UNIVERSITY OF SOUTHAMPTON

Development of selective non-metal based organocatalysts for asymmetric synthesis.

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Doctor of Philosophy

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
SCHOOL OF CHEMISTRY

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ABSTRACT

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DEVELOPMENT OF SELECTIVE NON-METAL BASED ORGANOCATALYSTS FOR ASYMMETRIC SYNTHESIS.

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This thesis is concerned with the design, synthesis and use of novel bifunctional organocatalysts for the asymmetric Michael addition of ketones and 1, 3 - dicarbonyl compounds to trans - β - nitrostyrene.

Chapter 1 describes the concept of organocatalysis, including history and mode of action. A detailed review is provided on the organocatalytic Michael addition of carbon nucleophiles to nitroolefins. The bifunctional organocatalyst design and programme of work is also discussed.

Chapter 2 details initial investigations conducted on the organocatalytic Michael addition of cyclohexanone to trans - β - nitrostyrene using monofunctional amine catalysts and hydrogen bond donor catalysts.

Chapters 3, 4 and 5 depict the synthesis and testing of a range of novel bifunctional organocatalysts for the Michael addition of cyclohexanone to trans - β - nitrostyrene.

Chapter 6 compares the different bifunctional organocatalysts and explores the scope of the catalysts and the Michael addition reaction.

dedicated to my Grandad

Mr Victor Thomas Carley (Senior)

July 15th 1927 - March 17th 2006

'always try your best, your best will be good enough'

Contents.

Preface.

The research described in this thesis was carried out under the supervision of Professor Jeremy Kilburn at the University of Southampton between October 2003 and January 2007. No part of this thesis has been previously submitted at this or any other University.

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Abbreviations.

Ac	acetyl
Ar	aryl
aq.	aqueous
Å	Ångström
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bmim	butylmethyl imidazolium
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
bs	broad singlet
° C	degrees centigrade
cat.	catalytic
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
d	doublet, day(s)
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNBS	2,4-dinitrobenzene sulfonic acid
d.r.	diastereomeric ratio
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
e.e.	enantiomeric excess
ES	electrospray
Et	ethyl
eq.	equivalent(s)
FT	fourier transform

h	hour(s)
HOBt	1-hydroxybenzotriazole
HOMO	highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IPA	isopropanol
IR	infrared spectroscopy
J	coupling constant
L.A.	Lewis acid
lit. ref.	literature reference
LRMS	low resolution mass spectroscopy
LUMO	lowest occupied molecular orbital
M	molar
$[M]^+$	positive molecule ion
$[M]^-$	negative molecule ion
m	multiplet, medium
m-	meta
Me	methyl
min	minute(s)
mol.	molecular
Mp	melting point
NMP	N-methyl-2-pyrrolidinone
NMO	N-methylmorpholine
NMR	nuclear magnetic reasonance
o-	ortho
p-	para
PEG	polyethylene glycol
Ph	phenyl
ppm	parts per million
ppt	precipitate
PTC	phase transfer catalysis
Pr	propyl

q	quartet
qn.	quintuplet
rt	room temperature
rxn	reaction
s	singlet, strong
sat.	saturated
sext	sextet
t	triplet
t	tertiary
TADDOL	α,α,α',α'-tetraaryl-4,5-dimethoxy-1,3-dioxolane
TBA.I	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
Temp	temperature
TFA	trifluoroacetic acid
TFPB	4,4,4-trifluoro-1-phenyl-1,3-butandionate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl, toluenesulphonic
TS	transition state
UV	ultraviolet
w	weak

Chapter 1 Introduction.

1.1 Organocatalysis.

1.1.1 Organocatalysis background.

The demand for enantiomerically pure compounds, particularly with pharmaceutical related materials, has led to the surge of interest in catalytic asymmetric reactions. Many advances have been made in catalytic asymmetric synthesis which, until recently, could be defined in two broad categories; transition metal catalysis and enzymatic processes[1]. Organocatalysis is emerging as a third new approach of asymmetric transformations with research in the area blossoming in the last decade. Organocatalysis is the catalysis of a reaction with an organic compound that does not contain a metal atom[2]. A prototypical example of an organocatalyst is the amino acid L - proline (**Figure 1**) which is capable of catalysing a wide range of reactions[1, 3-5].

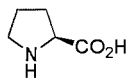

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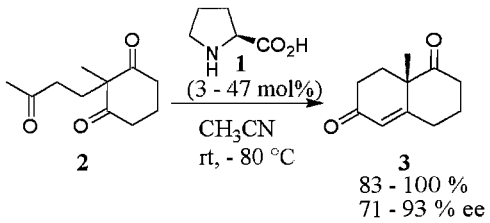
Figure 1: L - proline.

Organocatalysts have multiple advantages, for example many organocatalysts are readily available (or derived from) chiral pool compounds and as organocatalysts are stable to water and air they require no demanding reaction conditions. Organocatalysts have a reduced environmental impact compared to transition metal catalysts and some organocatalytic reactions have been carried out in water[6-14], brine[15, 16], sea water[16] or in solvent free conditions[17, 18].

Organocatalysis History.

David Macmillan first coined the term 'organocatalysis' in 2000 to describe reactions catalysed by small organic molecules. However the use of small organic molecules as catalysts is not a new concept; the German chemist Wolfgang Langenbeck published the idea of "organische katalysatoren" ("organic catalyst") in 1932[19]. As early as 1928 Langenbeck had published work entitled "Analogies in the catalytic action of enzymes and definite organic substances"[20], he also had the foresight to distinguish between covalent and non covalent catalysis.

The first asymmetric organocatalytic reaction was reported in 1912 where the alkaloids quinine and quinidine were used to catalyse the addition of HCN to benzaldehyde[21]. The first amino acid catalysed aldol reaction was reported as early as 1931[22]. Alkaloids (1 mol %) were again used in 1960 by Pracejus[23] to catalyse the asymmetric addition (74 % ee) of methanol to phenylmethylketene. The synthesis of the unsaturated Wieland - Miescher ketone **3** (**Scheme 1**) *via* the Hajos - Parrish - Eder - Sauer - Wiechert reaction, reported in 1971[24], is a well known organocatalytic reaction. The L - proline (**1**) catalysed intramolecular aldol cyclodehydration reaction to yield **3** is an efficient method of obtaining an important steroid intermediate with high enantioselectivity[25].

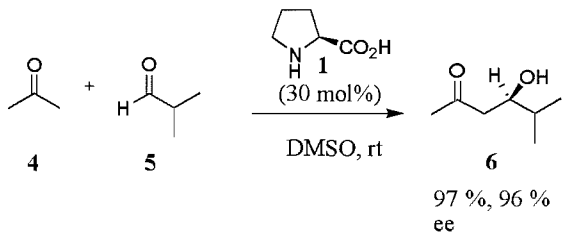


Scheme 1.

There have since been many papers published explaining the origin of enantioselectivity of the intramolecular aldol cyclodehydration reaction catalysed by L - proline[26-28] *via* a well defined transition state. In 1984 L - proline (**1**) was used as the catalyst in the synthesis of thiadecalins and thiahydrindans *via* the same Hajos - Parrish - Eder - Sauer - Wiechert reaction pathway[28]. The Hajos - Parrish -

Eder - Sauer - Wiechert reaction has recently been catalysed by the β amino acid cispentacin[29].

The early 1980s saw the publication of two further organocatalytic reactions; the hydrocyanation of benzaldehyde catalysed by a cyclic dipeptide[30] and the organocatalytic epoxidation of chalcones with a poly amino acid and hydrogen peroxide[31]. The few isolated examples of small organic molecule catalysis sparked little interest in the field of organocatalysis until the seminal work by List[32], Macmillan[33], Barbas[34], Jorgensen[35] and Jacobsen[36] in the late 1990s and early 2000s inspired a so called 'gold rush'[37] of research. **Scheme 2** illustrates the pioneering work by List *et al.*[32] of the L - proline (**1**) catalysed intermolecular aldol reaction. Since the pioneering work, numerous reactions have been mediated by organocatalysts including; Michael addition, aldol, Mannich, Morita - Baylis - Hillman, Diels Alder, kinetic resolution, alkylation, halogenation, oxidation and reduction reactions (see organocatalyst reviews for details[2, 37-49]). Due to the vast number of organocatalytic reactions reported, the following review will focus on the research subject of this work; the organocatalysed conjugate addition of carbon nucleophiles to nitroolefins.



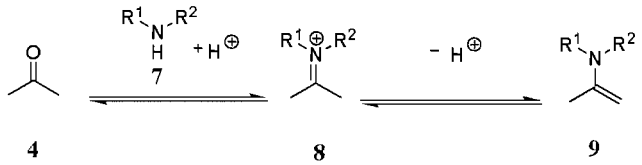
Scheme 2.

1.1.2 Mode of action.

There are many different types of organocatalysis; despite the differences, the type of catalysis can be categorised into two broad definitions depending on the interactions the catalysts employ; covalent catalysis and non - covalent catalysis.

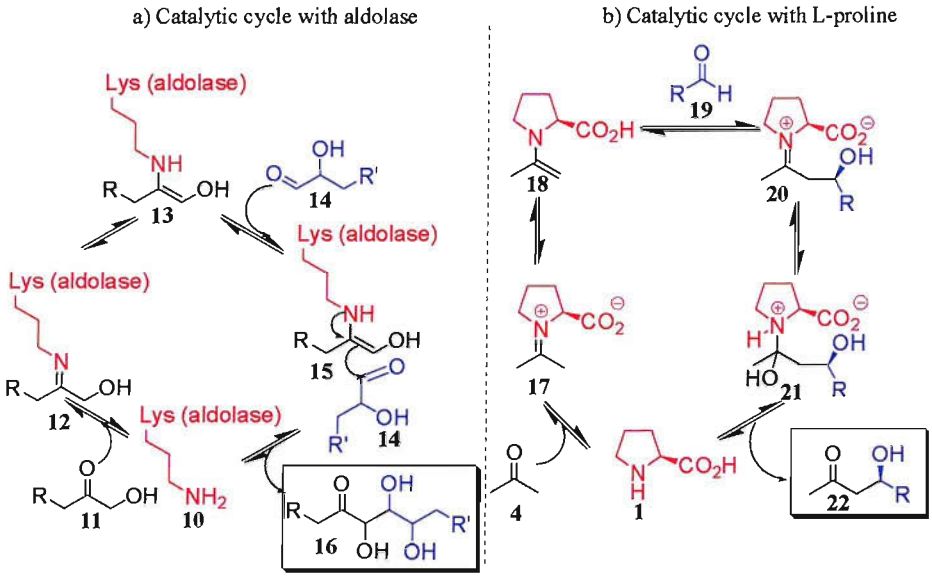
1.1.2.1 Covalent catalysis.

As the name suggests 'covalent catalysis' describes mechanisms by which the catalyst and substrate form a covalent bond(s). Examples of covalent catalysis are either by simple covalent bond forming interactions or by multi - step reactions involving the formation of enamine or iminium intermediates[37]. The process of using simple amines (**7**), often chiral, to facilitate reactions through an iminium pathway (**8**, electrophilic activation) or enamine (**9**, nucleophilic activation) is widely used throughout organocatalysis (**Scheme 3**).



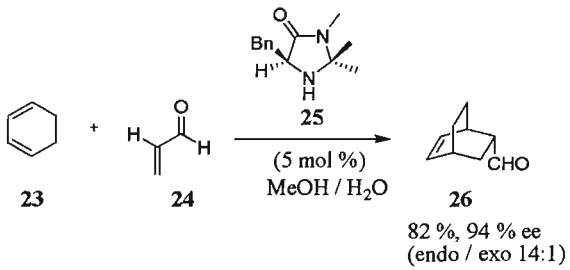
Scheme 3.

The use of enamine and iminium activation is frequently seen in enzyme catalysis; a well known example is the aldol reaction catalysed by aldolase which can be directly compared to the aldol reaction catalysed by L - proline (**1**). The comparison between the two different aldol reactions (**Scheme 4**) illustrates the mechanistic similarities between organocatalysis and enzymatic processes[3].



Scheme 4.

As previously mentioned, List[32] first reported the nucleophilic activation of the intermolecular aldol reaction *via* an enamine pathway, catalysed by L - proline (**1**, **Scheme 2**). Equally ground - breaking was the work by Macmillan *et al.*[33] who activated α, β - unsaturated aldehydes *via* an iminium reaction pathway by using catalyst **25** derived from phenylalanine (**Scheme 5**).

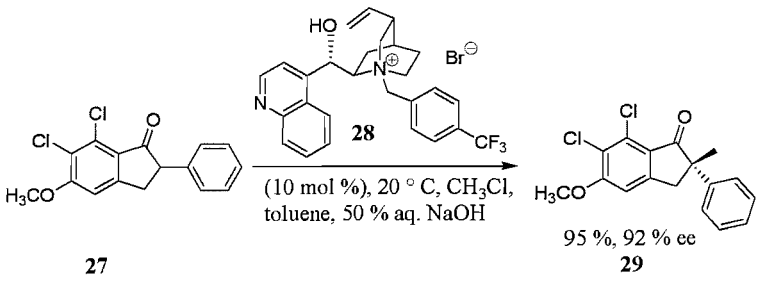


Scheme 5.

1.1.2.2 Non - covalent catalysis.

Non covalent catalysis relies on the activation of the substrates through non - covalent interactions such as hydrogen bonding or the formation of ion pairs. Phase transfer

catalysis is a unique ion pair mediated reaction useful for reactions in which charged intermediates are involved[2, 38]. Phase transfer catalysts (PTC) are used where two phase systems are used in the reaction and the PTC primarily acts as an ion shuttle between the two phases. Chiral PTCs act as templates to direct the approach of the reagent[2, 50, 51]. Coulombic interactions are the principal forces which hold together the rigid, well structured catalyst – substrate complex. The tight ion pair complex, which results from a combination of electrostatic and van der Waals forces, dictates that only one face of the substrate is available for reaction[38]. The majority of PTCs are quaternary ammonium salts derived from *Cinchona* alkaloids[52-57]; other examples include crown ethers[58-60], guanidinium cations[61, 62], binaphthyl derivatives[63-65] and tartaric acid derivatives[66-68]. PTCs catalyse a variety of reactions including Michael additions[54, 69, 70], epoxidations[71-73] and alkylation reactions[55, 61, 74]. PTCs are widely used in organocatalytic alkylation reactions; one of the first enantioselective alkylation reactions was reported in 1984 using the *Cinchona* derived phase transfer catalyst (**28**, **Scheme 6**) to yield an intermediate towards the synthesis of (+) - indacrinone[75].



27 29

Scheme 6.

Asymmetric organocatalysis using hydrogen bond donor catalysts is becoming a popular method of activating substrates and has inspired many reviews on the subject[76-80]. The use of hydrogen bonding is ubiquitous within nature in structure recognition and catalysis where enzymatic processes activate electrophiles to nucleophilic attack by hydrogen bonding. The use of small organic molecules to activate substrates *via* hydrogen bonding, by decreasing the electron density of the LUMO orbital of the electrophile, is a powerful method of catalysis[78]. Hydrogen bonding also has a crucial role in stabilising reactive intermediates. A simple

example of hydrogen bonding by a simple organocatalyst is the L - proline (**1**) catalysed aldol reaction (**Scheme 2** and **Scheme 4**) where the carboxylic acid hydrogen bonds to the aldehyde activating it toward nucleophilic attack from the nucleophilic enamine[39, 78].

Many organocatalysts that act as hydrogen bond donors are bidentate, examples (**Figure 2**) include ureas (**30**)[36, 81-86], thioureas (**31**)[76, 87-89], guanidiniums (**32**)[90-92], amidiniums (**33**)[93-95] and diols[96, 97] (specifically TADDOL (**34**)[98-103] and BINOL[103-105] (**35**) derivatives). The bidentate binding interaction benefits from increased strength (compared to one hydrogen bond) and removes some conformational degrees of freedom[76, 78]. There is a positive correlation between the acidity of the N - H bonds of amides, ureas, and thioureas and their catalytic ability[89].

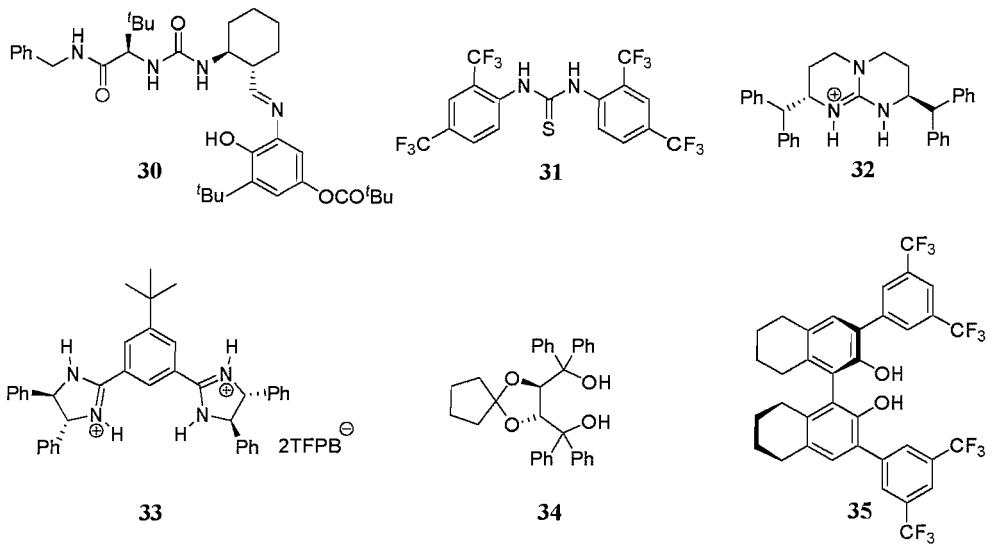
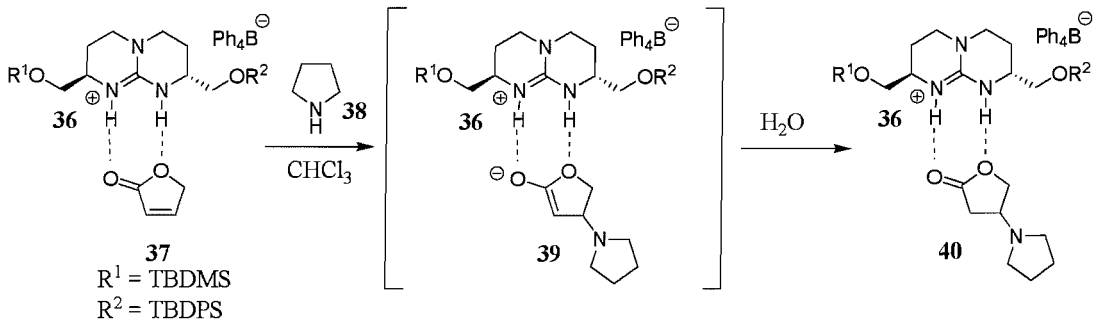


Figure 2: Examples of organocatalysts which are bidentate hydrogen bond donors.

Guanidinium, amidinium and thiouronium cations form strong zwitterionic hydrogen bonds with oxoanions due to the combination of highly polarised N - H bonds and coulombic interactions[76, 106]. Guanidiniums can effectively and enantioselectively catalyse a number of reactions including nitro aldol[90, 107] and Michael reactions[106, 108]. In the nitro aldol reaction the guanidinium cation forms strong hydrogen bonds with the nitronate anions, stabilising the negative charges developing in the transition state and therefore increasing the rate of the reaction. In the Michael addition reaction

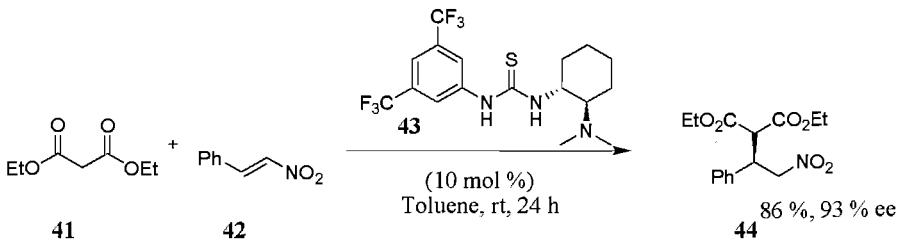
(**Scheme 7**) as well as activating the lactone (**37**) to nucleophilic attack, the transition state is stabilised by the hydrogen bonds between the guanidinium cation and the forming enolate. In a similar fashion, amidinium ions have been used in nitro aldol reactions[90] and to activate dienophiles in the Diels Alder reactions[94, 95, 109].



Scheme 7.

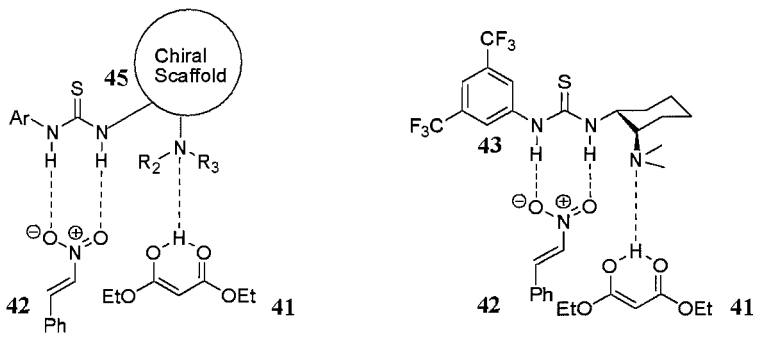
1.1.3 Bifunctional Organocatalysts.

An emerging class of organocatalysts are bifunctional catalysts; these are catalysts which can activate the electrophile and the nucleophile of the reaction in a synergistic fashion, integrating separate catalytic functionalities within one molecule. A simple chiral pool bifunctional organocatalyst is L - proline (**1**); the secondary amine serves to form a nucleophilic enamine (**Section 1.1.3.1**) whilst the carboxylic acid activates the electrophile by hydrogen bonding[1]. The idea of small organic bifunctional catalysts was investigated as early as 1977[110]. In 2003 Takemoto *et al.*[111] were the first to synthesise a bifunctional organocatalyst (**43**) that combined a basic amino group (Brønsted base) and a bidentate hydrogen bond donor group (Brønsted acid) that was used in the Michael addition of malonates to nitroolefins (**Scheme 8**).



Scheme 8.

A dual activation model (**Figure 3**) was proposed which illustrates the activation of the electrophile (**42**) *via* hydrogen bonding with the thiourea and also the simultaneous activation of the nucleophile (**41**) through the interaction between the tertiary amine group and the enolic form of the 1, 3 - dicarbonyl. The carbon - carbon bond formation takes place when both substrates are bound to the catalyst in a ternary complex. Takemoto *et al.*[111-113] postulates that the nucleophilic addition occurs to a single face of the thiourea bound olefin resulting in the enantioselectivity observed. Both the tertiary amine and the thiourea are essential for effective and selective catalysis[111-113].



DUAL ACTIVATION MODEL

DUAL ACTIVATION WITH CATALYST **43**

Figure 3: Proposed dual activation model of bifunctional catalyst **43**[113, 114].

Since the original publication in 2003, bifunctional organocatalyst **43** has catalysed a variety of different transformations including a number of different Michael additions[115-118], the asymmetric nitro Mannich (aza Henry)[112, 118, 119], dynamic kinetic resolution reactions[120] and polymerization reactions[121]. Catalyst **43** mediated the

asymmetric tandem Michael reaction to yield an important intermediate towards the synthesis of (-) - epibatidine[122, 123].

Numerous papers have been published on bifunctional organocatalysts since Takemoto's original work in 2003[111], the majority of the catalysts also employ an amino group and hydrogen bond donor group in a dual activation method. Many of the bifunctional organocatalysts are derived from natural sources of chirality such as *Cinchona* alkaloids[52, 117, 124-136]. The majority of the recent work has concentrated on Michael additions to nitroolefins[12, 117, 124, 127-130, 137-151], other examples of bifunctional catalysed reactions include Morita - Baylis - Hillman[152-158], nitro aldol[135, 159, 160], Friedel - Crafts[125] and Mannich reactions[126, 134, 161].

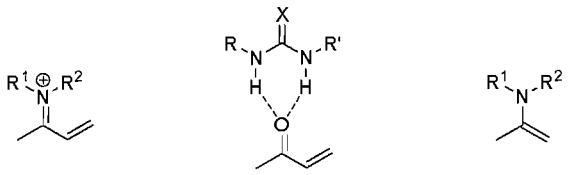
Bifunctional organocatalysis adds another dimension to catalyst design; the activation of both electrophile and nucleophile in a chemical reaction enhances the scope of rate enhancement and control of the chiral environment in which new bonds are formed. Bifunctional organocatalysts can be designed and altered in both the electronic and steric sense and can be envisioned to apply to many different reactions[79].

1.2 Organocatalytic addition to C=C.

1.2.1 Organocatalytic addition to C=C overview.

One of the most common carbon – carbon and carbon – heteroatom bond formations used in organic synthesis is the conjugate addition of nucleophiles to electron poor alkenes[38]. Traditionally Michael additions were carried out asymmetrically using a chiral base or chiral phase transfer catalysts. As well as being utilised as a chiral base or PTC, organocatalysts can also facilitate Michael reactions through the formation of reversible covalent bonds or with hydrogen bonding (**Section 1.1.3**). Michael acceptors, for example α, β - unsaturated ketones or aldehydes, are activated *via* the reversible formation of a chiral iminium ion (**46**) by condensation with a small chiral amine. Alternatively catalysts can activate Michael acceptors by decreasing the

electron density through hydrogen bonding (**47**). Michael donors, for example aldehydes and ketones, are activated by reversibly reacting with chiral amines to form enamines (**9**). Bifunctional organocatalysts are capable of interacting with both Michael acceptors and donors.

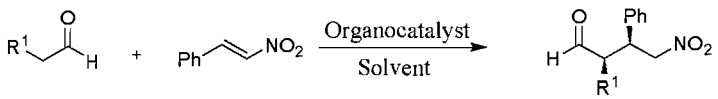


46 **47** **9**

Figure 4: Examples of organocatalytic activation in Michael reactions.

The capability of organocatalysts to react with both Michael acceptor and donor through a variety of different means suggests that a wide number of transformations can be carried out. This, combined with the diversity of Michael acceptors and donors available has resulted in the abundant publication of efficient and enantioselective organocatalysed Michael reactions.

1.2.2 Michael addition of aldehydes to nitroolefins.



48 **42** **49**

Scheme 9.

The Michael addition of nucleophiles to nitroolefins is a widely studied reaction because the resulting nitroalkanes are versatile synthetic intermediates as the nitro group can be transformed into other functionalities[162-164]. The organocatalytic Michael addition of aldehydes to β - nitrostyrenes (**Scheme 9**) was first studied by

Barbas and Bentacort[165] in 2001 with a variety of chiral amines (examples include **1**, **51**, **52** and **55**, **Figure 5**).

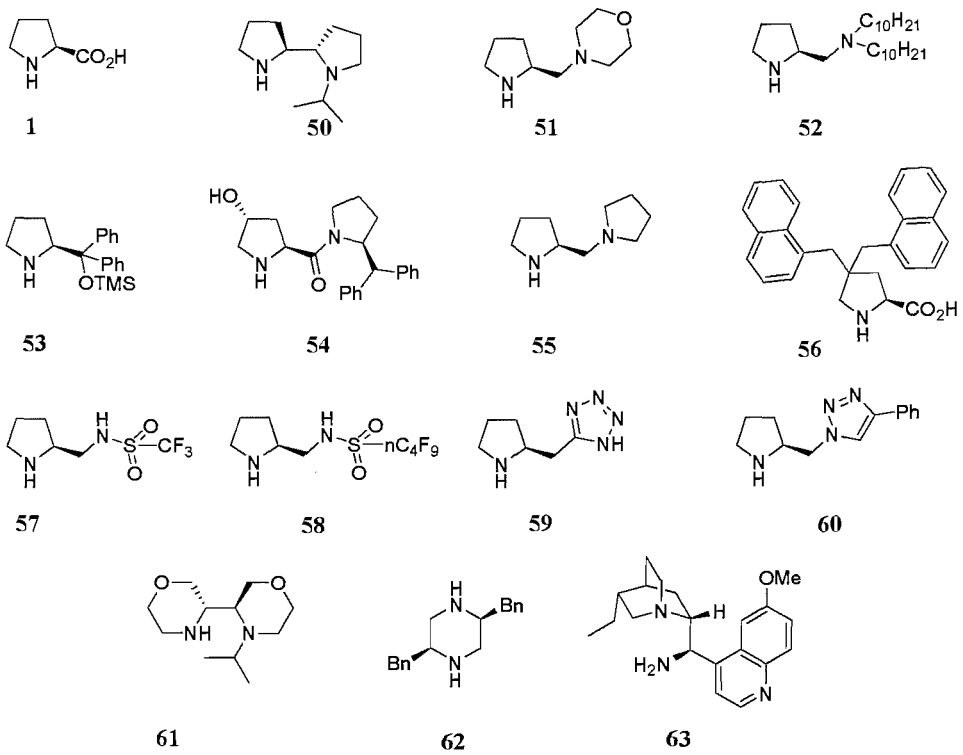


Figure 5: A selection of organocatalysts employed for the Michael addition of aldehydes to nitroolefins[165-177].

Since the initial investigations into the Michael addition of aldehydes to β - nitrostyrenes in 2001 many new organocatalysts have been shown as efficient catalysts for the transformation (examples are illustrated in **Figure 5**). The majority of the organocatalysts are chiral secondary amines, many of which are derived from L - proline (**1**), however there are a few examples of efficient primary amine catalysts[142, 175] for example *Cinchona* based catalyst **63** (**Figure 5**, entry 15; **Table 1**)[176]. The Michael addition of aldehydes to nitroolefins by the chiral amines proceeds through a catalytic enamine system usually producing high syn diastereoselectivities.

Entry	Catalyst	mol %	R^1	Time	Solvent	eq. aldehyde	Temp	Yield (%)	d.r.[a]	e.e. (%)[b]
1	**1**[165]	20	^{i}Pr	3 d	THF	10	rt	<5	93:7	25
2	**50**[166]	15	^{i}Pr	2 d	$CHCl_3$	10	rt	99	87:13	73
3	**51**[165]	20	^{i}Pr	3 d	THF	10	rt	78	92:8	72
4	**52**[165]	20	^{i}Pr	3 d	THF	10	rt	88	80:20	47
5	**53**[177]	20	^{i}Pr	1 d	Hexane	10	rt	77	94:6	99
6	**54**[167]	10	^{i}Pr	20 h	DCM	1.5	rt	75	95:5	91
7	**55**[165]	20	^{i}Pr	3 d	THF	10	rt	80	80:20	75
8[c]	**56**[168]	20	^{i}Pr	3 d	IPA	10	0 ° C	87	89:11	90
9	**57**[169]	20	^{n}Pr	1 d	IPA	10	0 ° C	99	98:2	96
10	**58**[170]	10	nC_7H_{15}	12 h	H_2O	10	rt	98	80:20	81
11	**59**[171]	15	^{i}Pr	1 d	IPA/EtOH	1.5	rt	39	95:5	37
12[d]	**60**[172]	20	^{i}Pr	1.5 d	Neat	20	rt	80	97:3	40
13	**61**[173]	15	^{i}Pr	3 d	$CHCl_3$	10	rt	85	94:6	88
14	**62**[174]	10	Et	2 d	DCM / Hexane	10	0 ° C	63	97:3	84
15[e]	**63**[176]	15	^{i}Pr	4 d	Neat	5	rt	76	67:1	95

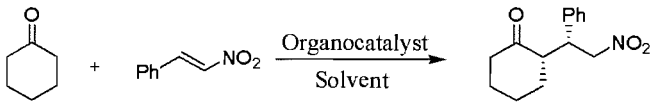
a: syn: anti; b: of syn diastereomer; c: DMAP additive (20 mol %); d: TFA additive (2.5 mol %); e: PhCOOH additive (15 mol %).

Table 1. Catalysts used for the addition of aldehydes to trans - β - nitrostyrene.

Table 1 indicates that organocatalysts are capable of facilitating the Michael addition of linear and branched aldehydes with sometimes excellent enantioselectivity (entry 5; **Table 1**). There are few diastereo and enantioselective examples of the addition of α, α - disubstituted aldehydes to nitroolefins to yield quaternary stereocentres. Catalysts **57**[169] and **61**[173] are capable of producing high enantioselectivities when symmetrically disubstituted aldehydes are used. A variety of different nitroolefins can be successfully used including β - substituted alkyl nitroolefins (catalysts **50**[166], **53**[177] and **54**[167]) and α - substituted alkyl nitroolefins (only with catalyst **50**[178]).

One of the drawbacks of the organocatalysed Michael additions is the need for a large excess of the aldehyde (see **Table 1**) due to competing aldol reactions. Palomo *et al.*[167] have successfully managed to decrease the aldehyde quantity to 1.5 equivalents using catalyst **54** without loss in yield or enantioselectivity. Other problems associated with the Michael addition reaction are the long reaction times and high catalyst loading. Alexakis *et al.*[179] have illustrated that reaction rates can be significantly improved using microwave irradiation without loss of selectivity. To overcome the necessary high catalyst loading some organocatalysts have been immobilised on a solid support to facilitate catalyst reuse and recovery[180, 181]. Catalyst **58** has catalysed the addition of aldehydes to trans - β - nitrostyrene (**42**) in water (entry 10, **Table 1**) and is easily recovered through fluorous solid phase extraction and reused[170].

1.2.3 Michael addition of ketones to nitroolefins.



64 **42** **65**

Scheme 10.

In 2001 List *et al.*[182] first reported the L - proline (**1**) catalysed addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) in DMSO with high diastereoselectivity but poor enantiomeric excess (**Scheme 10,** entry 1; **Table 2**). Later studies by Enders *et al.*[183] illustrated that the same reaction carried out in methanol (entry 2; **Table 2**) increases the enantioselectivity (from 23 % to 57 %) but with detriment to the reaction time. List *et al.*[184] later used N - terminal polypeptides to catalyse the addition of ketones to trans - β - nitrostyrene (**42**) in DMSO but with poor enantioselectivity also observed. The dipeptide (*S*) - ala - (*R*) - ala (**73**) has recently been shown to catalyse the enantioselective addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) with excellent diastereo and enantioselectivity (entry 15; **Table 2**)[175].

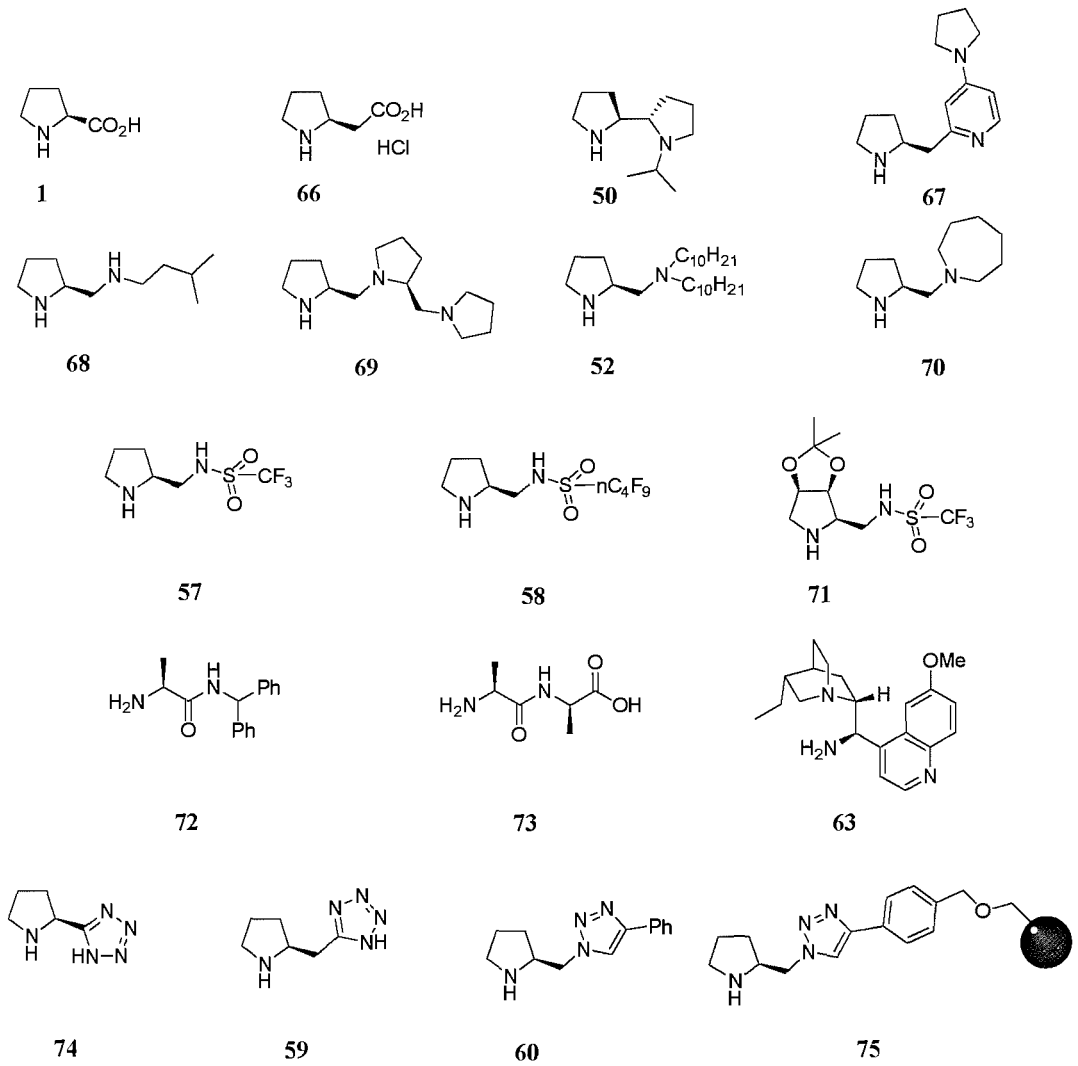


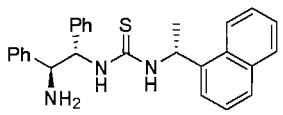
Figure 6: A selection of organocatalysts employed for the Michael addition of ketones to nitroolefins[10, 166, 169-171, 175, 176, 182, 185-193].

Entry	Catalyst	mol %	Time	Solvent	Additive (mol %)	eq. ketone	Temp	Yield (%)	d.r.[a]	e.e. (%)[b]
1	**1**[182]	15	16 h	DMSO	-	10	rt	94	95:5	23
2	**1**[183]	20	4 d	MeOH	-	10	rt	79	97:3	57
3	**66**[185]	20	20 h	^{t}BuOH	NMO (20 %)	2	rt	90	90:2	90
4	**50**[166]	15	3 d	$CHCl_3$	HCl (15 %)	10	rt	74	95:5	74
5	**50**[194]	15	15 h	$CHCl_3$	PhCOOH (15 %)	10	rt	76	92:8	77
6	**67**[186]	10	1 d	$CHCl_3$	DNBS (5 %)	20	0 ° C	95	98:2	99
7	**68**[187]	20	1 d	DMF	pTsOH (15 %)	5	rt	86	95:5	99
8	**69**[188]	15	3 d	Toluene	(+) CSA (7.5 %)	40	0 ° C	95	98:2	90
9	**52**[189]	20	22 h	THF	-	10	rt	92	98:2	90
10	**70**[189]	20	22 h	THF	-	10	rt	93	98:2	89
11	**57**[169]	20	10 h	IPA	-	10	0 ° C	96	98:2	97
12	**58**[170]	10	9 h	H_2O	-	10	rt	95	96:4	90
13	**71**[190]	15	16 h	$CHCl_3$	-	20	rt	96	97:3	90
14	**72**[191]	30	3 d	NMP	TsOH (15 %)	3	rt	92	67:33	93
15	**73**[175]	30	3 d	DMSO/ NMP	H_2O (10 eq.)	3	-20°C	62	94:6	97
16	**63**[176]	10	3 d	Neat	PhCOOH (10 %)	5	rt	91	88:12	84
17	**74**[192]	15	1 d	IPA/ EtOH	-	20	rt	96	75:25	62
18	**59**[171]	15	1 d	IPA/ EtOH	-	1.5	rt	88	95:5	91
19	**60**[10]	10	13 h	H_2O	-	5	rt	98	97:3	96
20	**75**[193]	10	1 d	H_2O	diMePEG (10 %)	20	rt	85	95:5	90

a: syn: anti; b: of syn diastereomer.

Table 2. Catalysts used for the addition of ketones to trans - β - nitrostyrene.

Many of the organocatalysts used for the addition of aldehydes to nitroolefins can also be employed for the activation of ketones (**Figure 6**). The reaction proceeds through a catalytic enamine pathway, indicated by ESMS[141, 143, 147, 195], usually yielding high syn diastereoselectivity. The organocatalytic Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) (**Scheme 10**, **Table 2**) usually gives high enantioselectivity depending on the catalyst employed. However, poor diastereo and enantioselectivity is often observed with acyclic or different cyclic ketones. Catalysts that show selectivity for acyclic ketones include (*S*) - homoproline **66**[185], *Cinchona* alkaloid derived **63**[176] and bifunctional catalysts **76**[147] and **77**[143]. Jacobsen's bifunctional organocatalyst **77**[143] is capable of catalysing the selective addition of cyclic and acyclic ketones to nitrostyrenes and also β - alkyl - nitroalkenes.



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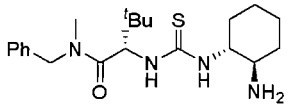

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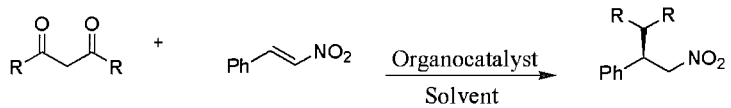
Figure 7: Bifunctional organocatalysts used for the addition of ketones to nitroolefins.

The tetrazole catalyst **74** has been used by several research groups[192, 196-198] in a variety of transformations. The tetrazole ring is often used as bioisostere for the carboxylic acid group due to the similar pK_a[171]. Ley *et al.*[192] illustrated that **74** catalysed the conjugate addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) with moderate to good selectivity (entry 17; **Table 2**). In the same year Ley *et al.*[171] developed a second tetrazole catalyst (**59**) which significantly improved the selectivity of the reaction without detriment to the reaction time and with only 1.5 equivalents of the ketone required (entry 18; **Table 2**). Later Liang *et al.*[10] developed similar triazole based catalysts by using 'click chemistry', aiming to optimise catalyst **74** by altering various electronic and steric properties. Triazole **60** efficiently and selectively catalysed the addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) in water with shorter reaction times (entry 19[10]; **Table 2**) with 5 equivalents of ketone. Recently catalyst **60** was immobilised on solid support to yield organocatalyst **75** which can be recovered and reused (entry 20; **Table 2**)[193].

The addition of ketones to nitroolefins suffers from the same drawbacks as for when aldehydes are used as the Michael donor; for example long reaction times, high catalyst loading and a large excess of ketone / aldehyde. Improvements to the Michael reaction are continually being made, for example, reaction rates can be enhanced by microwave irradiation[179]. Catalysts **66**, **72**, **73** and **59** use only 3 equivalents (or less) of the ketone (entries 3, 12, 15, and 18 respectively; **Table 2**)[171, 175, 185, 191]. The organocatalysed Michael addition reactions can be effectively carried out neat[176], in water[10, 170, 193] or in ionic liquids[195, 199, 200]. Catalysts **58** and **75** have been effectively recovered and reused utilising polymer supports[193] and fluorous solid phase extraction[170]. One area which has of yet seen little improvement is the catalyst loading, with 10 mol % the lowest organocatalyst amount used.

1.2.4 Michael addition of 1, 3-dicarbonyl compounds to nitroolefins.

The Michael addition of 1, 3 - dicarbonyl compounds (**78**) to nitroolefins (**Scheme 11**) provides synthetically versatile nitroalkanes (**79**) important in the synthesis of pharmaceutical and agrochemical compounds[122, 124, 201]. The first enantioselective organocatalytic Michael addition of malonate esters to trans - β - nitrostyrene (**42**) was carried out with Takemoto's bifunctional catalyst **43**[111] (**Scheme 8**, **Section 1.1.4**). Bifunctional catalyst **43** is compatible with a wide variety of β - nitrostyrenes, β - alkyl nitroolefins and malonate derivatives[111, 113, 122, 123].



78 **42** **79**

Scheme 11.

Since Takemoto's original work in 2003 there has been a number of organocatalysts developed for the addition of 1, 3 - dicarbonyl compounds to nitroolefins; examples are illustrated in **Figure 8**.

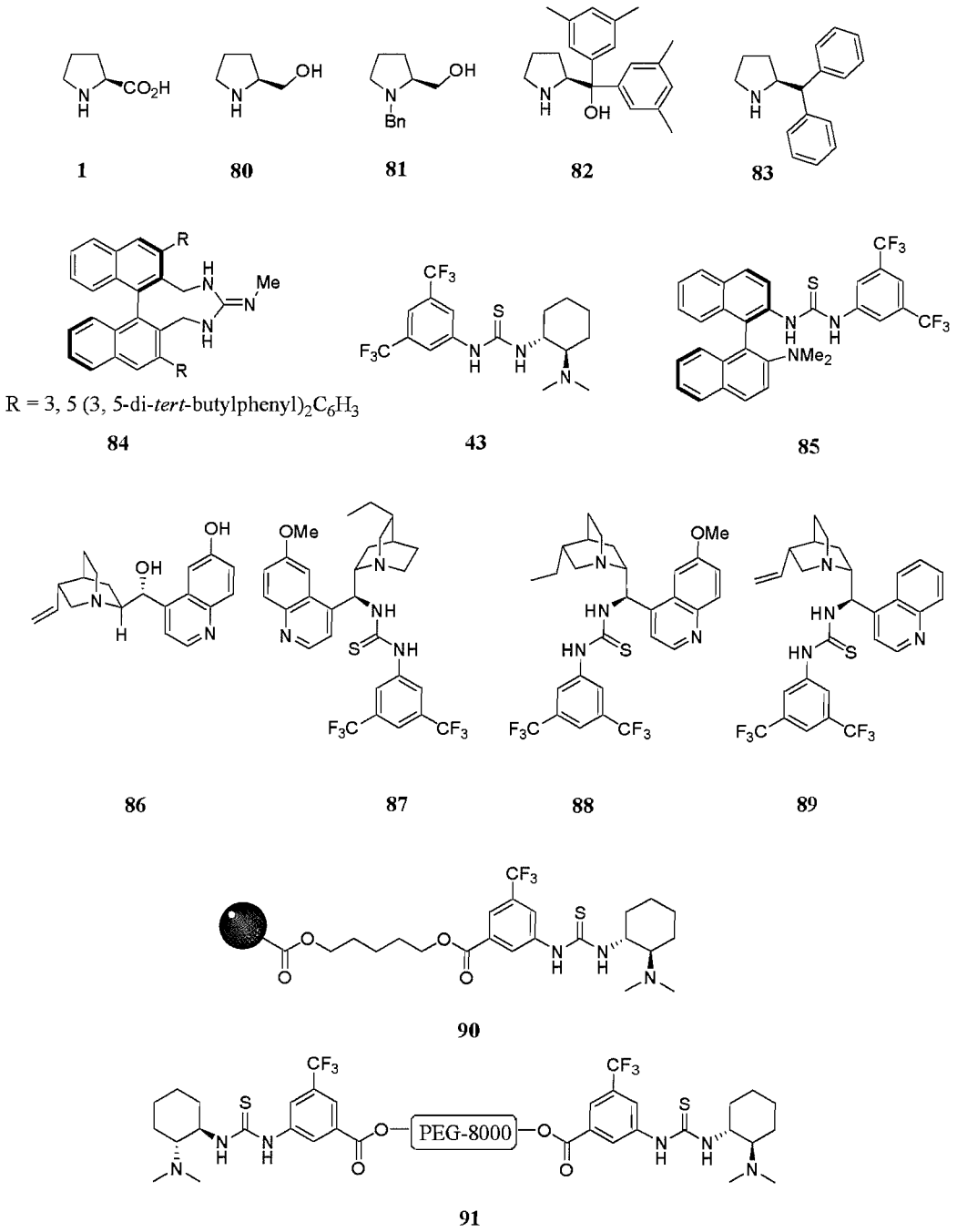


Figure 8: A selection of organocatalysts employed for the Michael addition of 1, 3 - dicarbonyl compounds to nitroolefins[113, 118, 124, 128, 129, 137, 138, 202].

Lattanzi[138] used L - proline (**1**), **80**, **81** and **82** as bifunctional organocatalysts where the secondary amine activates malonate esters and the hydroxyl proton hydrogen bonds to nitroolefins. The catalysts showed poor activity in terms of rate and enantioselectivity (entries 1 - 4; **Table 3**) with catalyst **82** demonstrating the best results but with still only moderate enantioselectivity. The importance of the

hydroxyl group in catalysts **80** - **82** was illustrated by the comparison with monofunctional catalyst **83** (entry 5; **Table 3**) where little activity was observed.

Entry	Catalyst	mol %	R	Time	Solvent	eq. 78	Temp	Yield (%)	79 config.	e.e. (%)
1	**1**[138]	30	OMe	3 d	Xylene	2	rt	<5	-	-
2	**80**[138]	20	OMe	3 d	Xylene	2	rt	62	S	4
3	**81**[138]	30	OMe	4 d	Xylene	2	rt	34	R	7
4	**82**[138]	30	OMe	3 d	Xylene	2	rt	93	S	44
5	**83**[138]	30	OMe	4 d	Xylene	2	rt	7	S	4
6	**84**[202]	2	OMe	2 h	Et_2O	5	- 40 °C	100	R	96
7	**43**[113]	10	OMe	9 h	Toluene	2	rt	89	R	86
8	**85**[137]	1	Me	26 h	Et_2O	2	rt	87	R	95
9	**86**[128]	10	OMe	1.5 d	THF	3	- 20 °C	97	S	96
10	**87**[129]	2	OMe	30 h	Toluene	2	- 20 °C	93	S	99
11	**88**[129]	2	OMe	30 h	Toluene	2	rt	98	R	85
12	**89**[124]	10	OMe	30 h	DCM	3	- 20 °C	95	R	94
13	**91**[118]	10	OEt	6 d	DCM	2	rt	71	S	86

Table 3. Catalysts used for the addition of 1, 3-dicarbonyl compounds to trans - β - nitrostyrene.

Catalyst **84**[202] utilises the strong basic nature of guanidines and the ability of guanidiniums to form strong bidentate hydrogen bonds. The guanidine unit in catalyst **84** is attached to an axially chiral binaphthyl backbone which provides a chiral environment for asymmetric reactions. Guanidine **84** catalyses the addition of 1, 3 - dicarbonyl compounds to nitroolefins (entry 6; **Table 3**) very efficiently and enantioselectively with catalyst loading as low as 0.4 %. Guanidine catalyst **84** tolerates a wide range of reactants including unsubstituted and α - substituted

malonate esters, β - ketoesters, and 1, 3 - diketones to a variety of aryl and alkyl β - nitroolefins and also sterically hindered γ - branched nitroolefins[202].

Deng *et al.*[128] researched *Cinchona* alkaloids as organocatalysts for the addition of malonates and β - ketoesters to nitroolefins. The 6' - demethylated quinine (**86**, entry 9, **Table 3**) and quinidine alkaloids were found to be considerably more active catalysts than their natural counterparts due to the hydrogen bonding provided by the hydroxyl group. In 2005 Dixon *et al.*[124] and Connon *et al.*[129] separately published work on *Cinchona* alkaloid derived bifunctional organocatalysts (**87**, **88** and **89**) for the addition of malonate esters to nitroolefins. Both research groups combined the basic bridgehead nitrogen and substituted the hydroxyl group at C9 of the alkaloids with different hydrogen bond donor groups. Dixon *et al.*[124] investigated a number of bifunctional catalysts with mono and bidentate hydrogen bond donor groups. Dixon *et al.*[124] identified bidentate hydrogen bond donor catalyst **89** (entry 12; **Table 3**) as the optimal catalyst yielding high activity and selectivity. Connon *et al.* [129] reported that inversion of the stereochemistry at the C9 position resulted (**87** and **88**, entries 10 and 11 respectively; **Table 3**) in much higher activity and selectivity than the natural alkaloid diastereoisomers without altering the sense of stereoinduction observed in the product. Similar thiourea - *Cinchona* based bifunctional organocatalysts have been developed for other Michael addition reactions[117, 130]. *Cinchona* derived catalysts **86 - 87**[124, 128, 129] all tolerate a wide range of nitroolefins bearing alkyl, aryl or heteroaryl groups.

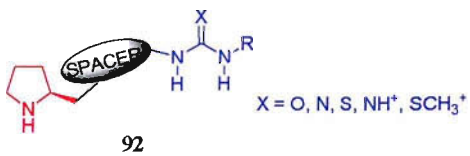
Kinetic studies carried out with organocatalysts **43**[113] and **86**[128] reveal that the Michael addition of 1, 3 - dicarbonyl compounds to nitroolefins follow a first order dependence on the catalyst, nucleophile and electrophile. Organocatalyst **84 - 89** and **43** catalyse the addition of 1, 3 - dicarbonyl compounds with good reaction times and excellent enantioselectivity with some catalysts (**84**, **85**, **87** and **88**) employed with low catalyst loadings. Following the success of organocatalyst **43**, Takemoto *et al.*[118] successfully produced immobilised forms of their catalyst (**90** and **91**). The soluble PEG bound catalyst (**91**, entry 13; **Table 3**) is more active than the analogous polystyrene or TentaGel™ bound catalyst (**90**) and was effectively recovered and reused without loss in activity or selectivity[118].

1.3 Catalyst design and programme of work.

1.3.1 Catalyst design.

A key feature of catalysis is the ability to stabilise the transition state of a reaction relative to that of the ground state. The stabilisation is due to the conjunction of several factors, for example, forming stronger hydrogen bonds with the transition state than that of the free substrate as well as neutralising the negative charge that develops as the reaction proceeds[108]. An ideal catalyst, therefore, should complement the transition state of the reaction more than either the starting material or the product, but also should be designed such that product release is a thermodynamically favourable process to prevent product inhibition[203].

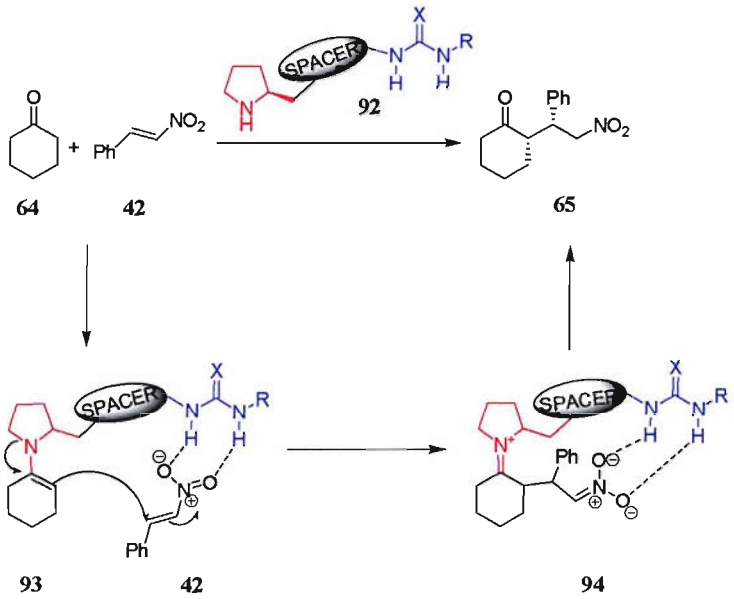
The pioneering work by List[32] and Macmillan[33] illustrated that small chiral amine molecules can effectively catalyse a range of reactions through either iminium or enamine mechanistic pathways (covalent catalysis). Many reactions have been catalysed by the use of bidentate hydrogen bond donor molecules (non - covalent catalysis) which are capable of activating the starting material and stabilising the transition state[106-108]. An effective catalyst would be one that combines the two catalytic components, covalent and non - covalent catalysis, tethered by a suitable spacer group to activate both the electrophile and nucleophile in the reaction. A proline derived modular catalyst could be synthesised which orientates both portions of the catalyst for efficient turnover (**Figure 9**). When our project commenced, the idea of using a small organic molecule to catalyse a reaction through the activation of both the electrophile and nucleophile synergistically was a novel concept; during the time of our research several bifunctional catalysts have been reported[111-161].



92

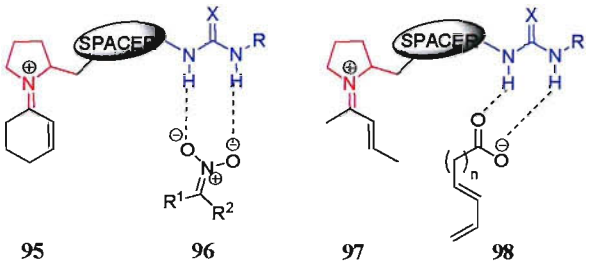
Figure 9: Proposed design of novel bifunctional catalyst.

In the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**, **Scheme 12**) the chiral secondary amine of the novel bifunctional catalyst (**92**) activates the ketone by forming a chiral enamine, whilst the bidentate hydrogen bond donor group orientates and activates the trans - β - nitrostyrene (**42**) towards nucleophilic attack (**93**). The hydrogen bond donor group can then further accelerate the reaction by stabilising the forming nitronate anion in the transition state (**94**). Hydrolysis of the resulting iminium ion releases the catalyst for further reaction and yields the desired product (**65**).



Scheme 12.

The bifunctional organocatalyst **92** can also be envisioned to catalyse other reactions (**Figure 10**) such as the conjugate addition of nitroalkanes to an enone where the enone is activated by forming an α, β - unsaturated iminium (**95**, **Figure 10**), and the nitronate anion (**96**) is stabilised and orientated through hydrogen bonding. Bifunctional organocatalyst **92** could potentially catalyse the Diels Alder reaction with dienes and α, β - unsaturated aldehydes or ketones; as before the electrophile is activated through the formation of an iminium (**97**, **Figure 10**) and the diene - carboxylate (**98**) is directed through hydrogen bonding.



95 96 97 98

Figure 10.

1.3.2 Programme of work.

The purpose of the work described in this thesis was to develop bifunctional catalysts incorporating a proline and a thiourea / thiouronium / guanidinium moiety with a suitable spacer. The programme of work was conducted as follows;

1. Optimisation of conditions for dual catalysis.

Initial work focused on the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) catalysed by a range of mono functional secondary amines and hydrogen bond donor molecules (thiourea, thiouronium, guanidinium). Conditions for catalysis were optimised by varying the solvent, concentration and stoichiometry and the rate monitored by HPLC assay; this work is discussed in Chapter 2.

2. Synthesis of novel bifunctional organocatalysts.

A series of different proline – hydrogen bond donor adducts were synthesised, with the two catalytic functionalities tethered by a simple spacer; the length of the spacer was also investigated; this work is discussed in Chapters 3, 4 and 5.

3. Catalyst screening.

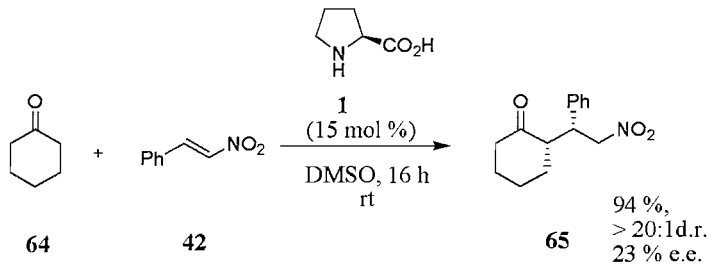
A range of synthesised bifunctional organocatalysts were screened primarily against the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**). Once the

optimum catalysts had been identified, work was undertaken to improve the catalyst conditions and widen the scope of the reaction reactants. The catalysts that showed the most activity were further tested to catalyse other types of reactions; this work is discussed in Chapters 3, 4, 5 and 6.

Chapter 2 Optimisation of conditions for dual catalysis.

2.1 Aims.

List *et al.*[182] first reported the L-proline (**1**) catalysed addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) in DMSO (**Scheme 13**) with high diastereoselectivity but poor enantioselectivity. The aim of our initial work was to optimise the same reaction by varying the solvent, concentration, stoichiometry and different mono functional secondary amine catalysts. The optimised conditions were then used to investigate the effect of dual catalysis by incorporating the use of hydrogen bond donor molecules (thiourea, thiouronium, guanidinium).



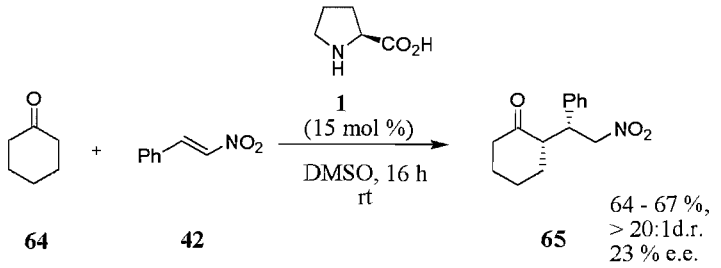
Scheme 13.

2.2 Solvent and concentration effects.

2.2.1 Sample assay development.

The synthesis of 2 - (2 - nitro - 1 - phenyl - ethyl) - cyclohexanone (**65**) was carried out according to the conditions given by List *et al.*[182] using L - proline (**1**, 15 mol %) and DMSO (8 mL) as the solvent (**Scheme 14**). After purification by column chromatography **65** was isolated as a white solid in moderate yields (64 % - 67 %)

with diastereoselectivity and enantioselectivity identical to the results reported by List *et al.* [182].



64 42 65

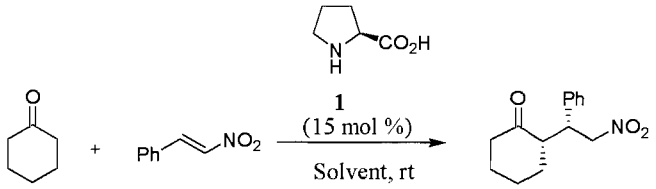
Scheme 14.

The isolated product **65** was used to develop a method for HPLC screening. To monitor the progress of the reactions under investigation; reaction mixture samples were effectively quenched by a dilution effect, taking 10 μL of the reaction mixture and diluting with 1.5 mL of acetonitrile. The sample preparation method is not only efficient but also accurate as a known amount of reaction mixture is sampled.

In order to ascertain the concentration of **42** and **65** in the samples taken from the reaction mixture (from the absorbance), calibration curves were obtained for both using the internal standard naphthalene. The calculated concentrations of trans - β - nitrostyrene (**42**) were used to produce a first order plot (Ln[concentration] against time) to give a rate constant (s^{-1}).

2.2.2 Catalyst L - proline.

In order to optimise the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) using the organocatalyst L - proline (**1**) four different experiments (**Table 4**) were investigated that varied the equivalents of cyclohexanone (**64**) and the volume of solvent used. For each set of four reactions, four different solvents were used; acetonitrile, methanol, DCM and THF (**Table 5**). The reactions were monitored regularly by HPLC (see **Appendix 1** for further results).



64 42 65

Scheme 15.

Volume of Solvent	Molar equivalents of 64	Concentration 64 / M
8 mL	10	1.2
8 mL	1.5	0.2
1.5 mL	10	5.0
1.5 mL	1.5	0.9

Table 4: Variation of concentration of cyclohexanone.

HPLC results indicate that all the reactions proceeded cleanly with one product formed. The reactions catalysed by L - proline (**1**) occur with high diastereoselectivity (confirmed by NMR). The results indicate that the fastest reactions contain the highest concentration of cyclohexanone (**64**) (our result has been subsequently confirmed by Ishii *et al.*[186]). There is also a marked increase in the rate of reaction where the volume of solvent used is decreased. Varying the solvent used in the Michael addition reaction has a significant effect on the rate (**Table 5**).

Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	Yield (%)	Time	e.e. (%)[a]
MeCN	1.5 mL	10	5.0	57 %	12.5 days	22 %
MeOH	1.5 mL	10	5.0	74 %	44 hours	40 %
THF	1.5 mL	10	5.0	60 %	19 days	35 %
DCM	1.5 mL	10	5.0	100 %*	13 days	24 %

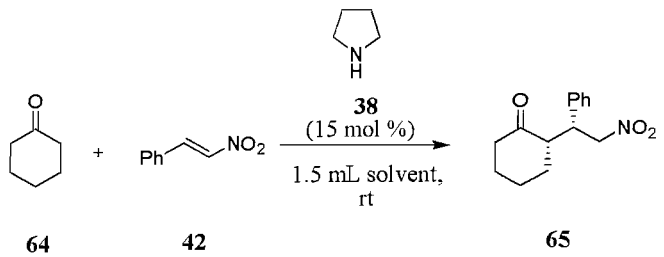
* Based on HPLC results; a: of syn diastereomer.

Table 5: The effect of solvent on the Michael addition catalysed by L - proline.

The Michael addition carried out in methanol is considerably faster than the same reaction carried out in other solvents. The use of methanol also increases the enantioselectivity observed; our result is analogous to work published by Enders *et al.*[183] and later by other groups[192, 198, 204]. The solvent used in the Michael addition reaction has a significant effect on the rate, which could be due to two reasons. Firstly the solubility of L - proline (**1**) may be increased in methanol. Secondly, methanol may be able to form hydrogen bonds to the nitronate anions in the developing transition state[205], analogous to the stabilising effect of hydrogen bond donors[90, 107]. The non - polar solvents investigated illustrate poor reaction times compared with DMSO and methanol probably due to poor solubility of the catalyst. In all solvents investigated no reaction was observed after 30 days with no catalyst employed.

2.2.3 Catalyst pyrrolidine.

As with L - proline (**1**), the organocatalyst pyrrolidine (**38**) was initially employed with the same conditions as List *et al.*[182] using DMSO. Multiple products were observed by TLC and only 14 % yield of the desired product was obtained. Having established the optimum concentration of cyclohexanone (**64**) for the synthesis of **65** catalysed by L - proline (**1**), the same reaction conditions were employed to investigate solvent effects when pyrrolidine (**38**) catalyses the Michael reaction (**Scheme 16**, **Table 6**).



64 **42** **65**

Scheme 16.

In contrast with L - proline (**1**), the reaction using pyrrolidine (**38**) to catalyse the Michael addition in methanol results in the formation of a precipitate on the addition of the organocatalyst. HPLC analysis indicates multiple impurities with only 20 % of the desired product formed. The precipitate formed is not soluble in DMSO, $CHCl_3$ or MeCN and has therefore not been identified (possibly the product of the polymerisation of nitrostyrene).

Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	Yield (%)	Time	e.e. (%)[a]
MeCN	1.5 mL	10	5.0	43 %	17 hours	0 %
MeOH	1.5 mL	10	5.0	20 %	19 days	0 %
THF	1.5 mL	10	5.0	45 %	5 hours	0 %
DCM	1.5 mL	10	5.0	58 %	2 hours	0 %

a: of syn diastereomer.

Table 6: The effect of solvent on the Michael addition catalysed by pyrrolidine.

It is evident from the above results that the Michael addition to form **65** catalysed by pyrrolidine (**38**) is much faster than L - proline (**1**), with the starting material trans - β - nitrostyrene (**42**) consumed within 2 hours when the reaction was conducted in DCM. Unfortunately, although the reactions catalysed by pyrrolidine (**38**) were comparatively fast, HPLC indicates the formation of multiple impurities. Careful column chromatography isolated the desired product in 58 % yield (80 % d.e.), five other products were also isolated. Mass spectra and NMR of the additional products indicate cyclohexanone (**64**) with a varying number of (2 - nitro - ethyl) - benzene units attached. It is clear that although pyrrolidine (**38**) can catalyse the Michael addition it exhibits no control as seen with L - proline (**1**) indicating that additional side groups are required to efficiently form the desired product.

To investigate the mechanism of the amine promoted Michael addition of ketones to nitroolefins a proton NMR (in d_6DMSO) was taken combining equimolar amounts of cyclohexanone (**64**) and pyrrolidine (**38**). The proton NMR (**Figure 11**) clearly

illustrates the presence of an alkene peak (4.10 ppm) indicating the formation of an enamine species[206].

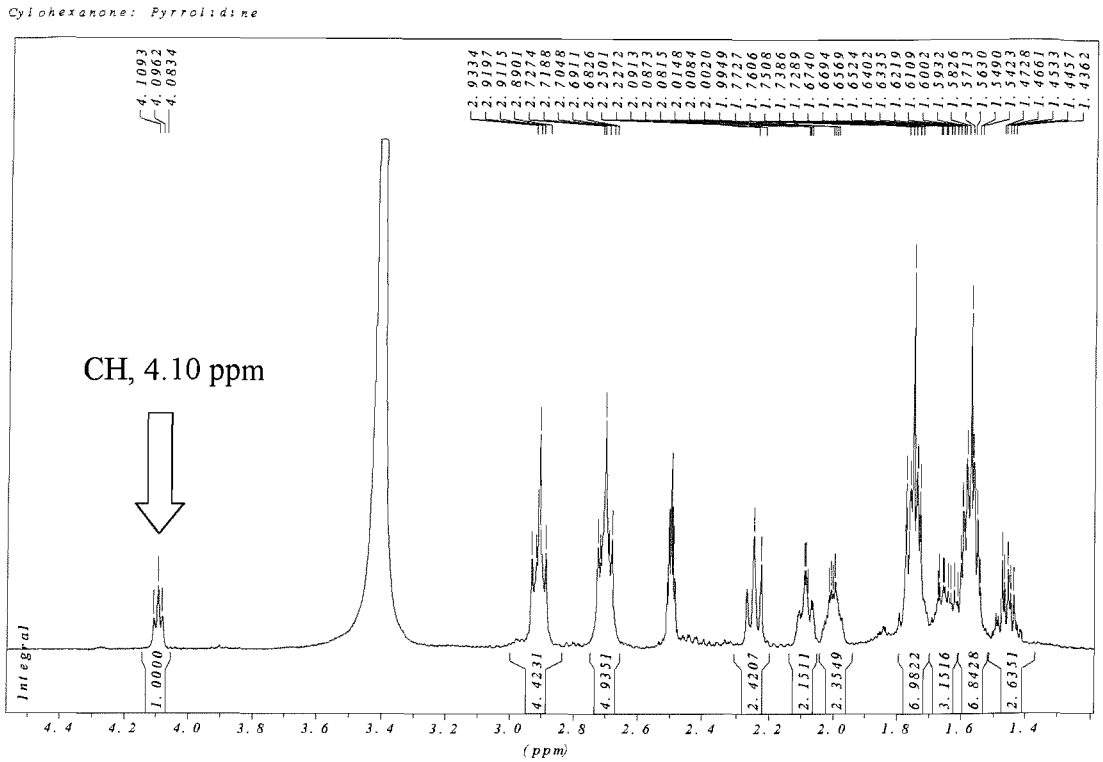
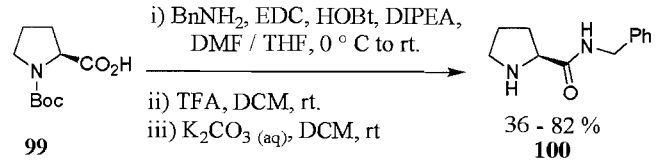


Figure 11: Proton NMR illustrating the formation of an enamine species.

The Michael addition was also investigated using piperidine as the organocatalyst. The reaction carried out in DCM (1.5 mL, 10 equivalents of cyclohexanone) was complete within four days and like pyrrolidine (**38**) gave multiple products. The desired product was isolated in 50 % yield (60 % d.e.). The result indicates that the size of the organocatalyst ring has an effect on the rate of the reaction[42, 206].

2.2.4 Catalyst pyrrolidine - 2 - carboxylic acid benzylamide.

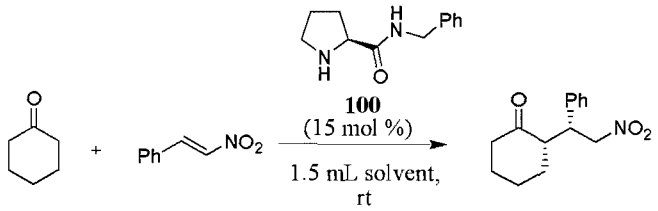
(*S*) - Pyrrolidine - 2 - carboxylic acid benzylamide (**100**) was synthesised as a potential organocatalyst to investigate the effect of the carboxylic acid group of L - proline (**1**). Catalyst **100** was efficiently synthesised (**Scheme 17**) by the coupling of N - ^{t}Boc - L - proline (**99**) and benzylamine; followed by ^{t}Boc deprotection and basic workup.



99 **100**

Scheme 17.

As with L - proline (**1**) and pyrrolidine (**38**); the solvent effects on the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) using **100** as an organocatalyst was also investigated (**Scheme 18**, **Table 7**). List's[182] conditions with DMSO did not yield the desired product.



64 42 65

Scheme 18.

Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	HPLC Yield (%)	Time	e.e. (%)[a]
MeCN	1.5 mL	10	5.0	83 %	26 days	19 %
MeOH	1.5 mL	10	5.0	35 %	32 days	38 %
THF	1.5 mL	10	5.0	100 %	10 days	19 %
DCM	1.5 mL	10	5.0	97 %	7 days	22 %

a: of syn diastereomer.

Table 7: The effect of solvent on the Michael addition catalysed by **100**.

The addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) catalysed by **100** proceeded cleanly in acetonitrile, THF and DCM. The results indicate that the reactions catalysed by **100** in DCM and THF are faster than the Michael addition reaction catalysed by L - proline (**1**) but with a slight detriment to the

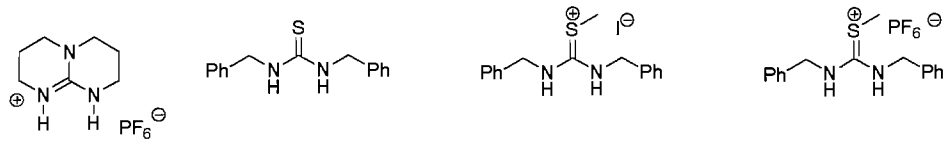
enantioselectivity observed. The Michael addition reaction carried out in acetonitrile show similar reaction rates and enantioselectivity with L - proline (**1**) and catalyst **100**. However, in contrast to the L - proline (**1**) example, the reactions in methanol and DMSO are slow and HPLC analysis indicates multiple impurities. The ability of pyrrolidine (**38**), piperidine and catalyst **100** to effectively catalyse the Michael addition reaction indicates that the carboxylic acid group is not essential to catalysis, as suggested by Wilken[3] and Miller[4].

Babu *et al.*[6] have used organocatalyst **100** to catalyse the aldol reaction between 4 - nitrobenzaldehyde and acetone in water. Babu reports that catalyst **100** illustrates greater activity compared with an analogous catalyst derived from L - proline (**1**) and aniline. The difference in rates is attributed to the small change in catalyst structure; the CH_2 spacer between the amide nitrogen and the phenyl ring in catalyst **100** gives the catalyst a degree of flexibility and means the active site of the catalyst is unhindered[6].

2.3 Co - catalysts.

Bidentate hydrogen bond donor molecules have been successfully used to catalyse a variety of reactions[90, 94, 95, 106-109]. Hydrogen bond donors can effectively catalyse nitro - aldol reactions[90, 107] by forming strong hydrogen bonds with nitronate anions and stabilising the developing negative charge in the transition state. It can be envisioned that the addition of hydrogen bond donors to the Michael addition of ketones to nitroolefins will catalyse the reaction by activation and stabilisation. The combination of covalent catalysis (*via* enamine formation) and non - covalent catalysis (hydrogen bonding) should lead to an optimal catalytic system.

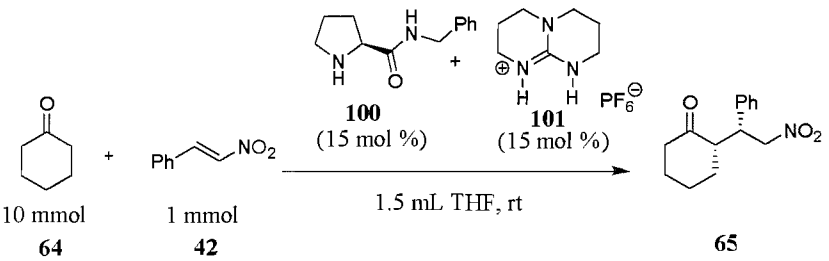
To investigate the effect of the addition of bidentate hydrogen bond donors to the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**); co - catalysts **101**, **102**, **103** and **104** (**Figure 12**) were synthesised according to literature procedure[207] in good yield.



101 **102** **103** **104**

Figure 12: Synthesised co - catalysts.

Organocatalyst **100** was used for the investigation as the carboxylic acid group on L - proline (**1**) may interact with the co - catalyst. THF was used as the solvent for the co - catalyst studies because the solvent consistently gave good results, also studies conducted by Bentacort *et al.*[165, 189] identified THF as the optimum solvent for a number of organocatalysts. For each co - catalyst under investigation several different reactions were set up in order to directly compare the effect to the reaction without the co - catalyst, if the co - catalyst can catalyse the reaction without catalyst **100**, and if an additional base is required[111]. The results are tabulated below (**Tables 8 -11**).

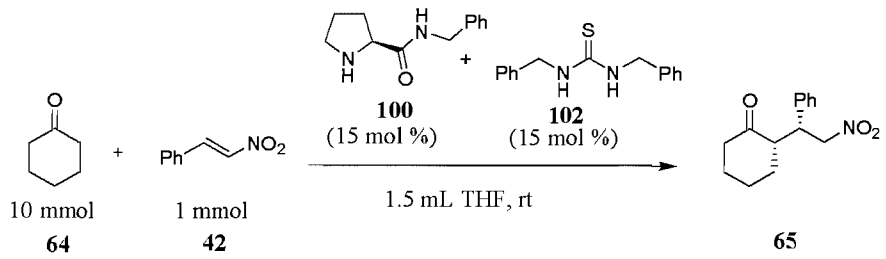


Scheme 19.

Catalyst / Co - catalyst	Additive (10 mol %)	HPLC Yield (%)	Time	e.e. (%)[a]
100	-	100 %	6 days	19 %
100 + 101	-	97 %	20 days	17 %
101	-	0 %	30 days	-
100 + 101	Et_3N	95 %	14 days	17 %
101	Et_3N	0 %	30 days	-
None	Et_3N	0 %	30 days	-

a: of syn diastereomer.

Table 8: The effect of co - catalyst **101**.

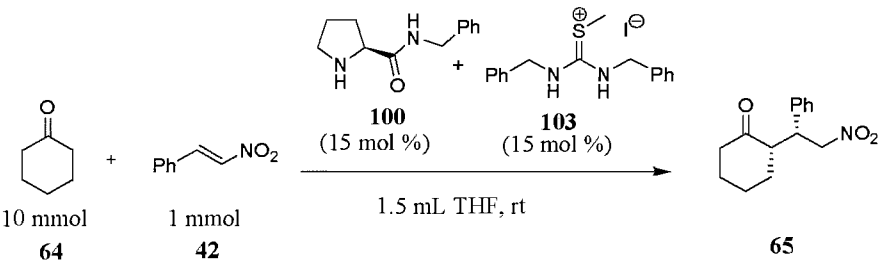


Scheme 20.

Catalyst / Co - catalyst	Additive (10 mol %)	HPLC Yield (%)	Time	e.e. (%)[a]
100	-	100 %	6 days	19 %
100 + 102	-	57 %	30 days	14 %
102	-	0 %	30 days	-
100 + 102	Et_3N	93 %	10 days	15 %
102	Et_3N	0 %	30 days	-

a: of syn diastereomer.

Table 9: The effect of co - catalyst **102**.

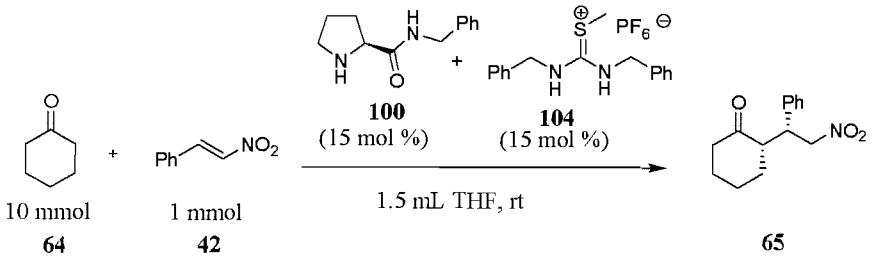


Scheme 21.

Catalyst / Co - catalyst	Additive (10 mol %)	HPLC Yield (%)	Time	e.e. (%)[a]
100	-	100 %	6 days	19 %
100 + 103	-	98 %	14 days	16 %
103	-	0 %	30 days	-
100 + 103	Et_3N	32 %	30 days	15 %
103	Et_3N	0 %	30 days	-

a: of syn diastereomer.

Table 10: The effect of co - catalyst **103**.



Scheme 22.

Catalyst / Co - catalyst	Additive (10 mol %)	HPLC Yield (%)	Time	e.e. (%)[a]
100	-	100 %	6 days	19 %
100 + 104	-	96 %	11 days	16 %
104	-	0 %	30 days	-
100 + 104	Et_3N	96 %	14 days	16 %
104	Et_3N	0 %	30 days	-

a: of syn diastereomer.

Table 11: The effect of co - catalyst **104**.

All the reactions were monitored by HPLC and no impurities were detected. It is evident from the results that for all the investigated co - catalysts, none are able to catalyse Michael reaction exclusively, with or without base. The results also indicate that the addition of a co–catalyst to the Michael addition reaction with catalyst **100** slows the reaction compared to the reaction catalysed by **100** alone. The Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) is not catalysed by the tertiary amine base triethylamine; supporting an enamine mechanism rather than a base mediated mechanism. The addition of co - catalysts causes a slight detriment to the enantioselectivity observed when catalyst **100** is used exclusively.

There appears to be no significant difference in changing the counter ion of the thiouronium (**103** and **104**), with the addition of a base to the reactions slowing the reactions further. In the cases of the co - catalysts **101** and **102** the opposite appears to be true, with the addition of base to the reaction mixture increasing the rate of the

reaction. Di - benzyl thiourea (**102**) co - catalyst has the most detrimental effect on the reaction with the Michael addition on 57 % complete after 30 days.

In contrast to our negative results; Dixon *et al.*[208] reported in 2006 the successful use of a number of bidentate hydrogen bond donors to accelerate the addition of preformed enamines to trans - β - nitrostyrene (**42**) in toluene. However, it was also reported that poor results were obtained when ethereal solvents were used due to the catalysts hydrogen bonding to the solvent leading to catalyst inhibition. Dixon's[208] results suggest that the use of toluene as the solvent to investigate the effect of the co - catalysts (**101 - 104**) may lead to more positive results. The effect of the hydrogen bonding of the co - catalysts (**101 - 104**) in the Michael addition reactions may be binding to the solvent and / or the carbonyl group of cyclohexanone (**64**) or the catalyst (**100**) preventing the formation of an enamine intermediate.

2.4 Conclusions.

L - Proline (**1**), pyrrolidine (**38**), piperidine, and (*S*) - pyrrolidine - 2 - carboxylic acid benzylamide (**100**) have all been employed as organocatalysts for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) with varying catalytic activity; generally imparting good diastereoselectivity but with poor enantioselectivity. Studies, using the catalyst L - proline (**1**), investigating concentration and stoichiometry identified that the highest concentration of cyclohexanone (**64**) as the optimum conditions for catalysis. Solvent studies with organocatalysts **1**, **38** and **100** gave conflicting results probably due to the different solubility of the catalysts.

