Acid–Catalysed Hydroaminations

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by

Laura Henderson

MChem (Hons.)

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School of Chemistry

Cardiff University

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

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DECLARATION

This work has not previously been accepted in substance for any degree and is not concurrently submitted in candidature for any degree.

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STATEMENT 1

This thesis is being submitted in partial fulfilment of the requirements for the degree of PhD

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This thesis is the result of my own independent work/investigation, except where otherwise stated.

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Abstract

The Knight group has for some time been utilising the acid-catalysed hydroamination to synthesise pyrrolidines **140**. This method was also utilised to produce poly-cyclic systems, of either a *spiro*-**220** or a fused-nature **12**, through cascade reactions using a sulfonamide as a terminator. This was examined further to establish some scope and limitation. In particular, we have shown that the reaction is not limited to the formation of tertiary carbenium ions but could be implemented for cyclisations *via* secondary carbenium ions **155**. The hydroamination was also shown to be most successful at forming highly hindered, bridged compounds **194**, which would be difficult to synthesise through other means.

The hydroamination reaction was then investigated in terms of its potential as a variant of the classical Pictet-Spengler reaction towards dihydroisoindoles **363** and tetrahydroisoquinolines **361**. This was briefly explored in terms of the type of remote functional groups that would be compatible with this method. The formation of the isoindoles and isoquinolines was successful and further investigations of compatible functional groups need to be performed.

The synthesis of the trisubstituted piperidine **447** was attempted using the acid-catalysed hydroamination method, believing that this would be a simple extension of the pyrrolidine synthesis. Unfortunately, this was not successful; instead the corresponding pyrrolidine **449** was isolated. This led us to further investigate the sensitivity of sterically crowded piperidines towards acid. Successful synthesis of trisubstituted piperidine **501** was achieved by changing the *N*-protecting group.

Contents

Abbreviations

Abbreviations in this text are:

Ac	Acetyl
APCI	Atmospheric Pressure Chemical Ionisation
Aq.	Aqueous
Ar	Aromatic
Boc	Butoxycarbonyl
9-BBN	9-Borabicyclo[3.3.1]nonane
Conc.	Concentrated
Cbz	Benxyl carbamate
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
d.e.	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DMAP	Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
dtbpf	Di-*tert*-butyl phosphine ferrocene
e.e.	Enantiomeric excess
Eq.	Equivalents
EI	Electro Ionisation
ES	Electro Spray
hr	Hour
hrs	Hours
HRMS	High Resolution Mass Spectrometry
IR	Infra red
LDA	Lithium diisopropylamine
LRMS	Low Resolution Mass Spectrometry
m.p.	Melting point
M	Molar (moles L^{-1})
mins	Minutes
MsCl	Mesyl chloride/ methanesulfonyl chloride
NMR	Nuclear Magnetic Resonance
Ns / nosyl	*para*-Nitrobenzenesulfonyl
i-Pr	*iso*-Propyl

Ppm	Parts per million
Py	Pyridine
r.t.	Room temperature
Sat.	Saturated
TBAF	tetra-*n*-Butylammonium fluoride
TBS	*tert*-Butylsilyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TfOH	Trifluoromethane sulfonic acid
PCy_3	Tricyclohexylphosphine
TsNHBoc	*N*-(*tert*-Butoxycarbonyl)-*p*-toluenesulfonamide
Ts / tosyl	*p*-Toluenesulfonyl
TsCl	*p*-Toluenesulfonyl chloride

Chapter 1

Chapter 1

Introduction to Acid-Catalysed Hydroamination

"Hydroamination is a highly atom-economical process in which an amine N-H functionality is added to an unsaturated carbon-carbon linkage."[1]

1.1. Hydroamination Development

Nitrogen-containing saturated heterocyclic systems are important core structures in organic chemistry because of their presence in many natural products;[2] making the development of simple procedures for the formation of heterocycles, such as pyrrolidines and piperidines, highly desirable.[3] Other nitrogen containing compounds including amines, enamines and imines, are valuable and commercially important bulk chemicals, speciality chemicals and pharmaceuticals.[4] Amongst various synthetic routes, hydroamination, the direct formation of a new carbon-nitrogen bond by addition of an amine to an unsaturated carbon-carbon bond, is of particular significance.[5] The reaction offers a potentially atom-efficient pathway starting from readily accessible alkenes and alkynes. [6,7,8,9,10]

The hydroamination of alkenes is more difficult compared to that of alkynes because of the lower reactivity and electron density of carbon-carbon double bonds.[11] A particular challenge is the reversal of stereochemistry to obtain the anti-Markovnikov product.[12] During recent years, hydroamination became a widely explored operation in the synthesis of nitrogen heterocycles and complex nitrogenous molecules in general. The Markovnikov addition of protected amines to alkynes is also now an established synthetic strategy. In early studies, hydroaminations were mostly triggered by alkali and lanthanide metals, followed by a shift in focus to the use of zirconium, titanium[5,13] and late transition metal catalysts.[14] Most of these are employed as homogenous catalysts, though new strategies for the immobilisation of these have gained and will undoubtedly continue to gain increased importance.[10a]

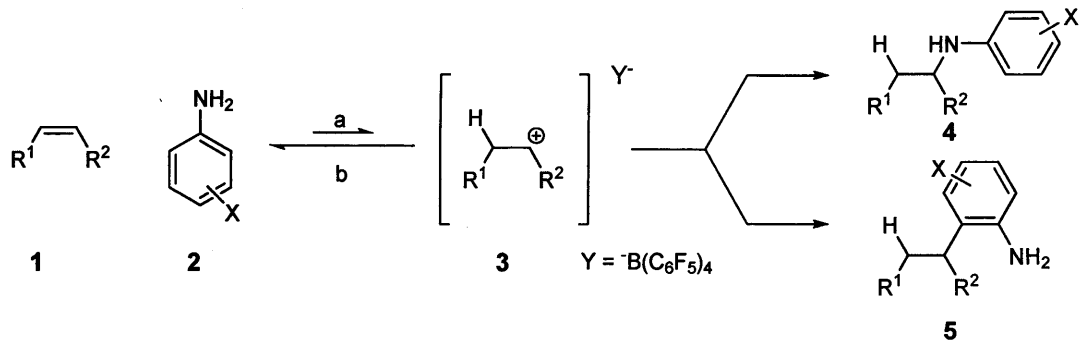
Acid-catalysed hydroaminations have been developed from related, well studied methods of carbon-oxygen bond formation using acid catalysts. Alkenes undergo hydration in moderately concentrated aqueous sulfuric acid to generate saturated alcohols .[15]

1.2. Brønsted Acid-Catalyzed Hydroamination of Alkenes and Alkynes

Except for solid acids, Brønsted acids had not been used extensively as catalysts in hydroamination processes involving alkenes and alkynes because of the more basic character of the nitrogen compared with the π-system of unsaturated compounds. This resulted in the preferential formation of ammonium salts instead of the carbenium ions, which result from proton addition to carbon-carbon double or triple bonds. In this way, the nucleophilic character of the nitrogen is removed and thus attack of the nucleophile on the π-system cannot occur. Despite these general considerations, it was found that catalytic amounts of Brønsted acids favoured the inter- and intramolecular hydroamination of alkenes and alkynes with homogeneous and heterogeneous catalysts.[16,17,18] A reaction pathway *via* intermediate protonation of styrenes was proposed by Hii for copper-catalysed hydroaminations.[19] In nearly all hydroamination reactions, the basicity of the amine or amine derivative plays a key role: more basic amines lead to lower rates of reaction.[20]

1.2.1. Intermolecular Brønsted Acid-Catalyzed Hydroamination of Alkenes

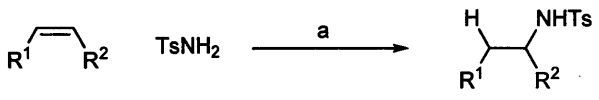
Hydroamination/hydroarylation of olefins **1** with anilines **2** was performed using $PhNH_3B(C_6F_5)_4.Et_2O$ (Scheme 1.1). [21]



Scheme 1.1. a) $PhNH_3B(C_6F_5)_4.Et_2O$ (5 mol%) b) C_6D_6

The addition reactions tolerate substitution on the nitrogen as well as in the aromatic ring of the aniline **2**. Electron-withdrawing substituents on the aniline ring increase the overall yield of the reaction and favour the formation of the hydroamination product. Stabilized carbocations **3** were postulated to act as a reaction intermediate, and either the nitrogen or the aromatic ring could act as the nucleophile to give, after proton loss, the hydroamination or hydroarylation products **4** or **5**, respectively.[21] Dupont found that intermolecular hydroamination or hydroarylation reactions of norbornene and cyclohexadiene performed with catalytic amounts of Brønsted acids in ionic liquids provided higher selectivity and yields than those obtained in classical organic solvents.[22]

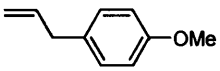
He and co-workers reported the hydroamination of simple olefins **6** with tosylamide **7** under relatively mild conditions mediated by trifluoromethanesulfonic acid at low concentrations to give compounds **8** (Scheme 1.2 and Table 1.1). Under the same reaction conditions, $CbzNH_2$ could be added to 1,3-dienes to afford allylamines in good yields.[23] Hartwig reported a very similar result, at almost the same time.[24]



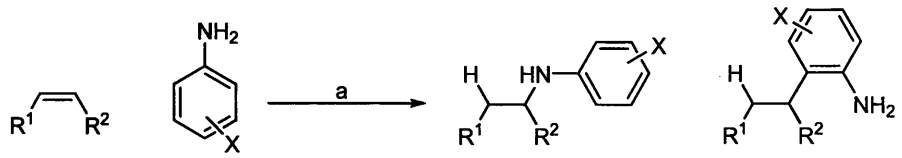
6 **7** **7**

Scheme 1.2. a) 5% TfOH, PhMe

Table 1.1. Examples of hydroamination of simple olefins with 5% trifluomethanesulfonic acid

Olefin 6	Temperature / °C	Time / hrs	Yield / %
	85	15	70
	85	15	85
	60	15	88

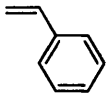
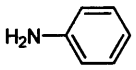
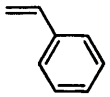
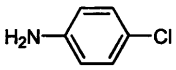
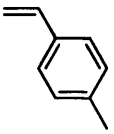
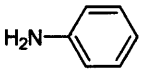
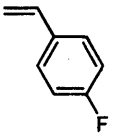
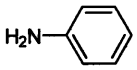
Marcseková and Doye found that substituted anilines **2** reacted with styrenes **1** in the presence of catalytic amounts of aqueous hydrogen iodide to give a mixture of the corresponding hydroamination and hydroarylation products, **4** and **5**, respectively (Scheme 1.3 and Table 1.2).[25]



1 **2** **4** **5**

Scheme 1.3. a) 5 mol% HI, PhMe

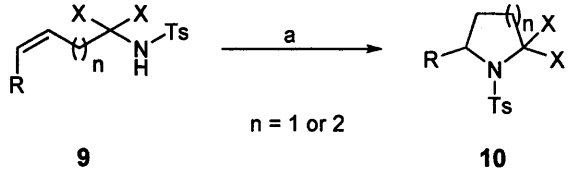
Table 1.2. Examples of hydroamination/hydroarylation of simple olefins with hydrogen iodide

Olefin 1	Anilines 2	Temperature / °C	Time / hrs	Ratio of 4 : 5	Yield / %
		135	4	3 : 2	98
		135	24	2 :3	86
		135	24	5 : 4	80
		135	24	7 : 3	82

The hydroamination reaction is the predominant process; however, the hydroarylation reaction becomes more important in the case of aryl-substituted olefins. The electronic properties of the amine and the olefin play important roles in the selectivity of the reaction. The proposed mechanism for this reaction involved an initial addition of hydrogen iodide to the olefin followed by a nucleophilic substitution.

1.2.2. Intramolecular Brønsted Acid-Catalyzed Hydroamination of Alkenes

Intramolecular hydroamination is of great interest, because nitrogen-containing heterocycles are synthesized from amino olefins. The first example of a Brønsted acid-catalyzed intramolecular hydroamination was reported by Schlummer and Hartwig.[2] Aminoalkenes **9** bearing an electron withdrawing group at the nitrogen atom led to pyrrolidines and piperidines **10** in excellent yields in the presence of a substoichiometric amount of triflic acid in hot toluene (Scheme 1.4). Lactams (**9**, X = O) were also prepared under the same reaction conditions starting from amides.



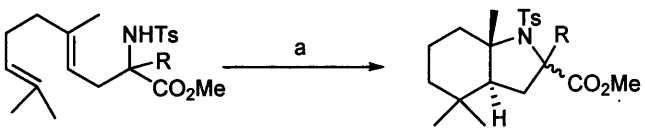
9 **10**

Scheme 1.4. a) 20 mol% TfOH, Toluene, 100 °C

During studies on palladium-catalyzed hydroamination[26] of tosylamides,[27] they discovered from control experiments that this Brønsted acid catalyzed cyclisation generates five- and six-membered heterocycles in good yield. The initial experiments showed that tosyl-protected aminoalkene **9**

cyclised in the presence of catalytic $Pd(PPh_3)_4$ and triflic acid. However, this reaction, in contrast to reactions of free amines, occurred in the absence of palladium to give heterocycles **10** in good yield. In the absence of acid, no product was observed, even upon prolonged heating at 100 °C in toluene.[2]

In the case of using sulfuric acid as catalyst, yields were generally lower. In a proposed mechanism, the alkenyl tosylamide is protonated first at the tosylamide group, the proton then transferred intramolecularly to the double bond, and finally, the resulting carbenium ion is trapped by the sulfonamide, which regenerates a protond rendering the process catalytic in acid. The regiochemistry of the process is determined mostly by the stability of the carbenium ion intermediate, thus, most of these transformations are overall unfavourable 5-*endo*-trig cyclisations, according to Baldwin's rules.[28] Yin and Zhao applied the former methodology to the synthesis of indolines and quinolines using *N*-arylsulfonyl-2-allylanilines as starting materials, the process being carried out in toluene at 80 °C in the presence of a catalytic amount of triflic acid.[29] Contemporaneously to the study of Schlummer and Hartwig,[2] Haskins and Knight demonstrated that triflic acid was an excellent catalyst for inducing overall 5-*endo*-trig cyclisation of homoallylic sulfonamides to give pyrrolidines.[30] They applied this methodology to the synthesis of polycyclic compounds through a cationic cascade terminated by a sulfonamide group. For instance, geranyl derivative **11** underwent rapid cyclisation at 0 °C to give 90% isolated yields of the *trans*-annulated pyrrolidine **12**, as a 3:2 epimeric mixture at the amino ester stereogenic centre (Scheme 1.5). This assignment of structure was confirmed by a single crystal X-ray crystallographic determination of a separated sample of the major isomer of the glycine derivative **12a**.

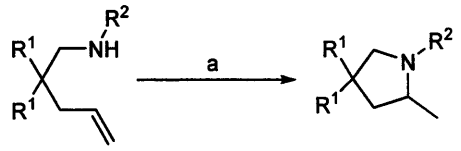


11a R = H
11b R = Me

12a R = H
12b R = Me

Scheme 1.5. a) 0.4 eq. TfOH, $CHCl_3$, 0 °C

Intramolecular hydroamination reactions of non-activated alkenes with basic alkylamines using Brønsted acid catalysis were unknown until Ackermann *et al.* found that ammonium salts of weakly coordinating anions enabled efficient catalysis but at elevated temperatures. The reaction conditions allowed the use of substrates bearing a variety of valuable functional groups, so *bis*-homoallyl amines **13** were converted into pyrrolidines **14** in high yields (Scheme 1.6).[31]



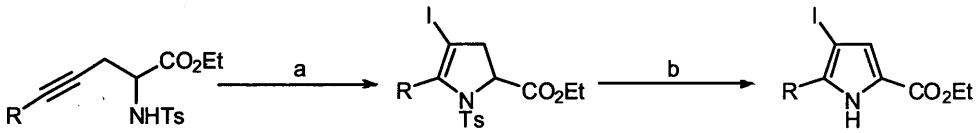
13 14

Scheme 1.6. a) 20 mol% R_3NHX, 1,4-dioxane, 120 - 130 °C, 24 hrs

This protocol is not restricted to *gem*-disubstituted substrates and can be applied to primary alkylamines.

1.3. Development of Acid-Catalysed Hydroamination in the Knight Group

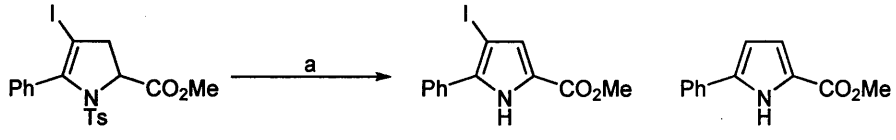
The development in acid-catalysed hydroaminations in the Knight group resulted directly from research into iodocyclisations. Sharland[32] of the Knight group discovered that iodopyrrole-2-carboxylates **17** could readily be obtained by base-induced elimination of the elements of *p*-toluenesulfinic acid upon exposure of the initial iodocyclisation product **16** to two equivalents of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) in DMF at ambient temperature (Scheme 1.7).



15 16 17

Scheme 1.7. a) 3 eq. I_2, K_2CO_3, MeCN b) 2 eq. DBU, DMF, 20 °C, ~2 hrs

However, in their initial investigations of this elimination reaction, they found that heating the iodo-dihydropyrrole **18** with one equivalent of DBU in DMF at 90 °C led to the formation of a mixture of the desired iodopyrrole **19** together with the deiodinated pyrrole **20** (Scheme 1.8).



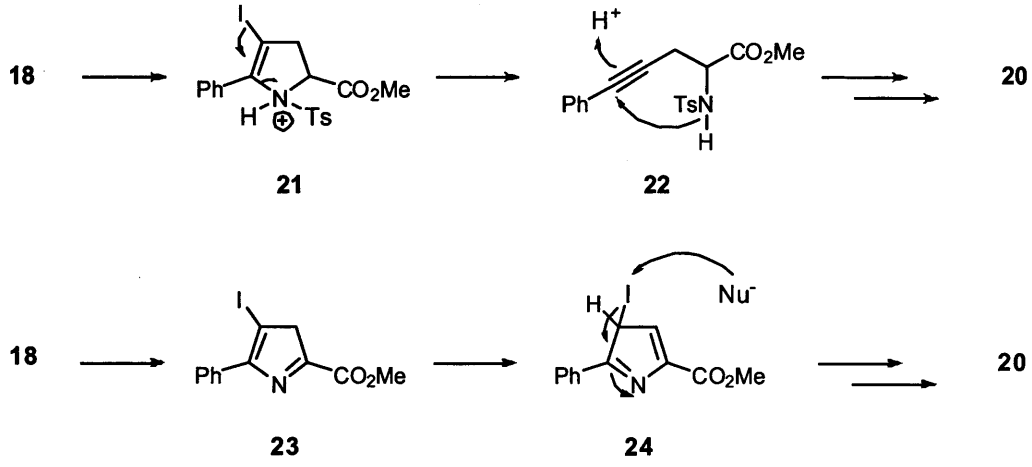
18 19 20

Scheme 1.8. a) 1 eq. DBU, DMF, 90 °C, ~2 hrs

It was reasoned that the dehalogenation was probably a result of protonation of the iodo-dihydropyrrole **18** at the nitrogen to give cation **21**, followed by ring opening with loss of an iodonium ion and subsequent acid-catalysed cyclisation of the starting material **22** to give the

observed deiodopyrrole **20** (Scheme 1.9). Initially, it was thought that some kind of radical chemistry was involved in this deiodination. However, extensive experimentation showed this not to be the case. Independent proton sources were shown to induce the same reaction, so it was concluded that protonated DBU was acting as such a proton source.

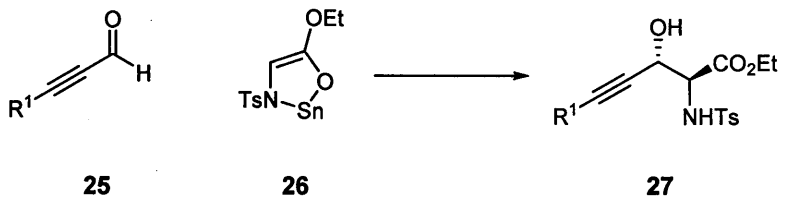
Another possibility is that the mechanism could involve a [1,5]-hydride shift of the initial elimination product **23** to the isomeric structure **24**, where the iodine could be removed by a nucleophile to give deprotonated **20** (Scheme 1.9).



Scheme 1.9.

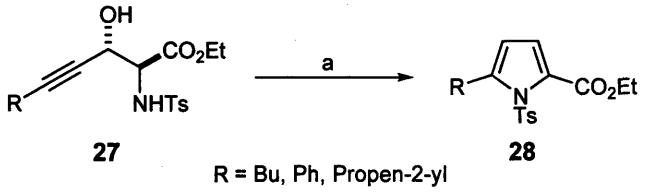
These observations suggested that it might be possible to trigger 5-*endo*-dig cyclisations using a proton source.

Sharland then found that treatment of representative γ-alkynyl-β-hydroxy-α-amino esters **27** with *p*-toluenesulfonic acid could be used to achieve the synthesis of highly substituted pyrroles. The precursors **27** were obtained from condensation of the corresponding ynals **25** with tin(II) enolates (Scheme 1.10).[32]



Scheme 1.10.

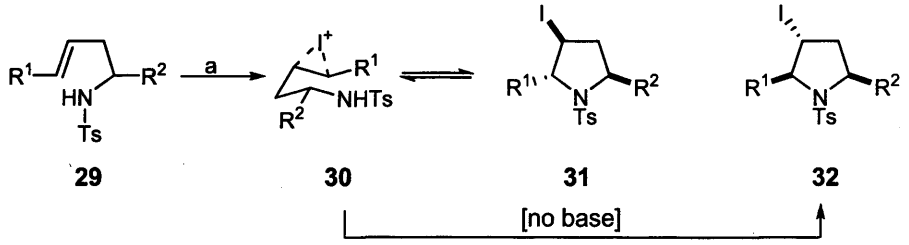
These precursors **27** were treated with 0.5 equivalents of *p*-toluenesulfinic acid resulting in excellent yields of about 70 - 90 % of *N*-tosyl derivative of the pyrroles **28** (Scheme 1.11).



Scheme 1.11. a) 0.5 eq. TolSOH, toluene, reflux, 6 hrs

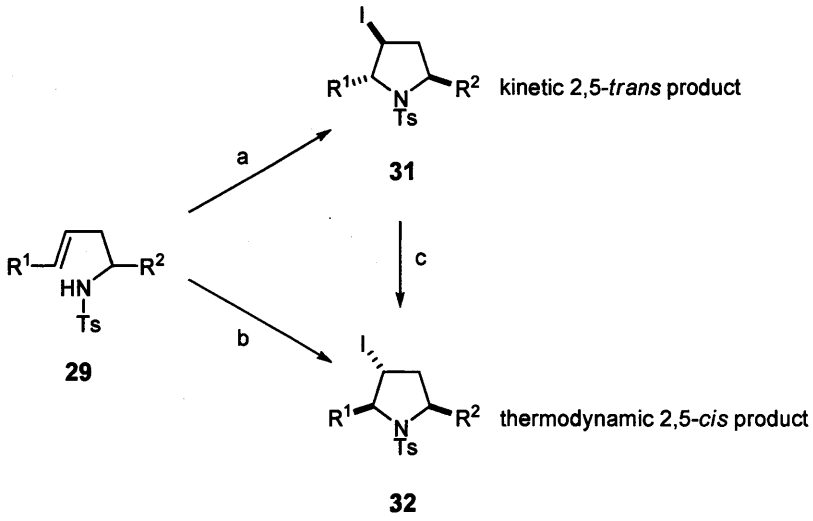
It was also shown that *p*-toluenesulfonic acid could be used with equal efficiency, which is a further support for an acid-catalysed mechanism (Scheme 1.9).

Amjad[33], also of the Knight group, showed that in pyrrolidine syntheses from (*E*)-homoallylic sulfonamides **29** using iodocyclisations in the presence of a proton source, the thermodynamically more stable 2,5-*cis* diastereoisomers **32** were formed, whereas exposure to excess iodine in the presence of potassium carbonate showed a distinct preference for the formation of the 2,5-*trans* isomers **31**. These results were thought to be due to an initial cyclisation *via* a chair-like transition state conformation **30**, which leads to the 2,5-*trans* isomers **31**, and which can then be followed by proton-induced cyclo-reversion and re-closure and hence equilibrium towards, and eventually only, the more thermodynamically stable 2,5-*cis* isomers **32** (Scheme 1.12).



Scheme 1.12. a) I_2, K_2CO_3

The stereochemical outcomes appear to follow largely the chair-like conformation **30**, wherein the sp^3-bonded group (R^2) adopts an equatorial position during the initial cyclisation, under basic conditions, hence leading to kinetic products, the 2,5-*trans* isomers **31**. Omission of the base leads to only the 2,5-*cis* isomers **32**. The pathways were proven by exposing a 2,5-*trans*-pyrrolidine **31** to a mixture of hydrogen iodine and iodine, when conversion into the *cis*-isomer **32** occurred rapidly. Acid-catalysed cyclo-reversion and equilibration to the thermodynamically more stable *cis*-isomers **32** then follows (Scheme 1.13).



Scheme 1.13. a) I_2, K_2CO_3 b) I_2, H^+ c) I_2, HI

Developing this theme, which clearly shows that a tosylamide group remains sufficiently nucleophilic in the presence of a strong acid (HI), Haskins[30] of the Knight group then later discovered that trifluoromethanesulfonic acid is an excellent catalyst for inducing such overall 5-*endo* cyclisations of homoallylic sulfonamides to give pyrrolidines in excellent yields (usually over 90%). Motivated by the prospects for discovering a rapid approach to highly substituted proline-derivatives, attempts were made to cyclise more highly substituted examples.

1.4. Conclusion

From the results shown, in particular those reported by Hartwig and Haskins, the acid-catalysed hydroamination has a great potential to be a powerful method for the synthesis of nitrogen containing heterocycles. This potential is explored in the following chapters.

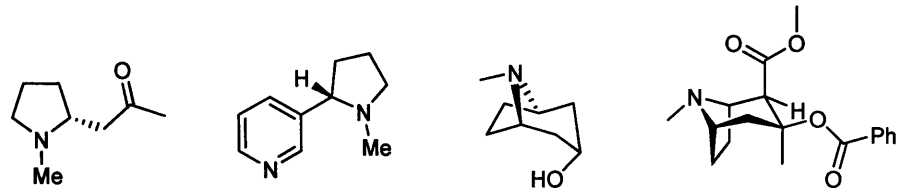
Chapter 2

Chapter 2

Acid-Catalysed Hydroaminations – Model Studies

2.1. Introduction

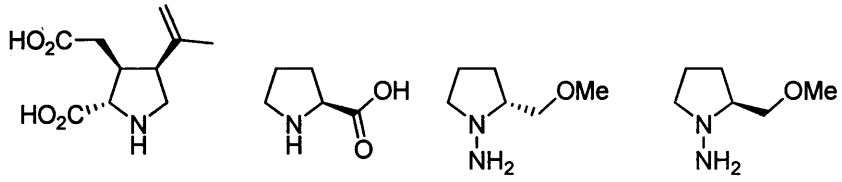
Pyrrolidines are important compounds, as their motif often appears in natural products, such as alkaloids: hygrine, nicotine, tropine, or cocaine (Figure 2.1), which showed significant biological activities. [34,35,36,37,38]



hygrine nicotine tropine cocaine

Figure 2.1. Structures of alkaloids containing pyrrolidine

Other compounds having this moiety include the amino acids and related derivatives, such as kainic acid or proline. In addition, prolinol derivatives, such as the (*S*)/(*R*)-1-amino-2-(methoxymethyl)-pyrrolidines (SAMP/RAMP), have found important applications as chiral auxiliaries, mainly in asymmetric alkylations (Figure 2.2).[39]



(+)-α-kainic acid proline RAMP SAMP

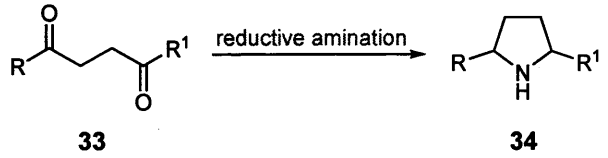
Figure 2.2. Structures of amino acid pyrrolidines and chiral auxiliaries

Due to their importance, many different strategies towards the synthesis of pyrrolidines have been developed. The methods to construct the pyrrolidine ring can be divided into intermolecular and intramolecular reactions. [3b,40,41,42,43]

2.1.1. Intermolecular Methods for Pyrrolidine Formation

Some of the oldest methods for pyrrolidine formation rely upon the disconnection of the two bonds alpha to the nitrogen in the final product, meaning that the nitrogen can be introduced as a primary amine.

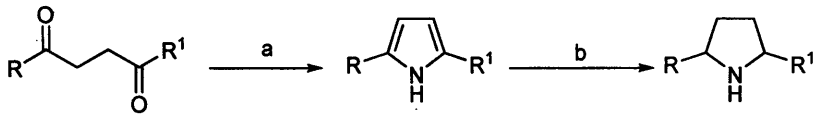
The reductive amination of 1,4-diketones **33** is one of the oldest methods for the preparation of 2,5-disubstituted pyrrolidines **34** (Scheme 2.1); this method has been used for the preparation of natural non-symmetrical 2,5-dialkyl-pyrrolidines.[44]



33 **34**

Scheme 2.1.

This method is not stereoselective, since a 1:1 mixture of *cis* and *trans* isomers is obtained. Further optimisation showed that treatment of 1,4-diketones **33** with an excess of ammonium carbonate allowed the formation of the not isolated pyrrole intermediates **35**, which were hydrogenated to give the *trans* isomers of the major compound (d.r. = 85 : 15) (Scheme 2.2). [45]



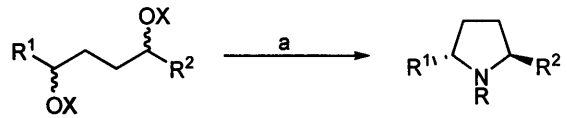
33 **35** **36**

a: R = $(CH_2)_6CH_3$, R^1 = $(CH_2)_3CH_3$
b: R = $(CH_2)_4CH_3$, R^1 = $(CH_2)_3CH_3$
c: R = $(CH_2)_5CH_3$, R^1 = $(CH_2)_4CH_3$

Scheme 2.2. a) $(NH_4)CO_3$ b) H_2, Rh/Al_2CO_3

Several factors, such as the size of the ring formed (*i.e.* pyrrolidine or piperidine), the nature of the substituents as well as the nature of the reducing agent, influences the *cis* : *trans* diastereomer ratio.[46]

The nucleophilic attack of primary amines upon 1,4-dihydroxy derivatives, results in direct cyclisation to form *trans* 2,5-disubstituted pyrrolidines (Scheme 2.3). This is a well known reaction directly derived from the studies on the aminocyclisations of 2,5-dibromoadipic acid esters, where *trans* : *cis* stereoselectivity can be improved by chiral auxiliaries.[47,48,49,50]



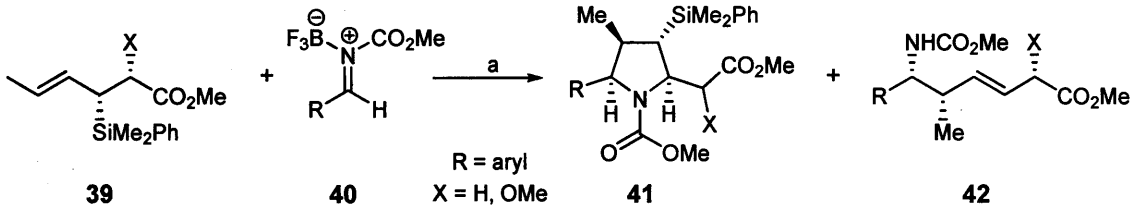
37 X = Ts, Ms, Tf **38**

Scheme 2.3. a) R-NH_2

Usually the stereoselectivity and the stereospecificity of these reactions are excellent when non-racemic starting materials are used. Chirality may be introduced in non-racemic cases by two methods: i) use of enantiomerically pure diols - both stereogenic centres are inverted, due to the cyclisation occurring through stereospecific S_N2-type reactions; ii) stereoselective formation of

enantiomerically pure pyrrolidines from racemic mixtures of 1,4-dihydroxy derivatives can be achieved through the implementation of chiral auxiliaries.[51,52,53,54,55,56,57,58]

In another approach, chiral allylsilanes **39** were treated with *N*-acylimines **40**, generated *in situ* from arylacetals or aldehydes to form *cis* *N*-acylpyrrolidines **41** as the major isomers at temperatures between –100 °C and –78 °C, whereas at temperatures between –78 °C and –20 °C, *N*-acylhomoallylic amines **42** were obtained (Scheme 2.4).[59]

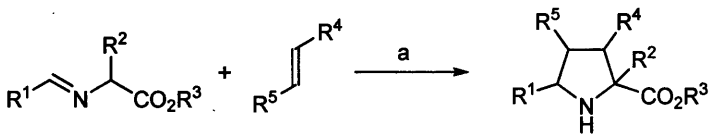


39 **40** **41** **42**

Scheme 2.4. a) –78 °C

Arylamines were generally more reactive and gave higher yields of pyrrolidines in comparison to acetals; aliphatic aldehydes, on the other hand, did not give rise to the corresponding pyrrolidines.

[1,3]-Dipolar cycloadditions are amongst the most efficient methods for the preparation of pyrrolidines and pyrrolines.[60,61] The reactions are usually concerted, regioselective and highly stereoselective. Imines of α-amino esters **43** are known for reacting with electron deficient alkenes **44** in the presence of a Lewis acid to give polysubstituted pyrrolidines (Scheme 2.5).



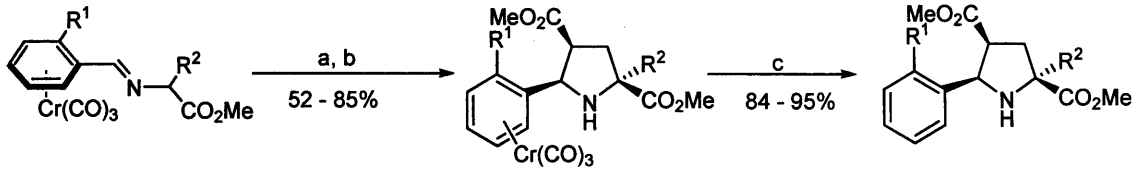
43 **44** **45**

R^1 = Ph	R^2 = Ph	R^2 = Me	R^4 = H	R^5 = Me	Lewis acid = LiBr	Yield = 100%
R^1 = Ph	R^2 = Me	R^3 = Me	R^4 = H	R^5 = CO_2Me	Lewis acid = AgOTs	Yield = 81%
R^1 = naphth	R^2 = Me	R^3 = Me	R^4 = H	R^5 = CO_2Me	Lewis acid = AgOAc	Yield = 100%
R^1 = Ph	R^2 = Me	R^3 = Me	R^4 = CO_2Me	R^5 = CO_2Me	Lewis acid = AgOAc	Yield = 90%
R^1 = Ph	R^2 = Ph	R^3 = Me	R^4 = CO_2Ph	R^5 = CO_2Ph	Lewis acid = LiBr	Yield = 85%

Scheme 2.5. a) NEt_3, Lewis acid

AgOAc appeared to be the most efficient catalyst, for the stereospecific preparation of 2,5-disubstituted pyrrolidines.[62] It has been shown that the use of LiBr as a Lewis acid reverses the *exo-endo* selectivity of the reaction, compared with those achieved with AgOTf.[63] Three main strategies for asymmetric [1,3]-dipolar cycloadditions of azomethine ylides have been exemplified by Grigg: i) use of chiral dipolarophiles,[64,65,66,67] ii) use of chiral azomethine ylides,[68,69,70] iii) use of chiral catalysts.[61,71]

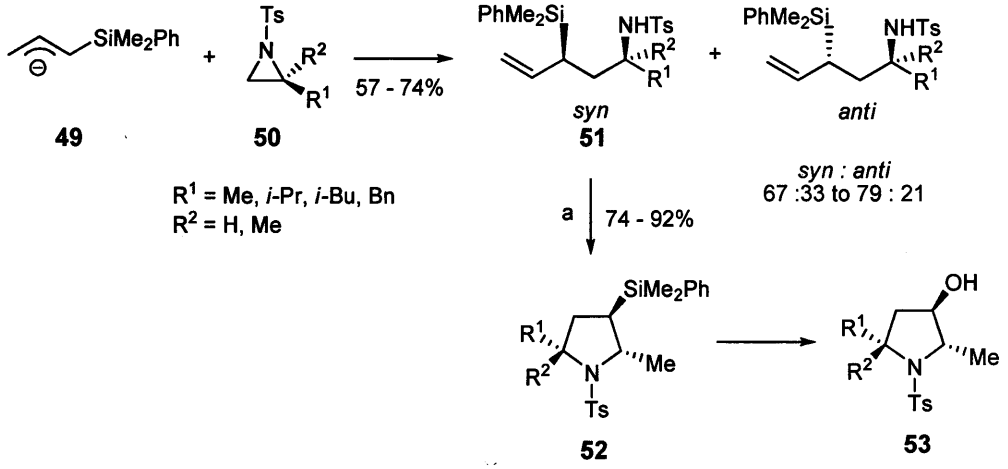
Highly diastereoselective [3 + 2] cycloadditions of azomethine ylides linked to planar arene chromium complex **46** and methyl acrylates have been found where only one diastereomer **47** was detected in the products. These were then oxidatively decomplexed to yield pyrrolidines **48** (Scheme 2.6). The use of a titanium Lewis acid resulted in reverse product regiochemistry.[72]



46 **47** **48**

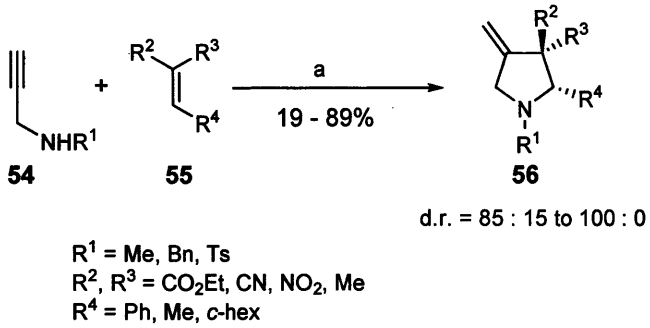
Scheme 2.6. a) LiBr, NEt_3 b) $CH_2=C(R^2)CO_2Me$ c) *hν*, air, MeCN

Nucleophilic opening of aziridines by phenylthiolate ions or azides, followed by cyclisation into pyrrolidines, usually gives a mixture of polysubstituted pyrrolidines and piperidines, mostly forming pyrrolidines as the major product, with yields ranging from 51 to 84%.[73] This was improved upon by the reaction of enantiopure aziridines, **50** with an allylsilyllithium species **49** and has been used in the chiral synthesis of 2,3,5,5-tetrasubstituted pyrrolidines **52**, *via* the predominant *syn*-intermediates **51** (Scheme 2.7).[74] Silypyrrolidine **52** can easily be converted to the corresponding alcohol **53**, as the silyl is essentially a masked hydroxyl group.



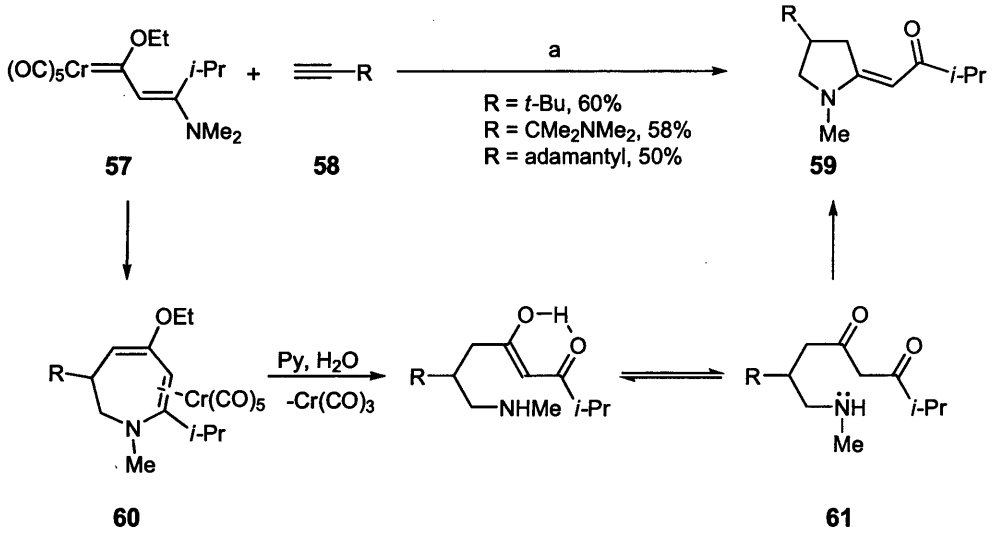
Scheme 2.7. a) *p*-TsOH, CH_2Cl_2

One-pot tandem Michael addition-cyclisation reactions of protected propargylamines **54** and Michael acceptors, catalysed by copper iodide, have successfully yielded pyrrolidines **56** in good yields, ranging from 19 – 89% with good stereoselectivity (Scheme 2.8).[75]



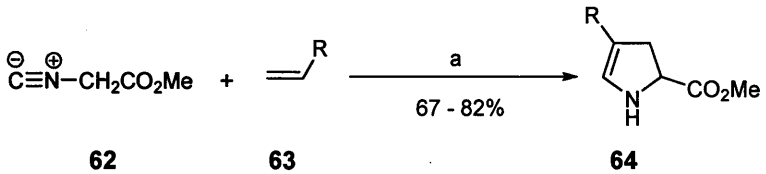
Scheme 2.8. a) *n*-BuLi (10 mol%), CuI (3 mol%), THF

A formal [5 + 2] cycloaddition between chromium complex **57** and a bulky terminal alkyne **58**, proceeded *via* cycloadduct **60**. This decomplexed in pyridine to diones **61**. Cyclisation and elimination of water then yielded pyrrolidines **59** (Scheme 2.9).[76]



Scheme 2.9. a) Pyridine, 80 °C

Silver acetate has been used as a catalyst for the cycloaddition of methyl isocyanoacetate **62** with activated alkenes **63**, yielding pyrrolidines **64** (Scheme 2.10). A stepwise mechanism was proposed, explaining the partial loss of stereochemistry observed when disubstituted alkenes were used.[77]



Scheme 2.10. a) cat. AgOAc, MeCN

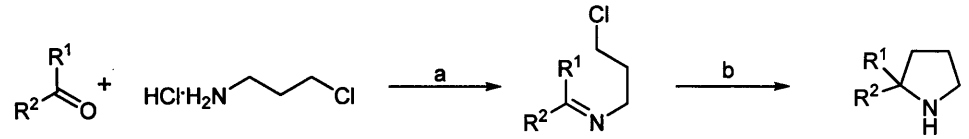
2.1.2. Intramolecular Methods to Afford Pyrrolidines

The reactions of amino-alcohol **65** derivatives are usually stereospecific and very little epimerisation occurs (Scheme 2.11).[78, 79, 80]

65 OX = leaving group **66**

Scheme 2.11.

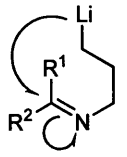
The reaction of different *N*-(3-chloropropyl) imines **69** with an excess of lithium powder and a catalytic amount of 4,4-di-*tert*-butylbiphenyl (DTBB) gave the expected pyrrolidines **70** (Scheme 2.12).



67 **68** **69** **70**

Scheme 2.12. a) H_2O (or MeOH), Na_2CO_3 b) LiDTBB (5%) c) H_2O

From a mechanistic point of view, it is hypothesised that a chlorine-lithium exchange takes place (without affecting the imine) giving an organolithium intermediate **71** (Figure 2.3), in which an intramolecular addition occurs *via* an 5-*endo*-trig process, generating the expected pyrrolidines after work-up.

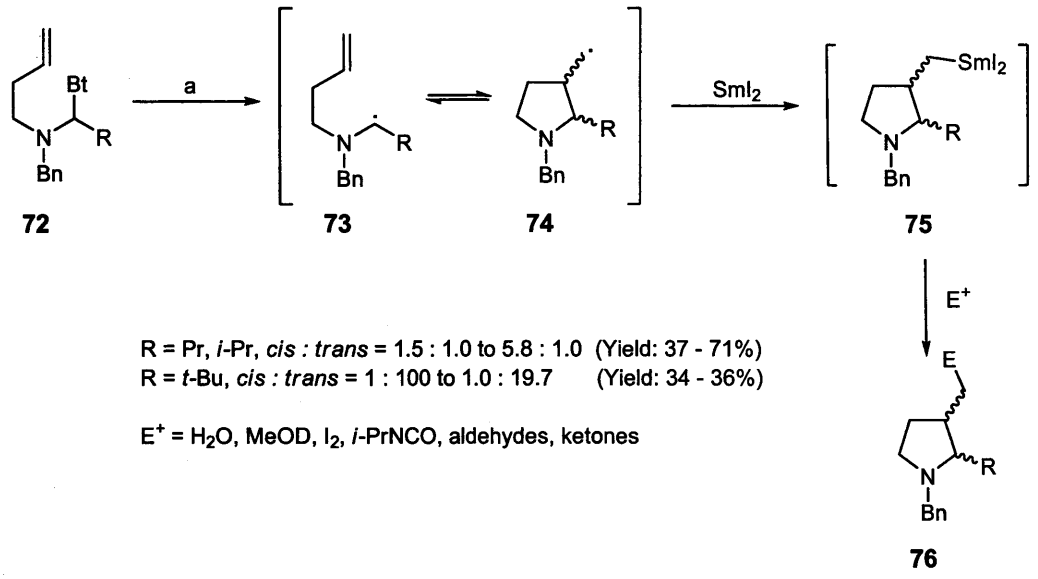


71

Figure 2.3. Proposed intermediate for *endo*-trig cyclisation to occur

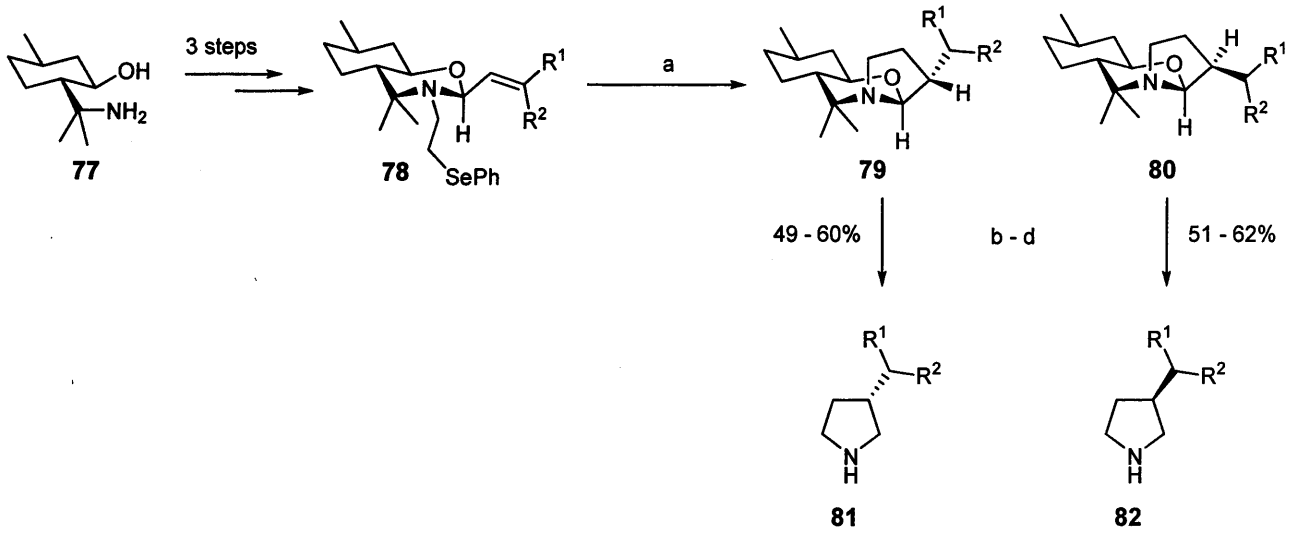
In the case of imines derived from aliphatic ketones and aldehydes, this method gave significantly lower yields.[3b]

Samarium iodide has been used in two procedures to facilitate pyrrolidine formation by the addition of α-aminoalkyl radicals to alkenes. Radicals **73** generated from α-amino-benzotriazoles **72** exist in equilibrium with cyclised radicals **74** (Scheme 2.13).[81]



Scheme 2.13. a) SmI_2, THF-HMPA

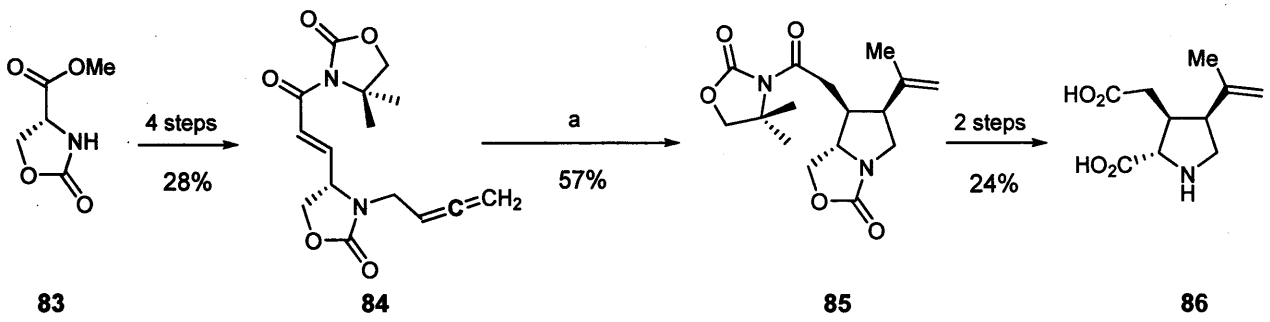
Modest diastereoselectivity was generally observed in radical pyrrolidine cyclisations, induced by a chiral perhydro-1,3-benzoxazine moiety (Scheme 2.14).[82]



Scheme 2.14. a) Bu_3SnH, C_6H_6, AIBN b) AlH_3, THF c) PCC d) KOH

The major diastereomer from the reaction shown was product **79**. Cleavage of the *N,O*-acetal moiety and two step removal of the chiral auxiliary, resulted in enantiopure 3-substituted pyrrolidines **81** and **82**.

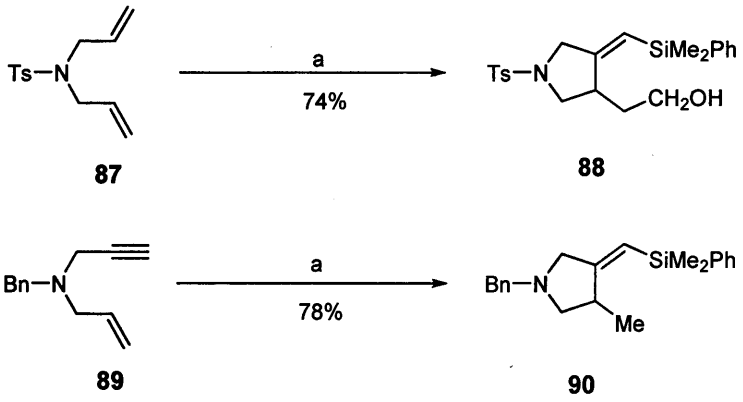
A synthesis of kainic acid **86** involved a nickel-catalysed allene cyclisation yielding product **85** in good yield and excellent stereoselectivity (d.r. = 98:2) (Scheme 2.15). The reaction mechanism was proposed to be identical to the extensively studied nickel-catalysed cyclisation of alkenes. [83]



83 **84** **85** **86**

Scheme 2.15. a) MeLi/$ZnCl_2$, $Ni(COD)_2$ (10mol%), $Ti(O\text{-}i\text{-}Pr)_4$

Ring-closing metathesis has often been employed for the synthesis of pyrrolidines. Recent substrates have included phenyl-substituted dienes[84] and the products from enantioselective allylic aminations of allylic carbonates.[85,86] Pyrrolidines prepared as part of a study on the rhodium-catalysed domino silylformylation of enynes showed that the nature of the *N*-substituent greatly affects the outcome of the reaction (*i.e.* **90** showed no incorporation of carbon monoxide) (Scheme 2.16).[87]

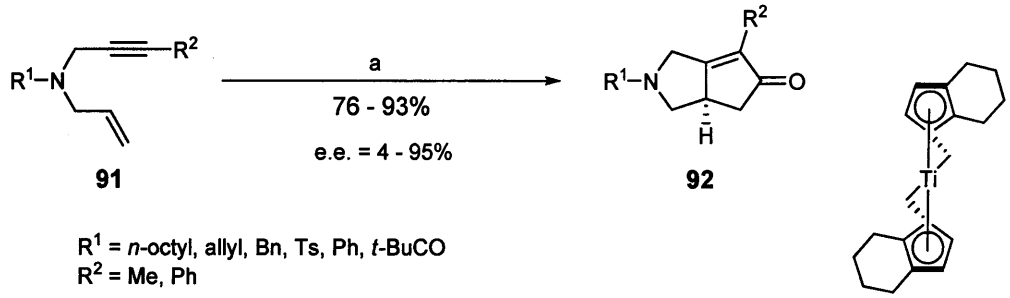


87 **88**

89 **90**

Scheme 2.16. a) Me_2PhSiH, CO (20 kg cm^{-2}), $Rh(CO)_2(acac)$ (0.5 mol%), C_6H_8, 90 °C

Buchwald and Sturla reported an asymmetric cyclocarbonylation of enynes, catalysed by an enantiomerically pure titanocene complex **93**. For the best enantioselectivity, an electron-rich nitrogen centre was required in the starting enyne **91** (Scheme 2.17).[88]

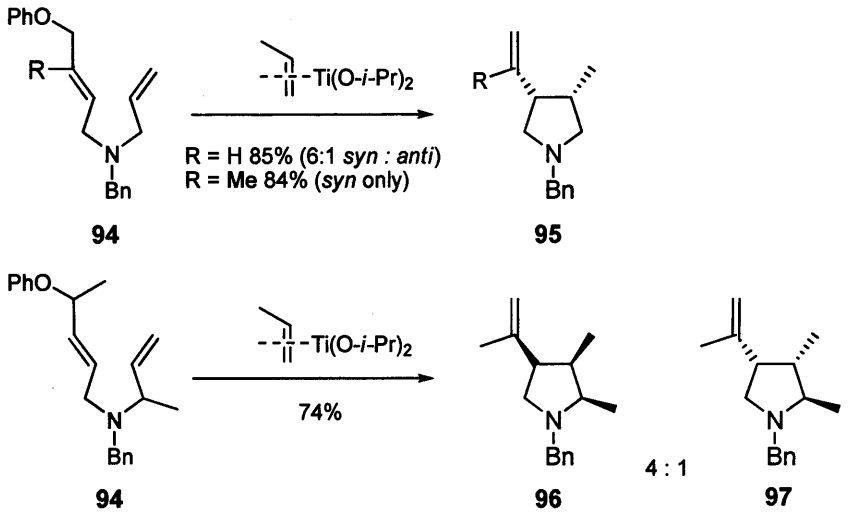


91 **92** **93**

R^1 = *n*-octyl, allyl, Bn, Ts, Ph, *t*-BuCO
R^2 = Me, Ph

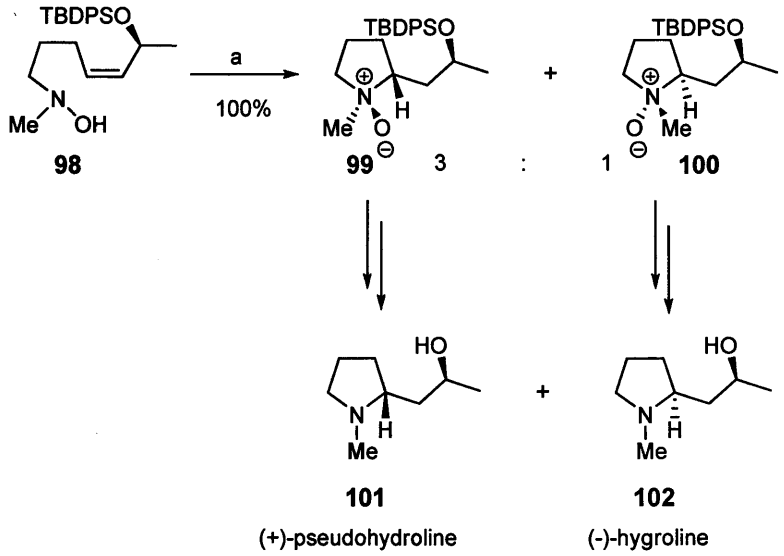
Scheme 2.17. a) **107** (10 – 15 mol%), CO (14 psig), toluene, 95 °C

During the course of these studies, Buchwald and co-workers also discovered a titanocene-catalysed cycloisomerisation of dienes **94**, one example of which yielded a pyrrolidine.[89] This method was used for the stereoselective preparation of *syn*-3,4-disubstitited **95** and *syn,syn*-2,3,4-trisubstituted pyrrolidine **96**, which was exploited in a new total synthesis of (-)-α-kainic acid (Scheme 2.18).[90]



Scheme 2.18.

The Knight group employed a reverse-Cope elimination in the synthesis of (–)-hygroline **102** and (+)-pseudohygroline **101** (Scheme 2.19).[91]

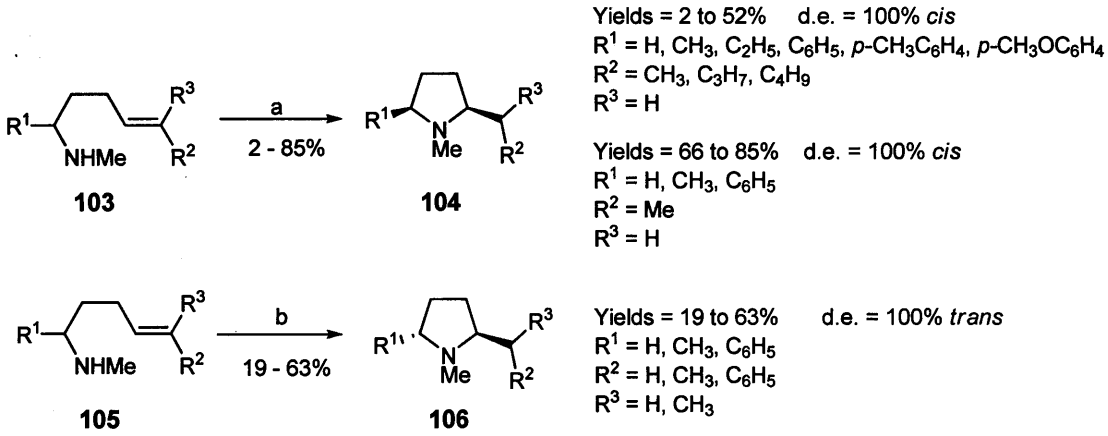


Scheme 2.19. a) $CHCl_3$, 60 °C

Contrary to earlier studies, which suggested that substituents at the distal end of the participating alkene greatly inhibited reaction, allylic oxygen groups were found to facilitate the cyclisation, though the stereoselectivity was found to be low.

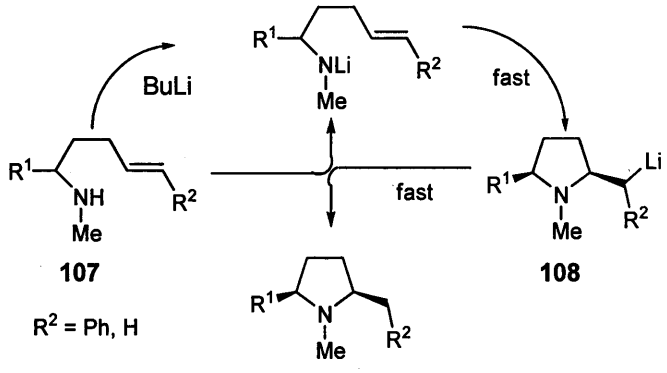
2.1.3. Reaction of Amino Alkenes

Numerous syntheses of substituted pyrrolidines by intramolecular cyclisation of 5-alkenyl amines *via* the aminyl radical have been reported: photolysis,[92] thermolysis of *N*-chloroamines[93] and anodic oxidation of lithium amides and hydroxylamines[94,95] are among the most encountered methods. Two procedures to note involve: i) the anodic oxidation of γ,δ-unsaturated lithium amides leading stereospecifically to *cis* 2,5-disubstituted pyrrolidines **104**,[96] and ii) the intramolecular cyclization of *N*-chloroalkenylamine in the presence of tributyltin hydride and azoisobutyronitrile (*n*-Bu_3SnH-AIBN) giving rise almost exclusively to *trans*-2,5-disubstituted pyrrolidines **106** (Scheme 2.20).[97]



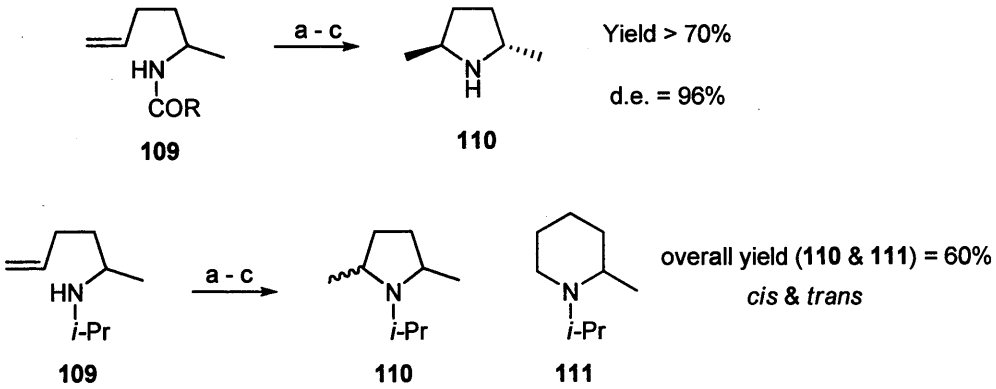
Scheme 2.20. a) BuLi, e⁻ b) NCS, *n*-Bu_3SnH, AIBN

Tokuda reported the stereoselective synthesis of *cis*-2,5-disubstituted *N*-methyl-pyrrolidines **108** as single diastereomers by treating δ-alkenyl amines **107** with a catalytic amount of *n*-BuLi (*i.e.* 0.1 equivalents of *n*-BuLi) (Scheme 2.21).[96]



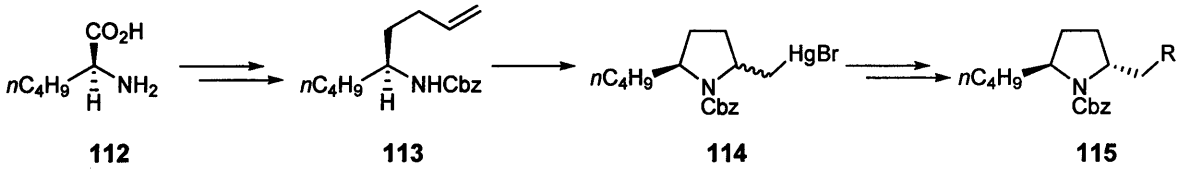
Scheme 2.21.

Aminomercuration (with $HgCl_2$) of δ-alkenylamines **109** resulted in a mixture of 2,5-disubstituted pyrrolidines **110** and piperidines **111** being obtained.[97] The regio- and stereoselectivities were better for the amidomercuration than for the aminomercuration and the *trans* isomer was always the major isomer formed *(cis : trans 2 : 98)* (Scheme 2.22).[98]



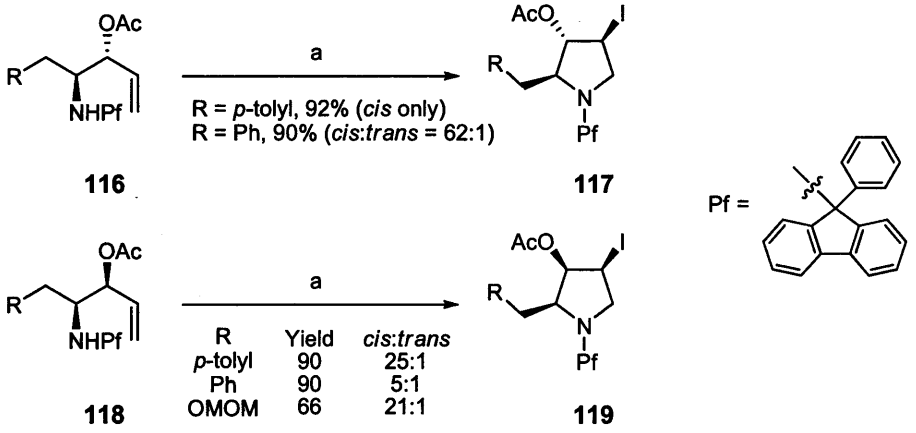
Scheme 2.22. a) $HgCl_2$ b) $NaBH_4$ c) HCl

Harding also showed that 5-alkenylamines, when treated by $Hg(OAc)_2$, led to 2,6-disubstituted piperidines; and observed an equilibrium between the *trans* and *cis* products.[99] Takahata used this to synthesise *trans*-2,5-dialkylpyrrolidines **115** from L-norleucine **112** (with d.r. *cis* : *trans* = 1 : 25 and e.e. = 98%) and has since then been used toward the synthesis of numerous 2,5-disubstituted pyrrolidines (Scheme 2.23).[100,101,102]



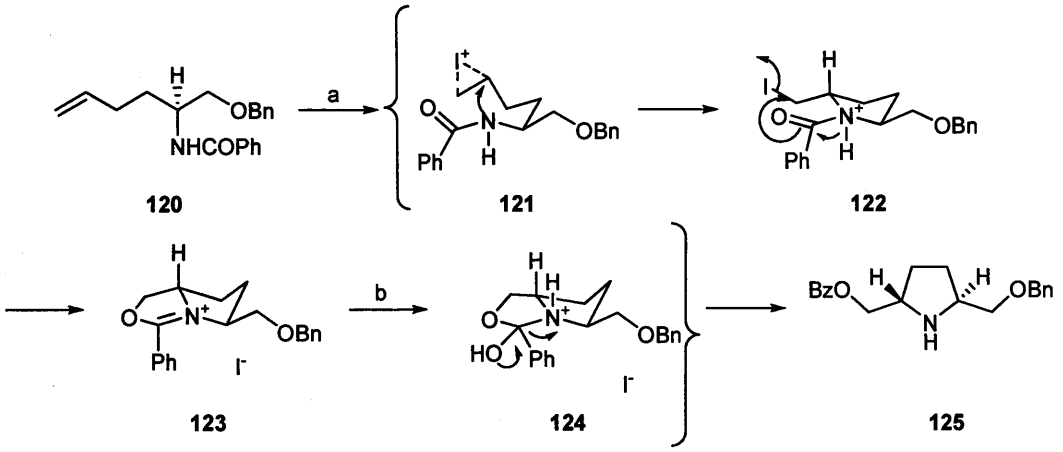
Scheme 2.23.

Diastereoselective iodoamination of 3-acetyloxybut-1-enylamine **116** and **118** have been performed, yielding pyrrolidines **117** and **119**.[103] The biphasic conditions shown in Scheme 2.24 were essential for the high yields and short reaction times, as was the very large *N*-substituent.



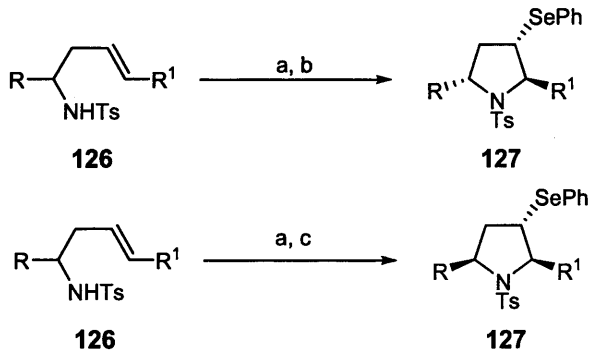
Scheme 2.24. a) I_2, $NaHCO_{3\,(aq)}$: THF : Et_2O (2:1:1)

A strategy related to the preparation of tetrahydrofurans was used in the stereoselective formation of *trans*-pyrrolidines (Scheme 2.25).[104]



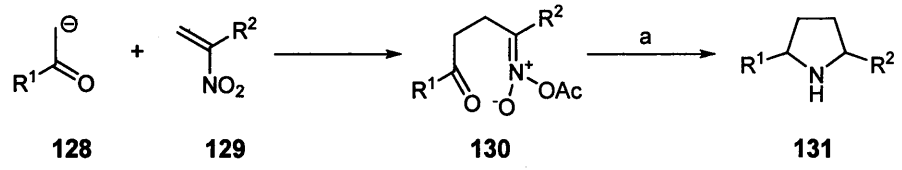
Scheme 2.25. a) I_2, MeCN b) H_2O

Selenocyclisations have largely been used for the synthesis of 2,5-disubstituted tetrahydrofurans,[105] though Clive used this method for the preparation of pyrrolidines substituted at C-2.[106] Selenocyclisations of homoallylic sulfonamides **126** have also been reported, but stereochemical outcome of the pyrrolidine products **127** were somewhat unpredictable (Scheme 2.26). [107,108]



Scheme 2.26. a) PhSeCl, CH_2Cl_2, –78 °C, 0.5 – 1 hr b) K_2CO_3, 5 mol% H_2O c) cat. 10 M HCl

Yoshikoshi described the synthesis of 2,5-dialkylated pyrrolidines **131** by hydrogenation of acetyl-nitronates **130** prepared from enolates **128** and nitroalkenes **129**. Unfortunately, diastereoselectivity is low: 64 to 72% in favour of the *cis* isomer (Scheme 2.27).[109]

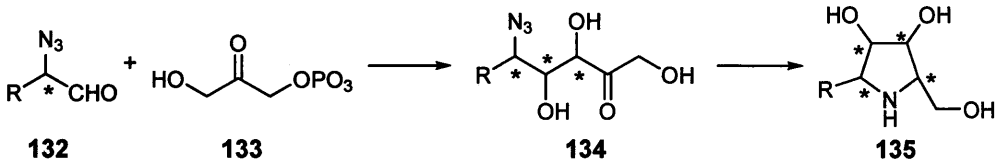


Scheme 2.27. a) H_2, PtO_2

This was improved by synthesising the pyrrolidines *via* cyclic and chiral nitrones obtained by electrophilic α-hydroxyamination of a chiral sultam. The pyrrolidines obtained were enantiomerically pure with overall yields ranging from 48 to 60%, depending on the nature of the substituents and with d.e. = 87 to 99% in favour of the *trans* isomers. [110]

The hydrogenation of γ-nitroketones to give *cis*-2,5-disubstituted pyrrolidines,[111,112] was achieved through the *syn*-addition of hydrogen on the intermediate pyrroline, resulting in the formation of *cis* pyrrolidines.[113,114]

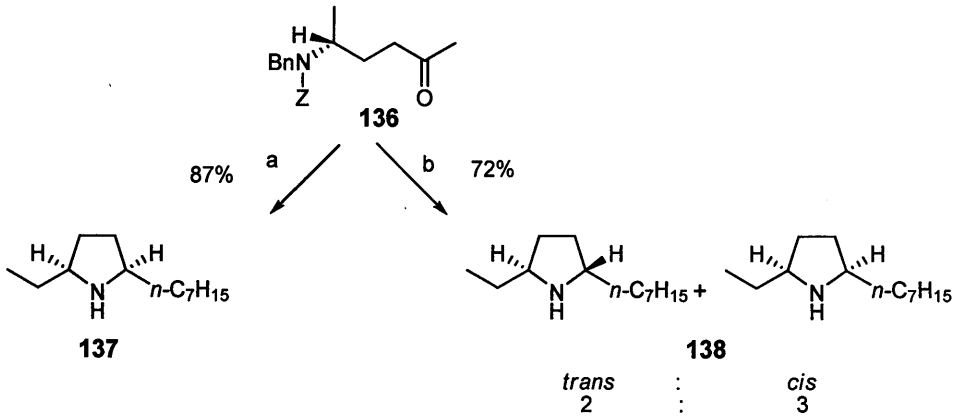
Most syntheses of 2,3,4,5-tetrasubstituted pyrrolidines **135** proceed *via* an azidoketone **134** to give enantiomerically pure pyrrolidines **135** (Scheme 2.28).[115,116,117]



132 **133** **134** **135**

Scheme 2.28.

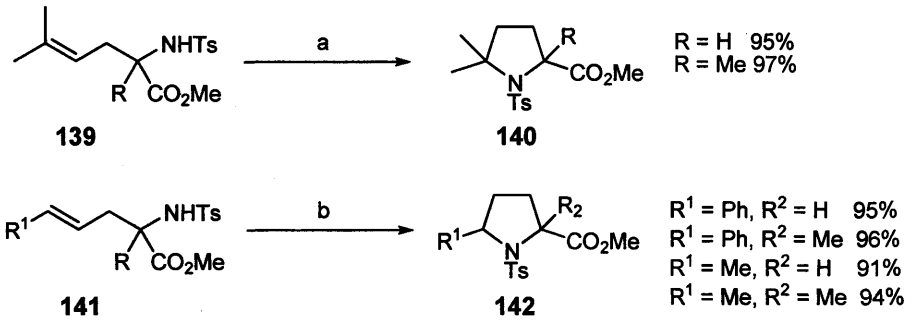
Aminoketones **136** can be hydrogenated in the same way as nitroketones and azidoketones Hydrogenation of aminoketone **136** in the presence of 10% palladium on charcoal in methanol cleaved the protecting group from the amino function as well as reduction of the ketone and the cyclisation leading to 2,5-disubstituted pyrrolidines **137** of exclusive *cis* configuration, whereas treatment of aminoketones **138** with ammonium formate in the presence of 10% palladium on charcoal in methanol under reflux, gave a mixture of *cis*- and *trans*-2,5-disubstituted pyrrolidines **138** (3 : 2) (Scheme 2.29).[118]



Scheme 2.29. a) H_2, 10% Pd/C b)HCO_2NH_4, 10% Pd/C

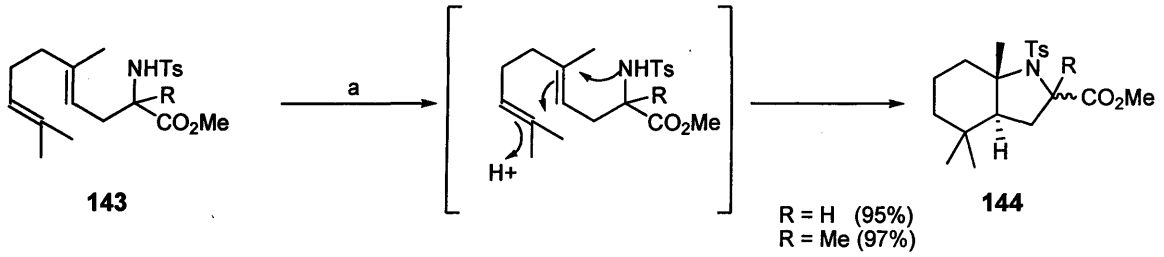
2.2 Background to Current Work

The synthesis of pyrrolidines through acid-catalysed hydroaminations has previously been developed within the Knight group. Pyrrolidines, such as **140** and **142** had been successfully isolated through cyclisation of homoallylic sulfonamide **139** and **141** with triflic acid (Scheme 2.30).[30]



Scheme 2.30. a) 0.4 eq. TfOH, $CHCl_3$, 0 °C, 2.5 hrs b) 0.4 eq. TfOH, $CHCl_3$, 25 °C, 4.5 hrs

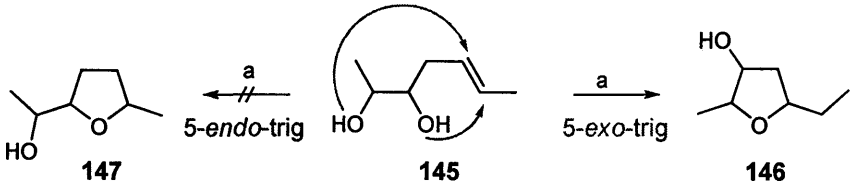
This cyclisation has also been used in the implementation of cascade reactions, where a multitude of rings can be formed, with the sulfonamide acting as the terminator (Scheme 2.31).



