave the reductive aldol products in high yields and excellent levels of diastereoselectivity under the modified conditions.

In an attempt to understand the superior reactivity of the nickel-catalysed reactions, a mechanistic investigation was undertaken partially based on previous reports of coupling reactions with nickel catalysts.[5] It is widely accepted that $Ni(acac)_2$ is re-



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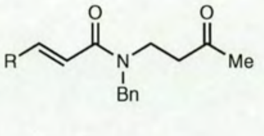
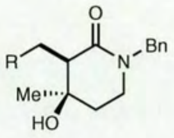
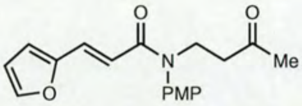
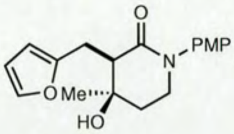
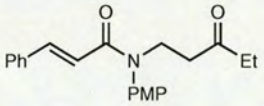
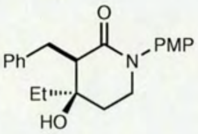
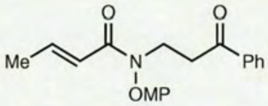
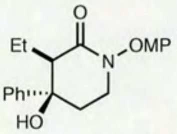
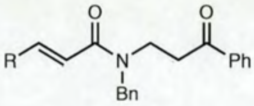
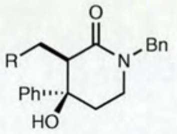
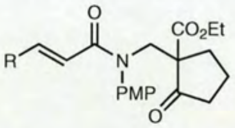
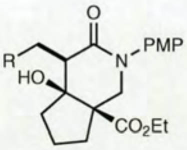
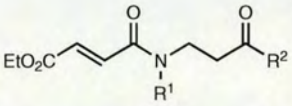
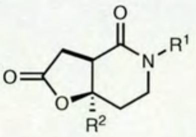
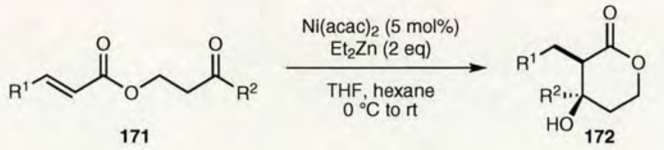
1		Me		> 19:1	97
2		*i*-Pr		12:1	98
3		$PhCH_2CH_2$		> 19:1	95
4		Ph		> 19:1	97
5		2-furyl		> 19:1	99
6				> 19:1	75
7				> 19:1	82
8				> 19:1	62
9		Me		9:1	84
10		*i*-Bu		12:1	84
11		2-furyl		> 19:1	79
12		Me		> 19:1	62
13		Ph		> 19:1	50
14		R^1 = PMP R^2 = Ph		> 19:1	62
15		R^1 = Bn R^2 = Me		> 19:1	50

Table 1.6: Nickel catalysed reductive aldol cyclisation to form 4-hydroxypiperidin-2-ones

duced with Et_2Zn to a nickel(0) species *in situ* and this intermediate acts as the active catalyst. Similarly cobalt(II) salts are also reduced with Et_2Zn to cobalt(0). However, the mode of action of these two low valent metal catalysts are uncertain. We have proposed two mechanisms that can explain the reactivity patterns observed in our studies.[27]



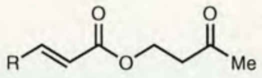
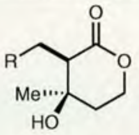
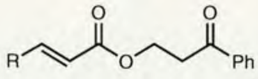
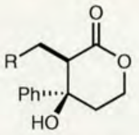
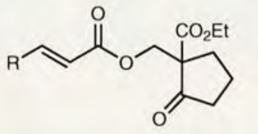
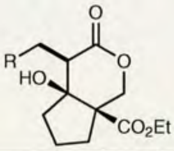
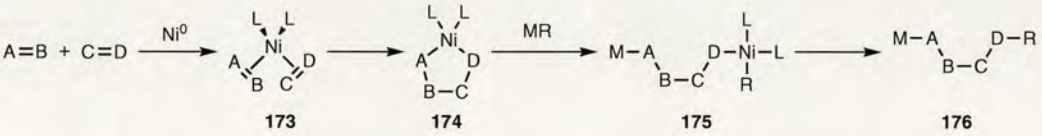
Entry	Substrate	R	Product	*dr*	Yield
1		*i*-Bu		> 19:1	77
2		$PhCH_2CH_2$		> 19:1	85
3		4-MeOPh		> 19:1	76
4		2-furyl		> 19:1	81
5		*i*-Bu		5.5:1	99
6		$PhCH_2CH_2$		> 19:1	76
7		Me		> 19:1	88
8		*i*-Pr		> 19:1	74
9		Ph		> 19:1	73

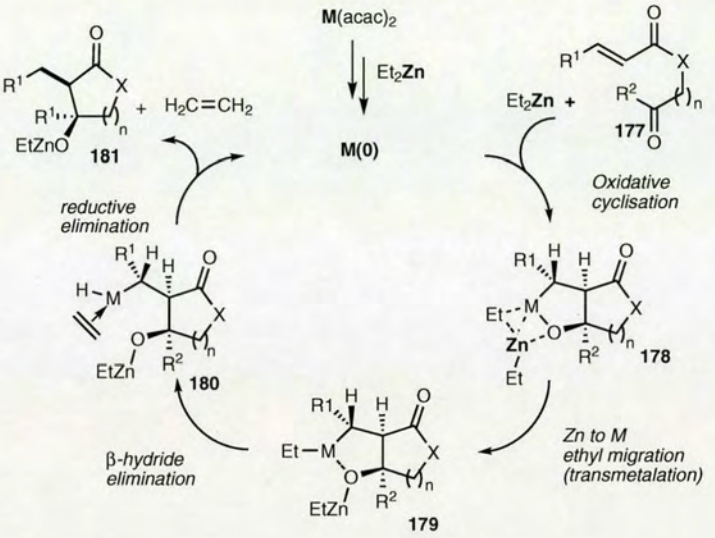
Table 1.7: Nickel-catalysed reductive aldol cyclisation to form β-hydroxylactones

A general mechanism for oxidative cyclisation with a low valent catalyst is shown on scheme 1.37. Initial coordination of the metal (nickel(0)) with two π-components is followed by oxidative cyclisation giving intermediate **174**. Transmetallation of **174** with a main group organometallic reagent gives **175**. Reductive elimination of nickel from **175** releases the final product **176** and regenerates the low valent catalyst.[5]



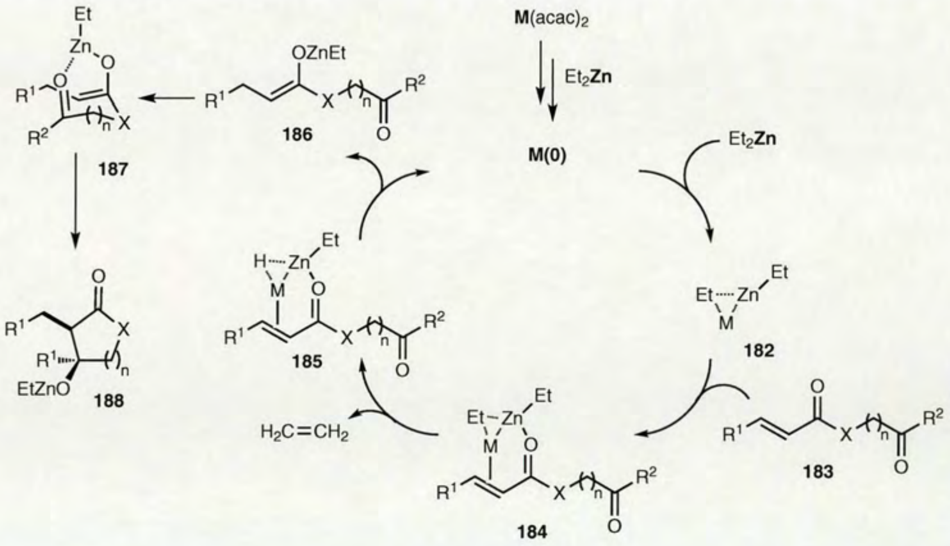
Scheme 1.37: Oxidative cyclisation of Ni(0) with two π-components

The mechanism for the reductive aldol cyclisation with nickel and cobalt catalysts and diethyl zinc reductant is proposed based on an oxidative cyclisation mechanism (Scheme 1.38). Cyclisation between alkene, ketone and low valent metal catalyst is most likely facilitated by the diethylzinc reagent through Lewis acid-based activation. Possibly a three-center-two-electron intermediate is formed **178**.[97] Transmetallation of an ethyl group from zinc to nickel/cobalt yields intermediate **179**. Upon β-hydride elimination from an ethyl substituent a metal hydride **180** is formed which undergoes reductive elimination to give the product in the form of alkoxide **181** and regenerates the metal catalyst. The alcohol product is isolated from reaction mixture upon acidic workup.



Scheme 1.38: First possible reaction mechanism: via formation of metallacycles

In this mechanism, the control of the relative stereochemistry is achieved through formation of metallacycle **178** that contain a *cis* arrangement of rings producing mainly the *syn* diastereoisomer of the final product.

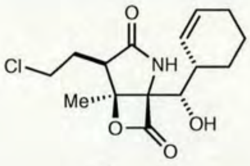


Scheme 1.39: Second possible reaction mechanism: via formation of a zinc enolate

An alternative mechanism has also been proposed. In this scenario only the α,β-unsaturated amide moiety is involved in the first steps of the catalytic cycle. Intermediate **182** is preformed from the metal catalyst and diethylzinc. Coordination of **182** to the starting material gives intermediate **184** that undergoes β-hydride elimination from an ethyl group to produce **185**. A concerted rearrangement of the **185** gives enolate **186** and regenerates the metal catalyst. Intermediate **186** undergoes aldol cyclisation through transition state **187** to produce the alkoxide **188**. Acidic workup of the reaction mixture allows isolation of the desired aldol product. The stereoselectivity of this mechanism is the result of a preferential formation of a Z-enolate in **187** and a chelated Zimmerman-Traxler transition state.

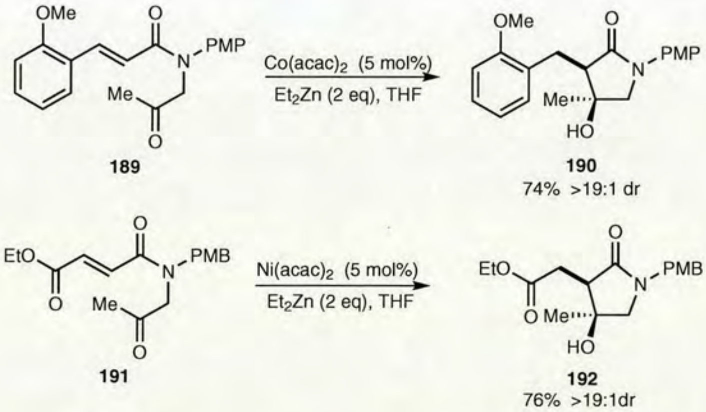
1.4 Results and discussion

Given the huge interest in salinosporamide A (**1**), and the resemblance of β-hydroxy-γ-lactam **3** to the core of **1**, we became interested in the possibility of applying our nickel-catalysed reductive aldol methodology[29] in a synthetic route towards this natural product.[†]


1

Scheme 1.40: Structure of Salinosporamide A

Reductive aldol cyclisation in the Lam group at that time was a well studied reaction. We believed to have an extensive understanding of reaction conditions that would allow us to successfully apply our reductive aldol cyclisation to substrates significantly more difficult than those previously studied. Our motivation came from examples like those depicted in scheme 1.41.



Scheme 1.41: Relevant examples of successful cyclisations to 5-membered ring -lactams

Although the nickel-catalysed reductive aldol cyclisations proceeded smoothly to give β-hyrdroxy-γ-lactams, the vast majority of starting materials did not contain large side chain substitutions and we were unsure how this would influence the key step in

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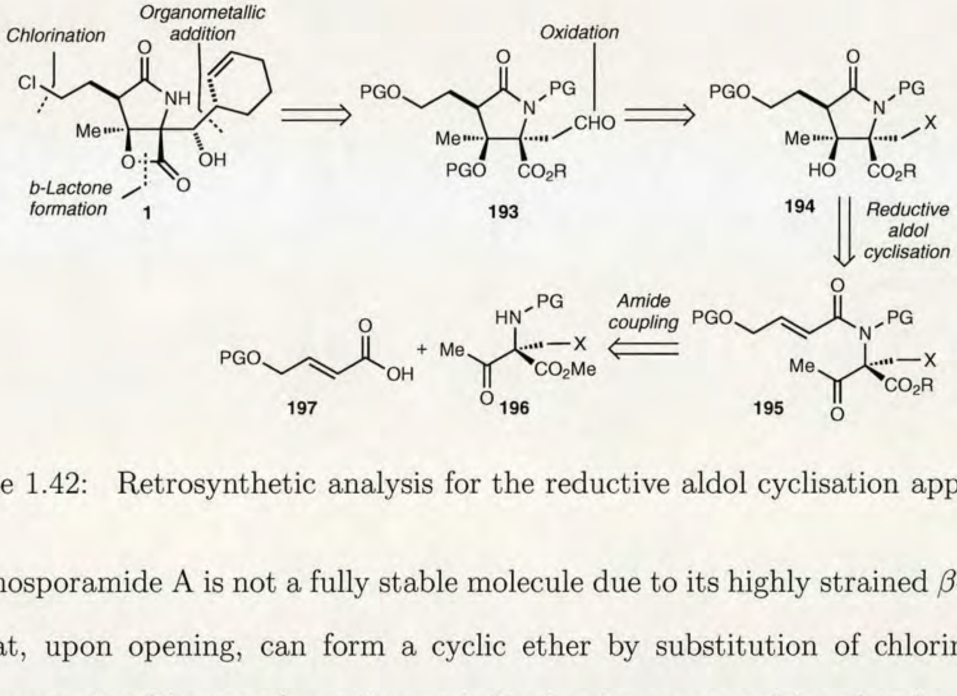
[†] Work done in cooperation with Isabel Villanueva, † is used to mark experiments conducted by Isabel.

our synthesis. We were lucky to observe high levels of *syn* diastereoselectivity in most of the reactions but no control of enantioselectivity was known. Hence, we had to be sure that our cyclisation precursor in the synthesis of salinosporamide A contained a preformed stereocentre to efficiently direct our *syn* selective reductive aldol cyclisation towards one diastereoisomer.

1.4.1 Retrosynthesis

Employing a reductive aldol cyclisation as our key step in the total synthesis of salinosporamide A placed a strong constraint on the possible synthetic pathway. Upon careful examination of previous total syntheses and difficulties that were observed by others we decided to follow a distinct (although similar in certain aspects) pathway (Scheme 1.42).



Scheme 1.42: Retrosynthetic analysis for the reductive aldol cyclisation approach

Salinosporamide A is not a fully stable molecule due to its highly strained β-lactone ring that, upon opening, can form a cyclic ether by substitution of chlorine. For these reasons the β-lactone formation and chlorination were envisioned to be our last steps. It was also important to plan the introduction of the cyclohexene moiety at a later stage in the synthesis and these disconnections lead to intermediate **193**. The aldehyde functionality in **193** has to be masked as group X (for example: silane, benzyl ether) during the reductive aldol cyclisation because of incompatibility with diethylzinc. Structure **194** represents an example of a reductive aldol cyclisation product that we hoped to obtain from the α,β-unsaturated amide **195** that in turn can be constructed by peptide coupling between acid **197** and amino-ketone **196**.

Compound **196** can be seen as a β-substituted derivative of amino acid. Transformation of L-threonine to **196** is a relatively common process involving oxazoline intermediates for control of the stereochemistry of the tetrasubstituted stereocentre.

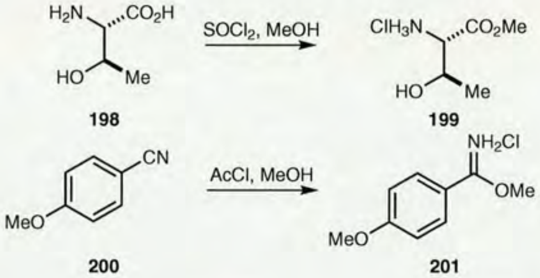
1.4.2 Formal synthesis

Using the retrosynthetic analysis as a guide we initiated studies towards the total synthesis of salinosporamide A. Surprisingly, because of unpredicted circumstances we managed to complete a formal synthesis by obtaining a different than expected product of the reductive aldol cyclisation. Our synthesis started with a relatively large scale preparation of basic starting materials.

Preparation of oxazoline

Esterification of L-threonine **198** gave the HCl salt of the methyl ester **199** in a high yield although with minor difficulties. Our product of esterification was obtained as a slightly yellow highly viscous solid instead of white powder. As there were no impurities observed by means of spectral analysis we assumed that our source of HCl (generated *in situ* from $SOCl_2$) was impure or a side reaction was taking place giving small quantities of sulphur that inhibited the crystallisation process. Changing $SOCl_2$ to AcCl did indeed help however, only a slight improvement was observed and the final product had to be washed several times in various solvents to achieve a nice white powder that was easier to handle then the viscous solid. After a search in scientific literature we found out that similar problems were observed by others and the only way to isolate L-threonine methyl ester as white powder is to conduct esterification in high purity methanol with HCl gas as a catalyst. Due to the of difficulties associated with handling large amounts of HCl gas we decided to continue our synthesis using the previous protocol of pregeneration of HCl *in situ* from methanol and thionyl chloride as depicted in scheme 1.43.

Following a known protocol[98] 4-methoxybenzonitrile **200** was smoothly transformed into **201** via an acid catalysed addition of methanol to nitrile. Product **201** was obtaine as a pure white solid on semi-industrial scale (up to 100g in one batch) and could be stored indefinitely in a fridge. Despite the use of AcCl, that caused difficulties in the crystallisation of ester **199**, this time the desired white powder of **201** was spontaneously crashing out of solution. One drawback of this reaction was the need to maintain a slight overpressure of generated HCl inside the sealed reaction flask. That required a significant degree of caution during the addition of acetyl chloride and the reaction flask was sealed only after most of the HCl was released to ensure safety.

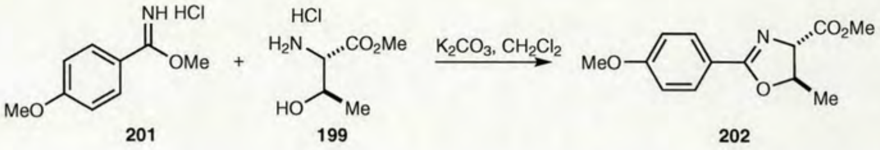


Scheme 1.43: Basic starting materials

Condensation of imine **201** and the methyl ester of L-threonine **199** was initially achieved using 1 equiv of triethylamine in refluxing DCM. This process gave 40% of the desired oxazoline **202**. However, upon scaling up, we found it to be a less reliable method because of difficulties with purification of the reaction mixture. Later we discovered that K_2CO_3 can be used instead of triethylamine and 65% yield of product was obtained. Oxazoline **202** is the same material that Corey obtained in his synthesis. Although our condensation approach with K_2CO_3 was giving slightly lower yields than Corey's procedure (acylation of methyl ester **199** with 4-methoxybenzoyl chloride and subsequent acid catalysed cyclisation[45]), this process involved only one step and allowed grater reliability.

Alkylation of α-position in oxazoline 202

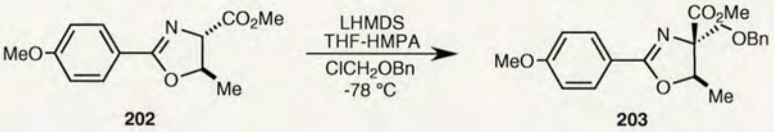
Alkylation of oxazoline **202** was achieved by Corey using LDA in the presence of HMPA to form the enolate intermediate and followed by addition of chloromethyl benzyl ether



Scheme 1.44: Preparation of oxazoline **202**

to give the desired product **203** in 69% yield. We decided to try to optimise this reaction.

Our desired product did not require the introduction of a benzyl ether substituent. It was enough to install any functional group that could be easily converted to an aldehyde. It was also desirable to avoid the use of unstable or toxic reagents.



Scheme 1.45: Optimisation of alkylation procedure

Upon testing many different conditions we came to the conclusion that phase-transfer catalysis is hopeless in this case (as expected) as only decomposition products were isolated. It was also not possible to exchange the chloromethyl benzyl ether with an iodomethyl silane reagent even when Corey's protocol of deprotonation was used. That can be explained due to the reduced electrophilicity and large steric bulk of iodomethyl silane in comparison to chloromethyl benzyl ether. Finally, we managed to improve Corey's yield using LHMDS instead of LDA to deprotonate the oxazoline **202**. This change of base also made it easier to conduct the alkylation steps because LHMDS is a stable commercial reagent as opposed to LDA that have to be preformed (Scheme 1.45 and Table 1.8).

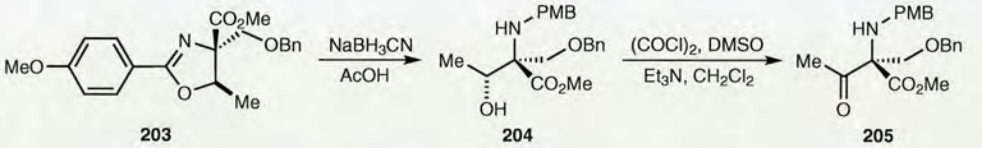
Preparation of α,β-unsaturated amide-ketone 212

Oxazoline **203** was reductively opened with sodium cyanoborohydride in acetic acid (Scheme 1.46). The desired amino-alcohol **204** was obtained in a good yield, unfortunately yields were variable between reaction runs (from 60 to 85%). Initially we

Entry	Acceptor	Base/Additive	Solvent	Results
1	$ICH_2Si(Me)_2Ph$	KOH, $BuNEt_3Cl$	PhMe	Decomp.
2	$ClCH_2OBn$	KOH, $BuNEt_3Cl$	PhMe	Decomp.
3	formaldehyde	KOH, $BuNEt_3Cl$	PhMe	Decomp.
4	$ICH_2Si(Me)_2Ph$	LHMDS, HMPA	THF	Decomp.
5	$ClCH_2OBn$	LHMDS, HMPA	THF	75%

Table 1.8: Alkylation trials

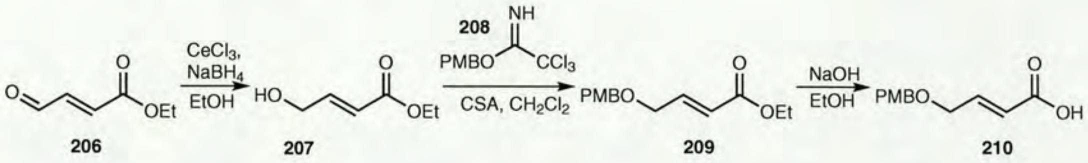
planned to protect the hydroxyl in **204** as a TMS ether, then perform a peptide coupling of the amine to a desired α,β-unsaturated acid. Deprotection of the TMS ether and oxidation of the alcohol to a ketone to afford compounds similar to **212**. The reason for this initial procedure was that reacting amino-alcohol **204** with Dess-Martin periodinane gave unidentified products of decomposition. Fortunately it was found that the same amino-alcohol can be readily oxidized with a *good old* Swern oxidation protocol. Using $(COCl)_2$, DMSO and Et_3N alcohol **204** was smoothly converted to the ketone **205** in 72% yield without the need for time consuming protection steps (conversion from the amino-alcohol to the amide-ketone was done in two steps instead of four).



Scheme 1.46: Oxazoline reduction and Swern oxidation

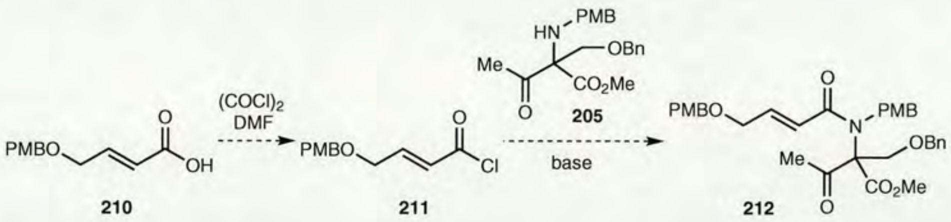
N-Acylation of 205

Amine-ketone **205** was an important intermediate in the synthesis of salinosporamide A. We were able to form several different α,β-unsaturated amides using this material and so test the efficiency of the reductive aldol cyclisation. Formation of an amide possessing the desired functionality was crucial in order to continue the synthesis of salinosporamide A because the side chain of the acid used would have to be converted in to the CH_2CH_2Cl side chain of final molecule at a later stage. We decided that the acid **210** with an OPMB protecting group would fulfil all the necessary requirements for a late stage chlorination. The acid **210** was made via a three steps synthesis with good yield (Scheme 1.47).



Scheme 1.47: Preparation of acid **210**†

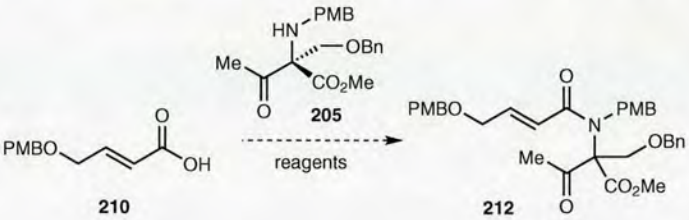
The formation of an amide bond between amine **205** and acid **210** proved to be more difficult than anticipated (Scheme 1.48). Initial trials concentrated on the *in situ* formation of an acid chloride **211** that was transferred to a solution of base and amine **205** without prior isolation. We have used two protocols to generate the acid chloride **211**. In the first procedure, a solution of acid **210**, oxalyl chloride and a catalytic amount of DMF was stirred until no further gas evolution was observed, that was a standard procedure used for amide coupling in our laboratory. In the second case, treatment of acid **210** with thionyl chloride for 3 h and vacuum distillation to remove the excess reagent was also tried. The solution of pregenerated acid chloride **211** was then added to a solution of amine **205** in the presence of a base (Et_3N, i-Pr_2EtN, pyridine, 2,6-di-tert-butylpyridine, Na_2CO_3 *aq*). Unfortunately, we were not able to isolate any product of amide coupling under any of these conditions.



Scheme 1.48: Trials of peptide coupling

Upon careful examination of our results we realized that PMB protecting group of the alcohol was susceptible to cleavage during acid chloride formation. This protecting group is known to be sensitive to acidic conditions. Additionally, the low nucleophilicity and steric hindrance of amine **205** made this amide coupling even more challenging.

To avoid PMB cleavage we tried to use peptide coupling reagents to mediate this difficult amide coupling. In theory, without the need to generate acid chloride derivatives, there would be no problem of PMB cleavage. Several different peptide coupling reagents were trialled in the presence of various additives (Table 1.9). Unfortunately, no desired product was observed and the starting amine **205** was recovered.



Entry	Reagent, Additive/Base	Solvent
1	DCC, DMAP	DCM
2	DCC, HOBt	DCM or DMF
3	DIC, DMAP	DCM or DMF
4	EDC, HOBt	DMF
5	EDC, DMAP	DCM or DMF

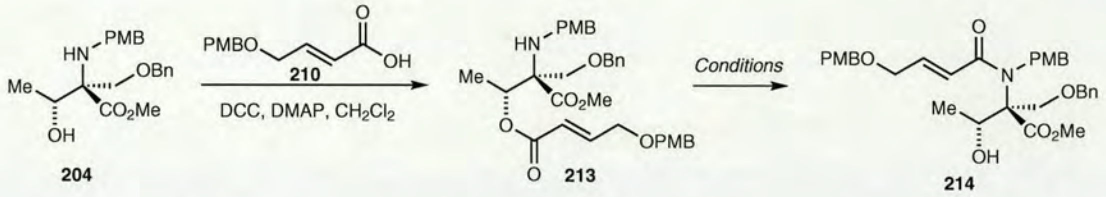
Table 1.9: Peptide coupling reagents

We speculated that the failure of peptide coupling reagents was caused by the low nucleophilicity and steric bulk of amine **205**. A possible solution to this amide coupling would be to use the benzyl protected version of acid **210** to avoid the cleavage of the protecting group during acid chloride formation. However, benzyl protection would not be compatible for later steps in the synthesis of salinosporamide A as there was already one benzyl ether protected group in **205** that would have to be selectively hydrogenated after the reductive aldol cyclisation step.

O-acylation and acyl transfer

After the difficulties with the amide coupling we turned to a procedure of acyl transfer that has been used previously in the synthesis of natural products (Scheme 1.49). When amino-alcohol **204** was used with acid **210** under peptide coupling conditions an ester **213** was smoothly isolated. This result confirmed our previous speculation concerning the large steric bulk of amine **205**. We hoped that a Lewis acid activation of ester **213** would facilitate an intramolecular attack of nitrogen onto the ester to yield amide

214. Upon examining several sets of conditions we obtained no product and only isomerisation of the double bond in the α,β-unsaturated ester moiety was observed.



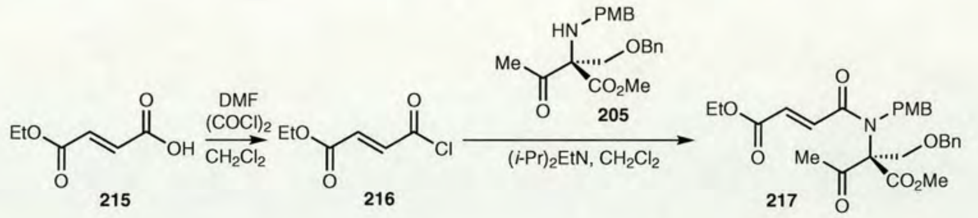
Scheme 1.49: Esterification of **204** and acyl transfer trials

Entry	Conditions	Results
1	$La(OTf)_3$, DCM, Reflux	SM
2	DBU, PhMe, Reflux	Isomerization
3	Me_3Al, DCM, Reflux	SM
4	Me_2AlCl, DCM, Reflux	SM
5	Me_3Al, PhMe, Reflux	SM
6	EtOH, H_2SO_4, Reflux	Isomerization

Table 1.10: Acyl transfer trials

Mono-ethylfumaric amide

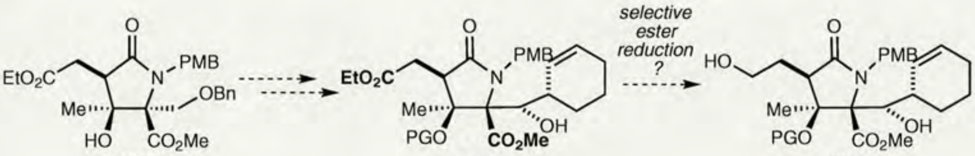
A long series of unsuccessful amide coupling attempts motivated us to survey some different α,β-unsaturated acids in an effort to at least verify that once we obtained the desired amide, a reductive aldol cyclisation can be conducted on this class of starting material.



Scheme 1.50: Preparation of **217**

Amide derived from mono-ethylfumaric acid **215** was a perfect candidate for such model studies. This acid was previously used during methodology studies giving good yields of five- and six-membered lactams. Pregeneration of the acid chloride **216** using a standard procedure was followed by addition of the amine **205** in presence of a base. The desired mono-ethylester fumaric amide **217** was isolated in good yield (Scheme 1.50).

Compound **217** was considered as a suitable model for the reductive aldol cyclisation studies. The product of this cyclisation **218** was not suitable to continue the synthesis of salinosporamide A because of the ethyl ester substitution in a side chain. This ethyl ester would have to be selectively reduced in the presence of a methyl ester later in course of synthesis (Scheme 1.51). A more suitable group than an ethyl ester would be a PMB protected hydroxyl group that contains carbon atom at the oxidation state of the final product (salinosporamide A) making it strategically much more valuable.



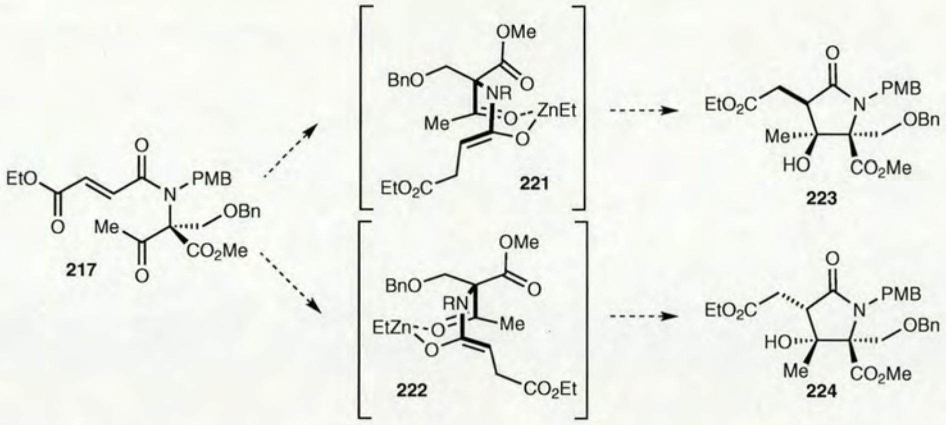
218 **219** **220**

Scheme 1.51: Possible difficulties caused by ethyl ester

Reductive aldol cyclisation of 217

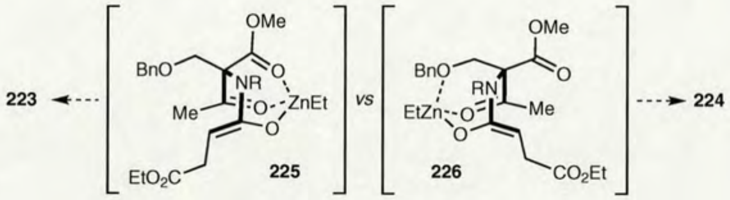
We planned to employ reductive aldol cyclisation methodology, developed in our group, to stereoselectively form the γ-lactam ring of salinosporamide A. High levels of *syn* selectivity in reductive aldol cyclisations are accounted for by the preferential formation of Z-enolates together with Zimmerman-Traxler[99] transition state.[26–29] For a successful synthesis of salinosporamide A it was desireable for the quaternary stereocentre to exert a strong effect on the face selectivity of *syn* cyclisation (Scheme 1.52).

Possible influence of the quaternary stereocentre on the reaction outcome would be by additional binding of the catalyst to one of its substituents. A strong interaction between the catalyst and methyl ester of the quaternary center would yield the desired diastereomer **223**. However, the benzyl ether group is also a suitable binding site and such binding would produce the undesired diastereomer **224**, although this interaction



Scheme 1.52: Transition states that give two *syn* products of cyclisation

should be weaker then catalyst-methyl ester (Scheme 1.53).



Scheme 1.53: Directing effect of quaternary stereocentre

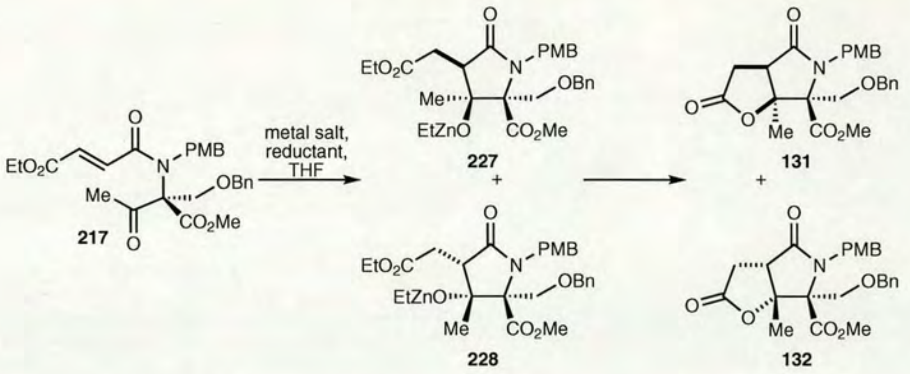
Ultimately, it was difficult to predict the diastereoselective outcome of this reductive aldol cyclisation since all proposed transition states could be formed in competition and it was hard to estimate the relative energies of them as well as kinetic effects. In addition, the precise nature of the reductive aldol cyclisation was not fully understood during methodology studies, adding to the confusion. It was becoming apparent that the cobalt- and nickel-catalysed processes did not undergo an enolate-type mechanism as was in operation under copper catalyses.

Our efforts to cyclise amide **217** concentrated around cobalt and nickel-catalysed reductive aldol cyclisations as copper was not a suitable catalyst for formation of five-membered lactam rings. Initially $Co(acac)_2$ and $Ni(acac)_2$ were used together with diethylzinc or triethylaluminum reagents. Unfortunately these standard sets of conditions were not effective in the cyclisation of **217**. Several combinations of catalyst, temperature and solvent were tried. The majority of these tests yielded mixtures of products. In an attempt to understand reaction mechanism several trials to isolate the major product from complex mixtures were conducted without success.

Further studies focused on the use of phosphine ligands together with nickel and cobalt salts. Addition of triphenylphosphine did not have an effect if small quantities were used. However, it was able to completely inhibit the catalyst when substoichiometric quantities were added. A large bis-phosphine ligand DPPF did not change the course of the reaction and afforded a complex mixture of products.

Upon analysis of the results obtained during the development of the reductive aldol cyclisations, we concluded that all possible reaction conditions from the methodology development studies had been exhausted. Any further search for a reaction catalyst would have to be conducted on the difficult starting material and not on simple models. After a time consuming synthesis of significant quantities of amide **217** we continued the search for a suitable catalyst system. A screening of transition metal salts and several potential reducing agents was undertaken. Fortuitously, one of the reagents surveyed was $(Ph_3P)_2NiBr_2$. Knowing that the addition of triphenylphosphine to $Ni(acac)_2$ did not yield any product we were not hopeful of this preformed Ni-triphenylphosphine complex. Surprisingly, the first trials of the cyclisation step yielded fairly clean TLC (as compared to previous ones) with two major products and small quantities of a third one. Upon purification, a 35% yield of product (in the form of a γ-lactone-γ-lactam) was obtained together with 30% of the undesired diastereomer. These results were further improved by the use of $(Me_3P)_2NiCl_2$ and starting reaction temperature of -15 °C. In this case, the desired product **131** was isolated in 42% yield (Table 1.11).

The observed low facial selectivity of the reductive aldol cyclisation indicated that the quaternary stereocentre was either ineffective at directing the approach of nickel catalyst or binding between nickel-methyl ester was comparable to nickel-benzyl ether. We speculated that the former is the case as the nickel catalyst is already occupied with two triphenylphosphine ligands. The only way to increase the effect of the quaternary stereocentre would be to use a catalyst without ligands but that in turn caused many side reactions to occur. This dead circle prompted us to continue the synthe-



Entry	Metal salt/ligand	Reductant	Result
1	$Ni(acac)_2$	Et_2Zn	intractable mixture
2	$CoCl_2$, Cy_2PPh	Et_2Zn	intractable mixture
3	$Co(acac)_2$	Et_2Zn	<10% conversion
4	$Ni(acac)_2$	Et_3Al	intractable mixture
5	$Co(acac)_2$	Et_2Al	intractable mixture
6	$CoCl_2$, PPh_3	Et_2Zn	**217** recovered
7	$CoCl_2$, DPPF	Et_2Zn	intractable mixture
8	$(Ph_3P)_2NiBr_2$	Et_2Zn	35% of **131**, 30% of **132**
9	$(Me_3P)_2NiCl_2$	Et_2Zn	42% of **131**, 30% of **132**

Table 1.11: Conditions attempted in the cyclisation of **217**

sis of salinosporamide A without further optimisation of the reductive aldol cyclisation conditions.

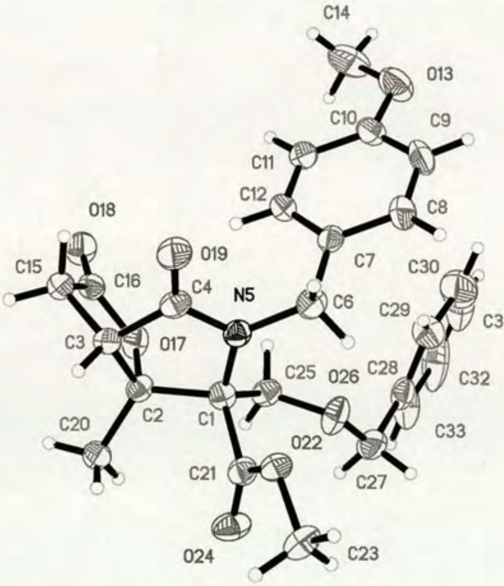
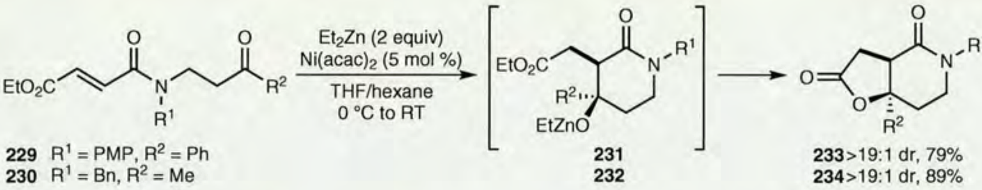


Figure 1.54: X-ray analysis of **132**

The formation of the additional γ-lactone ring during reductive aldol cyclisation was not anticipated. This process most likely occurred after zincalkoxide intermediates were formed. A highly probable mechanism involves an attack of the alkoxide anion onto the neighbouring ethyl ester with a release of zinc ethoxide. Similar processes were observed during methodology studies when a six-membered lactam of **229** and **230** was formed and only minor quantities were found in other cases. Compounds **131** and **132** were the first examples of γ-lactone-γ-lactam ring system formation during reductive aldol cyclisations in our studies. One possible explanation is that steric bulk around the quaternary stereocentre causes a high strain in the γ-lactam ring that brings the zincalkoxide and ethyl ester substituents in closer proximity to each other, facilitating the additional cyclisation.

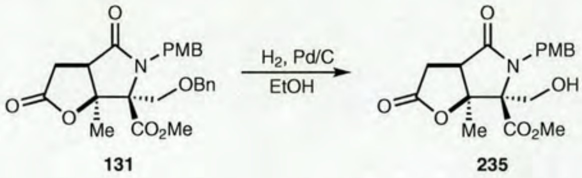


Scheme 1.55: Reductive aldol cyclisation leading to fused ring system

Although the cyclisation precursor **217** was considered as a model study of cyclisation, an additional lactonisation step could allow the completion of the synthesis of salinosporamide A. Without lactonisation a difficult late stage reduction of the ethyl ester in the presence of a methyl ester would have to be done. However, γ-lactone is relatively easy to reduce as this type of ester group is much more reactive then a linear methyl ester. Additionally, the γ-lactone ring delivered a stable protection for the tertiary β-hydroxyl substituent that otherwise would have to be protected in an additional step. The configuration of the undesired diastereoisomer was confirmed by X-ray crystallography (Figure 1.54).

Finishing formal synthesis

Upon optimisation of the reductive aldol cyclisation of **217** the desired diastereomer of the cyclized product **131** was transformed in a few steps to the triol **20** that was an intermediate in the total synthesis of salinosporamide A by Corey.[45]



Scheme 1.56: Deprotection of benzyl ether

After successful separation of the diastereomers by column chromatography, compound **131** was debenzylated by palladium-catalysed hydrogenation and the alcohol **235** was obtained in good yield (Scheme 1.56). Fortunately it was possible to obtain crystals suitable for X-ray analysis and in this way the absolute stereochemistry of **235** was confirmed(Figure 1.57).

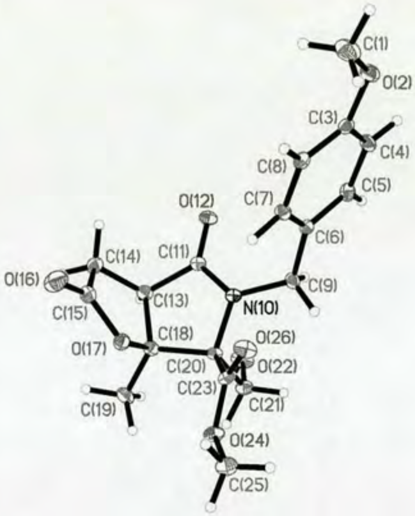
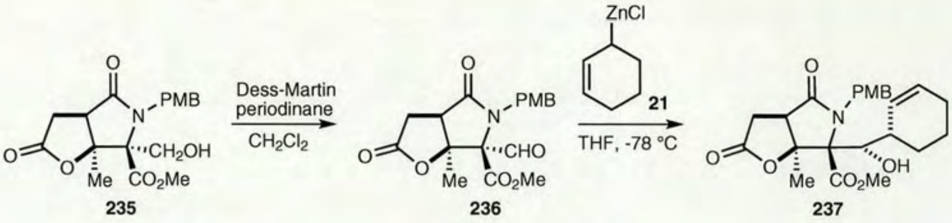


Figure 1.57: X-ray analysis of **235**

Dess-Martin oxidation[81,82] of the alcohol **235** provided **236** in good yield although the aldehyde product was unstable and so was quickly reacted with 2-cyclohexenylzinc chloride according to procedure of Corey.[45] Upon completion, the homoallylic alcohol **237** was isolated with very high diastereoselectivity (the minor diastereomer was not observed by ^{1}H NMR) and 61% yield over two steps (Scheme 1.58).

