Acid-catalysed hydroamination for targeted synthesis

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Abstract

Nitrogen-containing *spiro*-cyclic compounds mainly exist in naturally occurring compounds and pharmaceutical products. *Spiro*-cyclic frameworks are characterized by a unique special arrangement of their rings. The main challenge for the preparation of the spirocyclic motif is regio-controlled and stereo-controlled generation of a quaternary carbon center. Known methods for *spiro*-cyclic compounds include alkylation and cyclisation, condensation reactions, rearrangement reactions, metal-catalysed reactions, and ring closing metathesis are reviewed. Brønsted acid-catalysed hydroamination in the synthesis of pyrrolidines and *spiro*-pyrrolidines has been investigated in the Knight group for a long time. This methodology is of great convenience and can be efficient for targeted cyclic and *spiro*-cyclic compounds synthesis. A *tris*-piperidine structure, a potential lead compound for an ant-cancer drug, originates from a computer study carried out at Cancer Research UK. This small molecule was found which could bind to known sites present in various cancer cells.

This thesis describes the application of triflic acid-catalysed cyclisation in the synthesis of the targeted *spiro*-piperidines and *tris*-piperidines. In section one, an introduction of anticancer drugs and anticancer drugs discovery is given, together with the background of the current project. Section two summarizes known methods for *spiro*-cyclic compounds synthesis, and applications of triflic acid-catalysed cyclisation in the Knight group are reviewed in section three. Section four describes different synthetic routes towards the construction of amino-alkenes and cyclisation into *spiro*-cyclic compound *via* acid-catalysed hydroamination methodology. Attempts to synthesize 1,3-disubstituted-dithianes for the preparation of *spiro*-piperidine and *tris*-piperidine are also discussed. Chapter five contains the experimental data.

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Abbreviations

Abbreviations used in this thesis are listed below:

Ac	acetyl
APCI	atmosphere pressure chemical ionisation
br.	broad
Bn	benzy
Bz	benzoyl
BuLi	butyl lithium
cat.	catalytic
cy	cyclohexane
d	day(s)
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
dd	double doublet
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DNA	deoxyribonucleic acid
DPC	diphenyl chlorophosphine
DPPA	diphenylphosphoryl azide
dt	double triplet
DTBMP	2,6-di-tert-butyl-4-methylpyridine
eq.	equivalent(s)
g	gram
h	hour(s)

HTS	high throughput screening
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infra-red
J	coupling constant
m	multiplet
M	molar
Me	methyl
min.	minute(s)
ml	millilitre(s)
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
PABA	*p*-aminobenzoic acid
TBDMS	*ter*t-butyldimethylsilyl
ppm	parts per million
q	quartet
RCM	ring closing metathesis
RNA	ribonucleic acid
RRM	ring rearrangement metathesis
r.t.	room temperature
σ	sigma
s	singlet
t	triplet
THF	tetrahydrofuran

Section 1: Introduction

1.1 Cancer

Cancer is a large group of diseases characterized by abnormal cell growth. It has become the second leading cause of death worldwide. In 2012, there were 14.1 million new cancer cases and 8.2 million deaths resulted from cancers (Figure 1). It is estimated that the number of new cancer cases will rise to 22 million within the next decades.[1]

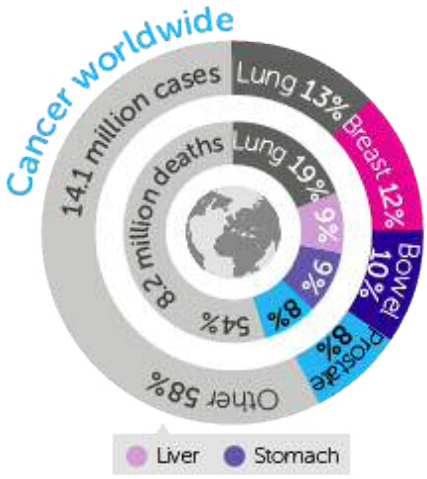


Figure 1. Worldwide cancer statistics in 2012 (Cancer research UK).