Scheme 2.31. a) 0.4 eq. TfOH, $CHCl_3$, 0 °C, 0.25 hrs

This all developed from previous work conducted in the Knight group on iodocyclisations (see Chapter 1).

The acid-catalysed hydroamination follow an overall 5-*endo*-trig process, but this does not mean that they are subject to Baldwin's rules. Because the cyclisation involves the formation of a carbocation, which is the driving force for the cyclisation, ring formations that are disfavoured according to Baldwin's rules are still possible under these conditions. Baldwin's rules are relevant to iodocylisations that are not driven by the formation of carbocations (Scheme 2.32).



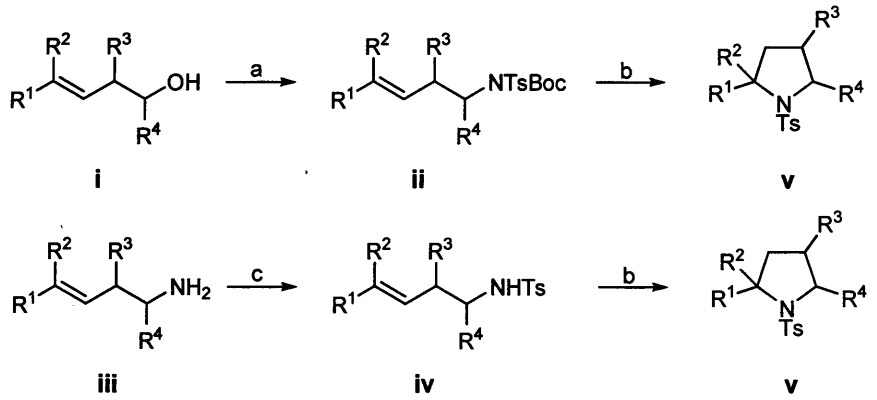
Scheme 2.32. a) 3 eq. I_2

2.3 Results and Discussion

2.3.1 Simple Pyrrolidines

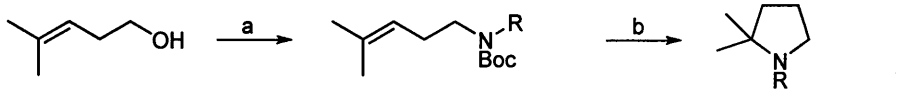
To further expand the work performed by Haskins, simple pyrrolidines were to be synthesised where the substitution patterns and the type of substituent are varied. This would give a good indication as to the scope of these hydroaminations. Previous work by Haskins always included an ester group, used in precursor synthesis, adjacent to the amine for synthetic ease.[30,119] A question that needs to be answered is whether the presence of the ester group actually necessary for the cyclisation to occur.

As a general limitation, a synthetic route was to be no more than five steps to the pyrrolidines (**v**). This generally involved the synthesis or purchase of either an alcohol (**i**) or the amines (**iii**). The alcohols (**i**) were reacted under Mitsunobu conditions (PPh_3, DIAD, THF, 0 °C, 24 hours) with the Weinreb reagent (TsNHBoc) to give the desired precursors (**ii**). The amines (**iii**) were tosylated to sulfonamides (**iv**) and then both precursors were reacted under acidic conditions to afford the pyrrolidines (**v**) (Scheme 2.33).



Scheme 2.33. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight b) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight c) 0.5 eq. TfOH, DCM 0 – 40 °C

The first pyrrolidine synthesised was synthetically straightforward: 4-methyl-3-penten-1-ol **148** was converted into the corresponding sulfonamide **149** followed by cyclisation to dimethylpyrrolidine **150** (Scheme 2.34).



148

R = Ts **149a** Yield: 42%
R = Ns **149b** Yield: 40%

R = Ts **150a** Yield: 95%
R = Ns **150b** Yield: 97%

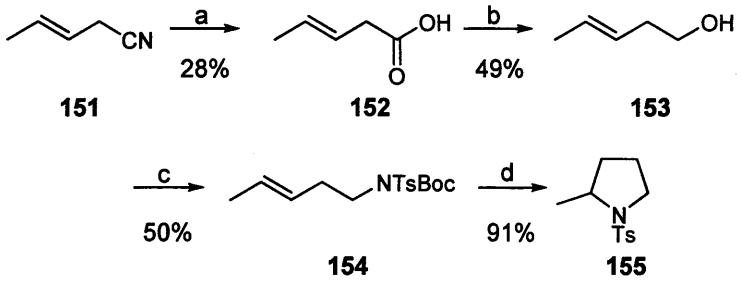
Scheme 2.34. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight b) 0.5 eq. TfOH, DCM 0 °C, 2.5 hrs

An unexpected bonus was the observation that both the Boc deprotection and cyclisation occurred in a single step. In hindsight, this was a reasonable observation, as standard removal of a Boc

group employs the use of trifluoroacetic acid (TFA) (pKa 0.3).[120] Since the hydroaminations are acid-catalysed, it is reasonable to expect that the triflic acid (pKa –13) would indeed be successful in removing the Boc group. The removal of the Boc group was achieved successfully with full conversion to pyrrolidines **150**. Another advantage of this cyclisation is that provided pure precursor (**ii**) is used and the reaction reaches completion, no purification of the produced pyrrolidine (**iii**) is required.

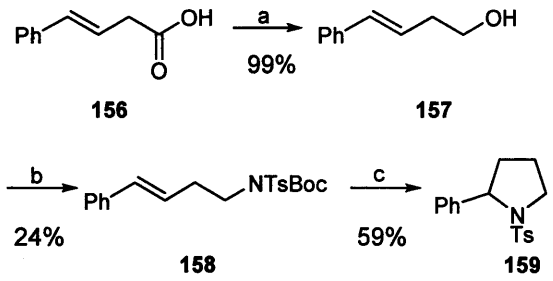
It seemed prudent to see whether this method could be expanded beyond the use of tertiary carbenium ion formation. Haskins had performed cyclisations on secondary and tertiary carbenium ions, though all of these had an ester adjacent to the nitrogen.[30,119] The result above (Scheme 2.34) shows that an ester is unnecessary for the cyclisation of tertiary carbenium ions to occur.

A simple example was sought that would be easily comparable to **150**. 2-Methyl-1-tosylpyrrolidine **155** is a viable and comparable target and was synthesised from commercial *trans*-3-pentenenitrile **151** (Scheme 2.35).



Scheme 2.35. a) 30% H_2O_2, 3 M NaOH, 80 °C for 1 hr then 20 °C for 1 hr b) $LiAlH_4$ Et_2O, 0 °C, 1 hr c) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight d) 0.5 eq. TfOH, DCM, 40 °C, 48 hrs

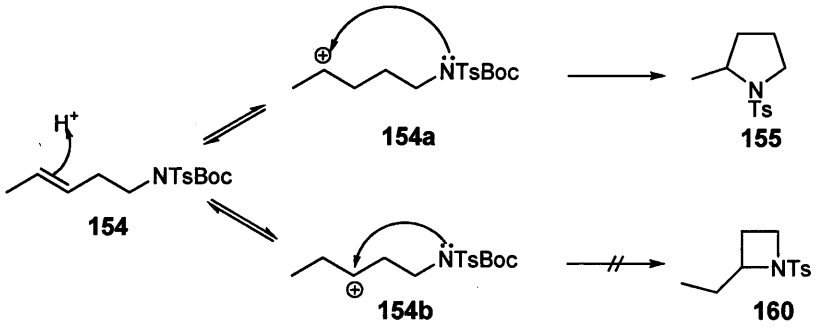
The cyclisation was successfully completed with an excellent yield of 91%. Heating was needed to reach full conversion to the pyrrolidine **155**, as well as a longer reaction time of 48 hours compared with that required for formation of pyrrolidine **150**. The requirement for moderate heating and the longer reaction time could be a symptom of the secondary carbenium ion generated from **154**. Could the inclusion of a charge stabilising group, such as a phenyl, help reduce the reaction time? Sulfonamide **158** was synthesised in a similar fashion to sulfonamide **154**, from commercial *trans*-styrylacetic acid **153** (Scheme 2.36).[121]



Scheme 2.36. a) $LiAlH_4$, Et_2O, 0 °C, 1 hr b) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight c) 0.5 eq. TfOH, DCM, 20 °C, 48 hrs

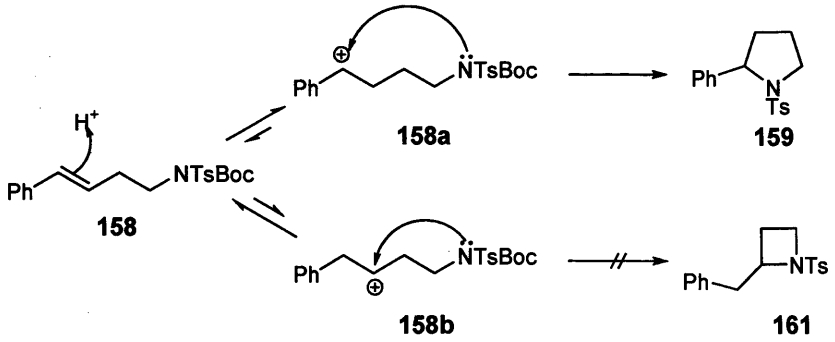
The cyclisation was successful for the formation of 2-phenylpyrrolidine **159** and occurred at lower temperature than the cyclisation to **155**. This appears to reflect the relative carbenium ion stabilities.

Secondary carbenium ions are more challenging to form than tertiary examples. There are two possible secondary carbenium ions that can form from sulfonamide **154**; these are both equally likely to form (Scheme 2.37). Trapping the secondary carbenium ion **154a** will form the observed pyrrolidine **155** through a formally disfavoured overall 5-*endo*-trig process. Carbenium ion **154b** would form the severely strained 4-membered ring **160**, though an overall 4-*exo*-trig process.



Scheme 2.37.

Two possible carbenium ions can form from **158**; however the benzylic carbenium ion **158a** is much more likely to form than **158b** due to the stabilisation afforded by the phenyl group, resulting in the exclusive formation of pyrrolidine **159** (Scheme 2.38).



Scheme 2.38.

Hence, cyclisations can occur without an ester in examples of both secondary and tertiary carbenium ions; though cyclisations involving secondary carbenium ions require higher temperatures and longer reaction times than tertiary carbenium ions. As reasonably expected, the presence of the ester was not necessary for the key cyclisation.

The next stage was to increase the substitution around the pyrrolidine ring by including a methyl group in the 5-position of the anticipated products to hopefully give 2,2,5-trisubstituted pyrrolidine **162** and 2,5-disubstituted pyrrolidine **163** (Figure 2.3).

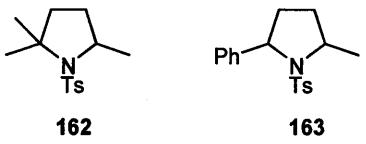
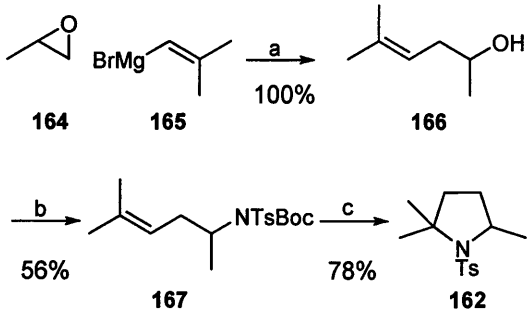


Figure 2.3. Structures of pyrrolidines with increased substitution

2,2,5-Trimethylpyrrolidine **162** was synthesised successfully *via* alcohol **166**, resulting from opening of propylene oxide **164** with 2-methyl-propenylmagnesium bromide **165** (Scheme 2.39).[122]

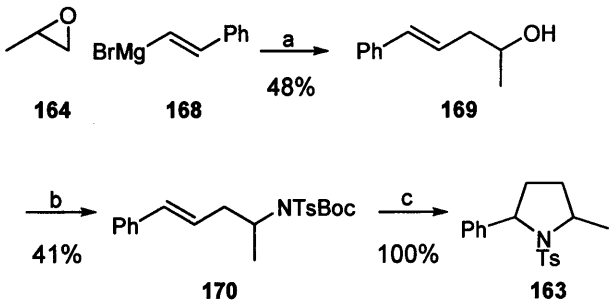


Scheme 2.39. a) CuI, THF, –35 °C, 1.5 hrs b) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight c) 0.5 eq. TfOH, DCM, 0 °C, 4 hrs

The cyclisation was high yielding and complete conversion was achieved without the need for purification of the product. Extra substitution had slightly increased the time required for the

production of 2,2,5-trimethylpyrrolidine **162** compared with 2,2-dimethylpyrrolidine **150** (Scheme 2.34), although both reactions proceeded relatively rapidly at 0 °C.

The same synthetic approach was used for the synthesis of 2-methyl-5-phenyl-1-tosylpyrrolidine **163**[122] using styrylmagnesium bromide **168** to open propylene oxide **164** (Scheme 2.40).



Scheme 2.40. a) CuI, THF, –35 °C, 1.5 hrs b) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight c) 0.5 eq. TfOH, DCM, 0 °C, 24 hrs

The ring opening of the epoxide **164** was successful, though not as high yielding as for the previous example **166**. The cyclisation was achieved in 100% yield, an improvement on the synthesis of 2-phenylpyrrolidine **159**. The reaction was performed at a lower temperature (0 °C rather than 20 °C) and had a shorter reaction time of 24 hours.

2.3.2 Terminal Double Bonds – Secondary vs. Primary Carbenium Ions

Formations of primary carbenium ions are expected to be so unfavourable that they would be most unlikely to participate in this type of hydroamination. This was a relatively easy concept to investigate, involving the movement of the double bond to a terminal position (**172**) (Figure 2.4).[123]

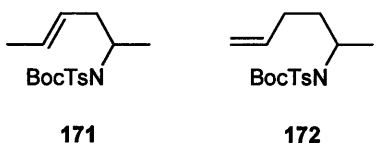
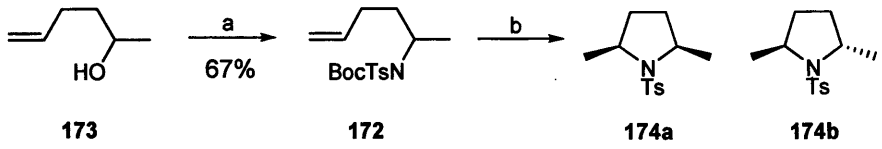


Figure 2.4. Structure of homoallylic sulfonamide **171** and *bis*-homoallylic sulfonamide **172**

If the primary carbenium ion was formed and underwent cyclisation *via* a favoured 6-*endo*-trig process, then the corresponding piperidine would be observed. If, as was expected, the primary carbenium ion was not formed, and instead the secondary was formed, then pyrrolidines **174** would be formed *via* a favoured 5-*exo*-trig process.

The terminal alkene sulfonamide **172** was synthesised from 5-hexen-2-ol **173**[124] using a Mitsunobu reaction (Scheme 2.41).



173 **172** **174a** **174b**

Scheme 2.41. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C overnight b) 0.5 eq. TfOH, DCM, 40 °C, 24 – 72 hrs

The results for the cyclisation of **172** are depicted in Table 2.1 below, along with the *cis* : *trans* ratios observed, which were estimated from ^{1}H NMR.

Table 2.1. Table showing *cis* : *trans* ratio for cyclisation of terminal alkene **172**

Acid[a]	**Temperature / °C**	**Time / hrs**	***trans* :*cis* ratio**	**Yield / %**
TfOH	20	24	Boc removal	0
TfOH	40	24	3.0 : 1.0	99
TfOH	40	72	3.0 : 1.0	88
H_2SO_4	40	72	1.0 : 1.0	88

[a] either 0.5 eq. TfOH in DCM or 2 drops of sulfuric acid in DCM

The cyclisation of (*R*)-*tert*-butyl hex-5-en-2-yl(tosyl)carbamate **172** at 40 °C overnight, showed successful formation of the desired products **174**, with a diastereomer ratio of 3.0 : 1.0. Leaving the cyclisation with triflic acid for 72 hours showed no change in the diastereomer ratio. Treating sulfonamide **172** with concentrated sulfuric acid at 40 °C for 72 hours resulted in a diastereomer ratio of 1.0 : 1.0.

The two diastereomer were separated by recrystallisation from dichloromethane, where the major isomer **174b** crystallised as a colourless solid and the minor isomer **174a** remained as a viscous oil. X-ray diffraction confirmed that the major diastereomer was *trans*-pyrrolidine **174b** (Figure 2.5).

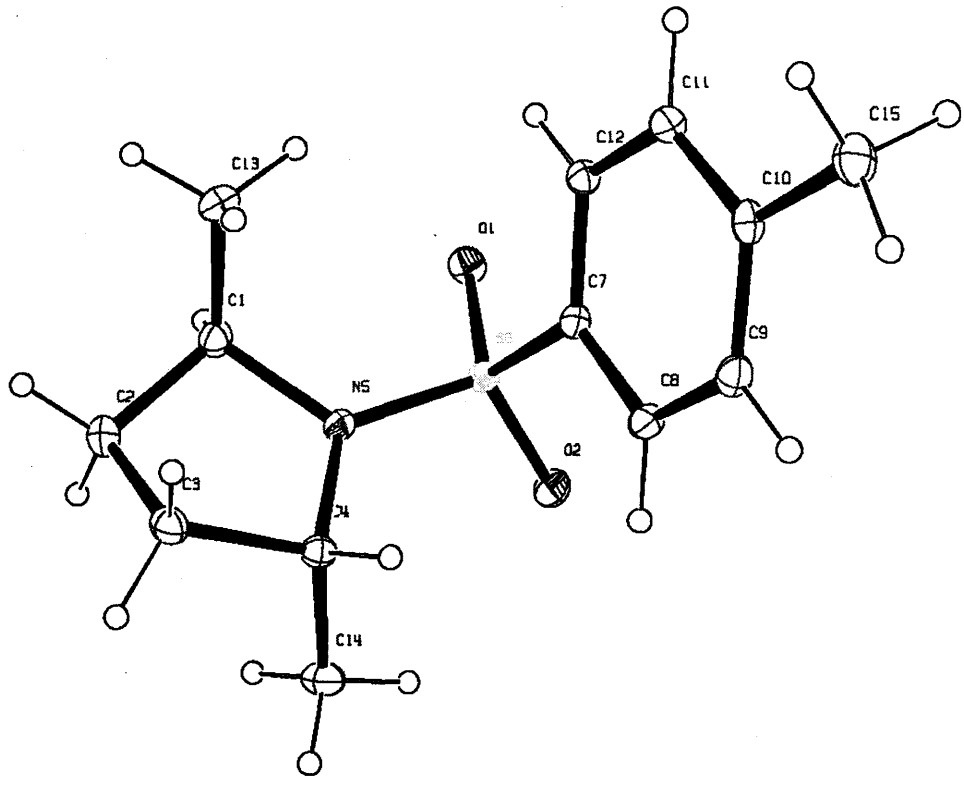


Figure 2.5. X-ray structure of major *trans*-pyrrolidine **174b**. Full crystallographic data is included in the appendix.

The structure in Figure 2.5 showed bond lengths and angles consistent with the five membered ring structure depicted in Figure 2.5.

The *trans* diastereomer was formed in greater abundance than the *cis* diastereomer when using triflic acid to catalyse the cyclisation. Sulfuric acid on the other hand showed an equal mixture of the two diastereomers, which may be due to the reaction having reached equilibrium.

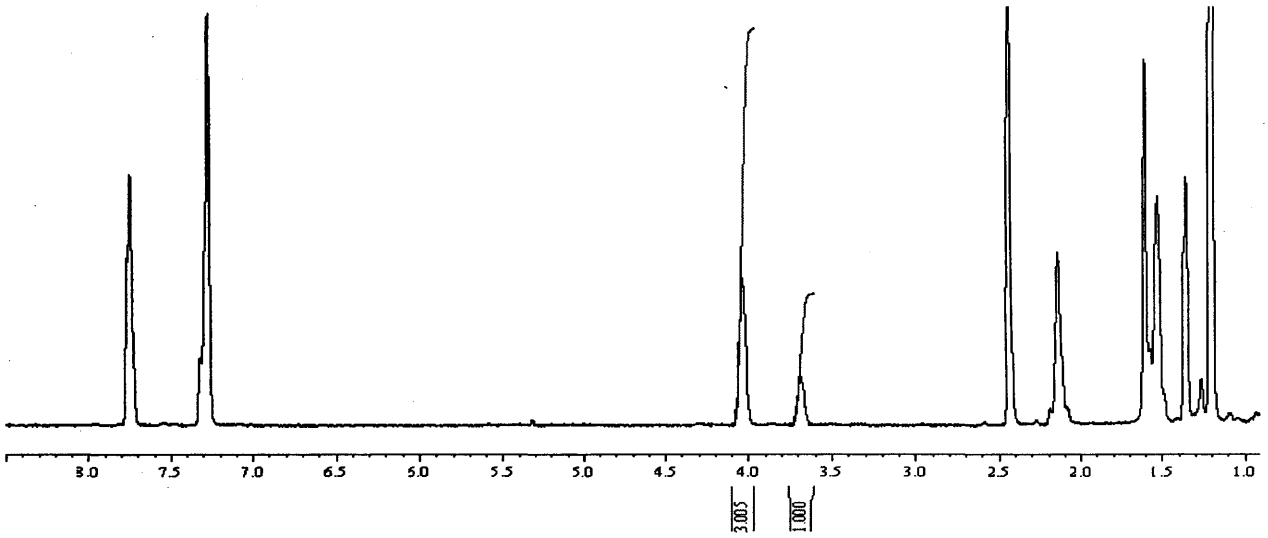


Figure 2.6. ^{1}NMR spectrum showing diastereomers **174a** and **174b** as a mixture

The CHs either side of the nitrogen for pyrrolidines **174a** and **174b**, were observed at 3.98 – 3.93 ppm for the *trans* and 3.62 – 3.59 ppm for the *cis*-diastereomer, respectively. The two tosyl Me groups were observed at 2.35 ppm and 2.34 ppm, respectively (Figure 2.6 and 2.7).

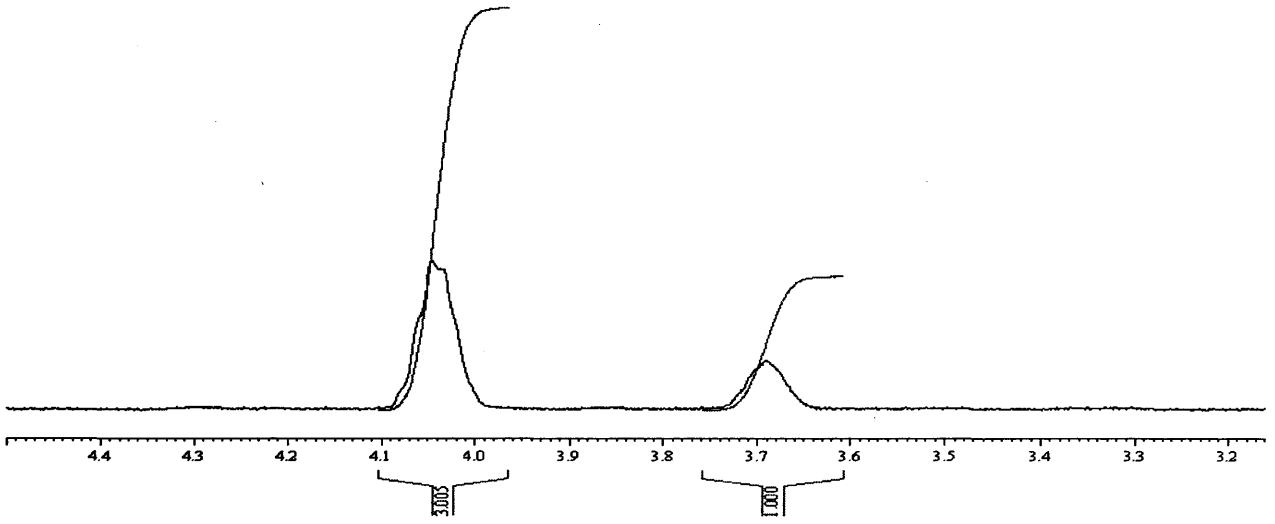


Figure 2.7. Expanded section of ^{1}H NMR spectrum for diastereomers **174a** and **174b**

Determination of the identity of each diastereomer was also possible by comparison with NMR data amassed on similar examples synthesised by Jones (Figure 2.8).[125] He had synthesised diastereomers **175** and **176** by iodocyclysation, followed by removal of the iodine (Figure 2.8). When the reactions had been performed under basic conditions then the major diastereomer isolated were the *trans* 2,5-disubstituted pyrrolidines **175**, however, when the reactions were conducted under acidic conditions then the major diastereomers isolated were the *cis* 2,5-disubstituted pyrrolidines, as was observed for **174** (Scheme 2.41).

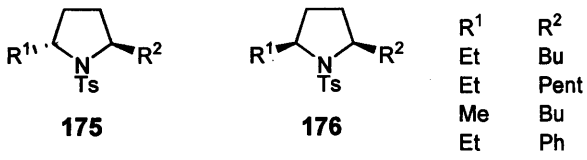


Figure 2.8. Structure of diastereomers synthesised by Jones[125]

Jones stated that for the 2,5-disubstituted pyrrolidines in Figure 2.7 "the resonance corresponding to the 2-CH and the 5-CH (*i.e.* the CHs alpha to the nitrogen) for the *trans*-pyrrolidines have a downfield shift of *ca.* 0.3 ppm by ^{1}H NMR relative to the corresponding *cis*-2,5-disubstituted pyrrolidine". This same phenomenon was observed for **174a** and **174b**.

2.3.3. Investigation intoRing Opening and Re-closure

Work previously carried out by Haskins showed the possibility of ring opening and re-closure. This is most obvious when there are groups either side of the nitrogen, as these can either be in *cis* or *trans* with respect to one another (Figure 2.9).[30,119]

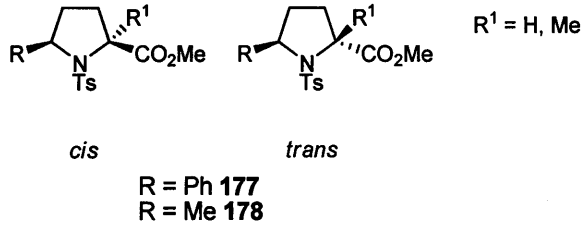
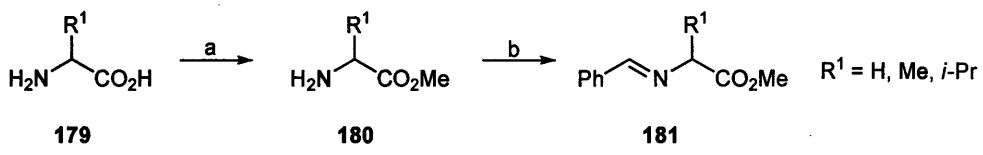


Figure 2.9. Structures of pyrrolidines used by Haskins to investigate ring-opening and re-closure

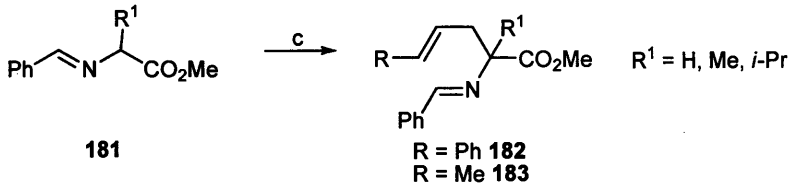
This observation was investigated further, using the forgoing examples and, in addition, an example where R^1 = *i*-Pr. These compounds are amino acid derivatives, which were synthesised from glycine, alanine or valine.

Amino acids **179** were converted into the corresponding methyl esters **180**, followed by formation of the benzyl imines **181** (Scheme 2.42). The imine acts as a protecting group for the next step of the synthesis.[30,119,126]



Scheme 2.42. a) $SOCl_2$, MeOH, 20 °C, overnight b) Benzaldehyde, $MgSO_4$, NEt_3, DCM, 20 °C, 30 hrs

Imines **181** were deprotonated with *in situ* generated LDA and then reacted with either cinnamyl or crotyl bromide (Scheme 2.43).

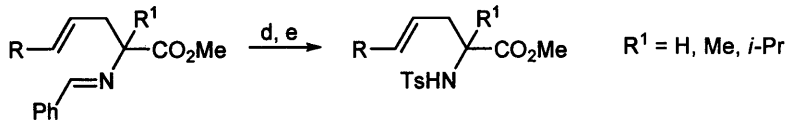


181

R = Ph **182**
R = Me **183**

Scheme 2.43. c) LDA, crotyl or cinnamyl bromide, THF, –78 °C, 1 hr, then r.t., 1 hr

N-Protecting group exchange was carried out, where imines **182** and **183** were hydrolysed to the corresponding amines, followed by immediate tosylation to give sulfonamides **184** and **185** (Scheme 2.44).

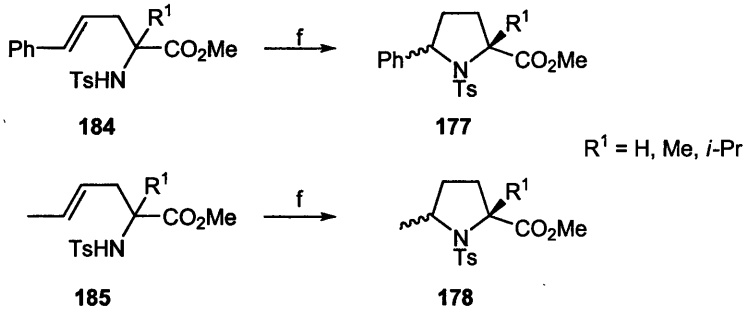


R = Ph **182**
R = Me **183**

R = Ph **184**
R = Me **185**

Scheme 2.44. d) 1 M HCl, Et_2O, 2 hrs e) *p*-TsCl, NEt_3, DCM, –78 °C, overnight

Sulfonamides **184** and **185** were cyclised with varying amounts of triflic acid to determine the effect this would have on the diastereomer ratio (Scheme 2.45).



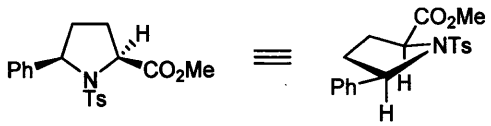
184 **177**

185 **178**

Scheme 2.45. f) 0.5 eq. TfOH, DCM, 0 °C

The standard conditions for the cyclisation with triflic acid involve the use of 0.5 equivalents of acid.[119] The amount of acid was then increased to 1, 2 and 5 equivalents. The data shown in the Tables 2.2 to 2.4 below have been calculated from ^{1}H NMR spectra.

The major isomer should be the 2,5-*cis* isomer. Due to what is known about energetic stability, the large substituents should be in the "pseudo-equatorial" position meaning that they would be *cis* to one another (Figure 2.10).



177a

Figure 2.10. Structural explanation of possible favourable *cis* diastereomer formation

The cinnamyl derivatives were cyclised and the diastereomer ratios evaluated (Table 2.2).[127]

184 R^1 = H, Me, *i*-Pr 177

Scheme 2.46. a) 0.5 eq. TfOH, DCM, 0 °C

Table 2.2. *Isomer ratios for the cinnamyl derivatives*

R^1	Equivalents	Isomer Ratios after 1 hr *trans* : *cis*	Isomer ratio after 24 hrs *trans* : *cis*
H	0.5	1.0 : 1.2	1.0 : 1.1
H	1	1.0 : 2.4 [a]	1.0 : 4.0
H	2	1.0 : 1.3	1.0 : 1. 1
H	5	1.0 : 1.0	1.0 : 1.0
Me	0.5	1.0 : 3.0 [a]	1.0 : 3.0 [a]
Me	1	1.0 : 3.1 [a]	1.0 : 2.2
Me	2	1.5 : 1.0	1.0 : 1.8
Me	5	1.6 : 1.0	1.0 : 2.2
i-Pr	0.5	1.0 : 38	1.0 : 4.3
i-Pr	1	1.0 : 5.5 [a]	1.0 : 3.6
i-Pr	2	1.0 : 4.0	1.0 : 4.0
i-Pr	5	5.0 : 1.0 : 5.0[b]	2.0 : 1.8 : 1.0[b]

[a] Starting material observed [b] second ring opened product observed

The glycine derivative overall, showed little change in diastereomer ratio when increasing the equivalents of acid added, stirring for either 1 hour or 24 hours. The reaction using 1 equivalent of acid for 24 hours had a diastereomer ratio of 1.0 : 4.0, the largest ratio observed for **177**.

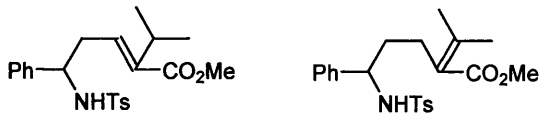
It was difficult to compare the three amino acid derivatives to one another. No apparent correlation seemed obvious between the use of the same equivalents or times exposed to the acid.
In comparison to Haskins' observations, the results obtained were rather different (Table 2.3).[119]

Table 2.3. *Comparison with the isomer ratios observed by Haskins*

	Haskins		New	
Derivative	**Equivalents**	**Isomer ratio after 1 h** ***cis* ; *trans***	**Equivalents**	**Isomer ratio after 1 h** ***cis* ; *trans***
Glycine	2	>20 : 1.0	2	1.3 : 1.0
Glycine	5	>20 : 1.0	5	1.0 : 1.0
Alanine	0.5	2.9 : 1.0	0.5	1.3 : 1.0
Alanine	1	3.5 : 1.0	1	1.3 : 1.0
Alanine	5	9.0 : 1.0	5	1.6 : 1.0

Haskins obtained isomer ratios of 20.0 : 1.0 with the glycine derivative when using 2 and 5 equivalents of TfOH. This could not be repeated; instead an isomer ration of 1.3 : 1.0 was observed for all the equivalents used apart from 1 equivalent of TfOH where a ratio of 1 : 4 was observed. For the alanine derivative, Haskins observed a 9.0 : 1.0 ratio for 5 equivalents, which again could not be repeated. Instead, a diastereomer ratio of 1.6 : 1.0 was observed. This difference in isomer ratio is difficult to explain but highlights the inherent difficulty associated with this method. The difference in diastereomer ratio observed by Haskins and those reported in Table 2.2 could possibly be due to varying levels of water present in the reaction.

The valine derivative had not been cyclised previously. Unfortunately, no significant differences in the isomer ratios were observed. This changed when using 5 equivalents; a third compound appeared. This new compound was tentatively identified as a ring opening product **186a** or **186b** by NMR, as essentially a single isomer (Figure 2.11).



186a **186b**

Figure 2.11. Possible structure for ring opening of valine derivative **177c**

The ^{1}H NMR showed a distinct NH peak as a doublet, suggesting that it must be adjacent to another proton. This was not the case in the synthesised starting material **184c** wherein the NH appeared as a broad singlet. To confirm that this doublet was in fact the NH, a D_2O shake was performed, resulting in the disappearance of the doublet and a change in the multiplicity of the CH adjacent to the NH, from a double double doublet (ddd) to a double doublet (dd). The lack of *i*-Pr and alkene protons in the NMR spectra also suggesting that ring opened product **186b** had been isolated and not **186a**. The methyl groups of the *i*-Pr group also show significant difference in

chemical shift than observed for the starting alkene **184c** and those expected for ring opened by-product **186a**. The methyl groups appeared as doublets at 1.05 and 0.89 ppm for alkene **184c**; a similar value and splitting would be expected for **186a**. The resonance observed, however, were two singlets at 2.37 and 1.96 ppm, giving further supporting the deduction that the minor ring opened byproduct observed is indeed **186b**.

Investigations into the *cis/trans* diastereomer ratios for the crotyl derivatives were also performed.

185 **178**

Scheme 2.47. a) 0.5 eq. TfOH, DCM, 0 °C

As for the cinnamyl derivative, the *cis* isomer was expected to be the major isomer observed, at least for R^1 = H, due to steric interactions (see Figure 2.9); and the results are depicted in Table 2.4.

Table 2.4. *Isomer ratios for crotyl derivatives*

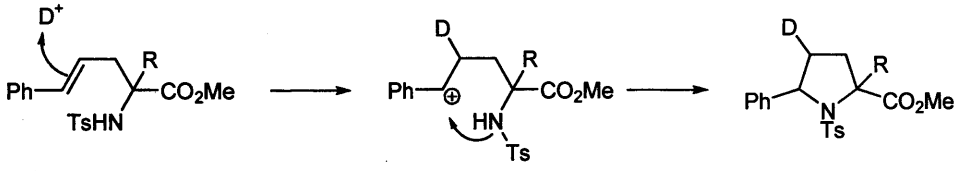
R^1	Equivalents	Isomer ratio after 1 hour *trans* : *cis*	Isomer ratio after 2 hours *trans* : *cis*	Isomer ratio after 3 hours *trans* : *cis*	Isomer ratio after 24 hours *trans* : *cis*
H	0.5	1.0 : 2.0	1.0 : 1.3	1.6 : 1.0	1.0 : 2.1
H	1	-	1.0 : 3.0	1.0 : 2.6	1.0 : 2.6
H	2	1.0 : 2.7	1.0 : 2.7	1.0 : 2.6	1.0 : 3.9
H	5	1.0 : 2.3	1.0 : 2.3	1.0 : 3.6	1.0 : 2.8
Me	0.5	2.0 : 1.0	1.4 : 1.0	2.0 : 1.0	1.9 : 1.0
Me	1	1.6 : 1.0	1.6 : 1.0	1.3 : 1.0	1.1 : 1.0
Me	2	1.7 : 1.0	1.5 : 1.0	1.7 : 1.0	1.5 : 1.0
Me	5	1.1 : 1.0	1.1 : 1.0	1.6 : 1.0	1.1 : 1.0

The glycine derivative showed inversion of ratios after 3 hours, which reverted back to the ratio observed after 1 hour using 0.5 equivalents of acid. This inversion was not observed for 1, 2 and 5 equivalents of acid added. The alanine derivative showed a gradual decline in diastereomer ratio over 24 hours although this could be due to experimental error. The valine derivative did not cyclise under any of the cyclisation conditions shown in Table 2.2. Presumably, the cyclisation could not occur because the short lived carbenium ion is difficult for the bulky sulfonamide to approach. The cyclisation for the valine cinnamyl derivative can occur, due to the generated

carbenium ion being stabilised by the phenyl group adjacent to it, meaning it will have a longer life time, thus giving the bulky sulfonamide a chance to approach it.

2.3.3.1 Investigations of the Mechanism

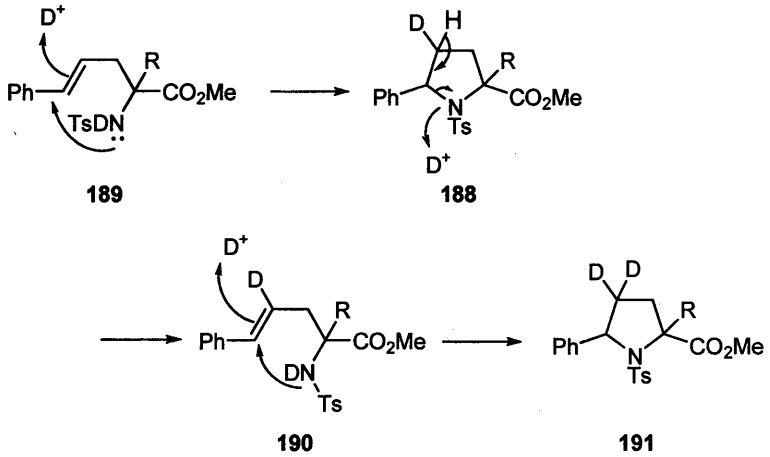
Investigating the reaction mechanism was performed with a deuterium study. This involved the implementation of deuterated triflic acid to perform the reaction with (Scheme 2.48). Deuterated triflic acid was diluted in dry DCM to give a 0.695 M stock solution to be used for the cyclisation.



184 **187** **188**

Scheme 2.48.

Cyclo-reversion is believed to occur from the beginning of the reaction, so double deuterium incorporation should be observed. Carbon-deuterium bonds are generally much stronger than carbon-hydrogen bonds; meaning that hydrogen would be preferentially lost over a deuterium (Scheme 2.49).



189 **188** **190** **191**

Scheme 2.49.

Unfortunately, there was no evidence of deuterium incorporation at all. This was rather unexpected as deuterated triflic acid was the only source of protonation and the cyclisations still occurred. The lack of deuterium incorporation was possibly due to the deuterium exchanging with hydrogen of DCM, thus meaning that the cyclisations were conducted with non-deuterated triflic acid.

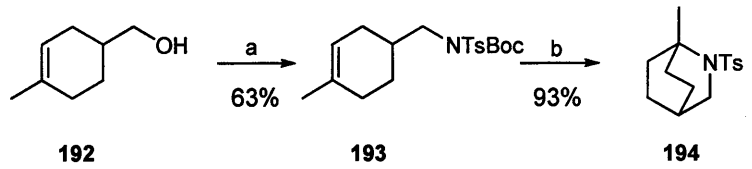
These deuteration experiments should be repeated with a solution of deuterated triflic acid in deuterated chloroform. A saturated solution of K_2CO_3 in D_2O should be used in the quenching of the reaction, to prevent further exchange. The strength of the nitrogen-deuterium bonds must also

be taken into consideration, as these are stronger than nitrogen-hydrogen bonds. The difference in bond strength could slow the removal of this and thus slow the rate of reaction. If this is still not observed, than one could conclude that N-H cleavage is not a rate determining step.

2.3.4 Transannular Cyclisations

The synthesis of pyrrolidines and other cyclic systems that have been discussed employed a planar mode of addition. Does this always have to be the case? Can the synthesis of bridged compounds through transannular hydroaminations be achieved?

Commercially available (4-methylcyclohex-3-enyl)methanol **192**[128] was converted into sulfonamide **193**, followed by cyclisation to give only the sterically crowded bridged piperidine **194** (Scheme 2.50); there is no evidence of formation of the alternative secondary carbocation, which would have resulted in the less hindered product.



Scheme 2.50. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight b) 0.5 eq. TfOH, DCM, 20 °C, 48 hrs

This is an example of *trans*-annular cyclisation and the compound formed **194** is an example of an isoquinuclidine, which are very important precursors to natural products, such as ibogaine, dioscorine and (+)-catharanthine (Figure 2.12).[129,130,131]

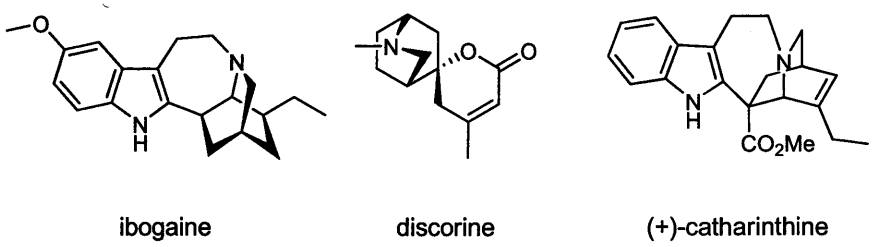
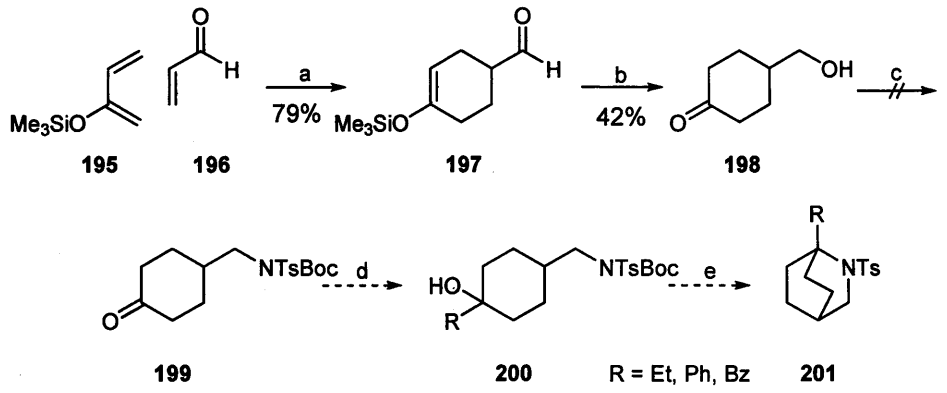


Figure 2.12. Structures of natural products containing an isoquinuclidine moiety

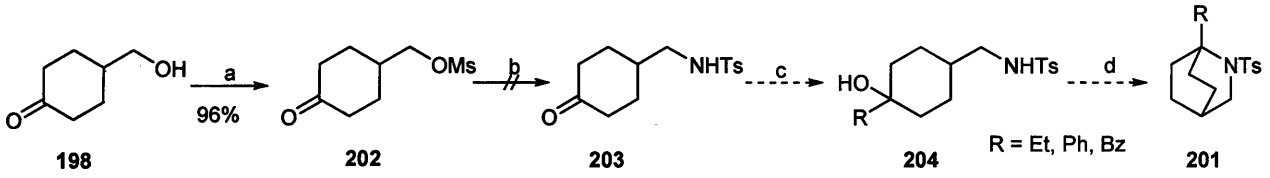
Since they are important, a new synthetic method of forming these hindered compounds using the hydroamination technique was investigated. The incorporation of different R groups, in place of the methyl group shown in **194** (Scheme 2.50) was desired. Ideally, the synthesis should allow access to different isoquinuclidines in as few steps as possible, meaning incorporation of these different functional groups should occur late on in the synthesis. This new methodology would be most suited for the elaboration of non-natural analogues substituted at a bridgehead carbon adjacent to the nitrogen, thus giving access to many new types of potentially bioactive derivatives.

The proposed synthetic approach to the desired isoquinuclidine derivatives **201** is outlined in Scheme 2.51.



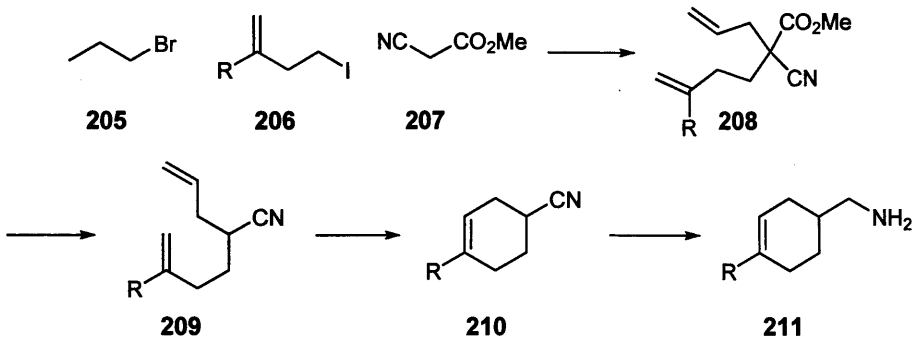
Scheme 2.51. a) Hydroquinone, toluene, 110 °C, 24 hrs b) i) $LiAlH_4$, THF ii) 15% NaOH, MeOH, 30 min c) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight d) RMgBr, THF, 0 °C e) 0.5 eq. TfOH, DCM 20 °C

The synthetic route up to keto-alcohol **198** followed literature procedure by Borden;[132] unfortunately the Mitsunobu reaction leading to sulfonamide **199** was not successful. An alternative route was sought starting from keto-alcohol **198** and is outlined in Scheme 2.52.



Scheme 2.52. a) MsCl, NEt_3, DCM, 20 °C, 2 hrs[133] b) *p*-$TsNH_2$, KOH, DMF, 100 °C, 24 hrs c) RMgBr, THF, 0 °C d) 0.5 eq. TfOH, DCM 20 °C

Conversion of the hydroxyl group of **198** into mesylate **202** was successful, though the subsequent reaction with *p*-toluenesulfonamide was not. The synthesis of isoquinuclidines **201** was abandoned and a new synthetic route towards **200** or **204** needs to be devised. The syntheses above (Schemes 2.51 and 2.52) could possibly be successful if the probable interference from the ketone was overcome through implementation of a protecting group, such as a dithiane. Alternatively, a completely different synthetic approach could be taken. Formation of the amine **211** through ring closing metathesis, where the substitution was incorporated prior to the ring closure (Scheme 2.53).



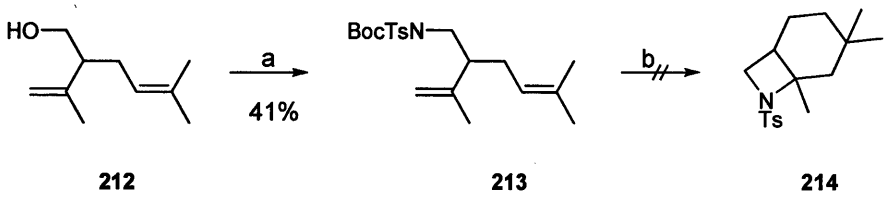
Scheme 2.53.

The synthetic approach shown in Scheme 2.53 could allow for additional substitution around the ring.

2.3.5 Cascades & Fused Systems

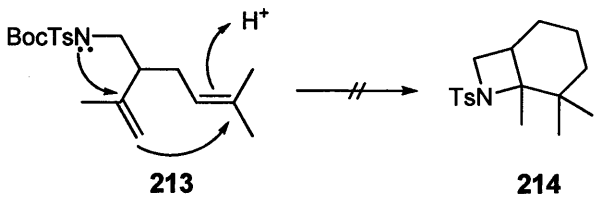
Cascade reactions, where multiple ring systems were formed in one step (Scheme 2.31) result in formation of compounds with interesting structural scaffolds, such as *spiro-* and fused systems. These are compounds that can be difficult to synthesise in just a few steps through means other than a hydroamination.[134]

Targeting a 4,6-fused system, lavandulol **212** was converted to sulfonamide **213** *via* a Mitsunobu reaction, followed by cyclisation (Scheme 2.54).



Scheme 2.54. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight b) 0.5 eq. TfOH, DCM, 40 °C, 24 hrs

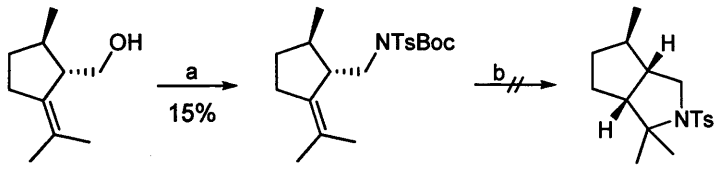
It was hoped that a four membered ring would be formed, despite the overall 4-*exo*-trig cyclisations being disfavoured by Baldwin's rules (Scheme 2.55). Cyclisations have already been proven to be possible despite being disfavoured by Baldwin's rules, such as **152** in Scheme 2.35.



Scheme 2.55.

The synthesis of **214** was unsuccessful, which was not particularly surprising, as the four membered ring formed would have been under considerable strain.

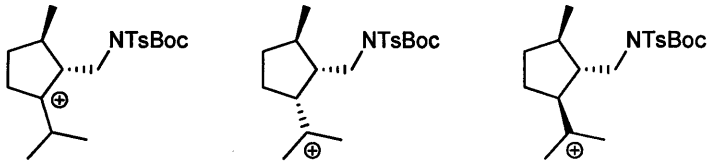
Formation of a 5,5-fused system was attempted next, through formation of the pyrrolidine ring upon an already present cyclopentane (Scheme 2.56).



215 **216** **217**

Scheme 2.56. a) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight b) 0.5 eq. TfOH, DCM, 40 °C, 48 hrs

The cyclisation was not successful, possibly due to steric crowding or due to the carbenium ion **216a** being formed at the ring junction rather than the isopropyl as expected. Also protonation at the isopropenyl would result in formation of two isomers **216b** and **216c**; where **216b** would favour cyclisation due to its proximity to the nitrogen required for the cyclisation to occur (Figure 2.13).

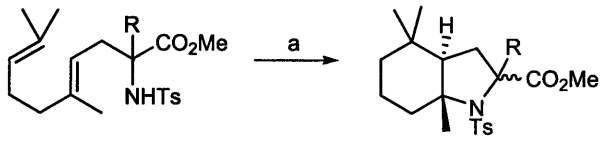


216a **261b** **216c**

Figure 2.13. Three possible carbenium ions formed from **216**

If the carbenium ion at the ring junction **216a** and **216c** were favoured, then this would explain the lack of cyclisation occurring. The resulting 4-membered ring formed from carbenium ion **216a** would be too strained to make its formation feasible.

A study was undertaken on the cyclisation of geranyl derivatives of glycine and valine (Scheme 2.57). These were synthesised by the same method as the cinnamyl and crotyl derivatives in Figure 2.8, employing geranyl bromide in the substitution reaction.[135]



218 R = H or *i*-Pr **219**

Scheme 2.57. a) 0.5 eq. TfOH, DCM

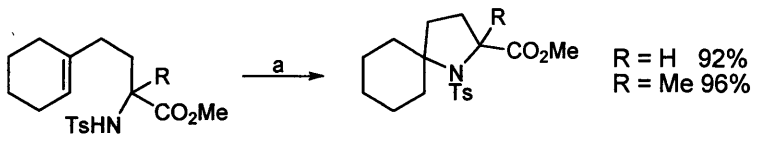
Table 2.5. *Comparison of genaryl glycinate and valinate derivatives*

R	Equivalents	Isomer ratio after 1 hour *trans* : *cis*	Isomer ratio after 24 hours *trans* : *cis*
H	2	1.0 : 10.0	1.0 : 2.5
i-Pr	2	1.0 : 10.0	1.0 : 5.0

The diastereomer ratios observed for the fused-cycle **219** were higher than those for the pyrrolidines **177** & **178**; reminiscent of the ratios observed by Haskins for the cinnamyl glycinate **177a** and alaninate **178a** derivatives.[119] The glycinate derivative **219** diastereomer ratio decreased from 1.0 : 10.0 after 1 hour to 1.0 : 2.5 after 24 hours. A similar but less marked decrease was observed for the alanine derivative, where the ratio decreased from 1.0 : 10.0 to 1.0 : 5.0. It is believed that the ratio shifts in favour of the *trans*-diastereomer, the thermodynamic product, after prolonged exposure to acid.[136]

2.3.6. Indene

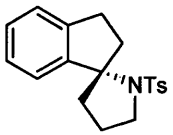
As well as synthesising simple pyrrolidines, previous work by Haskins has shown that *spiro*-cycles can be formed through acid-catalysed hydroaminations. These had ester functionality adjacent to the formed hindered amine (Scheme 2.58).[30]



219 **220**

Scheme 2.58. a) 0.5 eq. TfOH, $CHCl_3$, 0 °C, 0.25 hrs

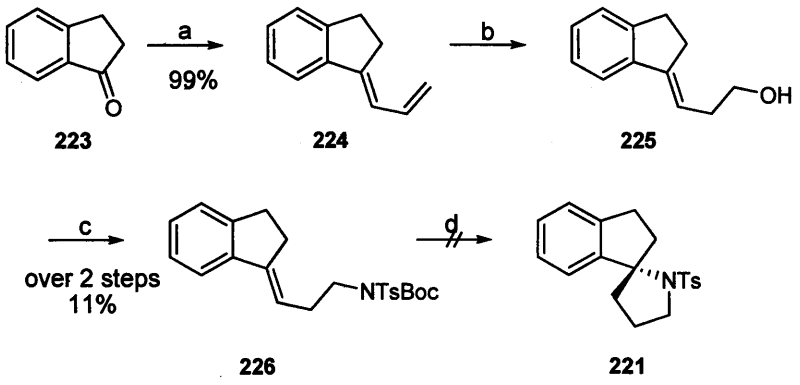
The ester adjacent to the sulfonamide is not needed for acid-catalysed hydroamination to occur. Is this also the case for *spiro*-cycles, such as **221**, which would also represent an extension to the present methods (Figure 2.14)?



221

Figure 2.14. Indanone derived *spiro-cycle*

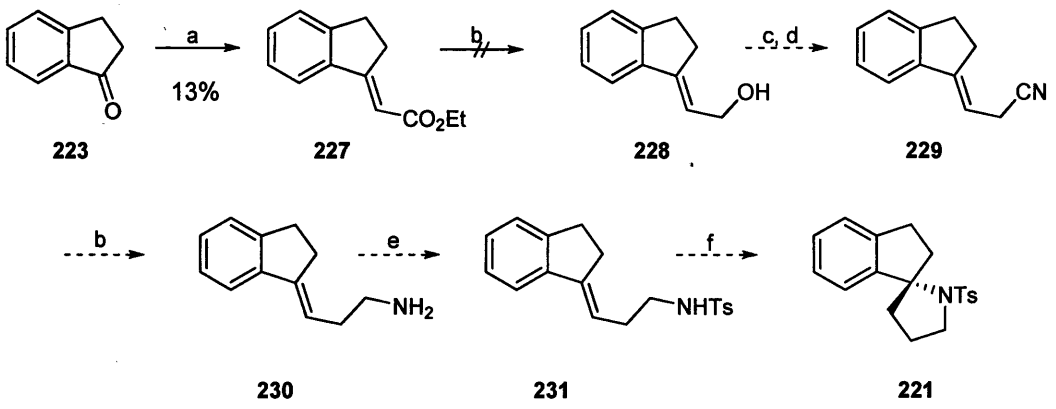
This was to be tested in the synthesis of indene-derived *spiro*-cycle **221**. The original synthetic route is outlined in Scheme 2.59.



Scheme 2.59. a) $CeCl_3$, allylMgBr, MsCl, NEt_3, conc. HCl, 20 °C, 3 hrs b) 9-BBN, aq. NaOH, H_2O_2, 80 °C, 2 hrs c) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C

The synthesis of alcohol **225** followed a known literature procedure.[137] The cerium chloride-mediated Grignard reaction was successful, but problems were encountered with the 9-BBN hydroboration/oxidation reaction. Alcohol **225** proved difficult to isolate, which is not something observed by Pearson. The problem of isolating alcohol **225** was eventually overcome by omitting its purification and instead carrying it forward to the Mitsunobu reaction to give sulfonamide **226**. Unfortunately, the cyclisation to the desired *spiro*-pyrrolidine **221** could not be achieved.

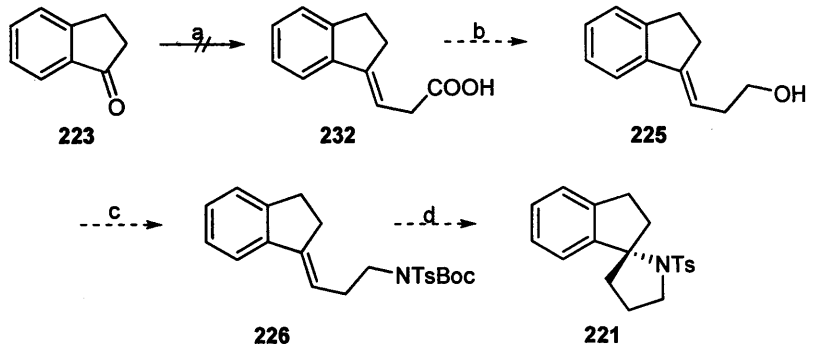
An alternative synthetic approach from indanone **223** involved the formation of an ethyl ester through a Horner-Wadsworth-Emmons reaction[138] was attempted, as outlined in Scheme 2.60.



Scheme 2.60. a) triethyl phosponoacetate, NaH, THF b) $LiAlH_4$, THF, 0 °C c) TsCl, pyridine, 0 °C d) NaCN, DMSO e) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C f) 0.5 eq. TfOH, DCM, 0 °C

Reduction to the alcohol **228** resulted in isolation of a residue that was deemed beyond purification.

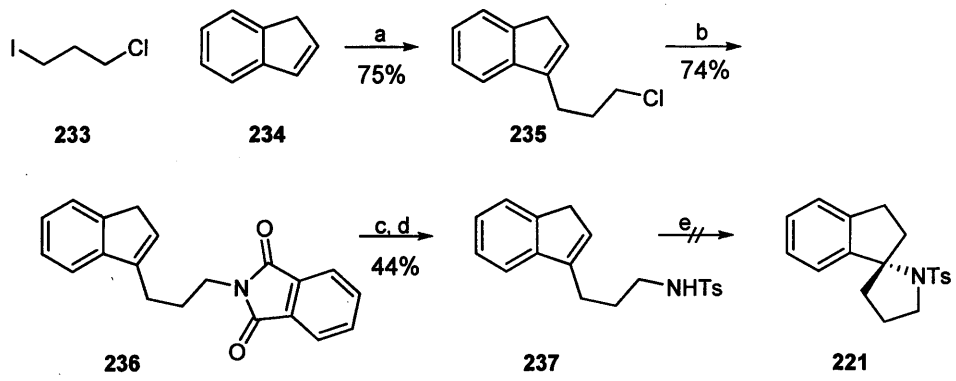
An alternative Horner-Wadsworth-Emmons reaction, to give acid **232**, which would negate the need for a cyanide reaction was attempted (Scheme 2.61).[139,140]



Scheme 2.61. a) 2-carboxyethyltriphenylphosphonium bromide, NaH, THF:DMSO (1:1) 0 °C, overnight b) $LiAlH_4$, THF, 0 °C c) PPh_3, DIAD, TsNHBoc, THF, 0 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C

The Horner-Wadsworth-Emmons reaction was unsuccessful, with no discernable amount of **232** visible in the proton spectra.

1-Chloro-3-iodopropane was reacted with indene **234**.[141] Chloride **235** was treated with potassium phthalimide through a Gabriel synthesis,[142] and converted to sulfonamide **237** (Scheme 2.62).



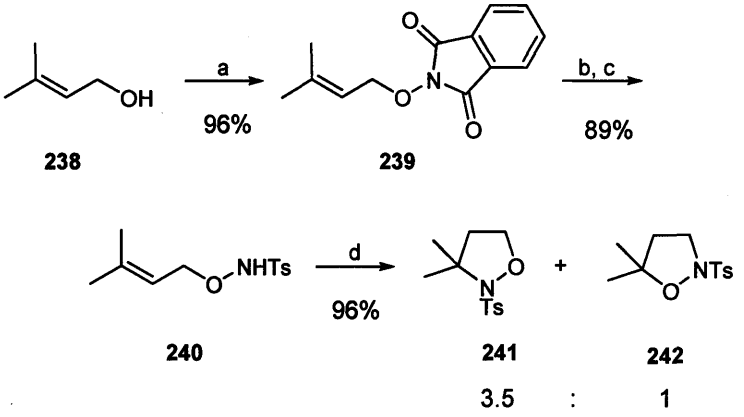
Scheme 2.62. a) *n*-BuLi, THF, 0 °C b) K^+ phthalimide c) H_2NNH_2, EtOH, 60 °C d) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C e) 0.5 eq. TfOH, DCM, 0 °C

Sulfonamide **237** was not successfully cyclised to the desired *spiro*-pyrrolidine **221**, as had been observed for sulfonamide **226** (Scheme 2.59). Why the cyclisation did not occur is still unknown. Possibly harsher conditions are needed for the reaction to occur. There is also the distinct possibility that the sulfonamide is unable to approach the reaction site due it being too hindered. If this is the case then the cyclisation should be attempted with a smaller *N*-protecting group, such as a mesylate or methoxycarbonyl.

2.3.7. O-N Compounds

2.3.7.1 Isoxazolidine vs. Morpholine

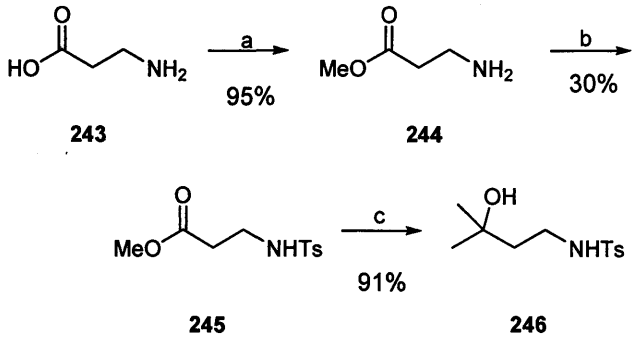
Proctor investigated whether suitably protected hydroxylamines could be used to trap an acid-generated carbenium ion. The first substrates that Proctor synthesised were isoxazolidines, such as **241** in Scheme 2.63.[143]



Scheme 2.63. a) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C b) $MeNH_2$, Et_2O c) *p*-TsCl, DMAP, pyridine, DCM, –78 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C, 10 min,

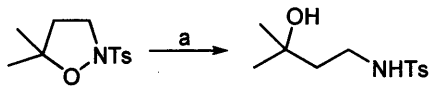
Complete conversion of the starting material was observed, though a minor product was also observed. The structure of the isoxazolidine **241** was confirmed by X-ray crystallography and the minor product was identified as a regioisomer of product **241**, isoxazolidine **242**.

The structure of this regioisomer was further confirmed by synthesis of **246**; the actual regioisomer was not synthesised, due to the possibility of the same kind of rearrangement occurring, especially during [1,3]-dipolar addition. Instead a derivative was synthesised, the corresponding amino-alcohol **246** resulting from nitrogen-oxygen bond cleavage, as laid out in Scheme 2.64.



Scheme 2.64. a) $SOCl_2$, MeOH b) *p*-TsCl, NEt_3, DMAP, DCM c) MeMgCl, THF, 0 °C

The cleavage of the nitrogen-oxygen bond was then attempted through hydrogenation;[144] this proved difficult, as after 7 days, proton spectrum of the crude product revealed only 40% conversion to the amino alcohol **246** (Scheme 2.65).

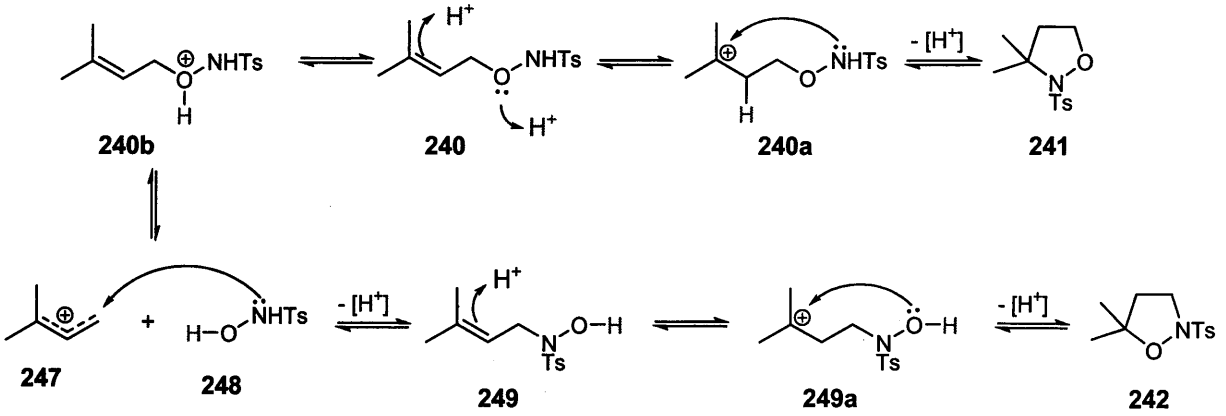


242 **246**

Scheme 2.65. a) H_2, Pd/C. MeOH, 48 hrs

Although a pure sample of the hydrogenolysed product was not isolated, the correlation of the new resonance in the proton NMR spectrum of this mixture of compound with the those found in the authentic sample of the amino alcohol **246**, showed an exact match. This provided excellent support for the structural assignment of the minor product and the hypothesis that the products of the cyclisation reaction were the isoxazolidine **241** and regioisomer **242** (Scheme 2.63).

Previous observations suggested that the major cyclisation product resulted from trapping of a carbenium ion generated by the protonation of an alkene bond in the tertiary position **240a**, under acidic conditions.[143] Protonation may also occur at the nitrogen nucleophile; however, although this would initially block its ability to act as a nucleophile, this may also assist in protonation of the alkene by allowing for intramolecular proton transfer. In the case of the *O*-allylic hydroxylamines, the hydroxylamine oxygen is a further potential site for protonation. Protonation at the oxygen **240b** would result in the hydroxylamine becoming a considerably better leaving group, generating *N*-tosyl hydroxylamine **248** and a relatively stabilised, allylic carbenium ion **247** (Scheme 2.66).

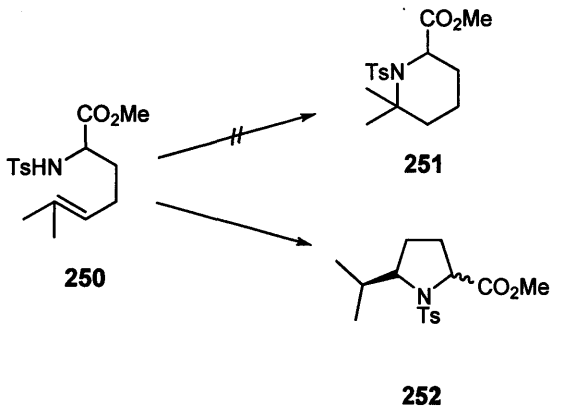


Scheme 2.66.

The loss of the hydroxylamine **248** was hypothesised to be a reversible process, with this portion of the molecule able to reattach through the nucleophilic oxygen and regenerate the starting

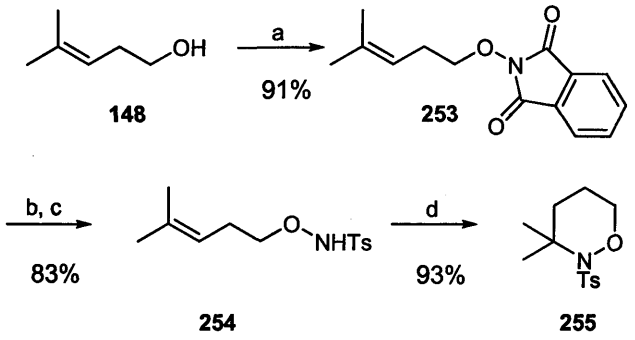
material **240**, which could then cyclise to give the expected product **241**. The hydroxylamine could also reattach to the carbenium ion through the nitrogen instead, resulting in the rearranged starting material **249**. This compound could then cyclise through generation of a tertiary carbenium ion **249a** followed by attack of the oxygen, yielding the minor product **242** (Scheme 2.66).

Studies into acid-catalysed cyclisations of sulphonamides, conducted by Haskins, showed a limitation in an apparent inability to synthesise piperidines *via* overall 6-*endo*-trig cyclisations. In one notable example, the sulfonamide **250**, designed for the synthesis of piperidine **251**, instead cyclised to yield pyrrolidine **252**, an overall 5-*exo*-trig cyclisation, presumably occurring *via* rearrangement to a secondary carbenium ion intermediate and cyclisation through this species (Scheme 2.67).[119]



Scheme 2.67. Cyclisation of sulfonamide **250** resulting in unexpected 5-*exo*-trig product **252**

In order to test whether a similar phenomenon would be observed in the cyclisation of hydroxylamines, suitable tosyl-protected hydroxylamine **254** was synthesised from the homo-prenyl alcohol **148**, which is commercially available (Scheme 2.68).[143]



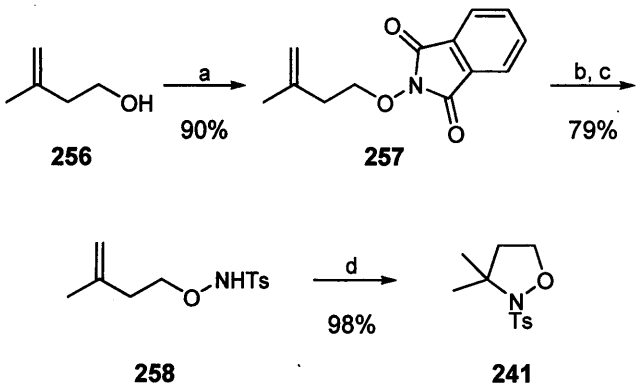
Scheme 2.68. a) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C, overnight b)$MeNH_2$, Et_2O, 40 °C, 2 hrs c) *p*-TsCl, DMAP, pyridine, DCM, –78 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C, 10 min

Application of the standard cyclisation conditions returned not only the desired six-membered cyclic product **255**, but delivered it as a single product and with no need for further purification.

In the case of the homoprenyl analogue **254**, loss of the hydroxylamine portion of the molecule would leave a primary carbenium ion, which is far less stable than the allylic carbenium ions shown in Scheme 2.67, thus resulting in none of the regioisomer being produced.

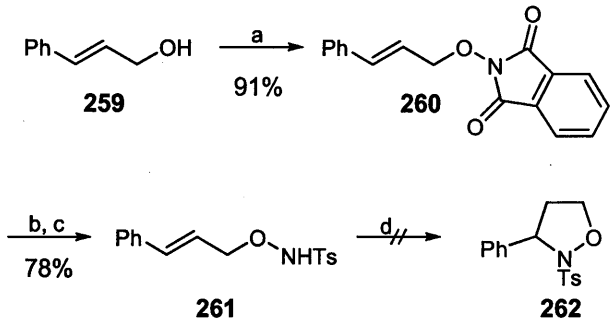
These findings suggested that if the hydroxylamine is not in an allylic (or perhaps similary stabilised) position, the rearrangement process does not occur and a single product is obtained. This effect was examined in the synthesis of isoxazolidine **241**, where the alkene bond was repositioned so that the hydroxylamine oxygen was no longer in an allylic position, taking care that the same tertiary carbenium ion was generated.

From commercially available, *iso*-prenyl alcohol **256**, the tosyl-protected hydroxylamine **258** was synthesised (Scheme 2.69). Exposure to triflic acid delivered the desired isoxazolidine **241**, as a single product and with no further purification required.



Scheme 2.69. a) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C, overnight b) $NeNH_2$, Et_2O, 2 hrs c) pyridine, DMAP, *p*-TsCl, DCM, –78 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C, 10 min

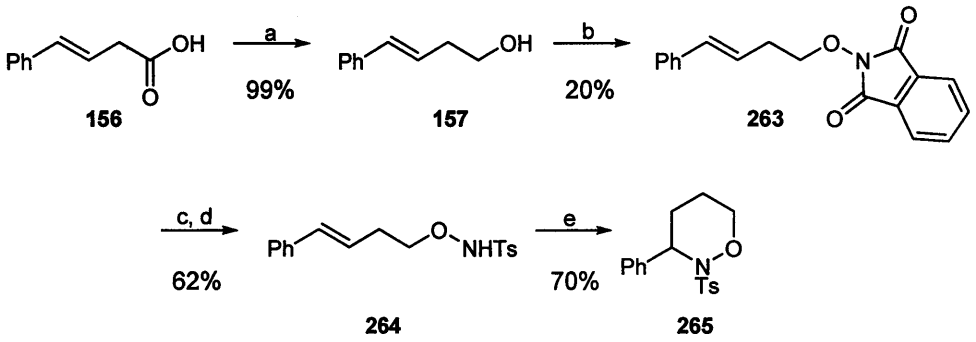
Proctor had attempted the synthesis of the isoxazolidine **262** with a phenyl substituent, from (*E*)-cinnamyl alcohol **259** (Scheme 2.70).