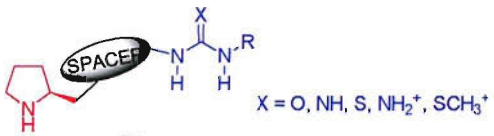
The different results obtained when pyrrolidine (**38**) and piperidine were used as the catalyst indicate that amine ring size is an important factor, as reported by Stork *et al.*[206] and later by List *et al.*[42]. NMR studies indicate an enamine mechanistic pathway, the result is further validated by the failure of triethylamine to catalyse the Michael reaction discounting a base mediated mechanism.

Investigations were carried out into the effects of the addition of bidentate hydrogen bonding co - catalysts (**101** - **104**) to the amine promoted Michael addition reaction. The use of co - catalysts slowed the reaction compared to the exclusively amine promoted reaction and with a slight detriment to the enantioselectivity. The Michael reaction failed when only the co - catalysts were used. The negative results obtained when using the bidentate hydrogen bond donor molecules could be due to hydrogen bonding to the ethereal solvent, to cyclohexanone (**64**) or to the catalyst resulting in catalyst inhibition.

Chapter 3 Bifunctional amide linked organocatalysts.

3.1 Aims.

Since the original work by List *et al.*[32] and Macmillan *et al.*[33] many transformations have been successfully carried out with organocatalysts which are either chiral amines (covalent catalysis) or hydrogen bond donors (non - covalent catalysis). As many groups have shown,[111-161] an optimal catalyst is one which combines both catalytic components to activate both the electrophile and the nucleophile of a reaction. The aim of our work was to synthesise and test a range of bifunctional organocatalysts derived from L - proline (**1**), incorporating a hydrogen bond donor group tethered by a spacer group (**Figure 9**). Different spacers were investigated to identify the optimal distance between the two catalytic functionalities for efficient turnover and enantioselectivity. A range of L - proline derived compounds were made which could be functionalised with thioureas, thiouroniums and guanidiniums.



92

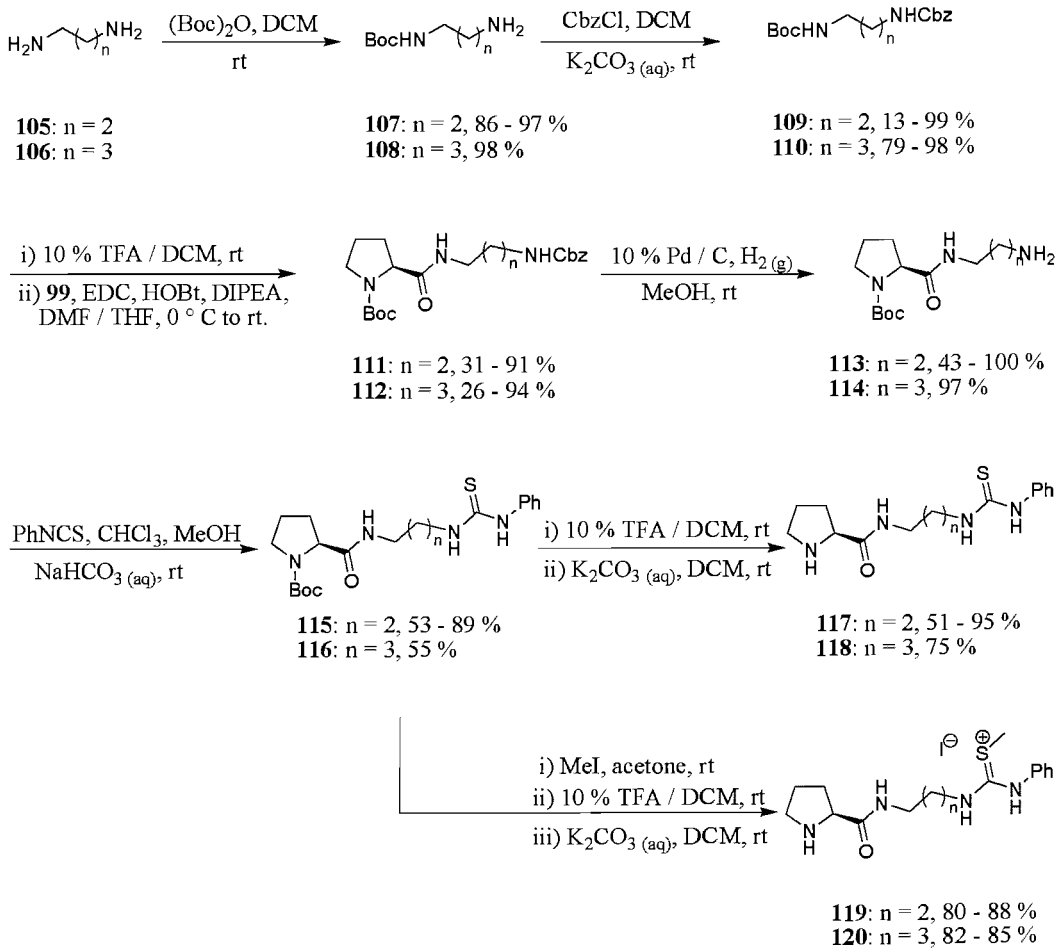
Figure 9: Proposed design of novel bifunctional catalyst.

3.2 Amide linked thiourea and thiouronium bifunctional organocatalysts.

3.2.1 Amide linked thiourea and thiouronium bifunctional organocatalysts synthesis.

A variety of bifunctional thiourea and thiouronium organocatalysts incorporating 2, 3 or 4 carbon chain length spacers were successfully synthesised in moderate to good yields (**Scheme 23** and **Scheme 24**). The synthesis of the catalysts uses orthogonal

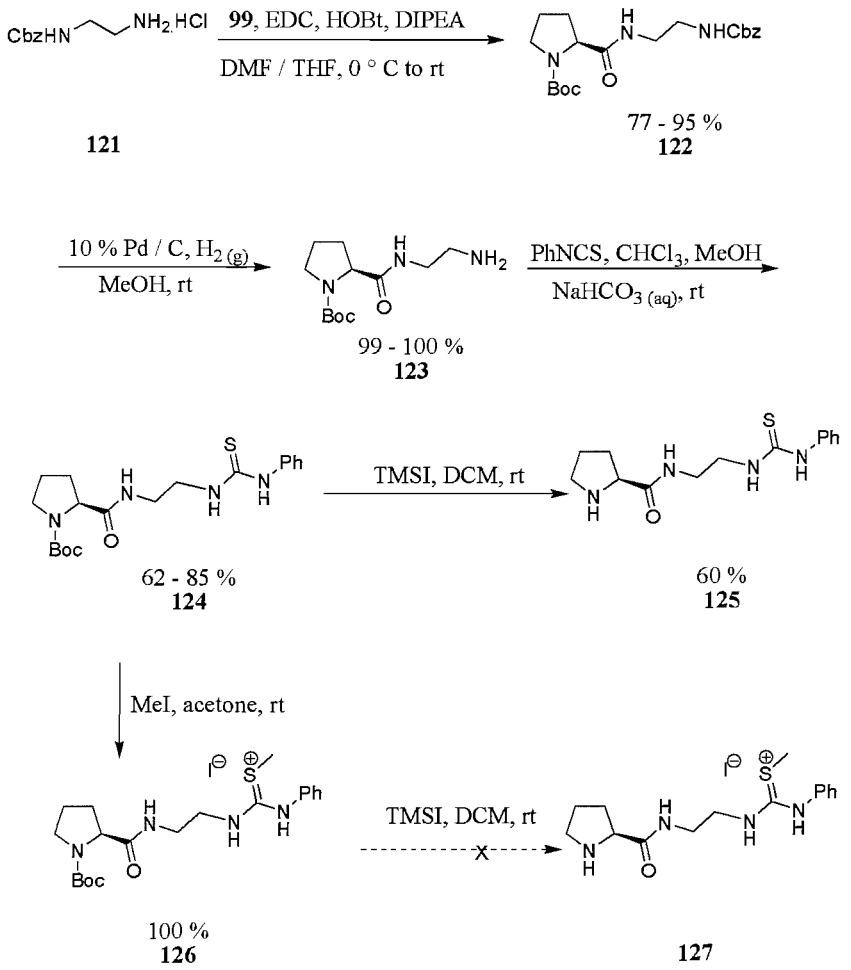
protecting group chemistry, to that end it was necessary to synthesise mono Cbz diamines. However, the synthesis of the mono Cbz diamines requires three steps *via* the di - protected diamines **109 - 110** and then subsequent Boc deprotection. Attempts were made to make the mono Cbz diamines in two steps using Pittelkow's[209] method, however, low yields were obtained.



Scheme 23.

Coupling of the mono Cbz diamines to N - ^{t}Boc - L - proline (**99**) was carried out using coupling agents EDC and HOBt[207] and the products (**111 - 112**) purified by crystallisation, generally in good yields. Cbz removal by hydrogenation occurred almost quantitatively to yield the L - proline derived primary amines **113 - 114**. Boc protected thiourea bifunctional organocatalysts (**115 - 116**) were produced in moderate to good yields *via* the coupling of primary amines **113 - 114** with phenyl isothiocyanate and purified by column chromatography. Bifunctional thiourea

organocatalysts **117** and **118**, incorporating 3 and 4 carbon chain spacers respectively, were straightforwardly prepared by TFA Boc deprotection and subsequent basic work up to isolate the free amine. Similarly thiouronium bifunctional organocatalysts **119** and **120**, incorporating 3 and 4 carbon chain spacers respectively, were readily prepared in good yields through alkylation of the thiourea with methyl iodide and subsequent Boc deprotection as before.

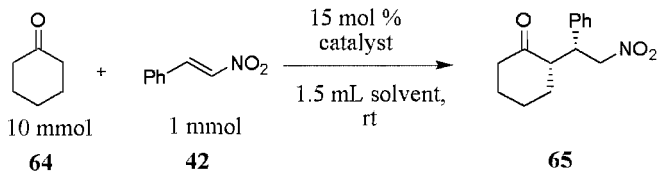


Scheme 24.

Boc protected catalyst **124** was prepared from commercially available diamine **121** utilising the same synthetic sequence used to produce analogous **115** and **116** (**Scheme 23**) in good yields. Despite the success obtained in the synthesis of thiourea and thiouronium bifunctional organocatalysts (**117 - 120**), with 3 or 4 carbon chain spacers, the synthesis of analogous catalysts containing 2 carbon chain length spacer failed on the TFA Boc deprotection step resulting in the formation of multiple

products. Later investigations found that trimethylsilyl iodide[210] facilitated the reaction cleanly to yield thiourea catalyst **125** (**Scheme 24**), however, this method was not successful for the deprotection of thiouronium **126** and therefore it was not possible to prepare **127**.

3.2.2 Amide linked thiourea and thiouronium bifunctional organocatalysts; catalyst comparison.

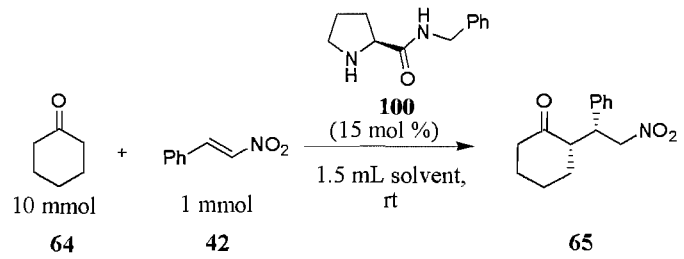


10 mmol **64** 1 mmol **42** **65**

Scheme 25.

In order to investigate the potential of organocatalysts **117**, **118**, **119** and **120**, they were each used to catalyse the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) using a variety of solvents (**Scheme 25**). The optimal conditions previously identified were used; 10 molar equivalents of ketone and 1.5 mL of solvent. As a comparison to observe what effect the tethered thiourea / thiouronium group has on the reaction, the L - proline benzylamide catalyst **100** was also screened (**Scheme 18**). The reaction mixtures were sampled regularly and monitored by HPLC. Reaction yields and diastereomeric ratios are calculated from HPLC data, enantiomeric excess was determined by chiral HPLC. Bifunctional thiourea organocatalyst **125** was not successfully synthesised until a much later time in our investigations and so solvent studies on this catalyst were not carried out.

3.2.2.1 (*S*) - Pyrrolidine - 2 - carboxylic acid benzylamide (100).



Scheme 18.

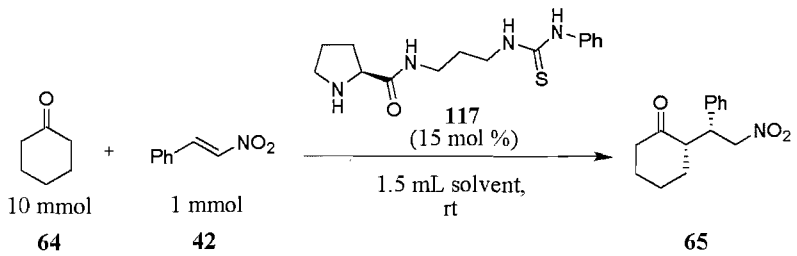
Solvent	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
DMSO	11 %	30 days	92:8	38 %
MeOH	4 %	30 days	90:10	38 %
EtOH	44 %	30 days	92:8	23 %
IPA	40 %	30 days	94:6	23 %
THF	> 90 %	9 days	95:5	19 %
MeCN	76 %	30 days	94:6	19 %
DCM	> 90 %	6 days	95:5	22 %
$CHCl_3$	> 90 %	7 days	96:4	19 %

a: syn: anti; b: of syn diastereomer.

Table 12: The effect of solvent on the Michael addition catalysed by **100**.

Analogous to the results using organocatalyst **100** reported in **Chapter 2**; the reactions carried out in non - polar solvents are considerably faster than in polar solvents, with methanol yielding only 4 % of the desired product after 30 days. All reactions proceed with high diastereoselectivity but with low enantiomeric excess.

3.2.2.2 (*S*)-Pyrrolidine-2-carboxylic acid [3-(3-phenyl-thioureido)-propyl]-amide (117).



Scheme 26.

Solvent	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
DMSO	63 %	30 days	94:6	13 %
MeOH	16 %	30 days	92:8	24 %
EtOH	> 90 %	30 days	94:6	12 %
IPA	50 %	30 days	95:5	4 %
THF	> 90 %	20 days	95:5	27 %
MeCN	71 %	30 days	95:5	22 %
DCM	> 90 %	17 days	95:5	31 %
$CHCl_3$	> 90 %	18 days	95:5	24 %

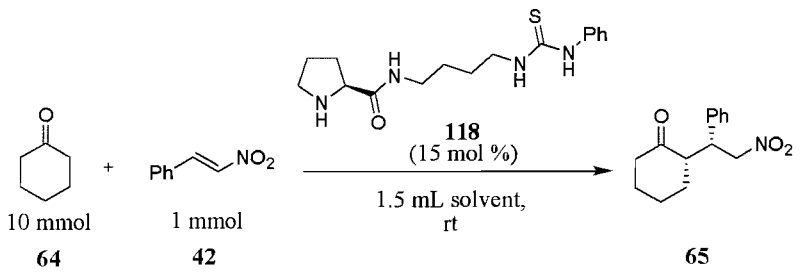
a: syn: anti; b: of syn diastereomer.

Table 13: The effect of solvent on the Michael addition catalysed by **117**.

The bifunctional thiourea organocatalyst **117** successfully catalyses the Michael reaction of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) at a similar rate to monofunctional catalyst **100**, again with the same trend of the less polar solvent giving increased reaction rates; this result is consistent with many literature papers[111, 116, 117, 130, 137, 138, 144-146, 149, 174, 211-216]. The reaction rate has increased in comparison to the Michael addition reactions catalysed by **100** in polar solvents, however, with THF, DCM and chloroform the rate is halved. The diastereoselectivity remains high, and there appears to be a small increase in enantioselectivity in the less polar solvents and

a decrease in enantioselectivity in the polar solvents. The general trend of better activity in non polar solvents is presumably due to the enhanced hydrogen bonding effects in these solvents, resulting in better interactions between the catalyst and substrates[145]. Although the bifunctional catalyst (**117**) shows no significant improvement in rate or enantioselectivity compared with monofunctional organocatalyst **100**, when the results are compared to the co-catalyst studies (**Chapter 2**), using amine **100** and thiourea **102**, the rate is more than doubled and the enantioselectivity improved.

3.2.2.3 (*S*)-Pyrrolidine-2-carboxylic acid [4-(3-phenylthioureido)butyl]-amide (118).



Scheme 27.

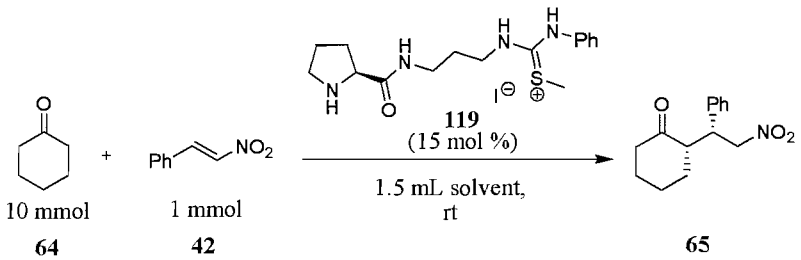
Solvent	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
DMSO	33 %	30 days	86:14	23 %
MeOH	10 %	30 days	92:8	25 %
EtOH	27 %	30 days	86:14	21 %
IPA	37 %	30 days	90:10	20 %
THF	0.4 %	30 days	-	-
MeCN	0.6 %	30 days	-	-
DCM	2 %	30 days	86:14	35 %
$CHCl_3$	2 %	30 days	86:14	11 %

a: syn: anti; b: of syn diastereomer.

Table 14: The effect of solvent on the Michael addition catalysed by **118**.

In contrast to the reasonable results obtained with catalyst **117**, the yields for the Michael reaction catalysed by **118** are low in all solvents after 1 month. It is clear here that the solvent trend with catalyst **118** has reversed with the more polar solvents enhancing the reaction rate. The rate of reaction with **118** is comparable to the reaction rate of the Michael addition catalysed by **100** in polar solvents; however the diastereoselectivity has fallen. It is postulated that the thiourea component of **118** is hydrogen bonding intramolecularly *via* the carbonyl group of the amide, resulting in catalyst inhibition. The rate enhancement observed in polar solvents may be due to the solvents perturbing the hydrogen bonding between the thiourea and carbonyl, allowing the catalyst to react. The results suggest that a 4 carbon chain as a spacer between the L - proline moiety and the thiourea is too long as it interacts with itself rather than the reactants.

3.2.2.4 ((*S*)-Pyrrolidine-2-carbonyl)-amino]-propylamino}-1-phenylamino-methylidene]-methyl-sulfonium iodide (119).



10 mmol **64** + 1 mmol **42** → **65**

Scheme 28.

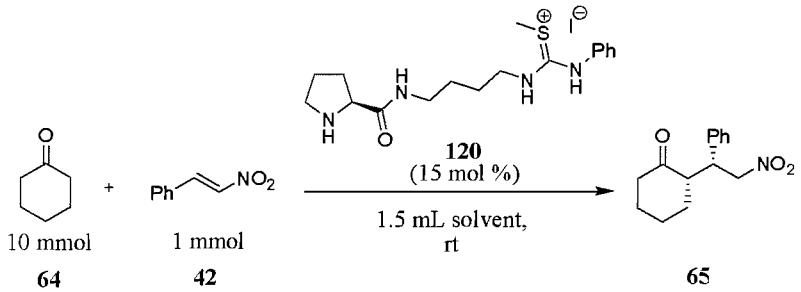
Solvent	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
DMSO	28 %	30 days	86:14	13 %
MeOH	2 %	30 days	-	-
EtOH	8 %	30 days	67:33	-
IPA	2 %	30 days	-	-
THF	3 %	30 days	83:17	15 %
MeCN	9 %	30 days	86:14	25 %
DCM	43 %	30 days	92:8	28 %
$CHCl_3$	13 %	30 days	80:20	37 %

a: syn: anti; b: of syn diastereomer.

Table 15: The effect of solvent on the Michael addition catalysed by **119**.

Thiouronium bifunctional organocatalyst **119**, incorporating a 3 carbon chain length spacer, demonstrated poor activity and enantioselectivity in all solvents investigated. There appears to be no real solvent effect with DMSO and DCM giving the highest conversion after 1 month; although the reactions appeared to be homogeneous, this result could be down to solubility issues. Disregarding the solvent effects, thiouronium organocatalyst **119** is a poor organocatalyst; the results indicate that the thiouronium is a detrimental component in comparison with the thiourea analogue **117**.

3.2.2.5 ((*S*)-Pyrrolidine-2-carbonyl)-amino]-butylamino}-1-phenylamino-methylidene]-methyl-sulfonium iodide (120).



Scheme 29.

Solvent	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
DMSO	> 90 %	30 days	80:20	5 %
MeOH	6 %	30 days	-	-
EtOH	7 %	30 days	-	18 %
IPA	24 %	30 days	92:8	1 %
THF	31 %	30 days	86:14	0 %
MeCN	32 %	30 days	86:14	6 %
DCM	> 90 %	10 days	92:8	13 %
$CHCl_3$	73 %	30 days	93:7	20 %

a: syn: anti; b: of syn diastereomer.

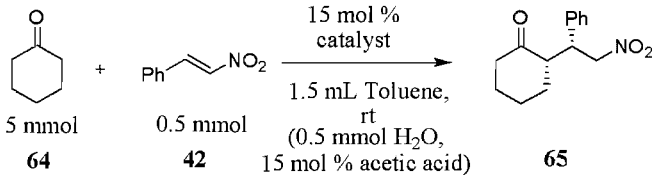
Table 16: The effect of solvent on the Michael addition catalysed by **120**.

Analogous to catalyst **119**, bifunctional thiouronium organocatalyst **120** exhibits poor activity and enantioselectivity in all solvents except DCM. Surprisingly in the solvent DCM, catalyst **120** imparts the highest conversion rate compared with bifunctional catalysts **117**, **118** and **119**, albeit with poor enantioselectivity however. As with thiouronium **119**, there appears no be no trend to the effect of solvent on the Michael addition reaction catalysed by **120**; as before DMSO and DCM exhibit the highest conversion rate over a month. Thiourea catalyst **118** and thiouronium **120** both contain four carbon length spacers, however thiourea **118** exhibited little to no activity but in contrast thiouronium **120** is able to catalyse the reaction within 10 days in DCM seemingly indicating the lack of intramolecular hydrogen bonding.

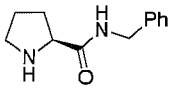
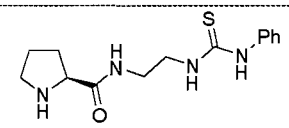
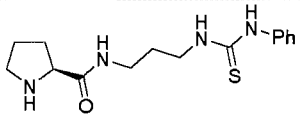
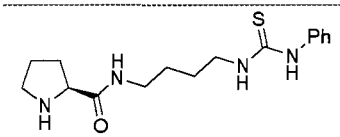
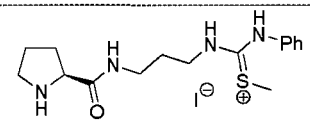
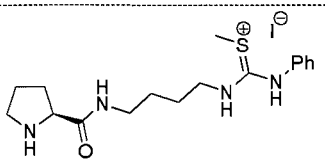
3.2.2.6 Solvent effect of toluene and additives.

During the course of our studies several research groups reported that the optimum conditions are achieved when toluene is used as the reaction medium[113, 115, 116, 122, 129, 130, 133, 136, 139, 143-145, 147, 148, 151, 159, 160, 176, 217-220] for many organocatalysed reactions, indicating that hydrogen bonding strength is significantly affected by the polarity of the solvent[145, 221]. A number of literature papers have also reported increased reaction rate and enantioselectivity when adding organic acids and / or water to organocatalysed Michael addition reactions[13, 15, 141-143, 145-148, 150, 151, 172, 175, 176, 186, 187, 191, 193, 199, 211, 216, 222-227]. Hine *et al.*[228] reported that primary amines formed imines with carbonyl compounds fifteen times faster in the presence of acid compared with the rate observed with amines alone, indicating the importance of acid in enamine formation from secondary amines. List *et al.*[39] and Cordova *et al.*[229] have both reported on the significance of water on enamine formation and regeneration of the catalyst in the catalytic system.

Our amide linked organocatalysts **100**, **117**, **118**, **119**, **120** and **125** were later reinvestigated following the work by Tsogoeva *et al.*[145, 147, 148] who found that the use of acetic acid and water significantly improved the rate of the organocatalysed Michael addition of ketones to trans - β - nitrostyrene in toluene (**Scheme 30**).



Scheme 30.

	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.**[a]	**e.e. (%)**[b]	**HPLC Yield (%)**	**Time**	**d.r.**[a]	**e.e. (%)**[b]
 **100**	> 90 %	6 days	92:8	8 %	> 90 %	24 hours	92:8	8 %
 **125**	3 %	30 days	-	-	5 %	30 days	-	-
 **117**	> 90 %	18 days	92:8	13 %	> 90 %	12 days	94:6	15 %
 **118**	> 90 %	25 days	92:8	30 %	> 90 %	11 days	95:5	25 %
 **119**	> 90 %	42 hours	94:6	24 %	> 90 %	15 hours	91:9	24 %
 **120**	1 %	30 days	-	-	3 %	30 days	-	-

a: syn: anti; b: of syn diastereomer

Table 17: Comparison of monofunctional and bifunctional amide linked catalysts.

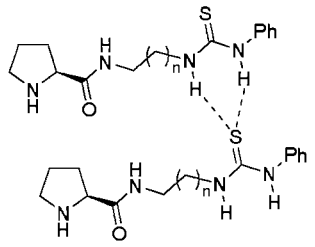
No reaction was observed in toluene or in toluene with the addition of acetic acid (15 mol %) and water (1 equivalent) after 30 days when no organocatalyst was employed. Monofunctional organocatalyst **100** and bifunctional thiourea organocatalyst **117** give similar reaction rates in toluene as the analogous Michael addition reaction carried out in DCM and chloroform (**Table 12** and **Table 13**), but with a loss of enantioselectivity. The results observed in toluene with catalysts **100** and **117** agree with the previous results that increased reaction rates are observed in non polar solvents. Bifunctional thiourea organocatalyst **125** and bifunctional thiouronium organocatalyst **120** exhibited little catalytic activity in toluene and in toluene with the addition of acetic acid and water.

In contrast to our previous solvent study results (**Section 3.2.2.3**), bifunctional thiourea organocatalyst **118** demonstrated enhanced catalytic ability in non polar solvent toluene, with similar selectivity. Correspondingly bifunctional thiouronium organocatalyst **119** exhibits a dramatic increase in the rate of reaction in toluene compared with the other solvents investigated (**Table 15**), again with little change in selectivity. The significant rate increase observed in toluene with organocatalysts **118** and **119**, compared to other solvents, cannot be easily explained; an important difference between toluene and the other solvents investigated is that toluene is an aromatic solvent, suggesting that toluene may have a stabilising effect on the organocatalysed reaction through π - π and / or π - cation interactions.

Organocatalysts **100**, **117**, **118** and **119** all result in faster reaction rates with the addition of acetic acid and water to the Michael addition reaction in toluene, with little change to the selectivity given. The enhancement in rate with the additives acetic acid and water agrees with Tsogoeva's[145, 147, 148] results and indicates that acid and water is important for enamine formation and catalyst regeneration[39, 145, 147, 148, 228, 229].

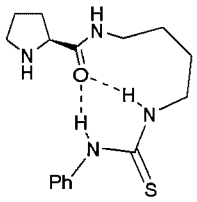
3.2.3 NMR Experiments.

Due to the generally poor activity and enantioselectivity displayed by bifunctional thiourea and thiouronium organocatalysts **117**, **118**, **119**, **120** and **125** it was postulated that the catalysts may be aggregating by hydrogen bonding intermolecularly (I, **Figure 13**) or possibly intramolecularly hydrogen bonding (II, **Figure 13**) between the thiourea / thiouronium and the carbonyl group of the amide, inhibiting catalysis.



125: n = 1
117: n = 2
118: n = 3

I

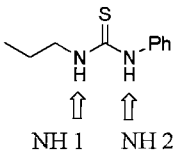


118

II

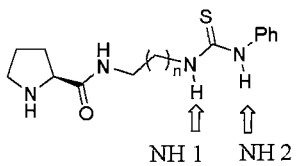
Figure 13: Postulated intermolecular (I) and intramolecular (II) hydrogen bonding.

To investigate the postulation of intra and intermolecular hydrogen bonding, NMR studies were carried out. Simple 1 - phenyl - 3 -propyl - thiourea (**128**) was synthesised as a comparison to the catalysts as a thiourea which has no possible intramolecular hydrogen bonding.



NH 1 NH 2

128



NH 1 NH 2

117: n = 2
118: n = 3

Figure 14: Thiourea **128** and bifunctional thiourea organocatalysts **117** and **118**.

Several proton NMR's of thiourea **128** were taken at different concentrations to examine intermolecular hydrogen bonding (**Table 18**).

	$CDCl_3$ ppm		CD_3CN ppm		d_6DMSO ppm	
	NH 1	NH 2	NH 1	NH 2	NH 1	NH 2
5 mM	-	-	6.59	7.99	7.74	9.43
25 mM	6.08	7.76	6.58	8.00	7.72	9.41
100 mM	6.03	7.96	6.59	8.05	7.72	9.40

Table 18: Chemical shift of the thiourea NH protons of **128** at different concentrations in different solvents.

The proton NMR experiments conducted on thiourea **128** indicate that no significant aggregation due to intermolecular hydrogen bonding has occurred as no significant change in NH chemical shift is observed when the concentration is changed. The shift downfield of the NH signals in d_6DMSO compared to $CDCl_3$ indicates hydrogen bonding between the thiourea and solvent. Wittkopp *et al.*[87, 88] have previously commented that due to the relative high acidity and poor hydrogen bond acceptor ability of thioureas (compared with ureas) there is little self association of these type of compounds.

	$CDCl_3$ ppm		d_6DMSO ppm	
Catalyst	NH 1	NH 2	NH 1	NH 2
128	6.03	7.96	7.72	9.40
117	6.99	7.90	7.78	8.02
118	8.13	8.23	7.98	8.35
119	-	7.90	6.45	8.04
120	-	7.76	6.41	7.98

Table 19: Chemical shift of the thiourea / thiouronium NH protons of organocatalysts **117 - 120** and thiourea **128** at 100 mM.

As observed for thiourea **128**, the chemical shifts of the bifunctional organocatalyst thiourea / thiouronium NH signals are shifted in different solvents for all catalysts (**Table 19**). In comparison with thiourea **128** all the catalysts show different chemical shifts for the thiourea NH's. Although there is little difference shown in the chemical shifts between the two thiouronium catalysts **119** and **120**, the difference between the two thiourea catalysts (**117** and **118**) is quite distinct. In $CDCl_3$ the difference is most noticeable with a large shift downfield in the chemical shifts for thiourea **118** (incorporating a 4 carbon chain length spacer) compared to thiourea **117** (incorporating a 3 carbon chain length spacer) and simple thiourea **128**, indicating hydrogen bonding. The difference between **117** and **118** indicates that the 3 carbon chain length spacer between the thiourea and the amide bond is too short to permit intramolecular hydrogen bonding, whereas the 4 carbon chain length spacer is long enough for intramolecular hydrogen bonding to occur. If organocatalyst **118** was indeed intramolecularly hydrogen bonding, as the results suggest, then the result explains why catalyst **118** failed to catalyse the Michael addition reaction in the majority of solvents.

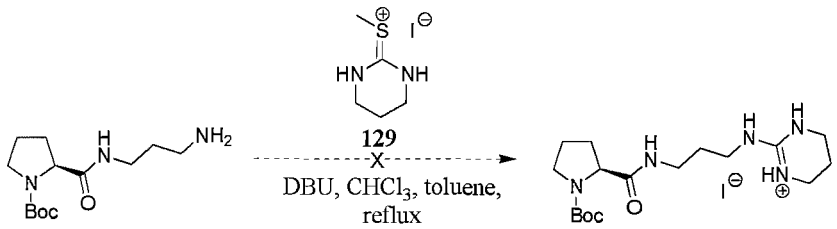
3.3 Amide linked guanidinium bifunctional organocatalysts.

3.3.1 Amide linked guanidinium bifunctional organocatalysts synthesis.

3.3.1.1 Cyclic guanidiniums.

There are numerous different methods of synthesising guanidinium adducts; a successful route often employed is the condensation of thiouroniums with amines, eliminating thiol and generating the guanidinium[207, 230-232]. Several research groups have successfully synthesised cyclic guanidiniums utilising thiouronium **129** (**Scheme 31**) and amines[233-238]. It was envisaged that a simple method of making the Boc protected bifunctional guanidinium organocatalyst **130** would be to condense the free amine **113** with the thiouronium **129** (**Scheme 31**). The thiouronium **129** was successfully synthesised by methylating the analogous thiourea, available from commercial suppliers. Attempts were made to make the PF_6 salt of the

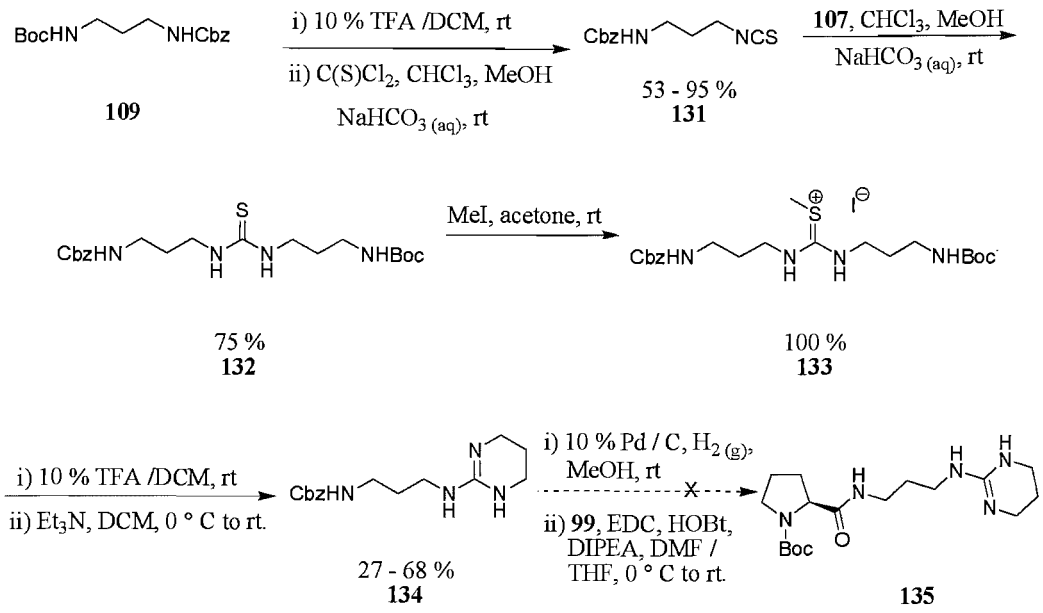
thiouronium (**129**), however, the salt was unstable and readily decomposed. The condensation of **113** and **129** was attempted using Kilburn's[232] method by treating with DBU and refluxing the two components in chloroform and toluene. An initial small scale reflux overnight gave multiple spots by TLC and the desired product was not isolated. Davis *et al.*[239] have reported low yields when attempting to introduce a cyclic guanidine unit using thiouronium **129**.



113 **130**

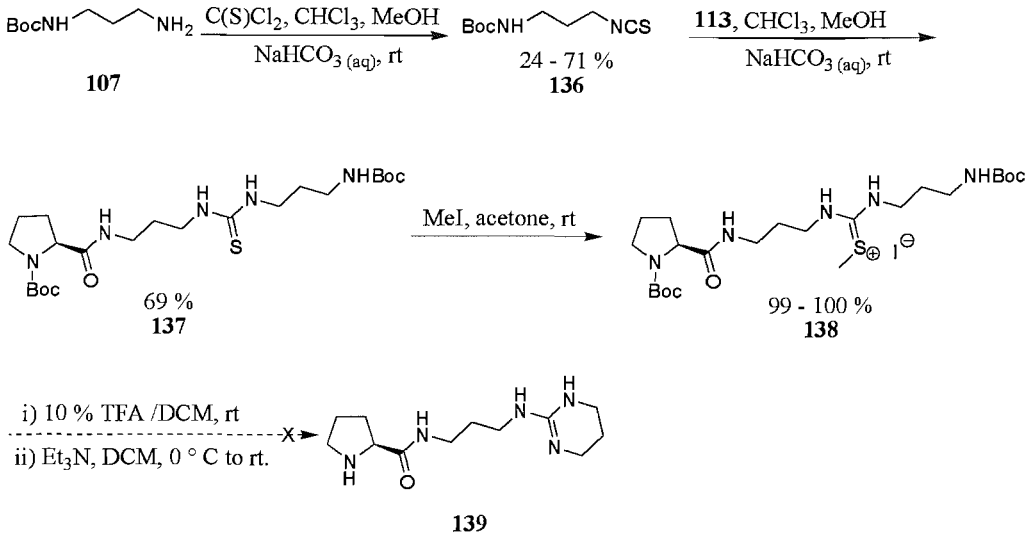
Scheme 31.

Attempts were made to optimise the condensation using thiouronium **129** and benzylamine using various literature procedures[234, 236]. Upon purification of the condensation reactions, however, only starting materials were isolated. Wellner *et al.*[240] suggest that the problem with the condensation reaction lies with the iodide salt of the thiouronium causing de - alkylation[240, 241]. The hexafluorophosphate salt of **129** decomposes, however, Wellner *et al.*[240, 241] utilise the trifluoroacetate thiouronium **129** with apparent success. The thiouronium counter ion was successfully changed to the trifluoroacetate and resulting thiouronium heated in a microwave (in a sealed tube) with benzylamine for 600 seconds (at 160 ° C) according to the literature procedure[241]. Although a new spot was observed by TLC no product was isolated after column chromatography.



Scheme 32.

Following the work of Davis *et al.*[242] and Anslyn *et al.*[243] another method was investigated for making the bifunctional guanidine organocatalyst **135** (**Scheme 32**). The proposed synthetic scheme involved the formation of the cyclic guanidine **134** *via* cyclisation, and subsequent Cbz removal and coupling to N - ^{t}Boc - L - proline (**99**) to yield Boc protected catalyst **135**. The synthesis of thiouronium **133** was synthesised using known literature procedures[207, 232] and in a good yield. The subsequent Boc deprotection of **133** was carried out successfully and the cyclisation conditions optimised by treating the ammonium salt with distilled Et_3N at 0 ° C followed by NaOH aqueous work up to afford cyclic guanidine **134** in 69 % yield. Unfortunately the subsequent removal of the Cbz group from guanidine **134** failed after several attempts of hydrogenation[207] or treatment with hydrobromic acid[244, 245].



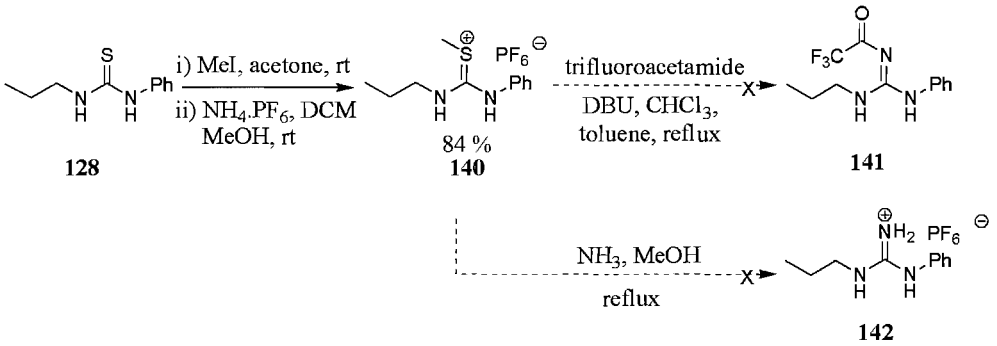
Scheme 33.

Following the previous failed attempts to synthesise a cyclic guanidinium bifunctional organocatalyst (**Scheme 31** and **Scheme 32**) a new synthetic route was examined (**Scheme 33**) utilising the cyclisation chemistry optimised in **Scheme 32**. The condensation of the isothiocyanate **136** and the L - proline derived amine **113** yielded thiourea **137** in good yield. The subsequent methylation with iodomethane was facile yielding **138**. Di - Boc thiouronium **138** was treated with a 10 % solution of TFA in DCM to remove the Boc groups, the resulting ammonium salt was dissolved in DCM, cooled over ice and treated with distilled Et_3N. Unlike the successful synthesis of cyclic guanidine **134**, the cyclisation reaction did not proceed cleanly giving multiple spots by TLC and the desired organocatalyst **139** was not isolated.

3.3.1.2 Acyclic guanidiniums.

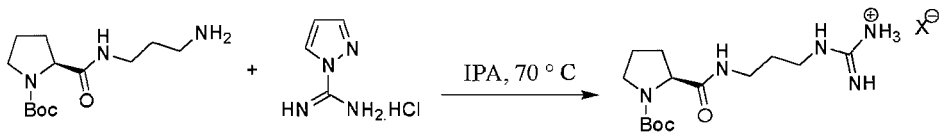
The failure to successfully produce bifunctional cyclic guanidinium catalysts led to investigations into the synthesis of acyclic guanidinium catalysts. Thiouronium **140** (**Scheme 34**) was used to research the synthesis of guanidiniums from thiouroniums analogous to thiouronium catalysts **119** and **120**. The synthesis of protected guanidines from bis alkyl thiouronium compounds is a technique frequently used within our research group[207, 232, 237, 238], however, the literature based reaction between trifluoroacetamide and thiouronium **140** failed to yield any product. Similarly, no

reaction was observed when thiouronium **140** was refluxed in ammonium saturated methanol[230].



Scheme 34.

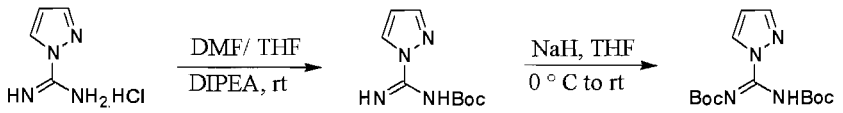
The guanylating agent **143** (**Scheme 35**) has been successfully employed in the synthesis of guanidiniums by several research groups[246-250]. The desired guanidinium chloride salt (**144**) was synthesised by heating L - proline derived amine **113** with guanylating agent **143** for 24 hours. However, attempts to crystallise the chloride salt (**144**) failed and column chromatography led to decomposition. Conversion of the anion to PF_6 (**145**) or BPh_4 (**146**) and attempts to crystallise were unsuccessful in purifying the crude product. The Boc deprotection of **144** with TFA and attempts to crystallise the ammonium salt as the TFA, PF_6 or BPh_4 salt also failed to yield clean material.



113 **143**

144: X =Cl
145: X = PF_6
146: X = BPh_4

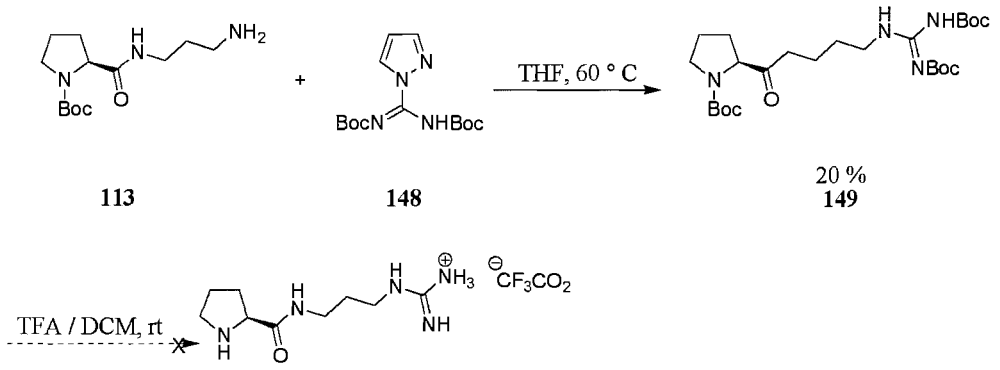
Scheme 35.



143 **147** **148**

Scheme 36.

Bernatowicz *et al.*[251] has reported that bis - protection with Boc or Cbz protecting groups activates the guanylating agent (**143**) to react with even non nucleophilic amines. Following known procedures[251] the activated guanylating agent (**148**) was synthesised in two steps (**Scheme 36**) in good overall yield (76 %).



113 **148** **149**

150

Scheme 37.

The activated guanylating agent (**148**) was reacted with L - proline derived primary amine **113** at room temperature in dry THF (**Scheme 37**). However, contrary to literature reports that **148** will react efficiently at room temperature[251], the reaction had to be warmed to 60 ° C to drive the reaction forward. The tri - Boc protected bifunctional guanidine organocatalyst **149** is stable to column chromatography purification and was isolated in 20 % yield, with 50 % of the starting materials also recovered. Subsequent treatment of **149** with a 20 % solution of TFA in DCM successfully removed all three Boc groups, however, only a small amount of the organocatalyst **150** was obtained and attempts to purify the catalyst were

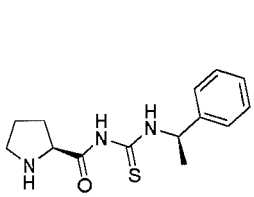
unsuccessful. Due to the low yielding coupling step to obtain protected **149** and the impurity of the final compound bifunctional organocatalyst **150** was not tested.

3.4 Conclusions.

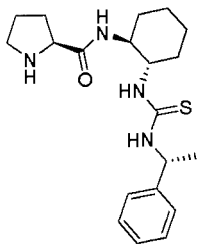
Bifunctional thiourea (**117**, **118** and **125**) and thiouronium (**119** and **120**) organocatalysts, incorporating either 2, 3 or 4 carbon length chain spacers, were successfully synthesised in good yields. The thiourea and thiouronium bifunctional organocatalysts (**117 - 120**) were tested as catalysts for the Michael reaction between cyclohexanone (**64**) to trans - β - nitrostyrene (**42**), with extensive solvent studies also conducted. Thiourea catalyst **117**, incorporating a 3 chain length spacer, was able to catalyse the reaction marginally more efficiently and enantioselectively than mono functional catalyst **100** in polar solvents. Co - catalyst studies (**Chapter 2**) illustrated that the addition of thioureas, thiouroniums and guanidiniums to the Michael addition catalysed by chiral amine **100** are detrimental to the rate of the reaction. In contrast to the results reported in **Chapter 2**, bifunctional organocatalyst **117** gives similar reaction rates to monofunctional catalyst **100**, indicating that the tethering of the two catalytic functionalities is preferred to the use of two separate catalysts.

Thiourea organocatalyst **118**, incorporating a 4 chain length spacer, exhibited very little activity in the majority of solvents; proton NMR studies indicate intramolecular hydrogen bonding resulting in catalyst inhibition. Both bifunctional thiouronium organocatalysts **119** and **120** are poor catalysts with poor conversion and enantioselectivity illustrated. There were no general trends in the solvent effects for catalysts **119** and **120** except both showed higher activity in DMSO and DCM suggesting better solubility in these solvents. Conversely thiourea **118** and thiouronium **119** both exhibit a significantly enhanced reaction rate with toluene compared with other solvents; it is postulated that toluene may have a stabilising effects through π - π and / or π - cation interactions.

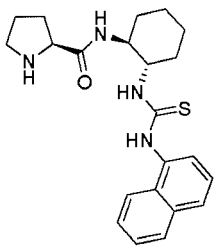
The majority of results given by bifunctional thiourea organocatalysts **125**, **117** and **118** (incorporating a 2, 3 or 4 carbon chain length spacer respectively) suggest that a 3 carbon chain length spacer is the optimal distance between the two catalytic functionalities. The addition of acetic acid and water to the Michael addition catalysed by organocatalysts **100**, **117**, **118** and **119** in toluene increases the rate of reaction, with no significant change to the selectivity and suggests that the additives are important for enamine formation and catalyst regeneration[39, 145, 147, 148, 228, 229]. Our results are analogous to other amide linked bifunctional organocatalysts reported in the literature which also failed to demonstrate high activity or enantioselectivity[147, 211] (**Figure 15**).



151



152



153

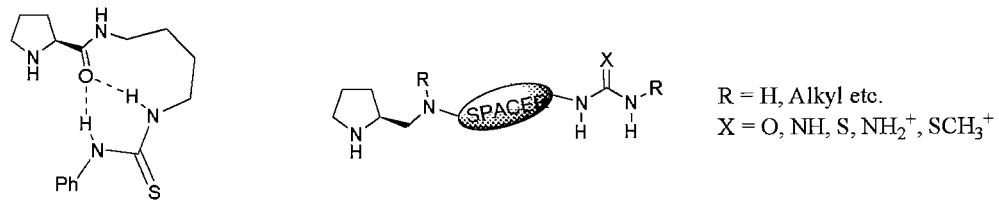
Figure 15.

Multiple attempts were made to synthesise bifunctional acyclic and cyclic guanidinium catalysts by reacting thiouroniums with amines but with little success. The cyclic guanidine **134** was efficiently prepared; however, the failure of the subsequent removal of Cbz halted the organocatalyst synthesis. The use of activated guanylating agent **148** accomplished the tri - Boc protected bifunctional guanidine organocatalyst **149** in low yield. Unfortunately the subsequent TFA removal of the Boc groups resulted impure organocatalyst **150** which could not be purified.

Chapter 4 Bifunctional amine linked organocatalysts.

4.1 Aims.

Several bifunctional organocatalysts, tethered by an amide group, were synthesised and tested, as described in Chapter 3. The amide liked catalysts exhibited poor activity and enantioselectivity; NMR studies indicated intramolecular hydrogen bonding in catalyst **118** (I, **Figure 16**) resulting in catalyst inhibition. A second generation of catalysts were therefore synthesised that tether the two catalytic components through an ether or amine linkage (**154**, II, **Figure 16**). It was postulated that the removal of the carbonyl group would reduce the possibility of intramolecular hydrogen bonding. Chapter 4 describes the synthesis and use of amine linked bifunctional organocatalysts incorporating a range of different spacers to identify the optimal distance between the two catalytic functionalities.



118 **154**

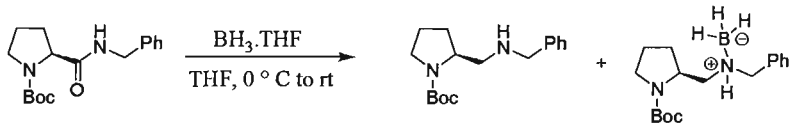
I II

Figure 16: Intramolecular hydrogen bonding in catalyst **118** (I) and amine linked bifunctional organocatalysts (II).

4.2 Amine linked thiourea, thiouronium and guanidinium bifunctional organocatalyst and monofunctional catalyst synthesis.

4.2.1 Monofunctional organocatalyst synthesis.

In order to ascertain the catalytic ability of amine linked bifunctional organocatalysts, a range of monofunctional chiral amine catalysts were synthesised and tested as comparison compounds. The reduction of the amide bond of **100** using borane[252] (**Scheme 38**) was slow and produced the amine **155** in poor yield. As well as recovering starting material from the reaction, the zwitterionic compound **156** was isolated as a by - product from the reaction. The structure of **156** was determined by x - ray crystallography (**Figure 17**).



Scheme 38.

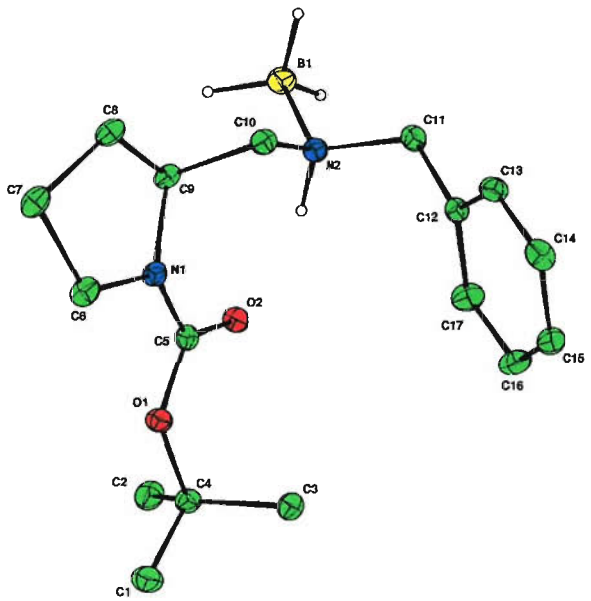
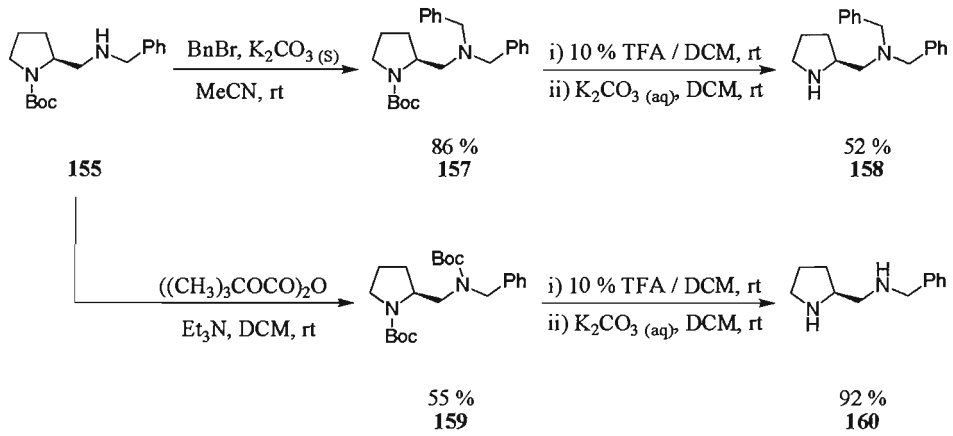


Figure 17: Crystal structure of zwitterion **156**.

Mono alkylation of **155** with benzyl bromide[253] yielded **157** in 86 % yield, followed by Boc deprotection and basic workup yielded catalyst **158**. A proportion of amine **155** was treated with di - *tert* - butyl dicarbonate to give di - protected **159** (crystal structure illustrated in **Figure 18**) to assist purification. Boc removal of **159** with a solution of TFA yielded monofunctional catalyst **160**.



Scheme 39.

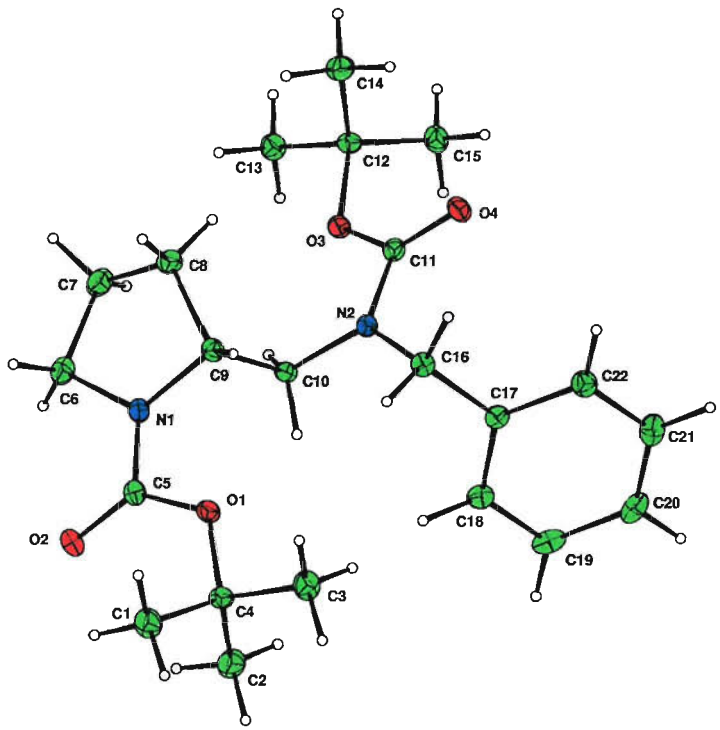
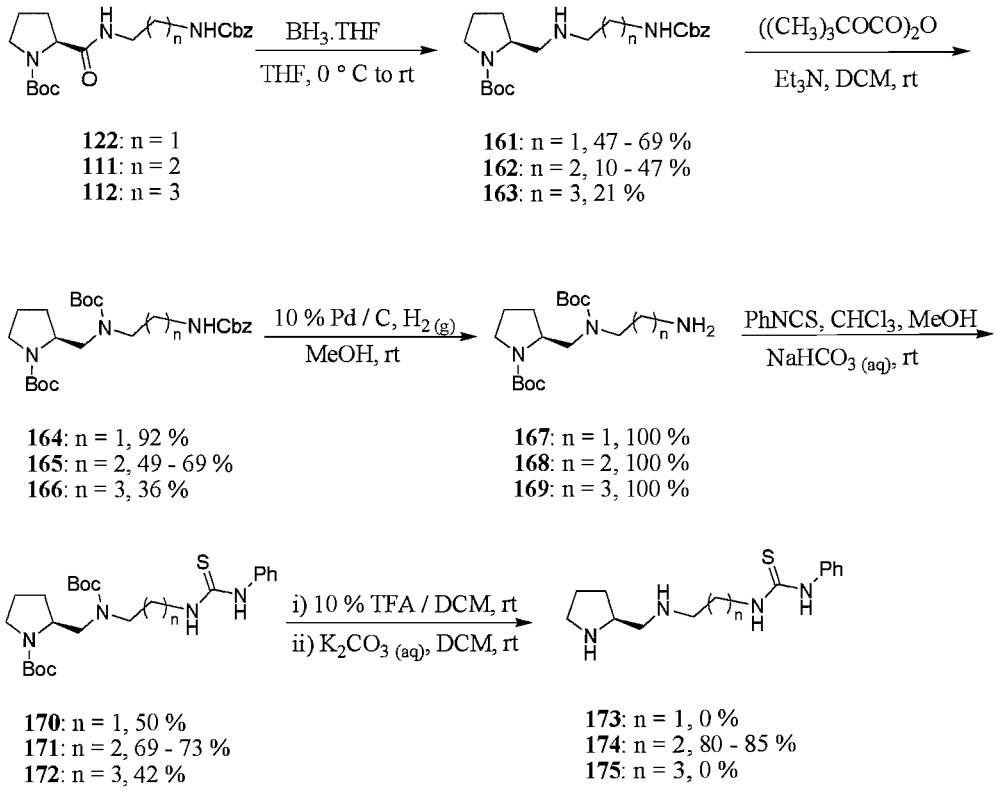


Figure 18: Crystal structure of **159**.

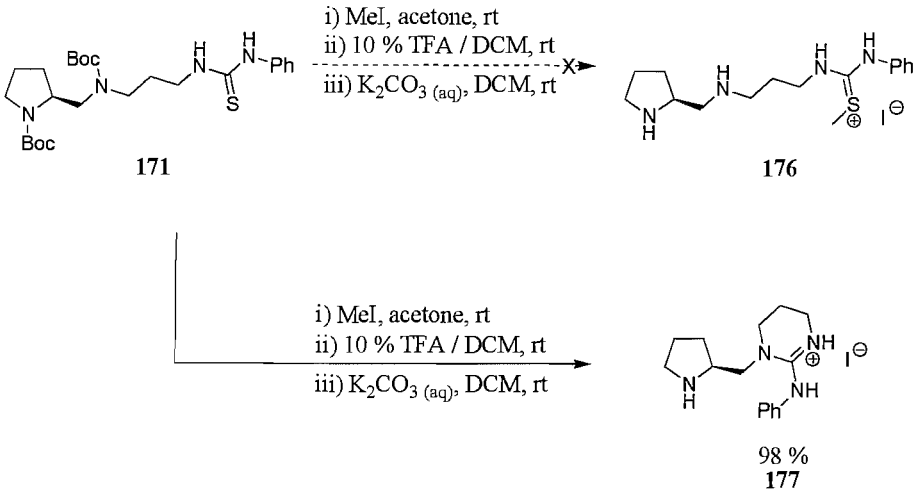
4.2.2 Secondary amine linked thiourea and guanidinium bifunctional organocatalyst synthesis.

The bis - protected compounds **111**, **112** and **122** **(Scheme 40)** were reduced (in the presence of two carbamate groups[254]), using borane[252] at room temperature, to yield the secondary amines **161** - **163** in low to moderate yields. The reduction of the amide group of compounds **111**, **112** and **122** required lengthy reaction times at room temperature, attempts were made to improve the rate by increasing the temperature but this led to reduced yields and some cleavage of the Cbz group[255]. Manipulation of protecting group[256, 257] chemistry yielded the L - proline derived primary amines **167** - **169**. Subsequent coupling[207] with phenyl isothiocyanate produced the di - Boc thiourea catalysts **170** - **172** in moderate yields. The Boc removal with TFA solution and basic workup produced organocatalyst **174** in good yield. Unfortunately, the desired catalysts **173** and **175**, incorporating a 2 or 4 carbon chain length spacer respectively, were not isolated because the treatment of **170** and **172** with a solution of TFA led to multiple products.



Scheme 40.

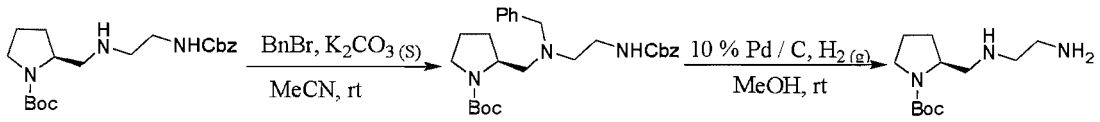
Efforts were made to synthesise the thiouronium bifunctional organocatalyst **176** (**Scheme 41**), alkylation and deprotection with TFA proceeded smoothly (ammonium salt of **176** observed by proton NMR), however, upon basic workup cyclisation between the secondary amine and the thiouronium resulted in the formation of guanidinium **177**.



Scheme 41.

4.2.3 Tertiary amine linked thiourea and thiouronium bifunctional organocatalyst synthesis.

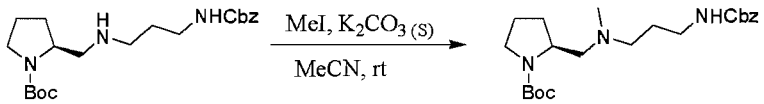
In order to diversify the secondary amine linked organocatalysts, work was undertaken to synthesise bifunctional catalysts incorporating tertiary amine tethers. Investigations were made into alkylation of the amine *via* reductive amination[258] or *via* the Eschweiler - Clark reaction[259], however, the Boc group proved unstable in the acidic conditions of both reactions. The secondary amine **161** (**Scheme 42**) was successfully mono - alkylated with benzyl bromide. It was thought that the amino benzyl group would be relatively stable to Cbz deprotection conditions, unfortunately after only 5 hours under hydrogenation conditions both the benzyl and Cbz groups were cleaved. Treatment of **178** with hydrobromic acid led to cleavage of the Boc group[244, 245].



161 43 - 79 % **178** 100 % **179**

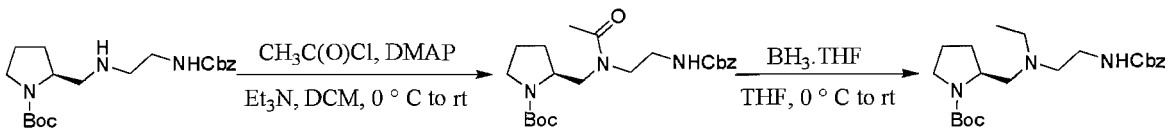
Scheme 42.

Due to the lability of the benzyl group to hydrogenation conditions, investigations were made to introduce other alkyl groups onto the secondary amine position. An attempt was made to make the methyl amine (**180**, **Scheme 43**) using iodomethane, however, only 15 % of the desired product was isolated in contrast to the benzyl analogue which was produced in good yield. Reduction of acetamide **181** (**Scheme 44**) was carried out using borane, the desired ethyl amine was isolated but in a very low yield.



162 15 % **180**

Scheme 43.

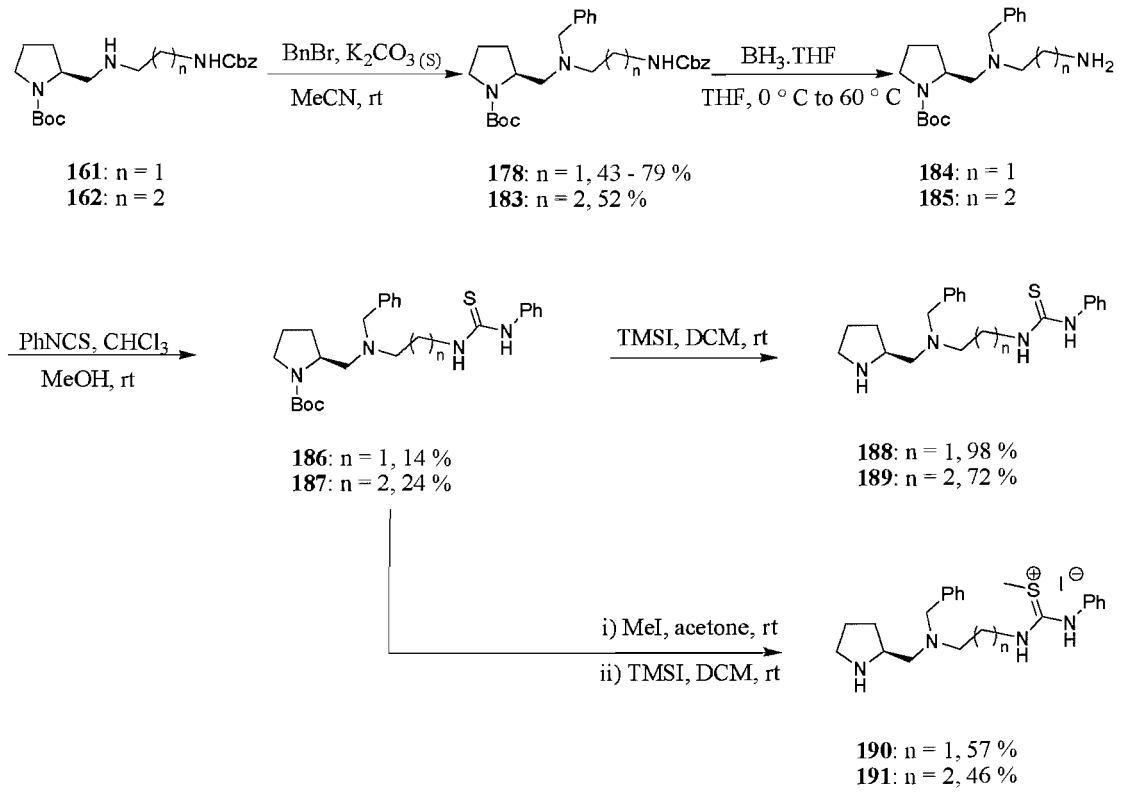


161 88 - 96 % **181** 9 % **182**

Scheme 44.

Due to the reasonable success of alkylating secondary amines **161** and **162** with benzyl bromide and the poor yields obtained using other methods; the selective removal of the Cbz protecting group was re - investigated. The reduction of amides **111**, **112** and **122** with borane led to a proportion of the material undergoing Cbz

cleavage when heated[255]. The side reaction was used to prepare primary amines (**184** and **185**) by heating the reduction of **178** and **183** at 60 ° C for 1 week (**Scheme 45**); the desired product was identified by crude NMR and mass spectroscopy. The crude material was used without further purification and subsequently reacted with phenyl isothiocyanate to yield the Boc protected thiourea catalysts **186** and **187** in low yields. Bifunctional thiourea organocatalysts **188** and **189** were produced by efficient deprotection with trimethylsilyl iodide[210]. Similarly thiouronium bifunctional organocatalysts **190** and **191** were successfully synthesised by alkylation followed by deprotection.

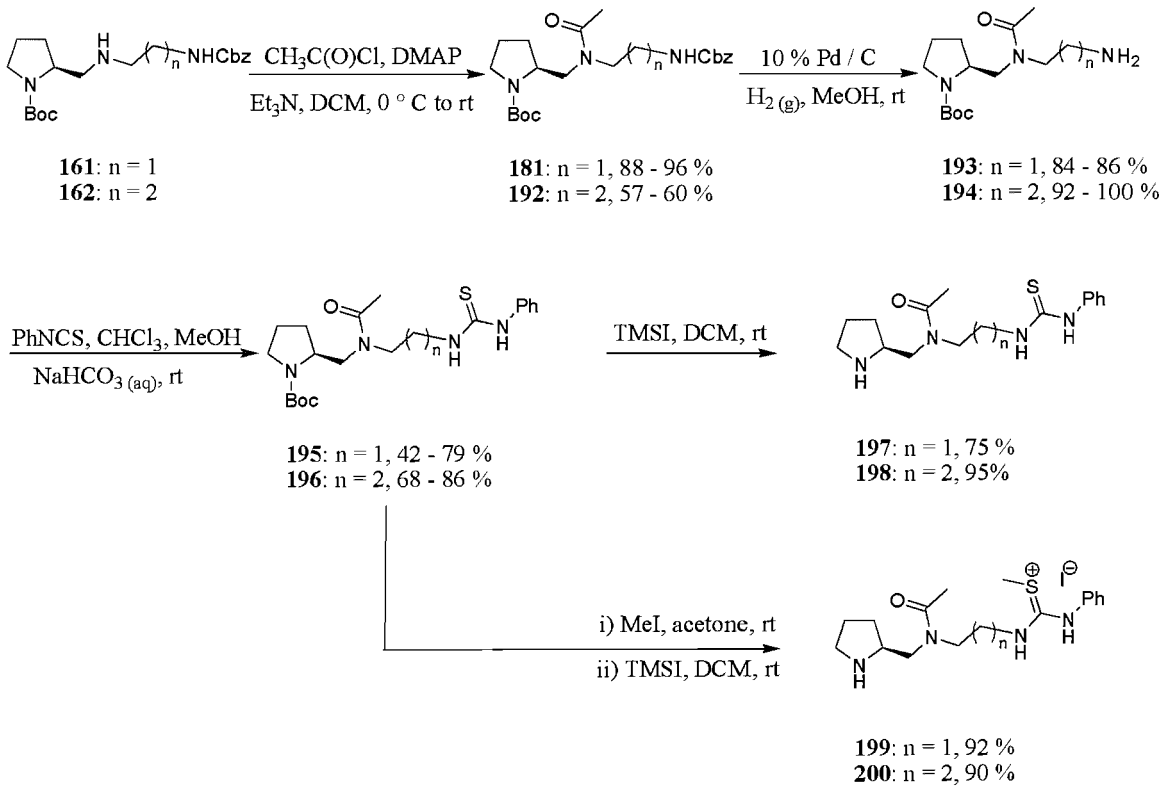


Scheme 45.

4.2.4 Acetamide linked thiourea and thiouronium bifunctional organocatalyst synthesis.

The synthesis of acetamide linked bifunctional organocatalysts utilised secondary amines **161** and **162**; acetylation, deprotection and subsequent coupling yielded Boc

protected thioureas **195** and **196** in moderate to good yields (**Scheme 46**). Problems arose with the synthesis when TFA was used to remove the Boc protecting groups; all four bifunctional organocatalysts **197 - 200** showed impurities by NMR after treatment with the acid solution. Several unsuccessful attempts were made to purify the thiourea and thiouronium catalysts by crystallisation and column chromatography. It was therefore necessary to treat the impure catalysts with di - *tert* - butyl dicarbonate to aid purification; the clean Boc protected catalysts were then successfully deprotected using trimethylsilyl iodide.

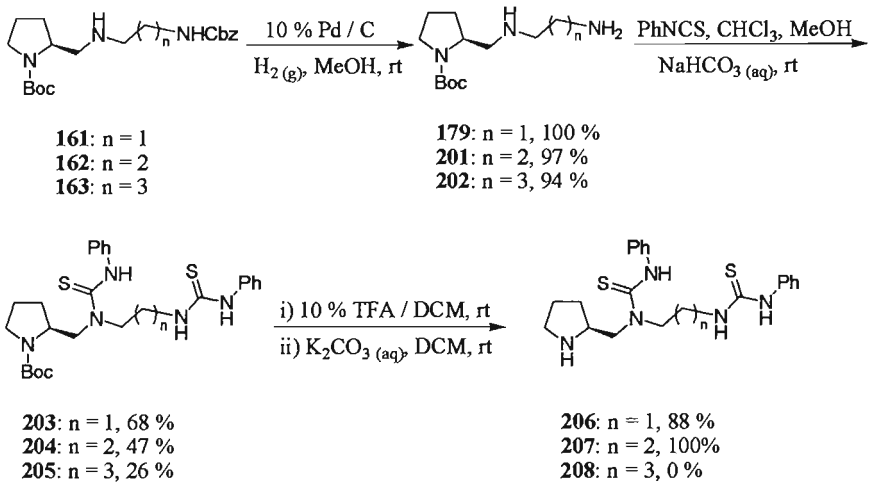


Scheme 46.

4.2.5 Bis thiourea bifunctional organocatalyst synthesis.

L - proline derived diamines **179**, **201** and **202** were straightforwardly synthesised by Cbz hydrogenation of secondary amine compounds **161 - 163** (**Scheme 47**). Coupling of the diamines with 2.5 equivalents of phenyl isothiocyanate yielded Boc protected bis thioureas **203 - 205** after column chromatography. The removal of the Boc protecting group with TFA and subsequent basic workup yielded bifunctional

organocatalysts **206** and **207** (crystal structure: **Figure 19**) in good yields, however, the same treatment of bis thiourea **205** led to multiple products and the desired product was not isolated.



Scheme 47.

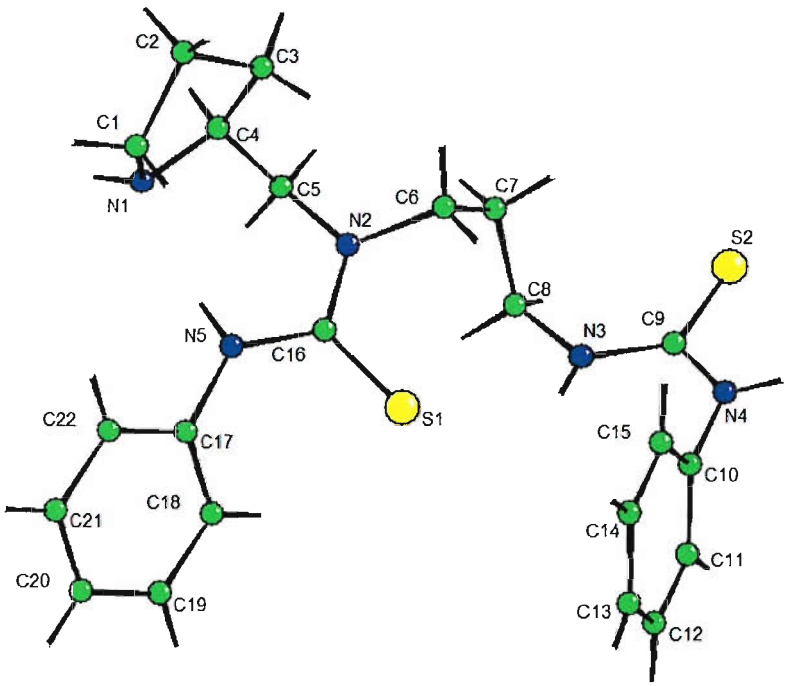
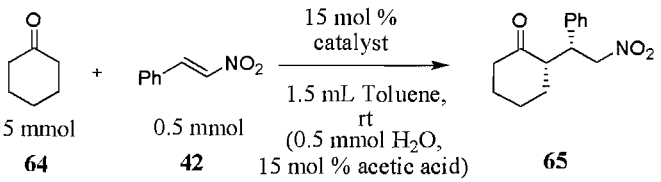


Figure 19: Crystal structure of catalyst **207**.

4.3 Amine linked thiourea, thiouronium and guanidinium bifunctional organocatalysts; catalyst comparison.

4.3.1 Solvent and additive effects.

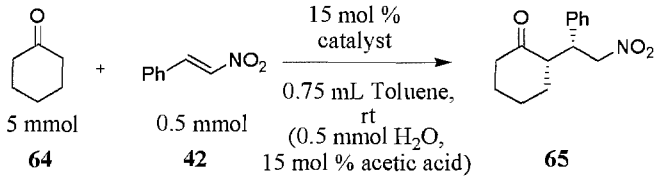
Our previous studies conducted with bifunctional amide linked organocatalysts (**Chapter 3**) on the solvent effects on the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) illustrated significant rate enhancement in toluene for catalysts **118** and **119**. The improvement of the reaction rate when toluene is used as the reaction medium in organocatalytic reactions is consistent with published results[113, 115, 116, 122, 129, 130, 133, 136, 139, 143-145, 147, 148, 151, 159, 160, 176, 217-220]. Investigations into the affect of the additives acetic acid and water[145, 147, 148] to the Michael addition catalysed by bifunctional amide linked organocatalysts in toluene demonstrated that the additives accelerated the reaction rate with little change to the selectivity (**Chapter 3**). The improved results observed with bifunctional amide linked organocatalysts in toluene and literature precedent[113, 115, 116, 122, 129, 130, 133, 136, 139, 143-145, 147, 148, 151, 159, 160, 176, 217-220] prompted the decision not to carry out any further solvent studies and only investigate the effect of toluene and the additives acetic acid and water (**Scheme 30**).



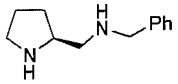
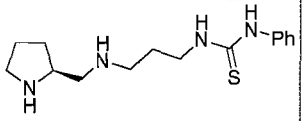
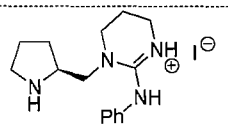
5 mmol **64** 0.5 mmol **42** **65**

Scheme 30.

4.3.2 Secondary amine linked thiourea and guanidinium bifunctional organocatalyst; catalyst comparison.



Scheme 30.

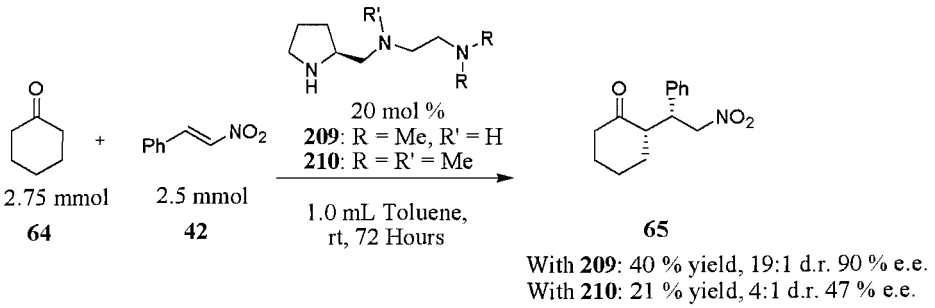
	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
None	0 %	30 days	-	-	0 %	30 days	-	-
 **160**	> 90 %	5 days	94:6	91 %	> 90 %	2 days	95:5	90 %
 **174**	> 90 %	20 hours	91:9	87 %	> 90 %	7 hours	92:8	85 %
 **177**					> 90 %	12 hours	94:6	87 %

a: syn: anti; b: of syn diastereomer.

Table 20: Comparison of monofunctional and bifunctional di - amine catalysts and guanidinium bifunctional catalyst **177**.

No reaction was observed in toluene or in toluene with additives acetic acid and water without the use of a catalyst after 30 days. Monofunctional diamine catalyst **160**

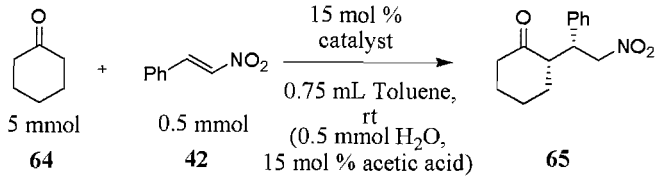
effectively catalysed the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) in toluene within 5 days and with excellent diastereo and enantioselectivity, contrary to results published by Alexakis *et al.*[166] who reported that a similar diamine catalyst formed aminals upon reaction with ketones. The result acquired with diamine catalyst **160** in toluene is comparable to results published by Pansare *et al.*[187] who used diamine catalyst **209** to catalyse the same reaction with good selectivity using only 1.1 equivalents of cyclohexanone (**64**) (**Scheme 48**). The addition of acetic acid and water to the Michael reaction catalysed by **160** led to an increase of reaction rate by more than double of that carried out in toluene alone, with an increase in the diastereoselectivity observed. The same observation was reported by Pansare *et al.*[187] when *p* - toluene sulfonic acid was used as an additive.



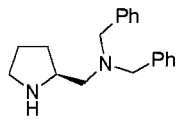
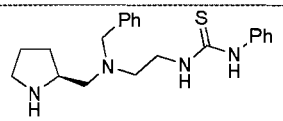
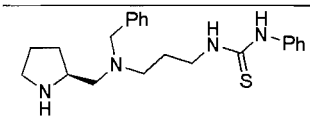
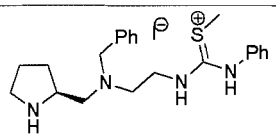
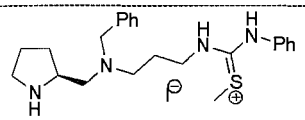
Scheme 48.

Pleasingly bifunctional diamine - thiourea organocatalyst **174** demonstrated a significant increase in the rate of reaction in toluene and with acid and water additives when compared to the monofunctional diamine catalyst **160**, with a slight detriment to the diastereo and enantioselectivity. As with catalyst **160**, the addition of acetic acid and water to the Michael addition catalysed by bifunctional organocatalyst **174** increased the rate of reaction by nearly three times, with no change in the selectivity observed. Similarly bifunctional guanidinium catalyst **177** illustrated good catalytic activity and selectivity (comparable to the results obtained with thiourea catalyst **174**) in the Michael addition reaction in toluene in the presence of acid and water (due to small amount of catalyst **177** available the Michael reaction in toluene alone was not carried out). Comparison of bifunctional organocatalysts **174** and **177** with monofunctional diamine catalyst **160** indicates that the tethering of a hydrogen bond donor group (thiourea or guanidinium) significantly increases the rate of the reaction but has no effect on the selectivity of the reaction.

4.3.3 Tertiary amine linked thiourea and thiouronium bifunctional organocatalyst; catalyst comparison.



Scheme 30.

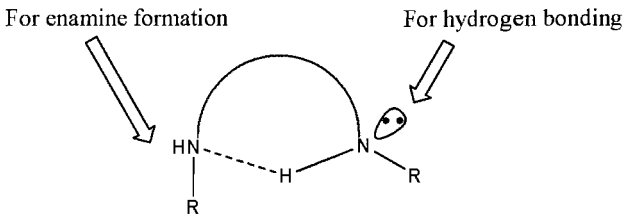
Catalyst	TOLUENE				TOLUENE / H^+ / H_2O			
	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
 **158**	62 %	30 days	94:6	95 %	> 90 %	20 days	94:6	90 %
 **188**	36 %	30 days	92:8	78 %	50 %	30 days	91:9	77 %
 **189**	36 %	30 days	86:14	76 %	64 %	30 days	83:17	75 %
 **190**	1 %	30 days	-	-	4 %	30 days	-	-
 **191**	8 %	30 days	92:8	90 %	11 %	30 days	92:8	88 %

a: syn: anti; b: of syn diastereomer.

Table 21: Comparison of monofunctional and bifunctional tertiary amine linked catalysts.