The alcohol **237** was a crystalline solid and so it was possible to confirm the configuration of the two newly created stereocenters using X-ray crystallography. (Figure 1.59)

To complete the formal synthesis a γ-lactone ring had to be selectively reduced in



Scheme 1.58: Dess-Martin oxidation and organozinc addition†

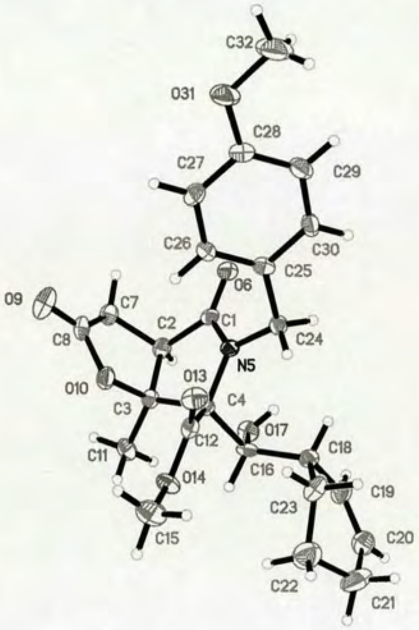
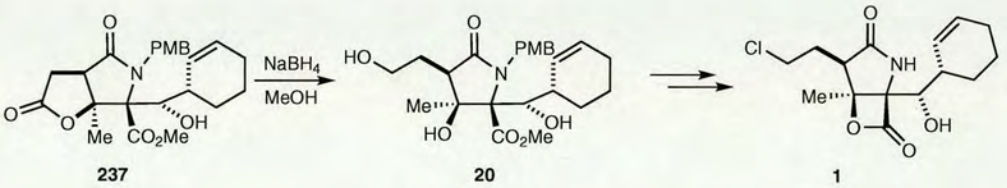


Figure 1.59: X-ray analysis of **237**

the presence of a methyl ester. Fortunately the much higher reactivity of the lactone carbonyl allowed a smooth reduction with $NaBH_4$ to give the triol **20** (Scheme 1.60). It was necessary to use a large excess of $NaBH_4$ to achieve full conversion of the starting material. The product **20** was structurally identical to intermediates obtained by Corey[45] and Pattenden[48] in their total synthesis of salinosporamide A. Four further steps are required to convert **20** into salinosporamide A (**1**).

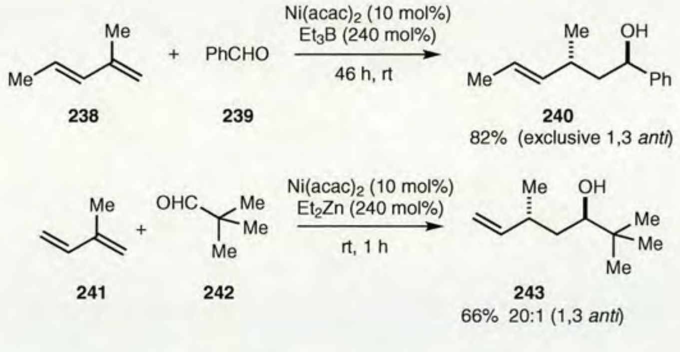


Scheme 1.60: Reduction of γ-lactone†

Upon careful examination of the NMR data for triol **20** we observed some small deviations from the values for the same compound reported by Corey and co-workers, these differences were most obvious in the ^{13}C NMR spectra.[45] We requested copies of NMR data from both the Corey and Pattenden groups and noticed that our results are in good agreement with the same compound obtained by Pattenden. It is possible that the chemical shifts of some ^{13}C NMR signals are slightly dependent on concentration (intermolecular hydrogen bonding between hydroxyl and ester groups can change electron density on adjacent carbon atoms) the data acquired by Pattenden and ourselves was from relatively dilute samples whereas Corey obtained his results using more highly concentrated samples.

1.4.3 Future work

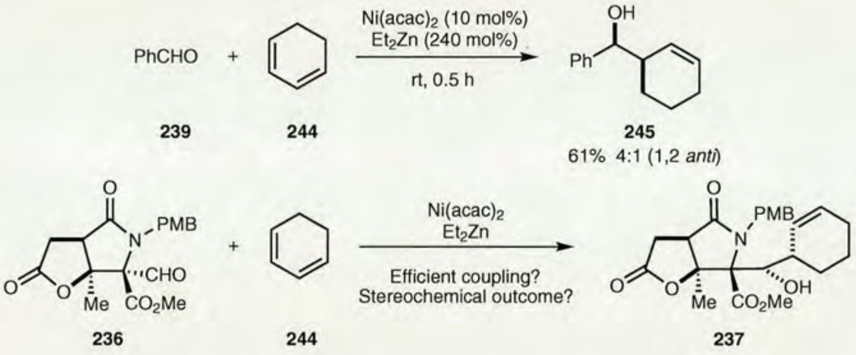
One important feature to improve in our formal synthesis of salinosporamide A could be a reductive aldol cyclisation step. However, it is rather difficult to imagine what could be done to make this reaction more selective without some modification of the starting material. Any optimisation of the catalyst system would at first require the development of a suitable model starting material that would be faster and cheaper to make followed by a careful screening of transition metals and analysis of products obtained.



Scheme 1.61: Homoallylation by Tamaru

Another interesting and more probable project would be to take advantage of an unusual type of addition of cyclohexadiene to aldehydes. So far almoust all total syntheses of salinosporamide A[45–51] have used Corey's procedure for the installation of the cyclohexenyl side-chain using a cyclohexenylzinc reagent. The high diastereoselectivity of this process is impressive. However, the preparation of cyclohexenylzinc reagents involves several synthetic steps using highly toxic tin reagent, is atom-inefficient and is practically troublesome. Instead, another route could be proposed using new methodology developed by Tamaru.[100] A new nickel-catalysed homoallylation of aromatic and aliphatic aldehydes has been demonstrated using triethylborane or diethylzinc (in the case of sterically hindered aliphatic aldehydes and ketones). High levels of regio- and stereoselectivity have been reported (Scheme 1.61).

In his original report, Tamaru gave an example of a reaction between 1,3-cyclohexadiene and benzaldehyde that afforded allylation product **245** in good yield and moderate diastereoselectivity (Scheme 1.62). If further improved, this type of reaction could be of great benefit for the synthesis of salinosporamide A as it uses more convenient reaction conditions and contains a single step



Scheme 1.62: Allylation example by Tamaru

1.5 Conclusions

We have successfully developed a formal synthesis of salinosporamide A. A reductive aldol cyclisation was used in the formation of the important γ-lactam ring. Optimization of the reductive aldol conditions revealed a new catalyst $(Me_3P)_2NiCl_2$ for this transformation and gave insight into the reaction mechanism. The desired diastereomer of the product was afforded in 42% yield together with 30% yield of the alternative product. The observed low levels of diastereoselectivity gave more information about the reaction mechanism.

The reductive aldol cyclisation was followed by an unexpected formation of γ-lactone ring. This surprising result appeared to be beneficial, thanks to the protection of the tertiary alcohol that it provided the possibility of a selective reduction of the γ-lactone in the presence of the methyl ester. The highly efficient reductive aldol cyclisation-lactonisation reaction allowed the completion of formal the synthesis using several less steps then planned. Only four synthetic steps were required to transform the cyclisation product **131** into the intermediate obtained by Corey. A further four steps would allow the formation of salinosporamide A.

We have developed a formal synthesis of salinosporamide A using 11 synthetic steps and 2.5% overall yield to intermediate **20**. If recalculated, a total synthesis of this natural product would be achieved in 15 steps and 1.4% yield. A comparison with other syntheses of salinosporamide A is presented in table 1.12.

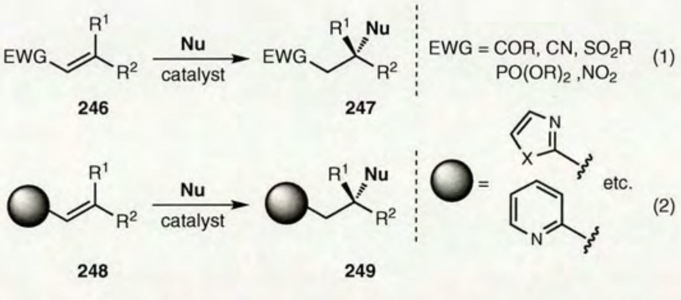
Entry	Author	No of steps	Overall yield	Asymmetric/racemic
1	Corey (Baylis-Hillman)	18	8.7%	asymmetric
2	Corey (Kulinkovich)	18	9.7%	asymmetric
3	Danishefsky	28	1.8%	asymmetric
4	Pattenden	14	11.5%	racemic
5	Langlois	18	4.0%	asymmetric
6	Romo	9	1.2%	racemic
7	Macherela	24	0.2%	asymmetric
8	Hatakeyama	21	4.4%	asymmeteric
9	Omura	36	2.0%	asymmetric
10	Bode	18	0.7%	asymmeteric
11	Lam	15	1.4%	asymmetric

Table 1.12: Comparison of reported syntheses of salinosporamide A (recalculated in case of formal synthesis)

Chapter 2

Copper catalysed asymmetric reduction of alkenylheteroarenes

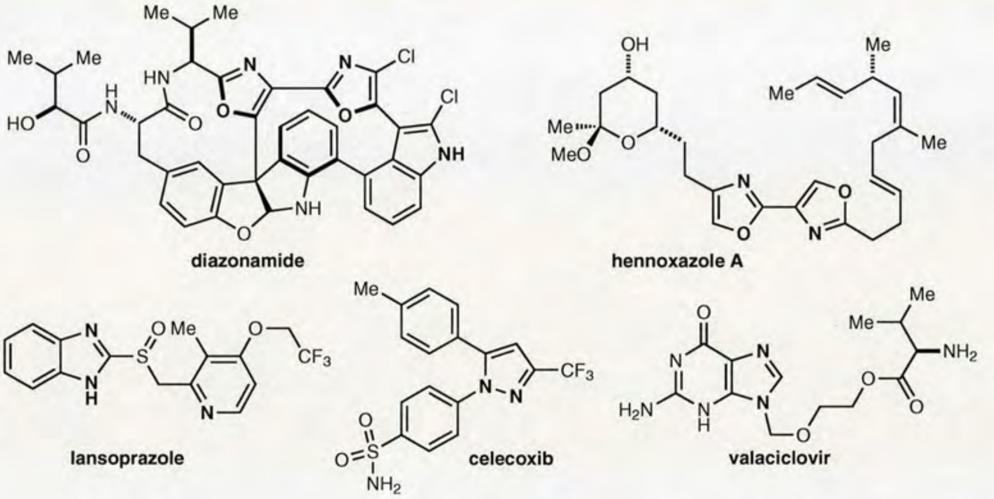
The development of modern pharmaceuticals requires increasingly more efficient and selective synthetic methods. Inspired by a growing number of procedures for enantioselective reductions and alkylations of alkenes (Scheme 2.1 eq 1)[101–108] conjugated to electron-withdrawing groups, we became interested in possible activation of a carbon-carbon double bond for nucleophilic attack with much weaker electron-withdrawing substituents.



Scheme 2.1: General Idea

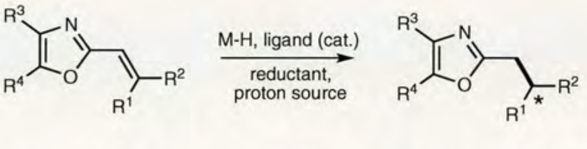
The most common functional groups used to activate alkenes towards asymmetric conjugate additions possess a central atom with a considerably large partial positive charge induced by several π-bonds to oxygen. This range includes carbonyls, sulfones, phosphonates, and nitro groups. It has also been shown that nitriles are suitable activating groups in this transformation, proving that a strong oxygen based activation is not necessary.

Given that heteroarenes such as oxazoles, thiazoles, pyridines, and others are ubiquitous in biologically active natural products, pharmaceuticals (Scheme 2.2), and agrochemicals, the ability to functionalise these privileged structures through a diverse set of asymmetric conjugate additions of 2-alkenyl derivatives (Scheme 2.1 eq 2) would open up broad-ranging applications.



Scheme 2.2: Examples of drugs containing electron-withdrawing heterocycle

Our objective was to develop a new synthetic transformation for the highly enantioselective reduction of α,β unsaturated heteroarenes (Scheme 2.3). This would require the optimization of reaction conditions and an initial investigation into the substrate scope of this new process. We hoped that this procedure would broaden the field of synthetic tools available to the medicinal chemist and allow the quick preparation of a diverse family of compounds for which currently there is no efficient synthetic route.



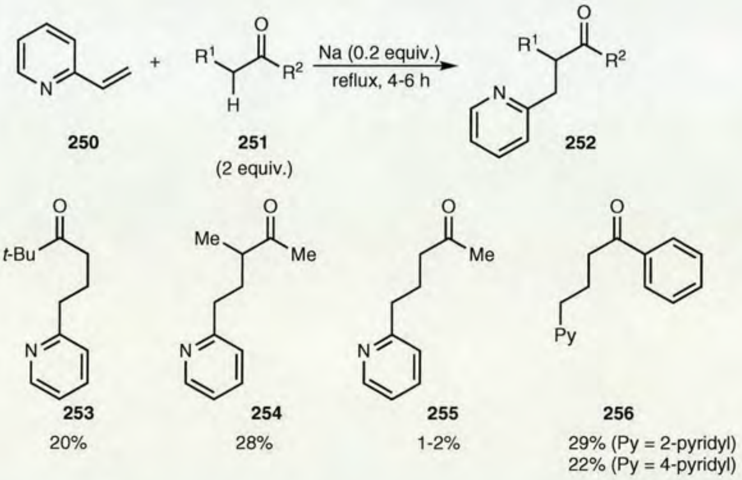
Scheme 2.3: Possible activation of alkene with oxazole heterocycle

2.1 Introduction

Addition of a nucleophile to an alkene is one of the most popular classes of reactions in organic chemistry, examples of which can be found in almost all total synthesis of natural compounds. Ordinary alkenes are not susceptible to a nucleophilic attack (apolar bond) and require activation from an electron-withdrawing substituent. Usually carbonyl groups like ketones or esters are used, reports of activation with aromatic substituents are also present in scientific literature.[109,110] An overview of research relevant to this project is presented below.

2.1.1 Nucleophilic addition reactions to alkenylheteroarenes

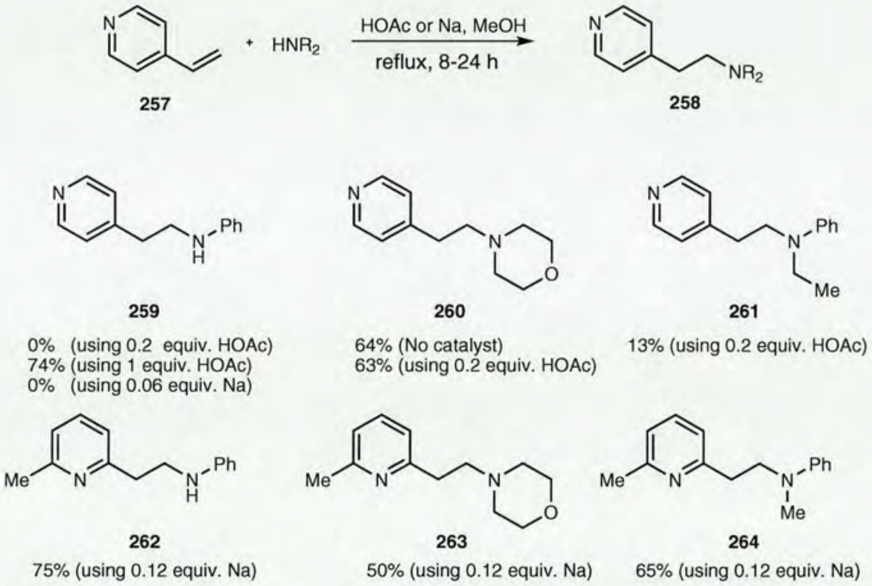
One of the earliest examples of a successful nucleophilic addition reaction to alkenylheteroarenes was published by Levine and Wilt in 1953.[111,112] They reported a reaction between 2- and 4-vinylpyridine and a ketone in presence of 0.2 equiv. of sodium (Scheme 2.4). The products of mono alkylation were obtained in modest yields.



Scheme 2.4: Alkylation of 2-vinylpyridine

The starting materials employed in this study contained several α-hydrogen and it was observed that varying levels of multiple alkylations can be obtained by changing the ratio of the starting materials used. When the starting ketone was in large excess only the mono-pyridylethylated products were observed, whereas multiple subsequent additions occurred when the ketone was the limiting reagent. Surprisingly acetone, showed very limited reactivity giving only 1-2% of product. It was also observed that the α-methylene carbon in **251** was more reactive than the α-methyl (giving product **254**). The last example **256** demonstrates that this reaction does not depend on a nitrogen atom in 2-position as there was only a small difference in the yields of products obtained with two different orientations of pyridine substituent. This methodology was later applied in the synthesis of biologically active compounds.[111,112]

Levine together with Magnus extended the previous methodology in 1956 publishing the results of the addition of amines, amides and nitriles to 2-, 4- and 5-vinylpyridines.[113] A mixture of starting materials in methanol were refluxed in the presence of concentrated acetic acid to promote the addition of nitrogen nucleophile to vinylpyridine, alternatively sodium was used in cases were acid catalysis did not afford good results (Scheme 2.5).



257

258

259
0% (using 0.2 equiv. HOAc)
74% (using 1 equiv. HOAc)
0% (using 0.06 equiv. Na)

260
64% (No catalyst)
63% (using 0.2 equiv. HOAc)

261
13% (using 0.2 equiv. HOAc)

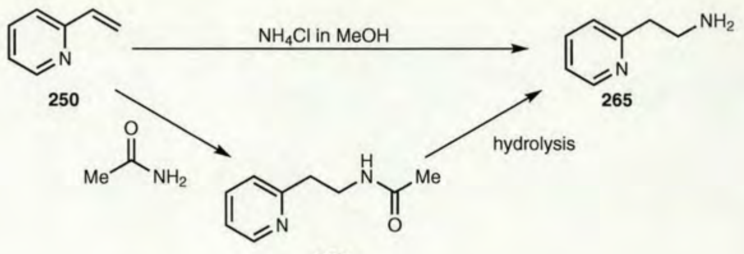
262
75% (using 0.12 equiv. Na)

263
50% (using 0.12 equiv. Na)

264
65% (using 0.12 equiv. Na)

Scheme 2.5: Addition of amines to 4-vinylpyridine

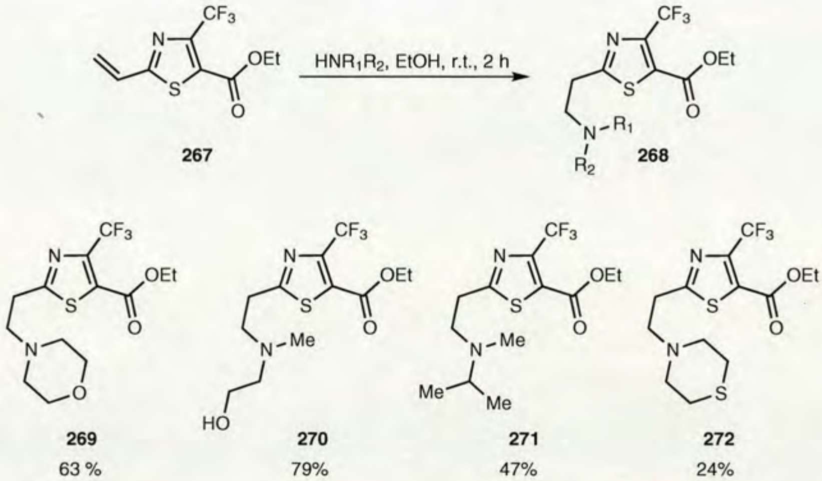
Although acetic acid was a good promoter for the reaction of 4-vinylpyridine, in the case of 2-methyl-5-vinylpyridine higher yields of addition were obtained with sodium. The paper also reports a very useful procedure for the formation of 2-(aminoethyl)pyridine from 2-vinylpyridine by either direct amination with ammonium chloride or addition of acetic amide followed by hydrolysis of the amide bond (Scheme 2.6).



Scheme 2.6: Direct amination and amide additoin/hydrolysis pathway

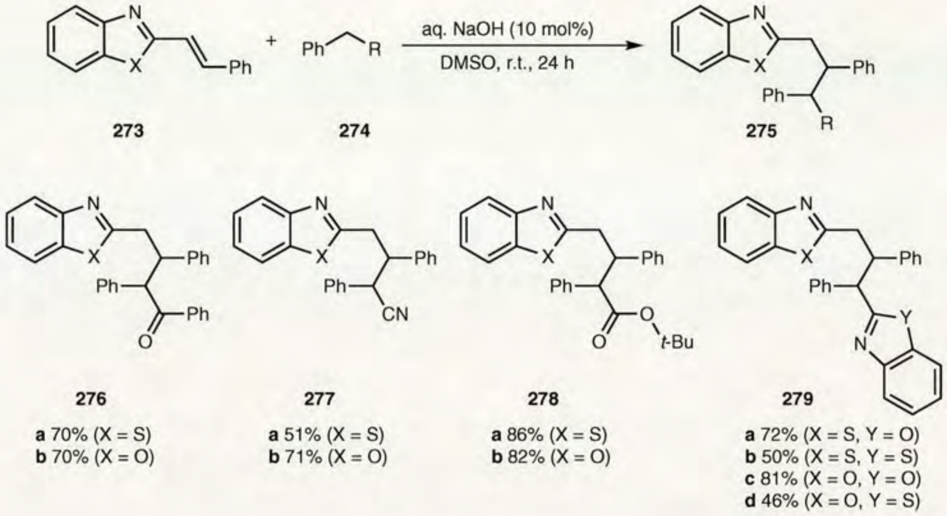
Following the first route, the reaction of 2-vinylpyridine with an aqueous methanolic solution of ammonium chloride gave 2-(aminoethyl)pyridine in 85% yield, and the corresponding reaction of 4-vinylpyridine with an aqueous methanolic solution of ammonium acetate gave 4-(aminoethyl)-pyridine in 77% yield. The second route also resulted in the formation of the desired product.

Boy and Guernon showed that other vinyl-heterocycles could undergo similar reactions (Scheme 2.7).[114] They succeeded in the addition of various aliphatic amines to the ethyl-4-(trifluoromethyl)-2-vinylthiazole-5-carboxylate **267**. Acyclic amines were observed to perform much better than cyclic amines suggesting strong influence of steric effects.



Scheme 2.7: Addition of amines to 2-vinylthiazole

Addition of carbon nucleophiles to 2-styrylbenzothiazole and 2-styryl-benzoxazole was reported by Dryanska and Ivanov in 1983 (Scheme 2.8).[115] A solution of the starting material **273**, NaOH and nucleophile was stirred at room temperature for 24 h to deliver good to high yields of products. A broad scope of nucleophiles including ketones, esters, nitriles, 2-benzoxazole and 2-styrylthiazole was showed tolerated under the reaction conditions demonstrating that vinyl benzoxazoles and benzothiazoles are good electrophiles for nucleophilic addition reactions.

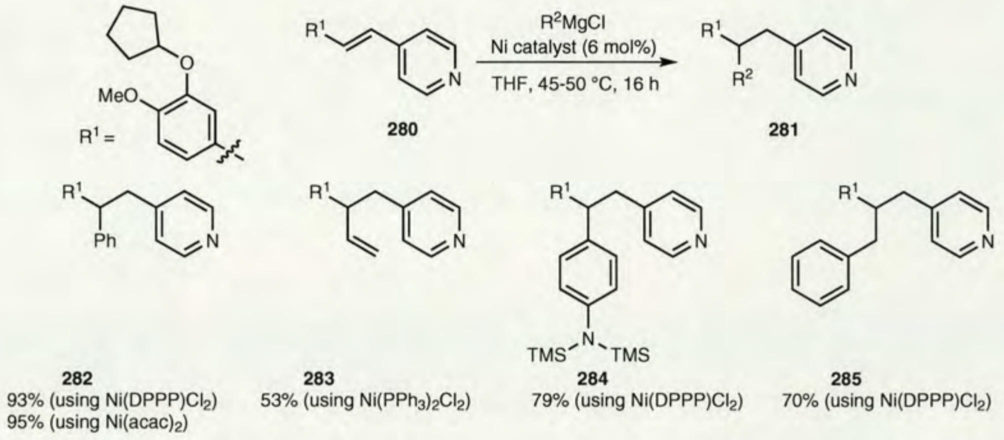


Scheme 2.8: Alkylation of 2-styrylbenzoxazole

An important research article was published by Houpis and co-workers involving nickel-catalysed nucleophilic conjugate addition of organometallic reagents to 4-vinylpyridines with various substitution patterns (Scheme 2.9).[116] Grignard and organo zinc reagents were effective alkylating agents in this transformation. It was observed that reactions at 45 °C gave much higher yields (product **282** was formed with 95% yield at 45 °C as compared to only 40% at 25 °C) and significantly lower amounts of side products.

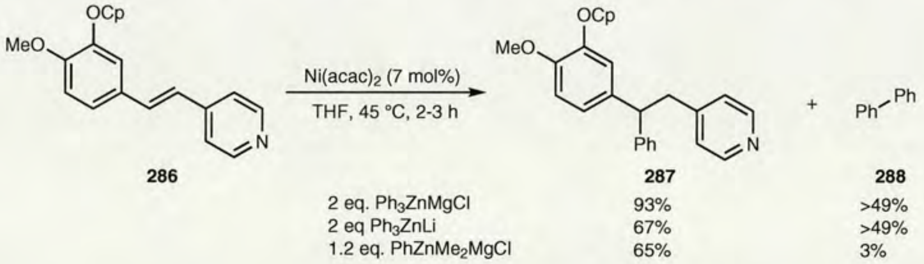
Various nickel catalysts were trialled however, different ligands did not improve the reaction rates or selectivity. Only moderate levels of enantioselectivity (<15% *ee*) were obtained when a broad screening of chiral ligands was undertaken (bisphosphines, diamines, aminoalcohols, bissulphonamide, and diols)

Finally it was also possible to successfully employ phenyl zincate reagents as nucleophiles when Ni(acac)$_2$ was used as a catalyst. However, no improvement was observed using zinc based reagents in place of Grignard reagents with respect to enantioselectivity (Scheme 2.10).



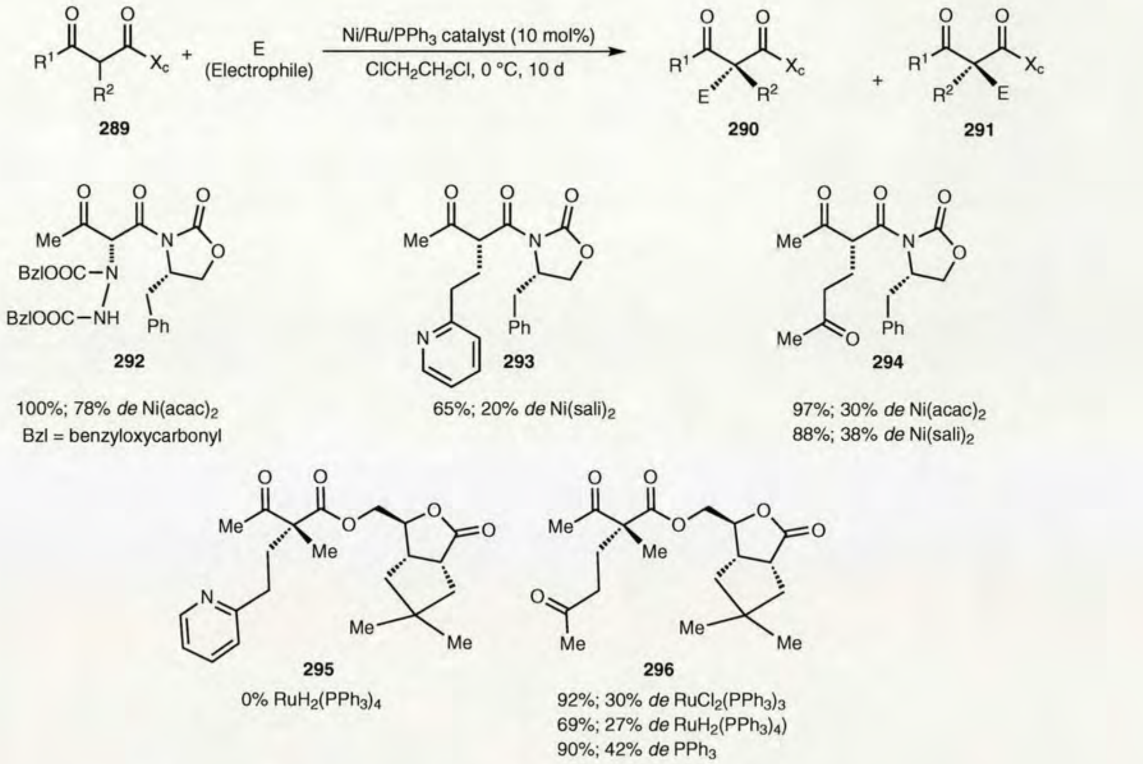
Scheme 2.9: Alkylation of 4-vinylpyridine with Grignard reagents

In 1999, Molins reported an approach for stereoselective nucleophilic additions using chiral auxiliaries as selectivity inducing agents (Scheme 2.11).[117] $Ni(sal)_2$ was used as an achiral catalyst for the addition of nucleophiles possessing a chiral auxiliary to various electrophiles. Later the same group published an improved procedure using a ruthenium based catalyst.[118] Several products were made with good yields and moderate diastereomeric excess. Most importantly, product **293**, derived from a 2-vinylpyridine electrophile, gave 65% yield and 20% de. Although this result is much lower then other described by Molins, it is an important precedent.



Scheme 2.10: Arylation of 4-vinylpyridine with zincate reagents

As discussed in the review above, the nucleophilic additions to alkenylheteroarenes have been well studied. Diverse set of possible conditions using various bases, acids and transition metals to promote this reaction have been described. Although some examples of stereoselective additions have been reported, they suffer from relatively low efficiency and stereoselectivity.



Scheme 2.11: Stereoselective additions using chiral auxiliaries

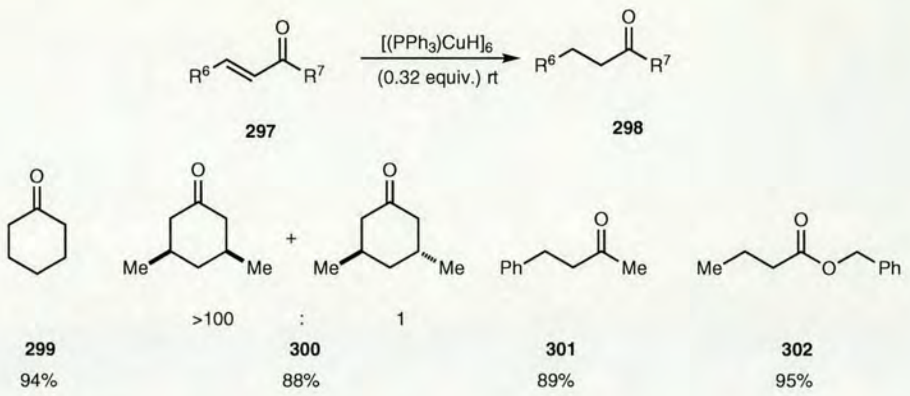
2.1.2 CuH-catalysed 1,4-conjugate reduction reactions

Conjugate reductions are a subset of nucleophilic addition reactions where the nucleophile is a hydride. This type of transformation usually requires transition metal catalysts to achieve high levels of regioselectivity.[119]

Historically the most significant example was the development of Stryker's reagent.[120] It is best described as a hexamer $[(Ph_3P)CuH]_6$ in which triphenylphospine plays a crucial role in stabilising a copper hydride intermediate. Stryker's reagent is an effective reducing agent for α,β-unsaturated carbonyl derivatives that can deliver high levels of selectivity[121] (Scheme 2.12).

Stryker's reagent can be efficiently prepared by pressurizing hydrogen gas over a solution of CuOt-Bu and triphenylphosphine in toluene. Although it is a stable solid when stored under an inert atmosphere (in fact can be exposed to the atmosphere without significant decomposition for short periods of time), in solution this copper hydride is very sensitive to oxygen.

Stryker's reagent is used as a stoichiometric reducing agent and a big disadvantage

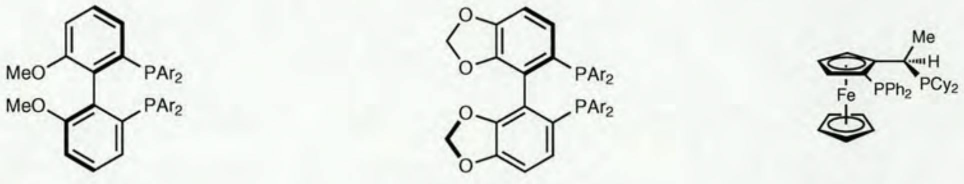


Scheme 2.12: Stryker's reagent

is the low atom efficiency of this reagent (326.8 g per 1 mol of hydride delivered) that limits its applicability in industrial processes. The first reports of trials to use this reagent catalytically came from the Stryker group itself. In their original paper they described an experiment in which CuO*t*-Bu and Ph_3P were stirred with cyclohexenone in toluene and subjected to 80 psi of hydrogen pressure. The product of reduction of cyclohexenone to cyclohexanone was observed albeit with a very slow rate (<1 turnover/hour). Further increasing the pressure of hydrogen to >200 psi led to a side reaction giving cyclohexenol as the main product.[121]

In later years, several groups reported the successful generation of stable and reactive copper hydrides *in situ* by treatment of CuO*t*-Bu with silanes as the stoichiometric reductant. A selection of silanes can be used in this process: polymethylhydrosilane (PMHS), tetramethyldisiloxane (TMDS), dimethylphenylsilane and phenylsilane being the most popular.

Although Stryker reported a high reactivity and good selectivity of $[(Ph_3P)CuH]_6$ in the reduction of α,β-unsaturated ketones, less activated alkenes require the use of more finely tuned copper hydride species. A broad scope of reactivity can be delivered by varying ligands.[122] Several enantioselective versions of this process have also been developed. The use of chiral non-racemic bisphosphines has proved to deliver remarkable levels of enantioselectivity. A broad range of ligands can be used in such processes, most notably biaryl and ferrocenyl bisphosphines have shown high levels of enantioselectivity. It is also worth mentioning that these ligands usually improve the reactivity of copper hydrides when compared with Stryker's reagent (Scheme 2.13).



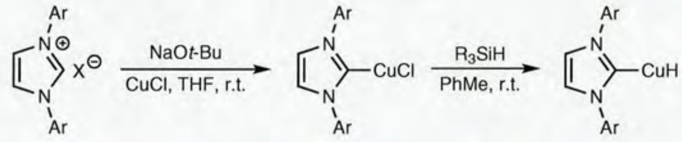
(*R*)-MeO-Biphep (Ar = Ph)
(*R*)-Xyl-MeO-Biphep (Ar = 3,5-$Me_2C_6H_3$)

(*R*)-Segphos (Ar = Ph)
(*R*)-DTBM-Segphos (Ar = 3,5-*t*-Bu_2-4-$MeOC_6H_2$)

(*R*,*S*)-Josiphos

Scheme 2.13: Phosphine ligands for fine tuning of copper hydride reactivity

More recent studies concentrate on further improving the reactivity of copper hydride by application of a relatively new class of ligands. N-heterocyclic carbenes have recently enabled a lot of progress in many types of transition metal-catalysed processes. Their particular electronic properties as σ-donors and π-acceptors exert a strong effect on the nucleophilic properties of copper hydride, increasing the reactivity of these species. A linear arrangement between carbene ligand, copper and hydrogen atom makes it possible to effectively access sterically hindered alkenes.



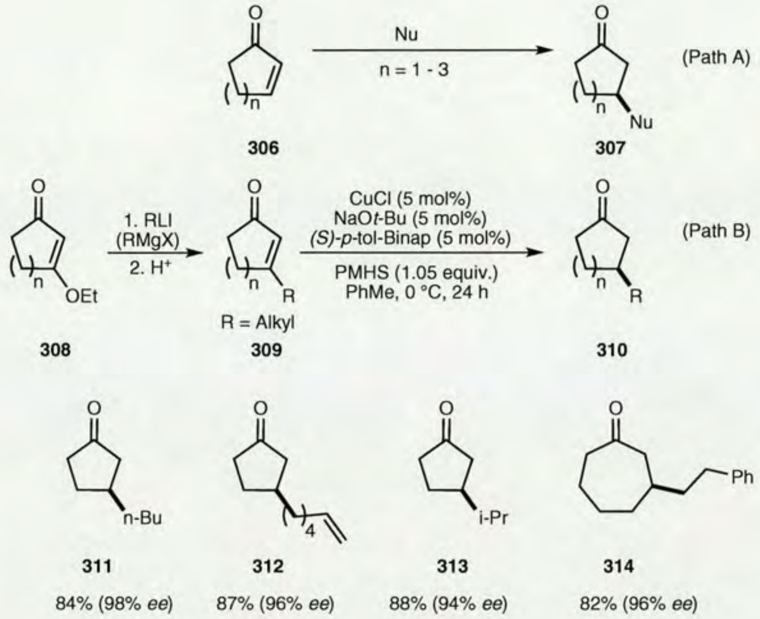
303 **304** **305**

Scheme 2.14: N-heterocyclic ligands for activation of copper hydride

Application of the right set of conditions is crucial to obtain high levels of reactivity in 1,4-conjugate reductions of substrates with various types of activating functional groups.

Reduction of α,β-unsaturated ketones

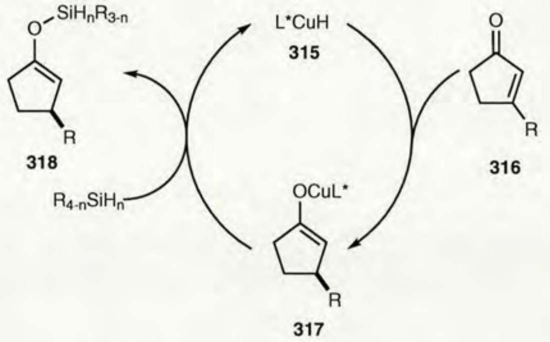
The first report of a copper-catalysed asymmetric conjugate reduction of cyclic enones came from Buchwald and co-workers[123] (Scheme 2.15 eq B). Although a shorter approach to this class of compounds, involving direct asymmetric addition of a carbon nucleophile to cyclic enones (Scheme 2.15 eq A) was already known,[124–127] Buchwald's new methodology delivered much higher enantioselectivity compared with other methods.



Scheme 2.15: Reduction of cyclic enones with copper hydride

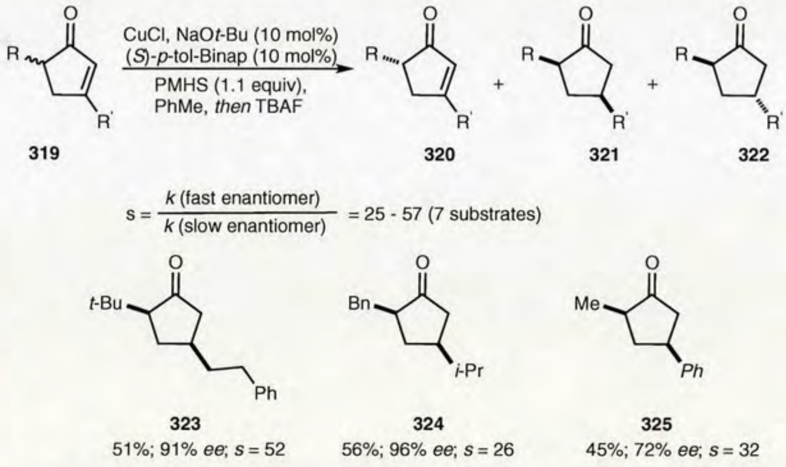
A solution of bisphosphine ligand, CuCl and NaO*t*-Bu in toluene was treated with PMHS to form an active copper hydride species, and the resulting mixture was transferred to a solution of the starting material in toluene. A catalyst loading of 5 mol% was usually sufficient to obtain complete conversion within 24 h. The β-substituted cyclopentanone products were obtained in high yield and excellent levels of enantioselectivity. The amount of PMHS added had to be precisely controlled (1.05 equiv. of PMHS in relation to starting material was used) as an excess of reducing agent led to an undesired 1,2-addition of hydride to form the alcohol. Significantly longer reaction times were needed when sterically hindered starting materials were used (Scheme 2.15 product **313**).

It was shown that this type of copper hydride is able to discriminate between activated and apolar carbon-carbon double bonds, as in example **312** the terminal double bond was left intact. The presence of an ester functionality was also tolerated. The best results were obtained with cyclohexenones. When the ring size was further increased (3-phenylethylcycloheptanone) a small amount of alcohol was observed from a competing 1,2-reduction together with desired product (**314**).



Scheme 2.16: Mechanism of copper catalysed reduction

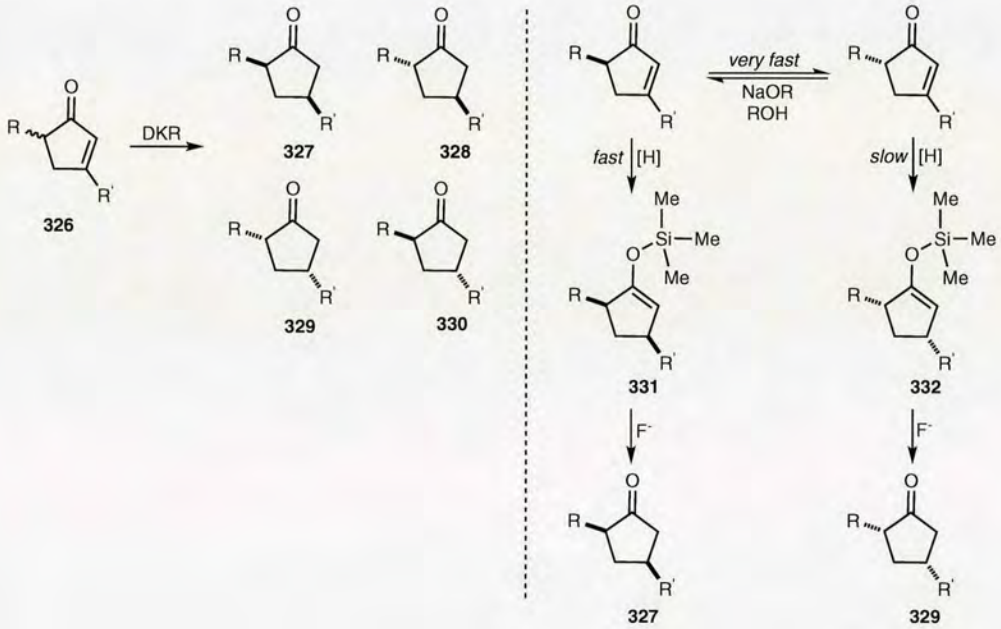
A possible catalytic cycle for this process is depicted in scheme 2.16. A 1,4-nucleophilic addition of copper hydride **315** to the starting enone **316** forms the copper enolate **317**, subsequently a σ-bond metathesis of this intermediate with a molecule of silane regenerates the copper hydride and produce silyl enol ether **318**. Upon reaction work up the silyl enol ether is hydrolysed releasing the desired product.



Scheme 2.17: Buchwald's results of kinetic resolution

Shortly after his original work, Buchwald in collaboration with Jurkauska developed a dynamic kinetic resolution variant of the nucleophilic 1,4-conjugate reduction of 2,4-dialkycyclopent-2-enones.[128] The initial experiments without addition of a base proved to deliver high levels of enantioselectivity in kinetic resolution (Scheme 2.17). Although 50% yield does not look good, this is a limiting factor in kinetic resolution processes where only half of starting material with matching chiral centers gets reacted while the other half remains intact.

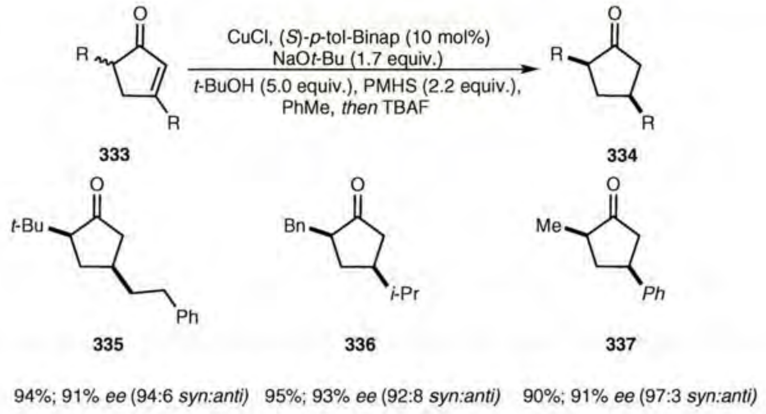
To obtain better yields than those of kinetic resolution a base was added in an approach to achieve dynamic kinetic resolution. In this case the starting material is rapidly epimerized during the course of a reaction, copper hydride adds to one of the enantiomers of the starting material to form the previously proposed enol intermediate that undergoes σ-bond metathesis with silane to give the silyl enol ether (Scheme 2.18). As the ketone functionality in the product is masked as silyl enol ether during the course of reaction, no further epimerization can occur.