Scheme 2.70. a) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C, overnight b) $MeNH_2$, Et_2O, 2 hrs c) pyridine, DMAP, *p*-TsCl, DCM, –78 °C, overnight d) 0.5 eq. TfOH, DCM, 0 °C

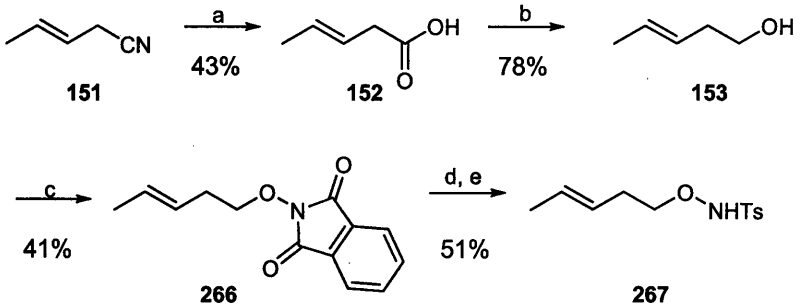
Unfortunately treatment with triflic acid resulted in the decomposition of the substrate. The decomposition could be attributed to the sensitivity of either the starting material or the reaction products to the acidic conditions. It was possible that the same kind of regioisomerisation was occurring for **261** as had been observed previously with allylic hydroxylamine **240** (Scheme 2.66). In this case an unstable intermediate carbenium species may have been generated; unfortunately, the possibility of synthesising an alternative non-allylic isomer did not exist.

Thus, in order to complete these model studies, some additional experiments were carried out at the outset of the present project. Homoallylic analogue **264** was synthesised, as this was not expected to participate in the isomerisation and could potentially deliver a 6-membered product by addition to a benzylic carbenium ion. This idea was vindicated by the isolation of the morpholine **265** in a very successful yield (Scheme 2.71).



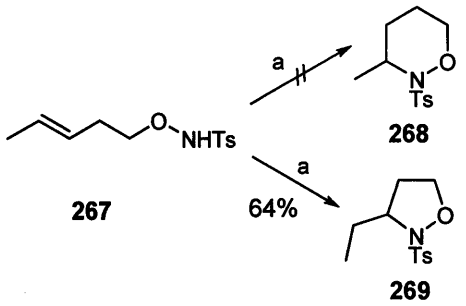
Scheme 2.71. a) $LiAlH_4$, Et_2O, 20 °C, 1 hr b) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C, overnight c) H_2NNH_2, EtOH, 60 °C, 2 hrs d) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight e) 0.5 eq.TfOH, DCM, 20 °C, 24 hrs

The successful isolation of morpholine **265** prompted the investigation into whether its formation was due to the stability of the benzylic carbenium ion generated or if this outcome would be true for all possible morpholine syntheses involving a secondary carbenium ion. The analogue of sulfonamide **254** (Scheme 2.68) was therefore synthesised from commercially available *trans*-3-pentenitrile **151** as shown in Scheme 2.72.



Scheme 2.72. a) 30% H_2O_2, 3 M NaOH, 80 °C, 2 hrs then 20 °C, 1 hr b) $LiAlH_4$ Et_2O, 20 °C, 1 hr c) PPh_3, DIAD, *N*-hydroxyphthalimide, THF, 0 °C, overnight d) H_2NNH_2, EtOH, 60 °C, 2 hrs e) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C, overnight

Unfortunately, the anticipated morpholine **268** was not isolated; instead isoxazolidine **269** was formed as a single product (Scheme 2.73).



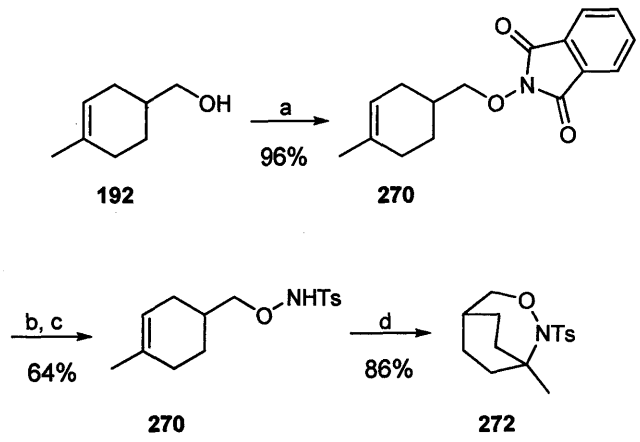
Scheme 2.73. 0.5 eq. TfOH, 24 hrs, 0 °C

Both the morpholine and isoxazolidine would have been formed through a secondary carbenium ion. The formation of isoxazolidine **269** was due to the 5-*exo*-trig cyclisation being favoured over the 6-*endo*-trig formation of morpholine **268**. Again, although not strictly a Baldwin-type cyclisation as it is cationic, when the formation of the two possible carbenium ions is equally likely, the reaction will follow the pattern set out by Baldwin. Presumably morpholine **268** would be made from the 4-hexenyl analogue. Hence, despite the sensitivity and weakness of an N-O bond, with the exception of the cinamyl (and possibly crotyl) examples, they all worked well with secondary carbenium cations.

This needs to be expanded further to see if other groups, such as electron donating and withdrawing, would favour the formation of a morpholines or isoxazolidines; as well as investigating the effect of substitution pattern.

2.3.7.2 Transannular Cyclisations

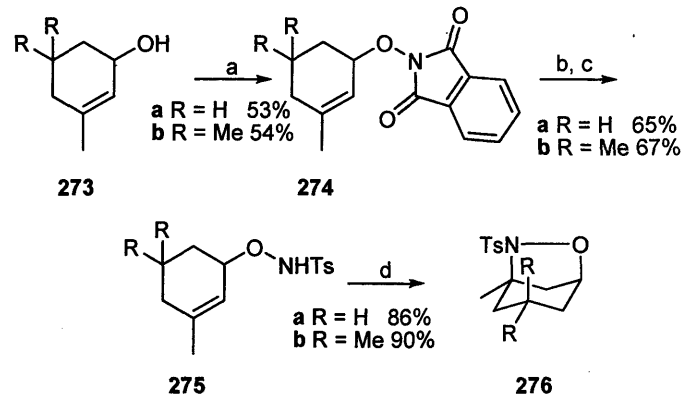
As transannular cyclisations were successful for sulfonamide **193** (Scheme 2.50), the possibility of this occurring with hydroxylamines derivatives was investigated (Scheme 2.74).



Scheme 2.74. a) PPh_3, DIAD, *N*-hydroxphthalimide, THF, 0 °C, overnight b) H_2NNH_2, EtOH, 60 °C 2 hrs c) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight d) 0.5 eq.TfOH, DCM, 0 °C, 2 hrs

The cyclisation to oxazepane **272** was successfully achieved in a good yield without further need for purification. No evidence of the alternative product, resulting from trapping of a secondary carbenium ion, was observed.

Examples of bridged-morpholines **276**, through *trans*-annular cyclisation were achieved from 3-methylcyclohex-2-enol **273a** and 3,5,5-trimethylcyclohex-2-enol **273b**, as shown in Scheme 2.75.

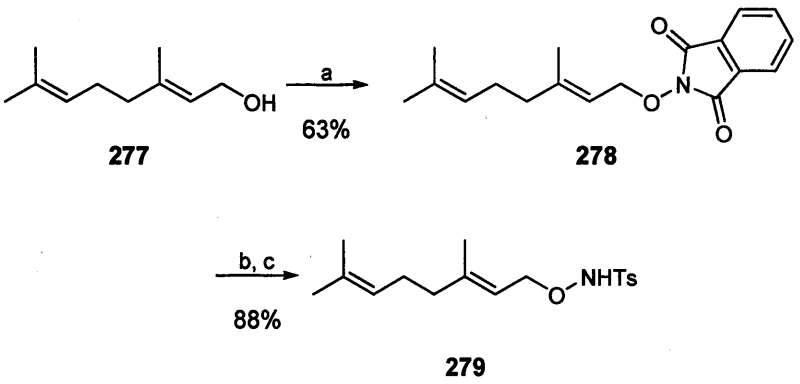


Scheme 2.75. a) PPh_3, DIAD, *N*-hydroxphthalimide, THF, 0 °C, overnight b) H_2NNH_2, EtOH, 60 °C, 2 hrs c) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight d) 0.5 eq.TfOH, DCM, 0 °C, 24 hrs

Both cyclisations were successful and high yielding. This was unexpected for isoxazolidine **276b**, as it was feared that the methyl groups may cause steric hindrance and therefore prevent the cyclisation from occurring. Both examples would be extremely difficult to synthesise in such a short sequence with excellent yields.

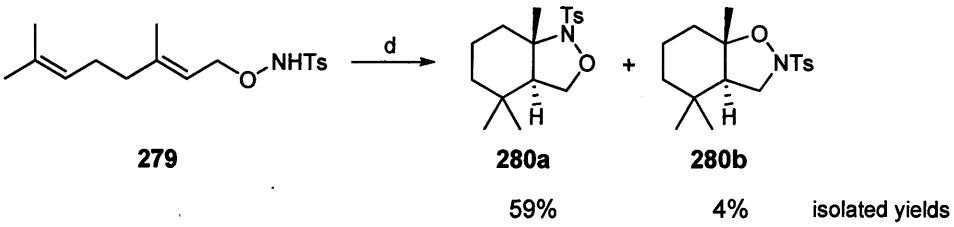
2.3.7.3 Spiro-Isoxazolidines

Haskins demonstrated the stability of the sulfonamides to trap acid-generated carbenium ions could be extended to the synthesis of fused ring systems *via* acid catalysed poly-ene cascade reactions (Scheme 2.31), with sulfonamides acting as terminators.[30,119] Both Brønsted and Lewis acid-catalysed cascade reactions had recently received considerable interest and have found applications in numerous total syntheses.[145] Proctor investigated this further and achieved the synthesis of a suitable cascade precursor, starting from commercially available geraniol **277** (Scheme 2.76).[143]



Scheme 2.76. a) PPh_3, DIAD, *N*-hydroxyphthalimide, DCM, 0 °C, overnight b) H_2NNH_2, EtOH, 60 °C, 2 hrs c) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight

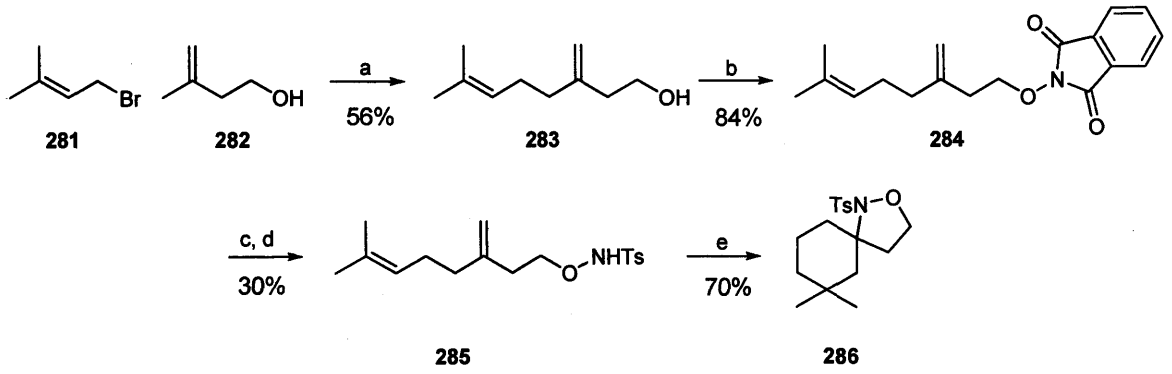
Exposure to a catalytic amount of triflic acid leads to rapid consumption of the starting material **279** and the formation of two products **280a** and **280b**, in the ratio ~ 4 : 1 (as judged by integration of resonance in the proton NMR of crude product), which were separated by silica gel chromatography (Scheme 2.77).



Scheme 2.77. f) 0.5 eq. TfOH, DCM, 40 °C, 48 hrs

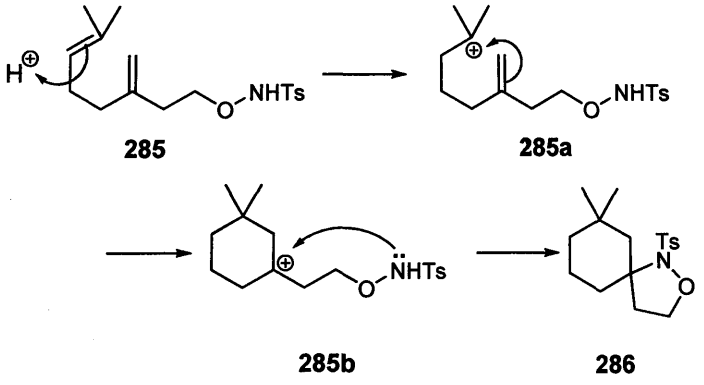
Working on the assessment that, in each of the cascade reactions described, the minor product resulted from isomerisation of the allylic *N*-tosyl hydroxylamine subunit, it seemed a logical approach to attempt the same tactic for preventing this isomerisation (see Scheme 2.66 on p.46) as had proved successful previously, *i.e.* repositioning of the double bond so that the hydroxylamine was no longer in the allylic position. The geraniol isomer **283** was synthesised using the method of Chong and elaborated in the standard manner.[146] Application of triflic acid resulted in an initially

surprising, yet in retrospect predictable result: synthesis of the *spiro*-cyclic isoxazolidine **286** (Scheme 2.78).



Scheme 2.78. a) TMEDA, 2 eq. *n*-BuLi, Et_2O, 0 °C for 6 hrs, then –78 °C overnight b) PPh_3, DIAD, *N*-hydroxphthalimide, THF, 0 °C, overnight c) H_2NNH_2, EtOH, 60 °C, 2 hrs d) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight e) 0.5 eq. TfOH, DCM, 0 °C, 1 hr

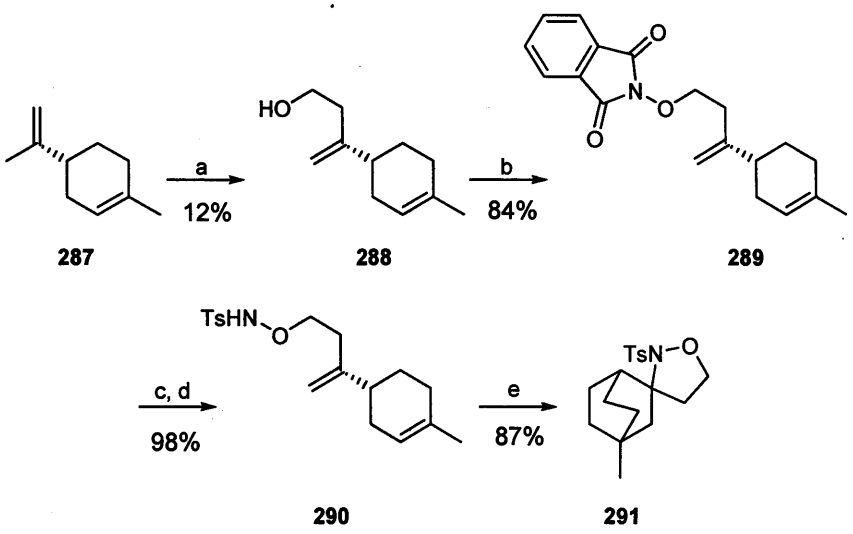
For formation of the carbocyclic ring to occur, this must take place prior to the formation of the isoxazolidine ring. Protonation of the double bond furthest from the hydroxylamine moiety, followed by attack by the second double bond, leaves a tertiary carbenium species **285a** that can be attacked by the hydroxylamine nucleophile to form the spirocyclic isoxazolidine **286** (Scheme 2.79).



Scheme 2.79.

The protonation seems unlikely to be so regiospecific that a series of rapid equilibria may be present to give the presumably thermodynamic product **286**.

Next the *spiro*-cyclic bridged isoxazolidine of homolimonenol was synthesised, through a cascade reaction to form both the bridge and the isoxazolidine. Homolimonenol **288** was first synthesised from (*R*)-limonene **287** utilising the method described by Blomquist,[147] using paraformaldehyde in an inefficient ene reaction. The original stereochemistry was destroyed in the cyclisation to bridge *spiro*-cycle **291** (Scheme 2.80).



Scheme 2.80. a) paraformaldehyde, $Sn(IV)Cl_4$, DCM, 20 °C, 3 days b) PPh_3, DIAD, *N*-hydroxphthalimide, THF, 0 °C, overnight c) H_2NNH_2, EtOH, 60 °C, 2 hrs d) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight e) 0.5 eq. TfOH, DCM, 0 °C, 1 hr

The spirocyclic bridged isoxazolidine **291** was isolated as a single isomer. The cyclisation could have occurred in either an *endo*- or *exo*-manner to give either **291a** or **291b**, respectively (Figure 2.15).

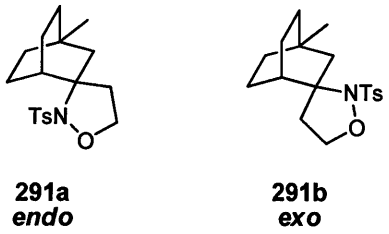
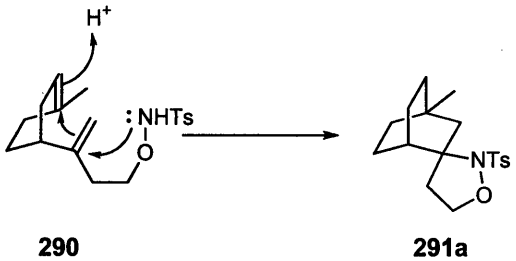


Figure 2.15. Two possible isomers of **x130**

According to NMR analysis it would appear that the single isomer is in fact the *exo*-product **291b**, which is sensible considering the reaction mechanism as shown in Scheme 2.81.



Scheme 2.81.

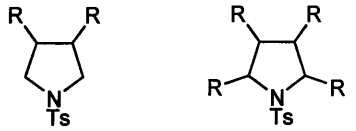
2.4. Conclusion and Future Work

From the eclectic mixture of reactions that have been performed in this chapter some conclusions can be drawn. First and foremost, it has been shown that an ester adjacent to the nitrogen involved in the cyclisation is not required. The acid-catalysed hydroamination cyclisations as a whole have been achieved in good yields without any need for purification. In those cases where the sulfonamide nitrogen is further protected with a Boc group; this can be removed *in situ* in the cyclisation step, thus negating a deprotection reaction.

The hydroamination has also been shown to be applicable to the formation of bridged compounds through a trans-annular cyclisation, such as isoquinuclidine **194**. Unfortunately, the designed synthetic approach to give a wider variety of isoquinuclidine derivatives was unsuccessful due to difficulties in forming sulfonamides **200** and **204**. An alternative approach for these is needed to allow cyclisation to isoquinuclidines **201** (Scheme 2.52 and 2.53).

The cyclisation has also been used in the synthesis of isoxazolidines as well as morpholines, as a continuation of work started by Proctor. This also allowed the synthesis of *spiro*-isoxazolidines **286** and **291**, which were isolated cleanly and as single isomers.

Though as a whole, the syntheses of the targeted compounds in this chapter have been successful, more still needs to be accomplished with this acid-catalysed hydroamination method. The synthesis of 3,4-disubstituted **292** and 2,3,4,5-tetrasubstituted **293** pyrrolidines still needs to be investigated (Figure 2.16).



292 **293**

Figure 2.16. 3,4-Disubstituted and 2,3,4,5-tetrasubstitued pyrrolidines

Difficulties with the use of triflic acid, in terms of its shelf-life and ease of use, resulted in the use of concentrated sulfuric acid in some syntheses, which have been successful. Further investigation into the use of sulfuric acid needs to be made, especially in terms of accuracy of measurement of the acid; and insolubility in dichloromethane. This will most likely evolve into testing of other acids, most likely chiral super-acids, which would hopefully allow control of stereochemistry in the synthesised pyrrolidines.

Chapter 3

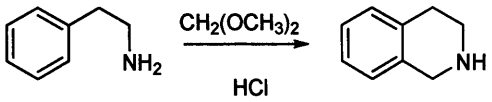
Chapter 3

A Hydroamination Variant of the Pictet-Spengler Reaction

3.1. Introduction

3.1.1. Development of the Pictet-Spengler Reaction

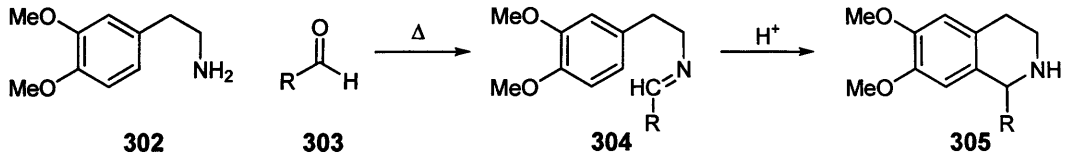
The condensation of β-phenethylamine **300** with carbonyl compounds in the presence of an acid catalyst to give 1,2,3,4-tetrahydroisoquinolines **301** (Scheme 3.1) is known as the Pictet-Spengler reaction and is a special case of the Mannich reaction.[148,149,150,151,152]



300 **301**

Scheme 3.1. a) $CH_2(OCH_3)_2$, HCl

The reaction was extended by Decker and Becker to the condensation of substituted phenethylamines **302** with various aliphatic and aromatic aldehydes **303**.[153]

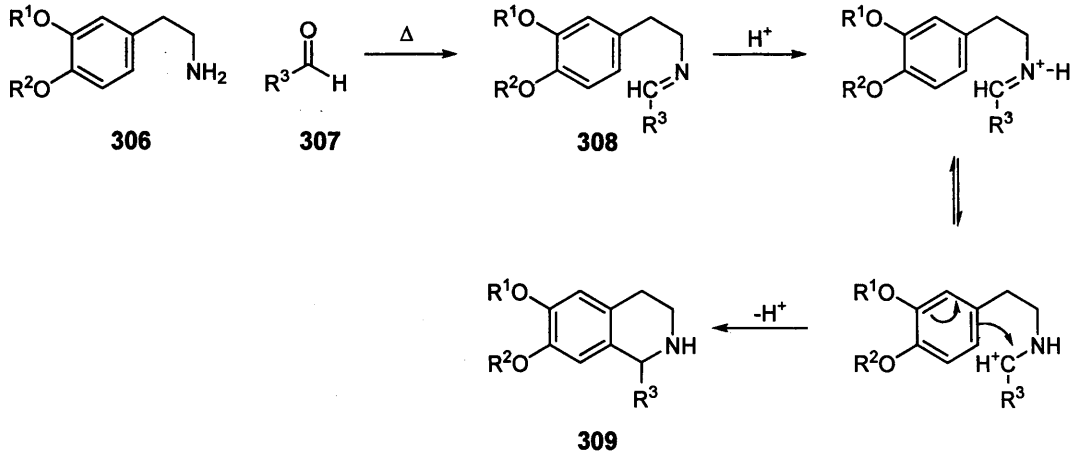


302 **303** **304** **305**

Scheme 3.2.

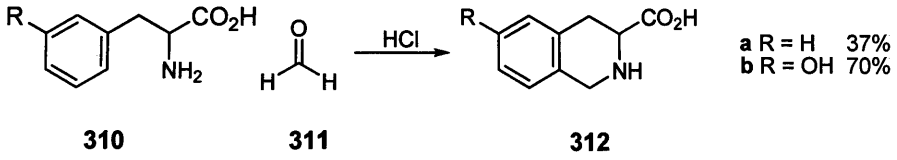
3.1.2. Tetrahydroisoquinolines

The Pictet-Spengler reaction has been used widely for the synthesis of a variety of 1,2,3,4-tetrahydroisoquinolines **309** because of the generally mild reaction conditions.[151,154,155] The proposed mechanism shown in Scheme 3.3, is believed to involve formation of a Schiff's base **308**. This intermediate Schiff's base **308** has in some cases been isolated and subsequently cyclised to the isoquinoline derivative **309** by exposure to acid.[155]



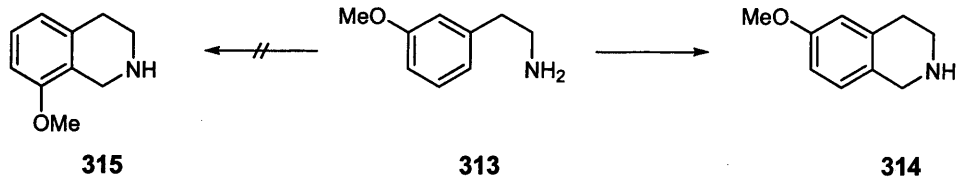
Scheme 3.3.

The electrophilic ring closure is induced by electron-donating substituents; this is illustrated by the cyclisation of phenylalanine **310a** and its *meta* hydroxyl derivative **310b** to the corresponding tetrahydroisoquinoline **312a** and **312b** by treatment with formaldehyde **311** and hydrochloric acid (Scheme 3.4). The fact that even unactivated phenethylamines can be cyclised under these conditions suggests that only a low activation energy is required for this cyclisation to occur.



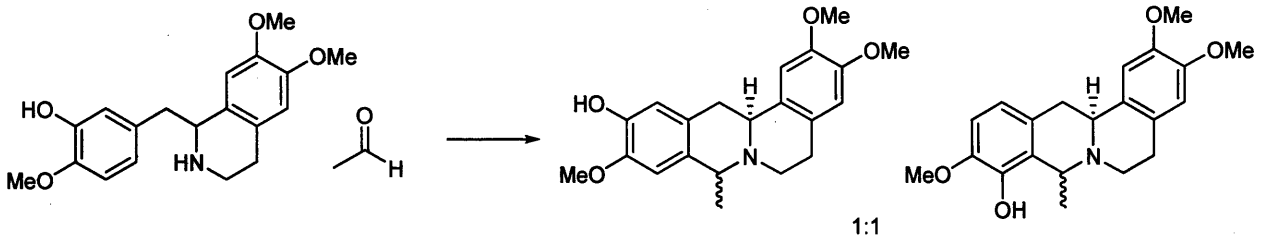
Scheme 3.4.

In general, alkoxyl groups direct the cyclisation to the *para* position. Thus the reaction of 3-methoxyphenethylamine **313** with formaldehyde yields only 1,2,3,4-tetrahydroisoquinoline **314** and none of the 8-methoxy compound **315**; the same observation is made in the related Bischler-Napieralski reaction.[152,156]



Scheme 3.5.

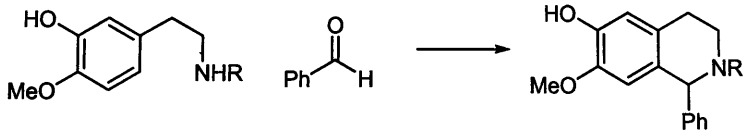
If the alkoxy groups are replaced by hydroxyl groups, the orientation rule becomes invalid and the ring closure proceeds to both *ortho* and *para* positions, such as for the treatment of phenolic compound **316** with acetaldehyde afforded a mixture of **317** and **318**, which are derivatives of xylopinine, in equal amounts (Scheme 3.6). [157,158]



316 317 318

Scheme 3.6.

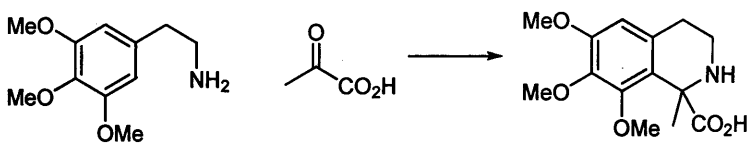
Hydrochloric acid has been the most commonly employed dehydrating agent, but sulfuric acid and acetic acid have found occasional use.[159] For preparation of isoquinolines sensitive to strong acid, a modification of the Pictet-Spengler reaction has been reported using formic acid and formaldehyde, conditions of the Eschweiler-Clarke reaction.[159,160] However, undesired *N*-methylisoquinolines are formed as minor products if primary amines are used. Preparation of acid-sensitive isoquinolines with a Pictet-Spengler reaction, employing a base (*e.g.* pyridine or triethylamine), have been reported. For example the condensation of *N*-methyl-3'-hydroxyphenethylamine **319** with benzaldehyde **320** in the presence of pyridine or triethylamine gives tetrahydroisoquinoline **321** (Scheme 3.7). [161,162]



319 320 321

Scheme 3.7.

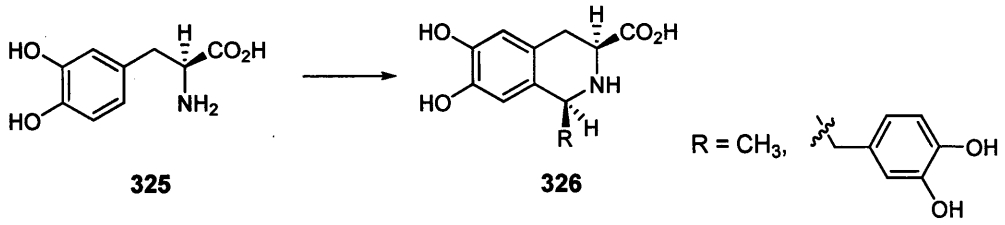
Formaldehyde, most frequently employed as the carbonyl compound in the Pictet-Spengler reaction,[155] generally gives the product in excellent yield and is used preferably to methylal or sodium hydroxymethanesulfonate.[163] However, pyruvic acid **323** reacts much more easily than aldehydes (Scheme 3.8).[164]



322 323 324

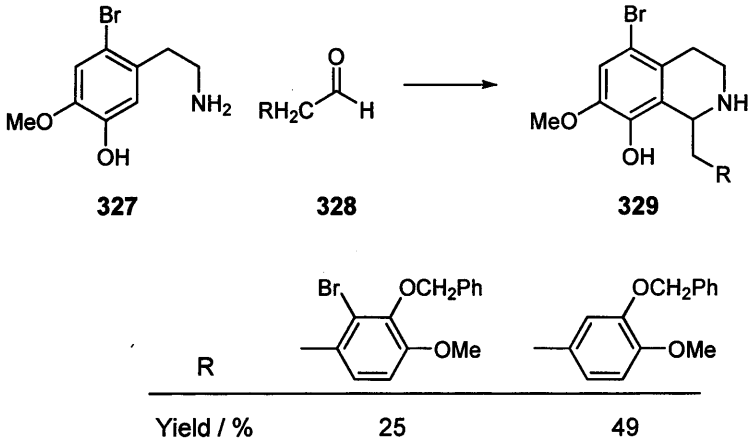
Scheme 3.8.

A biogenetically patterned asymmetric synthesis of (+)-laudanosine **326** from (-)-dopa **325** has been reported by Yamada.[165] Similar results were reported by Brossi,[166] and a stereospecific isoquinoline synthesis has also been achieved from amino acids.[167]



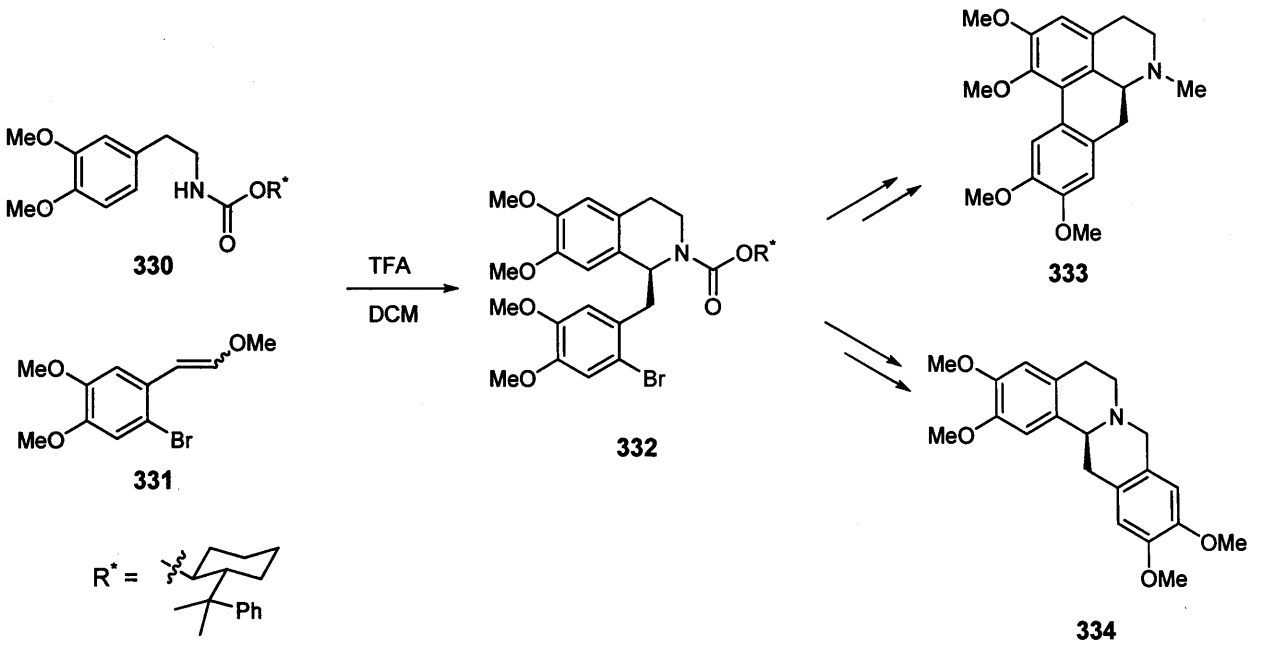
Scheme 3.9.

Stereopecificity in the Pictet-Spengler reaction was achieved for the synthesis of 7,8-dioxygenated isoquinoline; one of the cyclisation position was blocked with bromine (see Scheme 3.6), and the methoxy group replaced by a hydroxyl group to offset the inactivation of the nucleus caused by the *–I* effect of the bromine atom. These manipulations were anticipated to promote ring closure *ortho* to the hydroxyl group and the reaction of bromophenethylamine **327** with aldehyde **328** and hydrochloric acid gave the expected 1,2,3,4-tetrahydro-8-hydroxy-7-methoxyisoquinoline **329** (Scheme 3.10).[168] This tactic is now widely used for protoberberine alkaloid syntheses.[169]



Scheme 3.10.

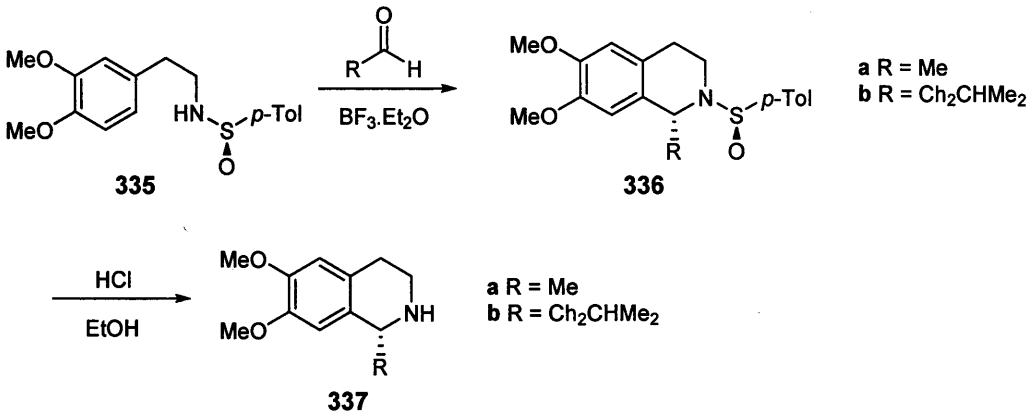
Asymmetric syntheses, where the chirality transfer occurs from a chiral auxiliary introduced to either the β-arylethylamine or the aldehyde component were continued from earlier studies on the Pictet-Spengler asymmetric synthesis of isoquinoline alkaloids.[170] Comins investigated the influence of a chiral auxiliary, *e.g.* (+)-*trans*-2-(α-cumyl)cyclohexyl, appended to the amine nitrogen in **330** as well as in the aldehyde equivalent **331**, which was substituted with a bromine at C-2, on the degree of stereoselectivity in the cyclisation step (Scheme 15). [171,172] The C-2 bromine not only caused an increase in stereoselectivity during the cyclisation step (tetrahydroisoquinoline **332** was formed as a mixture of diastereomers with 77% d.e.) but was helpful for separation of the diastereomeric products. The major (+)-**332** was converted into aporphine alkaloid (+)-glaucine **333**.



Scheme 3.11.

The diastereoselective Pictet-Spengler reaction has also been applied to the construction of various tetrahydroisoquinoline moieties of ecteinascidine and saframycine types of antitumor alkaloids. [173] ,174,175, 176,177,178,179,180

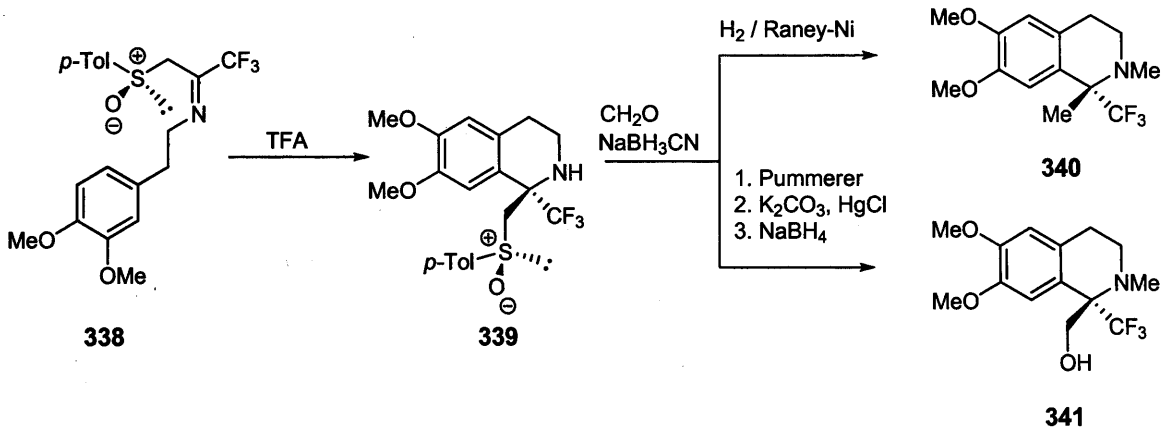
A number of asymmetric syntheses of isoquinoline alkaloids mediated by sulfur containing auxiliaries have been reported. The efficient synthesis of tetrahydroisoquinoline **337** carried out under very mild conditions has been developed from chiral *N*-*p*-tolylsulfinylphenylethylamine **335** and aliphatic aldehydes with excellent selectivity (e.e. = 93% and e.e. = 92% for **336a** and **336b**, respectively) (Scheme 3.12).[181]



Scheme 3.12.

The synthesis of 1-trifluoromethyl tetrahydroisoquinoline alkaloids **340** and **341**, based on the Pictet-Spengler cyclisation using a sulfinyl auxiliary to generate C-1 quaternary stereogenic centre, was reported by Bravo (Scheme 3.13).[182] The stereoselectivity achieved during the cyclisation of the sulfoxide **338** to give the tetrahydro derivative **339** was as a 6:1 mixture of (1*S*/*R*)/(1*R*/*R*)

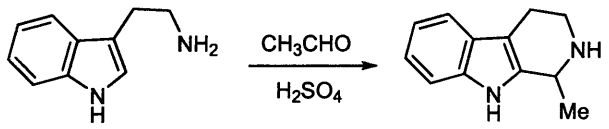
diastereomers which were postulated to result from a *cis* geometry of the C=N double bond in **338**, with the two aromatic rings on the same side of this bond, thus minimising the dipole-dipole interactions between the S=O and C=N bonds, and hindering the *si* face of the molecule.



Scheme 3.13.

3.1.3. Pictet-Spengler Reaction of Indoles

The reaction was originally utilised exclusively to prepare tetrahydroisoquinolines and became the standard method for their formation.[154] The use of an indole base was first shown by Tatsui in 1928 during the preparation of carboline **343** (Scheme 3.14). [183,184,185]



Scheme 3.14.

The development of the enantioselective Pictet-Spengler reaction in recent years has rendered this condensation an important synthetic method for formation of macroline/sarpagine/ajmaline indole alkaloids.[186,187] The interest in the total synthesis of indole alkaloid natural products stems from their complex structures and diverse medicinal properties. For example, vincristine and vinblastine from *Catharanthus roseus*[188] have long been established as antitumor alkaloids[189] of clinical significance, while reserpine[190] as well as ajmaline[191] exhibit very important cardiovascular effects (Figure 3.1).[192]

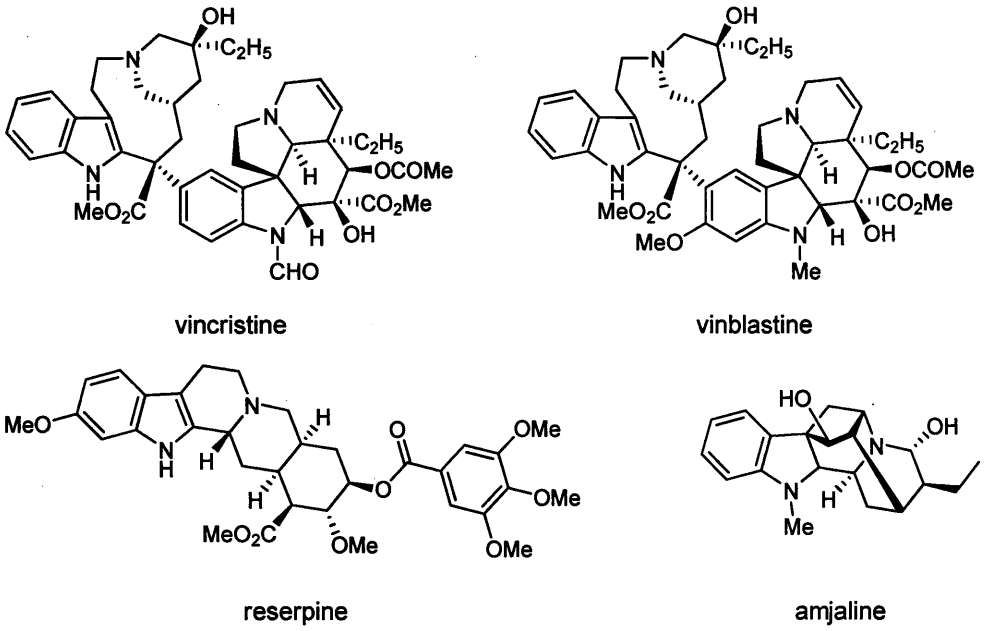
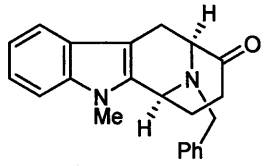


Figure 3.1.

Research on the stereospecific Pictet-Spengler condensation has lead to enantioselective intermediates, such as Cook's tetracyclic ketone **345** (Figure 3.2).[193]

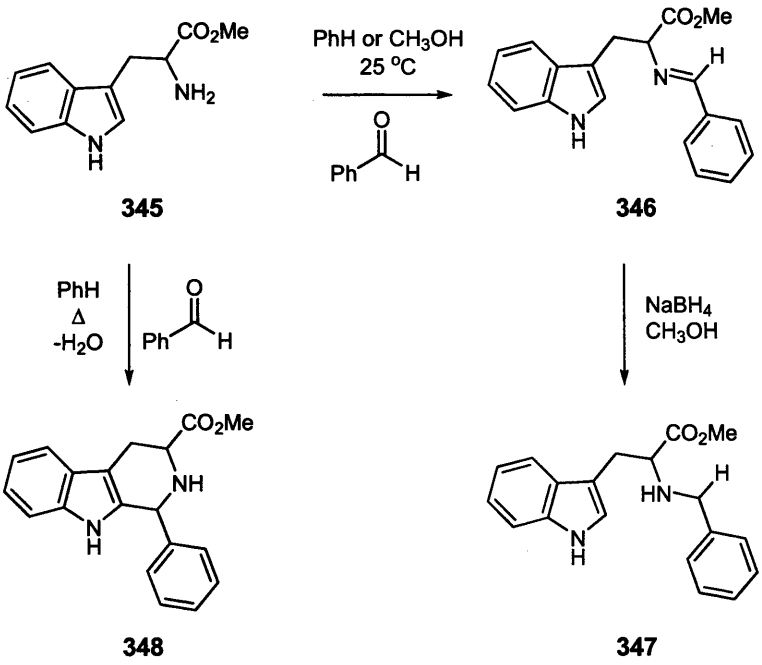


345

Figure 3.2. Cook's tetracyclic ketone intermediate

Work in this area was preceded by the discovery that the Pictet-Spengler reaction could be effected in non-acidic aprotic media as well as under the classical conditions of acid catalysis.

The synthesis of N_b-benzyltryptophan methyl ester **347** was achieved from tryptophan methyl ester **345** and benzaldehyde at room temperature, followed by reduction of the imine **346**.[194] To improve conversion of ester **345** into imine **346**, benzaldehyde and amine **345** were heated at reflux. Although the imine **346** was initially observed, after prolonged heating the products were the *cis* and *trans* diastereomers of 1-phenyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-β-carboline **348** in 95% yield (Scheme 3.15).

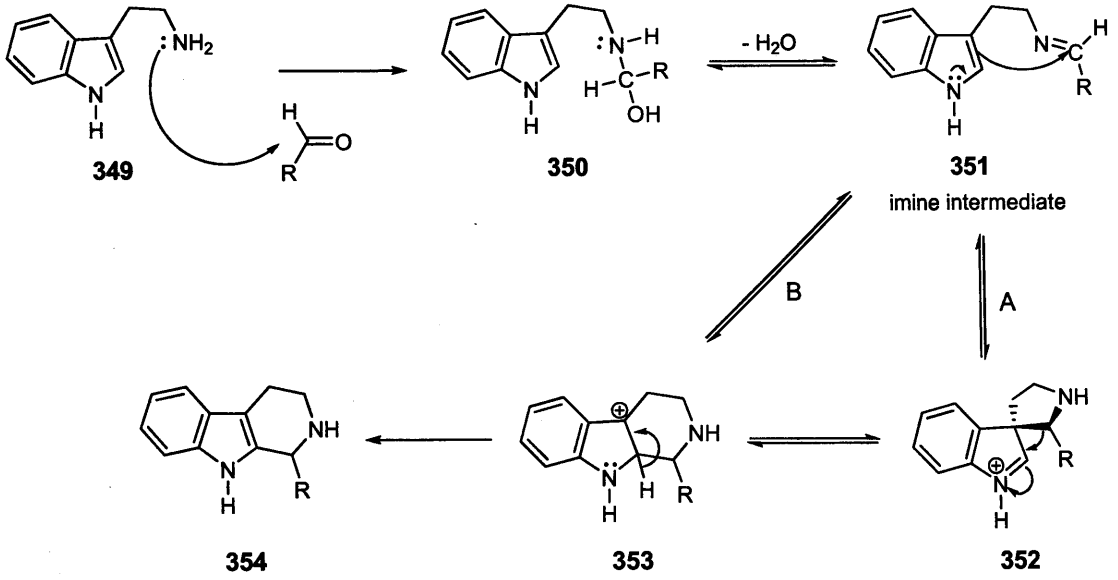


Scheme 3.15.

This result was surprising, for generally the Pictet-Spengler reaction had been carried out in a protic solvent with acid catalysts.[195] It was presumed that the Pictet-Spengler reaction with the tryptophan methyl ester **345** had occurred without the aid of acid catalysts, and detailed studies were carried out.

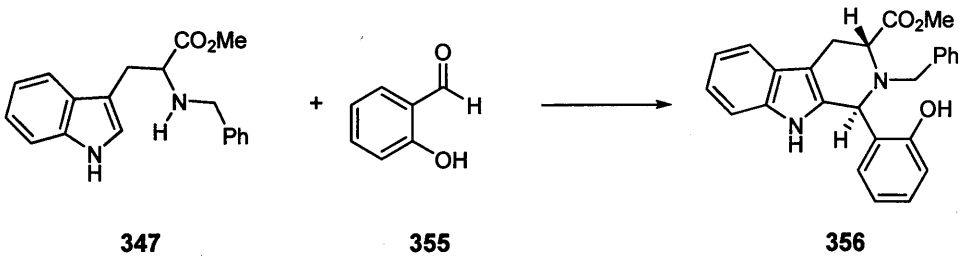
Excellent yields of tetrahydro-*β*-carbolines were obtained from tryptophan methyl ester **345** and a variety of aldehydes. It was apparent from examination of the data that yields of the Pictet-Spengler reaction could be improved in non-acidic aprotic media, which was even more apparent when acid-labile aldehydes were used as substrates, having substituents such as acetals, esters, amides and acetonides, heretofore too labile to be used in this condensation. [196,197] The yields for cyclisations carried out under non-acidic aprotic conditions were generally two or three times better than in aqueous acidic conditions.

There are two pathways for the Pictet-Spengler reaction between tryptamine derivatives **349** and carbonyl compounds (Scheme 3.16).[198] The Pictet-Spengler reaction (see **349** - **354)** has generally been thought to proceed *via* a spiroindolenine intermediate **352** as shown in Scheme 3.16 (path A), although Casnatiso has shown that cyclization can occur by direct attack at position 2 of the indole (path B) when very reactive electrophiles are employed.[199] No matter which path occurs, it is the electrophilic nature of the carbon double bond in **351** that is the driving force of the cyclisation.[200] Performing the reaction in non-acidic, aprotic media permitted the study of the correlation between the electron density on the aliphatic nitrogen atom with the ease of cyclisation, since protonation of the nitrogen atom by solvent was no longer a complicating factor.[201]



Scheme 3.16.

Several groups had investigated the *cis/trans* isomer ratios in the Pictet-Spengler reaction, all of which showed mixtures of *cis* and *trans*-isomers.[202] Ungemach discovered that the reaction of N_b-benzyltryptophan methyl ester **347** with salicylaldehyde **355** provided a single diastereomer **356** in 97% yield (Scheme 3.17). Steric interactions in this 1,2,3-trisubstituted β-carboline were too complex to permit an unequivocal assignment using ^{13}C NMR spectroscopy. [203] Removal of the N_b-benzyl function of this indole permitted comparison of the properties with authentic *cis*- and *trans*-1,3,-disubstituted β-carbolines prepared by an independent route.[200] In this case, the N_b-benzyl group clearly directed this condensation in a *trans* stereospecific manner. [204] This represented the first completely stereoselective result in the N_a-H tetrahydro- β-carboline methyl ester series.



Scheme 3.17.

The possibility that hydrogen bonding through the hydroxyl group of the salicylaldehyde **355** could have played a role in the stereoselectivity of this reaction led to the use of aldehydes devoid of the hydroxyl group. Examination of the ^{13}C NMR spectrum indicated the presence of only the *trans*-isomer in the reaction mixture, demonstrating that the hydroxyl group played no role in directing the stereochemical outcome of the condensation. In previous examples of this reaction

when performed in the absence of the N_b-benzyl function, formation of the *cis* and *trans*-isomer resulted.[200]

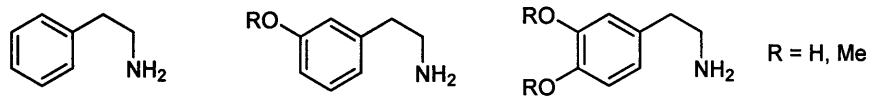
Previous studies have shown that strain between position 1 of the tetrahydro-β-carboline and the N_a-substituent could be the dominant factor in determining the *cis/trans* ratio in the Pictet-Spengler reaction in the N_b-series.[205] Smaller aldehydes were condensed with amine **347** and the *cis/trans* ratio examined, but no evidence of the *cis* isomer was seen.

3.1.4. Conclusion

Tetrahydroquinoline alkaloids, due to their widespread occurrence in nature, diverse biological activity (including the unnatural congeneres),[206] and useful chemical properties, have become attractive targets for organic synthesis. In the past decade, a wide range of synthetic methods have been reported for the synthesis of chiral non-racemic alkaloids.

Most of these methods have been based on diastereoselective syntheses using chiral auxiliaries, usually derived from natural products, appended either to or around the nitrogen of isoquinoline (or its precursor) or in the C-1 substituent (or its equivalent). In this context, the traditional Bischler-Napieralski cyclisation/reduction and Pictet-Spengler syntheses, as well as the addition of carbon nucleophiles to the C=N double bond have been the most explored strategies.[207]

The major limitation of the classic Pictet-Spengler reaction towards tetrahydroisoquinolines is that only a small number of phenylamines can successfully be used in the reaction (Figure 3.3).[151,208]



357 **358** **359**

Figure 3.3. Phenylamines used in the classic Pictet-Spengler reaction

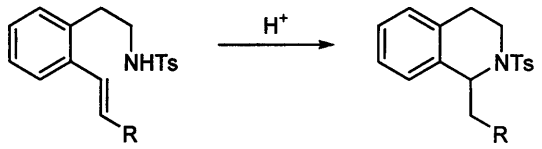
The detailed study of the Pictet-Spengler reaction has progressed from the discovery of improved non-acidic aprotic reaction conditions to probing the mechanistic phenomena involved. It is clear that enantiomerically pure N_b-benzyltryptophan alkyl esters can be condensed with aldehydes (acid labile or otherwise) to provide *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines in stereospecific fashion. Pictet-Spengler reaction of these same aldehydes and esters under acidic conditions should also provide the *trans* isomer with 100% diastereoselectivity, albeit with slightly lower yields.[154]

Although the 1-substituted tetrahydroisoquinoline alkaloids are readily synthesised in an asymmetric manner, there is no one general method that would secure preparation of all types of isoquinoline alkaloids with high optical purity employing simple procedures. Usually the applied

methodologies suffer from various limitations, such as, e.g. moderate to poor yields, unsatisfactory regio- and stereoselectivity, non-availability or cost of starting materials or reagents, multistep procedures, etc. Therefore, the question of finding a more efficient and/or simpler synthetic strategy that also has greater functional group compatibility is still open.[207]

3.2. Hypothesis

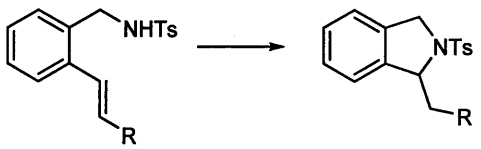
Due to the limitations seen with the Pictet-Spengler reaction for the production of tetrahydroisoquinolines **361**, a new synthetic approach was needed, preferably one that did not require the involvement of a directing group. It was hypothesised that if the appropriate precursors **360** could be synthesised, then a hydroamination variant of the Pictet-Spengler reaction should be possible (Scheme 3.18).[30]



360 **361**

Scheme 3.18.

This method could potentially also be used to form dihydroisoindoles **363**, through the same chemistry, with an appropriate precursor **362**. This is especially interesting, since formation of dihydroisoindoles **363** utilising a Pictet-Spengler reaction are not noted in the literature (Scheme 3.19).



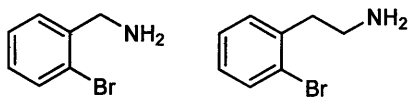
362 **363**

Scheme 3.19.

3.3. Results and Discussion

3.3.1. Proposed Synthetic Route

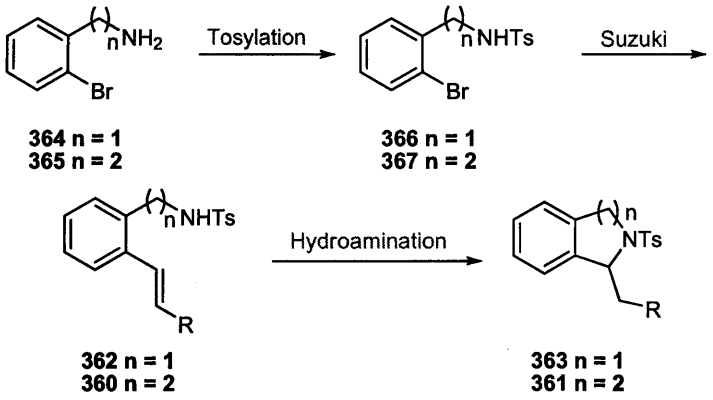
To arrive at the desired precursors needed for the cyclisation to give dihydroisoindoles and tetrahydroisoquinolines, a synthetic route was proposed that started from 2-bromobenzylamine **364** and 2-bromophenethylamine **365**, respectively (Figure 3.4).



364 **365**

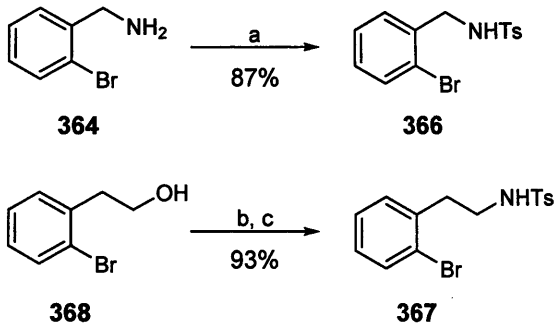
Figure 3.4.

These amines would be *N*-protected by tosyl groups to give sulfonamides **366** and **367**, which would then be treated with vinylboronic acids **369** to give the desired precursors. These were then hopefully to be cyclised using the hydroamination method developed by the Knight group to give either the dihydroisoindoles **363** or the tetrahydroisoquinolines **361** (Scheme 3.20).



Scheme 3.20.

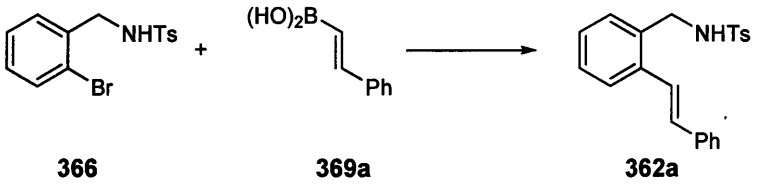
2-Bromobenzylamine **364** was readily available through commercial sources and converted into the corresponding sulfonamide **366** in excellent yield by reaction with *p*-toluenesulfonyl chloride. Commercial alcohol **368** was reacted under standard Mitsunobu conditions (see Chapter 1) to give the corresponding Boc-protected sulfonamide; the Boc group was removed to give sulfonamide **367** in excellent yield (Scheme 3.21)



Scheme 3.21. a) *p*-TsCl, DMAP, NEt_3, DCM, 0 °C b) PPh_3, DIAD, TsNHBoc, THF, –78 °C c) TFA, DCM

3.3.2. Suzuki Reaction

The sulfonamides were required to undergo Suzuki reactions with various vinylboronic acids to give the precursors needed for the cyclisations. The Suzuki reaction of sulfonamide **366** with *trans*-2-phenylvinylboronic acid **369a** was first tried with $[PPh_3]_4Pd$ and $NaHCO_3$ in DMF,[209] however, this reaction yielded none of the desired product **362a** even when heated at reflux for 72 hours or when the reaction was performed in a microwave oven (Scheme 3.22).



Scheme 3.22.

The failure of the Suzuki reaction may have been due to the electron rich nature of sulfonamide **366** and possibly also due to the steric hindrance that would be present at the reaction site as it is *ortho* to the sulfonamide.

The Eli Lilly Catalyst Laboratory provided a range of "pre-mixes" to trial for these Suzuki reactions. These pre-mixes consist of different combinations of catalyst, ligand and base and are designed to aid in the weighing of the small quantities of catalyst and ligand actually used in each reaction, especially when performed on a small scale. A selection of "pre-mixes" were screened on the reaction between sulfonamide **366** and *trans*-2-phenylboronic acid **369a** (Scheme 3.22) and the results are shown in Table 3.1. These reactions were all carried out in a microwave oven, as recent literature had showed this to be very successful for triggering Suzuki reactions.[246a,210]

Table 3.1. Results for a variety of catalyst, ligand and base mixtures for the Suzuki reaction

Catalyst / ligand / base mixture[a]	Solvent	Crude Yield of 362a / %
$Pd(PPh_3)_4$ / $NaHCO_3$[211]	DMF	0[b]
$Pd(OAc)_2$ / PCy_3 / K_3PO_4	DMF / H_2O[d]	61[c]
$Pd(OAc)_2$ / dtbpf[212] / K_3PO_4	DMF / H_2O[d]	63[c]
$Pd(dba)_2$ / dtbpf / K_3PO_4	DMF / H_2O[d]	43[a,b]
Pd(Quinoline-8-carboxylate)$_2$ / K_2CO_3[213]	DMF / H_2O[d]	58[b]
$Pd(PPh_3)_4$ / NaOH	DMF / H_2O[d]	47[b]
$Pd(OAc)_2$ / K_2CO_3	H_2O	37[b]

[a] 100 °C, 100W, 30 min; [b] starting material visible; [c] clean product isolated, no purification required, [d] 1 : 1 mixture

Though all reactions apart from the one involving $Pd(PPh_3)_4$ gave some moderate yields of the desired product, the best conditions for this transformation was the reaction using a combination of $Pd(OAc)_2$, 1,1'-bis(di-*tert*-butylphosphine)-ferrocene (dtbpf) and K_3PO_4, though the yield was far from ideal. It was reasoned that a change of solvent system could possibly improve this;[214] the results of this investigation are shown in Table 3.2.

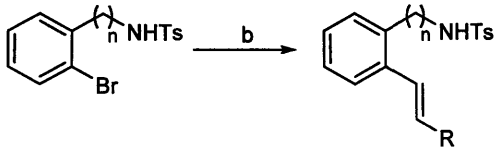
Table 3.2. Effect of Solvent upon the Suzuki reaction

Catalyst / ligand / base mixture[a]	Solvent	Crude Yield / %
$Pd(OAc)_2$ / dtbpf / K_3PO_4	Dioxane / H_2O	92[b]
$Pd(OAc)_2$ / dtbpf / K_3PO_4	Toluene / H_2O	89[b]
$Pd(OAc)_2$ / dtbpf / K_3PO_4	Ethanol / H_2O	90[c]
$Pd(OAc)_2$ / dtbpf / K_3PO_4	H_2O	72[b]

[a] 100 °C, 100W, 30 min; [b] starting material visible, [c] clean product isolated, no purification required

All of the new solvent combinations resulted in improved yields; however, all but one of these contained starting material. The reaction performed in ethanol and water gave an excellent yield, and most importantly none of the starting materials were visible by NMR.

This optimised Suzuki reaction was then applied to the synthesis of more dihydroisoindole and tetrahydroisoquinoline precursors **362** and **360** respectively (Scheme 3.23).

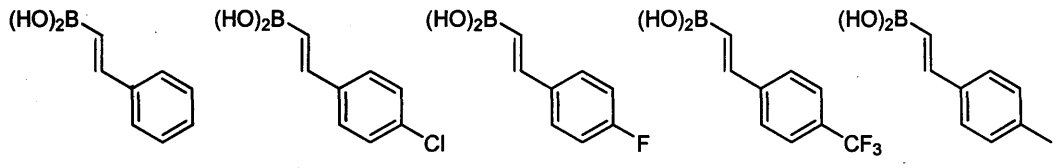


366 n = 1
367 n = 2

362 n = 1
360 n = 2

Scheme 3.23. b) $Pd(OAc)_2$, dtbpf, K_3PO_4, EtOH/Water, 100 W, 100 °C, 30 min

The boronic acids chosen for these reactions were a selection of styrylboronic acids with electron withdrawing and electron donating groups **369a - e** (Figure 3.5).

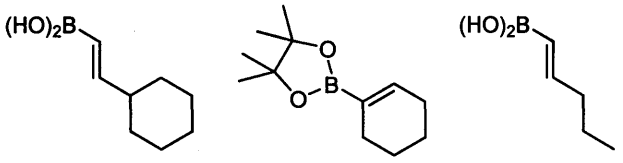


369a **369b** **369c** **369d** **369e**

Figure 3.5. Styrylboronic acids for the Suzuki reaction

This allowed the assessment as to whether the electron withdrawing or donating nature of the substituents would have an effect upon the rate of cyclisation.

Another set of boronic acids to be used in the Suzuki reaction were the alkylboronic acids **369f - h**, including a cyclohexenyl boronic acid **369g**, which upon cyclisation, if successful, would result in formation of a *spiro*-compound (Figure 3.6).



369f **369g** **369h**

Figure 3.6. Alkyboronic acids for the Suzuki reaction

The difference in the rates of cyclisation of the aryl and alkyl derivatives, if any, can be determined by comparing these two sets of compounds.

The boronic acids **369a - h** were reacted with sulfonamides **366** and **367**, to give the precursors **362** and **360** for the cyclisation hopefully to give the various dihydroisoindoles **363** and tetrahydroisoquinolines **361**. The yields for the Suzuki reactions are shown in Table 3.3.

Table 3.3. Yields of the Suzuki reaction for dihydroisoindol and tetrahydroisoquinoline precursors

Boronic Acid[a]	Yield / % (n = 1) 362	Yield / % (n = 2) 360
369a	90	99
369b	81	85
369c	91	60
369d	99	99
369e	95	96
369f	83	69
369g	97	94
369h	95	86

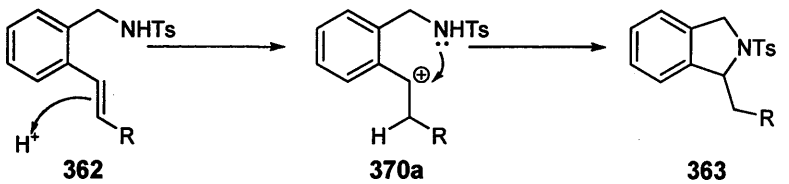
[a] $Pd(OAc)_2$, dtbpf, K_3PO_4, $EtOH/H_2O$, 100 °C, 100W, 30 min

The Suzuki couplings for both the dihydroisoindole **362** and tetrahydroisoquinoline **360** precursors were all achieved in excellent yield. No purification was required and they were able to be taken directly onto the new cyclisation step. Not much difference was observed in the yields between the dihydroisoindole precursors **362** and the tetrahydroisoquinoline precursors **360**; indeed, any difference observed may simply be due to experimental error.

3.3.3. Cyclisations

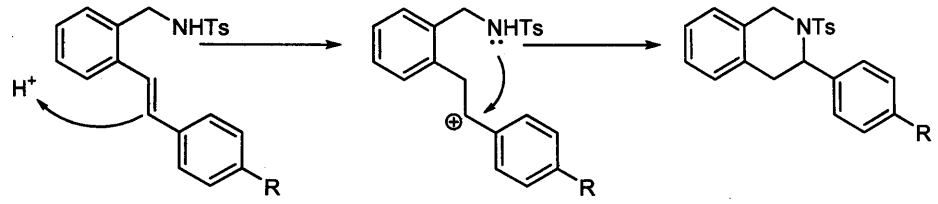
3.3.3.1. Dihydroisoindols

The successful synthesis of precursor **362a - h** meant that cyclisation to the dihydroisoindols **363** could be tested. This was expected to proceed through benzylic carbenium ions **370a**, which are then attacked by the lone pair of the sulfonamide nitrogen to give the desired product **363** *via* an overall 5-*exo*-trig process (Scheme 3.24).



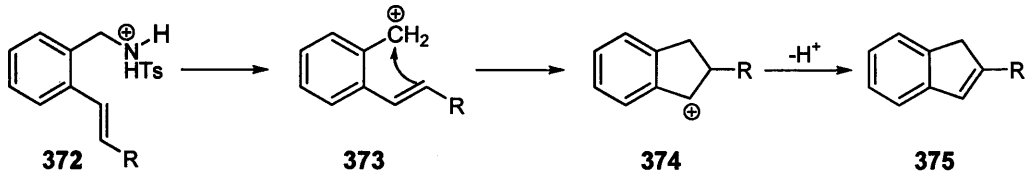
Scheme 3.24.

Of course, there is no guarantee that the carbenium ion formed is that depicted in Scheme 3.24: the protonation could occur at the other end of the double bond. In precursors **362a – e** this would also form a benzylic carbenium ion, **370b**, which would result in the formation of a tetrahydroisoquinoline **371**, through an overall 6-*endo*-trig process (Scheme 3.25).



Scheme 3.25.

There was also the distinct possibility that this cyclisation would not occur, due to *N*-protonation to **372**, followed by loss of tosylamine and cyclisation to indene **375** (Scheme 3.26).



Scheme 3.26.

Compounds **362f - h** (Scheme 3.23) would most likely form carbenium ion **370a** as this would be the more stable carbenium ion, as they do not include the benzyl functionality that **362a – e** possess. It was believed that the overall 5-*exo*-trig cyclisation would be the favoured process, resulting in formation of the dihydroisoindols shown in Figure 3.7.

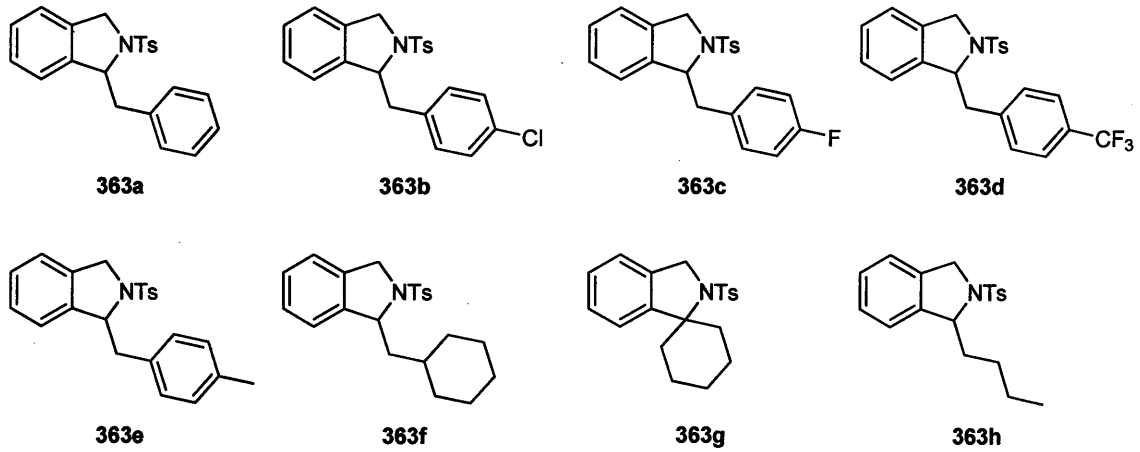


Figure 3.7.

Compounds **363a - h** were cyclised with triflic acid, the standard method for cyclisations performed by the Knight group[30] and the results are shown in Table 3.4.

Table 3.4. Yields and conditions for cyclisation to afford dihydroisoindols with TfOH

Starting Material	Product	Acid[a]	Temperature / °C	Time / hrs	Yield / %
362a	**363a**	TfOH	0	24	98
362b	**363b**	TfOH	40	24	81
362c	**363c**	TfOH	40	24	84
362d	**363d**	TfOH	40	24	71
362e	**363e**	TfOH	40	24	86
362f	**363f**	TfOH	40	2	93
362g	**363g**	TfOH	0	6	70
362h	**363h**	TfOH	40	3	100

[a] 0.5 eq. TfOH, DCM

In general, the cyclisations occurred in excellent yields and no starting material was visible. Some of the lower yields may be due to loss in the work up of the reaction, a relatively standard hazard when working on a small scale. All but two of the reactions needed heating to reflux; these were the phenyl and pentenyl derivatives **363a** and **363h**. All of the aryl derivatives **363a – e** required reaction times of 24 hours, whereas the alkyl substituted precursors all required less time to react. From the reaction of aryl derivatives, it can be deduced that the electron donating and withdrawing nature of the substituents have little overall effect equally, as these all required heating in comparison to the "neutral" phenyl derivative **363a**.

Some difficulties were encountered with the use of triflic acid as the catalyst for the hydroamination in these reactions. Triflic acid is very water sensitive, so the stock solution used would become less efficient over time as water contamination occurred. This was frustrating as it removed the certainty that what was being added to all the reactions over time was of the same concentration. It was observed in cyclisations in Chapter 1, in reactions that involved Boc removal as well as cyclisation in the same step, that "old" stock solutions would achieve the Boc removal but then stall at the cyclisation stage. The cyclisation could be achieved if more acid was added. If the reaction of the Boc compound was then carried out with a freshly made up stock solution of triflic acid, then the Boc deprotection and cyclisation would occur in one pot. One approach to solving this problem was to replace triflic acid with an acid that was not so water sensitive, such as sulfuric acid. Sulfuric acid is cheap and readily available in any organic laboratory, it is easier to handle that triflic acid and the reactions seemed less sensitive to the presence of water. To determine the effectiveness of sulfuric acid in comparison to triflic acid, the cyclisations were

repeated using concentrated sulfuric acid as the catalyst for the hydroaminations to give the desired dihydroisoindols (Table 3.5).

Table 3.5. Yields and conditions for cyclisation to afford dihydroisoindols with concentrated H_2SO_4

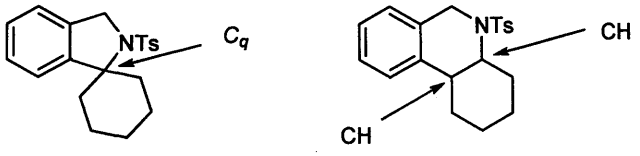
Starting Material	Product	Acid[a]	Temperature / °C	Time / hrs	Yield / %
362a	**363a**	H_2SO_4	20	48	92
362b	**363b**	H_2SO_4	40	48	70
362c	**363c**	H_2SO_4	40	24	73
362d	**363d**	H_2SO_4	40	24	67
362e	**363e**	H_2SO_4	40	24	67
362f	**363f**	H_2SO_4	40	4	100
362g	**363g**	H_2SO_4	0	24	78
362h	**363h**	H_2SO_4	40	3	98

[a] 2 drops of sulfuric acid, DCM

When comparing the cyclisations using triflic acid and sulfuric acid, not much difference in the reaction conditions can be seen. Some of the reaction times have increased but the reactions still proceeded cleanly, without any by-product formation. This was very encouraging as this showed that sulfuric acid was just as potent for these cyclisations as triflic acid, despite its insolubility in dichloromethane.

Showing that the products isolated are in fact the dihydroisoindoles **363** as expected and not the tetrahydroisoquinolines **371** is difficult to do. The indene **375** alternatives (Scheme 3.26) were quick to eliminate as the spectra would lack the tosyl group attached to the nitrogen; these were clearly present in all of the isolated compounds. But how can the dihydroisoindoles **363** and their isomers tetrahydroisoquinoline **371** be distinguished? As they are isomers, they have the same mass, though there is the possibility of a difference in fragmentation between the two isomers, it could be difficult to empirically assign the two. Unfortunately, none of the compounds are solids so X-ray crystallography was ruled out. One crude method involves analysis of the NMR spectra, looking at the likely resonances and coupling patterns for the isomers.

The simplest isomers to distinguish are those of *spiro*-dihydroisoindole **363g** and fused bicyclic tetrahydroisoquinoline **371g** (Figure 3.8). The most obvious distinction would be visible in the ^{13}C spectrum; the dihydroisoindole **363g** would have a quaternary for the *spiro*-center that would not be present in the fused compound **371g**. This quaternary is very clearly present in the ^{13}C spectrum at 74 ppm.

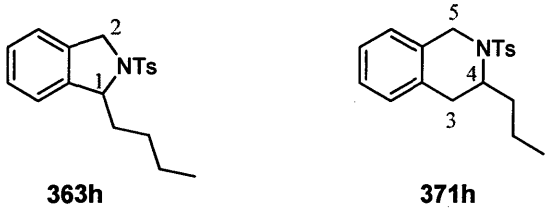


363g **371g**

Figure 3.8. Relevant resonances for *spiro*-dihydroisoindole **363g** and bicyclic tetrahydroisoquinoline **371g**

From this structure we can also extrapolate the possible resonances for the CH_2 adjacent to the nitrogen and benzene ring; which resonated as a singlet at 4.53 ppm for **363g**.

The next compound that was examined was **363h**. If the tetrahydroisoquinoline **371h** had been isolated instead of the desired isoindole derivative **363h**, then four benzylic protons would be visible, the four proton at positions 3 and 5 (Figure 3.9), rather than the three expected for **363h**, potions at positions 1 and 2 (Figure 3.9). This is true for all the of the dihydroisoindole derivatives **363**, apart from *spiro*-dihydroisoindole **363g**. The proton spectrum showed that only three benzylic protons were present; the two protons at position 2 were observed at 4.58 and 4.51 ppm as doublets with a spliting of 14.8 Hz. The proton adjacent to the nitrogen resonated at 4.92 as an apparent singlet. The resonance for the CH alpha to the nitrogen would also shift significantly upfield to around 3 ppm, if it were the tetrahydroisoquinoline **371**.