Cancer is caused by genetic alterations. In normal cells, the division and replication of cells is controlled by the activity of genes. When some genes are faulty, they can malfunction and cause excessive cell growth. Researchers found that genetic alterations were not only caused by mutation in oncogenes and tumor-suppressor genes, but also by epigenetic alterations.[2]

Cancer treatments have changed with the understanding of the underlying biological processes of neoplastic tumors. The most serious obstacle to cancer treatment is the complexity and plasticity of cancer cells. Depending on the type, location and grade of cancer, treatment of cancers will be different. Common primary treatments include surgery, chemotherapy, radiotherapy, hormonal therapy and targeted therapy. Surgery may play a role in prolongation of survival. However, the effectiveness of the treatment is often limited by metastasis. In combination with surgery, chemotherapy as a part of standardized treatment has proven useful in numerous cancers. The toxicity of the agents used in chemotherapy is still a problem, which needs to be considered.

Compared with many standard chemotherapy agents, targeted agents are more specific and less toxic. Survival rates of various types of cancer have dramatically improved as a result of the discovery and development of novel anti-cancer agents. Until now, there are more than ten targets, which have been developed in current cancer therapy (Figure 2).

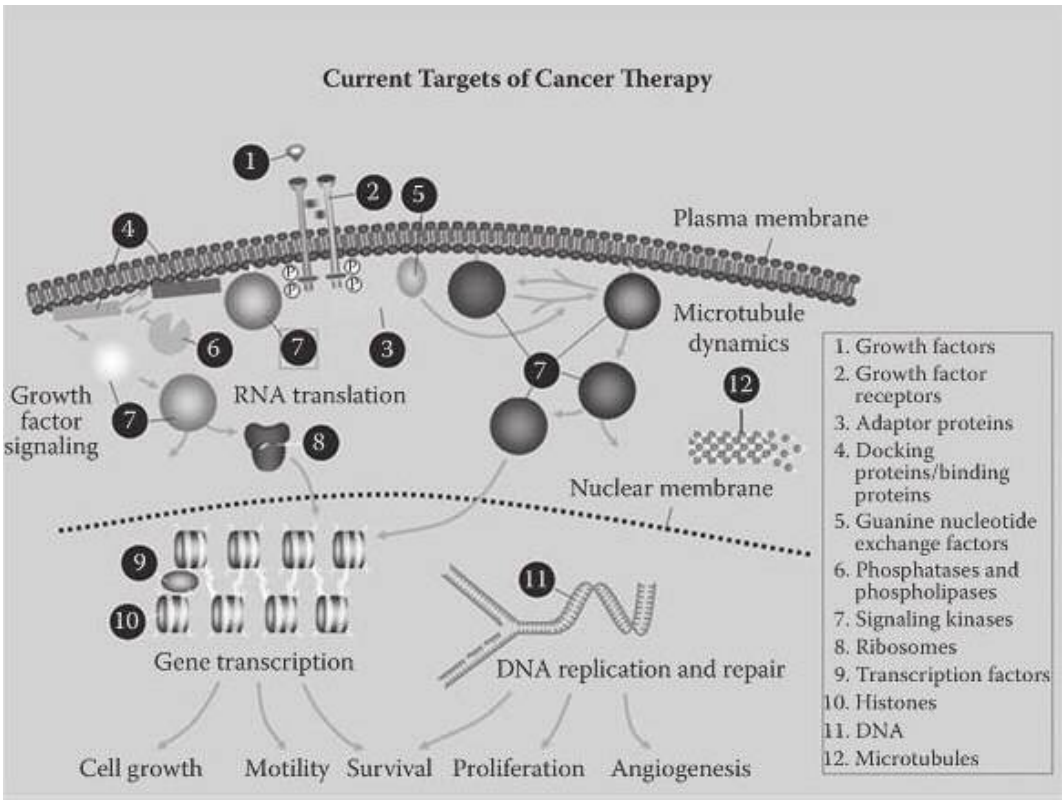


Figure 2. Various mechanism of action of anticancer agents.[3]

1.2 Anti-cancer drugs

Although various mechanisms of action of chemotherapeutic drugs have been described, the main aim of anticancer drugs is to interfere with tumor growth and progression. Agents that interact with deoxyribonucleic acid (DNA) processing are the largest and most diverse group of anticancer agents. Generally, there are seven classes of anticancer agents: alkylating agents, antimetabolites, anticancer antibiotics, natural products, miscellaneous agents, hormonal agents, and target-based agents.