Scheme 2.18: Dynamic kinetic resolution mechanism and possible isomers of product

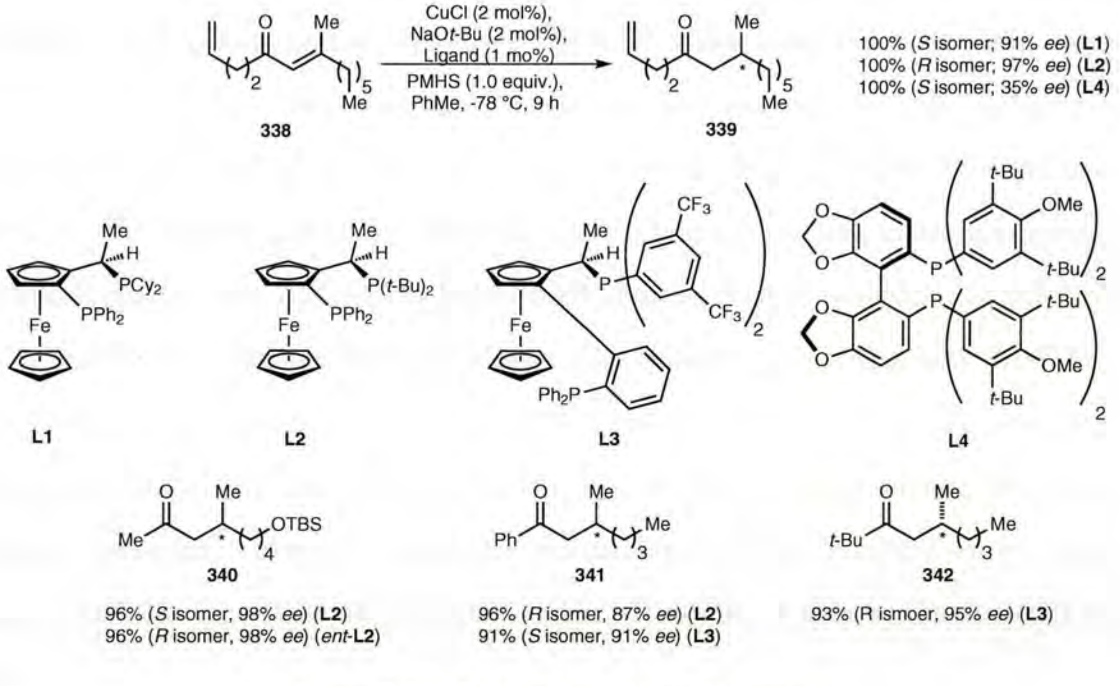
Initial studies indicated that amide bases yielded low conversions and poor enantioselectivities and so other bases were investigated. An excess of NaO*t*-Bu was able to effect the racemisation but this process was too slow when compared with the rate of conjugate reduction. Fortunately the addition of 5 equiv of *t*-BuOH accelerated the rate of racemisation dramatically and led to improved yields and high levels of enantiomeric and diastereomeric excess (Scheme 2.19).

Enantioselective conjugate reduction of acyclic enones was reported in 2003 by Lipshutz and Servesko (Scheme 2.20).[129] Such compounds possess more flexibility than cyclic enones and, for this reason, it is more difficult to achieve high levels of enantios-



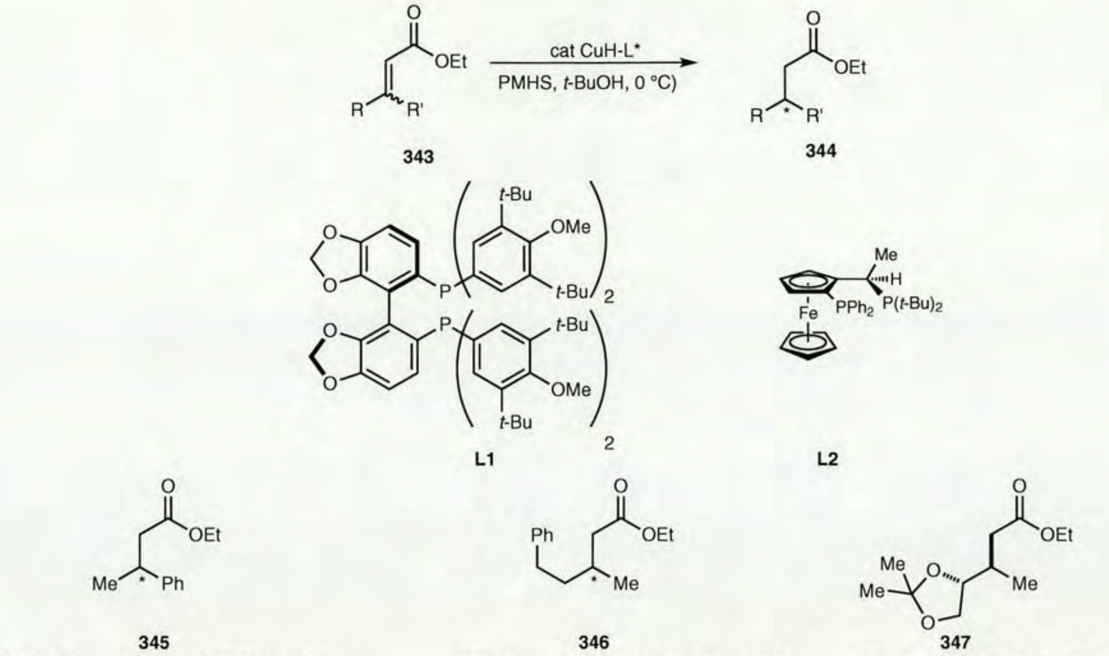
Scheme 2.19: Buchwald's results of dynamic kinetic resolution

electivity. Broad screening of ligands proved that those used previously by Buchwald and co-workers were delivering low *ee*. However, a family of Josiphos ligands were found to work particularly well, giving the reduced products with superior selectivity (Scheme 2.20). Testing different solvents yielded analogous results and toluene was used in later experiments.



Scheme 2.20: Reduction of acyclic enones

It is possible to control the stereoselective outcome of these reactions by changing the ligands. In example, ligand **L2** usually gives the S enantiomer while **ent-L2** proceeded to deliver the R enantiomers of starting materials (however in example **340** the



92% (*S* isomer; 99% *ee*) (*Z*-62a and **L1**)
94% (*R* isomer; 91% *ee*) (*E*-62a and **L1**)
92% (*R* isomer; 98% *ee*) (*Z*-62a, **L2**, and 7700:1 S:L)

98% (*S* isomer; 99% *ee*) (*E*-62b and **L2**)
96% (*R* isomer; 98% *ee*) (*E*-62b and *ent*-**L2**)

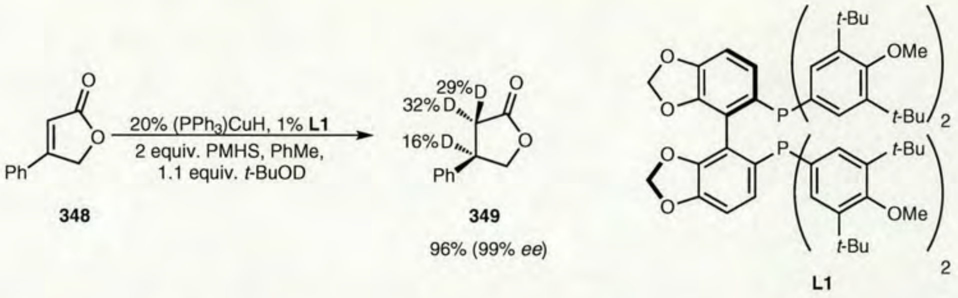
91% (98% *de*) (*E*-62c and **L2**)

Scheme 2.21: Reduction of α,β-unsaturated esters

diminished enantioselectivity. Variation of the ligand (**L2**) enantiomers whilst using the same E/Z isomer of the starting material gave opposite configurations in the product without significant lost of selectivity in starting material **346**. Similar to the previous work by Lipshutz, a very low ligand loading was required in these reactions (S:L 7700:1 for compound **345**).

The ligand choice was crucial when a starting material containing a preexisting stereocentre was employed. Reduction of an optically pure starting material with the R,S isomer of **L2**, produced matching product **347** with 98% *de* and 91% conversion. However, the same starting material was reduced with much lower selectivity and conversion when the S,R isomer of **L2** was employed (40% *de* and 70% conversion).

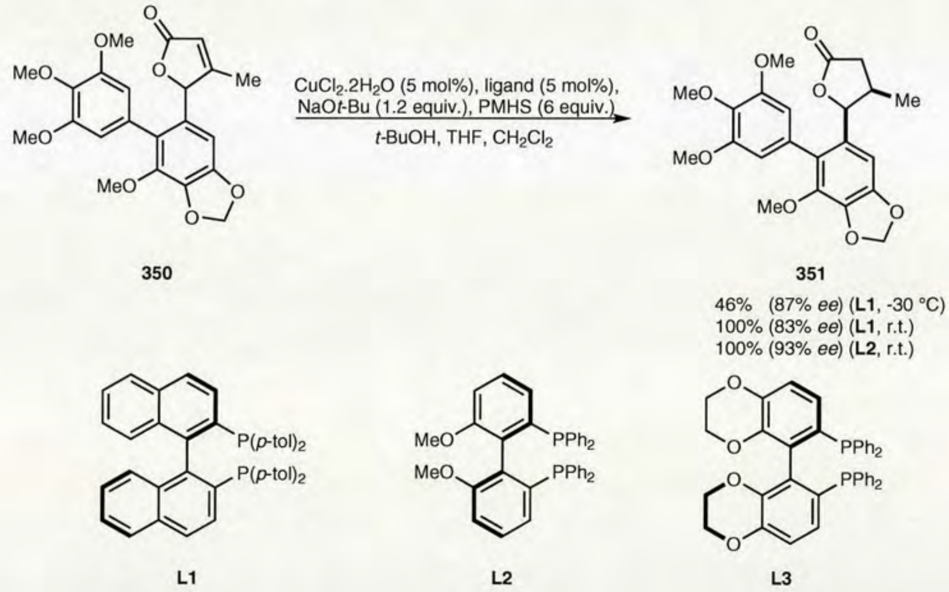
The effect of an alcohol additive on reaction rate was also studied. The reduction of α,β-unsaturated lactone **348** was done in the presence of t-BuOD in benzene-d6 (Scheme 2.22) and the reaction products were analyzed by proton NMR. It was observed that deuterium atoms were predominantly incorporated at the α position to the lactone **349**. A higher reaction rate in the presence of alcohol additive can be explained by a faster quenching of the copper enolate by the alcohol as compared to σ-bond metathesis



Scheme 2.22: Studies of reaction rate using isotope-labelled alcohol

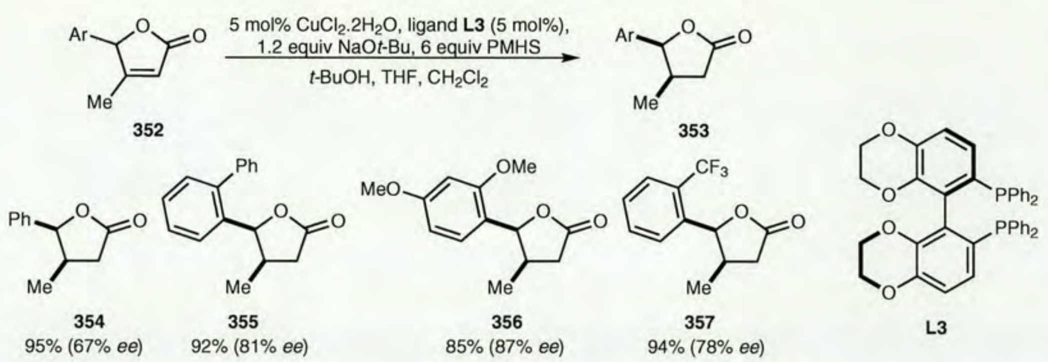
with PMHS.

Application of a copper hydride species in the asymmetric reduction of γ-lactones was reported by Buchwald and co-workers in the total synthesis of Eupomatilone-3 (Scheme 2.23).[131] In the key step, butenolide **350** was enantioselectively reduced to cis-4,5-disubstituted lactone **351**. The cis-stereoisomer was produced with no detectable levels of the trans-isomer. Once again ligand screening proved to be worthwile as different levels of reactivity and selectivity were observed.



Scheme 2.23: Comparison of ligand efficiency in the synthesis of Eupomatilone-3

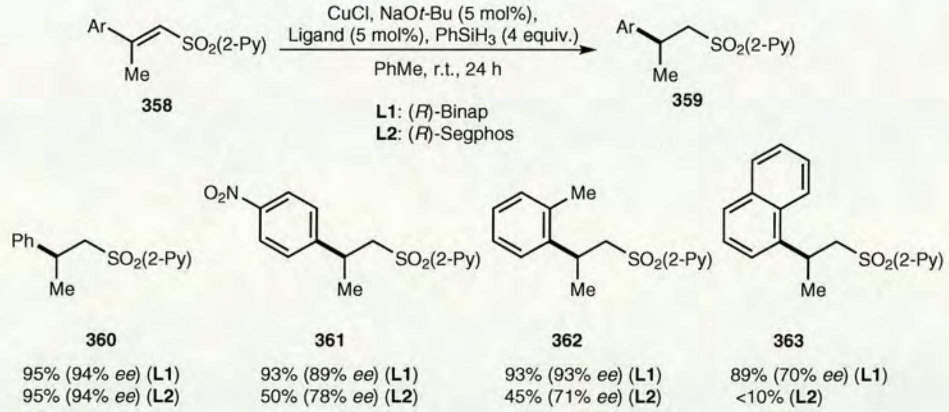
A wider range of γ-aryl substituted lactones were tested (Scheme 2.24). The ligand applied in the total synthesis of Eupomatilone-3 (MeO-BIPHEP) did not deliver satisfactory results. It was discovered that SYNPHOS **L3** was much more efficient both in terms of yield and diastereoselectivity although only moderate (as compared



Scheme 2.24: Reduction of γ-aryl-lactones

to the previous results) levels of enantioselectivity were produced. Poorer results were observed when starting materials containing γ-alkyl substituents were used. In these cases, a maximum of 50% conversion of starting materials was reported suggesting that the racemisation of preexisting stereocenters in the lactone starting materials did not occur or was to slow to occur when compared with the rate of reduction. Both cis and trans isomers of the product were present in the reaction mixture with the cis product having very low levels of enantiomeric enrichment (< 25% *ee*).

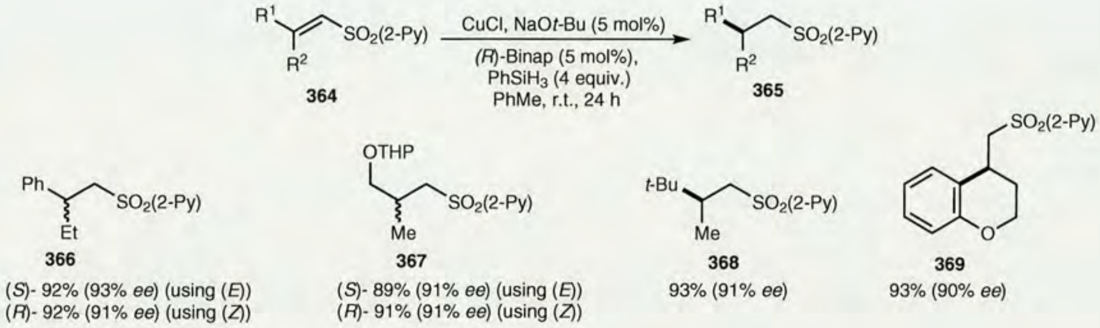
Reduction of α,β-unsaturated sulfones



Scheme 2.25: Reduction of α,β-unsaturated sulfones

The reduction of phenyl vinyl sulfones was investigated by Carretero and co-workers in 2007.[132] Despite broad screening of three copper sources ($Cu(OAc)_2$, $CuF(PPh_3)_3$ and CuCl/*t*-BuONa) with phenylsilane and two chiral ligands (BINAP, Josiphos) in toluene for 24 h, only unsuccessful results were obtained.

Later studies were based on Rh-catalysed conjugate addition of boronic acids to α,β-unsaturated sulfones.[133,134] Results of this research showed a significantly higher reactivity of 2-pyridylsulfones as compared to phenyl, tolyl or vinyl sulfones. Drawing precedent from these results, when compound **360**, containing a 2-pyridyl substituent was tested, a highly rewarding reaction was observed (Scheme 2.25). Screening of possible ligands revealed the superior performance of BINAP, SEGPHOS and DTMB-SEGPHOS ligands (with axial chirality) over Josiphos or Taniaphos with substrates containing β-aryl substituents on a carbon-carbon double bond.

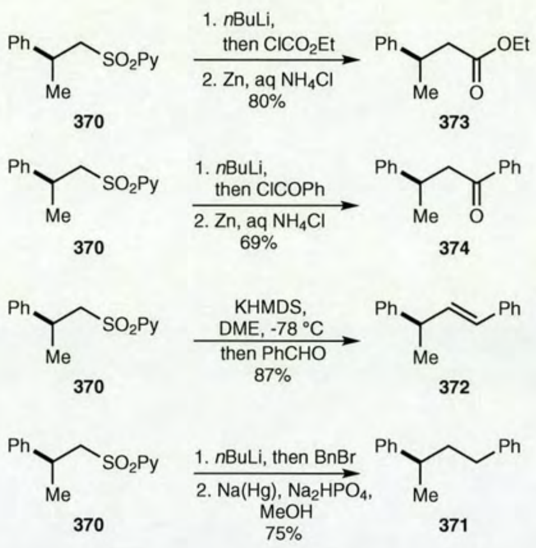


Scheme 2.26: Extension of previous results

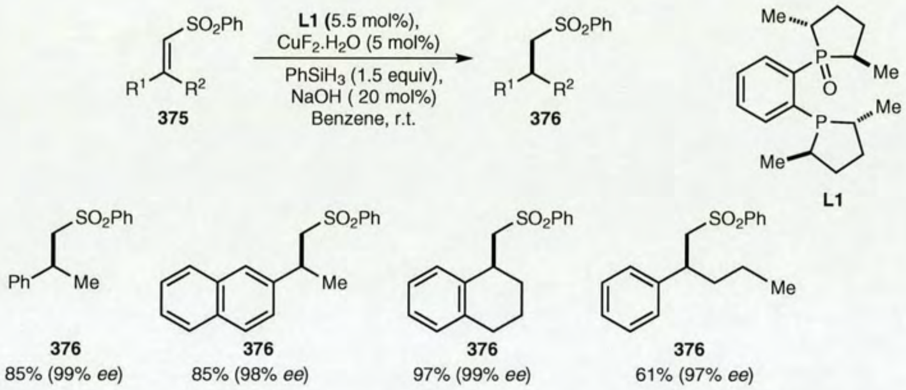
Extension of these results was done by testing the scope of the starting materials tolerated in this reaction. β,β-Dialkyl substituted starting materials were tested, along with cyclic substrates and E/Z isomers of double bonds (Scheme 2.26). Excellent results were obtained, with product yields above 90% and high enantiomeric excess. As predicted, the E/Z isomers produced opposite enantiomers of products.

The utility of compounds prepared was demonstrated by converting the sulfonyl group in a straightforward process (Scheme 2.27). In a one or two-step reaction it was possible to convert the sulfonyl substituents to an ester (**373**), a phenyl (**371**) and a phenyl ketone (**374**) whilst preserving the configuration of the preformed stereocentre. A Julia-Kocienski olefination of **370** provided alkene **372** with complete E stereoselectivity.

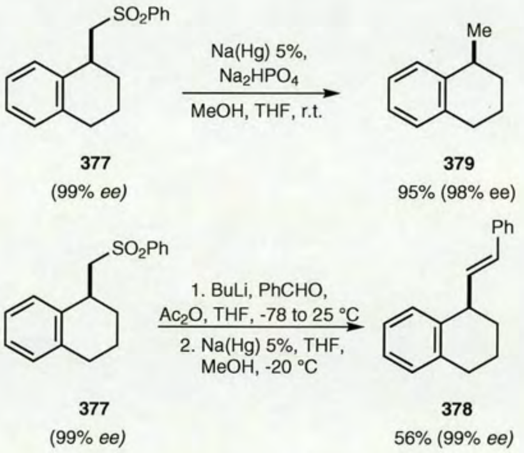
This process was initially limited to 2-pyridyl sulfones, this issue was resolved by Charette and co-workers.[135] A different copper source (CuF$_2$) and a hemilabile ligand (Me-Duphos monoxide **L1**) were employed (Scheme 2.28).



Scheme 2.27: Derivatization of sulfones



Scheme 2.28: Improved conditions for the reduction of α,β-unsaturated sulfones

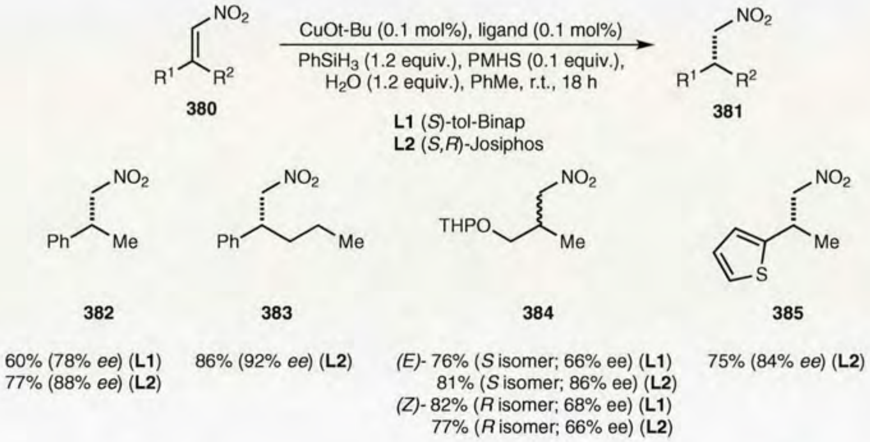


Scheme 2.29: Derivatisation of sulfones

Once more a possible transformation of sulfonyl groups was demonstrated with olefination and reduction (Scheme 2.29).

Reduction of nitroalkenes

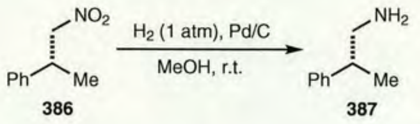
Despite their previous unsuccessful attempts to alkylate α,β-unsaturated nitroalkenes using dialkyl zinc reagents, Carreira and Czekelius managed to develop a copper catalysed asymmetric reduction procedure with tol-BINAP.[136] The commonly used system of CuCl, NaO*t*-Bu and tol-BINAP gave sluggish rates of reaction and only moderate yields. A significant improvement was achieved by the use of CuO*t*-Bu (instead of generating this reagent *in situ*). This copper source gave much higher reaction rates, good yields and enantiomeric excess (Scheme 2.30).



Scheme 2.30: Reduction of α,β-unsaturated nitroalkenes

Previous reports in the scientific literature suggest that the addition of inorganic salts such as LiCl or KCN can lead to reduced reaction rates. It was concluded that the NaCl generated *in situ*, as a by-product in the formation of CuO*t*-Bu, was inhibiting the activity of the copper phosphine catalyst. Interestingly, the best results were obtained when a combination of phenyl silane and PMHS were used. It was necessary to add 1.2 equiv. of water to the reaction mixture to suppress over reduction. However, yields obtained are still approximately 15% lower compared to previous reports (Scheme 2.30.

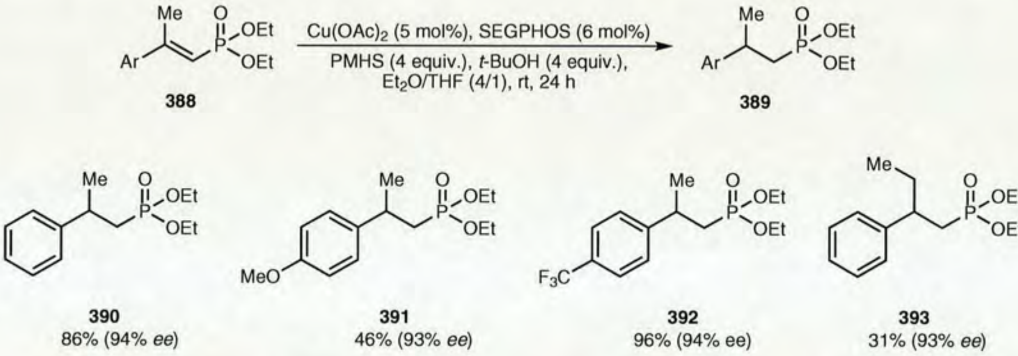
If required, enantioenriched products of copper catalysed asymmetric 1,4-conjugate reduction can be converted into corresponding amines with a known protocol without any loss of enantioenrichment (Scheme 2.31).



Scheme 2.31: Possible derivatisation of nitroalkanes

Reduction of α,β-unsaturated phosphonates

A very recent study by Xiang-Ping Hu and Zhuo Zheng demonstrated that phosphonates can also be a suitable activating group for enantioselective copper catalysed reduction of alkenes (Scheme 2.32).[137] After an extensive screening of conditions it was found that $Cu(OAc)_2$ and SEGPHOS, PMHS, t-BuOH in a 4:1 mixture of Et_2O/THF provided the best results. The desired optically active β-stereogenic alkylphosphonates were afforded in good to high yields and good levels of enantioselectivity (>90%).



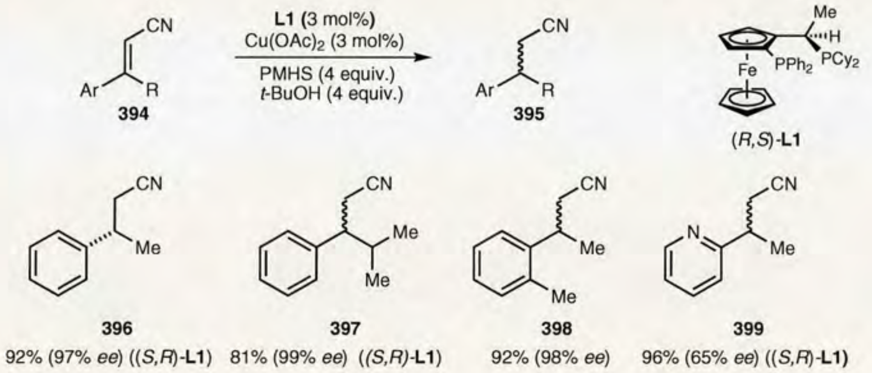
Scheme 2.32: Reduction of α,β-unsaturated phosphonates

It was shown that the addition of t-BuOH significantly increased the reaction rate whilst not affecting the enantioselectivity. A precise amount of t-BuOH and PMHS (4 equiv. of each) had to be used since a decrease in conversion was observed when suboptimal amounts were added. These results were in agreement with those obtained by Buchwald in his study of reduction of α,β-unsaturated esters.[138]

The effect of aryl substitution on the reaction efficiency was also studied. When starting materials having ortho-substituted aryl groups were used, a very low level of conversion was observed. The authors speculated that steric effects inhibit the copper hydride from coordinating to the alkene. Substrates having a para substitution were much more reactive and in those cases it was possible to study the electronic effect of the substituent. Starting materials having electron-withdrawing groups on the phenyl ring were reduced more effectively and the desired products were isolated in much higher yields. However, electron-withdrawing or electron-donating substituents were not observed to have an effect on the stereoselectivity of this reaction.

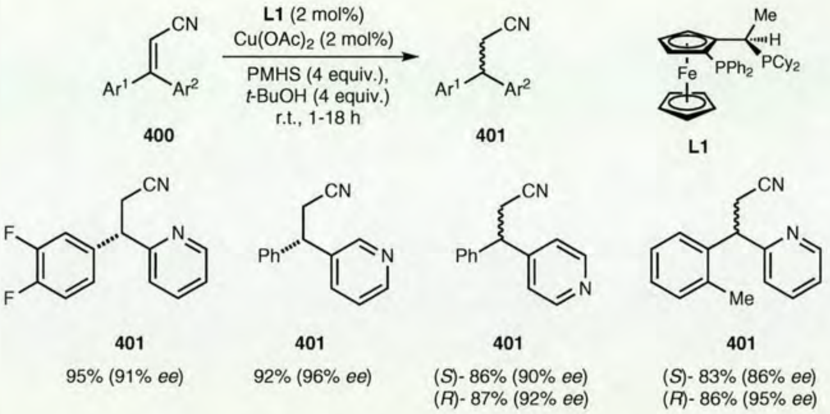
Reduction of α,β-unsaturated nitriles

A successful asymmetric conjugate reduction of α,β-unsaturated nitriles was published by Yun and co-workers in 2006.[139] This report is particularly interesting as the activation of the carbon-carbon double bond is done with the potentially troublesome nitrile group and as such, this class of compounds has not been extensively employed in the past. A nitrile substituent can coordinate to the metal catalyst in a linear fashion driving it away from possible reaction center. Yun and co-workers reported that $Cu(OAc)_2$ and Josiphos-type ligands can effectively overcome such problems in the reduction of β-aryl,β-alkyl substituted starting materials (Scheme 2.33).



Scheme 2.33: Reduction of α,β-unsaturated nitriles

Later, it was reported that this system can perform equally well with β,β-diaryl substituted starting materials (Scheme 2.34).[140] This process is highly competitive with Rh- and Ru-based hydrogenation catalysts that are known to underperform because of end-on coordination to metal. These catalysts usually require high pressure of hydrogen and an additional coordinating center next to the alkene moiety.[141–143] The catalyst developed by Yun is able to reduce acrylonitriles efficiently independent of the orientation of the pyridyl substituent (2, 3 or 4-pyridyl) with high yields and enantioselectivity. Contrary, usage of Ph-MeO-BIPHEP, Mandyphos and Walphos-type ligands proved to deliver sluggish yields with relatively low *ee*. Interestingly, a large variation of yield and *ee* were observed when the temperature was different from the optimal.



Scheme 2.34: Reduction of biaryl substituted α,β-unsaturated nitriles

Summary

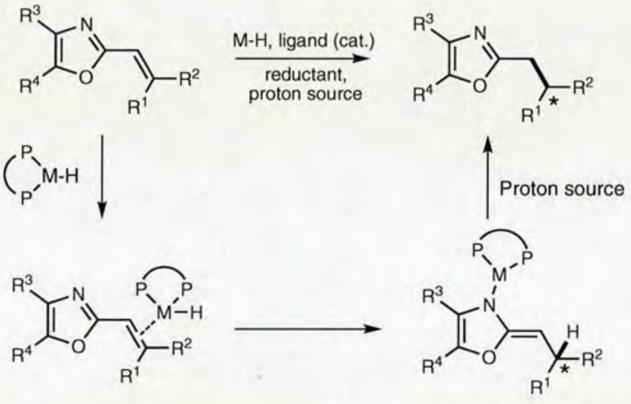
Asymmetric conjugate reduction of activated alkenes by copper hydride has received much attention in recent literature. Many groups have devoted a significant amount of time on the careful optimisation of reaction conditions. Reactivity problems were initially resolved by the use of stronger silanes but this in turn led to over reduction of products. Careful temperature control was crucial in obtaining high *ee* and reasonable reaction rates. The use of water and alcohols was introduced by Lipshutz to suppress side reactions and enhance the rate of the desired process. In the majority of cases, the key part of reaction development was to find a suitable ligand for particular class of starting materials, as all BINAP, SEGPHOS, Josiphos and others have performed well and yet none of them have proved to be the perfect solution in all cases.

An often underestimated part of research in organic chemistry methodology is the synthesis of starting materials. Although approaches to trisubstituted double bonds exist in organic chemistry, an efficient synthesis of a broad variety of compounds is still difficult. The supporting information of the above articles provided valuable insight into possible synthetic routes to the compounds used in our study.

2.2 Results and Discussion

2.2.1 Aims of project

Although, as discussed in the introduction, conjugate additions to 2-vinylheteroarenes (R_1 , R_2 = H in eq 2) are relatively common,[113,114,144–149] the corresponding reactions of mono-β-substituted substrates are much rarer.[115,116,150–155] Hypothetically, steric bulk around the β-carbon blocks attack of large nucleophiles, although there are no examples of successful alkylation of β,β-disubstituted alkenes. Furthermore, the only report of a catalytic enantioselective variant is limited to a poorly selective (15% *ee*) Grignard addition to 4-alkenylpyridines.[116] Therefore, we initiated a program targeted at addressing these deficiencies ‡.



Scheme 2.35: General idea

Several issues have to be addressed to fulfil this goal. The asymmetric copper-catalysed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks.[123,128–131,138,156–163] Whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent alkene in an analogous reaction was uncertain.

The predicted weak activation of the double bond was also potentially a restriction on the scope of starting material. Specifically whether substituents with large steric bulk would be tolerated under our reaction conditions, in contrast to the known

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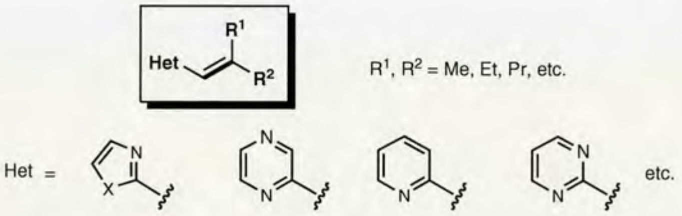
[‡] Work done in cooperation with Aakarsh Saxena, ‡ is used to mark experiments conducted by Aakarsh

procedures.

In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the copper catalyst would occur in such a process. Whether this interaction would be beneficial, inconsequential, or detrimental was not easy to predict.

However, the first and most pressing obstacle was the preparation of starting materials. We had to come up with an approach to prepare tri-substituted double bonds with high E/Z purity. Our preferred structure would have an electron-poor heterocycle at one end of the double bond and two aliphatic substituents at the other end.



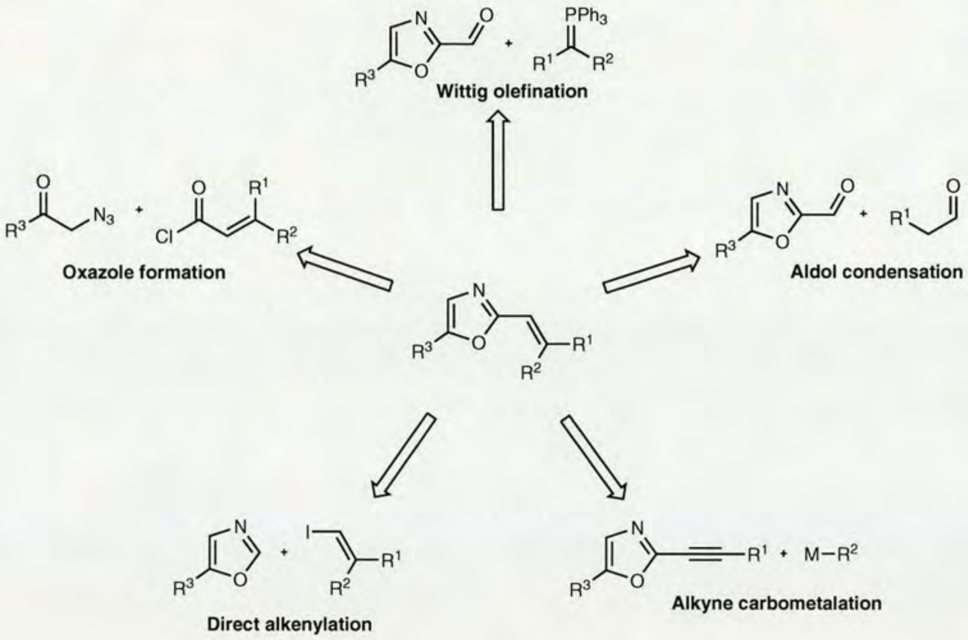
Scheme 2.36: General starting material

2.2.2 Preparation of starting materials

Preparation of tri-substituted double bonds is a challenging endeavour in synthetic chemistry. Despite many transformations described in the literature, there was no existing single approach that could be applied for this project. Instead, we devised several independent strategies that promised to deliver a high level of flexibility in the formation of our starting materials compounds.

Our initial target was 2-substituted oxazole (structure and potential retrosynthetic analysis on scheme 2.37). We anticipated that an aliphatic substitution on the alkene (R^1 and R^2) would be preferential for enantioselective reduction as aromatic groups can have a negative effect on the polarity of a carbon-carbon double bond and so, make our starting materials less reactive. Five main approaches were considered for the synthesis of desired compounds.

The preferred strategy would ideally start from commercially available starting materials and take no more then three synthetic steps to deliver the desired compounds.

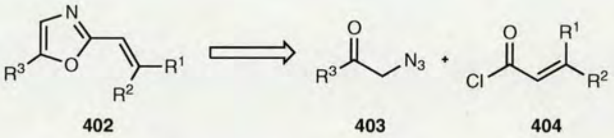


Scheme 2.37: Retrosynthesis of starting material

It would also be beneficial if the last step of a given strategy would allow some sort of diversity in the final product, reducing the total number of synthetic steps. However, none of depicted transformations have such properties.

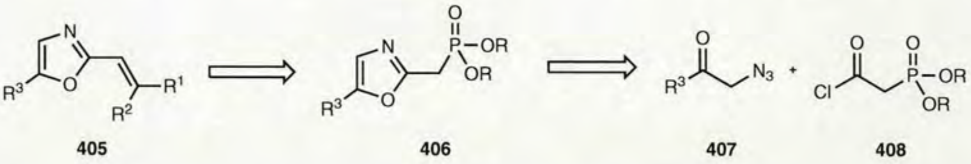
Oxazole formation and Horner-Wadsworth-Emmons olefination

The first approach we attempted in this project involved the formation of an oxazole ring as a key step. Our target was to prepare several simple 2-alkenyl-oxazoles for a proof of concept study. By reacting α-azido ketones (**403**) and α,β-unsaturated acid chlorides (**404**) in different combinations, we can potentially access a variety of desired 2-alkenyl-oxazoles (Scheme 2.38).



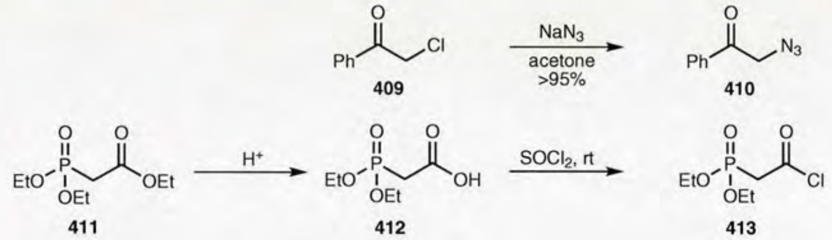
Scheme 2.38: Oxazole formation

It quickly became obvious that there was no easy method of synthesising acid chlorides with tri-substituted double bonds and this approach was modified to encompass a Horner-Wadsworth-Emmons reaction (Scheme 2.39). In this way, it was possible to generate several substitution patterns on the double bond by changing the ketone reagent in the Horner-Wadsworth-Emmons olefination of compound **406**.



Scheme 2.39: Oxazole formation and Horner-Wadsworth-Emmons olefination

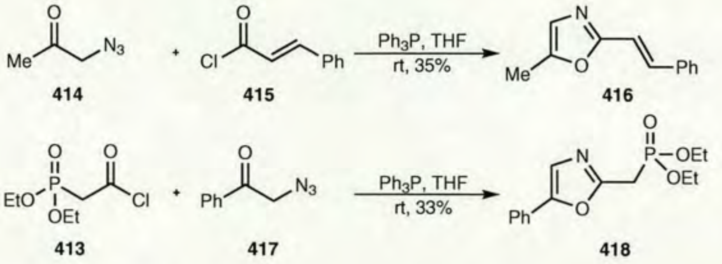
α-Azido ketones (**410**) have been easily prepared through halogen exchange of α-chloro ketones (**409**).[164] The acid catalysed hydrolysis of the commercially available ethyl ester **411** gave acid **412** after a very short purification procedure.[165] Conversion to the chloride derivative (**413**) was carried out with thionyl chloride, and the excess reagent was removed by vacuum distillation, no further purification was needed (Scheme 2.40).[165]



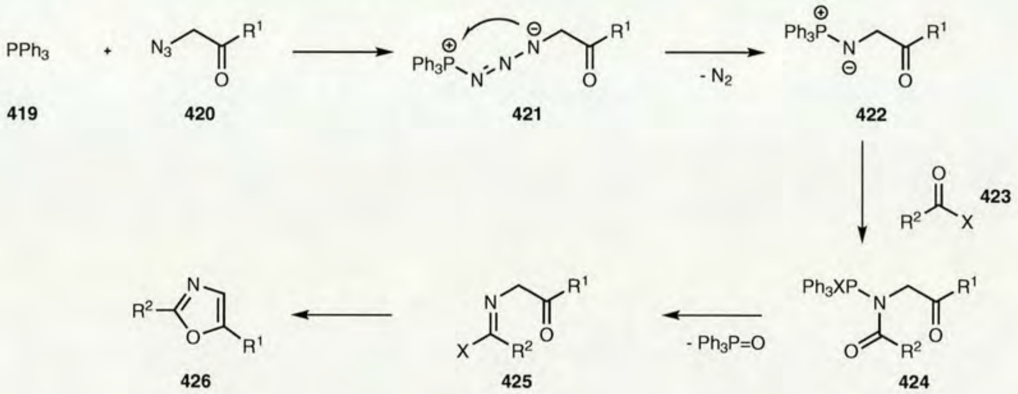
Scheme 2.40: Synthesis of β-azido-ketones and acid chlorides

Oxazole ring formation was conducted with stoichiometric amounts of triphenyl phosphine in THF. This reaction gave yields of around 33-35% (Scheme 2.41) that were in line with the original publication of this procedure.[166] Despite many trials it was not possible to reproduce yields (50-55%) published in a more recent article[167] even when the same starting materials were employed.

A possible mechanism of oxazole ring formation is depicted in scheme 2.42. Initially a complex between triphenylphosphine and the azide is formed. A release of a nitrogen molecule generates intermediate **422** that attacks an acid halogen derivative **423** to form **424**. This compound undergoes an aza-Wittig rearrangement generating **425** and triphenylphosphine oxide. An intramolecular cyclisation of **425** yields the final product **426**.



Scheme 2.41: Oxazole formation



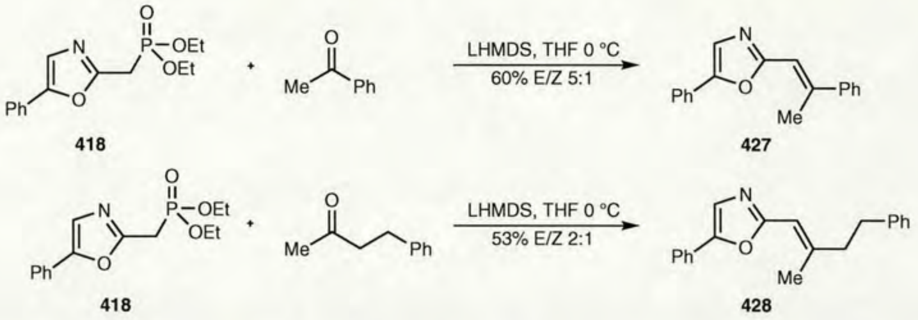
Scheme 2.42: Possible mechanism of oxazole ring formation

Compound **416** cannot serve as a starting material for an enantioselective reduction. Indeed, it was an easily obtainable target that could be used in a proof of concept study to verify whether our idea of copper catalysed reductions was valid.

Relatively low yields were not the only problem in during oxazole formation. Triphenyl phosphine oxide was produced as a by product in stoichiometric quantities making purification of the reaction mixture difficult in larger scale synthesis.

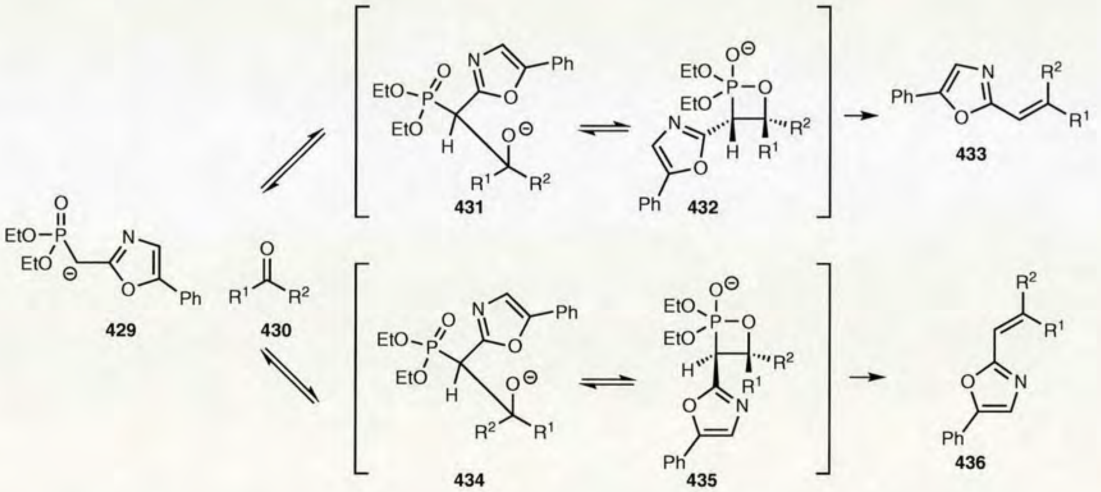
Oxazole derivative **418** was deprotonated with LHMDS in THF and the resulting anion was reacted with different ketones (in this case with acetophenone) to give the desired olefin **427**. Horner-Wadsworth-Emmons olefination proceeded with good yields unfortunately, only in a few cases was it possible to obtain a good E/Z selectivity (Scheme 2.43). This type of olefination is known to give high E/Z ratios with aldehydes, although ketones are usually much less selective. It was observed that good E/Z ratios were obtained for ketones with significantly different substituents (Me vs Ph) whereas dialiphatic ketones (Me vs Et or Et vs Bu) gave almost no selectivity.

The mechanism depicted in scheme 2.44 illustrates that the selectivity in the Horner-



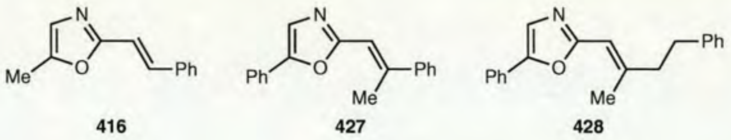
Scheme 2.43: Horner-Wadsworth-Emmons olefination

Wadsworth-Emmons olefination comes from the thermodynamic equilibration of reaction intermediates. Steric repulsion between the oxazole ring and one of the ketone substituents (R^1 and R^2) is the main factor that determines the energies of these intermediates and so their relative abundance in the reaction mixture. Large size differences between R^1 and R^2 are required to achieve good E/Z selectivity as demonstrated in the example with acetophenone (Scheme 2.43).