363h **371h**

Figure 3.9. Relevant ^1H resonance for dihydroisoindole **363h** and tetrahydroisoquinoline **371h**

A more challenging structure to assign was that of phenyl derivative **363a** (Figure 3.10). No significant difference in the resonances would be apparent between the two isomers. The assignment as to which isomer had been isolated was based purely on comparison to the resonances and splitting patterns observed for compounds that have been positively identified as dihydroisoindoles. The two protons at position 2, alpha to the nitrogen, resonated at 4.53 and 4.12 ppm as doublets with a coupling constant of 15.9 Hz, which is consistent with the coupling constant measured for dihydroisoindole **363h** and others.

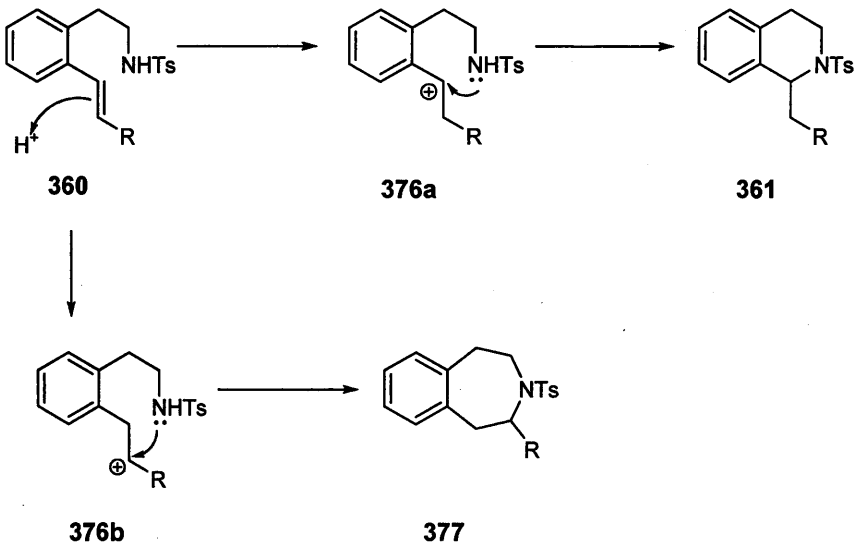
x61a **x71a**

Figure 3.10. Relevant resonaces for dihydroisoindole **363a** and tetrahydroisoquinoline **371a**

3.3.3.2. Tetrahydroisoquinolines

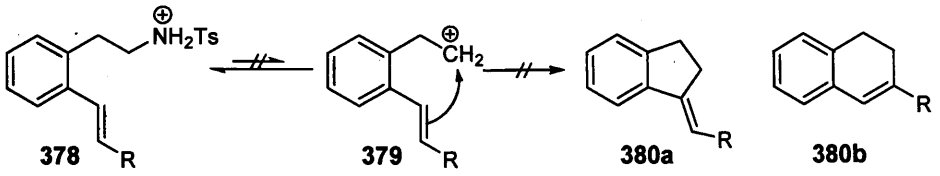
The success of the cyclisations towards the dihydroisoindole derivatives **363** gave hope that these cyclisations would also be successful for the tetrahydroisoquinoline derivatives **361** (Scheme 3.18).

As for the dihydroisoindole precursors **362**, two carbenium ions could be formed, after protonation of the double bond of **360** (Scheme 3.27). Carbenium ion **376a** would give the desired tetrahydroisoquinoline product **361** through an overall 6-*exo*-trig process, which is favoured according to Baldwin's rules; whereas carbenium ion **376b** would give the 7-membered ring **377**, which would occur through an overall 7-*endo*-trig process, which is also favoured by Baldwin's rules (Scheme 3.27).



Scheme 3.27.

For precursors **360** there was little concern that *N*-protonation could lead to the loss of tosylamine and thus give rise to alternative cyclisation products **380a** and/or **380b**. The carbenium ion **379** generated (Scheme 3.28) would not be stabilised as would have been the case for the dihydroisoindole precursors **362** as shown in Scheme 3.25.



Scheme 3.28.

Due to 6-membered rings generally being formed preferentially over 7-membered rings, the synthesis of the tetrahydroisoquinolines **361** (Figure 3.11) was believed to possible.

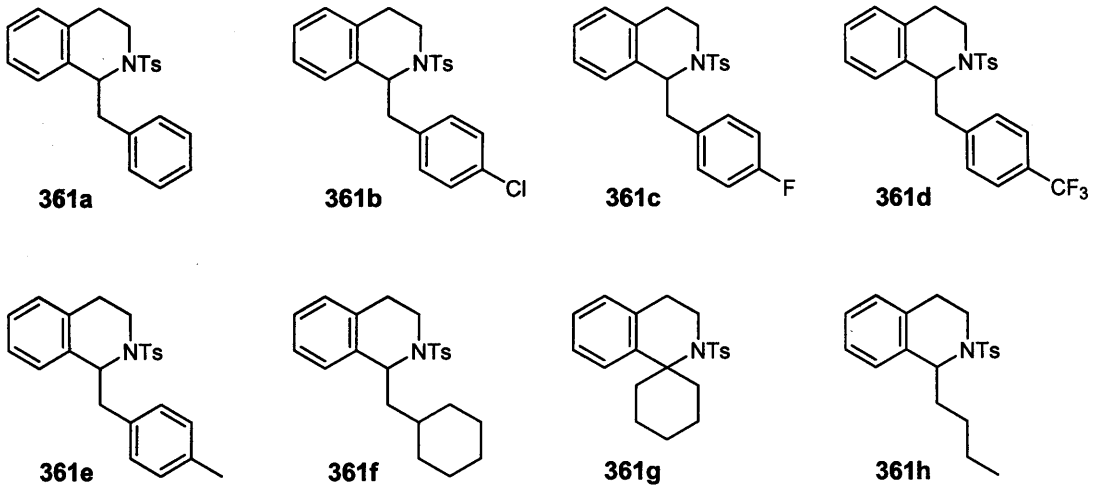


Figure 3.11.

The results for the cyclisation of **360** with triflic acid to give tetrahydroisoquinolines **361** are shown in Table 3.6.

Table 3.6. Yields and conditions for cyclisation to afford tetrahydroisoquinolines with TfOH

Starting Material	Product	Acid[a]	Temperature / °C	Time / hrs	Yield / %
360a	**361a**	TfOH	0	24	100
360b	**361b**	TfOH	40	24	87
360c	**361c**	TfOH	40	24	72
360d	**361d**	TfOH	40	24	75
360e	**361e**	TfOH	40	24	54
360f	**361f**	TfOH	40	24	90
360g	**361g**	TfOH	0	24	83
360h	**361h**	TfOH	0	24	92

[a] 0.5 eq. TfOH, DCM

As with the dihydroisoindoles **363**, the cyclisations were successful, high yielding and produced no discernable by-products. The reaction conditions, in terms of temperatures for the cyclisations to give both **363** and **361** were, overall, much the same, although the alkyl derivatives of the dihydroisoindoles **363f - g** were formed considerably faster than those of the tetrahydroisoquinolines **361f - g**. Again the aryl compounds showed no difference in reaction conditions when comparing the electron withdrawing and donating nature of the substituents. The alkyl derivatives **361f – h** reacted under milder conditions that the aryl derivatives **361a – e**, with the notable exception of **361f**, which requires heating, unlike the equivalent dihydroisoindole **363f**.

Some of the cyclisations were repeated with concentrated sulfuric acid, as with the dihydroisoindole **363**; the results are shown in Table 3.7.

Table 3.7. Yields and conditions for cyclisation to afford tetrahydroisoquinolines with concentrated H_2SO_4

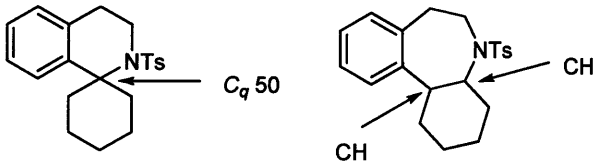
Starting Material	Product	Acid[a]	Temperature / °C	Time / hrs	Yield / %
360a	**361a**	H_2SO_4	20	48	99
360b	**361b**	H_2SO_4	-	-	-
360c	**361c**	H_2SO_4	-	-	-
360d	**361d**	H_2SO_4	40	48	56
360e	**361e**	H_2SO_4	40	48	80
360f	**361f**	H_2SO_4	-	-	-
360g	**361g**	H_2SO_4	20	24	81
360h	**361h**	H_2SO_4	40	4	89

[a] 2 drops of sulfuric acid, DCM

Again, when comparing the cyclisations with TfOH to those using concentrated sulfuric acid, the reactions are comparable except that the reaction times have again doubled in length, as was observed with the dihydroisoindols **363**.

Evidence for the formation of the desired tetrahydroisoquinolines **361** over the 7-membered system **377** and the carbocycles **380**, relied solely upon NMR data, as for the dihydroisoindoles **363** (Scheme 3.7). The carbocycles **380** could be eliminated quickly as the tosyl groups were clearly visible in the spectra. This was not unsurprising as the formation of carbocycles **380** would be mechanistically unreasonable. Formation of the 7-membered systems **377** also seems unfeasible, as generally six-membered ring formation is favoured over 7-membered rings.

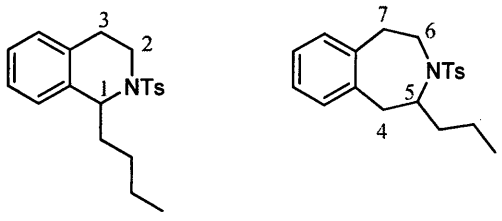
For *spiro*-cyclic compound **361g**, the obvious difference to that of the fused 7-ring system **377g** would be the absence of the quaternary in the carbon spectra (Figure 3.12). The quaternary carbon is quite clearly present in the spectrum (50.0 ppm) and thus confirming the successful synthesis of **361g**. The splitting pattern for the two protons adjacent to the nitrogen was expected to show a double double doublet for each proton in this type of system. The protons would have excibited large axial-axial couplings (*ca.* 14 Hz), two axial-equatorial interactions (*ca.* 4 - 10 Hz) and two equatorial-equatorial interactions (1 - 4 Hz). However, the two protons resonated at similar chemical shift to give the appearance of an apparent double double with $J = 13.6$ and 7.0 Hz.



361g **377g**

Figure 3.12 Relevant resonance for tetrahydroisoquinoline **361g** and the 7-membered derivative **377g**

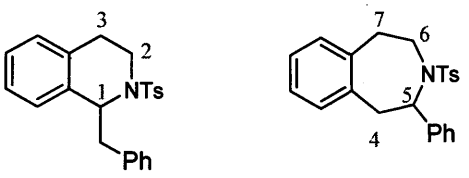
Analysis of the NMR data of the reaction to give tetrahydroisoquinoline **361h** showed that there were only three benzylic protons present, positions 1 and 3, rather than the four that would have been expected if the 7-membered ring **377h** had been isolated, position 4 and 7. Another important piece of evidence is the splitting for the CH adjacent to the nitrogen; a triplet was observed at 4.88 ppm with coupling constants of 6.5 Hz, which fits with the data that was expected for tetrahydroisoquinoline **361h**. A more complicated splitting pattern would have been present if **377h** had been isolated for this proton, position 4, as it is adjacent to two CH_2 groups. The two protons adjacent to the nitrogen, position 2, showed resonances between 3.81 and 3.35 ppm as multiplets.



361h **377h**

Figure 3.13. Relevant resonance for tetrahydroisoquinoline **361h** and the 7-membered derivative **377h**

As for dihydroisoindoles **363**, the phenyl derivative of the tetrahydroisoquinolines was the most challenging to assign, due to the similarity in shifts between the two isomers **361a** and **377a** (Figure 3.14). The triplet at 5.12 ppm with a coupling constant of 6.6 Hz, was attributed to the proton adjacent to the nitrogen of tetrahydroisoquinoline, position 1 as a more complicated splitting pattern would have been observed if **377a** had been isolated.

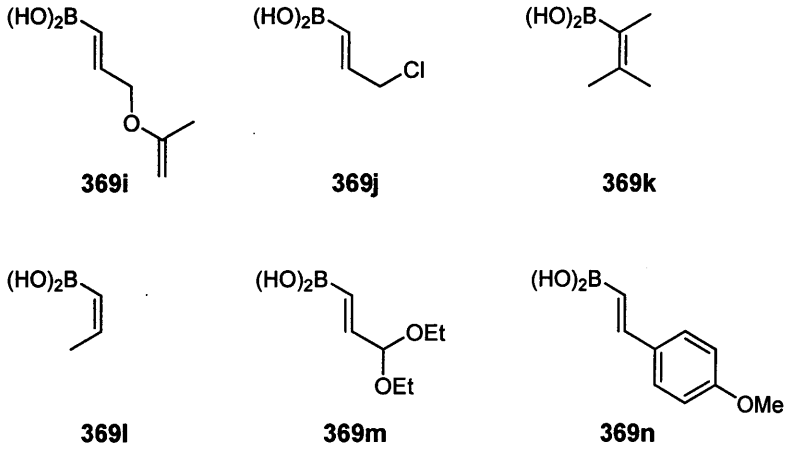


361a **377a**

Figure 3.14. Relevant resonance for tetrahydroisoquinoline **361a** and the 7-membered derivative **377a**

3.4. Remote Functional Groups

Though the derivatives of the dihydroisoindols **363** and tetrahydroisoquinolines **361** demonstrated the successful application of the acid-catalysed cyclisation from vinyl-precursors **362** and **360**, the functional groups were not overly inspiring and the scope of the reaction needed to be investigated further. This was to be done by determining if remote functional groups would successfully survive the acidic reaction conditions and not interfere where possible. Commercially available boronic acids **369i** - **n** (Figure 3.15) were reacted under the conditions used for the Suzuki reactions with boronic acids **369a** - **h** with sulfonamides **366** and **367**. Unfortunately the reactions were unsuccessful for boronic acids **369i** – **m**.



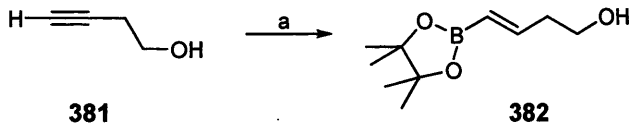
369i **369j** **369k**

369l **369m** **369n**

Figure 3.15. Boronic acids containg usefull remote functional groups

Some interest was seen in having a remote alcohol group present during the cyclisation to give the dihydroisoindols **363** and tetrahydroisoquinolines **361**. The Knight group has not performed any model cyclisations with an alcohol group present in the molecule. The Pictet-Spengler reaction seemed an ideal candidate to test this out. First of all, a method for the introduction of this remote alcohol group had to be devised. Recent literature discussed the conversion of alkynes **381** into allylboronates **382** using either a rhodium catalysed hydroboration[215] or a zirconium- mediated

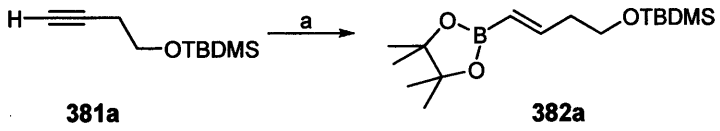
hydroboration; [216] both were tried and the rhodium-catalysed reaction was successful (Scheme 3.29).



381 382

Scheme 3.29. a) $RhHCl(CO)(PPh_3)_3$, pinacol borane, toluene, 20 °C, 4 hrs

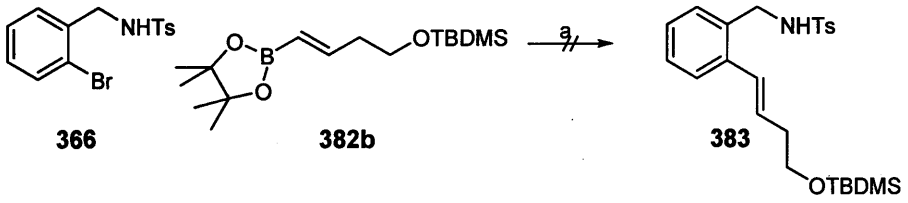
Unfortunately, the reaction of boronic acid pinacol ester **382** with sulfonamide **366** was unsuccessful. This could possibly have been due to the alcohol group interfering with the reaction. To avoid this, the alcohol was protected with a silyl group and then transformed into the corresponding pinacol ester **382a** (Scheme 3.30).[216]



381a 382a

Scheme 3.30. a) carbonchlorohydridotris(triphenylphospahen)Rh, pinacol borane

Unfortunately, the Suzuki reaction with the TBDMS protected alcohol **382a** was again unsuccessful (Scheme 3.31).



366 382b 383

Scheme 3.31. $Pd(OAc)_2$, dtbpf, K_3PO_4, EtOH/Water, 100 W, 100 °C, 30 min

An alternative method for the synthesis of **383** is through the utilisation of a Wittig reaction and will be discussed later.

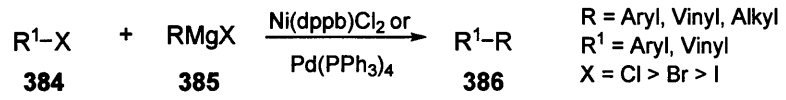
3.4.1. Alternatives to Suzuki

The difficulties encountered with the Suzuki reaction and its subsequent optimisation highlights the need to look at alternate methods for the formation of these vinyl precursors. The most obvious alternatives are other palladium-catalysed cross-coupling reactions, such as the Hiyama, Kumada, Negishi, Sonogashira, Stille and Heck reactions, which all belong to the same category of Pd-catalysed cross-coupling reactions of organic halides, triflates or other electrophiles with organometallic reagents and follow a general mechanistic cycle. There are slight variations for the Hiyama and Suzuki reactions, for which an additional activation step is required for the transmetallation to occur.[217] The Kumada and Negishi reaction have shown some incompatibility

with amines, therefore these reactions would require further protection of the amines **364** and **365**. Another viable reaction is the Wittig reaction

Kumada

The Kumada coupling was developed in 1972 and was the first Pd or Ni-catalyzed cross coupling reaction. It involves the coupling of Grignard reagents **385** with alkyl, vinyl or aryl halides (or triflates) **384** under Ni-catalysis provides an economic transformation, but the reaction was limited to halide partners that do not react with organomagnesium compounds. The advantage of this reaction is the direct coupling of Grignard reagents, which avoids additional reaction steps such as the conversion of Grignard reagents into zinc compounds, as for the starting materials in the Negishi coupling. [218,219]



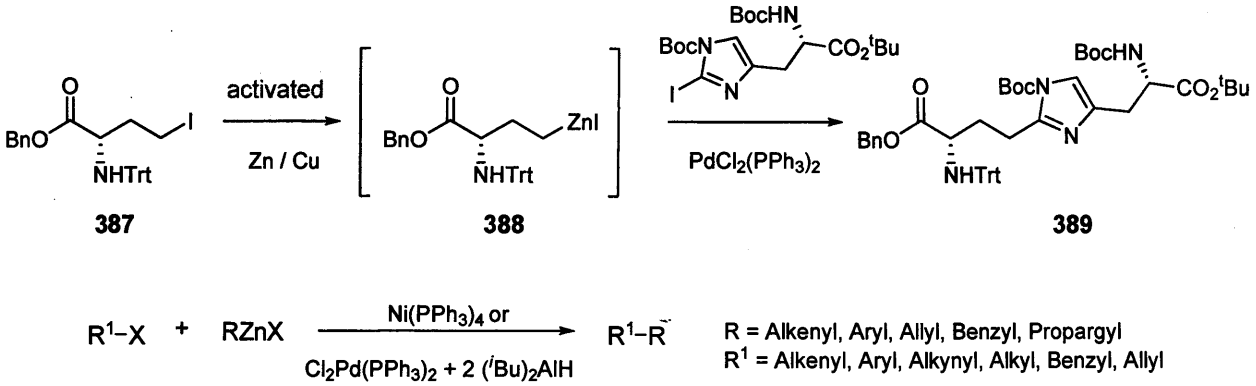
Scheme 3.33.

The ready availability and low cost of Grignard reagents make the Kumada coupling a valuable reaction for the formation of carbon-carbon bonds. Iron-catalysed Kumada coupling reactions of secondary alkyl halides encompass nearly entire reaction spectrum through bond formation with aryl, alkenyl, and alkyl Grignard reagents. The successful coupling of secondary alkyl halides with aryl Grignard reagents under iron catalysis were demonstrated by Nakamura, to produce excellent yields.[220] The iron-catalysed activation of the alkyl bromide out competes the nucleophilic attack of the Grignard reagent on functional groups such as keto, ester, chloride, and nitrile groups, which makes this method extremely powerful.[221]

Cobalt-catalysis has a great deal of potential with regard to the cross-coupling of alkyl halides. The coupling of primary, secondary and even tertiary alkyl electrophiles with Grignard reagents was developed,[222] though functional groups, such as amides, esters, and carbamates did not survive the reaction conditions. The scope of the cobalt-catalysed coupling of secondary alkyl halides and aryl Grignard reagents is limited when a phosphine ligand is used,[223] but with a diamine ligand[224] the reaction is quite efficient.[221]

Negishi

The Negishi coupling, published in 1977, was the first reaction that allowed the preparation of unsymmetrical biaryls in good yields. The versatile nickel- or palladium-catalyzed coupling of organozinc compounds with various halides (aryl, vinyl, benzyl, or allyl) has broad scope.[218,225] It is compatible with many functional groups including ketones, ester, amides, and nitriles.[226]

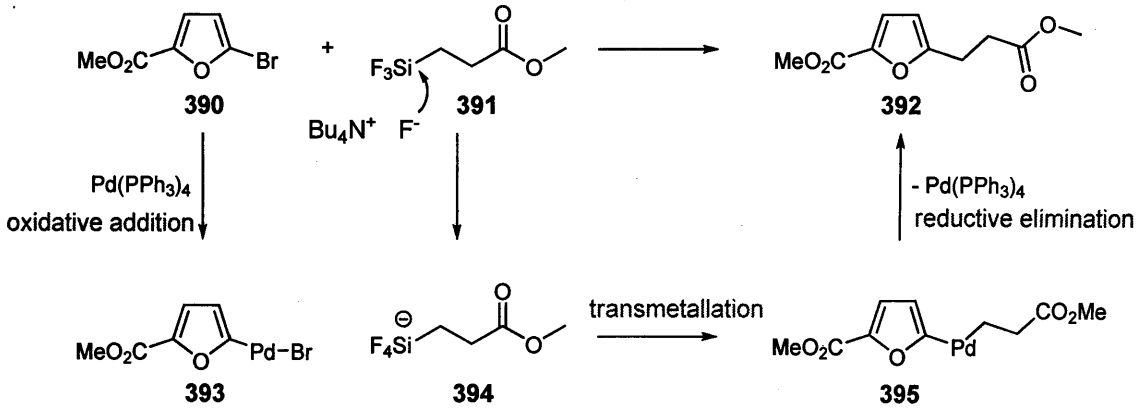


Scheme 3.34.

The reaction of a variety of secondary alkyl electrophiles with organozinc reagents at room temperature using [Ni(cod)$_2$]/*s*Bu-pybox,[227] proceeds in the presence of various functional groups, such as sulfonamides, ethers, acetals, esters, and amides. Alkyl chlorides, alkyl tosylates, and tertiary alkyl bromides do not react under these conditions.[228]

Hiyama

The Hiyama coupling is a palladium-catalyzed C-C bond formation between aryl, alkenyl, or alkyl halides or pseudohalides (*e.g.* triflates) **390** and organosilanes **391**; an activating agent such as fluoride ion or a base is required. The transmetallation step is reluctant to occur without the effect of an activating agent and lead to a pentavalent silicon compound **394** (Scheme 3.33). For the transmetallation to occur in the Hiyama coupling, fluoride activation and the formation of pentavalent silicon is essential.[218,229]

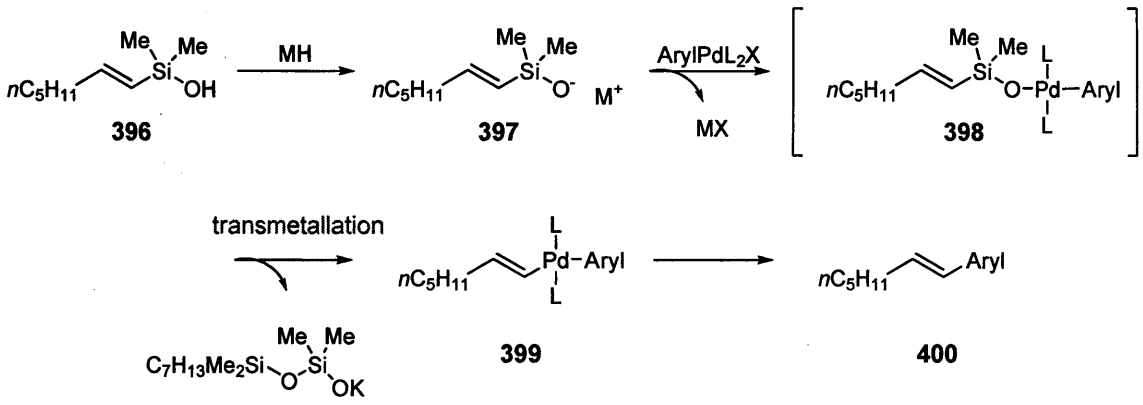


Scheme 3.35.

Organosilane reagents have many of the attractions of organoborane reagents, including availability, low toxicity, and high functional group compatibility. To further increase the scope of the reaction with secondary alkyl electrophiles, a nickel(II)-catalsyed coupling of aryl trifluorsilanes was developed.[230] A variety of cyclic and acyclic secondary bromides and cyclic

iodides can be used, and the substrates can contain ether, imide, ketone, and carbamate functional groups.[221]

The Hiyama-Denmark coupling is a modification of the Hiyama Coupling, in which the palladium-catalyzed coupling of deprotonated silanols **397** with vinyl and aryl halides leads to cross-coupled products **400**. Fluoride is not needed as activator, so the reaction is compatible with substrates bearing silyl-protecting groups and can be performed in large-scale reactors. The Hiyama-Denmark Coupling occurs in the presence of a base and strongly depends on the steric and electronic properties of the silicon centre. It was proposed that the mechanism for the transmetallation involves the formation of a pentavalent silicon species, suggesting that the *in situ*-generated silanolate forms an organopalladium complex, which is activated by a second equivalent of the silanolate prior to transmetallation. [218,231]



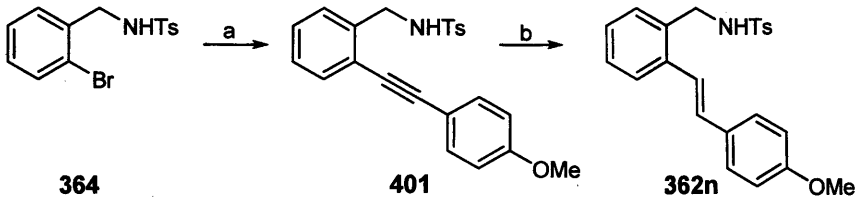
Scheme 3.36.

Sonogashira

The Sonogashira reaction is a Pd/Cu-catalysed cross-coupling reaction of organohalides with terminal alkynes. This is closely related to the Cadiot-Chodkiewicz coupling and Castro-Stephens reaction; In contrast to the Castro-Stephens coupling, which uses stoichiometric copper, the Sonogashira variant uses catalytic palladium and copper. [225,232,233,234]

In 2006, the first Sonogashira coupling of unactivated secondary alkyl bromides was reported.[235] The reaction proceeded well in the presence of a palladium complex with a *N*-heterocyclic carbene (NHC) ligand at elevated temperatures in polar solvents.[221]

The Sonogashira reaction could be a possibility for the synthesis of the *trans*-2-(4-methoxy)-phenyl derivative **362n**. [236,237,238] *trans*-2-(4-Methoxy)phenylboronic acid **369n** is expensive to, whereas the corresponding alkyne is relatively inexpensive. The produces alkyne could then be selectively reduced to the *trans*-alkene (Scheme 3.31).

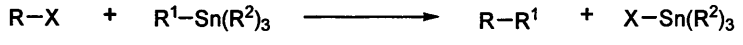


364 401 362n

Scheme 3.37. a) $(Ph_3P)_2PdCl_2$, CuI, Et_3N b) Lindlar catalyst, H_2

Stille

The Stille coupling was first reported in the 1970s and is a versatile C-C bond forming reaction between stannanes **403** and halides or pseudohalides (*e.g.* triflates) **402**, with very few limitations on the R-groups (Scheme 3.38). [239] Well-elaborated methods allow the preparation of different products from all of the combinations of halides and stannanes depicted below (Scheme 3.38). The main drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki coupling.[218] The triflates are more widely used, as they are readily prepared from phenols or enolisable aldehydes or ketones. In these reactions, the presence of a source of halide is needed, such as LiCl. [240,241]



402 **403** **405** **405**

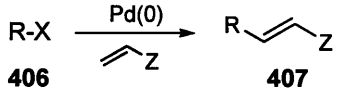
Scheme 3.38.

Nickel-catalysed processes with secondary electrophiles were also extended to the Still reaction by using monoorganotin reagents.[242] Monoorganotin reagents are especially useful, as they are not as toxic as triorganotin reagents and do not make product purification as difficult.[221]

There are many known side-reactions for the Stille reaction, which include homocoupling, transfer of "non-transferable" ligands, destannylation, cine substitution and aryl migration. The most common side-products are those involving a homocoupling event. [243,244,245,246,247,248,249] When electron-rich aryl- or heteroarylstannanes are used, destannylation can be a problem;[250,251] however, usually the volatile side-products can be removed during work-up. Some scattered examples of cine substitution have been reported in the case of 1-substituted 1-stannylethylenes. [252,253,254] A proposed mechanism involves insertion of the Pd^{II}-aryl species across the double bond of the alkene followed by β-elimination and protodestannylation.[225]

Heck

The palladium-catalyzed C-C coupling between aryl or vinyl halides and activated alkenes in the presence of a base is referred to as the Heck Reaction. The Heck reaction involves the reaction of an aryl or alkenyl halide or triflate with an alkene, resulting in an alkene product, whereby one of the C-H bonds has been substituted; [255,256] formally, this represents a direct functionalisation reaction.[225] Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction. One of the benefits of the Heck Reaction is its outstanding *trans* selectivity. [241,257]



Scheme 3.39.

Oshima *et al* developed a cobalt-catalysed version for the coupling of secondary alkyl bromides with styrene derivatives.[258] Secondary alkyl chlorides also participated in the coupling reaction, as well as a variety of styrene derivatives. A *tert*-butoxybarbonyl group and a carbamate group were tolerated.[221]

Wittig

The Wittig Reaction allows a completely different disconnection approach compared to that used in the cross-coupling reactions (Figure 3.16).

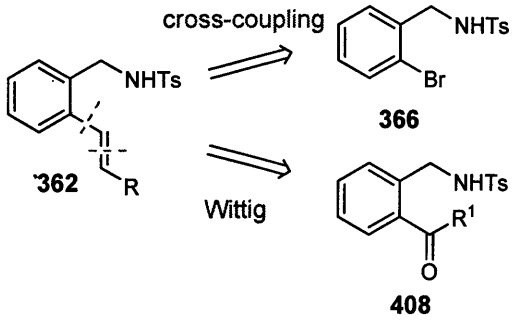
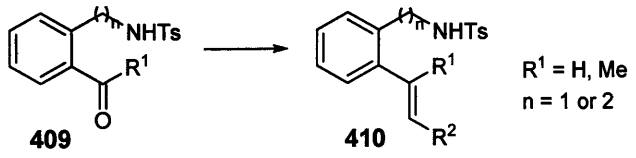


Figure 3.16. Disconnection for both the cross-coupling approach and the Wittig reaction

Alkenes are prepared by the reaction of an aldehyde or ketone with the ylide generated from a phosphonium salt. For the synthesis towards the cyclisation precursors **362** and **360** this means that the Wittig reaction could be performed with either the aldehyde (R = H) or the ketone (R = Me), thus allowing the inclusion of greater steric hindrance (Scheme 3.40).[259]



Scheme 3.40.

The geometry of the resulting alkene depends on the reactivity of the ylide. Stabilized ylides give (*E*)-alkenes whereas non-stabilized ylides lead to (*Z*)-alkenes, but it seems unlikely that this feature affects the outcome of the present acid-catalysed conditions.[217,241]

Any potential difficulties that could be encountered are most likely to be possible to overcome by using the Wittig modifications, such as the Julia and Peterson Olefinations.

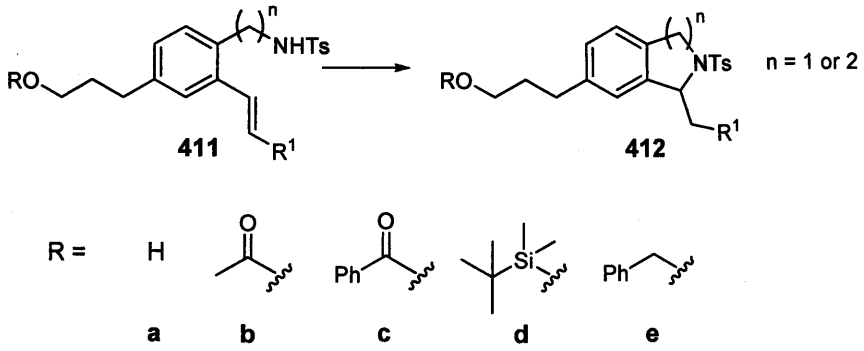
3.5. Conclusion and Future Work

The hydroamination variant of the Pictet-Spengler reaction has been successful for the synthesis of both the dihydroisoindoles **363** and tetrahydroisoquinolines **361**. Some problems were encountered with the Suzuki reaction but overcome by the use of a ferrocene bi-phosphine ligand (dtbpf) and heating in a microwave in an equal measure of ethanol and water. The inclusion of remote functional groups through a Suzuki cross-coupling failed (**369i – m**) and needs to be addressed.

Further investigations into determining whether remote functional groups can survive the cyclisation reaction conditions will need to be performed.

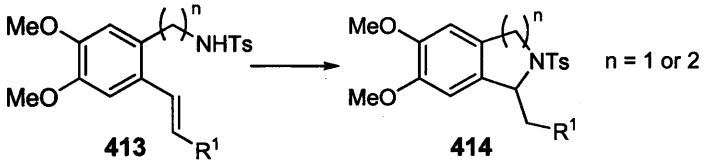
A viable synthetic route towards precursors **362i – m** and **360i - m** needs to be developed allowing an assessment of which groups will be able to withstand the cyclisation conditions. This will most likely involve the use of one of the alternatives to the Suzuki reaction, discussed above. Ideally, a reaction starting from sulfonamides **366** and **367**, such as other cross-coupling reactions, would be preferred. The chances are that more than one of these cross-coupling will need to be used to arrive at the various remote functional groups, due to commercial availability and synthetic ease. Most likely, any reaction chosen will involve more steps towards **362** and **360**, in comparison to the Suzuki.

Functional groups that are known to survive the cyclisations include esters, sulfones not connected to the reaction site, and remote allyl groups (see Chapter 2). One particular remote functional group of interest is the hydroxyl group. Can this survive the acidic cyclisation conditions? It is also of interest to see which alcohol protecting groups would be able to survive (Scheme 3.41).



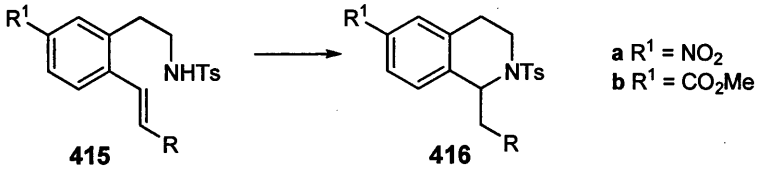
Scheme 3.41.

As discussed in the introduction to this chapter, Pictet-Spengler reactions towards tetrahydroisoquinolines contain a directing methoxy group. This is not necessary for the hydroamination variant of the Pictet-Spengler reaction to occur, as the reaction proceeds through a carbenium ion, which dictates the reaction site. The plan is to include this methoxy group, not as a directing group, but instead to possibly allow further substitution after the cyclisation has been achieved (Scheme 3.42).



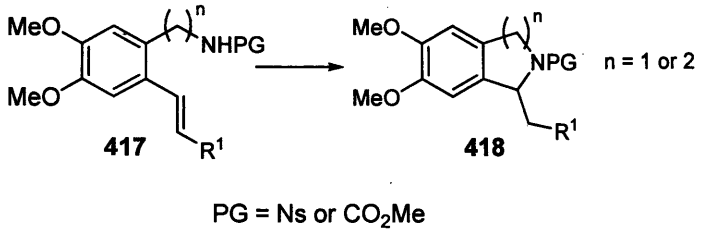
Scheme 3.42.

This could then also be expanded to the inclusion of other functionalities, which are incompatible with the classic Pictet-Spengler reaction, such as a nitro group **415a** or a methyl ester **415b** (Scheme 3.43).



Scheme 3.43.

Another area to investigate is the possibility of performing these reactions with nitrogen protecting groups that are easier to remove than the tosyl group that has been used for both the dihydroisoindols **363** and tetrahydroisoquinolines **361**. The tosyl group could easily be substituted with a nosyl group or a carbamate, both of which are fairly simple to remove (Scheme 3.44).



Scheme 3.44.

If the hydroamination variant of the Pictet-Spengler reaction can be shown to not only be successful in the classic Pictet-Spengler constraints but to also be able to overcome these limitations, then this could be a real alternative of the Pictet-Spengler reaction.

In the future, natural product synthesis may also be on the cards using the hydroamination variant of the Pictet-Spengler reaction.

The stereochemical implications of the acid-catalysed hydroamination variant of the Pictet-Spengler reaction need to be investigate (Figure 3.17). Would the inclusion of a substituent adjacent to the sulfonamide affect the cyclisation? Would the predominant isomer have the substituents either side of the nitrogen be *syn* to one another as has, on the most part, been observed for the pyrrolidines (see Chapter 2)?

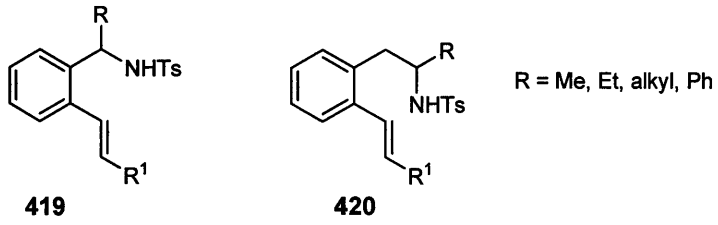


Figure 3.17. Inclusion of substituents adjacent to the nitrogen

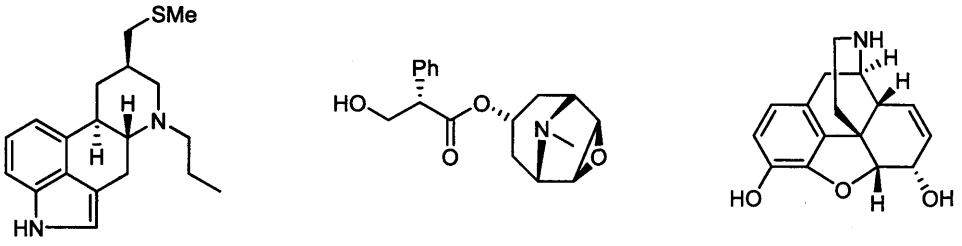
Chapter 4

Chapter 4

Ring-Contraction of Piperidines

4.1. Introduction

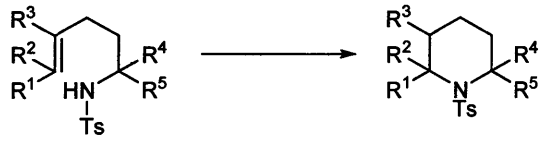
The synthesis of piperidines was deemed an important addition to the acid-catalysed hydroamination method, due to the synthetic importance of such compounds. Functionalised piperidines are among the most common building blocks in natural products, and, more interestingly, in many biologically active compounds such as pergoline, scopolamine and morphine (Figure 4.1).[260]



pergoline scopolamine morphine

Figure 4.1. Natural products containing a piperidine moitey

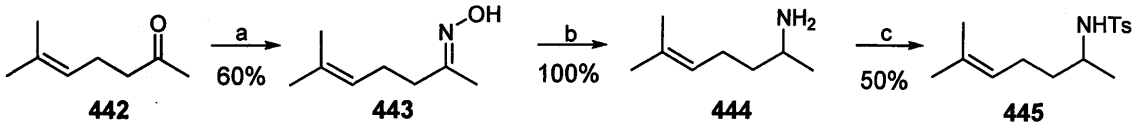
In Chapters 2 and 3, the acid-catalysed hydroamination had successfully been used in the formation of pyrrolidines and morpholines, as well as in the synthesis of dihydroisoindoles and tetrahydroisoquinolines. Surely this synthetic method should also be applicable to the synthesis of piperidines, especially if the distal terminus of the alkenes were fully substituted (Scheme 4.1).



440 **441**

Scheme 4.1.

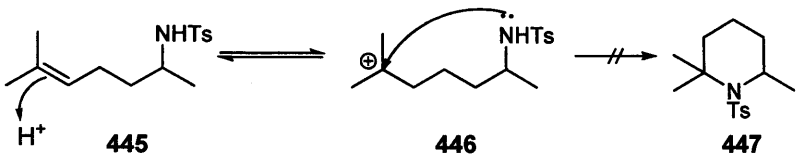
The anticipated synthesis of 2,2,6-trimethylpiperidine **447** from 6-methylhept-5-en-2-one **442**, *via* the oxime **443**[261] and amine **444**[262] to sulphonamide **445** was used to test this (Scheme 4.2).



442 **443** **444** **445**

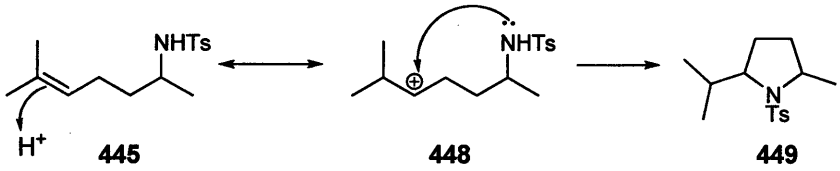
Scheme 4.2. a) Hydroxylamine.HCl, NaOAc, EtOH, 60 °C, 2 hrs b) $LiAlH_4$, THF, 70 °C, 3 hrs c) *p*-TsCl, NEt_3, DMAP, DCM, –78 °C, overnight

This particular example was chosen due to the tertiary carbenium ion **446** expected to form, which would facilitate an overall 6-*endo*-trig cyclisation, to hopefully give piperidine **447** (Scheme 4.3).



Scheme 4.3.

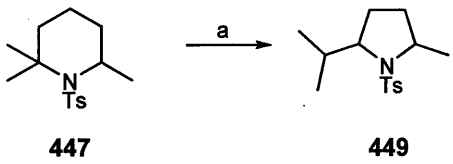
Most surprisingly, little of the desired **447** was isolated; instead the corresponding isopropyl pyrrolidine **449** was formed, which would have involved formation of a secondary carbenium ion **448** and an overall 5-*exo*-trig cyclisation (Scheme 4.4)



Scheme 4.4.

Though both cyclisations are favoured by Baldwin's rules, it was thought that formation of tertiary carbenium ion **446** would be favoured over secondary carbenium ion **448**. However, it would appear that this is not the case.

This was unexpected as this very principle had in fact been used by Hartwig to produce piperidines, as well as pyrrolidines.[2] Due to the small quantity of **447** formed in the reaction further investigations were needed. Was piperidine **447** formed initially and then converted to **449** during the course of the cyclisation reaction? The small quantity of **447** produced during the reaction was separated from pyrrolidine **449** and was exposed to the cyclisation conditions again (Scheme 4.5).



Scheme 4.5. a) 0.5 eq. TfOH, DCM, 20 °C

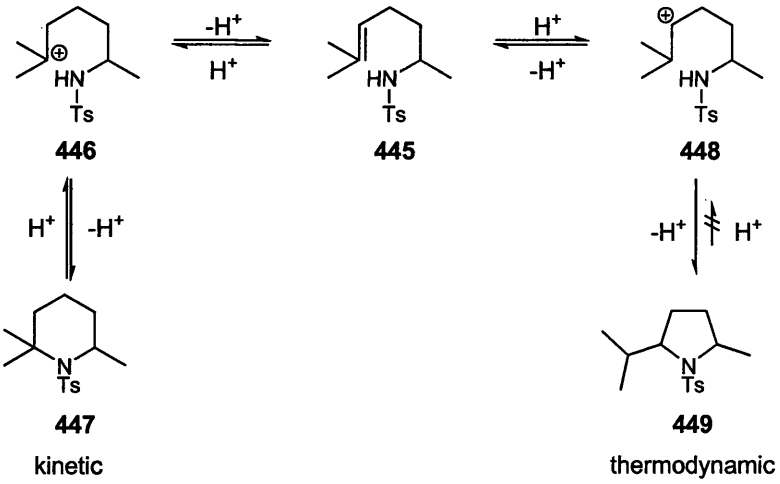
If pyrrolidine **449** was isolated, then this would suggest that piperidine **447** must ring open and re-close to give pyrrolidine **449**. The reaction was sampled at regular intervals (Table 4.1) and analysed by proton NMR.[263]

Table 4.1. Exposure of 2-methylpiperidine **447** to acidic conditions[a]

Time / mins	Major product	445 : 447 : 449 ratio / %[b]
5	Piperidine **447**	~ 10 : 85 : 5
15	Pyrrolidine **449**	~ 0 : 25 : 75
45	Pyrrolidine **449**	0: 7 : ≥93
75	Pyrrolidine **449**	0 : 0 : 100

[a] 0.5 eq. TfOH, dichloromethane, 20 °C [b] as approximated from ^{1}H NMR spectra

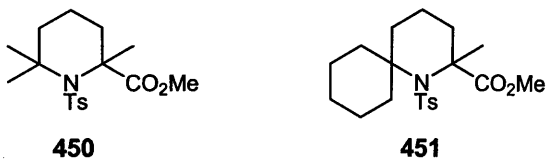
As can be seen in Table 4.1, piperidine **447** was still present after 5 minutes at 20 °C but after just 15 minutes pyrrolidine **449** was the major product present in the reaction mixture. During the subsequent hour, piperidine **447** was fully converted into the pyrrolidine **449**. This conversion could possibly occur though a series of equilibria, where piperidine **447** is the kinetic product and pyrrolidine **449** the thermodynamic product (Scheme 4.6).



Scheme 4.6.

This is very similar to the ring opening and re-closure mechanism proposed for the pyrrolidine formation from amino acids discussed in Chapter 2.

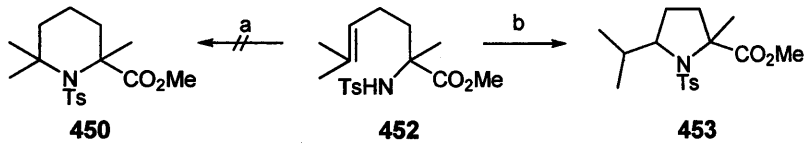
In hindsight, this had already been seen in work produced by the Knight group. Haskins had attempted the synthesis of piperidine **450** and *spiro*-piperidine **451** (Figure 4.2); in both cases the corresponding pyrrolidines were isolated cleanly. This was surprising as both pyrrolidines were again formed *via* a less stable secondary carbenium ion intermediate.



450 **451**

Figure 4.2. Piperidines **450** and **451**

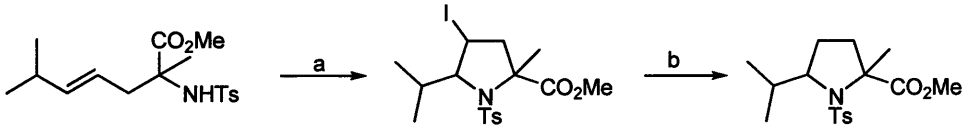
The pyrrolidine **453** was isolated instead of **450**, with a *cis* : *trans* ratio of *ca.* 3 : 2 (from ^{1}H NMR) (Scheme 4.7).[119]



450 **452** **453**

Scheme 4.7. (a) 0.4 eq. TfOH at 0 °C no cyclisation (b) 0.6 eq. TfOH, 20 °C 1 hr

Due to this unexpected result, confirmation of the pyrrolidine structure **453** was sought; the compound **453** was synthesised through an alternative method featuring an iodocyclisation (Scheme 4.8).

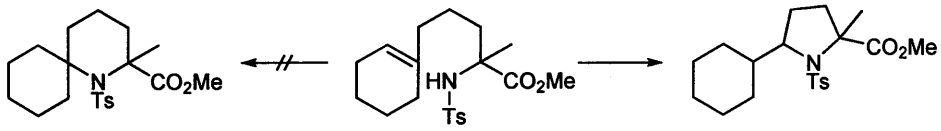


454 **455** **453**

Scheme 4.8. a) I_2, K_2CO_3, MeCN b) H_2, Pd/C, MeOH, Et_3N

Iodopyrrolidine **455** was isolated (*cis* : *trans* ratio of *ca.* 1 : 4) and was deiodinated to give pyrrolidine **453** and showed the same spectroscopic data as that generated by the acid-catalysed cyclisation, although the diastereomeric isomer ratios differed.

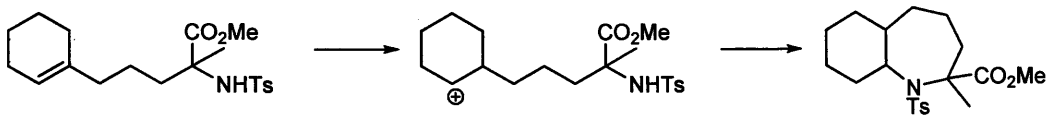
The cyclohexenyl derivative **456** also failed to give the desired *spiro*-piperidine **451** when treated with triflic acid; instead pyrrolidine **457** was formed essentially as a single isomer (Scheme 4.9).



451 **456** **457**

Scheme 4.9.

The lack of piperidine formation was evident from the ^{13}C data, as the quaternary carbon expected for the *spiro*-centre was not discernable. In addition two CH signals were present at 64.8 and 40.5 ppm. Originally, the possibility of a 6/7 fused system **459** was considered which would have formed *via* secondary carbocation **458** (Scheme 4.10).



456 **458** **459**

Scheme 4.10.

The pyrrolidine structure was, however, confirmed by X-ray crystallography. Pyrrolidine **457** was isolated as a single isomer, where the cyclohexyl and methyl ester substituents were *cis* to one another, as would be expected from this type of reaction and a result that was observed in the cinnamyl and crotyl derivatives **177** and **178** described in Chapter 2 (p. 35 and 37).

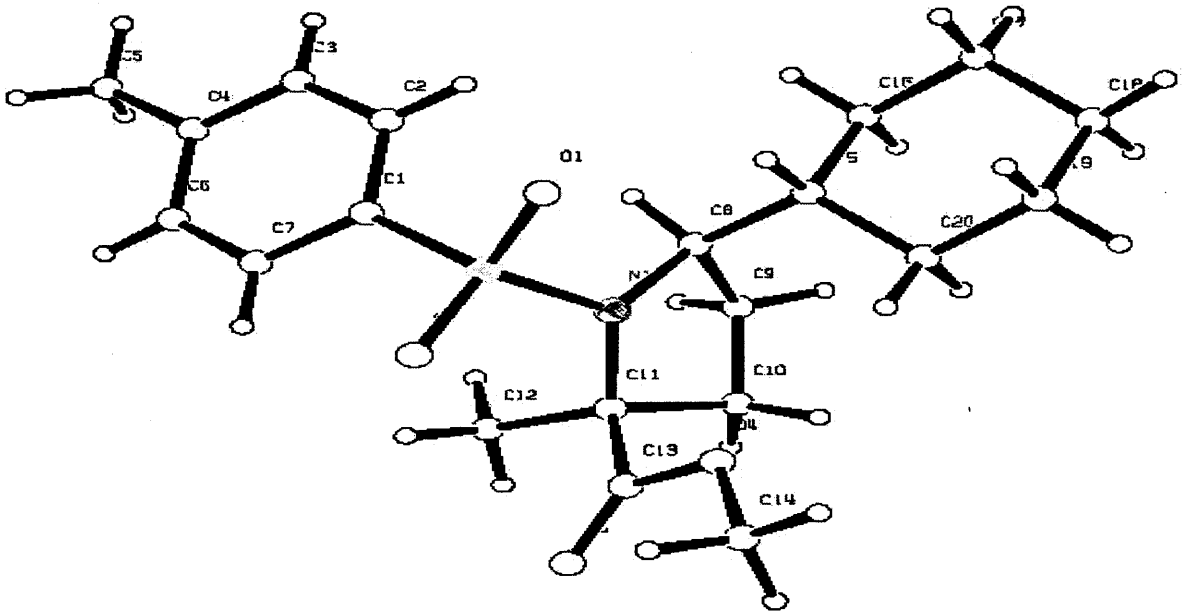
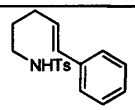
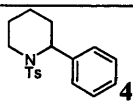
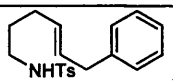
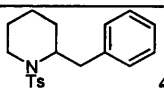


Figure 4.3. X-ray structure of **457**[119]

Haskin's observations, as well as the failure to cleanly synthesise trimethylpiperidine **447** from sulfonamide **445**, prompted further inspections of Hartwig's results.[2] These showed a successful, high yielding synthesis of 2-phenylpiperidine **460**; however, for the synthesis of 2-benzylpiperidine **461**, a very low yield was noted (Table 4.2).

Table 4.2. Hartwig's yields for the synthesis of piperidines;[2]

Starting Material	Product	Acid	Time	Yield [c]
	 **460**	$TfOH$ [a] H_2SO_4 [b]	2 24	83 80
	 **461**	$TfOH$ [a] H_2SO_4 [b]	2 24	51 0

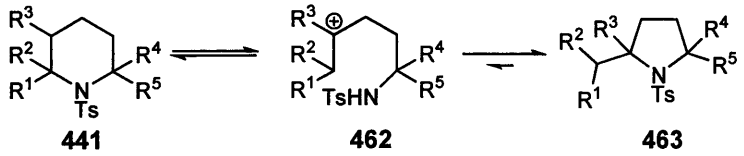
[a] 20 mol% TfOH, 100 °C [b] 20 mol% H_2SO_4, 100 °C [c] Isolated yield after column chromatography

The yields for the production of 2-phenylpiperidine **460** were high for the reactions with both acids, however, the 2-benzylpiperidine **461** yield was relatively low for the cyclisation with triflic acid and none of this product **461** was isolated when using sulfuric acid. No mention was made as to what was isolated for the sulfuric acid-catalysed reaction, or the nature of other product, which was formed during the reaction with triflic acid. All that was noted was that neither any starting material nor the alternate 7-membered product related to piperidine **461**, was recovered.

4.2. Results and Discussion

4.2.1. Ring Contraction of Piperidines

Since it has been observed that 2,2,6-trimethylpiperidine **447** was rapidly converted into the corresponding isopropyl pyrrolidine **449** under hydroamination conditions, it was felt that it would be worthwhile investigating if other piperidines would undergo the same transformation (Scheme 4.11).



Scheme 4.11.

A variety of piperidines were chosen to see what effect substitution type and pattern would have on the putative ring contraction under acidic conditions (Figure 4.4).

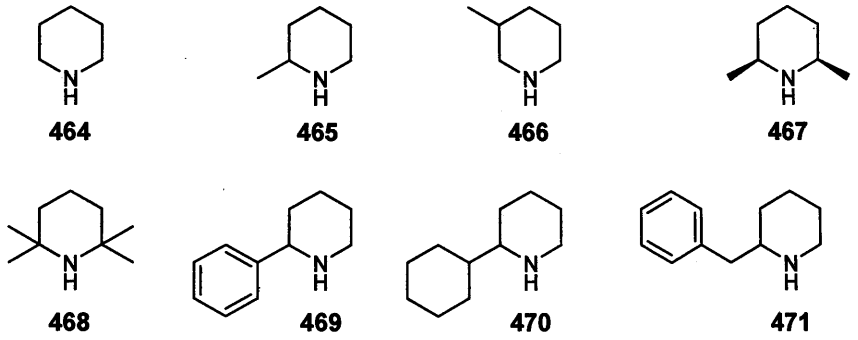
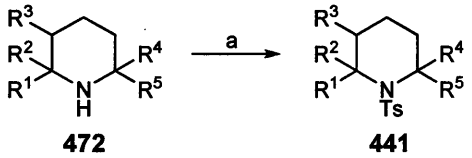


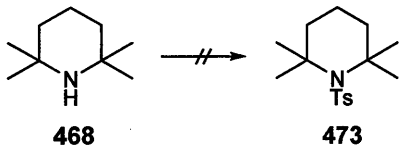
Figure 4.4. Piperidines proposed for rearrangement to pyrrolidines

Most of these piperidines **472** are commercially available and were treated with *p*-toluenesulfonyl chloride to give the corresponding tosylpiperidines **441** (Scheme 4.12).



Scheme 4.12. a) *p*-TsCl, NEt_3, DMAP, DCM

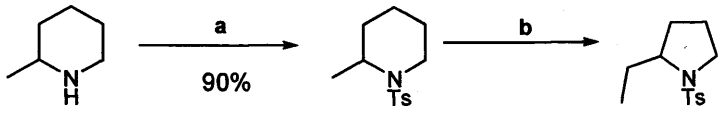
Tetramethylpiperidine **468** was unfortunately not successfully tosylated. Even a strong base, such as *n*-BuLi (pKa 51), was not able to successfully affect tosylation (Scheme 4.12). This was most likely due to the steric hindrance presented by the four methyl groups surounding the nitrogen. This is consistent with the literature.[264]



Scheme 4.12. a) *n*-BuLi, *p*-TsCl, THF, 65 °C, 72 hrs

The failure in the tosylation of piperidine **468** gave the indication that crowding due to α-substituents may have played a role in the ring-contraction of piperidine **447** to pyrrolidine **449** (Scheme 4.5).

2-Methyl-1-tosylpiperidine **474** was believed to be the very unlikely to rearrange to the related pyrrolidine **475**. 2-Methylpiperidine **465** is commercially available and was tosylated and then exposed to acid at a variety of temperatures (Scheme 4.13).



465 **474** **475**

Scheme 4.13. a) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C b) TfOH, DCM 0 - 40 °C *or* conc. H_2SO_4, toluene, 20 - 110 °C

As Hartwig had synthesised piperidines with both triflic acid and sulfuric acid, both of these were used for the attempted rearrangement of piperidines to pyrrolidines. The results for 2-methylpiperidine **474** at a variety of temperatures and times, are shown in Table 4.3.

Table 4.3. Exposure of 2-methylpiperidine to acid at different temperatures

Acid [a]	Solvent	Temperature / °C	Time / hrs	Conversion / % [c]
TfOH	DCM	20	3	0
H_2SO_4	DCM	20	3	0
TfOH	DCM	40	3	0
H_2SO_4	DCM	40	3	0
TfOH	Toluene	110	24	0
H_2SO_4	Toluene	110	72	9
TfOH	Toluene	110	72	5
H_2SO_4 [b]	Toluene	110	24	21
H_2SO_4 [b]	Toluene	110	72	6
-	Toluene	110	24	0

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4 unless otherwise stated; [b] 6 drops of conc. H_2SO_4; [c] amount of pyrrolidine formed from piperidine

At relatively low temperatures, none of piperidine **474** was ring contracted to the corresponding pyrrolidine **475**. However with increasing temperatures and the length of reaction time, then some conversion into pyrrolidine **475** was observed, the most pronounced example of which was a 21% conversion **475** with sulfuric acid when heated to 110 °C for 24 hours. Oddly, when the reaction was left for 72 hours the amount of pyrrolidine **475** seen was lower, almost a quarter less. What is important to note is the fact that this piperidine **474** was not expected to ring contract at all; nevertheless it had, and under fairly standard acidic conditions to which piperidines are often exposed. A control reaction was performed which omitted both acids to show that the contraction was not thermally induced.

The appearance of the pyrrolidine **475** peaks can clearly be seen between 3.0 and 3.5 ppm in the proton NMR spectra shown below (Figure 4.5). There is also clear evidence of doubling of the tosyl peaks both in the aromatic region as well as of the tosyl methyl, which appears at 2.33 ppm for the pyrrolidine **475** and 2.32 ppm for piperidine **474**.

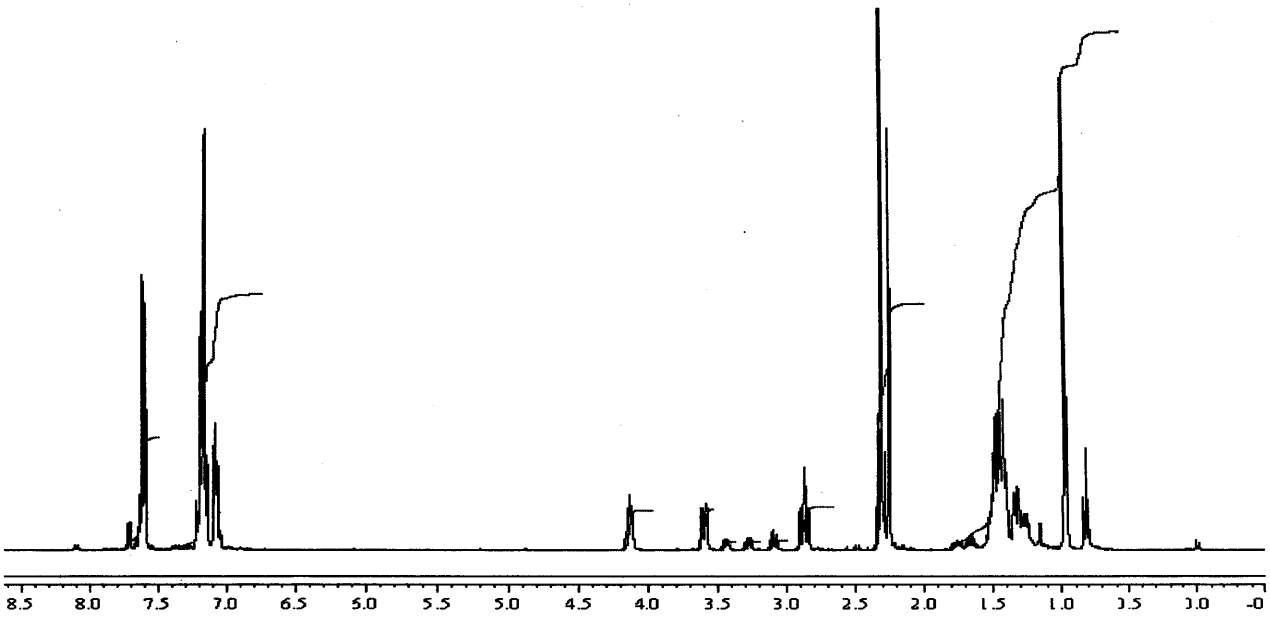
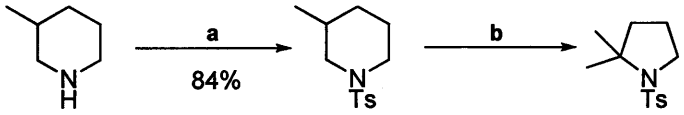


Figure 4.5. Appearance of pyrrolidine **475** peaks

Since 2-methylpiperidne **474** was partly converted into pyrrolidine **475**, would moving the methyl group to the 3-position improve or hinder this conversion (Scheme 4.14)?



466 **476** **477**

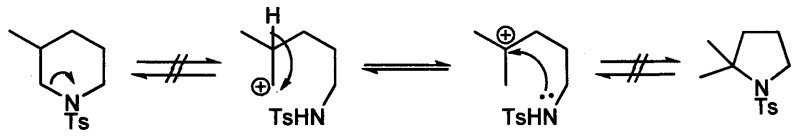
Scheme 4.14. a) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C b) TfOH, DCM 0 – 40 °C *or* conc. H_2SO_4, toluene, 20 - 110 °C

Table 4.4. Exposure of 3-methylpiperidine to acid at different temperatures

Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [b]
TfOH	DCM	20	3	0
H_2SO_4	DCM	20	3	0
TfOH	Toluene	110	24	0
H_2SO_4	Toluene	110	24	0
TfOH	Toluene	110	72	0

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4; [b] amount of pyrrolidine formed from piperidine

As can be seen in Table 4.4, none of piperidine **476** was ring contracted to pyrrolidine **477**. This was surprising, as it had been surmised that as a tertiary carbenium ion **479** could be formed in the 3-position of the piperidine at the methyl substitution this would then favour the formation of the pyrrolidine **477** (Scheme 4.15).

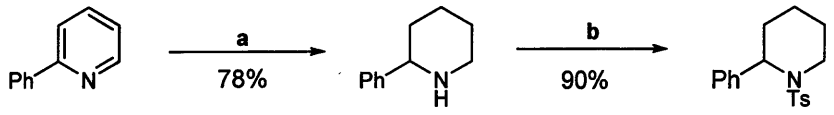


476 **478** **479** **477**

Scheme 4.15.

The ring contraction could not even be persuaded to occur when heating the reaction mixture at 110 °C for 72 hours. As this was felt to be the most extreme conditions that a piperidine is likely to be exposed to under acidic conditions, it was conceded that the rearrangement was unlikely to occur when a piperidine is substituted in the 3-position, rather than at its 2-position. Inital and presumably necessary carbon-nitrogen rupture by *N*-protonation to give secondary carbenium ion **478** would not be particularly favourable as there was no special steric inducement. From this it was concluded that it may not be possible to ring contract piperidines substituted at the 3-position. This is something that needs to be investigated further; unfortunately for this study no other piperidines substituted in the 3-position were available.

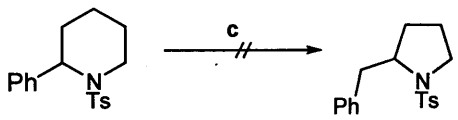
Returning to piperidines substituted at the 2-position, the ring contraction was then attempted on 2-phenylpiperidine **460**. This was synthesised by the reduction of 2-phenylpyrridine **480** with the aid of Adam's catalyst,[265] followed by conversion into the sulfonamide **460** (Scheme 4.16).[2]



480 **469** **460**

Scheme 4.16. a) PtO_2, H_2, EtOH, 1atm b) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C

Compound **460** was of particular interest, as it had been synthesised by Hartwig using hydroamination with an 83% yield using TfOH and 80% using sulfuric acid, meaning that in theory, the piperidine **460** should not rearrange to pyrrolidine **481**, or if it does, then only to a very small extent (Scheme 4.17).



460 **480**

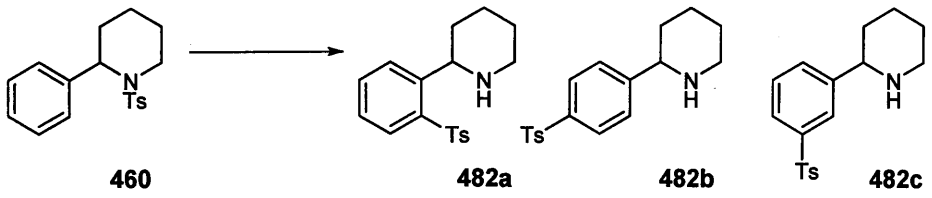
Scheme 4.17. c) TfOH, DCM 0 - 40 °C *or* conc. H_2SO_4, toluene 20 - 110 °C

Table 4.5. Exposure of 2-phenylpiperidine to acids at a variety of temperatures

Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [b]
TfOH	DCM	20	3	0
H_2SO_4	DCM	20	3	0
TfOH	DCM	20	24	0
TfOH	DCM	40	24	0
TfOH	Toluene	110	72	decomposed
H_2SO_4	Toluene	110	72	decomposed

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4; [b] amount of pyrrolidine formed from piperidine; decomposed: no piperidine detected

Exposure of piperidine **460** at low temperatures resulted in no conversion into pyrrolidine **481**, as was also observed when heating to 100 °C for 24 hours. An unexpected result occurred when piperidine **460** was heated at 100 °C for 72 hours with either acid: all of piperidine **460** had disappeared according to ^{1}H NMR analysis. At first it was though that pyrrolidine **481** had been formed, however upon closer inspection of the NMR data, it became apparent that this was not the case. 2-Benzylpyrrolidine **481** had recently been synthesised by Zhang and co workers[266] and comparing their spectroscopic data to that observed for the products obtained after 72 hours confirmed that the pyrrolidine **481** had definitely not been formed. This now left the issue of trying to determine what had been produced in the reaction. None of the starting piperidine **460** was evident in the spectra nor was any of the *N*-protected piperidine present.[267] In fact tosyl groups were clearly visible in the spectra, which could not be the tosylate salts due to the basic work up used. The piperidine had clearly changed and the only hypothesis that seemed reasonable was that the piperidine either ring opened in some fashion, or that the tosyl group may have come off the nitrogen and then added to the phenyl. This latter theory would fit best with the observations made in the NMR spectra, as there was clearly more than one tosyl group present; which could be explained by the phenyl have *ortho*- and *para*-tosyl substitution, and possible some *meta*-tosyl substitution, **482a-c** (Scheme 4.18).

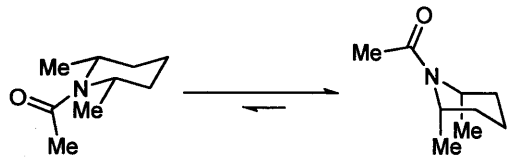


460 **482a** **482b** **482c**

Scheme 4.18.

The failure in the ring contraction of **460** was most curious, considering that 2-methylpiperidine **474** had rearranged and led to a further investigation of its structure to find an explanation of this. When searching the literature a NMR study on the conformational aspects of the acyl derivatives

of *cis*-2,6-dimethylpiperidines by Chow came to light. They found that the interaction between the oxygen of the acyl group and the α-equatorial methyl in **483a** was severe and thus the favoured structure was **483b**, where the acyl and α-methyl groups were in an axial orientation to one another (Figure 4.6).[268]

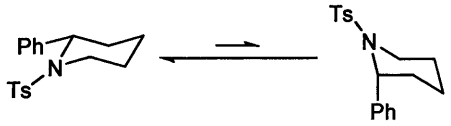


483a **483b**

Figure 4.6. Structures of axial and equatorial α-methyl of *cis*-2,6-dimethylpiperidine **483**

Comparison of the chemical shifts of the α-protons for acylpiperidine **483** with the corresponding data of *N*-benzoyl-4-*t*-butylpiperidine left no doubt that the α-protons were equatorially orientated in the former compound. The coupling patterns of the α-protons also agreed fully with this, showing coupling constants of *ca.* 8.8 Hz.

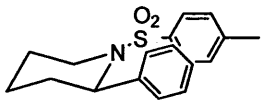
Examination of the proton NMR data for **460** showed that the phenyl group had not adopted an axial orientation towards the *N*-tosyl group **460b** but rather an equatorial orientation **460a**. This was confirmed by the coupling patterns, which showed that the α-proton at 3.84 ppm had a coupling constant of 15.4 Hz, very characteristic of an axial interaction (Figure 4.7).



460a **460b**

Figure 4.7. Structures showing axial and equatorial α-phenyl of 2-phenyl piperdine **460**

This equatorial orientation of the phenyl group was a little surprising due to the steric crowding that must be present. When considered this further, however, it seemed logical to presume that this structure may be favoured due to the possible π-stacking of the phenyl and tosyl groups (Figure 4.8).

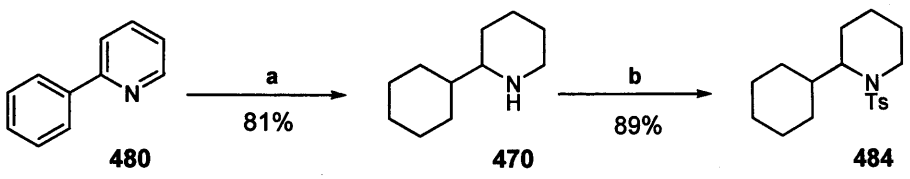


460a

Figure 4.8. Possible π-stacking between the phneyl and tosyl group

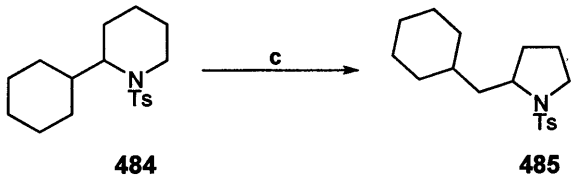
During the synthesis of 2-phenylpiperidine **469**, using the conditions described by Overberger and Herin,[265] 2-phenylpyridine **480** over reduced to give 2-cyclohexylpiperidine **470**. Though not a

compound that it had originally been planned to use in the testing of the ring contraction theory, **484** was also an appropriate compound to use and would be analogous to using an *iso*-propyl substituted piperidine.



Scheme 4.19. a) PtO_2, H_2, Etanol, 2 – 3 atm. b) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C

After piperidine **470** was tosylated, it was exposed to both triflic and sulfuric acid (Scheme 4.20), the results of which are shown in Table 4.6.



Scheme 4.20. c) TfOH, DCM 0 - 40 °C *or* conc. H_2SO_4 in toluene 20 - 110 °C

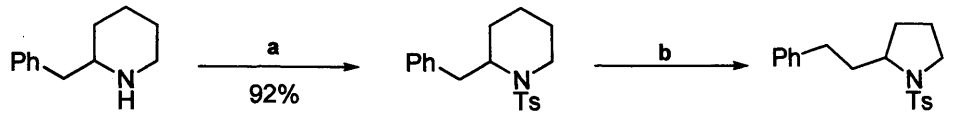
Table 4.6. 2-cyclohexylpiperidine exposed to acid at different temperatures

Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [b]
TfOH	DCM	20	3	0
TfOH	Toluene	110	24	32%
TfOH	Toluene	110	72	48%
H_2SO_4	Toluene	110	72	23%

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4; [b] amount of pyrrolidine formed from piperidine

When the cyclohexyl piperidine **484** was heated to 110 °C with both triflic and sulfuric acid, conversion into the pyrrolidine **485** was observed. In the case of triflic acid, longer exposure resulted in more pyrrolidine **485** being formed, 48% after 72 hours, however, when the compound **484** was refluxed with sulfuric acid for 72 hours only half that amount of pyrrolidine **484** was observed. From this it can be concluded that for this type of system, triflic acid appears to be more effective at inducing ring contraction, perhaps due to it being much more soluble in toluene.

Hartwig had also synthesised the 2-benzylpiperidine **461** using a hydroamination, although only in disappointing yields (see Table 4.2). He was unable to account for alternative products other than the lack of starting material present, so compound **461** was also exposed to the acids at different temperatures (Scheme 4.21) and the results are shown in Table 4.7.



471 461 486

Scheme 4.21. a) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C b) TfOH, DCM 0 - 40 °C *or* conc. H_2SO_4, toluene, 20 - 110 °C

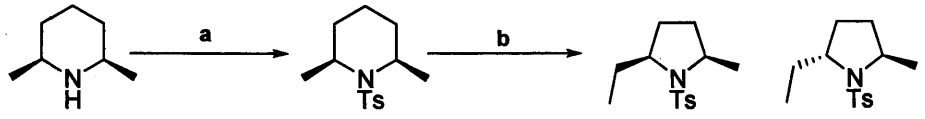
Table 4.7. Exposure of 2-benzylpiperidine to acid at different temperatures

Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [d]
TfOH	DCM	20	24	0
H_2SO_4	DCM	20	24	0
TfOH	DCM	40	24	0
H_2SO_4	DCM	40	24	0
H_2SO_4	Toluene	110	3	0
H_2SO_4	Toluene	110	24	27
TfOH	Toluene	110	72	44
TfOH [b]	Toluene	110	24	30
TfOH [c]	Toluene	110	24	57

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4 unless otherwise stated; [b] 1.0 eq. Of TfOH; [c] 2.0 eq. Of TfOH; [d] amount of pyrrolidine formed from piperidine

As expected, ring contraction occurred when the reaction was heated to 110 °C for 24 hours with sulfuric acid, giving a 27% conversion to pyrrolidine **486**. Triflic acid gave a 44% conversion when heated for 72 hours in toluene; increasing the amount of triflic acid but with shortened reaction time also resulted in conversion, the largest overall yield of 57% being seen for 2 equivalents of triflic acid for 24 hours at 110 °C

Piperidine **487** was exposed to the acidic hydroamination conditions in order to investigate the stereochemical aspects of the contraction. The pure *cis*-piperidine **467** was purchased and converted into the tosylated piperidine **487**. Would the stereochemistry be retained when the ring contraction occurred or would a mixture of products be seen? From previous experience with pyrrolidine ring formation (Chapter 2), it is known that the *cis*-pyrrolidine is usually favoured, though both the *cis*- and *trans*-diastereomers can easily be formed. The ratio of these diastereomers can also be affected by length of reaction time and the amount of acid used in the reaction. This same phenomenon was expected for *cis*-2,6-dimethyl-1-tosylpiperidine **487** (Scheme 4.22); the results shown in Table 4.8.