Alkylating agents play an important role in cancer treatment. These are cytotoxic drugs that attach an alkyl group to biomacromolecules such as DNA, ribonucleic acid (RNA) and enzymes. The

alkylated part is essential for anticancer activity and changes to the carrier part can improve pharmacokinetics properties in the body (Figure 3).

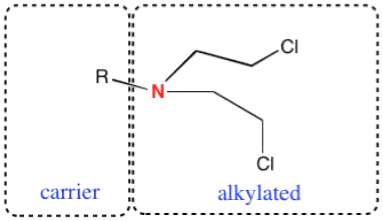


Figure 3. General structure of alkylating agents

The anticancer drug mechlorethamine is the prototype of alkylating agents. The successfully clinically used mechlorethamine promoted the later development of more alkylating agents including the nitrogen mustards, ethyleneamine derivatives, alkyl sulfonates, nitrosoureas and platinum coordination complexes. The usual reaction mechanism associated with such alkylating agents is first displacement of chloride to form an electrophilic aziridinium ion, which is then attacked by nucleophilic DNA bases (Figure 4**).** One of the other cross-link strands of DNA will repeat the reaction sequence, leading to DNA damage. This action works for all cells, but cancer cells are more sensitive because of their rapid dividing rate. Even though the newly developed anticancer drugs have been used to achieve better clinical outcomes, sometimes alkylating agents represent a unique treatment option for refractory tumors.[4]

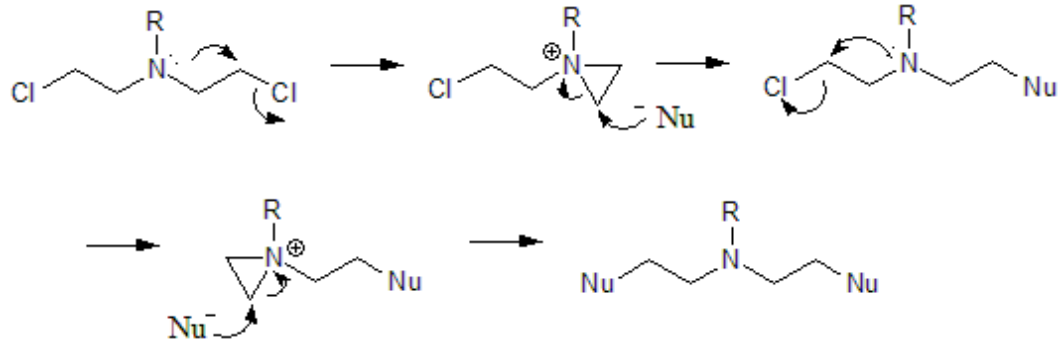


Figure 4. Reaction mechanism of alkylating agents

Antimetabolites have a similar chemical structure to naturally occurring molecules in DNA and RNA synthesis. Purine and pyrimidine analogues and anti-folate agents are widely used clinically to stop cell development and division (Figure 5). These are phase specific agents that only act on phase

S. These were thought to act on fast growing cancer cells, but cells in hair, bone marrow, and the gastrointestinal (GI) tract also respond and lead to unavoidable side effects. Moreover, the less active cells in older solid tumors make these types of agents less effective.