Scheme 2.44: Mechanism of Horner-Wadsworth-Emmons olefination with ketones

Considering the practicality of this approach in obtaining a good diversity of starting materials we decided to try and purify the mixtures of E/Z isomers. However, it was possible to separate these isomers by silica gel column chromatography with purity over 99% for a small number of examples. A high level of purity was required as it is known that the enantioselective reduction of such olefins commonly results in opposite enantiomers from the E and Z isomers of the olefin (Scheme 2.30).

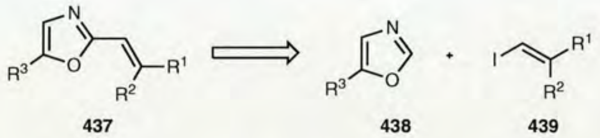


Scheme 2.45: Starting materials made with this approach

This synthetic approach to the desired starting materials only yielded three compounds (Scheme 2.45) with high purity. However, it was enough to test whether our idea of enantioselective reduction of α,β-unsaturated heteroarenes (in this case oxazoles) was viable. A preliminary catalyst screening gave postive results and so we decided to concentrate on the synthesis of starting materials before any further examinations.

Zirconium catalysed carboaluminations and direct couplings

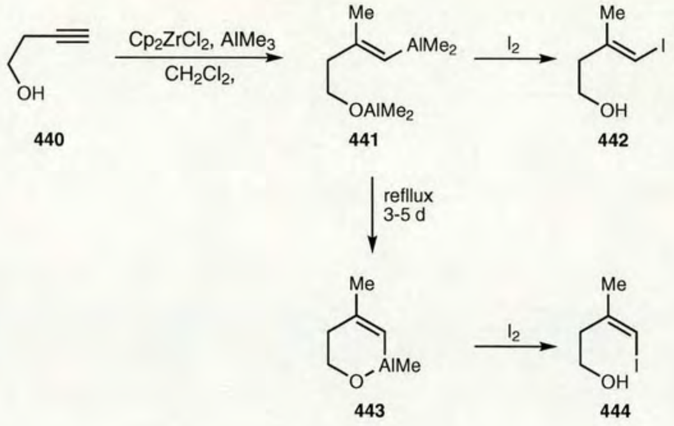
Inspired by a growing number of C-H activation methodology developments in recent literature we envisioned an efficient and unprecedented approach to our target compounds. A subproject was initiated to identify conditions that allow a direct coupling of vinyl iodides (**439**) to substituted oxazoles **438** (Scheme 2.46).



Scheme 2.46: Retrosynthetic disconnection

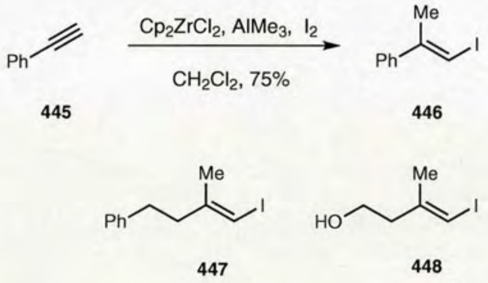
Vinyl iodides were obtained through carbo-alumination of substituted acetylenes with Cp_2ZrCl_2 and trimethyl aluminium followed by quenching of the aluminium intermediates with iodine (Scheme 2.48).[168–170] This procedure requires stoichiometric amounts of zirconium reagent and long reaction times. However, after careful literature studies we managed to reduce the amount of zirconium reagent to 20% by addition of precise amounts of water[171] or MAO.

This reaction is known to have superb selectivity producing E isomers with undetectable levels of Z isomers. It is also possible, in cases of starting material with



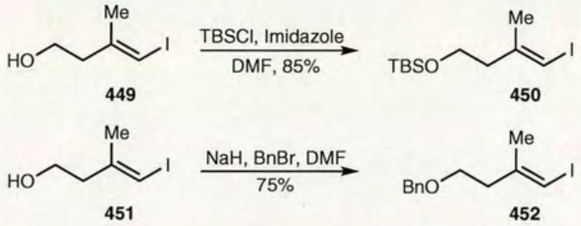
Scheme 2.47: Temperature induced E-to-Z isomerisation

hydroxyl groups, to reverse its selectivity by heating the reaction mixture to produce a metalacycle intermediate and upon quenching with iodine obtain only the Z isomers (Scheme 2.47). Optimised conditions for such E to Z isomerisation were recently published by Negishi.[172] A big disadvantage of this transformation is its low reactivity with larger trialkylaluminium reagents restricting the possible products to those containing methyl as one of the substituents of the double bond.



Scheme 2.48: Preparation of vinyl-iodides

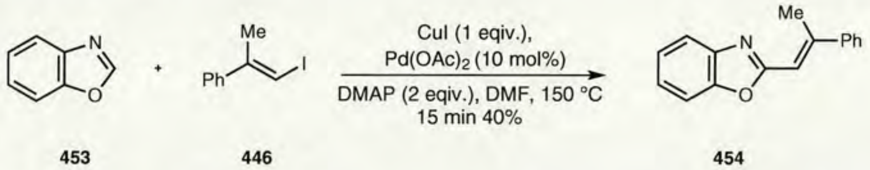
As a free hydroxyl group could interfere during coupling to oxazole moiety, it was protected with TBS or benzyl groups using standard procedures[173] (Scheme 2.49).



Scheme 2.49: Protection of vinyl-iodides

At the time of this study there were only a few examples of direct coupling to the 2-position of oxazoles and this subject was considered "hot" as demonstrated by the large number of articles recently appearing in the scientific literature.[174–176] We were surprised to see that all of the published coupling procedures used aromatic and heteroaromatic halides as coupling partners for oxazoles and there were no examples of direct coupling between oxazole and vinyl halides. However, during the course of our studies a highly relevant article was published describing the direct alkenylation at the 2-position of oxazoles.[177] Based on catalyst systems developed for aryl halides we decided to investigate the possibility of coupling vinyl halides to oxazole. Our general idea was to take advantage of the relatively high acidity of the proton at the 2-position of the oxazole and couple the *in-situ* generated anion using a copper or palladium catalyst to the vinyl halide.

Screening of known procedures for similar types of coupling involved many unsuccessful trials with no conversion of starting materials. We tested several copper sources, and the addition of palladium, ligands and bases. It was not until a discovery that 1 equiv. of CuI with 10% of $Pd(OAc)_2$ and KO*t*-Bu as a base gave full conversion of the starting vinyl iodide that we realized the full potential of this transformation. Unfortunately the desired product was obtained as a E/Z mixture of isomers, despite the isomeric purity of vinyl iodide.

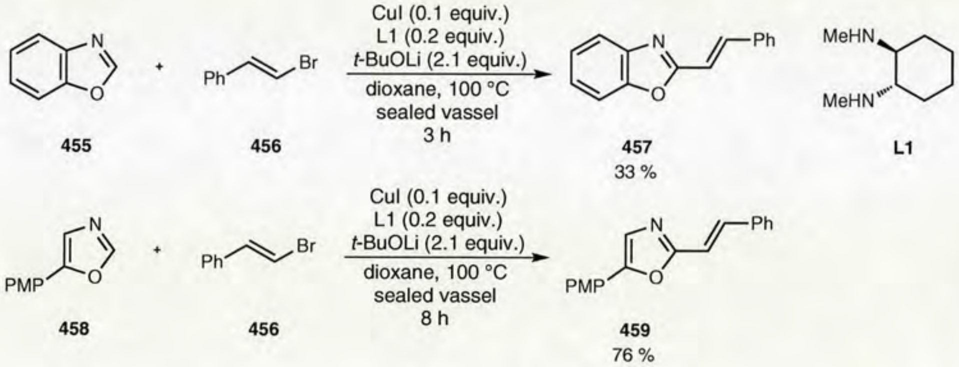


Scheme 2.50: Coupling of vinyl-iodides to benzoxazole

Extensive studies to improve this procedure were then undertaken. It was not possible to reduce the amount of CuI used as this led to a decline in conversion. Palladium was necessary in the reaction mixture, in its absence no product was formed. A breakthrough came with the application of DMAP as a base/ligand with CuI and $Pd(OAc)_2$. These conditions did not give full conversion but the product was formed as a single isomer (E/Z). Further studies indicated that quantitative conversion can be obtained using CuOAc although the reaction yields did not increase. As DMAP was the only example of an organic base we decided to screen several different nitrogen based ligand/bases, unfortunately these modified conditions did not offer any success. A short screening of solvents indicated that DMF with microwave heating is preferential. Interestingly it was observed that the addition of NaI or NaBr inhibits this process. The condition trialled during these studies are summarised below.

Conditions:

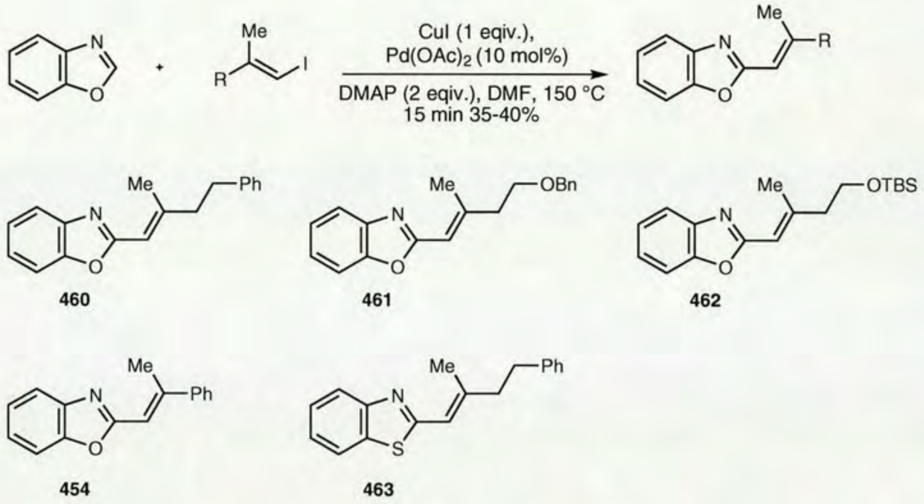
- Catalyst: CuI, CuOAc, Pd(OAc)$_2$, AgNO$_3$, Rh
- Ligands: PPh$_3$, 1,10-phenanthroline
- Bases: KO*t*-Bu, NaOMe, BuLi, DMAP, Et$_3$N
- Solvents: DMF, THF, Dioxane, DMSO



Scheme 2.51: Direct coupling to benzoxazole by Besselievre[177]

Unfortunately at the time of these studies an article appeared[177] describing the successful coupling of vinyl bromides to benzoxazole (Scheme 2.51). In their examples, there was no problem of E/Z isomerisation. However, the conditions used by group of Piguel gave E/Z isomeric mixtures of product with our starting materials. This suggests that methyl substituent in our examples can be deprotonated after forming the product therefore isomerising the double bond upon quenching.

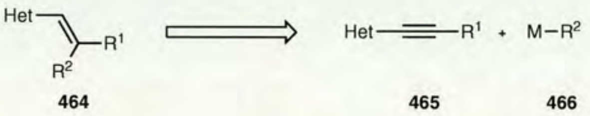
The appearance of this article placed strong limitations on the possibility of publishing our own work. Therefore we decided to stop further investigations and apply our suboptimal conditions (Scheme 2.50) to prepare starting materials for the main project. We managed to obtain the substrates in scheme 2.52 in 35-40% yield.



Scheme 2.52: Starting materials made with this approach

Carbometalation of alkynes

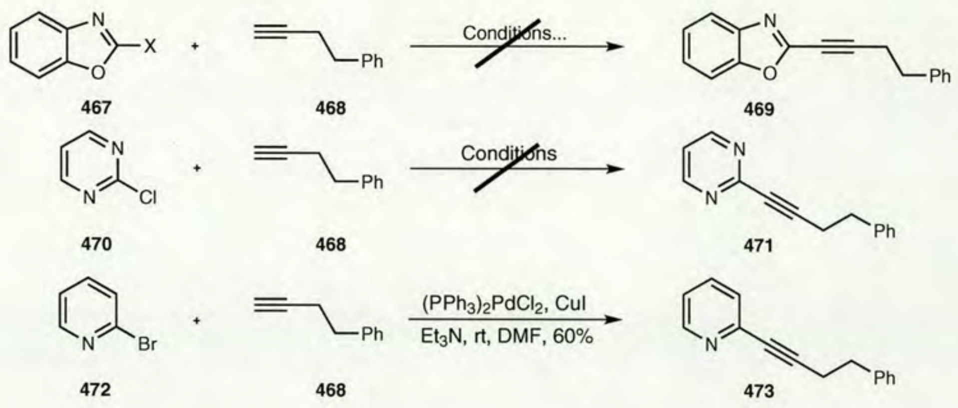
The majority of starting materials obtained at this point contained a methyl group as one of the substituents at the double bond. We decided to take another approach to try to diversify our substrate pool through the carbometalation of alkynes (Scheme 2.53).



Scheme 2.53: Retrosynthetic disconnection

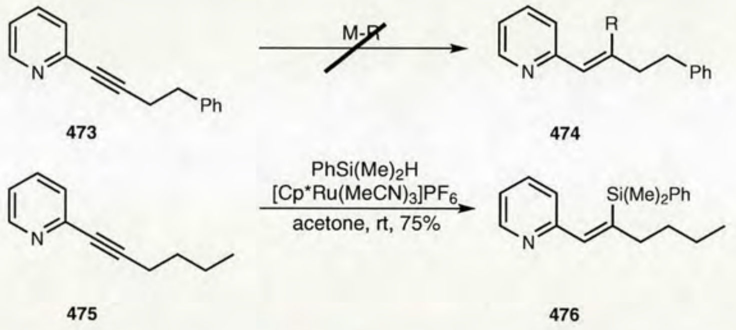
The first issue to address in this approach was the preparation of appropriate alkynes (**465**). The Sonogashira coupling of 2-chlorobenzoxazole (**467**) or 2-chloropyrazine (**470**) did not work. We then tried to obtain the triflate or iodine derivatives. Unfortunately, despite several published procedure,[178, 179] it was not possible to isolate these materials cleanly as they proved to be highly unstable compounds.

We also tried several procedures involving the direct coupling of benzoxazole to bromo-alkynes with no success. It was possible to obtain small quantities of product



Scheme 2.54: Sonogashira coupling trials

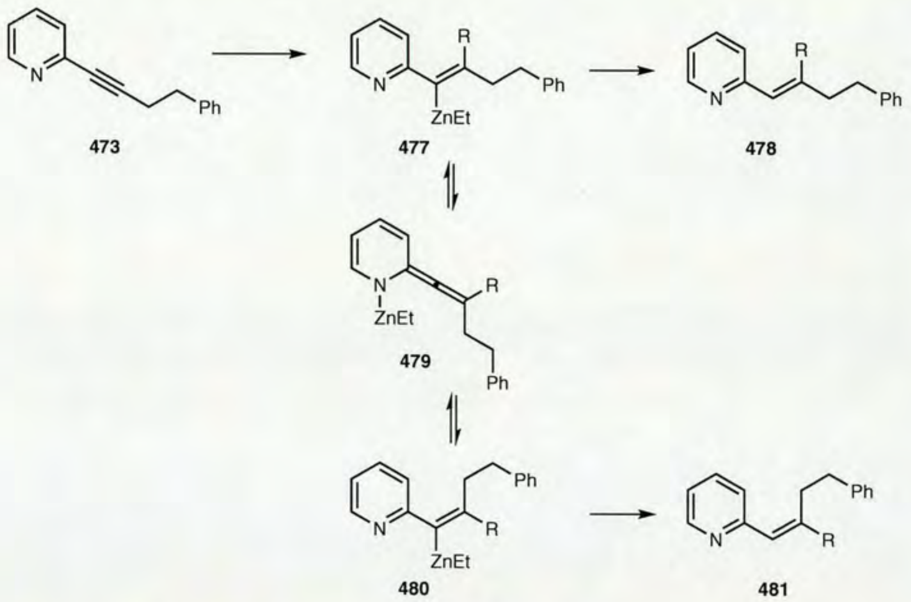
by deprotonating the phenylacetylene with butyl lithium first and then adding the 2-chlorobenzoxazole. However, the low yields of this process were highly discouraging. We turned to known procedures for Sonogashira coupling[180,181] of 2-bromopyridine (**472**) to terminal acetylenes (for example **468**) and obtained the product **473** in 60% yield (Scheme 2.54).



Scheme 2.55: Carbometalation of 2-pyridinealkynes

The addition of carbon nucleophiles to alkynes conjugated with a heterocycle proved to be more difficult than expected. Upon testing several catalyst systems (Rh, Ni, Cu) and alkylating agents (Et_2Zn, EtMgBr, Me_3Al) we were not able to cleanly isolate the desired products. This research was later continued by Yi Wang in our group, who after extensive studies, discovered a set of suitable condition that allowed the addition of diethylzinc to some 2-pyridinealkynes with varying levels of E/Z selectivity (1:2 to 1:4) and moderate yields. However, the low reliability of this process and limited scope (only 2-pyridinealkynes were tolerated) discouraged further investigation (Scheme 2.55).

The low E/Z selectivity of the carbometallation step can possibly be explained



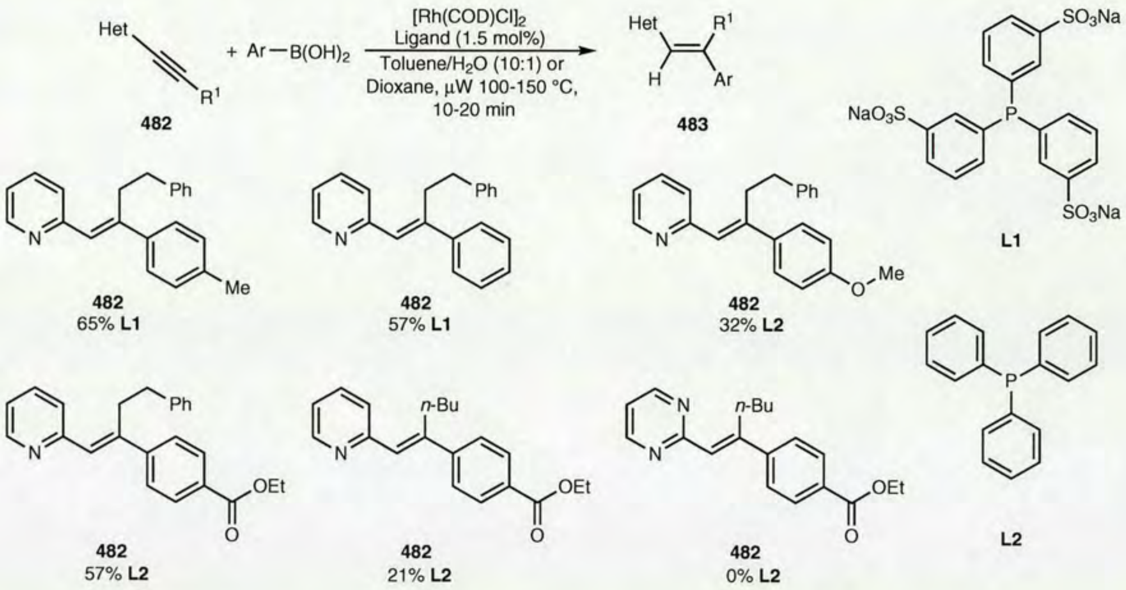
Scheme 2.56: Possible explanation of low E/Z

with reversible formation of an allene intermediate (**479** Scheme 2.56) which looses E/Z information and the distribution of isomers produced comes from the relative energy differences of both forms (**477** and **480**) and not from the kinetics of addition. Presumably this unstable allene can also take part in a series of undesirable reactions, reducing the yield of the final product.

Fortunately, it was possible to functionalise 2-pyridinealkynes through different reactions. Addition of dimethylphenylsilane proceeded smoothly with a ruthenium based catalyst.[182] Further studies were based on known protocols for rhodium catalysed hydroarylation of alkynes.[183, 184] Conditions modified by Aakarsh Saxena‡allowed the formation of differently substituted alkenes (Scheme 2.57).

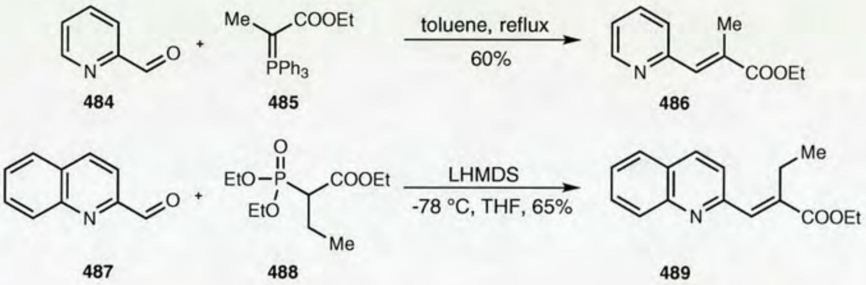
Wittig olefination and ester reduction

Fortunately a simpler approach to the preparation of pyridine series of starting materials was available. Wittig and Horner-Wadsworth-Emmons olefinations of pyridine and quinoline 2-carboxyaldehydes produced α,β-unsaturated esters (**486** and **489**) in good yields (Scheme 2.58). There were no problems in selectivity as aldehydes are known to give high E/Z ratios in this type of olefinations. In addition, if required it was also possible to separate the E and Z isomers by silica gel column chromatography as they



Scheme 2.57: Arylation of 2-alkenylpyridines by Aakarsh Saxena[‡]

showed significantly different retention factors.

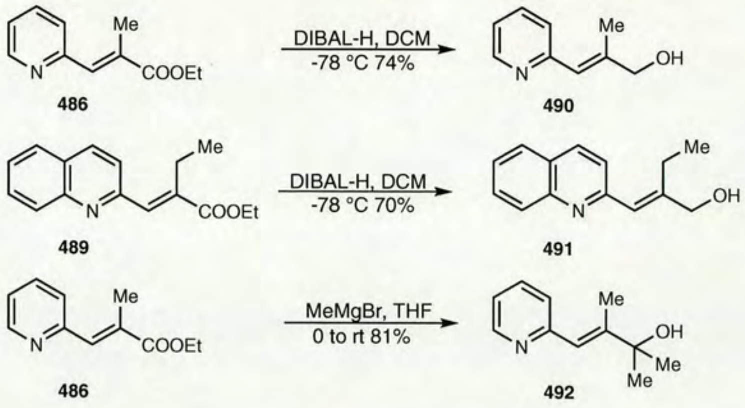


Scheme 2.58: Wittig olefination of aldehydes

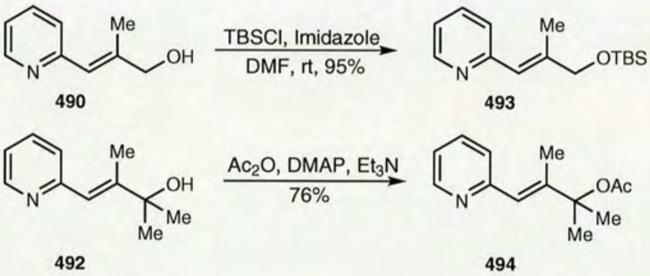
DIBAL reduction of these esters gave alcohols **490** and **491**, it was also possible to form the tertiary alcohol **492** by the addition of a Grignard reagent (Scheme 2.59). In the case of the DIBAL reduction it was observed that temperature plays a crucial role in the control of this reaction and low temperatures are required to avoid the subsequent reduction of the carbon-carbon double bond.

Protection of the obtained alcohol with TBSCl or acetic anhydride gave the desired starting materials (Scheme 2.60). Several other compounds were also prepared including a pivaloate and *p*-bromobenzoate ester ‡.

Despite the relatively large number of steps required, this approach proved to be highly valuable because of the simplicity of the chemical reactions. Several starting ma-

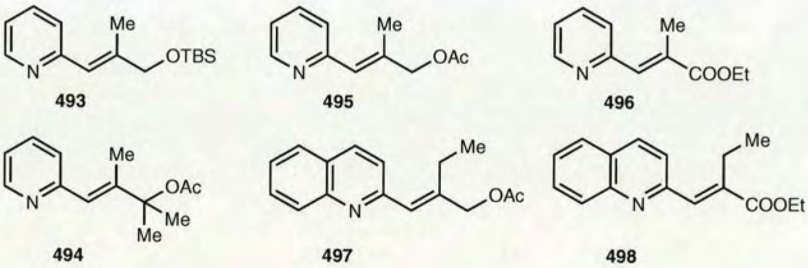


Scheme 2.59: Reduction of ethyl esters



Scheme 2.60: Protection of hydroxyl group

terials were prepared in this approach however, a major limitation was the commercial availability of the starting aldehydes.

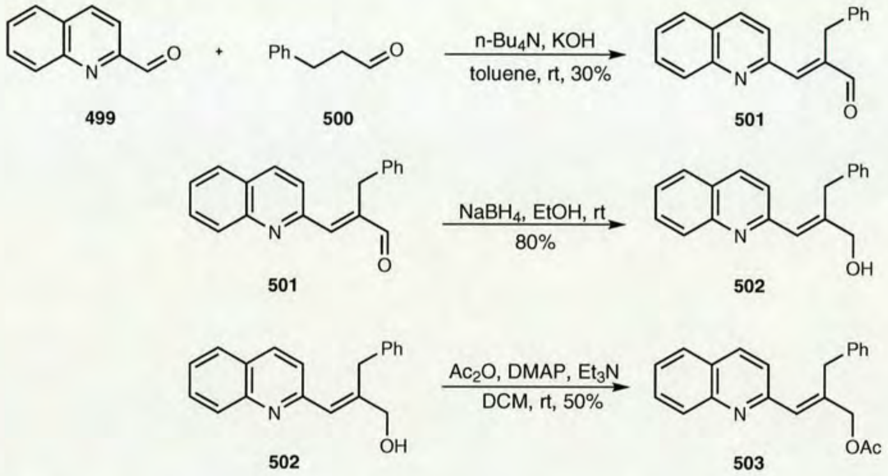


Scheme 2.61: Starting materials made with this approach

Aldol cross-condensation and aldehyde reduction

To extend the previous approach, the Wittig olefination was replaced with an aldol condensation-elimination sequence to form α,β-unsaturated aldehydes (Scheme 2.62). This type of reaction is usually promoted by sodium and potassium hydroxides with catalytic amounts of phase-transfer-catalyst[185] but there are also other methods to promote aldol condensation.[186]

As opposed to esters, α,β-unsaturated aldehydes can be easily reduced with milder and easier to handle reagents such as $NaBH_4$ in ethanol. Despite the relatively low yielding condensation-elimination step, this procedure is highly valuable because it allows a broader diversity of substituents on the carbon-carbon double bond by varying the aldol condensation partners.

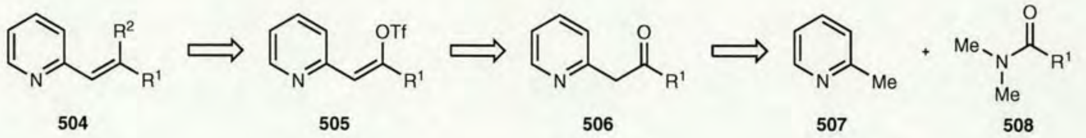


Scheme 2.62: Aldol condensation, aldehyde reduction and hydroxyl protection steps

Protection of the primary alcohol **544** with TBSCl or acetic anhydride provided the desired starting materials. Once again this approach was further extended by Aakarsh Saxena and several other compounds were prepared.

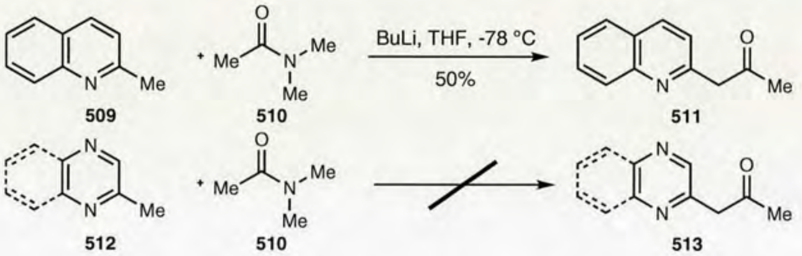
Formation of vinyl triflates and iron catalysed coupling of Grignard reagents

Additionally, another way to prepare the required starting materials was envisioned (Scheme 2.63). In this strategy, we tried to form a triflate intermediate **505** through a series of acylation-triflation steps of 2-methyl-heterocycles (**507**). This approach could possibly deliver a broad scope of desired compounds because of the availability of starting materials. It is also worth noticing that the triflation step can produce intermediates with good E/Z ratios and easy purification. Finally an iron catalysed coupling of an organometallic reagent to an α,β-unsaturated triflate **505** could give many variations of the desired compound (**504**)[187] in the last step of synthesis whilst preserving the E/Z configuration.



Scheme 2.63: Retrosynthetic analysis

Acylation of 2-methylquinoline with butyllithium and dimethylacetamide provided ketone **511** in moderate yield on a large scale (50 g). Unfortunately when the same procedure was tried with 2-methylquinoxaline (**512**), no product was formed. Instead, NMR analysis of the crude reaction mixture together with mass spectroscopy data suggested the formation of the addition product between 2-methylquinoxaline and butyllithium, despite the significant energy required to break the aromaticity of quinoxaline.

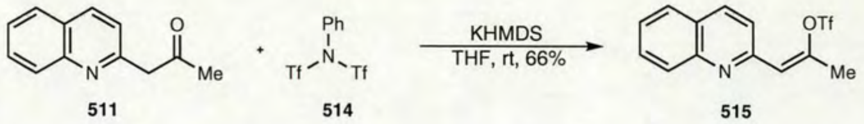


Scheme 2.64: Acylation of 2-methylheteroarenes

Trials with different bases and acceptors were made but we found acylation of the 2-methylpyrazine series of heterocycles in this way impossible. Surprisingly the same reaction involving 2-methylquinoline was unsuccessful when a larger acceptor (for example, dimethylpropionamide) was used.

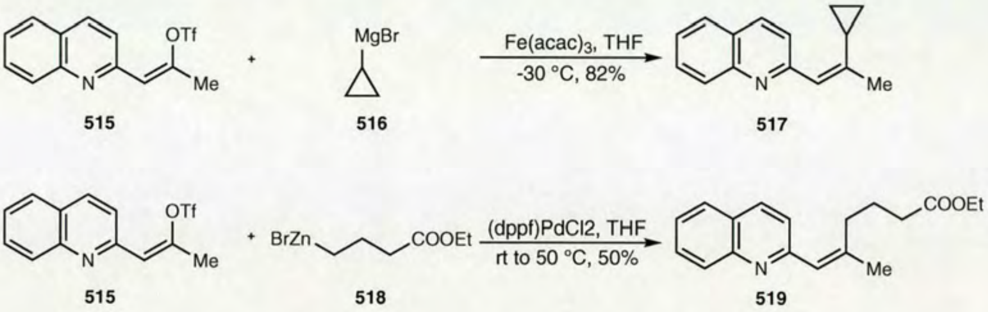
Addition of triethylamine and triflic anhydride to ketone **515** produced the desired α,β-unsaturated triflate ester, although with a low yield. After a short optimisation process, we decided to use another standard procedure for this type of reaction.[188] Deprotonation of ketone **511** with KHMDS and addition of Tf_2NPh gave the desired compound **515** as a single isomer in good yield.

The iron catalysed coupling of Grignard reagents to α,β-unsaturated triflates proceeded smoothly, with retention of E/Z geometry (Scheme 2.66).[187] Similarly, a Negishi coupling of organozinc reagent gave the desired compound **519** in moderate yield (no



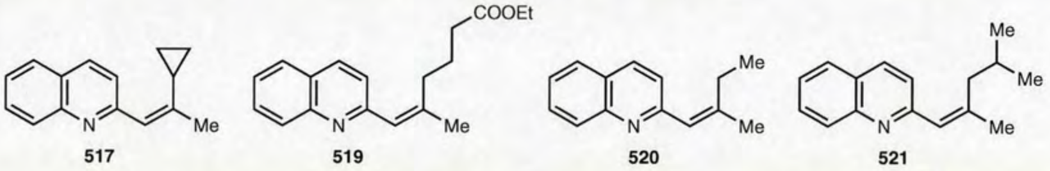
Scheme 2.65: Vinyl triflate formation

optimisation done).[189]



Scheme 2.66: Fe/Mg and Pd/Zn coupling

Despite a three step synthesis, by changing the organometallic reagent used in the final step, we managed to obtain several desired compounds.

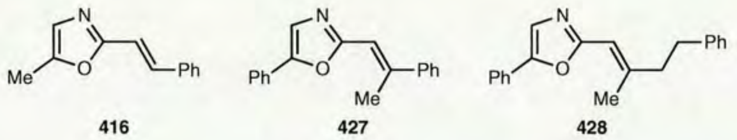


Scheme 2.67: Starting materials made with this approach

2.2.3 Preliminary screening of catalyst systems

Initial tests of catalyst systems for reduction of α,β-unsaturated heteroarenes began shortly after the preparation of the first starting materials. At first we concentrated our efforts on finding a set of conditions that allowed the mild reduction of the disubstituted carbon-carbon double bond in **416**

We assumed that this type of transformation could potentially be catalysed by copper in the presence of a bisphosphine ligand and a silane reducing agent. Upon testing only a few sets of condition we managed to achieve 50% conversion in a reaction involving **416**, $Cu(OAc)_2$, BINAP, and $PhSiH_3$ in toluene.



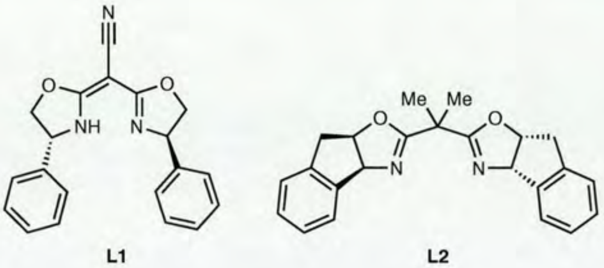
Scheme 2.68: Starting materials for preliminary screening

With a promising result in hand it was time to try our reductions on "real" starting materials that would allow a test of the enantioselectivity of this processes. Unfortunately when **427** (with methyl and phenyl substituents) was tried, almost no product was formed. An extensive screening was started to investigate many combinations of ligands, solvents, silanes and possible additives (summarised below).

- catalyst: $Cu(OAc)_2$
- ligands: BINAP SEGPHOS
- silanes: $PhSiH_3$, $(EtO)_3SiH$, PMHS
- additives: none, *t*-BuOH, NaOtBu
- solvents: THF, toluene, dichloromethane

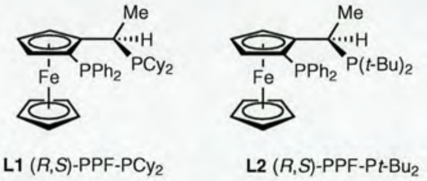
This screening did not produce a working catalyst system although it was possible to see some patterns in the data obtained. Clearly, dichloromethane was the poorest solvent as it gave negligible product in all cases. It was also observed that the presence of additives did improve the conversion of starting materials. The best results obtained at this stage employed $Cu(OAc)_2$, BINAP/SEGPHOS, $PhSiH_3$, *t*-BuOH/NaO*t*-Bu in toluene however, it was still far from our goal. Further screening of different copper sources ($Cu(OTf)_2$, CuF_2) and some rhodium catalysts proved to be unsuccessful and we decided to try a radically different approach.

After some literature research we tried cobalt as a catalyst with BOX ligands and $NaBH_4$ as the reducing agent in ethanol. Initial tests proved to be quite successful providing only the desired product with full conversion of starting material and 67% *ee*. Unfortunately further studies to improve the enantiomeric excess did not offer any significant improvements. We realized that this type of catalyst system was very unreliable, although 100% conversion was observed in every case, the same reaction conditions were producing varying (and usually low) levels of enantiomeric excess (Scheme 2.69).



Scheme 2.69: Bisoxazoline ligands

Once more we turned to copper catalysed reactions but this time with more elaborate ligands. Reduction of **428** (PhOx=Me,CH2CH2Ph) with $PhSiH_3$ was smoothly catalysed by $Cu(OAc)_2$ with Josiphos ligand and *t*-BuOH in toluene giving full conversion from the starting material and 97% *ee* (Scheme 2.70).



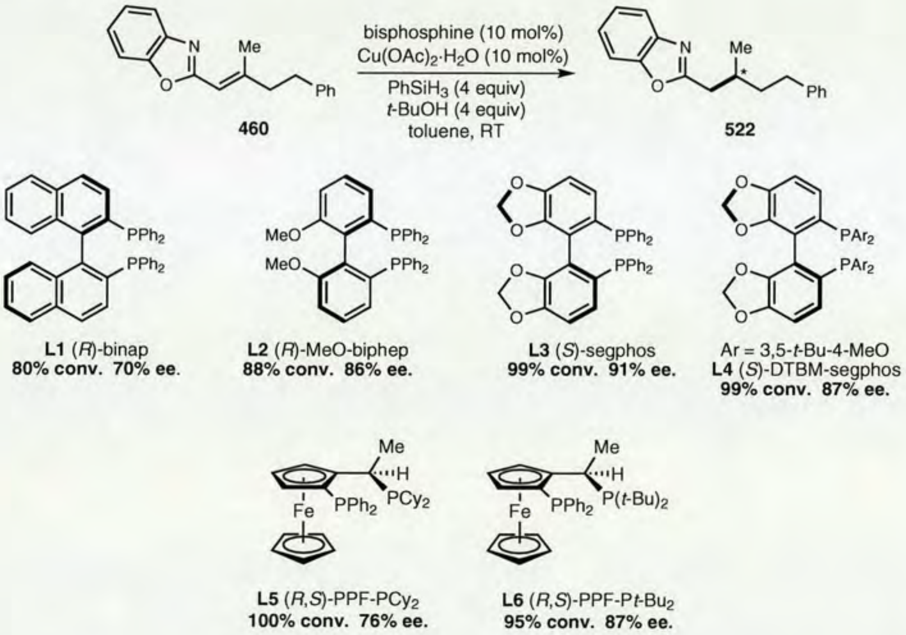
Scheme 2.70: Josiphos ligands

This surprising result prompted us to try more reactions with this particular ligand. It was observed that PMHS was not a strong enough reducing agent for this reaction and $PhSiH_3$ was employed in later studies. Compound **427** possessing a phenyl substituent on the double bond was still not reactive, while starting materials without aromatic substitution were being reduced with 100% conversion in 2-18 h and usually with good enantiomeric excess. Having a good insight into the requirements of this reaction we decided to undertake a careful ligand screening in order to further optimise the reaction conditions.

2.2.4 Ligand screening

Based on preliminary results we began with a survey of chiral bisphosphine ligands L1-L6 using 2-alkenylbenzoxazole **460** as a model substrate (Scheme 2.71). Using 10 mol % of $Cu(OAc)_2$, 10 mol % of ligand, and 4 equiv each of $PhSiH_3$ and *t*-BuOH in toluene at room temperature.

Compound **460** was chosen for the model studies as preliminary results indicated that benzoxazole heterocycles are good activating groups. This starting material was also preferred as it does not have aromatic substituents on the double bond which were problematic in preliminary screening. Relatively large catalyst and ligand loadings (10 mol %), an excess of $PhSiH_3$ and long reaction times (24 h) were used in this study to ensure that most reactions produced a sufficient amount of material for a precise analysis of the enantioselective excess obtained.



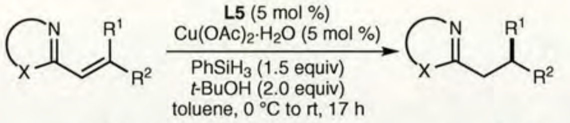
Scheme 2.71: Ligand screening

Biaryl-based ligands L1-L4 proved competent in promoting the conjugate reduction. With (R)-BINAP (L1), both conversion and enantioselectivity were only moderate. However, improved results were observed using (R)-MeO-BIPHEP (L2) and the SEGPHOS ligands L3 and L4, with 91% *ee* obtained using (S)-SEGPHOS (L3). The Josiphos ligands L5 and L6 were also effective, providing **522** in 89% and 87% *ee*, respectively. Of all the ligands, the highest reaction rates were observed with L4 and L5 (reactions were complete in 2 h). However, the superior selectivity provided by L5 prompted us to select this ligand for further optimization and investigation of the reaction scope.

2.2.5 Final Results

Using 5 mol % each of $Cu(OAc)_2$ and L5, $PhSiH_3$ (1.5 equiv), and *t*-BuOH (2.0 equiv) at an initial temperature of 0 °C, a range of β,β-disubstituted 2-alkenylheteroarenes underwent conjugate reduction with generally excellent levels of enantioselection (Table 2.1). In addition to benzoxazole (entries 1-4), other effective nitrogen-containing hetero-arenes in this process included 5-phenyloxazole (entry 5), benzothiazole (entry 6), pyridine (entries 7-9), quinoline (entry 10), and pyrazine (entry 11). Tolerated functionality at the β-positions of the alkene included simple aliphatic groups, a phenyl group (entry 4), a benzyl group (entry 9), various oxygenated alkyl groups (entries 2, 3, 7-9, and 11), and a cyclopropane (entry 10). The process is tolerant of lower loadings of copper and ligand. For example, reduction of **493** on a 1.0 mmol scale using 2 mol % each of $Cu(OAc)_2$ and L5 provided **557** in 92% yield and 96% *ee* (entry 7, values in parentheses).

The significantly lower *ee* reported in entry 4 can be explained in two fold. Aromatic substituents on carbon-carbon double bonds are known to be incompatible with Josiphos type ligands (examples of acyclic enones by Lipshutz[130]). However, its difficult to directly translate results obtained for different class of compounds as benzoxazole is a significantly different activating group. Additionally, the electron-withdrawing properties of phenyl substituents limits the polarisation of carbon-carbon double bonds. The main aspect of activation of alkene comes from the electron withdrawing properties of benzoxazole that causes polarisation of double bond and a partial positive charge on β carbon that can be then attacked by a copper hydride species. An additional electron-withdrawing group on the other end of alkene counters the electron withdrawing effect of the benzoxazole and so limits the difference of partial charges between α and β carbon (to benzoxazole), possibly resulting in the addition of hydride to α carbon. If this scenario is the case, then formation of the stereocentre at the β carbon occurs by a comparably unselective protonation mechanism.



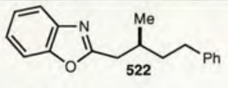
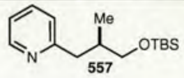
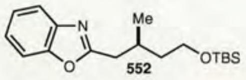
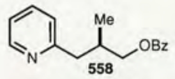
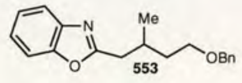
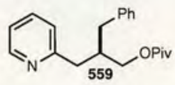
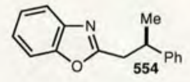
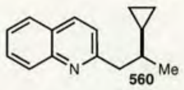
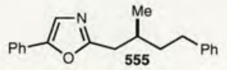
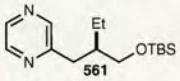
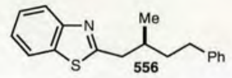
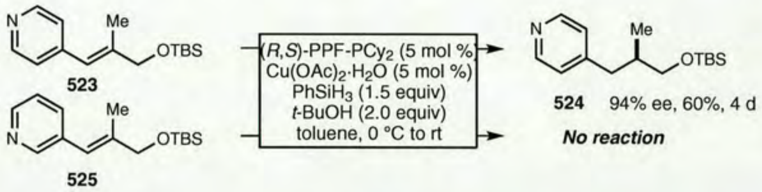
No.	product	yield / *ee* (%)	No.	product	yield / *ee* (%)
1	 **522**	90 / 93	7	 **557**	90(92) / 99(96)
2	 **552**	67 / 94	8	 **558**	81 / 98
3	 **553**	88 / 95	9	 **559**	90 / 97
4	 **554**	95 / 87	10	 **560**	90 / 96
5	 **555**	93 / 90	11	 **561**	89 / 96
6	 **556**	86 / 95			

Table 2.1: Scope of Cu-Catalyzed Asymmetric Conjugate Reduction

Reductions of 4- and 3-alkenylpyridine

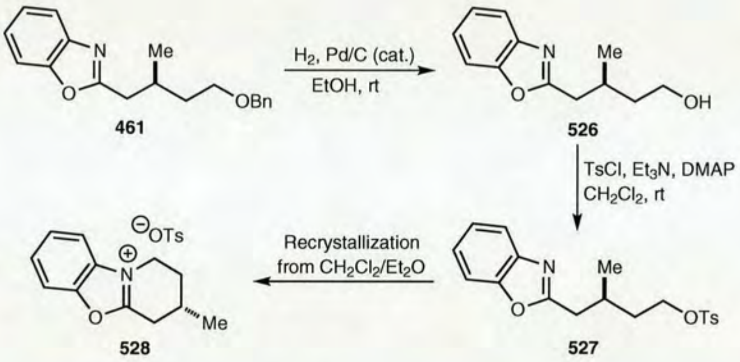
Experiments to explore the origins of the reactivity of the starting meterials were then conducted. We hypothesised that two main effects are important for a reaction to occur. An electronic activation of the alkene by conjugation with an electron-withdrawing heterocycle and a possible coordination of the opper catalyst to the nitrogen present in all of the starting materials that we used. To verify the latter hypothesis a reduction of 4-alkenylpyridine **523** was attempted. The substrate **523** does not allow coordination of copper next to the reaction center (alkene moiety) and therefore it should not react. Surprisingly, reduction of **523** provided **524** in 60% yield and 94% *ee*, albeit in a slower reaction that was incomplete even after 4 days. This result suggests that alkene reduction by copper hydride can occur without assistance of a directing effect from the nitrogen atom. In contrast, 3-alkenylpyridine **525** was nonreactive‡, demonstrating the importance of conjugation of the alkene to a C=N moiety for reactivity.



Scheme 2.72: Reductions of 4- and 3-alkenylpyridine‡

X-ray and absolute configuration

The stereochemistries of the products obtained herein were assigned tentatively by analogy with that of **491**, which was secured through X-ray crystallography of a derivative **528** (Scheme 2.73).