467 487 488a 488b

Scheme 4.22. a) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C b) TfOH, DCM 0 - 40 °C *or* conc. H_2SO_4, Toluene, 20 - 110 ° C

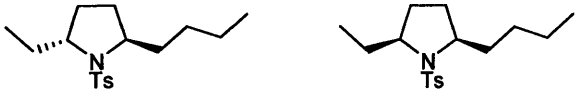
Table 4.8. Exposure of 2,6-dimethylpiperine to acid at different temperatures

Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [b] 487 : 488a : 488b
TfOH	DCM	20	3	0
H_2SO_4	DCM	20	3	0
H_2SO_4	DCM	40	3	0
TfOH	DCM	20	24	0
H_2SO_4	DCM	20	24	0
TfOH	DCM	40	24	0
H_2SO_4	Toluene	110	3	46 : 28 : 26
H_2SO_4	Toluene	110	24	28 : 50 : 22
H_2SO_4	Toluene	110	72	43 : 43 : 14
TfOH	Toluene	110	72	62 : 15 : 23
-	Toluene	110	24	0

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4; [b] amount of pyrrolidine formed from piperidine

As expected, **487** ring contracted to give two pyrrolidines, which were diastereomers of one another. From observations made by Haskins and those discussed in Chapter 2, the major pyrrolidine diastereomer was expected to be the *cis*-isomer **488a**. The major pyrrolidine isomer when the piperidine was reacted with concentrated sulfuric acid was pyrrolidine **488a**, however when using trifilic acid and refluxing in toluene for 72 hours this ratio was inverted. A control reaction was performed which omitted both acids to show that the contraction was not thermally induced.

The full assignment of these pyrrolidines cannot be made due to the difficulty in separating them from the remaining piperidine, however, from work carried out by Jones (Figure 4.9)[269] and comparison with pyrrolidine **174a** and **174b** synthesised in Chapter 2 (Figure 4.10), a provisional assignment was made. Jones had been able to separate the two diastereomers (Figure 4.9) and assign relevant NMR resonances,[269] which assisted in the assignment of diastereomer peaks for **174** (p. 31).



175 176

Figure 4.9. Structure of diastereomers synthesised by Jones [269]

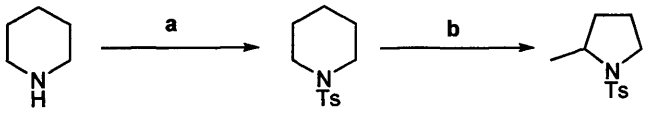
The two methine groups alpha to the nitrogen in the pyrrolidine ring, were determined through careful integration. For the *cis*-isomer these appeared at 3.55 – 3.45 ppm, whereas in the *trans*-isomer, the corresponding values were 3.84 – 3.70 ppm. There was also a minor difference in the shift of tosyl methyl peaks for the two diastereomers. The *cis* isomer methyl resonates at 2.42 ppm whereas the *trans*-isomer methyl appeared at 2.40 ppm. This concurred with trend in data exhibited by pyrrolidines **174a** and **174b** in Chapter 2 (Figure 4.10).

174a **174b**

Figure 4.10. Diastereomers **174a** and **174b**

From this it was concluded that major diastereomer is *cis*-pyrrolidine **488a** and the minor diastereomer is *trans*-pyrrolidine **488b**.

Was substitution even necessary for this type of ring contraction to occur? Evidence that changing the substitution pattern had an effect upon the ring contraction was seen, but did that really mean that it was necessary? Therefore, the ring contraction on the parent piperidine **489** with both acids at varying temperatures was examined (Scheme 4.23). The resulting pyrrolidine **155** (p. 26) was synthesised in Chapter 2, and therefore its characteristic NMR spectroscopic data were known.



464 **489** **155**

Scheme 4.23. a) *p*-TsCl, DIAD, NEt_3, DCM, –78 °C b) TfOH, DCM 0 – 40 °C or conc. H_2SO_4, toluene 110 °C

Table 4.9. Exposure of piperidine to acid at different temperatures

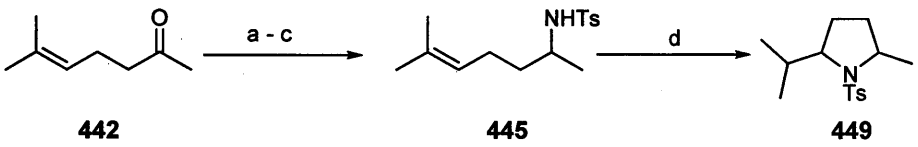
Acid [a]	Solvent	Temperature / °C	Time / h	Conversion / % [b]
TfOH	DCM	20	3	0
H_2SO_4	DCM	20	3	0
TfOH	DCM	20	24	0
H_2SO_4	DCM	20	24	0
TfOH	DCM	40	24	0
H_2SO_4	DCM	40	24	0
TfOH	Toluene	110	24	0
H_2SO_4	Toluene	110	24	0
TfOH	Toluene	110	72	0
-	Toluene	110	24	0

[a] 0.5 eq. Of TfOH or 2 drops of conc. H_2SO_4; [b] amount of pyrrolidine formed from piperidine

A pattern appeared to be emerging: as substitution α to the tosyl protected nitrogen increased and as the substitution increased in size, the contraction to the corresponding pyrrolidines appears to occur more readily. Thus the failure to contract the parent piperidine **489** to the corresponding pyrrolidine **155** was perhaps unsurprising. Could the ring-contraction of piperidines be mostly due to steric crowding α to the bulky tosyl group?

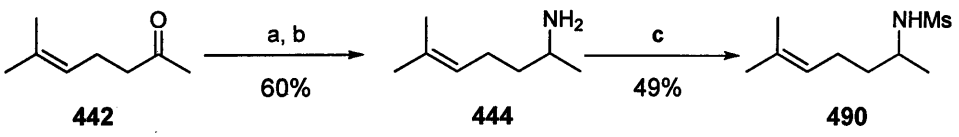
4.2.2. Synthesis towards Piperidines

As discussed in Schemes 4.3 and 4.4, the synthesis of piperidines **447** from *bis*-homoallylic sulfonamides **445** was unsuccessful, as the piperidine **447** ring contracted to give the corresponding pyrrolidine **449** (Scheme 4.24).



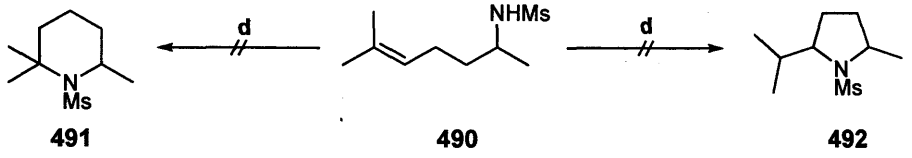
Scheme 4.24. a) Hydroxylamine, NaOAc, EtOH b) $LiAlH_4$, THF c) *p*-TsCl, DMAP, NEt_3, DCM, –78 °C d) TfOH, DCM, 0 °C, 1 hr

We have shown that this ring contraction can occur for other piperidines as well. The original purpose of the work described in this Chapter, however, was the synthesis of piperidines from *bis*-homoallylic sulfonamides. Steric factors seem key as the tosyl group is a fairly large group. It seemed reasonable that if the steric bulk of the tosyl group was playing a role in the favoured synthesis of pyrrolidines over the piperidines then surely changing the nitrogen protecting group could improve the chances of synthesising a piperidine. Returning to the proposed synthesis of 2,2,6-trimethylpiperidine (Scheme 4.3), two alternate protecting groups were tried. The first, a mesylate, was chosen due to its similarity to the tosyl protecting group. The mesylate belongs to the sulfonamide family of protecting groups but has less steric bulk and is less electron withdrawing than the tosyl. The mesyl sulfonamide **490** was to be prepared in the same manner as the tosyl sulfonamide **445** (Scheme 4.25).



Scheme 4.25. a) Hydroxylamine, NaOAc, EtOH, 60° C, 2 hrs b) $LiAlH_4$, THF, 70° C, 3 hrs c) MsCl, DMAP, NEt_3, DCM, –78 °C

As the tosylpiperidine **447** had been isolated after 5 minutes under the acidic cyclisation conditions but had then fully converted to the corresponding pyrrolidine **449** after 1 hour (Scheme 4.26), these two times were chosen to test the performance of the mesylate as a protecting/activating group.

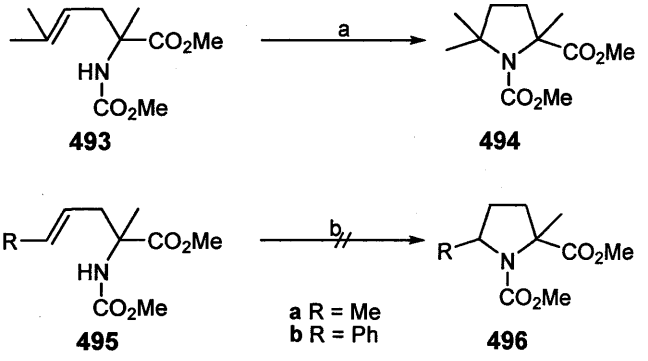


491 **490** **492**

Scheme 4.26. d) H_2SO_4, DCM, 0 °C, 5 min & 1 hr

Unfortunately, mesylate **490** gave neither clean piperidine **491** nor pyrrolidine **492**. In fact all that was observed was starting sulfonamide **490** and some of amine **444**, where the mesyl group had been removed, thus making it a totally inappropriate protecting/activating group for this type of reaction.

The second protecting group, a carbamate group (Moc group), was then tried, as this is a very versatile protecting group. Haskins had investigated the possibility of using the Moc group for the acid-catalysed hydroamination of homoallylic amides to give pyrrolidines, with disappointing results. When the cyclisation involved the formation of a tertiary carbenium ion, such as that generated from the prenyl derivative **493**, the cyclisation to pyrrolidine **494** occurred with a moderate yield of 69%. However, when the crotyl and cinammyl derivatives **495** were subjected to the acidic-conditions, no cyclisation occurred (Scheme 4.27).[119]



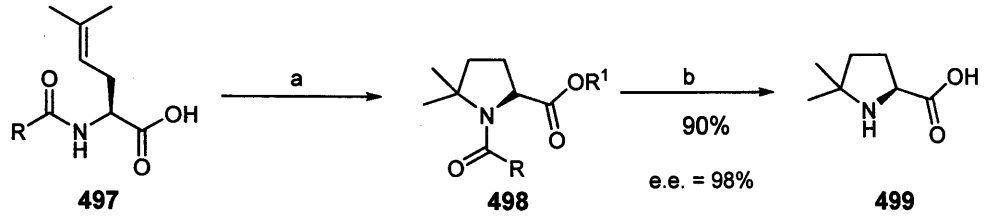
493 **494**

a R = Me
b R = Ph

495 **496**

Scheme 4.27. a) 2 eq. TfOH, $CHCl_3$, 25 °C, 2 hrs b) 5 eq. TfOH, $CHCl_3$, 62 °C, 48 hrs

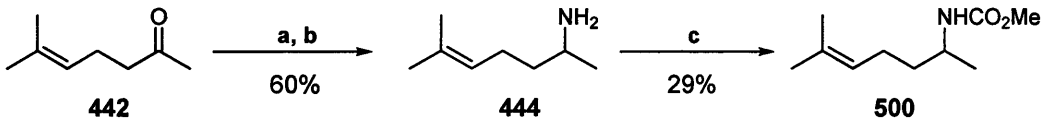
In the enantioselective cyclisation towards 5,5-dimethylproline **499** from *N*-protected prenylglycines **497**, Jackson encountered a similar protecting group issue.[270] Only the cyclisation of *N*-acetyl protected prenylglycine **497a** give 5,5-dimethyproline methy ester **498a**, which was successful deprotected to give enantiomerically pure proline analogue **499** (Scheme 4.28).



a R = Me R^1 = Me Yield = 96%
b R = Me R^1 = H Yield = 0%
c R = $(Me)_3CO$ R^1 = Me Yield = 0%
d R = $(Me)_3CO$ R^1 = H Yield = 0%

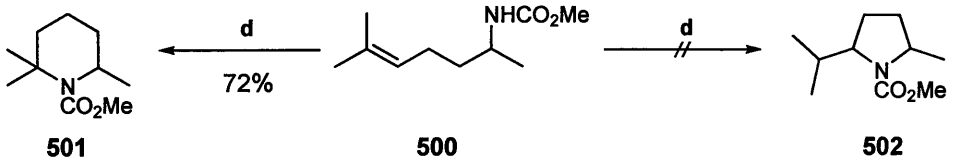
Scheme 4.28. a) 20% TfOH, Toluene, 110 °C, 4 hrs b) 1 M HCl, reflux, 90 min

Since cyclisations of *N*-carbamate protected, highly substituted homoallylic amines had been successful for both Haskins[119] and Jackson,[270] piperidine **501** was believed to be accessible with this type of protecting group. Carbamate **500** was synthesised in a similar manner to **445** and **490** (Scheme 4.29).



Scheme 4.29. a) Hydroxylamine, NaOAc, EtOH, 60° C, 2 hrs b) $LiAlH_4$, THF, 65° C c) Methyl chloroformate, $NaHCO_3$, 1:1 THF/H_2O, 20 °C, 24 hrs

The carbamate **500** was exposed to sulfuric acid for 5 minutes and 1 hour at 0 °C. The reaction after 5 minutes showed the appearance of piperidine **501** and starting carbamate **500** (Scheme 4.30).



Scheme 4.30. d) H_2SO_4, DCM, 0° C, 1 hr

Piperidine **501** was successfully isolated after 1 hour and no rearrangement to pyrrolidine **502** nor the starting sulfonamide **500** were observed. The reactions did not require any chromatography as the reaction proceeded cleanly without any by-products visible in the NMR spectra (see Figures 4.11 to 4.13). Both ^1H and ^{13}C NMR spectra support the successful synthesis of piperidine **501**; as can be seen from Figures 4.11 through to 4.13, carbamate **500** is clearly disappearing and piperdine **501** peaks are appearing. Most obvious is the disappearance of the allylic CH of **500** at 4.41 ppm and the appearance of the CHN of piperidine **501** at 4.14 ppm. Tantalisingly, Figure 4.12 shows the possible transient intermediate.

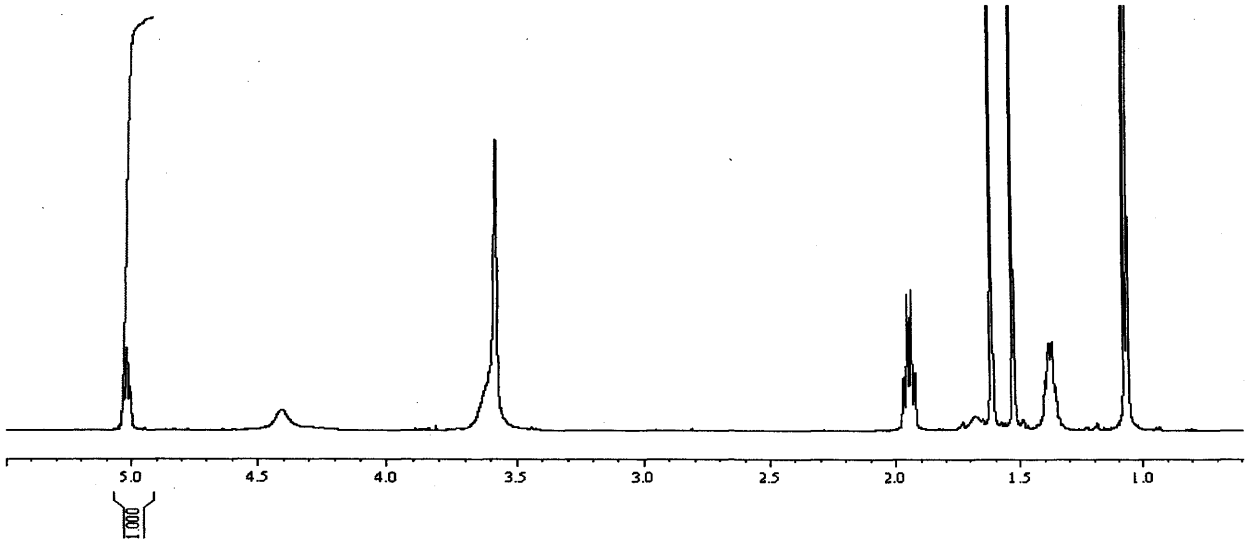


Figure 4.11. ^{1}NMR spectrum of carbamate **500**

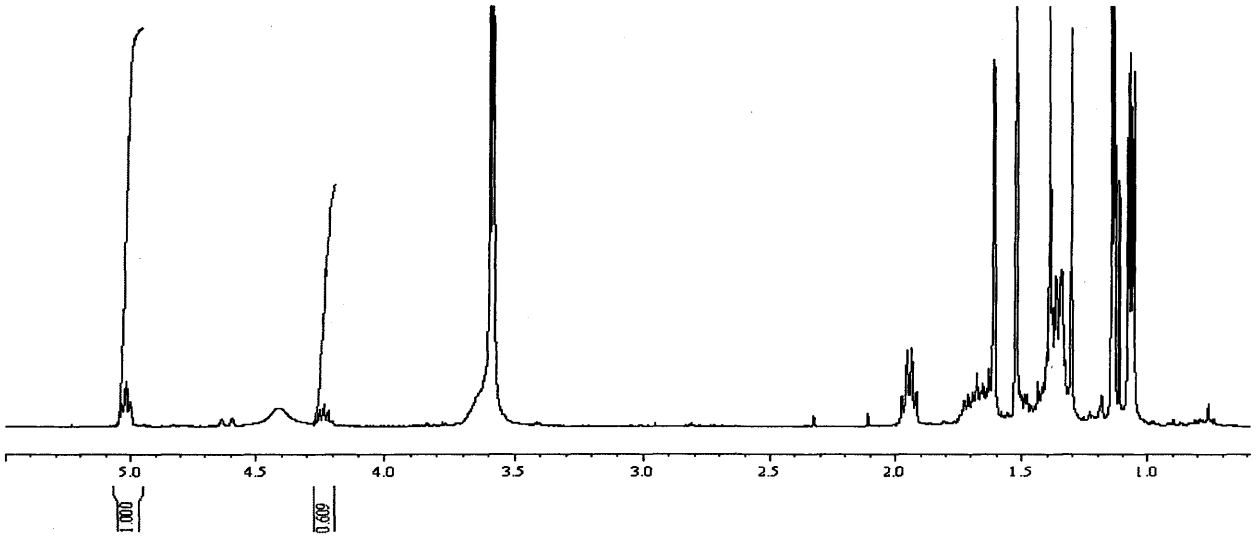


Figure 4.12. Reaction of carbamate **500** in acid after 5 minutes

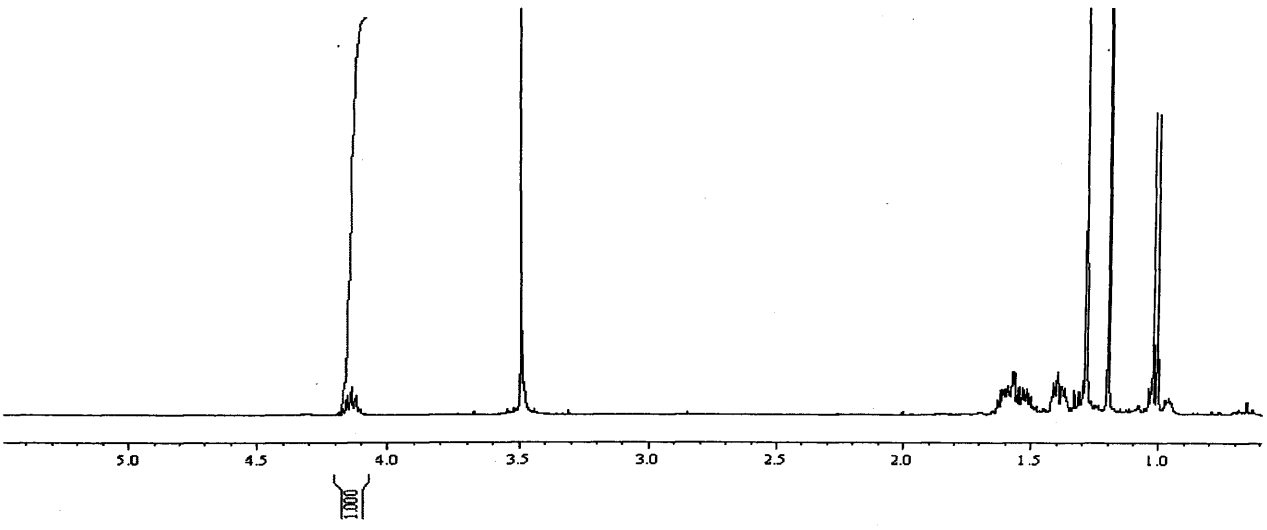


Figure 4.13. Reaction of carbamate **500** in acid after 1 hour, showing that only piperidine **501** was visible.

The ^{13}C NMR spectra in particular, showed that the characteristic quaternary carbon next to the nitrogen present in piperidine **501**, was visible at 54.3 ppm, as was the CH next to the nitrogen at 48.3 ppm (Figure 4.14).

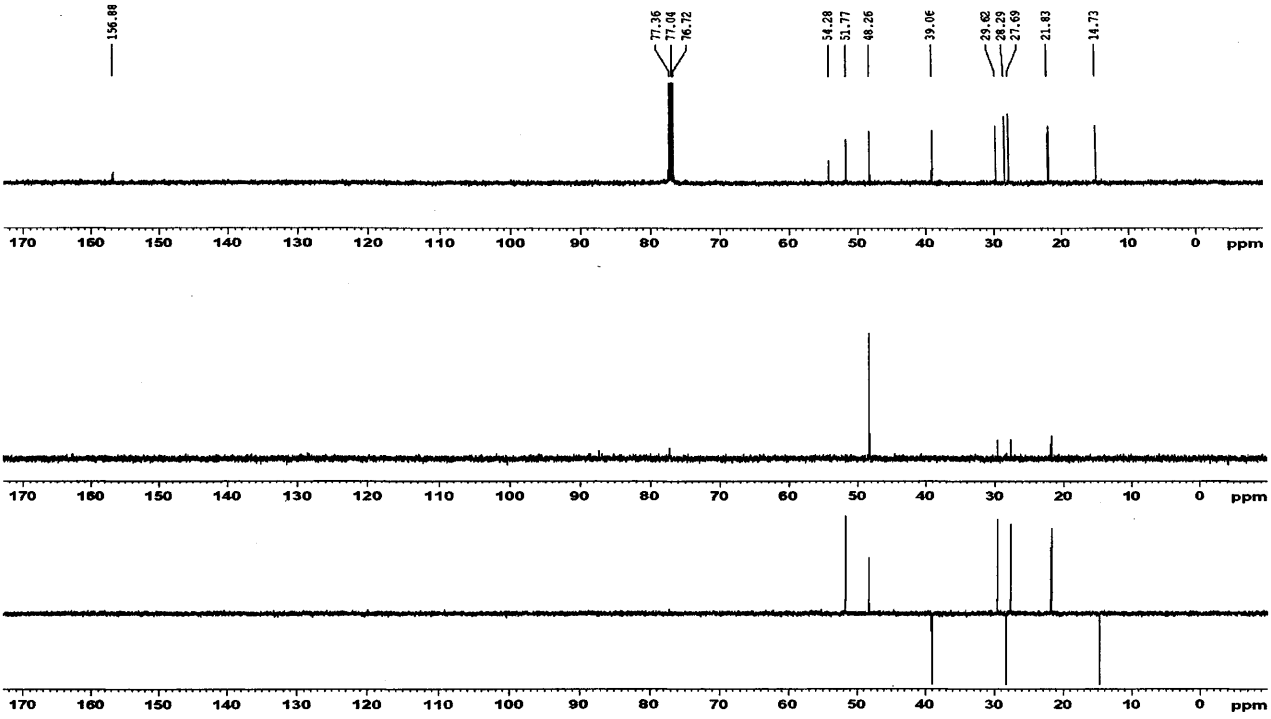


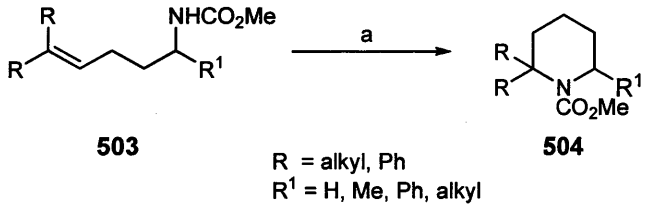
Figure 4.14. ^{13}C NMR spectrum of piperidine **501**

The quaternary carbon at 54.3 would not have been present at all if the pyrrolidine **502** had been isolated instead.

4.3. Conclusion and Future Work

From the work carried out in this chapter it can be concluded that piperidines will easily rearrange to the corresponding pyrrolidine under fairly standard acidic conditions, when contending with steric interference from large groups such as the tosyl group present in **464 - 471**. This should be taken as a synthetic warning when treating crowded piperidines to acidic conditions. More work need to be carried out on the ring-contraction of piperidines, especially piperidines substituted in the 3-position, and more highly substituted piperidines.

It has also been shown that the synthesis of 2,2,6-trimethylpiperidine **501** was achieved by changing from *N*-protecting group from a sulfonamide **445** to a carbamate **500**. This allowed piperidine **501** to be isolated cleanly without any visible traces of pyrrolidine **502**. This had directly lead from observations made by Haskins where a carbamate had successfully been used as a *N*-protecting group to effect the cyclisation of a prenyl derivative **493** to pyrrolidine **494**, through a tertiary carbenium ion. However, when a cyclisation was to be initiated through a secondary carbenium ion, as for derivatives **495**, none of the desired pyrrolidines **496** were observed (Scheme 4.27). This seems to indicate that the synthesis of piperidines through this method may be limited to highly substituted piperidines (Figure 4.15).



Scheme 4.31. a) 0.5 eq. TfOH, DCM, 0 °C

If the synthesis of highly hindered piperidines **504** can be successfully accomplished, then the synthesis of *spiro*-piperidines **505** should also be attempted. The synthesis of these *spiro*-cycles should also include cyclohexanes that contain heteroatoms (Figure 4.15).

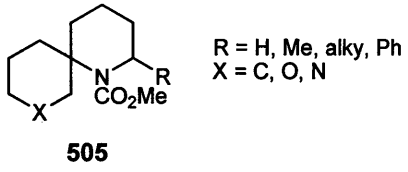
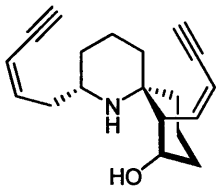


Figure 4.15. Possible *spiro*-piperidines

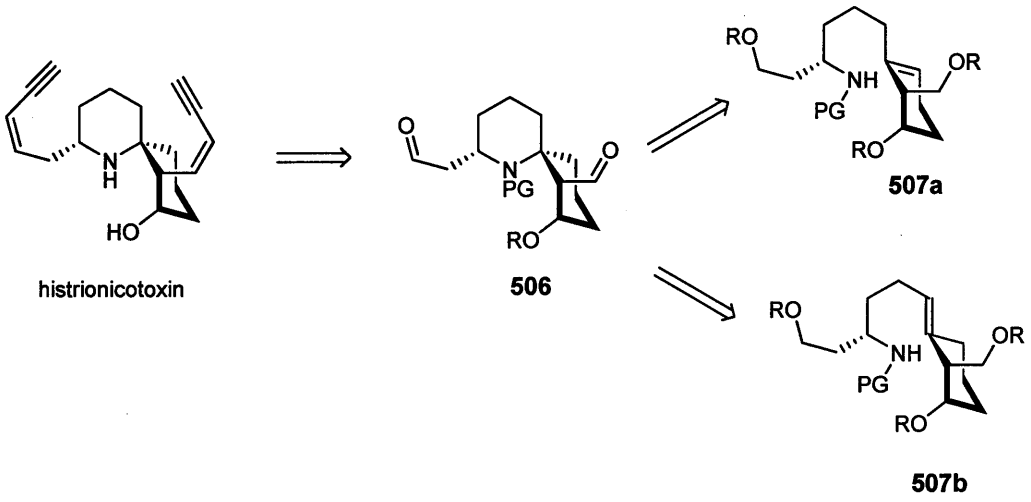
If this can all be conducted successfully, as has been suggested by Jackson[270,271] then the synthesis of a natural product should be attempted, such as the *spiro*-piperidine histrionicotoxin (Figure 4.16).



histrionicotoxin

Figure 4.16. Structure of histrionicotoxin

Retrosynthetic analysis of this compound shows that the *spiro*-piperidine core of the compound could be generated by acid-catalysed hydroamination. The location of the double bond is ambigous as either regioismer **507a** or **507b** would hopefully give the desired *spiro*-piperidine **506** (Scheme 4.32). The nature of the protecting group would need further investigations.



Scheme 4.32. Retrosynthetic analysis of histrionicotoxin

Chapter 5

Chapter 5

Experimental

6.1. General Details

All non-aqueous reactions were, unless otherwise stated, conducted using oven or flame-dried glassware and under an atmosphere of dry nitrogen. Reactions conducted at "-78°C" were cooled using an acetone-solid carbon dioxide bath. The triflic acid (TFOH) used in all cyclisation reaction was made as 0.695 M stock solution in dichloromethane. Reactions conducted at "0°C" were cooled using an ice-water bath. Heated reactions were conducted in a stirred oil bath heated on a hotplate. Unless otherwise stated, reactions were stirred magnetically. Dry tetrahydrofuran was obtained by fresh distillation from sodium wire and a benzophenone indicator. Dry dichloromethane was obtained by fresh distillation from calcium hydride. All other dry solvents were obtained commercially from Fisher Scientific Ltd. Silica gel chromatography and filtration was performed using Matrex Silica (35-70 μm). All reactions were monitored by tlc, using Merck silica gel 60 F254 pre-coated aluminium-backed plates and were visualised using ultraviolet light, potassium permanganate or ammonium molybdate. All melting points (mp °C) were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infrared Spectrometer, as nujol mulls on sodium chloride plates [nujol], as liquid films on sodium chloride plates [film] or as a solution in dichloromethane [DCM]. Unless otherwise stated, NMR spectra were recorded on a Bruker DPX 400 instrument with proton (^{1}H) NMR spectra recorded at 400 MHz and ^{13}C spectra recorded at 100 MHz. Proton (^{1}H) NMR spectra recorded at 500 MHz and ^{13}C spectra recorded at 125 MHz were obtained using a Bruker DRX500 instrument. Unless otherwise stated, spectra were obtained from dilute solutions in deuteriochloroform and at 298 K. Abbreviations used for the multiplicities are: singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent.), septet (sept.), unresolved multiplet (m) or combinations thereof. Apparent (app.) refers to overlapping peaks appearing to display a given multiplicity. Chemical shifts are reported relative to residual, undeuterated solvent (*e.g.* residual chloroform, 7.27 ppm in proton NMR). Mass spectra were recorded on a Fisons VG Platform II Mass Spectrometer using atmosphere pressure chemical ionisation [APCI]. Accurate high resolution mass spectral data were obtained at Cardiff University, using a Micromass Q-ToF Micromass Mass Spectrometer. "Evaporated" refers to solvent removal using a Buchi rotary evaporator with water pump vacuum and water bath at 25°C. Reactions performed in a microwave, were performed in a CEM Discover Microwave.

6.2. General Procedures

General Procedure A: Mitsunobu Reaction

Triphenylphosphine (1.2 eq.) was added to tetrahydrofuran (50 ml per mmol), cooled to 0 °C under N_2 and stirred for 10 min. Diisopropyl azodicarboxylate (1.01 eq.) was added and the solution stirred for 15 minutes after which it turned milky-white. Alcohol (1.0 eq.) was added and stirred for 20 min, followed by *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide or *N*-hydroxyphthalimide (1.01 eq.). The reaction mixture was allowed to warm slowly to room temperature over night; and the solvent was then evaporated.

Work up *1*:[272] The residue was dissolved in a minimum amount of dichloromethane (5 ml), filtered through silica and the silica, washed with dichloromethane (500 ml). The solution was reduced in volume to 200 ml and washed the solution with 15 wt. % hydrogen peroxide in water (40 ml). The two layers were separated and the organic layer washed with saturated aqueous sodium sulphite (30 ml) to neutralise excess hydrogen peroxide. The organic layer was dried over Na_2SO_4 and the solvent was evaporated.

Work up *2*: The residue was dissolved in dichloromethane (15 ml) and washed with 15 wt. % hydrogen peroxide in water (40 ml). The two layers were separated and the organic layer washed with saturated aqueous sodium sulphite (30 ml) to neutralise excess hydrogen peroxide. The organic layer was dried over Na_2SO_4 and the solvent was evaporated.

General Procedure B: Preparation of Sulfonamides from Phthalimide

Phthalimide (1.0 eq.) was dissolved in ethanol (10 ml mml^{-1}), to which was added hydrazine monohydrate (1 eq.) and the mixture was heated at 60 °C for 2 hours. The reaction mixture was cooled to room temperature, dried over $MgSO_4$ and evaporated to give the hydroxylamine, which was used in the next step without purification.

The hydroxylamine (1.0 eq.) was dissolved in dichloromethane (1 ml mml^{-1}) and cooled to –78 °C. Triethylamine (1.01 eq.) was added, followed by DMAP (a few crystals) and *p*-toluenesulphonyl chloride (1.0 eq.). The reaction was allowed to warm to room temperature over night. The reaction mixture was extracted with water (3 × 30 ml) and the combined organic layers washed with copper sulfate (30 ml), water (2 × 30 ml), dried over $NaSO_4$ and evaporated.

Genreal Procedure C: Tosylation of Amines

The amine (1.0 eq.) was dissolved in dichloromethane (1 ml $mmol^{-1}$) and cooled to –78 °C. Triethylamine (1.01 eq.) was added, followed by DMAP (a few crystals) and *p*-toluenesulphonyl chloride (1.0 eq.). The reaction was allowed to warm to room temperature over night. The reaction

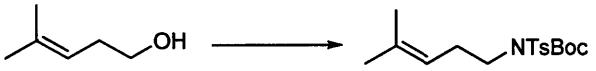
mixture was extracted with water (3 × 30 ml), 2M HCl (2 × 30 ml) and 2M NaOH (2 × 30 ml), then dried over Na_2SO_4 and evaporated.

General Procedure D: Suzuki Reaction

Sulfonamide (1.0 eq.) and vinylboronic acid or pinacol ester (1.3 eq.) were suspended in a 1:1 mixture of water and ethanol (3 ml per 100 mg of sulfonamide). To this suspension was then added the Suzuki premix (0.544 wt% $Pd(OAc)_2$, 1.11 wt% dtbpf and 98.4 wt% K_3PO_4) (0.425 g per 100 mg of sulfonamide) and the reaction placed in the microwave at 100W, 100 °C for 30 minutes. The cooled mixture was then extracted with diethyl ether (3 x 15 ml), and the combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and evaporated.

6.3. Experimental Data

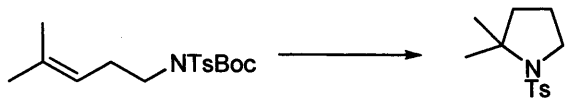
***tert*-Butyl 4-methylpent-3-enyl(tosyl)carbamate 149a**



148 **149a**

4-Methyl-3-penten-1-ol **148** (0.58 ml, 4.99 mmol, 1.0 eq.) was reacted with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.37 g, 5.04 mmol, 1.01 eq.) following general procedure **A** using work up ***1***. The crude product was recrystallised from diethyl ether to give *the title compound* **149a** as a white solid (741 mg, Yield: 42%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.71 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.22 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.10 - 5.04 (m, 1H, C*H*), 3.74 - 3.68 (m, 2H, CH_2N), 2.38 - 2.35 (m, 5H, Ts CH_3 & CH_2), 1.65 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.27 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 151.3 (C_q), 143.9 (C_q), 137.6 (C_q), 135.0 (C_q), 129.2 (2 × Ts *C*H), 127.8 (2 × Ts *C*H), 119.8 (*C*H), 84.0 (C_q), 46.7 (*C*H_2N), 29.0 (*C*H_2), 27.9 (Boc C(*C*H_3)$_3$), 25.8 (*C*H_3), 21.6 (Ts *C*H_3), 17.8 (*C*H_3). IR (neat) υ/cm^{-1}: 2981, 1717, 1456, 1380, 1132, 986, 864. HRMS (EI) *m/z* calcd. for $C_{14}H_{19}NO_4S$ [M-C_4H_8]$^+$ = 297.1035; found 297.1042.

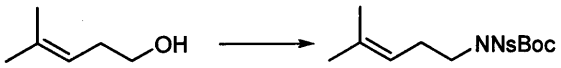
2,2-Dimethyl-1-tosylpyrrolidine 150a



149a **150a**

A solution of *tert*-butyl 4-methyl-3-enyl(tosyl)carbamate **149a** (741 mg, 20.90 mmol, 1.0 eq.) in dichloromethane (20 ml) was cooled to 0 °C for 5 minutes, after which triflic acid (1.50 ml, 10.45 mmol, 0.5 eq.) was added and the resulting solution stirred for 2.5 hours. The solution was quenched with saturated aqueous $NaHCO_3$ solution (10 ml), and the products extracted into dichloromethane (3 × 10 ml). The organic extracts were washed with water (3 × 30 ml), then dried over $MgSO_4$ and evaporated to give *the title compound* **150a** as a colourless solid (0.504 g, Yield: 95%). All data obtained was in accordance with that previously reported in the literature.[273] m.p.: 68 - 70 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.67 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.20 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.31 (t, 2H, J = 6.5 Hz, CH_2N), 2.34 (s, 3H, Ts CH_3), 1.76 - 1.67 (m, 4H, 2 × CH_2), 1.36 (s, 6H, 2 × CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 132.2 (C_q), 132.0 (C_q), 129.4 (2 × Ts *C*H), 127.1 (2 × Ts *C*H), 65.1 (C_q), 49.3 (CH_2), 42.9 (CH_2), 28.3 (2 × CH_3), 22.5 (CH_2), 21.5(Ts CH_3). IR (nujol) υ/cm^{-1}: 2926, 1331, 1151, 1093, 1010, 871, 811, 711, 677, 643. HRMS (EI) *m/z* calcd. for $C_{13}H_{19}NO_2S$ $[M]^+$ = 253.1136; found 253.1134.

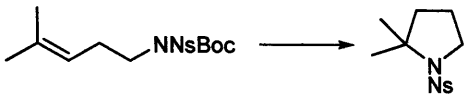
tert-Butyl 4-methylpent-3-enyl(2-nitrophenylsulfonyl)carbamate 149b



148 **149b**

4-Methyl-3-penten-1-ol **148** (0.58 ml, 4.99 mmol, 1.0 eq.) was reacted with *tert*-butyl-2-nitrophenylsulfonylcarbamate (1.53 g, 5.04 mmol, 1.01 eq.) following general procedure **A** using work up ***1***. The crude product was recrystallised from diethyl ether to give *the title compound* **149b** as a yellow oil (0.762 g, Yield: 40%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.25 - 8.22 (m, 1H, Ns, C*H*), 7.68 - 7.64 (m, 3H, 3 × Ns C*H*), 5.11 - 5.06 (m, 1H, C*H*), 3.69 - 3.64 (m, 2H, CH_2N), 2.38 - 2.32 (m, 2H, CH_2), 1.66 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.32 (s, 9H, Boc $C(CH_3)_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 150.5 (C_q), 135.2 (C_q), 134.0 (Ns *C*H) 133.3 (2 × Ns *C*H), 131.7 (C_q), 124.3 (Ns *C*H), 119.6 (*C*H), 84.9 (C_q), 47.7 (CH_2N), 29.0 (CH_2), 27.8 (Boc $C(CH_3)_3$), 25.8 (CH_3), 17.8 (CH_3). IR (neat) υ/cm^{-1}: 2981, 1717, 1456, 1380, 1350, 1132, 986, 750. HRMS (EI) *m/z* calcd. for $C_{13}H_{16}N_2O_6S$ $[M-C_4H_8]^+$ = 328.0729; found 328.0736.

2,2-Dimethyl-1-(2-nitrophenylsulfonyl)pyrrolidine 150b



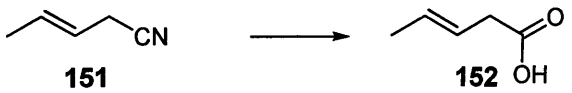
149b **150b**

A solution of *tert*-butyl 4-methylpent-3-enyl(2-nitrophenylsulfonyl)carbamate **149b** (50 mg, 0.013 mmol, 1.0 eq.) in dichloromethane (5 ml) was cooled to 0 °C for 5 minutes, after which triflic acid (1.50 ml, 10.45 mmol, 0.5 eq.) was added and the resulting solution stirred for 1.75 hours. The reaction was quenched with saturated aqueous K_2CO_3 solution (10 ml), and the products extracted into dichloromethane (3 × 30 ml). The organic extracts were washed with water (3 × 30 ml), dried over $MgSO_4$ and evaporated to give *the title compound* **150b** as a colourless solid (36 mg Yield: 97%).

A solution of *tert*-butyl 4-methylpent-3-enyl(2-nitrophenylsulfonyl)carbamate **149b** (50 mg 0.013 mmol, 1.0 eq.) in dry dichloromethane (5 ml) was cooled to 0 °C for 5 minutes, after which concentrated sulfuric acid (2 drops) was added and the resulting solution stirred 1.75 hours. The reaction was quenched with saturated aqueous K_2CO_3 solution (10 ml), and the products extracted into dichloromethane (3 × 30 ml). The organic extracts were washed with water (3 × 30 ml), then dried over $MgSO_4$ and evaporated to give *the title compound* **150b** as a colourless solid (22 mg Yield: 60%).

Both samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.97 - 7.94 (m, 1H, Ns C*H*), 7.61 - 7.57 (m, 1H, 2 × Ns C*H*), 7.52 - 7.48 (m, 1H, Ns C*H*), 3.45 (t, 2H, J = 6.8 Hz, CH_2N), 1.87 - 1.75 (m, 4H, 2 × CH_2), 1.36 (s, 6H, 2 × CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 148.5 (C_q), 135.0 (C_q), 133.2 (Ns *C*H), 131.4 (Ns *C*H), 130.2 (Ns *C*H), 123.8 (Ns *C*H), 66.2 (C_q), 50.0 (CH_2N), 42.7 (CH_2), 27.6 (2 × CH_3), 22.0 (CH_2). IR (neat) υ/cm^{-1}: 2970, 1545, 1456, 1380, 1350, 750. HRMS (APCI) *m/z* calcd. for $C_{12}H_{17}N_2O_4S$ $[M+H]^+$ = 285.0909; found 285.0897.

(*E*)-Pent-3-enoic acid 152[121]

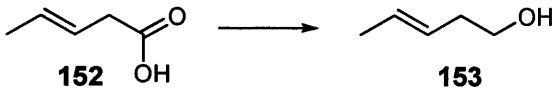


151 **152**

30 wt. % hydrogen peroxide (13.00 ml, 125 mmol, 2.6 eq.) was added dropwise over 20 minutes to a stirred solution of *trans*-3-pentenitrile **151** (5.00 ml, 48.6 mmol, 1.0 eq.) in 3 M aqueous NaOH (41.60 ml, 125 mmol, 2.6 eq.). The reaction mixture was heated to 80 °C for 2 hours and

then stirred for a further hour at room temperature. The solution was washed with diethyl ether (30 ml), which was discarded. The aqueous solution was cooled to 0 °C and the pH adjusted to 4 - 5 with 6 M HCl. The suspension was extracted with diethyl ether (3 × 30 ml) and the combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated to give *the title compound* **152** as a yellow oil (2.075 g, Yield: 43%). All data obtained was in accordance with that previously reported in the literature.[121] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.68 - 5.50 (m, 2H, 2 × C*H*), 3.09 (d, 2H, J = 6.8 Hz, CH_2), 1.64 (d, 3H, J = 2.9 Hz, CH_3).

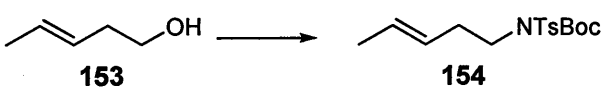
(*E*)-Pent-3-en-1-ol 153[121]



152 **153**

A solution of (*E*)-pent-3-enoic acid **152** (2.08 g, 2.08 mmol, 1.0 eq.) in diethyl ether (30 ml) was added dropwise to a stirred ice-cooled suspension of $LiAlH_4$ (945 mg, 2.49 mmol, 1.3 eq.) in diethyl ether (30 ml) over 20 minutes and then stirred at room temperature for 1 hour. Water (10 ml) was added carefully and the mixture was poured into ice-diluted H_2SO_4. The solution was extracted with diethyl ether (3 × 30 ml), the ether extracts were washed with water (30 ml) and brine (30 ml), then dried over $MgSO_4$ and concentrated *in vacuo* to give *the title compound* **153** as an orange oil (1.40 g, Yield: 78%). All data obtained was in accordance with that previously reported in the literature.[121] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.62 - 5.53 (m, 2H, 2 × C*H*), 3.63 (t, 2H, J = 6.3 Hz, CH_2O), 2.29 - 2.23 (m, 2H, CH_2), 1.69 (d, 3H, J = 6.3 Hz, CH_3).

(*E*)-*tert*-Butyl pent-3-enyl(tosyl)carbamate 154

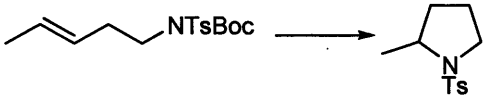


153 **154**

(*E*)-Pent-3-en-1-ol **153** (990 mg, 11.4 mmol, 1.0 eq.) was reacted with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (3.14 g, 11.6 mmol, 1.01 eq.) according to general procedure **A** using work up *2*. The crude product was purification by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **154** as a white solid (1.95 g, Yield 50%). All data obtained was in accordance with that previously reported in the literature.[274] m.p.: 45 - 48 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.72 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.23 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.51 - 5.43 (m, 1H, C*H*), 5.38 - 5.29 (m, 1H, C*H*), 3.73 - 3.69 (m, 2H, CH_2N), 2.37 (s, 3H, Ts

CH_3), 1.59 (dd, 2H, J = 1.2Hz , 6.3 Hz, CH_2), 1.27 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 153.8 (C_q), 141.4 (C_q), 139.6 (C_q), 129.4 (2 × Ts *C*H), 127.8 (*C*H), 127.0 (*C*H), 126.0 (2 × Ts *C*H), 82.0 (C_q), 42.0 (CH_2N), 28.9 (CH_2), 21.8 (Boc C(CH_3)$_3$), 21.4 (Ts CH_3), 14.2 (CH_3). IR (neat) υ/cm^{-1}: 2979, 2935, 2361, 1729, 1452, 1356, 1288, 1258, 1160, 1089, 971. HRMS (ES) *m/z* calcd. for $C_{17}H_{29}N_2O_4S$ $[M+NH_4]^+$ = 357.1848; found 357.1833.

2-Methyl-1-tosylpyrrolidine 155



154 **155**

(*E*)-*tert*-Butyl pent-3-enyl(tosyl)carbamate **154** (64 mg 0.19 mmol, 1.0 eq.) was dissolved in dichloromethane (5 ml), to which was added triflic acid (0.10 ml, 0.09 mmol, 0.5 eq.). The resultant solution was heated to 40 °C for 48 hours, cooled to room temperature and quenched with saturated aqueous K_2CO_3 (15 ml). The two layers were separated, the aqueous layer was extracted with dichloromethane (2 × 15 ml), the combined organic layers were dried over K_2CO_3 and concentrated to give *the title compound* **155** as a white solid (41 mg Yield: 91%). All data obtained was in accordance with that previously reported in the literature.[275] m.p.: 84 - 87 °C.^{1}H NMR (400 MHz / $CDCl_3$) δ 7.65 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.24 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 3.67 - 3.60 (m, 1H, C*H*N), 3.42 - 3.32 (m, 1H, CH_AH_BN), 3.11 - 3.04 (m, CH_AH_BN), 2.36 (s, 3H, Ts CH_3), 1.85 - 1.69 (m, 1H, CH_CH_D), 1.68 - 1.56 (m, 1H, CH_CH_D), 1.52 - 1.35 (m, 2H, CH_2), 1.25 (d, 3H, J = 6.3 Hz, CH_3), ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.2 (C_q), 134.8 (C_q), 129.6 (2 × Ts *C*H), 127.4 (2 × Ts *C*H), 56.1 (*C*H), 49.1 (CH_2N), 33.5 (CH_2), 23.9 (CH_2), 22.9 (CH_3), 21.6 (Ts CH_3). HRMS (APCI) *m/z* calcd. For $C_{12}H_{18}NO_2S$ $[M+H]^+$ = 240.1058; found 240.1070.

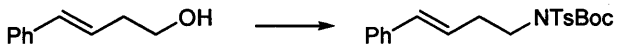
(*E*)-4-Phenylbut-3-en-1-ol 157[276]

156 **157**

trans-Styrylacetic acid **156** (1.50 g, 9.25 mmol, 1.0 eq.) was dissolved in dry diethyl ether (20 ml), added to a suspension of $LiAlH_4$ (460 mg, 12.2 mmol, 1.3 eq.) in diethyl ether (40 ml) and stirred at room temperature for 1 hour. The reaction was then quenched by the slow addition of water (20 ml). The mixture was then poured into ice-diluted H_2SO_4 (20 ml), which was extracted with

diethyl ether (3 × 30 ml). The combined organic fractions were washed with water (30 ml) and brine (30 ml), dried over $MgSO_4$ and concentrated to give *the alcohol* **157** as a yellow oil (1.36 g, Yield: 99%). All data obtained was in accordance with that previously reported in the literature.[277] ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.32 - 7.11 (m, 5H, 5 × Ar C*H*), 6.43 (d, 1H, J = 15.9 Hz, C*H*), 6.14 (td, 1H J = 7.2, 15.9 Hz, C*H*), 3.76 (app. t, 2H, J = 6.3 Hz, CH_2), 2.50 - 2.35 (m, 2H, CH_2O), 1.77 (br. s, 1H, O*H*). ^{13}C NMR (500 MHz / $CDCl_3$) δ 137.7 (C_q), 132.9 (Ar *C*H), 128.6 (2 × Ar *C*H), 127.3 (*C*H), 126.4 (*C*H), 126.1 (2 × Ar *C*H), 62.0 (CH_2O), 36.5 (CH_2). IR (neat) υ/cm^{-1}: 3375, 3026, 2934, 1721, 1598, 1462, 1115, 965, 750, 690. HRMS (EI) *m/z* calcd. for $C_{10}H_{10}O$ $[M-H_2]^+$ = 146.0732; found 146.0731.

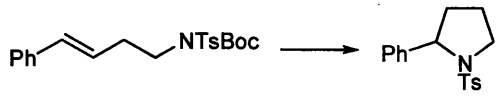
(*E*)-*tert*-Butyl 4-phenylbut-3-enyl(tosyl)carbamate 158



157 **158**

(*E*)-4-Phenylbut-3-en-1-ol **157** (1.37 g, 9.25 mmol, 1.0 eq.) was reacted with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (2.50 g, 9.34 mmol, 1.01 eq.) according to general procedure **A** using work up ***2***. The crude product was purification by flash column chromatography (elitung silica gel with dichloromethane) to give *the sulfonamide* **158** as a colourless oil (889 mg, Yield: 24%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.79 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.38 - 7.18 (m, 7H, 2 × Ts C*H* & 5 × Ar C*H*), 6.51 - 6.43 (m, 1H, C*H*), 6.24 - 6.14 (m, 1H, C*H*), 4.01 - 3.91 (m, 2H, CH_2N), 2.69 - 2.63 (m, 2H, CH_2), 2.42 (s, 3H Ts CH_3), 1.30 (s, 9H, Boc $C(CH_3)_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 151.0 (C_q), 144.1 (C_q), 137.4 (C_q), 137.3 (C_q), 132.6 (Ar *C*H), 129.3 (2 × Ts *C*H), 128.5 (2 × Ar *C*H), 127.9 (2 × Ts *C*H), 127.3 (*C*H), 126.1 (2 × Ar *C*H), 126.0 (*C*H), 84.3 (C_q), 46.6 (CH_2N), 34.0 (CH_2), 27.9 (Boc $C(CH_3)_3$), 21.6 (Ts CH_3). IR (neat) υ/cm^{-1}: 2980, 1733, 1597, 1462, 1152, 1100, 965, 845, 750, 690. HRMS (EI) *m/z* calcd. for $C_{22}H_{27}NO_4Na^{23}S$ $[M+Na]^+$ = 424.1559; found 424.1542.

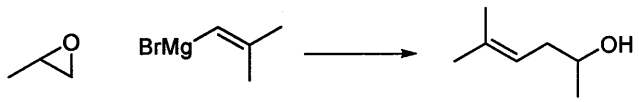
2-Phenyl-1-tosylpyrrolidine 159



158 **159**

(*E*)-*tert*-Butyl 4-phenylbut-3-enyl(tosyl)carbamate **158** (100 mg 0.25 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added triflic acid (0.20 ml, 0.13 mmol, 0.5 eq.) and the resultant solution stirred at room temperature for 48 hours. The reaction was quenched with saturated aqueous K_2CO_3. The two layers were separated and the aqueous layer extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **159** as a yellow solid (53 mg Yield: 70%). All data obtained was in accordance with that previously reported in the literature.[278] m.p: 77 - 82 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.61 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.14 - 7.25 (m, 7H, 2 × Ts C*H* & 5 × Ar C*H*), 4.72 (dd, 1H, J = 7.9, 3.6 Hz, C*H*N), 3.59 - 3.52 (m, 1H, CH_AH_BN), 3.39 - 3.31 (m, 1H, CH_ACH_BN), 2.36 (s, 3H, Ts CH_3), 1.94 - 1.86 (m, 1H, CH_ACH_B), 1.83 - 1.71 (m, 2H, CH_2), 1.63 - 1.54 (m, 1H, CH_ACH_B). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.3 (C_q), 129.6 (2 × Ts *C*H), 129.3 (C_q), 128.4 (2 × Ar *C*H), 127.5 (2 × Ts *C*H), 127.1 (C_q), 127.0 (Ar *C*H), 126.2 (2 × Ar *C*H), 63.3 (*C*HN), 49.4 (CH_2N), 31.4 (CH_2), 24.0 (CH_2), 21.6 (Ts CH_3). IR (neat) υ/cm^{-1}: 2961, 1598, 1462, 1152, 845, 750, 690. HRMS (APCI) *m/z* calcd. for $C_{17}H_{20}NO_2S$ $[M+H]^+$ = 302.1215; found 302.1228.

5-Methylhex-4-en-2-ol 166[122]



164 **165** **166**

A 0.5 M solution of 2-methyl-1-propenylmagnesium bromide **165** (35.0 ml, 17.4 mmol, 1.01 eq.) in tetrahydrofuran was cooled to –35 °C. Copper iodide (170 mg 0.86 mmol, 0.05 eq.) was introduced followed 15 minutes later by propylene oxide **164**, which was added dropwise. The resulting solution was stirred for 30 minutes, the flask was then removed from the cold bath and allowed to warm to room temperature and stirred for 45 minutes. The reaction was quenched by adding the reaction mixture into a separating funnel containing brine (100 ml) and 12 N HCl. After extracting with ethyl acetate (3 × 30 ml) the combined organic phases were dried over Na_2SO_4 to give *alcohol* **166** as a colourless oil (1.97 g, Yield: 100%). All data obtained was in accordance with that previously reported in the literature.[122] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.23 - 5.17

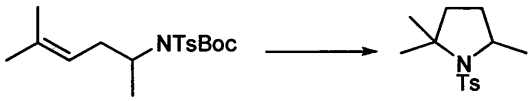
(m, 1H, C*H*), 4.14 – 4.07 (m, 1H, C*H*O), 3.67 - 3.59 (m, 1H, CH_AH_B), 3.47 – 3.43 (m, 1H, CH_AH_B), 1.72 (d, 3H, J = 1.7 Hz, CH_3), 1.62 (s, 3H, CH_3), 1.07 (d, 3H, J = 6.1 Hz, CH_3).

tert-Butyl 5-methylhex-4-en-2-yl(tosyl)carbamate 167

166 **167**

5-Methylhex-4-en-2-ol **166** (1.97 g, 17.3 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (3.52 g, 17.4 mmol, 1.01 eq.) according to general method **A** using work up *2*. The crude product was purified by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **167** as a yellow oil (3.53 g, Yield: 56%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.78 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.28 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 5.09 - 5.04 (m, 1H, C*H*), 4.52 - 4.43 (m, 1H, C*H*N), 2.71 - 2.63 (m, 1H, CH_AH_B), 2.43 (s, 3H, Ts CH_3), 2.34 - 2.36 (m, 1H, CH_AH_B), 1.67 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.46 (d, 3H, J = 6.9 Hz, CH_3), 1.36 (Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 150.7 (C_q), 143.6 (C_q), 138.2 (C_q), 134.2 (C_q), 129.1 (2 × Ts *C*H), 127.7 (2 × Ts *C*H), 121.3 (*C*H), 83.8 (C_q), 55.6 (*C*H), 29.6 (*C*H$_2$), 28.0 (Boc C(*C*H$_3$)$_3$), 25.8 (*C*H$_3$),19.7 (*C*H$_3$), 17.9 (*C*H$_3$). IR (neat) υ/cm^{-1}: 2977, 1733, 1598, 1462, 1152, 1100, 965, 845. HRMS (EI) *m/z* calcd. for $C_{19}H_{30}NO_4S$ $[M+H]^+$ = 368.1896; found 368.1905.

2,2,5-Trimethyl-1-tosylpyrrolidine 162



167 **162**

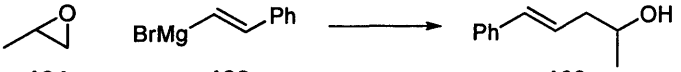
The sulfonamide **167** (100 mg 0.27 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added triflic acid (0.20 ml, 0.17 mmol, 0.5 eq.) and stirred at 0 °C for 3.5 hours. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 ml). The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 30 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **162** as a colourless oil (48 mg Yield: 66%).

The sulfonamide **167** (125 mg 0.34 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops) and stirred at 0 °C for 4 hours. The reaction

was quenched by the addition of saturated aqueous K_2CO_3 (15 ml). The two layers were separated, the aqueous layer extracted with dichloromethane (2 × 30 ml), the combined organic layers dried over K_2CO_3 and concentrated to give *the title compound* **162** as a colourless oil (71 mg Yield: 78%).

Both samples show identical spectroscopic and analytical data. All data obtained was in accordance with that previously reported in the literature.[279] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.26 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.97 - 3.91 (m, 1H, C*H*N), 2.41 (s, 3H, Ts CH_3), 2.04 - 1.87 (m, 2H, CH_2), 1.71 - 1.67 (m, 1H, CH_ACH$_B$), 1.58 (s, 3H, CH_3), 1.48 - 1.43 (m, 1H, CH$_A$$H_B$), 1.33 (s, 3H, C$H_3$), 1.21 (d, 3H, J = 6.4 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.5 (C_q), 139.9 (C_q), 129.3 (2 × Ts *C*H), 127.3 (2 × Ts *C*H), 66.2 (C_q), 57.6 (*C*HN), 40.6 (*C*H$_2$), 31.4 (*C*H$_3$), 30.3 (*C*H$_2$), 26.8 (*C*H$_3$), 22.7 (*C*H$_3$), 21.5 (Ts *C*H$_3$). IR (neat) υ/cm^{-1}: 2968, 1728, 1599, 1462, 1152, 845. HRMS (EI) *m/z* calcd. for $C_{14}H_{21}NO_2S$ $[M]^+$ = 267.1293; found 267.1296.

(*E*)-5-Phenylpent-4-en-2-ol 169[122]

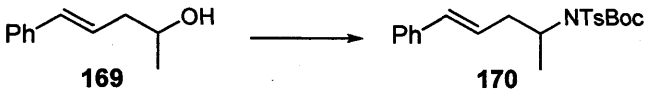


164 **168** **169**

A 0.5 M solution of (*E*)-styrylmagnesium bromide **168** was formed by the following method: Magnesium fillings (400 mg, 16.4 mmol, 1.0 eq.) were stirred under nitrogen for 24 hours and then suspended in tetrahydrofuran (33 ml). This suspension was treated with a crystal of iodine and β-bromostyrene (2.10 ml, 16.4 mmol, 1.0 eq.) and the suspension was stirred vigorously until decolourisation was observed. Copper iodide (160 mg 0.81 mmol, 0.05 eq.) was added to the freshly prepared grignard reagent **168** (1.01 eq.) at -30 °C, followed 15 minutes later by the dropwise addition of propylene oxide **164** (1.10 ml, 16.2 mmol, 1.0 eq.). After 30 minutes the reaction was allowed to warm to room temperature and stirred for a further 45 minutes. The reaction was quenched by pouring the reaction mixture into a separating funnel containing brine (100 ml) and 12 N HCl. After extracting with ethyl acetate (3 × 30 ml) the combined organic phases were dried over Na_2SO_4. The crude product was purified by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **169** as a yellow oil (1.32 g, Yield: 48%). All data obtained was in accordance with that previously reported in the literature.[280] ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.38 - 7.20 (m, 5H, 5 × Ar C*H*), 6.48 (d, 1H, J = 15.8, C*H*), 6.23 (app. dd, 1H, J = 6.2, 15.8 Hz, C*H*), 3.96 - 3.89 (m, 1H, C*H*O), 2.45 - 2.30 (m, 2H, CH_2), 1.25 (d, 3H, J = 6.2 Hz, CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 137.3 (C_q), 133.3 (Ar *C*H),

128.6 (2 × Ar *C*H), 127.3 (*C*H), 126.3 (*C*H), 126.1 (2 × Ar *C*H), 67.4 (*C*HO), 43.0 (CH_2), 22.9 (CH_3). IR (neat) υ/cm^{-1}: 3054, 1719, 1446, 1380, 965, 750, 690. HRMS (EI) *m/z* calcd. for $C_{11}H_{14}O$ $[M]^+$ = 162.1045; found 162.1041.

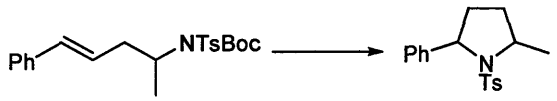
(*E*)-*tert*-Butyl 5-phenylpent-4-en-2-yl(tosyl)carbamate 170



169 **170**

(*E*)-5-Phenylpent-4-en-2-ol **169** (1.32 g, 8.2 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.70 g, 8.25 mmol, 1.01 eq.) according to general method **A** using work up *2*. The crude product was purified by flash column chromatography (eluting silica gel with 20% ethyl acetate in hexanes) to give *the title compound* **170** as a colourless oil (1.39 g, Yield: 41%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.73 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.35 - 7.20 (m, 5H, 5 × Ar C*H*), 7.07 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 6.39 (d, 1H, J = 15.6 Hz, C*H*), 6.05 (app. dd, 1H, J = 6.2, 15.6 Hz, C*H*), 4.75 - 4.66 (m, 1H, C*H*N), 2.96 - 2.87 (m, 1H, CH_AH_B), 2.60 - 2.52 (m, 1H, CH_AH_B), 2.34 (s, 3H, Ts CH_3), 1.53 (d, 3H, J = 6.2 Hz, CH_3), 1.36 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 157.2 (C_q), 143.7 (C_q), 137.7 (C_q), 136.8 (C_q), 129.7 (2 × Ts *C*H), 129.1 (2 × Ar *C*H), 128.5 (2 × Ar *C*H), 127.8 (2 × Ts *C*H), 127.2 (*C*H), 127.1 (Ar *C*H), 124.9 (*C*H), 84.0 (C_q), 40.6 (*C*H), 38.3 (CH_2), 28.0 (Boc C(CH_3)$_3$), 21.8 (Ts CH_3), 20.0 (CH_3). IR (neat) υ/cm^{-1}: 2979, 1786, 1725, 1598, 1446, 1380, 1135, 1112, 965, 827, 750, 690. LRMS (ES) 433.16 ($M+NH_4^+$, 47%), 438.18 ($M+Na^+$, 90%), 479.20 ($M+MeCNNa^+$, 100%).

2-Methyl-5-phenyl-1-tosylpyrrolidine 163



170 **163**

The sulfonamide **170** (100 mg 0.24 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added triflic acid (0.20 ml, 0.12 mmol, 0.5 eq.) and stirred at 0 °C for 4 hours. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 ml). The two layers were separated, the aqueous layer was extracted with dichloromethane (2 × 30 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **163** as a colourless oil (50 mg Yield: 66%).

The sulfonamide **170** (100 mg 0.24 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops) and stirred at 0 °C for overnight. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 ml). The two layers were separated, the aqueous layer was extracted with dichloromethane (2 × 30 ml), the combined organic layers were dried over K_2CO_3 and evaporated to give *the title compound* **163** as a colourless oil (75 mg Yield: 99%).

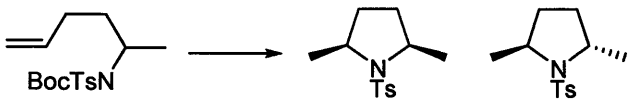
Both samples show identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.73 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.39 - 7.23 (m, 7H, 5 × Ar C*H* & 2 × Ts C*H*), 4.74 - 4.68 (m, 1H, C*H*N), 3.96 - 3.89 (m, 1H, C*H*N), 2.43 (s, 3H, Ts CH_3), 1.90 - 1.65 (m, 4H, 2 × CH_2), 1.26 (d, 3H, J = 6.4 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 141.7 (C_q), 140.7 (C_q), 137.8 (C_q), 129.7 (2 × Ts *C*H), 128.5 (2 × Ar *C*H), 127.1 (2 × Ts *C*H), 126.2 (2 × Ar *C*H), 124.9 (Ar *C*H), 50.1 (*C*H), 49.6 (*C*H), 40.6 (*C*H_2), 31.7 (*C*H_2), 21.8 (*C*H_3), 21.6 (Ts *C*H_3). IR (neat) υ/cm^{-1}: 2966, 1785, 1599, 1446, 1380, 1135, 827, 750, 690. HRMS (EI) *m/z* calcd. for $C_{18}H_{21}NO_2S$ $[M]^+$ = 315.1293; found 315.1303.

***tert*-Butyl hex-5-en-2-yl(tosyl)carbamate 172**

173 **172**

5-Hexen-2-ol **173** (1.00 g, 9.99 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (2.70 g, 10.1 mmol, 1.01 eq.) according to general method **A** using work up *2*. The crude product was purified by flash column chromatography (eluting the silica gel with 30% ethyl acetate in hexanes) to give *the title compound* **172** as a clear oil (2.63 g, Yield: 75%). Compound reported in the literature but not spectroscopic data given.[281] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.81 (d, 2H, J = 7.6 Hz, 2 × Ts C*H*), 7.31 (d, 2H, J = 7.6 Hz, 2 × Ts C*H*), 5.91 - 5.79 (m, 1H, C*H*), 5.10 - 4.97 (m, 2H, CH_2), 4.64 - 4.54 (m, 1H, C*H*N), 2.45 (s, 3H, Ts CH_3), 2.14 - 2.03 (m, 2H, CH_2), 1.86 - 1.75 (m, 2H, CH_2), 1.46 (d, 3H, J = 6.6 Hz, CH_3), 1.37 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 150.8 (C_q), 143.8 (C_q), 137.9 (C_q), 137.8 (*C*H), 129.2 (2 × Ts *C*H), 127.8 (2 × Ts *C*H), 115.1 (*C*H_2), 84.0 (C_q), 55.0 (*C*H), 34.2 (*C*H_2), 31.2 (*C*H_2), 28.0 (Boc C(*C*H_3)$_3$), 21.7 (Ts *C*H_3), 19.7 (*C*H_3). IR (neat) υ/cm^{-1}: 2978, 1729, 1641, 1598, 1462, 1380, 1145, 1100, 828. HRMS (EI) *m/z* calcd. for $C_{14}H_{19}NO_2S$ $[M\text{-}C_4H_8]^+$ = 297.1035; found 297.1039.

(2*S*,5*R*)-2,5-Dimethyl-1-tosylpyrrolidine (cis) **174a** **&** **(2*S*,5*S*)-2,5-dimethyl-1-tosylpyrrolidine** (trans) **174b**



172 **174a** **174b**

The sulfonamide **172** (100 mg, 0.28 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml) and cooled 0 °C, to which was added TfOH (0.20 ml, 0.14 mmol, 0.5 eq.). The resultant solution was heated to 40 °C for 12 hours. The reaction mixture was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), dried the combined organic layers over K_2CO_3 and evaporated to give *pyrrolidines* **174** as a clear oil (71 mg, Yield: 99%). **C*is* : *trans* 1.0 : 3.0**

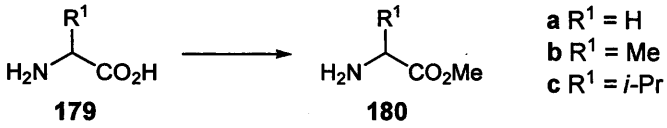
The sulfonamide **172** (100 mg, 0.28 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml) and cooled 0 °C, to which was added TfOH (0.20 ml, 0.14 mmol, 0.5 eq.). The resultant solution was heated to 40 °C for 12 hours. The reaction mixture was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), dried the combined organic layers over K_2CO_3 and evaporated to give *pyrrolidines* **174** as a clear oil (63 mg, Yield: 88%). ***Cis* : *trans* 1.0 : 3.0**

The sulfonamide **172** (100 mg, 0.28 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml) and cooled 0 °C, to which was added concentrated sulfuric acid (2 drops). The resultant solution was heated to 40 °C for 12 hours. The reaction mixture was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), dried the combined organic layers over K_2CO_3 and evaporated to give *pyrrolidines* **174** as a clear oil (63 mg, Yield: 88%). ***Cis* : *trans* 1.0 : 1.0**

See Table 2.1 on p. 31 for more details. All data obtained was in accordance with that previously reported in the literature.[282] All samples show identical spectroscopic and analytical data: m.p.: 99 - 102 °C. ^{1}H NMR (500 MHz / $CDCl_3$) *trans* isomer: δ 7.67 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.19 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.03 - 3.91 (m, 2H, 2 × C*H*N), 2.34 (s, 3H, Ts CH_3), 2.18 - 2.04 (m, 2H, CH_2), 1.46 - 1.41 (m, 2H, CH_2), 1.12 (d, 6H, J = 6.4 Hz, 2 × CH_3); *cis* isomer: δ 7.65 (d, 2H, J = 8.0 Hz, 2 × Ts C*H*), 7.23 (d, 2H, J = 8.0 Hz, 2 × Ts C*H*), 3.64 - 3.57 (m, 2H, 2 × C*H*N), 2.35 (s, 3H, Ts CH_3), 1.54 - 1.47 (m, 2H, CH_2), 1.46 - 1.41 (m, 2H, CH_2), 1.27 (d, 6H, J = 6.4 Hz, 2 × CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) *trans* isomer: δ 142.6 (C_q), 139.8 (C_q), 129.4 (2 × Ts *C*H), 127.0 (2 × Ts C*H*), 56.2 (2 × *C*HN), 31.2 (2 × CH_2), 23.7 (2 × CH_3), 21.3 (Ts CH_3); *cis* isomer: δ 143.1 (C_q), 135.3 (C_q), 129.6 (2 × Ts *C*H), 127.5 (2 × Ts *C*H), 57.6 (2 × *C*HN), 32.0

(2 × CH_2), 21.49 (2 × CH_3), 21.45 (Ts CH_3). IR (neat) υ/cm^{-1}: 2972, 1599, 1462, 1380, 1145, 828. HRMS (EI) *m/z* calcd. for $C_{13}H_{11}NSO_2$ [M] = 253.1137; found 253.1141.

Preparation of methyl esters 180 [126]



a R^1 = H
b R^1 = Me
c R^1 = *i*-Pr

The amino acid **179** (1.0 eq.) was suspended in methanol (1 ml mmol^{-1} of amino acid) and cooled to 0 °C. Thionyl chloride (1.5 eq.) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The solvent was evaporated to give *the amino acid methyl ester* **180**. All data obtained was in accordance with that previously reported in the literature.[126]

(R^1 = H) Methyl 2-aminoacetate 180a

Glycine **179a** (4.00 g, 53.0 mmol, 1.0 eq.) gave *the title compound* **180a** as a white solid (4.75 g, Yield: 100%). ^{1}H NMR (400 MHz / CD_3OD) δ 3.78 (s, CH_2N), 3.68 (s, 3H, CH_3).

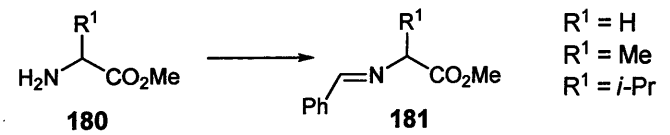
(R^1 = Me) Methyl 2-aminopropanoate 180b

Alanine **179b** (4.00 g, 44.9 mml, 1.0 eq.) gave *the title compound* **180b** as a clear oil (4.09 g, Yield: 100%). ^{1}H NMR (400 MHz / CD_3OD) δ 4.06 (q, 1H, J = 7.3 Hz, CH) 3.68 (s, 3H, CH_3) 1.41 (d, 3H, J = 7.3 Hz, CH_3).

(R^1 = *i*-Pr) Methyl 2-amino-3-methylbutanoate 180c

Valine **179c** (4.00 g, 34.2 mmol, 1.0 eq.) gave *the title compound* **180c** as a clear oil (4.48 g, Yield: 100%). ^{1}H NMR (400 MHz / CD_3OD) δ 3.89 (d, 1H, J = 4.7 Hz, CHN), 3.70 (s, 3H, CH_3), 2.25 - 2.16 (m, 1H, CH), 0.89 (d, 6H, J = 6.7 Hz, 2 × CH_3).

Preparation of imines 181 [126]



R^1 = H
R^1 = Me
R^1 = *i*-Pr

Amino acid methyl ester **180** (1.0 eq.) was dissolved in dichloromethane (1 ml mmol^{-1} of methyl ester); $MgSO_4$ (0.6 g g^{-1} of methyl ester) and triethylamine (2.0 eq.) are added and the resultant suspension is treated with benzaldehyde (0.95 eq.) and stirred for 30 hours. The suspension was

filtered and the solvent evaporated under reduced pressure. The residue was partitioned between water (30 ml) and ether (30 ml), the two layers were separated and the aqueous layer was further extracted with diethyl ether (2 × 30 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and the solvent evaporated to give *the imine* **181**. All data obtained was in accordance with that previously reported in the literature.[126]

(R^1 = H) (*E*)-Methyl 2-(benzylideneamino)acetate 181a

Methyl ester **180a** (4.75 g, 53.0 mmol, 1.0 eq.) gave *the title compound* **181a** as a colourless oil (5.83 g, Yield: 62%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 8.26 (br. s, 1H, C*H*N), 7.79 - 7.72 (m, 2H, 2 × Ar C*H*), 7.43 - 7.38 (m, 3H, 3 × Ar C*H*), 4.39 (s, 2H, CH_2N), 3.75 (s, 3H, CH_3).