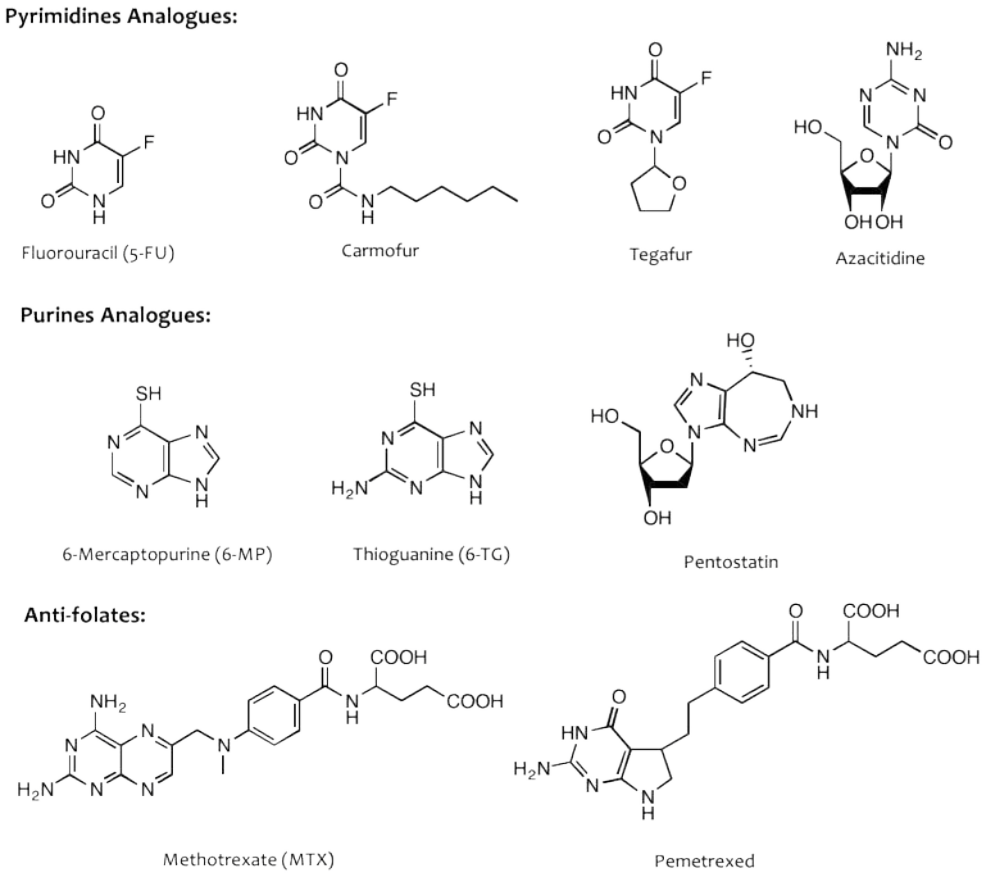
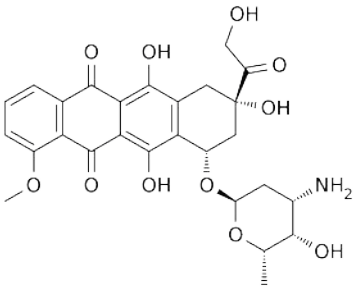


Figure 5. Clinically used antimetabolites.

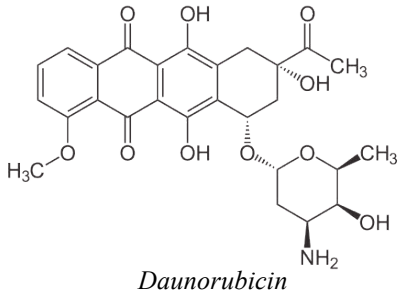
An antimetabolite may be an antibiotic. Sulfonamide antibiotics are a kind of *p*-aminobenzoic acid (PABA) inhibitor, which affect the production of folic acid by competitively inhibiting the enzymatic synthesis of PABA.

Many clinically used anticancer antibiotics have been derived from *Streptomyces* species. These antibiotics act by blocking the synthesis of DNA and RNA, or by affecting topoisomerase II. Compared with traditional chemotherapeutic agents, such antibiotics specifically bind to cancer cells to inhibit cell growth, while having limited effect on healthy cells and such antibiotics can also be used to treat or prevent infections during cancer treatment. Anticancer antibiotics have become an accepted treatment for some types of cancer. Doxorubicin and daunorubicin are the most important

and useful antibiotics that can be used to treat more than one type of cancer. Doxorubicin is mainly used to treat acute leukemia and the combination of daunorubicin and methotrexate may treat localized or disseminated gestational choriocarcinoma. Antiobiotics such as actinomycin D, epirubicin, bleomycins and mitomycin C have also been widely used in cancer treatment.