Scheme 2.73: Synthesis of derivative **528** for X-ray studies

Reduction and subsequent acetyl transfer of 495

An interesting observation has been made when reducing compounds containing an acetate ester in the γ position (**495**). In this case the reduction of the carbon-carbon double bond was followed by acetyl transfer from ester to the α position and intramolecular hemiacetal formation. Product **529** was isolated as a single diastereoisomers in 50% yield. Similar behaviour was observed with p-bromobenzoyl esters. However, pivaloate ester did not proceed through that pathway. Further studies are required to speculate on the utility of this process.

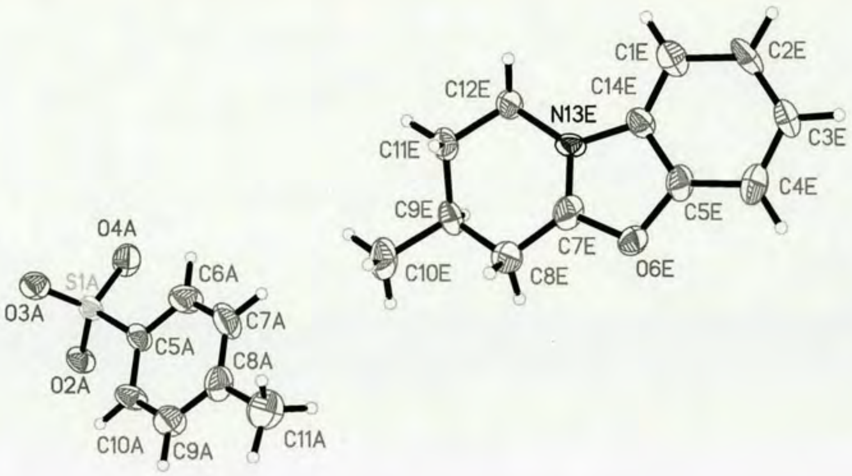
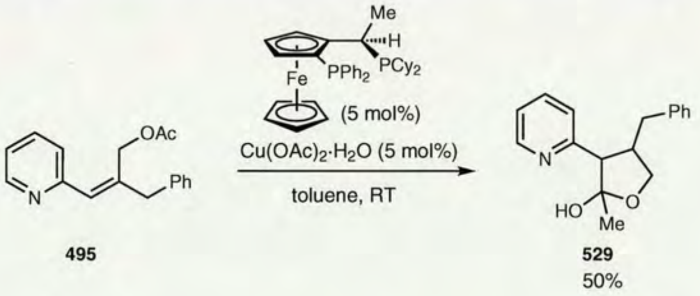


Figure 2.74: X-ray crystallography structure of **528**



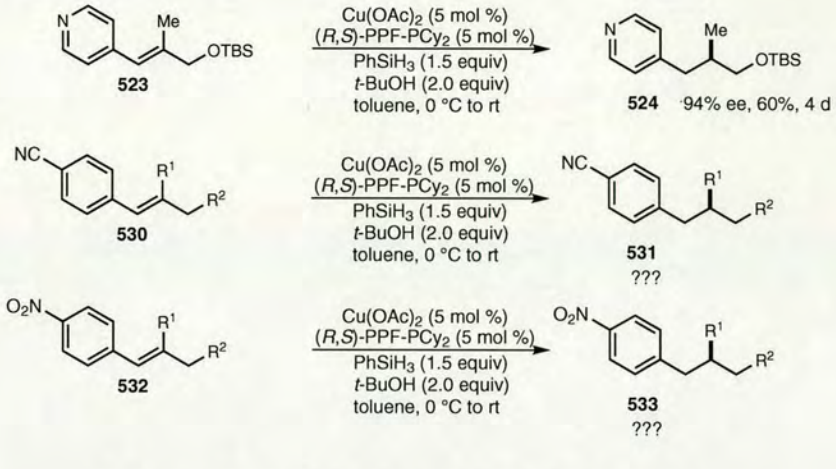
Scheme 2.75: Copper mediated reduction and acetyl transfer

2.3 Future Work

Possible future work could involve extensive screening of reaction conditions to find a way to improve the reaction scope in areas where this study has failed to deliver desired products. A probable improvement could come from the fine-tuning of ligand, as preliminary screening a showed huge correlation of reactivity with bisphosphine used. It would also be beneficial to change the reducing agent to the more stable TMDS or PMHDS as these are highly preferred in industry. Similar reactions could also proceed using boranes or even hydrogen as a reductant provided suitable catalysts can be found. These would offer huge advantages over the current conditions.

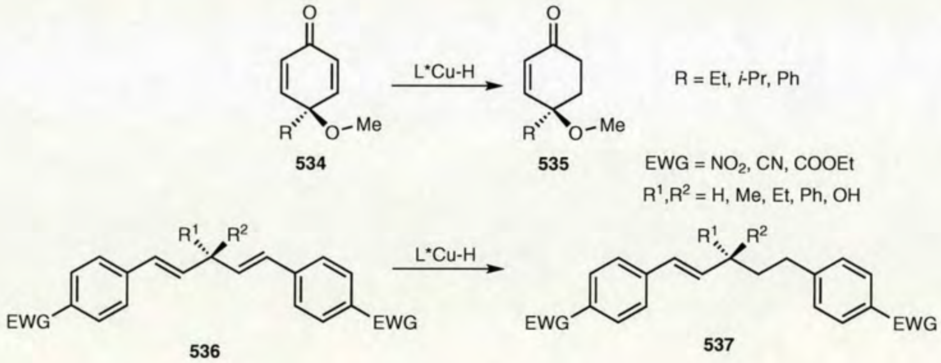
The substrate, 4-alkenylpyridine **523**, demonstrated that reduction by copper hydride can occur without the assistance of a directing effect from the nitrogen atom and it is easy to envision that 4-alkenylnitrobenzene **532** or 4-alkenylcyanobenzene **530** should give positive results. This research is currently under way in the Lam group

(Scheme 2.76).



Scheme 2.76: Extension of 4-alkenylpyridine

Further extension of the substrate scope can come from desymmetrization of C2 symmetric molecules (Scheme 2.77). In this process enantiomeric excess can be obtained if the catalyst (copper hydride) can differentiate between the two chemically identical parts of molecule.



Scheme 2.77: Enantioselective desymmetrization

In the long term it would be beneficial to investigate whether the addition of larger nucleophiles is possible. For example, $PhSiH_3$ could be substituted with allylSi$(OMe)_3$. These type of alkylation are known to occur, although they usually require strongly activated starting materials.[190]

2.4 Conclusions

In summary, copper-catalysed asymmetric conjugate reductions of β,β-disubstituted 2-alkenylheteroarenes are reported. In addition to serving as a further demonstration of the power of chiral copper hydride catalysis, this work has shown that nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate addition reactions. Extension of the general concept to other classes of asymmetric reactions should provide a range of useful tools for chemists working with heteroarenes.

Chapter 3

Experimental Data

3.1 General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Toluene and THF were dried and purified by passage through activated alumina columns using a solvent purification system from "Glass Contour Solvent Systems". All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[1] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DMX500 (500 MHz) spectrometer, a Bruker DPX360 (360 MHz) spectrometer, or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used

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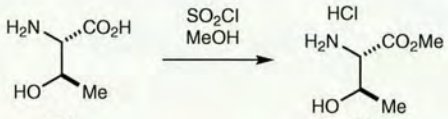
[1]. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

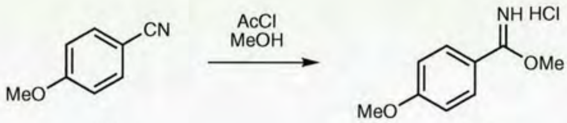
in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.1 MHz) spectrometer, a Bruker DPX360 (90.6 MHz) spectrometer, or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, CD_3OD at 49.9 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Microwave reactions were performed using a Biotage microwave synthesizer. Authentic racemic samples of products for chiral HPLC assay determinations were obtained by hydrogenation of the alkene substrates in EtOH using a Pd/C catalyst, except in the case of *rac*-**553** which was obtained by copper-catalyzed conjugate reduction of alkene **461** according to General Procedure C but using *rac*-BINAP as the ligand, and *rac*-**559**, which was obtained by hydrogenation of alkene **543** in EtOH using a Pt/C catalyst.

3.2 Formal Synthesis of Salinosporamide A



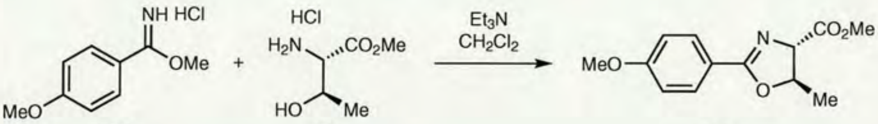
198 199

(*L*)-Threonine methyl ester (199) To a stirred solution of SOCl$_2$ (11.0 mL, 150 mmol) in MeOH (115 mL) at 0 ºC was added (*L*)-threonine (18.2 g, 150 mmol) in portions. After stirring for 30 min at room temperature, the reaction was heated to reflux for 14 h and then concentrated *in vacuo*, to obtain a thick colourless oil. Methyl ester **199** was used in the next step without further purification. ^{1}H NMRHH (360 MHz, CD$_3$OD) δ 5.11 (3H, bs, N**H$_2$** + O**H**), 4.52 (1H, dq, J = 6.5, 4.2 Hz, C**H**CH$_3$), 4.19 (1H, d, J = 4.2 Hz, C**H**CHOH), 4.08 (3H, s, OC**H$_3$**), 1.56 (3H, d, J = 6.5 Hz, C**H$_3$**CH); ^{13}C NMR (62.9 MHz, CD$_3$OD) δ 170.1 (C), 66.8 (CH), 60.3 (CH), 54.2 (CH$_3$), 20.9 (CH$_3$).



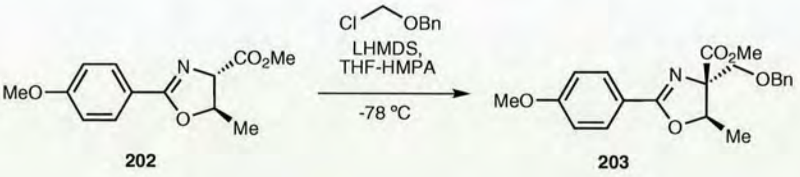
200 201

4-Methoxybenzimidate hydrochloride (201) To a stirred solution of *p*-methoxybenzonitrile **200** (22.4 g, 168.6 mmol) in MeOH (85 mL, 2.0 mol) at 0 ºC was added acetyl chloride (96.0 mL, 1.34 mol) slowly *via* syringe. The solution was stirred for 14 h at room temperature and then concentrated *in vacuo* which afforded **201** as a colourless solid. This solid was washed with Et$_2$O (5 x 30 mL), dried and used without further purification in the next step (30.5 g, 91%). m.p. 165-167 ºC; ^{1}H NMRHH (360 MHz, CDCl$_3$) δ 11.60 (1H, bs, N**H**), 8.39 (2H, d, J = 9.0 Hz, Ar**H**), 7.02 (2H, d, J = 9.0 Hz, Ar**H**), 4.51 (3H, s, OC**H$_3$**), 3.88 (3H, s, OC**H$_3$**); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 171.1 (C), 165.5 (C), 132.1 (2 x CH), 116.7 (C), 114.6 (2 x CH), 60.8 (CH$_3$), 55.6 (CH$_3$).

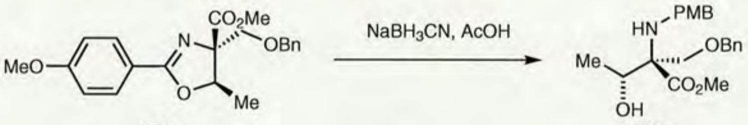


201 199 202

(4*S*,5*R*)-Methyl 4,5-dihydro-2 (4-methoxyphenyl)-5-methyloxazole-4-carboxylate (202)[26] To a stirred solution of threonine methyl ester **199**(25.5 g, 150 mmol) in CH_2Cl_2 (175 mL) at room temperature was added Et_3N (41.0 mL, 300 mmol) slowly *via* syringe, followed by the addition of **201** in one portion. The reaction was stirred for 1 h at room temperature, heated to reflux for 14 h, then it was quenched with saturated aqueous NH_4Cl solution (150 mL) and extracted with CH_2Cl_2 (3 x 70 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 40% EtOAc/petrol) afforded oxazoline **202** (12.8 g, 40%) as a pale yellow solid. R_f (30% EtOAc in hexane) = 0.29; m.p. 87-88 ºC, lit.[26] 86-87 ºC; $[\alpha]^{22}_{D}$ +76.5 (*c* 1.98, $CHCl_3$), lit.[26] +69.4 (*c* 2.0, $CHCl_3$); ^{1}H NMRHH (360 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.9 Hz, Ar**H**), 6.83 (2H, d, J = 8.9 Hz, Ar**H**), 4.89 (1H, dq, J = 7.4, 6.3 Hz, OC**H**CH_3), 4.38 (1H, d, J = 7.4 Hz, NC**H**), 3.75 (3H, s, OC**H₃**), 3.73 (3H, s, OC**H₃**), 1.45 (3H, d, J = 6.2 Hz, CHC**H₃**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.4 (C), 165.0 (C), 162.1 (C), 130.0 (2 x CH), 119.4 (C), 113.4 (2 x CH), 78.4 (CH), 74.8 (CH), 55.0 (CH_3), 52.2 (CH_3), 20.7 (CH_3).



(4*R*,5*R*)-Methyl 4-[(benzyloxy)methyl]-4,5-dihydro-2-(4-methoxyphenyl)-5-methyloxazole-4-carboxylate (203) To a stirred solution of LHMDS (56.6 mL, 1 M solution in THF, 56.5 mmol), in THF (200 mL) at –78 ºC was added HMPA (30.0 mL, 221 mmol), followed by the transfer of a solution of oxazoline **202** (12.8 g, 51.3 mmol) in THF (100 mL) *via* cannula. This solution was stirred at –78 ºC for 1 h to allow enolate formation. Benzyloxy chloromethyl ether (14.3 mL, 61.7 mmol) was then added and the reaction was stirred at –78 ºC for 3 h, when it was quenched with saturated aqueous NH_4Cl solution (150 mL) and warmed up to room temperature for 30 minutes. The aqueous layer was extracted with EtOAc (4 x 80 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (15% to 20% EtOAc/petrol) afforded alkylated oxazoline **203** (14.8 g, 75%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.53; $[\alpha]_D^{22}$ –6.0 (*c* 1.0, $CHCl_3$), lit.[26] –6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMRHH (360 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 9.0 Hz, Ar**H**), 7.29-7.24 (5H, m, Ar**H**), 6.90 (2H, d, J = 9.0 Hz, Ar**H**), 4.78 (1H, q, J = 6.6 Hz, OC**H**CH_3), 4.61 (2H, s, OC**H₂**Ar), 3.87 (1H, d, J = 9.9 Hz, C**H_A**H_BO), 3.81 (1H, d, J = 9.9 Hz, CH_A**H_B**O), 3.80 (3H, s, OC**H₃**), 3.73 (3H, s, OC**H₃**), 1.35 (3H, d, J = 6.6 Hz, CHC**H₃**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.8 (C), 165.0 (C), 162.2 (C), 137.8 (C), 130. 2 (2 x CH), 128.0 (2 x CH), 127.4 (2 x CH), 127.3 (CH), 119.7 (C), 113.4 (2 x CH), 81.0 (C), 79.5 (CH), 73.5 (CH_2), 73.0 (CH_2), 55.1 (CH_3), 52.0 (CH_3), 16.5 (CH_3).

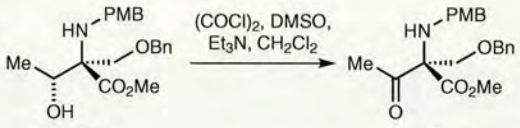


203

204

(2*R*,3*R*)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3- hydroxybutanoate (204) To a stirred solution of oxazoline **203** (14.8 g, 40.0 mmol) in HOAc (50 mL) at room temperature was added $NaCNBH_3$ (8.80 g, 132 mmol) in small portions over 2 h. The reaction mixture was stirred for 16 h at 50 ºC, when it was diluted in water (100 mL), neutralised with solid Na_2CO_3 and the aqueous layer was extracted with ethyl acetate (5 x 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 25% EtOAc/petrol) afforded aminoalcohol **204** (9.3 g, 65%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.21; $[\alpha]_D^{22}$ –5.8 (*c* 1.03, $CHCl_3$), lit.[26] –9.1 (*c* 1.0, $CHCl_3$); ^{1}H NMRHH (360 MHz, $CDCl_3$) δ 7.54-7.44 (5H, m, Ar**H**), 7.43 (2H, d, J = 8.7 Hz, Ar**H**), 7.02 (2H, d, J = 8.7 Hz, Ar**H**), 4.71 (2H, s, OC**H₂**Ph), 4.15 (1H, q, J = 6.4 Hz, HOC**H**CH_3), 4.03 (1H, d, J = 9.8 Hz, NC**H_A**H_BAr), 3.98 (1H, d, J = 9.8 Hz, NCH_A**H_B**Ar), 3.95 (3H, s, OC**H₃**), 3.92 (3H, s, OC**H₃**), 3.87 (1H, d, J = 11.8 Hz, C**H_C**H_DOBn), 3.79 (1H, d, J = 11.8 Hz, CH_C**H_D**OBn), 2.28 (1H, bs, O**H**), 1.35 (3H, d, J = 6.6 Hz, CHC**H₃**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.8 (C), 158.8

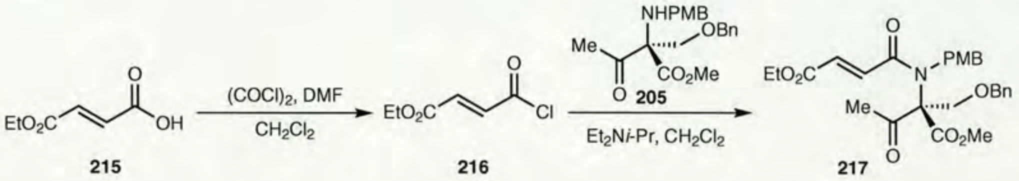
(C), 137.5 (C), 131.7 (C), 129.5 (2 x CH), 128.4 (2 x CH), 127.8 (CH), 127.7 (2 x CH), 113.8 (2 x CH), 73.5 (CH_2), 69.8 (C), 69.5 (CH_2), 69.4 (CH), 55.2 (CH_3), 52.1 (CH_3), 47.3 (CH_2), 17.9 (CH_3).



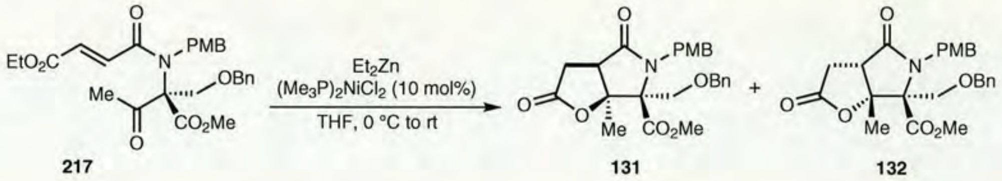
204 **205**

(*R*)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3-oxobutanoate (205) To a stirred solution of oxalyl chloride (1.70 mL, 18.8 mmol) in CH_2Cl_2 (40 mL) at −78 °C, was added DMSO (2.10 mL, 37.6 mmol) dropwise over 3 min. After stirring for 15 min, a solution of alcohol **204** (3.34 g, 8.94 mmol) in CH_2Cl_2 (30 mL) was added *via* cannula over 5 min. The reaction stirred at −78 °C for 1 h and Et_3N (5.25 mL, 37.6 mmol) was then added over 1 min. The reaction was stirred at −78 °C for 1 h, allowed to warm up to −40 °C over 2 h, and then quenched with saturated aqueous NH_4Cl solution (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10% to 20% EtOAc/petrol) gave *amino ketone* **205** (2.39 g, 72%) as a pale yellow solid. R_f (30% EtOAc in hexane) = 0.55; m.p. = 60-62 °C; $[\alpha]^{22}_{D}$ -12.7 (*c* 1.02, $CHCl_3$); IR (film) 3347 (NH), 2952, 2836, 1741 (C=O), 1718 (C=O), 1511, 1245, 1178, 1033, 700 cm^{-1}; ^1H NMRHH (250 MHz, $CDCl_3$) δ 7.39-7.28 (5H, m, Ar**H**), 7.25 (2H, d, J = 8.7 Hz, Ar**H**), 6.85 (2H, d, J = 8.7 Hz, Ar**H**), 4.59 (1H, d, J = 12.4 Hz, OC$\mathbf{H_A}$$H_B$Ph), 4.53 (1H, d, J = 12.4 Hz, OC$H_A$$\mathbf{H_B}$Ph), 4.02 (1H, d, J = 10.1 Hz, NHC$\mathbf{H_C}$$H_D$), 3.90 (1H, d, J = 10.1 Hz, NHC$H_C$$\mathbf{H_D}$), 3.80 (3H, s, OC$\mathbf{H_3}$), 3.74 (3H, s, OC$\mathbf{H_3}$), 3.59 (1H, d, J = 12.3 Hz, C$\mathbf{H_E}$$H_F$OBn), 3.46 (1H, d, J = 12.3 Hz, C$H_E$$\mathbf{H_F}$OBn), 2.53 (1H, br s, N**H**), 2.21 (3H, s, C$\mathbf{H_3}$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 203.3 (C), 169.8 (C), 158.7 (C), 137.6 (C), 131.7 (C), 129.3 (2 x CH), 128.4 (2 x CH), 127.8 (3 x CH), 113.7 (2 x CH), 74.8 (C), 73.4 (CH_2), 68.1 (CH_2), 55.3 (CH_3), 52.7 (CH_3), 46.7 (CH_2), 25.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1805, found:

372.1804.



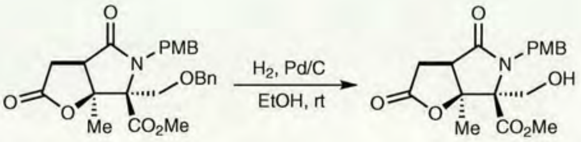
(*R*)-Ethyl (*E*)-3-[*N*-(1-benzyloxymethyl-1-carbomethoxy-2-oxopropyl)-*N*-(4-methoxybenzyl)carbamoyl]acrylate (217) To a stirred solution of fumaric acid monoethyl ester (858 mg, 5.65 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added oxalyl chloride (0.56 mL, 6.40 mmol) followed by DMF (one drop). This solution was stirred at room temperature for 1 h, and then transferred *via* cannula to a solution of the amine **205** (1.34 g, 3.60 mmol) and diisopropylethyl amine (1.10 mL, 6.40 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 ºC for 10 min and then at room temperature for 18 h, when it was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave *amide* **217** (1.7 g, 95%) as a pale yellow oil. R_f (30% EtOAc in hexane) = 0.45; $[\alpha]^{22}_{D}$ –18.2 (*c* 1.18, $CHCl_3$); IR (film) 2953, 2837, 1722 (C=O),1658 (C=O), 1513, 1408, 1294, 1175, 1032, 974 cm^{-1}; ^1H NMR (360 MHz, CDCl3) δ 7.35-7.27 (5H, m, Ar**H**), 7.22 (1H, d, J = 15.3 Hz, =C**H**), 7.17-7.12 (2H, m, Ar**H**), 6.95-6.89 (2H, dm, J = 8.8 Hz, Ar**H**), 6.80 (1H, d, J = 15.3 Hz, =C**H**), 4.95 (1H, d, J = 18.4 Hz, $OC\mathbf{H_A}H_BAr$), 4.81 (1H, d, J = 18.4 Hz, $OCH_A\mathbf{H_B}Ar$), 4.32 (1H, d, J = 11.9 Hz, $NC\mathbf{H_C}H_DAr$), 4.28 (1H, d, J = 11.9 Hz, $NCH_C\mathbf{H_D}Ar$), 4.19 (2H, q, J = 7.1 Hz, $OC\mathbf{H_2}CH_3$), 3.83 (3H, s, $OC\mathbf{H_3}$), 3.80 (3H, s, $OC\mathbf{H_3}$), 3.78 (2H, s, $C\mathbf{H_2}OBn$), 2.45 (3H, s, $C\mathbf{H_3}C{=}O$), 1.26 (3H, t, J = 7.1 Hz, $OCH_2C\mathbf{H_3}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.6 (C), 168.0 (C), 167.5 (C), 165.2 (C), 158.9 (C), 136.5 (C), 133.3 (CH), 133.1 (CH), 129.7 (C), 128.4 (2 x CH), 127.9 (CH), 127.5 (2 x CH), 127.1 (2 x CH) 114.2 (2 x CH), 77.5 (C), 73.7 (CH_2), 70.1 (CH_2), 61.1 (CH_2), 55.2 (CH_3), 52.9 (CH_3), 48.9 (CH_2), 27.9 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{27}H_{32}NO_8$ $[M+H]^+$: 498.2122, found: 498.2123.



(3a*R*,6*R*,6a*S*)-6-Benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahy *c*]pyrrole-6-carboxylic acid methyl ester (131) and (3a*S*,6*R*,6a*R*)-6-benzyloxymethy 5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-*c*]pyrrole-6-carboxylic acid methyl ester (132) A solution of amide **217** (875 mg, 1.75 mmol) and $(Me_3P)_2NiCl_2$ (115 mg, 0.175 mmol) in THF (75 mL) was stirred at room temperature for 30 min and then cooled to −15 °C (ice-salt bath). Et_2Zn (3.52 mL, 1 M solution in THF, 3.52 mmol) was then added *via* syringe. The reaction was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% to 35 % EtOAc/petrol) gave the *double cyclization product* **131** (354 mg, 42%) as a pale yellow oil, followed by the *double cyclization product* **132** (253 mg, 30%) as a colourless solid. Recrystallization of **132** from EtOAc/petrol gave colourless crystals that were suitable for X-ray crystallography.

Data for *desired* **131**: R_f (30% EtOAc in $CHCl_3$) = 0.19; $[\alpha]^{22}_D$ −33.3 (*c* 1.02, $CHCl_3$); IR (film) 2955, 1789 (C=O), 1733 (C=O), 1699 (C=O), 1612, 1513, 1439, 1404, 1248, 1178 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27-7.18 (3H + 2H, m, Ar**H**), 7.04-6.99 (2H, m, Ar**H**), 6.69 (2H, d, J = 8.7 Hz, Ar**H**), 4.97 (1H, d, J = 15.2 Hz, $OC\mathbf{H_A}H_BPh$), 4.21 (1H, d, J = 15.2 Hz, $OCH_A\mathbf{H_B}Ph$), 3.83 (1H, d, J = 11.5 Hz, $NC\mathbf{H_C}H_DAr$), 3.75 (1H, d, J = 10.4 Hz, $C\mathbf{H_E}H_FOBn$), 3.73 (1H, d, J = 11.5 Hz, $NCH_C\mathbf{H_D}Ar$), 3.73 (3H, s, $OC\mathbf{H}_3$), 3.66 (3H, s, $OC\mathbf{H}_3$), 3.13 (1H, d, J = 10.4 Hz, $CH_E\mathbf{H_F}OBn$), 2.97 (1H, dd, J = 9.3, 1.5 Hz, $CH_GH_HC\mathbf{H}$), 2.88 (1H, dd, J = 18.3, 1.5 Hz, $C\mathbf{H_G}H_HCH$), 2.72 (1H, dd, J = 18.3, 9.3 Hz, $CH_G\mathbf{H_H}CH$), 1.53 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.5 (C), 172.9 (C), 166.9 (C), 159.0 (C), 136.7 (C) 130.0 (2 x CH), 129.4 (C), 128.4 (2 x CH), 127.9 (CH), 127.3 (2 x CH), 113.6 (2 x CH), 88.4 (C), 75.8 (C), 72.8 (CH_2), 67.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 47.5 (CH), 45.1 (CH_2), 30.7 (CH_2), 19.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860 , found: 454.1856.

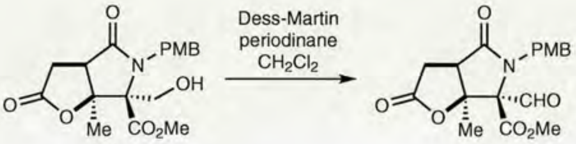
Data for *undesired* **132**: R_f (30% EtOAc in $CHCl_3$) = 0.08; m.p. = 105 ºC; $[\alpha]^{22}_{D}$ -17.9 (*c* 1.01, $CHCl_3$); IR (film) 2952, 2870, 1789 (C=O), 1743 (C=O), 1703 (C=O), 1613, 1512, 1434, 1246, 1128 cm-1; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38-7.21 (5H, m, Ar**H**), 7.12 (2H, d, J = 8.7 Hz, Ar**H**), 6.82 (2H, d, J = 8.7 Hz, Ar**H**), 4.72 (1H, d, J = 15.2 Hz, $O\mathbf{CH_A}H_BPh$), 4.40 (1H, d, J = 15.2 Hz, $OCH_A\mathbf{H_B}Ph$), 4.34 (1H, d, J = 11.7 Hz, $N\mathbf{CH_C}H_DAr$), 4.27 (1H, d, J = 11.7 Hz, $NCH_C\mathbf{H_D}Ar$), 3.94 (1H, d, J = 10.1 Hz, $\mathbf{CH_E}H_FOBn$), 3.82 (3H, s, $OC\mathbf{H_3}$), 3.74 (1H, d, J = 10.1 Hz, $CH_E\mathbf{H_F}OBn$), 3.67 (3H, s, $OC\mathbf{H_3}$), 3.07 (1H, dd, J = 9.7, 1.8 Hz, $CH_GH_H\mathbf{CH}$), 3.04 (1H, dd, J = 18.3, 1.9 Hz, $\mathbf{CH_G}H_HCH$), 2.88 (1H, dd, J = 18.3, 9.7 Hz, $CH_G\mathbf{H_H}CH$), 1.51 (3H, s, $C\mathbf{H_3}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.4 (C), 173.2 (C), 169.2 (C) 158.7 (C) 137.1 (C) 129.2 (2 x CH), 129.0 (C), 128.3 (2 x CH), 127.7 (3 x CH), 113.6 (2 x CH), 86.6 (C), 75.3 (C), 73.6 (CH_2), 68.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 46.9 (CH), 45.1 (CH_2), 30.9 (CH_2), 21.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860, found: 454.1858.



131 235

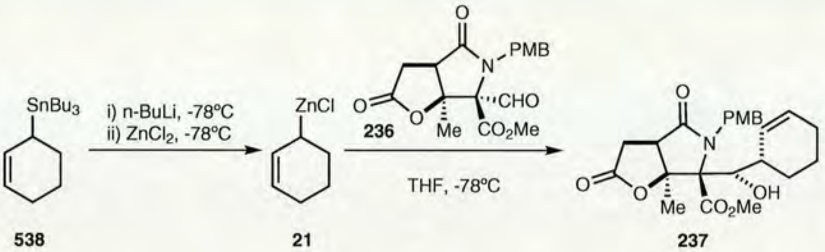
(3a*R*,6*R*,6a*S*)-6-Hydroxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydr c]pyrrole-6-carboxylic acid methyl ester (235) A mixture of benzyl ether **131** (354 mg, 0.78 mmol) and 10% Pd/C (99 mg, 0.093 mmol) in EtOH (5 mL) at room temperature was evacuated and flushed with H_2 (3 times) and then stirred vigorously under an atmosphere of H_2 (1 atm, H_2 balloon) at room temperature for 18 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/petrol) gave *alcohol* **235** (240 mg, 84%) as a white powder. R_f (100% EtOAc) = 0.52; m.p. 144-146 ºC; $[\alpha]^{22}_{D}$ –30.1

(c 0.95, $CHCl_3$); IR (film) 3437 (OH), 2955, 2253, 1787 (C=O), 1757 (C=O), 1692 (C=O), 1613, 1513, 1247, 1035, 951cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (2H, d, J = 8.6 Hz, Ar**H**), 6.87 (2H, d, J = 8.6 Hz, Ar**H**), 5.22 (1H, d, J = 15.2 Hz, NC$\mathbf{H_A}$$H_B$Ar), 4.24 (1H, d, J = 15.2 Hz, NC$H_A$$\mathbf{H_B}$Ar), 3.95 (1H, dd, J = 13.0, 8.9 Hz, C$\mathbf{H_C}$$H_D$OH), 3.83 (3H, s, OC$\mathbf{H}_3$), 3.80 (3H, s, OC$\mathbf{H}_3$), 3.43 (1H, dd, J = 13.0, 5.5 Hz, C$H_C$$\mathbf{H_D}$OH), 3.04 (1H, dd, J = 9.1, 1.7 Hz, C$H_E$$H_F$C**H**), 2.96 (1H, dd, J = 18.1, 1.7 Hz, C$\mathbf{H_E}$$H_F$CH), 2.85 (1H, dd, J = 18.1, 9.1 Hz, C$H_E$$\mathbf{H_F}$CH), 1.69 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.7 (C), 172.7 (C), 167.1 (C), 159.5 (C), 129.6 (2 x CH + C), 114.6 (2 x CH), 88.3 (C), 77.3 (C), 60.9 (CH_2), 55.3 (CH_3), 52.8 (CH_3), 47.6 (CH), 44.9 (CH_2), 30.5 (CH_2), 19.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{25}N_2O_7$ $[M+NH_4]^+$: 381.1656, found: 381.1660.



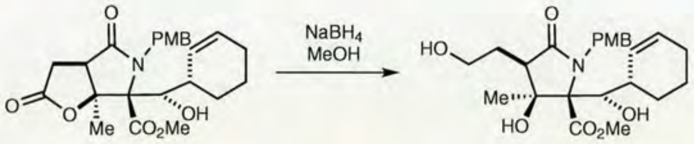
235 236

(3a*R*,6*R*,6a*S*)-6-Formyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2, c]pyrrole-6-carboxylic acid methyl ester (236) To a solution of alcohol **235** (30 mg, 0.082 mmol) in CH_2Cl_2 (0.8 mL) at room temperature was added Dess-Martin periodinane (43 mg, 0.099 mmol). The reaction mixture was stirred for 1.5 h, quenched with water and extracted with EtOAc (3 x mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo as an oil. This aldehyde proved to be unstable and was generally used immediately in the next step without purification. On one occasion, purification of a small amount of crude product by column chromatography (50% EtOAc/petrol) was performed for characterisation purposes. R_f (100% EtOAc) = 0.34; IR (film) 2956, 1788 (C=O), 1760 (C=O), 1728 (C=O), 1687 (C=O), 1513, 1438, 1246, 1176, 949 cm^{-1}; ^{1}H NMRHH (250 MHz, $CDCl_3$) δ 9.47 (1H, s, C**H**O), 7.05 (2, d, J = 8.7 Hz, Ar**H**), 6.81 (2H, d, J = 8.7 Hz, Ar**H**), 4.86 (1H, d, J = 14.4 Hz, NC$\mathbf{H_A}$$H_B$Ar), 4.39 (1H, d, J = 14.4 Hz, NC$H_A$$\mathbf{H_B}$Ar), 3.90 (3H, s, OC$\mathbf{H_3}$), 3.78 (3H, s, OC$\mathbf{H_3}$), 3.08 (1H, dd, J = 9.7, 1.8 Hz, C$H_C$$H_D$C**H**), 2.99 (1H, dd, J = 18.4, 1.8 Hz, CH$_C$H$_D$CH), 2.85 (1H, dd, J = 18.4, 9.7 Hz, CH$_C$**H$_D$**CH), 1.52 (3H, s, **CH$_3$**); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 195.5 (CH), 172.7 (C), 172.0 (C), 165.7 (C), 159.6 (C), 131.1 (2 x CH), 126.8 (C), 114.2 (2 x CH), 87.3 (C), 79.0 (C), 55.2 (CH$_3$), 53.4 (CH$_3$), 46.8 (CH), 45.6 (CH$_2$), 30.6 (CH$_2$), 20.5 (CH$_3$); LRMS (EI$^+$) Mass calcd. for $C_{18}H_{19}NO_7Na$ [M+Na]$^+$: 384.3, found: 383.7.



(3aR,6R,6aS)-6-[(7S)-(8S)-Cyclohex-2-enylhydroxymethyl]-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (237) To a solution of cyclohexenyltributyltin (**538**)[36] (89.6 mg, 0.206 mmol) in THF (0.6 mL) at –78 ºC was added n-BuLi (130 μL mL, 1.6 M solution in hexanes, 0.206 mmol). After stirring at –78 ºC for 1 h, ZnCl$_2$ (0.42 mL, 0.5 M solution in THF, 0.21 mmol) was added and stirring was continued at this temperature for another 1 h. A solution of the crude aldehyde **236** from the above experiment (theoretically 0.082 mmol) in THF (0.4 mL) was then added *via* cannula, and after stirring for 3 h at –78 ºC, the reaction was quenched with H$_2$O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo*, and purification of the residue by column chromatography (50% EtOAc/petrol) gave the *homoallylic alcohol* **237** (22.4 mg, 61% over two steps) as a colourless solid. R$_f$ (100% EtOAc) = 0.61; R$_f$ (70% EtOAc in CHCl$_3$) = 0.45; m.p. = 114-116 ºC; $[\alpha]^{22}_{D}$ +3.0 (c 1.47, CHCl$_3$); IR (film) 3438 (OH), 2931, 2359, 1790 (C=O), 1755 (C=O) 1687 (C=O), 1512, 1440, 1246, 1175, 807 cm^{-1}; ^{1}H NMRHH (250 MHz, CDCl$_3$) δ 7.18 (2H, d, J = 8.7 Hz, Ar**H**), 6.84 (2H, d, J = 8.7 Hz, Ar**H**), 5.91 (1H, dm, J = 10.2 Hz, **CH**=CH), 5.68 (1H, dm, J = 10.2 Hz, C**H**=CH), 4.79 (1H, d, J = 14.9 Hz, NC**H$_A$**H$_B$Ar), 4.54 (1H, d, J = 14.9 Hz, NCH$_A$**H$_B$**Ar), 4.12 (1H, t, J = 7.1 Hz, C**H**OH), 3.78 (6H, s, 2 x OC**H$_3$**), 3.13 (1H, dd, J = 6.8, 3.3 Hz, CH$_2$C**H**C=O), 2.92 (1H, br s, O**H**), 2.82-2.79

(2H, m, $\mathbf{CH_2}$CHC=O), 2.32 (1H, bs, CHOHC**H**), 2.02 (2H, bs, $\mathbf{CH_2}$), 1.81 (3H, s, $\mathbf{CH_3}$CO), 1.76-1-66 (2H, m, $\mathbf{CH_2}$), 1.57-1.46 (1H, m, $\mathbf{CH_2}$), 1.44-1.33 (1H, m, $\mathbf{CH_2}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.8 (C), 173.0 (C), 167.8 (C), 158.3 (C), 131.8 (CH), 129.3 (C), 127.6 (2 x CH), 125.2 (CH), 113.7 (2 x CH), 91.1 (C), 79.0 (C), 76.9 (CH), 55.2 (CH_3), 52.4 (CH_3), 47.9 (CH_2), 47.8 (CH), 38.3 (CH), 30.9 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 20.6 (CH_2), 19.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{24}H_{33}N_2O_7$ $[M+NH_4]^+$: 461.2282, found: 461.2283.



237

20

(2*R*,3*S*,4*R*)-2-[(6*S*)-(7*S*)-Cyclohex-2-enylhydroxymethyl]-3-hydroxy-4-(2-hydroxyet 1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (20) To a solution of the lactone **237**(19.3 mg, 0.043 mmol) in MeOH (0.6 mL) at room temperature was added $NaBH_4$ (75 mg, 2.0 mmol) portionwise over 2 min. The solution was stirred for 18 h, quenched with H_2O (4 mL) and extracted with EtOAc (3 x 4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (70% EtOAc/petrol) gave triol **20** (11.7 mg, 60%) as a white foam. R_f (70% EtOAc in $CHCl_3$) = 0.12; m.p. = 82-83 ºC, lit.^{26} 83-84 ºC; $[\alpha]^{22}_{D}$ +3.5 (*c* 0.56, $CHCl_3$), lit.^{26} +5.2 (*c* 0.60, $CHCl_3$); IR (film) 3331(OH), 2925, 2853, 1752 (C=O), 1670 (C=O), 1512, 1441, 1245, 1175, 1034 cm^{-1}; ^{1}H NMRHH (250 MHz, $CDCl_3$) δ 7.29 (2H, d, J = 8.7 Hz, Ar**H**), 6.85 (2H, d, J = 8.7 Hz, Ar**H**), 5.93 (1H, dm, J = 10.2 Hz, C**H**=CH), 5.62 (1H, dm, J = 10.2 Hz, C**H**=CH), 4.76 (1H, d, J = 15.2 Hz, $\mathbf{NCH_A}H_B$Ar), 4.39 (1H, d, J = 15.2 Hz, $NCH_A\mathbf{H_B}$Ar), 4.15 (1H, t, J = 6.3 Hz, C**H**OH), 3.87-3.81 (1H, m, $HOC\mathbf{H_C}H_DCH_2$), 3.80-3.75 (1H, m, $HOCH_C\mathbf{H_D}CH_2$), 3.79 (3H, s, $\mathbf{OCH_3}$), 3.71 (3H, s, $\mathbf{OCH_3}$), 3.02 (1H, dd, J = 8.1, 4.8 Hz, COC**H**), 2.20 (1H, bs, CHOHC**H**), 2.01 (2H, bs, $\mathbf{CH_2}$), 1.93-1.78 (2H, m, $\mathbf{CH_2}$), 1.76-1.65 (2H, m, $\mathbf{CH_2}$), 1.64 (3H, s, $\mathbf{CH_3}$CO), 1.54-1.41 (2H, m, $\mathbf{CH_2}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.5 (C), 169.7 (C), 158.2 (C), 132.9 (CH), 130.2 (C), 128.0 (2 x CH), 124.8 (CH), 113.6 (2 x CH), 81.8 (C), 80.6 (C), 77.2 (CH), 61.7 (CH_2), 55.2 (CH_3), 51.9 (CH), 51.3 (CH_3), 47.8 (CH_2), 38.6 (CH), 28.2 (CH_2), 26.8 (CH_2), 25.0 (CH_2), 21.2 (CH_3), 20.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{24}H_{33}NO_7Na$ $[M+Na]^+$: 470.2149, found: 470.2150.

Comparison of ^{13}C NMR in $CDCl_3$ for **20**.

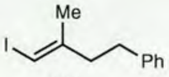
HWL data referenced at 77.0 ppm	Corey data referenced at 77.38 ppm (data referenced at 77.0 ppm)	Δ ppm	Pattenden data referenced at 77.03 ppm	Δ ppm
178.5	178.99 (178.61)	–0.11	178.8	–0.3
169.7	170.12 (169.74)	–0.04	169.7	0
158.2	158.27 (157.89)	+0.31	158.2	0
132.9	131.30 (130.92)	**+1.98**	132.6	+0.3
130.2	130.55 (130.17)	+0.03	130.7	–0.5
128.0	128.13 (127.75)	+0.25	128.2	–0.2
124.8	126.39 (126.01)	**–1.21**	125.1	–0.3
113.7	113.74 (113.36)	+0.34	113.7	0
81.8	81.93 (81.55)	+0.25	81.8	0
80.6	80.75 (80.37)	+0.23	80.6	0
77.2	76.87 (76.49)	**+0.71**	77.2	0
61.7	61.61 (61.23)	+0.47	61.6	+0.1
55.2	55.45 (55.07)	+0.13	55.2	0
51.9	51.97 (51.59)	+0.31	51.9	0
51.3	51.32 (50.94)	+0.36	51.3	0
47.8	48.07 (47.69)	+0.11	47.9	–0.1
38.6	39.17 (38.22)	+0.38	38.7	– 0.1
28.2	27.71 (27.82)	+0.38	28.0	+0.2
26.8	27.13 (26.75)	+0.05	26.8	0

25.0	25.22 (24.84)	+0.16	25.0	0
21.2	21.35 (20.97)	+0.23	21.1	+0.1
20.6	21.22 (20.84)	–0.62	20.7	–0.1

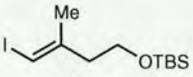
3.3 Reduction of α,β unsaturated heteroarenes

Preparation of Alkenyl Iodides

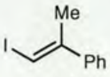
Alkenyl iodides **447**,[2] **450**,[3] and **446**[4] were prepared according to previously reported procedures.



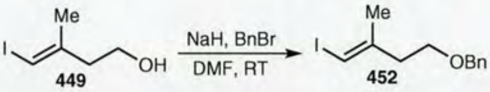
447



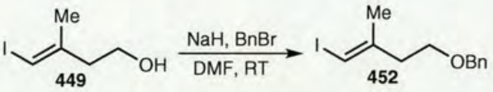
450



446



[(*E*)-4-Iodo-3-methylbut-3-enyloxymethyl]benzene (452) To a stirred suspension of NaH (60% dispersion in mineral oil, 280 mg, 7.00 mmol) in DMF (40 mL) at 0 °C was added the alcohol **449** (1.06 g, 5.00 mmol) in DMF (10 mL) *via* cannula over 2 min and the resulting mixture was stirred at room temperature for 15 min. BnBr (713 μL, 5.99 mmol) was then added over 1 min and the mixture was stirred at room temperature for 5 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→5% EtOAc/hexane) gave the *benzyl ether* **452**(1.43 g, 95%) as a pale yellow oil. IR (film) 3052, 2981, 2934, 1706, 1638, 1584, 1563, 1465, 1431, 1390, 1366, 1254, 1206, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.20 (5H, m, Ar**H**), 5.91 (1H, q, J = 1.0 Hz, C**H**=), 4.43 (2H, s, C**H**$_2$Ph), 3.48 (2H, t, J = 6.6 Hz, C**H**$_2$OCH$_2$Ph), 2.44 (2H, t, J = 6.6 Hz, C**H**$_2$CH$_2$O), 1.79 (3H, d, J = 1.0 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 145.0 (C), 138.1 (C), 128.4 (2 x CH), 127.6 (3 x CH), 76.4 (CH), 72.9 (CH_2), 68.0 (CH_2), 39.4 (CH_2), 24.2 (CH_3).