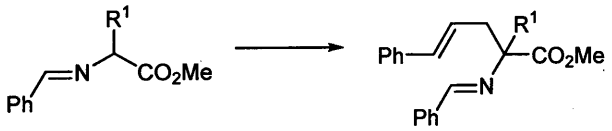
(R^1 = Me) (*E*)-Methyl 2-(benzylideneamino)propanoate 181b

Methyl ester **180b** (4.08 g, 44.9 mmol, 1.0 eq.) gave *the title compound* **181a** as a colourless oil (5.66 g, Yield: 65%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.29 (br. s, 1H, C*H*N), 7.79 - 7.76, (m, 2H, 2 × Ar C*H*), 7.43 - 7.37 (m, 3H, 3 × Ar C*H*), 4.15 (q, 1H, J = 6.9 Hz, C*H*), 3.72 (s, 3H, CH_3), 1.52 (d, 3H, J = 6.9 Hz, CH_3).

(R^1 = *i*-Pr) (*E*)-Methyl 2-(benzylideneamino)-3-methylbutanoate 181c

Methyl ester **180a** (4.474 g, 34.2 mmol, 1.0 eq.) gave *the title compound* **181a** as a colourless oil (3.19 g, Yield: 43%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.24 (br. s, 1H, C*H*N), 7.81 - 7.77 (m, 2H, 2 × Ar C*H*), 7.44 - 7.40 (m, 3H, 3 × Ar C*H*), 4.01 (d, 1H, J = 7.3 Hz, C*H*), 3.74 (s, 3H, CH_3), 2.44 - 2.35 (m, 1H, C*H*), 0.97 (d, 3H, J = 6.8 Hz, CH_3), 0.94 (d, 3H, J = 6.8 Hz, CH_3).

Cinnamyl Derivatives 182[119,126]



181

182a R^1 = Ph, R = H
182b R^1 = Ph, R = Me
182c R^1 = Ph, R = *i*-Pr

Lithium diisopropylamine was prepared by the dropwise addition of *n*-BuLi in hexanes (2.5 M solution in hexanes, 1.2 eq.) to a solution of diisopropylamine (1.2 eq.) in tetrahydrofuran (2 ml mmol^{-1} of diidopropylamine) at 0 °C. After 30 minutes the solution was cooled to –78 °C. A solution of the *N*-(benzlidine)amino ester **181** (1.0 eq.) in tetrahydrofuran (2 ml mmol^{-1}) was added dropwise *via* a syringe, and the resulting deep red solution was stirred for 30 minutes at –78 °C.

An solution of cinnamyl bromide (1.1 eq.) in tetrahydrofuran (1 ml $mmol^{-1}$) was added dropwise and the resulting solution stirred at –78 °C. After 1 hour the now orange solution was allowed to warm to room temperature, stirred for 1 hour, quenched with saturated aqueous ammonium chloride (4 ml $mmol^{-1}$) and diluted with ether (3 × 4 ml $mmol^{-1}$). The combined organic solutions were dried, filtered and evaporated to give *the crude imines* **182**, which were characterised by proton NMR only.

(R^1 = H) (*E*)-Methyl 2-((*E*)-benzylideneamino)-5-phenylpent-4-enoate 182a

(*E*)-Methyl 2-(benzylideneamino)acetate **181a** (3.02 g, 17.1 mmol, 1.0 eq.) gave *the title compound* **182a** as an orange oil (5.01 g, Yield: 100%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.24 (s, 1H, C*H*N), 7.82 - 7.13 (m, 10H, 10 × Ar C*H*), 6.48 (dt, 1H, J = 15.8, 6.4 Hz, C*H*), 6.43 (d, 1H, J = 15.8 Hz, C*H*), 4.06 (t, 1H, J = 6.5 Hz, C*H*N), 3.75 (s, 3H, CH_3), 2.97 - 2.73 (m, 2H, CH_2).

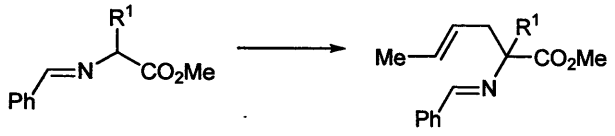
(R^1 = Me) (*E*)-Methyl 2-((*E*)-benzylideneamino)-2-methyl-5-phenylpent-4-enoate 182b

(*E*)-Methyl 2-(benzylideneamino)propanoate **181b** (1.12 g, 5.86 mmol, 1.0 eq.) gave *the title compund* **182b** as an orange oil (900 mg, Yield: 50%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.16 (s, 1H, C*H*N), 7.82 - 7.11 (m, 10H, 10 × Ar C*H*), 6.47 (dt, 1H, J = 15.8, 7.5 Hz, C*H*), 6.43 (d, 1H, J = 15.8 Hz, C*H*), 3.64 (s, 3H, CH_3), 2.73 (d, 2H, J = 7.5 Hz, CH_2), 1.45 (s, 3H, CH_3).

(R^1 = *i*-Pr) (*E*)-Methyl 2-((*E*)-benzylideneamino)-2-isopropyl-5-phenylpent-4-enoate 182c

(*E*)-Methyl 2-(benzylideneamino)-3-methylbutanoate **181c** (2.97 g, 13.6 mmol, 1.0 eq.) gave *the title compound* **182c** as an orange oil (2.50 g, Yield: 55%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.26 (s, 1H, C*H*N), 7.71 - 7.15 (m, 10H, 10 × Ar C*H*), 6.41 (dt, 1H, J = 15.4, 7.3 Hz, C*H*), 6.3 (d, 1H, J = 15.4 Hz, C*H*), 3.74 (s, 3H, CH_3), 2.84 - 2.73 (m, 2H, CH_2), 2.48 - 2.34 (m, 1H, C*H*), 1.04 (d, 6H, J = 7.1 Hz, 2 × CH_3).

Crotyl Derivatives 183[119,126]



181

183a R^1 = H
183b R^1 = Me
183c R^1 = *i*-Pr

Lithium diisopropylamine was prepared by the dropwise addition of *n*-BuLi in hexanes (2.5 M solution in hexanes, 1.2 eq.) to a solution of diisopropylamine (1.2 eq.) in tetrahydrofuran (2 ml $mmol^{-1}$ of diidopropylamine) at 0 °C. After 30 minutes the solution was cooled to –78 °C. A solution of the *N*-(benzlidine)amino ester **181** (1.0 eq.) in tetrahydrofuran (2 ml $mmol^{-1}$) was added dropwise *via* a syringe, and the resulting deep red solution was stirred for 30 minutes at –78 °C. A solution of crotyl bromide (1.1 eq.) in tetrahydrofuran (1 ml $mmol^{-1}$) was added dropwise and the resulting solution stirred at –78 °C. After 1 hour the now orange solution was allowed to warm to room temperature, stirred for 1 hour, quenched with saturated aqueous ammonium chloride (4 ml $mmol^{-1}$) and diluted with ether (3 × 4 ml $mmol^{-1}$). The combined organic solutions were dried, filtered and evaporated to give *the crude imines* **183**, which were characterised by proton NMR only.

(R^1 = H) (*E*)-Methyl 2-((*E*)-benzylideneamino)hex-4-enoate 183a

(*E*)-Methyl 2-(benzylideneamino)acetate **181a** (5.83 g, 32.0 mmol, 1.0 eq.) gave *the title compound* **183a** as an orange oil (6.88 g, Yield: 90%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.16 (s, 1H, C*H*N), 7.69 (dd, 2H, J = 7.6, 1.8 Hz, 2 × Ar C*H*), 7.36 - 7.30 (m, 3H, 3 × Ar C*H*), 5.53 - 5.37 (m, 1H, C*H*), 5.34 - 5.23 (m, 1H, C*H*), 3.92 (t, 1H, J = 5.9 Hz, C*H*N), 3.66 (s, 3H, CH_3), 2.69 - 2.40 (m, 2H, CH_2), 1.55 (d, 3H, J = 7.1 Hz, CH_3).

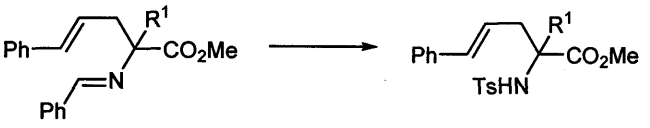
(R^1 = Me) (*E*)-Methyl 2-((*E*)-benzylideneamino)-2-methylhex-4-enoate 183b

(*E*)-Methyl 2-(benzylideneamino)propanoate **181b** (5.66 g, 29.6 mmol, 1.0 eq.) gave *the title compouns* **183b** as an orange oil (4.68 g, Yield: 65%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.23 (s, 1H, C*H*N), 7.71 - 7.66 (m, 2H, 2 × Ar C*H*), 7.36 - 7.30 (m, 3H, 3 × Ar C*H*), 5.55 - 5.40 (m, 1H, C*H*), 5.36 - 5.19 (m, 1H, C*H*), 3.65 (s, 3H, CH_3), 2.65 - 2.45 (m, 2H, CH_2), 1.57 (d, 3H, J = 6.3 Hz, CH_3), 1.39 (s, 3H, C*H*).

(R^1 = *i*-Pr) (*E*)-Methyl 2-((*E*)-benzylideneamino)-2-isopropylhex-4-enoate 183c

(*E*)-Methyl 2-(benzylideneamino)-3-methylbutanoate **181c** (3.19 g, 14.6 mmol, 1.0 eq.) gave *the title compound* **183c** as an orange oil (1.93 g, Yield: 49%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 8.24 (br. s, 1H, C*H*N), 7.82 - 7.76 (m, 2H, 2 × Ar C*H*), 7.44 - 7.40 (m, 3H, 3 × Ar C*H*), 5.55 - 5.40 (m, 1H, C*H*), 5.36 - 5.19 (m, 1H, C*H*), 3.74 (s, 3H, CH_3), 2.65 - 2.45 (m, 2H, CH_2), 2.44 - 2.35 (m, 1H, C*H*), 1.57 (d, 3H, J = 6.3 Hz, CH_3), 0.97 (d, 3H, J = 6.8 Hz, CH_3), 0.94 (d, 3H, J = 6.8 Hz, CH_3).

Preparation of homoallylic sulfonamides of cinammyl derivatives 184[119,126]



182a R^1 = H
182b R^1 = Me
182c R^1 = *i*-Pr

184a R^1 = H
184b R^1 = Me
184c R^1 = *i*-Pr

The crude imine **182** (1.0 eq.) was dissolved in ether (8 ml mmol^{-1}) and 1 M hydrochloric acid (8 ml mmol^{-1}) was added slowly. The resulting mixture was then stirred vigorously for 2 hours. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 4 ml mmol^{-1}); these organic solutions were discarded. The aqueous layer was adjusted to pH 9 with 2 M aqueous sodium hydroxide and the resulting solution extracted with dichloromethane (3 × 4 ml mmol^{-1}). The combined organic extracts were dried over Na_2SO_4 and evaporated to yield the corresponding amine, assigned by proton NMR. The amine (1.0 eq.) was then immediately dissolved in dichloromethane (5 ml mmol^{-1}) at –78 °C and treated with tosyl chloride (1.2 eq.), triethylamine (1.2 eq.) and a few crystals of DMAP. The resulting mixture was stirred overnight at room temperature, quenched by addition of 2 M hydrochloric acid (4 ml mmol^{-1}) and the organic phase separated. The aqueous phase was further extracted with dichloromethane (2 × 4 ml mmol^{-1}). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by recrystallisation from ethyl acetate / hexanes to give *the sulfonamide* **184**.

(R^1 = H) (*E*)-Methyl 2-(4-methylphenylsulfonamido)-5-phenylpent-4-enoate 184a

182a (3.99 g, 13.6 mmol, 1.0 eq.) gave *the title compound* **184a** as a white solid (300 mg Yield: 8.5%). All data obtained was in accordance with that previously reported in the literature.[30,283] m.p.: 88 - 92 °C. ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.76 - 7.63 (m, 2H, 2 × Ts C*H*), 7.22 - 7.16 (m, 7H, 5 × Ar C*H* & 2 × Ts C*H*), 6.32 (d, 1H, J = 15.7 Hz, C*H*), 5.94 (app. ddd, 1H,

J= 15.7, 7.9, 7.9 Hz, C*H*), 5.24 (s, 1H, N*H*), 4.03 (ddd, 1H, J = 7.9, 5.8, 5.8 Hz, C*H*N), 3.57 (s, 3H, CH_3), 2.67 - 2.54 (m, 2H, CH_2), 2.32 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 171.4 (C_q), 143.0 (C_q.), 136.8 (C_q), 136.6 (C_q), 134.6 (Ar *C*H), 129.7 (2 x Ts C*H*), 128.5 (2 x Ar *C*H), 127.7 (*C*H), 127.27 (2 x Ts *C*H), 126.3 (2 x Ar *C*H), 122.6 (*C*H), 55.5 (*C*HN), 52.6 (*C*H_3), 36.9 (*C*H_2), 21.5 (Ts *C*H_3). IR (nujol) υ/cm^{-1}: 3279, 1744, 1596, 1458, 1326, 1212, 1158, 1091, 968, 905, 857, 817, 744, 690, 665. HRMS (EI) *m/z* calcd. for $C_{19}H_{21}NO_4S$ [M+1] = 360.1270, found 360.1261.

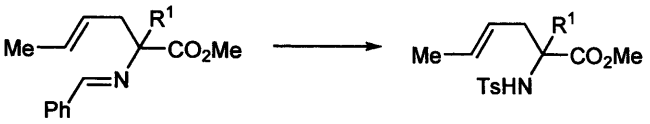
(R^1 = Me) (*E*)-Methyl 2-methyl-2-(4-methylphenylsulfonamido)-5-phenylpent-4-enoate 184b

182b (2.09 g, 6.82 mmol, 1.0 eq.) gave *the sulfonamide* **184b** as a white solid (700 mg Yield: 27.5%). All data obtained was in accordance with that previously reported in the literature.[30] m.p.: 130 - 133 °C. ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.71 - 7.70 (m, 2H, 2 × Ts C*H*) 7.22 - 7.16 (m, 7H, 5 × Ar C*H* & 2 × Ts C*H*), 6.36 (d, 1H, J= 15.8 Hz, C*H*), 5.91 (td, 1H, J= 7.5, 15.8 Hz, C*H*), 5.35 (s, 1H, N*H*), 3.63 (s, 3H, CH_3), 2.60 (dd, 1H, J= 7.5, 15.1 Hz, CH_AH$_B$), 2.55 (dd, 1H, J= 7.5, 15.1 Hz, CH$_A$$H_B$), 2.32 (s, 3H, Ts C$H_3$), 1.43 (s, 3H, C$H_3$). ^{13}C NMR (500 MHz / $CDCl_3$): 173.5 (C_q), 143.3 (C_q), 139.5 (C_q), 136.8 (C_q), 134.8 (Ar *C*H), 129.5 (2 x Ts *C*H), 128.5 (2 x Ar *C*H), 127.6 (*C*H), 127.11 (2 x Ts *C*H), 126.3 (2 x Ar *C*H), 122.7 (*C*H), 62.5 (C_q), 52.8 (*C*H_3), 43.0 (*C*H_2), 22.6 (*C*H_3), 21.5 (Ts *C*H_3). IR (nujol): 3297, 1724, 1339, 1261, 1220, 1157, 1122, 1091, 973, 849, 820, 747, 696, 673, 656. HRMS (EI) *m/z* calcd. for $C_{20}H_{23}NO_4S$ [M+1] = 374.1462, found 374.1425

(R^1 *i*-Pr) (*E*)-Methyl 2-isopropyl-2-(4-methylphenylsulfonamido)-5-phenylpent-4-enoate 184c

182c (2.48 g, 7.39 mmol,1.0 eq.) gave *the sulfonamide* **184c** as a white solid (2.00 g, Yield: 67.4%). m.p: 146 - 150 °C. ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.83 - 7.82 (m, 2H, 2 × Ts C*H*), 7.34 - 7.16 (m, 7H, 5 × Ar C*H* & 2 × Ts C*H*), 6.46 (dt, 1H, J= 15.9, 7.7 Hz, C*H*), 6.34 (d, 1H, J= 15.9 Hz, C*H*), 5.52 (s, 1H, N*H*), 3.74 (s, 3H, CH_3), 3.06 (m, 2H, CH_2), 2.40 - 2.38 (m, 4H, Ts CH_3 & C*H*), 1.05 (d, 3H, J = 6.9 Hz, CH_3), 0.89 (d, 3H, J= 6.9 Hz, CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 172.4 (C_q), 143.1 (C_q), 140.0 (C_q), 137.1 (C_q), 133.5 (Ar *C*H), 129.5 (2 x Ts *C*H), 128.4 (2 x Ar *C*H), 127.2 (*C*H), 126.9 (2 x Ts *C*H), 126.1 (2 x Ar *C*H), 124.3 (*C*H), 71.0 (C_q), 52.6 (*C*H_3), 36.5 (*C*H_2), 34.8 (*C*H), 21.4 (Ts *C*H_3), 17.7 (*C*H_3), 17.4 (*C*H_3). IR (nujol): 3282, 1708, 1596, 1457, 1325, 1261, 1154, 1094, 1006, 969, 910, 855, 813, 747, 693, 666. HRMS (EI) *m/z* calcd. for $C_{22}H_{27}NO_4S$ [M+1] = 402.1739, found 402.1730.

Preparation of homoallylic sulfonamides of cinammyl derivatives 185 [119,126]



183a R^1 = H
183b R^1 = Me
183c R^1 = *i*-Pr

185a R^1 = H
185b R^1 = Me
185c R^1 = *i*-Pr

The crude imine **183** (1.0 eq.) was dissolved in ether (8 ml $mmol^{-1}$) and 1 M hydrochloric acid (8 ml $mmol^{-1}$) was added slowly. The resulting mixture was then stirred vigorously for 2 hours. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 × 4 ml $mmol^{-1}$); these organic solutions were discarded. The aqueous layer was adjusted to pH 9 with 2 M aqueous sodium hydroxide and the resulting solution extracted with dichloromethane (3 × 4 ml $mmol^{-1}$). The combined organic extracts were dried over Na_2SO_4 and evaporated to yield the corresponding amine, assigned by proton NMR. The amine (1.0 eq.) was then immediately dissolved in dichloromethane (5 ml $mmol^{-1}$) at –78 °C and treated with tosyl chloride (1.2 eq.), triethylamine (1.2 eq.) and a few crystals of 4-dimethylaminopyridine (DMAP). The resulting mixture was stirred overnight at room temperature, quenched by addition of 2 M hydrochloric acid (4 ml $mmol^{-1}$) and the organic phase separated. The aqueous phase was further extracted with dichloromethane (2 × 4 ml $mmol^{-1}$). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the sulfonamides* **185**.

(R^1 = H) (*E*)-Methyl 2-(4-methylphenylsulfonamido)hex-4-enoate 185a

183a (6.88 g, 29.7 mmol, 1.0 eq.) gave *the sulfonamide* **185a** as a white solid (3.63 g, Yield: 41%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.72 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.29 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 5.65 - 5.44 (m, 1H, C*H*), 5.29 - 5.08 (m, 1H, C*H*), 4.04 - 3.95 (m, 1H, C*H*N), 3.52 (s, 3H, CH_3), 2.42 (s, 3H, Ts CH_3), 2.41 - 2.36 (m, 2H, CH_2), 1.62 (d, 3H, J = 6.4 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 171.4 (C_q), 142.0 (C_q), 136.8 (C_q), 129.7 (2 x Ts *C*H), 127.3 (*C*H), 127.2 (2 x Ts *C*H), 123.4 (*C*H), 55.5 (*C*HN), 52.6 (CH_3), 36.9 (CH_2), 21.5 (Ts CH_3), 18.5 (CH_3).

(R^1 = Me) (*E*)-Methyl 2-methyl-2-(4-methylphenylsulfonamido)hex-4-enoate 185b

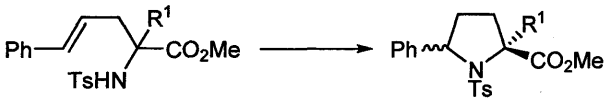
183b (4.68 g, 19.1 mmol, 1.0 eq.) gave *the sulfonamide* **185b** as a beige solid (1.30 g, Yield: 22%). All data obtained was in accordance with that previously reported in the literature.[30] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.75 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.28 (d, 2H, J = 8.3 Hz,

2 × Ts C*H*), 5.55 - 5.46 (m, 1H, C*H*), 5.26 - 5.17 (m, 1H, C*H*), 3.64 (s, 3H, CH_3), 2.51 - 2.44 (m, 1H, CH_AH$_B$), 2.39 - 2.34 (m, 1H, CH$_A$$H_B$), 2.41 (s, 3H, Ts C$H_3$), 2.05 (d, 3H, J = 6.5 Hz, CH_3), 1.40 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 173.4 (C_q), 142.3 (C_q), 138.6 (C_q), 131.7 (*C*H), 129.7 (2 × Ts *C*H), 127.2 (2 × Ts *C*H), 123.6 (*C*H), 62.5 (C_q), 53.2 (CH_3), 43.6 (CH_2), 22.4 (CH_3), 21.5 (Ts CH_3), 18.5 (CH_3).

(R^1 *i*-Pr) (*E*)-Methyl 2-isopropyl-2-(4-methylphenylsulfonamido)hex-4-enoate 185c

183c (1.93 g, 7.07 mmol, 1.0 eq.) gave *the sulfonamide* **185c** as a beige solid (815 mg, Yield: 34%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.71 - 7.70 (m, 2H, 2 × Ts C*H*) 7.22 - 7.16 (m, 2H, 2 × Ts C*H*), 6.36 (dq, 1H, J = 15.8, 7.2 Hz, C*H*), 5.91 (dt, 1H, J = 15.8, 7.5 Hz, C*H*), 3.63 (s, 3H, CH_3), 2.76 - 2.53 (m, 2H, CH_2), 2.32 (s, 3H, Ts CH_3), 1.43 (s, 3H, CH_3), 2.40 - 2.38 (m, 4H, Ts CH_3 & C*H*), 1.05 (d, 3H, J = 6.9 Hz, CH_3), 0.89 (d, 3H, J = 6.9 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 172.6 (C_q), 142.8 (C_q), 137.5 (C_q), 131.5 (*C*H), 129.7 (2 × Ts *C*H), 127.3 (2 × Ts *C*H), 124.1 (*C*H), 69.5 (C_q), 52.4 (CH_3), 37.4 (CH_2), 35.1 (*C*H), 21.6 (Ts CH_3), 17.7 (CH_3), 17.4 (CH_3). HRMS (EI) *m/z* calcd. for $C_{17}H_{26}NO_4S$ $[M+H]^+$ = 340.1538; found 340.1536.

Cyclisations of cinnamyl derivatives 177[30,119]



184a R^1 = H
184b R^1 = Me
184c R^1 = *i*-Pr

177a R^1 = H
177b R^1 = Me
177c R^1 = *i*-Pr

See Table 2.2 on p.36 form more details.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.5 eq.) was added. The reaction was allowed to warm to room temperature and stirred for 1 hour after which a sample (*ca.* 3 ml) was taken, which was quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated to give *the title compound* **177**.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (1.0 eq.) was added. The reaction was allowed to warm to room temperature and

stirred for 1 hour after which a sample (*ca.* 3 ml) was taken, which was quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated *the title compound* **177**.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (2.0 eq.) was added. The reaction was allowed to warm to room temperature and stirred for 1 hour after which a sample (*ca.* 3 ml) was taken, which was quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated *the title compound* **177**.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (5.0 eq.) was added. The reaction was allowed to warm to room temperature and stirred for 1 hour after which a sample (*ca.* 3 ml) was taken, which was quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated *the title compound* **177**.

(R^1 = H) (2*RS*, 5*RS*) and (2*RS*, 5*SR*)-Methyl 5-phenyl-1-tosylpyrrolidine-2-carboxylate 177a

All data obtained was in accordance with that previously reported in the literature.[30] All samples showed identical spectroscopic and analytical data of inseperable diastereoisomers: ^{1}H NMR (500 MHz / $CDCl_3$) major isomer: δ 7.36 (d 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.10 - 7.09 (m, 1H, 2 × Ar C*H*), 6.96 - 6.94 (m, 3H, 3 × Ar C*H*), 6.85 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.85 (d, 1H, J = 8.3 Hz, C*H*), 3.82 (s, 3H, CH_3), 2.52 - 2.24 (m, 2H, CH_2), 2.16 (s, 3H, Ts CH_3), 1.83 - 1.67 (m, 2H, CH_2), 1.77 (s, 3H, CH_3); minor isomer: δ 7.12 - 6.79 (m, 9H, 4 × Ts C*H* & 5 × Ar C*H*), 5.22 (dd, 1H, J = 2.6, 9.1 Hz, C*H*), 3.72 (s, 3H, CH_3), 2.57 - 2.46 (m, 1H, CH_AH$_B$), 2.13 - 2.04 (m, 2H, CH_2), 1.66 - 1.57 (m, 1H, CH$_A$*H$_B$*), 2.21 (s, 3H, Ts CH_3), 1.80 (s, 3H, CH_3). ^{13}C NMR

(500 MHz / $CDCl_3$) δ 172.8 (C_q), 143.4 (C_q), 141.2 (C_q), 129.3 (2 x Ts *C*H), 128.2 (Ar *C*H), 127.8 (2 × Ar *C*H), 127.2 (2 x Ts *C*H), 127.0 (2 x Ar *C*H), 62.0 (*C*H), 61.9 (*C*H), 52.4 (CO_2CH_3), 38.9 (CH_2), 29.5 (CH_2), 21.5 (Ts CH_3) (due to ratio between isomers, minor isomer was not visible in ^{13}C spectrum). IR (nujol) υ/cm^{-1}: 1261, 1095, 800. HRMS (EI) *m/z* calcd. for $C_{19}H_{22}NO_4S$ $[M+H]^+$ = 360.1270, found 360.1266.

(R^1 = Me) (2*RS*, 5*RS*) and (2*RS*, 5*SR*)-Methyl 2-methyl-5-phenyl-1-tosylpyrrolidine-2-carboxylate 177b

All data obtained was in accordance with that previously reported in the literature.[30] All samples showed identical spectroscopic and analytical data of inseperable diastereoisomers: ^1H NMR (500 MHz / $CDCl_3$) major isomer: δ 7.36 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.11 - 7.09 (m, 1H, 2 × Ar C*H*), 6.94 - 6.93 (m, 3H, 3 × Ar C*H*), 6.85 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.85 (d, 1H, J = 8.3 Hz, C*H*), 3.82 (s, 3H, CH_3), 2.52 - 2.24 (m, 2H, CH_2), 1.83 - 1.67 (m, 2H, CH_2), 2.16 (s, 3H, Ts CH_3), 1.77 (s, 3H, CH_3); minor isomer: δ 7.12 - 6.79 (m, 9H, 4 × Ts C*H* & 5 × Ar C*H*), 5.22 (dd, J = 2.6, 9.1 Hz, C*H*), 3.72 (s, 3H, CH_3), 2.57 - 2.46 (m, 1H, CH_AH_B), 2.13 - 2.04 (m, 2H, CH_2), 1.66 - 1.57 (m, 1H, CH_AH_B), 2.21 (s, 3H, Ts CH_3), 1.80 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$ / 500 MHz, ppm) major isomer: δ 175.4 (C_q), 142.8 (C_q), 142.2 (C_q), 139.2 (C_q), 129.1 (2 x Ts *C*H), 128.6 (2 x Ts *C*H), 127.5 (2 x Ar *C*H), 127.3 (2 x Ar *C*H), 126.9 (Ar *C*H), 70.4 (C_q), 65.9 (*C*H), 53.1 (CH_3), 39.0 (CH_2), 33.4 (CH_2), 24.6 (CH_3), 21.8 (CH_3); minor isomer: δ 175.1 (C_q), 143.3 (C_q), 142.4 (C_q), 137.3 (C_q), 129.0 (2 x Ts *C*H), 128.6 (2 x Ts *C*H), 128.3 (2 x Ar *C*H), 127.4 (2 x Ar *C*H), 127.0 (Ar *C*H), 71.3 (C_q), 63.5 (*C*H), 53.2 (CH_3), 37.9 (CH_2), 34.6 (CH_2), 24.6 (CH_3), 23.3 (CH_3). IR (neat): 2951, 1740, 1598, 1495, 1454, 1379, 1336, 1271, 1154, 1090, 1065, 996, 916, 876, 815, 757, 733, 702, 668. HRMS (EI) *m/z* calcd. for $C_{20}H_{23}NO_4S$ [M+1] = 374.1426, found 374.1412.

(R^1 = *i*-Pr) (2*RS*, 5*RS*) and (2*RS*, 5*SR*)-Methyl 2-isopropyl-5-phenyl-1-tosylpyrrolidine-2-carboxylate 177c

All samples showed identical spectroscopic and analytical data: ^1H NMR (500 MHz / $CDCl_3$) major isomer: δ 7.25 - 7.16 (m, 5H, 5 × Ar C*H*), 7.08 - 6.94 (m, 4H, 4 × Ar C*H*), 5.14 (app. dd, 1H, J = 5.2, 9.2 Hz, C*H*), 3.75 (s, 3H, CH_3), 3.06 - 2.98 (m, 1H, C*H*), 2.68 - 2.63 (m, 1H, CH_CH_D), 2.24 - 2.21 (m, 1H, CH_AH_BC), 2.21 (s, 3H, Ts CH_3), 2.05 - 2.00 (m, 1H, CH_AH_BC), 1.89 - 1.84 (m, 1H, CH_CH_DCH), 1.15 (d, 3H, J = 6.6 Hz, CH_3), 0.92 (d, 3H, J = 6.6 Hz, CH_3); minor isomer: δ 7.25 - 7.16 (m, 5H,5 × Ar C*H*), 7.08 - 6.94 (m, 4H, 4 × C*H*), 4.96 (t, 1H, J = 7.3 Hz, C*H*, minor), 3.77 (s, 3H, CH_3), 3.37 - 3.32 (m, 1H, C*H*), 2.51 - 2.47 (m, 1H, CH_AH_BC), 2.36 - 2.33 (m, 1H, CH_CH_DCH), 2.20 (s, 3H, Ts CH_3), 2.17 - 2.12 (m, 1H, CH_AH_BC), 1.99 - 1.94 (m, 1H, CH_CH_DCH), 1.17 (d, 3H, J = 6.8 Hz, CH_3, minor), 0.94 (d, 3H, J = 6.8 Hz, CH_3, minor). ^{13}C NMR (500 MHz /

$CDCl_3$) major & minor isomers: δ 173.4 (C_q), 141.6 (C_q), 141.5 (C_q), 136.9 (C_q), 127.6 (2 x Ts *C*H), 127.3 (2 x Ar *C*H) 126.9 (2 x Ts *C*H), 126.6 (2 x Ar *C*H), 126.4 (Ar *C*H.), 65.5 (C_q), 51.0 (CH_3), 32.6 (CH_2), 30.7 (*C*H), 29.2 (CH_2), 20.4 (CH_3), 19.2 (CH_3), 17.8 (CH_3). IR (nujol): 1748, 1597, 1463, 1377, 1347, 1242, 1152, 1089, 1043, 1002, 819, 762, 722, 702, 677. HRMS (EI) *m/z* calculated for $C_{22}H_{27}NO_4S$ [M+1] = 402.1739, found 402.1739.

Cyclisations for isomer ratio determination for crotyl derivatives 178

185a R^1 = H
185b R^1 = Me
185c R^1 = *i*-Pr

178a R^1 = H
178b R^1 = Me
178c R^1 = *i*-Pr

See Table 2.4 on p.38 for further details.

The sulphonamide **185** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.5 eq.) was added. The reaction was allowed to warm to room temperature; samples (*ca.* 3 ml) were taken after for 1 hour, 2 hours and 3 hours, which were quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated to give *the title compound* **178**.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.5 eq.) was added. The reaction was allowed to warm to room temperature; samples (*ca.* 3 ml) were taken after for 1 hour, 2 hours and 3 hours, which were quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated to give *the title compound* **178**.

The sulphonamide **184** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.5 eq.) was added. The reaction was allowed to warm to room temperature;

samples (*ca.* 3 ml) were taken after for 1 hour, 2 hours and 3 hours, which were quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated to give *the title compound* **178**.

The sulphonamide **185** (100 mg, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.5 eq.) was added. The reaction was allowed to warm to room temperature; samples (*ca.* 3 ml) were taken after for 1 hour, 2 hours and 3 hours, which were quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated. The remaining reaction mixture was allowed to stir at room temperature overnight, quenched with saturated aqueous K_2CO_3. The two phases were separated and the aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried over K_2CO_3, filtered and evaporated to give *the title compound* **178**.

(R^1 = H) (2*RS*, 5*RS*) and (2*RS*, 5*SR*)-Methyl 5-methyl-1-tosylpyrrolidine-2-carboxylate 178a

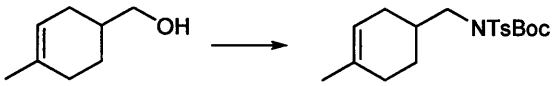
All data obtained was in accordance with that previously reported in the literature.[30] All samples showed identical spectroscopic and analytical data of inseperable diastereoisomers: ^{1}H NMR (400 MHz / $CDCl_3$) major isomer: δ 7.68 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.17 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.30 (dd, 1H, J = 7.8, 2.3 Hz, C*H*), 3.79 – 3.76 (m, 1H, C*H*), 3.72 (s, 3H, CH_3), 2.35 (s, 3H, Ts CH_3), 2.35 – 1.34 (m, 4H, 2 × CH_2), 1.26 (d, 3H, J = 6.5 Hz, CH_3); minor isomer: δ 7.72 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.12 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.39 (dd, 1H, J = 7.4, 2.8 Hz, C*H*), 4.07 – 4.05 (m, 1H, C*H*), 3.68 (s, 3H, CH_3), 2.34 (s, 3H, Ts CH_3), 2.27 - 1.31 (m, 4H, 2 × CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) major isomer: δ 174.4 (C_q), 148.7 (C_q), 142.6 (C_q), 128.8 (2 × Ts *C*H), 127.0 (2 × Ts *C*H), 66.5 (*C*H), 58.2 (*C*H), 52.7 (*C*H$_3$), 38.6 (*C*H$_2$), 31.2 (*C*H$_2$), 24.3 (*C*H$_3$), 21.9 (*C*H$_3$); minor isomer: δ 174.8 (C_q), 148.9 (C_q), 142.8 (C_q), 128.6 (2 × Ts *C*H), 127.3 (2 × Ts *C*H), 68.4 (*C*H), 57.6 (*C*H), 52.8 (*C*H$_3$), 38.3 (*C*H$_2$), 31.5 (*C*H$_2$), 23.9 (*C*H$_3$), 21.7 (*C*H$_3$).

(R^1 = Me) (2*RS*, 5*RS*) and (2*RS*, 5*SR*)-Methyl 2,5-dimethyl-1-tosylpyrrolidine-2-carboxylate 178b

All data obtained was in accordance with that previously reported in the literature.[30] All samples showed identical spectroscopic and analytical data of inseperable diastereoisomers: ^{1}H NMR (400 MHz / $CDCl_3$) major isomer: δ 7.69 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.12 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 3.87 - 3.86 (m, 1H, C*H*), 3.74 (s, 3H, CH_3), 2.34 (s, 3H, Ts CH_3), 2.32 - 1.39 (m, 4H,

2 × CH_2), 1.52 (s, 3H, CH_3), 1.15 (d, 3H, J = 6.5 Hz, CH_3); minor isomer: δ 7.72 (d, 2H, J = 8.2 Hz, 2 × Ts CH), 7.10 (d, 2H, J = 8.2 Hz, 2 × Ts CH), 4.07 - 4.06 (m, 1H, CH), 3.66 (s, 3H, CH_3), 2.34 (s, 3H, Ts CH_3), 2.21 - 1.27 (m, 4H, 2 × CH_2), 1.70 (s, 3H, CH_3), 1.03 (d, 3H, J = 6.5 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) major isomer: δ 174.6 (C_q), 149.2 (C_q), 143.9 (C_q), 129.8 (2 × Ts CH), 127.9 (2 × Ts CH), 67.4 (CH), 57.8 (CH), 52.9 (CH_3), 39.1 (CH_2), 32.0 (CH_2), 27.3 (CH_3), 22.2 (CH_3), 21.8 (Ts CH_3); minor isomer: δ 175.2 (C_q), 149.2 (C_q), 143.6 (C_q), 129.7 (2 × Ts CH), 127.3 (2 × Ts CH), 70.4 (CH), 57.9 (CH), 52.8 (CH_3), 38.3 (CH_2), 32.0 (CH_2), 27.3 (CH_3), 22.2 (CH_3), 21.8 (Ts CH_3).

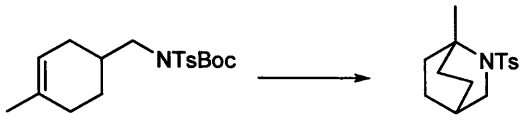
tert-Butyl (4-methylcyclohex-3-enyl)methyl(tosyl)carbamate 193



192 **193**

4-Methylenecyclohexyl methanol **192** (500 mg, 3.96 mmol, 1.0 eq.) was reacted with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (1.09 g, 4.00 mmol, 1.01 eq.) according to general procedure **A** using work up ***2***. The crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **193** as a white solid (940 mg, Yield 63%). m.p.: 99 - 101 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.77 (d, 2H, J = 8.4 Hz, 2 × Ts CH), 7.30 (d, 2H, J = 8.4 Hz, 2 × Ts CH), 5.37 (app. br. s, 1H, CH), 3.79 - 3.76 (m, 2H, CH_2N), 2.43 (s, 3H, Ts CH_3), 2.16 - 1.72 (m, 7H, 3 × CH_2 & CH), 1.65 (s, 3H, CH_3), 1.32 (s, 9H, Boc $C(CH_3)_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 151.2 (C_q), 144.0 (C_q), 137.5 (C_q), 134.0 (C_q), 129.2 (2 × Ts CH), 127.8 (2 × Ts CH), 119.6 (CH), 84.1 (C_q), 52.5 (CH_2N), 34.3 (CH), 29.7 (CH_2), 29.3 (CH_2), 27.9 (Boc $C(CH_3)_3$), 26.7 (CH_2), 23.5 (CH_3), 21.6 (Ts CH_3). IR (neat) υ/cm^{-1}: 3020, 2923, 1728, 1598, 1459, 1380, 1138, 1100, 839. HRMS (ES) *m/z* calcd. for $C_{22}H_{32}N_2O_4NaS$ $[M+MeCNNa]^+$ = 443.1980; found 443.1999.

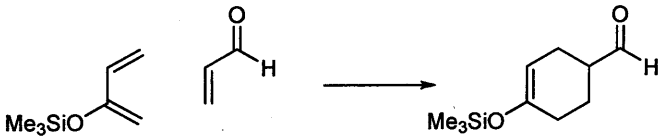
1-methyl-2-tosyl-2-azabicyclo[2.2.2]octane 194



193 **194**

The sulfonamide **193** (100 mg 0.26 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added triflic acid (0.20 ml, 0.13 mmol, 0.5 eq.) and stirred at 20 °C for 48 hours. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 ml) and the two layers were separated. The aqueous layer was extracted with dichloromethane (2 × 30 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **194** as a colourless oil (70 mg Yield: 96%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.65 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.21 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 2.75 (app. d, 2H, J = 6.4 Hz, 2 × CH_2N), 2.34 (s, 3H, Ts CH_3), 1.98 - 1.90 (m, 1H, C*H*), 1.84 - 1.77 (m, 1H, CH_AH$_B$), 1.69 - 1.57 (m, 2H, CH_2) 1.52 (s, 3H, CH_3), 1.50 - 1.44 (m, 3H, CH_2 & CH$_A$$H_B$), 1.33 - 1.24 (m, 2H, C$H_2$), 1.18 - 1.07 (m, 1H, C$H_AH_B$), 0.95 - 0.75 (m, 1H, CH$_A$$H_B$). ^{13}C NMR (500 MHz / $CDCl_3$) δ 144.6 (C_q), 134.1 (C_q), 129.7 (2 × Ts *C*H), 127.1 (2 × Ts *C*H), 52.7 (C_q), 48.5 (*C*H$_2$N), 34.6 (*C*H), 33.6 (*C*H$_2$), 31.0 (*C*H$_2$), 29.3 (*C*H$_2$), 25.9 (*C*H$_2$), 24.7 (*C*H$_3$), 21.5 (Ts *C*H$_3$). IR (neat) υ/cm^{-1}: 2928, 1710, 1598, 1459, 1380, 1138, 839. HRMS (APCI) *m/z* calcd. for $C_{15}H_{22}NO_2S$ $[M+H]^+$ = 280.1371; found 280.1380.

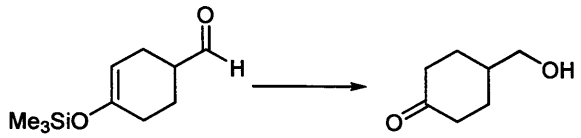
4-(Trimethylsilyloxy)cyclohexanecarbaldehyde 197[132]



195 **196** **197**

2-Trimethylsilyloxy-1,3-butadiene **195** (2.50 g, 17.6 mmol, 1.0 eq.) was mixed with acrolein **196** (2.40 ml, 35.2 mmol, 2.0 eq.), hydroquinone (0.2 g, 1.76 mmol, 0.1 eq.) and dry toluene (70 ml). The resulting solution was heated at 110 °C for 24 hours. The solvent and any unreacted starting materials were evaporated and the residue distilled by Kugelrohr at 67 - 70 °C (1.2 mm) to give *the title compound* **197** as an orange oil (2.75 g, Yield: 79%). All data obtained was in accordance with that previously reported in the literature.[132] ^{1}H NMR (400 MHz / $CDCl_3$) δ 9.46 (br. s, 1H, C*H*), 6.46 (br. s, 1H, C*H*), 2.32 - 1.51 (m, 7H, 3 × CH_2 & C*H*), 0.05 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 202.4 (*C*HO), 149.6 (C_q), 116.2 (*C*H), 47.3 (*C*H), 39.5 (*C*H$_2$), 29.5 (2 × *C*H$_2$), 1.09 (Si(*C*H$_3$)$_3$).

4-(Hydroxymethyl)cyclohexanone 198[132]



197 **198**

4-(Trimethylsilyloxy)cyclohexanecarbaldehyde **197** (4.00 g, 20.2 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (20 ml) and added dropwise to a suspension of $LiAlH_4$ (420 mg, 11,1 mmol, 0.55 eq.) in tetrahydrofuran (40 ml) at –78 °C over 30 minutes. The suspension was allowed to warm to room temperature over 2 hours; the solution was then cooled to 0 °C and water (12 ml), 15% $NaOH_{(aq)}$ and water (30 ml) were added sequentially. The solution was dried over $MgSO_4$ and evaporated to give a viscous orange oil. This oil was dissolved in methanol (50 ml), a few drops of 2 M HCl and were added and the resulting suspension stirred at 20 °C for 30 minutes. The methanol was evaporated and the residue dissolved in diethyl ether (30 ml), dried over $MgSO_4$ and evaporated to give *the title compound* **198** as a clear oil (1.54 g, Yield: 60%). All data obtained was in accordance with that previously reported in the literature.[132] ^{1}H NMR (400 MHz / $CDCl_3$) δ 3.51 (d, 2H, J = 6.4 Hz, CH_2O), 2.52 (br. s, 1H, O*H*), 2.40 - 1.84 (m, 7H 3 × CH_2 & C*H*), 1.44 - 1.34 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 202.4 (C_q), 47.3 (CH_2O), 39.8 (*C*H), 39.5 (2 × CH_2), 25.5 (2 × CH_2). HRMS (EI) *m/z* calcd. for $C_7H_{12}O_2$ $[M]^+$ = 128.0837; found 128.0837.

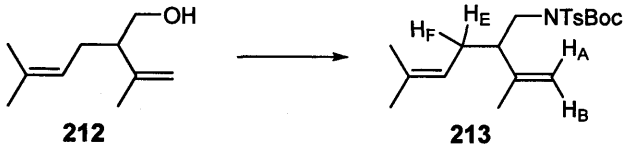
(4-Oxocyclohexyl)methyl methanesulfonate 202[133]

198 **202**

4-(Hydroxymethyl)cyclohexanone **198** (500 mg, 3.90 mmol, 1.0 eq.) and triethylamine (0.82 ml, 5.86 ml, 1.5 eq.) were stirred in dichloromethane (20 ml), to which was added mesyl chloride (0.36 ml, 4.68 mmol, 1.2 eq.) slowly and stirred at 20 °C for 30 minutes. The solution was then washed with water (2 × 30 ml), 1 M HCl (30 ml), water (30 ml), brine (30 ml), dried over Na_2SO_4 and evaporated to give *the title compound* **202** as a clear oil (769 mg, Yield: 96%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 4.09 (d, 2H, J = 6.5 Hz, CH_2O), 2.97 (s, 3H, Ms CH_3), 2.42 - 2.06 (m, 9H, 4 × CH_2 & C*H*). ^{13}C NMR (400 MHz / $CDCl_3$) δ 210.3 (C_q), 72.6 (CH_2O), 39.9 (2 × CH_2), 37.5

(Ms CH_3), 35.9 (*C*H), 28.7 (2 × CH_2). HRMS (EI) *m/z* calcd. for $C_8H_{14}O_4S$ $[M]^+ = 206.0613$; found 206.0612.

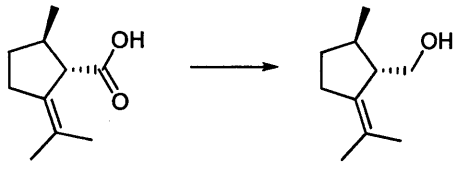
tert-Butyl 5-methyl-2-(prop-1-en-2-yl)hex-4-enyl(tosyl)carbamate 213



212 **213**

Lavandulol **212** (500 mg, 3.24 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (890 mg, 3.27 mmol, 1.01 eq.) according to general method **A** using work up ***2***. The crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **213** as a clear oil (509 mg, Yield: 41%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.80 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.36 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.12 - 5.05 (m, 1H, C*H*), 4.85 (s, 1H, CH_AH_B), 4.79 (s, 1H, CH_AH_B), 4.11 - 3.79 (m, 2H, CH_2N), 3.61 - 3.48 (m, 1H, C*H*), 2.46 (s, 3H, Ts CH_3), 2.39 - 2.27 (m, 1H, CH_EH_F), 2.13 - 1.99 (m, 1H, CH_EH_F), 1.72 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.22 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 151.1 (C_q), 144.6 (C_q), 143.9 (C_q), 137.6 (C_q), 132.5 (2 × Ts *C*H), 131.2 (C_q), 129.1 (2 × Ts *C*H), 123.1 (*C*H), 114.2 (*C*H$_2$), 84.0 (C_q), 49.7 (*C*H$_2$N), 47.7 (*C*H), 27.8 (Boc C(*C*H$_3$)$_3$), 26.4 (*C*H$_2$), 25.8 (*C*H$_3$), 21.6 (Ts *C*H$_3$), 19.7 (*C*H$_3$), 18.8 (*C*H$_3$). IR (neat) υ/cm^{-1}: 2979, 1732, 1645, 1598, 1459, 1380, 1138, 1100, 965, 839. HRMS (ES) *m/z* calcd. for $C_{24}H_{36}N_2O_4NaS$ $[M+MeCNNa]^+ = 471.2293$; found 471.2270.

((1*S*,2*R*)-2-Methyl-5-(propan-2-ylidene)cyclopentyl)methanol 215

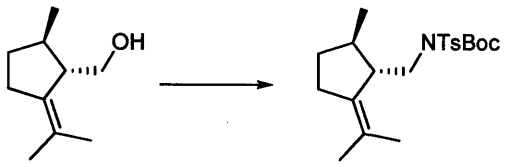


215a **215**

(1*S*,2*R*)-2-Methyl-5-(propan-2-ylidene)cyclopentanecarboxylic acid **215a** (1.00 g, 5.95 mmol, 1.0 eq.) in dry diethyl ether (15 ml) was added dropwise to a suspension of lithium aluminium hydride (300 mg, 7.74 mmol, 1.3 eq.) in dry diethyl ether (40 ml) at 0 °C. The suspension was stirred at room temperature for 1.5 hours; the reaction was cooled to 0 °C and aqueous 2 M NaOH

was added dropwise until a white precipitate had formed. The suspension was filtered and washed with diethyl ether (30 ml), the filtrate was dried over $MgSO_4$ and evaporated to give *alcohol* **215** as a clear oil (916 mg, Yield: 100%). All data obtained was in accordance with that previously reported in the literature.[284] ^1H (400 MHz / $CDCl_3$) δ 3.46 - 3.37 (m, 2H, C*H*$_2$O), 2.33 (br. s, 1H, O*H*), 2.28 - 2.21 (m, 1H, C*H*), 2.11 - 1.98 (m, 2H, C*H*$_2$), 1.86 - 1.74 (m, 1H, C*H*), 1..65 (s, 3H, C*H*$_3$), 1.56 (s, 3H, C*H*$_3$), 1.25 - 1.14 (m, 2H, C*H*$_2$) 0.88 (d, 3H, J = 7.0 Hz, C*H*$_3$).

***tert*-Butyl ((1*R*,2*R*)-2-methyl-5-(propan-2-ylidene)cyclopentyl)methyl(tosyl)carbamate 216**



215 **216**

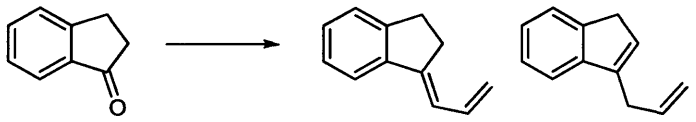
Alcohol **215** (916 mg, 5.95 mmol, 1.0 eq.) was treated with according to general method **A** using work up ***1*** to give *the title compound* **216** as a clear oil (376 mg, Yield: 15%). ^1H NMR (400 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.23 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 3.90 – 3.57 (m, 3H, C*H*$_2$N & C*H*), 2.73 - 2.69 (m, 1H, C*H*$_A$H$_B$), 2.39 - 2.35 (m, 1H, CH$_A$*H*$_B$), 1.79 – 1.67 (m, 3H, C*H*$_2$ & C*H*), 1.63 (s, 3H, C*H*$_3$), 1.63 (s, 3H, C*H*$_3$), 1.33 (s, 9H, Boc C(C*H*$_3$)$_3$), 1.23 (s, 3H, C*H*$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 157.6 (*C*$_q$), 142.3 (*C*$_q$), 140.1 (*C*$_q$), 137.2 (*C*$_q$), 129.7 (2 × Ts *C*H), 127.3 (2 × Ts *C*H), 123.3 (*C*$_q$), 84.6 (*C*$_q$), 44.7 (*C*H), 41.9 (*C*H$_2$N), 32.8 (*C*H), 29.5 (2 × *C*H$_2$), 28.6 (Boc C(*C*H$_3$)$_3$), 21.5 (Ts *C*H$_3$), 19.7 (2 × *C*H$_3$), 18.1 (*C*H$_3$). HRMS (ES) *m/z* calcd. for $C_{22}H_{37}N_2O_4$ [M+NH_4^+] = 425.2474; found 425.2480.

Preparation of anhydrous cerium (III) chloride from cerium (III) chloride heptahydrate ($CeCl_3.7H_2O$)

A 250 ml two-necked flask, round bottomed flask was equipped with a glass stopper and three-way stopcock, the flask is connected to a trap that is cooled to –78 °C and attached to a vacuum pump. The flask is charged with powdered cerium (III) chloride heptahydrate ($CeCl_3.7H_2O$) (1.38 g, 3.70 mmol) and evacuated to 0.1 - 0.2 mm. After gradual warming to 90 °C over 30 minutes with an oil bath, the flask is heated at 90 - 100 °C for 2 hours with intermittent shaking. The system is filled with dry N_2 and cooled to room temperature. The solid is transferred to a mortar and quickly pulverised with a pestle. The resulting white powder and magnetic stirring bar are placed in the original flask. Gradual warming to 90 °C at 0.1 - 0.2 mm over 30 minutes,

followed by evacuating at 90 - 100 °C for 1.5 hours with intermittent shaking, gives cerium (III) chloride monohydrate ($CeCl_3.H_2O$). The cerium (III) chloride monohydrate is gradually warmed to 140 °C over 30 minutes under reduced pressure (0.1 - 0.2 mm) without stirring. Heating at 140 - 150 °C at 0.1 - 0.2 mm for 2 hours with gentle stirring affords a fine, white powder of anhydrous cerium (III) chloride. While the flask is still hot, the area that was not immersed in the oil bath was heated with a heat gun in order to remove the last traces o water. After introduction of nitrogen gas into the flask, the resulting anhydrous cerium (III) chloride was cooled to room temperature. One of the glass stoppers is replaced by a rubber septum under a stream of dry nitrogen.

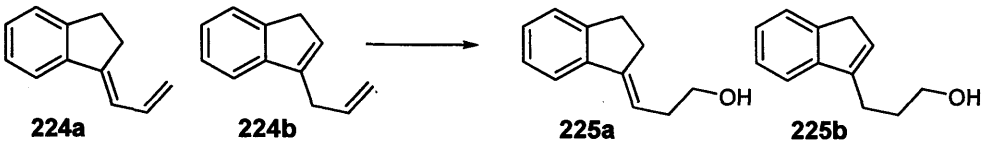
(*E*)-1-Allylidene-2,3-dihydro-1H-indene and 3-allyl-1H-indene 224



223 **224a** **224b**

$CeCl_3$ (3.70 g, 15 mmol, 1.5 eq.) was suspended in tetrahydrofuran (30 ml) and stirred overnight. The suspension was cooled to 0 °C and indanone **223** (1.32 g, 10 mmol, 1.0 eq.) in tetrahydrofuran (10 ml) was added and stirred at 20 °C for 1 hour. Allylmagnesium grignard (10 ml, 20 mmol, 2.0 eq.) was added, resulting in an orange colour. After 30 minutes the suspension was cooled to 0 °C, triethylamine (10.0 ml, 72 mmol, 7.2 eq.) and methanesulfonyl chloride (1.60 ml, 20 mmol, 2.0 eq.) were added sequentially and the suspension was warmed to 20 °C over 1 hour. Water (10 ml) and concentrated HCl (10 ml) were added, and stirred for 30 minutes. The yellow mixture was extracted with diethyl ether (3 × 30 ml) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (2 × 30 ml) and brine (30 ml). The organic phase was then dried over $MgSO_4$ and evaporated to afford *the title compounds* **224** as a brown oil (1.55 g, Yield: 99%). All data obtained was in accordance with that previously reported in the literature.[285] ^{1}H NMR (400 MHz / $CDCl_3$) (major = **224b**, minor = **224a**) δ 7.69 (dd, 1H, J = 0.5, 7.2 Hz, Ar C*H*, major), 7.52 (dt, 1H, J = 1.1, 7.4 Hz, Ar C*H*, major), 7.44 - 7.10 (m, 6H, 2 × Ar C*H*, major & 4 × Ar C*H*, minor), 6.59 - 6.23 (m, 2H, 2 × C*H*, minor), 6.18 - 6.16 (m, 1H, C*H*, major), 6.03 - 5.91 (m, 1H, C*H*, major), 5.20 (dd, 1H, J = 16.0, 1.7 Hz, CH_AH_B, minor) 5.11 (dd, 1H, J = 17.2, 1.6 Hz, CH_AH_B, major), 5.06 (dd, 1H, J = 10.1, 1.7 Hz, CH_AH_B, minor), 5.04 (dd, 1H, J = 10.1, 1.6 Hz, CH_AH_B, major), 3.70 - 3.65 (m, 2H, CH_2, major), 3.11 - 3.05 (m, 2H, CH_2, minor), 2.65 - 2.60 (m, 2H, CH_2, minor), 1.80 - 1.75 (m, 2H CH_2, major). IR (neat) υ/cm^{-1}: 3020, 2931, 1711, 1608, 1459, 750. LRMS (APCI) 174.09 (M+NH_4, 100%).

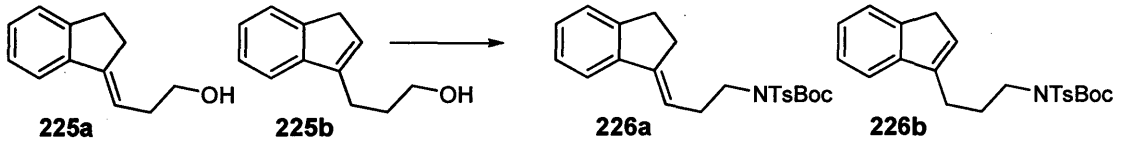
(*E*)-3-(2,3-Dihydro-1H-inden-1-ylidene)propan-1-ol and 3-(1H-inden-3-yl)propan-1-ol 225



224a 224b 225a 225b

9-BBN (21.0 ml, 10.3 mmol, 2.0 eq.) was added to **224** (800 mg 5.12 mmol, 1.0 eq.) and heated to 80 °C for 1 hour. The reaction mixture was then cooled to room temperature and carefully treated with 5 M NaOH (5 ml) followed by 30 wt. % hydrogen peroxide in water (5 ml) and heated at 60 °C for 1 hour. The reaction was cooled to room temperature and the aqueous layer was saturated with K_2CO_3; the organic layer was separated, dried over $MgSO_4$ and evaporated to give crude **225**, which was used in the next step without further purification.

(*E*)-*tert*-Butyl 3-(2,3-dihydro-1H-inden-1-ylidene)propyl(tosyl)carbamate and *tert*-butyl 3-(1H-inden-3-yl)propyl(tosyl)carbamate 226

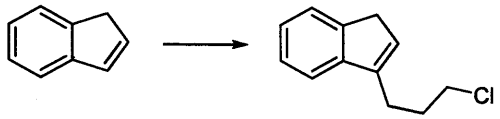


225a 225b 226a 226b

Crude alcohol **225** (2.29 g, 13.2 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (3.60 g, 13.3 mmol, 1.01 eq.) according to general procedure **A**, using work up ***2***. The crude product was purified by flash column chromatography (eluting silica gel with 20 - 40 % ethyl acetate in hexanes followed dichloromethane) to give *the sulfonamides* **226** as an orange oil (588 mg, Yield: 11%). ^{1}H NMR (400 MHz / $CDCl_3$) (major = **226b**, minor = **226a**) δ 7.85 (d, 4H, J = 8.3 Hz, 4 × Ts C*H*, major and minor), 7.73 - 7.65 (m, 2H, Ar. C*H*, major and minor), 7.60 - 7.56 (m, 2H, Ar. C*H*, major and minor), 7.48 (m, 2H, Ar. C*H*, major and minor), 7.31 - 7.10 (m, 6H, Ar. C*H*, major; Ar C*H*, minor; 2 × Ts C*H*, major; 2 × Ts C*H*, minor), 5.70 - 5.56 (m, 1H, C*H* minor isomer), 4.60 (t, 1H, J = 4.6 Hz, C*H* major isomer), 3.15 - 3.12 (m, 1H, CH_AH_B, major and minor), 2.70 - 2.67 (m, 1H, CH_AH_B, major and minor), 2.43 (s, 3H, Ts CH_3, major and minor), 2.21 - 2.12 (m, 2H, CH_2, major and minor), 1.82 - 1.80 (m, 2H, CH_2, major and minor), 1.68 - 1.47 (m, 2H, CH_2, major and minor), 1.38 (s, 9H, Boc $C(CH_3)_3$, major and minor). ^{13}C NMR (400 MHz / $CDCl_3$) (only the major isomer was visible) δ 155.2 (C_q), 150.7 (C_q), 143.9 (C_q), 137.8 (C_q), 137.1 (C_q), 134.6 (Ar *C*H), 133.6 (C_q), 129.4 (2 × Ts *C*H), 127.7 (2 × Ts *C*H), 127.3 (Ar *C*H), 126.7 (Ar *C*H), 126.2 (*C*H), 123.7 (Ar *C*H), 84.0 (C_q), 36.2 (CH_2N),

34.3 (2 × CH_2), 28.0 (Boc C(CH_3)$_3$), 25.8 (CH_2), 21.6 (Ts CH_3). HRMS (ES) *m/z* calc. for $C_{19}H_{22}NO_2S$ $[M+H]^+$ = 328.1371; found 328.1371.

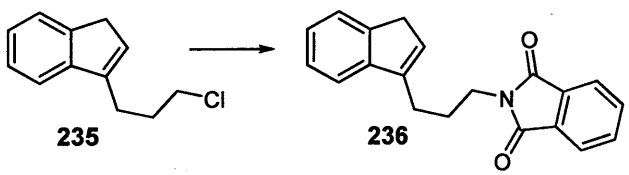
3-(3-Chloropropyl)-1H-indene 235



234 **235**

Indene **234** (1.00 g, 8.61 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (50 ml) and cooled to 0 °C, 2.5. M *n*-BuLi in hexanes (3.5 mmol, 8.69 mmol, 1.01 eq.) was added dropwise and the mixture was stirred for 30 minutes. The reaction mixture was then cooled to –78 °C, 1-chloro-3-iodopropane **233** (2.30 ml, 21.5 mmol, 2.5 eq.) was added and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with brine (2 × 30 ml), dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **235** as an orange oil (1.25 g, Yield: 75%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.41 - 7.12 (m, 4H, 4 × Ar C*H*), 6.26 - 6.24 (m, 1H, C*H*), 3.64 (t, 2H, J = 6.1 Hz, CH_2Cl), 3.33 (d, 2H, J = 6.5 Hz, CH_2), 2.25 - 2.19 (m, 2H, CH_2), 2.19 - 2.13 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 145.1 (C_q), 144.5 (C_q), 142.8 (C_q), 128.7 (Ar *C*H), 126.1 (Ar *C*H), 124.7 (Ar *C*H), 123.9 (Ar *C*H), 118.9 (*C*H), 44.8 (CH_2Cl), 37.8 (CH_2), 35.4 (CH_2), 31.8 (CH_2). IR (neat) υ/cm^{-1}: 3068, 2923, 1712, 1602, 1459, 750, 700. HRMS (EI) *m/z* calcd. for $C_{12}H_{13}Cl$ (Cl^{35}) $[M]^+$ = 192.0706; found 192.0705.

2-(3-(1H-Inden-3-yl)propyl)isoindoline-1,3-dione 236

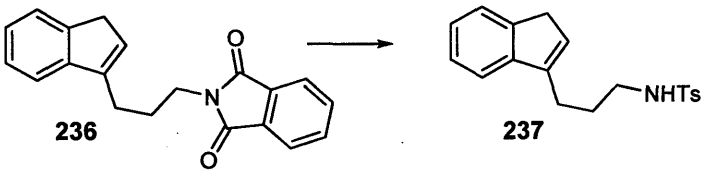


235 **236**

The chloride **235** (796 mg, 4.13 mmol, 1.0 eq.) was dissolved in *N,N*-dimethylformamide (50 ml), treated with phthalimide potassium salt (1.50 g, 8.25 mmol, 2.0 eq.) and heated to 90 °C for 2 hours. The reaction mixture was cooled to room temperature, water (30 ml) was added and the

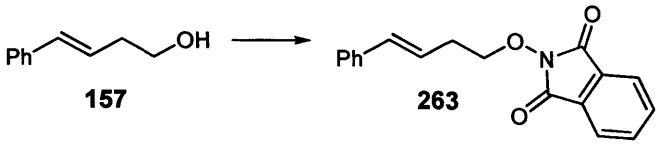
aqueous layer extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with water (3 × 30 ml), brine (30 ml), dried over $MgSO_4$ and evaporated to give *the title compound* **236** as orange oil (1.23 g, Yield: 98%). All data obtained was in accordance with that previously reported in the literature.[286] ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.77 – 7.64 (m, 4H, 4 × Ar C*H*), 7.35 - 7.09 (m, 4H, 4 × Ar C*H*), 6.23 - 6.21 (m, 1H, C*H*), 3.75 (t, 2H, J = 7.2 Hz, CH_2N), 3.23 (d, 2H, J = 1.9 Hz, CH_2), 2.55 (app. dt, 2H, J = 8.0, 1.7 Hz, CH_2), 2.08 - 2.01 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 168.5 (2 × C_q), 145.1 (C_q), 144.4 (C_q), 143.1 (C_q), 134.0 (2 × Ar *C*H), 132.3 (2 × C_q), 128.3 (Ar *C*H), 126.1 (Ar *C*H), 124.6 (Ar *C*H), 123.8 (Ar *C*H), 123.2 (2 × Ar *C*H), 118.9 (*C*H), 38.0 (*C*H_2N), 37.8 (*C*H_2), 26.7 (*C*H_2), 25.1 (*C*H_2). IR (neat) υ/cm^{-1}: 3063, 2939, 1712, 1612, 1459, 750. HRMS (CI) *m/z* calcd. for $C_{20}H_{18}NO_2$ $[M+H]^+$ = 304.1338; found 304.1336.

_N_-(3-(1H-Inden-3-yl)propyl)-4-methylbenzenesulfonamide 237



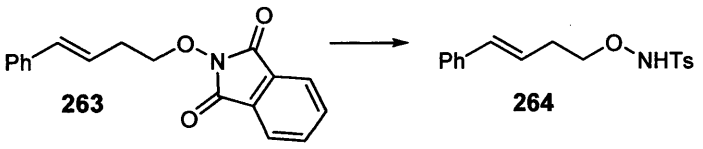
The phthalimide **236** (1.23 g, 4.06 mmol, 1.0 eq.) was treated according to general method **B** to give *the sulfonamide* **237** as a viscous orange oil (584 mg, Yield: 44%). All data obtained was in accordance with that previously reported in the literature.[287] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.55 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.28 (br. d, 1H, J = 7.3 Hz, Ar. C*H*), 7.36 - 7.00 (m, 5H, 3 × Ar. C*H* & 2 × Ts C*H*), 5.70 - 5.56 (m, 1H, C*H*), 3.15 - 3.12 (m, 1H, CH_AH$_B$), 2.70 - 2.67 (m, 1H, CH$_A$$H_B$), 2.43 (s, 3H, Ts C$H_3$), 2.21 - 2.12 (m, 2H, C$H_2$), 1.82 - 1.80 (m, 2H, C$H_2$), 1.68 - 1.47 (m, 2H, C$H_2$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.9 (2 × C_q), 137.8 (C_q), 137.1 (C_q), 133.4 (C_q), 134.6 (Ar *C*H), 129.4 (2 × Ts *C*H), 127.7 (2 × Ts *C*H), 127.3 (Ar *C*H), 126.7 (Ar *C*H), 123.7 (Ar *C*H), 60.0 (*C*H), 36.2 (*C*H_2N), 34.3 (2 × *C*H_2), 25.8 (*C*H_2), 21.6 (Ts *C*H_3). IR (neat) υ/cm^{-1}: 3280, 3064, 2926, 1712, 1598, 1459, 1380, 1139, 854, 750. HRMS (APCI) *m/z* calcd. for $C_{19}H_{22}NO_2S$ $[M+H]^+$ = 328.1371; found 328.1359.

(*E*)-2-(4-Phenylbut-3-enyloxy)isoindoline-1,3-dione 263



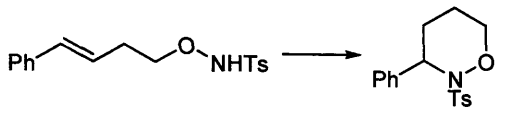
E)-Phenylbut-3-en-1-ol **157** (1.36 g, 9.22 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (1.52 g, 9.31 mmol, 1.01 eq.) according to general procedure **A** using work up ***2***. The crude product purified by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **263** as a yellow solid (535 mg, Yield: 20%). m.p.: 74 - 76 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.76 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 7.67 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 7.32 - 7.11 (m, 5H, 5 × Ar C*H*), 6.49 (d, 1H, J = 15.8 Hz, C*H*), 6.21 (td, 1H, J = 6.8, 15.8 Hz, C*H*), 4.27 (t, 2H, J = 6.8 Hz, CH_2O), 2.70 - 2.63 (m, 2H, CH_2). ^{13}C (400 MHz / $CDCl_3$) δ 163.7 (2 × C_q), 140.3 (2 × C_q), 137.2 (C_q), 134.5 (2 × Ar *C*H), 132.7 (Ar *C*H), 128.5 (2 × Ar *C*H), 127.3 (*C*H), 126.2 (2 × Ar *C*H), 124.7 (*C*H), 123.6 (2 × Ar *C*H), 77.4 (CH_2O), 31.9 (CH_2). HRMS (APCI) *m/z* calcd. for $C_{18}H_{16}NO_3$ $[M+H]^+$ = 294.1130; found 294.1133.

(*E*)-4-Methyl-*N*-(4-phenylbut-3-enyloxy)benzenesulfonamide 264



The phthalimide **263** (535 mg, 1.83 mmol, 1.0 eq.) was treated according to general method **B** and the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the sulfonamide* **264** as a yellow solid (462 mg, Yield: 62%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.77 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.38 - 7.18 (m, 7H, 5 × Ar C*H* & 2 × Ts C*H*), 6.42 (d, 1H, J = 15.8 Hz, C*H*), 6.16 (td, 1H, J = 6.9, 15.8 Hz, C*H*), 4.13 (t, 2H, J = 6.9 Hz, CH_2O), 2.54 - 2.49 (m, 2H, CH_2), 2.39 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 139.9 (C_q), 137.2 (C_q), 133.4 (C_q), 132.2 (*C*H), 129.7 (2 × Ts *C*H), 129.7 (2 × Ts *C*H), 128.7 (2 × Ar *C*H), 128.6 (2 × Ar *C*H), 127.3 (*C*H), 126.1 (Ar *C*H), 76.3 (CH_2O), 29.9 (CH_2), 21.7 (Ts CH_3). HRMS (APCI) *m/z* calcd. for $C_{17}H_{20}NO_3S$ $[M+H]^+$ = 318.1164; found 318.1170.

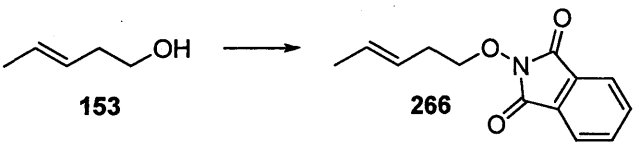
3-Phenyl-2-tosylmorpholine 265



264 **265**

The sulfonamide **264** (100 mg, 0.27 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.14 mmol, 0.5 eq.) and the resulting solution stirred at room temperature for 24 hours. The reaction was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **265** as a white solid (70 mg, Yield: 70%). m.p.: 92 - 95 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.62 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.33 - 7.20 (m, 7H, 5 x Ar C*H* & 2 × Ts C*H*), 4.89 (t, 1H, J = 4.9 Hz,C*H*N), 4.39 - 4.31 (m, 1H, CH_AH$_B$O), 4.10 - 4.03 (m, 1H, CH$_A$$H_B$O), 2.41 (s, 3H, Ts C$H_3$), 2.27 - 2.19 (m, 1H, C$H_CH_D$), 2.06 - 1.98 (m, 1H, CH$_C$$H_D$), 1.65 - 1.53 (m, 2H, C$H_2$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 144.1 (C_q), 139.3 (C_q), 133.6 (C_q), 129.2 (2 × Ts *C*H), 128.8 (2 × Ar *C*H), 128.1 (2 × Ar *C*H), 127.6 (2 × Ts *C*H), 127.2 (Ar *C*H), 71.4 (*C*H$_2$O), 59.7 (*C*HN), 30.0 (*C*H$_2$), 21.7 (Ts *C*H$_3$), 20.8 (*C*H$_2$). IR (neat) υ/cm^{-1}: 2954, 1598, 1462, 1139, 1100, 825, 750, 690. HRMS (APCI) *m/z* calcd. for $C_{17}H_{20}NO_3S$ $[M+H]^+$ = 318.1164; found 318.1171.

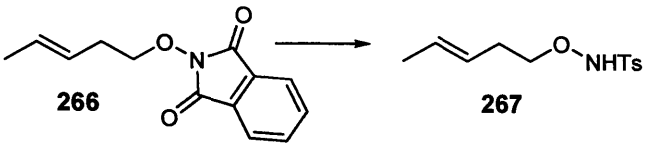
(*E*)-2-(Pent-3-enyloxy)isoindoline-1,3-dione 266



153 **266**

(*E*)-Pent-3-en-1-ol **153** (1.19 g, 13.79 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (2.30 g, 13.93 mmol, 1.01 eq.) according to general method **A** using work up *2*. The crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **266** as a clear oil (1.29 g, Yield: 41%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.77 (app. dd, 2H, J= 7.7, 1.3 Hz, 2 × Ar C*H*), 7.66 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 5.49 - 5.59 (m, 1H, C*H*), 5.37 - 5.44 (m, 1H, C*H*), 4.14 (t, 2H, J = 7.0 Hz, CH_2O), 2.40 - 2.46 (m, 2H, CH_2), 1.59 (d, 3H, J = 6.3 Hz, CH_3). LRMS (ES) 232.09 ($M+H^+$, 86%), 288 ($M+NH_4^+$, 59%).

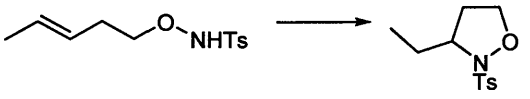
(*E*)-4-Methyl-*N*-(pent-3-enyloxy)benzenesulfonamide 267



266 267

(*E*)-2-(Pent-3-enyloxy)isoindoline-1,3-dione **266** (1.29 g, 5.56 mmol, 1.0 eq.) was treated according to general method **B** and the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the sulfonamide* **267** as a yellow solid (716 mg, Yield: 51%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.80 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.35 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.63 - 5.48 (m, 1H, C*H*), 5.42 - 5.33 (m, 1H, C*H*), 4.15 - 4.10 (m, 2H, CH_2O), 2.46 (s, 3H, Ts CH_3), 2.34 - 2.26 (m, 2H, CH_2), 1.70 (d, 3H, J = 6.2 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 144.7 (C_q), 133.3 (C_q), 131.5 (*C*H), 130.41 (*C*H), 129.9 (2 × Ts *C*H), 127.9 (2 × Ts *C*H), 66.9 (*C*H_2O), 31.2 (*C*H_2), 21.7 (Ts *C*H_3), 14.7 (*C*H_3). HRMS (ES) *m/z* calcd. for $C_{12}H_{18}NO_3S$ $[M+H]^+$ = 256.1007; found 256.1019.

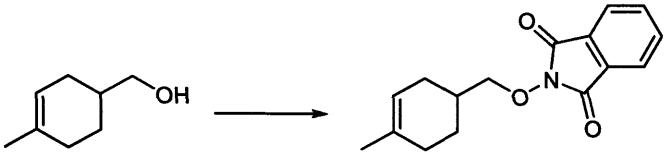
3-Ethyl-2-tosylisoxazolidine 269



267 269

The sulfonamide **267** (50 mg 0.19 mmol, 1.0 eq.) was dissolved in dichloromethane (5 ml), to which was added triflic acid (0.15 ml, 0.09 mmol, 0.5 eq.). The resulting solution was stirred at 0 °C for 24 hours and then quenched with saturated aqueous K_2CO_3 (15 ml). The two layers were separated, the aqueous layer was extracted with dichloromethane (2 × 15 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **269** as an orange oil (32 mg Yield: 64%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.75 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.27 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.13 - 3.87 (m, 2H, CH_2O), 2.38 (s, 3H, Ts CH_3), 2.31 - 2.23 (m, 1H, C*H*N), 1.92 - 1.84 (m, 2H, CH_2), 1.69 - 1.60 (m, 2H, CH_2), 1.14 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.6 (C_q), 139.8 (C_q), 129.4 (2 × Ts *C*H), 127.1 (2 × Ts *C*H), 69.9 (*C*H_2O), 66.8 (*C*HN), 34.5 (*C*H_2), 28.8 (*C*H_2), 21.6 (Ts *C*H_3), 10.9 (*C*H_3). IR (neat) υ/cm^{-1}: 2965, 1597, 1459, 1380, 1138, 1100, 839. HRMS (ES) *m/z* calcd. for $C_{12}H_{18}NO_3S$ $[M+H]^+$ = 256.1007; found 256.1009.