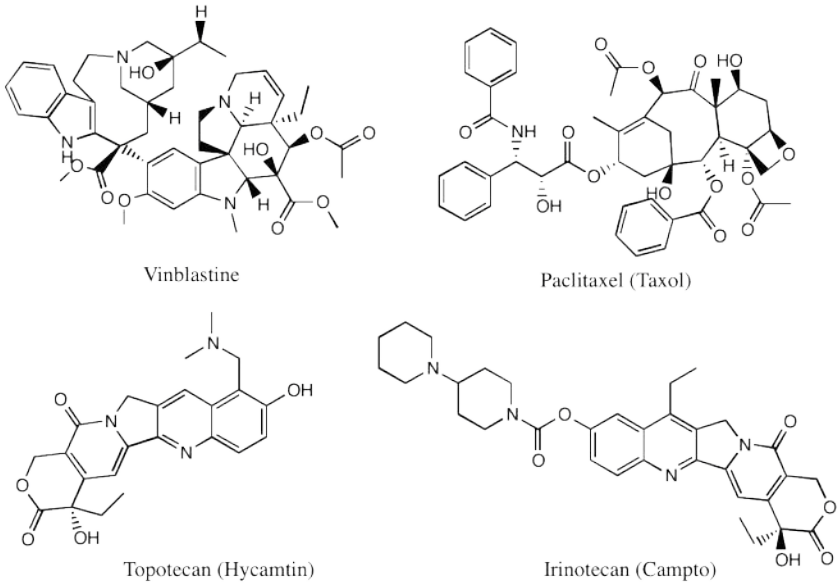


Doxorubicin



Daunorubicin

Natural products and their derivatives are a most important source of anticancer agents, either in their naturally occurring forms or as synthetically modified derivatives (Figure 6).[5] Much effort has been put into the isolation of lead compounds with potential bioactivity, chemical modification of effective constituents from natural products and the development of efficient total synthesis or semi-synthesis routes.



Vinblastine

Paclitaxel (Taxol)

Topotecan (Hycamtin)

Irinotecan (Campto)

Figure 6. Anticancer drugs from natural source.

Vinblastine is an important basic medicine that is on the list of essential medicines. It is a phase specific agent that arrests phase M in a cell cycle. Vinblastine works by inhibiting mitosis and has been used to treat numerous cancers including Hodgkin's lymphoma, bladder and brain cancer and non-small cell lung cancer. The combination of vinblastine, methotrexate and bleomycin has been reported effective in the treatment of early stage Hodgkin's lymphoma.[6] Paclitacel (Taxol®) is another well-known anticancer agent isolated from yew, which is currently used to treat lung and breast cancer. Two camptothecin analogues, topotecan and irinotecan, have been approved in cancer chemotherapy.[7] Resveratrol, a widely occurring natural phenol, was found to be a potential cancer chemo-preventive agent that can affect progression though S phase and G2 phase of a cell cycle.[8,9]

Hormones are substances made naturally in the body that stimulate and regulate body functions. Hormone-sensitive or hormone-dependent cancers, such as breast and prostate cancer, can be managed by blocking the effects of these or lowering their levels. Treatment of breast cancer in premenopausal and postmenopausal women is different due to the way that production of oestrogen is different. Aromatase inhibitors such as anastrozole, exemestane and letrozole are used to treat early breast cancer in postmenopausal women by blocking the production of oestrogen in body fat. For premenopausal women with breast cancer, luteinising hormone (LH) blockers act on a hormone produced in the pituitary gland to stop the production and release of oestrogen from ovaries. Ovary removal by surgery is another treatment option for premenopausal women. Hormone agents cannot only treat hormone sensitive or hormone dependent cancers, but also prevent such cancers from occurring and recurrence. A large international clinical trial showed that taking tamoxifen for 10 years after primary treatment of breast cancer leads to a noticeable reduction in cancer recurrence and death.[10]

In the past five years, 40% of the best-selling anticancer drugs are targeted agents. Targeted therapy seems more effective than traditional chemotherapy and provides more individualized and effective treatment for cancer patients. It interferes with specifically targeted molecules needed for tumor growth rather than with a rapidly dividing cell. G-protein-coupled receptors, protein kinases and monoclonal antibodies have become a very important group of anticancer drug targets.[11] Monoclonal antibodies are man-made versions of immune system proteins that can be designed to

attack specific cancer cells. Immunotherapy is another biologically targeted therapy that is designed to stimulate the body's immune system to attack cancer cells.