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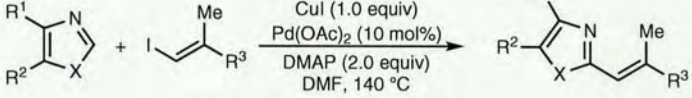
[2]. Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2007**, *9*, 2047–2049.

[3]. Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445–448.

[4]. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

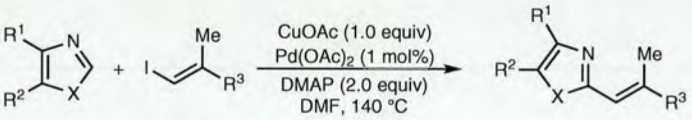
Preparation of 2-Alkenylheteroarenes

General Procedure A

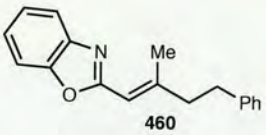


A solution of the appropriate heterocycle (2.00 mmol), the appropriate vinyl iodide (1.00 mmol), $Pd(OAc)_2$ (23 mg, 0.10 mmol), CuI (191 mg, 1.00 mmol), and DMAP (244 mg, 2.00 mmol) in DMF (2 mL) was heated at 140 °C for 15 min in a microwave synthesizer. The mixture was diluted with Et_2O (10 mL) and washed with saturated aqueous NH_4Cl solution (3 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the 2-alkenylheteroarene.

General procedure B



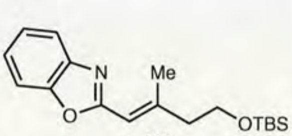
A solution of the appropriate heterocycle (2.00 mmol), the appropriate vinyl iodide (1.00 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), CuOAc (126 mg, 1.00 mmol), and DMAP (244 mg, 2.00 mmol) in DMF (2 mL) was heated at 140 °C for 15 min in a microwave synthesizer. The mixture was diluted with Et_2O (10 mL) and washed with saturated aqueous NH_4Cl solution (3 x 15 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the 2-alkenylheteroarene.



460

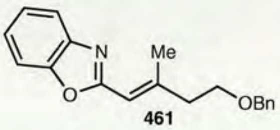
2-[(*E*)-2-Methyl-4-phenylbut-1-enyl]benzooxazole (**460**). The title compound was prepared according to General Procedure A from benzoxazole (243 mg, 2.00 mmol) and vinyl iodide **447** (272 mg, 1.00 mmol) and purified by column chromatography (hexane→1% EtOAc/hexane) to give a colorless oil (141 mg, 53%). IR (film)

3061, 3027, 2926, 2858, 1942, 1885, 1653, 1603, 1547, 1454, 1247, 1134, 1003, 953, 744, 699 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66-7.64 (1H, m, Ar**H**), 7.39-7.38 (1H, m, Ar**H**), 7.24-7.19 (4H, m, Ar**H**), 7.14-7.13 (3H, m, Ar**H**), 6.20 (1H, br s, C**H**=), 2.80-2.77 (2H, m, C**H$_2$**), 2.51-2.48 (2H, m, C**H$_2$**), 2.33 (3H, d, J = 0.8 Hz, C**H$_3$**); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 162.8 (C), 153.2 (C), 149.7 (C), 142.0 (C), 141.1 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.1 (CH), 124.5 (CH), 124.2 (CH), 119.6 (CH), 111.8 (CH), 110.2 (CH), 42.9, 34.2 (CH$_2$), 19.7 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{18}H_{18}NO$ [M+H]$^+$: 264.1383, found: 264.1383.



462

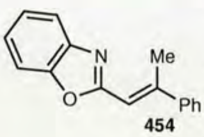
2-[(*E*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbut-1-enyl]benzooxazole (462). The title compound was prepared according to General Procedure B from benzoxazole (243 mg, 2.00 mmol) and vinyl iodide **450** (326 mg, 1.00 mmol) and purified by column chromatography (hexane→2% EtOAc/hexane) to give a colorless oil (133 mg, 42%). IR (film) 3054, 2954, 2928, 2901, 2857, 1936, 1773, 1651, 1548, 1454, 1361, 1250, 1101, 1003, 837, 776, 744 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72-7.70 (1H, m, Ar**H**), 7.51-7.49 (1H, m, Ar**H**), 7.33-7.29 (2H, m, Ar**H**), 6.31-6.30 (1H, m, C**H**=CCH$_3$), 3.85 (2H, t, J = 6.6 Hz, C**H$_2$**O), 2.51 (2H, dt, J = 6.6, 0.9 Hz, C**H$_2$**CH$_2$O), 2.39 (3H, d, J = 1.3 Hz, =CC**H$_3$**), 0.90 (9H, s, C(C**H$_3$**)$_3$), 0.07 (6H, s, Si(C**H$_3$**)$_2$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 162.7 (C), 151.2 (C), 149.7 (C), 141.9 (C), 124.5 (CH), 124.1 (CH), 119.6 (CH), 112.9 (CH), 110.2 (CH), 61.5 (CH$_2$), 44.3 (CH$_2$), 25.9 (3 x CH$_3$), 19.9 (CH$_3$), 18.2 (C), –5.4 (2 x CH$_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{28}NO_2Si$ [M+H]$^+$: 318.1884, found: 318.1879.



461

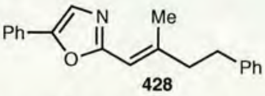
2-[(*E*)-4-Benzyloxy-2-methylbut-1-enyl]benzooxazole (461). The title compound was prepared according to General Procedure B from benzoxazole (243 mg, 2.00 mmol) and vinyl iodide **452** (302 mg, 1.00 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a colorless oil (116 mg, 39%). IR (film) 3062, 3029, 2858, 1652, 1546, 1453, 1361, 1247, 1101, 1076 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$)

δ 7.72-7.71 (1H, m, Ar**H**), 7.51-7.49 (1H, m, Ar**H**), 7.36-7.35 (4H, m, Ar**H**), 7.32-7.30 (3H, m, Ar**H**), 6.36-6.35 (1H, m, C**H**=CCH$_3$), 4.57 (2H, s, C**H**$_2$Ph), 3.71 (2H, t, J = 6.6 Hz, CH$_2$C**H**$_2$O), 2.62 (2H, td, J = 6.6, 0.9 Hz, C**H**$_2$CH$_2$O), 2.40 (3H, d, J = 1.3 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 162.5 (C), 150.8 (C), 149.6 (C), 141.8 (C), 138.0 (C), 128.3 (2 x CH), 127.5 (3 x CH), 124.4 (CH), 124.0 (CH), 119.5 (CH), 112.6 (CH), 110.1 (CH), 72.9 (CH$_2$), 67.9 (CH$_2$), 40.9 (CH$_2$), 19.6 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{19}$H$_{20}$NO$_2$ [M+H]$^+$: 294.1489, found: 249.1482.



454

(*E*)-2-Phenylpropenyl]benzooxazole (454). The title compound was prepared according to General Procedure A from benzoxazole (243 mg, 2.00 mmol) and vinyl iodide **446** (244 mg, 1.00 mmol) and purified by column chromatography (hexane→1% EtOAc/hexane) to give a colorless oil (93 mg, 39%). IR (CHCl$_3$) 3059, 2919, 1945, 1890, 1630, 1541, 1452, 1249, 1150, 1140, 1003, 763, 744 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.79-7.77 (1H, m, Ar**H**), 7.62-7.60 (2H, m, Ar**H**), 7.56-7.54 (1H, m, Ar**H**), 7.46-7.33 (5H, m, Ar**H**), 6.82 (1H, br d, J = 1.2 Hz, C**H**=), 2.83 (3H, d, J = 1.2 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 162.9 (C), 149.8 (C), 142.2 (C), 142.0 (C), 128.7 (CH), 128.5 (2 x CH), 126.2 (2 x CH), 124.8 (CH), 124.3, (CH) 119.8 (CH), 112.7 (CH), 110.2 (CH), 18.7 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{16}$H$_{14}$NO [M+H]$^+$: 236.1070, found: 236.1066.



428

2-[(*E*)-2-Methyl-4-phenylbut-1-enyl]-5-phenyloxazole (428). The title compound was prepared according to a slight modification of General Procedure A from 5-phenyloxazole[5] (581 mg, 4.00 mmol), vinyl iodide **447** (544 mg, 2.00 mmol), Pd(OAc)$_2$ (65 mg, 0.29 mmol), CuI (381 mg, 2.00 mmol), and DMAP (489 mg, 4.00 mmol) in DMF (5 mL) at 150 °C for 20 min and purified by column chromatography (hexane→3% EtOAc/hexane) to give a yellow gum (126 mg, 22%). IR (CHCl$_3$) 3061, 3027, 2927, 1694, 1494, 1450, 1226, 1025 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.56-7.52 (2H, m, Ar**H**), 7.34-7.27 (3H, m, Ar**H**), 7.25-7.19 (3H, m, Ar**H**) 7.14-7.11 (3H, m, Ar**H**), 6.12 (1H, s, C**H**=CCH$_3$), 2.80-2.74 (2H,

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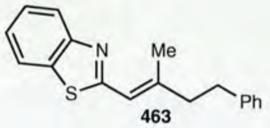
[5]. Besselievre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278–3280.

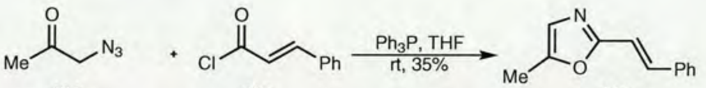
m, C**H**$_2$), 2.49-2.43 (2H, m, C**H**$_2$), 2.24 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 161.1 (C), 149.6 (C), 148.4 (C), 141.2 (C), 128.8 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 128.1 (C), 128.0 (CH), 126.0 (CH), 123.9 (2 x CH), 122.8 (CH), 111.7 (CH), 42.6 (CH$_2$), 34.2 (CH$_2$), 19.2 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{20}NO$ [M+H]$^+$: 290.1539, found: 290.1536.



463

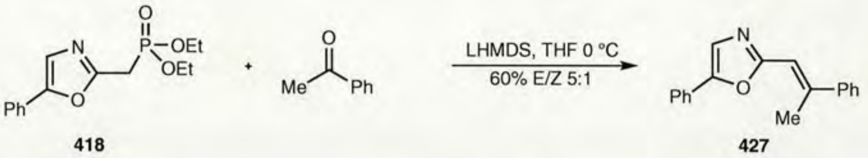
2-[(*E*)-2-Methyl-4-phenylbut-1-enyl]benzothiazole (463). The title compound was prepared according to General Procedure A from benzothiazole (270 mg, 2.00 mmol) and vinyl iodide **447** (272 mg, 1.00 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a pale yellow solid (242 mg, 43%). m.p. 56-58 °C; IR (CHCl$_3$) 3060, 3026, 2925, 1635, 1495, 1454, 1433, 1311, 1107, 758, 727, 698 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.02 (1H, dm, J = 8.1 Hz, Ar**H**), 7.87 (1H, dm, J = 8.1 Hz, Ar**H**), 7.49-7.46 (1H, m, Ar**H**), 7.38-7.31 (3H, m, Ar**H**), 7.25-7.21 (3H, m, Ar**H**), 6.65 (1H, q, J = 1.2 Hz, C**H**=CCH$_3$), 2.93-2.89 (2H, m, C**H**$_2$), 2.63-2.60 (2H, m, C**H**$_2$), 2.33 (3H, d, J = 1.2 Hz, C**H**$_3$); ^{13}C NMR (201.1 MHz, CDCl$_3$) δ 165.3 (C), 153.1 (C), 148.6 (C), 141.1 (C), 134.7 (C), 128.4 (2 x CH), 128.2 (2 x CH), 126.0 (2 x CH), 124.6 (CH), 122.6 (CH), 121.1 (CH), 119.6 (CH), 43.1 (CH$_2$), 34.2 (CH$_2$), 19.6 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{18}NS$ [M+H]$^+$: 280.1154, found: 280.1157.

Initial approach through oxazol formation

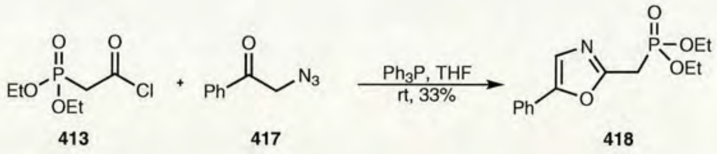


414 415 416

(E)-5-methyl-2-styryloxazole (416) To a solution of Ph$_3$P (4.45 g, 17 mmol) in THF (50 mL) at rt was added azide (0.99 g, 10 mmol) and acid chloride (1.66 g, 10 mmol). The resultant mixture was stirred for 12 h and then filtered. Purification of the residue by column chromatography (15% EtOAc/hexane → 25% EtOAc/hexane) gave **416** (690 mg, 37%). ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.44 (3H, m, Ar**H**), 7.29 (3H, m, Ar**H** + =C**H**), 6.88 (1H, d, J = 16.4, =C**H**), 6.75 (1H, bs, Ox**H**), 2.27 (3H, d, J = 1.1, C$\mathbf{H}_3$); LRMS (ESI) $[M+H]^+$: 186.1. [6]



(E)-5-phenyl-2-(2-phenylprop-1-enyl)oxazole (427) To a solution of phosphonoacetate **418** (1.18 g, 4 mmol) in THF (50 mL) was added LHMDS dropwise at 0 °C under nitrogen. After 30 min, acetophenone (0.56 mL, 4.8 mmol) was added. After 3 d reaction was quenched with NH_4Cl(aq), extracted with DCM dried over Na_2SO_4. Crude mixture was dissolved in small amount of EtOH and 400 mg of $NaBH_4$ was added to reduce excess of acetophenone after 30 min quenched with NH_4Cl(aq), extracted with DCM dried over Na_2SO_4. Purification of the residue by column chromatography (10% EtOAc/hexane → 20% EtOAc/hexane) gave **427** (624 mg, 60%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73–7.26 (11H, m, Ar**H**), 6.72 (1H, q, J = 1.1 Hz, =C**H**), 2.71 (3H, d, J = 1.3 Hz, C$\mathbf{H}_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.3 (C) , 150.1 (C), 145.5 (C) , 142.5 (C), 128.9 (2 x CH), 128.5 (CH), 128.2 (CH), 128.0 (C), 126.0 (CH), 124.1 (CH), 123.3 (CH), 112.7 (CH) , 18.3 (CH_3); LRMS (ESI) $[M+H]^+$: 262.1.



diethyl (5-phenyloxazol-2-yl)methylphosphonate (418) To a solution of Ph_3P (47 g, 179 mmol) in THF (150 mL) at rt was added azide (17 g, 105 mmol) and acid chloride (22.6 g, 105 mmol). The resultant mixture was stirred for 12 h and then filtered. Purification of the residue by column chromatography (10% EtOAc/hexane → 30% EtOAc/hexane) gave **418** (9.3 g, 30%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.66–7.17 (6H, m, Ar**H**), 4.17–4.05 (4H, m, 2 x OC$\mathbf{H}_2$CH$_3$), 3.40 (2H, d, J = 21.3 Hz, PC$\mathbf{H}_2$),

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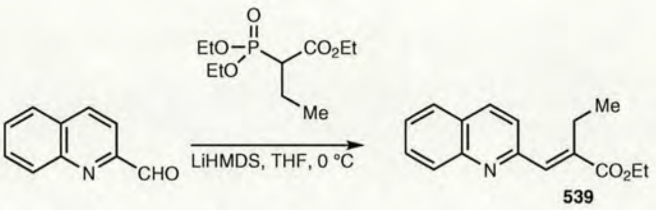
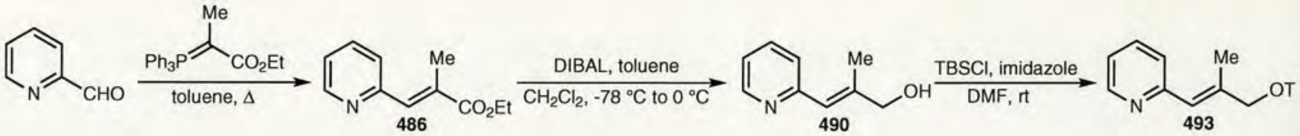
[6]. Stephen, A.; Hashmi, K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, 6, 4391–4394.

1.25 (6H, bt, J = 7.1 Hz, 2 x $OCH_2C\mathbf{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 154.8 (C), 151.0 (C), 132.9 (C), 127.8 (CH), 127.4 (CH), 123.1 (CH), 121.4 (CH), 61.8 (2 x CH_2), 26.5 (CH_2), 15.4 (2 x CH_3); LRMS (ESI) $[M+H]^+$: 296.2.

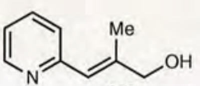


(E/Z)-ethyl 2-(quinolin-2-ylmethylene)butanoate (495) To a solution of triethyl 2-phosphonobutyrate (1.26 g, 5 mmol) in THF (50 mL) at –78 °C was added LiHMDS (1 M in THF, 6.0 mL, 6.0 mmol) over 5 min, and the resulting solution was stirred at the same temperature for 15 min and then warmed to 0 °C. 2-Quinolinecarboxaldehyde (643 mg, 6.0 mmol) was then added over 1 min and the mixture was stirred at 0 °C for 4 h before being quenched carefully with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with Et_2O (3 x 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) gave the alkene **495** (114 g, 45%) as a pale yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.31 (2H, dd, J = 8.3, 5.0 Hz, Ar**H**), 8.00 (1H, m, Ar**H**), 7.97 (s, 1H, =C**H**), 7.91 (1H ddd, J = 8.4, 6.9, 1.5 Hz, Ar**H**), 7.73 (1H, dd, J = 11.2, 3.8 Hz, Ar**H**), 7.64 (1H, d, J = 8.5 Hz, Ar**H**), 4.53 (1H, q, J = 7.1 Hz, $OC\mathbf{H}_2$), 3.19 (2H, q, J = 7.4 Hz, $=CC\mathbf{H}_2$), 1.58 (3H, t, J = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.46 (3H, t, J = 7.4 Hz, $=CCH_2C\mathbf{H}_3$); LRMS (ESI) $[M+H]^+$: 256.1.

Preparation of Alkene 493



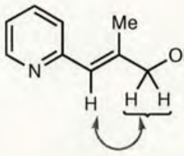
Ethyl($\boldsymbol{E}$)-2-methyl-3-(pyridin-2-yl)propenoate (486). A solution of 2-pyridinecarboxal (1.90 mL, 20.0 mmol) and (carbethoxyethylidene)-triphenylphosphorane (94%, 8.70 g, 22.6 mmol) in toluene (200 mL) was heated under reflux for 18 h and then cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give the *alkene* **486** (1.91 g, 50%) as a pale yellow oil. IR (film) 3052, 2981, 2934, 1706, 1638, 1584, 1563, 1465, 1431, 1390, 1366, 1254, 1206, 1120 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.68 (1H, ddd, J = 4.8, 1.8, 1.0 Hz, Ar**H**), 7.70 (1H, dt, J = 7.7, 1.8 Hz, Ar**H**), 7.64 (1H, app q, J = 1.5 Hz, C**H**=CCH_3), 7.37 (1H, app d, J = 7.9 Hz, Ar**H**), 7.19 (1H, ddd, J = 7.7, 4.8, 1.0 Hz, Ar**H**), 4.28 (2H, q, J = 7.1 Hz, $OC\mathbf{H}_2$), 2.33 (3H, d, J = 1.5 Hz, =$C\mathbf{H}_3$), 1.35 (3H, t, J = 7.1 Hz, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 168.6 (C), 155.2 (C), 149.5 (CH), 136.6 (CH), 136.1 (CH), 132.4 (C), 125.7 (CH), 122.4 (CH), 70.0 (CH_2), 14.2 (CH_3), 14.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{14}NO_2$ $[M+H]^+$: 192.1019, found: 192.1022.



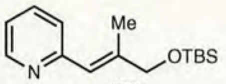
490

(*E*)-Methyl-3-(pyridin-2-yl)prop-2-en-1-ol (490). To a solution of the ester **486** (956 mg, 5.00 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added DIBAL (1.2 M in toluene, 8.75 mL, 10.5 mmol) over 2 min, and the resulting mixture was stirred at –78 °C for 2 h and then at 0 °C for 1 h. The reaction was quenched carefully with saturated aqueous Rochelle's salt solution (50 mL) and the resulting mixture was stirred vigorously for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/hexane) gave the *alcohol* **490** (553 mg, 74%) as a yellow oil. IR (film) 3273, 2910, 2852, 1662, 1589, 1564, 1471, 1433, 1375, 1076 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.57-8.55 (1H, m, Ar**H**), 7.66-7.61 (1H, m, Ar**H**), 7.24 (1H, app d, J = 7.9 Hz, Ar**H**), 7.11-7.08 (1H, m, Ar**H**), 6.65 (1H, br d, J = 1.1 Hz, C**H**=CCH_3), 4.19 (2H, s, $C\mathbf{H}_2O$), 3.72 (1H, br s, O**H**), 2.01 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.8 (C), 148.8 (CH), 143.0 (C), 136.1 (CH), 124.0 (CH), 123.1 (CH), 121.0 (CH), 67.8 (CH_2), 15.4 (CH_3); HRMS (ES) Exact mass calcd for $C_9H_{12}NO$ $[M+H]^+$: 150.0913, found: 150.0911.

The stereochemistry of alcohol **490** was determined using an NOE experiment, which displayed the following diagnostic enhancement:



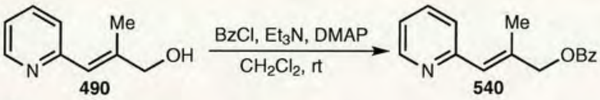
490



493

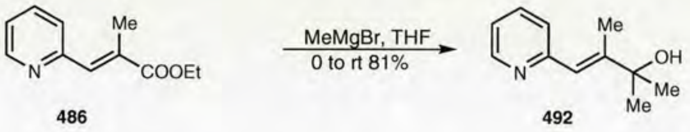
2-[(*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropenyl]pyrid (493). To a solution of the alcohol **490** (298 mg, 2.00 mmol) and imidazole (340 mg, 5.00 mmol) in DMF (10 mL) at room temperature was added a solution of TBSCl (392 mg, 2.60 mmol) in DMF (10 mL) *via* cannula over 3 min and the mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *silyl ether* **1g** (501 mg, 95%) as a pale yellow oil. IR (film) 2954, 2928, 2855, 1664, 1586, 1561, 1471, 1430, 1252, 1111, 1089 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.59 (1H, app d, $J = 4.7$ Hz, Ar**H**), 7.60 (1H, dt, $J = 7.7, 1.8$ Hz, Ar**H**), 7.22 (1H, app d, $J = 7.9$ Hz, Ar**H**), 7.08-7.04 (1H, m, Ar**H**), 6.61 (3H, s, C**H**=CCH_3), 4.20 (2H, s, $\mathbf{CH_2}O$), 2.03 (3H, s, $\mathbf{CH_3}$), 0.95 (9H, s, $C(\mathbf{CH_3})_3$), 0.12 (6H, s, $Si(\mathbf{CH_3})_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.2 (C), 149.1 (CH), 142.1 (C), 135.8 (CH), 124.0 (CH), 122.8 (CH), 120.7 (CH), 68.1 (CH_2), 25.9 (3 x CH_3), 18.4 (C), 15.2 (CH_3), –5.3 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{26}NOSi$ $[M+H]^+$: 264.1778, found: 264.1779.

(*E*)-2-Methyl-3-pyridin-2-ylpropenyl benzoate (540)



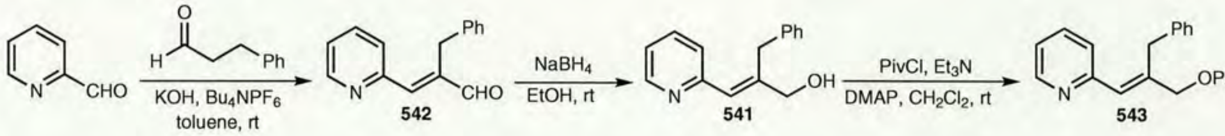
To a solution of the alcohol **490** (84 mg, 0.56 mmol), Et_3N (390 μL, 2.80 mmol), and DMAP (17 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at room temperature was added BzCl

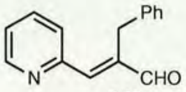
(140 μL, 1.21 mmol), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo.* Purification of the residue by column chromatography (20% EtOAc/hexane) gave the *benzoate ester* **540** (83 mg, 58%) as a colorless oil. IR (film) 2922, 1718 (C=O), 1585, 1450, 1313, 1269, 1111, 1068, 1026, 712 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (1H, d, J = 4.2 Hz, Ar**H**), 8.05-8.08 (2H, m, Ar**H**), 7.60-7.46 (2H, m, Ar**H**), 7.40-7.34 (2H, m, Ar**H**), 7.20-7.16 (1H, m, Ar**H**), 7.06-7.02 (1H, m, Ar**H**), 6.59 (1H, app br d, J = 1.2 Hz, C**H**=CCH_3), 4.84 (2H, s, C**H**$_2$O), 2.11 (3H, br d, J = 0.9 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.2 (C), 156.1 (C), 149.2 (CH), 137.2 (C), 136.0 (CH), 133.0 (CH), 130.0 (C), 129.6 (2 x CH), 128.3 (2 x CH), 126.7 (CH), 124.2 (CH), 121.3 (CH), 69.9 (CH_2), 15.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1176, found: 254.1172.



(E)-2,3-dimethyl-4-(pyridin-2-yl)but-3-en-2-ol (492) Purification of the residue by column chromatography (10% EtOAc/hexane → 30% EtOAc/hexane) gave **418** (9.3 g, 30%). A solution of methylmagnesium bromide (2 mL, 6 mmol, 3 M in THF) was added to ester **486** in 20 mL of THF at 0 °CReaction mixture was allowed to warm up to rt and was quanched after 1 h with NH_4Cl (aq). Crude product was extracted with EtOAc and dried over $MgSO_4$. Purification of the residue by column chromatography (10% EtOAc/hexane → 40% EtOAc/hexane) gave **492** (286 mg, 81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 4.1 Hz, Ar**H**), 7.71 (1H, td, J = 7.7, 1.9 Hz, Ar**H**), 7.31 (1H, d, J = 7.9 Hz, Ar**H**), 7.17 (1H, ddd, J = 7.5, 4.9, 1.0 Hz, **H**), 6.87 (1H, bs, =C**H**), 2.87 (1H, s, O**H**), 2.15 (3H, d, J = 1.3 Hz, =CC**H**$_3$), 1.54 (6H, s, 2 x C**H**$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 158.5 (C), 150.3 (C), 149.9 (CH), 136.9 (CH), 125.3 (CH), 122.9 (CH), 121.8 (CH), 74.8 (C), 29.8 (2 x CH_3), 15.7 (CH_3); LRMS (ESI) $[M+H]^+$: 178.1.

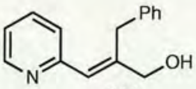
Preparation of Alkene 543





542

(Z)-2-Benzyl-3-pyridin-2-ylpropenal (542). Following a slight modification of a literature procedure for a similar compound, [7] to a vigorously stirred suspension of Bu_4NPF_6 (387 mg, 1.00 mmol) and KOH (84 mg, 1.50 mmol) in toluene (15 mL) was added 2-pyridinecarboxaldehyde (0.95 mL, 10.0 mmol) dropwise over 1 min, followed by hydrocinnamaldehyde (1.76 mL, 12.0 mmol) dropwise over 2 min. The reaction was stirred vigorously at room temperature for 5 h, and then partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→60% EtOAc/hexane) gave the *enal* **542** (819 mg, 37%) as a red-brown solid. m.p. 46-48 °C; IR ($CHCl_3$) 3059, 2924, 2823, 2717, 2360, 1684 (C=O), 1631 (C=C), 1579, 1308, 1136, 739; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (1H, s, C**H**O), 8.61-8.59 (1H, m, Ar**H**), 7.57 (1H, dt, J = 7.8, 1.9 Hz, Ar**H**), 7.29 (1H, d, J = 7.8 Hz, Ar**H**), 7.21-6.98 (7H, m, Ar**H** and C**H**=CCH$_2$Ph), 4.24 (2H, s, C**H**$_2$Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.3 (CH), 153.7 (C), 149.8 (CH), 147.6 (CH), 143.7 (C), 139.0 (C), 136.4 (CH), 128.6 (2 x CH), 128.1 (2 x CH), 126.2 (CH), 125.8 (CH), 123.7 (CH), 29.8 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{14}NO$ $[M+H]^+$: 224.1070, found: 224.1065.



541

(Z)-2-Benzyl-3-pyridin-2-ylprop-2-en-1-ol (541). To a solution of aldehyde **542**(447 mg, 2.00 mmol) in EtOH (10 mL) at room temperature was added $NaBH_4$ (227 mg, 6.00 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature for 1 h and quenched carefully with saturated aqueous NH_4Cl solution (20 mL). Most

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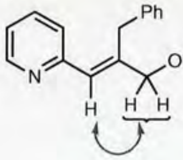
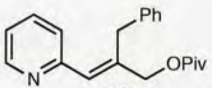
[7] Kryshtal, G. V.; Zhdankina, G. M.; Zlotin, S. G. *Eur. J. Org. Chem.* **2005**, 2822–2827.

of the EtOH was removed *in vacuo*, and the aqueous residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/hexane) gave the *alcohol* **541** (451 mg, 99%) as a cream solid. m.p. 67-69 °C; IR (film) 3273 (OH), 3025, 2906, 1659 (C=C), 1585, 1472, 1151, 1052, 733, 620 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.46-8.40 (1H, m, Ar**H**), 7.49 (1H, dt, J = 7.7, 1.8 Hz, Ar**H**), 7.16-7.03 (6H, m, Ar**H**), 7.00 (1H, ddd, J = 7.5, 4.9, 0.9 Hz, Ar**H**), 6.75 (1H, s, C**H**=CCH_2Ph), 4.04 (2H, d, J = 1.2 Hz, $\mathbf{CH_2}OH$), 3.88 (2H, s, $\mathbf{CH_2}Ph$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.3 (C), 148.8 (CH), 145.0 (C), 139.2 (C), 136.3 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 125.9 (CH), 124.3 (CH), 123.7 (CH), 121.3 (CH), 65.2 (CH_2), 34.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226, found: 226.1223.

The stereochemistry of alcohol **541** was determined using an NOE experiment, which displayed the following diagnostic enhancement:

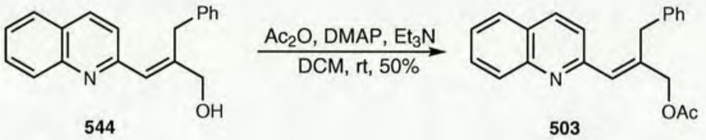


541



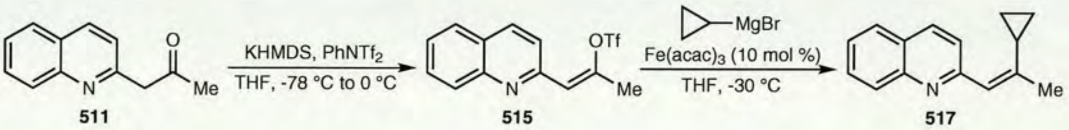
543

(Z)-2-Benzyl-3-pyridin-2-ylpropenyl pivaloate (543). To a solution of the alcohol **541**(338 mg, 1.50 mmol), Et_3N (638 μL, 4.50 mmol), and DMAP (18 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) at room temperature was added trimethylacetyl chloride (370 μL, 3.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *pivaloate ester* **543** (458 mg, 99%) as a colorless oil. IR (film) 2973, 1729 (C=O), 1658 (C=C), 1585, 1479, 1280, 1149, 1031, 740, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.50-8.48 (1H, m, Ar**H**), 7.49 (1H, dt, J = 7.7, 1.9 Hz, Ar**H**), 7.18-7.04 (6H, m, Ar**H**), 6.99 (1H, d, J = 7.6, 4.8, 1.1 Hz, Ar**H**), 6.59 (1H, s, C**H**=CCH$_2$Ph), 4.48 (2H, d, J = 1.3 Hz, C**H**$_2$O), 4.05 (2H, s, C**H**$_2$Ph), 1.10 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (90.6 MHz, CDCl$_3$) δ 177.8 (C), 155.6 (C), 149.1 (CH), 139.7 (C), 138.9 (C), 136.0 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.4 (CH), 126.0 (CH), 124.1 (CH), 121.6 (CH), 67.4 (CH$_2$), 38.7 (C), 34.4 (CH$_2$), 27.1 (3 x CH$_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_2$ [M+H]$^+$: 310.1802, found: 310.1802.



(E)-2-benzyl-3-(quinolin-2-yl)allyl acetate (503) To a solution of alcohol **544** (826 mg, 3 mmol), DMAP (91 mg, 0.75 mmol), Et$_3$N (1.6 mL, 12 mmol) in 20 mL of DCM at rt, was added acetic anhydride (643 mg, 6.3 mmol). After 2 h reaction mixture was quenched with NH$_4$Cl (aq). Crude product was extracted with EtOAc and dried over MgSO$_4$. Purification of the residue by column chromatography (10% EtOAc/hexane → 30% EtOAc/hexane) gave **503** (476 mg, 50%). ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.92 (1H, d, J = 8.5 Hz, Ar**H**), 7.87 (1H, d, J = 8.1 Hz, Ar**H**), 7.59 (1H, d, J = 8.0 Hz, Ar**H**), 7.50 (1H, ddd, J = 8.5, 6.9, 1.4 Hz, Ar**H**), 7.32 (1H, t, J = 7.5 Hz, Ar**H**), 7.24–6.91 (6H, m, Ar**H**), 6.70 (1H, s, =C**H**), 4.48 (2H, s, C**H**$_2$), 4.07 (2H, s, C**H**$_2$), 1.89 (3H, s, C**H**$_3$); ^{13}C NMR (63 MHz, CDCl$_3$) δ 171.0 (C), 156.1 (C), 148.3 (C), 141.5 (C), 139.5 (C), 136.5 (CH), 129.9 (CH), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.2 (CH), 127.8 (CH), 127.2 (C), 126.7 (CH), 126.6 (CH), 122.9 (CH), 67.8 (CH$_2$), 35.2 (CH$_2$), 21.3 (CH$_3$); LRMS (ESI) [M+H]$^+$: 317.1.

Preparation of Alkene 517



Trifluoromethanesulfonic acid (*Z*)-1-methyl-2-quinolin-2-yl vinyl ester (515). To a solution of the ketone **511**[8] (370 mg, 2.00 mmol) in THF (15 mL) at

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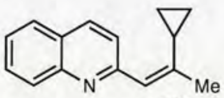
[8]. (a) Wolfe, J. F.; Murray, T. P. *J. Org. Chem.* **1971**, *36*, 354–357. (b) Langer, P.; Döring, M.; Seyferth, D.; Görls, H. *Chem. Eur. J.* **2001**, *7*, 573–584.

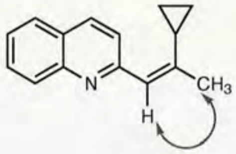
–78 °C was added KHMDS (0.5 M in toluene, 4.4 mL, 2.2 mmol) over 2 min. After 15 min, a solution of $PhNTf_2$ (857 mg, 2.40 mmol) in THF (5 mL) was added *via* cannula over 2 min and the mixture was stirred at –78 °C for 30 min before being warmed slowly to 0 °C over 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and the mixture was diluted with Et_2O (30 mL). The aqueous layer was separated an extracted with Et_2O (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by recrystallization from hot hexane gave the *vinyl triflate* **515** (423 mg, 67%) as an amorphous yellow solid. IR ($CHCl_3$) 3061, 2926, 1685, 1597, 1503, 1419, 1240, 1208, 1143, 1113, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.18-8.16 (2H, m, Ar**H**), 7.81-7.79 (1H, m, Ar**H**), 7.73 (1H, ddd, J = 8.4, 6.9, 1.4 Hz, Ar**H**), 7.57-7.53 (2H, m, Ar**H**), 6.53 (1H, q, J = 1.0 Hz, **CH**=CCH_3), 2.34 (3H, s, **CH$_3$**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 151.2 (C), 148.0 (C), 136.7 (CH), 130.0 (CH), 129.3 (CH), 127.4 (CH), 127.1 (CH), 127.1 (C), 121.4 (CH), 120.8 (CH), 118.3 (C, q, J_F = 320.0 Hz), 21.0 (CH_3); Exact mass calcd for $C_{13}H_{11}F_3NO_3S$ $[M+H]^+$: 318.0406, found: 310.0403.



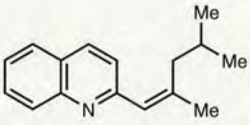
517

2-[(*Z*)-2-Cyclopropylpropenyl]quinoline (517). To a solution of the vinyl triflate **515** (317 mg, 1.00 mmol) and $Fe(acac)_3$ (35 mg, 0.10 mmol) in THF (20 mL) at –30 °C was added a solution of cyclopropylmagnesium bromide (0.5 M in THF, 4.0 mL, 2.0 mmol) rapidly in one portion and the mixture was stirred at –30 °C for 1 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL) and the mixture was diluted with Et_2O (30 mL). The aqueous layer was separated and extracted with Et_2O (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→5% EtOAc/hexane) gave the *trisubstituted alkene* **517** 172 mg, 82%) as a pale brown oil. IR (film) 3056, 3006, 2915, 1635, 1597, 1553, 1500, 1422, 1304, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.07-8.02 (2H, m, Ar**H**), 7.75 (1H, dd, J = 8.1, 1.3 Hz, Ar**H**), 7.66 (1H, ddd, J = 8.4, 6.9, 1.5 Hz, Ar**H**), 7.49-7.44 (2H, m, Ar**H**), 6.59 (1H, br s, **CH**=CCH_3), 2.89-2.81 (1H, m, =C**CH**), 1.70 (3H, d, J = 1.4 Hz, **CH$_3$**), 0.80-0.75 (4H, m, CH_2CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 157.6 (C), 147.9 (C), 146.0 (C), 135.5 (CH), 129.2 (CH), 129.1 (CH), 127.3 (CH), 126.3 (C), 126.1 (CH), 125.6 (CH), 122.7 (CH), 19.5 (CH_3), 13.8 (CH), 5.9 (2 x CH_2); Exact mass calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1277, found: 210.1281.

The stereochemistry of alkene **517** was determined using an NOE experiment, which displayed the following diagnostic enhancement:

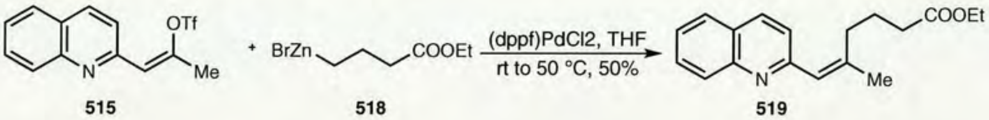


517



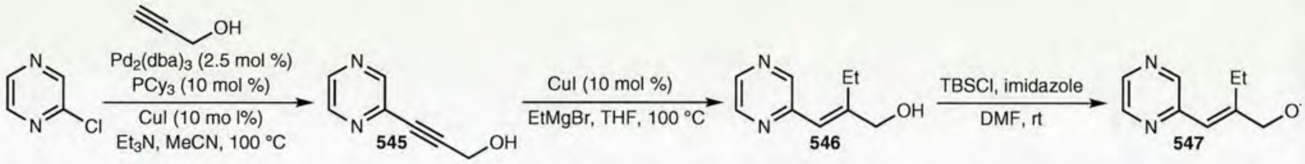
521

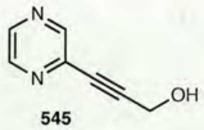
(Z)-2-(2,4-dimethylpent-1-enyl)quinoline (521) To a solution of the vinyl triflate **515** (1.26 g, 4.0 mmol) and $Fe(acac)_3$ (141 mg, 0.40 mmol) in THF (80 mL) at –30 °C was added a solution of isobutylmagnesium chloride (2.0 M in THF, 4.0 mL, 8.0 mmol) rapidly in one portion and the mixture was stirred at –30 °C for 1 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (60 mL) and the mixture was diluted with Et_2O (120 mL). The aqueous layer was separated and extracted with Et_2O (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the residue by column chromatography (hexane→5% EtOAc/hexane) gave the *trisubstituted alkene* **521** 567 mg, 63%) as a pale brown oil. ^1H NMR (250 MHz, $CDCl_3$) δ 7.96 (2H, dd, J = 8.3, 2.0 Hz, Ar**H**), 7.67 (1H, dd, J = 8.0, 1.3 Hz, Ar**H**), 7.59 (1H, ddd, J = 8.5, 6.9, 1.5 Hz, Ar**H**), 7.39 (1H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar**H**), 7.23 (1H, d, J = 8.5 Hz, Ar**H**), 6.48 (1H, s, =C**H**), 2.51 (2H, dd, J = 7.3, 0.7 Hz, =C$\mathbf{H_2}$), 1.98–1.79 (1H, m, C**H**$(CH_3)_2$) 1.91 (3H, d, J = 1.4 Hz, =C$\mathbf{H_3}$), 0.81 (6H, d, J = 6.7 Hz, 2 x C$\mathbf{H_3}$); LRMS (ESI) $[M+H]^+$: 226.2.



(Z)-ethyl 5-methyl-6-(quinolin-2-yl)hex-5-enoate (519) To a solution of enol triflate **515** (634 mg, 2.0 mmol) and $PdCl_2(dppf)$ (7 mg, 0.06 mmol) in THF (6 mL) was added a 0.5 M THF solution of 3-(ethoxycarbmetyl)-propylzinc bromide **518** (8.2 mL, 4.1 mmol). After being stirred for 2 h at 50 °C, a saturated aqueous $NaHCO_3$ solution was carefully added. Crude product was extracted with EtOAc and dried over $MgSO_4$. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave the *trisubstituted alkene* **519** 283 mg, 50%) as a pale brown oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.98 (2H, dd, J = 12.6, 8.5 Hz, Ar**H**), 7.68 (1H, dd, J = 8.1, 1.3 Hz, Ar**H**), 7.59 (1H, ddd, J = 8.4, 6.9, 1.5 Hz, Ar**H**), 7.40 (1H, ddd, J = 8.1, 6.9, 1.2 Hz, Ar**H**), 7.24–7.17 (1H, m, Ar**H**), 6.44 (1H, s, =C**H**), 3.97 (2H, q, J = 7.1 Hz, $COC\mathbf{H}_2$), 2.66–2.56 (2H, m, $=CC\mathbf{H}_2$), 2.28 (2H, t, J = 7.5 Hz, $EtO_2CC\mathbf{H}_2$), 1.91 (3H, d, J = 1.5 Hz, $=CC\mathbf{H}_3$), 1.89–1.79 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.10 (3H, t, J = 7.2 Hz, $OCH_2C\mathbf{H}_3$); LRMS (ESI) $[M+H]^+$: 284.2.

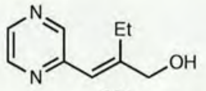
Preparation of Alkene 547





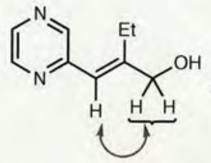
545

3-Pyrazin-2-ylprop-2-yn-1-ol (545). A solution of 2-chloropyrazine (440 μL, 5.00 mmol), $Pd_2(dba)_3$ (115 mg, 0.125 mmol), PCy_3 (140 mg, 0.50 mmol), CuI (95 mg, 0.50 mmol), and Et_3N (2.1 mL, 15 mmol) in MeCN (15 mL) was stirred at room temperature for 15 min. Propargyl alcohol (437 μL, 7.50 mmol) was then added and the mixture was heated at 100 °C for 24 h. After cooling to room temperature, the mixture was filtered through a short plug of celite, eluting with EtOAc (200 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution (200 mL), and aqueous layer was separated and extracted with EtOAc (200 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/hexane→ EtOAc) gave the *alkyne* **545** (147 mg, 22%) as a red amorphous solid. IR ($CHCl_3$) 3387 (OH), 2924, 1642, 1464, 1397, 1277, 1143, 1037, 964, 851 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.65 (1H, d, J = 1.5 Hz, Ar**H**), 8.52 (1H, dd, J = 2.6, 1.5 Hz, Ar**H**), 8.48 (1H, d, J = 2.6 Hz, Ar**H**), 4.54 (2H, s, **CH_2**O), 2.76 (1H, br s, O**H**); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 147.5 (CH), 144.2 (CH), 143.1 (CH), 139.6 (C), 92.4 (C), 81.5 (C), 50.8 (CH_2); Exact mass calcd for $C_7H_7N_2O$ $[M+H]^+$: 135.0553, found: 135.0554.