Unlike the secondary diamine organocatalysts (**Table 20**), the monofunctional and bifunctional catalysts incorporating a tertiary amine linker showed poor catalytic activity in all cases (**Table 21**). Despite the poor catalytic activity, high diastereo and enantioselectivity was exhibited. The addition of acetic acid and water increased the rate of reaction with all tertiary amine tethered organocatalysts (compared with the reaction carried out in toluene exclusively), with a small decrease in enantioselectivity observed. Bifunctional thiourea catalysts **188** and **189** illustrate similar conversion rates and enantioselectivity, however, the diastereoselectivity given by organocatalyst **189**, incorporating a 3 carbon chain length spacer, is significantly less than that observed with thiourea **188** and analogous thiouronium catalyst **191**. Bifunctional thiouronium catalysts **190** and **191** illustrate the least catalytic ability with only a small amount of the desired product observed after 30 days.

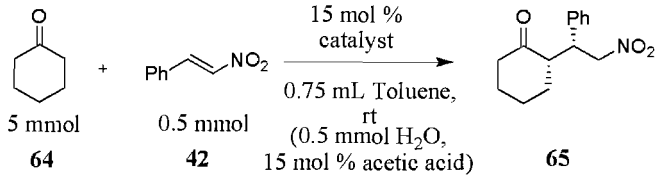
Pansare *et al.*[187] reported lower activity and selectivity when tertiary amine catalyst **210** (**Scheme 48**) was used compared with secondary diamine catalyst **209**. Reports by Pansare *et al.*[187] and Yamamoto *et al.*[260] both comment on the importance of a secondary - secondary diamine motif (compared with secondary - tertiary diamine catalysts) due to the possibility of additional hydrogen bonding (**Figure 20**) which could lead to a more stabilised and structured transition state. In contrast to the reports by Pansare[187] and Yamamoto[260], many groups have reported good activity with secondary - tertiary diamine organocatalysts[15, 165, 166, 173, 178, 179, 189, 194, 215, 226, 261-263].



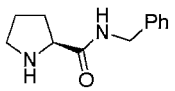
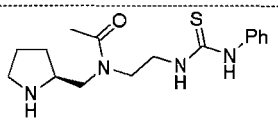
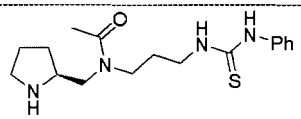
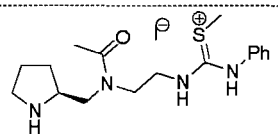
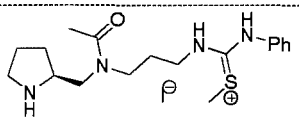
211

Figure 20: Proposed hydrogen bonding present in secondary diamine organocatalysts[260]

4.3.4 Acetamide linked thiourea and thiouronium bifunctional organocatalyst; catalyst comparison.



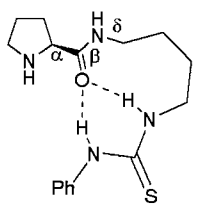
Scheme 30.

	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
 **100**	> 90 %	6 days	92:8	8 %	> 90 %	24 hours	92:8	8 %
 **197**	4 %	30 days	-	-	12 %	30 days	95:5	85 %
 **198**	1 %	30 days	-	-	4 %	30 days	-	-
 **199**	0 %	30 days	-	-	0 %	30 days	-	-
 **200**	3 %	30 days	-	-	8 %	30 days	-	-

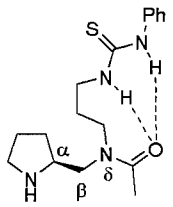
a: syn: anti; b: of syn diastereomer.

Table 22: Comparison of bifunctional acetamide linked catalysts with amide monofunctional catalyst **100**.

All bifunctional organocatalysts tethered by an acetamide group demonstrated little to no catalytic ability with only a small increase in yield obtained when the additives acetic acid and water were employed. The small amount of product **65** (**Scheme 30**) obtained from the Michael reaction was produced with good selectivity when bifunctional organocatalyst **197** and additives acetic acid and water were tested. As with the amide linked bifunctional organocatalysts (**118**, **Figure 21**), the inactivity of the acetamide linked organocatalysts could be due to intramolecular hydrogen bonding between the carbonyl of the amide and the thiourea NH's (**198**) resulting in catalyst inhibition.



118

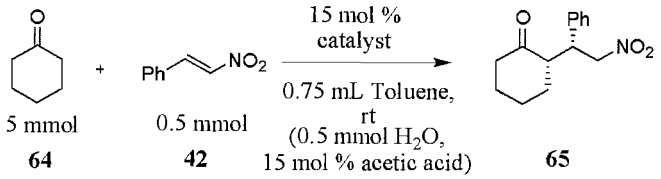


198

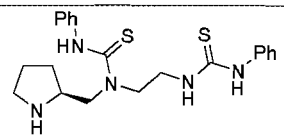
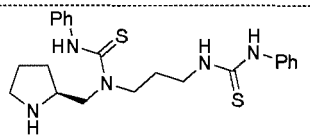
Figure 21: Proposed intramolecular hydrogen bonding in bifunctional organocatalysts **118** and **198**.

Despite the poor catalytic activity observed with acetamide linked bifunctional organocatalysts, the selectivity observed with catalyst **197** is significantly higher than the selectivity obtained with amide linked bifunctional organocatalysts (for example **118**, **Figure 21**). The results given by acetamide linked bifunctional organocatalysts (**Table 22**) and the high selectivity observed with secondary amine (**Table 20**) and tertiary amine (**Table 21**) tethered bifunctional organocatalysts indicates that the carbonyl functionality at the β position (**Figure 21**) significantly impairs the selectivity of the catalysts.

4.3.5 Bis thiourea bifunctional organocatalyst; catalyst comparison.



Scheme 30.

	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
 **206**	> 90 %	5 days	89:11	91 %	> 90 %	9 hours	91:9	97 %
 **207**	> 90 %	6 days	90:10	85 %	> 90 %	4 hours	92:8	92 %

a: syn: anti; b: of syn diastereomer.

Table 23: Comparison of bifunctional bis thiourea catalysts.

Both bis thiourea bifunctional organocatalysts **206** and **207** demonstrate moderate activity when the Michael addition reaction is carried out in toluene, although good selectivity is observed. Gratifyingly both bis thiourea bifunctional organocatalysts exhibited a dramatic increase in the rate of reaction when the additives acetic acid and water were employed. The use of the additives with the bis thiourea catalysts not only increased the rate by up to a multiple of 36, but also slightly increased the

diastereoselectivity and the enantioselectivity by up to 7 %. Bis thiourea organocatalysts have successfully been used for Baylis - Hillman[264, 265] and Henry (nitro - aldol) reactions[159, 160, 218], however, as of yet bis thiourea catalysts have not been used for the Michael addition of ketones to nitroolefins. A recent literature search indicates that bis thiourea organocatalyst **207,** in combination with acetic acid and water, is as good as or better than many published organocatalysts in terms of both catalytic activity and selectivity for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**).

4.4 Conclusions.

The synthesis of two monofunctional organocatalysts, eleven thiourea / thiouronium bifunctional organocatalysts and one guanidinium bifunctional organocatalysts were successfully synthesised, unfortunately the synthesis of three additional bifunctional organocatalysts failed on the final deprotection step. The bifunctional organocatalysts incorporated several variations; the nature of the hydrogen bond donor group (thiourea, thiouronium and guanidinium), the tethering group (secondary amine, tertiary amine, acetamide or thiourea) and the spacer group between the two catalytic functionalities (2 or 3 carbon chain length spacers). The monofunctional and bifunctional organocatalysts were tested as catalysts for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) in toluene and the effect of adding water and acetic acid additives investigated.

The organocatalysts incorporating tertiary amine or acetamide linkers exhibited little catalytic activity but good selectivity, in the case of the acetamide linked bifunctional catalysts it is postulated that intramolecular hydrogen bonding may be leading to catalyst inhibition. Secondary amine linked thiourea bifunctional organocatalyst **174**, guanidinium bifunctional organocatalyst **177** and bis thiourea bifunctional organocatalysts **206** and **207** demonstrated good to excellent catalytic activity and selectivity. When bifunctional organocatalyst **174** and **177** are compared with analogous monofunctional organocatalyst **160**, it is evident that the tethering of the

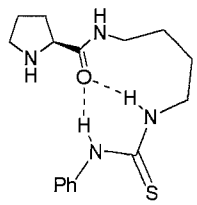
two catalytic functionalities (chiral amine and hydrogen bond donor group) results in a more active, although no more selective, catalyst. There is no marked difference in the catalytic activity and selectivity illustrated between the two different carbon chain length spacers. Comparing the results from **Chapter 4** with previously tested amide linked bifunctional organocatalysts (**Chapter 3**), which gave little selectivity, suggests that the C=O bond at the β position (**Figure 21**) results in the loss of chiral control of the catalysts.

For all of the organocatalysts tested, the addition of acetic acid and water increased the rate of reaction, sometimes significantly, with little effect on the selectivity observed. The rate enhancement observed with the addition of acetic acid and water agrees with published work that states that acid and water play an important role in enamine formation and catalyst regeneration[39, 145, 147, 148, 228, 229].

Chapter 5 Bifunctional ether linked organocatalysts.

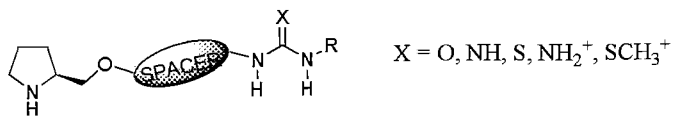
5.1 Aims.

Bifunctional amide liked organocatalysts exhibited poor catalytic activity and selectivity in the Michael addition reaction between cyclohexanone (**64**) and trans - β - nitrostyrene (**42**) (**Chapter 3**). NMR studies indicated that catalyst inhibition is due to intramolecular hydrogen bonding (I, **Figure 22**). Bifunctional organocatalysts that tether the two catalytic components through an amine linkage to reduce the possibility of intramolecular hydrogen bonding were described in **Chapter 4** and positive results were achieved with several such amine linked bifunctional organocatalysts. **Chapter 5** describes the synthesis and use of ether linked bifunctional organocatalysts (**212**, II, **Figure 22**) which also avoid intramolecular hydrogen bonding.



118

I



212

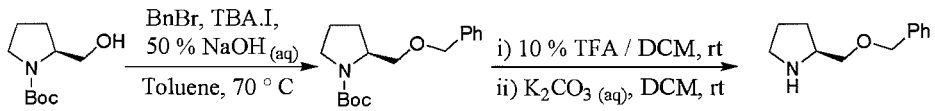
II

Figure 22: Intramolecular hydrogen bonding in catalyst **118** (I) and ether linked bifunctional organocatalysts (II).

5.2 Ether linked thiourea, thiouronium and guanidinium bifunctional organocatalyst and monofunctional catalyst synthesis.

5.2.1 Monofunctional organocatalyst synthesis.

To determine the effect of ether linked bifunctional organocatalysts compared with monofunctional catalysts, the chiral amine **215** was synthesised and tested as a comparison. ^{t}Boc - L - prolinol (**213**) was efficiently synthesised *via* the reduction of ^{t}Boc - L - proline (**99**) with borane[252] (**Scheme 49**). Ether **214** was successfully synthesised *via* the alkylation of ^{t}Boc - L - prolinol (**213**) using Williamson[266] ether synthesis phase transfer conditions with tetrabutyl ammonium iodide. Boc removal with TFA solution and basic aqueous work up gave monofunctional organocatalyst **215** in moderate yield.



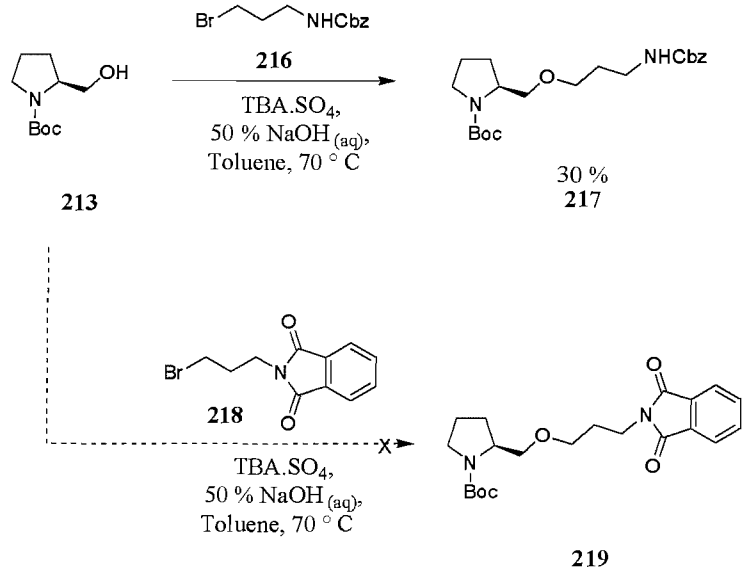
213 87 % **214** 59 % **215**

Scheme 49.

5.2.2 Ether linked thiourea and thiouronium bifunctional organocatalyst synthesis.

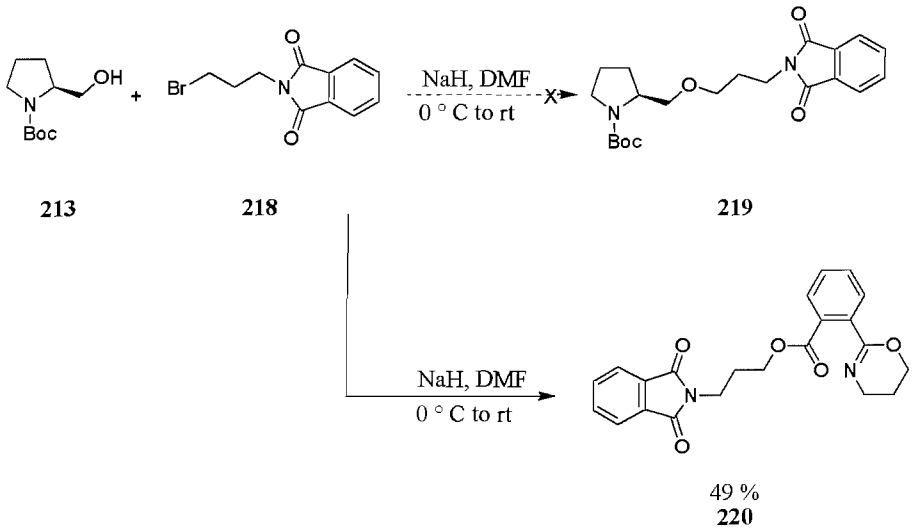
In order to make bifunctional ether linked organocatalysts, it was decided to try to alkylate ^{t}Boc - L - prolinol (**213**) with an alkyl halide that incorporates a protected amine so that once deprotected a guanidinium or thiourea could be attached onto the molecule. Attempts to alkylate ^{t}Boc - L - prolinol (**213**) employing the Williamson ether synthesis conditions[266] with carbamate **216** (synthesised from 3 - bromopropyl amine hydrobromide) resulted in only 30 % of the desired product (**217**, **Scheme 50**).

The same reactions conditions were employed to alkylate ^{t}Boc - L - prolinol (**213**) with phthalimide **218**. Unfortunately multiple products were observed by TLC and ether **219** was not isolated with 12 % of the alcohol **213** recovered.



Scheme 50

Further attempts to alkylate ^{t}Boc - L - prolinol (**213**) by generating the alkoxide with sodium hydride with subsequent treatment of either carbamate **216** or phthalimide **218** (**Scheme 51**) failed in both cases with the majority of the alcohol recovered[267, 268]. The reaction with sodium hydride and phthalimide **218** (**Scheme 51**) resulted in the isolation of a crystalline product oxazine **220** (crystal structure: **Figure 23**).



Scheme 51.

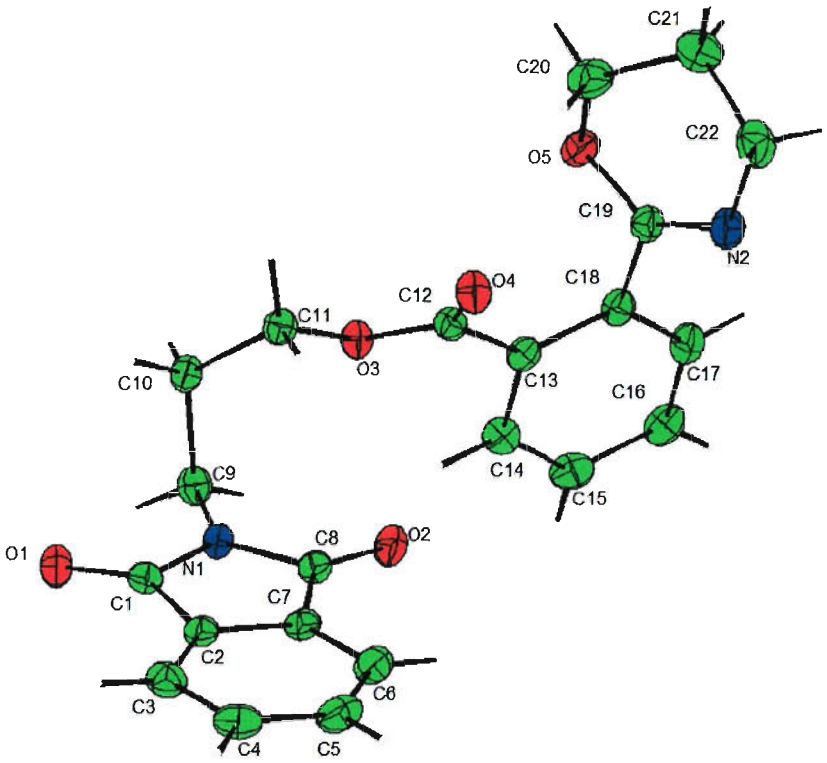
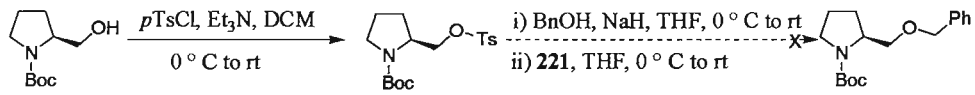


Figure 23: Crystal structure of **220**.

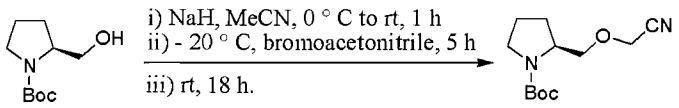


213 65 % **221** **214**

Scheme 52.

As an alternative approach 'Boc - L - prolinol (**213**) was activated by conversion into the tosylate **221** (**Scheme 52**), however, the subsequent reaction with benzyl alkoxide failed to yield any products despite positive results reported with the same method by Lee *et al.*[269].

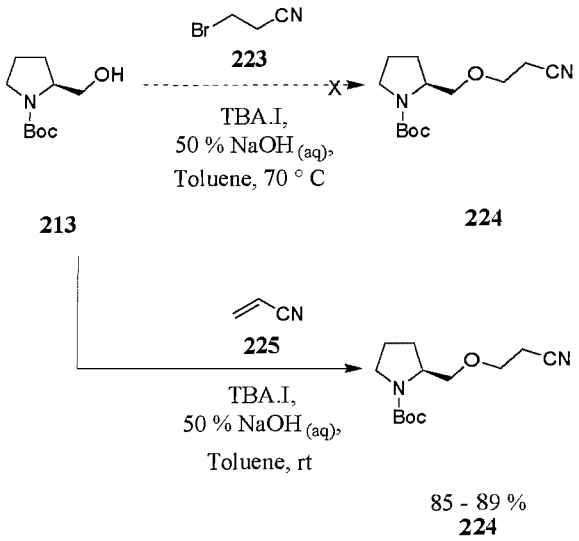
Hindsgaul *et al.*[270] have previously alkylated alcohols with bromo - nitriles in good yields using sodium hydride. Following Hindsgaul's[270] procedure, **213** was successfully alkylated with bromo acetonitrile in low yield (**Scheme 53**), with recovery of **213** and also deprotected L - prolinol (**80**). Ether compound **222** was not reacted further due to the low yields obtained using Hindsgaul's[270] method.



213 5 -13 % **222**

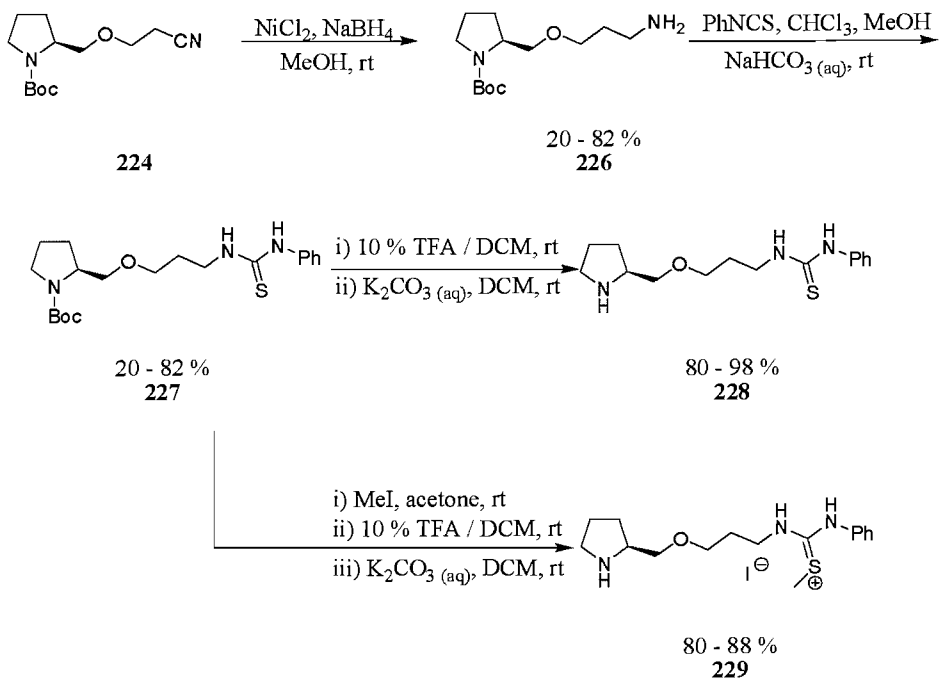
Scheme 53.

Hindsgaul's *et al.* [270] method (**Scheme 53**) with sodium hydride and Williamson ether phase transfer conditions[266] were attempted with 3 - bromo - propionitrile **223** (**Scheme 54**), unfortunately, neither method gave the desired product (**224**). However, ether **224** was successfully prepared in good yields by the Michael addition of ^{t}Boc - L - prolinol (**213**) with acrylonitrile (**225**) using phase transfer conditions[271] with aqueous sodium hydroxide (**Scheme 54**).



Scheme 54.

Ether **224** could be successfully synthesised in large scale (5.3 g) and in good yield, the synthesis of the catalysts from **224** seemed straightforward, however, problems arose in the reduction of the nitrile group. The reduction was first attempted with $LiAlH_4$[272, 273] and under these conditions the nitrile group was reduced but the Boc group was also cleaved. Attempted hydrogenation of the nitrile group with 10 % palladium on carbon resulted in formation of multiple products in the reaction mixture. Borane reduction[274] gave the desired primary amine product (**226**) but in only 17 % yield. Reduction of the nitrile group with $NaBH_4$ (2 equivalents) and $NiCl_2$ (5 equivalents)[275] led to the isolation of **226** in 20 % yield with 26 % recovery of the starting material (**224**). A subsequent reaction with 6 equivalents of $NaBH_4$ and 2 equivalents $NiCl_2$, following a procedure by Yang *et al.*[276], gave the primary amine **226** in 82 % yield after column chromatography (**Scheme 55**).



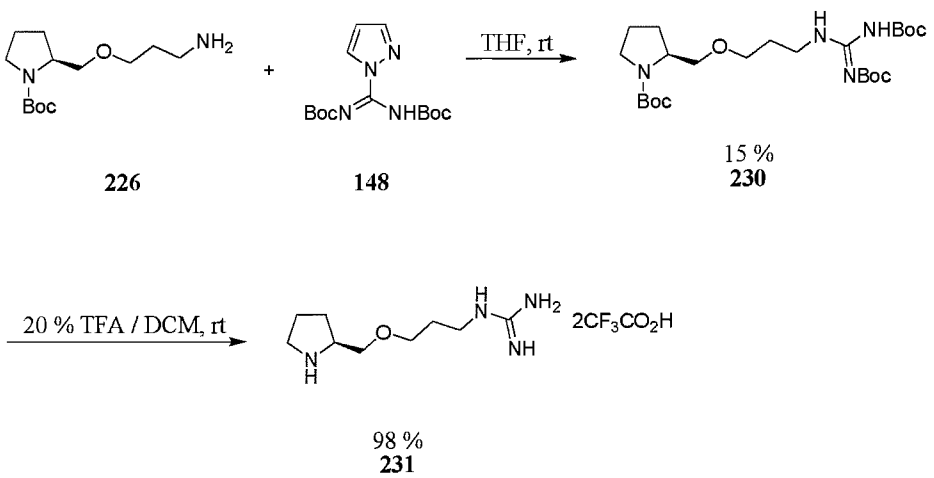
Scheme 55.

The coupling[207] of primary amine **226** to phenyl isothiocyanate was straightforward and led to the production of Boc protected thiourea organocatalyst **227** in good yield. Removal of the Boc protecting group from **227** with a solution of TFA in DCM and subsequent basic workup gave ether linked thiourea organocatalyst **228**. Similarly

thiouronium organocatalyst **229** was readily prepared by alkylation of thiourea **227** with iodomethane followed by Boc deprotection with TFA.

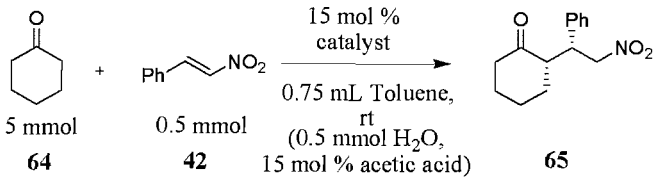
5.2.3 Ether linked guanidinium bifunctional organocatalyst synthesis.

The reaction between activated guanylating agent **148** and primary amine[251] **226** successfully produced the tri - Boc protected guanidinium bifunctional organocatalyst **230** but in a disappointingly low yield after careful column chromatography (**Scheme 56**). Unlike previous attempts to synthesise guanidinium organocatalysts following the same route, the treatment of **230** with a solution of TFA did not lead to decomposition and the bifunctional organocatalyst **231** was isolated as the TFA salt in excellent yield.

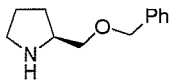
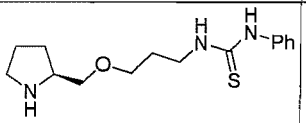
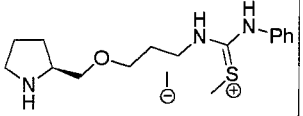
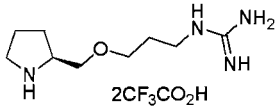


Scheme 56.

5.3 Ether linked thiourea, thiouronium and guanidinium bifunctional organocatalysts; catalyst comparison.



Scheme 30.

	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
 **215**	23 %	30 days	91:9	94 %	10 %	30 days	91:9	93 %
 **228**	> 90 %	24 hours	94:6	86 %	> 90 %	7 hours	94:6	78 %
 **229**	> 90 %	24 hours	94:6	86 %	> 90 %	4 hours	94:6	80 %
 **231** 15 mol % Et_3N	> 90 %	4 days	92:8	71 %				

a: syn: anti; b: of syn diastereomer.

Table 24: Comparison of monofunctional and bifunctional ether linked catalysts.

Monofunctional organocatalyst **215** demonstrates poor catalytic activity, but good selectivity, for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**, **Scheme 30**) in toluene and also with the addition of acetic acid and water. Contrary to previous results, the additives acetic acid and water has a detrimental effect on the reaction rate on the Michael addition catalysed by monofunctional catalyst **215**. Pleasingly the bifunctional thiourea organocatalyst **228** proved to be a more effective and diastereoselective catalyst than **215** with the reaction complete within one day in toluene, although with a slight loss in the enantioselectivity observed. Analogous thiouronium bifunctional organocatalyst **229** demonstrated the same selectivity and catalytic activity as thiourea **228** in toluene. Both thiourea (**228**) and thiouronium (**229**) bifunctional organocatalysts exhibited a marked increase in activity when combined with additives acetic acid and water with a slight loss in enantioselectivity.

Bifunctional guanidinium organocatalyst **231** was tested in toluene with 15 mol % triethylamine to generate the secondary chiral amine for catalysis *in situ* (previous experiments indicate that triethylamine does not catalyse the reaction). The bifunctional organocatalyst **231** is significantly more active than monofunctional organocatalyst **215** but not as enantioselective. Guanidinium bifunctional organocatalyst **231** is not as active or as selective as analogous bifunctional thiourea **228** and thiouronium **229** organocatalysts. The limited amount of catalyst **231** meant that only one experiment could be conducted and therefore the effect of additives combined with the organocatalyst was not investigated.

5.4 Conclusions.

After many failed reactions, bifunctional thiourea (**228**) and thiouronium (**229**) organocatalysts were synthesised in good yields. Bifunctional guanidinium organocatalyst **231** was synthesised using an activated guanylating agent in poor yield. All three bifunctional organocatalysts and monofunctional organocatalyst **215** were tested as catalysts for the Michael addition reaction between cyclohexanone (**64**)

and trans - β - nitrostyrene (**42**) in toluene, with and without additives acetic acid and water. Bifunctional organocatalysts **228**, **229** and **231** exhibited a marked increase in catalytic activity compared with monofunctional catalyst **215**, although with a slight loss in enantioselectivity. The increased catalytic activity observed with ether linked bifunctional organocatalysts agree with the results obtained with amine linked bifunctional organocatalysts, indicating that the tethering the two catalytic functionalities gives a more efficient, although not a more selective, catalyst. The addition of acetic acid and water increased the rate of the Michael addition reaction when catalysts **228** and **229** were employed, again signifying the importance of acid and water for enamine formation and catalyst regeneration[39, 145, 147, 148, 228, 229]. Comparison of the hydrogen bond donor groups indicates that the thiouronium functionality exhibits the best catalytic activity. Unfortunately attempts to synthesise ether linked bifunctional organocatalysts with different carbon chain length spacers were not successful and so evaluation of optimal spacer length between the two catalytic functionalities of bifunctional ether linked organocatalysts could not be carried out.

Chapter 6 Organocatalyst comparison and applications.

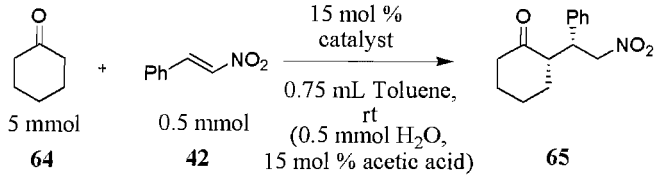
6.1 Aims.

Numerous bifunctional organocatalysts were successfully synthesised and tested for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) with a number of these catalysts demonstrating excellent results (**Table 25** and **Table 26**). However, to achieve the positive results a large excess of the ketone (10 equivalents) and a relatively high catalyst loading (15 mol %) is required, a common problem in many organocatalytic reactions[2, 37-49]. Investigations were carried out into the capability of the bifunctional organocatalysts at lower catalyst loading and with fewer equivalents of cyclohexanone (**64**). The scope of our bifunctional organocatalysts to promote the Michael addition reaction of acyclic ketones or malonates to trans - β - nitrostyrene (**42**) was also studied.

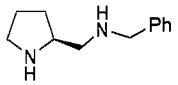
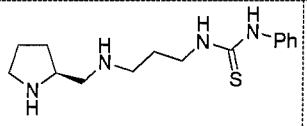
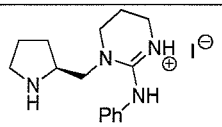
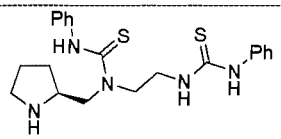
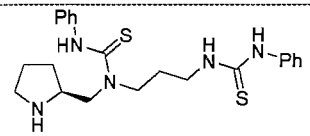
6.2 Michael addition of cyclohexanone and trans - β - nitrostyrene; catalyst comparison and capability.

6.2.1 Catalyst comparison.

Table 25 and **Table 26** summarise the results demonstrated by the more active and selective bifunctional organocatalysts used to catalyse the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**, **Scheme 30**), monofunctional organocatalysts are included for comparison. All the bifunctional organocatalysts tested exhibited greater catalytic ability than the corresponding monofunctional organocatalysts, although no significant difference in selectivity was observed.

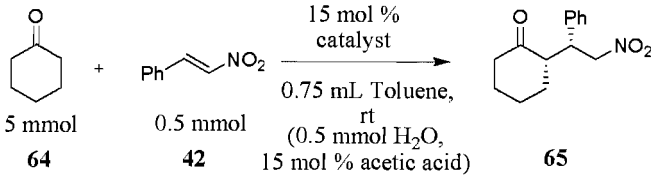


Scheme 30.

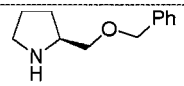
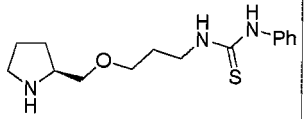
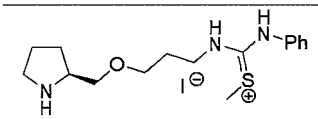
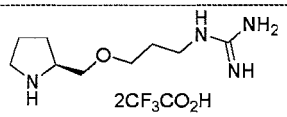
	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
None	0 %	30 days	-	-	0 %	30 days	-	-
 **160**	> 90 %	5 days	94:6	91 %	> 90 %	2 days	95:5	90 %
 **174**	> 90 %	20 hours	91:9	87 %	> 90 %	7 hours	92:8	85 %
 **177**					> 90 %	12 hours	94:6	87 %
 **206**	> 90 %	5 days	89:11	91 %	> 90 %	9 hours	91:9	97 %
 **207**	> 90 %	6 days	90:10	85 %	> 90 %	4 hours	92:8	92 %

a: syn: anti; b: of syn diastereomer.

Table 25: Comparison of amine linked bifunctional organocatalysts



Scheme 30.

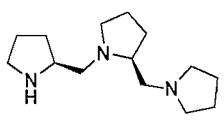
	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.**[a]	**e.e. (%)**[b]	**HPLC Yield (%)**	**Time**	**d.r.**[a]	**e.e. (%)**[b]
None	0 %	30 days	-	-	0 %	30 days	-	-
 **215**	23 %	30 days	91:9	94 %	10 %	30 days	91:9	93 %
 **228**	> 90 %	24 hours	94:6	86 %	> 90 %	7 hours	94:6	78 %
 **229**	> 90 %	24 hours	94:6	86 %	> 90 %	4 hours	94:6	80 %
 **231** 15 mol % Et_3N	> 90 %	4 days	92:8	71 %				

a: syn: anti; b: of syn diastereomer.

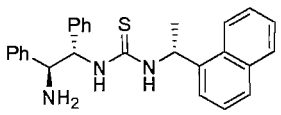
Table 26: Comparison of ether linked bifunctional organocatalysts.

The addition of acetic acid and water to the Michael reaction catalysed by bifunctional organocatalysts significantly increased the rate of reaction, with little effect on the selectivity, indicating that acid and water is significant in the formation of enamine species and catalyst regeneration[39, 145, 147, 148, 228, 229]. Comparison of the hydrogen

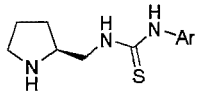
bond donor functionality indicates that thiourea and thiouronium demonstrate greater catalytic activity than analogous guanidinium bifunctional organocatalysts. Evaluation of ether linked and amine linked bifunctional organocatalysts indicates that the type of linkage makes little difference on the catalytic activity of the bifunctional organocatalysts, with the amine linked bifunctional organocatalysts demonstrating slightly enhanced selectivity. Bis thiourea bifunctional organocatalyst **207** and ether linked thiouronium bifunctional organocatalyst **229** demonstrated excellent catalytic activity, in the presence of acetic acid and water, completing the reaction in 4 hours with good selectivity.



69



76



232: Ar = Ph
233: Ar = 4-MeC_6H_4
234: Ar =3, 5-$(CF_3)_2C_6H_3$

Figure 24: Literature organocatalysts[12, 146, 147, 151, 211, 277].

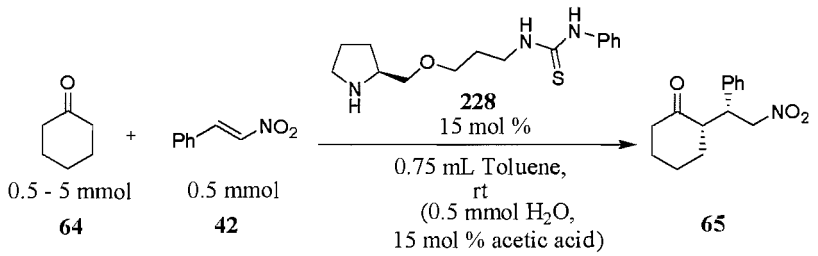
Catalyst	mol %	Time	Solvent	Additive (mol %)	eq. ketone	Temp	Yield (%)	d.r.[a]	e.e. (%)[b]
69[277]	20	5 hours	DMSO	TFA (20 %)	10	rt	95	92:8	89
76[147]	15	72 hours	Toluene	Acetic acid (15 %) H_2O (2 eq.)	10	rt	82	80:20	96
232[151]	20	2 days	Toluene	-	10	rt	53	99:1	99
233[12, 211]	10	11 hours	Hexane	PhCOOH (10 %)	10	rt	93	96:4	92
234[146]	20	12 hours	neat	Butyric acid (10 %)	20	rt	100	94:6	87

a: syn: anti; b: of syn diastereomer.

Table 27: Comparison of literature thiourea bifunctional organocatalysts for the Michael addition of cyclohexanone to trans - β - nitrostyrene[12, 146, 147, 151, 211, 277].

Figure 24 illustrates recent organocatalysts reported in the literature for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) (**Table 27**) [12, 146, 147, 151, 211, 277]. Although catalysts **76** and **232** exhibit slightly greater selectivity, only triamine organocatalyst **69** (**Figure 24** and **Table 27**) displays similar reaction times as those demonstrated by bis thiourea **207** and thiouronium **229** bifunctional organocatalyst. Tsogoeva *et al.*[147] stated that for good catalytic activity and enantioselectivity the two catalytic functionalities need to be directly adjacent to a stereogenic centre, however, the hydrogen bond donor group and the stereo centre in bis thiourea organocatalyst **207** and thiouronium **229** bifunctional organocatalysts are separated by five atoms and both exhibit good catalytic activity and enantioselectivity.

6.2.2 Catalyst capabilities; catalyst loading and equivalents of ketone.



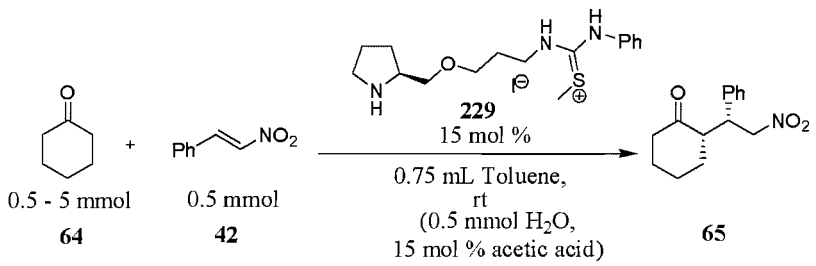
Scheme 57.

TOLUENE					TOLUENE / H_2O / H^+				
eq. of 64	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]	eq. of 64	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)[b]
10	> 90 %	24 hours	94:6	81 %	10	> 90 %	11 hours	94:6	87 %
5	> 90 %	34 hours	94:6	87 %	5	> 90 %	24 hours	94:6	86 %
1	> 90 %	28 days	94:6	76 %	1	> 90 %	14 days	94:6	81 %

a: syn: anti; b: of syn diastereomer.

Table 28: Investigating cyclohexanone equivalents with organocatalyst **228**.

A common drawback of organocatalytic Michael addition reactions is that a large excess of the nucleophile is required[2, 37-49] for efficient reaction times. Investigations were carried out on the effect of reducing the number of equivalents of cyclohexanone (**64**) used in the Michael addition reaction with bifunctional organocatalysts **228** and **229**. With the addition of acetic acid and water, thiourea bifunctional organocatalyst **228** (15 mol %, **Scheme 57** and **Table 28**) efficiently catalyses the reaction in 1 day with 5 equivalents of cyclohexanone (**64**), however, the use of 1 equivalent of the ketone significantly reduces the reaction time to 14 days. The results indicate (**Table 28**) that reducing the amount of cyclohexanone (**64**) used in the reaction has a slightly detrimental effect on the enantioselectivity.



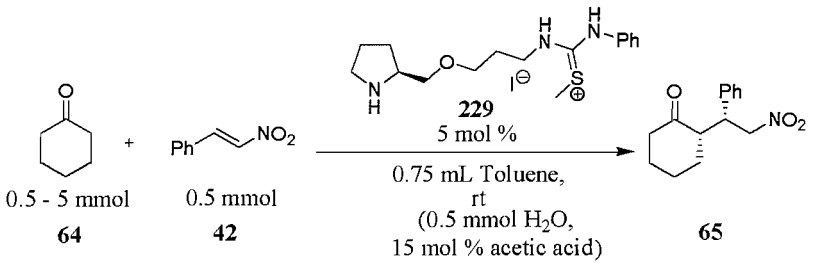
Scheme 58.

TOLUENE					TOLUENE / H_2O / H^+				
eq. of 64	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**eq. of 64**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
10	> 90 %	24 hours	94:6	88 %	10	> 90 %	5 hours	94:6	90 %
5	> 90 %	2 days	91:9	84 %	5	> 90 %	8 hours	92:8	90 %
1	> 90 %	3 days	91:9	86 %	1	> 90 %	30 hours	91:9	85 %

a: syn: anti; b: of syn diastereomer.

Table 29: Investigating cyclohexanone equivalents with organocatalyst **229**.

Pleasingly 15 mol % of bifunctional thiouronium organocatalyst **229** effectively catalyses the Michael addition reaction with only 1 equivalent of cyclohexanone (**64**) in 30 hours in the presence of acid and water, and within 3 days without the use of additives (**Scheme 58**, **Table 29**). Analogous to the results demonstrated by thiourea catalyst **228**, decreasing the equivalents of cyclohexanone (**64**) employed only has a marginal effect on the enantioselectivity observed with thiouronium catalyst **229**.



Scheme 59.

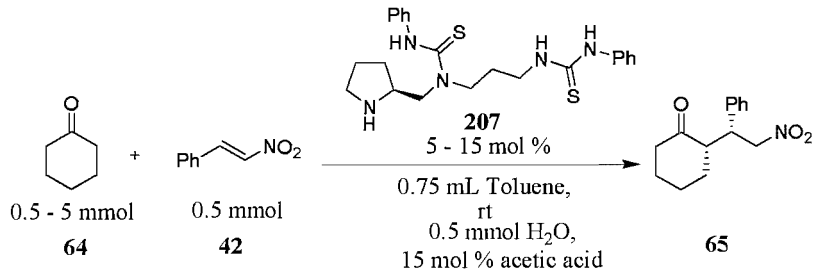
TOLUENE					TOLUENE / H_2O / H^+				
eq. of 64	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**eq. of 64**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
10	59 %	30 days	91:9	82 %	10	> 90 %	24 hours	92:8	85 %
5	43 %	30 days	90:10	81 %	5	> 90 %	48 hours	92:8	86 %
1	34 %	30 days	90:10	82 %	1	> 90 %	5 days	92:8	84 %

a: syn: anti; b: of syn diastereomer.

Table 30: Investigating cyclohexanone equivalents and catalyst loading with organocatalyst **229**.

Another widespread problem encountered with organocatalysis is the high catalyst loading required for efficient turnover[2, 37-49]. Studies were conducted to determine the effect of reducing the amount of catalyst and the amount of cyclohexanone (**64**)

utilised for the Michael addition catalysed by bifunctional organocatalysts **207** and **229**. Poor catalytic activity was observed with 5 mol % of thiouronium catalyst **229** (**Scheme 59** and **Table 30**) in toluene, however, excellent results were obtained with the addition of acetic acid and water, resulting in completion of the reaction within 5 days with the use of only 1 equivalent of the ketone. Reducing the catalyst loading to 5 mol % from 15 mol % resulted in a small decrease in the enantioselectivity given.



Scheme 60.

TOLUENE / H_2O / H^+					
eq. of 64	**mol %**	**HPLC Yield (%)**	**Time**	**d.r.**[a]	**e.e. (%)**[b]
10	15	> 90 %	4 hours	92:8	92 %
1	15	>90 %	21 days	92:8	84 %
1	5	28 %	30 days	91:9	80 %

a: syn: anti; b: of syn diastereomer.

Table 31: Investigating cyclohexanone equivalents and catalyst loading with organocatalyst **207**.

Although bis thiourea bifunctional organocatalyst **207** demonstrated the same catalytic activity time as thiouronium **229** under the normal reaction conditions (utilising 15 mol % of catalyst, 10 equivalents of cyclohexanone (**64**), acetic acid and water), unfortunately the results were not mirrored when 1 equivalent of

cyclohexanone (**64**) was used or when the catalyst loading was reduced to 5 mol % with poor reaction rates observed. Analogous with the data obtained with thiourea **228** and thiouronium **229**, the reduction in ketone and catalyst amounts resulted in a small loss in enantioselectivity. Although a few research groups have successfully lowered number of equivalents of ketone (1.5 – 5 equivalents) used, a high catalyst loading is still required for efficient turnover[15, 143, 171, 175, 187, 191, 192, 198, 225]. A recent search of the literature could not find another organocatalyst that was capable of efficiently catalysing the Michael addition of ketones to trans - β - nitrostyrene (**42**) employing only 5 mol % of the catalyst combined with equimolar amounts of ketone. The small loss in enantioselectivity observed when lowering the equivalents of ketone or the catalyst loading agrees with results published by Ley *et al.*[171, 192, 198] and Pericàs *et al.*[193].

6.2.3 Stereochemistry.

The high syn diastereoselectivity observed with all catalysts is in agreement with Seebach's synclinal transition state model for the conjugate addition of enamines to nitroolefins[278]. Seebach *et al.* proposed that the syn selectivity was due to favourable electrostatic interactions between the nitrogen of the enamine and the nitro group giving the transition states **235** and **236 (Figure 25)**.

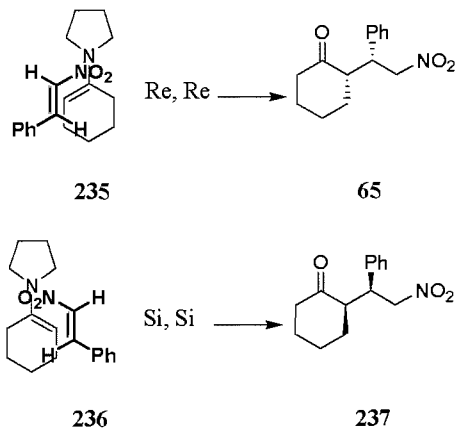
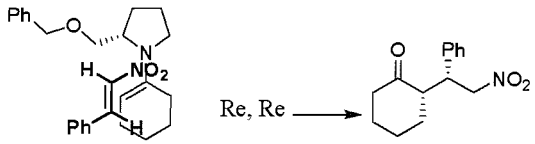


Figure 25: Seebach's synclinal transition state model[278].

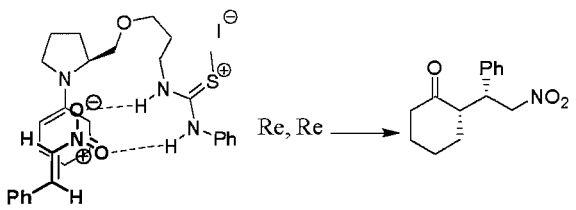
The major enantiomer observed with all the monofunctional and bifunctional organocatalysts is the *2S,1R* enantiomer (**65**), the observed absolute configuration can be explained using the synclinal transition state model[278]. For monofunctional organocatalysts, with no hydrogen bond capability, the stereochemistry is explained by the proposed transition state (**238**, **Figure 26**), the substituent on the 2 position of the pyrrolidine ring shields the *Si* face of the enamine double bond promoting *Re* face attack by the nitrostyrene[186, 188, 189, 200, 277].



238 **65**

Figure 26: Proposed transition state for asymmetric Michael addition with monofunctional organocatalysts.

With bifunctional organocatalysts the hydrogen bond donor group activates and directs the nitrostyrene, through hydrogen bonding, to the *Re* face of the enamine (**239**, **Figure 27**) resulting in the observed high selectivity for the *2S,1R* enantiomer (**65**)[145-148, 169, 187, 211, 279].



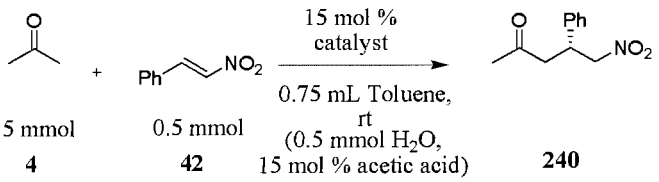
239 **65**

Figure 27: Proposed transition state for asymmetric Michael addition with bifunctional organocatalysts.

6.3 Organocatalyst scope; acyclic ketones.

Following the success obtained with a variety of bifunctional organocatalysts employed for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**), investigations were carried out to broaden the substrate scope of the reaction with acyclic ketones acetone (**4**) and butanone (**241**). The same reaction conditions tested for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) were employed with acetone (**4**) and butanone (**241**), again investigating the effect of the addition of acetic acid and water. Extensive research was carried out with a numerous monofunctional and bifunctional organocatalysts, the results from the more active catalysts are tabulated (**Table 32** and **Table 33**) the remaining results are detailed in **Appendix 1**.

6.3.1 Acetone.



5 mmol **4** + 0.5 mmol **42** → **240**

Scheme 61

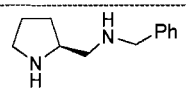
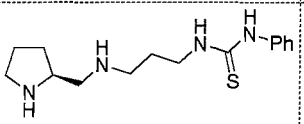
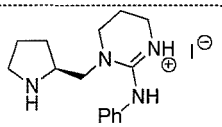
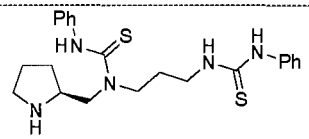
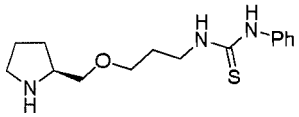
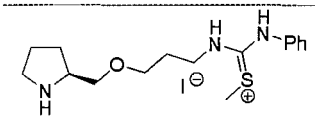
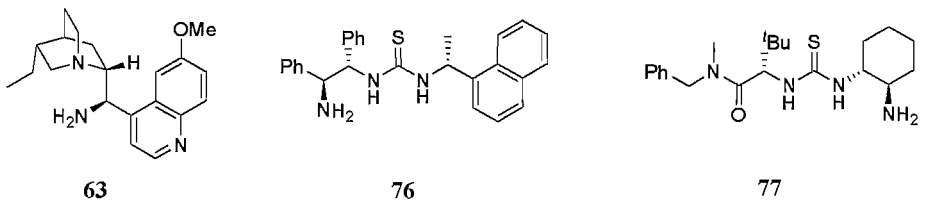
	TOLUENE			TOLUENE / H^+ / H_2O		
Catalyst	**HPLC Yield (%)**	**Time**	**e.e. (%)**	**HPLC Yield (%)**	**Time**	**e.e. (%)**
None	0 %	30 days	-	0 %	30 days	-
 **160**	39 %	30 days	10 %	> 90 %	4 days	19 %
 **174**	> 90 %	21 days	5 %	> 90 %	3 days	5 %
 **177**				> 90 %	7 days	30 %
 **207**				> 90 %	10 days	22 %
 **228**	> 90 %	34 hours	5 %	> 90 %	24 hours	9 %
 **229**	> 90 %	9 days	17 %	> 90 %	24 hours	18 %

Table 32: Comparison of organocatalysts on the Michael addition of acetone to trans - β - nitrostyrene.

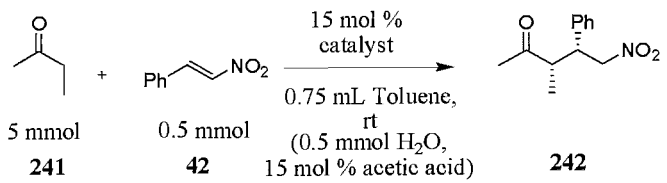
Despite the promising results given with the Michael addition reaction between cyclohexanone (**64**) and trans - β - nitrostyrene (**42**), switching the ketone to acetone (**4**) gave rise to extended reaction times and a dramatic loss in enantioselectivity. Ether linked bifunctional organocatalysts exhibit the shortest reaction times with the addition of acetic acid and water but with poor selectivity. The additives acetic acid and water resulted in shorter reaction times and a small increase in enantioselectivity[39, 145, 147, 148, 228, 229]. Although the results obtained with acetone (**4**) are disappointing they are comparable with many literature organocatalysts that report poor enantioselectivity with acyclic ketones [12, 13, 15, 141, 166, 169, 171, 172, 182-184, 189, 191, 192, 194, 198-200, 279]. A few organocatalysts are capable of enantioselectively catalysing the Michael addition of acyclic ketones to trans - β - nitrostyrene (**42**) including *Cinchona* alkaloid derived **63**[176] and bifunctional organocatalysts **76**[144, 145, 147, 148] and **77**[143] (**Figure 28**).



63 **76** **77**

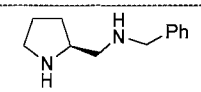
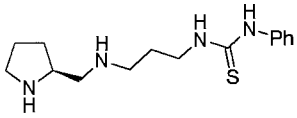
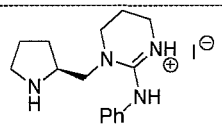
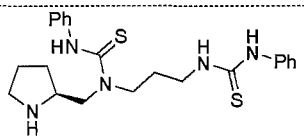
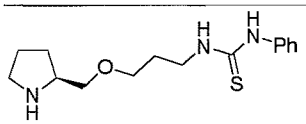
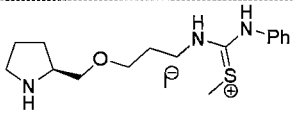
Figure 28: Selective organocatalysts for Michael addition reactions with cyclic and acyclic ketones.

6.3.2 Butanone.



5 mmol **241** 0.5 mmol **42** **242**

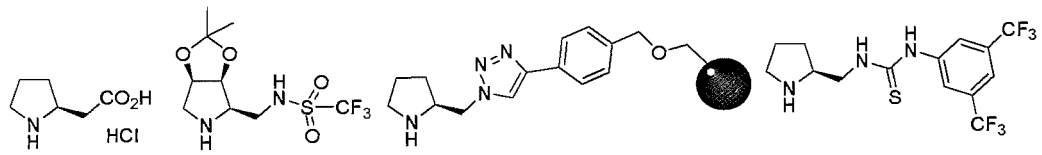
Scheme 62.

	TOLUENE					TOLUENE / H^+ / H_2O				
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)**		**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)**	
				s[b]	**a[c]**				**s[b]**	**a[c]**
None	0 %	30 days	-	-	-	1 %	30 days	-	-	-
 **160**	13 %	30 days	50:50	77 %	41 %	> 90 %	8 days	67:33	77 %	44 %
 **174**	16 %	30 days	75:25	70 %	16 %	66 %	30 days	67:33	55 %	40 %
 **177**						22 %	30 days	50:50	39 %	47 %
 **207**						70 %	30 days	50:50	42 %	51 %
 **228**	> 90 %	5 days	50:50	58 %	35 %	> 90 %	48 hours	50:50	8 %	85 %
 **229**	> 90 %	12 days	50:50	55 %	56 %	> 90 %	5 days	50:50	39 %	19 %

a: syn: anti; b: syn diastereomer; c: anti diastereomer

Table 33: Comparison of bifunctional organocatalysts on the Michael addition of butanone to trans - β - nitrostyrene.

Analogous to the results obtained with acetone (**4**), the organocatalysed Michael addition of butanone (**241**) to trans - β - nitrostyrene (**42**) exhibited generally poor reaction times and selectivity. The ether linked bifunctional organocatalysts **228** and **229** again demonstrated the greatest catalytic ability and although both exhibited poor diastereoselectivity, thiourea **228** yielded the anti diastereomer in good enantiomeric excess. Conversely diamine organocatalysts **160** and **174** gave the syn diastereomer in good enantiomeric excess and the anti diastereomer with poor selectivity. The addition of acetic acid and water successfully increased the rate of reaction for all tested organocatalysts but the effect on the selectivity is inconsistent. Many research groups that have reported positive results from the Michael addition reaction with cyclic ketones have also reported poor selectivity with acyclic ketones[13, 15, 141, 166, 169, 171, 172, 182-184, 189, 191, 192, 194, 198-200, 279]. **Figure 28** illustrates a few primary amine based organocatalysts[143-145, 147, 148, 176] that selectively catalyse Michael addition reactions with cyclic and acyclic ketones; analogous to the results tabulated in **Table 33** some research groups have reported improved selectivity utilising butanone (**241**) compared with acetone (**4**) (**Figure 29**)[146, 185, 190, 193].



66 **71** **75** **234**

Figure 29: Selective organocatalysts for Michael addition reactions with butanone.

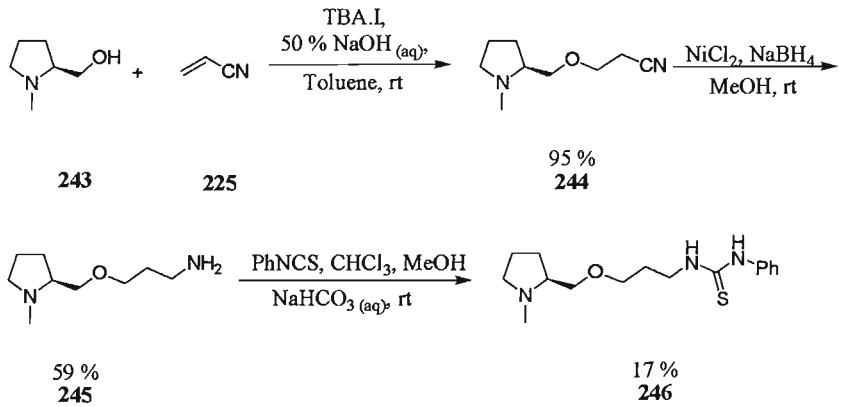
6.4 Michael addition of diethyl malonate to trans - β - nitrostyrene.

Many organocatalysts have successfully mediated the Michael addition of 1, 3 - dicarbonyl compounds to nitroolefins (**Section 1.2.4**) providing synthetically versatile nitroalkanes important in the synthesis of pharmaceutical and agrochemical compounds[122, 124, 201]. Investigations were carried out to determine if the organocatalysts synthesised for the Michael addition of ketones to trans - β -

nitrostyrene (**42**) could be further employed for the selective addition of malonates. Extensive research was carried out with numerous organocatalysts, the more relevant results are tabulated below (**Table 34** and **Table 35**) and the remaining results are detailed in **Appendix 1**. The organocatalytic reactions are carried out according to literature procedure by Dixon *et al.*[124].

6.4.1 Bifunctional organocatalyst synthesis.

Bifunctional thiourea catalyst **246** was synthesised to investigate the effect of incorporating a tertiary amine group compared with the secondary amine group in analogous catalyst **228**. The synthesis of bifunctional organocatalyst was straightforward (**Scheme 63**), utilising the chemistry optimised for the synthesis of catalyst **228** (**Section 5.2.2**).



Scheme 63.

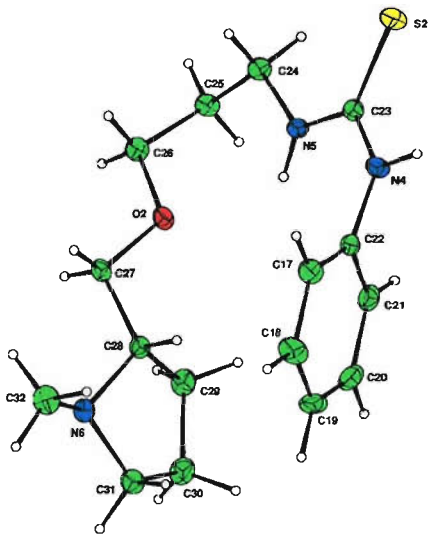
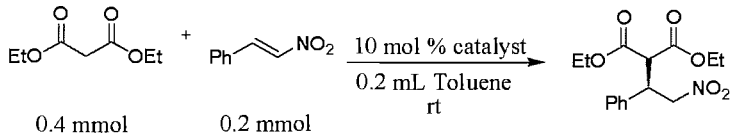


Figure 30: Crystal structure of bifunctional organocatalyst **246**.

6.4.2 Catalyst comparison.



0.4 mmol **41** 0.2 mmol **42** **44**

Scheme 64.

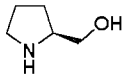
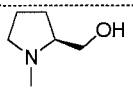
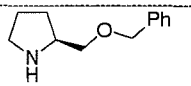
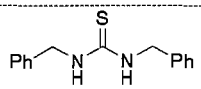
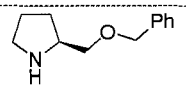
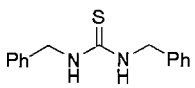
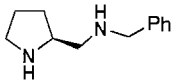
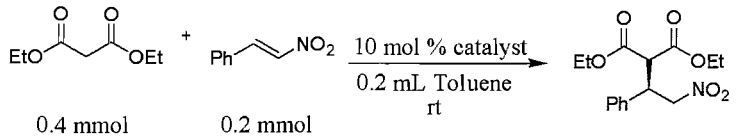
Catalyst	HPLC Yield (%)	Time	e.e. (%)
None	0 %	30 days	-
 **80**	> 90 %	24 hours	9 %
 **243**	> 90 %	24 hours	4 %
 **215**	0 %	30 days	-
 **102**	0 %	30 days	-
 **215** and  **102**	2 %	30 days	-
 **160**	41 %	30 days	6 %

Table 34: Comparison of monofunctional organocatalysts on the Michael addition of diethyl malonate to trans - β - nitrostyrene.



Scheme 64.

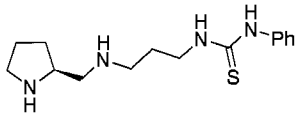
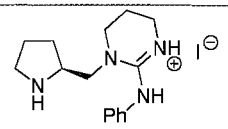
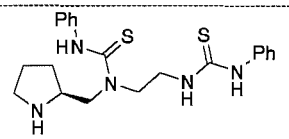
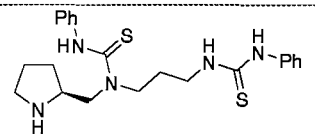
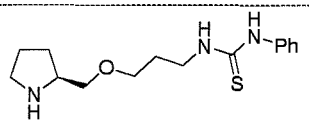
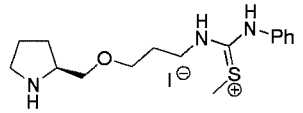
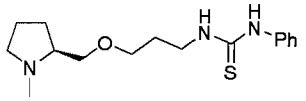
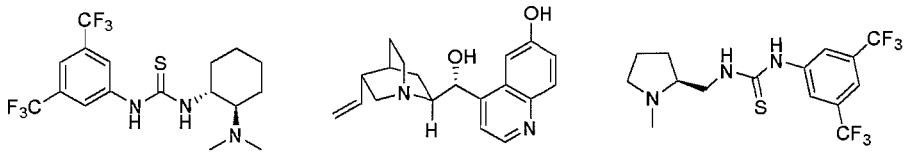
Catalyst	HPLC Yield (%)	Time	e.e. (%)
 **174**	> 90 %	29 hours	60 %
 **177**	> 90 %	24 hours	66 %
 **206**	> 90 %	34 hours	15 %
 **207**	> 90 %	5 days	20 %
 **228**	> 90 %	18 hours	77 %
 **229**	> 90 %	3 days	59 %
 **246**	> 90 %	24 hours	25 %

Table 35: Comparison of bifunctional organocatalysts on the Michael addition of diethyl malonate to trans - β - nitrostyrene.

In accordance with results published by Lattanzi *et al.*[138], monofunctional amine catalysts (**Table 34**) generally exhibited poor catalytic activity and selectivity, with organocatalysts incorporating a hydroxyl group (**80** and **243**) demonstrating the most activity. Co - catalyst dibenzyl thiourea **102** failed to catalyse the reaction, as did the combination of amine **215** and co - catalyst **102**, demonstrating that the two separate types of organocatalysts combined does not give enhanced catalysis.

Bifunctional organocatalysts (**Table 35**) demonstrated much shorter reaction times and generally higher selectivity. Bis thiourea organocatalysts **206** and **207** illustrated poor selectivity, whereas guanidinium **177** and thioureas **174** and **228** yielded the product in moderate to good enantioselectivity. There is no obvious trend in the results to determine which linker functionality or hydrogen bond donor group gives an optimal catalyst. Thiouronium bifunctional organocatalyst **229** demonstrates longer reaction times and poor selectivity compared with analogous thiourea catalyst **228**; similarly the use of N - methyl analogue **246** led to a dramatic decrease in enantioselectivity, although not in rate, indicating that the secondary amine in the pyrrolidine ring may be important for chiral control. Chen *et al.*[133] also reported low selectivity when using similar bifunctional tertiary amine organocatalyst **247** (**Figure 31**) for the Michael addition of α - cyanoacetate to chalcones.



43 **86** **247**

Figure 31: Bifunctional organocatalyst for the Michael addition to nitroolefins.

Bifunctional thiourea organocatalyst **228** gives similar results to the results reported by Deng *et al.*[128] using *Cinchona* derived organocatalyst **86** (**Figure 31**) at room temperature. Despite the good reaction time given with bifunctional thiourea organocatalyst **228**, the modest enantioselectivity cannot compete with the excellent results obtained by Takemoto's[111, 113] original bifunctional organocatalyst **43** (**Figure 31** and **Scheme 8**, **Section 1.1.4**) and the following work by Dixon *et al.*[124], Connon *et al.*[129], and Yaguchi *et al.*[202].

6.5 Conclusions.

Several bifunctional organocatalysts were successfully synthesised and used to catalyse the Michael addition of cyclohexanone (**64**), acetone (**4**), butanone (**241**) and diethyl malonate (**41**) to trans - β - nitrostyrene (**42**) with varied results. The addition of acetic acid and water to the Michael addition of ketones to trans - β - nitrostyrene (**42**) catalysed by monofunctional and bifunctional organocatalysts significantly improved the rate of reaction, with little effect to the selectivity, indicating that acid and water is significant in the formation of enamine species and catalyst release[39, 145, 147, 148, 228, 229].

A number of the bifunctional organocatalysts tested exhibited good to excellent results in terms of reaction rates and selectivity for the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**), some of which rival organocatalysts published in the literature for the same reaction. Pleasingly bifunctional thiouronium organocatalyst **229** efficiently and selectively catalyses the Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**) with only one equivalent of the cyclohexanone (**64**) and 5 mol % of the catalyst.

Attempts were made to expand the substrate scope for the synthesised bifunctional organocatalysts, investigating acyclic ketones. Unfortunately, despite the positive results obtained with cyclohexanone (**64**), poor catalytic activity and enantioselectivity were observed for the Michael addition of acetone (**4**) to trans - β - nitrostyrene (**42**) with all monofunctional and bifunctional organocatalysts investigated, our results are mirrored in many literature papers[13, 15, 141, 166, 169, 171, 172, 182-184, 189, 191, 192, 194, 198-200, 279]. Similarly poor reaction rates, diastereoselectivity and enantioselectivity were observed when the Michael addition of butanone (**241**) to trans - β - nitrostyrene (**42**) was investigated. Bifunctional thiourea organocatalyst **228** yielded the anti diastereomer in good enantiomeric excess; conversely diamine organocatalysts **160** and **174** gave the syn diastereomer in good enantiomeric excess and the anti diastereomer with poor selectivity.

Investigations were also carried out into the Michael addition of malonate esters to trans - β - nitrostyrene (**42**) with a variety of monofunctional and bifunctional organocatalysts. In agreement with literature results, monofunctional organocatalysts exhibit poor catalytic activity and enantioselectivity[138]; bifunctional organocatalysts demonstrate much shorter reaction times and improved selectivity. Bifunctional, ether linked, thiourea organocatalyst **228** gave the shortest reaction time of 18 hours and the highest enantioselectivity at 77 %, unfortunately this modest selectivity is not as good as results already reported in the literature[111, 113, 118, 128, 129, 202].

Unfortunately due to synthesis problems, a wide range of bifunctional organocatalysts incorporating a different number of carbon chain spacer lengths between the two catalytic functionalities were not tested and so no conclusions can be drawn to determine what length of spacer yields a more optimal catalyst. Similarly, due to the varied results obtained with different linker functionalities and hydrogen bond donor groups (thiourea, thiouronium and guanidinium) it is not possible to distinguish which combination gives the best catalytic effects.

At the time of our proposal, the idea of a bifunctional organocatalyst to catalyse a reaction through the activation of both the electrophile and nucleophile synergistically was a novel concept. Our extensive and detailed research into Michael addition reactions catalysed by monofunctional organocatalysts, co - catalysts and bifunctional organocatalysts validates our original proposal by concluding that tethering the two catalytic functionalities (chiral amine and hydrogen bond donor) does indeed give an optimal catalyst. The synthesis and testing of numerous monofunctional and bifunctional organocatalysts for the Michael addition reaction allows for some conclusions to be drawn about our organocatalysts structural features, for example in terms of linker groups and reducing the possibility of catalyst intramolecular hydrogen bonding. Bifunctional organocatalysts **207** and **229** give excellent results for the organocatalysed Michael addition of cyclohexanone (**64**) to trans - β - nitrostyrene (**42**), results which are as good as or better than current results published in the literature for the same reaction. It is envisioned our more active and selective organocatalysts could give excellent results if used for other types of organocatalytic reactions.

Experimental.

General experimental.

Reactions requiring anhydrous conditions were conducted in oven - dried or flame - dried glassware. All anhydrous solvents were prepared by refluxing with an appropriate drying agent and purified by distillation. THF was refluxed from sodium and benzophenone under argon until a persistent purple colour was maintained. DCM and triethylamine were refluxed from CaH_2. The distilled solvents were taken using the usual syringe techniques. Solvents were of commercial grade and were used without further purification unless otherwise stated. All chemicals were attained from commercial suppliers without further purification unless otherwise stated.

Thin layer chromatography was performed on aluminium backed sheets coated with silica gel (0.25 mm) containing the fluorescent indicator UV_{254}. The plates were visualised under UV lamp at 254 nm and / or using $KMnO_4$ or ninhydrin stains. Flash chromatography was performed on Sorbil C_{60}, 35 - 70 mesh silica, following a procedure by Still *et al.*[280]. The eluent solvent ratios are reported by volume prior to mixing.

Instrumentation.

Infrared spectra were obtained on a Thermo Nicolet 380 FT - IR spectrometer. Absorptions are given in wavenumbers (cm^{-1}). The relative intensity of the peaks are reported within the brackets using the following abbreviations; strong (s), medium (m) and weak (w). All samples were run either as neat solids or as oils. Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected.

^{1}H NMR spectra were recorded at 300 MHz on a Bruker AC 300 spectrometer or 400 MHz on a Bruker DPX 400 spectrometer using the deuterated solvent as the lock and the residual protons as internal standard. Peak positions are quoted against the δ scale relative to the residual solvent signal[281], using the following abbreviations; singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), quintuplet (qn), sextet (sext) and multiplet (m). ^{13}C NMR (proton decoupled) spectra were obtained at 75.5 MHz on a Bruker AC 300 or at 100 MHz on a Bruker DPX 400 spectrometer using the solvent as lock and internal standard. Coupling constants, *J*, are measured in Hertz (Hz).

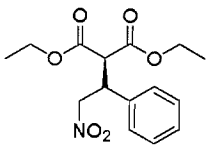
Low resolution ES^{+} and ES^{-} mass spectra were obtained on a Micromass platform with a quadrupole mass analyser. High resolution ES^{+} mass spectra were obtained on a Bruker Apex III FT - ICR mass spectrometer, or on a Micromass Q - Tof 1 mass spectrometer. M/z signals are reported in atomic mass units followed in brackets by the ion found and peak intensity. Microanalysis were performed by MEDAC Ltd., Surrey.

X - Ray diffraction data was obtained on an Enraf Nonius KappaCCD diffractometer, and the structures were determined by direct methods using the program SHELXS97 and refined using SHELXL97.

All HPLC chromatograms were recorded on a LaChrom D - 7000 instrument, using a Phenomenex 150 mm x 4.6 mm reverse phase column (flow rate of 1 mL / minute, 20 minutes). All reverse phase HPLC chromatograms were recorded at 220 nm.

Enantioselectivities were determined using a LaChrom D - 7000 instrument, with a Chiralpak AI chiral HPLC column (250 mm x 4.6 mm, flow rate of 0.5 mL / minute). Chiral HPLC chromatograms were recorded at 215 nm.

2-((*R*)-2-Nitro-1-phenyl-ethyl)-malonic acid diethyl ester (44).



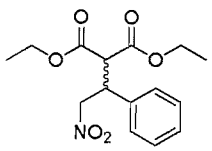
Prepared according to the procedure given by Dixon *et al.*[161]

Diethyl malonate (**41**, 304 μL, 2.00 mmol) was dissolved in THF (1.5 mL) and treated with trans - β - nitrostyrene (**42**, 149 mg, 1.00 mmol) and pyrrolidine (**38**, 12.5 μL, 0.150 mmol). The reaction mixture was stirred at room temperature for 2 weeks. Hydrochloric acid (2M, 3 mL) was added to the reaction mixture and stirred for 30 minutes at room temperature. The phases were separated and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % ethyl acetate / petroleum ether) to give ester **44** as an off white crystalline solid (194 mg, 0.628 mmol, 63 %). 62 – 64 ° C (ethyl acetate) (Literature Mp.: 64.0 - 64.5 ° C)[282]; MS (ES^+): m/z (%) 332 (100) $[M+Na]^+$; IR (film): ν_{max} = 1728 (s), 1555 (s), 1255 (m), 1177 (m), 1027 (m), 909 (s), 728 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 - 7.23 (m, 5H, 5C**H**), 4.93 (dd, *J* = 13.1, 5.1 Hz, 1H, CHCH**H**'NO_2), 4.87 (dd, *J* = 13.1, 8.9 Hz, 1H, CHC**H**H'NO_2), 4.27 - 4.19 (m, 3H, $CH_3C\mathbf{H}_2O$ and CHC**H**(Ph)CH_2), 4.00 (q, *J* = 7.14 Hz, 2H, $CH_3C\mathbf{H}_2O$), 3.82 (d, *J* = 9.2 Hz, 1H, $(C(O))_2C\mathbf{H}CH(Ph)$), 1.27 (t, *J* = 7.14 Hz, 3H, $CH_2C\mathbf{H}_3$), 1.07 (t, *J* = 7.14 Hz, 3H, $CH_2C\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6 (**C**), 166.9 (**C**), 136.4 (**C**), 129.0 (2**C**H), 128.4 (2**C**H), 128.2 (**C**H), 77.8 ($\mathbf{C}H_2$), 62.2 ($\mathbf{C}H_2$), 62.0 ($\mathbf{C}H_2$), 55.1 (**C**H), 43.1 (**C**H), 14.1 ($\mathbf{C}H_3$), 13.8 ($\mathbf{C}H_3$) ppm.
Spectroscopic data agrees with literature[283].

Highest enantioselectivity (77 %) of **44** observed with organocatalyst **228** determined by chiral HPLC. (2-((*R*)-2-Nitro-1-phenyl-ethyl)-malonic acid diethyl ester configuration determined by comparison of optical rotation values with literature

references; $[\alpha]_D$ = - 4.7 ° (c = 1.0, $CHCl_3$, 24 ° C) (Literature $[\alpha]_D$ = - 6.0 ° (c = 1.0, $CHCl_3$, 30 ° C), e.e. = 93 %)[111].

2-(2-Nitro-1-phenyl-ethyl)-malonic acid diethyl ester (44) kinetic experiments.



According to the procedure given by Dixon *et al.*[161]

The majority of kinetic experiments were carried out at least twice to check for consistency. The organocatalyst under investigation (0.0200 mmol) was stirred in a solution of trans - β - nitrostyrene (**42**, 29.8 mg, 0.200 mmol) and diethyl malonate (**41**, 60.7 μL, 0.400 mmol) in toluene (0.2 mL) at room temperature. The solvent contained naphthalene as an internal standard (1 mg / mL). The progress of the reactions were monitored by reverse phase HPLC. To sample the reactions; 5 μL was taken from the reaction mixture and diluted with acetonitrile (HPLC grade, 1.5 mL). Upon completion the crude reaction mixture was not purified. Reverse phase HPLC retention time: 5.7 minutes (60 % acetonitrile / 40 % water). Chiralpak IA normal phase retention times: 47 minutes (enantiomer 1) and 54 minutes (enantiomer 2) (3 % isopropanol / 97 % hexane).

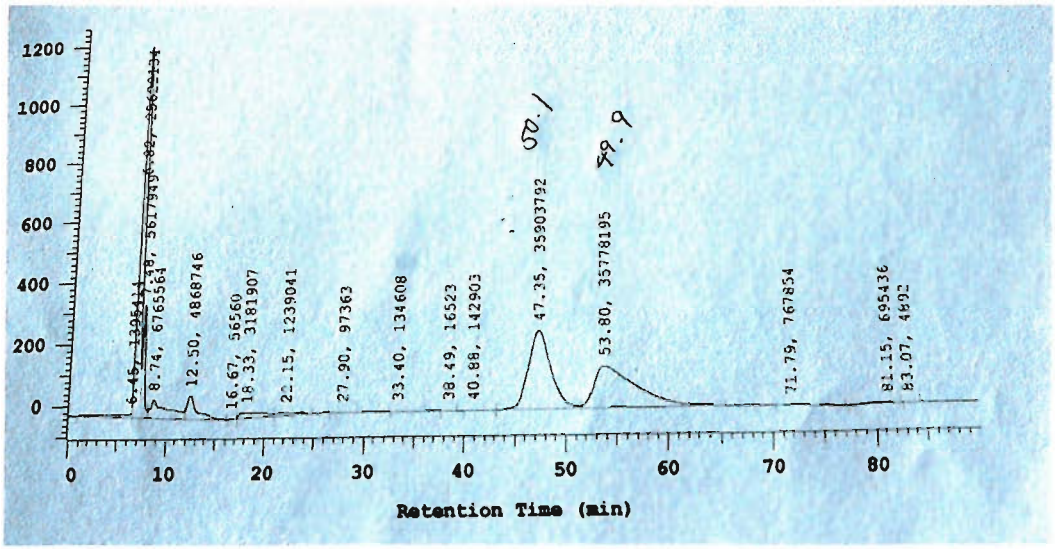
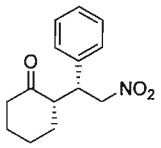


Figure 32: Chiral HPLC trace of **44** (Chiralpak IA, 3 % isopropanol / 97 % hexane).

(*S*)-2-((*R*)-2-Nitro-1-phenyl-ethyl))-cyclohexanone (65).



Prepared according to the procedure given by List *et al.*[182]

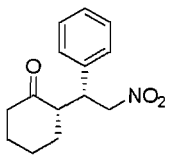
A suspension of L - proline (**1**, 17.0 mg, 0.150 mmol) was stirred in a solution of trans - β - nitrostyrene (**42**, 150 mg, 1.00 mmol) and cyclohexanone (**64**, 1.04 mL, 10.0 mmol) in DMSO (8 mL) at room temperature for 16 hours. The reaction mixture was then treated with ethyl acetate (10 mL) and saturated ammonium chloride aqueous solution (10 mL), the phases were separated and the aqueous phase extracted with ethyl acetate (3 x 30 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil. The crude product was purified by column chromatography (25 % ethyl acetate / 75 % hexane) to give ketone **65** as a white solid (156 mg, 0.645 mmol, 65 %). Mp.: 98 – 100 ° C (ethyl acetate / petroleum ether) (Literature Mp.: 106.1 – 106.4 ° C)[278]; Mixture of diastereoisomers, major

diastereoisomer syn reported; MS (ES^+): m/z (%) 270 (100) $[M+Na]^+$; IR (film): ν_{max} = 2955 (w), 2855 (w), 1697 (m), 1549 (s), 1384 (w), 696 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 - 7.24 (m, 3H, 3C**H**), 7.18(m, 2H, 2C**H**), 4.92 (dd, *J* = 12.4, 4.5 Hz, 1H, CH(Ph)CH**H**'NO_2), 4.64 (dd, *J* = 12.4, 9.8 Hz, 1H, CH(Ph)CH**H**'NO_2), 3.77 (dt, *J* = 9.8, 4.5 Hz, 1H, CHC**H**(Ph)CH_2), 2.68 (dt, *J* = 10.9, 4.9 Hz, 1H, C(O)C**H**CH_2), 2.46 (td, *J* = 12.8, 4.9 Hz, 1H, C(O)C**H**H'CH_2), 2.38 (dt, *J* = 12.0, 5.9 Hz, 1H, C(O)CH**H**'CH_2), 2.79 - 2.72 (m, 1H, C**H**H'CH_2), 1.81 - 1.52 (m, 4H, 2C$\mathbf{H_2}$), 1.24 (ddd, *J* = 25.1, 12.1, 3.5 Hz, 1H, CH_2CH**H**'CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0 (**C**), 137.9 (**C**), 129.1 (2C**H**), 128.3 (2C**H**), 127.9 (C**H**), 79.0 (C$\mathbf{H_2}$), 52.7 (C**H**), 44.1 (C**H**), 42.9 (C$\mathbf{H_2}$), 33.3 (C$\mathbf{H_2}$), 28.7 (C$\mathbf{H_2}$), 25.2 (C$\mathbf{H_2}$) ppm.

Spectroscopic data agrees with literature reference[278, 284].

Highest enantioselectivity (97 %) of **65** observed with organocatalyst **206** determined by chiral HPLC. (*S*)-2-((*R*)-2-Nitro-1-phenylethyl)cyclohexanone (**65**) configuration determined by comparison of optical rotation values and the HPLC elution order[147] with literature references; $[\alpha]_D$ = - 26.7 ° (c = 1.0, $CHCl_3$, 24 ° C) (Literature $[\alpha]_D$ = - 28.0 ° (c = 1.0, $CHCl_3$, 25 ° C))[278].

2-(2-Nitro-1-phenyl-ethyl)-cyclohexanone (65) general kinetic experiments.



According to the procedure given by List *et al.*[182]

The majority of kinetic experiments were carried out at least twice to check for consistency. The organocatalyst under investigation (0.150 mmol) was stirred in a solution of trans - β - nitrostyrene (**42**, 150 mg, 1.00 mmol) and cyclohexanone (**64**, 1.0 mL, 10.0 mmol) in solvent (1.5 mL) at room temperature. The solvent contained naphthalene as an internal standard (1.00 mg / mL). The progress of the reactions

were monitored by reverse phase HPLC. To sample the reactions; 10 μL was taken from the reaction mixture and diluted with acetonitrile (HPLC grade, 1.5 mL). Upon completion the crude reaction mixture was not purified. Reverse phase HPLC retention times: 4.9 (anti diastereomer: minor) and 5.5 minutes (syn diastereomer: major) (60 % acetonitrile / 40 % water). Chiralpak IA normal phase retention times: 33 minutes (syn enantiomer 1: minor), 37 minutes (anti enantiomer 1: minor), 53 minutes (anti enantiomer 2: major) and 55 minutes (syn enantiomer 2: major) (3 % isopropanol / 97 % hexane).