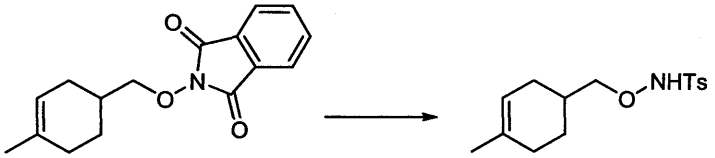
2-((4-Methylcyclohex-3-enyl)methoxy)isoindoline-1,3-dione 270



192 **270**

4-Methyl-cyclohex-3-enyl)-methanol **192** (500 mg, 3.97 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (650 mg, 4.01 mmol, 1.01 eq.) according to general procedure **A** using work up ***1*** to give *the title compound* **270** as a clear oil (1.08 g, Yield: 100%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.60 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 7.47 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 5.40 - 5.35 (m, 1H, C*H*), 3.70 - 3.65 (d, 2H, J = 6.5 Hz, CH_2O), 2.21 - 1.91 (m, 3H, 3 × CH_AH_B), 1.81 - 1.76 (m, 1H, C*H*), 1.65 (s, 3H, CH_3), 1.43 - 1.32 (m, 3H, 3 × CH_AH_B). ^{13}C NMR (400 MHz / $CDCl_3$) δ 161.0 (2 × C_q), 134.4 (3 × C_q), 132.2 (2 × Ar *C*H), 128.5 (2 × Ar *C*H), 123.5 (*C*H), 82.9 (CH_2O), 32.5 (*C*H), 29.0 (CH_2), 28.1 (CH_2), 25.5 (CH_2), 21.9 (CH_3). IR (neat) υ/cm^{-1}: 3020, 2980, 1733, 1458, 1380, 1100, 964, 750.

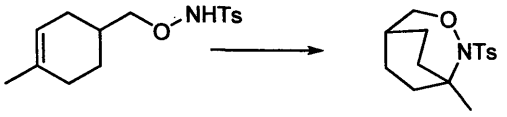
4-Methyl-*N*-((4-methylcyclohex-3-enyl)methoxy)benzenesulfonamide 271



270 **271**

2-((4-Methylcyclohex-3-enyl)methoxy)isoindoline-1,3-dione **270** (1.08 g, 3.97 mmol, 1.0 eq.) was treated according to general procedure **B** and the crude product purified by flash column chromatography to give *the sulfonamide* **271** as a white solid (749 mg, Yield: 64%). m.p: 119 - 124 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.67 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.20 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 5.36 - 5.32 (m, 1H, C*H*), 4.11 - 3.97 (m, 2H, CH_2O) 2.42 (s, 3H, Ts CH_3), 2.10 – 1.71 (m, 4H, 2 × CH_2), 1.65 (s, 3H, CH_3), 1.36 - 1.23 (m, 3H, CH_2 & C*H*). IR (neat) υ/cm^{-1}: 3060, 2956, 1597, 1459, 1380, 1100, 964, 839. HRMS (ES) calcd. for $C_{15}H_{20}NO_3S$ $[M–H]^+$ = 294.1164; found 294.1151.

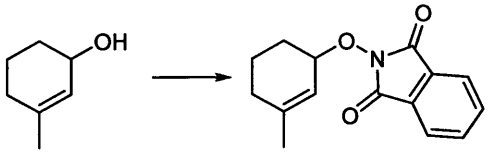
2-tosyl-3-oxa-2-azabicyclo[3.2.2]nonane 272



271 **272**

The sulfonamide **271** (50 mg 0.17 mmol, 1.0 eq.) was dissolved in dichloromethane (5 ml), to which was added TfOH (0.13 ml, 0.09 mmol, 0.5 eq.) and the resulting solution stirred at 0 °C for 24 hours. The reaction was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and evaporated to give *the title compound* **272** as an orange oil (43 mg Yield: 86%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.59 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.12 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.04 - 3.74 (m, 2H, CH_2O), 2.33 (s, 3H, Ts CH_3), 2.00 - 0.70 (m, 9H, 4 × CH_2 & C*H*), 1.55 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 134.0 (C_q), 132.8 (C_q), 129.4 (2 × Ts *C*H), 127.3 (2 × Ts *C*H), 73.4 (*C*H_2O), 54.1 (C_q), 36.7 (*C*H), 32.8 (2 × *C*H_2), 23.6 (2 × *C*H_2), 21.8 (*C*H_3), 21.5 (Ts *C*H_3). IR (neat) υ/cm^{-1}: 2925, 1597, 1469, 1380, 1148, 1100, 845. HRMS (EI) *m/z* calcd. for $C_{18}H_{17}NO_3S$ $[M]^+$ = 295.1208; found 295.1217.

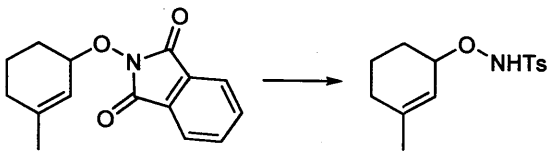
2-(3-Methylcyclohex-2-enyloxy)isoindoline-1,3-dione 274a



273a **274a**

3-Methyl-2-cyclohexen-1-ol **273a** (500 mg, 4.46 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (735 mg, 4.5 mmol, 1.01 eq.) according to general method **A** using work up *2* and purified the crude product by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **274a** as a white solid (606 mg, Yield: 53%). m.p: 105 - 107 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.78 (app. dd, 2H, J = 7.71.3 Hz, 2 × Ar C*H*), 7.68 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 5.60 (s, 1H, C*H*), 4.70 - 4.65 (m, 1H, C*H*O), 1.66 (s, 3H, CH_3), 1.65 - 1.56 (m, 6H, 3 × CH_2). HRMS (ES) *m/z* calcd. for $C_{15}H_{19}N_2O_3$ $[M+NH_4]^+$ = 275.1396; found 275.1399.

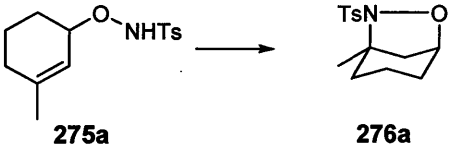
4-Methyl-*N*-(3-methylcyclohex-2-enyloxy)benzenesulfonamide x275a



274a **275a**

The phthalimide **274a** (606 mg, 2.36 mmol, 1.0 eq.) was treated according to general procedure **B** and the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the sulfonamide* **275a** as a yellow oil (414 mg, Yield: 65%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.82 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.34 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.51 - 447 (m, 1H, C*H*), 4.51 - 4.45 (m, 1H, C*H*O), 2.44 (s, 3H, Ts CH_3), 1.93 - 1.86 (m, 3H, 3 × CH_AH$_B$), 1.68 (s, 3H, CH_3), 1.67 - 1.52 (m, 3H, 3 × CH$_A$$H_B$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.6 (C_q), 140.7 (C_q), 136.4 (C_q), 129.6 (2 × Ts *C*H), 129.4 (2 × Ts *C*H), 125.6 (*C*H), 77.0 (*C*H$_2$), 36.6 (*C*H), 30.6 (2 × *C*H$_2$), 23.4 (*C*H$_3$), 21.8 (*C*H$_3$). HRMS (ES) *m/z* calcd. for $C_{14}H_{20}NO_3S$ $[M+H]^+$ = 282.1164; found 282.1154.

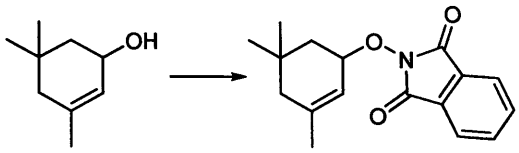
(1*R*,5*S*)-1-Methyl-7-tosyl-6-oxa-7-azabicyclo[3.2.1]octane 276a



275a **276a**

The sulfonamide **275a** (100 mg 0.36 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.26 ml, 0.18 mmol, 0.5 eq.) and the resulting solution stirred at 0 °C for 24 hours. The reaction was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and concentrated to give *the title compound* **276a** a yellow oil (86 mg Yield: 86%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.28 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.39 - 4.30 (m, 1H, C*H*O), 2.39 (s, 3H, Ts CH_3), 2.21 - 1.84 (m, 2H, CH_2), 1.67 - 1.52 (m, 2H, CH_2), 1.35 - 1.21 (m, 2H, CH_2), 1.13 (s, 3H, CH_3), 0.96 - 0.90 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 144.9 (C_q), 132.4 (C_q), 129.6 (2 × Ts *C*H), 129.4 (2 × Ts *C*H), 85.9 (C_q), 60.4 (*C*HO), 42.7 (*C*H$_2$), 36.7 (*C*H$_2$), 30.6 (*C*H$_2$), 23.4 (*C*H$_3$), 21.8 (*C*H$_3$), 18.8 (*C*H$_2$). IR (neat) υ/cm^{-1}: 2930, 1710, 1597, 1449, 1380, 1138, 1100, 839. HRMS (EI) *m/z* calcd. for $C_{14}H_{20}NSO_3$ $[M+H]^+$ = 282.1164 observed $[M+H^+]$ = 282.1171.

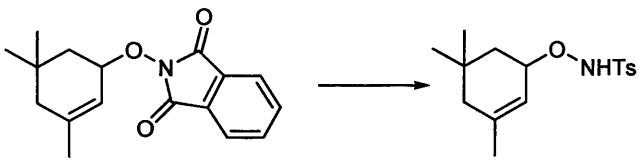
2-(3,5,5-Trimethylcyclohex-2-enyloxy)isoindoline-1,3-dione 274b



273b **274b**

3,5,5-trimethyl-2-cyclohexen-1-ol **273b** (0.60 ml, 3.57 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (0.588 g, 3.60 mmol, 1.01 eq.) according to general procedure **A** using work up *2* and purified the crude product by flash column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **274b** as a white solid (504 mg, Yield: 54%). m.p.: 91 - 94 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.78 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 7.68 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 5.63 - 5.58 (m, 1H, C*H*), 4.75 - 4.67 (m, 1H, C*H*O), 1.66 (s, 3H, CH_3), 1.65 - 1.56 (m, 4H, 2 × CH_2), 0.99 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 160.1 (2 × C_q), 140.0 (2 × C_q), 134.4 (2 × Ar *C*H), 129.0 (C_q), 123.5 (2 × Ar *C*H), 118.1 (*C*H), 84.1 (*C*HO), 44.2 (*C*H_2), 40.1 (*C*H_2), 31.2 (C_q), 30.8 (*C*H_3), 26.5 (*C*H_3), 23.8 (*C*H_3). HRMS (ES) *m/z* calcd. for $C_{34}H_{42}N_3O_6$ $[(2 \times M)+NH_4^+]^+$ = 588.3074; found 588.3062.

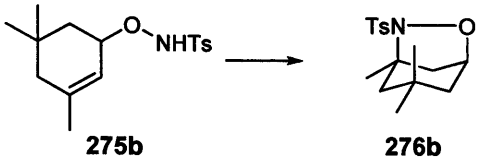
4-Methyl-*N*-(3,5,5-trimethylcyclohex-2-enyloxy)benzenesulfonamide 275b



274b **275b**

The phthalimide **274b** (488 mg 1.71 mmol, 1.0 eq.) was treated according to general procedure **B** and the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the sulfonamide* **275b** as an orange oil (526 mg, Yield: 90%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.82 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.34 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.54 - 5.48 (m, 1H, C*H*), 4.74 - 4.69 (m, 1H, C*H*O), 2.44 (s, 3H, Ts CH_3), 1.68 (s, 3H, CH_3), 1.67 - 1.52 (m, 4H, 2 × CH_2), 0.99 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 149.5 (C_q), 143.7 (C_q), 136.7 (C_q), 129.3 (2 × Ts *C*H), 127.6 (2 × Ts *C*H), 123.1 (*C*H), 77.0 (*C*H), 46.7 (*C*H_2), 43.4 (*C*H_2), 31.8 (C_q), 29.4 (2 × *C*H_3), 27.5 (*C*H_3), 21.4 (*C*H_3). IR (neat) υ/cm^{-1}: 3054, 2961, 1712, 1598, 1449, 1380, 1138, 1100, 839. LRMS (ES) 308 (M-H$^+$, 86%), 294 (M-CH_3, 73%).

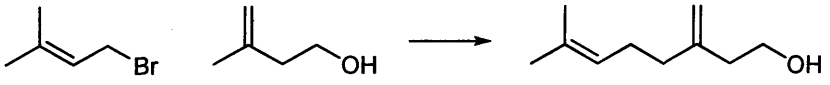
(1*R*,5*S*)-1,3,3-Trimethyl-7-tosyl-6-oxa-7-azabicyclo[3.2.1]octane 276b



275b **276b**

The sulfonamide **275b** (100 mg 0.32 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.26 ml, 0.16 mmol, 0.5 eq.) and the resulting solution stirred at 0 °C for 24 hours. The reaction was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and concentrated to give *the title compound* **276b** a yellow oil (90 mg Yield: 90%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.28 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.40 - 4.36 (m, 1H, C*H*O), 2.39 (s, 3H, Ts CH_3), 2.21 - 1.84 (m, 2H, CH_2), 1.67 - 1.52 (m, 2H, CH_2), 1.15 (s, 3H, CH_3), 1.03 (s, 6H, 2 × CH_3), 0.96 - 0.90 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 144.9 (C_q), 132.4 (C_q), 129.6 (2 × Ts *C*H), 129.4 (2 × Ts *C*H), 85.9 (C_q), 60.4 (*C*HO), 48.2 (C_q), 42.7 (CH_2), 36.7 (CH_2), 33.5 (2 × CH_3), 30.6 (CH_2), 23.4 (CH_3), 21.8 (CH_3). IR (neat) υ/cm^{-1}: 2930, 1710, 1597, 1449, 1380, 1138, 1100, 839. HRMS (EI) *m/z* calcd. for $C_{16}H_{24}NO_3S$ $[M+H]^+$ = 310.1432; found 310.1438.

7-Methyl-3-methyleneoct-6-en-1-ol 283[288]

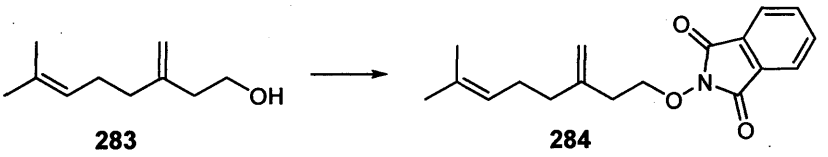


281 **282** **283**

TMEDA (9.10 ml, 0.604 mmol, 2.6 eq.) and diethyl ether (50 ml) were stirred together and cooled to 0 °C. To this was then added 1.6M *n*-BuLi in hexanes (31.0 ml, 0.51 mmol, 2.2 eq.) and the resulting pale yellow solution was stirred at room temperature for 1 hour. The solution was then cooled to 0 °C and 3-methyl-3-buten-1-ol **282** (2.40 ml, 0.232 mmol, 1.0 eq.) was added dropwise and the solution turned to an intense yellow colour. The reaction mixture was then stirred at room temperature for 6 hours to give the desired dianion as a yellow slurry. The slurry was the cooled to –78 °C and 3,3-dimethylallyl bromide **281** (3.20 ml, 0.279 mmol, 1.2 eq.) in ether (6 ml) was added slowly. The reaction was then allowed to warm to room temperature slowly over 16 hours. Stirred at room temperature for another further 3 hours; the reaction was then quenched by the careful addition of saturated aqueous NH_4Cl (20 ml). The resulting layers were then separated and

the aqueous layer was extracted with ether (3 × 30 ml), the combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. 1 g of the 3.587 g of the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **283** as a clear oil (348 mg, Yield: 97%). All data obtained were in accordance with those previously reported in the literature.[288] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.13 - 5.05 (m, 1H, C*H*), 4.86 (br. s, 1H, C*H*), 4.82 (br. s, 1H, C*H*), 3.69 (t, 2H, J = 6.3 Hz, CH_2), 2.29 (t, 2H, J = 6.3 Hz, CH_2), 2.15 - 2.00 (m, 4H, 2 × CH_2), 1.67 (s, 3H, CH_3), 1.59 (s, 3H, CH_3). ^{13}C (400 MHz / $CDCl_3$) 145.9 (C_q), 132.0 (C_q), 123.8 (CH), 111.8 (CH_2), 60.3 (CH_2), 39.3 (CH_2), 35.7 (CH_2), 26.3 (CH_3), 27.5 (CH_3), 17.8 (CH_3). LRMS *m/z* (APCI) 137.1 (M^+ + H, 100%).

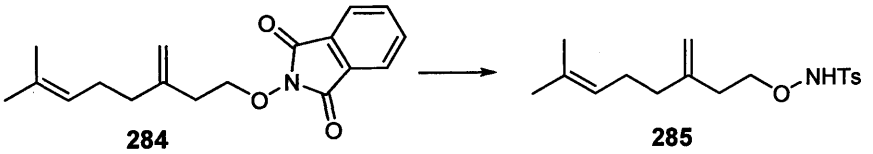
2-(7-Methyl-3-methyleneoct-6-enyloxy)isoindoline-1,3-dione 284



283 **284**

7-Methyl-3-methyleneoct-6-en-1-ol **283** (348 mg, 2.259 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalamide (372 mg, 2.282 mmol, 1.01 eq.) according to general method **F**. The *crude product* **284** was not purified before use in the next step.

4-Methyl-N-(7-methyl-3-methyleneoct-6-enyloxy)benzenesulfonamide 285[289]

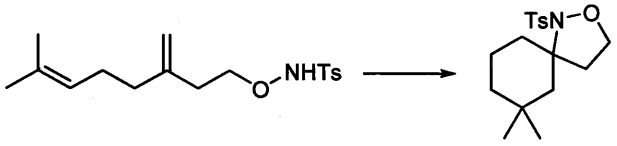


284 **285**

Crude phthalimide **284** (1.05 g, 3.512 mmol, 1.0 eq.) was treated according to general method **F** and the crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the sulfonamide* **285** as a clear oil (340 mg Yield: 30%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.81 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.34 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.12 (br, s, 1H, N*H*), 5.08 (br. t, 1H, J = 6.7 Hz, C*H*), 4.80 (br. s, 1H, C*H*), 4.76 (m, 1H, C*H*), 4.10 (t, 2H, J = 6.8 Hz, CH_2O), 2.45 (s, 3H, Ts CH_3), 2.33 (t, 2H, J = 6.8 Hz, CH_2), 2.13 - 1.99 (m, 4H, 2 × CH_2), 1.68 (s, 3H, CH_3), 1.60 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 145.5 (C_q), 144.8 (C_q), 133.6 (C_q), 131.8 (C_q), 129.7 (2 × Ts CH), 128.6 (2 × Ts CH), 123.8 (CH_2), 111.1 (CH), 75.6

(CH_2), 36.0 (CH_2), 34.6 (CH_2), 26.3 (CH_3), 25.7 (CH_3), 21.7 (Ts CH_3), 17.7 (CH_2). HRMS (EI) *m/z* calcd. for $C_{17}H_{26}NO_3S$ $[M + H]^+$ = 324.1633; found 324.1636.

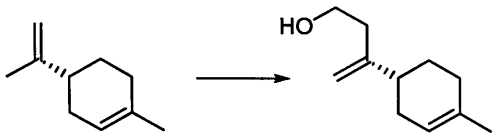
6,6-Dimethyl-1-tosyl-2-oxa-1-azaspiro[4.5]decane 286



285 **286**

The sulfonamide **285** (100 mg 0.31 mmol, 1 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.31 ml, 0.15 mmol, 0.5 eq.) and the resulting solution stirred at 0 °C for 1 hour. The reaction was quenched with saturated aqueous K_2CO_3 and the two layers separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml), the combined organic layers dried over K_2CO_3 and evaporated. The crude product was purified by flash column chromatography (eluting silica gel with dichloromethane) to give *the title compound* **286** as a yellow oil (70 mg Yield: 70%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.83 (2H, d, J = 8.3 Hz, 2 x Ts C*H*), 7.32 (2H, d, J = 8.5 Hz, 2 x Ts C*H*), 4.23 - 4.11 (m, 2H, CH_2O), 2.47 (ddd, 1H, J = 11.8, 9.4, 6.2 Hz, CH_AH$_B$), 2.43 (s, 3H, Ts CH_3), 2.21 (ddd, 1H, J = 11.8, 9.4, 5.9 Hz, CH$_A$$H_B$), 2.17 - 2.09 (m, 1H, C$H_CH_D$), 2.01 (d, 1H, J = 13.4 Hz, CH_EH$_F$), 1.97 – 1.88 (1H, m, CH$_C$$H_D$), 1.77 (app. dddd, 1H, J = 13.7, 7.9, 3.6, 0.9 Hz, CH_GH$_H$), 1.57 - 1.51 (m, 1H, CH$_G$$H_H$), 1.49 (d, 1H, J = 13.4, CH$_E$$H_F$), 1.40 - 1.29 (m, 2H, CH$_2$), 1.07 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). ^{13}C NMR (500MHz / $CDCl_3$) δ 144.2 (C_q), 136.0 (C_q), 129.3 (2 × Ts *C*H), 128.6 (2 × Ts *C*H), 71.2 (*C*H$_2$O), 69.5 (C_q), 47.1(*C*H$_2$), 40.7 (*C*H$_2$), 38.7 (*C*H$_2$), 33.8 (*C*H$_2$), 31.4 (C_q), 21.7 (Ts *C*H$_3$), 21.6 (2 × *C*H$_3$) 20.0 (*C*H$_2$). IR (neat) υ/cm^{-1}: 2952, 1598, 1455, 1327, 1156, 1089, 814, 670. HRMS (EI) *m/z* calcd. for $C_{17}H_{25}NO_3S$ $[M]^+$ = 323.1555; found 323.1552.

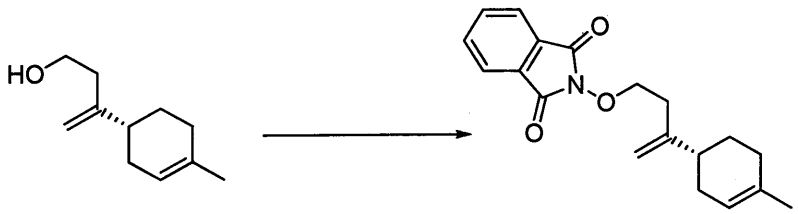
3-(4-methylcyclohex-3-enyl)but-3-en-1-ol 288[147]



287 **288**

A mixture of (*R*)-limonene **287** (25.0 g, 183.5 mmol, 1.0 eq.), paraformaldehyde (2.65 g, 88.1 mmol, 0.48 eq.) and dichloromethane (200ml) were stirred at 0 °C for 10 minutes. Then fuming stannic chloride (0.10 ml, 222.6 mmol, 1.2 eq.) was added dropwise, forming a heterogeneous orange solution. This solution was stirred at 20 °C for 3 days, after which the solution had turned a tan colour. Under vigorous stirring, dilute aqueous NaOH (20 ml) was added. The two phases were separated and the aqueous phase was further extracted with ether (3 × 30 ml), the combined organics were dried over Na_2SO_4 and evaporated. The resulting oil was filtered through silica with petroleum ether to remove any residual starting materials, followed by methanol to give *the title compound* **288** as a clear oil (3.70 g, Yield: 12%). All data obtained was in accordance with that previously reported in the literature.[290] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.43 - 5.37 (m, 1H, C*H*), 5.17 - 4.98 (m, 2H, CH_2), 3.48 (t, 2H, J = 7.0 Hz, CH_2O), 2.40 - 2.32 (m, 1H, C*H*), 2.15 - 1.87 (m, 4H, 2 × CH_2), 1.83 - 1.76 (m, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.52 - 1.41 (m, 2H, CH_2).

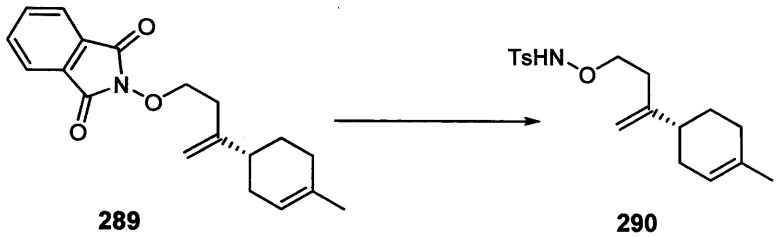
2-(3-(4-Methylcyclohex-3-enyl)but-3-enyloxy)isoindoline-1,3-dione 289



288 **289**

Alcohol **288** (500 mg, 3.01 mmol, 1.0 eq.) was treated with *N*-hydroxyphthalimide (495 mg, 3.04 mmol, 1.01 eq.) according to general procedure **A** using work up ***1*** to give *the title compound* **289** as a yellow solid (576 mg, Yield: 62%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.85 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 7.76 (app. dd, 2H, J = 7.7, 1.3 Hz, 2 × Ar C*H*), 5.41 - 5.35 (m, 1H, C*H*), 4.98 -4.96 (m, 2H, CH_2), 3.59 (t, 2H, J = 7.3 Hz, CH_2O), 2.19 – 1.80 (m, 7H, 3 × CH_2 & C*H*), 1.65 (s, 3H, CH_3), 1.54 - 1.41 (m, 2H, CH_2). IR (neat) υ/cm^{-1}: 2962, 2921, 1786, 1730, 1641, 1449, 1380, 1138, 1100, 839. LRMS (ES) 310.14 (M-H$^+$, 54%).

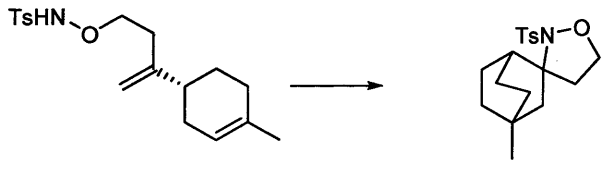
4-Methyl-*N*-(3-(4-methylcyclohex-3-enyl)but-3-enyloxy)benzenesulfonamide 290



289 **290**

The phthalimide **289** (576 mg, 1.85 mmol, 1.0 eq.) was treated according to general procedure **B** and the crude product was purified by flash column chromatography (eluting silica with dichloromethane) to give *the title compound* **290** as a yellow solid (218 mg, Yield: 24%). m.p.: 74 - 76 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.74 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.27 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 5.33 - 5.29 (m, 1H, C*H*), 4.76 - 4.74 (m, 1H, CH_AH_B), 4.70 - 4.68 (m, 1H, CH_AH_B), 4.04 (t, 2H, J = 7.0 Hz, CH_2O), 2.38 (s, 3H, Ts CH_3), 2.28 (t, 2H, J = 7.0 Hz, CH_2), 2.09 - 1.60 (m, 7H, 3 × CH_2 & C*H*), 1.58 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 150.0 (C_q), 133.8 (C_q), 133.6 (C_q), 129.8 (C_q), 129.7 (2 × Ts *C*H), 128.6 (2 × Ts *C*H), 120.5 (*C*H), 109.4 (CH_2), 76.1 (CH_2), 39.7 (*C*H), 33.2 (CH_2), 31.2 (CH_2), 30.6 (CH_2), 28.1 (CH_2), 23.5 (CH_3), 21.7 (Ts CH_3). IR (neat) υ/cm^{-1}: 3222, 3069, 2921, 1641, 1597, 1449, 1380, 1138, 1100, 839. HRMS (ES) *m/z* calcd. for $C_{18}H_{26}NO_3S$ $[M+H]^+$ = 336.1633; found 336.1629.

4-Methyl-2'-tosylspiro[bicyclo[2.2.2]octane-2,3'-isoxazolidine] 291

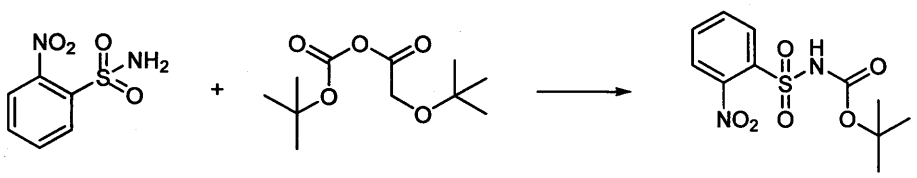


290 **291**

The sulfonamide **290** (201 mg, 0.59 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), cooled to 0 °C and triflic acid (0.40 ml, 0.29 mmol, 0.5 eq.) was added. The resulting solution was stirred at 0 °C for 1 hour, after which the reaction was quenched with saturated aqueous K_2CO_3, the two layers were separated, the aqueous layer extracted with dichloromethane (2 × 10 ml), the combined organics dried over K_2CO_3 and evaporated to give *the title compound* **291** as a yellow oil (174 mg, Yield: 87%).^{1}H NMR (400 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.25 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 4.39 - 4.13 (m, 2H, CH_2O), 2.36 (s, 3H, Ts CH_3), 1.73 - 0.84 (m, 15H, 6 × CH_2 & C*H*), 0.75 (CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.3 (C_q), 130.4 (C_q), 129.4 (2 × Ts *C*H), 128.7 (2 × Ts *C*H), 69.4 (CH_2O), 62.7 (C_q), 42.1 (CH_2), 31.8 (CH_2), 31.7

(CH_2), 31.6 (CH_2), 30.8 (CH), 27.9 (CH_3), 23.4 (CH_2), 23.1 (CH_2), 21.6 (Ts CH_3), 20.4 (C_q). IR (neat) υ/cm^{-1}: 2959, 1597, 1449, 1380, 1138, 1100, 839. HRMS calcd. for $C_{18}H_{26}NO_3S$ $[M+H]^+ = 336.1633$; found 336.1635.

***tert*-Butyl 2-nitrophenylsulfonylcarbamate**[291]



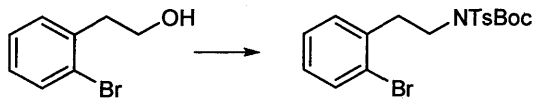
Boc_2O (1.78 g, 8.17 mmol, 1.1 eq.) was added in one portion to a stirred solution of 2-nitrobenzenesulfonamide (1.49 g, 7.38 mmol, 1.0 eq.), triethylamine (1.14 ml, 8.17 mmol, 1.1 eq.) and DMAP (92 mg mmol, eq.) in dichloromethane (20 ml) under nitrogen. After 2 hours the solvent was removed under vacuum, and the residue dissolved in ethyl acetate (60 ml), washed with 1 M HCl (50 ml), water (50 ml), brine (50 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was recrystallised from ethyl acetate / petrol to give *the title compound* as a white solid (982 mg, Yield: 44%). All data obtained was in accordance with that previously reported in the literature.[291] ^1H NMR (400 MHz / $CDCl_3$) δ 8.39 - 8.365 (m, 1H, Ns C*H*), 7.91 - 7.88 (m, 1H, Ns C*H*), 7.84 - 7.80 (m, 2H, 2 × Ns C*H*), 1.45 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 148.5 (C_q), 135.6 (2 × C_q), 134.7 (Ns *C*H), 133.3 (Ns *C*H), 132.5 (Ns *C*H), 125.1 (Ns *C*H), 84.9 (C_q), 27.9 (Boc C(CH_3)$_3$). HRMS (EI) *m/z* calcd. for $C_6H_6N_2SO_4$ $[M\text{-Boc}]^+ = 202.0048$; found 202.0049.

_N_-(2-Bromobenzyl)-4-methylbenzenesulfonamide 366

364 **366**

2-Bromobenzylamine **364** (2.00 g, 10.8 mmol, 1.0 eq.) was treated according to general procedure **C** and the crude product was purified by column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the sulfonamide* **366** as a white crystalline solid (3.17 g, Yield: 87%). All data obtained was in accordance with that previously reported in the literature.[292] m.p.: 78 - 80 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.73 (d, 2H, J = 8.0, 2 × Ts C*H*), 7.48 (dd, 1H, J = 8.0 Hz, Ar C*H*), 7.33 (d, 1H, J = 8.0 Hz, Ar C*H*), 7.28 (d, 2H, J = 8.0 Hz, 2 × Ts C*H*), 7.24 (d, 1H, J = 8.0 Hz, Ar C*H*), 4.90 (app. t, 1H, J = 6.5 Hz, N*H*), 4.26 (app. d, 2H, J = 6.5 Hz, CH_2N), 2.43 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.5 (C_q), 137.0 (C_q), 135.5 (C_q), 132.8 (Ar *C*H), 130.6 (Ar *C*H), 129.7 (2 × Ts *C*H), 129.6 (Ar *C*H), 127.7 (Ar *C*H), 127.1 (2 × Ts *C*H), 123.5 (C_q), 47.5 (CH_2N), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3290, 1441, 1328, 1158, 1093, 1026, 814, 750. HRMS (ES) *m/z* calcd. for $C_{14}H_{16}BrNO_2S$ $[M+H]^+$ = 341.9908 (Br^{81}) and 339.9929 (Br^{79}); found 341.9982 (Br^{81}) and 339.9998 (Br^{79}).

***tert*-Butyl 2-bromophenethyl(tosyl)carbamate 368a**

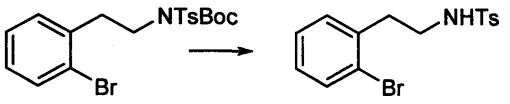


368 **368a**

2-Bromophenylethanol **368** (2.20 ml, 16.2 mmol, 1.0 eq.) was treated with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (4.50 g, 16.14 mmol, 1.01 eq.) according to general procedure **A** using work up *2*. The crude product was purified by column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **368a** as a colourless oil (6.89 g, Yield: 94%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.77 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.57 - 7.54 (m, 1H, Ar C*H*), 7.34 - 7.32 (m, 1H, Ar C*H*), 7.29 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.25 - 7.23 (m, 1H, Ar C*H*), 7.14 - 7.11 (m, 1H, Ar C*H*), 4.09 (t, 2H, J = 7.4 Hz, CH_2N), 3.21 (t, 2H, J = 7.4 Hz, CH_2), 2.44 (s, 3H, Ts CH_3), 1.29 (s, 9H, Boc C(CH_3)$_3$). ^{13}C NMR (500 MHZ / $CDCl_3$) δ 150.9 (C_q), 144.2 (C_q), 137.8 (C_q), 137.2 (C_q), 132.9 (Ar *C*H), 131.6 (Ar *C*H), 129.2 (2 x Ts *C*H), 128.3 (Ar *C*H), 128.1 (2 x Ts *C*H), 127.7 (Ar *C*H), 84.2 (Boc C_q(CH_3)$_3$), 46.7 (CH_2N), 36.9 (CH_2), 27.8 (Boc C(CH_3)$_3$), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 2932, 1728, 1448,

1247, 815, 753, 539. HRMS (ES) *m/z* calcd. for $C_{20}H_{28}BrN_2O_4S$ $[M+NH_4]^+ = 471.0953$ (Br^{79}); found 471.0956 (Br^{79}).

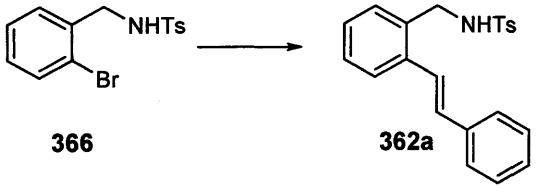
_N_-(2-Bromophenethyl)-4-methylbenzenesulfonamide 367[120]



368a **367**

Trifluoroacetic acid (3.00 ml, 40.4 mmol, 5.0 eq.) was added dropwise to the forgoing sulfonamide **368a** (3.61 g, 7.94 mmol, 1.0 eq.) in dichloromethane (20 ml) and stirred at room temperature for 2 hours. Water (20 ml) was then added and the organic layer washed with water (2 x 20 ml), dried over Na_2SO_4 and evaporated to give *the sulfonamide* **367** as a white solid (2.79 g, Yield: 99%). All data obtained was in accordance with that previously reported in the literature.[293] m.p.: 62 - 63 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.63 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.43 – 7.391 (m, 1H, Ar C*H*), 7.20 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.14 – 7.01 (m, 3H, 3 × ArC*H*), 4.38 (app. br. s, 1H, N*H*), 3.16 (t, 2H, J = 7.1 Hz, CH_2N), 2.84 (t, 2H, J = 7.1 Hz, CH_2), 2.34 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.5 (C_q), 132.2 (C_q), 131.8 (C_q), 133.1 (Ar *C*H), 131.2 (Ar *C*H), 129.8 (2 x Ts *C*H), 128.7 (Ar *C*H), 127.6 (Ar *C*H), 126.1 (2 x Ts *C*H), 124.4 (C_q), 42.6 (CH_2N), 36.3 (CH_2), 21.5 (Ts CH_3). IR (neat), υ / cm^{-1}: 3062, 2932, 1448, 815, 753, 539. HRMS (ES) *m/z* calcd. for $C_{15}H_{16}BrNO_2S$ $[M]^+ = 354.0163$ (Br^{79}); found 354.0176 (Br^{79}).

(*E*)-4-Methyl-*N*-(2-styrylbenzyl)benzenesulfonamide 362a

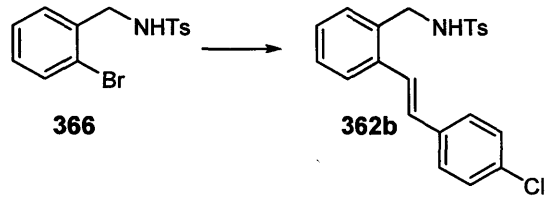


366 **362a**

By the general procedure **D**, reaction between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and *trans*-2-phenylvinylboronic acid **369a** (57 mg, 0.384 mmol, 1.3 eq.) to give *the title compound* **362a** as a brown oil (107 mg, Yield: 99%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.69 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.55 - 7.53 (m, 1H, Ar C*H*), 7.42 - 7.37 (m, 1H, Ar C*H*), 7.32 - 7.07 (m, 10H, 7 x Ar C*H* & 2 x Ts C*H* & C*H*), 6.91 (d, 1H, J = 16.1 Hz, C*H*), 4.40 (app. t, 1H, J = 5.7 Hz, N*H*), 4.16 (app. d, 2H, J = 5.7 Hz, CH_2N), 2.37 (s, 3H, Ts CH_3). ^{13}C NMR

(400 MHz / $CDCl_3$) δ 143.5 (2 x C_q), 137.0 (2 x C_q), 132.5 (C_q), 132.0 (Ar *C*H), 129.9 (Ar *C*H), 129.8 (2 x Ts *C*H), 128.9 (Ar *C*H), 128.8 (2 x Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar CH), 127.2 (2 x Ts *C*H), 126.8 (2 x Ar *C*H), 126.2 (*C*H), 124.5 (*C*H), 45.5 (CH_2N), 21.9 (CH_3). IR (neat), υ / cm^{-1}: 3290, 1598, 1327, 1158, 1092, 1042, 963, 815, 761, 691. HRMS (APCI) *m/z* calculated for $C_{22}H_{22}NO_2S$ $[M+H]^+$ = 364.1371, found 364.1389.

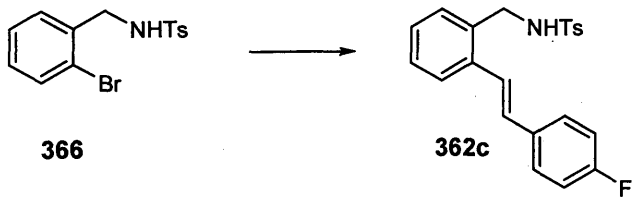
(*E*)-N-(2-(4-Chlorostyryl)benzyl)-4-methylbenzenesulfonamide 362b



366 **362b**

Reaction according to general procedure **D**, between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and *trans*-2-(4-chlorophenyl)vinylboronic acid **369b** (70 mg, 0.384 mmol, 1.3 eq.) gave *the title compound* **362b** as a brown oil (116 mg, Yield: 99%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.69 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.54 - 7.52 (m, 1H, Ar C*H*), 7.41 - 7.05 (m, 10H, 2 x Ts C*H*, 7 x Ar C*H* & C*H*), 6.89 (d, 1H, J = 16.3 Hz, C*H*), 4.39 (app. t, 1H, J = 5.9 Hz, N*H*), 4.15 (app. d, 2H, J = 5.9 Hz, CH_2N), 2.37 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 139.7 (C_q), 134.6 (2 × C_q), 133.6 (C_q), 133.0 (C_q), 132.6 (C_q), 132.0 (Ar *C*H), 130.5 (Ar *C*H), 129.8 (2 × Ts *C*H), 128.8 (Ar *C*H), 128.7 (2 × Ar *C*H), 128.0 (Ar *C*H), 127.3 (2 × Ts *C*H), 127.3 (Ar *C*H), 126.8 (*C*H), 125.4 (Ar *C*H), 124.6 (*C*H), 45.6 (CH_2N), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3277, 3026, 2921, 1597, 1448, 815, 753, 658. HRMS (EI) *m/z* calcd. for $C_{22}H_{20}ClNO_2S$ $[M]^+$ = 397.0903 (Cl^{35}); found 397.0906 (Cl^{35}).

(*E*)-*N*-(2-(4-Fluorostyryl)benzyl)-4-methylbenzenesulfonamide 362c

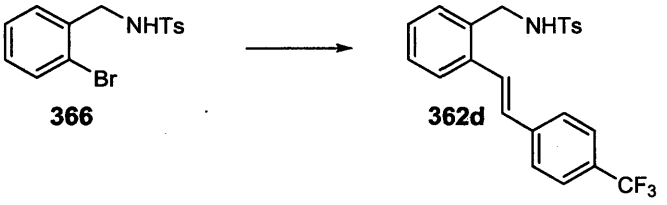


366 **362c**

By general procedure **D**, reaction between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and *trans*-2-(4-fluorophenyl)vinylboronic acid **369c** (64 mg, 0.384 mmol, 1.3 eq.) gave *the sulfonamide* **362c** as a dark brown oil (111 mg, Yield: 99%). ^{1}H NMR

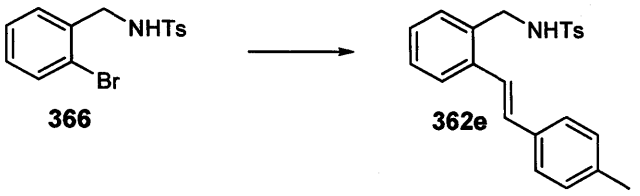
(400 MHz / $CDCl_3$) δ 7.64 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.55 – 7.48 (m, 1H, Ar C*H*), 7.39 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.27 – 7.11 (m, 6H, 6 × Ar C*H*), 7.08 – 6.86 (m, 3H, Ar C*H* & 2 × C*H*), 4.16 (app. d, 2H, J = 6.6 Hz, CH_2N), 2.34 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 162.3 (C_q), 134.3 (2 × C_q), 133.7 (C_q), 133.0 (C_q), 132.6 (C_q), 132.2 (Ar *C*H), 130.5 (Ar *C*H), 129.7 (2 × Ts *C*H), 128.5 (Ar *C*H), 128.3 (2 × *C*H), 127.6 (Ar *C*H), 127.3 (Ar *C*H), 127.2 (Ar *C*H), 126.8 (*C*H), 125.4 (Ar *C*H), 124.6 (*C*H), 45.6 (CH_2N), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3280, 3026, 2922, 1598, 1448, 1074, 815, 750, 706. HRMS (APCI) *m/z* calcd. for $C_{22}H_{21}FNO_2S$ $[M+H]^+$ = 382.1277; found 382.1268.

(*E*)-4-Methyl-*N*-(2-(4-(trifluoromethyl)styryl)benzyl)benzenesulfonamide 362d



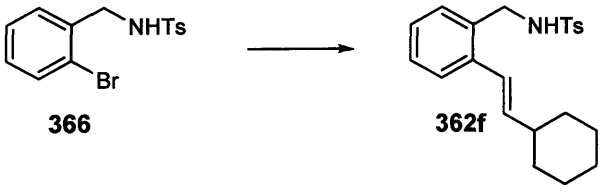
Reaction according to general procedure **D** between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and *trans*-2-[4-(fluoromethyl)phenyl]vinylboronic acid **369d** (83 mg, 0.384 mmol, 1.3 eq.), gave the product **362d** as a dark brown oil (121 mg, Yield: 95%). ^1H NMR (500 MHz / $CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz, 2 x Ts C*H*), 7.58 - 7.47 (m, 6H, 2 x Ts C*H* & 4 x Ar C*H*), 7.39 - 7.08 (m, 5H, 4 x Ar C*H* & C*H*), 6.95 (d, 2H, J = 16.1 Hz, C*H*), 4.41 (app. t, 1H, J = 6.0 Hz, N*H*), 4.16 (app. d, 2H, J = 6.0 Hz, CH_2N), 2.37 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 145.2 (C_q), 144.5 (C_q), 142.5 (C_q), 135.8 (C_q), 135.6 (2 × Ar *C*H), 129.6 (C_q), 129.4 (C_q), 128.9 (2 x Ts *C*H), 128.7 (2 × *C*H), 126.0 (2 x Ts *C*H), 125.7 (2 × Ar *C*H), 125.5 (C_q), 125.6 (2 x Ar *C*H), 123.7 (2 x Ar *C*H), 45.5 (CH_2N), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3274, 3028, 2928, 1614, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{20}F_3NO_2S$ $[M^+]$ = 431.1167; found 431.1169.

(*E*)-4-Methyl-*N*-(2-(4-methylstyryl)benzyl)benzenesulfonamide 362e



By general procedure **D**, reaction between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and *trans*-2-(4-methylphenyl)vinylboronic acid **369e** (62 mg, 0.384 mmol, 1.3 eq.), gave *the sulfonamide* **362e** as dark yellow oil (106 mg, Yield: 96%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.64 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.39 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.30 – 7.11 (m, 6H, 6 × Ar C*H*), 7.10 – 7.02 (m, 3H, 2 × Ar C*H* & C*H*), 6.95 (d, 1H, J = 15.8 Hz, C*H*), 4.16 (app. d, 2H, J = 6.6 Hz, CH_2N), 2.34 (s, 6H, 2 × Ar CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 146.5 (C_q), 136.9 (2 × C_q), 135.5 (3 × C_q), 132.8 (2 × Ar *C*H), 130.5 (2 × Ar *C*H), 129.8 (2 × Ar *C*H), 129.7 (2 × Ts *C*H), 129.6 (2 × Ar *C*H), 127.8 (*C*H), 127.2 (2 × Ts *C*H), 123.5 (*C*H), 41.5 (CH_2N), 21.6 (2 × Ar CH_3). IR (neat), υ / cm^{-1}: 3289, 3021, 2921, 1598, 1512, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{23}NO_2S$ $[M]^+$ = 377.1450; found 377.1438.

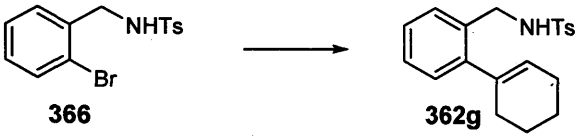
(*E*)-*N*-(2-(2-Cyclohexylvinyl)benzyl)-4-methylbenzenesulfonamide 362f



Reacted according to general procedure **D** between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and 2-cyclohexylvinylboronic acid **369f** (59 mg, 0.384 mmol, 1.3 eq.) to give *the sulfonamide* **362f** as a light brown oil (78 mg, Yield: 72%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.69 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.33 - 7.30 (m, 1H, Ar C*H*), 7.25 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.17 - 7.14 (m, 1H, Ar C*H*), 7.07 – 7.01 (m, 2H, 2 × Ar C*H*), 6.23 (d, 1H, J = 15.7 Hz, C*H*), 5.94 (dd, 1H, J = 15.7, 7.1 Hz, C*H*), 4.08 (app. d, 2H, J = 5.8 Hz, CH_2N), 2.38 (s, 3H, Ts CH_3), 1.99 - 1.92 (m, 1H, C*H*), 1.74 – 1.60 (m, 5H, 5 × C*H*), 1.29 - 1.00 (m, 5H, 5 × C*H*). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.5 (2 × C_q), 140.6 (Ar *C*H), 137.0 (C_q), 132.2 (C_q), 129.7 (2 × Ts *C*H), 129.6 (Ar *C*H), 128.6 (Ar *C*H), 127.3 (2 × Ts *C*H), 127.1 (Ar *C*H), 126.4 (*C*H), 123.4 (*C*H), 45.5 (CH_2N), 41.4 (*C*H), 32.9 (2 × CH_2), 26.1

(3 × CH_2), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3271, 2924, 2851, 1704, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{22}H_{27}NO_2S$ $[M]^+$ = 369.1763; found 369. 1762.

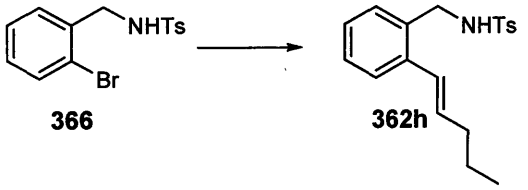
N-(2-Cyclohexenylbenzyl)-4-methylbenzenesulfonamide 362g



366 **362g**

By general procedure **D**, reaction between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and 1-cyclohexen-1-yl boronic acid pinacol ester **369g** (80 mg, 0.384 mmol, 1.3 eq.) gave *the sulfonamide* **362g** as a light brown oil (94 mg, Yield: 93%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.68 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.24 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.16 – 7.07 (m, 4H, 4 × Ar C*H*), 7.02 - 6.99 (m, 1H, C*H*), 4.01 (app. d, 2H, J = 5.9 Hz, CH_2N), 2.37 (s, 3H, Ts CH_3), 1.98 – 1.95 (m, 4H, 2 × CH_2), 1.57 – 1.51 (m, 4H, 2 × CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 144.5 (C_q), 143.5 (C_q), 137.5 (C_q), 136.8 (C_q), 132.9 (C_q), 129.7 (2 × Ts *C*H), 129.2 (Ar *C*H), 128.8 (Ar *C*H), 127.9 (Ar *C*H), 127.2 (2 × Ts *C*H), 127.0 (Ar *C*H), 126.9 (*C*H), 45.2 (CH_2N), 30.8 (CH_2), 25.4 (CH_2), 22.9 (CH_2), 21.9 (CH_2), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3279, 3026, 1498, 1448, 1274, 990, 815, 750. HRMS (ES) *m/z* calcd. for $C_{20}H_{25}NO_2S$ $[M+H]^+$ = 342.1528; found 342.1520.

(*E*)-4-Methyl-*N*-(2-(pent-1-enyl)benzyl)benzenesulfonamide 362h

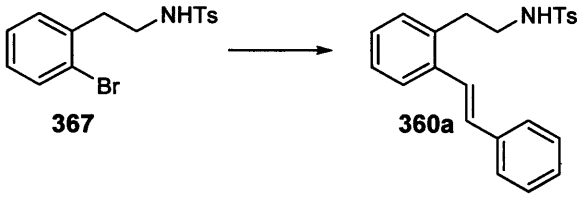


366 **362h**

Reaction according to general procedure **D**, between *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide **366** (100 mg 0.294 mmol, 1.0 eq.) and 1-penten-1-ylboronic acid pinacol ester **369h** (75 mg, 0.382 mmol, 1.3 eq.) to gave *the sulfonamide* **362h** as a brown oil (68 mg, Yield: 70%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.69 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.34 - 7.31 (m, 1H, Ar C*H*), 7.24 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.18 - 7.00 (m, 3H, 3 × Ar C*H*), 6.31 - 6.28 (m, 1H, C*H*), 6.04 - 5.95 (m, 1H, C*H*), 4.05 (app. d, 2H, J = 5.9 Hz, CH_2N), 2.37 (s, 3H, Ts CH_3), 2.06 - 1.98 (m, 2H, CH_2), 1.43 - 1.35 (m, 2H, CH_2) , 0.86 (t, 3H, J = 7.3 Hz,

CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.8 (C_q), 137.2 (2 × C_q), 134.8 (Ar *C*H), 132.1 (C_q), 129.9 (2 × Ts *C*H), 129.6 (*C*H), 128.5 (Ar *C*H), 127.3 (2 × Ts *C*H), 127.1 (*C*H), 126.3 (Ar *C*H), 125.8 (Ar *C*H), 45.5 (CH_2N), 30.7 (CH_2), 22.6 (Ts CH_3), 21.5 (CH_2), 13.9 (CH_3). IR (neat), υ / cm^{-1}: 3029, 1648, 1598, 1441, 1328, 1158, 1093, 1026, 814, 750. HRMS (EI) *m/z* calcd. for $C_{19}H_{23}NO_2S$ $[M]^+$ = 329.1450; found 329.1449.

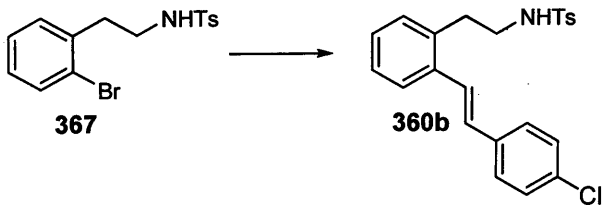
(*E*)-4-Methyl-*N*-(2-styrylphenethyl)benzenesulfonamide 360a



367 **360a**

By general procedure **D**, reaction between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and *trans*-2-phenylvinylboronic acid **369a** (55 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360a** as a brown oil (106 mg, Yield: 99%). ^1H NMR (500 MHz / $CDCl_3$) δ 7.53 (d, 2H, J = 8.0 Hz, 2 × Ts C*H*), 7.41 (d, 2H, J = 8.0 Hz, 2 × Ts C*H*), 7.35 – 6.96 (m, 10H, 9 × Ar C*H* & C*H*), 6.84 (d, 1H, J = 16.2 Hz, C*H*), 3.82 (t, 2H, J = 8.4 Hz, CH_2N), 2.79 (t, 2H, J = 8.4 Hz, CH_2), 2.26 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 137.5 (2 × C_q), 136.5 (2 × C_q), 135.4 (C_q), 129.7 (2 x Ts *C*H), 128.8 (2 x Ar *C*H), 127.9 (2 x Ts *C*H), 127.3 (2 x Ar *C*H), 127.1 (2 x Ar *C*H), 126.7 (2 x Ar *C*H), 126.4 (Ar *CH*), 126.3 (*C*H), 125.4 (*C*H), 43.5 (CH_2N), 33.9 (CH_2), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3286, 3028, 2922, 1598, 1448, 1274, 990, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{23}NO_2S$ $[M]^+$ = 377.1450; found 377.1450.

(*E*)-*N*-(2-(4-Chlorostyryl)phenethyl)-4-methylbenzenesulfonamide 360b

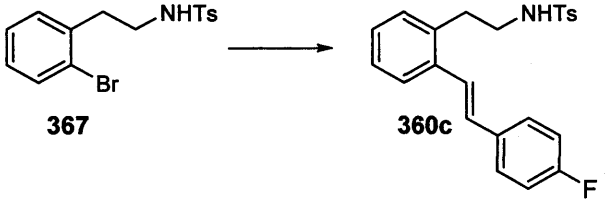


367 **360b**

Reaction according to general procedure **D** between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and *trans*-2-(4-chlorophenyl)vinylboronic acid **369b** (67 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360b** as an orange oil (66 mg, Yield: 85%). ^1H NMR (400 MHz / $CDCl_3$) δ 7.56 (d, 2H, J = 8.3 Hz,

2 × Ts C*H*), 7.37 (d, 2H, *J* = 8.3 Hz, 2 × Ts C*H*), 7.29 - 7.26 (m, 2H, 2 × Ar C*H*), 7.23 – 7.10 (m, 6H, 5 × Ar C*H* & C*H*), 7.05 - 7.03 (m, 1H, Ar C*H*), 6.82 (d, 1H, *J* = 16.1 Hz, C*H*), 3.84 (t, 2H, *J* = 8.3 Hz, CH_2N), 2.84 (t, 2H, *J* = 8.3 Hz, CH_2), 2.35 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 138.4 (C_q), 137.8 (C_q), 137.3 (C_q), 135.5 (2 × C_q), 134.9 (C_q), 129.3 (2 × Ts *C*H), 128.6 (2 × Ar *C*H), 127.9 (2 × Ar *C*H), 127.7 (2 × Ts *C*H), 126.9 (2 × Ar *C*H), 126.4 (Ar *C*H), 125.8 (*C*H), 125.7 (Ar *C*H), 125.2 (*C*H), 43.5 (CH_2N), 33.4 (CH_2), 21.3 (Ts, CH_3). IR (neat), υ / cm^{-1}: 3285, 3064, 2924, 1703, 1598, 1448, 1274, 990, 815, 750, 657. HRMS (EI) *m/z* calcd for $C_{23}H_{23}ClNO_2S$ $[M+H]^+ = 412.1138$ (Cl^{35}); found 412.1136 (Cl^{35}).

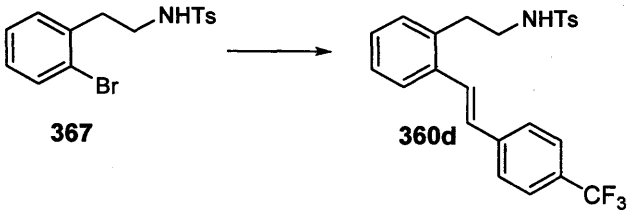
(*E*)-*N*-(2-(4-Fluorostyryl)phenethyl)-4-methylbenzenesulfonamide 360c



367 **360c**

By general procedure **D**, reaction between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and *trans*-2-(4-fluorophenyl)vinylboronic acid **369c** (60 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360c** as an orange oil (44 mg, Yield: 60%). ^1H NMR (400 MHz / $CDCl_3$) δ 7.66 – 7.54 (m, 4H, 2 × Ar C*H* & 2 x Ts C*H*), 7.51 - 7.48 (m, 1H, Ar C*H*), 7.44 – 7.39 (m, 2H, 2 × Ar C*H*), 7.23 – 7.07 (m, 3H, Ar C*H* & 2 × Ts C*H*), 7.04 – 6.97 (m, 3H, 2 × Ar C*H* & C*H*), 6.84 (d, 1H, *J* = 16.1 Hz, C*H*), 3.84 (t, 2H, *J* = 8.5 Hz, CH_2N), 2.82 (t, 2H, *J* = 8.5 Hz, CH_2), 2.35 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 138.6 (C_q), 137.8 (C_q), 137.5 (C_q), 135.5 (2 × C_q), 134.9 (C_q), 129.5 (2 × Ts *C*H), 128.6 (2 × Ar *C*H), 127.8 (2 × Ar *C*H), 127.8 (2 × Ts *C*H), 127.0 (2 × Ar *C*H), 126.4 (Ar *C*H), 125.8 (*C*H), 125.7 (Ar *C*H), 125.2 (*C*H), 43.5 (CH_2N), 33.4 (CH_2), 21.3 (Ts, CH_3). IR (neat), υ / cm^{-1}: 3283, 2924, 1718, 1598, 1508, 1448, 1274, 1074, 990, 815, 750. HRMS (EI) *m/z* calcd for $C_{23}H_{22}FNO_2S$ $[M]^+ = 395.1355$; found 395.1354.

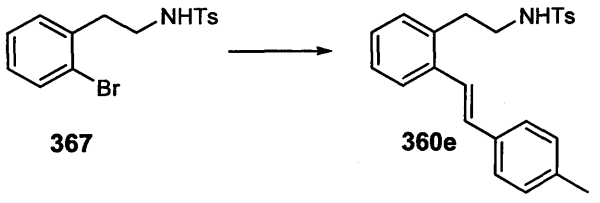
(*E*)-4-Methyl-*N*-(2-(4-(trifluoromethyl)styryl)phenethyl)benzenesulfonamide 360d



367 360d

Reaction according to general procedure **D** between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and trans-2-[4-(trifluoromethyl)phenyl]vinylboronic acid **369d** (80 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360d** as a brown oil (125 mg, Yield: 99%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.62 - 7.49 (m, 5H, 3 × Ar C*H* & 2 × Ts C*H*), 7.23 – 7.09 (m, 5H, 3 × Ar C*H* & 2 × Ts C*H*), 7.06 – 6.87 (m, 4H, 2 × Ar C*H* & 2 × C*H*), 3.84 (t, 2H, J = 8.4 Hz, CH_2N), 2.82 (t, 2H, J = 8.4 Hz, CH_2), 2.29 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.5 (C_q), 140.9 (C_q), 140.5 (C_q), 137.7 (C_q), 135.7 (C_q), 130.3 (C_q), 129.7 (2 × Ts *C*H), 128.5 (Ar *C*H), 128.1 (Ar *C*H), 127.7 (Ar *C*H), 127.5 (Ar *C*H), 127.3 (2 × Ts *C*H), 126.8 (2 × Ar *C*H), 126.6 (Ar *C*H), 126.3 (*C*H), 125.7 (Ar *C*H), 125.1 (*C*H), 123.7 (C_q), 43.8 (CH_2N), 34.1 (CH_2), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3283, 3065, 2926, 1613, 1599, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{24}H_{22}F_3NO_2S$ $[M]^+$ = 445.1323; found 445.1329.

(*E*)-4-Methyl-*N*-(2-(4-methylstyryl)phenethyl)benzenesulfonamide 360e

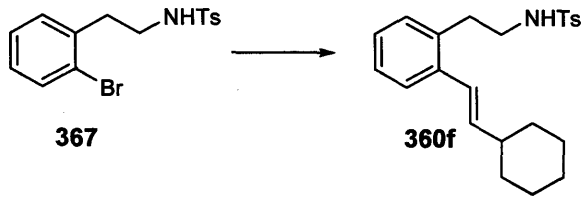


367 360e

By general procedure **D**, reaction between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and *trans*-2-(4-methylphenyl)vinylboronic acid **369e** (60 mg, 0.367 mmol, 1.3 eq.) to give *the sulfonamide* **360e** as a brown oil (109 mg, Yield: 99%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.65 – 7.55 (m, 4H, 2 × Ar C*H* & 2 × Ts C*H*), 7.45 - 7.42 (m, 2H, 2 × Ar C*H*), 7.23 - 7.21 (m, 2H, Ar C*H* & C*H*), 7.17 – 6.99 (m, 6H, 3 × Ar C*H*, 2 × Ts C*H* & C*H*), 3.84 (t, 2H, J = 8.4 Hz, CH_2N), 2.82 (t, 2H, J = 8.4 Hz, CH_2), 2.35 (s, 6H, 2 × Ar CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.4 (C_q), 137.2 (2 × C_q), 137.0 (2 × C_q), 135.3 (C_q), 133.1 (Ar *C*H), 131.2 (Ar *C*H), 129.7 (2 × Ts *C*H), 129.4 (2 × Ar *C*H), 128.6 (2 × Ar *C*H), 127.7 (2 × Ts *C*H), 127.4

(*C*H), 127.1 (2 × Ar *C*H), 127.0 (*C*H), 42.5 (*C*H_2N), 36.4 (*C*H_2), 21.6 (Ar *C*H_3), 21.5 (Ar *C*H_3). IR (neat) υ / cm^{-1}: 3286, 2922, 1598, 1513, 1448, 1274, 815, 750. LRMS (EI) 274.09 (M-C_9H_9, 68%).

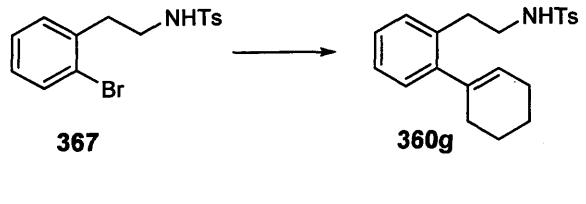
(*E*)-*N*-(2-(2-Cyclohexylvinyl)phenethyl)-4-methylbenzenesulfonamide 360f



367 **360f**

Reaction according to general procedure **D** between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and 2-cyclohexyl vinyl boronic acid **369f** (57 mg, 0.367mmol, 1.3 eq.) gave *the sulfonamide* **360f** as a yellow oil (73 mg, Yield: 69%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.59 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.31 - 7.28 (m, 1H, Ar C*H*), 7.19 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.17 – 6.98 (m, 2H, 2 × Ar C*H*), 6.95 - 6.93 (m, 1H, Ar C*H*), 6.37 (br. d, 1H, J = 15.7 Hz, C*H*), 5.89 (dd, 1H, J = 15.7, 7.1 Hz, C*H*), 3.08 (t, 2H, J = 7.0 Hz, CH_2N), 2.77 (t, 2H, J = 7.0 Hz, CH_2), 2.34 (s, 3H, Ts CH_3), 2.07 – 1.97 (m, 1H, C*H*), 1.74 - 1.57 (m, 5H, 5 × C*H*), 1.30 – 1.00 (m, 5H, 5 × C*H*). ^{13}C NMR (500 MHz / $CDCl_3$) δ 138.4 (2 × C_q), 137.6 (C_q), 137.2 (C_q), 129.4 (2 × Ts *C*H), 128.5 (Ar *C*H), 127.9 (2 × Ts *C*H), 127.7 (Ar *C*H), 126.8 (Ar *C*H), 126.5 (*C*H), 125.8 (Ar *C*H), 123.8 (*C*H), 43.6 (*C*H_2N), 38.4 (*C*H), 33.7 (2 × *C*H_2), 33.2 (*C*H_2), 26.4 (2 × *C*H_2), 25.3 (*C*H_2), 21.3 (Ts *C*H_3). IR (neat) υ / cm^{-1}: 3283, 2924, 2850, 1707, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{30}NO_2S$ $[M+H]^+$ = 384.1997; found 384.1993.

***N*-(2-Cyclohexenylphenethyl)-4-methylbenzenesulfonamide 360g**

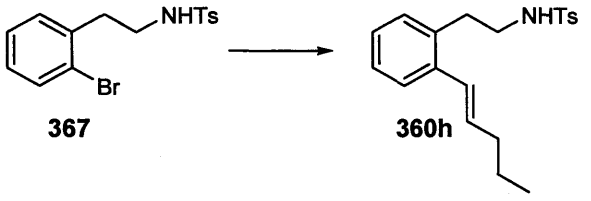


367 **360g**

By general procedure **D**, reaction between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, 0.282 mmol, 1.0 eq.) and 1-cyclohexen-ylboronic acid pinacol ester **369g** (76 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360g** as a yellow oil (94 mg, Yield: 94%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.60 (d, 2H, J = 8.3 Hz, 2 × Ts, C*H*), 7.32 - 7.29 (m, 2H, 2 × Ar C*H*), 7.15 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.13 – 7.04 (m, 1H, Ar C*H*), 7.02 – 6.95 (m, 1H, Ar C*H*), 6.90

(app. t, 1H, J = 7.5 Hz, C*H*), 3.85 (t, 2H, J = 8.4 Hz, CH_2N), 2.82 (t, 2H, J = 8.4 Hz, CH_2), 2.30 (s, 3H, Ts CH_3), 2.04 – 1.98 (m, 4H, 2 × CH_2), 1.64 – 1.54 (m, 4H, 2 × CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.0 (C_q), 138.2 (2 × C_q), 131.7 (C_q), 129.6 (2 × Ts *C*H), 129.1 (Ar *C*H), 127.4 (2 × Ts *C*H), 127.1 (Ar *C*H), 127.0 (C_q), 125.1 (Ar *C*H), 123.7 (Ar *C*H) 115.0 (*C*H), 43.9 (*C*H_2N), 33.1 (*C*H_2), 30.9 (*C*H_2), 25.3 (*C*H_2), 23.0 (*C*H_2), 22.0 (*C*H_2), 21.5 (Ts *C*H_3). IR (neat) υ / cm^{-1}: 3292, 2926, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{21}H_{25}NO_2S$ $[M]^+$ = 355.1606; found 355.1612.

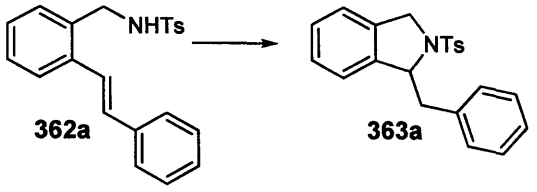
(*E*)-4-Methyl-*N*-(2-(pent-1-enyl)phenethyl)benzenesulfonamide 360h



367 **360h**

Reaction according to general procedure **D** between *N*-(2-bromophenethyl)-4-methylbenzenesulfonamide **367** (100 mg, mmol, 1.0 eq) and penten-1-yl boronic acid **369h** (40 mg, 0.367 mmol, 1.3 eq.) gave *the sulfonamide* **360h** as a brown oil (83 mg, Yield: 97%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.60 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.15 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.14 – 6.87 (m, 4H, 4 × Ar C*H*), 6.43 - 4.380 (m, 1H, C*H*), 5.95 (d, 1H, J = 15.5 Hz, C*H*), 3.84 (t, 2H, J = 8.4 Hz, CH_2N), 2.82 (t, 2H, J = 8.4 Hz, CH_2), 2.30 (s, 3H, Ts CH_3), 2.12 - 2.03 (m, 2H, CH_2), 1.43 – 1.34 (m, 2H, CH_2), 0.88 – 0.82 (m, 3H, CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 142.0 (C_q), 137.2 (C_q), 137.0 (C_q), 133.8 (Ar *C*H), 133.1 (C_q), 129.7 (2 × Ts *C*H), 127.7 (Ar *C*H), 127.3 (2 × Ts *C*H), 126.8 (Ar *C*H), 126.5 (Ar *C*H), 125.1 (*C*H), 123.7 (*C*H), 43.5 (*C*H_2N), 35.3 (*C*H_2), 33.4 (*C*H_2), 27.9 (*C*H_2), 21.6 (Ts *C*H_3), 13.8 (*C*H_3). IR (neat) υ / cm^{-1}: 3291, 3028, 2957, 2926, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{20}H_{25}NO_2S$ $[M]^+$ = 343.1606; found 343.1600.

1-Benzyl-2-tosylisoindoline 363a

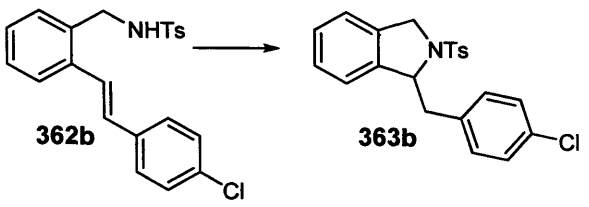


The sulfonamide **362a** (20 mg, 0.055 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.10 ml, 0.028 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 2 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic solutions were dried over K_2CO_3 and evaporated to give *the isoindole* **363a** as a yellow oil (19.5 mg, Yield: 98%).

The sulfonamide **362a** (102 mg, 0.28 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 20 °C for 48 hours and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363a** as a yellow oil (94 mg, Yield: 92%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.66 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.54 - 7.52 (md, 2H, 2 × Ar C*H*), 7.37 - 7.35 (m, 2H, 2 × Ar C*H*), 7.27 - 7.24 (m, 2H, 2 × Ar C*H*), 7.21 – 7.14 (m, 3H, 3 × Ar C*H*), 7.10 – 7.00 (m, 1H, Ar C*H*), 6.95 – 6.84 (m, 1H, Ar C*H*), 5.28 (t, 1H, J = 6.4 Hz, C*H*N), 4.53 (d, 1H, J = 15.9 Hz, CH_AH$_B$N), 4.12 (d, 1H, J = 15.9 Hz, CH$_A$$H_B$N), 2.95 (d, 2H, J = 6.4 Hz, CH_2), 2.25 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.2 (C_q), 139.8 (C_q), 137.0 (C_q), 132.9 (C_q), 132.6 (C_q), 129.8 (2 × Ts *C*H), 129.5 (2 × Ar *C*H), 128.8 (Ar *C*H), 128.1 (Ar *C*H), 127.8 (Ar *C*H), 127.1 (2 × Ts *C*H), 126.9 (Ar *C*H), 126.5 (Ar *C*H), 125.9 (Ar *C*H), 124.6 (Ar *C*H), 54.7 (*C*HN), 45.6 (*C*H$_2$N), 32.3 (*C*H$_2$), 21.6 (Ts *C*H$_3$). IR (neat) υ / cm^{-1}: 3278, 3059 3029, 2917, 2848, 1599, 1448, 1274, 815, 750. HRMS (APCI) *m/z* calcd. for $C_{22}H_{22}NO_2S$ $[M+H]^+$ = 364.1371; found 364.1386.

1-(4-Chlorobenzyl)-2-tosylisoindoline 363b

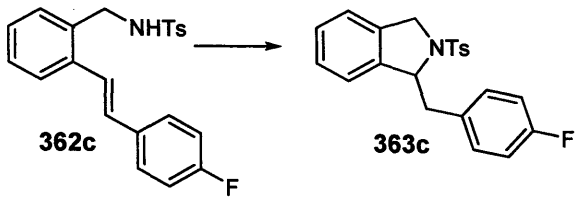


The sulfonamide **362b** (95 mg, 0.238 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.119 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363b** as a yellow oil (77 mg, Yield: 81%).

The sulfonamide **362b** (106 mg, 0.267 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363b** as a yellow oil (74 mg, Yield: 70%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.75 – 7.52 (m, 4H, 2 × Ts C*H* & 2 × Ar C*H*), 7.35 – 6.88 (m, 8H, 2 × Ts C*H* & 6 × Ar C*H*), 5.31 (d, 1H, J = 15.4 Hz, CH_AH_BN), 4.59 (d, 1H, J = 15.4 Hz, CH_AH_BN), 4.11 (t, 1H, J = 6.2 Hz, C*H*N), 2.98 (app. br. s, 2H, CH_2), 2.28 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.2 (C_q), 139.8 (C_q), 137.0 (C_q), 132.6 (C_q), 132.4 (C_q), 132.2 (C_q), 129.6 (Ar *C*H), 129.5 (2 × Ts *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.4 (Ar *C*H), 127.4 (Ar *C*H), 127.2 (Ar *C*H), 127.1 (2 × Ts *C*H), 126.5 (Ar *C*H), 125.9 (Ar *C*H), 54.7 (*C*HN), 44.0 (CH_2N), 32.3 (CH_2), 21.6 (Ts CH_3). IR υ / cm^{-1}: 3277, 3062 3028, 2923, 2855, 1598, 1448, 1274, 815, 750, 658. HRMS (APCI) *m/z* calcd. for $C_{22}H_{21}ClNO_2S$ $[M+H]^+$ = 398.0982 (Cl^{35}); found 398.0983 (Cl^{35}).

1-(4-Fluorobenzyl)-2-tosylisoindoline 363c

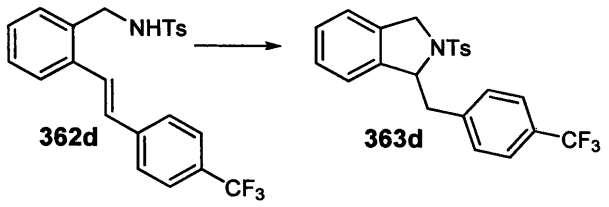


The sulfonamide **362c** (97 mg, 0.255 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.127 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363c** as a brown oil (81 mg, Yield: 84%).