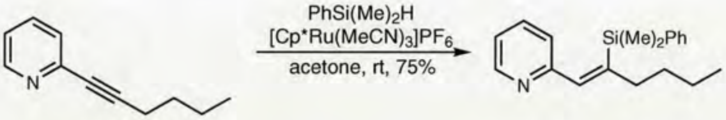

546

2-[(*E*)-1-Pyrazin-2-ylmethylidene]butan-1-ol (546). To a solution of CuI (19 mg, 0.10 mmol) in THF (4 mL) at room temperature was added EtMgBr (1 M in THF, 2.5 mL, 2.5 mmol), and the resulting dark brown solution was stirred for 10 min. The solution was then added *via* cannula to a suspension of the propargylic alcohol **545** (134 mg, 1.00 mmol) in THF (5 mL) in a microwave vial, using further THF (1 mL) as a rinse. The mixture was then heated to 100 °C for 10 min in a microwave synthesizer. After cooling to room temperature, the reaction was quenched carefully with 2 M HCl (20 mL), and saturated aqueous Na_2CO_3 solution (30 mL) was then added carefully. The mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (60% EtOAc/hexane→EtOAc) gave the *alkene* **546** (95 mg, 71%) as a yellow oil. IR (film) 3848, 2968, 1651, 1517, 1463, 1404, 1128, 1086, 1018, 873 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50 (1H, dd, J = 2.5, 1.5 Hz, Ar**H**), 8.44 (1H, br s, Ar**H**), 8.29 (1H, d, J = 2.5 Hz, Ar**H**), 6.55 (1H, s, C**H**=CCH_2), 4.25 (2H, d, J = 1.2 Hz, **CH_2**O), 3.58 (1H, br s, O**H**), 2.54 (2H, q, J = 7.5 Hz, **CH_2**CH_3), 1.08 (3H, t, J = 7.5 Hz, CH_2**CH_3**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.6 (C), 152.4 (C), 144.9 (CH), 143.8 (CH), 141.0 (CH), 118.3 (CH), 65.6 (CH_2), 22.3 (CH_2), 12.8 (CH_3); Exact mass calcd for $C_9H_{13}N_2O$ $[M+H]^+$: 165.1022, found: 165.1023.

The stereochemistry of alkene **546** was determined using an NOE experiment, which displayed the following diagnostic enhancement:


546

2-[(*E*)-2-(*tert*-Butyldimethylsilyloxymethyl)but-1-enyl]pyrazine (547). To a solution of the alcohol **546** (82 mg, 0.50 mmol) and imidazole (85 mg, 1.25 mmol) in DMF (2 mL) at room temperature was added TBSCl (98 mg, 0.65 mmol) in one portion, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture was extract with Et_2O (2 x 25 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (2.5% EtOAc/hexane→5% EtOAc/hexane) gave the *silyl ether* **547** (100 mg, 72%) as a yellow oil. IR (film) 3424, 2955, 2929, 2856, 1654 (C=C), 1463, 1258, 1115, 837, 768 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53 (1H, s, Ar**H**), 8.46 (1H, s, Ar**H**), 8.31 (1H, s, Ar**H**), 6.56 (1H, s, **CH**=CCH_2), 4.26 (2H, d, J = 1.6 Hz, $\mathbf{CH_2}O$), 2.56 (2H, q, J = 7.5 Hz, $\mathbf{CH_2}CH_3$), 1.11 (3H, t, J = 7.5 Hz, $CH_2\mathbf{CH_3}$), 0.96 (9H, s, $C(\mathbf{CH_3})_3$), 0.12 (6H, s, $Si(\mathbf{CH_3})_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.8 (C), 152.0 (C), 145.3 (CH), 143.8 (CH), 141.0 (CH), 117.9 (CH), 66.0 (CH_2), 25.9 (3 x CH_3), 22.2 (CH_2), 18.4 (C), 13.0 (CH_3), –5.4 (2 x CH_3); Exact mass calcd for $C_{15}H_{27}N_2OSi$ $[M+H]^+$: 279.1887, found: 279.1887.

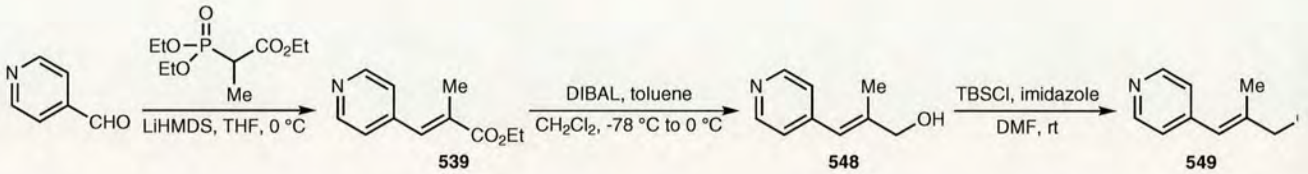


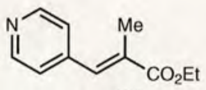
475

476

(Z)-2-(2-(dimethyl(phenyl)silyl)hex-1-enyl)pyridine (476) The alkyne **475** (318 mg, 2 mmol), was dissolved in DCM (0.5 M solution) and treated with diethylphenylsilane (327 mg, 2.4 mmol). The flask was cooled to 0 °C, and catalyst (10 mg, 0.02 mmol) was added at this temperature. The flask was immediately allowed to warm to ambient temperature and stirred for 30 min. The crude reaction mixture was concentrated under reduced pressure. Purification of the residue by column chromatography (hexane → 15% EtOAc/hexane) gave **476** (449 mg, 75%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.15 (1H, dd, J = 4.8, 0.9 Hz, Ar**H**), 7.48–7.31 (3H, m, Ar**H**), 7.21–7.09 (3H, m, Ar**H**), 6.97 (1H, d, J = 7.8 Hz, Ar**H**), 7.03 (1H, s, =**CH**), 6.84 (1H, ddd, J = 7.3, 4.8, 0.9 Hz, Ar**H**), 2.39–2.17 (2H, m, =CC**H**$_2$), 1.47–1.14 (4H, m, CH$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.79 (3H, t, J = 7.2 Hz, C**H**$_3$), 0.31 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (63 MHz, CDCl$_3$) δ 155.9 (C), 148.0 (C), 147.7 (CH), 141.7 (C), 140.5 (CH), 135.6 (CH), 133.2 (CH), 127.7 (CH), 127.1 (CH), 122.9 (CH), 121.1 (CH), 39.3 (CH$_2$), 32.7 (CH$_2$), 22.5 (CH$_2$), 13.9 (CH$_3$), 0.0 (CH$_3$); LRMS (ESI) [M+H]$^+$: 196.2.

Preparation of Alkene 549

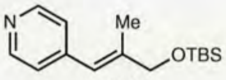




539

Ethyl (*E*)-2-methyl-3-(pyridin-4-yl)propenoate (539). To a solution of triethyl 2-phosphonopropionate (5.1 mL, 24 mmol) in THF (200 mL) at –78 °C was added LiHMDS (1 M in THF, 28.0 mL, 28.0 mmol) over 5 min, and the resulting solution was stirred at the same temperature for 15 min and then warmed to 0 °C. 4-Pyridinecarboxaldehyde (1.90 mL, 20.0 mmol) was then added over 1 min and the mixture was stirred at 0 °C for 4 h before being quenched carefully with saturated aqueous NH$_4$Cl (100 mL). The mixture was extracted with Et$_2$O (3 x 150 mL), and the combined organic layers were dried (MgSO$_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) gave the alkene **539** (1.60 g, 41%) as a pale yellow oil. IR (film) 3430, 1710 (C=O), 1641 (C=C), 1366, 1330, 1261, 1198, 1114, 1030, 809 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.67 (2H, br s, Ar**H**), 7.57 (1H, s, C**H**=CCH$_3$), 7.26 (2H, br s, Ar**H**), 4.29 (2H, q, J = 7.1 Hz, OC**H**$_2$), 2.10 (3H, d, J = 1.5 Hz, =CC**H**$_3$), 1.36 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (90.6 MHz, CDCl$_3$) δ 167.8 (C), 149.9 (2 x CH), 143.5 (C), 135.5 (3 x CH), 132.6 (C) , 61.2 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); Exact mass calcd for C$_{11}$H$_{14}$NO$_2$ [M+H]$^+$: 192.1019, found: 192.1020.

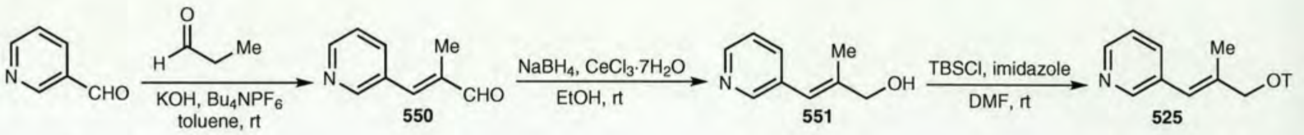
(*E*)-Methyl-3-(pyridin-4-yl)prop-2-en-1-ol (548). To a solution of the ester **539** (382 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added DIBAL (25 wt. % in toluene, 3.1 mL, 4.6 mmol) over 2 min, and the resulting mixture was stirred at –78 °C for 1.5 h, then at –20 °C for 1 h, and finally at –10 °C for 2 h. The reaction was quenched carefully with saturated aqueous Rochelle's salt solution (50 mL) and the resulting mixture was stirred vigorously for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to leave the *alcohol* **548** as a white solid which was used immediately in the next step without further purification.

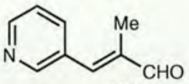


549

4-[(*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropenyl]-pyridine (549). To a solution of the above alcohol **548** (theoretically 2.00 mmol) in DMF (10 mL) at room temperature was added imidazole (340 mg, 5.00 mmol) followed by TBSCl (452 mg, 3.00 mmol) in one portion. The mixture was stirred at room temperature for 1 h and then partitioned between Et_2O (80 mL) and saturated aqueous NH_4Cl solution (100 mL). The organic layer was separated and washed with further saturated aqueous NH_4Cl solution (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→15% EtOAc/hexane) gave the *silyl ether* **549** (402 mg, 76% over two steps) as a colorless oil. IR (film) 3431, 2954, 2856, 1596 (C=C), 1471, 1255, 1169, 1111, 838, 777 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53 (2H, d, J = 5.2 Hz, Ar**H**), 7.16 (2H, m, Ar**H**), 6.48 (1H, br s, C**H**=CCH$_3$), 4.18 (2H, d, J = 0.8 Hz, C**H**$_2$O), 1.84 (3H, d, J = 0.7 Hz, =CC**H**$_3$), 0.95 (9H, s, C(C**H**$_3$)$_3$), 0.12 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.5 (2 x CH), 145.6 (C), 142.0 (C), 123.6 (2 x CH), 120.9 (CH), 67.7 (CH_2), 25.9 (3 x CH_3), 18.4 (C), 15.1 (CH_3), –5.4 (2 x CH_3); Exact mass calcd for $C_{15}H_{26}NOSi$ $[M+H]^+$: 264.1778, found: 264.1778.

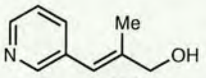
Preparation of Alkene 525





550

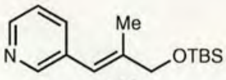
(*E*)-2-Methyl-3-pyridin-3-ylpropenal (550). Following a literature procedure for a similar compound, to a vigorously stirred suspension of Bu_4NPF_6 (194 mg, 0.50 mmol) and KOH (42 mg, 0.75 mmol) in toluene (8 mL) was added 3-pyridinecarboxaldehyde (469 μL, 5.00 mmol) dropwise over 1 min, followed by propionaldehyde (437 μL, 6.00 mmol) dropwise over 2 min. The reaction was stirred vigorously at room temperature for 5 h, diluted with toluene (10 mL), and washed with H_2O (2 x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→40% EtOAc/hexane) gave the *enal* **550** (551 mg, 75%) as a white solid. m.p. 36-38 °C; IR ($CHCl_3$) 3433, 2110, 1675 (C=O), 1640 (C=C), 1430, 1361, 1260, 1200, 1013, 709 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.60 (1H, s, C**H**O), 8.75 (1H, br s, Ar**H**), 8.58 (1H, app dd, J = 4.8, 1.4 Hz, Ar**H**), 7.87 (1H, app dt, J = 8.0, 1.8 Hz, Ar**H**), 7.41-7.36 (1H, m, Ar**H**), 7.27 (1H, br s, C**H**=CCH_3), 2.03 (3H, d, J = 1.4 Hz, C**H$_3$**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.0 (CH), 150.1 (CH), 149.4 (CH), 144.8 (CH), 139.3 (C), 135.8 (CH), 130.3 (C), 122.8 (CH), 10.2 (CH_3); LRMS (ES) 148 ($[M+H]^+$, 100).



551

(*E*)-Methyl-3-(pyridin-3-yl)prop-2-en-1-ol (551). To a solution of aldehyde **550** (545 mg, 3.70 mmol) and $CeCl_3 \cdot 7H_2O$ (1.65 g, 4.44 mmol) in EtOH (30 mL) at room temperature was added $NaBH_4$ (148 mg, 3.89 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature for 18 h and quenched carefully with saturated aqueous NH_4Cl solution (25 mL). Most of the EtOH was removed *in vacuo*, and the aqueous residue was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc) gave the *alcohol* **551** (410 mg, 74%) as a yellow oil. IR (film) 3398 (OH), 2857, 1645 (C=C), 1479, 1416, 1197, 1074, 1027, 843, 713 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ

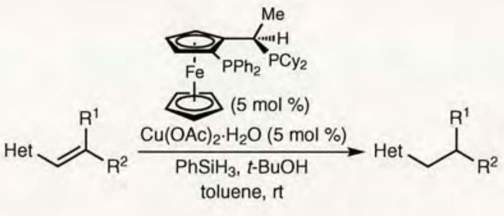
8.34 (1H, br s, Ar**H**), 8.25 (1H, app d, J = 4.4 Hz, Ar**H**), 7.49-7.44 (1H, m, Ar**H**), 7.13 (app dd, J = 7.8, 4.9 Hz, Ar**H**), 6.42 (1H, s, C**H**=CCH_3), 5.56 (1H, s, O**H**), 4.10 (2H, s, $\mathbf{CH_2}O$), 1.73 (3H, br s, $\mathbf{CH_3}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.1 (CH), 146.2 (CH), 141.2 (C), 135.9 (CH), 133.6 (C), 123.0 (CH), 119.4 (CH), 67.0 (CH_2), 14.9 (CH_3); LRMS (ES) 150 ($[M+H]^+$, 100).



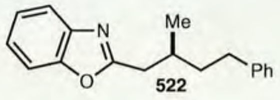
525

3-[(*E*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropenyl]pyrid (525). To a solution of the alcohol **551** (149 mg, 1.00 mmol) and imidazole (170 mg, 2.50 mmol) in DMF (2 mL) at room temperature was added TBSCl (196 mg, 1.30 mmol) in one portion, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine (20 mL). The brine layer was separated and extracted with Et_2O (2 x 25 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *silyl ether* **525** (247 mg, 94%) as a yellow oil. IR (film) 3432, 2954, 2856, 1642 (C=C), 1472, 1415, 1254, 1110, 837, 776 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.53 (1H, br s, Ar**H**), 8.42 (1H, br s, Ar**H**), 7.58 (1H, br d, J = 7.8 Hz, Ar**H**), 7.27-7.24 (1H, m, Ar**H**), 6.48 (1H, s, C**H**=CCH_3), 4.17 (2H, s, $\mathbf{CH_2}O$), 0.93 (9H, s, $C(\mathbf{CH_3})_3$), 0.10 (6H, s, $Si(\mathbf{CH_3})_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 149.9 (CH), 147.0 (CH), 139.9 (C), 135.7 (CH), 133.5 (C), 122.9 (CH), 119.7 (CH), 67.8 (CH_2), 25.8 (3 x CH_3), 18.3 (C), 14.8 (CH_3), –5.4 (2 x CH_3); LRMS (ES) 264 ($[M+H]^+$, 100).

Enantioselective Copper-Catalyzed Reductions: General Procedure C



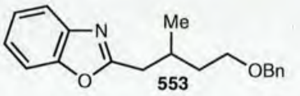
A solution of the appropriate alkene (0.20 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol), Josiphos ligand (6.1 mg, 0.01 mmol), and *t*-BuOH (38 μL, 0.40 mmol) in toluene (1 mL) was stirred at 0 °C for 15 min. $PhSiH_3$ (37 μL, 0.30 mmol) was then added dropwise. The mixture was stirred at 0 °C for 2 h, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short pad of silica gel using EtOAc (20 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reduced product.



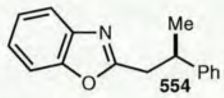
522

2-[(*S*)-2-Methyl-4-phenybutyl]benzooxazole (522). The title compound was prepared according to General Procedure C from alkene **460** (53 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a colorless oil (48 mg, 90%). $[\alpha]_D^{24}$ –26.9 (*c* 0.52, $CHCl_3$); IR (film) 3060, 3026, 2927, 2860, 1940, 1614, 1570, 1454, 1242, 746, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.66 (1H, m, Ar**H**), 7.48-7.46 (1H, m, Ar**H**), 7.30-7.24 (4H, m, Ar**H**), 7.18-7.16 (3H, m, Ar**H**), 2.97 (1H, dd, J = 14.8, 6.0 Hz, N=C$\mathbf{CH_2}$), 2.80 (1H, dd, J = 14.8, 8.1 Hz, N=C$\mathbf{CH_2}$), 2.73 (1H, ddd, J = 13.8, 10.5, 5.7 Hz, $\mathbf{CH_2}$Ph), 2.64 (1H, ddd, J = 13.8, 10.5, 6.1 Hz, $\mathbf{CH_2}$Ph), 2.25-2.16 (1H, m, **CH**CH_3), 1.80-1.73 (1H, m, $\mathbf{CH_2}CH_2$Ph), 1.65-1.57 (1H, m, $\mathbf{CH_2}CH_2$Ph), 1.07 (3H, d, J = 6.7 Hz, $\mathbf{CH_3}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.4 (C), 150.8 (C), 142.2 (C), 141.4 (C), 128.3 (2 x CH), 125.8 (CH), 124.4 (CH), 124.0 (CH), 119.6 (CH), 110.3 (CH), 38.4 (CH_2), 35.9 (CH_2), 33.3 (CH_2), 31.8 (CH), 19.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{20}NO$ $[M+H]^+$: 266.1539, found: 266.1532. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 9.8 min; t_r (minor) = 14.4 min, 93% ee.

2-[(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbutyl]benzooxazole (552). The title compound was prepared according to General Procedure C from alkene **462** (63 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a pale yellow oil (43 mg, 67%). $[\alpha]_D^{21}$ +2.0 (*c* 1.00, $CHCl_3$); IR (film) 2960, 2929, 2856, 1614, 1572, 1456, 1244, 1099, 837, 775, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.66 (1H, m, Ar**H**), 7.51-7.47 (1H, m, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 3.76-3.67 (2H, m, $C\mathbf{H}_2O$), 2.98 (1H, dd, J = 14.7, 6.1 Hz, $N{=}C\mathbf{CH}_2$), 2.80 (1H, dd, J = 14.7, 8.1 Hz, $N{=}C\mathbf{CH}_2$), 2.38-2.28 (1H, m, $\mathbf{CH}CH_3$), 1.72-1.65 (1H, m, $\mathbf{CH}_2CH_2O$), 1.55-1.49 (1H, m, $\mathbf{CH}_2CH_2O$), 1.04 (3H, d, J = 6.7 Hz, $CH\mathbf{CH}_3$), 0.89 (9H, s, $SiC(\mathbf{CH}_3)_3$), 0.05 (3H, s, $Si\mathbf{CH}_3$), 0.04 (3H, s, $Si\mathbf{CH}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.4 (C), 150.8 (C), 141.4 (C), 124.4 (CH), 124.0 (CH), 119.5 (CH), 110.3 (CH), 60.9 (CH_2), 39.4 (CH_2), 36.0 (CH_2), 29.1 (CH), 25.9 (3 x CH_3), 19.7 (CH_3), 18.3 (C), –5.4 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{30}NO_2Si$ $[M+H]^+$: 320.2040, found: 320.2045. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 5.3 min; t_r (minor) = 5.7 min; 94% ee.

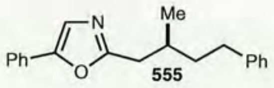


2-[(*S*)-4-Benzyloxy-2-methylbutyl]benzooxazole (553). The title compound was prepared according to General Procedure C from alkene **461** (59 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a pale yellow oil (52 mg, 88%). $[\alpha]_D^{24}$ +3.8 (*c* 1.04, $CHCl_3$); IR (film) 3060, 3030, 2958, 2927, 2858, 1614, 1570, 1454, 1365, 1242, 1101, 937, 839, 746, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.68 (1H, m, Ar**H**), 7.50-7.48 (1H, m, Ar**H**), 7.35-7.28 (7H, m, Ar**H**), 4.50 (2H, s, $\mathbf{CH}_2Ph$), 3.61-3.54 (2H, m, $CH_2\mathbf{CH}_2O$), 2.99 (1H, dd, J = 14.7, 5.9 Hz, $N{=}C\mathbf{CH}_2$), 2.81 (1H, dd, J = 14.8, 8.1 Hz, $N{=}C\mathbf{CH}_2$), 2.43-2.33 (1H, m, $\mathbf{CH}CH_3$), 1.84-1.78 (1H, m, $\mathbf{CH}_2CH_2O$), 1.66-1.59 (1H, m, $\mathbf{CH}_2CH_2O$), 1.04 (3H, d, J = 6.7 Hz, $\mathbf{CH}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (2 quaternary carbon signals unresolved) 141.4 (C), 138.4 (C), 128.3 (2 x CH), 127.6 (2 x CH), 127.5 (CH), 124.4 (CH), 124.0 (CH), 119.5 (CH), 110.3 (CH), 72.9 (CH_2), 68.1 (CH_2), 36.3 (CH_2), 35.9 (CH_2), 29.3 (CH), 19.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{22}NO_2$ $[M+H]^+$: 296.1645, found: 296.1653. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 12.0 min; t_r (minor) = 19.6 min; 95% ee.



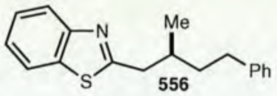
554

2-[(*R*)-2-Phenylpropyl]benzooxazole (554). The title compound was prepared according to a modification of General Procedure C from alkene **454** (36.5 mg, 0.155 mmol), $Cu(OAc)_2{\cdot}2H_2O$ (1.4 mg, 0.008 mmol), josiphos ligand **L5** (4.9 mg, 0.008 mmol), *t*-BuOH (29 μL, 0.31 mmol), and $PhSiH_3$ (29 μL, 0.23 mmol) in toluene (0.5 mL) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a pale pink oil (35 mg, 95%). $[\alpha]_D^{24}$ –45.2 (c. 0.57, $CHCl_3$); IR (film) 3060, 3028, 2964, 2927, 1614, 1570, 1495, 1454, 1242, 1146, 762, 746, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.66 (1H, m, Ar**H**), 7.50-7.47 (1H, m, Ar**H**), 7.34-7.29 (6H, m, Ar**H**), 7.24-7.21 (1H, m, Ar**H**), 3.55-3.48 (1H, m, C**H**CH$_3$), 3.26 (1H, dd, J = 14.9, 6.2 Hz, N=CC**H$_2$**), 3.16 (1H, dd, J = 14.9, 9.0 Hz, N=CC**H$_2$**), 1.39 (3H, d, J = 7.0 Hz, C**H$_3$**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 165.8 (C), 150.8 (C), 145.4 (C), 141.3 (C), 128.6 (2 x CH), 126.7 (2 x CH), 126.6 (CH), 124.5 (CH), 124.1 (CH), 119.6 (CH), 110.3 (CH), 38.2 (CH), 37.3 (CH$_2$), 21.5 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1226, found: 238.1226. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t$_r$ (major) = 10.1 min; t$_r$ (minor) = 11.8 min; 87% ee.



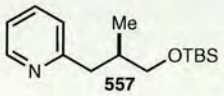
555

2-[(*S*)-2-Methyl-4-phenylbutyl]-5-phenyloxazole (555). The title compound was prepared according to General Procedure C from alkene **428** (58 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a colorless oil (54 mg, 93%) that solidified on standing. m.p. 50-52 °C; $[\alpha]_D^{24}$ –21.0 (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) 3060, 3026, 2925, 2848, 1554, 1493, 1454, 1122, 1026, 941, 825, 760, 649 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (2H, m, Ar**H**), 7.44-7.40 (2H, m, Ar**H**), 7.34-7.27 (3H, m, Ar**H**), 7.25 (1H, br s, Ar**H**), 7.20-7.17 (3H, m, Ar**H**), 2.89 (1H, dd, J = 14.8, 6.1 Hz, N=CC**H$_2$**), 2.77-2.71 (2H, m, N=CC**H$_2$** and C**H$_2$**Ph), 2.66 (1H, ddd, J = 13.7, 10.2, 6.2 Hz, C**H$_2$**Ph), 2.19-2.09 (1H, m, C**H**CH$_3$), 1.80-1.73 (1H, m, C**H$_2$**CH$_2$Ph), 1.64-1.57 (1H, m, C**H$_2$**CH$_2$Ph), 1.08 (3H, d, J = 6.7 Hz, C**H$_3$**); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.7 (C), 150.9 (C), 142.3 (C), 128.8 (2 x CH), 128.3 (4 x CH and C), 128.1 (CH), 125.7 (CH), 124.0 (2 x CH), 121.8 (CH), 38.3 (CH_2), 35.4 (CH_2), 33.3 (CH_2), 31.9 (CH), 19.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO$ $[M+H]^+$: 292.1696, found: 292.1699. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 16.6 min, t_r (major) = 17.6 min; 90% ee.



556

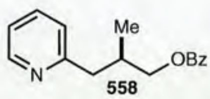
2-[(*S*)-2-Methyl-4-phenybutyl]benzothiazole (556). The title compound was prepared according to General Procedure C from alkene **463** (56 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a colorless amorphous solid (48 mg, 86%). $[\alpha]_D^{24}$ –32.7 (c 0.61, $CHCl_3$); IR ($CHCl_3$) 3060, 3026, 2956, 2925, 1518, 1454, 1435, 1311, 1124, 912, 760, 729, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (1H, d, J = 8.1 Hz, Ar**H**), 8.00 (1H, dm, J = 8.0 Hz, Ar**H**), 7.48-7.45 (1H, m, Ar**H**), 7.38-7.35 (1H, m, Ar**H**), 7.30-7.27 (2H, m, Ar**H**), 7.20-7.18 (3H, m, Ar**H**), 3.18 (1H, dd, J = 14.4, 6.2 Hz, N=C$\mathbf{CH_2}$), 2.99 (1H, dd, J = 14.4, 8.1 Hz, N=C$\mathbf{CH_2}$), 2.77 (1H, ddd, J = 13.7, 10.6, 5.5 Hz, $\mathbf{CH_2}$Ph), 2.66 (1H, ddd, J = 13.7, 10.5, 6.0 Hz, $\mathbf{CH_2}$Ph), 2.21-2.12 (1H, m, C**H**CH_3), 1.85-1.78 (1H, m, $\mathbf{CH_2}CH_2$Ph), 1.66-1.59 (1H, m, $\mathbf{CH_2}CH_2$Ph), 1.10 (3H, d, J = 6.6 Hz, $\mathbf{CH_3}$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.9 (C), 153.2 (C), 142.2 (C), 135.2 (C), 128.3 (4 x CH), 125.8 (CH), 125.7 (CH), 124.6 (CH), 122.5 (CH), 121.4 (CH), 41.5 (CH_2), 38.4 (CH_2), 34.0 (CH), 33.3 (CH_2), 19.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{20}NS$ $[M+H]^+$: 282.1311, found: 282.1310. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 12.9 min; t_r (minor) = 19.7 min; 95% ee.



557

2-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]py (557). The title compound was prepared according to General Procedure C from alkene **493** (53 mg, 0.20 mmol) and purified by column chromatography (hexane→2% EtOAc/hexane) to give a colorless oil (48 mg, 90%). $[\alpha]_D^{24}$ –8.0 (c 0.75, $CHCl_3$); IR (film) 2954, 2894, 2856, 1560, 1569, 1472, 1433, 1257, 1089, 1006 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (1H, app d, J = 2.8 Hz, Ar**H**), 7.58 (1H, app d, J = 7.4 Hz, ArH), 7.14 (1H, d, J = 7.1 Hz, ArH), 7.10 (1H, app t, J = 5.6 Hz, ArH), 3.51-3.45 (2H, m, CH_2O), 2.94 (1H, dd, J = 13.1, 5.9 Hz, N=CCH_2), 2.54 (1H, dd, J = 13.1, 8.5 Hz, N=CCH_2), 2.16-2.09 (1H, m, $CHCH_3$), 0.90 (12H, br s, $CHCH_3$ and $SiC(CH_3)_3$), 0.03 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.3 (C), 149.1 (CH), 136.0 (CH), 123.5 (CH), 120.8 (CH), 67.6 (CH_2), 42.0 (CH_2), 36.7 (CH), 25.9 (3 x CH_3), 18.3 (C), 16.5 (CH_3), –5.4 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{28}NOSi$ $[M+H]^+$: 266.1935, found: 266.1933. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.5:0.5 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (major) = 12.2 min, t_r (minor) *ca* 15 min (not detected); >99% ee.

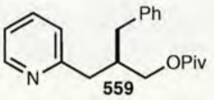
A similar experiment conducted using alkene **493** (264 mg, 1.00 mmol), $Cu(OAc)_2 \cdot H_2O$ (3.9 mg, 0.02 mmol), josiphos ligand **L5** (12.3 mg, 0.02 mmol), *t*-BuOH (190 μL, 2.00 mmol), and $PhSiH_3$ (185 μL, 1.50 mmol) in toluene (5 mL) gave *pyridine* **557** (244 mg, 92%) in 96% ee after a total reaction time of 17 h. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.5:0.5 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (major) = 12.7 min, t_r (minor) = 15.1 min; 96% ee.



558

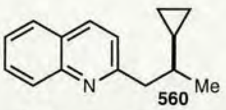
(*R*)-2-Methyl-3-pyridin-2-ylpropyl benzoate (558). The title compound was prepared according to a modification of General Procedure C from alkene **540** (25 mg, 0.10 mmol), $Cu(OAc)_2 \cdot 2H_2O$ (1.0 mg, 0.005 mmol), josiphos ligand **L5** (3.2 mg, 0.005 mmol), *t*-BuOH (19 μL, 0.20 mmol), and $PhSiH_3$ (25 μL, 0.20 mmol) in toluene (0.5 mL) for 72 h and purified by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give a yellow oil (21 mg, 81%). $[\alpha]_D^{24}$ –8.8 (*c* 0.45, $CHCl_3$); IR (film) 2924, 2852, 1718 (C=O), 1589, 1452, 1273, 1111, 1026, 756, 712 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.57 (1H, br s, ArH), 8.05-8.01 (2H, m, ArH), 7.61-7.54 (2H, m, ArH), 7.46-7.42 (2H, m, ArH), 7.18-7.11 (2H, m, ArH), 4.27 (1H, dd, J = 10.9, 5.8 Hz, CH_2O), 4.22 (1H, dd, J = 10.9, 6.0 Hz, CH_2O), 3.00 (1H, dd, J = 13.5, 6.6 Hz, N=CCH_2), 2.76 (1H, dd, J = 13.5, 7.8 Hz, N=CCH_2), 2.63-2.50 (1H, m, $CHCH_3$), 1.07 (3H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 166.6 (C), 160.2 (C), 149.3 (CH), 136.2 (CH), 132.8 (CH), 130.3 (C), 129.5 (2 x CH), 128.3 (2 x CH), 123.6 (CH), 121.2 (CH), 69.2 (CH_2), 42.4

(CH_2), 33.5 (CH), 16.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332, found: 256.1334. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 20.6 min, t_r (major) = 22.9 min; 98% ee.



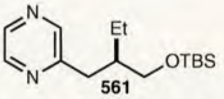
559

(*R*)-2-Benzyl-3-pyridin-2-ylpropyl pivaloate (559). The title compound was prepared according to General Procedure C from alkene **543** (62 mg, 0.20 mmol) but using half the volume of toluene (0.5 mL) as solvent. Purification by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave a dark brown oil (56 mg, 90%). $[\alpha]_D^{24}$ –2.0 (*c* 1.00, $CHCl_3$); IR (film) 3420, 2931, 2360, 1726 (C=O), 1653, 1570, 1476, 1283, 1158, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.56-8.55 (1H, m, Ar**H**), 7.59 (1H, dt, 7.6, 1.6 Hz, Ar**H**), 7.29-7.27 (2H, m, Ar**H**), 7.20-7.10 (5H, m, Ar**H**), 3.91 (2H, app d, J = 4.6 Hz, $\mathbf{CH_2}$O), 2.86 (2H, app d, J = 7.1 Hz, $\mathbf{CH_2}$Ar), 2.74-2.72 (2H, m, $\mathbf{CH_2}$Ar), 2.68-2.60 (1H, m, **CH**CH_2Ph), 1.24 (9H, s, C($\mathbf{CH_3}$)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 178.4 (C), 160.0 (C), 149.4 (CH), 139.6 (C), 136.3 (CH), 129.1 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 123.7 (CH), 121.3 (CH), 65.2 (CH_2), 40.1 (CH), 40.0 (CH_2), 38.9 (C), 37.5 (CH_2), 27.3 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1958, found: 312.1954. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98.2 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 17.9 min, t_r (major) = 19.0 min; 97% ee.

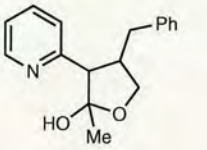


560

2-[(*S*)-2-Cyclopropylpropyl]quinoline (560). The title compound was prepared according to General Procedure C from alkene **517** (42 mg, 0.20 mmol) and purified by column chromatography (hexane→3% EtOAc/hexane) to give a brown oil (38 mg, 90%). $[\alpha]_D^{21}$ +22.0 (*c* 1.00, $CHCl_3$); IR (film) 3073, 2955, 2925, 2870, 1619, 1599, 1563, 1504, 1455, 1426, 1116, 1016 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.07-8.03 (2H, m, Ar**H**), 7.78 (1H, dd, J = 8.1, 1.3 Hz, Ar**H**), 7.68 (1H, ddd, J = 8.5, 6.9, 1.3 Hz, Ar**H**), 7.48 (1H, ddd, J = 8.1, 6.9, 1.3 Hz, Ar**H**), 7.29 (1H, d, J = 8.5 Hz, Ar**H**), 3.13 (1H, dd, J = 13.0, 6.6 Hz, N=C**H**$_2$), 2.94 (1H, dd, J = 13.0, 8.0 Hz, N=C**H**$_2$), 1.42-1.30 (1H, m, **C**HCH$_3$), 1.02 (3H, d, J = 6.7 Hz, C**H**$_3$), 0.72-0.62 (1H, m, C**H**(CH$_2$CH$_2$)), 0.72-0.28 (2H, m, C**H**(C**H**$_2$C**H**$_2$)), 0.11-0.04 (1H, m, C**H**(C**H**$_2$C**H**$_2$)), –0.02 to –0.09 (1H, m, C**H**(C**H**$_2$C**H**$_2$)); ^{13}C NMR (90.6 MHz, CDCl$_3$), δ 162.1 (C), 147.8 (C), 135.7 (CH), 129.2 (CH), 128.8 (CH), 127.4 (CH), 126.6 (C), 125.6 (CH), 122.3 (CH), 46.8 (CH$_2$), 39.8 (CH), 19.7 (CH$_3$), 18.0 (CH), 4.5 (CH$_2$), 3.3 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{15}H_{18}N$ [M+H]$^+$: 212.1434, found: 212.1436. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98.2 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t$_r$ (minor) = 7.2 min, t$_r$ (major) = 7.9 min; 96% ee.


561

2-[(*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)butyl]-pyrazine (561). The title compound was prepared according to General Procedure C from alkene **547** (56 mg, 0.20 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a yellow oil (50 mg, 89%). $[\alpha]_D^{21}$ –18.0 (c 0.78, CHCl$_3$); IR (film) 3436, 2928, 2857, 2098, 1643, 1402, 1258, 1084, 835, 749 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.58 (3H, br s, Ar**H**), 3.54-3.46 (2H, m, C**H**$_2$O), 2.92 (1H, dd, J = 13.7, 7.5 Hz, ArC**H**$_2$), 2.76 (1H, dd, J = 13.7, 6.7 Hz, ArC**H**$_2$), 2.05-1.91 (1H, m, C**H**CH$_2$O), 1.51-1.29 (2H, m, C**H**$_2$CH$_3$), 0.92 (3H, t, J = 7.4 Hz, CH$_2$C**H**$_3$), 0.90 (9H, s, C(C**H**$_3$)$_3$), 0.02 (3H, SiC**H**$_3$), 0.01 (3H, SiC**H**$_3$); ^{13}C NMR (125.1 MHz, CD$_3$OD, 348 K) δ 160.1 (C), 147.1 (CH), 146.4 (CH), 143.8 (CH), 66.5 (CH$_2$), 45.0 (CH), 38.9 (CH$_2$), 27.3 (3 x CH$_3$), 25.7 (CH$_2$), 20.0 (C), 12.5 (CH$_3$), –4.5 (2 x CH)$_3$; Exact mass calcd for $C_{15}H_{29}N_2OSi$ [M+H]$^+$: 281.2044, found: 281.2042. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.5:0.5) hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t$_r$ (minor) = 10.3 min, t$_r$ (major) = 11.0 min; 96% ee.

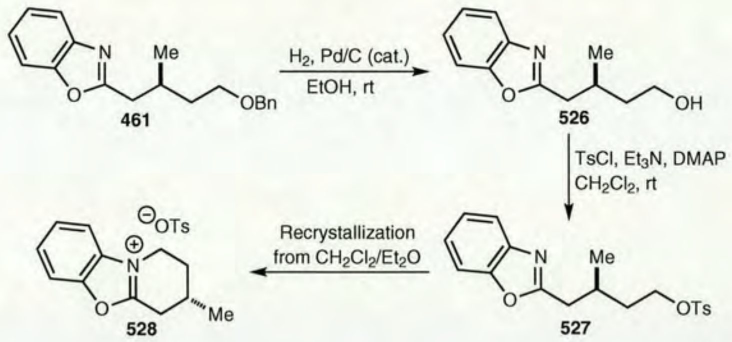

529

4-benzyl-2-methyl-3-(pyridin-2-yl)tetrahydrofuran-2-ol (529) The title compound was prepared according to General Procedure C and purified by column chromatography (hexane→10% EtOAc/hexane) to give a pale yellow oil (26 mg, 50%) ^{1}H NMR (800 MHz, CDCl$_3$) δ

8.56–8.54 (1H, m, Ar**H**), 7.60 (1H, td, J = 7.7, 1.7 Hz, Ar**H**), 7.22–7.17 (3H, m, Ar**H**), 7.16–7.12 (1H, m, Ar**H**), 7.08–7.02 (3H, m, Ar**H**), 4.25 (1H, t, J = 8.5 Hz, CH$\mathbf{CH_2}$O), 3.76 (1H, dd, J = 8.5, 7.2 Hz, CH$\mathbf{CH_2}$O), 3.21–3.15 (1H, m, PhCH$_2$**CH**), 2.94 (1H, d, J = 10.2), 2.78 (1H, dd, J = 13.8, 6.0 Hz, Ph$\mathbf{CH_2}$), 2.73 (1H, dd, J = 14.0, 9.2 Hz, Ph$\mathbf{CH_2}$), 1.45 (3H, s, $\mathbf{CH_3}$); ^{13}C NMR (201 MHz, CDCl$_3$) δ 161.20 (C), 151.33 (CH), 142.17 (C), 139.70 (CH), 131.23 (CH), 131.00 (CH), 128.85 (CH) , 127.89 (CH) , 124.82 (CH) , 107.73 (C), 73.85 (CH$_2$), 62.52 (CH), 49.64 (CH), 41.99 (CH$_2$), 28.80 (CH$_3$); LRMS (ESI) [M-H$_2$O]$^+$: 252.1, [M+Na]$^+$: 292.1.

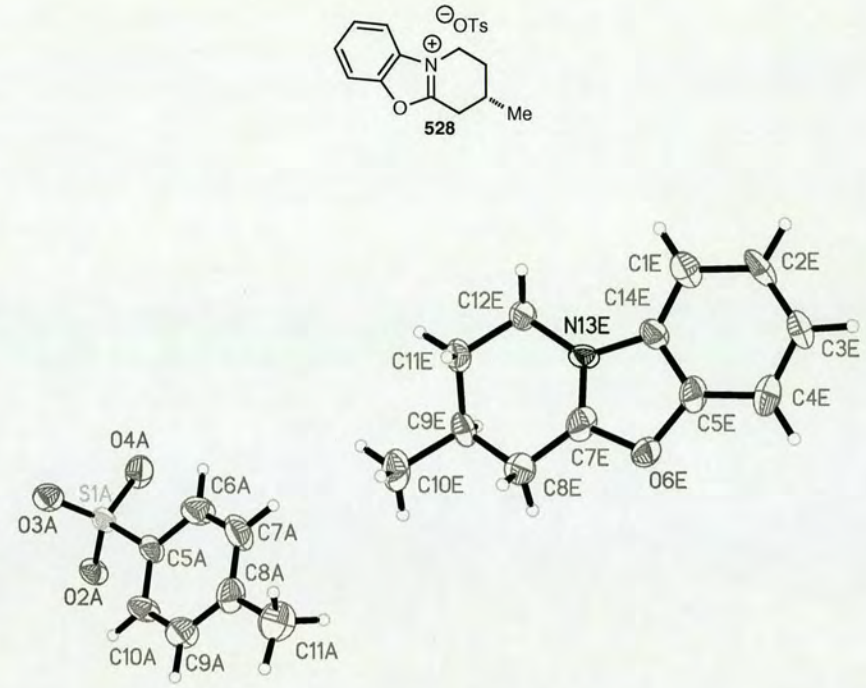
4-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropyl]pyridine (4). The title compound was prepared according to General Procedure C from alkene **3** (53 mg, 0.20 mmol) for a reaction time of 4 days and purified by column chromatography (hexane→15% EtOAc/hexane) to give a yellow oil (32 mg, 60%). $[\alpha]_D^{21}$ +2.6 (c 0.75, CHCl$_3$); IR (film) 3417, 2955, 2857, 1603, 1471, 1255, 1097, 1027, 837, 776 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 8.49 (2H, d, J = 5.7 Hz, Ar**H**), 7.10 (2H, d, J = 5.7 Hz, Ar**H**), 3.46 (1H, dd, J = 9.9, 5.4 Hz, $\mathbf{CH_2}$O), 3.40 (1H, dd, J = 9.9, 6.2 Hz, $\mathbf{CH_2}$O), 2.83 (1H, dd, J = 13.3, 5.9 Hz, Ar$\mathbf{CH_2}$), 2.33 (1H, dd, J = 13.3, 8.4 Hz, Ar$\mathbf{CH_2}$), 1.99-1.86 (1H, m, **CH**CH$_3$), 0.92 (9H, s, Si($\mathbf{CH_3}$)$_3$), 0.86 (3H, d, J = 6.7 Hz, CH$\mathbf{CH_3}$), 0.05 (6H, s, 2 x Si$\mathbf{CH_3}$); ^{13}C NMR (90.6 MHz, CDCl$_3$) δ 150.3 (C), 149.5 (2 x CH), 124.7 (2 x CH), 67.1 (CH$_2$), 38.9 (CH$_2$), 37.2 (CH), 25.9 (3 x CH$_3$), 18.3 (C), 16.3 (CH$_3$), –5.4 (2 x CH$_3$); Exact mass calcd for C$_{15}$H$_{28}$NOSi [M+H]$^+$: 266.1935, found: 266.1931. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.3:0.5:0.2 hexane:isopropanol:diethylamine, 0.8 mL/min, 254 nm, 25 °C); t$_r$ (minor) = 29.1 min, t$_r$ (major) = 30.0 min; 94% ee.

Determination of Absolute Configurations



A suspension of the benzoxazole **553** (131 mg, 0.44 mmol) and 10% Pd/C (26 mg) in EtOH (1 mL) was stirred at room temperature under an atmosphere of H_2 (1 atm) for 30 min. The mixture was then filtered through a short plug of celite, eluting with EtOAc (20 mL), and the filtrate was concentrated *in vacuo* to leave the alcohol **526** which used directly in the next step without purification. To a solution of the alcohol **526**, Et_3N (139 μL, 1.00 mmol), and DMAP (6 mg, 0.05 mmol) in CH_2Cl_2 (3 mL) was added a solution of TsCl (143 mg) in CH_2Cl_2 (2 mL) *via* cannula and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and rextracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave the *sulfonate ester* **527** (80 mg, 51%) as a light brown solid. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.78 (2H, dm, J = 8.3 Hz, Ar**H**), 7.69-7.63 (1H, m, Ar**H**), 7.52-7.47 (1H, m, Ar**H**), 7.34-7.30 (4H, m, Ar**H**), 4.19-4.08 (2H, $\mathbf{CH_2}$O), 2.88 (1H, dd, J = 14.9, 6.3 Hz, N=C$\mathbf{H_2}$), 2.78 (1H, dd, J = 14.9, 7.6 Hz, N=CC$\mathbf{H_2}$), 2.43 (3H, s, ArC$\mathbf{H_3}$), 2.35-2.26 (1H, m, C**H**CH_3), 1.89-1.80 (1H, m, $\mathbf{CH_2}CH_2O$), 1.68-1.58 (1H, m, $\mathbf{CH_2}CH_2O$), 0.99 (3H, d, J = 6.7 Hz, CHC$\mathbf{H_3}$).

This material was not stable, and was found to cyclize to the corresponding tosylate salt during recrystallization, which was conducted by gently layering Et_2O on top of a solution of **527** in CH_2Cl_2. The resulting crystals **528** were suitable for X-ray crystallography, which allowed determination of the absolute configuration of benzoxazole **553**:



Scheme 3.1: X-ray crystalography structure

The stereochemical outcome of the conjugate reduction to produce **553** is consistent with other reports of copper-catalyzed enantioselective conjugate reductions using josiphos ligands.[9] The absolute configurations of the remaining conjugate reduction products were assigned tentatively by analogy.

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[9]. (a) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789–4792. (b) Lipshutz, B. H.;Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353. (c) Lipshutz, B. H.;Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963–1966. (d) Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4793–4795. (e) Czekelius, C.; Carreira, E. M.; *Org. Lett.* **2004**, *6*, 4575–4577. (f) Lee, D.; Kim, D.; Yun, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 2785–2787. (g) Yoo, K.; Kim, H.; Yun, J. *J. Org. Chem.* **2009**, *74*, 4232–4235.