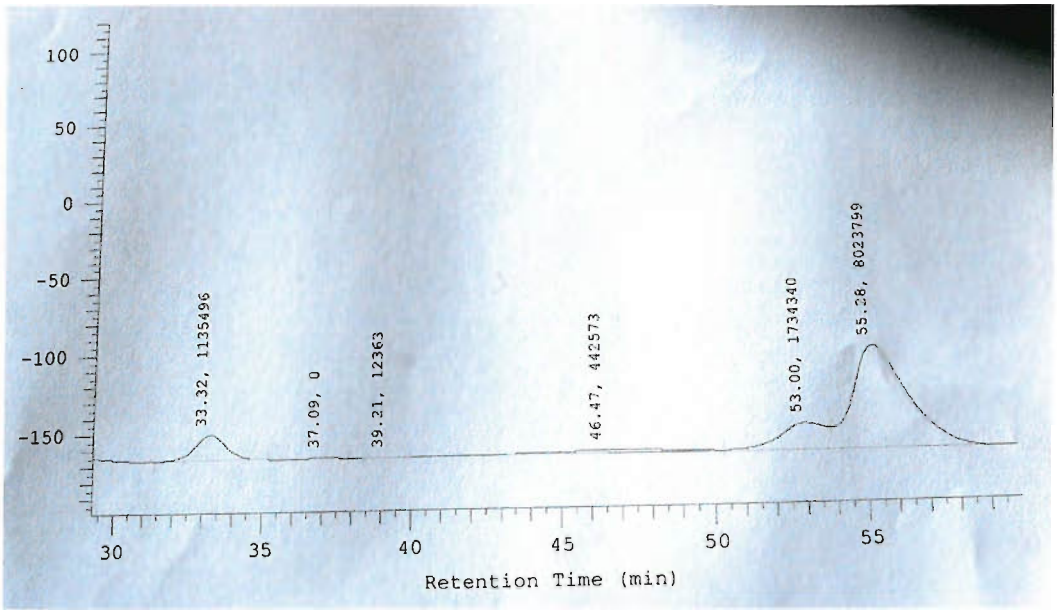
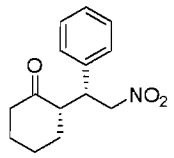


Figure 33: Chiral HPLC trace of **65** (Chiralpak IA, 3 % isopropanol / 97 % hexane).

2-(2-Nitro-1-phenyl-ethyl)-cyclohexanone (65) kinetic experiments investigating toluene and additives.

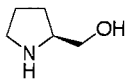


According to the procedure given by List *et al.*[182] and Tsogoeva *et al.*[147]

The majority of kinetic experiments were carried out at least twice to check for consistency. The organocatalyst under investigation (0.075 mmol) was stirred in a solution of trans - β - nitrostyrene (**42**, 74.6 mg, 0.500 mmol) and cyclohexanone (**64**, 520 μL, 5.00 mmol) in toluene (0.75 mL) at room temperature. The solvent contained naphthalene as an internal standard (1.00 mg / mL). The progress of the reactions were monitored by reverse phase HPLC. To sample the reactions; 10 μL was taken from the reaction mixture and diluted with acetonitrile (HPLC grade, 1.5 mL). Upon completion the crude reaction mixture was not purified. Reverse phase HPLC retention times: 4.9 (anti diastereomer: minor) and 5.5 minutes (syn diastereomer: major) (60 % acetonitrile / 40 % water). Chiralpak IA normal phase retention times: 33 minutes (syn enantiomer 1: minor), 37 minutes (anti enantiomer 1: minor), 53 minutes (anti enantiomer 2: major) and 55 minutes (syn enantiomer 2: major) (3 % isopropanol / 97 % hexane).

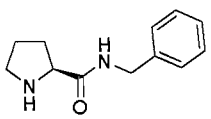
Kinetic reactions that investigated the effect of additives were carried out as above with the addition of acetic acid (2.20 μL, 0.0375 mmol) and water (9.00 μL, 0.500 mmol) from the onset.

(*S*)-1-Pyrrolidin-2-yl-methanol (80).



213 (250 mg, 1.24 mmol) was dissolved in a 10 % solution of TFA (1 mL) in DCM (9 mL) and stirred at room temperature for 3 hours. The solvent and residual TFA were removed under reduced pressure to give a yellow oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a colourless oil. The crude material was purified by column chromatography (10 % methanol / DCM) to give L - prolinol (**80**) as a colourless oil (88.5 mg, 0.875 mmol, 71 %). $[\alpha]_D = 37.8$ ° (c = 1.0, $CHCl_3$, 23 ° C, 589 nm) (Literature $[\alpha]_D = 41.0$ ° (c = 1.0, toluene))[285]; MS (ES^+): m/z (%) 143 (40) $[M+H+MeCN]^+$; IR (film): ν_{max} = 3287 (w), 2955 (m), 2869 (m), 1457 (w), 1047 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.49 (dd, *J* = 10.5, 3.8 Hz, 1H, CHCH**H**'O), 3.31 (dd, *J* = 10.5, 7.3 Hz, 1H, CHC**H**H'O), 3.22 (m, 1H, C**H**CH_2), 3.10 (bs, 2H, N**H** and O**H**), 2.86 (t, *J* = 6.8 Hz, 2H, CH_2CH_2NH), 1.83 - 1.55 (m, 3H, CH_2CH_2CHH'), 1.37 (m, 1H, CHC**H**H'CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.0 (**C**H_2), 60.0 (**C**H), 46.6 (**C**H_2), 27.8 (**C**H_2), 26.1 (**C**H_2) ppm.
Spectroscopic data agrees with literature reference[286].

(*S*)-Pyrrolidine-2-carboxylic acid benzylamide (100).



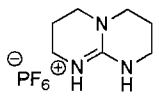
Prepared according to the procedure given by Bartoli *et al.*[207]

^{t}Boc - L - proline (**99**, 1.00 g, 4.65 mmol) was dissolved in a 1:1 mixture of DMF (20 mL) and THF (20 mL) and cooled to 0 ° C (over ice) before the addition of benzyl

amine (508 μL, 5.11 mmol), HOBt (942 mg, 7.00 mmol), EDC (980 mg, 5.11 mmol) and DIPEA (4.05 mL, 23.2 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed under reduced pressure to give a pale brown oil. The resulting oil was redissolved in DCM (50 mL) and washed with 1M $KHSO_4$ aqueous solution (3 x 50 mL), saturated $NaHCO_3$ aqueous solution (2 x 50 mL) and brine (50 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by crystallisation with ethyl acetate and hexane to give the amide as a white solid (1.18 g, 3.88 mmol, 83 %). ^{t}Boc - N protected amine (1.07 g, 3.52 mmol) was dissolved in a solution of 10 % TFA (5 mL) in DCM (45 mL) and stirred for 4 hours at room temperature after which the solvents and TFA were removed under reduced pressure to yield a pale yellow oil. The ammonium salt was then redissolved in DCM (30 mL) and the resulting solution was treated with saturated aqueous K_2CO_3 solution (2 mL) and solid K_2CO_3 (500 mg). The biphasic solution was stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (3 x 15 mL), the combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvents removed under reduced pressure to give amine **100** as a yellow oil (673 mg, 3.30 mmol, 94 %). $[\alpha]_D$ = - 30.3 ° (c = 1.0, $CHCl_3$, 29 ° C) (Literature $[\alpha]_D$ = - 29.0 ° (c = 0.6, methanol))[287]; MS (ES^+): m/z (%) 205 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{12}H_{17}N_2O$ requires m/z: 205.1336, found m/z: 205.1340; IR (film): ν_{max} = 3319 (w), 2969 (w), 2871 (w), 1657 (s), 1516 (s), 1454 (m), 731 (s), 697 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (bs, 1H, N**H**), 7.28 - 7.15 (m, 5H, 5C**H**), 4.34 (d, *J* = 5.9 Hz, 2H, PhC**H**$_2$NH), 3.73 (dd, *J* = 9.2, 5.4 Hz, 1H, CH_2C**H**NH), 2.92 (td, *J* = 10.2, 6.8 Hz, 1H, CH_2CH**H**'NH), 2.80 (td, *J* = 10.2, 6.3 Hz, 1H, CH_2C**H**H'NH), 2.43 (bs, 1H, N**H**), 2.10 (m, 1H,CH_2CH**H**'CH), 1.87 (m, 1H, CH_2C**H**H'CH), 1.69 - 1.59 (m, 2H, CH_2C**H**$_2$$CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0 (**C**), 138.8 (**C**), 128.7 (2**C**H), 127.7 (2**C**H), 127.4 (**C**H), 60.7 (**C**H), 47.3 (**C**H_2), 43.1 (**C**H_2), 30.9 (**C**H_2), 26.3 (**C**H_2) ppm.

Spectroscopic data agrees with literature reference[287].

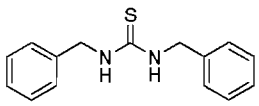
3,4,6,7,8,9-Hexahydro-2H-pyrimido-pyrimidin-1-ium hexafluoro phosphate (101).



Prepared according to the procedure given by Bartoli *et al.*[207]

1,3,4,6,7,8-Hexahydro-2H-pyrimido-pyrimidine (0.500 g, 3.59 mmol) was dissolved in chloroform (15 mL) and methanol (15 mL). To this solution ammonium hexafluorophosphate (0.585 g, 3.59 mmol) was added and the reaction mixture stirred at room temperature for 30 minutes. The solvents were removed under reduced pressure to give a white solid which was redissolved in DCM (20 mL) and then the organic phase was washed with water (5 mL). The aqueous phase was extracted with DCM (3 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give guanidinium **101** as a white 'fluffy' solid (0.988 g, 3.46 mmol, 97 %).
Mp.: 78 - 80 ° C (DCM); MS (ES^+): m/z (%) 140 (100) $[M]^+$; MS (ES^-): m/z (%) 145 (100) $[PF_6]^-$; HRMS (ES^+): $[M]^+$ $C_7H_{14}N_3^+$ requires m/z: 140.1182 found m/z: 140.1182; IR (solid): ν_{max} = 3429 (m), 2900 (w), 1619 (s), 1323 (m), 752 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.95 (bs, 2H, 2N**H**), 3.36 (t, J = 6.0 Hz, 8H, 2NHC**H**$_2$CH$_2$C**H**$_2$N), 2.06 (qn, J = 6.0 Hz, 4H, 2CH$_2$C**H**$_2$CH$_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.1 (**C**), 46.9 (2**C**H$_2$), 38.1 (2**C**H$_2$), 20.6 (**2C**H$_2$) ppm.

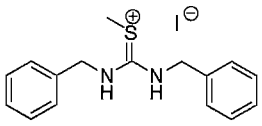
1, 3-Dibenzyl-thiourea (102).



Prepared according to the procedure given by Bartoli *et al.*[207]

Benzylamine (1.31 mL, 11.9 mmol) was dissolved in chloroform (100 mL). To this solution, saturated $NaHCO_3$ aqueous solution (30 mL) was added, followed by methanol (10 mL). Thiophosgene (297 μL, 4.00 mmol) was added to this biphasic solution and the reaction mixture stirred at room temperature for 20 hours. The phases were separated, the aqueous phase extracted with chloroform (3 x 30 mL) and the combined organic phase was washed with water (2 x 50 mL), dried over anhydrous magnesium sulfate, filtered and the solvents removed under reduced pressure to give a beige solid. The crude material was purified by column chromatography (10 % ethyl acetate in petroleum ether) to give thiourea **102** as a beige solid which was recrystallised in petroleum ether and DCM (769 mg, 3.00 mmol, 75 %). Mp.: 146 - 148 ° C (DCM / petroleum ether) (Literature Mp.: 146 - 148 ° C)[288]; MS (ES^+): m/z (%) 279 (100) $[M+Na]^+$; IR (solid): ν_{max} = 3283 (m), 3062 (w), 3031 (w), 1553 (s), 1497 (s), 1213 (m), 957 (m), 739 (s) cm^{-1}; ^1H NMR (300 MHz, d_6DMSO): δ = 7.96 (bs, 2H, 2N**H**), 7.35 - 7.22 (m, 10H, 10C**H**), 4.61 - 4.72 (m, 4H, 2NHC$\mathbf{H_2}$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 183.2 (**C**), 138.4 (2**C**), 128.5 (4**C**H), 127.7 (4**C**H), 127.2 (2**C**H), 48.4 (2$\mathbf{C}H_2$) ppm. Spectroscopic data agrees with literature reference[288, 289].

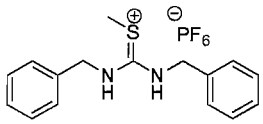
(Bis-benzylamino-methylene)-methyl-sulfonium iodide (103).



Prepared according to the procedure given by Bartoli *et al.*[207]

Dibenzyl thiourea (**102**, 769 mg, 3.00 mmol) was dissolved in reagent grade acetone (20 mL). To this solution iodomethane (747 μL, 12.0 mmol) was added and the reaction stirred at room temperature. A further 4 equivalents of iodomethane (747 μL, 12.0 mmol) was added to the reaction mixture after 2 hours. The solvent and residual iodomethane were removed under reduced pressure to give thiouronium **103** as an orange oil which gave a foam under a high vacuum line (1.16 g, 2.91 mmol, 97 %). Mp.: 122 – 124 ° C (ethyl acetate), (Literature Mp.: 119.5 - 120.5 ° C)[290]; MS (ES^+): m/z (%) 271 (100) $[M]^+$, MS (ES^-): m/z (%) 127 (100) $[I]^-$; IR (solid): ν_{max} = 3151 (w), 3029 (w), 1601 (s), 1505 (m), 735 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 - 7.10 (m, 10H, 10C**H**), 4.89 - 4.76 (m, 4H, 2NHC**H**$_2$), 2.82 (s, 3H, C**H**$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 168.3 (**C**), 134.7 (2**C**), 129.0 (4**C**H), 128.5 (4**C**H), 128.0 (2**C**H), 47.7 (2**C**H$_2$), 16.7 (**C**H$_3$) ppm.
Spectroscopic data agrees with literature reference[290].

(Bis-benzylamino-methylene)-methyl-sulfonium; hexafluoro phosphate (104).

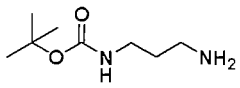


Prepared according to the procedure given by Bartoli *et al.*[207]

Thiouronium **103** (1.10 g, 2.77 mmol) was dissolved in DCM (10 mL) and methanol (10 mL). To this solution ammonium hexafluorophosphate (0.677g, 4.15 mmol) was added and the reaction mixture stirred at room temperature for 6 hours. The solvents

were removed from the reaction mixture to give an orange oil and this was redissolved in DCM (50 mL). The organic phase was washed with water (3 x 20 mL) and the aqueous phase extracted with DCM (2 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give an orange oil which yielded thiouronium **104** as an orange foam under a high vacuum line (1.14 g, 2.74 mmol, 99 %). Mp.: 85 – 87 ° C (DCM); MS (ES^+): m/z (%) 271 (100) $[M]^+$, MS (ES^-): m/z (%) 145 (100) $[PF_6]^-$; IR (solid): ν_{max} = 3155 (w), 3069 (w), 3029 (w), 1601 (s), 825 (s), 735 (s) cm^{-1}; ^1H NMR (300 MHz, d_6DMSO): δ = 9.60 (bs, 2H, 2N**H**), 7.39 - 7.20 (m, 10H, 10C**H**), 4.71 - 4.63 (m, 4H, 2NHC$\mathbf{H}_2$), 2.70 (s, 3H, C$\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 168.4 (**C**), 136.2 (**C**), 135.2 (**C**), 128.6 (4**C**H), 127.7 (4**C**H), 127.1 (2**C**H), 47.5 (**C**H_2), 46.6 (**C**H_2), 14.0 (**C**H_3) ppm.

(3-Amino-propyl)-carbamic acid *tert*-butyl ester (107).

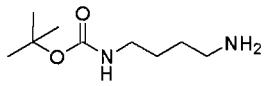


Prepared according to the procedure given by Montero *et al.*[256]

1, 3 Diaminopropane (**105**, 21.0 mL, 250 mmol) was dissolved in DCM (75 mL). A separate solution of di - *tert*butyl dicarbonate (9.10 g, 42.0 mmol) was prepared in DCM (600 mL) and was added dropwise to the diamine solution, whilst stirring at room temperature, over 7 hours. On complete addition of the di - *tert*butyl dicarbonate solution; the reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was transferred to a separating funnel and washed with K_2CO_3 saturated aqueous solution (2 x 230 mL) and water (2 x 75 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give amine **107** as a colourless oil (7.05 g, 40.4 mmol, 96 %). (ES^+): m/z (%) 175 (100) $[M+H]^+$; IR (solid): ν_{max} = 3358 (w), 2932 (w), 2871 (w), 1687 (s), 1518 (m), 1365 (m), 1250 (m), 1169 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.97 (bs, 1H, N**H**), 3.16 (q, J = 6.2 Hz, 2H, $CH_2C\mathbf{H}_2NH$),

2.74 (t, J = 6.7 Hz, 2H, $CH_2CH_2NH_2$), 1.69 (bs, 2H, NH_2), 1.59 (qn, J = 6.7 Hz, 2H, $CH_2CH_2CH_2$), 1.41 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3 (**C**), 79.1 (**C**), 39.7 (CH_2), 88.5 (CH_2), 33.4 (CH_2), 28.5 ($3CH_3$) ppm.
Spectroscopic data agrees with literature reference[209, 256]

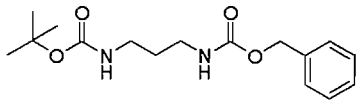
(4-Amino-butyl)-carbamic acid *tert*-butyl ester (108).



Prepared according to the procedure given by Montero *et al.*[256]

1, 4 Diaminobutane (**106**, 28.5 mL, 284 mmol) was dissolved in DCM (85 mL). A separate solution of di - *tert*butyl dicarbonate (0.07 M) was prepared from a 1M solution in THF (47.3 mL, 47.0 mmol) diluted with DCM (830 mL). The di - *tert*butyl dicarbonate solution was added dropwise to the diamine solution, whilst stirring vigorously at room temperature over 8 hours. On complete addition of the di - *tert*butyl dicarbonate solution, the reaction mixture was stirred at room temperature for 23 hours. The reaction mixture was transferred to a separating funnel and washed with K_2CO_3 saturated aqueous solution (2 x 250 mL) and water (2 x 100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give amine **108** as a colourless oil (8.64 g, 45.8 mmol, 97 %). MS (ES^+): m/z (%) 211 (100) $[M+Na]^+$; IR (solid): ν_{max} = 3364 (w), 2976 (w), 2931 (w), 2863 (w), 1694 (s), 1524 (m), 1365 (m), 1249 (m), 1169 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.68 (bs, 1H, N**H**), 3.11 (q, J = 6.2 Hz, 2H, CH_2CH_2NH), 2.72 (t, J = 6.7 Hz, 2H, $CH_2CH_2NH_2$), 1.80 (bs, 2H, NH_2), 1.52 - 1.45 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.43 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (**C**), 78.6 (**C**), 41.8 (CH_2), 41.6 (CH_2), 30.7 (CH_2), 28.2 ($3CH_3$), 27.2 (CH_2) ppm.
Spectroscopic data agrees with literature reference[291].

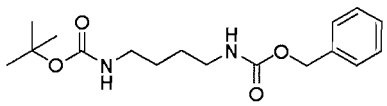
(3-*tert*-Butoxycarbonylamino-propyl)-carbamic acid benzyl ester (109).



Prepared according to the procedure given by Montero *et al.*[256]

Benzyl chloroformate (8.84 mL, 61.9 mmol) was added to a biphasic solution of **107** (9.81 g, 56.3 mmol) in DCM (440 mL) and K_2CO_3 saturated aqueous solution (270 mL). The reaction mixture was stirred at room temperature for 17 hours, at which time further benzyl chloroformate was added (4.00 mL, 28.1 mmol). The reaction was complete after 36 hours stirring at room temperature. The reaction mixture was transferred to a separating funnel, the phases separated and the aqueous phase extracted with DCM (2 x 200 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (2 % methanol / DCM) to give diamine **109** as a white solid (15.1 g, 50.0 mmol, 89 %).
Mp.: 52 – 54 ° C (DCM) (Literature Mp.: 45 - 46 ° C)[256]; MS (ES^+): m/z (%) 331 (100) $[M+Na]^+$; IR (solid): ν_{max} = 3360 (w), 3345 (w), 1686 (s), 1523 (m), 1244 (m), 1169 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 - 7.31 (m, 5H, 5C**H**), 5.09 (s, 2H, OC$\mathbf{H}_2$Ph), 4.84 (bs, 1H, N**H**), 3.24 (q, J = 6.1 Hz 2H, $CH_2C\mathbf{H}_2NH$), 3.17 - 3.11 (m, 2H, $CH_2C\mathbf{H}_2NH$), 1.77 (bs, 1H, N**H**), 1.64 (qn, J = 6.5 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.43 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.9 (**C**), 156.2 (**C**), 136.8 (**C**), 128.6 (2**C**H), 128.2 (2**C**H), 128.1 (**C**H), 79.5 (**C**), 66.6 ($\mathbf{C}H_2$), 37.8 ($\mathbf{C}H_2$), 37.2 ($\mathbf{C}H_2$), 30.6 ($\mathbf{C}H_2$), 28.4 ($3\mathbf{C}H_3$) ppm.
Spectroscopic data agrees with literature reference[256].

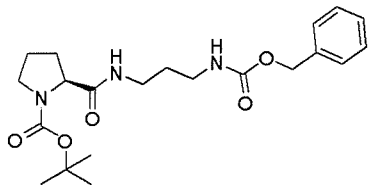
(4-*tert*-Butoxycarbonylamino-buyyl)-carbamic acid benzyl ester (110).



Prepared according to the procedure given by Montero *et al.*[256]

Benzyl chloroformate (7.12 mL, 50.0 mmol) was added to a biphasic solution of **108** (8.52 g, 45.3 mmol) in DCM (360 mL) and K_2CO_3 saturated aqueous solution (220 mL). The reaction mixture was stirred at room temperature for 17 hours, at which time further benzyl chloroformate was added (3.20 mL, 22.6 mmol). The reaction was complete after 36 hours stirring at room temperature. The reaction mixture was transferred to a separating funnel, the phases separated and the aqueous phase extracted with DCM (2 x 150 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (1 % methanol / DCM) to give diamine **110** as a white solid (11.5 g, 35.6 mmol, 79 %).
Mp.: 95 – 97 ° C (DCM) (Literature Mp.: 94 - 95 ° C)[292]; MS (ES^+): m/z (%) 323 (100) $[M+H]^+$; IR (solid): ν_{max} = 3334 (m), 2976 (w), 1683 (s), 1526 (m), 1366 (w), 1283 (m), 1169 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 - 7.19 (m, 5H, 5C**H**), 5.01 (s, 2H, OC$\mathbf{H}_2$Ph), 4.82 (bs, 1H, N**H**), 4.49 (bs, 1H, N**H**), 3.15 - 3.07 (m, 2H, $CH_2C\mathbf{H}_2NH$), 3.02 (t, J = 6.1 Hz, 2H, $CH_2C\mathbf{H}_2NH$), 1.43 - 1.41 (m, 4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$), 1.35 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6 (**C**), 156.1 (**C**), 136.7 (**C**), 128.6 (2**C**H), 128.3 (2**C**H), 128.2 (**C**H), 79.3 (**C**), 66.7 ($\mathbf{C}H_2$), 40.8 ($\mathbf{C}H_2$), 40.4 ($\mathbf{C}H_2$), 28.5 ($3\mathbf{C}H_3$), 27.5 ($2\mathbf{C}H_2$) ppm.
Spectroscopic data agrees with literature reference[292].

(*S*)-2-(3-Benzyloxycarbonylamino-propylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (111).

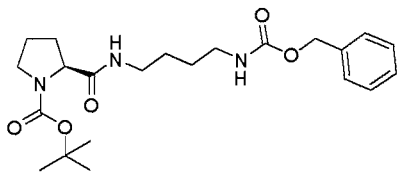


Prepared according to the procedure given by Bartoli *et al.*[207]

109 (6.27 g, 20.3 mmol) was dissolved in a 20 % mixture of TFA and DCM (150 mL) and stirred at room temperature for 1 hour. After 1 hour the TFA and DCM were removed from the reaction mixture under reduced pressure to give a beige solid that was recrystallised using ethyl acetate and hexane (6.53 g, 20.3 mmol, 100 %). ^{t}Boc - L - proline (**99**, 0.95 g, 4.43 mmol) was dissolved in a 1:1 mixture of DMF (30 mL) and THF (30 mL) and cooled to 0 ° C before the addition of 3 - benzyloxycarbonylamino - propyl - ammonium trifluoroacetate (1.57 g, 4.87 mmol), HOBt (898 mg, 6.65 mmol), EDC (934 mg, 4.87 mmol), and DIPEA (3.39 mL, 19.5 mmol). The reaction mixture was warmed to room temperature and stirred for 17 hours. The solvents were removed from the reaction mixture under reduced pressure and redissolved in DCM (50 mL). The solution was washed with 1M $KHSO_4$ aqueous solution (2 x 30 mL), saturated $NaHCO_3$ aqueous solution (2 x 30 mL) and brine (30 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by crystallisation with ethyl acetate and hexane to give carbamate **111** as an off - white crystalline solid (1.28 g, 3.16 mmol, 71 %). Mp.: 98 - 100 ° C (ethyl acetate / hexane); $[\alpha]_D$ = - 72.3 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 428 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{21}H_{31}N_3NaO_5$ requires m/z: 428.2156, found m/z: 428.2146; IR (solid): ν_{max} = 3283 (m), 2974 (w), 2879 (w), 1713 (m), 1662 (s), 1543 (m), 1409 (m), 1240 (s), 1160 (m), 1125 (m), 1020 (m) cm^{-1}; ^{1}H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.48 (bs, 1H, N**H**), 7.38 - 7.33 (m, 4H, 4C**H**), 7.29 (m, 1H, C**H**), 6.82 (bs, 1H, N**H**), 5.04 (s, 2H, C**H**$_2$Ph), 4.04 (dd, *J* = 8.4, 3.4 Hz, 1H, C**H**CO), 3.39 (1H, m, NCH**H**'), 3.31 (m, 1H, NC**H**H'), 3.16 - 3.10 (m, 2H, CH_2C**H**$_2$NH), 3.06 (t, *J* = 6.1 Hz, 2H,

NHC**H**$_2$CH$_2$), 2.07 (dt, J = 7.7, 3.8 Hz, 1H, CHCH**H**'), 1.85 - 1.74 (m, 3H, C**H**$_2$C**H**H'), 1.59 (qn, J = 6.9 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.38 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (**C**), 157.5 (**C**), 156.9 (**C**), 136.8 (**C**), 128.5 (2**C**H), 128.2 (2**C**H), 128.1 (**C**H), 80.4 (**C**), 66.6 (**C**H$_2$), 60.6 (**C**H), 47.1 (**C**H$_2$), 37.6 (**C**H$_2$), 35.9 (**C**H$_2$), 30.2 (**C**H$_2$), 28.4 (3**C**H$_3$), 24.5 (**C**H$_2$), 22.7 (**C**H$_2$) ppm; For crystal structure see **Appendix 2**.

(*S*)-2-(4-Benzyloxycarbonylamino-butylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (112).

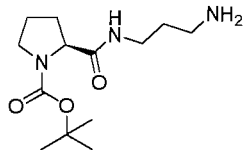


Prepared according to the procedure given by Bartoli *et al.*[207]

110 (13.4 g, 41.6 mmol) was dissolved in a 20 % mixture of TFA and DCM (250 mL) and stirred at room temperature for 1 hour. The TFA and DCM were removed from the reaction mixture under reduced pressure to give a brown oil (14.0 g, 41.6 mmol, 100 %). ^{t}Boc- L - proline (**99**, 3.78 g, 17.6 mmol) was dissolved in a 1:1 mixture of DMF and THF (200 mL) and cooled to 0 ° C before the addition of 3 - benzyloxycarbonylamino - butyl - ammonium trifluoroacetate (6.48 g, 19.3 mmol), HOBt (3.57 g, 26.4 mmol), EDC (3.70 g, 19.3 mmol) and DIPEA (15.3 mL, 87.8 mmol). The reaction mixture was warmed to room temperature and stirred for 24 hours. The solvents were removed from the reaction mixture under reduced pressure and redissolved in DCM (300 mL) and washed with 1M $KHSO_4$ aqueous solution (3 x 300 mL), saturated $NaHCO_3$ aqueous solution (2 x 300 mL) and brine (300 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by crystallisation with ethyl acetate and hexane to give carbamate **112** as an off - white crystalline solid (6.95 g, 16.6 mmol, 94 %). Mp.: 98 - 100 ° C (ethyl acetate / hexane); $[\alpha]_D$ = - 70.6 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+):

m/z (%) 442 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{22}H_{33}N_3NaO_5$ requires m/z: 442.2312, found m/z: 442.2312; IR (solid): ν_{max} = 3320 (w), 2977 (w), 2935 (w), 1667 (s), 1531 (m), 1391 (m), 1252 (m), 1162 (m), 1125 (m), 909 (m), 726 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.43 (bs, 1H, N**H**), 7.38 - 7.35 (m, 4H, 4C**H**), 7.29 (m, 1H, C**H**), 6.81 (bs, 1H, N**H**), 5.04 (s, 2H, C$\mathbf{H}_2$Ph), 4.06 (dd, *J* = 8.4, 3.4 Hz, 1H, C**H**CO), 3.38 (1H, m, NCH**H**'), 3.31 (m, 1H, NC**H**H'), 3.16 - 3.02 (m, 4H, 2NHC$\mathbf{H}_2$$CH_2$), 2.07 (m, 1H, CHCH**H**'), 1.87 - 1.73 (m, 3H, C$\mathbf{H}_2$C**H**H'), 1.45 (qn, *J* = 6.6 Hz, 4H, 2CH_2C$\mathbf{H}_2$$CH_2$), 1.38 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 172.3 (**C**), 156.1 (**C**), 153.6 (**C**), 137.3 (**C**), 128.2 (2**C**H), 127.7 (2**C**H), 127.6 (**C**), 78.3 (**C**), 65.1 (**C**H_2), 59.8 (**C**H), 46.4 (**C**H_2), 40.0 (**C**H_2), 38.1 (**C**H_2), 31.1 (**C**H_2), 28.0 (3**C**H_3), 26.8 (**C**H_2), 26.5 (**C**H_2), 23.1 (**C**H_2) ppm.

(*S*)-2-(3-Amino-propylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (113)

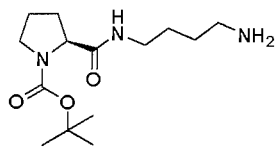


Prepared according to the procedure given by Montero *et al.*[256]

Palladium on activated carbon (dry, 10 %, 315 mg, 2.95 mmol) was added to a solution of **111** (1.20 g, 2.95 mmol) in methanol (40 mL). The flask containing the suspension was evacuated and the air replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature overnight. After 17 hours the hydrogen gas was removed from the reaction vessel and the palladium removed by filtering the reaction mixture through a pad of celite. The filtrate was reduced to give amine **113** as a low melting white solid (738 mg, 2.72 mmol, 92 %). $[\alpha]_D$ = - 43.6 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 272 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{13}H_{26}N_3O_3$ requires m/z: 272.1969, found m/z: 272.1967; IR (solid): ν_{max} = 3274 (m), 2974 (w), 1657 (s), 1393 (s), 1161 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 70 ° C): δ = 8.04 (bs, 1H, N**H**), 7.88 (t, *J* = 5.3 Hz, 2H, CH_2N$\mathbf{H}_2$), 4.07 (dd,

J = 8.4, 3.6 Hz, 1H, **CH**CO), 3.40 (m, 1H, NCH**H**'), 3.33 (m, 1H, NC**H**H'), 3.23 - 3.13 (m, 2H, NHC**H**$_2$CH$_2$), 2.80 (t, J = 7.2 Hz, 2H, CH$_2$C**H**$_2$NH$_2$), 2.10 (m, 1H, CHCH**H**'), 1.88 - 1.73 (m, 5H, **CH**$_2$ and C**H**$_2$C**H**H'), 1.38 (s, 9H, C(**CH**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d$_6$DMSO, 70 ° C): δ = 172.8 (**C**), 153.6 (**C**), 79.1 (**C**), 59.8 (**CH**), 46.4 (**CH**$_2$), 36.5 (**CH**$_2$), 35.5 (**CH**$_2$), 31.6 (**CH**$_2$), 31.0 (**CH**$_2$), 28.0 (3**CH**$_3$), 23.1 (**CH**$_2$) ppm.

(*S*)-2-(3-Amino-propylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (114)

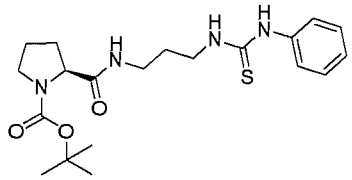


Prepared according to the procedure given by Montero *et al.*[256]

A hydrogenation conical flask was evacuated and the air replaced with nitrogen at atmospheric pressure, this process was repeated 3 times. Palladium on activated carbon (5 %, wet, 4.70 g, 21.7 mmol) was added to the flask and again purged with nitrogen 3 times. A solution of **112** (4.55 g, 10.8 mmol) in n - propanol (430 mL) was added to the flask and the purging procedure repeated. The flask was again evacuated and the nitrogen gas replaced with hydrogen gas, this process was repeated 3 times. The reaction suspension was stirred vigorously under an atmosphere of hydrogen gas, at room temperature, for 3 days. The hydrogen gas was removed from the reaction vessel and the palladium removed by filtering through a pad of celite. The filtrate was reduced to give amine **114** as a pale yellow oil (2.99 g, 10.4 mmol, 96 %). $[\alpha]_D$ = - 45.1 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 286 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{14}H_{28}N_3O_3$ requires m/z: 286.2125, found m/z: 286.2126. IR (film): ν_{max} = 3301 (w), 2976 (w), 2934(w), 1660 (s), 1548(m), 1392 (s), 1256 (m), 1161 (s) 732 (s) cm^{-1}; ^{1}H NMR (400 MHz, d$_6$DMSO, 80 ° C): δ = 7.54 (bs, 1H, N**H**), 4.06 (dd, J = 8.4, 3.3 Hz, 1H, **CH**CO), 3.96 (bs, 2H, N**H**$_2$), 3.39 (m, 1H, NCH**H**'), 3.32 (m, 1H, NC**H**H'), 3.15 - 3.03 (m, 2H, NHC**H**$_2$CH$_2$), 2.70 (t,

J = 6.6 Hz, 2H, $CH_2CH_2NH_2$), 2.09 (m, 1H, CHCHH'), 1.90 - 1.72 (m, 3H, CH_2CHH'), 1.49 (qn, J = 6.6 Hz, 4H, $2CH_2CH_2CH_2$), 1.38 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 172.3 (**C**), 153.3 (**C**), 78.3 (**C**), 59.8 (**C**H), 46.4 (CH_2), 39.2 (CH_2), 37.9 (CH_2), 31.1 (CH_2), 30.1 (CH_2), 28.0 ($3CH_3$), 26.3 (CH_2), 23.1 (CH_2) ppm.

(*S*)-2-[3-(3-Phenyl-thioureido)-propylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (115).

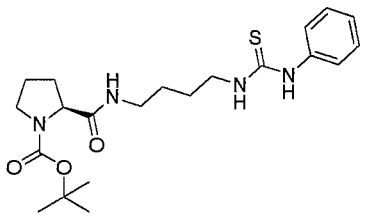


Prepared according to the procedure given by Bartoli *et al.*[207]

113 (391 mg, 1.44 mmol) and phenylisothiocyanate (173 μL, 1.44 mmol) were dissolved in a biphasic solution of chloroform (50 mL), methanol (14 mL) and saturated $NaHCO_3$ aqueous solution (14 mL). The reaction mixture was stirred vigorously for 18 hours at room temperature. On completion the phases were separated, the organic phase was washed with water (2 x 40 mL) and the aqueous phase was extracted with DCM (3 x 40 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to obtain thiourea **115** as a white foam (520 mg, 1.28 mmol, 89 %). $[\alpha]_D$ = - 29.1 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 429 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{20}H_{30}N_4NaO_3S$ requires m/z: 429.1931, found m/z: 429.1930; IR (solid): ν_{max} = 3283 (m), 2972 (w), 1656 (s), 1534 (s), 1391 (m), 1162 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 9.44 (bs, 1H, N**H**), 7.72 (bs, 1H, N**H**), 7.58 (bs, 1H, N**H**), 7.48 (dd, J = 8.7, 1.3 Hz, 2H, 2CC**H**), 7.29 (t, J = 7.4 Hz, 2H, 2CHC**H**CH), 7.08 (tt, J = 7.4, 0.9 Hz, 1H, CHC**H**CH), 4.07 (dd, J = 8.6, 3.2 Hz, 1H, C**H**CO), 3.54 (m, 1H, NC**H**H'), 3.39 - 3.31 (m, 3H, NCH**H**' and $NHCH_2$), 3.19 - 3.12 (m, 2H, $NHCH_2$), 2.10 (m, 1H, CHCH**H**'), 1.81 - 1.70 (m, 3H,

CH_2CHH'), 1.71 (qn, J = 6.7 Hz, 2H, $CH_2CH_2CH_2$), 1.39 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8 (**C**), 173.1 (**C**), 155.4 (**C**), 136.8 (**C**), 129.8 (2**C**H), 126.7 (2**C**H), 125.0 (**C**H), 80.4 (**C**), 60.4 (**C**H), 47.1 ($\mathbf{C}H_2$), 41.9 ($\mathbf{C}H_2$), 36.1 ($\mathbf{C}H_2$), 29.4 ($2\mathbf{C}H_2$), 28.4 ($3\mathbf{C}H_3$), 24.4 ($\mathbf{C}H_2$) ppm.

(*S*)-2-[3-(3-Phenyl-thioureido)-butylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (116).

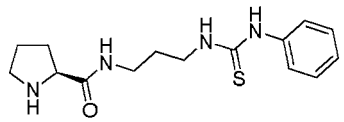


Prepared according to the procedure given by Bartoli *et al.*[207]

114 (2.22 g, 7.77 mmol) and phenylisothiocyanate (929 μL, 7.77 mmol) were dissolved in a biphasic solution of chloroform (200 mL), methanol (60 mL) and saturated $NaHCO_3$ aqueous solution (60 mL). The reaction mixture stirred vigorously for 64 hours at room temperature. On completion, the phases were separated and the organic phase washed with water (3 x 100 mL) and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (using a *Argonaut* Flash Master Personal with a prepacked 20 g silica cartridge, 2 % methanol / DCM) to obtain the thiourea **116** as a white foam (1.81 g, 4.31 mmol, 55 %). $[\alpha]_D$ = - 30.5 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 443 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{21}H_{32}N_4NaO_3S$ requires m/z: 443.2087, found m/z: 443.2094; IR (solid): ν_{max} = 3301 (w), 2976 (w), 1657 (s), 1533 (s), 1392 (m), 1160 (m), 731 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 9.20 (bs, 1H, N**H**), 7.50 (bs, 1H, N**H**), 7.46 (d, J = 7.6 Hz, 2H, 2CC**H**), 7.30 (t, J = 7.5 Hz, 2H, 2CHC**H**CH), 7.09 (t, J = 7.4 Hz, 1H, CHC**H**CH), 4.06 (dd, J = 8.5, 3.4 Hz, 1H, C**H**CO), 3.51 (q, J = 6.8 Hz, 2H, NHC$\mathbf{H}_2$), 3.38 (m, 1H, NC**H**H'), 3.31 (m, 1H, NCH**H**'), 3.18 - 3.06

(m, 3H, NHC**H**$_2$), 2.09 (dt, J = 7.8, 4.0 Hz, 1H, CHCH**H**'), 1.86 - 1.74 (m, 3H, C**H**$_2$C**H**H'), 1.58 (qn, J = 7.1 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.49 (qn, J = 6.9 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.38 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d$_6$DMSO): δ = 180.3 (**C**), 173.1 (**C**), 158.4 (**C**), 139.3 (**C**), 128.5 (2**C**H), 123.9 (2**C**H), 122.9 (**C**H), 78.3 (**C**), 59.9 (**C**H), 46.4 (**C**H$_2$), 43.5 (**C**H$_2$), 38.2 (**C**H$_2$), 31.1 (**C**H$_2$), 28.0 (3**C**H$_3$), 26.7 (**C**H$_2$), 26.0 (**C**H$_2$), 23.1 (**C**H$_2$) ppm.

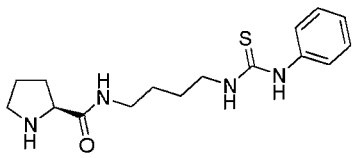
(*S*)-Pyrrolidine-2-carboxylic acid [3-(3-phenyl-thioureido)-propyl]-amide (117)



^{t}Boc protected thiourea **115** (232 mg, 0.571 mmol) was dissolved in a solution of 20 % TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 3 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (20 mL) and treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously at room temperature for 1 hour. The phases were separated and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **117** as a colourless oil (134 mg, 0.438 mmol, 77 %). $[\alpha]_D$ = - 34.1 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES$^+$): m/z (%) 329 (100) [M+Na]$^+$; HRMS (ES$^+$): [M+H]$^+$ $C_{15}H_{23}N_4OS$ requires m/z: 307.1587, found m/z: 307.1587; IR (film): ν_{max} = 3283 (w), 2938 (w), 2868 (w), 1643 (m), 1526 (s), 1495 (s), 1313 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (bs, 1H, N**H**), 7.86 (t, J = 6.0 Hz, 1H, CH$_2$N**H**), 7.36 (t, J = 7.6 Hz, 2H, 2CC**H**), 7.26 (dd, J = 8.4, 1.2 Hz, 1H, CHC**H**CH), 7.18 (t, J = 7.7 Hz, 2H, 2CHC**H**CH), 7.01 (t, J = 5.5 Hz, 1H, CH$_2$N**H**), 3.70 - 3.50 (m, 3H, C**H**CO and NHC**H**$_2$CH$_2$), 3.21 (q, J = 6.4 Hz, 2H, NHC**H**$_2$CH$_2$), 2.95 (dt, J = 10.2, 6.8 Hz, 1H, NHCH**H**'), 2.88 (dt, J = 10.1, 6.3 Hz, 1H, NHC**H**H'), 2.54 (bs, 1H, N**H**), 2.07 (m, 1H, CHCH**H**'), 1.80 (m, 1H, CHC**H**H'), 1.75 (qn, J = 6.4 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.66 (qn, J = 6.8 Hz, 2H, CH$_2$C**H**$_2$CH$_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.7 (**C**),

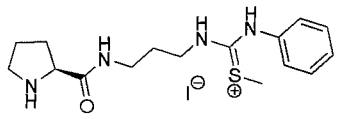
175.9 (**C**), 137.0 (**C**), 129.7 (2**C**H), 126.4 (2**C**H), 124.7 (**C**H), 60.5 (**C**H), 47.2 (**C**H_2), 42.0 (**C**H_2), 35.9 (**C**H_2), 30.8 (**C**H_2), 29.4 (**C**H_2), 26.1 (**C**H_2) ppm.

(*S*)-Pyrrolidine-2-carboxylic acid [4-(3-phenylthioureido)butyl]-amide (118).



^{t}Boc protected thiourea **116** (1.16 g, 2.77 mmol) was dissolved in a solution of 10 % TFA (2 mL) in DCM (18 mL) and stirred at room temperature for 3 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (40 mL) and treated with saturated K_2CO_3 aqueous solution (2 mL) and stirred vigorously at room temperature for 3 hours. The phases were separated and the aqueous phase extracted with DCM (4 x 20 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **118** as a pale yellow oil (666 mg, 2.08 mmol, 75 %). $[\alpha]_D$ = - 36.2 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 321 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{16}H_{25}N_4OS$ requires m/z: 321.1744, found m/z: 321.1745; IR (film): ν_{max} = 3279 (w), 2939 (w), 2868 (w), 1644 (m), 1529 (s), 1312 (m), 1263 (m), 696 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (bs, 1H, N**H**), 7.78 (t, 1H, CH_2N**H**), 7.38 (t, *J* = 7.3 Hz, 2H, 2CHC**H**CH), 7.26 - 7.21 (m, 3H, 3C**H**), 6.49 (bs, 1H, N**H**), 3.73 (dd, *J* = 9.1, 5.4 Hz, 1H, C**H**CO), 3.61 (q, *J* = 6.6 Hz, 2H, NHC$\mathbf{H}_2$), 3.21 (q, *J* = 6.6 Hz, 2H, NHC$\mathbf{H}_2$), 3.00 (dt, *J* = 10.3, 6.8 Hz, 1H, NHCH**H**'), 2.90 (dt, *J* = 10.3, 6.4 Hz, 1H, NHCH**H**'), 2.64 (bs, 1H, N**H**), 2.10 (m, 1H, CHC**H**H'), 1.85 (dt, *J* = 12.6, 6.9 Hz, 1H, CHCH**H**'), 1.68 (qn, *J* = 6.7 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.58 (qn, *J* = 7.3 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.51 (qn, *J* = 6.8 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.8 (**C**), 175.0 (**C**), 136.8 (**C**), 129.8 (2**C**H), 126.8 (2**C**H), 125.0 (**C**H), 60.4 (**C**H), 47.1 (**C**H_2), 44.8 (**C**H_2), 38.5 (**C**H_2), 30.7 (**C**H_2), 27.1 (**C**H_2), 26.0 (**C**H_2), 24.4 (**C**H_2) ppm.

((*S*)-Pyrrolidine-2-carbonyl)-amino]-propylamino}-1-phenylamino-methylidene]-methyl-sulfonium iodide (119).

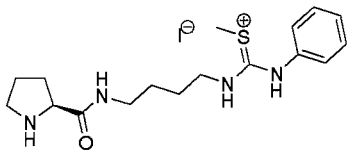


Prepared according to the procedure given by Bartoli *et al.*[207]

115 (677 mg, 1.66 mmol) was dissolved in chloroform (30 mL) and subsequently treated with iodomethane (1.55 mL, 24.9 mmol). The reaction mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure to give the ^{t}Boc protected thiouronium as a yellow foam (700 mg, 1.28 mmol, 77 %). ^{t}Boc protected thiouronium (700 mg, 1.28 mmol) was dissolved in a solution of 20 % TFA (6 mL) in DCM (24 mL) and stirred at room temperature for 3 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (30 mL) and treated with saturated K_2CO_3 aqueous solution (2 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **119** as a pale yellow oil (504 mg, 1.12 mmol, 88 %).
$[\alpha]_D$ = - 17.1 ° (c = 0.8, $CHCl_3$, 28 ° C, 589 nm); MS (ES^+): m/z (%) 321 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{16}H_{25}N_4OS^+$ requires m/z: 321.1744, found m/z: 321.1741; IR (film): ν_{max} = 3318 (w), 2941 (w), 2869 (w), 1647 (m), 1585 (s), 1516 (m), 1164 (m), 727 (s), 695 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (bs, 2H, 2N**H**), 7.28 (dt, *J* = 7.8, 1.2 Hz, 2H, 2CHC**H**CH), 7.02 (tt, *J* = 7.4, 1.2 Hz, 1H, CHC**H**CH), 6.90 (dd, *J* = 8.0, 1.2 Hz, 2H, 2CC**H**CH), 5.60 (bs, 1H, N**H**), 3.76 (dd, *J* = 9.1, 5.2 Hz, 1H, C**H**CO), 3.41 - 3.37 (m, 4H, 2NHC$\mathbf{H}_2$), 3.00 (dt, *J* = 10.1, 6.9 Hz, 1H, NHCH**H**'), 2.90 (dt, *J* = 10.2, 6.3 Hz, 1H, NHC**H**H'), 2.39 (s, 3H, C$\mathbf{H}_3$), 2.17 (qd, *J* = 12.9, 7.5 Hz, 1H, CHC**H**H'), 2.05 (bs, 1H, N**H**), 1.91 (qd, *J* = 12.6, 5.4 Hz, 1H, CHCH**H**'), 1.77 (qn, *J* = 6.3 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.72 (qn, *J* = 6.8 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$) ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 177.5 (**C**),

158.4 (**C**), 152.1 (**C**), 130.8 (2**C**H), 124.1 (2**C**H), 124.7 (**C**H), 62.7 (**C**H), 44.7 (**C**H_2), 41.0 (**C**H_2), 33.1 (**C**H_2), 28.9 (**C**H_2), 28.7 (**C**H_2), 27.91 (**C**H_2), 15.3 (**C**H_3) ppm.

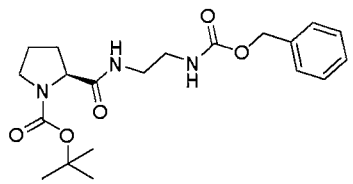
((*S*)-Pyrrolidine-2-carbonyl)-amino]-butylamino}-1-phenylamino-methylidene]-methyl-sulfonium iodide (120).



116 (846 mg, 2.01 mmol) was dissolved in chloroform (30 mL) and subsequently treated with iodomethane (1.25 mL, 20.1 mmol). The reaction mixture was stirred at room temperature for 12 hours. The solvent was removed under reduced pressure to give the ^{t}Boc protected thiouronium as a yellow foam (1.13 g, 2.01 mmol, 100 %). ^{t}Boc protected thiouronium (1.13 g, 2.01 mmol) was dissolved in a solution of 20 % TFA (6 mL) in DCM (24 mL) and stirred at room temperature for 2 hours. Once the reaction was complete, the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (30 mL) and treated with saturated K_2CO_3 aqueous solution (2 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **120** as a yellow oil (788 mg, 1.71 mmol, 85 %). $[\alpha]_D$ = - 15.8 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 335 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{17}H_{27}N_4OS^+$ requires m/z: 335.1900, found m/z: 335.1900; IR (film): ν_{max} = 3315 (w), 2930 (w), 2869 (w), 1607 (m), 1582 (s), 1485 (m), 1163 (m), 907 (m), 726 (s), 695 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (bs, 1H, N**H**), 7.29 (td, *J* = 8.2, 1.4 Hz, 2H, 2CHC**H**CH), 7.03 (tt, *J* = 7.5, 1.4 Hz, 1H, CHC**H**CH), 6.91 (dd, *J* = 8.2, 1.4 Hz, 2H, 2CC**H**CH), 3.75 (dd, *J* = 9.2, 5.5 Hz, 1H, C**H**CO), 3.38 (t, *J* = 6.6 Hz, 2H, NHC**H**$_2$), 3.28 (q, *J* = 6.8 Hz, 2H, NHC**H**$_2$), 3.01 (dt, *J* = 10.2, 6.7 Hz, 1H, NHCH**H**'), 2.92 (dt, *J* = 10.4, 6.5 Hz, 1H, NHCH**H**'), 2.31 (s, 3H, C**H**$_3$), 2.15 (m, 1H, CHC**H**H'), 1.91 (td, *J* = 12.5, 6.8 Hz, 1H,

CHCH**H'**), 1.72 (qn, J = 6.6 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.70 - 1.58 (m, 4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2 (**C**), 149.7 (**C**), 129.0 (**C**), 123.1 (2**C**H), 122.6 (2**C**H), 122.2 (**C**H), 60.5 (**C**H), 53.5 ($\mathbf{C}H_2$), 47.3 ($\mathbf{C}H_2$), 42.9 ($\mathbf{C}H_2$), 38.4 ($\mathbf{C}H_2$), 30.8 ($\mathbf{C}H_2$), 27.2 ($\mathbf{C}H_2$), 26.2 ($\mathbf{C}H_2$), 14.0 ($\mathbf{C}H_3$) ppm.

(*S*)-2-[3-(3-Phenyl-thioureido)-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (122).

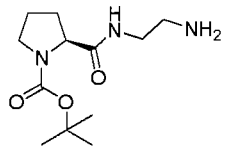


Prepared according to the procedure given by Bartoli *et al.*[207]

^{t}Boc- L - proline (**99**, 4.85 g, 22.5 mmol), was dissolved in a 1:1 mixture of DMF (110 mL) and THF (110 mL) and cooled to 0 ° C (over ice) before the addition of 2 - benzyloxycarbonylamino - ethyl - ammonium chloride (**121**, 4.81 g, 24.8 mmol), HOBt (4.57 g, 33.8 mmol), EDC (4.76 g, 24.8 mmol) and DIPEA (19.6 mL, 113 mmol). The reaction mixture was warmed to room temperature and stirred for 17 hours. The solvent was removed under reduced pressure to give a pale yellow oil. The resulting oil was redissolved in DCM (200 mL) and washed with 1M $KHSO_4$ aqueous solution (3 x 150 mL), saturated $NaHCO_3$ aqueous solution (2 x 150 mL) and brine (150 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by crystallisation with ethyl acetate and hexane to give carbamate **122** as an off - white crystalline solid (6.92 g, 17.8 mmol, 79 %). Mp.: 108 - 110 ° C (ethyl acetate); $[\alpha]_D$ = - 74.2 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 414 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{20}H_{29}N_3NaO_5$ requires m/z: 414.1999, found m/z: 414.1991; IR (solid): ν_{max} = 3323 (w), 2970 (w), 2880 (w), 1677 (s), 1527 (m), 1396 (m), 1255 (m) cm^{-1}; ^{1}H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 7.47 (bs, 1H, N**H**), 7.34 - 7.28 (m, 5H, 5C**H**), 6.71 (bs, 1H, N**H**), 5.04 (s, 2H, $C\mathbf{H}_2Ph$), 4.05

(dd, J = 8.4, 3.6 Hz, 1H, C**H**CO), 3.41 - 3.29 (m, 2H, NC**H**$_2$), 3.30 (dt, J = 12.0, 5.9 Hz, 2H, NHC**H**$_2$), 3.16 (dt, J = 13.1, 6.0 Hz, 2H, NHC**H**$_2$), 2.07 (m, 1H, CHCH**H**'), 1.88 - 1.71 (m, 3H, C**H**$_2$CHC**H**H'), 1.38 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (**C**), 156.8 (**C**), 154.6 (**C**), 136.5 (**C**), 129.2 (2**C**H), 128.5 (2**C**H), 128.1 (**C**H), 80.5 (**C**), 66.7 (**C**H$_2$), 60.5 (**C**H), 47.1 (**C**H$_2$), 41.0 (**C**H$_2$), 39.8 (**C**H$_2$), 31.4 (**C**H$_2$), 28.4 (3**C**H$_3$), 24.6 (**C**H$_2$) ppm.

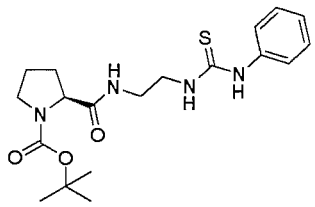
(*S*)-2-(3-Amino-ethylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (123).



Prepared according to the procedure given by Montero *et al.*[256]

Palladium on activated carbon (5 %, wet, 2.17 g, 10.2 mmol) was added to a solution of **122** (2.00 g, 5.11 mmol) in isopropanol (185 mL). The flask containing the suspension was evacuated and the air was replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature overnight. After 17 hours the hydrogen gas was removed from the reaction vessel and the palladium was removed by filtering the reaction mixture through a pad of celite. The filtrate was reduced to give amine **123** as a colourless oil (1.31 g, 5.10 mmol, 100 %). $[\alpha]_D$ = - 42.8 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 258 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{12}H_{24}N_3O_3$ requires m/z: 258.1812, found m/z: 258.1810; IR (film): ν_{max} = 3309 (w), 2972 (w), 1659 (s), 1537 (m), 1364 (s), 1158 (s) cm^{-1}; ^{1}H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 7.39 (bs, 1H, N**H**), 4.06 (dd, J = 8.3, 3.5 Hz, 1H, C**H**CO), 3.41 - 3.29 (m, 2H, NHC**H**$_2$), 3.19 - 3.04 (m, 2H, NC**H**$_2$), 2.68 - 2.57 (m, 4H, C**H**$_2$N**H**$_2$), 2.07 (m, 1H, CHCH**H**'), 1.87 - 1.73 (m, 3H, CH$_2$C**H**$_2$CH$_2$ and CHC**H**H'), 1.38 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO, 70 ° C): δ = 172.0 (**C**), 153.2 (**C**), 78.2 (**C**), 59.6 (**C**H), 46.2 (**C**H$_2$), 41.7 (**C**H$_2$), 40.9 (**C**H$_2$), 30.1 (**C**H$_2$), 27.7 (3**C**H$_3$), 23.1 (**C**H$_2$) ppm.

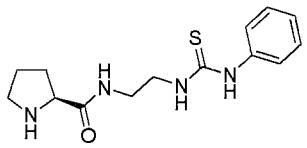
(*S*)-2-[3-(3-Phenyl-thioureido)-ethylcarbamoyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (124).



Prepared according to the procedure given by Bartoli *et al.*[207]

123 (99.0 mg, 0.384 mmol) and phenylisothiocyanate (45.9 μL, 0.384 mmol) were dissolved in a biphasic solution of chloroform (10 mL), methanol (3 mL) and saturated $NaHCO_3$ aqueous solution (3 mL). The reaction mixture was stirred vigorously for 17 hours at room temperature. On completion the phases were separated and the organic phase was washed with water (3 x 10 mL) and the aqueous phase extracted with DCM (3 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to obtain the thiourea **124** as a white foam (128 mg, 0.327 mmol, 85 %). $[\alpha]_D$ = - 28.6 ° (c = 1.0, $CHCl_3$, 28 ° C, 589 nm); MS (ES^+): m/z (%) 415 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{19}H_{28}N_4NaO_3S$ requires m/z: 415.1774, found m/z: 415.1778; IR (solid): ν_{max} = 3272 (w), 2972 (w), 1657 (s), 1525 (s), 1378 (m), 1158 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.28 (bs, 1H, N**H**), 7.59 (bs, 1H, N**H**), 7.51 (bs, 1H, N**H**), 7.41 (dd, *J* = 8.5, 1.2 Hz, 2H, 2CC**H**), 7.30 (t, *J* = 7.6 Hz, 2H, 2CHC**H**CH), 7.10 (tt, *J* = 7.8, 1.2 Hz, 1H, CHC**H**CH), 4.06 (dd, *J* = 8.5, 3.5 Hz, 1H, C**H**CO), 3.62 (ddd, *J* = 23.5, 12.5, 6.4 Hz, 1H, NC**H**H'), 3.43 - 3.24 (m, 5H, 2NHC$\mathbf{H}_2$ and NCH**H**'), 2.08 (m, 1H, CHCH**H**'), 1.89 - 1.70 (m, 3H, C$\mathbf{H}_2$C**H**H'CH), 1.38 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz,$CDCl_3$): δ = 180.3 (**C**), 173.1 (**C**), 158.4 (**C**), 136.7 (**C**), 129.9 (2**C**H), 126.7 (2**C**H), 125.3 (**C**H), 80.6 (**C**), 59.9 (**C**H), 47.3 (**C**H_2), 45.4 (**C**H_2), 39.4 (**C**H_2), 31.1 (**C**H_2), 28.5 (3**C**H_3), 24.6 (**C**H_2) ppm.

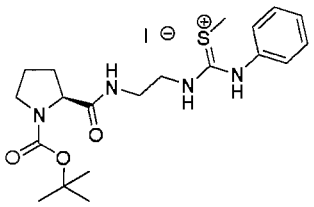
(*S*)-Pyrrolidine-2-carboxylic acid [3-(3-phenyl-thioureido)-ethyl]-amide (125).



Prepared according to the procedure given by Quaranta *et al.*[210]

The reaction was carried out with oven - dried glassware under an atmosphere of nitrogen gas. ^{t}Boc protected thiourea **124** (50.0 mg, 0.128 mmol) was dissolved in DCM (450 μL) and the solution treated with neat trimethylsilyl iodide (27.0 μL, 0.190 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (228 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (20 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (2 mL). The aqueous phase was then extracted with DCM (3 x 50 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **125** as a colourless oil (23.0 mg, 0.0787 mmol, 62 %). $[\alpha]_D$ = - 33.6 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 293 (100) $[M+H]^+$; IR (film): ν_{max} = 3265 (w), 2945 (w), 1646 (m), 1525 (s), 1261 (m) cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.95 (bs, 1H, N**H**), 7.46 - 7.35 (m, 4H, 4C**H**), 7.29 (tt, *J* = 7.2, 1.5 Hz, 1H, CHC**H**CH), 4.31 (dd, *J* = 8.6, 6.6 Hz, 1H, C**H**CO), 3.88 - 3.78 (m, 2H, NHC**H$_2$**), 3.60 - 3.33 (m, 6H, 2NHC**H$_2$** and 2N**H**), 2.46 (m, 1H, CHCH**H'**), 2.18 - 2.02 (m, 3H, C**H$_2$**C**H**H') ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 182.9 (**C**), 170.5 (**C**), 139.4 (**C**), 130.5 (2**C**H), 127.0 (2**C**H), 126.0 (**C**H), 61.5 (**C**H), 47.6 (**C**H_2), 45.0 (**C**H_2), 40.8 (**C**H_2), 31.2 (**C**H_2), 25.4 (**C**H_2) ppm.

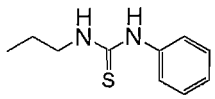
[1-{2-[((*S*)-1-*tert*-Butoxycarbonyl-pyrrolidine-2-carbonyl)-amino]-ethylamino}-1-phenylamino-methylidene]-methyl-sulfonium; iodide (126).



Prepared according to the procedure given by Bartoli *et al.*[207]

124 (232 mg, 0.591 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (366 μL, 5.91 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give thiouronium **126** as a yellow foam (300 mg, 0.561 mmol, 95 %). $[\alpha]_D$ = - 30.6 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 407 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; IR (film): ν_{max} = 2972 (w), 1605 (s), 1584 (s), 1391 (m), 1163 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.10 (bs, 1H, N**H**), 8.80 (bs, 1H, N**H**), 8.07 (bs, 1H, N**H**), 7.39 - 7.24 (m, 5H, 5C**H**), 4.19 (dd, *J* = 8.5, 4.7 Hz, 1H, C**H**CO), 4.05 - 3.80 (m, 2H, NHC$\mathbf{H}_2$), 3.58 (t, *J* = 5.6 Hz, 2H, NHC$\mathbf{H}_2$), 3.45 (m, 1H, NC**H**H'), 3.28 (m, 1H, NC**H**H'), 2.63 (s, 3H, C$\mathbf{H}_3$), 1.95 - 1.68 (m, 4H, 2C$\mathbf{H}_2$), 1.34 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz,$CDCl_3$): δ = 175.8 (**C**), 169.3 (**C**), 154.9 (**C**), 134.5 (**C**), 129.5 (2**C**H), 129.1 (2**C**H), 127.4 (**C**H), 80.1 (**C**), 60.3 (**C**H), 47.2 (**C**H_2), 46.3 (**C**H_2), 37.8 (**C**H_2), 28.4 (3**C**H_3), 24.4 (**C**H_2), 23.8 (**C**H_2), 15.6 (**C**H_3) ppm.

1-phenyl-3-propylthiourea (128).

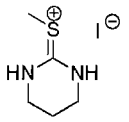


Prepared according to the procedure given by Bartoli *et al.*[207]

Propylamine (615 μL, 7.49 mmol) and phenylisothiocyanate (896 μL, 7.49 mmol) were dissolved in a biphasic solution of chloroform (130 mL), methanol (40 mL) and saturated $NaHCO_3$ aqueous solution (40 mL). The reaction mixture was stirred vigorously for 5 days at room temperature. On completion the phases were separated and the organic phase was washed with water (2 x 100 mL) and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (3 % methanol / DCM) to obtain the thiourea **128** as a white solid (1.29 g, 6.63 mmol, 89 %). Mp.: 57 - 59 ° C (DCM) (Literature Mp.: 59 – 60 ° C)[293]; MS (ES^+): m/z (%) 217 (100) $[M+Na]^+$; IR (film): ν_{max} = 3240 (m), 3073 (w), 2949 (m), 2873 (m), 1603 (m), 1537 (s), 1496 (s), 1324 (m) 1222 (m), 704 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (bs, 1H, N**H**), 7.42 (tt, *J* = 7.8, 1.7 Hz, 2H, 2CHC**H**CH), 7.29 (tt, *J* = 8.2, 1.9 Hz, 1H, CHC**H**CH), 7.20 (dd, *J* = 9.1, 3.0 Hz, 2H, 2CC**H**CH), 6.05 (bs, 1H, N**H**), 3.57 (t, *J* = 7.2 Hz, 2H, $CH_2C\mathbf{H}_2NH$), 1.62 (sext, *J* = 7.2 Hz, 2H, $CH_2C\mathbf{H}_2CH_3$), 0.89 (t, *J* = 7.4 Hz, 3H, $CH_2C\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.6 (**C**), 136.3 (**C**), 130.3 (2**C**H), 127.3 (2**C**H), 125.3 (**C**H), 47.3 ($\mathbf{C}H_2$), 22.3 ($\mathbf{C}H_2$), 11.4 ($\mathbf{C}H_3$) ppm.

Spectroscopic data agrees with literature reference[293].

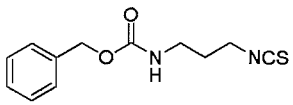
Methyl-(tetrahydro-pyrimidin-2-ylidene)-sulfonium; iodide (129).



Prepared according to the procedure given by Bartoli *et al.*[207]

Tetrahydro - pyrimidine - 2 - thione (0.511 g, 4.40 mmol) was dissolved in chloroform (20 mL). To this solution iodomethane (1.09 mL, 17.6 mmol) was added and the reaction stirred at room temperature for 3 hours. After 3 hours the solvent and excess iodomethane were removed under reduced pressure to give thiouronium **129** as a white solid (1.10 g, 4.27 mmol, 97 %). Mp.: 140 - 142 ° C (ethanol) (Literature Mp.: 146 – 148 ° C)[236]; MS (ES^+): m/z (%) 131 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; IR (solid): ν_{max} = 3150 (m), 2966 (w), 2867 (w), 1619 (s), 1561 (s), 1421 (m), 1234 (m), 1204 (s) cm^{-1}; ^1H NMR (300 MHz, d_6DMSO): δ = 9.53 (bs, 2H, 2N**H**), 3.38 (t, J = 5.8 Hz, 4H, 2NHC**H**$_2$CH$_2$), 2.58 (s, 3H, C**H**$_3$), 1.89 (qn, J = 5.8 Hz, 2H, CH$_2$C**H**$_2$CH$_2$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 162.9 (**C**), 40.0 (2**C**H$_2$), 18.1 (**C**H$_2$), 13.2 (**C**H$_3$) ppm.
Spectroscopic data agrees with literature reference[236].

(3-Isothiocyanato-propyl)-carbamic acid benzyl ester (131).

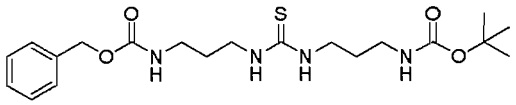


Prepared according to the procedure given by Jensen *et al.*[232]

109 (478 mg, 1.55 mmol) was dissolved in a 20 % mixture of TFA and DCM (150 mL) and stirred at room temperature for 1 hour. After 1 hour the TFA and DCM were removed from the reaction mixture under reduced pressure to give a beige solid that was recrystallised using ethyl acetate and hexane (500 mg, 1.55 mmol, 100 %). The trifluoroacetate salt (500 mg, 1.55 mmol) was dissolved in chloroform (30 mL)

and methanol (10 mL). To this solution saturated $NaHCO_3$ aqueous solution (10 mL) and thiophosgene (118 μL, 1.55 mmol) were added and the biphasic reaction mixture stirred at room temperature for 17 hours. On completion, the phase was separated and the organic phase washed with water (3 x 20 mL) and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil. The crude product was purified by column chromatography (1 % methanol / DCM) to give isothiocyanate **131** as a yellow oil (368 mg, 1.47 mmol, 95 %). MS (ES^+): m/z (%) 273 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{12}H_{14}N_2NaO_2S$ requires m/z: 273.0668, found m/z: 273.0666; IR (film): ν_{max} = 3321 (w), 2187 (m), 2108 (s), 1697 (s), 1531 (m), 1258 (s), 737 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 - 7.30 (m, 5H, 5C**H**), 5.10 (s, 2H, C$\mathbf{H_2}$O), 4.99 (bs, 1H, N**H**), 3.57 (t, *J* = 6.4 Hz, 2H, C$\mathbf{H_2}$NCS), 3.30 (q, *J* = 6.4 Hz, 2H, NHC$\mathbf{H_2}$), 1.89 (qn, *J* = 6.4 Hz, 2H, $CH_2C\mathbf{H_2}CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4 (**C**), 136.3 (**C**), 131.04 (**C**), 128.6 (2**C**H), 128.3 (2**C**H), 128.2 (**C**H), 66.9 ($\mathbf{C}H_2$), 42.6 ($\mathbf{C}H_2$), 38.2 ($\mathbf{C}H_2$), 30.2 ($\mathbf{C}H_2$) ppm.

{3-[3-(3-benzyloxycarbonylamino-propyl)-thioureido]-propyl} carbamic acid *tert*-butyl ester (132).

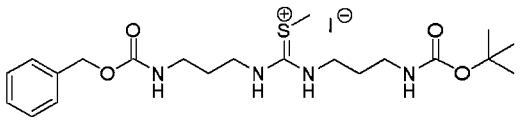


Prepared according to the procedure given by Bartoli *et al.*[207]

131 (3.94 g, 15.7 mmol) and **107** (2.73 g, 15.7 mmol) were dissolved into a biphasic solution of chloroform (300 mL), methanol (50 mL) and saturated $NaHCO_3$ aqueous solution (100 mL). The reaction mixture was stirred vigorously for 17 hours at room temperature. On completion the phases were separated and the organic phase was washed with water (2 x 100 mL) and the aqueous phase extracted with DCM (2 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material

was purified by column chromatography (0.2 % methanol / DCM) to obtain thiourea **132** as a colourless oil (4.96 g, 11.7 mmol, 75 %). MS (ES^+): m/z (%) 447 (100) $[M+Na]^+$; HRMS (ES^+) $[M+Na]^+$ $C_{20}H_{32}N_4NaO_4S$ requires m/z: 447.2036, found m/z: 447.2033; IR (film): ν_{max} = 3319 (w), 2939 (w), 1691 (m), 1529 (m), 1254 (m), 724 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO): δ = 8.28 (s, 1H, N**H**), 7.39 - 7.26 (m, 6H, 5C**H** and N**H**), 7.22 (t, 1H, J = 3.8 Hz, N**H**CH_2), 6.76 (t, 1H, J = 4.5 Hz, N**H**CH_2), 5.01 (s, 2H, C$\mathbf{H_2}$O), 3.52 - 3.32 (bs, 4H, 2NHC$\mathbf{H_2}$), 3.02 (q, J = 6.9 Hz, 2H, NHC$\mathbf{H_2}$), 2.91 (q, J = 6.6 Hz, 2H, NHC$\mathbf{H_2}$), 1.59 (qn, 2H, J = 6.8 Hz, $CH_2C\mathbf{H_2}CH_2$), 1.54 (qn, 2H, J = 6.8 Hz, $CH_2C\mathbf{H_2}CH_2$), 1.38 (s, 9H, C(C$\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 180.3 (**C**), 154.2 (**C**), 153.7 (**C**), 135.3 (**C**), 128.8 (2**C**H), 128.2 (2**C**H), 128.1 (**C**H), 79.6 (**C**), 65.7 (**C**H_2), 41.5 (**C**H_2), 38.5 (**C**H_2), 37.9 (**C**H_2), 29.7 (**C**H_2), 28.8 (2**C**H_2), 28.7 (3**C**H_3) ppm.

[1-(3-Benzyloxycarbonylamino-propylamino)-1-(3-*tert* butoxycarbonylamino-propylamino)-methylidene]-methyl-sulfonium; iodide (133).

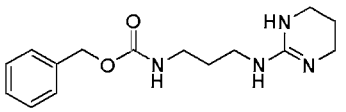


Prepared according to the procedure given by Bartoli *et al.*[207]

132 (4.82 g, 11.4 mmol) was dissolved in acetone (200 mL). To this solution iodomethane (7.07 mL, 114 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give thiouronium **133** as a yellow foam (6.44 g, 11.4 mmol, 100 %). MS (ES^+): m/z (%) 439 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{21}H_{35}N_4O_4S^+$ requires m/z: 439.2374, found m/z: 439.2369; IR (solid): ν_{max} = 3264 (w), 2977 (w), 2878 (w), 1690 (s), 1607 (s), 1517 (s), 1253 (s), 1166 (m), 728 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO): δ = 9.00 (bs, 1H, N**H**), 8.61 (bs, 1H, N**H**), 7.45 - 7.34 (m, 5H, 5C**H**), 6.87 (bs, 1H, N**H**), 5.07 (s, 2H, C$\mathbf{H_2}$O), 4.10 (bs, 1H, N**H**), 3.30 (t, J = 5.7 Hz, 4H, 2NHC$\mathbf{H_2}$), 3.25 - 3.20 (m, 4H, 2NHC$\mathbf{H_2}$), 2.79 (s, 3H, C$\mathbf{H_3}$), 1.85 (qn, J = 5.4 Hz, 2H, $CH_2C\mathbf{H_2}CH_2$), 1.76 (qn,

J = 5.4 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.37 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 167.5 (**C**), 156.7 (**C**), 156.2 (**C**), 137.5 (**C**), 128.8 (2**C**H), 128.3 (2**C**H), 128.2 (**C**H), 78.3 (**C**), 65.8 ($\mathbf{C}H_2$), 42.9 ($\mathbf{C}H_2$), 41.9 ($\mathbf{C}H_2$), 38.0 ($\mathbf{C}H_2$), 37.5 ($\mathbf{C}H_2$), 29.5 ($\mathbf{C}H_2$), 28.1 ($3\mathbf{C}H_3$), 27.5 ($\mathbf{C}H_2$), 14.4 ($\mathbf{C}H_3$) ppm.

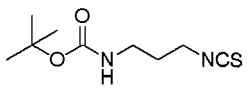
[3-(1,4,5,6-Tetrahydro-pyrimidin-2-ylamino)-propyl]-carbamic acid benzyl ester (134).



133 (500 mg, 0.880 mmol) was dissolved in a solution of 10 % TFA in DCM (10 mL) and stirred at room temperature for 3 hours. Once the deprotection was complete the solvent and residual TFA were removed under reduced pressure to give a brown oil. The resulting oil was redissolved in DCM (dry, 10 mL) to give an orange solution. To this solution Et_3N (distilled, 123 μL, 0.880 mmol) was added, after a few minutes stirring at room temperature the reaction mixture turned from orange to pale yellow. After 6 hours stirring at room temperature a further equivalent of Et_3N (123 μL, 0.880 mmol) was added to the reaction mixture and then stirred overnight. After 17 hours the reaction mixture was washed with 0.5 M NaOH (2 x 2.5 mL), and the aqueous phase extracted with DCM (5 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield guanidine **134** as a colourless oil (174 mg, 0.600 mmol, 68 %). MS (ES^+): m/z (%) 291 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{15}H_{23}N_4O_2$ requires m/z: 291.1816, found m/z: 291.1812; IR (film): ν_{max} = 3298 (w), 2925 (w), 1694 (w), 1649 (w), 1525 (w), 1260 (w), 1215 (w), 1133 (w) 750 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (t, J = 5.5 Hz, 1H, $CH_2N\mathbf{H}$), 7.41 - 7.23 (m, 5H, 5**C**H), 5.80 (bs, 1H, N**H**), 5.05 (s, 2H, $C\mathbf{H}_2O$), 3.27 (t, J = 5.6 Hz, 4H, $NHC\mathbf{H}_2CH_2C\mathbf{H}_2NH$), 3.14 (td, J = 11.4, 6.2 Hz, 4H, $NHC\mathbf{H}_2CH_2C\mathbf{H}_2NH$), 2.59 (bs, 1H, N**H**), 1.85 (qn, J = 5.6 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.75 (qn, J = 6.2 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (**C**), 153.6 (**C**), 136.4 (**C**), 128.5 (2**C**H),

128.1 (2**C**H), 127.8 (**C**H), 66.8 (**C**H_2), 38.7 (**C**H_2), 38.5 (**C**H_2), 38.2 (**C**H_2), 30.1 (**C**H_2), 20.1 (2**C**H_2), ppm.

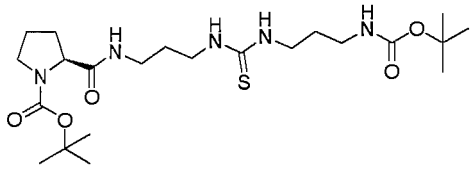
(3-Isothiocyanato-propyl)-carbamic acid tert-butyl ester (136).



Prepared according to the procedure given by Jensen *et al.*[232]

107 (214 mg, 1.22 mmol) was dissolved in chloroform (10 mL) and methanol (3 mL). To this solution saturated $NaHCO_3$ aqueous solution (3 mL) and thiophosgene (93.6 μL, 1.22 mmol) were added and the biphasic reaction mixture stirred at room temperature for 17 hours. On completion, the phases were separated and the organic phase washed with water (3 x 20 mL) and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil. The crude product was purified by column chromatography (3 % methanol / DCM) to give isothiocyanate **136** as a yellow oil (188 mg, 0.871 mmol, 71 % yield). MS (ES^+): m/z (%) 239 (100) $[M+Na]^+$; IR (film): ν_{max} = 3365 (w), 2977 (w), 2097 (s), 1686 (s), 1513 (m), 1249 (s), 1164 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.60 (bs, 1H, N**H**), 3.58 (t, *J* = 6.6 Hz, 2H, **CH**$_2$NCS), 3.23 (t, *J* = 6.6 Hz, 2H, NHC**H**$_2$), 1.89 (qn, *J* = 6.6 Hz, 2H, CH_2**CH**$_2$$CH_2$), 1.44 (s, 9H, C(**CH**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.1 (**C**), 131.04 (**C**), 79.9 (**C**), 42.8 (**C**H_2), 38.0 (**C**H_2), 30.6 (**C**H_2), 28.5 (3**C**H_3) ppm.
Spectroscopic data agrees with literature reference[243].

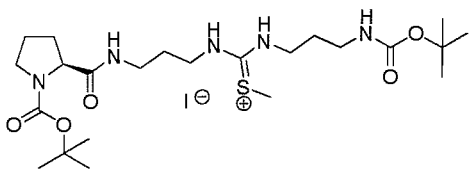
(*S*)-2-{2-[3-(3-*tert*-Butoxycarbonylamino-propyl)-thioureido] propylcarbamoyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (137).



Prepared according to the procedure given by Bartoli *et al.*[207]

136 (162 mg, 0.748 mmol) and **113** (203 mg, 0.748 mmol) was dissolved into a biphasic solution of chloroform (20 mL), methanol (6 mL) and saturated $NaHCO_3$ aqueous solution (6 mL). The reaction mixture was stirred vigorously for 17 days at room temperature. On completion the phases were separated and the organic phase washed with water (3 x 10 mL) and the aqueous phase extracted with DCM (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to obtain thiourea **137** as a white solid (252 mg, 0.516 mmol, 69 %). Mp.: 72 - 74 ° C (DCM); $[\alpha]_D$ = - 35.2 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 510 (100) $[M+Na]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{42}N_5O_5S$ requires m/z: 488.2901, found m/z: 488.2890; IR (solid): ν_{max} = 3302 (w), 2974 (w), 1675 (m), 1529 (m), 1392 (m), 1249 (m), 1161(s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 7.46 (bs, 1H, N**H**), 7.14 (bs, 2H, N**H**), 6.29 (bs, 1H, N**H**), 4.07 (dd, *J* = 8.8, 6.4 Hz, 1H, C**H**CO), 3.44 - 3.37 (m, 5H, NC**H**H' and 2NHC**H**$_2$), 3.33 (m, 1H, NCH**H**'), 3.16 - 3.06 (m, 2H, NHC**H**$_2$), 2.99 (q, *J* = 5.1 Hz, 2H, NHC**H**$_2$), 2.09 (m, 1H, CHCH**H**'), 1.88 - 1.73 (m, 3H, CHC**H**H' and C**H**$_2$), 1.67 (qn, *J* = 5.1 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.63 (qn, *J* = 5.1 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.40 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.39 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO, 70 ° C): δ = 182.2 (**C**), 172.0 (**C**), 155.2 (**C**), 153.2 (**C**), 78.2 (**C**), 77.2 (**C**), 59.7 (**C**H), 46.2 (**C**H$_2$), 40.8 (**C**H$_2$), 40.7 (**C**H$_2$), 37.5 (**C**H$_2$), 35.8 (**C**H$_2$), 29.1 (**C**H$_2$), 28.9 (2**C**H$_2$), 27.9 (3**C**H$_3$), 27.8 (3**C**H$_3$), 23.0 (**C**H$_2$) ppm.

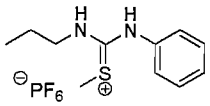
[1-(3-*tert*-Butoxycarbonylamino-propylamino)-1-{2-[((*S*)-1-*tert*-butoxycarbonyl-pyrrolidine-2-carbonyl)-amino]-propylamino}-methylidene]-methyl-sulfonium; iodide (138).



Prepared according to the procedure given by Bartoli *et al.*[207]

137 (105 mg, 0.214 mmol) was dissolved in acetone (4 mL). To this solution iodomethane (128 μL, 2.14 mmol) was added and the reaction mixture stirred at room temperature for 3 hours. On completion the solvent and excess iodomethane was removed under reduced pressure to give thiouronium **138** as a colourless oil (132 mg, 0.210 mmol, 98 %). $[\alpha]_D$ = - 36.1 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 502 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{23}H_{44}N_5O_5S^+$ requires m/z: 502.3058, found m/z: 502.3047; IR (film): ν_{max} = 3246 (w), 2970 (w), 2879 (w), 1676 (s), 1604 (s), 1509 (s), 1390 (s), 1161 (m), 732 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 8.74 (bs, 2H, N**H**), 7.65 (bs, 1H, N**H**), 6.46 (bs, 1H, N**H**), 4.09 (dd, *J* = 8.4, 3.4 Hz, 1H, C**H**CO), 3.43 (t, *J* = 7.0 Hz, 4H, 2NHC**H**$_2$), 3.38 - 3.30 (m, 2H, NC**H**$_2$), 3.20 - 3.13 (m, 2H, NHC**H**$_2$), 3.04 (q, *J* = 6.6 Hz, 2H, NHC**H**$_2$), 2.69 (s, 3H, C**H**$_3$), 2.11 (m, 1H, CHCH**H**'), 1.88 - 1.73 (m, 7H, CHC**H**H' and 3CH$_2$C**H**$_2$CH$_2$), 1.41 (s, 9H, C(C**H**$_3$)$_3$), 1.39 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (**C**), 167.0 (**C**), 155.2 (**C**), 153.2 (**C**), 80.3 (**C**), 79.6 (**C**), 60.7 (**C**H), 47.4 (**C**H$_2$), 41.9 (**C**H$_2$), 41.3 (**C**H$_2$), 37.0 (**C**H$_2$), 35.6 (**C**H$_2$), 29.2 (2**C**H$_2$), 28.5 (3**C**H$_3$), 28.4 (3**C**H$_3$), 24.6 (**C**H$_2$), 28.8 (**C**H$_2$), 15.0 (**C**H$_3$) ppm.

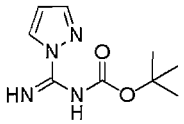
[1-Phenylamino-1-propylamino-methylidene]-methyl-sulfonium; hexafluoro phosphate (140).