The sulfonamide **362c** (115 mg, 0.302 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363c** as a brown oil (84 mg, Yield: 73%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.57 (d, 2H, J = 8.2, 2 × Ts C*H*), 7.33 - 7.30 (m, 2H, 2 × Ar C*H*), 7.20 - 7.17 (m, 2H, 2 × Ar C*H*), 7.11 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.10 - 6.94 (m, 2H, 2 × Ar C*H*), 6.90 - 6.84 (m, 1H, Ar C*H*), 6.75 - 6.72 (m, 1H, Ar C*H*), 5.22 (t, 1H, J = 6.4 Hz, C*H*N), 4.98 (d, 1H, J = 16.1 Hz, CH_AH$_B$N), 4.08 (d, 2H, J = 16.1 Hz, CH_AH$_B$N), 3.97 (d, 2H, J = 6.4 Hz, CH_2), 2.26 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.5 (2 × C_q), 137.0 (C_q), 135.6 (2 × C_q), 132.8 (Ar *C*H), 132.4 (C_q), 130.5 (Ar *C*H), 129.7 (2 × Ts *C*H), 129.5 (2 × Ar *C*H), 127.7 (2 × Ar *C*H), 127.1 (2 × Ts *C*H), 126.5 (Ar *C*H), 115.2 (Ar *C*H), 70.2 (*C*HN), 54.2 (*C*H$_2$N), 32.6 (*C*H$_2$), 21.5 (Ts *C*H$_3$). IR υ / cm^{-1}: 3278, 3059 3029, 2917, 2848, 1599, 1448, 1274, 815, 750, 706. HRMS (APCI) *m/z* calcd. for $C_{22}H_{21}FNO_2S$ $[M+H]^+$ = 382.1277; found 382.1268.

2-Tosyl-1-(4-(trifluoromethyl)benzyl)isoindoline 363d

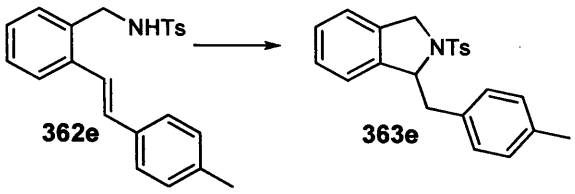


The sulfonamide **362d** (132 mg, 0.305 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.153 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363d** as a yellow oil (93 mg, Yield: 71%).

The sulfonamide **362d** (100 mg, 0.265 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363d** as a yellow oil (67 mg, Yield: 67%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.32 – 7.28 (m, 4H, 2 × Ts C*H* & 2 × Ar C*H*), 7.01 – 6.94 (m, 6H, 2 × Ts C*H* & 4 × Ar C*H*), 6.86 – 6.73 (m, 1H, Ar C*H*), 6.76 – 6.73 (m, 1H, Ar C*H*), 5.20 (t, 1H, J = 6.5 Hz, C*H*N), 4.98 (d, 1H, J = 16.1 Hz, CH_AH$_B$N), 4.11 (d, 1H, J = 16.1 Hz, CH_AH$_B$N), 3.65 (d, 2H, J = 6.5 Hz, CH_2), 2.19 (s, 3H, Ts CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.3 (C_q), 141.7 (2 × C_q), 135.5 (C_q), 135.2 (C_q), 133.6 (C_q), 130.2 (2 × Ar *C*H), 129.5 (2 × Ts *C*H), 128.9 (Ar *C*H), 127.1 (Ar *C*H), 127.0 (2 × Ts *C*H), 126.2 (2 × Ar *C*H), 125.1 (Ar *C*H), 125.0 (Ar *C*H), 123.9 (C_q), 70.7 (*C*HN), 52.6 (*C*H$_2$N), 33.5 (*C*H$_2$), 21.4 (Ts *C*H$_3$). IR (neat), υ / cm^{-1}: 3357, 3261, 3063, 2924, 1615, 1599, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{20}F_3NO_2S$ [M$^+$] = 431.1167; found 431.1168.

1-(4-Methylbenzyl)-2-tosylisoindoline 363e

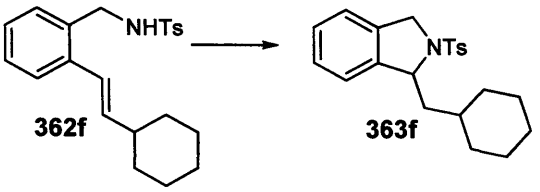


The sulfonamide **362e** (78 mg, 0.207 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.103 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363e** as a brown oil (67 mg, Yield: 86%).

The sulfonamide **362e** (100 mg, 0.265 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363e** as a brown oil (67 mg, Yield: 67%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.64 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.38 - 7.35 (m, 2H, 2 × Ar C*H*), 7.25 - 7.23 (m, 2H, 2 × Ar C*H*), 7.17 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.14 – 7.10 (m, 2H, 2 × Ar C*H*), 7.09 - 7.02 (m, 2H, 2 × Ar C*H*), 5.27 (t, 1H, J = 6.5 Hz, C*H*N), 4.62 (d, 1H, J = 15.9, CH_AH_BN), 4.27 (d, 1H, J = 15.9 Hz, CH_AH_BN), 2.96 (d, 2H, J = 6.5 Hz, CH_2), 2.33 (s, 6H, 2 × Ar CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.5 (C_q), 140.5 (C_q), 137.1 (C_q), 135.1 (2 × C_q), 132.0 (C_q), 132.8 (2 × Ar *C*H), 130.5 (2 × Ar *C*H), 129.7 (2 × Ts *C*H), 129.5 (2 × Ar *C*H), 127.7 (2 × Ar *C*H), 127.2 (2 × Ts *C*H), 77.3 (*C*HN), 49.0 (*C*H_2N), 30.0 (*C*H_2), 21.5 (2 × Ar *C*H_3). IR (neat), υ / cm^{-1}: 329, 3054, 3023, 2922, 2864, 1598, 1512, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{23}NO_2S$ $[M]^+$ = 377.1450; found 377.1448.

1-(Cyclohexylmethyl)-2-tosylisoindoline 363f

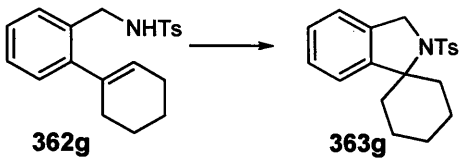


The sulfonamide **362f** (90 mg, 0.250 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.125 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 2 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363f** as a brown oil (84 mg, Yield: 93%).

The sulfonamide **362f** (64 mg, 0.265 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 40 °C for 4 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363f** as a brown oil (64 mg, Yield: 100%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.52 (d, 2H, J = 7.8 Hz, 2 × Ts C*H*), 7.20 – 6.89 (m, 6H, 4 × Ar C*H* & 2 × Ts C*H*), 4.85 (app. br. s, 1H, C*H*N), 4.53 (d, 1H, J = 14.8 Hz, CH_AH_BN), 4.47 (d, 1H, J = 14.8 Hz, CH_AH_BN), 2.87 (dd, 2H, J = 10.3, 2.8 Hz, CH_2) 2.18 (s, 3H, Ts CH_3), 1.74 – 1.40 (m, 7H, C*H* & 3 × CH_2), 1.13 - 0.76 (m, 4H, 2 × CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.4 (C_q), 141.2 (C_q), 136.8 (C_q), 134.9 (C_q), 129.6 (2 × Ts *C*H), 127.5 (Ar *C*H), 127.5 (Ar *C*H), 127.4 (Ar *C*H), 127.3 (2 × Ts *C*H), 122.6 (Ar *C*H), 64.4 (*C*HN), 53.5 (CH_2N), 44.8 (CH_2), 33.7 (*C*H), 33.9 (CH_2), 33.5 (CH_2), 26.5 (CH_2), 26.2 (2 × CH_2), 21.5 (Ts CH_3). IR (neat) υ / cm^{-1}: 3031, 2922, 2850, 1707, 1598, 1448, 1274, 815, 750. HRMS (ES) *m/z* calcd. for $C_{22}H_{28}NO_2S$ $[M+H]^+$ = 370.1841; found 370.1843.

2'-Tosylspiro[cyclohexane-1,1'-isoindoline] 363g



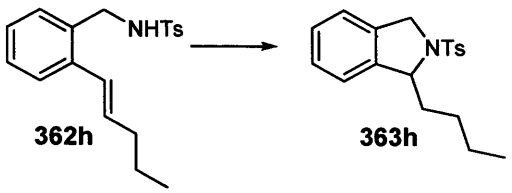
362g 363g

The sulfonamide **362g** (97 mg, 0.283 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.20 ml, 0.142 mmol, 0.5 eq.). The resulting solution was stirred at 0 °C for 6 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363g** as a yellow oil (68 mg, Yield: 70%).

The sulfonamide **362g** (82 mg, 0.240 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 0 °C for 24 hours and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363g** as a brown oil (64 mg, Yield: 78%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.72 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.57 - 7.54 (m, 1H, Ar C*H*), 7.21 – 7.15 (m, 4H, 2 × Ar C*H* & 2 × Ts C*H*), 7.10 - 7.07 (m, 1H, Ar C*H*), 4.53 (app. s, 2H, CH_2N), 2.74 - 2.71 (m, 2H, CH_2), 2.32 (s, 3H, Ts CH_3), 1.82 – 1.67 (m, 8H, 4 × CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 145.8 (C_q), 142.9 (C_q), 138.6 (C_q), 134.3 (C_q), 129.4 (2 × Ts *C*H), 127.4 (Ar *C*H), 127.2 (2 × Ts *C*H), 127.0 (Ar *C*H), 124.0 (Ar *C*H), 122.5 (Ar *C*H), 74.4 (C_q), 52.9 (CH_2N), 36.4 (2 × CH_2), 24.4 (2 × CH_2), 22.8 (CH_2), 21.6 (Ts CH_3). IR (neat), υ / cm^{-1}: 3045, 2927, 2879, 1728, 1598, 1498, 1448, 1274, 990, 815, 750. HRMS (EI) *m/z* calcd. for $C_{20}H_{24}NO_2S$ $[M+H]^+$ = 342.1528; found 342.1528.

1-Butyl-2-tosylisoindoline 363h

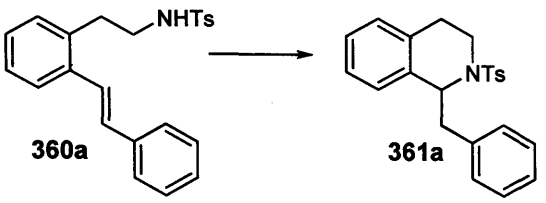


The sulfonamide **362h** (66 mg, 0.185 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.13 ml, 0.093 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 3 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363h** as a brown oil (66 mg, Yield: 100%).

The sulfonamide **362h** (28 mg, 0.085 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was heated to 40 °C for 3 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoindole* **363h** as a brown oil (27 mg, Yield: 98%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.26 (d, 2H, J = 8.1 Hz, 2 × Ts C*H*), 7.14 (d, 2H, J = 8.1 Hz, 2 × Ts C*H*), 7.12 - 7.09 (m, 2H, 2 × Ar C*H*), 7.04 – 6.97 (m, 2H, 2 × Ar C*H*), 4.92 (app. br. s, 1H, C*H*N), 4.58 (d, 1H, J = 14.8 Hz, CH_AH_BN), 4.51 (d, 1H, J = 14.8 Hz, CH_AH_BN), 2.26 (s, 3H, Ts CH_3), 2.10 – 2.02 (m, 1H, CH_CH_D), 1.80 – 1.73 (m, 1H, CH_CH_D), 1.32 – 1.11 (m, 3H, CH_2 & CH_EH_F), 0.91 – 0.81 (m, 1H, CH_EH_F), 0.73 (t, 3H, J = 7.3 Hz, CH_3). ^{13}C NMR (500 MHz / $CDCl_3$) δ 143.3 (C_q), 140.2 (C_q), 135.9 (C_q), 135.1 (C_q), 129.7 (2 × Ts *C*H), 127.6 (Ar *C*H), 127.5 (Ar *C*H), 127.3 (2 × Ts *C*H), 122.4 (Ar *C*H), 122.3 (Ar *C*H), 66.1 (*C*HN), 54.1 (CH_2N), 33.1 (CH_2), 25.5 (CH_2), 22.7 (CH_2), 21.5 (Ts CH_3), 14.0 (CH_3). IR υ / cm^{-1}: 3281, 3054, 2957, 2871, 1728, 1597, 1448, 1274, 815, 750. HRMS (APCI) *m/z* calcd. for $C_{19}H_{24}NO_2S$ $[M+H]^+$ = 330.1528; found 330.1523.

1-Benzyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361a

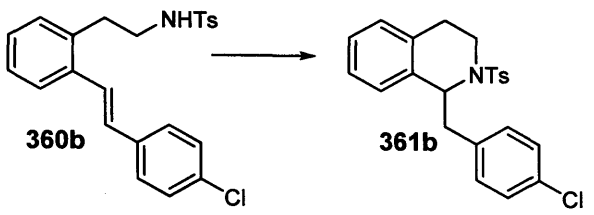


The sulfonamide **360a** (22 mg, 0.058 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.10 ml, 0.029 mmol, 0.5 eq.). The resulting solution mixture was stirred at 0 °C for 24 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361a** as a yellow oil (22 mg, Yield: 100%).

The sulfonamide **360a** (97 mg, 0.257 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 20 °C for 48 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361a** as a brown oil (96 mg, Yield: 99%).

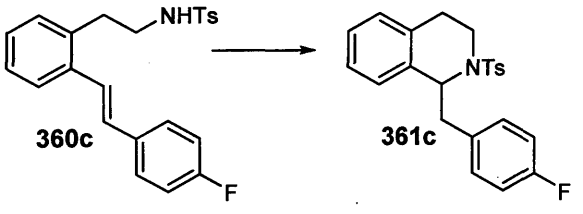
The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.37 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.13 – 6.85 (m, 10H, 2 × Ts C*H* & 8 × Ar C*H*), 6.75 - 6.71 (m, 1H, Ar C*H*), 5.12 (t, 1H, J = 6.6 Hz, C*H*N), 3.48 – 3.42 (m 1H, CH_AH$_B$N), 3.36 - 3.28 (m, 1H, CH$_A$$H_B$N), 3.07 – 3.02 (m, 2H, CH_2), 2.64 – 2.55 (m, 1H, CH_CH$_D$), 2.42 – 2.34 (m, 1H, CH$_C$$H_D$), 2.23 (s, 3H, Ts C$H_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.0 (C_q), 137.7 (C_q), 136.9 (C_q), 135.6 (C_q), 133.5 (C_q), 129.9 (2 × Ar *C*H), 129.5 (2 × Ts *C*H), 128.7 (Ar *C*H), 128.3 (2 × Ar *C*H), 127.3 (Ar *C*H), 127.2 (2 × Ts *C*H), 126.9 (Ar *C*H), 126.6 (Ar *C*H), 125.0 (Ar *C*H), 57.9 (*C*HN), 44.5 (*C*H$_2$N), 40.0 (*C*H$_2$), 27.2 (*C*H$_2$), 21.5 (Ts *C*H$_3$). IR (neat), υ / cm^{-1}: 3290, 3060, 3027, 2925, 2874, 1652, 1598, 1448, 1274, 990, 815, 750. HRMS (ES) *m/z* calcd. for $C_{23}H_{24}NO_2S$ $[M+H]^+$ = 378.1528; found 378.1539.

1-(4-Chlorobenzyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361b



The sulfonamide **360b** (52 mg, 0.126 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added TfOH (0.10 ml, 0.063 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361b** as a brown oil (44 mg, Yield: 87%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.65 – 7.55 (m, 3H, 2 × Ts C*H* & Ar C*H*), 7.39 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.16 – 6.99 (m, 4H, 4 × Ar C*H*), 6.93 – 6.75 (m, 3H, 3 × Ar C*H*), 5.07 (t, 1H, J = 6.6 Hz, C*H*N), 3.53 – 3.47 (m, 1H, CH_AH_BN),, 3.37 – 3.30 (m, 1H, CH_AH_BN), 3.09 - 3.00 (m, 2H, CH_2), 2.93 - 2.78 (m, 2H, CH_2), 2.28 (s, 2H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 144.1 (C_q), 143.2 (2 × C_q), 138.0 (C_q), 136.0 (C_q), 134.8 (C_q), 131.2 (Ar *C*H), 129.7 (Ar *C*H), 129.5 (2 × Ts *C*H), 128.8 (Ar *C*H), 128.3 (Ar *C*H), 127.2 (Ar *C*H), 127.1 (2 × Ts *C*H), 127.0 (Ar *C*H), 126.1 (Ar *C*H), 125.1 (Ar *C*H), 57.9 (*C*HN), 43.9 (CH_2N), 40.1 (CH_2), 28.9 (CH_2), 21.5 (Ts *C*H). IR (neat), υ / cm^{-1}: 3062, 3028, 2925, 2874, 1916, 1694, 1598, 1448, 815, 753, 658. HRMS (EI) *m/z* calcd for $C_{23}H_{23}ClNO_2S$ $[M+H]^+$ = 412.1138 (Cl^{35}); found 412.1135 (Cl^{35}).

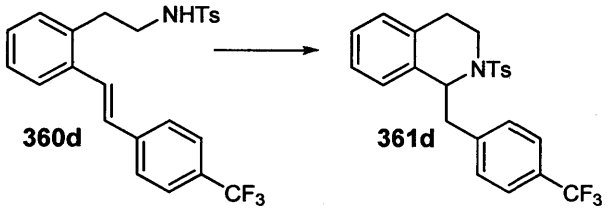
1-(4-Fluorobenzyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361c



The sulfonamide **360c** (42 mg, 0.106 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.10 ml, 0.051 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361c** as a brown oil (30 mg, Yield: 72%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.64 (d, 2H,

J = 8.3 Hz, 2 × Ts C*H*), 7.42 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.25 - 7.21 (m, 2H, 2 × Ar C*H*), 7.16 – 6.99 (m, 3H, 3 × Ar C*H*), 6.91 – 6.76 (m, 3H, 3 × Ar C*H*), 4.33 (t, 1H, J = 6.3 Hz, C*H*N), 3.89 - 3.82 (m, 2H, CH_2N), 3.20 – 3.14 (m, 2H, CH_2), 3.05 (d, 2H, J = 6.3 Hz, CH_2), 2.35 (s, 3H, Ts CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 174.5 (C_q), 143.5 (2 × C_q), 138.4 (C_q), 137.1 (C_q), 133.7 (C_q), 133.1 (Ar *C*H), 131.2 (Ar *C*H), 129.7 (2 × Ts *C*H), 129.3 (Ar *C*H), 128.6 (Ar *C*H), 127.7 (Ar *C*H), 127.1 (2 × Ts *C*H), 126.0 (Ar *C*H), 115.2 (Ar *C*H), 114.9 (Ar *C*H), 58.1 (*C*HN), 42.6 (*C*H_2N), 36.4 (*C*H_2), 27.4 (*C*H_2), 21.6 (Ts *C*H_3). IR (neat), υ / cm^{-1}: 3063, 2926, 2874, 1599, 1509, 1448, 1274, 1074, 990, 815, 750. HRMS (APCI) *m/z* calcd. for $C_{22}H_{21}FNO_2S$ $[M+H]^+$ = 382.1277; found 382.1268.

2-Tosyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline 361d



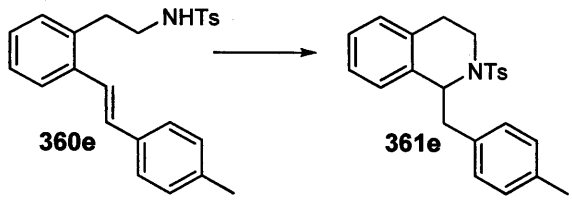
The sulfonamide **360d** (47 mg, 0.106 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.10 ml, 0.053 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361d** as a brown oil (35 mg, Yield: 75%).

The sulfonamide **360d** (116 mg, 0.261 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was heated to 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361d** as a brown oil (65 mg, Yield: 56%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.32 – 7.28 (m, 4H, 2 × Ts C*H* & 2 × Ar C*H*), 7.01 – 6.94 (m, 6H, 2 × Ts C*H* & 4 × Ar C*H*), 6.86 – 6.73 (m, 1H, Ar C*H*), 6.76 – 6.73 (m, 1H, Ar C*H*), 5.05 (t, 1H, J = 6.6 Hz, C*H*N), 3.46 - 3.43 (m, 1H, C$H_A$$H_B$N), 3.31 - 3.24 (m, 1H, CH$_A$$H_B$N), 3.05 (d, 2H, J = 6.6 Hz, CH_2), 2.60 - 2.57 (m, 1H, CH_CH$_D$), 2.37 – 2.24 (m, 1H, CH$_C$$H_D$), 2.19 (s, 3H, Ts C$H_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.3 (2 × C_q), 141.7 (2 × C_q), 135.5 (C_q), 135.2 (C_q), 133.6 (C_q), 130.2

(2 × Ar *C*H), 129.5 (2 × Ts *C*H), 128.9 (Ar *C*H), 127.1 (Ar *C*H), 127.0 (2 × Ts *C*H), 126.2 (2 × Ar *C*H), 125.1 (Ar *C*H), 125.0 (Ar *C*H), 57.7 (*C*HN), 44.3 (CH_2N), 40.1 (CH_2), 27.3 (CH_2), 21.4 (Ts CH_3). IR (neat), υ / cm^{-1}: 3063, 2931, 2874, 1617, 1599, 1555, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{24}H_{22}F_3NO_2S$ $[M]^+$ = 445.1323; found 445.1312.

1-(4-Methylbenzyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361e

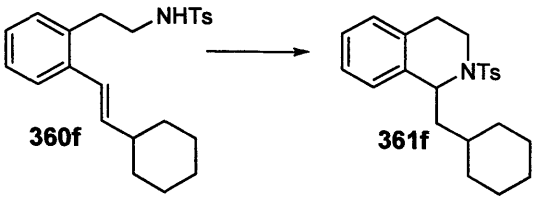


The sulfonamide **360e** (52 mg, 0.133 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added TfOH (0.10 ml, 0.066 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361e** as a brown oil (28 mg, Yield: 54%).

The sulfonamide **360e** (121 mg, 0.309 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added concentrated sulfuric acid (2 drops). The resulting suspension was heated to 40 °C for 48 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361e** as a brown oil (97 mg, Yield: 80%).

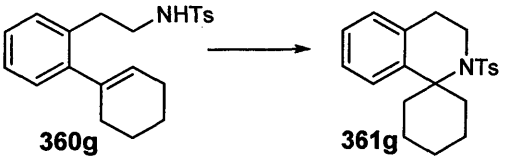
The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.64 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.45 - 7.42 (m, 4H, 4 × Ar C*H*), 7.21 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.12 – 6.99 (m, 4H, 4 × Ar C*H*), 5.06 (t, 1H, J = 6.3 Hz, C*H*N), 3.42 - 3.37 (m, 2H, CH_2N), 3.29 - 3.14 (m, 2H, CH_2), 3.01 (d, 2H, J = 6.4 Hz, CH_2), 2.35 (s, 6H, 2 × Ar CH_3), 2.34 - 2.21 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.4 (2 × C_q), 137.2 (2 × C_q), 136.9 (C_q), 133.0 (C_q), 131.2 (2 × Ar *C*H), 129.7 (2 × Ts *C*H), 128.6 (2 × Ar *C*H), 127.7 (2 × Ar *C*H), 127.1 (2 × Ts *C*H), 124.4 (2 × Ar *C*H), 77.3 (*C*HN), 42.5 (CH_2N), 36.4 (2 × CH_2), 21.6 (2 × Ar CH_3). IR (neat) υ / cm^{-1}: 3051, 3020, 2922, 2867, 1598, 1512, 1448, 1274, 815, 750. HRMS (EI) calcd. for $C_{24}H_{26}NO_2S$ $[M+H]^+$ = 392.1684; found 392.1689.

1-(Cyclohexylmethyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361f



The sulfonamide **360f** (39 mg, 0.102 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added TfOH (0.10 ml, 0.059 mmol, 0.5 eq.). The resulting solution was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361f** as a brown oil (35 mg, Yield: 90%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.51 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.06 - 6.90 (m, 5H, 2 × Ts C*H* & 3 × Ar C*H*), 6.79 - 6.76 (m, 1H, Ar C*H*), 4.98 (t, 1H, J = 6.9 Hz, C*H*N), 3.85 – 3.79 (m, 2H, CH_2N), 3.44 – 3.35 (m, 2H, CH_2), 2.25 (s, 3H, Ts CH_3), 1.72 - 0.78 (m, 13H, C*H* & 6 × CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 137.6 (2 × C_q), 137.4 (C_q), 134.0 (C_q), 129.2 (2 × Ts *C*H), 127.9 (2 × Ts *C*H), 127.7 (2 × Ar *C*H), 126.4 (Ar *C*H), 15.9 (Ar *C*H), 57.6 (*C*HN), 48.6 (*C*H_2N), 38.4 (*C*H_2), 33.9 (2 × *C*H_2), 31.3 (*C*H), 25.8 (2 × *C*H_2), 25.2 (2 × *C*H_2), 21.3 (Ts *C*H_3). IR (neat) υ / cm^{-1}: 3061, 3024, 2922, 2850, 1699, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* calcd. for $C_{23}H_{30}NO_2S$ $[M+H]^+$ = 384.1997; found 384.1980.

2'-Tosyl-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-isoquinoline] 361g



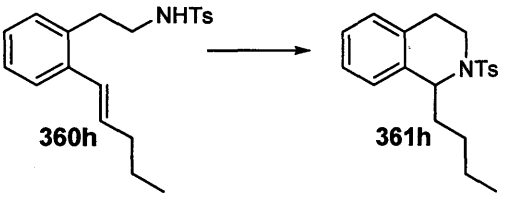
The sulfonamide **360g** (40 mg, 0.115 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added TfOH (0.10 ml, 0.058 mmol, 0.5 eq.). The resulting solution was stirred at 0 °C for 24 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361g** as a brown oil (33 mg, Yield: 83%).

The sulfonamide **360g** (90 mg, 0.253 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was added concentrated sulfuric acid (2 drops). The resulting suspension was stirred at 20

°C for 24 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **360g** as a brown oil (73 mg, Yield: 81%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.63 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.23 – 6.99 (m, 6H, 2 × Ts C*H* & 4 × Ar C*H*), 3.17 (app. dd, 2H, J = 13.6, 7.0 Hz, CH_2N), 2.61 - 2.85 (m, 2H, CH_2), 2.35 (s, 3H, Ts CH_3), 1.80 – 1.09 (m, 10H, 5 × CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.0 (C_q), 140.0 (C_q), 134.0 (C_q), 131.8 (C_q), 129.6 (2 × Ts *C*H), 129.4 (Ar *C*H), 127.3 (2 × Ts *C*H), 126.9 (Ar *C*H), 126.7 (Ar *C*H), 126.5 (Ar *C*H), 50.0 (C_q), 44.0 (*C*H$_2$N), 33.1 (*C*H$_2$), 30.9 (*C*H$_2$), 26.4 (*C*H$_2$), 25.3 (*C*H$_2$), 23.1 (*C*H$_2$), 22.0 (*C*H$_2$), 21.5 (Ts *C*H$_3$). IR (neat) υ / cm^{-1}: 3063, 3028, 2926, 2857, 1598, 1448, 1274, 815, 750. HRMS (EI) *m/z* cald. for $C_{21}H_{25}NO_2S$ $[M]^+$ = 355.1606; found 355.1601.

1-Butyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 361h



The sulfonamide **360h** (54 mg, 0.157 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added TfOH (0.10 ml, 0.079 mmol, 0.5 eq.). The resulting solution was stirred at 0 °C for 24 hours and then quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361h** as a brown oil (50 mg, Yield: 92%).

The sulfonamide **360h** (72 mg, 0.209 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml), to which was then added concentrated sulfuric (2 drops). The resulting suspension was heated to 40 °C for 24 hours, then cooled to room temperature and quenched with saturated aqueous K_2CO_3. The quenched solution was then separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and evaporated to give *the isoquinoline* **361h** as brown oil (64 mg, Yield: 89%).

The two samples showed identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.51 (d, 2H, J = 8.1 Hz, 2 × Ts C*H*), 7.07 – 6.94 (m, 5H, 3 × Ar C*H* & 2 × Ts C*H*), 6.82 - 6.79 (m, 1H, Ar C*H*), 4.88 (t, 1H, J = 6.5 Hz, C*H*N), 3.81 - 3.77 (m, 1H, CH_AH_BN), 3.43 – 3.35 (m, 1H,

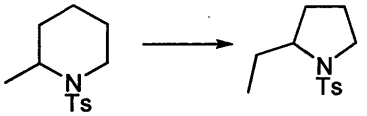
CH_AH_BN), 2.46 – 2.41 (m, 2H, CH_2), 2.24 (s, 3H, Ts CH_3), 1.78 – 1.58 (m, 2H, CH_2), 1.44 – 1.16 (m, 4H, 2 × CH_2), 0.82 (t, 3H, J = 7.1 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.9 (C_q), 137.9 (C_q), 137.0 (C_q), 132.6 (C_q), 129.3 (2 × Ts *C*H), 128.9 (Ar *C*H), 127.0 (2 × Ts *C*H), 126.9 (Ar *C*H), 126.5 (Ar *C*H), 126.0 (Ar *C*H), 56.8 (*C*HN), 38.7 (CH_2N), 37.5 (CH_2), 28.6 (CH_2), 26.2 (CH_2), 22.5 (CH_2), 21.5 (Ts CH_3), 14.1 (CH_3). IR (neat) υ / cm^{-1}: 3063, 3025, 2955, 2930, 1598, 1448, 1274, 815, 750. HRMS (ES) *m/z* calcd. for $C_{20}H_{26}NO_2S$ $[M+H]^+$ = 344.1684; found 344.1694.

2-Methyl-1-tosylpiperidine 474[294]

465 **474**

2-Methylpiperidine **465** (2.40 ml, 20.2 mmol, 1.0 eq.) was treated according to general procedure **C** to give *the title compound* **474** as a white solid (4.57 g, Yield: 90%). All data obtained was in accordance with that previously reported in the literature.[294] m.p.: 56 - 58 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.63 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.20 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.16 (app. pent, 1H, J = 6.9 Hz, C*H*N), 3.66 - 3.59 (m, 1H, CH_AH_BN), 2.93 - 2.87 (m, 1H, CH_AH_BN), 2.34 (s, 3H, Ts CH_3), 1.60 - 1.21 (m, 6H, 3 × CH_2), 0.99 (d, 3H, J = 6.9 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.8 (C_q), 138.3 (C_q), 129.7 (2 × Ts *C*H), 126.9 (2 × Ts *C*H), 48.5 (*C*HN), 40.5 (CH_2N), 30.4 (CH_2), 25.2 (CH_2), 21.6 (Ts CH_3), 18.3 (CH_2), 15.4 (CH_3). IR (neat) υ/cm^{-1}: 2939, 1597, 1263, 1037, 995. HRMS (EI) *m/z* calcd. for $C_{13}H_{19}NO_2S$ $[M]^+$ = 253.1137; found: 253.1133.

2-Ethyl-1-tosylpyrrolidine 475[295]



474 **475**

2-Methyl-1-tosylpiperidine **474** (100 mg, 0.39 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml) and to this concentrated sulfuric acid (2 drops) was added and the reaction mixture stirred at 40 °C under nitrogen for 72 hours. The reaction was allowed to cool and was then quenched with saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous

layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a white solid (72 mg, Yield: 72%). **9% pyrrolidine 475. (11.24 : 1 ratio)**

2-Methyl-1-tosylpiperidine **474** (100 mg, 0.39 mmol, 1.0 eq.) was dissolved in Toluene (10 ml) and to this TfOH (0.30 ml, 0.197 mmol, 0.5 eq.) was added and the reaction mixture stirred at 110 °C under nitrogen for 72 hours. The reaction was allowed to cool and was then quenched with saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a white solid (66 mg, Yield: 66%). **5% pyrrolidine 475. (19 : 1 ratio)**

2-Methyl-1-tosylpiperidine **474** (100 mg, 0.39 mmol, 1.0 eq.) was dissolved in Toluene (10 ml) and to this concentrated sulfuric acid (6 drops) was added and the reaction mixture stirred at 110 °C under nitrogen for 24 hours. The reaction was allowed to cool and was then quenched with saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a white solid (72 mg, Yield: 72%). **21% pyrrolidine 475. (4.62: 1.0 ratio)**

2-Methyl-1-tosylpiperidine **474** (100 mg, 0.39 mmol, 1.0 eq.) was dissolved in Toluene (10 ml) and to this concentrated sulfuric acid (6 drops) was added and the reaction mixture stirred at 40 °C under nitrogen for 72 hours. The reaction was allowed to cool and was then quenched with saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a white solid (21 mg, Yield: 21%). **6% pyrrolidine 475. (15.98 : 1 ratio)**

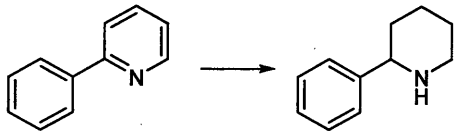
See Table 4.3, p. 101 for further details. All data obtained was in accordance with that previously reported in the literature.[295] The four samples showed identical spectroscopic and analytical data: m.p.: 49 – 51 °C. ^{1}H NMR (400 MHz / $CDCl_3$) <u>piperidine:</u> δ 7.61 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.18 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.17 – 4.11 (m, 1H, C*H*N), 3.63 – 3.57 (m, 1H, CH_AH_BN), 2.90 – 2.85 (m, 1H, CH_AH_BN), 2.32 (s, 3H, Ts CH_3), 1.55 – 1.24 (m, 6H, 3 × CH_2), 0.97 (d, 3H, J = 6.9 Hz, CH_3); <u>pyrrolidine</u> : δ 7.72 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.08 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 3.49 – 3.43 (m, 1H, C*H*N), 3.33 - 3.27 (m, 1H, CH_AH_BN), 3.20 – 3.16 (m, 1H, CH_AH_BN),2.33 (s, 3H, Ts CH_3, minor), 1.82 – 1.63 (m, 2H, CH_2), 1.55 – 1.24 (m, 4H, 2 × CH_2), 0.82 (t, 3H, J = 7.1 Hz, CH_3). IR (neat) υ/cm^{-1}: 2939, 2866, 1598, 1038, 996.

3-Methyl-1-tosylpiperidine 476[296]

466 **476**

3-Methylpiperidine **466** (2.00 g, 20.2 mmol, 1.0 eq.) was treated according to general procedure **C** to give the *title compound* **476** as a white solid (4.27 g, Yield: 84%). All data obtained was in accordance with that previously reported in the literature.[296] m.p.: 104 - 107 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.57 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.25 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.58 - 3.36 (m, 4H, 2 × CH_2N), 2.37 (s, 3H, Ts CH_3), 1.74 - 1.51 (m, 5H, 2 × CH_2 & C*H*), 0.80 (d, 3H, J = 6.5 Hz, CH_3). IR (neat) υ/cm^{-1}: 2939, 1597, 1263, 1037, 995. HRMS (EI) *m/z* calcd. for $C_{13}H_{19}NO_2S$ $[M]^+$ = 253.1137; found: 253.1134.

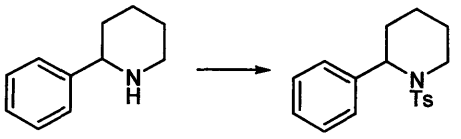
2-Phenylpiperidine 469[297]



480 **469**

A mixture of 2-phenylpiperidine **480** (4.60 ml, 32 mmol, 1.0 eq.) concentrated HCl (4 ml) and ethanol (20 ml) with PtO_2 (300 mg, 1.3 mmol, 0.04 eq.) was placed in a Paar apparatus and subjected to catalytic hydrogenation at a pressure of 1 atmosphere at room temperature for 24 hours. The catalyst was removed by filtration through a plug of celite and washed with EtOH (100 ml). The solvent was evaporated to dryness. The solid residue was treated with 2M NaOH (30 ml) and the free base extracted with diethyl ether (3 × 30 ml). The ether extracts were combined and dried over $MgSO_4$ and evaporated to give *the title compound* **469** as a white solid (4.04 g, Yield: 78%). All data obtained was in accordance with that previously reported in the literature.[297] m.p.: 105 - 108 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.40 - 7.23 (m, 5H, 5 × Ar C*H*), 3.61 (dd, 1H, J = 7.9, 2.5 Hz, C*H*N), 3.25 - 3.19 (m, 1H, CH_AH$_B$N), 2.82 (td, 1H, J = 11.5, 2.5, CH$_A$$H_B$N), 1.98 - 1.65 (m, 5H, 2 × CH_2 & N*H*), 1.60 - 1.46 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 145.6 (C_q), 128.4 (2 × Ar *C*H), 127.1 (Ar *C*H), 126.7 (2 × Ar *C*H), 62.4 (*C*HN), 47.8 (*C*H$_2$N), 35.0 (*C*H$_2$), 26.0 (*C*H$_2$), 25.5 (*C*H$_2$). IR neat υ/cm^{-1}: 3026, 2932, 2851, 2787, 1602, 1106, 996, 698. HRMS (EI) *m/z* calcd. for $C_{11}H_{15}N$ $[M]^+$ = 161.1204; found: 161.1200.

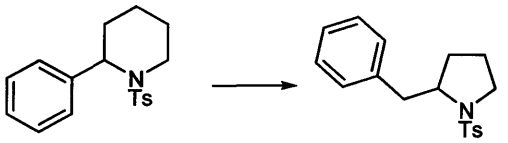
2-Phenyl-1-tosylpiperidine 460[298]



469 **460**

3-Methylpiperidine **469** (4.04 g, 25.1 mmol, 1.0 eq.) was treated according to general procedure **C** to give *the title compound* **460** as a white solid (7.11 g, Yield: 90%). All data obtained was in accordance with that previously reported in the literature.[298] m.p.: 109 - 112 °C. ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.76 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.35 - 7.28 (m, 6H, 2 × Ts C*H* & 4 × Ar C*H*), 7.26 - 7.22 (m, 1H, Ar C*H*), 3.84 (d, 1H, J = 13 Hz, C*H*N), 3.04 - 2.98 (m, 1H, , CH_AH_BN), 2.44 (s, 3H, Ts CH_3), 2.26 - 2.21 (m, 1H, CH_AH_BN), 1.67 -1.62 (m, 1H, CH_CH_D), 1.47 - 1.43 (m, 1H, CH_CH_D), 1.42 - 1.36 (m, 2H, CH_2), 1.33 - 1.24 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 142.9 (C_q), 138.9 (C_q), 138.7 (C_q), 129.7 (2 × Ts *C*H), 128.6 (2 × Ar *C*H), 127.05 (2 × Ts *C*H), 127.0 (2 × Ar *C*H), 126.8 (Ar *C*H), 55.3 (*C*HN), 41.9 (CH_2N), 27.2 (CH_2), 24.3 (CH_2), 21.6 (Ts CH_3), 18.9 (CH_2). IR neat υ/cm^{-1}: 2939, 2866, 1598, 1106, 996, 698. HRMS (APCI) *m/z* calcd. for $C_{18}H_{22}NO_2S$ $[M+H]^+$ = 316.1371; found: 316.1363.

2-Benzyl-1-tosylpyrrolidine 481[299]



460 **481**

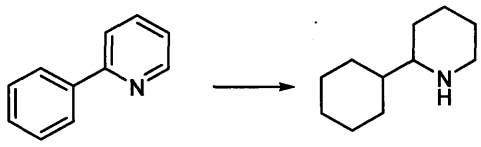
2-Phenyl-1-tosylpiperidine **460** (100 mg, 0.317 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.20 ml, 0.159 mmol, 0.5 eq.) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (80 mg, Yield: 80%).

2-Phenyl-1-tosylpiperidine **460** (100 mg, 0.317 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. . Concentrated H_2SO_4 (2 drops) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was

washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (80 mg, Yield: 80%).

Both samples showed decomposition of the piperidine and no isolation of the desired pyrrolidine **481**. This was shown by comparison with literature spectroscopic data for 2-benzyl-1-tosylpyrrolidine.[299]

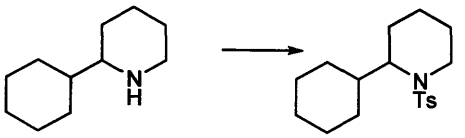
2-Cyclohexylpiperidine 470 [265,300]



480 **470**

A mixture of 2-phenylpiperidine **480** (4.60 ml, 32 mmol, 1.0 eq.) concentrated HCl (4 ml) and ethanol (20 ml) with PtO_2 (0.3 g, 1.3 mmol, 0.04 eq.) was placed in a Paar apparatus and subjected to catalytic hydrogenation at a pressure of 2 to 3 atmospheres at room temperature for 48 hours. The catalyst was removed by filtration through a plug of celite and washed with ethanol (100 ml). The solvent was evaporated to dryness. The solid residue was treated with 2 M NaOH (30 ml) and the free base extracted with diethyl ether (3 × 30 ml). The ether extracts were combined, dried over $MgSO_4$ and evaporated to give *the title compound* **470** as a yellow oil (4.358 g, Yield: 81%). All data obtained was in accordance with that previously reported in the literature.[300] ^{1}H NMR (500 MHz / $CDCl_3$) δ 3.08 (app. dq, 1H, J = 11.7, 2.3 Hz, C*H*N), 2.62 – 2.57 (m, 1H, CH_AH_BN), 2.23 – 2.16 (m, 1H, CH_AH_BN), 1.83 - 1.55 (m, 8H, 4 × CH_2), 1.43 - 1.25 (m, 2H, CH_2), 1.24 - 1.05 (m, 5H, 2 × CH_2 & C*H*), 1.02 - 0.92 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 62.0 (*C*HN), 47.6 (CH_2N), 43.5 (*C*H), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.2 (CH_2). IR neat υ/cm^{-1}: 2927, 2852, 1629, 1106, 996. HRMS (EI) *m/z* calcd. for $C_{11}H_{21}N$ $[M]^+$ = 167.1674; found: 167.1677.

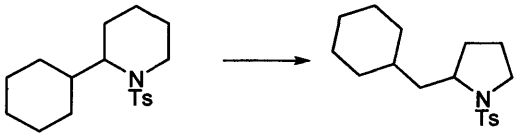
2-Cyclohexyl-1-tosylpiperidine 484



470 **484**

2-Cyclohexylpiperidine **470** (1.00 g, 5.99 mmol, 1.0 eq.) was treated according to general procedure **C** to give *the title compound* **484** as a clear oil (1.71 g, Yield: 89%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.73 (d, 2H, J = 8.3 Hz, 2 × Ts *CH*), 7.27 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.80 – 3.77 (m, 1H, CH_AH$_B$N), 3.69 – 3.61 (m, 1H, C*H*N), 3.00 - 2.94 (m, 1H, CH$_A$$H_B$N), 2.42 (s, 3H, Ts C$H_3$), 1.85 - 1.08 (m, 17H, 8 × CH_2 and C*H*). ^{13}C NMR (500 MHz / $CDCl_3$) δ 142.5 (C_q), 139.5 (C_q), 129.7 (2 × Ts *C*H), 127.0 (2 × Ts *C*H), 58.6 (*C*HN), 41.5 (*C*H$_2$N), 34.8 (*C*H), 30.5 (*C*H$_2$), 30.0 (*C*H$_2$), 26.4 (*C*H$_2$), 26.3 (*C*H$_2$), 26.2 (*C*H$_2$), 24.4 (2 × *C*H$_2$), 23.9 (*C*H$_2$), 21.4 (Ts *C*H$_3$), 18.6 (*C*H$_2$). IR (neat) υ/cm^{-1}: 2929, 2852, 1716, 1598, 1106, 996. HRMS (APCI) *m/z* calcd. for $C_{18}H_{28}NO_2S$ $[M+H]^+$ = 322.1841; found: 322.1845.

2-(Cyclohexylmethyl)-1-tosylpyrrolidine 485



484 **485**

2-Cyclohexyl-1-tosylpiperidine **484** (100 mg, 0.312 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.20 ml, 0.156 mmol, 0.5 eq.) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (31 mg, Yield: 31%). **32% pyrrolidine 485. (2.41 : 1.0 ratio)**

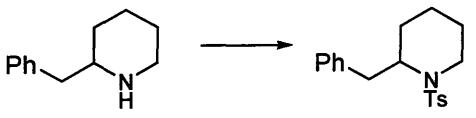
2-Cyclohexyl-1-tosylpiperidine **484** (100 mg, 0.312 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.20 ml, 0.156 mmol, 0.5 eq.) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over

solid K_2CO_3 and evaporated to give a yellow oil (73 mg, Yield: 73%). **48% pyrrolidine 485. (1.10 : 1.0 ratio)**

2-Cyclohexyl-1-tosylpiperidine **484** (100 mg, 0.312 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (56 mg, Yield: 56%). **23% pyrrolidine 485. (3.29 : 1.0 ratio)**

See Table 4.6, p. 106 for further deatils. The three samples showed identical spectroscopic and analytical data: ^{1}H NMR (500 MHz / $CDCl_3$) piperidine: δ 7.65 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.20 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 3.73 – 3.68 (m, 1H, C*H*N), , 3.57 – 3.54 (m, 1H, CH_AH$_B$N), 2.92 - 2.85 (m, 1H, CH$_A$$H_B$N), 2.34 (s, 3H, Ts C$H_3$), 1.79 – 1.76 (m, 1H, C*H*), 1.72 - 1.65 (m, 6H, 3 × CH_2), 1.64 – 1.06 (m, 10H, 5 × CH_2); pyrrolidine: δ 7.73 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.23 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.64 – 3.58 (m, 1H, C*H*N), 3.34 – 3.30 (m, 1H, CH_AH$_B$N), 3.14 – 3.10 (m, 1H, CH$_A$$H_B$N), 2.35 (s, 3H, Ts C$H_3$), 1.72 - 1.65 (m, 7H, 3 × CH_2 & C*H*), 1.64 – 1.06 (m, 10H, 5 × CH_2). ^{13}NMR (500 MHz / $CDCl_3$) piperidine: δ 142.6 (C_q), 139.5 (C_q), 129.5 (2 × Ts *C*H), 127.0 (2 × Ts *C*H), 58.3 (*C*HN), 41.1 (*C*H_2N), 34.9 (*C*H), 30.3 (*C*H_2), 30.0 (2 × *C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2), 26.2 (*C*H_2), 24.4 (*C*H_2), 23.9 (*C*H_2), 21.5 (Ts *C*H_3), pyrrolidine: δ 143.1 (C_q), 139.1 (C_q), 129.6 (2 × Ts *C*H), 127.5 (2 × Ts *C*H), 58.4 (*C*HN), 48.7 (*C*H_2N), 35.0 (*C*H), 34.1 (*C*H_2), 32.7 (*C*H_2), 31.1 (2 × *C*H_2), 30.3 26.6 (*C*H_2), 24.0 (*C*H_2), 21.7 (Ts *C*H_3), 18.6 (2 × *C*H_2). IR (neat) υ/cm^{-1}: 2926, 2853, 1598, 1106, 996.

2-Benzyl-1-tosylpiperidine 461[2]

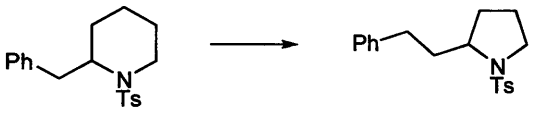


471 **461**

2-Benzylpiperidine **471** (200 mg, 1.14 mmol, 1.0 eq.) was treated according to general procedure **C** to give *the title compound* **461** as a colourless solid (346 mg, Yield: 92%). All data obtained was in accordance with that previously reported in the literature.[2] m.p.: 78 - 81 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.54 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.23 - 7.13 (m, 6H, 2 × Ts C*H* & 4 × Ar C*H*), 7.09 - 7.06 (m, 1H, Ar C*H*), 4.22 (app. t, 1H, J = 6.8, C*H*N), 3.74 - 3.67 (m, 1H, CH_AH$_B$N),

3.04 - 2.97 (m, 1H, CH_AH_BN), 2.76 (app. q, 2H, J = 6.8 Hz, CH_2), 2.32 (s, 3H, Ts CH_3), 1.61 - 1.54 (m, 4H, 2 × CH_2), 1.40 - 1.27 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) δ 142.8 (C_q), 138.7 (C_q), 138.5 (C_q), 129.6 (2 × Ar CH), 129.2 (2 × Ts CH), 128.5 (2 × Ar CH), 127.0 (2 × Ts CH), 126.4 (Ar CH), 54.3 (CHN), 40.9 (CH_2N), 35.7 (CH_2), 26.0 (CH_2), 24.9 (CH_2), 21.5 (Ts CH_3), 18.3 (CH_2). IR neat υ/cm^{-1}: 2940, 2864, 1598, 1108, 996, 698. HRMS (APCI) *m/z* calc. for $C_{19}H_{24}NO_2S$ $[M+H]^+$ = 330.1528; found: 330.1522.

2-Phenethyl-1-tosylpyrrolidine 486[301]



461 **486**

2-Benzyl-1-tosylpiperidine **461** (100 mg, 0.304 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (85 mg, Yield: 85%). **27% pyrrolidine 486. (2.71 : 1 ratio)**

2-Benzyl-1-tosylpiperidine **461** (100 mg, 0.304 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.20 ml, 0.152 mmol, 0.5 eq.) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (61 mg, Yield: 61%). **43.7% pyrrolidine 486. (1.29 : 1 ratio)**

2-Benzyl-1-tosylpiperidine **461** (100 mg, 0.304 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.40 ml, 0.304 mmol, 1.0 eq.) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over

solid K_2CO_3 and evaporated to give a yellow oil (80 mg, Yield: 80%). **30% pyrrolidine 486. (2.43 : 1 ratio)**

2-Benzyl-1-tosylpiperidine **461** (100 mg, 0.304 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.90 ml, 0.608 mmol, 2.0 eq.) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (83 mg, Yield: 83%). **57% pyrrolidine 486. (1 : 1.33 ratio)**

See Table 4.7, p. 107 for further details. All samples show identical spectroscopic and analytical data: All data obtained was in accordance with that previously reported in the literature.[301] ^{1}H NMR (500 MHz / $CDCl_3$) piperidine: δ 7.52 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 7.22 – 7.15 (m, 3H, 3 × Ar C*H*), 7.14 – 7.10 (m, 2H, 2 × Ar C*H*), 7.05 (d, 2H, J = 8.4 Hz, 2 × Ts C*H*), 4.22 - 4.16 (m, 1H, C*H*N), 3.73 – 3.66 (m, 1H, CH_AH_BN), 3.04 - 2.97 (m, 1H, CH_AH_BN), 2.73 (q, 2H, J = 6.8 Hz, CH_2), 2.29 (s, 3H, Ts CH_3), 1.62 – 1.43 (m, 4H, 2 × CH_2) , 1.39 - 1.25 (m, 2H, CH_2),; pyrrolidine: δ 7.22 – 7.15 (m, 5H, 2 × Ts C*H* 3 × Ar C*H*), 7.14 – 7.10 (m, 4H, 2 × Ts C*H* & 2 × Ar C*H*), 3.00 - 2.90 (m, 1H, C*H*N), 2.69 – 2.63 (m, 1H, CH_AH_BN), 2.60 – 2.56 (m, 1H, CH_AH_BN), 2.50 – 2.39 (m, 2H, CH_2), 2.28 (s, 3H, Ts CH_3), 1.69 (app. br. s, 2H, CH_2), 1.39 - 1.25 (m,2H, CH_2), 1.24 - 0.97 (m, 2H, CH_2). ^{13}C NMR (500 MHz / $CDCl_3$) piperidine: δ 142.8 (C_q), 138.7 (C_q), 138.6 (C_q), 129.6 (2 × Ar *C*H), 129.2 (2 × Ts *C*H), 128.5 (2 × Ar *C*H), 127.0 (2 × Ts *C*H), 126.4 (Ar *C*H), 54.4 (*C*HN), 40.9 (CH_2N), 35.8 (CH_2), 26.0 (CH_2), 24.9 (CH_2), 21.4 (Ts CH_3), 18.3 (CH_2); pyrrolidine: δ 139.3 (C_q), 139.1 (C_q), 138.7 (C_q), 129.9 (2 × Ar *C*H), 129.3 (2 × Ts *C*H), 128.4 (2 × Ar *C*H), 127.6 (2 × Ts *C*H), 126.2 (Ar *C*H), 58.3 (*C*HN), 47.2 (CH_2N), 44.0 (CH_2), 33.0 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 21.5 (Ts CH_3). IR (neat) υ/cm^{-1}: 2938, 2861, 1598, 1108, 996, 698.

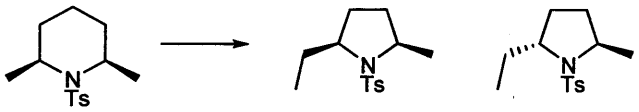
(2*S*,6*R*)-2,6-Dimethyl-1-tosylpiperidine 487[302]

467 **487**

2,6-Dimethylpiperidine **467** (2.00 g, 17.7 mmol, 1.0 eq.) was treated according to general procedure **C** and the crude product was purified using column chromatography (eluting silica gel

with 30% ethyl acetate in hexanes) to give *the title compound* **487** as a white solid (1.50 g, Yield: 32%). All data obtained was in accordance with that previously reported in the literature.[302] m.p: 63 - 65 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.63 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.20 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.11 (app. p, 2H, J = 7.1 Hz, 2 × C*H*N), 2.34 (s, 3H, Ts CH_3), 1.73 - 1.61 (m, 2H, CH_2), 1.40 - 1.29 (m, 4H, 2 × CH_2), 1.27 (d, 6H, J = 7.1 Hz, 2 × CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 142.6 (C_q), 139.0 (C_q), 129.6 (2 × Ts *CH*), 126.7 (2 × Ts *CH*), 47.9 (2 × *CH*N), 29.6 (2 × CH_2), 22.4 (CH_2), 21.5 (Ts CH_3), 13.4 (2 × CH_3). IR (neat) υ/cm^{-1}: 3026, 2924, 1599, 1265, 1108, 996. HRMS (EI) *m/z* calcd. for $C_{14}H_{21}NO_2S$ $[M]^+$ = 367.1293; found: 367.1284.

(2*S*,5*R*)-2-Ethyl-5-methyl-1-tosylpyrrolidine 488a & (2*R*,5*R*)-2-ethyl-5-methyl-1-tosylpyrrolidine 488b



487 **488a** **488b**

2,6-Dimethyl-1-tosylpiperidine **487** (100 mg, 0.374 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (77 mg, Yield: 77%). **487: 1 (28%); 488a: 1.83 (50%); 488b: 0.81 (22%)**

2,6-Dimethyl-1-tosylpiperidine **487** (100 mg, 0.374 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 3 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (78 mg, Yield: 78%). **487: 1 (46%); 488a: 0.61 (28%); 488b: 0.58 (26%)**

2,6-Dimethyl-1-tosylpiperidine **487** (100 mg, 0.374 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 24 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous

layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (77 mg, Yield: 77%). **487: 1 (23%); 488a: 2.46 (54%); 488b: 1(23%)**

2,6-Dimethyl-1-tosylpiperidine **487** (100 mg, 0.374 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. Concentrated sulfuric acid (2 drops) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (59 mg, Yield: 59%). **487: 1 (43%); 488a: 1 (43%); 488b: 0.43 (14%)**

2,6-Dimethyl-1-tosylpiperidine **487** (100 mg, 0.374 mmol, 1.0 eq.) was dissolved in toluene (10 ml) and stirred under nitrogen. TfOH (0.20 ml, 0.187 mmol, 0.5 eq.) was added to the solution and stirred at 110 °C for 72 hours. The reaction was allowed to cool and quenched by the addition of saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over solid K_2CO_3 and evaporated to give a yellow oil (69 mg, Yield: 69%). **487: 4 (62%); 488a: 0.25 (15%); 488b: 0.37 (23%)**

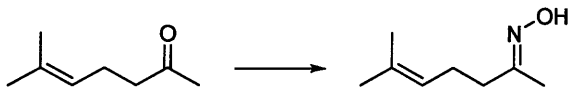
See Table 4.8, p. 108 for further details. All samples show identical spectroscopic and analytical data: ^{1}H NMR (400 MHz / $CDCl_3$) piperidine: δ 7.61 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 7.17 (d, 2H, J = 8.2 Hz, 2 × Ts C*H*), 4.09 (app. p, 2H, J = 7.1 Hz, 2 × C*H*N), 2.32 (s, 3H, Ts CH_3), 1.70 – 1.57 (m, 2H, CH_2), 1.40 - 1.29 (M, 2H, 2 × CH_2), 1.24 (d, 6H, J = 7.1 Hz, 2 × CH_3); *cis* pyrrolidine **488a**: δ 7.83 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.08 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.62 - 3.57 (m, 1H, C*H*N), 3.45 - 3.39 (m, 1H, C*H*N), 2.32 (s, 3H, Ts CH_3),, 2.02 – 1.72 (m, 2H, CH_2), 1.51 – 1.28 (m, 4H, 2 × CH_2), 1.09 (d, 3H, J = 6.4 Hz, CH_3). 0.83 (t, 3H, J = 7.5 Hz, CH_3); *trans* pyrrolidine **488b**: δ 7.71 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.32 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 3.96 - 3.89 (m, 1H, C*H*N), 3.69 - 3.63 (m, 1H, C*H*N), 2.29 (s, 3H, Ts CH_3), 2.02 – 1.72 (m, 2H, CH_2), 1.51 – 1.28 (m, 4H, 2 × CH_2), 1.09 (d, 3H, J = 6.4 Hz, CH_3), 0.71 (t, 3H, J = 7.4 Hz, CH_3). IR (neat) υ/cm^{-1}: 2968, 1599, 1265, 1108, 996.

1-Tosylpiperidine 489[303]

464 **489**

Piperidine **464** (1.20 ml, 11.8 mmol, 1.0 eq.) was treated according to general procedure **C** to give *1-tosylpiperidine* **489** as a colourless solid (2.61 g, Yield: 92%). All data obtained was in accordance with that previously reported in the literature.[304] m.p.: 89 - 92 °C. ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.57 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.25 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 2.89 (app. t, 4H, J = 5.8 Hz, 2 × CH_2N), 2.37 (s, 3H, Ts CH_3), 1.60 – 1.55 (m, 4H, 2 × CH_2), 1.37 – 1.30 (m, 2H, CH_2). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.3 (C_q), 133.2 (C_q), 129.5 (2 × Ts *C*H), 127.8 (2 × Ts *C*H), 47.0 (2 × *C*H_2N), 25.1 (2 × *C*H_2), 23.5 (*C*H_2), 21.6 (Ts *C*H_3). IR (neat) υ/cm^{-1}: 3056, 2938, 2925, 1596, 1154, 994. HRMS (APCI) *m/z* calcd. for $C_{12}H_{18}NO_2S$ $[M+H]^+$ = 240.1058; found: 240.1059.

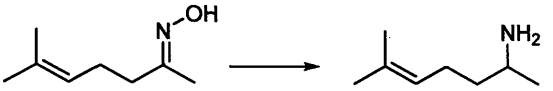
(*E*)-6-Methylhept-5-en-2-one oxime 443[261]



442 **443**

6-Methylhept-5-en-2-one **442** (2.90 ml, 1.98 mmol, 1.0 eq.) was suspended in ethanol (30 ml), to this suspension was then added hydroxylamine hydrochloride salt (2.60 g, 3.96 mmol, 2.0 eq.) and sodium acetate (small spatula). The suspension was heated to reflux for 2 hours. Once the reaction had cooled, the ethanol was evaporated off and the residue was partitioned between water (30 ml) and diethyl ether (30 ml). The aqueous layer was then extracted with ether (3 × 30 ml) and the combined organic fractions were dried over $MgSO_4$ and concentrate *in vacuo*. The oil was purified by column chromatography (eluting silica gel with 20% ethyl actetate in hexanes) to give *the title compound* **443** as a clear oil (1.66 g, Yield: 60%). All data obtained was in accordance with that previously reported in the literature.[305] ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.07 – 5.01 (m, 1H, C*H*), 2.24 – 2.21 (m, 4H, 2 × CH_2), 1.91 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.63 (s, 3H, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 158.7 (C_q), 132.7 (C_q), 123.12 (*C*H), 35.9 (*C*H_2), 25.7 (*C*H_3), 24.9 (*C*H_2), 17.7 (*C*H_3), 13.4 (*C*H_3). IR (neat) υ/cm^{-1}: 3246, 2924, 1736, 1262. HRMS (APCI) *m/z* calcd. for $C_8H_{16}NO$ $[M+H]^+$ = 142.1232; found: 142.1230.

6-Methylhept-5-en-2-amine 444[262]



443 444

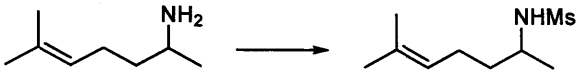
Oxime **443** (430 mg, 3.02 mmol, 1.0 eq.) dissolved in tetrahydrofuran (20 ml) and added dropwise to a suspension of $LiAlH_4$ (0.41 g, 10.9 mmol, 3.6 eq.) in tetrahydrofuran (40 ml) at 20 °C. The suspension was then heated to reflux for 3 hours and the subsequently cooled to 20 °C. When cooled, water (4 ml), 15% NaOH (4 ml) and water (4 ml) were added sequentially and the reaction then stirred for a further hour. The reaction mixture was filtered and washed with tetrahydrofuran (40 ml), dried over $MgSO_4$ and concentrated to give *the title compound* **444** as a clear oil. (383 mg, Yield: 100%). All data obtained was in accordance with that previously reported in the literature.[306] ^{1}H NMR (400 MHz / $CDCl_3$) δ 4.99 - 4.93 (m, 1H, C*H*), 2.75 (app. sext, 1H, J = 6.3 Hz, C*H*N), 1.91 - 1.79 (m, 2H, CH_2), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.29 - 1.18 (m, 2H, CH_2), 0.93 (d, 3H, J = 6.3 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 131.8 (C_q), 124.0 (*C*H), 46.8 (*C*HN), 39.5 (*C*H_2), 25.7 (*C*H_3), 24.9 (*C*H_3), 23.3 (*C*H_2), 17.7 (*C*H_3). IR (neat) υ/cm^{-1}: 3472, 2925, 1649, 1262.

4-Methyl-*N*-(6-methylhept-5-en-2-yl)benzenesulfonamide 445

444 445

6-Methylhept-5-en-2-amine **444** (141 mg, 1.11 mmol, 1.0 eq.) was treated according to general procedure **C** and the crude product was purified using column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **445** as a yellow oil (155 mg, Yield: 50%). %). All data obtained was in accordance with that previously reported in the literature.[307] ^{1}H NMR (400 MHz / $CDCl_3$) δ 7.69 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 7.23 (d, 2H, J = 8.3 Hz, 2 × Ts C*H*), 4.87 - 4.82 (m, 1H, C*H*), 3.28 - 3.24 (m, 1H, C*H*N), 2.36 (s, 3H, Ts CH_3), 1.90 - 1.71 (m, 2H, CH_2), 1.57 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.40 - 1.30 (m, 2H, CH_2), 0.97 (d, 3H, J = 6.6 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 143.2 (C_q), 138.2 (C_q), 132.4 (C_q), 129.7 (2 × Ts *C*H), 127.1 (2 × Ts *C*H), 123.2 (*C*H), 49.8 (*C*HN), 37.5 (*C*H_2), 25.7 (*C*H_3), 24.2 (*C*H_3), 21.8 (*C*H_2), 21.5 (Ts *C*H_3), 17.7 (*C*H_3). IR (neat) υ/cm^{-1}: 3279, 2924, 1918, 1598, 1262. HRMS (APCI) *m/z* calcd. for $C_{15}H_{24}NO_2S$ $[M+H]^+$ = 282.1528; found: 282.1530.

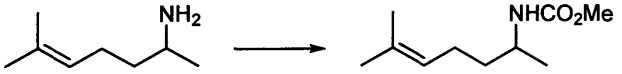
N-(6-methylhept-5-en-2-yl)methanesulfonamide 490



444 **490**

6-Methylhept-5-en-2-amine **444** (383 mg, 3.02 mmol, 1.0 eq.) was dissolved in dichloromethane (30 ml) and cooled to –78 °C under N_2. To this was then added triethylamine (0.43 ml, 3.05 mmol, 1.01 eq.), DMAP (4 crystal) and MsCl (0.23 ml, 17.7 mmol, 1.0 eq.). The reaction mixture was allowed to warm to room temperature over 16 hours. The mixture was washed with water (3 × 30 ml), 2 M HCl (2 × 30 ml) and 2 M NaOH (2 × 30 ml), then dried over Na_2SO_4 and concentrated. Purified using column chromatography (eluting silica gel with 40% ethyl acetate in hexanes) to give *the title compound* **490** as a clear oil (305 mg, Yield: 49%). ^{1}H NMR (400 MHz / $CDCl_3$) δ 5.04 - 5.00 (m, 1H, C*H*), 3.46 - 3.38 (m, 1H, C*H*N), 2.90 (s, 3H, Ms C*H*$_3$), 2.05 - 1.95 (m, 2H, C*H*$_2$), 1.62 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 1.47 – 1.42 (m, 2H, C*H*$_2$), 1.18 (d, 3H, J = 6.5 Hz, C*H*$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 137.7 (C_q), 123.1 (*C*H), 50.1 (*C*HN), 44.2 (Ms *C*H$_3$), 37.7 (*C*H$_2$), 25.7 (*C*H$_3$), 24.4 (*C*H$_3$), 22.4 (*C*H$_2$), 17.8 (*C*H$_3$). IR (neat) υ/cm^{-1}: 3291, 2926, 1673, 1262. HRMS (EI) *m/z* calcd. for $C_9H_{19}NO_2S$ $[M]^+$ = 205.1137; found: 205.1138.

Methyl 6-methylhept-5-en-2-ylcarbamate 500[308]

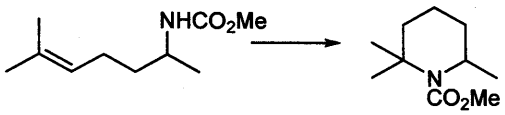


444 **500**

Methyl chloroformate (0.75 ml, 9.64 mmol, 1.1 eq.) was added to a suspension of 6-methylhept-5-en-2-amine **444** (1.11 g, 8.77 mmol, 1.0 eq.) and $NaHCO_3$ (2.20 g, 26.3 mmol, 2.0 eq.) in a 50/50 mixture of tetrahydrofuran and water (60 ml). The mixture was stirred at room temperature over night and then diluted with water (50 ml) and washed with diethyl ether (30 ml). The aqueous layer was acidified with 2 M HCl and washed with ethyl acetate (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over $MgSO_4$ and concentrates to a viscous oil. This was purified by column chromatography (eluting silica gel with 0 - 40% ethyl acetate in hexanes) to give *the title compound* **500** as a clear oil (0.469 g, Yield: 29%). ^{1}H NMR (500 MHz / $CDCl_3$) δ 7.20 (s, 1H, N*H*), 5.08 - 4.95 (m, 1H, C*H*), 4.41 (app. s, 1H, C*H*N), 3.59 (s, 3H, C*H*$_3$), 1.99 - 1.94 (m, 2H, C*H*$_2$), 1.61 (s, 3H, C*H*$_3$), 1.52 (s, 3H, C*H*$_3$), 1.39 - 1.35 (m, 2H, C*H*$_2$), 1.06 (d, 3H, J = 6.6 Hz, C*H*$_3$). ^{13}C NMR (400 MHz / $CDCl_3$) δ 156.5 (C_q), 132.1 (C_q), 123.6 (*C*H), 51.8 (*C*H$_3$), 46.9 (*C*HN), 37.2 (*C*H$_2$), 25.7 (*C*H$_3$), 24.6 (CH$_3$), 21.9 (*C*H$_2$), 17.7 (*C*H$_3$). IR (neat)

υ/cm^{-1}: 3329, 2967, 1699, 1538, 1262. HRMS (APCI) *m/z* calculated for $C_{10}H_{20}NO_2$ $[M+H]^+$ = 186.1494; found: 186.1491.

Methyl 2,2,6-trimethylpiperidine-1-carboxylate 501



500 **501**

Methyl 6-methylhept-5-en-2-ylcarbamate **500** (50 mg, 0.27 mmol, 1.0 eq.) was dissolved in dichloromethane (10 ml) and cooled to 0 °C under nitrogen. Concentrated sulfuric acid (2 drops) was added and the reaction stirred for 1 hour. The reaction mixture was quenched with saturated aqueous K_2CO_3 (10 ml). The quenched solution was then separated and the aqueous layer was washed with dichloromethane (3 x 10 ml). The combined organic layers were dried over K_2CO_3 and concentrated *in vacuo* to give *the title compound* **501** as a clear oil (36 mg, Yield: 72%). ^1H NMR (400 MHz / $CDCl_3$) δ 4.14 (app. dp, 1H, J = 7.0, 2.2 Hz, C*H*N), 3.49 (s, 3H, CH_3), 1.65 - 1.48 (m, 4H, 2 × CH_2), 1.43 – 1.36 (m, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.02 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR (400 MHz / $CDCl_3$) δ 156.9 (C_q), 54.3 (C_q), 51.8 (CH_3), 48.3 (*C*HN), 39.1 (CH_2), 29.6 (CH_3), 28.3 (CH_2), 27.7 (CH_3), 21.8 (CH_3), 14.7 (CH_2). IR (neat) υ/cm^{-1}: 3328, 2965, 1699, 1538, 1262. HRMS (EI) *m/z* calcd. for $C_{10}H_{19}NO_2$ $[M]^+$ = 185.1416; found: 185.1411.

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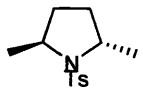
Appendix



174b

Table 1. Crystal data and structure refinement for dwk0901.

Identification code	dwk0901	
Empirical formula	C_{13} H_{19} N O_2 S	
Formula weight	253.35	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 6.2975(2) Å	α= 90°.
	b = 11.1070(3) Å	β= 90°.
	c = 18.1443(5) Å	γ = 90°.
Volume	1269.13(6) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.245 mm^{-1}	
F(000)	544	
Crystal size	0.30 x 0.30 x 0.30 mm^3	
Theta range for data collection	2.24 to 27.46°.	
Index ranges	-8<=h<=8, -14<=k<=14, -23<=l<=23	
Reflections collected	2863	
Independent reflections	2863 [R(int) = 0.0000]	
Completeness to theta = 27.46°	98.3 %	
Max. and min. transmission	0.9301 and 0.9301	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2863 / 0 / 158	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0786	
R indices (all data)	R1 = 0.0348, wR2 = 0.0803	
Absolute structure parameter	0.07(7)	
Extinction coefficient	0.159(10)	
Largest diff. peak and hole	0.213 and -0.317 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for wk0901. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5856(3)	2754(2)	6489(1)	26(1)
C(2)	7415(3)	3770(2)	6661(1)	30(1)
C(3)	9597(3)	3244(2)	6472(1)	27(1)
C(4)	9472(3)	1949(2)	6769(1)	22(1)
C(7)	7342(2)	-285(2)	5783(1)	22(1)
C(8)	9402(3)	-742(2)	5754(1)	24(1)
C(9)	10151(3)	-1222(2)	5096(1)	26(1)
C(10)	8894(3)	-1267(1)	4466(1)	24(1)
C(11)	6828(3)	-803(2)	4510(1)	25(1)
C(12)	6059(2)	-308(2)	5158(1)	23(1)
C(13)	5134(3)	2760(2)	5687(1)	32(1)
C(14)	10234(3)	1847(2)	7559(1)	31(1)
C(15)	9696(4)	-1830(2)	3764(1)	33(1)
N(5)	7153(2)	1678(1)	6694(1)	22(1)
O(1)	4066(2)	341(1)	6567(1)	28(1)
O(2)	7316(2)	-386(1)	7194(1)	30(1)
S(6)	6344(1)	309(1)	6620(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for dwk0901.

C(1)-N(5)	1.494(2)
C(1)-C(13)	1.524(2)
C(1)-C(2)	1.528(2)
C(2)-C(3)	1.532(3)
C(3)-C(4)	1.537(2)
C(4)-N(5)	1.497(2)
C(4)-C(14)	1.516(2)
C(7)-C(12)	1.392(2)
C(7)-C(8)	1.394(2)
C(7)-S(6)	1.7720(16)
C(8)-C(9)	1.390(2)
C(9)-C(10)	1.391(2)
C(10)-C(11)	1.402(2)
C(10)-C(15)	1.506(2)
C(11)-C(12)	1.386(2)
N(5)-S(6)	1.6098(14)
O(1)-S(6)	1.4379(12)
O(2)-S(6)	1.4333(13)
N(5)-C(1)-C(13)	113.78(14)
N(5)-C(1)-C(2)	100.85(13)
C(13)-C(1)-C(2)	112.56(15)
C(1)-C(2)-C(3)	104.43(14)
C(2)-C(3)-C(4)	103.40(14)
N(5)-C(4)-C(14)	112.32(14)
N(5)-C(4)-C(3)	101.90(13)
C(14)-C(4)-C(3)	112.68(14)
C(12)-C(7)-C(8)	120.19(15)
C(12)-C(7)-S(6)	119.91(12)
C(8)-C(7)-S(6)	119.89(13)
C(9)-C(8)-C(7)	119.22(15)
C(8)-C(9)-C(10)	121.72(16)
C(9)-C(10)-C(11)	117.97(16)
C(9)-C(10)-C(15)	121.21(17)
C(11)-C(10)-C(15)	120.80(16)
C(12)-C(11)-C(10)	121.21(15)
C(11)-C(12)-C(7)	119.69(15)
C(1)-N(5)-C(4)	113.26(13)

C(1)-N(5)-S(6)	124.19(11)
C(4)-N(5)-S(6)	120.42(11)
O(2)-S(6)-O(1)	119.22(8)
O(2)-S(6)-N(5)	108.25(8)
O(1)-S(6)-N(5)	107.32(8)
O(2)-S(6)-C(7)	105.72(8)
O(1)-S(6)-C(7)	107.81(8)
N(5)-S(6)-C(7)	108.10(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for dwk0901. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(1)	23(1)	30(1)	-1(1)	1(1)	4(1)
C(2)	34(1)	21(1)	36(1)	-2(1)	-2(1)	2(1)
C(3)	29(1)	25(1)	26(1)	3(1)	-2(1)	-5(1)
C(4)	18(1)	24(1)	22(1)	0(1)	0(1)	0(1)
C(7)	23(1)	17(1)	25(1)	1(1)	-1(1)	1(1)
C(8)	24(1)	22(1)	28(1)	3(1)	-4(1)	1(1)
C(9)	22(1)	21(1)	35(1)	1(1)	2(1)	0(1)
C(10)	28(1)	16(1)	28(1)	0(1)	3(1)	-2(1)
C(11)	29(1)	22(1)	26(1)	-1(1)	-5(1)	-1(1)
C(12)	21(1)	19(1)	28(1)	0(1)	-2(1)	0(1)
C(13)	32(1)	31(1)	34(1)	4(1)	-9(1)	4(1)
C(14)	28(1)	38(1)	27(1)	4(1)	-6(1)	-5(1)
C(15)	37(1)	30(1)	31(1)	-3(1)	6(1)	4(1)
N(5)	19(1)	20(1)	26(1)	1(1)	-2(1)	2(1)
O(1)	20(1)	31(1)	32(1)	0(1)	4(1)	-4(1)
O(2)	36(1)	27(1)	26(1)	7(1)	-2(1)	0(1)
S(6)	21(1)	21(1)	22(1)	2(1)	1(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for dwk0901.

	x	y	z	U(eq)
H(1)	4594	2814	6822	31
H(2A)	7342	3998	7188	36
H(2B)	7110	4488	6357	36
H(3A)	10747	3701	6717	32
H(3B)	9843	3249	5933	32
H(4)	10313	1398	6446	26
H(8)	10283	-726	6179	29
H(9)	11559	-1527	5075	31
H(11)	5939	-827	4087	31
H(12)	4662	13	5177	27
H(13A)	6375	2690	5364	49
H(13B)	4386	3514	5582	49
H(13C)	4178	2078	5601	49
H(14A)	9467	2427	7867	47
H(14B)	11760	2018	7581	47
H(14C)	9970	1030	7740	47
H(15A)	11238	-1937	3796	49
H(15B)	9358	-1305	3347	49
H(15C)	9015	-2615	3694	49