Tetrahedron 64 (2008) 7896–7901

Contents lists available at ScienceDirect

Tetrahedron

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Formal synthesis of salinosporamide A using a nickel-catalyzed reductive aldol cyclization–lactonization as a key step

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ARTICLE INFO

Article history:
Received 5 April 2008
Received in revised form 28 May 2008
Accepted 12 June 2008
Available online 14 June 2008

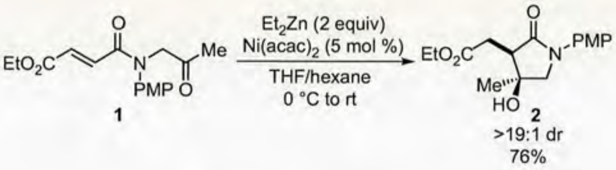
ABSTRACT

Application of a sequential nickel-catalyzed reductive aldol cyclization–lactonization reaction in a short formal synthesis of salinsporamide A, a potent 20S proteasome inhibitor and anti-cancer compound, is described.

1. Introduction

Advances in transition-metal-catalyzed cyclization reactions provide the means to access increasingly diverse carbocyclic and heterocyclic compounds from relatively simple starting materials, with often impressive levels of diastereo- and enantioselectivity.[1,2,3] Reductive cyclizations, where reaction is promoted by stoichiometric reductants such as molecular hydrogen, silanes, formic acid, stannanes, borohydrides or main-group organometallic reagents, represent an important class of these transformations.[2,3] Many of these reactions have been developed to a level of utility that enable their application in natural product synthesis.[4]

Our research in this area has led to the development of a series of metal-catalyzed reductive aldol cyclization reactions that form β-hydroxylactones and β-hydroxylactams in highly diastereoselective fashion.[5] A notable result is the cyclization of **1** using $Ni(acac)_2$ as the precatalyst and Et_2Zn as the stoichiometric reductant, which provided β-hydroxy-γ-lactam **2** as a single diastereomer (Eq. 1).[5d,6] This outcome was of interest because examination of the structure of **2** revealed similarities with the core of salinosporamide A (**3**) (Fig. 1), a secondary metabolite isolated by Fenical and co-workers from marine actinomycete bacteria of *Salinospora* strain CNB-392.[7] This compound has attracted significant attention because of its impressive biological activity.[7] Not only is **3** a highly potent inhibitor of the 20S proteasome, an abundant complex within cells that plays an important role in the degradation and removal of misfolded proteins,[8] it also exhibits promising potential as an anti-cancer therapeutic agent. Indeed, **3** is currently in clinical trials for this purpose.[9]



(1)

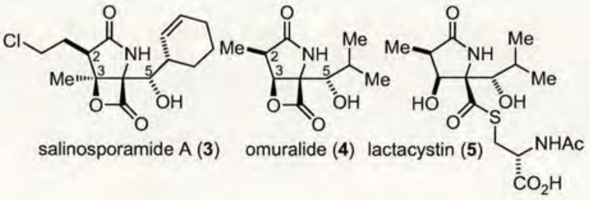


Figure 1.

Structurally, salinosporamide A (**3**) shares its fused γ-lactam-β-lactone bicyclic core with omuralide (**4**), a product derived from the terrestrial microbial metabolite lactacystin (**5**).[10,11] Although omuralide (**4**) is also an effective 20S proteasome inhibitor, differences between **3** and **4** at C2, C3 and C5 render **3** approximately 35 times more potent than **4**.[7] Salinosporamide A (**3**) has also elicited significant interest from a synthetic perspective, with a number of total and partial syntheses having been reported.[11c,12]

Given the huge interest in salinosporamide A (**3**), and the resemblance of β-hydroxy-γ-lactam **2** to the core of **3**, we became interested in the possibility of applying our nickel-catalyzed reductive aldol methodology[5d] in a synthetic route towards this natural product. Strategically, construction of the γ-lactam of **3** by formation of the C2–C3 bond has already been accomplished by Corey and co-workers (Scheme 1).[12a,b] In their original

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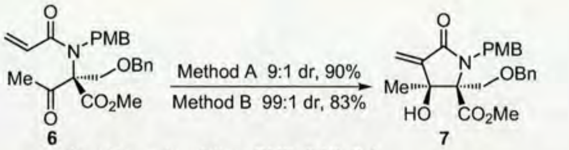
doi:10.1016/j.tet.2008.06.038

total synthesis of salinosporamide A (**3**), acrylamide **6** was cyclized in a Baylis–Hillman reaction[13] (method A) to provide γ-lactam **7** as a 9:1 mixture of diastereomers after 1 week.[12a] The same group subsequently developed improved conditions for this cyclization, involving the Kulinkovich reagent[14] formed from $Ti(O\textit{i}\text{-}Pr)_4$ and cyclopentylmagnesium chloride (method B).[12b] A sequence of several steps including a tin hydride-mediated radical cyclization was then required to transform the exomethylene group of **7** into the chloroethyl functionality of salinosporamide A (**3**).[12a]



Method A: quinuclidine, DME, 0 °C, 7 d.
Method B: (i) $Ti(O\textit{i}\text{-}Pr)_4$, $c\text{-}C_5H_9MgCl$, *t*-BuOMe, -40 °C, 30 min, then I_2, -40 °C, 2 h, then 0 °C, 2 h.
(ii) Et_3N, CH_2Cl_2, rt, 30 min.

Scheme 1. Construction of γ-lactam **7** by Corey and co-workers.[12a,b]

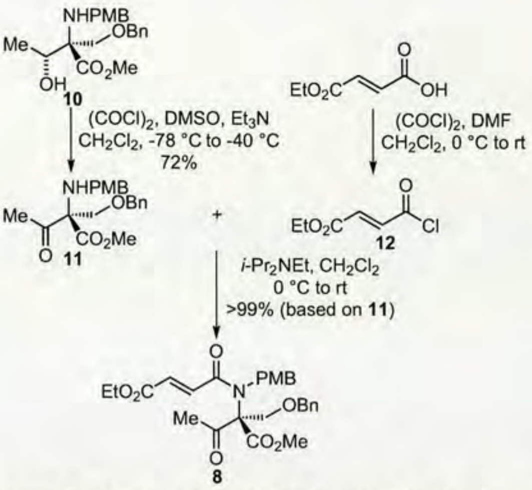
Since the ethyl ester-containing side-chain in **2** can be converted into the chloroethyl group of salinosporamide A (**3**) without further carbon–carbon bond formation, we envisaged that a suitably more functionalized variant of Eq. 1 might prove advantageous in a synthetic route towards **3**. Accordingly, α,β-unsaturated amide **8** became a target for our investigations (Scheme 2).

Scheme 2. Reductive aldol cyclization strategy towards **3**.

Compared with **1**, substrate **8** possesses a more densely functionalized, more sterically congested structure containing several Lewis basic groups that could potentially bind the catalyst and organometallic reductant and divert the course of the proposed cyclization towards deleterious side reactions. Furthermore, we would be reliant upon the single stereocenter present in **8** to control the absolute configurations of the two new stereocenters formed in the cyclization to provide **9** preferentially, and prediction of the sense of diastereoselectivity (if any) was by no means straightforward. Therefore, substrate **8** would provide a challenging test for our methodology. In this article, we describe the successful utilization of **8** in a formal synthesis of salinosporamide A (**3**).

2. Results and discussion

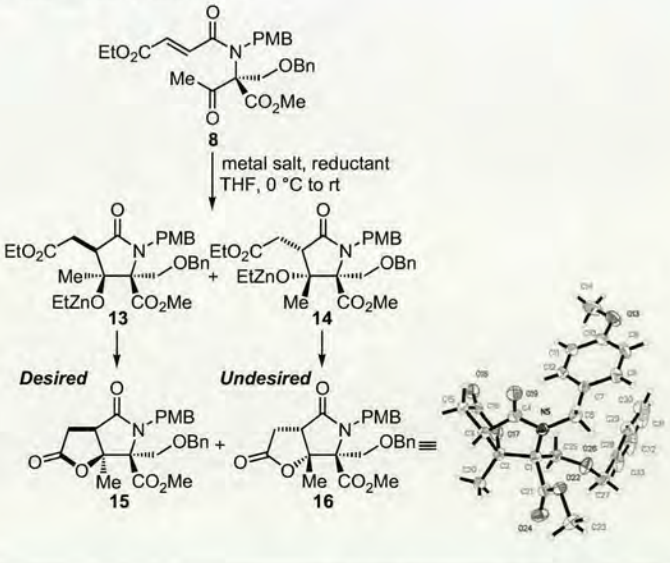
Cyclization precursor **8** was prepared in straightforward fashion as illustrated in Scheme 3. Swern oxidation[15] of the previously described amino alcohol **10**[12a] provided aminoketone **11**, which was then acylated with the acid chloride **12** derived from mono-ethyl fumarate[16] to afford α,β-unsaturated amide **8** in high yield.



Scheme 3. Preparation of substrate **8** for reductive aldol cyclization.

With **8** in hand, the crucial reductive aldol cyclization was attempted (Table 1). Unfortunately, exposure of **8** to $Ni(acac)_2$ and Et_2Zn (as in Eq. 1)[5d] provided only an intractable mixture of products (entry 1). The situation was not improved upon replacing Et_2Zn with Et_3Al[5c] (entry 2), or by replacing $Ni(acac)_2$ with $Co(acac)_2 \cdot 2H_2O$[5c] (entries 3 and 4). The effect of phosphine ligands on the reaction was then examined. Although the combination of $CoCl_2$ and DPPF offered no improvement (entry 5), it was found that commercially available nickel–phosphine complexes were effective precatalysts. Using $(Ph_3P)_2NiBr_2$ (entry 6), none of the initially desired product **9** was isolated. Instead, fused γ-lactone-γ-lactam **15** containing the

Table 1
Reductive aldol cyclization of **8**



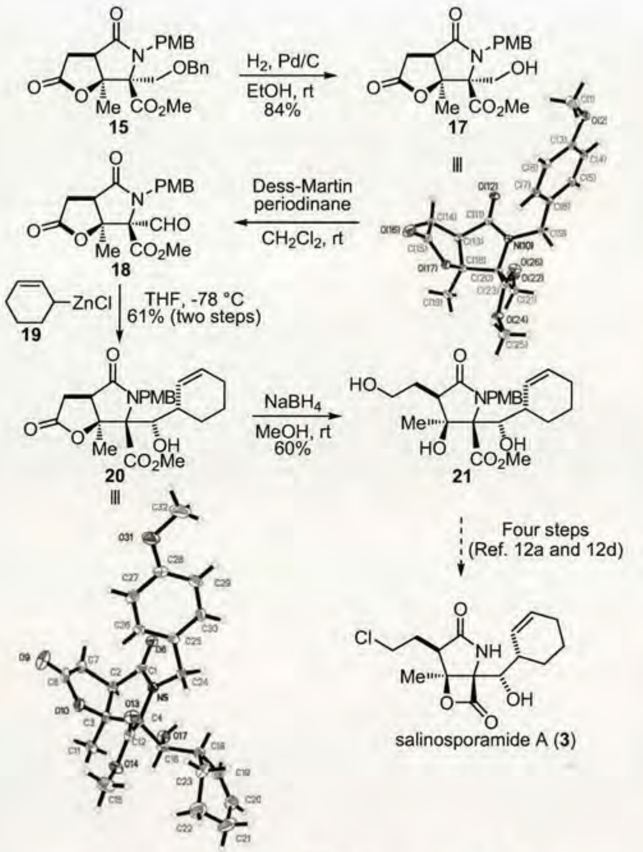
Entry	Precatalyst (10 mol %)	Reductant (2 equiv)	Result/yields
1	$Ni(acac)_2$	Et_2Zn	Intractable mixture
2	$Ni(acac)_2$	Et_3Al	Intractable mixture
3	$Co(acac)_2$	Et_2Zn	<10% Conversion
4	$Co(acac)_2$	Et_3Al	Intractable mixture
5	$CoCl_2$/DPPF	Et_2Zn	Intractable mixture
6	$(Ph_3P)_2NiBr_2$	Et_2Zn	35% of **15**,[a] 30% of **16**[a]
7[b]	$(Me_3P)_2NiCl_2$	Et_2Zn	42% of **15**,[a] 30% of **16**[a]

[a] Isolated yield.
[b] Initial reaction temperature of −15 °C. DPPF=1,1′-bis(diphenylphosphino)-ferrocene.

desired stereochemistry was isolated in 35% yield, along with a comparable amount of the alternative diastereomer **16**, the stereochemistry of which was established by X-ray crystallography.[17] Marginally superior results were obtained using $(Me_3P)_2NiCl_2$ at an initial temperature of −15 °C (entry 7). Attempts to increase the diastereoselectivity of the reaction in favor of **15** by further modification of the conditions have so far been unsuccessful.

The lactones **15** and **16** are produced presumably as a result of the zinc alkoxides **13** and **14**, formed upon reductive aldol reaction, cyclizing onto the pendant ethyl esters. Although lactonization was unexpected in light of the reaction shown in Eq. 1, it turned out to be a useful bonus, since it conveniently protected the tertiary alcohol towards subsequent transformations.[18]

The desired diastereomer **15** was subjected to palladium-catalyzed debenzylation to provide alcohol **17** (84% yield) (Scheme 4). X-ray crystallography of this compound allowed confirmation of its stereochemistry, and hence that of its immediate precursor **15**.[17] Oxidation of **17** to aldehyde **18** in readiness for installation of the cyclohexenyl group was accomplished using the Dess–Martin periodinane.[19] Aldehyde **18** proved to be somewhat unstable, and was immediately reacted with 2-cyclohexenylzinc chloride (**19**) as described by Corey and co-workers[12a] to give homoallylic alcohol **20** in highly selective fashion (one observable diastereomer by ^{1}H NMR analysis). X-ray crystallography of **20** showed that the desired stereochemistry had been obtained in the allylation.[17] Finally, reductive ring-opening of the lactone in **20** was accomplished using $NaBH_4$ to give triol **21**, the conversion of which into salinosporamide A (**1**) has already been described by the groups of Corey[12a] and Pattenden.[12d]



Scheme 4. Completion of the formal synthesis of **3**.

3. Conclusion

Largely following the strategy of Corey and co-workers,[12a] a concise formal synthesis of salinosporamide A (**3**) has been achieved. The distinguishing feature of the work described herein is the use of a sequential nickel-catalyzed reductive aldol cyclization–lactonization reaction of **8** to construct the γ-lactam of **3**. Although the diastereoselectivity of this transformation remains to be improved, this approach represents an attractive method to install the C2 side-chain with simultaneous protection of the C5 oxygen, and further demonstrates the utility of nickel catalysis in complex molecule synthesis.[1b,4a–c,f] Further applications of our reductive aldol cyclization methodology will be reported in due course.

4. Experimental section

4.1. General

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40–60 °C. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 μm). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^{1}H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), app (apparent) and br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

*4.1.1. (R)-Methyl 2-benzyloxymethyl-2-(4-methoxybenzylamino)-3-oxobutanoate (**11**)*

To a stirred solution of $(COCl)_2$ (1.67 mL, 18.8 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DMSO (2.70 mL, 37.6 mmol) dropwise over 3 min. After stirring for 15 min, a solution of the alcohol **10**[12a] (3.34 g, 8.94 mmol) in CH_2Cl_2 (30 mL) was added via cannula over 5 min. The reaction mixture was stirred at −78 °C for 1 h and Et_3N (5.23 mL, 37.6 mmol) was then added over 1 min. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to −40 °C over 2 h, and then quenched with saturated aqueous NH_4Cl

solution (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/petrol→20% EtOAc/petrol) gave the ketone **11** (2.39 g, 72%) as a pale yellow solid. R_f=0.55 (30% EtOAc/hexane); mp 60–62 °C; $[\alpha]_D^{25}$ −12.7 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3347 (NH), 2952, 2836, 1741 (C=O), 1718 (C=O), 1511, 1245, 1178, 1033, 700 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.28 (5H, m, Ar*H*), 7.25 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.85 (2H, dm, *J*=8.7 Hz, Ar*H*), 4.59 (1H, d, *J*=12.4 Hz, CH_2Ar), 4.53 (1H, d, *J*=12.4 Hz, CH_2Ar), 4.02 (1H, d, *J*=10.1 Hz, CH_2Ar), 3.90 (1H, d, *J*=10.1 Hz, CH_2Ar), 3.80 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.59 (1H, d, *J*=12.3 Hz, CH_2OBn), 3.46 (1H, d, *J*=12.3 Hz, CH_2OBn), 2.53 (1H, br s, N*H*), 2.21 (3H, s, $COCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 203.3 (C), 169.8 (C), 158.7 (C), 137.6 (C), 131.7 (C), 129.4 (2×CH), 128.4 (2×CH), 127.8 (3×CH), 113.7 (2×CH), 74.9 (C), 73.5 (CH_2), 68.1 (CH_2), 55.3 (CH_3), 52.7 (CH_3), 46.7 (CH_2), 25.7 (CH_3); HRMS (ES) exact mass calcd for $C_{21}H_{26}NO_5$ $[M+H]^+$: 372.1805, found: 372.1804.

4.1.2. (R)-Ethyl (E)-3-[N-(1-benzyloxymethyl-1-carbomethoxy-2-oxopropyl)-N-(4-methoxybenzyl)carbamoyl]acrylate (**8**)

To a stirred solution of mono-ethyl fumarate[16] (858 mg, 5.65 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $(COCl)_2$ (0.56 mL, 6.40 mmol) followed by DMF (one drop). The resulting mixture was stirred for 1 h at room temperature, and then transferred via cannula to a solution of the amine **11** (1.33 g, 3.60 mmol) and *i*-Pr_2NEt (1.10 mL, 6.40 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 18 h, when it was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *amide* **8** (1.79 g, >99%) as a pale yellow oil. R_f=0.45 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −18.2 (*c* 1.18, $CHCl_3$); IR (film) 2953, 2837, 1722 (C=O), 1658 (C=O), 1513, 1408, 1294, 1248, 1175, 1032, 974, 822 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35–7.27 (5H, m, Ar*H*), 7.21 (1H, d, *J*=15.3 Hz, =C*H*), 7.14–7.11 (2H, m, Ar*H*), 6.91 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.82 (1H, d, *J*=15.3 Hz, =C*H*), 4.94 (1H, d, *J*=18.3 Hz, CH_2Ar), 4.79 (1H, d, *J*=18.3 Hz, CH_2Ar), 4.31 (1H, d, *J*=11.9 Hz, CH_2Ar), 4.27 (1H, d, *J*=11.9 Hz, CH_2Ar), 4.18 (2H, q, *J*=7.1 Hz, OCH_2CH_3), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.76 (2H, br s, CH_2OBn), 2.43 (3H, s, CH_3C=O), 1.25 (3H, t, *J*=7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.6 (C), 168.0 (C), 167.5 (C), 165.2 (C), 158.9 (C), 136.5 (C), 133.3 (CH), 133.1 (CH), 129.7 (C), 128.4 (2×CH), 127.9 (CH), 127.5 (2×CH), 127.1 (2×CH), 114.1 (2×CH), 77.5 (C), 73.7 (CH_2), 70.1 (CH_2), 61.1 (CH_2), 55.2 (CH_3), 52.9 (CH_3), 48.9 (CH_2), 27.9 (CH_3), 14.0 (CH_3); HRMS (ES) exact mass calcd for $C_{27}H_{32}NO_8$ $[M+H]^+$: 498.2122, found: 498.2123.

4.1.3. (3aR,6R,6aS)-6-Benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**15**) and (3aS,6R,6aR)-6-benzyloxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**16**)

A solution of α,β-unsaturated amide **8** (875 mg, 1.76 mmol) and $(Me_3P)_2NiCl_2$ (115 mg, 0.175 mmol) in THF (75 mL) was stirred at room temperature for 30 min and then cooled to −15 °C (ice/salt bath). Et_2Zn (3.52 mL, 1 M solution in THF, 3.52 mmol) was then added over 0.5 min. The reaction mixture was allowed to warm slowly to room temperature over 18 h, and then quenched carefully with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/petrol→35% EtOAc/petrol) gave the *double cyclization product* **15** (354 mg, 42%) as a pale yellow oil, followed by the *double cyclization product* **16** (253 mg, 30%) as a white solid. Recrystallization of **16** from EtOAc/petrol gave colorless blocks that were suitable for X-ray crystallography.

Data for **15**: R_f=0.19 (30% EtOAc/$CHCl_3$); $[\alpha]_D^{25}$ −33.3 (*c* 1.02, $CHCl_3$); IR (film) 2955, 1789 (C=O), 1733 (C=O), 1699 (C=O), 1612, 1513, 1439, 1404, 1248, 1178, 1129, 736 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.25 (5H, m, Ar*H*), 7.12–7.08 (2H, m, Ar*H*), 6.60 (2H, dm, *J*=8.7 Hz, Ar*H*), 5.05 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.28 (1H, d, *J*=15.2 Hz, CH_2Ar), 3.91 (1H, d, *J*=11.5 Hz, CH_2O), 3.83 (1H, d, *J*=10.4 Hz, CH_2O), 3.81 (1H, d, *J*=11.5 Hz, CH_2O), 3.81 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.21 (1H, d, *J*=10.4 Hz, CH_2O), 3.05 (1H, dd, *J*=9.3, 1.5 Hz, CH_2CH), 2.96 (1H, dd, *J*=18.3, 1.5 Hz, CH_2CH), 2.79 (1H, dd, *J*=18.3, 9.3 Hz, CH_2CH), 1.61 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.5 (C), 172.9 (C), 166.9 (C), 158.9 (C), 136.7 (C), 130.0 (2×CH), 129.4 (C), 128.5 (2×CH), 127.9 (CH), 127.3 (2×CH), 113.6 (2×CH), 88.5 (C), 75.8 (C), 72.8 (CH_2), 67.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 47.5 (CH), 45.1 (CH_2), 30.7 (CH_2), 19.4 (CH_3); HRMS (ES) exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860, found: 454.1856.

Data for **16**: R_f=0.08 (30% EtOAc/$CHCl_3$); mp 105–106 °C; $[\alpha]_D^{25}$ −17.9 (*c* 1.01, $CHCl_3$); IR (film) 2952, 2870, 1789 (C=O), 1743 (C=O), 1703 (C=O), 1613, 1512, 1434, 1246, 1128, 739 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.28 (3H, m, Ar*H*), 7.22–7.19 (2H, m, Ar*H*), 7.09 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.78 (2H, d, *J*=8.8 Hz, Ar*H*), 4.68 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.37 (1H, d, *J*=15.2 Hz, CH_2Ar), 4.30 (1H, d, *J*=11.7 Hz, CH_2Ar), 4.23 (1H, d, *J*=11.7 Hz, CH_2Ar), 3.90 (1H, d, *J*=10.2 Hz, CH_2OBn), 3.78 (3H, s, OCH_3), 3.71 (1H, d, *J*=10.2 Hz, CH_2OBn), 3.64 (3H, s, OCH_3), 3.03 (1H, dd, *J*=9.7, 1.9 Hz, CH_2CH), 3.00 (1H, dd, *J*=18.3, 1.9 Hz, CH_2CH), 2.84 (1H, dd, *J*=18.3, 9.7 Hz, CH_2CH), 1.47 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.4 (C), 173.2 (C), 169.2 (C), 158.7 (C), 137.1 (C), 129.2 (2×CH), 129.0 (C), 128.3 (2×CH), 127.7 (3×CH), 113.6 (2×CH), 86.6 (C), 75.3 (C), 73.6 (CH_2), 68.7 (CH_2), 55.2 (CH_3), 52.8 (CH_3), 46.9 (CH), 45.1 (CH_2), 30.9 (CH_2), 21.8 (CH_3); HRMS (ES) exact mass calcd for $C_{25}H_{28}NO_7$ $[M+H]^+$: 454.1860, found: 454.1858.

4.1.4. (3aR,6R,6aS)-6-Hydroxymethyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**17**)

A mixture of benzyl ether **15** (354 mg, 0.78 mmol) and 10% Pd/C (99 mg, 0.093 mmol) in EtOH (5 mL) at room temperature was evacuated and flushed with H_2 (three times) and then stirred vigorously under an atmosphere of H_2 (1 atm, H_2 balloon) at room temperature for 18 h. The reaction mixture was filtered through Celite and concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/petrol) gave the *alcohol* **17** (240 mg, 84%) as a white powder. Recrystallization of **17** from CH_2Cl_2/Et_2O gave colorless blocks that were suitable for X-ray crystallography. R_f=0.52 (100% EtOAc); mp 144–146 °C; $[\alpha]_D^{25}$ −30.1 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3437 (OH), 2955, 2837, 2253, 1787 (C=O), 1757 (C=O), 1692 (C=O), 1613, 1513, 1247, 1035, 951, 914, 731 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (2H, dm, *J*=8.6 Hz, Ar*H*), 6.87 (2H, dm, *J*=8.6 Hz, Ar*H*), 5.22 (1H, d, *J*=15.2 Hz, NCH_2), 4.24 (1H, d, *J*=15.2 Hz, NCH_2), 3.95 (1H, dd, *J*=13.0, 8.9 Hz, CH_2OH), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.43 (1H, dd, *J*=13.0, 5.5 Hz, CH_2OH), 3.04 (1H, dd, *J*=9.1, 1.7 Hz, CH_2CH), 2.96 (1H, dd, *J*=18.1, 1.7 Hz, CH_2CH), 2.85 (1H, dd, *J*=18.1, 9.1 Hz, CH_2CH), 1.69 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.7 (C), 172.7 (C), 167.1 (C), 159.5 (C), 129.6 (2×CH and C), 114.6 (2×CH), 88.3 (C), 77.3 (C), 60.9 (CH_2), 55.3 (CH_3), 52.8 (CH_3), 47.6 (CH), 44.9 (CH_2), 30.5 (CH_2), 19.8 (CH_3); HRMS (ES) exact mass calcd for $C_{18}H_{25}N_2O_7$ $[M+NH_4]^+$: 381.1656, found: 381.1660.

4.1.5. (3aR,6R,6aS)-6-Formyl-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro[2,3-c]pyrrole-6-carboxylic acid methyl ester (**18**)

To a solution of the alcohol **17** (30 mg, 0.082 mmol) in CH_2Cl_2 (0.8 mL) at room temperature was added Dess–Martin periodinane

(43 mg, 0.099 mmol). The reaction mixture was stirred for 1.5 h, quenched with H_2O (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to leave the *aldehyde* **18** as a pale yellow oil. This aldehyde was not very stable and was generally used immediately in the next step without purification. On one occasion, purification of a small amount of crude product by column chromatography (50% EtOAc/petrol) was performed for characterization purposes. R_f=0.34 (100% EtOAc); IR ($CHCl_3$) 2956, 1788 (C=O), 1760 (C=O), 1728 (C=O), 1687 (C=O), 1513, 1438, 1246, 1176, 949 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.47 (1H, s, C*H*O), 7.05 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.81 (2H, dm, *J*=8.7 Hz, Ar*H*), 4.86 (1H, d, *J*=14.4 Hz, NCH_2), 4.39 (1H, d, *J*=14.4 Hz, NCH_2), 3.90 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.08 (1H, dd, *J*=9.7, 1.8 Hz, CH_2CH), 2.99 (1H, dd, *J*=18.4, 1.8 Hz, CH_2CH), 2.85 (1H, dd, *J*=18.4, 9.7 Hz, CH_2CH), 1.52 (3H, s, CH_3CO); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 195.5 (CH), 172.7 (C), 172.0 (C), 165.7 (C), 159.6 (C), 131.1 (2×CH), 126.8 (C), 114.2 (2×CH), 87.3 (C), 79.0 (C), 55.2 (CH_3), 53.4 (CH_3), 46.8 (CH), 45.6 (CH_2), 30.7 (CH_2), 20.5 (CH_3); LRMS (ES) 384 $[M+Na]^+$.

*4.1.6. (3aR,6R,6aS)-6-[(S)-{(S)-Cyclohex-2-eny}hydroxymethyl]-5-(4-methoxybenzyl)-6a-methyl-2,4-dioxohexahydrofuro [2,3-c]pyrrole-6-carboxylic acid methyl ester (**20**)*

To a solution of cyclohexenyltributyltin (**19**)[20] (ca. 85% pure by ^1H NMR analysis, 90 mg, 0.21 mmol) in THF (0.6 mL) at −78 °C was added *n*-BuLi (130 μL, 1.6 M solution in hexanes, 0.21 mmol). After stirring at −78 °C for 1 h, $ZnCl_2$ (420 μL, 0.5 M solution in THF, 0.21 mmol) was added and stirring was continued at this temperature for another 1 h. A solution of the unpurified aldehyde **18** from the above experiment (theoretically 0.082 mmol) in THF (0.4 mL) was then added via cannula, and after stirring for 3 h at −78 °C, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo, and purification of the residue by column chromatography (50% EtOAc/petrol) gave the *homoallylic alcohol* **20** (22.4 mg, 61% over two steps) as a white solid. Recrystallization from **20** from a mixture of EtOAc/hexane and acetone (a few drops) gave colorless needles that were suitable for X-ray diffraction. R_f=0.61 (100% EtOAc); mp 114–116 °C; $[\alpha]_D^{25}$ +3.0 (*c* 1.47, $CHCl_3$); IR ($CHCl_3$) 3438 (OH), 2931, 2359, 1790 (C=O), 1755 (C=O), 1687 (C=O), 1512, 1440, 1246, 1175, 807 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19 (2H, dm, *J*=8.7 Hz, Ar*H*), 6.84 (2H, dm, *J*=8.7 Hz, Ar*H*), 5.92 (1H, dm, *J*=10.3 Hz, =C*H*), 5.68 (1H, dm, *J*=10.3 Hz, =C*H*), 4.80 (1H, d, *J*=14.9 Hz, NCH_2), 4.54 (1H, d, *J*=14.9 Hz, NCH_2), 4.13 (1H, t, *J*=7.1 Hz, C*H*OH), 3.78 (6H, s, 2×OCH_3), 3.13 (1H, dd, *J*=6.8, 3.3 Hz, CH_2CHC=O), 2.92 (1H, br s, O*H*), 2.82–2.80 (2H, m, CH_2CHC=O), 2.32 (1H, br s, C*H*CHOH), 2.02 (2H, br s, $(CH_2)_3$), 1.81 (3H, s, CH_3CO), 1.76–1.66 (2H, m, $(CH_2)_3$), 1.57–1.46 (1H, m, $(CH_2)_3$), 1.44–1.33 (1H, m, $(CH_2)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.8 (C), 173.0 (C), 167.8 (C), 158.3 (C), 131.8 (CH), 129.3 (C), 127.6 (2×CH), 125.2 (CH), 113.7 (2×CH), 91.1 (C), 79.0 (C), 76.9 (CH), 55.2 (CH_3), 52.4 (CH_3), 47.9 (CH_2), 47.8 (CH), 38.3 (CH), 30.9 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 20.6 (CH_2), 19.6 (CH_3); HRMS (ES) exact mass calcd for $C_{24}H_{33}N_2O_7$ $[M+NH_4]^+$: 461.2282, found: 461.2283.

*4.1.7. (2R,3S,4R)-2-[(S)-{(S)-Cyclohex-2-enyl}hydroxymethyl]-3-hydroxy-4-(2-hydroxyethyl)-1-(4-methoxybenzyl)-3-methyl-5-oxopyrrolidine-2-carboxylic acid methyl ester (**21**)[12a]*

To a solution of the lactone **20** (19.3 mg, 0.043 mmol) in MeOH (0.6 mL) at room temperature was added $NaBH_4$ (75 mg, 2.0 mmol) portionwise over 2 min. The solution was stirred for 18 h, quenched with H_2O (4 mL) and extracted with EtOAc (3×4 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography (70% EtOAc/petrol) gave the triol **21** (11.7 mg, 60%) as a white foam. R_f=0.12 (70% EtOAc/$CHCl_3$); mp 83–84 °C; $[\alpha]_D^{25}$ +3.5 (*c* 0.565, $CHCl_3$); IR ($CHCl_3$) 3331 (OH), 2925, 2853, 1752 (C=O), 1670 (C=O), 1512, 1441, 1245, 1175, 1034, 801 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (2H, dm, *J*=8.8 Hz, Ar*H*), 6.85 (2H, dm, *J*=8.8 Hz, Ar*H*), 5.97–5.91 (1H, m, =C*H*), 5.65–5.60 (1H, m, =C*H*), 4.77 (1H, d, *J*=15.2 Hz, NCH_2), 4.58 (1H, d, *J*=15.2 Hz, NCH_2), 4.15 (1H, app t, *J*=6.3 Hz, C*H*OH), 3.87–3.81 (1H, m, CH_2OH), 3.80–3.75 (1H, m, CH_2OH), 3.79 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.02 (1H, dd, *J*=8.1, 4.8 Hz, C*H*C=O), 2.20 (1H, br s, C*H*CHOH), 2.01 (2H, br s, $(CH_2)_3$ and/or CH_2CH_2OH), 1.93–1.78 (2H, m, $(CH_2)_3$ and/or CH_2CH_2OH), 1.76–1.65 (4H, m, $(CH_2)_3$ and/or CH_2CH_2OH), 1.64 (3H, s, CH_3CO), 1.54–1.41 (2H, m, $(CH_2)_3$ and/or CH_2CH_2OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 178.5 (C), 169.7 (C), 158.2 (C), 132.9 (CH), 130.2 (C), 128.0 (2×CH), 124.8 (CH), 113.7 (2×CH), 81.8 (C), 80.6 (C), 77.2 (CH), 61.7 (CH_2), 55.2 (CH_3), 51.9 (CH), 51.3 (CH_3), 47.8 (CH_2), 38.6 (CH), 28.2 (CH_2), 26.8 (CH_2), 25.0 (CH_2), 21.2 (CH_3), 20.6 (CH_2); HRMS (ES) exact mass calcd for $C_{24}H_{33}NO_7Na$ $[M+Na]^+$: 470.2149, found: 470.2150.

Interestingly, the NMR data we obtained for triol **21** (recorded above) displayed subtle but appreciable differences to those reported by Corey and co-workers for the same compound,[12a] most notably in the ^{13}C NMR chemical shifts. However, we have also obtained from Pattenden and co-workers copies of the NMR spectra for the same compound that was prepared in their total synthesis of salinosporamide A,[12d] and our ^{13}C NMR data are a good match for theirs (^{13}C NMR spectrum supplied by Pattenden in Supplementary data). The most likely explanation for this observation is that the values of the ^{13}C NMR chemical shifts for triol **21** are concentration-dependent; both our and the Pattenden group's ^{13}C NMR spectra were run at relatively low concentration, whereas the Corey group's ^{13}C NMR spectrum was run at relatively high concentration. Due to limited quantities of triol **21**, we were unable to verify this hypothesis.

Acknowledgements

This work was supported by the EPSRC (GR/T07466/01) and the European Commission (Project No. MEST-CT-2005-020744). We thank Professor Gerald Pattenden at the University of Nottingham and Professor Elias J. Corey at Harvard University for helpful discussions. In addition, we thank Professor Pattenden and Dr. Leleti Rajender Reddy (Corey group) for providing copies of ^1H NMR and ^{13}C NMR spectra of triol **21**. We are grateful to Professor Simon Parsons, Dr. Anna Collins and Laura E. Budd at the School of Chemistry, University of Edinburgh for assistance with X-ray crystallography. The EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea is thanked for providing high resolution mass spectra.

Supplementary data

Copies of ^1H and ^{13}C NMR spectra for new compounds, and ^{13}C NMR spectrum of triol **21** supplied by Pattenden and co-workers. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.038.

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COMMUNICATIONS

Aromatic Heterocycles as Activating Groups for Asymmetric Conjugate Addition Reactions. Enantioselective Copper-Catalyzed Reduction of 2-Alkenylheteroarenes

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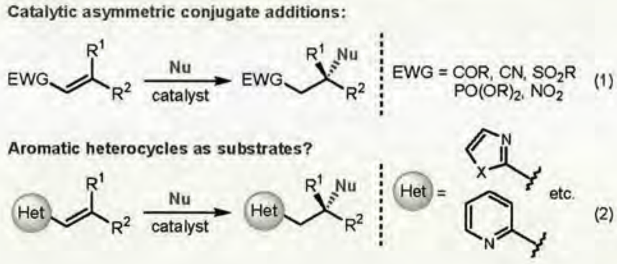
The 1,4-addition of a nucleophile to an alkene conjugated to an electron-withdrawing group is a fundamental reaction in organic chemistry, and numerous catalytic asymmetric variants (eq 1) of this process are now routinely employed in the synthesis of molecules of interest.[1,2] The most common functional groups used to activate alkenes toward asymmetric conjugate additions include carbonyls, nitriles, sulfones, phosphonates, and nitro groups. We recently questioned whether other rarely considered yet common functional groups might also be employed in this capacity, and our attention focused on nitrogen-containing aromatic heterocycles. Given that heteroarenes such as oxazoles, thiazoles, pyridines, and others are ubiquitous in biologically active natural products, pharmaceuticals, and agrochemicals, the ability to functionalize these privileged structures through a diverse set of asymmetric conjugate additions of 2-alkenyl derivatives (eq 2) would open up broad-ranging applications.

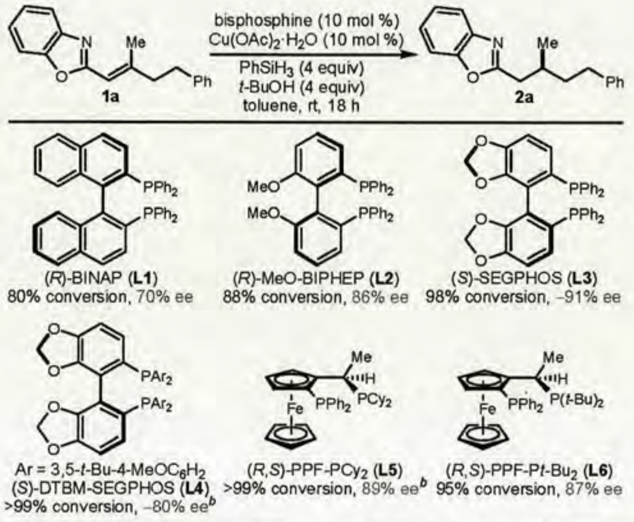


Although conjugate additions to 2-vinylheteroarenes (R^1, R^2 = H in eq 2) are relatively common,[3] the corresponding reactions of substrates containing a β-substituent are much rarer, presumably for steric reasons.[4,5] Furthermore, the only report of a catalytic enantioselective variant is limited to poorly selective (≤15% ee) Grignard additions to 4-alkenylpyridines.[5] Therefore, we recently initiated a program targeted at addressing these deficiencies, and in this communication, our preliminary findings involving highly enantioselective copper-catalyzed reductions[6] of β,β'-disubstituted 2-alkenylheteroarenes are presented.

The asymmetric copper-catalyzed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks.[6−10] Whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent alkene in an analogous reaction was, however, uncertain. In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the copper catalyst would occur in such a process, and whether this interaction would be beneficial, inconsequential, or detrimental was not easy to predict.

Our investigations began with a survey of chiral bisphosphines **L1**−**L6** using 2-alkenylbenzoxazole **1a** as a test substrate (Table 1). Using 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 10 mol % of ligand, and 4 equiv each of $PhSiH_3$ and *t*-BuOH in toluene at room temperature, biaryl-based ligands **L1**−**L4** proved competent in promoting conjugate reduction.[11] With (*R*)-BINAP (**L1**), both conversion and enantioselectivity were only moderate. However, improved results were observed using (*R*)-MeO-BIPHEP (**L2**) and the SEGPHOS ligands **L3** and **L4**, with 91% ee obtained using (*S*)-SEGPHOS (**L3**). The Josiphos ligands **L5** and **L6** were also effective, providing **2a** in 89% and 87% ee, respectively. Of all the ligands, the highest reaction rates were observed with **L4** and **L5** (reactions were complete in 2 h). However, the superior selectivity provided by **L5** prompted us to select this ligand for further optimization and investigation of the reaction scope.

Table 1. Ligand Optimization for the Asymmetric Reduction of **1a**[a]



(*R*)-BINAP (**L1**)
80% conversion, 70% ee

(*R*)-MeO-BIPHEP (**L2**)
88% conversion, 86% ee

(*S*)-SEGPHOS (**L3**)
98% conversion, −91% ee

Ar = 3,5-*t*-Bu-4-MeOC_6H_2
(*S*)-DTBM-SEGPHOS (**L4**)
>99% conversion, −80% ee[b]

(*R*,*S*)-PPF-PCy_2 (**L5**)
>99% conversion, 89% ee[b]

(*R*,*S*)-PPF-P*t*-Bu_2 (**L6**)
95% conversion, 87% ee

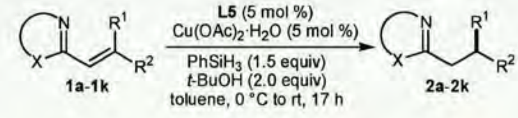
[a] Reactions were conducted using 0.20 mmol of **1a** in toluene (1 mL). Conversions were determined by GC analysis. Enantioselectivities were determined by chiral HPLC analysis. [b] Reactions complete after 2 h.

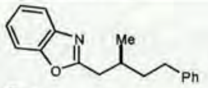
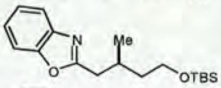
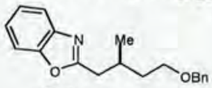
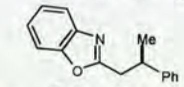
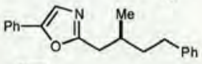
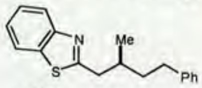
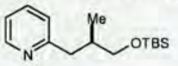
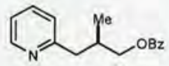
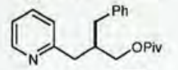
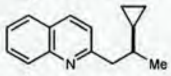
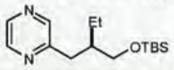
Using 5 mol % each of $Cu(OAc)_2 \cdot H_2O$ and **L5**, $PhSiH_3$ (1.5 equiv), and *t*-BuOH (2.0 equiv) at an initial temperature of 0 °C, a range of β,β'-disubstituted 2-alkenylheteroarenes underwent conjugate reduction with generally excellent levels of enantioselection (Table 2).[11] In addition to benzoxazole (entries 1−4), other effective nitrogen-containing heteroarenes in this process included 5-phenyloxazole (entry 5), benzothiazole (entry 6), pyridine (entries 7−9), quinoline (entry 10), and pyrazine (entry 11). Tolerated functionality at the β-positions of the alkene included simple aliphatic groups, a phenyl group (entry 4), a benzyl group (entry 9), various oxygenated alkyl groups (entries 2, 3, 7−9, and 11), and a cyclopropane (entry 10). The process is tolerant of lower loadings of copper and ligand. For example, reduction of **1g** on a 1.0 mmol scale using 2 mol % each of $Cu(OAc)_2 \cdot H_2O$ and **L5** provided **2g** in 92% yield and 96% ee (entry 7, values in parentheses).

Experiments to explore the origins of reactivity were then conducted. Reduction of 4-alkenylpyridine **3** provided **4** in 60% yield and 94% ee, albeit in a slower reaction that was incomplete even after 4 days (eq 3). This result suggests that alkene reduction by copper hydride can occur without assistance of a directing effect from the nitrogen atom. In contrast,

10.1021/ja904365h CCC: $40.75

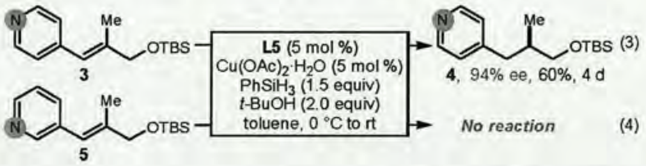
Table 2. Scope of Cu-Catalyzed Asymmetric Conjugate Reduction[a]



entry	product		yield (%)[b]	ee (%)[c]
1		**2a**	90	93
2		**2b**	67	94
3		**2c**	88	95
4[d]		**2d**	95	87
5		**2e**	93	90
6		**2f**	86	95
7		**2g**	90 (92)[e]	>99 (96)[e]
8[f]		**2h**	81	98
9		**2i**	90	97
10		**2j**	90	96
11		**2k**	89	96

[a] Reactions were conducted using 0.20 mmol of **1a**−**1k** unless otherwise stated. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Using 0.155 mmol of **1d**. [e] Values in parentheses refer to a reaction conducted using 1.0 mmol of **1g**, 2 mol % Cu, and 2 mol % **L5**. [f] Using 0.10 mmol of **1h** and 2.0 equiv of PhSiH$_3$.

3-alkenylpyridine **5** was unreactive (eq 4), demonstrating the importance of conjugation of the alkene to a C═N moiety for reactivity.



In summary, copper-catalyzed asymmetric conjugate reductions of β,β'-disubstituted 2-alkenylheteroarenes are reported. In addition to serving as a further demonstration of the power of chiral copper hydride catalysis,[6] this work has shown nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate addition reactions. Extension of the general concept to other classes of asymmetric reactions should provide a range of useful tools for chemists working with heteroarenes. Future studies from our laboratory will be directed toward this goal.

Acknowledgment. This work was supported by the European Commission (Project No. MEST-CT-2005-020744). Drs. Izuru Nagasaki (Takasago), Rudolf Schmid (Hoffmann-La Roche), and Matthias Lotz (Solvias AG) are gratefully acknowledged for supplying the SEGPHOS, MeO-BIPHEP, and Josiphos ligands, respectively, used in this study. We thank the EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea, for providing high resolution mass spectra. Dr. Fraser J. White is thanked for assistance with X-ray crystallography.

Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA904365H

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