Prepared according to the procedure given by Bartoli *et al.*[207]

128 (260 mg, 1.33 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (833 μL, 13.3 mmol) was added and the reaction mixture was stirred at room temperature for 5 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (447 mg, 1.33 mmol, 100 %). The thiouronium iodide (447 mg, 1.33 mmol) was dissolved in DCM (15 mL) and methanol (15 mL), to this solution ammonium hexafluorophosphate (261 mg, 1.6 mmol) was added and the solution stirred at room temperature for 18 hours. The solvents were removed from the reaction mixture and the resulting oil was redissolved in DCM (100 mL). The organic phase was washed with water (80 mL). The combined organic was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow foam which yielded thiouronium **140** (405 mg, 1.14 mmol, 86 %). MS (ES^+): m/z (%) 209 (100) $[M]^+$; MS (ES^-): m/z (%) 145 (100) $[PF_6]^-$; IR (film): ν_{max} = 2962 (w), 2873 (w), 1607 (s), 1582 (s), 1284 (m), 837 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (tt, *J* = 7.4, 1.8 Hz, 2H, 2CHC**H**CH), 7.17 (tt, *J* = 7.4, 1.2 Hz, 1H, CHC**H**CH), 7.07 (dd, *J* = 8.4, 1.2 Hz, 2H, 2CC**H**CH), 3.40 (t, *J* = 7.3 Hz, 2H, NHC$\mathbf{H}_2$$CH_2$), 2.41 (s, 3H, C$\mathbf{H}_3$), 1.67 (sext, *J* = 7.4 Hz, 2H, CH_2C$\mathbf{H}_2$$CH_3$), 0.97 (t, *J* = 7.4 Hz, 3H, CH_2C$\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.5 (**C**), 137.0 (**C**), 129.7 (2**C**H), 125.3 (2**C**H), 123.9 (**C**H), 46.1 ($\mathbf{C}H_2$), 22.8 ($\mathbf{C}H_2$), 14.5 ($\mathbf{C}H_3$), 11.4 ($\mathbf{C}H_3$) ppm.

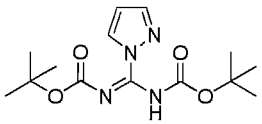
(Imino-pyrazol-1-yl-methyl)-carbamic acid *tert*-butyl ester (147).



Prepared according to the procedure given by Bernatowicz *et al.*[251]

143 (1.00 g, 6.82 mmol) was dissolved in DMF (10 mL) and THF (10 mL) and treated with DIPEA (2.98 mL, 17.1 mmol) before the addition of di - *tert* - butyl dicarbonate (1.49 g, 6.82 mmol). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure to yield a white solid. The crude material was dissolved in DCM (50 mL) and washed with 1M $KHSO_4$ aqueous solution (50 mL), saturated K_2CO_3 aqueous solution (50 mL) and brine (20 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to yield guanidine **147** as a pale pink solid (1.27 g, 6.05 mmol, 89 %). Mp.: 95 – 97 ° C (ethyl acetate) (Literature Mp.: 98 - 99 ° C)[251]; MS (ES^+): m/z (%) 233 (100) $[M+Na]^+$; IR (film): ν_{max} = 3433 (m), 3315 (m), 2977 (m), 2964 (m), 1653 (s), 1607 (s), 1509 (m), 1308 (s), 1153 (s), 758 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.06 (bs, 1H, N**H**), 8.44 (dd, J = 2.8, 0.6 Hz, 1H, NC**H**CH), 7.65 (dd, J = 1.6, 0.6 Hz, 1H, NC**H**CH), 7.60 (bs, 1H, N**H**), 6.38 (dd, J = 2.8, 1.6 Hz, 1H, CHC**H**CH), 1.53 (s, 9H, C($C\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5 (**C**), 155.2 (**C**), 143.5 (**C**H), 129.0 (**C**H), 109.0 (**C**H), 80.3 (**C**), 28.3 (3**C**H_3) ppm.

(*tert*-Butoxycarbonylimino-pyrazol-1-yl-methyl)-carbamic acid *tert*-butyl ester (148).

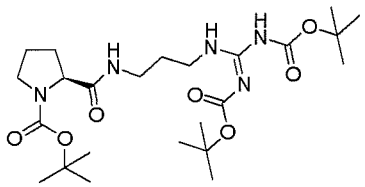


Prepared according to the procedure given by Bernatowicz *et al.*[251]

All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. To a stirring suspension of sodium hydride (825 mg, 20.6 mmol) in THF (40 mL) cooled to - 5 ° C, (**147**) was added (1.24 g, 5.90 mmol) as a solution in THF (20 mL) dropwise over 20 minutes. The resulting solution was stirred at - 5 ° C for 30 minutes before the addition di - *tert* - butyl dicarbonate (1.9 g, 8.8 mmol) as a solution in THF (20 mL) dropwise over 10 minutes. The reaction was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature. The reaction was stirred at room temperature for 48 hours. The reaction was cooled to - 5 ° C and quenched by the addition of cold water (20 mL) dropwise over 20 minutes. The reaction was extracted with ethyl acetate (3 x 50 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to give guanidine **148** as a white solid (1.55 g, 4.99 mmol, 85 %). Mp.: 107 - 108 ° C (methanol / water) (Literature Mp.: 108 - 109 ° C)[251]; MS (ES^+): m/z (%) 333 (100) $[M+Na]^+$; IR (film): ν_{max} = 2979 (w), 1763 (m), 1495 (s), 1236 (s), 1127 (s), 905 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.93 (bs, 1H, N**H**), 8.32 (dd, J = 2.8, 0.7 Hz, 1H, NC**H**CH), 7.63 (dd, J = 1.6, 0.7 Hz, 1H, NC**H**CH), 6.42 (dd, J = 2.8, 1.6 Hz, 1H, CHC**H**CH), 1.56 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.51 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5 (**C**), 149.5 (**C**), 142.8 (**C**H), 139.2 (**C**), 129.1 (**C**H), 109.9 (**C**H), 83.4 (**C**), 81.5 (**C**), 28.2 ($3\mathbf{C}H_3$), 27.8 ($3\mathbf{C}H_3$) ppm.

Spectroscopic data agrees with literature reference[294].

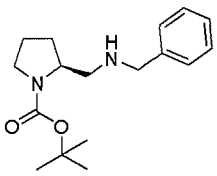
(*S*)-2-(*tert*-Butoxycarbonylimino 3-guanidino-propylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (149).



Prepared according to the procedure given by Bernatowicz *et al.*[251]

113 (383 mg, 1.41 mmol) was dissolved in dry THF (0.6 mL) and treated with **148** (438 mg, 1.41 mmol) and stirred at 60 ° C for 24 hours. The reaction was cooled to room temperature and the solvent removed under reduced pressure to give a pale yellow oil. The crude material was purified by column chromatography (5 % methanol / DCM) to yield guanidine **149** as a yellow oil (141 mg, 0.275 mmol, 20 %). $[\alpha]_D$ = - 27.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 536 (100) $[M+Na]^+$; HRMS (ES^+): $[M+H]^+$ $C_{24}H_{43}N_5NaO_7$ requires m/z: 536.3055, found m/z: 536.3048; IR (film): ν_{max} = 3330 (m), 2967 (w), 1697 (m), 1642 (s), 1559 (m), 1394 (m), 1161 (s), 1134 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 11.41 (bs, 1H, N**H**), 8.48 (bs, 1H, N**H**), 7.00 (bs, 1H, N**H**), 4.20 (dd, *J* = 8.4, 3.4 Hz, 1H, C**H**CO), 3.42 - 3.39 (m, 5H, 2NC$\mathbf{H}_2$ and NC**H**H'), 3.16 (m, 1H, NCH**H**'), 2.11 (m, 1H, C**H**H'), 2.00 (m, 1H, CH**H**'), 1.88 (m, 1H, C**H**H'), 1.77 (m, 1H, CH**H**'), 1.67 (qn, *J* = 6.4 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.44 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.43 (s, 9H, $C(C\mathbf{H}_3)_3$), 1.38 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8 (**C**), 163.6 (**C**), 160.9 (**C**), 156.6 (**C**), 153.2 (**C**), 83.3 (**C**), 80.0 (**C**), 79.3 (**C**), 60.8 (**C**H), 47.0 ($\mathbf{C}H_2$), 37.7 ($\mathbf{C}H_2$), 36.1 ($\mathbf{C}H_2$), 29.5 ($\mathbf{C}H_2$), 28.4 ($3\mathbf{C}H_3$), 28.3 ($3\mathbf{C}H_3$), 28.1 ($3\mathbf{C}H_3$), 24.5 ($\mathbf{C}H_2$), 23.6 ($\mathbf{C}H_2$) ppm.

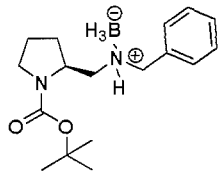
(*S*)-2-(Benzylamino-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (155).



Prepared according to the procedure given by Bartoli *et al.*[252]

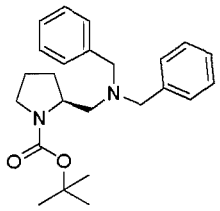
All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **100** (1.00 g, 3.29 mmol) was dissolved in THF (4 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.00 M, 6.57 mL, 6.57 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 7 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (20 mL) added dropwise over 20 minutes. The reaction mixture was then extracted with ethyl acetate (150 mL) and the organic phase was washed with brine (25 mL), saturated $NaHCO_3$ aqueous solution (25 mL) and water (2 x 25 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) to yield amine **155** as a white solid (252 mg, 0.868 mmol, 26 %). Mp.: 158 – 160 ° C ($CHCl_3$); $[\alpha]_D$ = - 33.5 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 291 (100) $[M+H]^+$; IR (film): ν_{max} = 2972 (w), 2874 (w), 1686 (s), 1453 (m), 1389 (s), 1164 (s), 1104 (s), 733 (s), 698 (s) cm^{-1}; (400 MHz, d_6DMSO, 90 ° C): δ = 9.26 (bs, 1H, N**H**), 7.59 - 7.57 (m, 2H, 2C**H**), 7.45 - 7.40 (m, 2H, 2C**H**), 7.30 (m, 1H, C**H**), 4.17 (dd, *J* = 12.5, 9.5 Hz, 1H, CHCH**H**'N), 4.07 (m, 1H, C**H**CH_2), 3.36 - 3.16 (m, 2H, N$C\mathbf{H}_2$), 3.07 - 2.91 (m, 3H, NH$C\mathbf{H}_2$ and CHC**H**H'N), 1.98 (m, 1H, CHC**H**H'), 1.89 - 1.72 (m, 3H, CH**H**'$C\mathbf{H}_2$), 1.39 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2 (**C**), 141.6 (**C**), 128.5 (2**C**H), 128.2 (2**C**H), 127.1 (**C**H), 79.4 (**C**), 57.3 (**C**H), 53.9 ($\mathbf{C}H_2$), 52.7 ($\mathbf{C}H_2$), 46.6 ($\mathbf{C}H_2$), 29.7 ($\mathbf{C}H_2$), 28.6 ($3\mathbf{C}H_3$), 23.5 ($\mathbf{C}H_2$) ppm.

(*S*)-Benzyl-((s)-1-*tert*-butoxycarbonyl-pyrrolidin-2-ylmethyl) ammonium borane (156).



Colourless crystals: Mp.: 118 - 119 ° C (DCM); MS (ES^+): m/z (%) 327 (100) $[M+Na]^+$; IR (film): ν_{max} = 2971 (w), 2862 (w), 2363 (w), 1689 (s), 1454 (m), 1393 (s), 1163 (s), 1134 (s), 774 (s), 698 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO): δ = 7.49 - 7.23 (m, 5H, 5C**H**), 6.63 (bs, 1H, N**H**), 4.35 (m, 1H, C**H**CH_2), 4.17 (dd, *J* = 14.2, 3.0 Hz, 1H, CHC**H**H'N), 3.39 (dd, *J* = 13.8, 10.2 Hz, 1H, CHCH**H**'N), 3.34 - 3.21 (m, 2H, NC$\mathbf{H}_2$), 2.59 (s, 2H, C$\mathbf{H}_2$Ph), 1.98 - 1.78 (m, 2H, C$\mathbf{H}_2$$CH_2$), 1.72 - 1.57 (m, 2H, CH_2C$\mathbf{H}_2$), 1.42 (s, 3H, B$\mathbf{H}_3$), 1.37 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 (**C**), 134.5 (**C**), 130.2 (2**C**H), 129.6 (2**C**H), 128.7 (**C**H), 80.7 (**C**), 61.3 (**C**H_2), 59.8 (**C**H_2), 55.1 (**C**H), 47.3 (**C**H_2), 31.2 (**C**H_2), 28.8 (3**C**H_3), 24.1 (**C**H_2) ppm; For crystal structure see **Appendix 2**.

(*S*)-2-[(Dibenzylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (157).

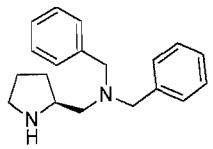


Prepared according to the procedure given by Miller *et al.*[253]

155 (191 mg, 0.658 mmol) was dissolved in acetonitrile (3 mL) and treated with K_2CO_3 (182 mg, 1.32 mmol) and benzyl bromide (78.2 μL, 0.658 mmol) and the resulting suspension stirred vigorously for 3 hours. The reaction mixture was treated with water (10 mL) and the reaction mixture extracted with ethyl acetate (4 x 20 mL).

The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % ethyl acetate / petroleum ether) to yield amine **157** as a colourless oil (217 mg, 0.570 mmol, 87 %). $[\alpha]_D$ = - 127.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 381 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{24}H_{33}N_2O_2$ requires m/z: 381.2537, found m/z: 381.2530; IR (film): ν_{max} = 2967 (w), 2873 (w), 1688 (s), 1390 (s), 1167 (s), 1109 (s), 733 (s), 698 (s) cm^{-1}; (400 MHz, d_6DMSO, 80 ° C): δ = 7.36 - 7.29 (m, 8H, 8C**H**), 7.23 (tt, *J* = 6.7, 1.9 Hz, 2H, 2CHC**H**CH), 3.85 (dt, *J* = 9.5, 4.8 Hz, 1H, C**H**CH_2), 3.73 (d, *J* = 13.6 Hz, 2H, N$C\mathbf{H}_2$), 3.43 (d, *J* = 13.8 Hz, 2H, N$C\mathbf{H}_2$), 3.18 (m, 1H, NC**H**H'), 3.06 (ddd, *J* = 10.7, 8.1, 3.7 Hz, 1H, NCH**H**'), 2.59 (dd, *J* = 12.5, 3.8 Hz, 1H, CHCH**H**'N), 2.31 (dd, *J* = 12.5, 9.5 Hz, 1H, CHCH**H**'N), 1.77 - 1.72 (m, 2H, $CH_2C\mathbf{H}_2$), 1.60 (m, 1H, CHC**H**H'), 1.47 (m, 1H, CHCH**H**'), 1.41 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6 (**C**), 139.8 (2**C**), 129.0 (4**C**H), 128.2 (4**C**H), 127.0 (2**C**H), 79.2 (**C**), 59.3 ($\mathbf{C}H_2$), 59.1 ($\mathbf{C}H_2$), 56.2 ($\mathbf{C}H_2$), 55.6 (**C**H), 46.1 ($\mathbf{C}H_2$), 29.1 ($\mathbf{C}H_2$), 28.1 ($3\mathbf{C}H_3$), 22.3 ($\mathbf{C}H_2$) ppm.

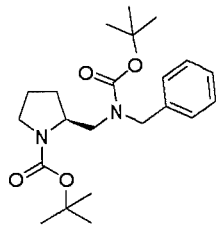
Dibenzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amine (158).



157 (200 mg, 0.526 mmol) was dissolved in a 20 % solution of TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 48 hours. The solvent and residual TFA were removed under reduced pressure to give a yellow oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give amine **158** as a colourless oil (76.0 mg, 0.271 mmol, 52 %).

$[\alpha]_D$ = + 11.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 281 (100) $[M+H]^+$; IR (film): ν_{max} = 2960 (w), 1670 (s), 1198 (s), 1125 (m), 699 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54 (bs, 1H, N**H**), 7.37 - 7.26 (m, 10H, 10C**H**), 3.76 - 3.71 (m, 3H, C**H**CH_2 and NC**H**$_2$Ph), 3.54 (d, *J* = 13.2 Hz, 2H, NC**H**$_2$Ph), 3.07 (m, 1H, NHCH**H**'CH_2), 2.61 - 2.53 (m, 3H, NHC**H**H'CH_2 and CHC**H**$_2$N), 2.06 (dt, *J* = 13.0, 6.2 Hz, 1H, CHCH**H**'CH_2), 1.84 (dt, *J* = 13.0, 6.2 Hz, 1H, CHC**H**H'CH_2), 1.66 - 1.49 (m, 2H, CH_2C**H**$_2$$CH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (2**C**), 129.3 (4**C**H), 128.8 (4**C**H), 127.7 (2**C**H), 58.7 (2**C**H_2), 56.5 (**C**H), 54.2 (**C**H_2), 44.1 (**C**H_2), 28.2 (**C**H_2), 23.3 (**C**H_2) ppm.

(*S*)-2-[(Benzyl-*tert*-butoxycarbonyl-amino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (159).

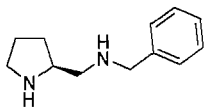


Prepared according to the procedure given by Nakanishi *et al.*[295]

155 (410 mg, 1.41 mmol) was dissolved in DCM (15 mL) and treated with di - *tert* - butyldicarbonate (339 mg, 1.56 mmol) and Et_3N (217 µL, 1.56 mmol) and stirred at room temperature for 18 hours. The reaction mixture was washed with saturated K_2CO_3 aqueous solution (3 x 10 mL) and the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to give the carbamate **159** as a white crystalline solid (303 mg, 0.776 mmol, 55 %). Mp.: 79 - 81 ° C ($CHCl_3$); $[\alpha]_D$ = - 9.9 ° (c = 0.8, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 391 (80) $[M+H]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{22}H_{34}N_2NaO_4$ requires m/z: 413.2411, found m/z: 413.2408; IR (solid): ν_{max} = 2973 (w), 2873 (w), 1686 (s), 1391 (m), 1159 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.33 (tt, *J* = 7.6, 1.5 Hz, 2H, 2CHC**H**CH), 7.26 (m, 1H, CHC**H**CH), 7.20 (m, 2H, 2CC**H**CH), 4.43 (d,

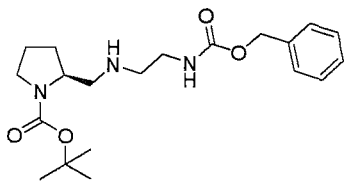
J = 15.8 Hz, 1H, NCH**H**'), 4.36 (d, J = 15.7 Hz, 1H, NCH**H**'), 3.95 (m, 1H, C**H**CH_2), 3.32 - 3.13 (m, 4H, 2NC**H**$_2$), 1.87 - 1.76 (m, 4H, 2C**H**$_2$), 1.41 (s, 9H, C(C**H**$_3$)$_3$), 1.38 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 155.1 (**C**), 153.6 (**C**), 138.5 (**C**), 128.4 (2**C**H), 126.9 (2**C**H), 126.6 (**C**H), 79.0 (**C**), 78.4 (**C**), 54.8 (**C**H), 49.2 (**C**H_2), 47.9 (**C**H_2), 45.7 (**C**H_2), 28.1 (3**C**H_3), 28.0 (3**C**H_3), 23.0 (**C**H_2), 22.0 (**C**H_2) ppm; For crystal structure see **Appendix 2**.

Benzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amine (160).



159 (273 mg, 0.699 mmol) was dissolved in a 20 % solution of TFA (1 mL) in DCM (4 mL) and stirred at room temperature for 4 hours. The solvent and residual TFA were removed under reduced pressure to give a yellow oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give diamine **160** as a pale yellow oil (123 mg, 0.646 mmol, 92 %). $[\alpha]_D$ = + 17.2 ° (c = 0.9, $CHCl_3$, 31 ° C, 589 nm) (Literature $[\alpha]_D$ = + 15.6 ° (c = 1.01, EtOH, 20 ° C))[296]; MS (ES^+): m/z (%) 191 (100) $[M+H]^+$; IR (film): ν_{max} = 2956 (w), 1670 (s), 1198 (s), 1125 (m), 699 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 - 7.21 (m, 5H, 5C**H**), 5.29 (bs, 2H, 2N**H**), 3.56 (s, 2H, NHC**H**$_2$Ph), 3.48 (m, 1H, C**H**CH_2), 3.05 (t, J = 7.3 Hz, 2H, CH_2C**H**$_2$NH), 2.75 (dd, J = 12.5, 4.5 Hz, 1H, CHCH**H**'NH), 2.67 (dd, J = 12.5, 9.0 Hz, 1H, CHC**H**H'NH), 1.95 (ddd, J = 12.7, 7.6, 2.6 Hz, 1H, CHCH**H**'CH_2), 1.91 - 1.78 (m, 2H, CH_2C**H**$_2$$CH_2$), 1.51 (ddd, J = 15.6, 12.7, 7.6 Hz, 1H, CHC**H**H'CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8 (**C**), 128.6 (2**C**H), 128.3 (2**C**H), 127.2 (**C**H), 59.0 (**C**H), 53.8 (**C**H_2), 51.4 (**C**H_2), 45.4 (**C**H_2), 28.9 (**C**H_2), 24.6 (**C**H_2) ppm.
Spectroscopic data agrees with literature reference[296].

(*S*)-2-[(2-Benzyloxycarbonylamino-ethylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (161).

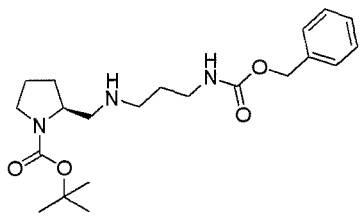


Prepared according to the procedure given by Bartoli *et al.*[252]

All glassware used for the reaction was flame dried, the reaction was carried out under an atmosphere of nitrogen gas and solvents were used distilled. **122** (7.29 g, 18.6 mmol) was dissolved in THF (22 mL) and the resulting solution was cooled to - 5 ° C. Borane - THF complex (1.00 M, 37.2 mL, 37.2 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 7 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (40 mL) added dropwise over 30 minutes. The reaction mixture was then extracted with ethyl acetate (3 x 250 mL) and the organic phase was washed with brine (100 mL), saturated $NaHCO_3$ aqueous solution (100 mL) and water (2 x 100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (20 % methanol / DCM) to yield carbamate **161** as a colourless oil (4.87 g, 12.9 mmol, 69 %). $[\alpha]_D$ = - 24.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 378 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{20}H_{32}N_3O_4$ requires m/z: 378.2387, found m/z: 378.2381; IR (film): ν_{max} = 3326 (w), 2973 (w), 2880 (w), 1675 (s), 1533 (m), 1392 (s), 1247 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.37 - 7.34 (m, 4H, 4C**H**), 7.28 (m, 1H, CHC**H**CH), 6.71 (bs, 1H, N**H**), 5.03 (s, 2H, C**H**$_2$Ph), 3.71 (ddd, *J* = 10.8, 7.0, 3.6 Hz, 1H, C**H**CH$_2$), 3.26 (m, 1H, NCH**H**'), 3.17 (m, 1H, NC**H**H'), 3.15 - 3.09 (m, 3H, N**H**C**H**$_2$), 2.70 (dd, *J* = 11.8, 4.1 Hz, 1H, CHCH**H**'), 2.64 (dt, *J* = 6.6, 1.3 Hz, 2H, NHC**H**$_2$), 2.50 (dd, *J* = 11.9, 7.9 Hz, 1H, CHC**H**H'), 1.87 - 1.67 (m, 4H, 2C**H**$_2$), 1.40 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 155.9 (**C**), 153.3 (**C**), 136.9 (**C**),

128.3 (2**C**H), 128.1 (2**C**H), 127.7 (**C**H), 77.8 (**C**), 64.8 (**C**H_2), 56.4 (**C**H), 51.1 (**C**H_2), 48.6 (**C**H_2), 45.9 (**C**H_2), 40.3 (**C**H_2), 28.4 (**C**H_2), 27.8 (3**C**H_3), 22.9 (**C**H_2) ppm.

(*S*)-2-[(3-Benzyloxycarbonylamino-propylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (162).

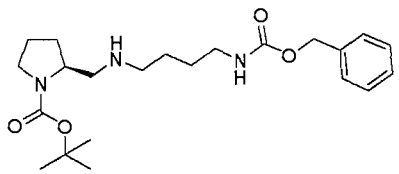


Prepared according to the procedure given by Bartoli *et al.*[252]

All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **111** (3.67 g, 9.05 mmol) was dissolved in THF (11 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.00 M, 18.1 mL, 18.1 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 7 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (40 mL) added dropwise over 20 minutes. The reaction mixture was then extracted with ethyl acetate (200 mL) and the organic phase washed saturated $NaHCO_3$ aqueous solution (200 mL) and brine (200 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) to yield carbamate **162** as a colourless oil (2.13 g, 5.43 mmol, 60 %). $[\alpha]_D$ = - 25.6 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 392 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{21}H_{34}N_3O_4$ requires m/z: 392.2544, found m/z: 392.2536; IR (film): ν_{max} = 3305 (w), 2973 (w), 1678 (s), 1530 (w), 1392 (s), 1165 (m), 749 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.38 - 7.29 (m, 5H, 5C**H**), 6.96 (bs, 1H, N**H**), 5.04 (s, 2H, C$\mathbf{H}_2$Ph), 3.89 (m, 1H, C**H**CH_2), 3.32 (m, 1H, NCH**H**'), 3.24 (m, 1H, NC**H**H'), 3.10 (q, *J* = 6.7 Hz, 2H, NHC$\mathbf{H}_2$), 3.05 (bs, 1H, N**H**), 2.85 (dd,

J = 12.2, 4.9 Hz, 1H, CHCH**H**'N), 2.75 (t, J = 7.1 Hz, 2H, NHC**H**$_2$), 2.70 (dd, J = 12.2, 7.3 Hz, 1H, CHC**H**H'N), 1.92 (m, 1H, CHC**H**H'), 1.86 - 1.79 (m, 3H, CH**H**'C**H**$_2$), 1.70 (qn, J = 7.2 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.43 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.9 (**C**H$_2$), 25.7 (**C**H$_2$), 28.6 (3**C**H$_3$), 29.7 (**C**H$_2$), 40.7 (**C**H$_2$), 46.8 (**C**H$_2$), 48.6 (**C**H$_2$), 53.1 (**C**H$_2$), 56.9 (**C**H), 66.7 (**C**H$_2$), 79.7 (**C**), 128.1 (**C**H), 128.2 (2**C**H), 128.6 (2**C**H), 136.8 (**C**), 156.7 (**C**), 158.3 (**C**) ppm.

(*S*)-2-[(3-benzyloxycarbonylamino-butylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (163).

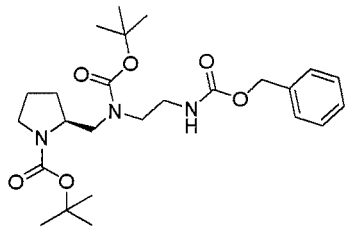


Prepared according to the procedure given by Bartoli *et al.*[252]

All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **112** (6.83 g, 16.3 mmol) was dissolved in THF (20 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.0 M, 32.6 mL, 32.6 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 7 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (10 mL) added dropwise over 20 minutes. The reaction mixture was then extracted with ethyl acetate (3 x 250 mL) and the organic phase washed with brine (50 mL), saturated $NaHCO_3$ aqueous solution (50 mL) and water (2 x 50 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) to yield carbamate **163** as a cloudy pale yellow oil (1.36 g, 3.35 mmol, 21 %). $[\alpha]_D$ = - 23.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 406 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{36}N_3O_4$ requires m/z: 406.2700, found m/z: 406.2690; IR (film): ν_{max} = 3305 (m), 2975 (w), 2933 (w), 1669 (s),

1540 (w), 1395 (s), 1162 (s), 735 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.38 - 7.30 (m, 5H, 5C**H**), 6.90 (bs, 1H, N**H**), 5.03 (s, 2H, C$\mathbf{H}_2$Ph), 4.06 (m, 1H, C**H**CH_2), 3.95 (bs, 1H, N**H**), 3.30 (m, 1H, NCH**H**'), 3.25 (m, 1H, NC**H**H'), 3.04 (t, *J* = 6.0 Hz, 2H, NHC$\mathbf{H}_2$), 2.91 (dd, *J* = 12.2, 5.1 Hz, 1H, CHCH**H**'N), 2.86 (dd, *J* = 12.0, 7.1 Hz, 1H, CHC**H**H'N), 2.77 (t, *J* = 7.7 Hz, 2H, NHC$\mathbf{H}_2$), 1.95 - 1.70 (m, 4H, 2C$\mathbf{H}_2$), 1.59 (qn, *J* = 7.1 Hz, 2H, CH_2C$\mathbf{H}_2$$CH_2$), 1.50 (qn, *J* = 7.1 Hz, 2H CH_2C$\mathbf{H}_2$$CH_2$), 1.43 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3 (**C**), 156.7 (**C**), 136.8 (**C**), 128.8 (2**C**H), 128.6 (2**C**H), 128.1 (**C**H), 80.5 (**C**), 66.6 (**C**H_2), 60.7 (**C**H), 51.3 (**C**H_2), 47.3 (**C**H_2), 40.8 (**C**H_2), 38.5 (**C**H_2), 30.8 (**C**H_2), 28.5 (3**C**H_3), 27.4 (**C**H_2), 27.1 (**C**H_2), 26.3 (**C**H_2) ppm.

(*S*)-2-{[(2-Benzyloxycarbonylamino-ethyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (164).

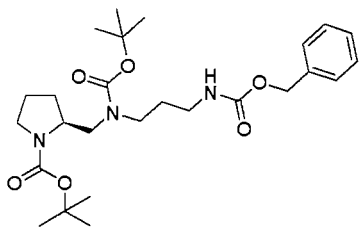


Prepared according to the procedure given by Nakanishi *et al.*[295]

161 (415 mg, 1.10 mmol) was dissolved in DCM (10 mL) and treated with di - *tert* - butyl dicarbonate (239 mg, 1.1 mmol) and Et_3N (153 μL, 1.10 mmol) and stirred at room temperature for 18 hours. The reaction mixture was washed with saturated K_2CO_3 aqueous solution (3 x 10 mL) and the organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude material was purified by column chromatography (100 % DCM) to give the carbamate **164** as a colourless oil (483 mg, 1.01 mmol, 92 %). $[\alpha]_D$ = - 15.8 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 500 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{25}H_{39}N_3NaO_6$ requires m/z: 500.2731, found m/z: 500.2727; IR (film): ν_{max} = 3338 (w), 2973 (w), 1686 (s), 1365 (m), 1159 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.37 - 7.30 (m, 5H, 5C**H**), 6.82 (bs, 1H, N**H**), 5.04 (s, 2H, C$\mathbf{H}_2$Ph), 3.95 (dq, *J* = 6.7, 2.3 Hz, 1H, C**H**CH_2), 3.33 - 3.16 (m,

8H, NHC**H**$_2$ and 3NC**H**$_2$), 1.84 - 1.71 (m, 4H, 2C**H**$_2$), 1.42 (s, 9H, C(C**H**$_3$)$_3$), 1.41 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 156.1 (**C**), 154.7 (**C**), 153.4 (**C**), 137.1 (**C**), 128.3 (2**C**H), 127.8 (2**C**H), 127.7 (**C**H), 78.7 (**C**), 78.4 (**C**), 65.2 (**C**H$_2$), 55.3 (**C**H), 48.8 (**C**H$_2$), 46.7 (**C**H$_2$), 45.7 (**C**H$_2$), 38.3 (**C**H$_2$), 28.1 (3**C**H$_3$), 28.0 (3**C**H$_3$), 22.9 (**C**H$_2$), 22.0 (**C**H$_2$) ppm.

(*S*)-2-{[(2-Benzyloxycarbonylamino-propyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (165).

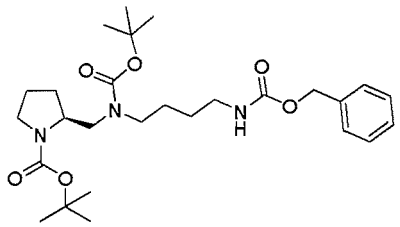


Prepared according to the procedure given by Nakanishi *et al.*[295]

162 (1.68 g, 4.29 mmol) was dissolved in DCM (200 mL) and treated with di - *tert* - butyl dicarbonate (1.03 g, 4.72 mmol) and Et_3N (658 μL, 4.72 mmol) and stirred at room temperature for 18 hours. The reaction mixture was washed with saturated K_2CO_3 aqueous solution (3 x 40 mL) and the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (100 % DCM) to give the carbamate **165** as a colourless oil (1.45 g, 2.95 mmol, 69 %). $[\alpha]_D$ = - 16.7 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 492 (100) $[M+H]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{26}H_{41}N_3NaO_6$ requires m/z: 514.2888, found m/z: 514.2885; IR (film): ν_{max} = 3339 (w), 2973 (w), 1686 (s), 1365 (m), 1159 (s) cm^{-1}; ^{1}H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.38 - 7.33 (m, 4H, 4C**H**), 7.31 (m, 1H, C**H**), 6.81 (bs, 1H, N**H**), 5.03 (s, 2H, C**H**$_2$Ph), 3.91 (m, 1H, C**H**CH$_2$), 3.32 - 3.23 (m, 2H, NC**H**$_2$), 3.21 - 3.15 (m, 2H, NC**H**$_2$), 3.03 (apparent q, *J* = 6.9 Hz, 4H, 2NC**H**$_2$), 1.83 - 1.74 (m, 4H, 2C**H**$_2$), 1.68 (apparent dqn, *J* = 7.3, 2.1 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.42 (s, 18H, 2C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6 (**C**), 156.2 (**C**), 154.7 (**C**), 136.9 (**C**), 128.5 (2**C**H), 128.1 (2**C**H), 127.9 (**C**H), 79.9 (**C**), 79.4 (**C**), 66.5 (**C**H$_2$),

55.8 (**C**H), 47.9 (**C**H_2), 46.7 (**C**H_2), 43.2 (**C**H_2), 37.9 (**C**H_2), 28.6 (3**C**H_3), 28.5 (3**C**H_3), 28.0 (**C**H_2), 23.6 (**C**H_2), 22.6 (**C**H_2) ppm.

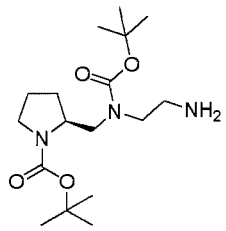
(*S*)-2-{[(2-Benzyloxycarbonylamino-butyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (166).



Prepared according to the procedure given by Nakanishi *et al.*[295]

163 (681 mg, 1.35 mmol) was dissolved in DCM (15 mL) and treated with di - *tert* - butyldicarbonate (325 mg, 1.48 mmol) and Et_3N (207 μL, 1.48 mmol) and stirred at room temperature for 18 hours. The reaction mixture was washed with saturated K_2CO_3 aqueous solution (3 x 10 mL) and the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to give the carbamate **166** as a colourless oil (244 mg, 0.483 mmol, 36 %). $[\alpha]_D$ = - 17.1 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 528 (100) $[M+Na]^+$; HRMS (ES^+): $[M+H]^+$ $C_{27}H_{43}N_3NaO_6$ requires m/z: 528.3044, found m/z: 528.3047; IR (film): ν_{max} = 3341 (w), 2973 (w), 1674 (s), 1391 (m), 1159 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.37 - 7.33 (m, 4H, 4C**H**), 7.30 (m, 1H, C**H**), 6.85 (bs, 1H, N**H**), 5.03 (s, 2H, CH_2Ph), 3.91 (m, 1H, C**H**CH_2), 3.32 - 3.21 (m, 4H, 2NCH_2), 3.19 - 3.10 (m, 4H, 2NCH_2), 1.85 - 1.75 (m, 5H, CHCH**H**' and 2CH_2), 1.57 - 1.44 (m, 3H, CHC**H**H' and CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 1.41 (s, 9H, C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5 (**C**), 154.7 (**C**), 154.4 (**C**), 136.8 (**C**), 128.6 (2**C**H), 128.4 (2**C**H), 128.2 (**C**H), 79.5 (2**C**), 66.6 (**C**H_2), 55.9 (**C**H), 48.2 (**C**H_2), 46.7 (**C**H_2), 46.3 (**C**H_2), 40.6 (**C**H_2), 28.7 (3**C**H_3), 28.6 (3**C**H_3), 27.1 (**C**H_2), 25.4 (**C**H_2), 23.6 (**C**H_2), 22.7 (**C**H_2) ppm.

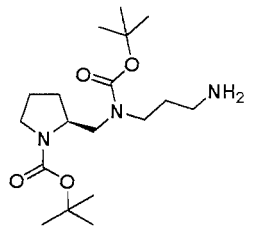
(*S*)-2-{[(2-Amino-ethyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (167).



Prepared according to the procedure given by Montero *et al.*[256]

164 (480 mg, 1.05 mmol) was dissolved in methanol (40 mL) and treated with palladium on activated carbon (dry, 10 %, 112 mg, 1.05 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature overnight. After 24 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give amine **167** as a colourless oil (345 mg, 1.01 mmol, 96 %). $[\alpha]_D$ = - 16.7 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z 344 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{17}H_{34}N_3O_4$ requires m/z: 344.2544, found m/z: 344.2534; IR (film): ν_{max} = 2973 (w), 1683 (s), 1389 (s), 1158 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 3.95 (m, 1H, **CH**CH_2), 3.31 - 3.15 (m, 6H, 3N**C**$\mathbf{H_2}$), 2.73 (t, *J* = 6.8 Hz, 2H, **C**$\mathbf{H_2}NH_2$), 2.65 (t, *J* = 6.7 Hz, 1H, N**H**), 2.33 (bs, 1H, N**H**), 1.84 - 1.74 (m, 4H, 2**C**$\mathbf{H_2}$), 1.43 (s, 9H, C(**C**$\mathbf{H_3}$)$_3$), 1.42 (s, 9H, C(**C**$\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 152.4 (**C**), 150.3 (**C**), 78.5 (**C**), 78.4 (**C**), 55.2 (**C**H), 49.7 (**C**H_2), 48.3 (**C**H_2), 46.1 (**C**H_2), 38.6 (**C**H_2), 28.1 (3**C**H_3), 28.0 (3**C**H_3), 23.0 (**C**H_2), 22.0 (**C**H_2) ppm.

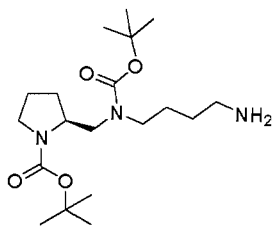
(*S*)-2-{[(2-Amino-propyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (168).



Prepared according to the procedure given by Montero *et al.*[256]

165 (1.39 g, 2.82 mmol) was dissolved in methanol (40 mL) and treated with palladium on activated carbon (dry, 10 %, 301 mg, 2.82 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature overnight. After 18 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give amine **168** as a colourless oil (1.01 g, 2.82 mmol, 100 %). $[\alpha]_D$ = - 17.6 ° (c = 1.0, $CHCl_3$, 29.5 ° C, 589 nm); MS (ES^+): m/z 358 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{18}H_{36}N_3O_4$ requires m/z: 358.2700, found m/z: 358.2701; IR (film): ν_{max} = 2967 (w), 2926 (w), 1683 (s), 1389 (s), 1158 (s), 1108 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 3.82 (m, 1H, **CH**CH_2), 3.32 - 3.14 (m, 6H, 3N**C**H_2), 2.62 - 2.52 (m, 4H, **C**H_2NH_2), 1.88 - 1.74 (m, 4H, **C**H_2**C**H_2), 1.60 (qn, *J* = 6.5 Hz, 2H, CH_2**C**$H_2$$CH_2$), 1.43 (s, 9H, C(**C**$H_3$)$_3$), 1.42 (s, 9H, C(**C**$H_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.4 (**C**), 154.3 (**C**), 79.7 (**C**), 79.6 (**C**), 55.9 (**C**H), 50.6 (**C**H_2), 48.0 (**C**H_2), 46.3 (**C**H_2), 39.1 (**C**H_2), 31.2 (**C**H_2), 28.7 (3**C**H_3), 28.6 (3**C**H_3), 23.6 (**C**H_2), 22.7 (**C**H_2) ppm.

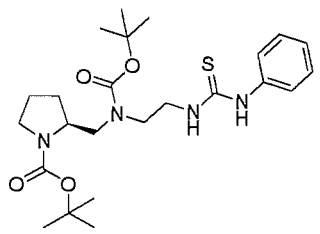
(*S*)-2-{[(2-Amino-butyl)-*tert*-butoxycarbonyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (169).



Prepared according to the procedure given by Montero *et al.*[256]

166 (223 mg, 0.441 mmol) was dissolved in methanol (8 mL) and treated with palladium on activated carbon (dry, 10 %, 47 mg, 0.441 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature overnight. After 18 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give amine **169** as a colourless oil (169 mg, 0.441 mmol, 100 %). $[\alpha]_D$ = - 18.2 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z 372 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{19}H_{38}N_3O_4$ requires m/z: 372.2857, found m/z: 372.2854; IR (film): ν_{max} = 2973 (w), 2930 (w), 1683 (s), 1389 (s), 1158 (s), 1108 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 3.92 (m, 1H, C**H**CH_2), 3.54 (bs, 2H, N**H**$_2$), 3.30 - 3.25 (m, 4H, 2NC**H**$_2$), 3.22 - 3.15 (m, 3H, CHCH**H**'N and C**H**$_2$$NH_2$), 2.74 (dd, *J* = 11.7, 6.8 Hz, 1H, CHC**H**H'N), 1.86 - 1.75 (m, 5H, CHCH**H**' and 2C**H**$_2$), 1.59 - 1.46 (m, 3H, CHC**H**H' and C**H**$_2$), 1.42 (s, 9H, C(C**H**$_3$)$_3$), 1.41 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.8 (**C**), 154.6 (**C**), 79.6 (**C**), 79.5 (**C**), 55.9 (**C**H), 48.3 (**C**H_2), 46.6 (**C**H_2), 46.4 (**C**H_2), 41.1 (**C**H_2), 28.7 (3**C**H_3), 28.6 (3**C**H_3), 26.0 (**C**H_2), 25.2 (**C**H_2), 23.5 (**C**H_2), 22.7 (**C**H_2) ppm.

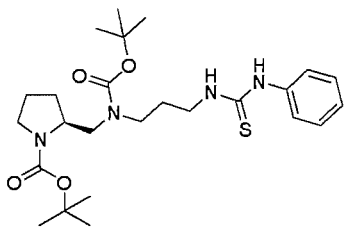
(*S*)-2-({*tert*-Butoxycarbonyl-[2-(3-phenyl-thioureido)-ethyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (170).



Prepared according to the procedure given by Bartoli *et al.*[207]

167 (345 mg, 1.01 mmol) was dissolved in a biphasic solution of chloroform (40 mL), methanol (40 mL) and saturated $NaHCO_3$ aqueous solution (10 mL) and treated with phenyl isothiocyanate (125 µL, 1.05 mmol). The reaction mixture was stirred vigorously at room temperature for 36 hours. The phases of the reaction mixture were separated and the organic phase washed with water (2 x 40 mL) and the aqueous phase extracted with DCM (3 x 40 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield the thiourea **170** as a colourless oil (240 mg, 0.501 mmol, 50 %). $[\alpha]_D$ = - 19.8 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z 501 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{24}H_{38}N_4NaO_4S$ requires m/z: 501.2506, found m/z: 501.2518; IR (film): ν_{max} = 3292 (w), 2974 (w), 1675 (s), 1534 (m), 1157 (s), 728 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 8.76 (bs, 1H, N**H**), 7.48 (bs, 1H, N**H**), 7.44 - 7.41 (m, 2H, 2C**H**), 7.38 - 7.26 (m, 2H, 2C**H**), 7.12 (m, 1H, CHC**H**CH), 4.03 (m, 1H, C**H**CH_2), 3.69 (ddd, *J* = 25.8, 13.5, 6.6 Hz, 1H, NCH**H**'), 3.50 (dd, *J* = 12.8, 6.6 Hz, 1H, CHCH**H**'N), 3.42 (dt, *J* = 6.6, 3.5 Hz, 1H, NC**H**H'), 3.29 - 3.25 (m, 5H, N**C**H_2**C**H_2NH and CHC**H**H'N), 1.87- 1.73 (m, 4H, 2**C**H_2), 1.44 (s, 9H, C(**C**H_3)$_3$), 1.42 (s, 9H, C(**C**H_3)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 180.3 (**C**), 154.8 (**C**), 153.2 (**C**), 140.7 (**C**), 128.4 (2**C**H), 127.6 (2**C**H), 126.0 (**C**H), 78.6 (**C**), 78.2 (**C**), 54.8 (**C**H), 47.7 (**C**H_2), 45.8 (**C**H_2), 45.5 (**C**H_2), 41.8 (**C**H_2), 27.9 (3**C**H_3), 27.8 (3**C**H_3), 22.8 (**C**H_2), 21.8 (**C**H_2) ppm.

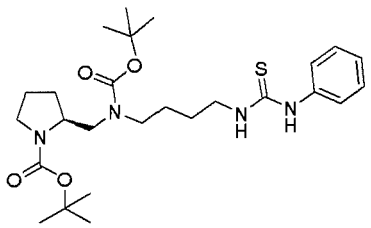
(*S*)-2-({*tert*-Butoxycarbonyl-[2-(3-phenyl-thioureido)-propyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (171).



Prepared according to the procedure given by Bartoli *et al.*[207]

168 (500 mg, 1.39 mmol) was dissolved in a biphasic solution of chloroform (85 mL), methanol (25 mL) and saturated $NaHCO_3$ aqueous solution (25 mL) and treated with phenyl isothiocyanate (167 μL, 1.39 mmol). The reaction mixture was stirred vigorously at room temperature for 36 hours. The phases of the reaction mixture were separated and the organic phase washed with water (2 x 55 mL) and the aqueous phase extracted with DCM (2 x 55 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield the thiourea **171** as a pale yellow oil (500 mg, 1.02 mmol, 73 %). $[\alpha]_D$ = - 21.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z 515 (100) $[M+Na]^+$ HRMS (ES^+): $[M+Na]^+$ $C_{25}H_{40}N_4NaO_4S$ requires m/z: 515.2662, found m/z: 515.2658; IR (film): ν_{max} = 3271 (w), 2974 (w), 2926 (w), 1675 (s), 1536 (m), 1158 (s), 728 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 9.33 (bs, 1H, N**H**), 7.61 (bs, 1H, N**H**), 7.45 (dd, *J* = 8.7, 1.3 Hz, 2H, 2C**H**), 7.30 (td, *J* = 7.5, 2.0 Hz, 2H, 2C**H**), 7.09 (tt, *J* = 7.5, 1.1 Hz, 1H, CHC**H**CH), 3.94 (m, 1H, C**H**CH_2), 3.50 (q, *J* = 7.1 Hz, 2H, CH_2NH), 3.30 - 3.25 (m, 4H, 2NCH_2), 3.23 (dd, *J* = 14.5, 7.2 Hz, 2H, CHCH_2N), 1.88 - 1.75 (m, 6H, 3CH_2), 1.43 (s, 9H, C(CH_3)$_3$), 1.42 (s, 9H, C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.4 (**C**), 159.4 (**C**), 156.5 (**C**), 136.4 (**C**), 129.8 (2**C**H), 126.6 (2**C**H), 125.3 (**C**H), 80.5 (**C**), 80.2 (**C**), 55.6 (**C**H), 47.7 (**C**H_2), 46.2 (**C**H_2), 42.6 (**C**H_2), 41.6 (**C**H_2), 29.7 (**C**H_2), 28.6 (3**C**H_3), 28.3 (3**C**H_3), 23.4 (**C**H_2), 22.5 (**C**H_2) ppm.

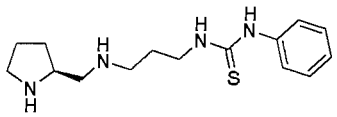
(*S*)-2-({*tert*-Butoxycarbonyl-[2-(3-phenyl-thioureido)-butyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (172).



Prepared according to the procedure given by Bartoli *et al.*[207]

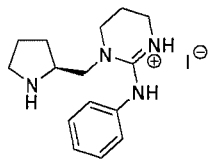
169 (152 mg, 0.409 mmol) was dissolved in a solution of chloroform (3 mL) and methanol (1 mL) and treated with phenyl isothiocyanate (54.0 μL, 0.450 mmol). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to yield the thiourea **172** as a white foam (87.0 mg, 0.172 mmol, 42 %). $[\alpha]_D$ = - 22.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z 507 (60) $[M+H]^+$; IR (solid): ν_{max} = 3292 (w), 2974 (w), 1675 (s), 1157 (s), 728 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.12 (bs, 1H, N**H**), 7.48 (bs, 1H, N**H**), 7.45 (dd, *J* = 8.3, 1.2 Hz, 2H, CC**H**CH), 7.30 (tt, *J* = 8.3, 2.0 Hz, 2H, 2CHC**H**CH), 7.09 (tt, *J* = 7.4, 1.1 Hz, 1H, CHC**H**CH), 3.95 (m, 1H, C**H**CH_2), 3.51 (q, *J* = 6.7 Hz, 2H, NHC$\mathbf{H}_2$), 3.32 - 3.18 (m, 6H, 3NC$\mathbf{H}_2$), 1.83 - 1.77 (m, 4H, 2C$\mathbf{H}_2$), 1.55 (qn, *J* = 6.8 Hz, 4H, 2CH_2C$\mathbf{H}_2$$CH_2$), 1.43 (s, 9H, C(C$\mathbf{H}_3$)$_3$), 1.42 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 180.3 (**C**), 154.5 (**C**), 153.3 (**C**), 139.2 (**C**), 128.5 (2**C**H), 124.0 (2**C**H), 123.0 (**C**H), 78.5 (**C**), 78.4 (**C**), 55.1 (**C**H), 47.5 (**C**H_2), 46.1 (**C**H_2), 45.8 (**C**H_2), 43.6 (**C**H_2), 28.1 (3**C**H_3), 28.0 (3**C**H_3), 26.0 (**C**H_2), 24.9 (**C**H_2), 23.0 (**C**H_2), 22.0 (**C**H_2) ppm.

1-Phenyl-3-{3-[((*S*)-1-pyrrolidin-2-ylmethyl)-amino]-propyl}-thiourea (174).



171 (371 mg, 0.753 mmol) was dissolved in a solution of 20 % TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 3 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (10 mL) and treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **174** as a pale yellow oil (186 mg, 0.636 mmol, 85 %). $[\alpha]_D$ = - 6.8 ° (c = 0.9, $CHCl_3$, 28.5 ° C, 589 nm); MS (ES^+): m/z (%) 293 (100) $[M+H]^+$; IR (film): ν_{max} = 2956 (w), 1668 (m), 1200 (m), 1132 (m), 722 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.87 (bs, 1H, N**H**), 7.38 - 7.29 (m, 4H, 4C**H**), 7.16 (t, *J* = 7.0 Hz, 1H, CHC**H**CH), 5.20 (bs, 2H, 2N**H**), 3.77 - 3.66 (m, 2H, C$\mathbf{H}_2$NH), 3.30 (m, 1H, C**H**CH_2), 3.05 - 3.00 (m, 2H, NHC$\mathbf{H}_2$), 2.75 - 2.63 (m, 3H, CHCH**H**'NH and NHC$\mathbf{H}_2$), 2.55 (dd, *J* = 12.6, 9.7 Hz, 1H, CHC**H**H'NH), 1.90 - 1.79 (m, 3H, CH**H**'C$\mathbf{H}_2$), 1.71 (qn, *J* = 6.0 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.42 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.0 (**C**), 138.4 (**C**), 129.3 (2**C**H), 125.8 (2**C**H), 124.8 (**C**H), 58.6 (**C**H), 51.9 (**C**H_2), 47.3 (**C**H_2), 45.4 (**C**H_2), 43.7 (**C**H_2), 28.8 (**C**H_2), 28.4 (**C**H_2), 24.7 (**C**H_2) ppm; Microanalysis: Calculated for $C_{15}H_{24}N_4S$; C, 61.61; H, 8.27; N, 19.15, found; C, 52.91; H, 7.06; N, 11.91.

2-Phenylamino-3-(*S*)-1-pyrrolidin-2-ylmethyl-3,4,5,6-tetrahydro-pyrimidinium; iodide (177).

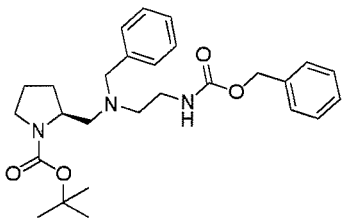


Prepared according to the procedure given by Bartoli *et al.*[207]

171 (389 mg, 0.793 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (494 μL, 7.93 mmol) was added and the reaction mixture was stirred at room temperature for 5 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give thiouronium iodide as a yellow foam (503 mg, 0.793 mmol, 100 %). The thiouronium iodide (340 mg, 0.537 mmol) was dissolved in a solution of 20 % TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 4 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (10 mL) and treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield guanidinium **177** as a colourless oil (205 mg, 0.531 mmol, 98 %). $[\alpha]_D$ = + 6.0 ° (c = 1, $CHCl_3$, 21 ° C, 589 nm); MS (ES^+): m/z (%) 293 (100) $[M+H]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{15}H_{23}N_4^+$ requires m/z: 259.1917, found m/z: 259.1920; IR (film): ν_{max} = 3432 (w), 2963 (w), 1579 (m), 1199 (m), 1125 (m), 752 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (bs, 2H, 2N**H**), 7.29 (t, *J* = 7.6 Hz, 2H, 2CHC**H**CH), 7.08 (tt, *J* = 7.4, 1.0 Hz, 1H, CHC**H**CH), 6.99 (dd, *J* = 8.5, 1.1 Hz, 2H, 2CC**H**CH), 4.01 (apparent dq, *J* = 7.6, 2.0 Hz, 1H, C**H**CH_2), 3.78 (dd, *J* = 15.1, 9.5 Hz, 1H, CHCH**H**'N), 3.66 (m, 1H, NHCH**H**'), 3.35 - 3.20 (m, 5H, 2NC$\mathbf{H}_2$ and CHC**H**H'N), 2.88 (td, *J* = 11.0, 7.1 Hz, 1H, NHC**H**H'), 2.09 - 2.00 (m, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.97 (m, 1H, CHH**H**'), 1.95 - 1.87 (m, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.49 (td, *J* = 12.8, 7.7 Hz, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (**C**), 141.1 (**C**), 130.0 (2**C**H), 124.8 (2**C**H), 124.0 (**C**H),

58.2 (**C**H), 55.4 (**C**H_2), 48.2 (**C**H_2), 44.9 (**C**H_2), 39.4 (**C**H_2), 28.5 (**C**H_2), 26.2 (**C**H_2), 21.9 (**C**H_2) ppm; Microanalysis: Calculated for $C_{15}H_{23}IN_4$; C, 46.64; H, 6.00; N, 14.50, found; C, 50.85; H, 6.66; N, 14.94.

(*S*)-2-{[Benzyl-(2-benzyloxycarbonylamino-ethyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (178).

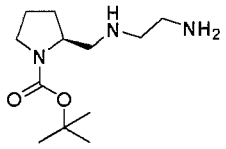


Prepared according to the procedure given by Miller *et al.*[253]

161 (200 mg, 0.530 mmol) was dissolved in acetonitrile (2.5 mL) and treated with K_2CO_3 (147 mg, 1.06 mmol) and benzyl bromide (63.0 μL, 0.530 mmol) and the resulting suspension stirred vigorously for 1 hour. The reaction mixture was treated with water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % ethyl acetate / petroleum ether) to yield amine **178** as a colourless oil (196 mg, 0.420 mmol, 79 %). $[\alpha]_D$ = - 65.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 468 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{27}H_{38}N_3O_4$ requires m/z: 468.2857, found m/z: 468.2858; IR (film): ν_{max} = 3325 (w), 2972 (w), 1676 (s), 1525 (m), 1392 (m), 1167 (m), 749 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 7.32 - 7.20 (m, 10H, 10C**H**), 6.61 (bs, 1H, N**H**), 5.03 (s, 2H, C$\mathbf{H}_2$Ph), 3.81 (m, 1H, C**H**CH_2), 3.77 (d, *J* = 14.0 Hz, 1H, NC**H**H'Ph), 3.53 (d, *J* = 13.9 Hz, 1H, NCH**H**'Ph), 3.24 (td, *J* = 11.1, 7.6 Hz, 1H, NC**H**H'), 3.16 (t, *J* = 7.0 Hz, 2H, NC$\mathbf{H}_2$), 3.11 (dt, *J* = 7.7, 4.2 Hz, 1H, NCH**H**'), 2.67 (td, *J* = 13.1, 7.1 Hz, 1H, C**H**H'NH), 2.61 (dd, *J* = 12.6, 3.9 Hz, 1H, CHCH**H**'N), 2.55 (q, *J* = 6.6 Hz, 1H, CH**H**'NH), 2.32 (dd, *J* = 12.5, 9.5 Hz, 1H, CHC**H**H'N), 1.81 - 1.73 (m, 2H, CH_2C$\mathbf{H}_2$), 1.70 - 1.57 (m, 2H, CHC$\mathbf{H}_2$), 1.42 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR

(100 MHz, d_6DMSO): δ = 157.6 (**C**), 154.6 (**C**), 141.0 (**C**), 138.8 (**C**), 130.2 (2**C**H), 129.8 (2**C**H), 129.5 (2**C**H), 129.2 (2**C**H), 128.2 (2**C**H), 79.7 (**C**), 66.6 (**C**H_2), 60.2 (**C**H_2), 56.4 (**C**H), 55.2 (**C**H_2), 47.4 (**C**H_2), 46.0 (**C**H_2), 40.2 (**C**H_2), 30.0 (3**C**H_3), 24.3 (**C**H_2), 23.3 (**C**H_2) ppm.

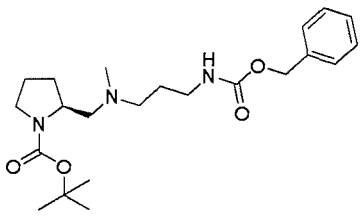
(*S*)-2-[(2-Amino-ethylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (179).



Prepared according to the procedure given by Montero *et al.*[256]

161 (573 mg, 1.52 mmol) was dissolved in methanol (30 mL) and treated with palladium on activated carbon (dry, 10 %, 162 mg, 1.52 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature for 5 hours. After 5 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give diamine **179** as a colourless oil (364 mg, 1.50 mmol, 98 %). $[\alpha]_D$ = - 18.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 244 (100) $[M+H]^+$; IR (film): ν_{max} = 2973 (w), 1683 (s), 1389 (s), 1158 (s) cm^{-1}; (400 MHz, d_6DMSO, 80 ° C): δ = 3.72 (m, 1H, C**H**CH_2), 3.40 (bs, 2H, N**H**$_2$), 3.29 - 3.23 (m, 2H, NC**H**$_2$), 3.21 - 3.17 (m, 2H, NHC**H**$_2$), 2.76 (t, *J* = 5.7 Hz, 2H, NHC**H**$_2$), 2.71 (t, *J* = 5.6 Hz, 2H, NHC**H**$_2$), 1.88 - 1.69 (m, 5H, 2C**H**$_2$ and N**H**), 1.37 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 153.6 (**C**), 78.0 (**C**), 56.6 (**C**H), 51.5 (**C**H_2), 50.0 (**C**H_2), 46.1 (**C**H_2), 40.3 (**C**H_2), 28.5 (**C**H_2), 28.1 (3**C**H_3), 22.5 (**C**H_2) ppm.

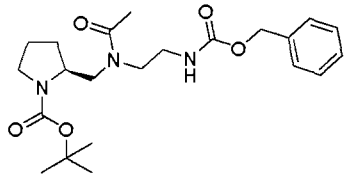
(*S*)-2-{[(3-Benzyloxycarbonylamino-propyl)-methyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (180).



Prepared according to the procedure given by Miller *et al.*[253]

162 (230 mg, 0.587 mmol) was dissolved in acetonitrile (2.5 mL) and treated with K_2CO_3 (141 mg, 1.17 mmol) and methyl iodide (36.6 μL, 0.587 mmol) and the resulting suspension stirred vigorously for 3 hours. The reaction mixture was treated with water (10 mL) and the reaction mixture extracted with ethyl acetate (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to yield amine **180** as a colourless oil (36.8 mg, 0.0907 mmol, 15 %). $[\alpha]_D$ = - 43.3 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 406 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{36}N_3O_4$ requires m/z: 406.2700, found m/z: 406.2702; IR (film): ν_{max} = 3335 (w), 2971 (w), 1691 (s), 1394 (m), 1248 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO): δ = 7.45 (bs, 1H, N**H**), 7.38 - 7.28 (m, 5H, 5C**H**), 5.01 (s, 2H, C**H**$_2$Ph), 3.94 (m, 1H, C**H**CH$_2$), 3.50 (m, 1H, NCH**H**'), 3.42 - 3.28 (m, 5H, 2C**H**$_2$ and NCH**H**'), 3.12 - 2.98 (m, 2H, NC**H**$_2$), 2.23 (s, 3H, NC**H**$_3$), 1.98 - 1.55 (m, 6H, 3C**H**$_2$), 1.40 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5 (**C**), 156.5 (**C**), 136.9 (**C**), 129.0 (2**C**H), 128.5 (2**C**H), 128.0 (**C**H), 79.8 (**C**), 66.5 (**C**H$_2$), 60.8 (**C**H$_2$), 55.9 (**C**H$_2$), 54.7 (**C**H), 47.0 (**C**H$_2$), 42.4 (**C**H$_3$), 40.7 (**C**H$_2$), 29.8 (**C**H$_2$), 28.8 (3**C**H$_3$), 25.9 (**C**H$_2$), 23.7 (**C**H$_2$) ppm.

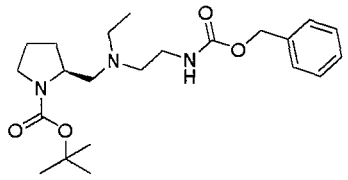
(*S*)-2-{[Acetyl-(2-benzyloxycarbonylamino-ethyl)-amino]-methyl}-pyrrolidine-1 carboxylic acid *tert*-butyl ester (181).



Prepared according to the procedure given by Li *et al.*[297]

161 (2.26 g, 5.99 mmol) was dissolved in DCM (distilled, 90 mL) and the solution cooled to 0 ° C before the addition of DMAP (670 mg, 5.99 mmol), Et_3N (distilled, 916 µL, 6.57 mmol) and acetyl chloride (467 µL, 6.57 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. Upon completion the reaction mixture was cooled to 0 ° C before the addition of aqueous $KHSO_4$ aqueous solution (1M, 25 mL). The phases were separated and the organic phase washed with aqueous $KHSO_4$ solution (1M, 2 x 500 mL) and the aqueous phase extracted with DCM (3 x 500 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (100 % ethyl acetate) to yield acetamide **181** as a white solid (2.42 g, 5.78 mmol, 96 %). Mp.; 68 – 70 ° C ($CHCl_3$); $[\alpha]_D$ = - 19.0 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 420 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{34}N_3O_5$ requires m/z: 420.2493, found m/z: 420.2486; IR (solid): ν_{max} = 3390 (m), 2975 (w), 2778 (w), 1668 (s), 1395 (s), 1162 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.38 - 7.28 (m, 5H, 5C**H**), 6.91 (bs, 1H, N**H**), 5.04 (s, 2H, C$\mathbf{H_2}$Ph), 4.00 (m, 1H, C**H**CH_2), 3.52 - 3.29 (m, 4H, 2NC$\mathbf{H_2}$), 3.25 - 3.17 (m, 4H, NC$\mathbf{H_2}$ and NHC$\mathbf{H_2}$), 1.98 (s, 3H, C$\mathbf{H_3}$), 1.88 - 1.79 (m, 3H, C**H**H'C$\mathbf{H_2}$), 1.65 (m, 1H, CHCH**H**'), 1.42 (s, 9H, C(C$\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (**C**), 156.7 (**C**), 154.8 (**C**), 136.8 (**C**), 128.5 (2**C**H), 128.4 (2**C**H), 128.0 (**C**H), 77.3 (**C**), 66.5 ($\mathbf{CH_2}$), 55.7 (**C**H), 51.7 ($\mathbf{CH_2}$), 48.4 ($\mathbf{CH_2}$), 46.2 ($\mathbf{CH_2}$), 39.6 ($\mathbf{CH_2}$), 28.5 (3**C**H_3), 23.5 ($\mathbf{CH_2}$), 22.7 ($\mathbf{CH_2}$), 21.5 ($\mathbf{CH_3}$) ppm.

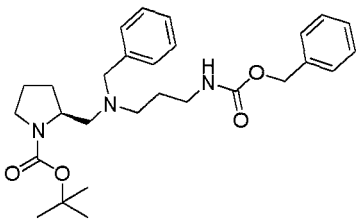
(*S*)-2-{[(2-Benzyloxycarbonylamino-ethyl)-ethyl-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (182).



Prepared according to the procedure given by Bartoli *et al.*[252]

All glassware used for the reaction was oven dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **181** (438 mg, 1.04 mmol) was dissolved in THF (5 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.0 M, 2.09 mL, 2.09 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 6 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (10 mL) added dropwise over 5 minutes. The reaction mixture was then extracted with ethyl acetate (150 mL) and the organic phase washed with brine (80 mL) and saturated $NaHCO_3$ aqueous solution (80 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) to yield amine **182** as a yellow oil (38.7 mg, 0.0954 mmol, 9 %). $[\alpha]_D$ = - 8.8 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 406 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{36}N_3O_4$ requires m/z: 406.2700, found m/z: 406.2691; IR (film): ν_{max} = 3336 (w), 2971 (w), 2869 (w), 1691 (s), 1394 (s), 1248 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.34 - 7.28 (m, 5H, 5C**H**), 6.67 (bs, 1H, N**H**), 5.03 (s, 2H, C$\mathbf{H_2}$Ph), 3.73 (m, 1H, C**H**CH_2), 3.29 - 3.18 (m, 2H, NC$\mathbf{H_2}$), 3.09 (q, J = 7.0 Hz, 2H, C$\mathbf{H_2}CH_3$), 3.07 - 2.92 (m, 2H, NC$\mathbf{H_2}$), 2.67 - 2.56 (m, 3H, CHCH**H**'N and NHC$\mathbf{H_2}$), 2.26 (m, 1H, CHC**H**H'N), 1.86 - 1.65 (m, 4H, 2C$\mathbf{H_2}$), 1.41 (s, 9H, C(C$\mathbf{H_3}$)$_3$), 0.97 (t, J = 7.1 Hz, 3H, CH_2C$\mathbf{H_3}$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9 (**C**), 153.3 (**C**), 136.9 (**C**), 128.7 (2**C**H), 128.6 (2**C**H), 128.2 (**C**H), 77.8 (**C**), 66.6 (**C**H_2), 56.7 (**C**H_2), 55.9 (**C**H), 53.3 (**C**H_2), 48.2 (**C**H_2), 46.5 (**C**H_2), 38.9 (**C**H_2), 29.8 (**C**H_2), 28.7 (3**C**H_3), 22.6 (**C**H_2), 12.0 (**C**H_3) ppm.

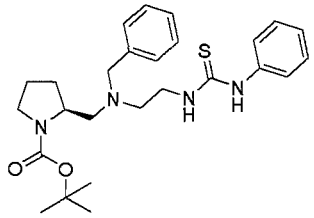
2-{[Benzyl-(2-benzyloxycarbonylamino-propyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (183).



Prepared according to the procedure given by Miller *et al.*[253]

162 (1.99 g, 5.07 mmol) was dissolved in acetonitrile (22 mL) and treated with K_2CO_3 (771 mg, 5.58 mmol) and benzyl bromide (603 μL, 5.07 mmol) and the resulting suspension stirred vigorously for 2 hour. The reaction mixture was treated with water (100 mL) and the reaction mixture extracted with ethyl acetate (3 x 200 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % ethyl acetate / petroleum ether) to yield amine **183** as a colourless oil (1.37 mg, 2.84 mmol, 56 %). $[\alpha]_D$ = - 63.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 482 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{28}H_{40}N_3O_4$ requires m/z: 482.3013, found m/z: 482.3014; IR (film): ν_{max} = 3336 (w), 2971 (w), 1691 (s), 1394 (m), 1248 (m), 1169 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 7.37 - 7.27 (m, 8H, 8C**H**), 7.25 (m, 1H, CHC**H**CH), 7.19 (m, 1H, CHC**H**CH), 5.03 (s, 2H, OC**H**$_2$Ph), 3.85 - 3.79 (m, 2H, C**H**CH$_2$ and N**H**), 3.33 (s, 2H, NC**H**$_2$Ph), 3.19 - 3.10 (m, 2H, NHC**H**$_2$), 3.06 (ddd, *J* = 26.5, 13.2, 6.2 Hz, 2H, NC**H**$_2$), 2.61 - 2.54 (m, 2H, C**H**$_2$N), 2.35 (m, 1H, CHCH**H**'N), 2.21 (m, 1H, CHC**H**H'N), 1.85 - 1.75 (m, 3H, C**H**$_2$CH**H**'CH), 1.64 (qn, *J* = 7.0 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.52 (m, 1H, CH$_2$C**H**H'CH), 1.42 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 156.0 (**C**), 153.3 (**C**), 139.6 (**C**), 137.3 (**C**), 128.6 (2**C**H), 128.2 (2**C**H), 128.0 (**C**H), 127.6 (2**C**H), 127.5 (2**C**H), 126.7 (**C**H), 78.2 (**C**), 65.0 (**C**H$_2$), 58.7 (**C**H$_2$), 56.4 (**C**H$_2$), 55.2 (**C**H), 51.6 (**C**H$_2$), 45.8 (**C**H$_2$), 38.6 (**C**H$_2$), 28.6 (**C**H$_2$), 28.1 (3**C**H$_3$), 22.7 (**C**H$_2$), 21.8 (**C**H$_2$) ppm.

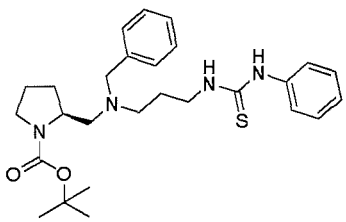
(*S*)-2-({Benzyl-[2-(3-phenyl-thioureido)-ethyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (186).



All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **178** (1.78 g, 3.82 mmol) was dissolved in THF (6 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.0 M, 7.63 mL, 7.63 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was then warmed to room temperature and subsequently refluxed for 14 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (20 mL) added dropwise over 10 minutes. The reaction mixture was then extracted with ethyl acetate (3 x 200 mL) and the organic phase washed with saturated $NaHCO_3$ aqueous solution (100 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow oil (1.43 g, 4.29 mmol, 112 %). The crude material (**184,** 1.33 g, 3.99 mmol) was used without further purification and was subsequently dissolved in a solution of chloroform (30 mL) and methanol (5 mL) and treated with phenyl isothiocyanate (525 µL, 4.39 mmol). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The crude material was purified by column chromatography (20 % ethyl acetate / petroleum ether) to yield thiourea **186** as a pale yellow oil (261 mg, 0.557 mmol, 14 %). $[\alpha]_D$ = - 55.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 469 (100) $[M+H]^+$; IR (film): ν_{max} = 3285 (w), 2971 (w), 1689 (s), 1529 (m), 1393 (m), 1170 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 11.70 (bs, 1H, N**H**), 7.37 - 7.22 (m, 9H, 9C**H**), 7.10 (t, *J* = 7.3 Hz, 1H, CHC**H**CH), 3.95 (m, 1H, C**H**CH_2), 3.89 - 3.85 (m, 2H, CH_2CH**H**'N and NC**H**H'Ph), 3.58 (d, *J* = 13.8 Hz, 1H, NCH**H**'Ph), 3.28 - 3.24 (m, 3H, NHC$\mathbf{H}_2$ and N**H**), 3.16 (dt, *J* = 7.6, 4.4 Hz, 1H, CH_2C**H**H'N), 2.96 (m, 1H, CH_2C**H**H'N), 2.75 (m, 1H, CH_2CH**H**'N), 2.66 (dd, *J* = 12.6, 3.7 Hz, 1H, CHCH**H**'N), 2.39 (dd, *J* = 12.5,

9.5 Hz, 1H, CHC**H**H'N), 1.83 - 1.80 (m, 2H, $CH_2C\mathbf{H}_2$), 1.71 - 1.64 (m, 2H, $CH_2C\mathbf{H}_2$), 1.43 (s, 9H, $C(C\mathbf{H}_3)_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 181.0 (**C**), 153.3 (**C**), 141.0 (**C**), 139.1 (**C**), 128.9 (2**C**H), 128.0 (2**C**H), 127.7 (**C**H), 126.8 (2**C**H), 125.8 (2**C**H), 124.3 (**C**H), 78.2 (**C**), 58.8 ($\mathbf{C}H_2$), 56.7 ($\mathbf{C}H_2$), 55.3 (**C**H), 51.5 ($\mathbf{C}H_2$), 45.9 ($\mathbf{C}H_2$), 38.3 ($\mathbf{C}H_2$), 28.1 ($3\mathbf{C}H_3$), 22.8 ($\mathbf{C}H_2$), 21.8 ($\mathbf{C}H_2$) ppm.

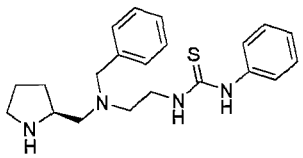
(*S*)-2-({Benzyl-[2-(3-phenyl-thioureido)-propyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (187).



All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. **183** (1.25 g, 2.59 mmol) was dissolved in THF (4 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.0 M, 5.18 mL, 5.18 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was then warmed to room temperature and subsequently refluxed for 14 days. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (20 mL) added dropwise over 10 minutes. The reaction mixture was then extracted with ethyl acetate (3 x 200 mL) and the organic phase washed with saturated $NaHCO_3$ aqueous solution (100 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield a yellow oil (1.01 g, 2.91 mmol, 112 %). The crude material (**185**, 910 mg, 2.62 mmol) was used without further purification and was subsequently dissolved in a solution of chloroform (30 mL) and methanol (5 mL) and treated with phenyl isothiocyanate (344 μL, 2.88 mmol). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The crude material was purified by column chromatography (20 % ethyl acetate / petroleum ether) to yield thiourea **187** as a pale yellow oil (307 mg, 0.636 mmol, 24 %). $[\alpha]_D$ = - 53.2 ° (c = 1.0, $CHCl_3$,

31 ° C, 589 nm); MS (ES^+): m/z (%) 483 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{27}H_{39}N_4O_2S$ requires m/z: 483.2788, found m/z: 483.2786; IR (film): ν_{max} = 3274 (w), 2971 (w), 1689 (s), 1393 (s), 1170 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 8.65 (bs, 1H, N**H**), 7.36 - 7.17 (m, 9H, 9C**H**), 7.10 (t, *J* = 7.3 Hz, 1H, CHC**H**CH), 3.88 - 3.82 (m, 2H, C**H**H'N and C**H**CH_2), 3.78 - 3.71 (m, 2H, CH**H**'N and NC**H**H'Ph), 3.51 (d, *J* = 13.9 Hz, 1H, NCH**H**'Ph), 3.29 - 3.14 (m, 3H, NHC$\mathbf{H}_2$ and N**H**), 2.65 - 2.59 (m, 2H, C$\mathbf{H}_2$N), 2.50 (m, 1H, CHCH**H**'N), 2.35 (dd, *J* = 12.5, 9.7 Hz, 1H, CHC**H**H'N), 1.89 - 1.81 (m, 4H, 2C$\mathbf{H}_2$), 1.73 - 1.62 (m, 2H, CH_2C$\mathbf{H}_2$), 1.44 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 181.8 (**C**), 153.3 (**C**), 141.1 (**C**), 139.5 (**C**), 128.7 (2**C**H), 128.0 (2**C**H), 127.7 (**C**H), 126.7 (2**C**H), 125.9 (2**C**H), 124.3 (**C**H), 78.2 (**C**), 58.7 (**C**H_2), 56.4 (**C**H_2), 55.2 (**C**H), 51.6 (**C**H_2), 45.9 (**C**H_2), 38.3 (**C**H_2), 28.1 (3**C**H_3), 24.3 (**C**H_2), 22.8 (**C**H_2), 21.8 (**C**H_2) ppm.

1-[3-(Benzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-ethyl]-3-phenyl-thiourea (188).

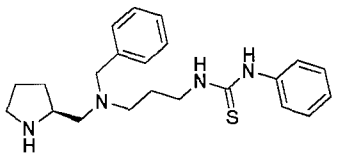


Prepared according to the procedure given by Quaranta *et al.*[210]

The reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. **186** (117 mg, 0.250 mmol) was dissolved in DCM (865 μL) and the solution treated with neat trimethylsilyl iodide (53 μL, 0.375 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (438 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (5 x 100 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under

reduced pressure to yield thiourea **188** as pale yellow oil (90.0 mg, 0.244 mmol, 98 %). $[\alpha]_D$ = - 31.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 369 (100) $[M+H]^+$; IR (film): ν_{max} = 3422 (w), 2925 (w), 1526 (m), 1338 (m), 1144 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.44 - 7.26 (m, 9H, 9C**H**), 7.22 (m, 1H, CHC**H**CH), 4.75 (bs, 1H, N**H**), 4.08 - 3.92 (m, 2H, C**H**CH_2 and NC**H**H'Ph), 3.52 - 3.41 (m, 2H, C**H**H'NH and NCH**H**'Ph), 3.26 (bs, 1H, N**H**), 3.21 (dt, *J* = 7.1, 2.8 Hz, 1H, CH**H**'NH), 2.98 - 2.88 (m, 2H, C$\mathbf{H}_2$NH), 2.87 - 2.81 (m, 3H, C$\mathbf{H}_2$N and N**H**), 2.75 (dd, *J* = 13.6, 4.4 Hz, 1H, CHC**H**H'N), 2.59 (dd, *J* = 14.2, 4.4 Hz, 1H, CHCH**H**'N), 2.20 (dt, *J* = 13.3, 7.4 Hz, 1H, CHC**H**H'), 2.00 (qn, *J* = 7.2 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.71 (dt, *J* = 13.1, 7.2 Hz, 1H, CHCH**H**') ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 182.2 (**C**), 141.8 (**C**), 139.7 (**C**), 130.5 (2**C**H), 129.6 (2CH), 129.4 (**C**H), 128.5 (2CH), 128.2 (2CH), 126.9 (CH), 59.2 (CH_2), 58.4 (CH), 56.9 (CH_2), 52.9 (CH_2), 52.4 (CH_2), 46.4 (CH_2), 29.4 (CH_2), 24.8 (CH_2) ppm.

1-[3-(Benzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-propyl]-3-phenyl-thiourea (189).

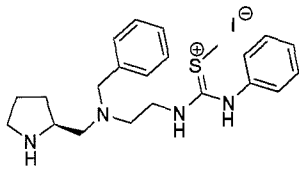


Prepared according to the procedure given by Quaranta *et al.*[210]

The reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. **187** (159 mg, 0.329 mmol) was dissolved in DCM (1.14 mL) and the solution treated with neat trimethylsilyl iodide (70.3 μL, 0.494 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (579 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (5 x 100 mL) and the combined organic phase

dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **189** as pale yellow oil (90.0 mg, 0.235 mmol, 71 %). $[\alpha]_D$ = - 29.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 383 (100) $[M+H]^+$; IR (film): ν_{max} = 3433 (w), 2925 (w), 1526 (m), 1337 (m), 1025 (m) cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.44 - 7.39 (m, 2H, 2C**H**), 7.35 - 7.24 (m, 7H, 7C**H**), 7.16 (m, 1H, CHC**H**CH), 4.03 (dt, *J* = 13.9, 7.6 Hz, 1H, C**H**H'NH), 3.95 (dt, *J* = 7.2, 2.4 Hz, 1H, C**H**CH_2), 3.85 (d, *J* = 13.4 Hz, 1H, NC**H**H'Ph), 3.76 (dt, *J* = 13.9, 7.6 Hz, 1H, CH**H**'NH), 3.60 (d, *J* = 13.4 Hz, 1H, NCH**H**'Ph), 3.35 (bs, 1H, N**H**), 3.30 - 3.20 (m, 2H, C**H**$_2$NH), 3.18 (bs, 1H, N**H**), 2.78 (bs, 1H, N**H**), 2.73 (t, *J* = 5.6 Hz, 2H, C**H**$_2$N), 2.63 (dd, *J* = 13.1, 6.1 Hz, 1H, CHCH**H**'N), 2.56 (dd, *J* = 13.2, 6.6 Hz, 1H, CHC**H**H'N), 2.14 (dt, *J* = 13.3, 7.4 Hz, 1H, CHCH**H**'), 2.04 - 1.89 (m, 4H, 2C**H**$_2$), 1.67 (dt, *J* = 13.0, 7.4 Hz, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 182.3 (**C**), 141.9 (**C**), 139.5 (**C**), 130.6 (2**C**H), 129.5 (2**C**H), 129.2 (**C**H), 128.4 (2**C**H), 127.6 (2**C**H), 126.4 (**C**H), 59.2 (**C**H), 59.0 (**C**H_2), 56.1 (**C**H_2), 53.4 (**C**H_2), 51.9 (**C**H_2), 46.2 (**C**H_2), 29.1 (**C**H_2), 25.2 (**C**H_2), 24.2 (**C**H_2) ppm.

[1-[2-(Benzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-ethylamino]-1-phenylamino-methylidene]-methyl-sulfonium; iodide (190).

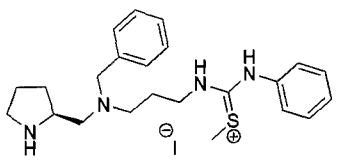


Prepared according to the procedure given by Bartoli *et al.*[207] and Quaranta *et al.*[210]

186 (142 mg, 0.303 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (187 μL, 3.03 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (160 mg, 0.262 mmol, 86 %). The deprotection reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. The thiouronium

iodide (160 mg, 0.262 mmol) was dissolved in DCM (1.05 mL) and the solution treated with neat trimethylsilyl iodide (64.6 μL, 0.454 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (531 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (5 x 100 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **190** as pale yellow oil (102 mg, 0.200 mmol, 76 %). $[\alpha]_D$ = - 34.3 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 383 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; IR (film): ν_{max} = 3433 (w), 2947 (w), 1578 (s), 1451 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.86 (bs, 1H, N**H**), 7.44 - 7.24 (m, 10H, 10C**H**), 4.15 - 4.06 (m, 2H, C**H**CH_2 and N**H**), 3.96 - 3.90 (m, 2H, NHC$\mathbf{H}_2$), 3.65 - 3.51 (m, 4H, 2NC$\mathbf{H}_2$), 3.43 (s, 2H, NC$\mathbf{H}_2$Ph), 3.10 - 2.95 (m, 3H, C$\mathbf{H}_2$N and N**H**), 2.17 - 2.12 (m, 5H, C$\mathbf{H}_2$ and C$\mathbf{H}_3$), 2.02 (m, 1H, CHCH**H**'), 1.78 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7 (**C**), 137.9 (**C**), 136.5 (**C**), 130.2 (2**C**H), 129.9 (2**C**H), 128.7 (**C**H), 128.0 (2**C**H), 127.4 (2**C**H), 123.7 (**C**H), 58.1 (**C**H_2), 57.5 (**C**H_2), 54.9 (**C**H), 51.3 (**C**H_2), 45.5 (**C**H_2), 44.3 (**C**H_2), 29.0 (**C**H_2), 23.5 (**C**H_2), 17.4 (**C**H_3) ppm.

[1-[2-(Benzyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-propylamino]-1-phenylamino-methylidene]-methyl-sulfonium; iodide (191).

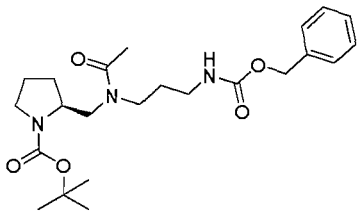


Prepared according to the procedure given by Bartoli *et al.*[207] and Quaranta *et al.*[210]

187 (177 mg, 0.367 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (227 μL, 3.67 mmol) was added and the reaction mixture was stirred at

room temperature for 3 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (174 mg, 0.279 mmol, 76 % yield). The deprotection reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. The thiouronium iodide (174 mg, 0.279 mmol) was dissolved in DCM (1.27 mL) and the solution treated with neat trimethylsilyl iodide (78 μL, 0.550 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (644 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (5 x 100 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **191** as pale yellow oil (117 mg, 0.223 mmol, 80 %). $[\alpha]_D$ = - 32.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 397 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M+MeOH]^+$ $C_{24}H_{37}N_4OS^+$ requires m/z: 429.2683, found m/z: 429.1931; IR (film): ν_{max} = 3434 (w), 2947 (w), 1578 (s), 1451 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.8 Hz, 2H, 2CHC**H**CH), 7.58 (t, *J* = 8.0 Hz, 4H, 4CC**H**CH), 7.46 (t, *J* = 7.9 Hz, 4H, 4CHC**H**CH), 4.41 - 4.19 (m, 3H, C**H**CH_2 and 2N**H**), 4.14 (d, *J* = 13.5 Hz, 1H, NC**H**H'Ph), 3.97 (d, *J* = 13.3 Hz, 1H, NCH**H**'Ph), 3.76 - 3.67 (m, 2H, C$\mathbf{H}_2$NH), 3.66 - 3.41 (m, 4H, 2NC$\mathbf{H}_2$), 3.15 - 2.85 (m, 3H, C$\mathbf{H}_2$NH and N**H**), 2.41 - 2.25 (m, 5H, C$\mathbf{H}_2$ and C$\mathbf{H}_3$), 2.24 - 2.12 (m, 3H, CHCH**H**'C$\mathbf{H}_2$), 1.90 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1 (**C**), 136.7 (**C**), 136.1 (**C**), 130.1 (2**C**H), 129.8 (2**C**H), 128.7 (**C**H), 127.8 (2**C**H), 127.4 (2**C**H), 123.9 (**C**H), 58.0 (**C**H), 57.3 (**C**H_2), 54.9 (**C**H_2), 54.7 (**C**H_2), 50.1 (**C**H_2), 45.4 (**C**H_2), 28.7 (**C**H_2), 25.6 (**C**H_2), 23.6 (**C**H_2), 17.5 (**C**H_3) ppm.

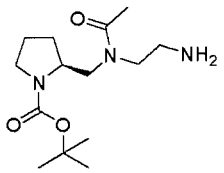
(*S*)-2-{[Acetyl-(2-benzyloxycarbonylamino-propyl)-amino]-methyl}-pyrrolidine-1 carboxylic acid *tert*-butyl ester (192).



Prepared according to the procedure given by Li *et al.*[297]

162 (1.09 g, 2.78 mmol) was dissolved in DCM (distilled, 40 mL) and the solution cooled to 0 ° C before the addition of DMAP (312 mg, 2.78 mmol), Et_3N (distilled, 427 µL, 3.06 mmol) and acetyl chloride (218 µL, 3.06 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. Upon completion the reaction mixture was cooled to 0 ° C before the addition of aqueous $KHSO_4$ solution (1M, 10 mL). The phases were separated and the organic phase washed with aqueous $KHSO_4$ solution (1M, 2 x 300 mL) and the aqueous phase extracted with DCM (3 x 400 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (100 % ethyl acetate) to yield acetamide **192** as a pale yellow oil (650 mg, 1.50 mmol, 54 %). $[\alpha]_D$ = - 21.9 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 456 (100) $[M+Na]^+$; HRMS (ES^+): $[M+H]^+$ $C_{23}H_{36}N_3O_5$ requires m/z: 434.2649, found m/z: 434.2649; IR (film): ν_{max} = 3391 (m), 2976 (w), 1663 (s), 1402 (s), 1162 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 - 7.27 (m, 5H, 5C**H**), 5.78 (bs, 1H, N**H**), 5.06 (s, 2H, C**H**$_2$Ph), 4.04 (m, 1H, C**H**CH_2), 3.77 (m, 1H, NC**H**H'), 3.52 (m, 1H, NCH**H**'), 3.49 - 3.25 (m, 3H, NC**H**$_2$ and CHC**H**H'N), 3.18 (m, 1H, CHCH**H**'N), 3.07 (t, *J* = 6.7 Hz, 2H, NHC**H**$_2$), 2.09 (s, 3H, C**H**$_3$), 1.92 - 1.76 (m, 4H, 2C**H**$_2$), 1.68 (qn, *J* = 6.5 Hz, 2H, CH_2C**H**$_2CH_2$), 1.43 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9 (**C**), 156.6 (**C**), 154.9 (**C**), 136.9 (**C**), 128.5 (2**C**H), 128.0 (2**C**H), 127.9 (**C**H), 79.5 (**C**), 66.4 (**C**H_2), 55.8 (**C**H), 50.5 (**C**H_2), 46.6 (**C**H_2), 43.0 (**C**H_2), 37.9 (**C**H_2), 28.5 (3**C**H_3), 27.7 (**C**H_2), 23.7 (**C**H_2), 22.8 (**C**H_2), 21.4 (**C**H_3) ppm.

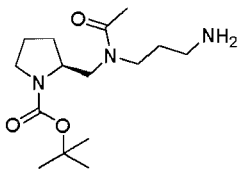
(*S*)-2-{[Acetyl-(2-amino-ethyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert* butyl ester (193).



Prepared according to the procedure given by Montero *et al.*[256]

181 (479 mg, 1.14 mmol) was dissolved in methanol (20 mL) and treated with palladium on activated carbon (dry, 10 %, 121 mg, 1.14 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature for 18 hours. Upon completion the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give amine **193** as a colourless oil (254 mg, 0.890 mmol, 78 %). $[\alpha]_D$ = - 7.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 286 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{14}H_{28}N_3O_3$ requires m/z: 286.2125, found m/z: 286.2125; IR (film): ν_{max} = 3293 (w), 2961 (w), 2929 (w), 1670 (s), 1392 (s), 1166 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.00 (m, 1H, C**H**CH_2), 3.40 (bs, 2H, N**H**$_2$), 3.36 - 3.20 (m, 2H, NC**H**$_2$), 2.87 (m, 1H, CHC**H**H'N), 2.76 (t, *J* = 6.5 Hz, 2H, NC**H**$_2$), 2.51 (m, 1H, CHCH**H**'N), 2.15 - 2.02 (m, 2H, C**H**$_2$$NH_2$), 1.93 (s, 3H, C**H**$_3$), 1.89 - 1.70 (m, 4H, 2C**H**$_2$), 1.41 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (**C**), 153.6 (**C**), 79.7 (**C**), 56.8 (**C**H), 53.0 (**C**H_2), 50.4 (**C**H_2), 48.2 (**C**H_2), 38.9 (**C**H_2), 29.8 (**C**H_2), 28.6 (3**C**H_3), 23.8 (**C**H_2), 23.2 (**C**H_3) ppm.

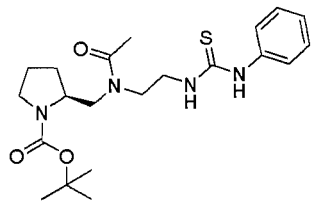
(*S*)-2-{[Acetyl-(2-amino-propyl)-amino]-methyl}-pyrrolidine-1-carboxylic acid *tert* butyl ester (194).



Prepared according to the procedure given by Montero *et al.*[256]

192 (1.20 g, 2.76 mmol) was dissolved in methanol (50 mL) and treated with palladium on activated carbon (dry, 10 %, 294 mg, 2.76 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature for 18 hours. Upon completion the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give amine **194** as a colourless oil (760 mg, 2.54 mmol, 92 %). $[\alpha]_D$ = - 6.0 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 300 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{15}H_{30}N_3O_3$ requires m/z: 300.2282, found m/z: 300.2280; IR (film): ν_{max} = 3293 (w), 2961 (w), 2930 (w), 1669 (s), 1392 (s), 1166 (s), 1109 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 4.08 (dd, *J* = 8.4, 4.0 Hz, 1H, CHCH**H**'), 3.98 (ddd, *J* = 11.4, 7.6, 4.5 Hz, 1H, C**H**CH_2), 3.42 (dt, *J* = 6.3, 1.8 Hz, 2H, **C**H_2NH_2), 3.36 - 3.22 (m, 2H, N**C**H_2), 2.99 (t, *J* = 6.3 Hz, 2H, N**C**H_2), 2.84 (dd, *J* = 12.2, 8.1 Hz, 1H, CHC**H**H'N), 2.57 (bs, 2H, N**H**$_2$), 2.55 (s, 3H, **C**H_3), 2.11 (m, 1H, CHCH**H**'N), 1.98 (qn, *J* = 7.6 Hz, 2H, CH_2**C**H_2CH_2), 1.92 - 1.82 (m, 2H, CH_2**C**H_2), 1.78 (m, 1H, CHC**H**H'), 1.44 (s, 9H, C(**C**H_3)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1 (**C**), 154.8 (**C**), 79.3 (**C**), 55.8 (**C**H), 46.5 (**C**H_2), 43.6 (**C**H_2), 39.5 (**C**H_2), 39.2 (**C**H_2), 31.0 (**C**H_2), 28.6 (3**C**H_3), 23.6 (**C**H_2), 23.3 (**C**H_2), 21.5 (**C**H_3) ppm.

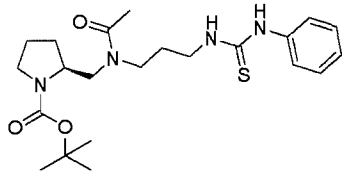
(*S*)-2-({Acetyl-[2-(3-phenyl-thioureido)-ethyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (195).



Prepared according to the procedure given by Bartoli *et al.*[207]

193 (250 mg, 0.876 mmol) was dissolved in a biphasic solution of chloroform (55 mL), methanol (16 mL) and saturated $NaHCO_3$ aqueous solution (16 mL) and treated with phenyl isothiocyanate (105 μL, 0.876 mmol). The reaction mixture was stirred vigorously at room temperature for 3 days. The phases of the reaction mixture were separated and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to yield the thiourea **195** as a white foam (293 mg, 0.697 mmol, 79 %). $[\alpha]_D$ = - 11.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z 421 (100) $[M+H]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{21}H_{32}N_4NaO_3S$ requires m/z: 443.2087, found m/z: 443.2078; IR (solid): ν_{max} = 3272 (w), 2974 (w), 2926 (w), 1682 (s), 1391 (m), 1163 (s), 1106 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 9.33 (bs, 1H, N**H**), 7.58 (bs, 1H, N**H**), 7.39 (d, *J* = 7.8 Hz, 2H, 2CC**H**CH), 7.31 (t, *J* = 7.5 Hz, 2H, 2CHC**H**CH), 7.12 (t, *J* = 7.3 Hz, 1H, CHC**H**CH), 4.06 (m, 1H, C**H**CH_2), 3.72 - 3.61 (m, 2H, NC**H**$_2$), 3.56 - 3.46 (m, 2H, NC**H**$_2$), 3.44 - 3.29 (m, 2H, NC**H**$_2$), 3.27 - 3.22 (m, 2H, NC**H**$_2$), 2.03 (s, 3H, C**H**$_3$), 1.87 - 1.80 (m, 3H, C**H**$_2$CH**H**'), 1.68 (m, 1H, CHC**H**H'), 1.41 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 180.7 (**C**), 170.0 (**C**), 153.6 (**C**), 138.7 (**C**), 128.7 (2**C**H), 124.5 (2**C**H), 123.6 (**C**H), 78.2 (**C**), 55.3 (**C**H), 50.7 (**C**H_2), 46.8 (**C**H_2), 44.8 (**C**H_2), 41.8 (**C**H_2), 28.1 (3**C**H_3), 22.9 (**C**H_2), 22.1 (**C**H_2), 21.2 (**C**H_3) ppm.

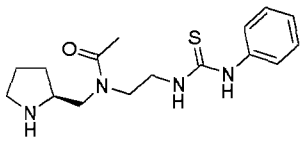
(*S*)-2-({Acetyl-[2-(3-phenyl-thioureido)-propyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (196).



Prepared according to the procedure given by Bartoli *et al.*[207]

194 (323 mg, 1.08 mmol) was dissolved in a biphasic solution of chloroform (55 mL), methanol (16 mL) and saturated $NaHCO_3$ aqueous solution (16 mL) and treated with phenyl isothiocyanate (132 μL, 1.08 mmol). The reaction mixture was stirred vigorously at room temperature for 3 days. The phases of the reaction mixture were separated and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (1 % methanol / DCM) to yield the thiourea **196** as a white foam (413 mg, 0.952 mmol, 88 %). $[\alpha]_D$ = - 12.2 ° (c = 1.0, $CHCl_3$, 28 ° C, 589 nm); MS (ES^+): m/z 435 (100) $[M+H]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{22}H_{34}N_4NaO_3S$ requires m/z: 457.2244, found m/z: 457.2233; IR (solid): ν_{max} = 3272 (w), 2974 (w), 2926 (w), 1682 (s), 1391 (m), 1163 (s), 1106 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 9.22 (bs, 1H, N**H**), 7.51 (bs, 1H, N**H**), 7.42 (dd, *J* = 8.7, 1.2 Hz, 2H, 2CC**H**CH), 7.31 (t, *J* = 7.5 Hz, 2H, 2CHC**H**CH), 7.11 (t, *J* = 7.4 Hz, 1H, CHC**H**CH), 4.02 (m, 1H, C**H**CH_2), 3.56 - 3.43 (m, 2H, NC$\mathbf{H}_2$), 3.42 - 3.38 (m, 2H, NC$\mathbf{H}_2$), 3.37 - 3.27 (m, 2H, NC$\mathbf{H}_2$), 3.26 - 3.24 (m, 2H, NHC$\mathbf{H}_2$), 2.01 (s, 3H, C$\mathbf{H}_3$), 1.92 - 1.73 (m, 5H, CH_2CH**H**' and C$\mathbf{H}_2$), 1.68 (m, 1H, CHC**H**H'), 1.42 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 180.3 (**C**), 169.8 (**C**), 153.5 (**C**), 139.1 (**C**), 128.6 (2**C**H), 124.1 (2**C**H), 123.2 (**C**H), 78.3 (**C**), 55.1 (**C**H), 50.0 (**C**H_2), 45.9 (**C**H_2), 43.0 (**C**H_2), 41.4 (**C**H_2), 28.1 (3**C**H_3), 28.0 (**C**H_2), 26.7 (**C**H_2), 22.1 (**C**H_2), 21.2 (**C**H_3) ppm.

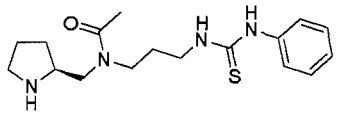
N-[2-(3-Phenyl-thioureido)-ethyl]-N-(*S*)-1-pyrrolidin-2-ylmethyl-acetamide (197).



Prepared according to the procedure given by Quaranta *et al.*[210]

The reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. ^{t}Boc protected thiourea **195** (260 mg, 0.618 mmol) was dissolved in DCM (2.14 mL) and the solution treated with neat trimethylsilyl iodide (132 μL, 0.927 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (1.08 mL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (50 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (2 mL). The aqueous phase was then extracted with DCM (3 x 100 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **197** as a white foam (148 mg, 0.462 mmol, 75 %). $[\alpha]_D$ = - 7.8 ° (c = 1.0, $CHCl_3$, 29.5 ° C, 589 nm); MS (ES^+): m/z (%) 321 (100) $[M+H]^+$; HRMS (ES^+): $[M + H]^+$ $C_{16}H_{25}N_4OS$ requires m/z: 321.1744, found m/z: 321.1741; IR (film): ν_{max} = 3271 (w), 2974 (w), 1682 (m), 1529 (m), 1391 (s) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ = 7.41 (t, *J* = 7.2 Hz, 2H, 2CHC**H**CH), 7.32 (dd, *J* = 8.7, 1.7 Hz, 2H, 2CC**H**CH), 7.25 (tt, *J* = 7.2, 1.5 Hz, 1H, CHC**H**CH), 3.96 (dd, *J* = 14.7, 9.0 Hz, 1H, CHCH**H**'N), 3.85 - 3.74 (m, 3H, NC**H**$_2$ and CH_2C**H**), 3.66 (dt, *J* = 6.5, 2.5 Hz, 2H, $CH_2C\mathbf{H}_2NH$), 3.50 (dd, *J* = 14.7, 3.0 Hz, 1H, CHC**H**H'N), 3.37 (m, 1H, NHCH**H**'CH_2), 3.25 (ddd, *J* = 11.6, 8.7, 5.9 Hz, 1H, NHC**H**H'CH_2), 2.22 (s, 3H, C**H**$_3$), 2.17 (m, 1H, CHCH**H**'), 2.14 - 1.96 (m, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.74 (ddd, *J* = 18.0, 12.7, 8.8 Hz, 1H, CHC**H**H') ppm; ^{13}C NMR (75 MHz, CD_3OD): δ = 183.1 (**C**), 175.8 (**C**), 139.2 (**C**), 130.2 (2**C**H), 127.2 (2**C**H), 126.0 (**C**H), 61.9 (**C**H), 49.6 (**C**H_2), 48.8 (**C**H_2), 46.4 (**C**H_2), 43.3 (**C**H_2), 28.8 (**C**H_2), 23.9 (**C**H_2), 21.5 (**C**H_3) ppm.

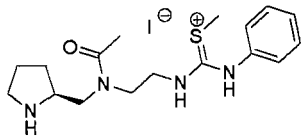
N-[2-(3-Phenyl-thioureido)-propyl]-N-(*S*)-1-pyrrolidin-2-ylmethyl-acetamide (198).



Prepared according to the procedure given by Quaranta *et al.*[210]

The reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. ^{t}Boc protected thiourea **196** (136 mg, 0.313 mmol) was dissolved in DCM (782 μL) and the solution treated with neat trimethylsilyl iodide (66.9 μL, 0.470 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (549 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (3 x 50 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **198** as pale yellow oil (102 mg, 0.305 mmol, 97 %). $[\alpha]_D$ = - 8.4 ° (c = 1.0, $CHCl_3$, 28 ° C, 589 nm); MS (ES^+): m/z (%) 335 (100) $[M+H]^+$; HRMS (ES^+): $[M + H]^+$ $C_{17}H_{27}N_4OS$ requires m/z: 335.1900, found m/z: 335.1905; IR (film): ν_{max} = 3245 (w), 2948 (w), 1614 (s), 1537 (s), 1450 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (bs, 1H, N**H**), 7.40 - 7.18 (m, 6H, 5C**H** and N**H**), 6.76 (bs, 1H, N**H**), 3.70 - 3.21 (m, 6H, 2C$\mathbf{H}_2$N and C**H**CH**H**'N), 3.12 (dd, *J* = 7.1, 1.4 Hz, 1H, CHC**H**H'N), 2.83 (t, *J* = 6.7 Hz, 2H, NHC$\mathbf{H}_2$CH_2), 1.99 (s, 3H, C$\mathbf{H}_3$), 1.95 - 1.60 (m, 5H, 2CH_2C$\mathbf{H}_2$CH_2 and CHCH**H**'), 1.25 (ddd, *J* = 15.4, 12.1, 7.2 Hz, 1H, CHC**H**H') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.4 (**C**), 171.9 (**C**), 136.8 (**C**), 129.8 (2**C**H), 126.6 (2**C**H), 124.8 (**C**H), 57.5 (**C**H), 53.9 (**C**H_2), 46.5 (**C**H_2), 42.9 (**C**H_2), 42.3 (**C**H_2), 29.6 (**C**H_2), 27.1 (**C**H_2), 25.3 (**C**H_2), 21.9 (**C**H_3) ppm.

[1-[2-(Acetyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-ethylamino]-1-phenylamino-methylidene]-methyl-sulfonium; iodide (199).

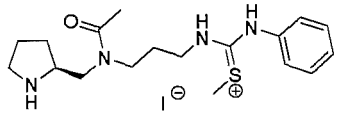


Prepared according to the procedure given by Bartoli *et al.*[207] and Quaranta *et al.*[210]

195 (291 mg, 0.692 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (428 μL, 6.92 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (388 mg, 0.690 mmol, 100 % yield). The deprotection reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. The thiouronium iodide (388 mg, 0.690 mmol) was dissolved in DCM (2.39 mL) and the solution treated with neat trimethylsilyl iodide (148 μL, 1.04 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (1.21 mL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (50 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (2 mL). The aqueous phase was then extracted with DCM (3 x 100 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **199** as a colourless oil (294 mg, 0.636 mmol, 92 %). $[\alpha]_D$ = - 11.1 ° (c = 1.0, $CHCl_3$, 27.5 ° C, 589 nm); MS (ES^+): m/z (%) 335 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{17}H_{27}N_4OS^+$ requires m/z: 335.1900, found m/z: 335.1905; IR (film): ν_{max} = 3418 (w), 2969 (m), 1606 (m), 1585 (m), 1494 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 - 7.20 (m, 2H, 2C**H**), 6.99 (tt, *J* = 7.4, 1.2 Hz, 1H, CHC**H**CH), 6.88 - 6.81 (m, 2H, 2C**H**), 6.58 (bs, 1H, N**H**), 5.96 (bs, 1H, N**H**), 3.79 - 3.52 (m, 4H, NC**H**$_2$ and **CHCH**H'N), 3.40 - 3.32 (m, 2H, NHC**H**$_2$), 3.28 (d, *J* = 6.4 Hz, 1H, CHCH**H**'N), 2.92 (t, *J* = 6.7 Hz, 2H, NHC**H**$_2$), 2.55 (bs, 1H, N**H**), 2.29 (s, 3H, C**H**$_3$), 2.17 (s, 3H, C**H**$_3$),

1.98 - 1.64 (m, 3H, CH**H**'CH_2), 1.33 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (**C**), 172.8 (**C**), 128.8 (**C**), 122.8 (2**C**H), 122.6 (2**C**H), 122.3 (**C**H), 57.7 (**C**H), 55.1 ($**C**H_2$), 51.7 ($**C**H_2$), 46.6 ($**C**H_2$), 46.4 ($**C**H_2$), 30.3 ($**C**H_2$), 25.5 ($**C**H_2$), 21.9 ($**C**H_3$), 14.0 ($**C**H_3$) ppm.

[1-[2-(Acetyl-(*S*)-1-pyrrolidin-2-ylmethyl-amino)-propylamino]-1-phenylamino-methylidene]-methyl-sulfonium; iodide (200).

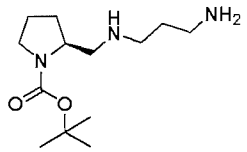


Prepared according to the procedure given by Bartoli *et al.*[207] and Quaranta *et al.*[210]

196 (299 mg, 0.688 mmol) was dissolved in acetone (5 mL). To this solution iodomethane (425 μL, 6.88 mmol) was added and the reaction mixture was stirred at room temperature for 4 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (397 mg, 0.688 mmol, 100 % yield). The deprotection reaction was carried out with oven - dried glassware and under an atmosphere of nitrogen gas. The thiouronium iodide (108 mg, 0.187 mmol) was dissolved in DCM (650 μL) and the solution treated with neat trimethylsilyl iodide (40 μL, 0.281 mmol). The reaction mixture was stirred at room temperature for 20 minutes before the addition of methanol (328 μL). The resulting yellow solution was stirred at room temperature for a further 2 hours. Upon completion the solvent was removed from the reaction mixture under reduced pressure. The resulting foam was redissolved in DCM (25 mL) and washed with saturated $Na_2S_2O_3$ aqueous solution (1 mL). The aqueous phase was then extracted with DCM (3 x 50 mL) and the combined organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **200** as colourless oil (80.0 mg, 0.168 mmol, 90 %). $[\alpha]_D$ = - 6.0 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 349 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+): $[M]^+$ $C_{18}H_{29}N_4OS^+$ requires m/z: 349.2057, found m/z: 349.2063; IR (film): ν_{max} = 3423 (w), 2971 (w), 1606 (s),

1585 (s), 1494 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 7.7 Hz, 2H, 2CHC**H**CH), 6.97 (tt, *J* = 7.4, 1.1 Hz, 1H, CHC**H**CH), 6.89 (dd, *J* = 8.4, 1.1 Hz, 2H, 2CC**H**CH), 5.80 (bs, 1H, N**H**), 3.64 (m, 1H, C**H**CH_2), 3.50 - 3.27 (m, 5H, 2C$\mathbf{H}_2$N and CHCH**H**'N), 3.23 (dd, *J* = 7.2, 3.4 Hz, 1H, CHC**H**H'N), 2.94 (t, *J* = 6.8 Hz, 2H, NHC$\mathbf{H}_2CH_2$), 2.38 (s, 3H, C$\mathbf{H}_3$), 2.28 (bs, 1H, N**H**), 2.19 (s, 3H, C$\mathbf{H}_3$), 1.98 - 1.64 (m, 6H, 2$CH_2C\mathbf{H}_2CH_2$ and CHCH**H**' and N**H**), 1.35 (ddd, *J* = 15.6, 12.2, 7.2 Hz, 1H, CHC**H**H') ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 175.0 (**C**), 167.6 (**C**), 138.6 (**C**), 130.4 (2**C**H), 128.7 (2**C**H), 126.9 (**C**H), 61.8 (**C**H), 48.4 (**C**H_2), 48.1 (**C**H_2), 45.9 (**C**H_2), 42.8 (**C**H_2), 28.4 (**C**H_2), 28.3 (**C**H_2), 23.6 (**C**H_2), 21.9 (**C**H_3), 15.3 (**C**H_3) ppm.

(*S*)-2-[(3-Amino-propylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (201).

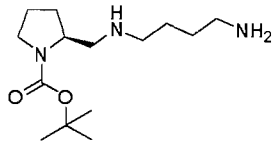


Prepared according to the procedure given by Montero *et al.*[256]

162 (539 mg, 1.38 mmol) was dissolved in methanol (25 mL) and treated with palladium on activated carbon (dry, 10 %, 147 mg, 1.4 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature for 18 hours. After 18 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give diamine **201** as a pale yellow oil (343 mg, 1.33 mmol, 96 %). $[\alpha]_D$ = - 19.1 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 258 (100) $[M+H]^+$; IR (film): ν_{max} = 2973 (w), 1683 (s), 1389 (s), 1158 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 8.14 (bs, 1H, N**H**), 3.76 (m, 1H, C**H**CH_2), 3.53 (bs, 2H, N$\mathbf{H}_2$), 3.28 (m, 1H, NC**H**H'), 3.20 (m, 1H, NCH**H**'), 2.79 (t, *J* = 7.0 Hz, 2H, C$\mathbf{H}_2NH_2$), 2.70 (m, 1H, CHC**H**H'NH), 2.64 (t, *J* = 6.6 Hz, 2H, C$\mathbf{H}_2$NH), 2.52 (m, 1H, CHCH**H**'NH),

1.90 - 1.78 (m, 3H, C**H**H'C$\mathbf{H}_2$), 1.72 (m, 1H, CHCH**H**'), 1.66 (qn, J = 6.7 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.41 (s, 9H, C($\mathbf{CH}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 153.5 (**C**), 78.1 (**C**), 56.6 (**C**H), 51.8 ($\mathbf{C}H_2$), 46.7 ($\mathbf{C}H_2$), 46.1 ($\mathbf{C}H_2$), 38.2 ($\mathbf{C}H_2$), 29.2 ($\mathbf{C}H_2$), 28.2 (3$\mathbf{C}H_3$), 23.1 ($\mathbf{C}H_2$), 22.4 ($\mathbf{C}H_2$) ppm.

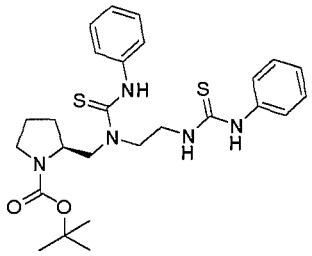
(*S*)-2-[(3-Amino-butylamino)-methyl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (202).



Prepared according to the procedure given by Montero *et al.*[256]

163 (319 mg, 0.787 mmol) was dissolved in methanol (15 mL) and treated with palladium on activated carbon (dry, 10 %, 84.0 mg, 0.787 mmol). The flask containing the suspension was evacuated, purged with nitrogen gas, and then replaced with hydrogen gas. The reaction was left to stir under hydrogen gas at room temperature for 18 hours. After 18 hours the hydrogen gas was removed from the reaction vessel and the reaction mixture filtered through a pad of celite. The filtrate was reduced to give diamine **202** as a pale yellow oil (200 mg, 0.737 mmol, 94 %). $[\alpha]_D$ = - 17.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 272 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{14}H_{30}N_3O_2$ requires m/z: 272.2338, found m/z: 272.1970; IR (film): ν_{max} = 2973 (w), 1683 (s), 1389 (s), 1158 (s), 1108 (m) cm^{-1}; ^{1}H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 3.74 (m, 1H, C**H**CH_2), 3.26 (bs, 2H, $\mathbf{NH}_2$), 3.19 - 3.06 (m, 2H, N$\mathbf{C}H_2$), 2.85 (m, 1H, CHCH**H**'NH), 2.73 (m, 1H, CHC**H**H'NH), 2.71 (t, J = 6.7 Hz, 2H, $\mathbf{C}H_2NH_2$), 2.56 (t, J = 6.5 Hz, 2H, $\mathbf{C}H_2NH$), 2.03 (bs, 1H, N**H**), 1.89 - 1.69 (m, 4H, 2$\mathbf{C}H_2$), 1.63 - 1.44 (m, 4H, 2$\mathbf{C}H_2$), 1.41 (s, 9H, C($\mathbf{CH}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 153.6 (**C**), 78.2 (**C**), 56.6 (**C**H), 51.6 ($\mathbf{C}H_2$), 49.0 ($\mathbf{C}H_2$), 46.7 ($\mathbf{C}H_2$), 38.3 ($\mathbf{C}H_2$), 28.2 (3$\mathbf{C}H_3$), 26.7 ($\mathbf{C}H_2$), 25.8 ($\mathbf{C}H_2$), 23.2 ($\mathbf{C}H_2$), 22.4 ($\mathbf{C}H_2$) ppm.

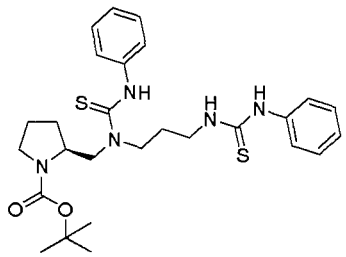
(*S*)-2-{3-Phenyl-1-[2-(3-phenyl-thioureido)-ethyl]-thioureidomethyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (203).



Prepared according to the procedure given by Bartoli *et al.*[207]

179 (324 mg, 1.33 mmol) was dissolved in a biphasic solution of chloroform (65 mL), methanol (20 mL) and saturated $NaHCO_3$ aqueous solution (20 mL) and treated with phenyl isothiocyanate (398 µL, 3.33 mmol). The reaction mixture was stirred vigorously at room temperature for 3 days. The phases of the reaction mixture were separated and the organic phase washed with water (2 x 50 mL) and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield the bis thiourea **203** as a white foam (462 mg, 0.899 mmol, 68 %). $[\alpha]_D$ = - 8.1 ° (c = 0.7, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 514 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{26}H_{36}N_5O_2S_2$ requires m/z: 514.2305, found m/z: 514.2303; IR (solid): ν_{max} = 3277 (w), 2963 (w), 2926 (m), 1671 (s), 1397 (s), 1165 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.37 (bs, 1H, N**H**), 9.14 (bs, 1H, N**H**), 7.65 (bs, 1H, N**H**), 7.42 (dt, *J* = 8.3, 1.2 Hz, 4H, 4CHC**H**CH), 7.35 - 7.28 (m, 4H, 4C**H**), 7.16 - 7.12 (m, 2H, 2C**H**), 4.21 (m, 1H, C**H**CH_2), 4.10 (m, 1H, CHCH**H**'N), 4.02 - 3.91 (m, 2H, NHC**H**$_2$), 3.88 - 3.82 (m, 3H, CHC**H**H'N and NC**H**$_2$), 3.39 - 3.29 (m, 2H, NC**H**$_2$), 2.01 - 1.81 (m, 4H, C**H**$_2$C**H**$_2$CH), 1.44 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 181.0 (**C**), 180.7 (**C**), 154.3 (**C**), 140.1 (**C**), 138.6 (**C**), 128.8 (2**C**H), 127.8 (2**C**H), 126.4 (2**C**H), 125.8 (2**C**H), 124.7 (**C**H), 123.7 (**C**H), 78.6 (**C**), 55.1 (**C**H), 53.0 (**C**H_2), 48.7 (**C**H_2), 45.7 (**C**H_2), 40.8 (**C**H_2), 28.1 (3**C**H_3), 23.3 (**C**H_2), 22.2 (**C**H_2) ppm.

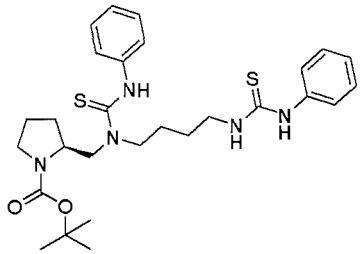
(*S*)-2-{3-Phenyl-1-[2-(3-phenyl-thioureido)-propyl]-thioureidomethyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (204).



Prepared according to the procedure given by Bartoli *et al.*[207]

201 (300 mg, 1.17 mmol) was dissolved in a biphasic solution of chloroform (65 mL), methanol (20 mL) and saturated $NaHCO_3$ aqueous solution (20 mL) and treated with phenyl isothiocyanate (349 µL, 2.91 mmol). The reaction mixture was stirred vigorously at room temperature for 3 days. The phases of the reaction mixture were separated and the organic phase washed with water (2 x 50 mL) and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield the bis thiourea **204** as a white foam (290 mg, 0.550 mmol, 47 %). $[\alpha]_D$ = - 12.2 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 528 (100) $[M+H]^+$; IR (solid): ν_{max} = 2962 (w), 2925 (m), 1671 (s), 1395 (s), 1165 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.16 (bs, 1H, N**H**), 8.98 (bs, 1H, N**H**), 7.52 (bs, 1H, N**H**), 7.47 - 7.41 (m, 4H, 4C**H**), 7.33 - 7.27 (m, 4H, 4C**H**), 7.14 - 7.09 (m, 2H, 2C**H**), 4.14 (m, 1H, C**H**CH_2), 4.01 (m, 1H, CHCH**H**'N), 3.91 - 3.75 (m, 3H, CHC**H**H'N and N$C\mathbf{H}_2$), 3.58 (q, *J* = 6.8 Hz, 2H, NH$C\mathbf{H}_2$), 3.38 - 3.27 (m, 2H, N$C\mathbf{H}_2$), 2.04 - 1.79 (m, 6H, 3$C\mathbf{H}_2$), 1.45 (s, 9H, C($C\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 180.5 (**C**), 180.2 (**C**), 154.4 (**C**), 140.9 (**C**), 139.0 (**C**), 129.9 (2**C**H), 128.6 (2**C**H), 127.8 (2**C**H), 125.9 (2**C**H), 124.2 (**C**H), 123.3 (**C**H), 78.9 (**C**), 55.4 (**C**H), 52.0 ($\mathbf{C}H_2$), 49.3 ($\mathbf{C}H_2$), 45.9 ($\mathbf{C}H_2$), 41.5 ($\mathbf{C}H_2$), 28.1 (3$\mathbf{C}H_3$), 26.4 ($\mathbf{C}H_2$), 23.2 ($\mathbf{C}H_2$), 22.2 ($\mathbf{C}H_2$) ppm.

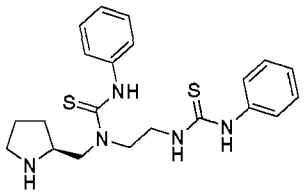
(*S*)-2-{3-Phenyl-1-[2-(3-phenyl-thioureido)-butyl]-thioureidomethyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (205).



Prepared according to the procedure given by Bartoli *et al.*[207]

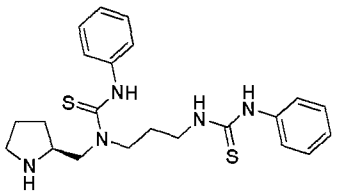
202 (176 mg, 0.648 mmol) was dissolved in a biphasic solution of chloroform (25 mL), methanol (8 mL) and saturated $NaHCO_3$ aqueous solution (8 mL) and treated with phenyl isothiocyanate (200 µL, 1.62 mmol). The reaction mixture was stirred vigorously at room temperature for 3 days. The phases of the reaction mixture were separated and the organic phase washed with water (2 x 20 mL) and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield the bis thiourea **205** as a white foam (93.0 mg, 0.172 mmol, 26 %); $[\alpha]_D$ = - 9.9 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 542 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{28}H_{40}N_5O_2S_2$ requires m/z: 542.2618, found m/z: 542.2622; IR (solid): ν_{max} = 2962 (w), 2925 (m), 1671 (s), 1395 (s), 1165 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.14 (bs, 1H, N**H**), 8.95 (bs, 1H, N**H**), 7.49 (bs, 1H, N**H**), 7.46 - 7.39 (m, 4H, 4C**H**), 7.32 - 7.27 (m, 4H, 4C**H**), 7.13 - 7.08 (m, 2H, 2C**H**), 4.13 (m, 1H, C**H**CH_2), 3.97 - 3.91 (m, 2H, NC$\mathbf{H}_2$), 3.84 - 3.72 (m, 2H, NC$\mathbf{H}_2$), 3.57 (q, J = 6.8 Hz, 2H, NHC$\mathbf{H}_2$), 3.35 - 3.27 (m, 2H, NC$\mathbf{H}_2$), 1.99 - 1.85 (m, 3H, C$\mathbf{H}_2$ and CH_2CH**H'**), 1.82 - 1.71 (m, 3H, C$\mathbf{H}_2$C**H**H'), 1.62 (qn, J = 7.1 Hz, 2H, CH_2C$\mathbf{H}_2$$CH_2$), 1.44 (s, 9H, C(C$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 180.6 (**C**), 180.3 (**C**), 153.9 (**C**), 140.9 (**C**), 139.2 (**C**), 128.5 (2**C**H), 127.8 (2**C**H), 126.5 (2**C**H), 124.5 (2**C**H), 124.0 (**C**H), 123.0 (**C**H), 79.0 (**C**), 55.4 (**C**H), 52.0 (**C**H_2), 46.0 (**C**H_2), 43.5 (**C**H_2), 40.4 (**C**H_2), 28.1 (3**C**H_3), 26.0 (**C**H_2), 24.2 (**C**H_2), 23.3 (**C**H_2), 22.3 (**C**H_2) ppm.

(*S*)-2-{3-Phenyl-1-[2-(3-phenyl-thioureido)-ethyl]-thioureidomethyl}-pyrrolidine (206).



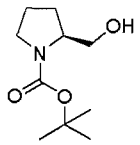
203 (355 mg, 0.691 mmol) was dissolved in a 20 % solution of TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 3 hours. The solvent and residual TFA were removed under reduced pressure to give a colourless oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give bis thiourea **206** as a white foam (251 mg, 0.607 mmol, 88 %). $[\alpha]_D$ = - 64.0 ° (c = 1.0, $CHCl_3$, 27 ° C, 589 nm); MS (ES^+): m/z (%) 414 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{21}H_{28}N_5S_2$ requires m/z: 414.1781, found m/z: 414.1785; IR (solid): ν_{max} = 3243 (w), 2926 (w), 1538 (s), 1496 (s), 1347 (s), 1311 (s), 1255 (s) 695 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO): δ = 9.71 (bs, 1H, N**H**), 8.06 (bs, 1H, N**H**), 7.41 - 7.34 (m, 4H, 4CC**H**), 7.33 (t, *J* = 7.7 Hz, 2H, CHC**H**CH), 7.28 (t, *J* = 7.6 Hz, 2H, CHC**H**CH), 7.13 (t, *J* = 7.3 Hz, 1H, CHC**H**CH), 7.05 (t, *J* = 7.3 Hz, 1H, CHC**H**CH), 4.42 - 3.59 (m, 6H, C**H**$_2$NC**H**$_2$ and NHC**H**$_2$), 3.41 (m, 1H, C**H**CH_2), 3.00 (m, 1H, NHC**H**H'CH_2), 2.75 (m, 1H, NHCH**H**'CH_2), 1.92 (m, 1H, CH_2C**H**H'), 1.79 (m, 1H, CH_2CH**H**'), 1.61 (dt, *J* = 15.8, 7.9 Hz, 1H, CHC**H**H'), 1.40 (dt, *J* = 14.6, 7.5 Hz, 1H, CHCH**H**') ppm; ^{13}C NMR (100 MHz, d_6DMSO): δ = 182.6 (**C**), 180.7 (**C**), 141.5 (**C**), 138.9 (**C**), 128.6 (2**C**H), 128.0 (2**C**H), 124.4 (2**C**H), 123.5 (2**C**H), 123.3 (**C**H), 123.2 (**C**H), 57.8 (**C**H), 56.3 (**C**H_2), 50.3 (**C**H_2), 45.2 (**C**H_2), 41.3 (**C**H_2), 28.8 (**C**H_2), 26.1 (**C**H_2) ppm; Microanalysis: Calculated for $C_{21}H_{27}N_5S_2$; C, 60.98; H, 6.58; N, 16.92; S, 15.52, found; C, 52.19; H, 6.53; N, 12.89; S, 15.81.

(*S*)-2-{3-Phenyl-1-[2-(3-phenyl-thioureido)-propyl]-thioureidomethyl}-pyrrolidine (207).



204 (201 mg, 0.381 mmol) was dissolved in a 20 % solution of TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 3 hours. The solvent and residual TFA were removed under reduced pressure to give a colourless oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give bis thiourea **207** as a white foam (163 mg, 0.381 mmol, 100 %). $[\alpha]_D$ = - 55.9 ° (c = 1.0, $CHCl_3$, 27 ° C, 589 nm). MS (ES^+): m/z (%) 428 (100) $[M+H]^+$; HRMS (ES^+) $[M+H]^+$ $C_{22}H_{30}N_5S_2$ requires m/z: 428.1937, found m/z: 428.1937; IR (solid): ν_{max} = 3247 (w), 2926 (w), 1538 (s), 1496 (s), 1347 (s), 1311 (s), 1255 (s), 695 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 12.48 (bs, 1H, N**H**), 7.76 (bs, 1H, N**H**), 7.51 (bs, 1H, N**H**), 7.21 - 7.18 (m, 9H, 9C**H**), 7.07 (tt, *J* = 7.0, 1.6 Hz, 1H, CHC**H**CH), 4.00 (dd, *J* = 13.8, 6.8 Hz, 1H, CHCH**H**'N), 3.82 (q, *J* = 6.5 Hz, 2H, C**H**$_2$NH), 3.72 - 3.63 (m, 3H, C**H**$_2$N and C**H**CH$_2$), 3.25 (d, *J* = 13.6 Hz, 1H, CHC**H**H'N), 3.09 (m, 1H, NHC**H**H'CH$_2$), 2.84 (ddd, *J* = 11.0, 8.5, 6.2 Hz, 1H, NHCH**H**'CH$_2$), 2.09 - 1.97 (m, 3H, CH$_2$C**H**H' and CH$_2$C**H**$_2$CH$_2$), 1.89 (m, 1H, CH$_2$CH**H**'), 1.70 (ddd, *J* = 19.9, 15.9, 7.4 Hz, 1H, CHC**H**H'), 1.42 (dt, *J* = 14.0, 7.3 Hz, 1H, CHCH**H**') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3 (**C**), 180.4 (**C**), 141.3 (**C**), 136.2 (**C**), 130.1 (2**C**H), 128.5 (2**C**H), 127.2 (2**C**H), 125.3 (2**C**H), 124.1 (**C**H), 123.4 (**C**H), 58.4 (**C**H), 56.4 (**C**H$_2$), 49.4 (**C**H$_2$), 46.3 (**C**H$_2$), 42.2 (**C**H$_2$), 29.7 (**C**H$_2$), 27.1 (**C**H$_2$), 26.7 (**C**H$_2$) ppm; Microanalysis: Calculated for $C_{22}H_{29}N_5S_2$; C, 61.79; H, 6.84; N, 16.37; S, 15.00, found; C, 58.87; H, 6.46; N, 15.18; S, 10.15; For crystal structure see **Appendix 2**.

(*S*)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (213).

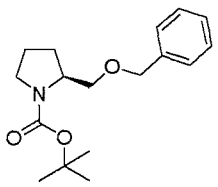


Prepared according to the procedure given by Bartoli *et al.*[252]

All glassware used for the reaction was flame dried, the reaction was carried out under an atmosphere of nitrogen gas and solvents were used distilled. ^{t}Boc - L - proline (**99**, 2.00 g, 9.29 mmol) was dissolved in THF (14 mL) and the resulting solution cooled to - 5 ° C. Borane - THF complex (1.00 M, 18.6 mL, 18.6 mmol) was added dropwise to the cold solution over 10 minutes. The reaction mixture was stirred at - 5 ° C to 0 ° C for 2 hours and then warmed to room temperature and stirred for a further 2 hours. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (32 mL) added dropwise over 30 minutes. The reaction mixture was then extracted with ethyl acetate (200 mL) and the organic phase was washed with brine (50 mL), saturated $NaHCO_3$ aqueous solution (50 mL) and water (2 x 50 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (3 % methanol / DCM) to yield ^{t}Boc - L - prolinol **213** as a white crystalline solid (1.87 g, 9.27 mmol, 99 %). Mp.: 52 - 54 ° C (DCM) (Literature Mp.: 56 - 58 ° C) [298]. $[\alpha]_D$ = - 49.9 ° (c = 1.0, $CHCl_3$, 27.5 ° C, 589 nm) (Literature $[\alpha]_D$ = - 47.3 ° (c = 1.0, $CHCl_3$))[252]; MS (ES^+): m/z (%) 224 (100) $[M+Na]^+$; IR (film): ν_{max} = 3431 (m), 2971 (w), 2869 (w), 1660 (s), 1404 (s), 1367 (s), 1404 (s), 1166 (s), 1126 (s), 1048 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (bs, 1H, **OH**), 3.89 (m, 1H, **CH**CH_2), 3.60 - 3.53 (m, 2H, CH**C**H_2O), 3.40 (m, 1H, CH_2CH**H**'N), 3,26 (m, 1H, CH_2C**H**H'N), 1.95 (m, 1H, CHCH**H**'CH_2), 1.82 - 1.69 (m, 2H, CH_2C**H**$_2$$CH_2$), 1.50 (m, 1H, CHC**H**H'CH_2), 1.42 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (**C**), 80.2 (**C**), 67.4 (**C**H_2), 60.2 (**C**H), 47.6 (**C**H_2), 28.7 (**C**H_2), 28.5 (3**C**H_3), 24.1 (**C**H_2) ppm.

Spectroscopic data agrees with literature reference[252, 299].

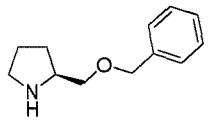
(*S*)-2-Benzyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (214).



Prepared according to the procedure given by Kokotos *et al.* [266]

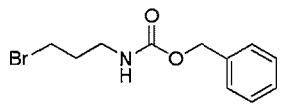
213 (250 mg, 1.24 mmol) was dissolved in toluene (3.00 mL) and treated with 50 % NaOH aqueous solution (4.60 mL) and tetrabutyl ammonium iodide (32.7 mg, 0.0885 mmol). The reaction mixture was warmed to 70 ° C, whilst stirring, before the addition of benzyl bromide (740 μL, 6.21 mmol). The reaction was stirred vigorously at 70 ° C for 48 hours. The phases were then separated and the aqueous phase extracted with ethyl acetate (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to give the ether **214** as a colourless oil (313 mg, 1.07 mmol, 87 %). $[\alpha]_D$ = - 49.0 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 314 (100) $[M+Na]^+$; IR (film): ν_{max} = 2975 (w), 2875 (w), 1684 (s), 1390 (s), 1365 (s), 1166 (s), 1097 (s), 749 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 - 7.26 (m, 5H, 5C**H**), 4.52 (m, 2H, O**C**$\mathbf{H}_2$Ph), 3.91 (m, 1H, **C**$\mathbf{H}$$CH_2$), 3.60 - 3.33 (m, 4H, CH_2**C**$\mathbf{H}_2$NH and CH**C**$\mathbf{H}_2$O), 1.98 - 1.78 (m, 4H, **C**$\mathbf{H}_2$**C**$\mathbf{H}_2$), 1.44 (s, 9H, C(**C**$\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6 (**C**), 138.6 (**C**), 128.4 (2**C**H), 127.6 (2**C**H), 127.5 (**C**H), 79.3 (**C**), 73.4 (**C**H_2), 71.2 (**C**H_2), 56.6 (**C**H), 46.8 (**C**H_2), 28.6 (3**C**H_3), 23.8 (**C**H_2), 23.1 (**C**H_2) ppm.
Spectroscopic data agrees with literature reference[300].

(*S*)-2-((Benzyloxy)methyl)pyrrolidine (215).



214 (280 mg, 0.96 mmol) was dissolved in a 10 % solution of TFA (1 mL) in DCM (9 mL) and stirred at room temperature for 3 hours. The solvent and residual TFA was removed under reduced pressure to give a yellow oil. The ammonium salt was redissolved in DCM (10 mL), treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a colourless oil. The crude material was purified by column chromatography (5 % methanol / DCM) to give ether **215** as a colourless oil (108 mg, 0.565 mmol, 59 %). $[\alpha]_D$ = - 22.1 ° (c = 1.0, H_2O, 27 ° C, 589 nm) (Literature $[\alpha]_D$ = - 19 ° (c = 1.0, H_2O))[301]; MS (ES^+): m/z (%) 192 (100) $[M+H]^+$; IR (film): ν_{max} = 2982 (w), 1669 (s), 1177 (s), 1127 (s), 720 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.85 (bs, 1H, N**H**), 7.32 - 7.26 (m, 5H, 5C**H**), 4.55 - 4.45 (m, 2H, O**C**H_2Ph), 3.78 (m, 1H, C**H**CH_2), 3.63 (dd, *J* = 10.3, 3.5 Hz, 1H, CHCH**H**'O), 3.57 (dd, *J* = 10.3, 6.6 Hz, 1H, CHC**H**H'O), 3.28 - 3.12 (m, 2H, $CH_2C\mathbf{H}_2NH$), 2.09 - 1.86 (m, 3H, $CH_2C\mathbf{H}_2CH\mathbf{H}'$), 1.77 (m, 1H, $CHC\mathbf{H}H'CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4 (**C**), 128.5 (2**C**H), 128.3 (2**C**H), 128.0 (**C**H), 73.4 ($\mathbf{C}H_2$), 68.7 ($\mathbf{C}H_2$), 58.9 (**C**H), 45.7 ($\mathbf{C}H_2$), 27.0 ($\mathbf{C}H_2$), 24.0 ($\mathbf{C}H_2$) ppm.
Spectroscopic data agrees with literature reference[301, 302].

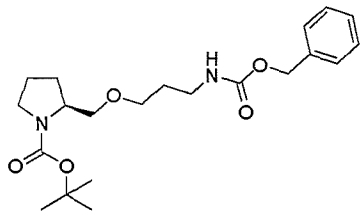
(3-Bromo-propyl)-carbamic acid benzyl ester (216).



Prepared according to the procedure given by Forsch *et al.* [303]

3 - Bromopropylamine hydrobromide (1.00 g, 4.57 mmol) was dissolved in a biphasic solution of DCM (35 mL) and saturated K_2CO_3 aqueous solution (20 mL) and treated with benzyl chloroformate (717 μL, 5.02 mmol). The reaction mixture was stirred vigorously at room temperature for 18 hours. The phases of the reaction mixture were separated and aqueous phase extracted with DCM (3 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give colourless oil. The crude material was purified by column chromatography (100 % DCM) to yield bromide **216** as a colourless oil (717 mg, 2.63 mmol, 58 %). MS (ES^+): m/z (%) 294 (100) $[M+Na]^+$; IR (film): ν_{max} = 3326 (w), 2929 (w), 1692 (s), 1521 (m), 1242 (s), 1131 (w), 1001 (w), 695 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.33 (m, 5H, 5C**H**), 5.10 (bs, 3H, OC$\mathbf{H}_2$Ph and N**H**), 3.41 (t, J = 6.5 Hz, 2H, BrC$\mathbf{H}_2$$CH_2$), 3.33 (q, J = 6.0 Hz, 2H, CH_2C$\mathbf{H}_2$NH), 2.05 (qn, J = 6.4 Hz, 2H, CH_2C$\mathbf{H}_2$$CH_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5 (**C**), 136.5 (**C**), 128.6 (2**C**H), 128.4 (2**C**H), 128.1 (**C**H), 66.8 (**C**H_2), 39.5 (**C**H_2), 32.5 (**C**H_2), 30.7 (**C**H_2) ppm.
Spectroscopic data agrees with literature reference[304].

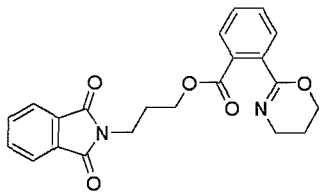
(*S*)-2-(3-Benzyloxycarbonylamino-propoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (217).



Prepared according to the procedure given by Kokotos *et al.*[266]

213 (250 mg, 1.24 mmol) was dissolved in a biphasic solution of toluene (3 mL) and NaOH aqueous solution (50 %, 4.2 mL) and treated with $TBA.HSO_4$ (29.1 mg, 0.0857 mmol). The mixture was warmed to 70 ° C before the dropwise addition of **216** (343 mg, 1.26 mmol) as a solution in toluene (1 mL). The reaction mixture was stirred vigorously at 70 ° C for 3 days. The phases were separated and the aqueous phase extracted with ethyl acetate (5 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % ethyl acetate / petroleum ether) to yield ether **217** as a pale yellow oil (14.4 mg, 0.0367 mmol, 3 %). $[\alpha]_D$ = - 20.5 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 393 (100) $[M+H]^+$; IR (film): ν_{max} = 2973 (w), 2874 (w), 1694 (s), 1392 (m), 1169 (m), 1100 (m) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 8.21 (bs, 1H, N**H**), 7.37 - 7.25 (m, 5H, 5C**H**), 4.50 (s, 2H, C$\mathbf{H}_2$Ph), 3.85 (m, 1H, C**H**CH_2), 3.57 (dd, *J* = 9.4, 3.5 Hz, 1H, CHCH**H**'O), 3.43 (dd, *J* = 9.4, 7.2 Hz, 1H, CHC**H**H'O), 3.29 (m, 1H, NCH**H**'), 3.22 (m, 1H, NC**H**H'), 3.10 - 2.95 (m, 4H, O$\mathbf{CH}_2$ and N$\mathbf{CH}_2$), 1.95 - 1.80 (m, 4H, 2$\mathbf{CH}_2$), 1.75 (m, 1H, CHC**H**H'), 1.46 (m, 1H, CHCH**H**'), 1.39 (s, 9H, C($\mathbf{CH}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8 (**C**), 154.7 (**C**), 138.7 (**C**), 128.5 (2**C**H), 128.3 (2**C**H), 127.6 (**C**H), 79.4 (**C**), 73.3 ($\mathbf{CH}_2$), 71.2 ($\mathbf{CH}_2$), 71.0 ($\mathbf{CH}_2$), 56.7 (**C**H), 47.0 ($\mathbf{CH}_2$), 46.6 ($\mathbf{CH}_2$), 29.8 ($\mathbf{CH}_2$), 28.7 (3$\mathbf{CH}_3$), 23.9 ($\mathbf{CH}_2$), 23.1 ($\mathbf{CH}_2$) ppm.

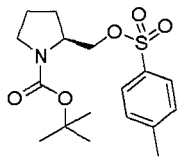
2-(5,6-Dihydro-4H-[1,3]oxazin-2-yl)-benzoic acid 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl ester (220).



All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of nitrogen gas and solvents were used distilled. A stirring suspension of NaH (56.8 mg, 1.42 mmol) in DMF (15 mL) was cooled to - 5 ° C before the addition of ^{t}Boc - L - prolinol (**213**, 300 mg, 1.49 mmol) as a solution in DMF (2 mL). The resulting suspension was stirred at - 5 ° C for 30 minutes before the addition of N - (3 - bromo - propyl) - phthalimide (381 mg, 1.42 mmol) as a solution in DMF (2 mL). The resulting reaction mixture was stirred at - 5 ° C for 1 hour. The reaction was then stirred at room temperature for 20 hours. The reaction was then cooled to - 5 ° C and quenched by the addition of cold water (15 mL) added dropwise over 10 minutes. The reaction mixture was then extracted with ethyl acetate (3 x 20 mL) and the organic phase dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The major product was isolated by crystallisation (ethyl acetate / hexane) to yield oxazine **220** as a white crystalline solid (147 mg, 0.375 mmol, 53 %). Mp.: 112 – 114 ° C (ethyl acetate / hexane); MS (ES^+): m/z (%) 393 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{22}H_{21}N_2O_5$ requires m/z: 393.1445, found m/z: 393.1438; IR (solid): ν_{max} = 3374 (w), 3202 (w), 2964 (w), 1728 (s), 1642 (s), 1589 (s), 1477 (m), 1241 (s), 1142 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H, 2CC**H**CH), 7.67 (apparent dd, *J* = 5.5, 3.1 Hz, 2H, 2CHC**H**CH), 7.64 (m, 1H, CC**H**CH), 7.56 (dd, *J* = 7.5, 1.3 Hz, 1H, CC**H**CH), 7.43 (dt, *J* = 7.5, 1.4 Hz, 1H, CHC**H**CH), 7.37 (dt, *J* = 7.5, 1.4 Hz, 1H, CHC**H**CH), 4.35 (t, *J* = 6.3 Hz, 2H, OC**H**$_2$), 4.29 (t, *J* = 5.4 Hz, 2H, OC**H**$_2$), 3.86 (t, *J* = 6.9 Hz, 2H, NC**H**$_2$), 3.57 (t, *J* = 6.0 Hz, 2H, NC**H**$_2$), 2.15 (qn, *J* = 6.5 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$), 2.00 (qn, *J* = 5.7 Hz, 2H, $CH_2C\mathbf{H}_2CH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4 (2**C**), 168.1 (**C**), 156.6 (**C**), 135.0 (**C**), 134.0 (2**C**H), 132.2 (2**C**), 131.4 (**C**), 131.0 (**C**H), 129.4 (2**C**H), 128.9 (**C**H), 123.3 (2**C**H), 65.6 (**C**H$_2$),

63.0 (**C**H_2), 42.9 (**C**H_2), 35.5 (**C**H_2), 27.9 (**C**H_2), 21.9 (**C**H_2) ppm; For crystal structure see **Appendix 2**.

(*S*)-2-(Toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (221).

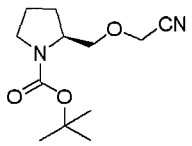


Prepared according to the procedure given by Bartoli *et al.*[252]

213 (1.00 g, 4.97 mmol) was dissolved in DCM (distilled, 35 mL) and cooled to 0 ° C before the addition of Et_3N (distilled, 4.16 mL, 29.8 mmol) and *p* - toluenesulfonyl chloride (4.74 g, 24.8 mmol). The reaction mixture was warmed to room temperature and stirred for 20 hours. The reaction mixture was washed with $KHSO_4$ aqueous solution (1M, 3 x 10 mL). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to yield tosylate **221** as a colourless oil (1.15 g, 3.23 mmol, 65 %). $[\alpha]_D$ = - 44.2 ° (c = 1.0, $CHCl_3$, 22 ° C, 589 nm) (Literature $[\alpha]_D$ = - 43.5 ° (c = 0.7, DCM, 25 ° C))[252]; MS (ES^+): m/z (%) 378 (100) $[M+Na]^+$; IR (film): ν_{max} = 2975 (w), 1744 (m), 1396 (m), 1364 (m), 1174 (s), 1009 (m), 728 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2H, 2CC**H**CH), 7.34 (d, *J* = 8.1 Hz, 2H, 2CHC**H**C), 4.07 (m, 1H, C**H**CH_2), 3.99 - 3.85 (m, 2H, CHC$\mathbf{H_2}$O), 3.29 - 3.25 (m, 2H, $CH_2C\mathbf{H_2}N$), 2.43 (s, 3H, C$\mathbf{H_3}$), 1.95 - 1.78 (m, 4H, 2C$\mathbf{H_2}$), 1.37 (s, 9H, 3C$\mathbf{H_3}$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6 (**C**), 144.9 (**C**), 133.1 (**C**), 130.0 (2**C**H), 128.0 (2**C**H), 79.9 (**C**), 70.1 (**C**H_2), 56.7 (**C**H), 46.6 (**C**H_2), 28.5 (3**C**H_3), 23.9 (**C**H_2), 23.0 (**C**H_2), 21.7 (**C**H_3) ppm.

Spectroscopic data agrees with literature[252].

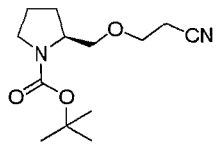
(*S*)-2-Cyanomethoxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (222).



Prepared according to the procedure given by Malet *et al.*[270]

All glassware used for the reaction was flame dried, the reaction carried out under an atmosphere of argon gas and solvents were used distilled. **213** (250 mg, 1.24 mmol) dissolved in acetonitrile (4 mL) was added to a suspension of sodium hydride (248 mg, 6.21 mmol) in acetonitrile (2 mL), cooled to 0 ° C. The reaction mixture was stirred for 1 hour at 0 ° C and 1 hour at room temperature. The reaction mixture was then cooled to - 20 ° C before the addition of bromoacetonitrile (475 μL, 6.82 mmol) dropwise over 5 minutes. The reaction mixture turned bright yellow and then to dark brown within 10 minutes. The reaction mixture was stirred at - 20 ° C for 5 hours before being allowed to warm to room temperature and stirred for 18 hours. A further 10 equivalents of bromoacetonitrile (865 μL, 12.4 mmol) was added at - 20 ° C and stirred at room temperature for a further 24 hours. The reaction was cooled to - 5 ° C and quenched with cold water (20 mL) over 20 minutes. The solvents were removed under reduced pressure and the resulting brown solid washed DCM (500 mL). The filtrate was reduced to give a bright yellow oil. The crude material was purified by column chromatography (25 % ethyl acetate / petroleum ether) to yield nitrile **222** as a colourless oil (38.9 mg, 0.162 mmol, 13 %). $[\alpha]_D$ = - 53.2 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 263 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{12}H_{20}N_2NaO_3$ requires m/z: 263.1366, found m/z: 263.1369; IR (film): ν_{max} = 2975 (w), 2878 (w), 1685 (s), 1390 (s), 1165 (s), 1100 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 4.43 (s, 2H, C**H**$_2$CN), 3.85 (m, 1H, C**H**CH$_2$), 3.63 (dd, *J* = 9.2, 3.5 Hz, 1H, CHCH**H**'O), 3.49 (dd, *J* = 9.2, 7.1 Hz, 1H, CHC**H**H'O), 3.29 (m, 1H, NC**H**H'), 3.22 (m, 1H, NCH**H**'), 1.94 (m, 1H, CHC**H**H'), 1.86 - 1.75 (m, 3H, C**H**$_2$CH**H**'), 1.43 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5 (**C**), 116.0 (**C**), 78.7 (**C**), 72.5 (**C**H$_2$), 56.8 (**C**H$_2$), 56.1 (**C**H), 46.9 (**C**H$_2$), 28.6 (3**C**H$_3$), 23.9 (**C**H$_2$), 23.6 (**C**H$_2$) ppm.

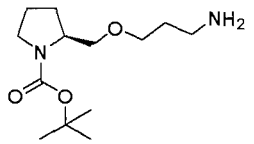
(*S*)-2-(2-Cyano-ethoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (224).



Prepared according to the procedure given by Krishna *et al.*[271]

213 (2.00 g, 9.94 mmol) was dissolved in a biphasic solution of toluene (4 mL) and NaOH aqueous solution (40 %, 40 mL) and treated with TBA.I (260 mg, 0.703 mmol) and acrylonitrile (**225**, 3.2 mL, 50.0 mmol) and stirred vigorously for room temperature for 20 hours. The phases were separated and the aqueous phase extracted with ethyl acetate (4 x 500 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (20 % ethyl acetate / petroleum ether) to yield nitrile **224** as a pale yellow oil (2.50 g, 9.83 mmol, 99 %). $[\alpha]_D$ = - 57.2 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 277 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{13}H_{22}N_2NaO_3$ requires m/z: 277.1523, found m/z: 277.1522; IR (film): ν_{max} = 2973 (w), 2877 (w), 1685 (s), 1390 (m), 1167 (s), 1103 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 80 ° C): δ = 3.83 (m, 1H, C**H**CH_2), 3.63 (t, *J* = 6.0 Hz, 2H, C$\mathbf{H_2}$O), 3.56 (dd, *J* = 9.5, 3.4 Hz, 1H, CHCH**H**'O), 3.41 (dd, *J* = 9.6, 7.2 Hz, 1H, CHC**H**H'O), 3.32 - 3.20 (m, 2H, NC$\mathbf{H_2}$), 2.67 (t, *J* = 6.1 Hz, 2H, C$\mathbf{H_2}$CN), 1.94 - 1.85 (m, 3H, C$\mathbf{H_2}$CH**H**'), 1.77 (m, 1H, CHC**H**H'), 1.43 (s, 9H, C(C$\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6 (**C**), 117.8 (**C**), 79.3 (**C**), 71.7 (**C**H_2), 65.7 (**C**H_2), 56.3 (**C**H), 46.7 (**C**H_2), 30.5 (**C**H_2), 28.5 (3**C**H_3), 23.0 (**C**H_2), 18.9 (**C**H_2) ppm.

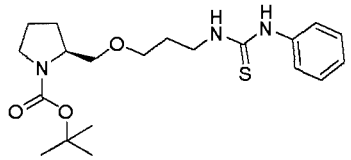
(*S*)-2-(3-Amino-propoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (226).



Prepared according to the procedure given by Khurana *et al.*[275]

224 (200 mg, 0.786 mmol) was dissolved in methanol (6 mL) and the round bottomed flask fitted with a condenser. The solution was treated with $NiCl_2$ (204 mg, 1.57 mmol) followed by water (1 mL), the solution turned from colourless to pale green. Sodium borohydride (179 mg, 4.70 mmol) was added to the reaction mixture portion wise, the addition caused the solution to turn black and effervesce; the condenser was immediately fitted after each addition. The reaction mixture was stirred at room temperature for 3 hours; at this time TLC confirmed the reaction was complete. The reaction was treated with methanol (10 mL) and filtered through a pad of celite, and the resulting black solid washed with methanol (20 mL). Water (50 mL) was added to the pale green filtrate and then extracted with DCM (3 x 200 mL). The combined organic phase was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give an orange oil. The crude material was purified with column chromatography (20 % methanol / DCM) to yield amine **226** as an orange oil (167 mg, 0.646 mmol, 82 %). $[\alpha]_D$ = + 20.5 ° (c = 1.0, $CHCl_3$, 29.5 ° C, 589 nm); MS (ES^+): m/z (%) 259 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{13}H_{27}N_2O_3$ requires m/z: 259.2016, found m/z: 259.2021; IR (film): ν_{max} = 3420 (w), 2970 (m), 2874 (m), 1689 (s), 1390 (m), 1167 (s), 1101 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 3.81 (m, 1H, C**H**CH_2), 3.52 - 3.42 (m, 3H, CHCH**H**'O and C$\mathbf{H_2}$O), 3.33 (dd, *J* = 9.5, 7.2 Hz, 1H, CHC**H**H'O), 3.30 (m, 1H, NCH**H**'), 3.20 (m, 1H, NC**H**H'), 2.66 (t, *J* = 6.6 Hz, 2H, C$\mathbf{H_2}$$NH_2$), 2.20 (bs, 2H, N$\mathbf{H_2}$), 1.90 - 1.81 (m, 3H, C$\mathbf{H_2}$CH**H**'), 1.74 (m, 1H, CHC**H**H'), 1.59 (qn, *J* = 6.6 Hz, 2H, CH_2C$\mathbf{H_2}$$CH_2$), 1.43 (s, 9H, C(C$\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 153.4 (**C**), 78.2 (**C**), 71.0 (**C**H_2), 68.6 (**C**H_2), 56.0 (**C**H), 46.1 (**C**H_2), 38.7 (**C**H_2), 33.4 (**C**H_2), 28.0 (3**C**H_3), 23.1 (**C**H_2), 22.3 (**C**H_2) ppm.

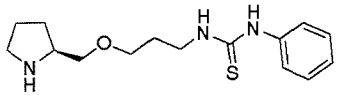
(*S*)-2-[3-(3-Phenyl-thioureido)-propoxymethyl]-pyrrolidine-1-carboxylic acid *tert* butyl ester (227).



Prepared according to the procedure given by Bartoli *et al.*[207]

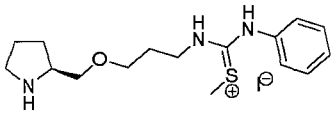
226 (800 mg, 3.10 mmol) and phenylisothiocyanate (370 μL, 3.10 mmol) were dissolved in a biphasic solution of chloroform (95 mL), methanol (30 mL) and saturated $NaHCO_3$ aqueous solution (30 mL). The reaction mixture stirred vigorously for 18 hours at room temperature. On completion the phases were separated and the organic phase washed with water (2 x 100 mL) and the aqueous phase extracted with DCM (3 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (5 % methanol / DCM) to obtain the thiourea **227** as a white foam (1.00 g, 2.54 mmol, 82 %). $[\alpha]_D$ = + 15.5 ° (c = 1.0, $CHCl_3$, 30.5 ° C, 589 nm); MS (ES^+): m/z (%) 416 (100) $[M+Na]^+$; HRMS (ES^+): $[M+Na]^+$ $C_{20}H_{31}N_3NaO_3S$ requires m/z: 416.1978 found m/z: 416.1969; IR (solid): ν_{max} = 3312 (w), 2975 (w), 1675 (m), 1398 (m), 1168 (m), 1108 (m), 726 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 9.14 (bs, 1H, N**H**), 7.44 (dd, *J* = 8.3, 1.1 Hz, 2H, 2CC**H**CH), 7.31 (tt, *J* = 7.3, 1.9 Hz, 2H, 2CHC**H**CH), 7.10 (tt, *J* = 7.3, 1.1 Hz, 1H, CHC**H**CH), 3.81 (m, 1H, C**H**CH_2), 3.56 (q, *J* = 6.8 Hz, 2H, C**H**$_2$NH), 3.59 - 3.49 (m, 3H, CHC**H**H'O and C**H**$_2$O), 3.33 (dd, *J* = 9.6, 7.2 Hz, 1H, CHC**H**H'O), 3.29 (m, 1H, NCH**H**'CH_2), 3.22 (m, 1H, NC**H**H'CH_2), 1.91 - 1.78 (m, 5H, CHCH**H**' and 2CH_2C**H**$_2$$CH_2$), 1.75 (m, 1H, CHC**H**H'), 1.42 (s, 9H, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, d_6DMSO): δ = 180.4 (**C**), 153.5 (**C**), 139.2 (**C**), 128.6 (2**C**H), 124.0 (2**C**H), 123.1 (**C**H), 78.3 (**C**), 71.1 (**C**H_2), 68.5 (**C**H_2), 55.9 (**C**H), 46.2 (**C**H_2), 41.5 (**C**H_2), 28.7 (**C**H_2), 28.1 (3**C**H_3), 23.2 (**C**H_2), 22.3 (**C**H_2), ppm.

1-Phenyl-3-[3-((*S*)-1-pyrrolidin-2-ylmethoxy)-propyl]-thiourea (228).



227 (412 mg, 1.05 mmol) was dissolved in a solution of 20 % TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 2 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (15 mL) and treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiourea **228** as a colourless oil (302 mg, 1.03 mmol, 98 %). $[\alpha]_D$ = + 6.2 ° (c = 1.0, $CHCl_3$, 21 ° C, 589 nm); MS (ES^+): m/z (%) 294 (100) $[M+H]^+$; HRMS (ES^+): $[M]^+$ $C_{15}H_{24}N_3OS^+$ requires m/z: 294.1635, found m/z: 294.1640; IR (film): ν_{max} = 2974 (w), 2875 (w), 1684 (s), 1392 (s), 1102 (s), 732 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 - 7.28 (m, 5H, 4C**H** and N**H**), 7.18 (tt, *J* = 6.7, 1.9 Hz, 1H, CHC**H**CH), 3.80 - 3.65 (m, 2H, C**H**$_2$O), 3.54 (q, *J* = 5.6 Hz, 2H, NHC**H**$_2$), 3.38 (dd, *J* = 9.5, 3.9 Hz, 1H, CHCH**H**'O), 3.25 (dd, *J* = 9.5, 7.9 Hz, 1H, CHC**H**H'O), 3.15 (m, 1H, C**H**CH$_2$), 2.96 - 2.80 (m, 2H, NHC**H**$_2$), 1.86 (qn, *J* = 5.7 Hz, 2H, CH$_2$C**H**$_2$CH$_2$), 1.78 - 1.60 (m, 3H, CHH**H**'C**H**$_2$), 1.30 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9 (**C**), 137.8 (**C**), 129.5 (2**C**H), 126.1 (2**C**H), 124.8 (**C**H), 73.5 (**C**H$_2$), 70.2 (**C**H$_2$), 58.1 (**C**H), 46.3 (**C**H$_2$), 44.1 (**C**H$_2$), 28.4 (**C**H$_2$), 27.7 (**C**H$_2$), 25.2 (**C**H$_2$) ppm. Microanalysis: Calculated for $C_{15}H_{23}N_3OS$; C, 61.40; H, 7.90; N, 14.31; S, 10.93, found; C, 57.21; H, 7.23; N, 12.53; S, 5.00.

Methyl-[1-phenylamino-1-[3-((*S*)-1-pyrrolidin-2-ylmethoxy)-propylamino]-methylidene]-sulfonium; iodide (229).

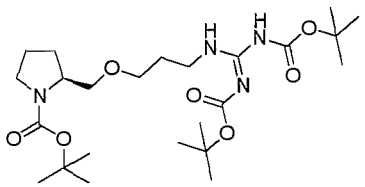


Prepared according to the procedure given by Bartoli *et al.*[207]

227 (682 mg, 1.73 mmol) was dissolved in acetone (10 mL). To this solution iodomethane (1.08 mL, 17.3 mmol) was added and the reaction mixture was stirred at room temperature for 5 hours. On completion the solvent and excess iodomethane were removed under reduced pressure to give the thiouronium iodide as a yellow foam (926 mg, 1.73 mmol, 100 %). The thiouronium iodide (439 mg, 0.820 mmol) was dissolved in a solution of 20 % TFA (2 mL) in DCM (8 mL) and stirred at room temperature for 3 hours. Once the reaction was complete the solvent and residual TFA were removed under reduced pressure. The resulting ammonium salt was redissolved in DCM (10 mL) and treated with saturated K_2CO_3 aqueous solution (1 mL) and stirred vigorously at room temperature for 30 minutes. The phases were separated and the aqueous phase extracted with DCM (5 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield thiouronium **229** as a pale yellow oil (314 mg, 0.721 mmol, 88 %). $[\alpha]_D$ = + 6.3 ° (c = 1.0, $CHCl_3$, 21 ° C, 589 nm); MS (ES^+): m/z (%) 308 (100) $[M]^+$; MS (ES^-): m/z (%) 127 (100) $[I]^-$; HRMS (ES^+) $[M]^+$ $C_{16}H_{26}N_3OS^+$ requires m/z: 308.1791, found m/z: 308.1789. IR (film): ν_{max} = 3315 (w), 3051 (w), 2870 (w), 1581 (s), 1484 (m), 1118 (s), 696 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.3 Hz, 2H, 2CHC**H**CH), 7.02 (tt, *J* = 7.4, 1.2 Hz, 1H, CHC**H**CH), 6.90 (dd, *J* = 8.3, 1.2 Hz, 2H, 2CC**H**CH), 3.81 (ddd, *J* = 15.1, 7.6, 3.8 Hz, 1H, C**H**CH_2), 3.68 (dd, *J* = 10.2, 3.8 Hz, 1H, CHCH**H**'O), 3.63 - 3.55 (m, 3H, CH_2O and CHC**H**H'O), 3.49 (dt, *J* = 6.4, 4.1 Hz, 2H, NHCH_2), 3.23 (t, *J* = 7.2 Hz, 2H, NHCH_2), 2.28 (s, 3H, CH_3), 2.12 - 1.84 (m, 5H, CH**H**'CH_2 and $CH_2CH_2CH_2$), 1.75 (m, 1H, CHC**H**H') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6 (**C**), 149.1 (**C**), 129.1 (2**C**H), 123.2 (2**C**H), 122.8 (**C**H), 69.7 (**C**H_2), 69.1 (**C**H_2), 59.1 (**C**H), 45.7 (**C**H_2), 40.6 (**C**H_2), 29.4 (**C**H_2), 27.0 (**C**H_2), 24.2 (**C**H_2), 14.2 (**C**H_3) ppm;

Microanalysis: Calculated for $C_{16}H_{26}IN_3OS$; C, 44.14; H, 6.02; N, 9.65; S, 7.36, found; C, 56.60; H, 7.71; N, 11.30; S, 3.18.

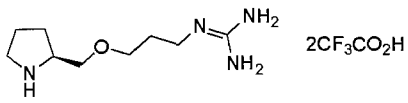
(*S*)-2-(*tert*-Butoxycarbonylimino 3-guanidino-propoxymethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (230).



Prepared according to the procedure given by Bernatowicz *et al.*[251]

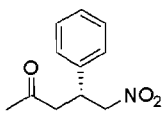
226 (200 mg, 0.774 mmol) was dissolved in dry THF (1 mL) and treated with **148** (240 mg, 0.774 mmol) and stirred at room temperature for 8 hours. The solvent was removed under reduced pressure to give a pale yellow oil. The crude material was purified by column chromatography (3 % methanol / DCM) to yield guanidine **230** as a colourless oil (120 mg, 0.240 mmol, 31 %). $[\alpha]_D$ = - 7.3 ° (c = 1.0, $CHCl_3$, 30 ° C, 589 nm); MS (ES^+): m/z (%) 501 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{24}H_{45}N_4O_7$ requires m/z: 501.3283, found m/z: 501.3275; IR (film): ν_{max} = 3330 (m), 2964 (w), 1788 (m), 1392 (m), 1130 (s) cm^{-1}; ^1H NMR (400 MHz, d_6DMSO, 90 ° C): δ = 8.21 (bs, 1H, N**H**), 7.55 (bs, 1H, N**H**), 3.82 (ddd, *J* = 10.6, 7.1, 3.4 Hz, 1H, **CH**CH_2), 3.50 (m, 1H, CHCH**H**'O), 3.47 (t, *J* = 5.9 Hz, 2H, O**C**H_2), 3.31 (dd, *J* = 9.5, 7.4 Hz, 1H, CHC**H**H'O), 3.27 - 3.17 (m, 2H, N**C**H_2), 3.18 (t, *J* = 6.9 Hz, 2H, NH**C**H_2), 1.89 - 1.83 (m, 3H, **C**H_2CH**H**'), 1.76 (m, 1H, CHC**H**H'), 1.69 (qn, *J* = 6.6 Hz, 2H, CH_2**C**$H_2$$CH_2$), 1.47 (s, 9H, C(**C**$H_3$)$_3$), 1.42 (s, 9H, C(**C**$H_3$)$_3$), 1.39 (s, 9H, C(**C**$H_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7 (**C**), 156.2 (**C**), 153.2 (**C**), 149.4 (**C**), 83.3 (**C**), 82.9 (**C**), 79.2 (**C**), 72.1 (**C**H_2), 69.6 (**C**H_2), 56.4 (**C**H), 46.5 (**C**H_2), 39.1 (**C**H_2), 29.8 (**C**H_2), 28.6 (**C**H_2), 28.4 (3**C**H_3), 28.2 (3**C**H_3), 28.1 (3**C**H_3), 22.8 (**C**H_2) ppm.

2-(3-(((*S*)-pyrrolidin-2-yl)methoxy)propyl)guanidininium; trifluroacetate (231).



230 (48 mg, 0.0959 mmol) was dissolved in a 20 % solution of TFA (1 mL) in DCM (4 mL) and stirred at room temperature for 4 hours. The solvent and residual TFA were removed under reduced pressure to give a yellow oil. The excess TFA was removed by repeatedly adding toluene and removing the solvent under reduced pressure. Guanidinium **231** was isolated as a cloudy white oil (40 mg, 0.0934 mmol, 97 %). $[\alpha]_D$ = + 7.2 ° (c = 0.9, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 239 (100) $[M+K]^+$; (ES^-): m/z (%) 113 (100) $[CF_3CO_2]^-$; IR (film): ν_{max} = 3374 (w), 3202 (w), 2964 (w), 1642 (s), 1589 (s), 1477 (m), 1397 (m), 1241 (s), 1142 (s) cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.78 (bs, 1H, N**H**), 6.45 (bs, 1H, N**H**), 3.79 (ddd, *J* = 15.8, 7.9, 3.6 Hz, 1H, C**H**CH_2), 3.67 (dd, *J* = 10.6, 3.6 Hz, 1H, CHCH**H**'O), 3.54 - 3.44 (m, 3H, C**H**H'OCH_2), 3.22 - 3.19 (m, 4H, 2NCH_2), 2.09 (ddd, *J* = 15.8, 7.8, 4.8 Hz, 1H, CHCH**H**'CH_2), 2.00 - 1.89 (m, 2H, $CH_2CH_2CH_2$), 1.77 (qn, *J* = 6.7 Hz, 2H, $CH_2CH_2CH_2$), 1.68 (ddd, *J* = 16.3, 12.4, 7.9 Hz, 1H, CHCHH'CH_2) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ = 158.8 (**C**), 70.6 (CH_2), 69.3 (CH_2), 60.8 (**C**H), 46.7 (CH_2), 39.4 (CH_2), 29.8 (CH_2), 27.4 (CH_2), 24.8 (CH_2) ppm.

(*R*)-5-Nitro-4-phenylpentan-2-one (240).



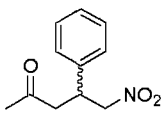
Prepared according to the procedure given by List *et al.* [182]

Trans - β - nitrostyrene (**42**, 74.6 mg, 0.500 mmol), acetone (**4**, 367 μL, 5.00 mmol) and catalyst **100** (15.3 mg, 0.0750 mmol) was dissolved in THF (0.75 mL) and stirred at room temperature for 7 days. The solvent was removed from the reaction mixture under reduced pressure and the crude product was purified by column

chromatography (20 % ethyl acetate / 80 % petroleum ether) to give ketone **240** as a white crystalline solid (73.0 mg, 0.352 mmol, 70 %). Mp.: 99 – 100 ° C (ethyl acetate) (Literature Mp.: 99 – 100 ° C (methanol))[305]; MS (ES^+): m/z (%) 230 (100) $[M+Na]^+$; IR (film): ν_{max} = 1711 (s), 1545 (s), 1360 (m), 1324 (m), 1161 (m), 695 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37 - 7.21 (m, 5H, 5C**H**), 4.71 (dd, *J* = 12.4, 6.9 Hz, 1H, CHCH**H**'NO_2), 4.60 (dd, *J* = 12.4, 7.7 Hz, 1H, CHC**H**H'NO_2), 4.01 (qn, *J* = 7.14 Hz, 1H, CH_2C**H**(Ph)CH_2), 2.91 (d, *J* = 6.9 Hz, 2H, C(O)C$\mathbf{H}_2$CH), 2.12 (s, 3H, C(O)C$\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4 (**C**), 139.0 (**C**), 129.2 (2**C**H), 128.0 (2**C**H), 127.5 (**C**H), 79.6 (**C**H_2), 46.3 (**C**H_2), 39.2 (**C**H_3), 30.5 (**C**H) ppm.
Spectroscopic data agrees with literature reference[306].

Highest enantioselectivity (30 %) of **235** observed with organocatalyst **177** determined by chiral HPLC. (*R*)-5-Nitro-4-phenylpentan-2-one configuration determined by comparison of optical rotation values and the HPLC elution order[147] with literature references; $[\alpha]_D$ = - 6.2 ° (c = 1.0, $CHCl_3$, 24 ° C) (Literature $[\alpha]_D$ = - 3.2 ° (c = 1.0, $CHCl_3$, 25 ° C), e.e. = 16 %)[13].

5-Nitro-4-phenylpentan-2-one (240) kinetic experiments.



According to the procedure given by List *et al.*[182] and Tsogoeva *et al.*[147]

The majority of kinetic experiments were carried out at least twice to check for consistency. The organocatalyst under investigation (0.0750 mmol) was stirred in a solution of trans - β - nitrostyrene (**42**, 74.6 mg, 0.500 mmol) and acetone (**4**, 367 μL, 5.00 mmol) in toluene (0.75 mL) at room temperature. The solvent contained naphthalene as an internal standard (1.00 mg / mL). The progress of the reactions were monitored by reverse phase HPLC. To sample the reactions; 10 μL was taken from the reaction mixture and diluted with acetonitrile (HPLC grade, 1.5 mL). Upon

completion the crude reaction mixture was not purified. Reverse phase HPLC retention time: 3.3 minutes (60 % acetonitrile / 40 % water). Chiralpak IA normal phase retention times: 44 minutes (enantiomer 1) and 47 minutes (enantiomer 2: major) (2 % isopropanol / 98 % hexane).

Kinetic reactions that investigated the effect of additives were carried out as above with the addition of acetic acid (2.20 μL, 0.0375 mmol) and water (9.00 μL, 0.500 mmol) from the onset.

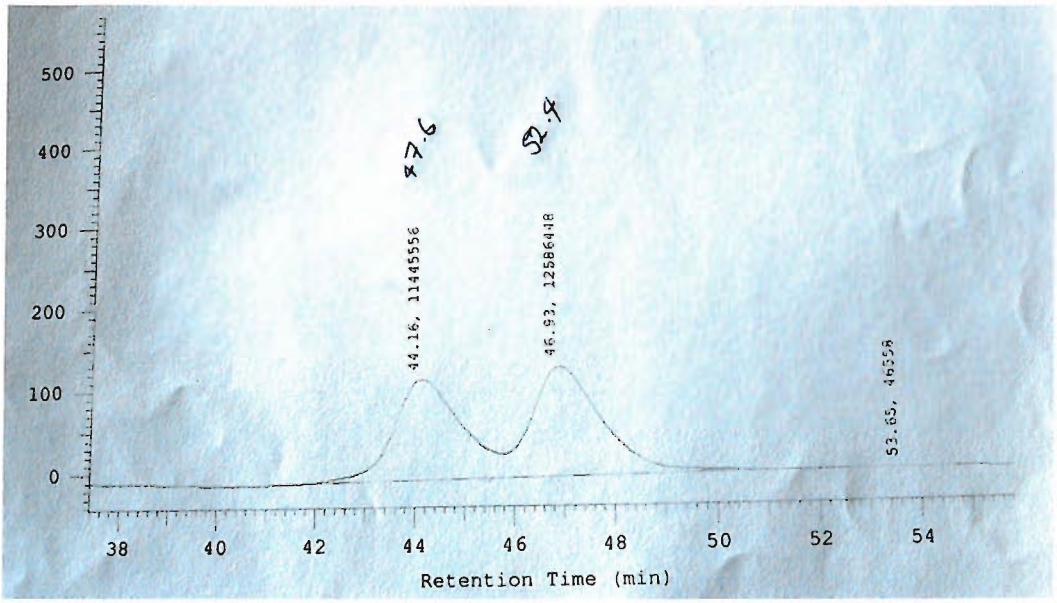
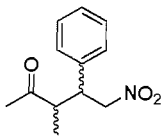


Figure 34: Chiral HPLC trace of **240** (Chiralpak IA, 2 % isopropanol / 98 % hexane).

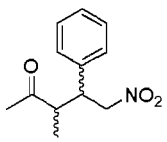
3-Methyl-5-nitro-4-phenylpentan-2-one (242).



Prepared according to the procedure given by List *et al.*[182]

Trans - β - nitrostyrene (**42**, 74.6 mg, 0.500 mmol), butanone (**241**, 450 μL, 5.00 mmol) and catalyst **100** (15.3 mg, 0.0750 mmol) was dissolved in THF (0.75 mL) and stirred at room temperature for 7 days. The solvent was removed from the reaction mixture under reduced pressure and the crude product was purified by column chromatography (20 % ethyl acetate / 80 % petroleum ether) to give ketone **242** as a colourless oil (82.0 mg, 0.371 mmol, 74 %). Mixture of diastereoisomers, major diastereoisomer syn reported; MS (ES^+): m/z (%) 244 (100) $[M+Na]^+$; IR (film): ν_{max} = 1711 (s), 1545 (s), 1360 (m), 1161 (m), 695 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 - 7.09 (m, 5H, 5C**H**), 4.65 - 4.53 (m, 2H, CHC**H**H'NO_2), 3.61 (ddd, *J* = 9.2, 8.4, 5.31 Hz, 1H, CHC**H**(Ph)CHH'), 2.90 (dq, *J* = 9.7, 7.1 Hz, 1H, CH_3C**H**CH), 2.14 (s, 3H, C(O)C$\mathbf{H}_3$), 0.89 (d, *J* =7.1 Hz, 3H, CHC$\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.8 (**C**), 137.6 (**C**), 129.1 (2**C**H), 128.1 (2**C**H), 127.5 (**C**H), 78.6 (**C**H_2), 49.3 (**C**H), 46.0 (**C**H), 29.2 (**C**H_3), 16.0 (**C**H_3) ppm.
Spectroscopic data agrees with literature reference[182, 307].

3-Methyl-5-nitro-4-phenylpentan-2-one (242) kinetic experiments.



According to the procedure given by List *et al.*[182] and Tsogoeva *et al.*[147]

The majority of kinetic experiments were carried out at least twice to check for consistency. The organocatalyst under investigation (0.0750 mmol) was stirred in a

solution of trans - β - nitrostyrene (**42**, 74.6 mg, 0.500 mmol) and butanone (**241**, 450 μL, 5.00 mmol) in toluene (0.75 mL) at room temperature. The solvent contained naphthalene as an internal standard (1 mg / mL). The progress of the reactions were monitored by reverse phase HPLC. To sample the reactions; 10 μL was taken from the reaction mixture and diluted with acetonitrile (HPLC grade, 1.5 mL). Upon completion the crude reaction mixture was not purified. Reverse phase HPLC retention time: 4.1 minutes (60 % acetonitrile / 40 % water). Chiralpak IA normal phase retention times: 43 minutes (syn enantiomer 1), 53 minutes (syn enantiomer 2), 57 minutes (anti enantiomer 1), 61 minutes (anti enantiomer 2)[147] (2 % isopropanol / 98 % hexane).

Kinetic reactions that investigated the effect of additives were carried out as above with the addition of acetic acid (2.20μL, 0.0375 mmol) and water (9.00 μL, 0.500 mmol) from the onset.

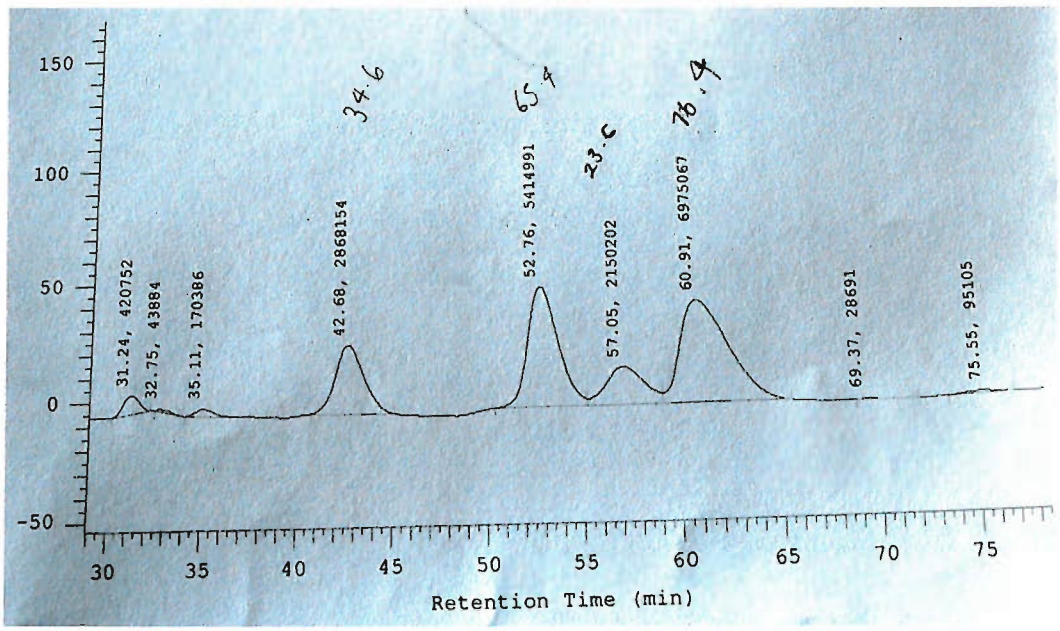
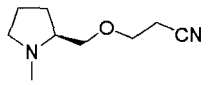


Figure 35: Chiral HPLC trace of **242** (Chiralpak IA, 2 % isopropanol / 98 % hexane).

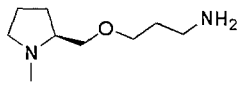
3-((*S*)-1-Methyl-pyrrolidin-2-ylmethoxy)-propionitrile (244).



Prepared according to the procedure given by Krishna *et al.*[271]

((*S*) - 1 - methylpyrrolidin - 2 - yl)methanol (**243**, 1.00 g, 8.68 mmol) was dissolved in a biphasic solution of toluene (3.5 mL) and NaOH aqueous solution (40 %, 35 mL) and treated with TBA.I (227 mg, 0.615 mmol) and acrylonitrile (2.81 mL, 43.4 mmol) and stirred vigorously at room temperature for 6 hours. The phases were separated and the aqueous phase extracted with ethyl acetate (4 x 500 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) to yield nitrile **244** as a pale yellow oil (1.39 g, 8.27 mmol, 95 %). $[\alpha]_D$ = - 42.2 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 169 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_9H_{17}N_2O$ requires m/z: 169.1335, found m/z: 169.1336; IR (film): ν_{max} = 2949 (w), 2876 (w), 1110 (s), 1068 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.65 (t, *J* = 6.3 Hz, 2H, CH_2CH_2O), 3.51 (dd, *J* = 9.4, 5.6 Hz, 1H, CHC**H**H'O), 3.43 (dd, *J* = 9.4, 5.0 Hz, 1H, CHCH**H**'O), 3.04 (dt, *J* = 9.2, 2.6 Hz, 1H, C**H**H'N), 2.59 (t, *J* = 6.3 Hz, 2H, CH_2CH_2CN), 2.43 (m, 1H, CH_2CH), 2.39 (s, 3H, CH_3), 2.21 (dt, *J* = 9.2, 7.6 Hz, 1H, CH**H**'N), 1.90 (m, 1H, CHC**H**H'), 1.81 - 1.66 (m, 2H, CH_2CH_2), 1.59 (m, 1H, CHCH**H**') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.9 (**C**), 74.2 (CH_2), 65.9 (CH_2), 64.8 (**C**H), 57.8 (CH_2), 41.7 (CH_3), 28.4 (CH_2), 22.9 (CH_2), 18.9 (CH_2) ppm.

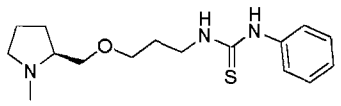
3-((*S*)-1-Methyl-pyrrolidin-2-ylmethoxy)-propylamine (245).



Prepared according to the procedure given by Khurana *et al.*[275]

244 (1.59 g, 9.43 mmol) was dissolved in methanol (72 mL) and the round bottomed flask fitted with a condenser. The solution was treated with $NiCl_2$ (2.45 g, 18.9 mmol) followed by water (12 mL), the solution turned from colourless to pale green. Sodium borohydride (2.14 g, 56.6 mmol) was added to the reaction mixture portion wise, the addition caused the solution to turn black and effervesce; the condenser was immediately fitted after each addition. The reaction mixture was stirred at room temperature for 6 hours; at this time TLC confirmed the reaction was complete. The reaction was treated with methanol (100 mL) and filtered through a pad of celite, and the resulting black solid washed with methanol (200 mL). Water (500 mL) was added to the pale green filtrate and then the methanol removed under reduced pressure. The resulting aqueous filtrate was extracted with DCM (6 x 500 mL). The combined organic phase was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give amine **245** as a yellow oil. The product was used crude (953 mg, 5.53 mmol, 59 %). $[\alpha]_D$ = - 35.3 ° (c = 1.0, $CHCl_3$, 29 ° C, 589 nm); MS (ES^+): m/z (%) 173 (100) $[M+H]^+$; IR (film): ν_{max} = 3368 (m), 2943 (m), 2871 (m), 1456 (m), 1109 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.46 (t, *J* = 5.9 Hz, 2H, CH_2CH_2O), 3.37 (m, 1H, CHCHH'O), 3.29 (m, 1H, CHCHH'O), 2.98 (m, 1H, CHH'N), 2.63 (t, *J* = 5.3 Hz, 2H, $CH_2CH_2NH_2$), 2.34 (s, 3H, CH_3), 2.29 (m, 1H, CH_2CH), 2.17 - 2.10 (m, 3H, CHH'N and NH_2), 1.85 (m, 1H, CHCHH'), 1.74 - 1.62 (m, 4H, $2CH_2$), 1.51 (m, 1H, CHCHH') ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.4 (CH_2), 70.0 (CH_2), 64.9 (CH), 57.8 (CH_2), 47.4 (CH_2), 41.7 (CH_3), 30.0 (CH_2), 28.8 (CH_2), 22.8 (CH_2) ppm.

1-[3-((*S*)-1-Methyl-pyrrolidin-2-ylmethoxy)-propyl]-3-phenyl-thiourea (246).



245 (912 mg, 5.29 mmol) was dissolved in a solution of chloroform (30 mL) and methanol (5 mL) and treated with phenyl isothiocyanate (697 μL, 5.82 mmol). The reaction mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure. The crude material was purified by column chromatography (10 % methanol / DCM) and then crystallised (diethyl ether) to yield the thiourea **246** as a white crystalline solid (272 mg, 0.885 mmol, 17 %).
Mp.: 83 - 85 ° C (diethyl ether); $[\alpha]_D$ = - 26.6 ° (c = 1.0, $CHCl_3$, 31 ° C, 589 nm); MS (ES^+): m/z (%) 308 (100) $[M+H]^+$; HRMS (ES^+): $[M+H]^+$ $C_{16}H_{26}N_3OS$ requires m/z: 308.1791, found m/z: 308.1791; IR (solid): ν_{max} = 3243 (w), 2918 (w), 2865 (w), 1496 (s), 1261 (s), 1101 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (bs, 1H, N**H**), 7.41 - 7.34 (m, 2H, 2C**H**), 7.26 - 7.19 (m, 3H, 3C**H**), 7.00 (bs, 1H, N**H**), 3.84 - 3.66 (m, 2H, CH_2CH_2NH), 3.52 (t, *J* = 5.3 Hz, 2H, CH_2CH_2O), 3.34 (dd, *J* = 9.7, 5.1 Hz, 1H, CHCHH'O), 3.20 (dd, *J* = 9.7, 5.7 Hz, 1H, CHCHH'O), 2.96 (m, 1H, CHH'N), 2.28 (s, 3H, CH_3), 2.16 - 2.02 (m, 2H, CHH'N and CH_2CH), 1.84 (qn, *J* = 6.0 Hz, 2H, $CH_2CH_2CH_2$), 1.73 - 1.57 (m, 3H, CHCHH'CH_2), 1.36 (m, 1H, CHCHH') ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.8 (**C**), 137.1 (**C**), 129.9 (2CH), 126.7 (2CH), 125.0 (CH), 73.9 (CH_2), 70.7 (CH_2), 64.8 (CH), 57.7 (CH_2), 44.9 (CH_2), 41.7 (CH_3), 28.6 (CH_2), 28.4 (CH_2), 22.8 (CH_2) ppm; Microanalysis: Calculated for $C_{16}H_{25}N_3OS$; C, 62.51; H, 8.20; N, 13.66; S, 10.43, found; C, 62.37; H, 8.17; N, 13.87; S, 4.84; For crystal structure see **Appendix 2**.

References.

1. List, B., *Tetrahedron* **2002**, *58*, 5573-5590.
2. Dalko, P. I.; Moisan, L., *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.
3. Groger, H.; Wilken, J., *Angew. Chem. Int. Ed.* **2001**, *40*, 529-532.
4. Jarvo, E. R.; Miller, S. J., *Tetrahedron* **2002**, *58*, 2481-2495.
5. Sorensen, E. J.; Sammis, G. M., *Science* **2004**, *305*, 1725-1726.
6. Chimni, S. S.; Mahajan, D.; Babu, V. V. S., *Tetrahedron Lett.* **2005**, *46*, 5617-5619.
7. Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M., *Angew. Chem. Int. Ed.* **2006**, *45*, 958-961.
8. Jiang, Z. Q.; Liang, Z.; Wu, X. Y.; Lu, Y. X., *Chem. Commun.* **2006**, 2801-2803.
9. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., *J. Am. Chem. Soc.* **2006**, *128*, 734-735.
10. Yan, Z. Y.; Niu, Y. N.; Wei, H. L.; Wu, L. Y.; Zhao, Y. B.; Liang, Y. M., *Tetrahedron: Asymmetry* **2006**, *17*, 3288-3293.
11. Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y., *Chem. Commun.* **2007**, 2524-2526.
12. Cao, Y. J.; Lai, Y. Y.; Wang, X.; Li, Y. H.; Xiao, W. J., *Tetrahedron Lett.* **2007**, *48*, 21-24.
13. Vishnumaya; Singh, V. K., *Org. Lett.* **2007**, *9*, 1117-1119.
14. Wu, X. Y.; Jiang, Z. Q.; Shen, H. M.; Lua, Y. X., *Adv. Synth. Catal.* **2007**, *349*, 812-816.
15. Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., *J. Am. Chem. Soc.* **2006**, *128*, 4966-4967.
16. Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jorgensen, K. A., *Chem. Commun.* **2006**, 4928-4930.
17. Rodriguez, B.; Rantanen, T.; Bolm, C., *Angew. Chem. Int. Ed.* **2006**, *45*, 6924-6926.
18. Rodriguez, B.; Bruckmann, A.; Bolm, C., *Chem. Eur. J.* **2007**, *13*, 4710-4722.
19. Langenbeck, W., *Angew. Chem.* **1932**, *45*, 97 - 99.
20. Langenbeck, W., *Angew. Chem.* **1928**, *41*, 740 - 745.

21. Bredig, G.; S., F. W., *Biochem. Z.* **1912**, *46*, 7.

22. Fischer, F. G.; Marschall, A., *Ber.* **1931**, *64*, 2825 - 2827.

23. Pracejus, H., *Justus Liebigs Ann.* **1960**, *634*, 9 - 22.

24. Eder, U.; Sauer, G.; Weichert, R., *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.

25. Hajos, Z. G.; Parrish, D. R., *J. Org. Chem.* **1974**, *39*, 1615-1621.

26. Agami, C.; Sevestre, H., *J. Chem. Soc., Chem. Commun.* **1984**, 1385-1386.

27. Agami, C.; Levisalles, J.; Sevestre, H., *J. Chem. Soc., Chem. Commun.* **1984**, 418-420.

28. Kozikowski, A. P.; Mugrage, B. B., *J. Org. Chem.* **1989**, *54*, 2274-2275.

29. Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E., *Chem. Commun.* **2005**, 3802-3804.

30. Oku, J. I.; Inoue, S., *J. Chem. Soc., Chem, Commun.* **1981**, 229-230.

31. Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H., *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317-1324.

32. List, B.; Lerner, R. A.; Barbas, C. F., *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

33. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C., *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.

34. Bui, T.; Barbas, C. F., *Tetrahedron Lett.* **2000**, *41*, 6951-6954.

35. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A., *J. Am. Chem. Soc.* **2002**, *124*, 6254-6255.

36. Vachal, P.; Jacobsen, E. N., *Org. Lett.* **2000**, *2*, 867 - 870.

37. Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis*. 1st ed.; Wiley-VCH: Weinheim: 2005.

38. Dalko, P. I.; Moisan, L., *Angew. Chem. Int. Ed.* **2001**, *40*, 3726-3748.

39. List, B., *Synlett* **2001**, 1675-1686.

40. Rouhi, A. M., *Chem. Eng. News,* **2004**, *82*, 41-45.

41. Notz, W.; Tanaka, F.; Barbas, C. F., *Acc. Chem. Res.* **2004**, *37*, 580-591.

42. List, B., *Acc. Chem. Res.* **2004**, *37*, 548 - 557.

43. Seayad, J.; List, B., *Org. Biomol. Chem.* **2005**, *3*, 719-724.

44. Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T., *Drug Discovery Today* **2007**, *12*, 8-27.

45. List, B., *Chem. Commun.* **2006**, 819-824.

46. Ikunaka, M., *Org. Process Res. Dev.* **2007**, *11*, 495-502.

47. Dalko, P. I., *Enantioselective Organocatalysis*. Wiley-VCH: Weinheim: 2007.

48. Almasi, D.; Alonso, D. A.; Najera, C., *Tetrahedron: Asymmetry*, **2007**, *18*, 299-365.

49. Tsogoeva, S. B., *Eur. J. Org. Chem.* **2007**, 1701-1716.

50. Albanese, D., *Mini-Rev. Org. Chem.* **2006**, *3*, 195-217.

51. Ooi, T.; Maruoka, K., *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266.

52. Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H., *Angew. Chem. Int. Ed.* **2006**, *45*, 7496-7504.

53. Hoffmann, H. M. R.; Frackenpohl, J., *Eur. J. Org. Chem.* **2004**, 4293-4312.

54. Ceccarelli, R.; Insogna, S.; Bella, M., *Org, Biomol. Chem.* **2006**, *4*, 4281-4284.

55. Chinchilla, R.; Najera, C.; Ortega, F. J., *Tetrahedron: Asymmetry* **2006**, *17*, 3423-3429.

56. Ishii, Y.; Fujimoto, R.; Mikami, M.; Murakami, S.; Miki, Y.; Furukawa, Y., *Org. Process Res. Dev.* **2007**, *11*, 609-615.

57. Andrus, M. B.; Ye, Z. F.; Zhang, J. Q., *Tetrahedron Lett.* **2005**, *46*, 3839-3842.

58. Bako, P.; Novak, T.; Ludanyi, K.; Pete, B.; Toke, L.; Keglevich, G., *Tetrahedron: Asymmetry* **1999**, *10*, 2373-2380.

59. Bako, P.; Kiss, T.; Toke, L., *Tetrahedron Lett.* **1997**, *38*, 7259-7262.

60. Bako, P.; Szollosy, A.; Bombicz, P.; Toke, L., *Synlett* **1997**, 291-292.

61. Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K., *Angew. Chem. Int. Ed.* **2002**, *41*, 2832-2834.

62. Nagasawa, K.; Georgieva, A.; Takahashi, H.; Nakata, T., *Tetrahedron* **2001**, *57*, 8959-8964.

63. Maruoka, K., *J. Synth. Org. Chem Jpn.* **2005**, *63*, 686-695.

64. Maruoka, K.; Ooi, T.; Kano, T., *Chem. Commun.* **2007**, 1487-1495.

65. Kano, T.; Lan, Q.; Wang, X. S.; Maruoka, K., *Adv. Synth. Catal.* **2007**, *349*, 556-560.

66. Rueffer, M. E.; Fort, L. K.; MacFarland, D. K., *Tetrahedron: Asymmetry* **2004**, *15*, 3297-3300.

67. Lippur, K.; Kanger, T.; Kriis, K.; Kailas, T.; Muurisepp, A. M.; Pehk, T.; Lopp, M., *Tetrahedron: Asymmetry* **2007**, *18*, 137-141.

68. Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M., *Tetrahedron* **2004**, *60*, 7743-7754.

69. Zhang, F. Y.; Corey, E. J., *Org. Lett.* **2001**, *3*, 639-641.

70. Corey, E. J.; Zhang, F. Y., *Org. Lett.* **2000**, *2*, 4257-4259.

71. Lygo, B.; To, D. C. M., *Tetrahedron Lett.* **2001**, *42*, 1343-1346.

72. Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K., *J. Org. Chem.* **1998**, *63*, 3526-3527.

73. Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K., *Tetrahedron Lett.* **1998**, *39*, 5433-5436.

74. Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V., *Adv. Synth. Catal.* **2006**, *348*, 2043-2046.

75. Dolling, U. H.; Davis, P.; Grabowski, E. J. J., *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

76. Schreiner, P. R., *Chem. Soc. Rev.* **2003**, *32*, 289-296.

77. Pihko, P. M., *Angew. Chem. Int. Ed.* **2004**, *43*, 2062-2064.

78. Taylor, M. S.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543.

79. Connon, S. J., *Chem. Eur. J.* **2006**, *12*, 5418-5427.

80. Akiyama, T.; Itoh, J.; Fuchibe, K., *Adv. Synth. Catal.* **2006**, *348*, 999-1010.

81. Curran, D. P.; Kuo, L. H., *J. Org. Chem.* **1994**, *59*, 3259 - 3261.

82. Vachal, P.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2002**, *124*, 10012 - 10014.

83. Su, J. T.; Vachal, P.; Jacobsen, E. N., *Adv. Synth. Catal.* **2001**, *343*, 197-200.

84. Sigman, M. S.; Vachal, P.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281.

85. Sigman, M. S.; Jacobsen, E. N., *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.

86. Curran, D. P.; Kuo, L. H., *Tetrahedron Lett.* **1995**, *36*, 6647 - 6650.

87. Schreiner, P. R.; Wittkopp, A., *Org. Lett.* **2002**, *4*, 217 - 220.

88. Wittkopp, A.; Schreiner, P. R., *Chem. Eur. J.* **2003**, *9*, 407-414.

89. Takemoto, Y., *Org. Biomol. Chem.* **2005**, *3*, 4299-4306.

90. Davis, A. P.; Dempsey, K. J., *Tetrahedron: Asymmetry* **1995**, *6*, 2829 - 2840.

91. Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R., *J. Org. Chem.* **1999**, *64*, 1039-1041.

92. Kitani, Y.; Kumamoto, T.; Isobe, T.; Fukuda, K.; Ishikawa, T., *Adv. Synth. Catal.* **2005**, *347*, 1653 - 1658.

93. Lohmeijer, B. G. G.; Pratt, R. C.; Leibfarth, F.; Logan, J. W.; Long, D. A.; Dove, A. P.; Nederberg, F.; Choi, J.; Wade, C.; Waymouth, R. M.; Hedrick, J. L., *Macromolecules* **2006**, *39*, 8574-8583.

94. Schuster, T.; Bauch, M.; Durner, G.; Gobel, M. W., *Org. Lett.* **2000**, *2*, 179-181.

95. Tsogoeva, S. B.; Durner, G.; Bolte, M.; Gobel, M. W., *Eur. J. Org. Chem.* **2003**, 1661-1664.

96. Zhou, Y.; Shan, Z. X., *J. Org. Chem.* **2006**, *71*, 9510-9512.

97. Hine, J.; Linden, S. M.; Kanagasabapathy, V. M., *J. Am. Chem. Soc.* **1985**, *107*, 1082-1083.

98. Tanaka, K.; Toda, F., *J. Chem. Soc., Chem. Commun.* **1983**, 593-594.

99. Harriman, D. J.; Lambropoulos, A.; Deslongchamps, G., *Tetrahedron Lett.* **2007**, *48*, 689-692.

100. Voituriez, A.; Charette, A. B., *Adv. Synth. Catal.* **2006**, *348*, 2363-2370.

101. Harriman, D. J.; Deslongchamps, G., *J. Mol. Model.* **2006**, *12*, 793-797.

102. Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K., *Adv. Synth. Catal.* **2005**, *347*, 1523-1526.

103. Rueping, M.; Sugiono, E.; Moreth, S. A., *Adv. Synth. Catal.* **2007**, *349*, 759-764.

104. McDougal, N. T.; Schaus, S. E., *J. Am. Chem. Soc.* **2003**, *125*, 12094-12095.

105. Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R., *J. Am. Chem. Soc.* **2007**, *129*, 3846 - 3847.

106. Alcázar, V.; Morán, J. R.; de Mendoza, J., *Tetrahedron Lett.* **1995**, *36*, 3941 - 3944.

107. Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P., *Tetrahedron; Asymmetry* **1994**, *7*, 1393 - 1402.

108. Martin-Portugues, M.; Alcazar, V.; Prados, P.; de Mendoza, J., *Tetrahedron* **2002**, *58*, 2951 - 2955.

109. Akalay, D.; Durner, G.; Bats, J. W.; Bolte, M.; Gobel, M. W., *J. Org. Chem.* **2007**, *72*, 5618-5624.

110. Hine, J., *Acc. Chem. Res.* **1978**, *11*, 1-7.

111. Okino, T.; Hoashi, Y.; Takemoto, Y., *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.

112. Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y., *Org. Lett.* **2004**, *6*, 625 - 627.

113. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y., *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

114. Hamza, A.; Schubert, G.; Soos, T.; Papai, I., *J. Am. Chem. Soc.* **2006**, *128*, 13151-13160.

115. Hoashi, Y.; Okino, T.; Takemoto, Y., *Angew. Chem. Int. Ed.* **2005**, *44*, 4032-4035.

116. Inokuma, T.; Hoashi, Y.; Takemoto, Y., *J. Am. Chem. Soc.* **2006**, *128*, 9413-9419.

117. Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y., *Synlett* **2005**, 603-606.

118. Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y., *Synthesis* **2006**, 3295-3300.

119. Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y., *Chem. Eur. J.* **2005**, *12*, 466-476.

120. Berkessel, A.; Cleemann, F.; Mukherjee, S.; Muller, T. N.; Lex, J., *Angew. Chem. Int. Ed.* **2005**, *44*, 807-811.

121. Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L., *J. Am. Chem. Soc.* **2005**, *127*, 13798-13799.

122. Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y., *Tetrahedron* **2006**, *62*, 365-374.

123. Hoashi, Y.; Yabuta, T.; Takemoto, Y., *Tetrahedron Lett.* **2004**, *45*, 9185-9188.

124. Ye, J. X.; Dixon, D. J.; Hynes, P. S., *Chem. Commun.* **2005**, 4481-4483.

125. Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L., *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157.

126. Song, J.; Shih, H. W.; Deng, L., *Org. Lett.* **2007**, *9*, 603-606.

127. Perdicchia, D.; Jorgensen, K. A., *J. Org. Chem.* **2007**, *72*, 3565-3568.

128. Li, H. M.; Wang, Y.; Tang, L.; Deng, L., *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907.

129. McCooey, S. H.; Connon, S. J., *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370.

130. Vakulya, B.; Varga, S.; Csampai, A.; Soos, T., *Org. Lett.* **2005**, *7*, 1967-1969.

131. Wu, F. H.; Hong, R.; Khan, J. H.; Liu, X. F.; Deng, L., *Angew. Chem. Int. Ed.* **2006**, *45*, 4301-4305.

132. Wang, B. M.; Wu, F. H.; Wang, Y.; Liu, X. F.; Deng, L., *J. Am. Chem. Soc.* **2007**, *129*, 768-769.

133. Gu, C. L.; Liu, L.; Sui, Y.; Zhao, J. L.; Wang, D.; Chen, Y. J., *Tetrahedron: Asymmetry* **2007**, *18*, 455-463.

134. Song, J.; Wang, Y.; Deng, L., *J. Am. Chem. Soc.* **2006**, *128*, 6048-6049.

135. Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H., *Synlett* **2005**, 2817-2819.

136. Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V., *Tetrahedron* **2006**, *62*, 375-380.

137. Wang, J.; Li, H.; Duan, W. H.; Zu, L. S.; Wang, W., *Org. Lett.* **2005**, *7*, 4713-4716.

138. Lattanzi, A., *Tetrahedron: Asymmetry* **2006**, *17*, 837-841.

139. Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Jiang, W.; Wang, W., *J. Am. Chem. Soc.* **2007**, *129*, 1036-1037.

140. Liu, K.; Cui, H. F.; Nie, J.; Dong, K. Y.; Li, X. J.; Ma, J. A., *Org. Lett.* **2007**, *9*, 923-925.

141. Almasi, D.; Alonso, D. A.; Gomez-Bengoa, E.; Nagel, Y.; Najera, C., *Eur. J. Org. Chem.* **2007**, 2328-2343.

142. Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N., *Angew. Chem. Int. Ed.* **2006**, *45*, 6366-6370.

143. Huang, H. B.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2006**, *128*, 7170-7171.

144. Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K., *Eur. J. Org. Chem.* **2005**, 4995-5000.

145. Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S., *Adv. Synth. Catal.* **2006**, *348*, 826-832.

146. Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y., *Org. Lett.* **2006**, *8*, 2901-2904.

147. Tsogoeva, S. B.; Wei, S. W., *Chem. Comm.* **2006**, 1451-1453.

148. Wei, S. W.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S., *Catal. Today*, **2007**, *121*, 151-157.

149. Clarke, M. L.; Fuentes, J. A., *Angew. Chem. Int. Ed.* **2007**, *46*, 930-933.

150. Cao, C. L.; Sun, X. L.; Zhou, J. L.; Tang, Y., *J. Org. Chem.* **2007**, *72*, 4073-4076.

151. Shen, Z. X.; Mang, Y. Q.; Jiao, C. J.; Li, B.; Ding, J.; Zhang, Y. W., *Chirality* **2007**, *19*, 307-312.

152. Matsui, K.; Takizawa, S.; Sasai, H., *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681.

153. Raheem, I. T.; Jacobsen, E. N., *Adv. Synth. Catal.* **2005**, *347*, 1701-1708.

154. Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W., *Org. Lett.* **2005**, *7*, 4293-4296.

155. Kwong, C. K. W.; Huang, R.; Zhang, M.; Shi, M.; Toy, P. H., *Chem. Eur. J.* **2007**, *13*, 2369-2376.

156. Matsui, K.; Tanaka, K.; Horii, A.; Takizawa, S.; Sasai, H., *Tetrahedron: Asymmetry* **2006**, *17*, 578-583.

157. Matsui, K.; Takizawa, S.; Sasai, H., *Synlett* **2006**, 761-765.

158. Mocquet, C. M.; Warriner, S. L., *Synlett* **2004**, 356-358.

159. Sohtome, Y.; Hashimoto, Y.; Nagasawa, K., *Adv. Synth. Catal.* **2005**, *347*, 1643-1648.

160. Sohtome, Y.; Hashimoto, Y.; Nagasawa, K., *Eur. J. Org. Chem.* **2006**, 2894-2897.

161. Tillman, A. L.; Ye, J. X.; Dixon, D. J., *Chem. Comm.* **2006**, 1191-1193.

162. Berner, O. M.; Tedeschi, L.; Enders, D., *Eur. J. Org. Chem.* **2002**, *12*, 1877-1894.

163. Ono, N., *The Nitro Group in Organic Synthesis*. Wiley-VCH: Weinheim: 2005.

164. Nichols, P. J.; DeMattei, J. A.; Barnett, B. R.; LeFur, N. A.; Chuang, T. H.; Piscopio, A. D.; Koch, K., *Org. Lett.* **2006**, *8*, 1495-1498.

165. Betancort, J. M.; Barbas, C. F., *Org. Lett.* **2001**, *3*, 3737 - 3740.

166. Alexakis, A.; Andrey, O., *Org. Lett.* **2002**, *4*, 3611 - 3614.

167. Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E., *Angew. Chem. Int. Ed.* **2006**, *45*, 5984-5987.

168. Gu, L.; Zhao, G., *Adv. Synth. Catal.* **2007**, *349*, 1629-1632.

169. Wang, J.; Li, H.; Lou, B. S.; Zu, L. S.; Guo, H.; Wang, W., *Chem. Eur. J.* **2006**, *12*, 4321-4332.

170. Zu, L. S.; Wang, J.; Li, H.; Wang, W., *Org. Lett.* **2006**, *8*, 3077-3079.

171. Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V., *Synlett* **2005**, 611-614.

172. Luo, S. Z.; Xu, H.; Mi, X. L.; Li, J. Y.; Zheng, X. X.; Cheng, J. P., *J. Org. Chem.* **2006**, *71*, 9244-9247.

173. Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A., *Org. Lett.* **2006**, *8*, 2559-2562.

174. Barros, M. T.; Phillips, A. M. F., *Eur. J. Org. Chem.* **2007**, 178-185.

175. Xu, Y. M.; Zou, W. B.; Sunden, H.; Ibrahem, S.; Cordova, A., *Adv. Synth. Catal.* **2006**, *348*, 418-424.

176. McCooey, S. H.; Connon, S. J., *Org. Lett.* **2007**, *9*, 599-602.

177. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M., *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.

178. Andrey, O.; Vidonne, A.; Alexakis, A., *Tetrahedron Lett.* **2003**, *44*, 7901-7904.

179. Mosse, S.; Alexakis, A., *Org. Lett.* **2006**, *8*, 3577-3580.

180. Cozzi, F., *Adv. Synth. Catal.* **2006**, *348*, 1367-1390.

181. Zu, L. S.; Li, H.; Wang, J.; Yu, X. H.; Wang, W., *Tetrahedron Lett.* **2006**, *47*, 5131-5134.

182. List, B.; Pojarliev, P.; Martin, H. J., *Org. Lett.* **2001**, *3*, 2423-2425.

183. Enders, D.; Seki, A., *Synlett* **2002**, 26-28.

184. Martin, H. J.; List, B., *Synlett* **2003**, 1901-1902.

185. Terakado, D.; Takano, M.; Oriyama, T., *Chem. Lett.* **2005**, *34*, 962-963.

186. Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H., *J. Am. Chem. Soc.* **2004**, *126*, 9558 - 9559.

187. Pansare, S. V.; Pandya, K., *J. Am. Chem. Soc.* **2006**, *128*, 9624-9625.

188. Zhu, M. K.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z., *Tetrahedron: Asymmetry* **2006**, *17*, 491-493.

189. Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., *Synthesis* **2004**, 1509-1521.

190. Diez, D.; Gil, M. J.; Moro, R. F.; Marcos, I. S.; Garcia, P.; Basabe, P.; Garrido, N. M.; Broughton, H. B.; Urones, J. G., *Tetrahedron* **2007**, *63*, 740-747.

191. Xu, Y. M.; Cordova, A., *Chem. Commun.* **2006**, 460-462.

192. Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V., *Chem. Commun.* **2004**, 1808-1809.

193. Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericas, M. A., *Org. Lett.* **2007**, *9*, 3717-3720.

194. Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G., *Adv. Synth. Catal.* **2004**, *346*, 1147-1168.

195. Luo, S. Z.; Mi, X. L.; Liu, S.; Xu, H.; Cheng, J. P., *Chem. Commun.* **2006**, 3687-3689.

196. Cobb, A. J. A.; Shaw, D. M.; Ley, S. V., *Synlett* **2004**, 558-560.

197. Hartikka, A.; Arvidsson, P. I., *Tetrahedron: Asymmetry* **2004**, *15*, 1831-1834.

198. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V., *Org. Biomol. Chem.* **2005**, *3*, 84-96.

199. Luo, S. Z.; Mi, X. L.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. P., *Angew. Chem. Int. Ed.* **2006**, *45*, 3093-3097.

200. Xu, D. Q.; Luo, S. P.; Yue, H. D.; Wang, L. P.; Liu, Y. K.; Xu, Z. Y., *Synlett* **2006**, 2569-2572.

201. Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J., *J. Am. Chem. Soc.* **2002**, *124*, 13097-13105.

202. Terada, M.; Ube, H.; Yaguchi, Y., *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455.

203. Motherwell, W. B.; Bingham, M. J.; Six, Y., *Tetrahedron* **2001**, *57*, 4663 - 4686.

204. Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M., *J. Mol. Catal. A: Chem.* **2005**, *235*, 267-270.

205. McNally, A.; Evans, B.; Gaunt, M. J., *Angew. Chem. Int. Ed.* **2006**, *45*, 2116-2119.

206. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R., *J. Am. Chem. Soc.* **1963**, *85*, 207 - 222.

207. Bartoli, S.; Jensen, K. B.; Kilburn, J. D., *J. Org. Chem.* **2003**, *68*, 9416 - 9422.

208. Dixon, D. J.; Richardson, R. D., *Synlett* **2006**, 81-85.

209. Pittelkow, M.; Lewinsky, R.; Christensen, J. B., *Synthesis* **2002**, *15*, 2195 - 2202.

210. Quaranta, L.; Corminboeuf, O.; Renaud, P., *Org. Lett.* **2002**, *4*, 39-42.

211. Cao, Y. J.; Lu, H. H.; Lai, Y. Y.; Lu, L. Q.; Xiao, W. J., *Synthesis* **2006**, 3795-3800.

212. Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Wang, W., *Adv. Synth. Catal.* **2007**, *349*, 1052-1056.

213. Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V., *Chem. Commun.* **2005**, 5346-5348.

214. Mitchell, C. E. T.; Brenner, S. E.; Garcia-Fortanet, J.; Ley, S. V., *Org. Biomol. Chem.* **2006**, *4*, 2039-2049.

215. Mosse, S.; Alexakis, A., *Org. Lett.* **2005**, *7*, 4361-4364.

216. Xie, J. W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J. G.; Chen, Y. C., *Org. Lett.* **2007**, *9*, 413-415.

217. Liu, T. Y.; Li, R.; Chai, Q.; Long, J.; Li, B. J.; Wu, Y.; Ding, L. S.; Chen, Y. C., *Chem. Eur. J.* **2007**, *13*, 319-327.

218. Sohtome, Y.; Takemura, N.; Iguchi, T.; Hashimoto, Y.; Nagasawa, K., *Synlett* **2006**, 144-146.

219. Tillman, A. L.; Dixon, D. J., *Org. Biomol. Chem.* **2007**, *5*, 606 - 609.

220. McDaid, P.; Chen, Y. G.; Deng, L., *Angew. Chem. Int. Ed.* **2001**, *41*, 338-340.

221. Zou, W. B.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Cordova, A., *Chem. Commun.* **2005**, 4946-4948.

222. Peelen, T. J.; Chi, Y. G.; Gellman, S. H., *J. Am. Chem. Soc.* **2005**, *127*, 11598-11599.

223. Davies, H. J.; Ruda, A. M.; Tomkinson, N. C. O., *Tetrahedron Lett.* **2007**, *48*, 1461-1464.

224. Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., *Tetrahedron Lett.* **2004**, *45*, 325-328.

225. Enders, D.; Chow, S., *Eur. J. Org. Chem.* **2006**, 4578-4584.

226. Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., *Org. Lett.* **2004**, *6*, 2527-2530.

227. Ishino, T.; Oriyama, T., *Chem. Lett.* **2007**, *36*, 550-551.

228. Hine, J.; Chou, Y., *J. Org. Chem.* **1981**, *46*, 649-652.

229. Cordova, A.; Zou, W. B.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W. W., *Chem. Commun.* **2005**, 3586-3588.

230. Dietrich, B.; Fyles, D. L.; Fyles, T. M.; Lehn, J.-M., *Helv. Chem. Acta* **1979**, *62*, 2763 - 2787.

231. Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A.; Anslyn, E. V., *Tetrahedron* **1998**, *54*, 15063 - 15086.

232. Jensen, K. B.; Braxmeier, T. M.; Demarcus, M.; Frey, J. G.; Kilburn, J. D., *Chem. Eur. J.* **2002**, *8*, 1300 - 1309.

233. McKay, A. F.; Hatton, W. G., *J. Am. Chem. Soc.* **1956**, *78*, 1618 - 1620.

234. Grosso, J. A.; Nichols, D. E., *J. Med. Chem.* **1980**, *23*, 1261 - 1264.

235. Kennedy, K. J.; Simandan, T. L.; Dix, T. A., *Synth. Commun.* **1998**, *28*, 741-746.

236. Marmillon, C.; Bompart, J.; Calas, M.; Escale, R.; Bonnet, P.-A., *Heterocycles* **2000**, *53*, 1317 - 1328.

237. Shepherd, J.; Gale, T.; Jensen, K. B.; Kilburn, J. D., *Chem. Eur. J.* **2006**, *12*, 713-720.

238. Shepherd, J.; Langley, G. J.; Herniman, J. M.; Kilburn, J. D., *Eur. J. Org. Chem.* **2007**, 1345-1356.

239. Lawless, L. J.; Blackburn, A. G.; Ayling, A. J.; Perez-Payan, N.; Davis, A. P., *J. Chem. Soc., Perkin Trans. 1.* **2001**, *11*, 1329 - 1341.

240. Wellner, E.; Sandin, H.; Swanstein, M., *J. Org. Chem.* **2004**, *69*, 1571 – 1580.

241. Wellner, E.; Sandin, H.; Swanstein, M., *Synlett* **2004**, 1817 – 1819.

242. Davis, A. P.; Lawless, L. J., *Chem. Commun.* **1999**, *1*, 9 - 10.

243. Kneeland, D. M.; Ariga, K.; Lynch, V. M.; Huang, C.-Y.; Anslyn, E. V., *J. Am. Chem. Soc.* **1993**, *115*, 10042 - 10055.

244. Kato, S.; Harada, H.; Morie, T., *J. Chem. Soc., Perkin Trans. 1* **1997**, 3219 - 3225.

245. Ben-Ishai, D.; Berger, A., *J. Am. Chem. Soc.* **1952**, *74*, 1564 - 1570.

246. Bernatowicz, M. S.; Wu, Y. L.; Matsueda, G. R., *J. Org. Chem.* **1992**, *57*, 2497-2502.

247. Hirsh, A. J.; Molino, B. F.; Zhang, J. Z.; Astakhova, N.; Geiss, W. B.; Sargent, B. J.; Swenson, B. D.; Usyatinsky, A.; Wyle, M. J.; Boucher, R. C.; Smith, R. T.; Zamurs, A.; Johnson, M. R., *J. Med. Chem.* **2006**, *49*, 4098-4115.

248. Baillet, S.; Buisine, E.; Horvath, D.; Maes, L.; Bonnet, B.; Sergheraert, C., *Bioorg. Med. Chem.* **1996**, *4*, 891-899.

249. Iqbal, N.; Knaus, E. E., *J. Heterocycl. Chem.* **1996**, *33*, 157-160.

250. Ciccotosto, S.; Vonitzstein, M., *Tetrahedron Lett.* **1995**, *36*, 5405-5408.

251. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R., *Tetrahedron Lett.* **1993**, *34*, 3389 - 3392.

252. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Giuliani, A.; Marcantoni, E.; Mecozzi, T.; Sambri, L.; Torregiani, E., *J. Org. Chem.* **2002**, *67*, 9111-9114.

253. Miller, K. M.; Jamison, T. F., *J. Am. Chem. Soc.* **2004**, *126*, 15342-15343.

254. Humphrey, J. M.; Liao, Y. S.; Ali, A.; Rein, T.; Wong, Y. L.; Chen, H. J.; Courtney, A. K.; Martin, S. F., *J. Am. Chem. Soc.* **2002**, *124*, 8584-8592.

255. Ginos, J. Z.; Cotzias, G. C.; Doroski, D., *J. Med. Chem.* **1978**, *21*, 160-165.

256. Montero, A.; Goya, P.; Jagerovic, N.; Callado, L. F.; Meana, J. J.; Giron, R.; Goicoechea, C.; Martin, M. I., *J. Med. Chem.* **2002**, *10*, 1009 - 1018.

257. Sakai, N.; Ohfune, Y., *J. Am. Chem. Soc.* **1992**, *114*, 998-1010.

258. Russell, M. G. N.; Matassa, V. G.; Pengilley, R. R.; van Niel, M. B.; Sohal, B.; Watt, A. P.; Hitzel, L.; Beer, M. S.; Stanton, J. A.; Broughton, H. B.; Castro, J. L., *J. Med. Chem.* **1999**, *42*, 4981-5001.

259. Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V.; Zaidlewicz, M., *J. Org. Chem.* **1999**, *64*, 6263-6274.

260. Saito, S.; Yamamoto, H., *Acc. Chem. Res.* **2004**, *37*, 570 - 579.

261. Melchiorre, P.; Jorgensen, K. A., *J. Org. Chem.* **2003**, *68*, 4151-4157.

262. Thayumanavan, R.; Dhevalapally, B.; Sakthivel, K.; Tanaka, F.; Barbas, C. F., *Tetrahedron Lett.* **2002**, *43*, 3817-3820.

263. Andrey, O.; Alexakis, A.; Bernardinelli, G., *Org. Lett.* **2003**, *5*, 2559-2561.

264. Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K., *Tetrahedron Lett.* **2004**, *45*, 5589-5592.

265. Berkessel, A.; Roland, K.; Neudorfl, J. M., *Org. Lett.* **2006**, *8*, 4195-4198.

266. Kokotos, G.; Verger, R.; Chiou, A., *Chem. Eur. J.* **2000**, *6*, 4211-4217.

267. Buchynskyy, A.; Stembera, K.; Knoll, D.; Vogel, S.; Kempin, U.; Biallass, A.; Henning, L.; Findeisen, M.; Muller, D.; Welzel, P., *Tetrahedron* **2002**, *58*, 7741-7760.

268. Mougenot, P.; Mertens, P.; Nguyen, M.; Touillaux, R.; MarchandBrynaert, J., *J. Org. Chem.* **1996**, *61*, 408-412.

269. Lee, D.; Long, S. A.; Murray, J. H.; Adams, J. L.; Nuttall, M. E.; Nadeau, D. P.; Kikly, K.; Winkler, J. D.; Sung, C. M.; Ryan, M. D.; Levy, M. A.; Keller, P. M.; DeWolf, W. E., *J. Med. Chem.* **2001**, *44*, 2015-2026.

270. Malet, C.; Hindsgaul, O., *J. Org. Chem.* **1996**, *61*, 4649-4654.

271. Krishna, T. R.; Jain, S.; Tatu, U. S.; Jayaraman, N., *Tetrahedron* **2005**, *61*, 4281-4288.

272. Bender, C. F.; Widenhoefer, R. A., *J. Am. Chem. Soc.* **2005**, *127*, 1070 - 1071.

273. Jarvinen, A. J.; Cerrada-Gimenez, M.; Grigorenko, N. A.; Khomutov, A. R.; Vepsalainen, J. J.; Sinervirta, R. M.; Keinanen, T. A.; Alhonen, L. I.; Janne, J. E., *J. Med. Chem.* **2006**, *49*, 399-406.

274. Leclerc, V.; Beaurain, N.; Depreux, P.; Bennejean, C.; Delagrange, P.; Boutin, J.; Lesieur, D., *Pharm. Pharmacol. Commun.* **2000**, *6*, 61 - 65.

275. Khurana, J. M.; Sharma, P., *Bull. Chem. Soc. Jap.* **2004**, *77*, 549-552.

276. Back, T. G.; Baron, D. L.; Yang, K., *J. Org. Chem.* **1993**, *58*, 2407 - 2413.

277. Chen, H. B.; Wang, Y.; Wei, S. Y.; Sun, J., *Tetrahedron: Asymmetry,* **2007**, *18*, 1308-1312.

278. Blarer, S. J.; Schweizer, W. B.; Seebach, D., *Helv. Chem. Acta* **1982**, *65*, 1637 - 1654.

279. Xu, D.-Q.; Wang, L.-P.; Luo, S.-P.; Wang, Y.-F.; Zhang, S.; Xu, Z.-Y., *Eur. J. Org. Chem.* **2008**, *2008*, 1049-1053.

280. Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, *43*, 2923-2925.

281. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A., *J. Org. Chem.* **1997**, *62*, 7512-7515.

282. Nelson, J. H.; Howells, P. N.; Delullo, G. C.; Landen, G. L.; Henry, R. A., *J. Org. Chem.* **1980**, *45*, 1246-1249.

283. Kao, K. H.; Yang, C. S.; Liu, J. T.; Lin, W. W.; Fang, H. Y.; Yao, C. F.; Chen, K. M., *Tetrahedron* **1998**, *54*, 13997-14014.

284. Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D., *Synthesis* **1993**, *12*, 1271 - 1290.

285. Dieter, R.; Tokles, M., *J. Am. Chem. Soc.* **1987**, *109*, 2040-2046.

286. Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M., *Tetrahedron: Asymmetry* **2004**, *15*, 2661-2666.

287. Chimni, S. S.; Mahajan, D., *Tetrahedron: Asymmetry* **2006**, *17*, 2108-2119.

288. Boas, U.; H., J. M., *J. Chem. Soc., Chem. Commun.* **1995**, 1995 - 1996.

289. Mohanta, P. K.; Dhar, S.; Samal, S. K.; Ila, H.; Junijappa, H., *Tetrahedron* **2000**, *56*, 629 - 637.

290. Percival, D. F.; M., H. R., *J. Org. Chem.* **1957**, *22*, 925 - 931.

291. Dardonville, C.; Fernandez-Fernandez, C.; Gibbons, S.-L.; Ryan, G. J.; Jagerovic, N.; Gabilondo, A. M.; Meana, J. J.; Callado, L. F., *Bioorg. Med. Chem.* **2006**, *14*, 6570-6580.

292. Arasujo, M.; Joso, S. M. P.; Ragnarsson, U.; Trigo, M.; Joaquina, S. A.; Amaral, A.; Lurdes, S., *J. Chem. Res. Miniprint,* **1996**, *8*, 2143 - 2161.

293. Ottana, R.; Maccari, R.; Barreca, M. L.; Bruno, G.; Rotondo, A.; Rossi, A.; Chiricosta, G.; Di Paola, R.; Sautebin, L.; Cuzzocrea, S.; Vigorita, M. G., *Bioorg. Med. Chem.* **2005**, *13*, 4243-4252.

294. Wu, Y.; Matsueda, G.; Bernatowicz, M., *Synth. Commun.* **1993**, *23*, 3055 - 3060.

295. Nakanishi, K.; Huang, X. F.; Jiang, H.; Liu, Y.; Fang, K.; Huang, D. W.; Choi, S. K.; Katz, E.; Eldefrawi, M., *Bioorg. Med. Chem.* **1997**, *5*, 1969-1988.

296. Amedjkouh, M.; Ahlberg, P., *Tetrahedron: Asymmetry* **2002**, *13*, 2229-2234.

297. Li, X.; Schenkel, L. B.; Kozlowski, M. C., *Org. Lett.* **2000**, *2*, 875-878.

298. Reed, P. E.; Katzenellenbogen, J. A., *J. Org. Chem.* **1991**, *56*, 2624-2634.

299. Correa, A.; Denis, J. N.; Greene, A. E., *Synth. Commun.* **1991**, *21*, 1-9.

300. Sternfeld, F.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Heald, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J., *J. Med. Chem.* **1999**, *42*, 677-690.

301. Madsen, R.; Roberts, C.; Fraserreid, B., *J. Org. Chem.* **1995**, *60*, 7920-7926.

302. Bernauer, K.; Chuard, T.; Stoecklievans, H., *Helv. Chim. Acta* **1993**, *76*, 2263-2273.

303. Forsch, R. A.; Wright, J. E.; Rosowsky, A., *Heterocycles* **1999**, *51*, 1789-1805.

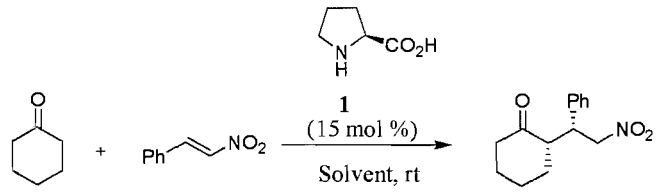
304. Robarge, M. J.; Husbands, S. M.; Kieltyka, A.; Brodbeck, R.; Thurkauf, A.; Newman, A. H., *J. Med. Chem.* **2001**, *44*, 3175-3186.

305. Kohler, E. P.; Drake, N. L., *J. Am. Chem. Soc.* **1923**, *45*, 2144-2150.

306. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., *J. Am. Chem. Soc.* **2001**, *123*, 5260 - 5267.

307. Yamamoto, Y.; Nishii, S., *J. Org. Chem.* **1988**, *53*, 3597-3603.

Appendix 1



64 42 65

Scheme 15.

Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	Yield (%)	Time	e.e. (%)[a]
MeCN	8 mL	10	1.2	71 %	14 days	24 %
MeCN	8 mL	1.5	0.2	26 %	53 days	20 %
MeCN	1.5 mL	10	5.0	57 %	13 days	22 %
MeCN	1.5 mL	1.5	0.9	83 %	52 days	20 %

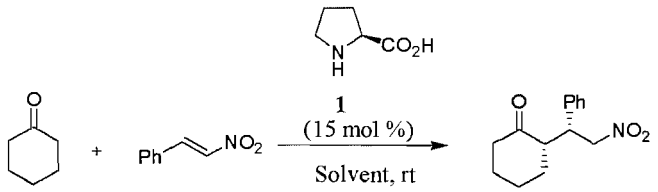
a: of syn diastereomer.

Table 36: The effect of concentration of cyclohexanone on the L - proline catalysed Michael addition in acetonitrile.

Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	Yield (%)	Time	e.e. (%)[a]
MeOH	8 mL	10	1.2	74 %	11 days	53 %
MeOH	8 mL	1.5	0.2	83 %	46 days	38 %
MeOH	1.5 mL	10	5.0	74 %	44 hours	40 %
MeOH	1.5 mL	1.5	0.9	58 %	4 days	34 %

a: of syn diastereomer.

Table 37: The effect of concentration of cyclohexanone on the L - proline catalysed Michael addition in methanol.



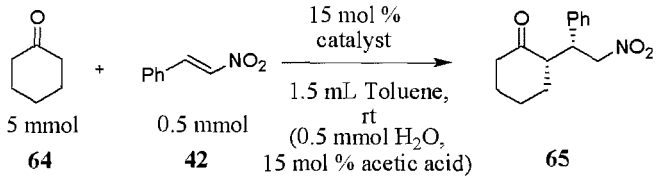
64 42 65

Scheme 15.

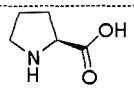
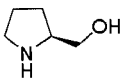
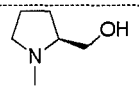
Solvent	Volume of Solvent	Molar equivalents of 64	Concentration 64 / M	Yield (%)	Time	e.e. (%)[a]
THF	8 mL	10	1.2	39 %	36 days	30 %
THF	8 mL	1.5	0.2	12 %	36 days	32 %
THF	1.5 mL	10	5.0	60 %	19 days	35 %
THF	1.5 mL	1.5	0.9	69 %	30 days	34 %

a: of syn diastereomer.

Table 38: The effect of concentration of cyclohexanone on the L - proline catalysed Michael addition in THF.

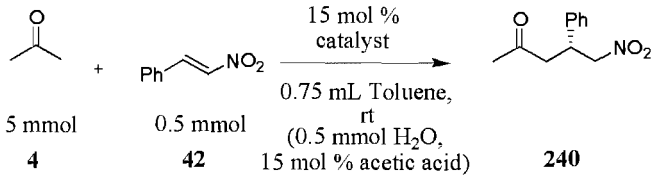


Scheme 30.

	TOLUENE				TOLUENE / H^+ / H_2O			
Catalyst	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**	**HPLC Yield (%)**	**Time**	**d.r.[a]**	**e.e. (%)[b]**
 **1**	41 %	30 days	94:6	17 %	5 %	30 days	94:6	-
 **80**	81 %	30 days	94:6	86 %	> 90 %	10 days	87:3	87 %
 **243**	2 %	30 days	-	-	3 %	30 days	-	-

a: syn: anti; b: of syn diastereomer

Table 39: Additional results for the organocatalysed Michael addition of cyclohexanone to trans - β - nitrostyrene.



Scheme 61

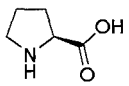
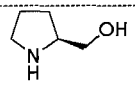
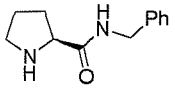
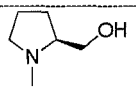
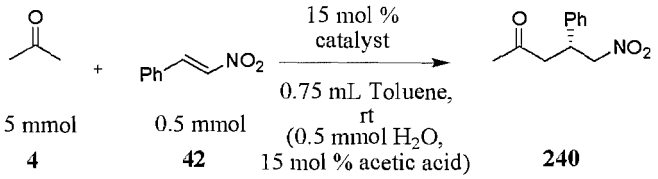
	TOLUENE			TOLUENE / H^+ / H_2O		
Catalyst	**HPLC Yield (%)**	**Time**	**e.e. (%)**	**HPLC Yield (%)**	**Time**	**e.e. (%)**
 **1**	2 %	30 days	-	0 %	30 days	-
 **80**	> 90 %	12 days	23 %	> 90 %	9 days	16 %
 **100**	61 %	30 days	19 %	> 90 %	2 days	29 %
 **243**	11 %	30 days	11 %	0 %	30 days	-

Table 40: Additional results for the organocatalysed Michael addition of acetone to trans - β - nitrostyrene.



Scheme 61

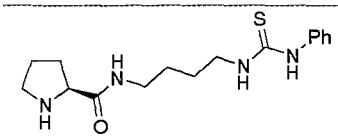
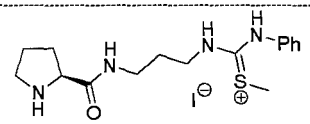
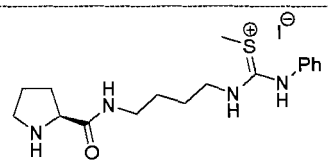
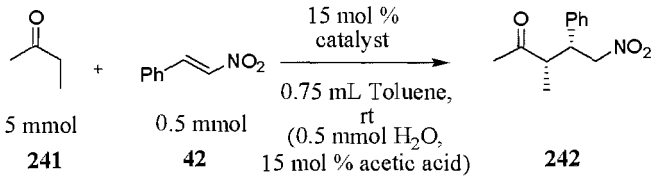
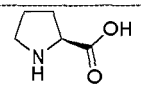
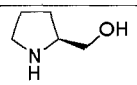
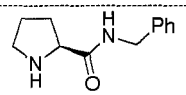
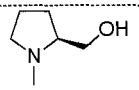
	TOLUENE			TOLUENE / H^+ / H_2O		
Catalyst	**HPLC Yield (%)**	**Time**	**e.e. (%)**	**HPLC Yield (%)**	**Time**	**e.e. (%)**
 **118**				32 %	30 days	16 %
 **119**				> 90 %	7 days	11 %
 **120**	0 %	30 days	-	0 %	30 days	-

Table 41: Additional results for the organocatalysed Michael addition of acetone to trans - β - nitrostyrene.

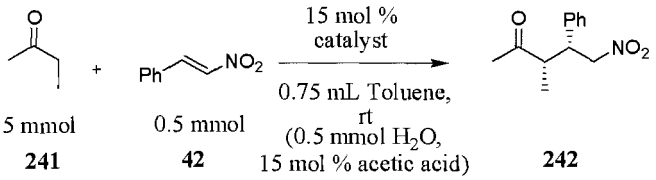


Scheme 62.

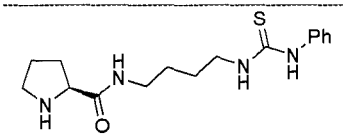
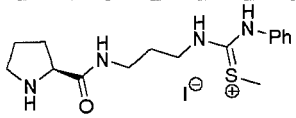
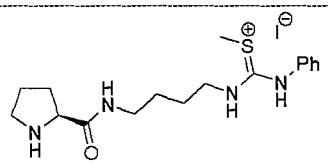
Catalyst	TOLUENE					TOLUENE / H^+ / H_2O				
	HPLC Yield (%)	Time	d.r.[a]	e.e. (%) s[b]	e.e. (%) a[c]	HPLC Yield (%)	Time	d.r.[a]	e.e. (%) s[b]	e.e. (%) a[c]
 **1**	2 %	30 days	-	-	-	2 %	30 days	-	-	-
 **80**	20 %	30 days	50:50	50 %	33 %	38 %	30 days	50:50	39 %	47 %
 **100**	> 90 %	30 days	75:25	29 %	49 %	> 90 %	4 days	75:25	37 %	49 %
 **243**	0 %	30 days	-	-	-	3 %	30 days	-	-	-

a: syn: anti; b: syn diastereomer; c: anti diastereomer

Table 42: Additional results for the organocatalysed Michael addition of butanone to trans - β - nitrostyrene.

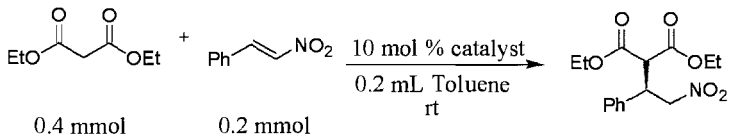


Scheme 62.

Catalyst	TOLUENE					TOLUENE / H^+ / H_2O				
	HPLC Yield (%)	Time	d.r.[a]	e.e. (%)		HPLC Yield (%)	Time	d.r.[a]	e.e. (%)	
				s[b]	a[c]				s[b]	a[c]
 **118**						63 %	30 days	80:20	17 %	42 %
 **119**						> 90 %	5 days	75:25	18 %	15 %
 **120**	0 %	30 days	-	-	-	0 %	30 days	-	-	-

a: syn: anti; b: syn diastereomer; c: anti diastereomer

Table 43: Additional results for the organocatalysed Michael addition of butanone to trans - β - nitrostyrene.



0.4 mmol **41** 0.2 mmol **42** **44**

Scheme 64.

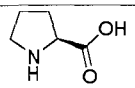
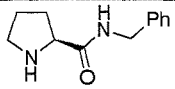
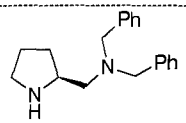
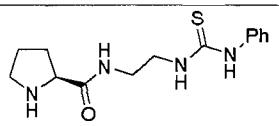
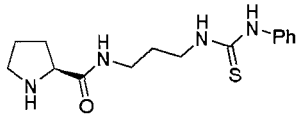
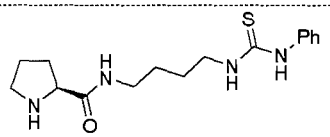
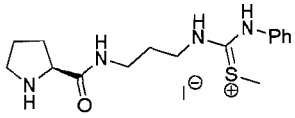
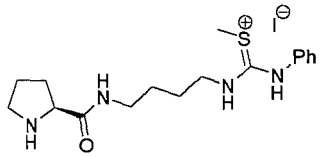
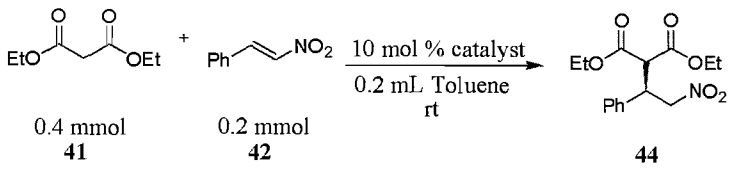
Catalyst	HPLC Yield (%)	Time	e.e. (%)
 **1**	1 %	30 days	-
 **100**	80 %	30 days	34 %
 **158**	20 %	30 days	52 %
 **125**	0 %	30 days	-
 **117**	41 %	30 days	20 %
 **118**	3 %	30 days	-
 **119**	52 %	30 days	28 %
 **120**	0 %	30 days	-

Table 44: Additional results for the organocatalysed Michael addition of diethyl malonate to trans - β - nitrostyrene.



0.4 mmol **41** 0.2 mmol **42** **44**

Scheme 64.

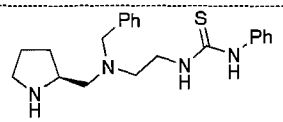
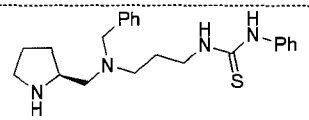
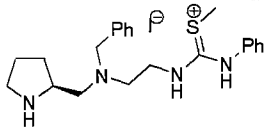
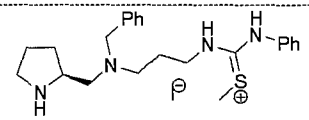
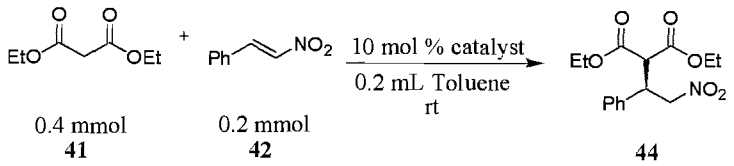
Catalyst	HPLC Yield (%)	Time	e.e. (%)
 **188**	20 %	30 days	2 %
 **189**	> 90 %	7 days	0 %
 **190**	0 %	30 days	-
 **191**	0 %	30 days	-

Table 45: Additional results for the organocatalysed Michael addition of diethyl malonate to trans - β - nitrostyrene.



Scheme 64.

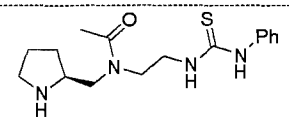
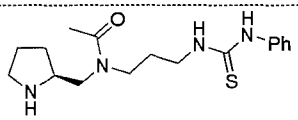
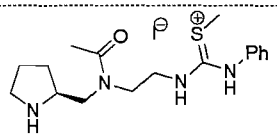
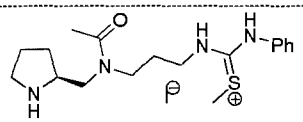
Catalyst	HPLC Yield (%)	Time	e.e. (%)
 **197**	0 %	30 days	-
 **198**	0 %	30 days	-
 **199**	0 %	30 days	-
 **200**	8 %	30 days	-

Table 46: Additional results for the organocatalysed Michael addition of diethyl malonate to trans - β - nitrostyrene.

Appendix 2

Table 1. Crystal data and structure refinement.

Identification code	**2007sot0665**	
Empirical formula	$C_{21}H_{31}N_3O_5$	
Formula weight	405.49	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	**a = 6.4937(5) Å**	**α = 90°**
	b = 18.6629(16) Å	**β = 99.643(5)°**
	c = 9.0686(7) Å	**γ = 90°**
Volume	1083.51(15) Å^3	
Z	2	
Density (calculated)	1.243 Mg / m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	436	
Crystal	Plate; Colourless	
Crystal size	0.20 x 0.06 x 0.01 mm^3	
θ range for data collection	3.16 – 27.48°	
Index ranges	$-8 \le h \le 8$, $-24 \le k \le 24$, $-11 \le l \le 11$	
Reflections collected	9886	
Independent reflections	2522 [R_{int} = 0.0531]	
Completeness to θ = 27.48°	98.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9991 and 0.9824	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2522 / 1 / 265	
Goodness-of-fit on F^2	1.102	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0666, $wR2$ = 0.1584	
R indices (all data)	$R1$ = 0.0853, $wR2$ = 0.1755	
Absolute structure parameter	10(10)	
Largest diff. peak and hole	0.279 and –0.242 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Gõttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	8711(7)	6701(3)	6012(5)	47(1)	1
C2	6921(8)	7036(3)	4952(6)	53(1)	1
C3	5114(8)	6537(3)	4991(6)	53(1)	1
C4	5418(6)	6247(2)	6617(5)	40(1)	1
C5	8667(6)	6119(2)	8445(5)	39(1)	1
C6	7951(8)	5497(3)	10720(5)	47(1)	1
C7	9110(9)	4822(3)	10450(6)	55(1)	1
C8	5850(9)	5325(4)	11165(7)	68(2)	1
C9	9250(11)	5989(3)	11829(6)	69(2)	1
C10	4843(6)	5462(3)	6590(5)	40(1)	1
C11	2093(8)	4609(3)	6867(5)	48(1)	1
C12	767(7)	4530(3)	5320(5)	46(1)	1
C13	−266(8)	3809(3)	5064(6)	53(1)	1
C14	−1862(7)	3116(3)	6848(5)	43(1)	1
C15	−3417(8)	2562(3)	8736(5)	49(1)	1
C16	−4693(7)	2813(2)	9878(5)	41(1)	1
C17	−3749(8)	2935(3)	11335(6)	54(1)	1
C18	−4946(9)	3223(4)	12347(6)	64(2)	1
C19	−7022(9)	3354(3)	11907(6)	57(1)	1
C20	−7963(8)	3213(3)	10448(6)	52(1)	1
C21	−6798(8)	2938(3)	9461(6)	49(1)	1
N1	7670(5)	6353(2)	7132(4)	42(1)	1
N2	3059(5)	5307(2)	7063(4)	41(1)	1
N3	−1792(6)	3710(2)	6074(5)	49(1)	1
O1	10580(5)	6141(2)	8833(4)	47(1)	1
O2	7291(5)	5874(2)	9273(3)	45(1)	1
O3	5888(6)	5016(2)	6050(4)	55(1)	1
O4	−843(6)	2575(2)	6736(4)	57(1)	1
O5	−3240(5)	3181(2)	7796(4)	46(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–N1	1.463(5)
C1–C2	1.514(7)
C1–H1A	0.9900
C1–H1B	0.9900
C2–C3	1.503(7)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C4	1.552(7)
C3–H3A	0.9900
C3–H3B	0.9900
C4–N1	1.472(5)
C4–C10	1.512(6)
C4–H4	1.0000
C5–O1	1.234(5)
C5–N1	1.329(6)
C5–O2	1.340(5)
C6–O2	1.487(5)
C6–C7	1.509(7)
C6–C9	1.510(8)
C6–C8	1.521(7)
C7–H7A	0.9800
C7–H7B	0.9800
C7–H7C	0.9800
C8–H8A	0.9800
C8–H8B	0.9800
C8–H8C	0.9800
C9–H9A	0.9800
C9–H9B	0.9800
C9–H9C	0.9800
C10–O3	1.227(5)
C10–N2	1.333(5)
C11–N2	1.444(6)
C11–C12	1.525(7)
C11–H11A	0.9900
C11–H11B	0.9900
C12–C13	1.505(8)
C12–H12A	0.9900
C12–H12B	0.9900
C13–N3	1.470(6)
C13–H13A	0.9900
C13–H13B	0.9900
C14–O4	1.221(6)
C14–N3	1.317(6)
C14–O5	1.346(5)
C15–O5	1.452(6)
C15–C16	1.505(6)
C15–H15A	0.9900
C15–H15B	0.9900
C16–C21	1.375(7)
C16–C17	1.379(7)
C17–C18	1.405(8)
C17–H17	0.9500
C18–C19	1.362(8)
C18–H18	0.9500
C19–C20	1.386(8)
C19–H19	0.9500
C20–C21	1.366(7)
C20–H20	0.9500
C21–H21	0.9500

N2–H2	0.8800
N3–H3	0.8800
N1–C1–C2	103.3(4)
N1–C1–H1A	111.1
C2–C1–H1A	111.1
N1–C1–H1B	111.1
C2–C1–H1B	111.1
H1A–C1–H1B	109.1
C3–C2–C1	104.4(4)
C3–C2–H2A	110.9
C1–C2–H2A	110.9
C3–C2–H2B	110.9
C1–C2–H2B	110.9
H2A–C2–H2B	108.9
C2–C3–C4	105.2(4)
C2–C3–H3A	110.7
C4–C3–H3A	110.7
C2–C3–H3B	110.7
C4–C3–H3B	110.7
H3A–C3–H3B	108.8
N1–C4–C10	111.4(4)
N1–C4–C3	102.5(3)
C10–C4–C3	109.3(4)
N1–C4–H4	111.1
C10–C4–H4	111.1
C3–C4–H4	111.1
O1–C5–N1	124.1(4)
O1–C5–O2	125.8(4)
N1–C5–O2	110.1(3)
O2–C6–C7	109.2(4)
O2–C6–C9	110.3(4)
C7–C6–C9	112.2(5)
O2–C6–C8	101.3(4)
C7–C6–C8	111.2(5)
C9–C6–C8	112.2(5)
C6–C7–H7A	109.5
C6–C7–H7B	109.5
H7A–C7–H7B	109.5
C6–C7–H7C	109.5
H7A–C7–H7C	109.5
H7B–C7–H7C	109.5
C6–C8–H8A	109.5
C6–C8–H8B	109.5
H8A–C8–H8B	109.5
C6–C8–H8C	109.5
H8A–C8–H8C	109.5
H8B–C8–H8C	109.5
C6–C9–H9A	109.5
C6–C9–H9B	109.5
H9A–C9–H9B	109.5
C6–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
O3–C10–N2	123.4(4)
O3–C10–C4	120.9(4)
N2–C10–C4	115.5(4)
N2–C11–C12	111.5(4)
N2–C11–H11A	109.3
C12–C11–H11A	109.3
N2–C11–H11B	109.3

C12–C11–H11B	109.3
H11A–C11–H11B	108.0
C13–C12–C11	113.4(4)
C13–C12–H12A	108.9
C11–C12–H12A	108.9
C13–C12–H12B	108.9
C11–C12–H12B	108.9
H12A–C12–H12B	107.7
N3–C13–C12	110.2(4)
N3–C13–H13A	109.6
C12–C13–H13A	109.6
N3–C13–H13B	109.6
C12–C13–H13B	109.6
H13A–C13–H13B	108.1
O4–C14–N3	125.8(4)
O4–C14–O5	123.7(4)
N3–C14–O5	110.5(4)
O5–C15–C16	105.2(4)
O5–C15–H15A	110.7
C16–C15–H15A	110.7
O5–C15–H15B	110.7
C16–C15–H15B	110.7
H15A–C15–H15B	108.8
C21–C16–C17	119.8(4)
C21–C16–C15	120.0(4)
C17–C16–C15	120.1(4)
C16–C17–C18	118.9(5)
C16–C17–H17	120.6
C18–C17–H17	120.6
C19–C18–C17	120.4(5)
C19–C18–H18	119.8
C17–C18–H18	119.8
C18–C19–C20	120.2(5)
C18–C19–H19	119.9
C20–C19–H19	119.9
C21–C20–C19	119.5(5)
C21–C20–H20	120.2
C19–C20–H20	120.2
C20–C21–C16	121.2(5)
C20–C21–H21	119.4
C16–C21–H21	119.4
C5–N1–C1	123.7(4)
C5–N1–C4	123.3(4)
C1–N1–C4	112.9(4)
C10–N2–C11	122.6(4)
C10–N2–H2	118.7
C11–N2–H2	118.7
C14–N3–C13	121.7(4)
C14–N3–H3	119.2
C13–N3–H3	119.2
C5–O2–C6	122.4(3)
C14–O5–C15	115.4(4)

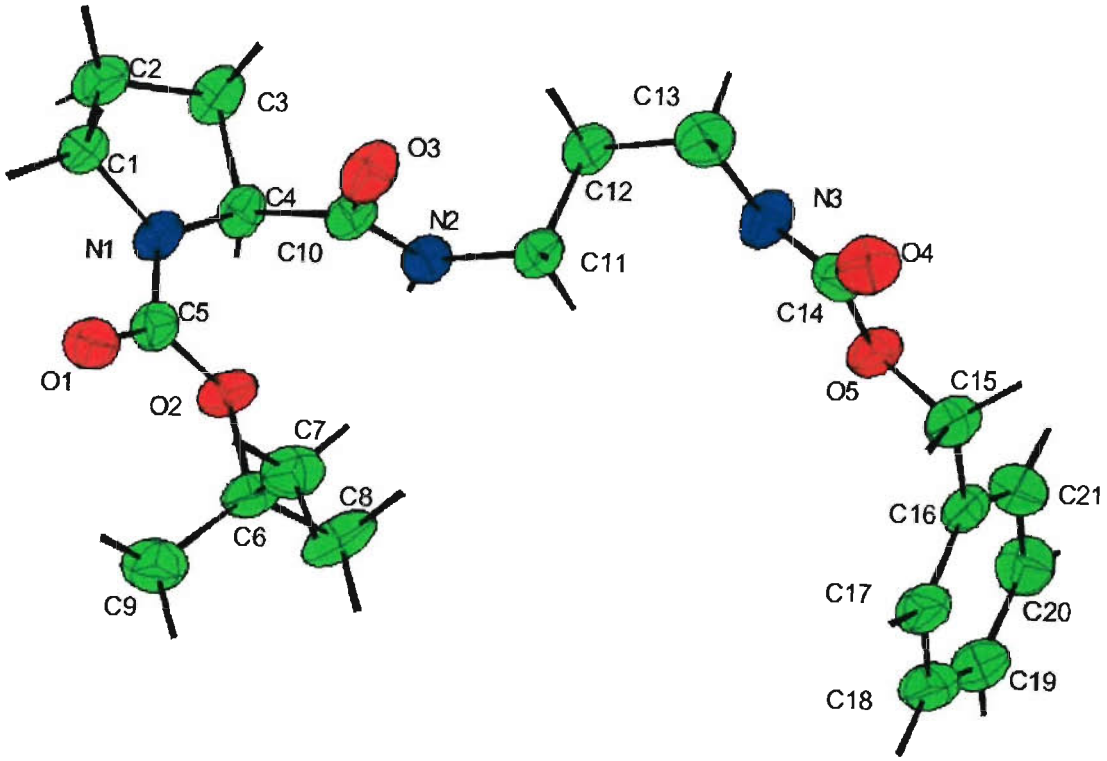
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	47(2)	56(3)	41(3)	0(2)	14(2)	−14(2)
C2	52(3)	66(3)	46(3)	7(2)	21(2)	−4(2)
C3	45(2)	56(3)	58(3)	16(2)	10(2)	−3(2)
C4	30(2)	42(2)	49(3)	8(2)	10(2)	1(2)
C5	39(2)	39(2)	42(2)	−3(2)	15(2)	−2(2)
C6	63(3)	45(3)	36(2)	5(2)	18(2)	6(2)
C7	70(3)	49(3)	47(3)	1(2)	16(2)	11(2)
C8	71(4)	84(4)	59(3)	25(3)	37(3)	9(3)
C9	105(5)	56(3)	48(3)	−6(3)	21(3)	−4(3)
C10	35(2)	46(2)	41(2)	5(2)	15(2)	0(2)
C11	57(3)	48(3)	43(3)	−2(2)	21(2)	−11(2)
C12	44(2)	53(3)	44(3)	0(2)	19(2)	−4(2)
C13	47(3)	64(3)	52(3)	−8(2)	21(2)	−1(2)
C14	40(2)	49(3)	38(2)	−9(2)	7(2)	−1(2)
C15	57(3)	46(3)	46(3)	4(2)	16(2)	3(2)
C16	48(2)	38(2)	39(2)	8(2)	14(2)	−3(2)
C17	42(2)	79(4)	42(3)	5(2)	12(2)	−14(2)
C18	61(3)	95(4)	39(3)	2(3)	16(2)	−20(3)
C19	61(3)	68(3)	48(3)	−2(3)	25(2)	−7(3)
C20	48(3)	53(3)	59(3)	−1(2)	16(2)	3(2)
C21	52(3)	52(3)	43(3)	−5(2)	6(2)	0(2)
N1	33(2)	52(2)	42(2)	9(2)	12(2)	−4(2)
N2	38(2)	47(2)	40(2)	−4(2)	16(2)	−4(2)
N3	49(2)	44(2)	59(3)	0(2)	30(2)	3(2)
O1	38(2)	60(2)	43(2)	−2(2)	9(1)	−1(2)
O2	42(2)	58(2)	40(2)	10(2)	16(1)	6(2)
O3	60(2)	42(2)	71(2)	2(2)	38(2)	6(2)
O4	58(2)	58(2)	57(2)	−1(2)	17(2)	14(2)
O5	55(2)	43(2)	44(2)	2(1)	22(2)	3(1)

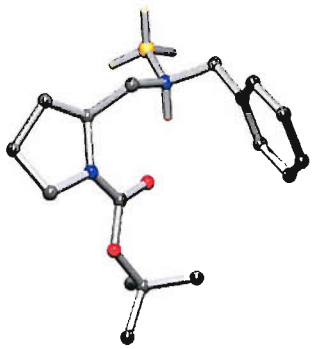
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	9465	6347	5489	57	1
H1B	9709	7070	6476	57	1
H2A	6606	7522	5293	63	1
H2B	7256	7070	3928	63	1
H3A	5130	6140	4269	64	1
H3B	3771	6797	4743	64	1
H4	4573	6528	7241	48	1
H7A	10423	4948	10116	82	1
H7B	8248	4534	9678	82	1
H7C	9411	4545	11379	82	1
H8A	5097	4982	10452	103	1
H8B	5028	5766	11159	103	1
H8C	6070	5117	12171	103	1
H9A	8553	6454	11831	103	1
H9B	10629	6054	11544	103	1
H9C	9411	5777	12830	103	1
H11A	1202	4536	7639	57	1
H11B	3191	4236	7003	57	1
H12A	−324	4906	5190	55	1
H12B	1664	4609	4554	55	1
H13A	−979	3772	4013	63	1
H13B	806	3427	5244	63	1
H15A	−2019	2399	9230	58	1
H15B	−4124	2162	8138	58	1
H17	−2314	2826	11649	65	1
H18	−4304	3328	13343	77	1
H19	−7827	3542	12601	68	1
H20	−9408	3308	10138	63	1
H21	−7453	2830	8469	59	1
H2	2445	5644	7513	49	1
H3	−2683	4056	6163	58	1



Departmental Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
Contact: Dr Mark E Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2007sot0082 (AC4671–81TOP)**
Empirical formula	$C_{17}H_{29}BN_2O_2$
Formula weight	304.23
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 11.2324(3) Å
	b = 11.8099(2) Å
	c = 13.6686(3) Å
Volume	1813.19(7) Å^3
Z	4
Density (calculated)	1.114 Mg / m^3
Absorption coefficient	0.072 mm^{-1}
F(000)	664
Crystal	Block; Colourless
Crystal size	0.45 × 0.35 × 0.2 mm^3
θ range for data collection	2.91 – 27.48°
Index ranges	$-14 \le h \le 14$, $-15 \le k \le 15$, $-17 \le l \le 17$
Reflections collected	18553
Independent reflections	2363 [R_{int} = 0.0508]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9858 and 0.9585
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2363 / 0 / 219
Goodness-of-fit on F^2	1.140
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0375, $wR2$ = 0.0869
R indices (all data)	$R1$ = 0.0469, $wR2$ = 0.0924
Extinction coefficient	0.065(6)
Largest diff. peak and hole	0.200 and –0.200 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the NH and BH3 which were freely refined

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
B1	−318(2)	2837(2)	4801(2)	31(1)	1
C1	−76(2)	2942(2)	−983(1)	36(1)	1
C2	1482(2)	2903(2)	330(2)	32(1)	1
C3	−116(2)	1392(2)	265(1)	27(1)	1
C4	195(2)	2625(2)	74(1)	25(1)	1
C5	−692(2)	3304(1)	1609(1)	22(1)	1
C6	−2083(2)	4942(2)	1416(1)	30(1)	1
C7	−2291(2)	5863(2)	2179(2)	32(1)	1
C8	−2491(2)	5189(2)	3118(1)	29(1)	1
C9	−1617(2)	4199(1)	3051(1)	23(1)	1
C10	−2089(2)	3181(2)	3616(1)	25(1)	1
C11	−1717(2)	1267(2)	4240(1)	29(1)	1
C12	−2325(2)	616(1)	3434(1)	23(1)	1
C13	−3552(2)	462(2)	3448(1)	28(1)	1
C14	−4095(2)	−212(2)	2746(1)	34(1)	1
C15	−3432(2)	−725(2)	2020(2)	33(1)	1
C16	−2212(2)	−556(2)	1990(2)	36(1)	1
C17	−1667(2)	109(2)	2694(1)	31(1)	1
N1	−1499(1)	4031(1)	1979(1)	23(1)	1
N2	−1157(1)	2361(1)	3934(1)	24(1)	1
O1	−623(1)	3382(1)	627(1)	25(1)	1
O2	−102(1)	2650(1)	2110(1)	25(1)	1

Table 3. Bond lengths [Å] and angles [°].

B1–N2	1.615(3)	C9–N1	1.484(2)
C1–C4	1.524(3)	C9–C10	1.524(2)
C2–C4	1.524(3)	C10–N2	1.492(2)
C3–C4	1.520(3)	C11–N2	1.496(2)
C4–O1	1.487(2)	C11–C12	1.508(2)
C5–O2	1.227(2)	C12–C13	1.390(3)
C5–N1	1.347(2)	C12–C17	1.388(3)
C5–O1	1.347(2)	C13–C14	1.387(3)
C6–N1	1.476(2)	C14–C15	1.381(3)
C6–C7	1.524(3)	C15–C16	1.386(3)
C7–C8	1.527(3)	C16–C17	1.384(3)
C8–C9	1.531(2)		
O1–C4–C3	110.28(14)	N2–C11–C12	115.21(15)
O1–C4–C2	109.90(15)	C13–C12–C17	118.74(17)
C3–C4–C2	112.66(16)	C13–C12–C11	120.43(17)
O1–C4–C1	102.19(14)	C17–C12–C11	120.74(17)
C3–C4–C1	110.60(16)	C14–C13–C12	120.11(18)
C2–C4–C1	110.72(17)	C15–C14–C13	120.78(19)
O2–C5–N1	123.74(16)	C14–C15–C16	119.39(19)
O2–C5–O1	124.59(16)	C17–C16–C15	119.90(19)
N1–C5–O1	111.66(15)	C16–C17–C12	121.06(19)
N1–C6–C7	103.34(15)	C5–N1–C6	124.58(15)
C6–C7–C8	103.07(15)	C5–N1–C9	120.99(15)
C7–C8–C9	104.68(15)	C6–N1–C9	112.24(13)
N1–C9–C10	115.23(14)	C10–N2–C11	110.33(14)
N1–C9–C8	102.56(14)	C10–N2–B1	113.41(14)
C10–C9–C8	110.42(14)	C11–N2–B1	109.92(14)
N2–C10–C9	114.55(15)	C5–O1–C4	120.03(14)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

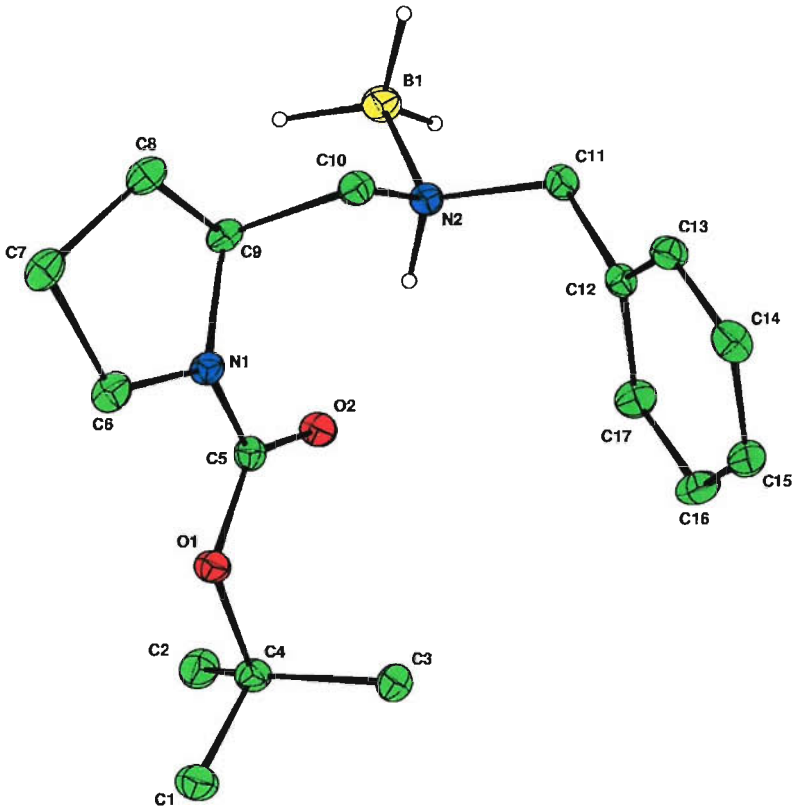
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
B1	34(1)	35(1)	24(1)	−2(1)	−5(1)	−6(1)
C1	47(1)	34(1)	26(1)	2(1)	4(1)	10(1)
C2	28(1)	30(1)	39(1)	−4(1)	7(1)	0(1)
C3	28(1)	25(1)	29(1)	−1(1)	0(1)	2(1)
C4	26(1)	25(1)	24(1)	−1(1)	4(1)	5(1)
C5	20(1)	21(1)	25(1)	1(1)	0(1)	−1(1)
C6	30(1)	26(1)	33(1)	−1(1)	−7(1)	9(1)
C7	31(1)	25(1)	40(1)	−4(1)	−5(1)	8(1)
C8	24(1)	28(1)	34(1)	−8(1)	−3(1)	5(1)
C9	18(1)	24(1)	26(1)	−6(1)	−2(1)	1(1)
C10	22(1)	27(1)	27(1)	−2(1)	2(1)	−2(1)
C11	37(1)	28(1)	22(1)	2(1)	−1(1)	−7(1)
C12	29(1)	21(1)	21(1)	3(1)	−1(1)	−1(1)
C13	29(1)	31(1)	24(1)	1(1)	5(1)	0(1)
C14	28(1)	42(1)	32(1)	5(1)	−3(1)	−6(1)
C15	44(1)	31(1)	25(1)	−2(1)	−5(1)	−6(1)
C16	42(1)	35(1)	30(1)	−10(1)	3(1)	4(1)
C17	26(1)	33(1)	33(1)	−3(1)	1(1)	3(1)
N1	25(1)	21(1)	23(1)	−1(1)	−1(1)	4(1)
N2	26(1)	24(1)	22(1)	−1(1)	−1(1)	−2(1)
O1	29(1)	25(1)	22(1)	2(1)	2(1)	7(1)
O2	24(1)	26(1)	25(1)	2(1)	1(1)	5(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H99	−680(20)	2254(18)	3358(16)	34(6)	1
H98	110(20)	3651(17)	4550(15)	33(6)	1
H97	−930(20)	2946(19)	5419(16)	38(6)	1
H96	420(20)	2180(20)	4962(18)	48(7)	1
H1A	−899	2736	−1139	53	1
H1B	468	2535	−1420	53	1
H1C	31	3759	−1071	53	1
H2A	1641	3701	184	48	1
H2B	2017	2424	−57	48	1
H2C	1617	2763	1028	48	1
H3A	65	1202	947	41	1
H3B	352	906	−171	41	1
H3C	−966	1271	141	41	1
H6A	−2845	4679	1132	36	1
H6B	−1561	5217	882	36	1
H7A	−2997	6326	2014	38	1
H7B	−1588	6364	2238	38	1
H8A	−3322	4912	3155	35	1
H8B	−2323	5661	3700	35	1
H9	−831	4432	3329	27	1
H10A	−2518	3458	4202	31	1
H10B	−2673	2777	3199	31	1
H11A	−2308	1428	4759	35	1
H11B	−1093	779	4530	35	1
H13	−4019	818	3939	33	1
H14	−4932	−321	2766	41	1
H15	−3810	−1189	1544	40	1
H16	−1749	−896	1488	43	1
H17	−830	220	2671	37	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N2–H99···O2	0.96(2)	1.89(2)	2.782(2)	154.6(19)



Thermal ellipsoids drawn at the 35% probability level, non-hetero atom hydrogens omitted for clarity.

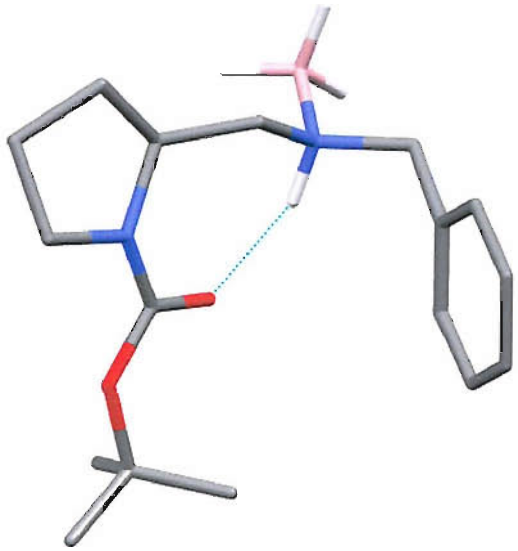
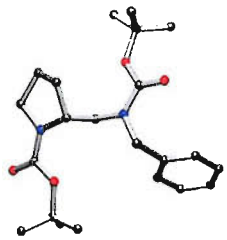


Table 1. Crystal data and structure refinement details.



Identification code	**2006sot1521 (AC4671–97)**
Empirical formula	$C_{22}H_{34}N_2O_4$
Formula weight	390.51
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.7839(4) Å
	b = 6.13470(10) Å β = 98.8050(10)°
	c = 16.4361(6) Å
Volume	1074.53(6) Å^3
Z	2
Density (calculated)	1.207 Mg / m^3
Absorption coefficient	0.083 mm^{-1}
$F(000)$	424
Crystal	Block; Colourless
Crystal size	0.2 × 0.2 × 0.2 mm^3
θ range for data collection	2.91 – 27.48°
Index ranges	$-13 \le h \le 12$, $-7 \le k \le 7$, $-21 \le l \le 21$
Reflections collected	8690
Independent reflections	2672 [R_{int} = 0.0354]
Completeness to θ = 27.48°	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9837 and 0.9737
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2672 / 1 / 260
Goodness-of-fit on F^2	1.186
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0430, $wR2$ = 0.0974
R indices (all data)	$R1$ = 0.0519, $wR2$ = 0.1026
Extinction coefficient	0.166(11)
Largest diff. peak and hole	0.439 and –0.438 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	13757(2)	–3404(4)	4719(2)	31(1)	1
C2	13480(2)	–4427(4)	3214(2)	32(1)	1
C3	13635(2)	–506(4)	3640(2)	26(1)	1
C4	13194(2)	–2768(3)	3844(1)	21(1)	1
C5	11070(2)	–4094(3)	3950(1)	19(1)	1
C6	8854(2)	–4817(4)	4030(2)	27(1)	1
C7	7671(2)	–3536(4)	3687(2)	31(1)	1
C8	8113(2)	–1168(4)	3727(1)	25(1)	1
C9	9424(2)	–1290(4)	3479(1)	19(1)	1
C10	9416(2)	–1208(4)	2538(1)	18(1)	1
C11	8126(2)	1861(3)	1862(1)	18(1)	1
C12	5896(2)	853(3)	1500(1)	20(1)	1
C13	5268(2)	–1354(4)	1555(1)	24(1)	1
C14	5417(2)	2493(4)	2068(1)	27(1)	1
C15	5730(2)	1657(4)	613(1)	25(1)	1
C16	10360(2)	2421(4)	2276(1)	19(1)	1
C17	10929(2)	2453(4)	1484(1)	19(1)	1
C18	11567(2)	659(4)	1238(1)	24(1)	1
C19	12007(2)	655(4)	485(2)	28(1)	1
C20	11833(2)	2470(4)	–23(1)	29(1)	1
C21	11230(2)	4294(4)	224(1)	30(1)	1
C22	10769(2)	4278(4)	973(1)	24(1)	1
N1	9859(2)	–3446(3)	3799(1)	20(1)	1
N2	9247(2)	1017(3)	2220(1)	18(1)	1
O1	11831(1)	–2459(2)	3769(1)	21(1)	1
O2	11413(1)	–5904(2)	4207(1)	24(1)	1
O3	7217(1)	311(2)	1796(1)	20(1)	1
O4	7975(1)	3740(3)	1633(1)	24(1)	1

Table 3. Bond lengths [Å] and angles [°].

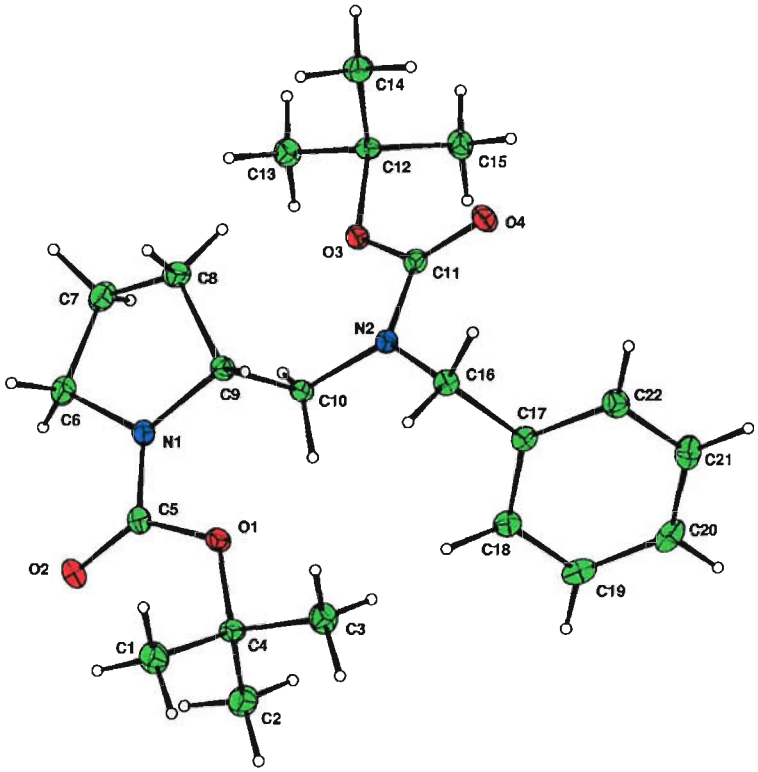
C1–C4	1.524(3)	C11–O3	1.358(3)
C2–C4	1.517(3)	C11–N2	1.363(3)
C3–C4	1.521(3)	C12–O3	1.472(2)
C4–O1	1.468(2)	C12–C14	1.515(3)
C5–O2	1.225(3)	C12–C13	1.522(3)
C5–N1	1.351(3)	C12–C15	1.524(3)
C5–O1	1.358(3)	C16–N2	1.469(3)
C6–N1	1.468(3)	C16–C17	1.521(3)
C6–C7	1.530(3)	C17–C18	1.391(3)
C7–C8	1.527(4)	C17–C22	1.395(3)
C8–C9	1.533(3)	C18–C19	1.392(3)
C9–N1	1.473(3)	C19–C20	1.387(4)
C9–C10	1.546(3)	C20–C21	1.386(4)
C10–N2	1.463(3)	C21–C22	1.396(3)
C11–O4	1.216(3)		
O1–C4–C2	109.53(18)	C14–C12–C13	110.96(17)
O1–C4–C3	101.89(17)	O3–C12–C15	110.78(16)
C2–C4–C3	111.00(18)	C14–C12–C15	111.91(18)
O1–C4–C1	111.21(17)	C13–C12–C15	110.85(18)
C2–C4–C1	112.3(2)	N2–C16–C17	112.76(16)
C3–C4–C1	110.44(19)	C18–C17–C22	118.78(19)
O2–C5–N1	124.2(2)	C18–C17–C16	121.36(19)
O2–C5–O1	125.8(2)	C22–C17–C16	119.82(19)
N1–C5–O1	110.02(18)	C19–C18–C17	120.7(2)
N1–C6–C7	102.54(18)	C20–C19–C18	120.1(2)
C8–C7–C6	103.65(19)	C21–C20–C19	119.9(2)
C7–C8–C9	103.68(19)	C20–C21–C22	119.9(2)
N1–C9–C8	101.81(17)	C21–C22–C17	120.6(2)
N1–C9–C10	109.81(16)	C5–N1–C6	121.02(18)
C8–C9–C10	113.62(17)	C5–N1–C9	125.12(18)
N2–C10–C9	111.63(16)	C6–N1–C9	113.57(17)
O4–C11–O3	125.4(2)	C11–N2–C10	124.21(17)
O4–C11–N2	124.1(2)	C11–N2–C16	117.83(18)
O3–C11–N2	110.48(17)	C10–N2–C16	117.95(17)
O3–C12–C14	110.56(17)	C5–O1–C4	121.14(16)
O3–C12–C13	101.32(16)	C11–O3–C12	121.22(16)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(1)	37(1)	29(1)	8(1)	−2(1)	−1(1)
C2	38(1)	25(1)	35(1)	−1(1)	15(1)	1(1)
C3	24(1)	24(1)	30(1)	2(1)	2(1)	−4(1)
C4	16(1)	20(1)	25(1)	2(1)	3(1)	2(1)
C5	22(1)	20(1)	13(1)	0(1)	0(1)	−1(1)
C6	24(1)	28(1)	29(1)	7(1)	7(1)	−3(1)
C7	23(1)	40(1)	30(1)	8(1)	7(1)	−1(1)
C8	24(1)	32(1)	19(1)	2(1)	6(1)	6(1)
C9	21(1)	19(1)	16(1)	0(1)	2(1)	2(1)
C10	18(1)	18(1)	17(1)	1(1)	3(1)	4(1)
C11	21(1)	18(1)	17(1)	0(1)	5(1)	0(1)
C12	15(1)	21(1)	23(1)	1(1)	2(1)	2(1)
C13	22(1)	23(1)	28(1)	2(1)	2(1)	−3(1)
C14	25(1)	24(1)	32(1)	0(1)	9(1)	3(1)
C15	24(1)	28(1)	24(1)	6(1)	1(1)	1(1)
C16	19(1)	19(1)	20(1)	−1(1)	1(1)	−2(1)
C17	15(1)	21(1)	20(1)	−1(1)	0(1)	−3(1)
C18	21(1)	26(1)	26(1)	1(1)	4(1)	1(1)
C19	21(1)	34(1)	32(1)	−5(1)	8(1)	0(1)
C20	23(1)	43(1)	23(1)	−1(1)	6(1)	−9(1)
C21	30(1)	34(1)	24(1)	6(1)	3(1)	−5(1)
C22	24(1)	24(1)	25(1)	2(1)	2(1)	−1(1)
N1	20(1)	19(1)	20(1)	4(1)	4(1)	0(1)
N2	17(1)	17(1)	19(1)	2(1)	3(1)	−1(1)
O1	16(1)	18(1)	29(1)	4(1)	2(1)	0(1)
O2	29(1)	18(1)	23(1)	5(1)	0(1)	2(1)
O3	16(1)	18(1)	23(1)	3(1)	1(1)	−1(1)
O4	24(1)	18(1)	31(1)	6(1)	2(1)	2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	13448	−2411	5110	46	1
H1B	14674	−3309	4782	46	1
H1C	13512	−4901	4829	46	1
H2A	13150	−5853	3343	47	1
H2B	14390	−4528	3228	47	1
H2C	13084	−3970	2664	47	1
H3A	13247	−104	3082	40	1
H3B	14550	−507	3673	40	1
H3C	13391	551	4034	40	1
H6A	8935	−4980	4635	32	1
H6B	8853	−6279	3775	32	1
H7A	7354	−3973	3113	37	1
H7B	7001	−3763	4028	37	1
H8A	8151	−575	4291	30	1
H8B	7547	−246	3339	30	1
H9	9975	−115	3759	23	1
H10A	10218	−1799	2409	21	1
H10B	8728	−2139	2261	21	1
H13A	5620	−2402	1203	37	1
H13B	4364	−1212	1370	37	1
H13C	5416	−1867	2126	37	1
H14A	5605	1976	2638	40	1
H14B	4507	2661	1914	40	1
H14C	5828	3901	2019	40	1
H15A	6108	3105	596	38	1
H15B	4833	1741	394	38	1
H15C	6141	642	279	38	1
H16A	11000	1900	2731	23	1
H16B	10126	3925	2409	23	1
H18	11704	−579	1588	29	1
H19	12426	−592	319	34	1
H20	12127	2463	−539	35	1
H21	11130	5554	−116	36	1
H22	10342	5522	1135	29	1



Thermal ellipsoids drawn at the 35% probability level

Table 1. Crystal data and structure refinement.

Identification code	**2007sot0754a**	
Empirical formula	$C_{22}H_{29}N_5S_2$	
Formula weight	427.62	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = **8.7606(4) Å**	α = **90°**
	b = **23.2204(9) Å**	β = 102.882(2)°
	c = **11.6562(3) Å**	γ = **90°**
Volume	2311.48(15) Å^3	
Z	4	
Density (calculated)	1.229 Mg / m^3	
Absorption coefficient	0.248 mm^{-1}	
F(000)	912	
Crystal	Fragment; Colourless	
Crystal size	0.20 × 0.16 × 0.06 mm^3	
θ range for data collection	3.17 – 27.48°	
Index ranges	$-10 \le h \le 11$, $-30 \le k \le 29$, $-15 \le l \le 15$	
Reflections collected	31490	
Independent reflections	10439 [R_{int} = 0.1223]	
Completeness to θ = 27.48°	99.4 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9853 and 0.9521	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10439 / 9 / 529	
Goodness-of-fit on F^2	0.993	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0671, $wR2$ = 0.1215	
R indices (all data)	$R1$ = 0.1232, $wR2$ = 0.1466	
Absolute structure parameter	0.1(4)	
Largest diff. peak and hole	0.299 and –0.379 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Gōttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	7607(7)	1455(2)	2817(5)	27(1)	1
S2	10118(8)	332(3)	7430(5)	32(1)	1
N1	9720(30)	3465(9)	2856(17)	33(5)	1
N2	9500(20)	2247(8)	4112(14)	24(4)	1
N3	9260(20)	691(8)	5183(15)	28(4)	1
N4	7640(30)	58(9)	5805(16)	38(5)	1
N5	9100(20)	2352(8)	2126(15)	28(4)	1
C1	8290(30)	3816(11)	2810(30)	47(8)	1
C2	8380(30)	4030(12)	4050(20)	44(7)	1
C3	9130(30)	3517(10)	4770(20)	36(6)	1
C4	10350(30)	3297(10)	4116(18)	25(5)	1
C5	10790(30)	2676(10)	4271(19)	26(5)	1
C6	9140(30)	2025(10)	5206(18)	28(5)	1
C7	10420(30)	1636(9)	5903(18)	29(5)	1
C8	10620(30)	1068(10)	5319(19)	28(5)	1
C9	8940(30)	364(10)	6052(18)	28(5)	1
C10	6600(30)	−3(11)	4660(20)	32(6)	1
C11	6810(40)	−436(12)	3910(20)	50(8)	1
C12	5780(50)	−494(14)	2830(30)	65(10)	1
C13	4540(40)	−138(16)	2520(30)	61(10)	1
C14	4330(40)	303(18)	3250(30)	70(10)	1
C15	5360(30)	370(15)	4340(30)	54(8)	1
C16	8800(30)	2040(9)	3029(18)	24(5)	1
C17	8740(30)	2205(10)	910(17)	25(5)	1
C18	9070(30)	1667(10)	504(19)	29(5)	1
C19	8800(30)	1561(12)	−700(20)	37(6)	1
C20	8210(30)	1996(12)	−1490(20)	39(6)	1
C21	7900(30)	2529(11)	−1094(19)	33(6)	1
C22	8150(30)	2635(11)	114(18)	29(5)	1
S101	2204(7)	3033(2)	−2182(5)	30(1)	1
S102	3348(7)	4001(3)	2678(5)	32(1)	1
N101	3760(20)	987(8)	−1963(17)	32(5)	1
N102	3480(20)	2175(7)	−730(14)	22(4)	1
N103	2970(20)	3679(8)	443(16)	29(4)	1
N104	1290(20)	4374(8)	811(16)	30(5)	1
N105	4090(20)	2159(8)	−2526(14)	25(4)	1
C101	4720(40)	471(11)	−2050(20)	52(8)	1
C102	4830(40)	148(11)	−910(20)	47(7)	1
C103	5020(40)	639(11)	−50(20)	51(8)	1
C104	3920(30)	1113(10)	−680(20)	31(5)	1
C105	4580(30)	1702(9)	−342(18)	25(5)	1
C106	2570(30)	2351(10)	130(19)	29(5)	1
C107	3580(30)	2682(10)	1154(19)	33(6)	1
C108	4200(30)	3249(10)	780(20)	31(6)	1
C109	2480(30)	4017(10)	1218(18)	26(5)	1
C110	600(30)	4470(10)	−413(19)	27(5)	1
C111	820(30)	4987(11)	−930(20)	37(6)	1
C112	190(30)	5072(12)	−2130(20)	42(7)	1
C113	−670(30)	4630(11)	−2800(20)	41(7)	1
C114	−920(30)	4124(11)	−2250(20)	34(6)	1
C115	−300(30)	4041(11)	−1060(20)	32(5)	1
C116	3320(30)	2437(9)	−1786(18)	22(5)	1
C117	4440(30)	2366(10)	−3569(18)	25(5)	1
C118	4780(30)	2942(10)	−3749(19)	30(5)	1
C119	5140(30)	3103(12)	−4800(20)	36(6)	1
C120	5190(30)	2706(12)	−5660(20)	37(6)	1
C121	4900(30)	2129(13)	−5490(19)	38(6)	1
C122	4510(30)	1965(11)	−4451(19)	33(6)	1

Table 3. Bond lengths [Å] and angles [°].

Symmetry transformations used to generate equivalent atoms:

Table 4. Bond lengths [Å] and angles [°].

S1–C16	1.70(2)
S2–C9	1.71(2)
N1–C1	1.49(4)
N1–C4	1.50(3)
N1–H1	0.90(10)
N2–C16	1.36(3)
N2–C6	1.47(3)
N2–C5	1.49(3)
N3–C9	1.34(3)
N3–C8	1.46(3)
N3–H3	0.8800
N4–C9	1.32(3)
N4–C10	1.45(3)
N4–H4N	0.8800
N5–C16	1.35(3)
N5–C17	1.42(3)
N5–H5	0.8800
C1–C2	1.51(4)
C1–H1A	0.9900
C1–H1B	0.9900
C2–C3	1.52(3)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C4	1.53(3)
C3–H3A	0.9900
C3–H3B	0.9900
C4–C5	1.49(3)
C4–H4	1.0000
C5–H5A	0.9900
C5–H5B	0.9900
C6–C7	1.53(3)
C6–H6A	0.9900
C6–H6B	0.9900
C7–C8	1.51(3)
C7–H7A	0.9900
C7–H7B	0.9900
C8–H8A	0.9900
C8–H8B	0.9900
C10–C11	1.37(4)
C10–C15	1.37(4)
C11–C12	1.39(4)
C11–H11	0.9500
C12–C13	1.35(5)
C12–H12	0.9500
C13–C14	1.37(5)
C13–H13	0.9500
C14–C15	1.40(4)
C14–H14	0.9500
C15–H15	0.9500
C17–C22	1.38(3)
C17–C18	1.39(3)
C18–C19	1.39(3)
C18–H18	0.9500
C19–C20	1.39(4)

C19–H19	0.9500
C20–C21	1.37(4)
C20–H20	0.9500
C21–C22	1.40(3)
C21–H21	0.9500
C22–H22	0.9500
S101–C116	1.70(2)
S102–C109	1.70(2)
N101–C101	1.48(3)
N101–C104	1.50(3)
N101–H101	0.91(10)
N102–C116	1.35(3)
N102–C105	1.46(3)
N102–C106	1.47(3)
N103–C109	1.34(3)
N103–C108	1.46(3)
N103–H103	0.8800
N104–C109	1.34(3)
N104–C110	1.44(3)
N104–H14N	0.8800
N105–C116	1.37(3)
N105–C117	1.40(3)
N105–H105	0.8800
C101–C102	1.51(4)
C101–H10A	0.9900
C101–H10B	0.9900
C102–C103	1.50(3)
C102–H10C	0.9900
C102–H10D	0.9900
C103–C104	1.54(3)
C103–H10E	0.9900
C103–H10F	0.9900
C104–C105	1.50(3)
C104–H104	1.0000
C105–H10G	0.9900
C105–H10H	0.9900
C106–C107	1.52(3)
C106–H10I	0.9900
C106–H10J	0.9900
C107–C108	1.52(3)
C107–H10K	0.9900
C107–H10L	0.9900
C108–H10M	0.9900
C108–H10N	0.9900
C110–C111	1.38(3)
C110–C115	1.39(3)
C111–C112	1.39(3)
C111–H111	0.9500
C112–C113	1.40(4)
C112–H112	0.9500
C113–C114	1.37(4)
C113–H113	0.9500
C114–C115	1.38(3)
C114–H114	0.9500
C115–H115	0.9500
C117–C118	1.39(3)
C117–C122	1.40(3)
C118–C119	1.39(3)
C118–H118	0.9500
C119–C120	1.37(4)
C119–H119	0.9500

C120–C121	1.39(4)
C120–H120	0.9500
C121–C122	1.38(3)
C121–H121	0.9500
C122–H122	0.9500

C1–N1–C4	107.3(19)
C1–N1–H1	115(10)
C4–N1–H1	109(10)
C16–N2–C6	122.6(18)
C16–N2–C5	121.8(18)
C6–N2–C5	115.4(17)
C9–N3–C8	124.0(18)
C9–N3–H3	118.0
C8–N3–H3	118.0
C9–N4–C10	126(2)
C9–N4–H4N	116.9
C10–N4–H4N	116.9
C16–N5–C17	127.4(19)
C16–N5–H5	116.3
C17–N5–H5	116.3
N1–C1–C2	106(2)
N1–C1–H1A	110.4
C2–C1–H1A	110.4
N1–C1–H1B	110.4
C2–C1–H1B	110.4
H1A–C1–H1B	108.6
C1–C2–C3	101(2)
C1–C2–H2A	111.5
C3–C2–H2A	111.5
C1–C2–H2B	111.5
C3–C2–H2B	111.5
H2A–C2–H2B	109.3
C2–C3–C4	104(2)
C2–C3–H3A	110.9
C4–C3–H3A	110.9
C2–C3–H3B	110.9
C4–C3–H3B	110.9
H3A–C3–H3B	108.9
C5–C4–N1	113.5(18)
C5–C4–C3	117(2)
N1–C4–C3	105.1(18)
C5–C4–H4	106.9
N1–C4–H4	106.9
C3–C4–H4	106.9
N2–C5–C4	117.4(19)
N2–C5–H5A	108.0
C4–C5–H5A	108.0
N2–C5–H5B	108.0
C4–C5–H5B	108.0
H5A–C5–H5B	107.2
N2–C6–C7	113(2)
N2–C6–H6A	108.9
C7–C6–H6A	108.9
N2–C6–H6B	108.9
C7–C6–H6B	108.9
H6A–C6–H6B	107.7
C8–C7–C6	115.0(18)
C8–C7–H7A	108.5
C6–C7–H7A	108.5
C8–C7–H7B	108.5

C6–C7–H7B	108.5
H7A–C7–H7B	107.5
N3–C8–C7	113(2)
N3–C8–H8A	108.9
C7–C8–H8A	108.9
N3–C8–H8B	108.9
C7–C8–H8B	108.9
H8A–C8–H8B	107.7
N4–C9–N3	117.0(19)
N4–C9–S2	119.6(17)
N3–C9–S2	123.4(17)
C11–C10–C15	120(2)
C11–C10–N4	121(2)
C15–C10–N4	119(2)
C10–C11–C12	120(3)
C10–C11–H11	120.0
C12–C11–H11	120.0
C13–C12–C11	120(3)
C13–C12–H12	120.0
C11–C12–H12	120.0
C12–C13–C14	120(3)
C12–C13–H13	119.8
C14–C13–H13	119.8
C13–C14–C15	120(3)
C13–C14–H14	119.9
C15–C14–H14	119.9
C10–C15–C14	119(3)
C10–C15–H15	120.5
C14–C15–H15	120.5
N5–C16–N2	113.8(19)
N5–C16–S1	122.5(16)
N2–C16–S1	123.6(16)
C22–C17–C18	119.7(19)
C22–C17–N5	118(2)
C18–C17–N5	123(2)
C19–C18–C17	120(2)
C19–C18–H18	120.0
C17–C18–H18	120.0
C18–C19–C20	120(2)
C18–C19–H19	120.0
C20–C19–H19	120.0
C21–C20–C19	120(2)
C21–C20–H20	120.0
C19–C20–H20	120.0
C20–C21–C22	120(2)
C20–C21–H21	119.9
C22–C21–H21	119.9
C17–C22–C21	120(2)
C17–C22–H22	120.0
C21–C22–H22	120.0
C101–N101–C104	107.3(19)
C101–N101–H101	107(10)
C104–N101–H101	111(10)
C116–N102–C105	123.1(18)
C116–N102–C106	122.2(18)
C105–N102–C106	114.7(17)
C109–N103–C108	123.3(18)
C109–N103–H103	118.4
C108–N103–H103	118.4
C109–N104–C110	124.9(19)
C109–N104–H14N	117.6

C110–N104–H14N	117.6
C116–N105–C117	128.2(18)
C116–N105–H105	115.9
C117–N105–H105	115.9
N101–C101–C102	106(2)
N101–C101–H10A	110.6
C102–C101–H10A	110.6
N101–C101–H10B	110.6
C102–C101–H10B	110.6
H10A–C101–H10B	108.8
C103–C102–C101	101(2)
C103–C102–H10C	111.6
C101–C102–H10C	111.6
C103–C102–H10D	111.6
C101–C102–H10D	111.6
H10C–C102–H10D	109.4
C102–C103–C104	105(2)
C102–C103–H10E	110.8
C104–C103–H10E	110.8
C102–C103–H10F	110.8
C104–C103–H10F	110.8
H10E–C103–H10F	108.8
C105–C104–N101	112.2(19)
C105–C104–C103	111(2)
N101–C104–C103	104(2)
C105–C104–H104	109.7
N101–C104–H104	109.7
C103–C104–H104	109.7
N102–C105–C104	114.3(18)
N102–C105–H10G	108.7
C104–C105–H10G	108.7
N102–C105–H10H	108.7
C104–C105–H10H	108.7
H10G–C105–H10H	107.6
N102–C106–C107	112(2)
N102–C106–H10I	109.3
C107–C106–H10I	109.3
N102–C106–H10J	109.3
C107–C106–H10J	109.3
H10I–C106–H10J	108.0
C106–C107–C108	113.2(19)
C106–C107–H10K	108.9
C108–C107–H10K	108.9
C106–C107–H10L	108.9
C108–C107–H10L	108.9
H10K–C107–H10L	107.8
N103–C108–C107	112(2)
N103–C108–H10M	109.1
C107–C108–H10M	109.1
N103–C108–H10N	109.1
C107–C108–H10N	109.1
H10M–C108–H10N	107.9
N103–C109–N104	117.9(19)
N103–C109–S102	121.6(17)
N104–C109–S102	120.5(17)
C111–C110–C115	120(2)
C111–C110–N104	120(2)
C115–C110–N104	120(2)
C110–C111–C112	120(2)
C110–C111–H111	119.9
C112–C111–H111	119.9

C111–C112–C113	120(2)
C111–C112–H112	120.1
C113–C112–H112	120.1
C114–C113–C112	119(2)
C114–C113–H113	120.3
C112–C113–H113	120.3
C113–C114–C115	121(2)
C113–C114–H114	119.6
C115–C114–H114	119.6
C110–C115–C114	120(2)
C110–C115–H115	120.2
C114–C115–H115	120.2
N102–C116–N105	113.3(18)
N102–C116–S101	123.4(17)
N105–C116–S101	123.2(16)
C118–C117–C122	119(2)
C118–C117–N105	124(2)
C122–C117–N105	118(2)
C119–C118–C117	119(2)
C119–C118–H118	120.3
C117–C118–H118	120.3
C120–C119–C118	121(2)
C120–C119–H119	119.4
C118–C119–H119	119.4
C119–C120–C121	121(2)
C119–C120–H120	119.7
C121–C120–H120	119.7
C122–C121–C120	119(2)
C122–C121–H121	120.6
C120–C121–H121	120.6
C121–C122–C117	121(2)
C121–C122–H122	119.3
C117–C122–H122	119.3

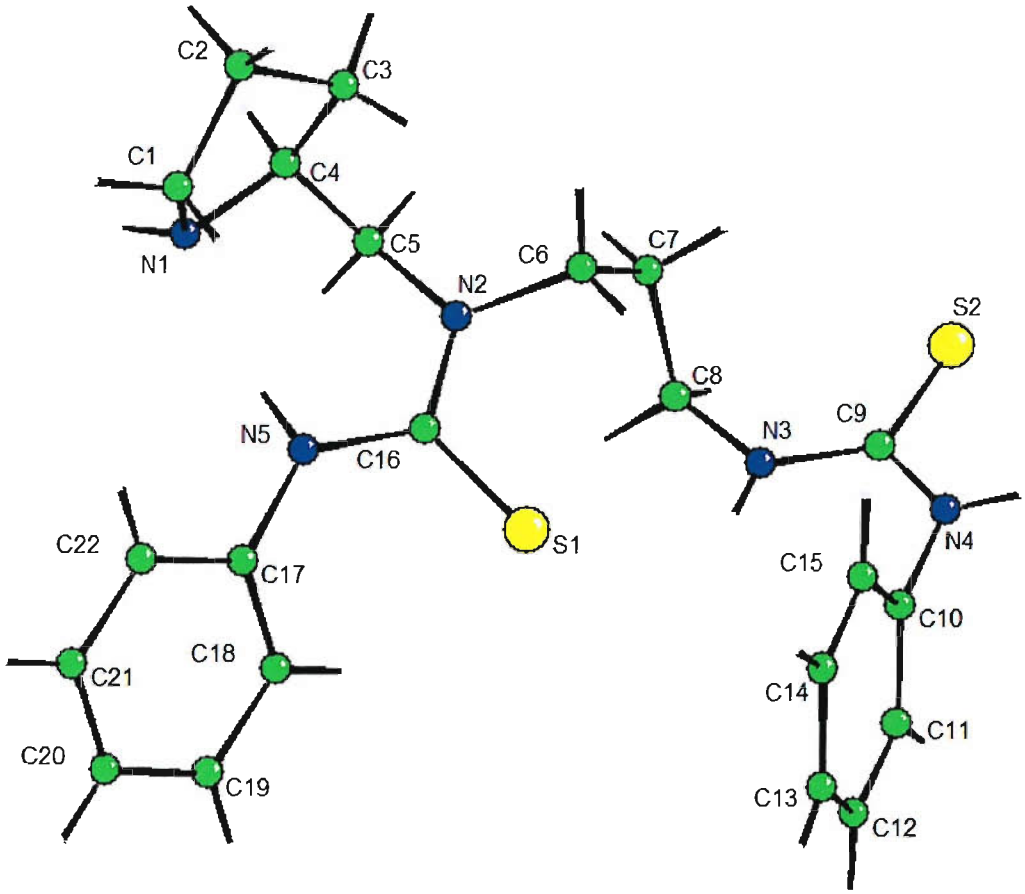
Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	31(3)	27(3)	23(3)	−2(2)	4(2)	−5(2)
S2	39(4)	31(3)	24(3)	5(3)	2(2)	−3(3)
N1	37(13)	34(12)	25(10)	5(9)	1(9)	−5(9)
N2	26(10)	29(10)	15(8)	−1(8)	2(7)	−3(8)
N3	32(12)	28(10)	21(9)	0(8)	2(8)	−9(8)
N4	43(14)	44(13)	25(10)	10(10)	1(9)	−13(10)
N5	35(12)	31(11)	17(9)	1(8)	2(8)	−6(9)
C1	44(18)	32(14)	56(18)	10(13)	−11(14)	0(12)
C2	40(16)	30(13)	62(18)	2(14)	10(13)	2(12)
C3	44(16)	28(13)	38(14)	4(11)	14(12)	0(11)
C4	25(13)	29(12)	19(10)	2(9)	0(9)	−5(9)
C5	26(13)	30(12)	21(11)	−1(10)	0(9)	−2(10)
C6	34(14)	29(12)	19(10)	1(10)	3(9)	1(10)
C7	36(14)	27(12)	20(10)	1(10)	1(10)	−3(10)
C8	29(13)	32(13)	24(11)	4(10)	6(10)	−3(10)
C9	31(13)	24(11)	28(11)	0(10)	7(10)	−3(10)
C10	33(15)	35(14)	27(12)	6(11)	2(10)	−9(11)
C11	70(20)	35(16)	38(15)	2(13)	8(15)	9(14)
C12	110(30)	43(18)	37(16)	−5(14)	12(18)	−21(19)
C13	70(20)	70(20)	35(15)	8(17)	−3(16)	−37(19)
C14	43(19)	90(30)	60(20)	10(20)	−9(15)	11(19)
C15	42(17)	62(19)	52(16)	−4(16)	−1(13)	11(15)
C16	25(12)	24(12)	20(10)	−2(9)	1(9)	2(9)
C17	28(13)	29(12)	19(10)	−2(10)	4(9)	−8(10)
C18	26(13)	34(13)	27(11)	−3(10)	4(10)	−3(10)
C19	34(14)	47(17)	32(13)	−13(12)	13(11)	−5(12)
C20	38(16)	56(17)	23(12)	−6(12)	8(11)	−13(13)
C21	32(14)	43(15)	20(11)	6(11)	1(10)	−9(11)
C22	29(14)	35(13)	23(11)	0(10)	3(10)	−9(10)
S101	34(3)	31(3)	24(3)	1(3)	2(2)	9(3)
S102	40(4)	31(3)	23(3)	−2(3)	4(2)	4(3)
N101	38(12)	28(11)	26(10)	−5(9)	2(9)	0(9)
N102	26(11)	21(9)	20(9)	0(8)	5(8)	3(8)
N103	25(11)	37(12)	23(9)	−4(9)	3(8)	−1(9)
N104	38(12)	31(11)	22(9)	0(9)	7(9)	9(9)
N105	28(11)	28(10)	20(9)	2(8)	7(8)	7(8)
C101	70(20)	36(16)	50(16)	−8(13)	14(15)	16(14)
C102	56(19)	31(14)	47(16)	−5(12)	−5(14)	9(13)
C103	70(20)	31(15)	39(14)	2(12)	−2(14)	13(14)
C104	37(14)	26(12)	30(12)	−3(10)	8(10)	0(11)
C105	28(13)	26(11)	19(10)	−2(9)	3(9)	3(9)
C106	36(14)	30(13)	25(11)	2(10)	14(10)	5(11)
C107	38(15)	35(13)	22(11)	−1(11)	2(10)	11(11)
C108	28(14)	36(14)	27(12)	−9(10)	2(10)	5(10)
C109	29(13)	23(11)	27(11)	−2(11)	7(9)	0(10)
C110	25(13)	28(12)	30(12)	3(10)	8(10)	5(10)
C111	41(16)	33(14)	35(13)	5(11)	2(11)	0(11)
C112	57(19)	37(15)	30(13)	6(12)	5(12)	3(13)
C113	46(17)	45(17)	30(13)	1(12)	5(12)	8(13)
C114	30(14)	40(15)	28(12)	−8(11)	2(10)	2(11)
C115	35(14)	29(13)	33(12)	−3(11)	11(10)	−4(11)
C116	23(12)	22(11)	20(10)	−3(9)	0(9)	−2(9)
C117	24(12)	32(13)	19(10)	4(10)	2(9)	9(10)
C118	30(13)	34(14)	24(11)	−1(10)	2(10)	1(11)
C119	32(14)	44(15)	31(12)	15(12)	6(10)	1(11)
C120	29(15)	61(18)	23(12)	9(12)	8(10)	4(12)
C121	26(14)	70(20)	21(11)	−7(12)	4(10)	8(12)
C122	31(14)	40(14)	27(12)	−1(11)	7(10)	6(11)

Table 6. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	10500(200)	3640(110)	2600(200)	50	1
H3	8604	678	4490	42	1
H4N	7379	−126	6393	58	1
H5	9582	2683	2312	42	1
H1A	7338	3579	2541	57	1
H1B	8253	4144	2264	57	1
H2A	7328	4114	4184	53	1
H2B	9042	4379	4218	53	1
H3A	8342	3217	4811	43	1
H3B	9638	3637	5583	43	1
H4	11322	3526	4406	30	1
H5A	11449	2582	3708	32	1
H5B	11451	2627	5073	32	1
H6A	8147	1807	5008	33	1
H6B	8988	2355	5708	33	1
H7A	11428	1847	6045	34	1
H7B	10182	1556	6679	34	1
H8A	10831	1145	4532	34	1
H8B	11545	867	5792	34	1
H11	7654	−698	4144	60	1
H12	5958	−784	2294	77	1
H13	3805	−194	1796	73	1
H14	3487	564	3010	84	1
H15	5209	670	4860	65	1
H18	9485	1371	1048	35	1
H19	9015	1192	−973	44	1
H20	8022	1924	−2315	47	1
H21	7504	2827	−1639	39	1
H22	7917	3003	388	35	1
H101	2750(160)	890(120)	−2300(200)	47	1
H103	2531	3718	−308	43	1
H14N	896	4565	1331	46	1
H105	4406	1807	−2321	38	1
H10A	5770	583	−2146	62	1
H10B	4208	230	−2728	62	1
H10C	3862	−74	−911	57	1
H10D	5741	−114	−741	57	1
H10E	6122	775	145	61	1
H10F	4728	519	690	61	1
H104	2874	1076	−470	37	1
H10G	4942	1721	524	30	1
H10H	5509	1758	−685	30	1
H10I	2135	2006	436	35	1
H10J	1688	2597	−265	35	1
H10K	4479	2438	1533	39	1
H10L	2954	2762	1745	39	1
H10M	5015	3401	1442	37	1
H10N	4696	3178	110	37	1
H111	1398	5286	−479	45	1
H112	350	5427	−2488	50	1
H113	−1072	4680	−3615	49	1
H114	−1522	3828	−2700	40	1
H115	−482	3690	−698	38	1
H118	4756	3221	−3157	36	1
H119	5358	3495	−4931	43	1
H120	5433	2827	−6380	45	1
H121	4969	1852	−6076	46	1
H122	4281	1572	−4335	39	1



N.B. 1). One molecule of two independent molecules in the asymmetric unit shown

2). Absolute configuration of C4 derived from reaction scheme alone, crystal enantiomerically pure.

Table 1. Crystal data and structure refinement.

Identification code	**2007sot0755**	
Empirical formula	$C_{22}H_{20}N_2O_5$	
Formula weight	392.40	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = **17.3383(7) Å**	α = **90°**
	b = **9.0472(3) Å**	β = **102.052(2)°**
	c = **12.3247(4) Å**	γ = **90°**
Volume	1890.68(12) Å^3	
Z	4	
Density (calculated)	1.379 Mg / m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	824	
Crystal	Blade; Colourless	
Crystal size	0.40 × 0.22 × 0.20 mm^3	
θ range for data collection	3.72 – 27.48°	
Index ranges	$-22 \le h \le 22$, $-11 \le k \le 11$, $-15 \le l \le 15$	
Reflections collected	21509	
Independent reflections	4306 [R_{int} = 0.0544]	
Completeness to θ = 27.48°	99.5 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.7456 and 0.5979	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4306 / 0 / 263	
Goodness-of-fit on F^2	1.055	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0493, $wR2$ = 0.1075	
R indices (all data)	$R1$ = 0.0724, $wR2$ = 0.1183	
Extinction coefficient	0.019(3)	
Largest diff. peak and hole	0.340 and –0.200 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. **A51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) **A46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	−243(1)	4440(1)	7298(1)	32(1)	1
O2	1289(1)	7081(1)	10115(1)	31(1)	1
O3	2582(1)	7269(1)	8746(1)	23(1)	1
O4	2463(1)	9716(1)	8985(1)	28(1)	1
O5	4013(1)	10710(1)	9226(1)	29(1)	1
N1	689(1)	5624(2)	8626(1)	23(1)	1
N2	3815(1)	12064(2)	10788(1)	29(1)	1
C1	−78(1)	5302(2)	8066(1)	24(1)	1
C2	−609(1)	6214(2)	8604(1)	23(1)	1
C3	−1423(1)	6348(2)	8360(1)	29(1)	1
C4	−1753(1)	7330(2)	9006(2)	32(1)	1
C5	−1284(1)	8144(2)	9852(2)	33(1)	1
C6	−468(1)	7999(2)	10092(1)	30(1)	1
C7	−142(1)	7018(2)	9452(1)	24(1)	1
C8	700(1)	6641(2)	9488(1)	25(1)	1
C9	1390(1)	4936(2)	8365(1)	25(1)	1
C10	1702(1)	5765(2)	7466(1)	24(1)	1
C11	1936(1)	7341(2)	7775(1)	23(1)	1
C12	2753(1)	8538(2)	9299(1)	21(1)	1
C13	3331(1)	8307(2)	10372(1)	21(1)	1
C14	3298(1)	7002(2)	10964(1)	25(1)	1
C15	3776(1)	6810(2)	12008(1)	29(1)	1
C16	4291(1)	7914(2)	12465(1)	30(1)	1
C17	4332(1)	9209(2)	11886(1)	28(1)	1
C18	3851(1)	9433(2)	10838(1)	23(1)	1
C19	3891(1)	10874(2)	10274(1)	24(1)	1
C20	3828(1)	12023(2)	8546(2)	36(1)	1
C21	4196(1)	13353(2)	9193(2)	41(1)	1
C22	3864(1)	13474(2)	10228(2)	37(1)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C1	1.214(2)
O2–C8	1.212(2)
O3–C12	1.3362(19)
O3–C11	1.4601(18)
O4–C12	1.2075(19)
O5–C19	1.359(2)
O5–C20	1.451(2)
N1–C1	1.395(2)
N1–C8	1.402(2)
N1–C9	1.461(2)
N2–C19	1.270(2)
N2–C22	1.461(2)
C1–C2	1.491(2)
C2–C3	1.386(2)
C2–C7	1.387(2)
C3–C4	1.393(3)
C3–H3	0.9300
C4–C5	1.392(3)
C4–H4	0.9300
C5–C6	1.390(3)
C5–H5	0.9300
C6–C7	1.383(2)
C6–H6	0.9300
C7–C8	1.491(2)
C9–C10	1.526(2)
C9–H9A	0.9700
C9–H9B	0.9700
C10–C11	1.509(2)
C10–H10A	0.9700
C10–H10B	0.9700
C11–H11A	0.9700
C11–H11B	0.9700
C12–C13	1.498(2)
C13–C14	1.396(2)
C13–C18	1.401(2)
C14–C15	1.388(2)
C14–H14	0.9300
C15–C16	1.378(3)
C15–H15	0.9300
C16–C17	1.382(3)
C16–H16	0.9300
C17–C18	1.398(2)
C17–H17	0.9300
C18–C19	1.486(2)
C20–C21	1.510(3)
C20–H20A	0.9700
C20–H20B	0.9700
C21–C22	1.510(3)
C21–H21A	0.9700
C21–H21B	0.9700
C22–H22A	0.9700
C22–H22B	0.9700
C12–O3–C11	115.50(12)
C19–O5–C20	113.57(13)
C1–N1–C8	111.90(14)
C1–N1–C9	123.59(13)
C8–N1–C9	124.48(14)
C19–N2–C22	118.83(15)

O1–C1–N1	124.41(16)
O1–C1–C2	129.50(16)
N1–C1–C2	106.10(13)
C3–C2–C7	121.67(16)
C3–C2–C1	130.36(15)
C7–C2–C1	107.95(14)
C2–C3–C4	116.97(17)
C2–C3–H3	121.5
C4–C3–H3	121.5
C5–C4–C3	121.31(17)
C5–C4–H4	119.3
C3–C4–H4	119.3
C6–C5–C4	121.29(16)
C6–C5–H5	119.4
C4–C5–H5	119.4
C7–C6–C5	117.24(17)
C7–C6–H6	121.4
C5–C6–H6	121.4
C6–C7–C2	121.51(16)
C6–C7–C8	130.04(15)
C2–C7–C8	108.44(14)
O2–C8–N1	125.07(16)
O2–C8–C7	129.33(15)
N1–C8–C7	105.61(14)
N1–C9–C10	112.80(14)
N1–C9–H9A	109.0
C10–C9–H9A	109.0
N1–C9–H9B	109.0
C10–C9–H9B	109.0
H9A–C9–H9B	107.8
C11–C10–C9	113.50(13)
C11–C10–H10A	108.9
C9–C10–H10A	108.9
C11–C10–H10B	108.9
C9–C10–H10B	108.9
H10A–C10–H10B	107.7
O3–C11–C10	106.54(13)
O3–C11–H11A	110.4
C10–C11–H11A	110.4
O3–C11–H11B	110.4
C10–C11–H11B	110.4
H11A–C11–H11B	108.6
O4–C12–O3	124.17(14)
O4–C12–C13	124.30(15)
O3–C12–C13	111.51(13)
C14–C13–C18	119.61(15)
C14–C13–C12	119.10(14)
C18–C13–C12	121.01(14)
C15–C14–C13	120.54(16)
C15–C14–H14	119.7
C13–C14–H14	119.7
C16–C15–C14	119.91(16)
C16–C15–H15	120.0
C14–C15–H15	120.0
C15–C16–C17	120.15(16)
C15–C16–H16	119.9
C17–C16–H16	119.9
C16–C17–C18	120.96(16)
C16–C17–H17	119.5
C18–C17–H17	119.5
C17–C18–C13	118.82(15)

C17–C18–C19	118.78(15)
C13–C18–C19	122.37(14)
N2–C19–O5	128.29(16)
N2–C19–C18	119.36(15)
O5–C19–C18	112.35(14)
O5–C20–C21	109.17(15)
O5–C20–H20A	109.8
C21–C20–H20A	109.8
O5–C20–H20B	109.8
C21–C20–H20B	109.8
H20A–C20–H20B	108.3
C20–C21–C22	108.08(16)
C20–C21–H21A	110.1
C22–C21–H21A	110.1
C20–C21–H21B	110.1
C22–C21–H21B	110.1
H21A–C21–H21B	108.4
N2–C22–C21	113.94(16)
N2–C22–H22A	108.8
C21–C22–H22A	108.8
N2–C22–H22B	108.8
C21–C22–H22B	108.8
H22A–C22–H22B	107.7

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	33(1)	33(1)	29(1)	−11(1)	6(1)	−7(1)
O2	32(1)	38(1)	22(1)	−7(1)	2(1)	−6(1)
O3	23(1)	21(1)	22(1)	−2(1)	1(1)	0(1)
O4	31(1)	21(1)	27(1)	1(1)	−2(1)	3(1)
O5	37(1)	27(1)	22(1)	0(1)	8(1)	−1(1)
N1	26(1)	23(1)	20(1)	−3(1)	4(1)	−2(1)
N2	35(1)	26(1)	26(1)	−3(1)	4(1)	−1(1)
C1	28(1)	21(1)	21(1)	2(1)	5(1)	−4(1)
C2	31(1)	20(1)	20(1)	2(1)	8(1)	−3(1)
C3	30(1)	28(1)	28(1)	6(1)	4(1)	−2(1)
C4	31(1)	31(1)	36(1)	11(1)	11(1)	4(1)
C5	45(1)	28(1)	31(1)	4(1)	18(1)	8(1)
C6	41(1)	26(1)	26(1)	0(1)	11(1)	0(1)
C7	32(1)	23(1)	19(1)	4(1)	7(1)	−1(1)
C8	32(1)	23(1)	19(1)	1(1)	6(1)	−5(1)
C9	26(1)	22(1)	27(1)	−2(1)	4(1)	1(1)
C10	25(1)	26(1)	22(1)	−5(1)	5(1)	−2(1)
C11	23(1)	27(1)	19(1)	1(1)	1(1)	−1(1)
C12	20(1)	22(1)	22(1)	−1(1)	5(1)	−1(1)
C13	21(1)	23(1)	20(1)	0(1)	5(1)	3(1)
C14	24(1)	24(1)	27(1)	0(1)	5(1)	2(1)
C15	32(1)	28(1)	27(1)	7(1)	7(1)	6(1)
C16	31(1)	35(1)	21(1)	4(1)	1(1)	6(1)
C17	27(1)	31(1)	24(1)	−4(1)	2(1)	0(1)
C18	23(1)	25(1)	22(1)	−3(1)	4(1)	2(1)
C19	22(1)	26(1)	21(1)	−3(1)	2(1)	−2(1)
C20	46(1)	34(1)	28(1)	7(1)	9(1)	1(1)
C21	54(1)	30(1)	41(1)	5(1)	12(1)	−5(1)
C22	47(1)	24(1)	40(1)	−3(1)	5(1)	−1(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	−1735	5807	7792	34	1
H4	−2298	7444	8868	38	1
H5	−1521	8797	10265	40	1
H6	−154	8540	10658	36	1
H9A	1265	3929	8120	30	1
H9B	1801	4896	9033	30	1
H10A	2156	5241	7316	29	1
H10B	1298	5766	6790	29	1
H11A	2106	7834	7167	28	1
H11B	1494	7882	7947	28	1
H14	2953	6254	10656	30	1
H15	3749	5939	12398	34	1
H16	4611	7786	13164	36	1
H17	4685	9944	12198	33	1
H20A	3260	12149	8338	43	1
H20B	4030	11920	7873	43	1
H21A	4076	14240	8748	50	1
H21B	4764	13239	9390	50	1
H22A	4191	14144	10742	45	1
H22B	3340	13901	10033	45	1

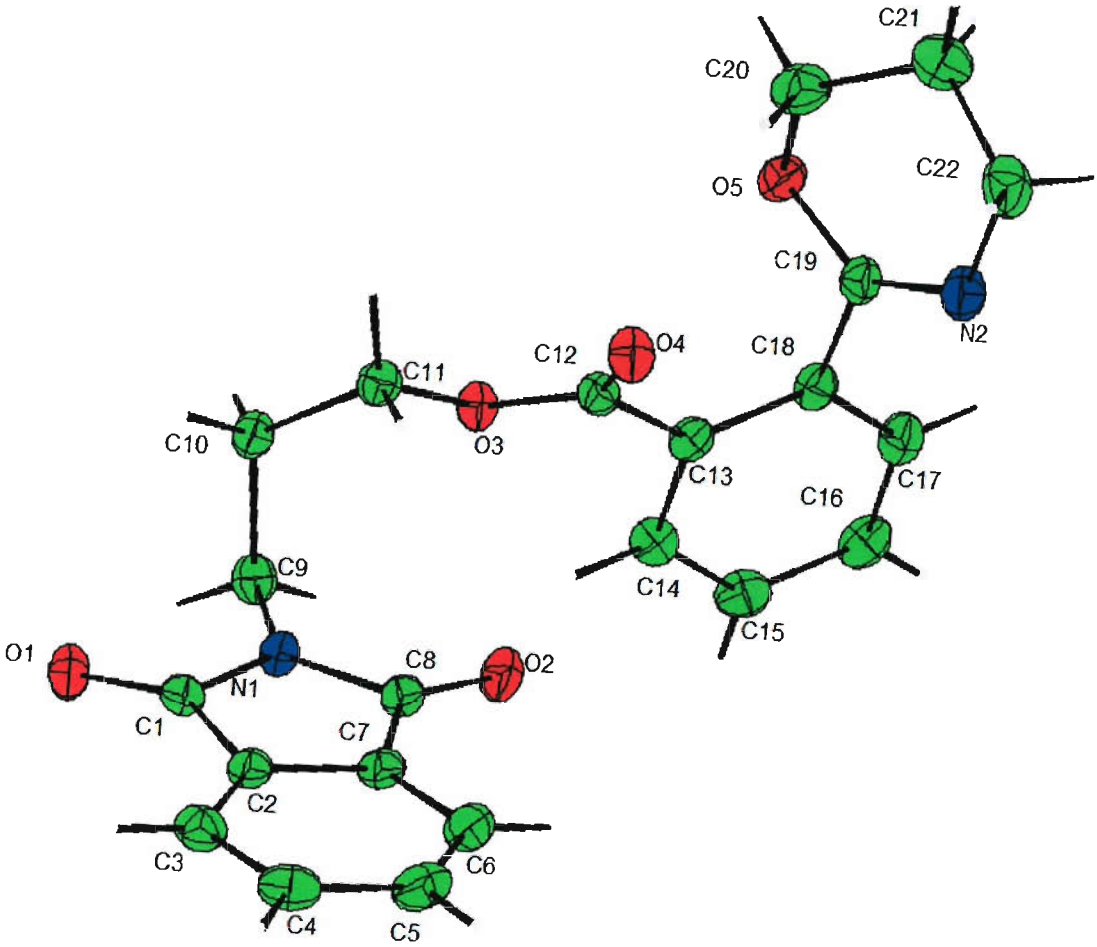
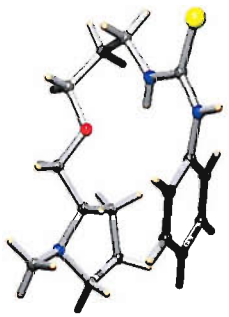

C21
C20
C22
O5
C19
N2
C18
C12
O4
C11
O3
C10
C13
C17
C16
C9
C14
C15
O1
C8
O2
N1
C1
C7
C2
C3
C6
C4
C5

Table 1. Crystal data and structure refinement details.



Identification code	**2007sot0346 (AC4818–88)**
Empirical formula	$C_{16}H_{25}N_3OS$
Formula weight	307.45
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	*C*2
Unit cell dimensions	a = 21.9260(4) Å
	b = 10.0530(2) Å β = 112.1693(10)°
	c = 16.1041(3) Å
Volume	3287.28(11) Å^3
Z	8
Density (calculated)	1.242 Mg / m^3
Absorption coefficient	0.200 mm^{-1}
F(000)	1328
Crystal	Fragment; Colourless
Crystal size	0.25 × 0.07 × 0.05 mm^3
θ range for data collection	3.24 – 27.48°
Index ranges	$-28 \le h \le 28$, $-13 \le k \le 12$, $-20 \le l \le 20$
Reflections collected	19596
Independent reflections	7038 [R_{int} = 0.0518]
Completeness to θ = 27.48°	99.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9842 and 0.9510
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7038 / 28 / 400
Goodness-of-fit on F^2	1.063
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0595, *wR2* = 0.1101
R indices (all data)	*R1* = 0.0801, *wR2* = 0.1213
Absolute structure parameter	0.15(9)
Largest diff. peak and hole	0.287 and –0.283 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. The -CH_2-O-CH_2-CH_2-CH_2- chain of the 1st molecule is disordered over 2 configurations

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	952(2)	−1985(4)	7276(2)	32(1)	1
C2	1032(2)	−635(5)	7469(3)	42(1)	1
C3	1655(2)	−71(4)	7788(2)	42(1)	1
C4	2193(2)	−854(4)	7926(2)	38(1)	1
C5	2123(2)	−2204(4)	7738(2)	30(1)	1
C6	1501(2)	−2756(4)	7409(2)	25(1)	1
C7	1163(2)	−5152(4)	7375(2)	27(1)	1
N2A	917(19)	−4920(40)	8054(15)	23(3)	0.468(4)
C8A	715(11)	−5960(20)	8525(7)	29(1)	0.468(4)
C9A	557(3)	−5420(7)	9304(4)	28(1)	0.468(4)
C10A	1142(4)	−4920(7)	10087(4)	30(1)	0.468(4)
O1A	1380(3)	−3702(6)	9858(5)	29(1)	0.468(4)
C11A	1092(18)	−2554(9)	10080(30)	44(3)	0.468(4)
N2B	1014(16)	−4940(30)	8068(14)	23(3)	0.532(4)
C8B	717(9)	−5985(19)	8425(6)	29(1)	0.532(4)
C9B	945(3)	−5915(5)	9441(4)	28(1)	0.532(4)
C10B	748(3)	−4678(5)	9803(4)	30(1)	0.532(4)
O1B	1057(3)	−3542(5)	9592(4)	29(1)	0.532(4)
C11B	983(16)	−2366(9)	10040(20)	44(3)	0.532(4)
C12	1407(2)	−1319(4)	9854(2)	36(1)	1
C13	2151(2)	−1378(4)	10339(3)	45(1)	1
C14	2360(2)	43(4)	10674(3)	42(1)	1
C15	1752(2)	872(4)	10198(2)	29(1)	1
C16	585(2)	469(5)	9500(3)	49(1)	1
C17	−1903(2)	−1862(4)	7411(2)	32(1)	1
C18	−1984(2)	−3202(4)	7207(3)	45(1)	1
C19	−1458(3)	−3995(4)	7283(3)	51(1)	1
C20	−835(2)	−3450(5)	7560(3)	47(1)	1
C21	−739(2)	−2104(4)	7767(2)	32(1)	1
C22	−1275(2)	−1314(4)	7711(2)	24(1)	1
C23	−999(2)	1080(4)	7685(2)	22(1)	1
N5	−875(1)	889(3)	6936(2)	23(1)	1
C24	−749(2)	1983(3)	6425(2)	27(1)	1
C25	−539(2)	1493(3)	5678(2)	27(1)	1
C26	−1054(2)	719(3)	4944(2)	29(1)	1
O2	−1156(1)	−524(2)	5302(1)	29(1)	1
C27	−1557(2)	−1426(3)	4639(2)	25(1)	1
C28	−1457(2)	−2780(4)	5079(2)	24(1)	1
C29	−743(2)	−3262(4)	5404(2)	32(1)	1
C30	−790(2)	−4782(4)	5392(3)	38(1)	1

C31	−1529(2)	−5068(4)	4993(2)	30(1)	1
C32	−2523(2)	−3805(4)	4228(2)	36(1)	1
N1	1437(1)	−4116(3)	7104(2)	29(1)	1
N3	1217(1)	−46(3)	10136(2)	29(1)	1
N4	−1184(1)	23(3)	8041(2)	26(1)	1
N6	−1813(1)	−3860(3)	4475(2)	24(1)	1
S1	1094(1)	−6640(1)	6866(1)	37(1)	1
S2	−945(1)	2589(1)	8173(1)	28(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C6	1.378(5)	C14–C15	1.512(5)
C1–C2	1.388(6)	C15–N3	1.467(4)
C2–C3	1.385(6)	C16–N3	1.471(5)
C3–C4	1.365(6)	C17–C18	1.383(5)
C4–C5	1.387(5)	C17–C22	1.390(5)
C5–C6	1.379(5)	C18–C19	1.370(7)
C6–N1	1.442(5)	C19–C20	1.380(7)
C7–N2B	1.293(17)	C20–C21	1.391(6)
C7–N1	1.354(4)	C21–C22	1.392(5)
C7–N2A	1.41(2)	C22–N4	1.431(4)
C7–S1	1.685(4)	C23–N4	1.341(4)
N2A–C8A	1.459(4)	C23–N5	1.347(4)
C8A–C9A	1.522(6)	C23–S2	1.693(4)
C9A–C10A	1.506(5)	N5–C24	1.461(3)
C10A–O1A	1.432(4)	C24–C25	1.523(4)
O1A–C11A	1.423(6)	C25–C26	1.506(4)
C11A–C12	1.530(14)	C26–O2	1.429(3)
N2B–C8B	1.459(4)	O2–C27	1.423(4)
C8B–C9B	1.521(6)	C27–C28	1.512(5)
C9B–C10B	1.505(5)	C28–N6	1.470(4)
C10B–O1B	1.432(4)	C28–C29	1.529(5)
O1B–C11B	1.423(6)	C29–C30	1.531(5)
C11B–C12	1.505(13)	C30–C31	1.528(5)
C12–N3	1.470(5)	C31–N6	1.472(4)
C12–C13	1.520(6)	C32–N6	1.455(4)
C13–C14	1.535(6)		

C6–C1–C2	119.1(4)	C11A–O1A–C10A	113.0(5)
C3–C2–C1	120.4(4)	O1A–C11A–C12	108.4(10)
C4–C3–C2	119.6(4)	C7–N2B–C8B	121(2)
C3–C4–C5	120.7(4)	N2B–C8B–C9B	112.1(7)
C6–C5–C4	119.3(4)	C10B–C9B–C8B	115.5(7)
C1–C6–C5	120.8(4)	O1B–C10B–C9B	109.6(4)
C1–C6–N1	120.9(3)	C11B–O1B–C10B	112.9(5)
C5–C6–N1	117.9(3)	O1B–C11B–C12	106.6(8)
N2B–C7–N1	116.1(14)	N3–C12–C11B	106.2(4)
N1–C7–N2A	117.8(15)	N3–C12–C13	104.5(3)
N2B–C7–S1	124.0(14)	C11B–C12–C13	119.7(14)
N1–C7–S1	119.7(3)	N3–C12–C11A	115.3(5)
N2A–C7–S1	122.5(15)	C13–C12–C11A	109.9(15)
C7–N2A–C8A	124(3)	C12–C13–C14	105.3(3)
N2A–C8A–C9A	112.2(7)	C15–C14–C13	104.2(3)
C10A–C9A–C8A	115.0(7)	N3–C15–C14	102.6(3)
O1A–C10A–C9A	110.4(4)	C18–C17–C22	119.4(4)

C19–C18–C17	121.1(4)	O2–C27–C28	106.4(2)
C18–C19–C20	119.8(4)	N6–C28–C27	114.1(2)
C19–C20–C21	120.3(4)	N6–C28–C29	102.2(3)
C20–C21–C22	119.5(4)	C27–C28–C29	113.2(3)
C17–C22–C21	119.9(4)	C28–C29–C30	104.9(3)
C17–C22–N4	118.7(3)	C31–C30–C29	104.4(3)
C21–C22–N4	121.1(3)	N6–C31–C30	103.8(3)
N4–C23–N5	117.8(3)	C7–N1–C6	128.2(3)
N4–C23–S2	119.4(2)	C15–N3–C12	104.8(3)
N5–C23–S2	122.8(3)	C15–N3–C16	110.2(3)
C23–N5–C24	122.8(3)	C12–N3–C16	113.3(3)
N5–C24–C25	112.2(3)	C23–N4–C22	127.3(3)
C26–C25–C24	115.2(3)	C32–N6–C28	113.6(3)
O2–C26–C25	108.7(2)	C32–N6–C31	111.5(3)
C27–O2–C26	113.7(2)	C28–N6–C31	103.2(2)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	29(2)	46(3)	21(2)	5(2)	10(1)	1(2)
C2	61(3)	43(3)	26(2)	12(2)	23(2)	20(2)
C3	82(3)	24(2)	28(2)	2(2)	29(2)	−5(2)
C4	52(2)	36(2)	24(2)	1(2)	12(2)	−18(2)
C5	33(2)	33(2)	22(2)	7(2)	10(1)	−4(2)
C6	32(2)	26(2)	18(2)	2(1)	10(1)	−6(1)
C7	24(2)	29(2)	23(2)	0(2)	4(1)	−6(1)
N2A	22(8)	22(2)	26(2)	−2(1)	10(3)	−7(4)
C8A	35(2)	25(2)	32(2)	0(2)	20(2)	−5(2)
C9A	28(3)	29(3)	30(2)	4(2)	15(3)	−7(2)
C10A	43(4)	26(3)	30(3)	−2(2)	22(3)	−9(3)
O1A	39(3)	23(2)	35(3)	−8(2)	24(3)	−7(2)
C11A	66(9)	40(3)	41(3)	−14(4)	37(6)	−14(5)
N2B	22(8)	22(2)	26(2)	−2(1)	10(3)	−7(4)
C8B	35(2)	25(2)	32(2)	0(2)	20(2)	−5(2)
C9B	28(3)	29(3)	30(2)	4(2)	15(3)	−7(2)
C10B	43(4)	26(3)	30(3)	−2(2)	22(3)	−9(3)
O1B	39(3)	23(2)	35(3)	−8(2)	24(3)	−7(2)
C11B	66(9)	40(3)	41(3)	−14(4)	37(6)	−14(5)
C12	58(2)	32(2)	27(2)	−9(2)	27(2)	−10(2)
C13	60(3)	36(2)	51(2)	5(2)	35(2)	14(2)
C14	28(2)	50(3)	46(2)	−11(2)	11(2)	−1(2)
C15	36(2)	25(2)	30(2)	−4(2)	15(2)	−2(2)
C16	26(2)	79(4)	36(2)	−12(2)	6(2)	3(2)
C17	43(2)	29(2)	28(2)	1(2)	18(2)	−8(2)
C18	71(3)	33(3)	36(2)	−2(2)	26(2)	−27(2)
C19	109(4)	20(2)	30(2)	4(2)	31(2)	2(3)
C20	77(3)	37(3)	26(2)	9(2)	19(2)	26(2)
C21	39(2)	37(2)	21(2)	4(1)	11(2)	9(2)
C22	34(2)	22(2)	18(2)	1(1)	12(1)	−1(2)
C23	20(2)	23(2)	23(2)	0(1)	7(1)	−3(1)
N5	29(1)	18(2)	23(1)	1(1)	11(1)	−3(1)
C24	31(2)	25(2)	27(2)	2(1)	14(1)	−8(1)
C25	32(2)	26(2)	29(2)	0(1)	18(2)	−6(2)
C26	36(2)	29(2)	26(2)	0(2)	18(2)	−5(2)
O2	41(1)	26(2)	20(1)	−2(1)	13(1)	−11(1)
C27	29(2)	28(2)	20(2)	−4(1)	11(1)	1(2)
C28	27(2)	25(2)	21(2)	1(1)	10(1)	−3(1)
C29	24(2)	36(2)	34(2)	2(2)	7(2)	−5(2)
C30	35(2)	39(2)	35(2)	2(2)	9(2)	8(2)
C31	36(2)	30(2)	28(2)	−1(2)	15(2)	−4(2)

C32	26(2)	43(2)	39(2)	−2(2)	12(2)	−4(2)
N1	42(2)	27(2)	23(1)	−4(1)	18(1)	−11(1)
N3	28(2)	30(2)	29(1)	−6(1)	11(1)	−7(1)
N4	37(2)	22(2)	25(1)	−3(1)	18(1)	−4(1)
N6	21(1)	29(2)	24(1)	0(1)	8(1)	−1(1)
S1	49(1)	25(1)	36(1)	−7(1)	16(1)	−10(1)
S2	34(1)	24(1)	30(1)	−5(1)	16(1)	−5(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

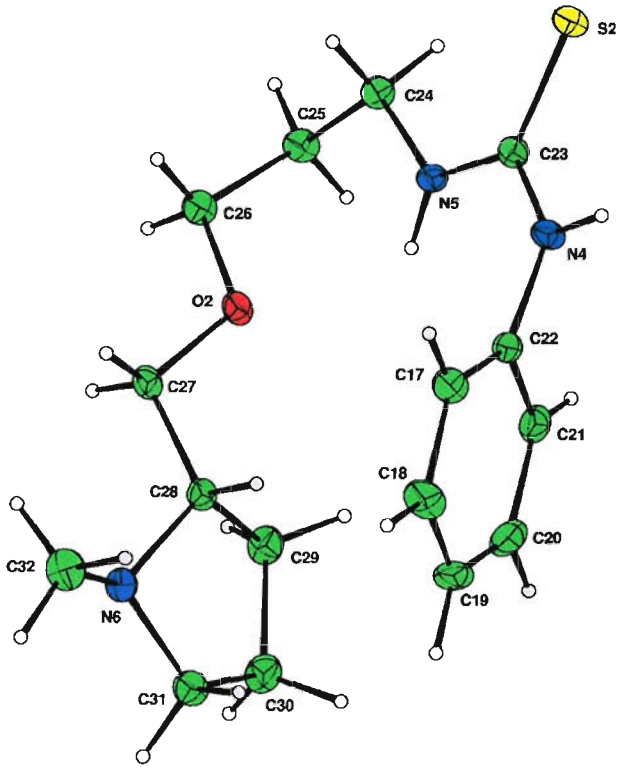
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	525	−2371	7055	38	1
H2	658	−94	7381	50	1
H3	1707	855	7911	50	1
H4	2620	−470	8153	45	1
H5	2499	−2744	7834	36	1
H2A	883	−4085	8203	28	0.468(4)
H8A1	1073	−6627	8754	34	0.468(4)
H8A2	321	−6417	8097	34	0.468(4)
H9A1	237	−4683	9080	33	0.468(4)
H9A2	341	−6132	9519	33	0.468(4)
H10A	1015	−4772	10607	36	0.468(4)
H10B	1497	−5596	10258	36	0.468(4)
H11A	1168	−2561	10725	53	0.468(4)
H11B	611	−2549	9731	53	0.468(4)
H2B	1094	−4160	8331	28	0.532(4)
H8B1	835	−6865	8252	34	0.532(4)
H8B2	232	−5896	8155	34	0.532(4)
H9B1	766	−6695	9648	33	0.532(4)
H9B2	1431	−5986	9701	33	0.532(4)
H10C	264	−4572	9537	36	0.532(4)
H10D	884	−4753	10462	36	0.532(4)
H11C	1125	−2525	10689	53	0.532(4)
H11D	516	−2079	9802	53	0.532(4)
H12	1299	−1294	9193	43	1
H13A	2364	−1664	9925	54	1
H13B	2273	−2009	10847	54	1
H14A	2491	99	11333	51	1
H14B	2733	342	10516	51	1
H15A	1743	1674	10550	35	1
H15B	1728	1147	9596	35	1
H16A	464	1269	9750	73	1
H16B	243	−209	9395	73	1
H16C	627	691	8932	73	1
H17	−2273	−1320	7348	39	1
H18	−2413	−3580	7011	54	1
H19	−1521	−4915	7144	61	1
H20	−469	−3998	7610	56	1
H21	−311	−1726	7946	39	1
H5A	−869	70	6746	28	1
H24A	−399	2560	6836	32	1
H24B	−1154	2526	6161	32	1

H25A	−409	2271	5406	33	1
H25B	−145	923	5947	33	1
H26A	−1471	1228	4712	34	1
H26B	−906	565	4443	34	1
H27A	−1424	−1439	4116	30	1
H27B	−2026	−1160	4433	30	1
H28	−1598	−2745	5601	29	1
H29A	−489	−2934	6017	39	1
H29B	−528	−2950	4998	39	1
H30A	−568	−5172	5016	45	1
H30B	−587	−5149	6006	45	1
H31A	−1625	−5860	4599	36	1
H31B	−1702	−5216	5470	36	1
H32A	−2725	−4607	3890	54	1
H32B	−2700	−3018	3855	54	1
H32C	−2623	−3753	4771	54	1
H1A	1596	−4296	6690	35	1
H4A	−1259	168	8533	31	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N2A–H2A···O1A	0.88	2.50	2.96(3)	113.0
N2B–H2B···O1B	0.88	2.15	2.80(3)	129.7
N5–H5A···O2	0.88	2.25	2.845(3)	124.9
N1–H1A···N6^{i}	0.88	2.15	2.967(4)	154.4
N4–H4A···N3^{ii}	0.88	2.12	2.965(4)	160.3

Symmetry transformations used to generate equivalent atoms:
(i) −x,y,−z+1 (ii) −x,y,−z+2



Second of the 2 independent molecules in the asymmetric unit; the first shows disorder of the $-CH_2-O-CH_2-CH_2-CH_2-$ chain.