1.3 Anti-cancer drug discovery

Drug discovery is a time-consuming and expensive business. Generally, there are seven stages (Figure 7)**.** Target identification is the first and crucial step in the drug discovery process. It can take many years to build up supporting evidence before selecting a target in a drug discovery program. A good target should be efficacious, safe and also meet clinical and commercial needs. Genomics and proteomics technologies have been used to identify a biological target that presents a common feature of a particular disease. Newly developed phenotypic screening is successfully used to isolate human monoclonal antibodies (mAbs). Once a target is identified, this then needs to be validated. Target validation is a multifunctional process: it is often considered that drugs failing to reach the clinic are the result of sloppy early target validation.[12]

Figure 7. Drug discovery process

A hit is the output of a compound screening that can be defined as a compound with a desired activity. Based on the knowledge of the target, hits are selected from numerous molecular sources and chemical libraries. Nowadays, high throughput screening (HTS) methods are widely used to generate a series of compounds with the desired activity. A chemistry program is started after screening to improve both the potency and selectivity of the initial hit.

Hit series are generated and selected to further develop to make "druglike" molecules. A potential winner is finally generated from such a hit series. This is one of the most challenging processes in drug discovery due to the difficulties of making and designing a molecule that is "drug-like".

Lipinski's rule of five is a useful rule to predict drug-likeness. It is used to indicate if a certain compound with pharmacological or biological activity can be an orally active drug in humans. Good absorption or permeation of a compound is more likely when a particular molecule has less than five hydrogen bond donors, less than ten hydrogen bond acceptors, a molecular weight under 500 and a partition coefficient (LogP) value under five. Increasing molecular weight may lead to safety and tolerability issues. If there are two parameters are out of the range, poor solubility or permeability is considered likely.[13] The majority of clinically marketed drugs normally have molecular weights of less than 350 and LogP values of less than 3.[14] Ultrafast shape recognition (USR) software has been developed recently to help identify drug-like molecules that have beneficial biological properties. This newly developed technique is 1,400 times faster than other technique currently used in virtual screening for drug discovery.

The goal of lead optimization is to find a drug candidate that has the desired biological properties as well as good absorption and is effective and safe. Data related to efficacy, stability, bioavailability and toxicity also have to been tested. Combinations of rapid *in vivo* and *in vitro* drug metabolism and pharmacokinetics (DMPK) screening tools have been used in the development of compounds with acceptable DMPK parameters.[15] The most-performing compound will then be chosen to enter pre-clinical studies.

Combinatorial chemistry is a new techniques developed to create a large population of chemical libraries in a short time. It speeds up drug discovery. Numerous structurally different molecules will be screened for biological activity by high throughout screening or used for pharmacological assay.[16] Combinatorial chemistry was first used in syntheses of peptide libraries that might be active in regulating human physiological responses. Some polypeptide libraries were found to be useful in the treatment of cancer.[17] There is a natural product-like library that has been built that contains 2.81 million polycyclic compounds. These compounds will be used to explore biological pathways

by combining with chemical genetic assays and biological functions by reverse chemical genetic assays.[18]

An important aspect of natural products is to provide biodiversity. Plant-derived compounds have been an important source of clinically useful agents. One in four drugs used in the past 20 years is directly derived from plants, while another 25% are chemically altered natural products.[19] Compounds isolated from plants, marine flora and microorganisms can be lead compounds for further research.[20] More than 3000 plant species have been found that can be used in the treatment of cancer.[21] The taxoids such as Paclitaxel (Taxol®) and Docetaxel (Taxotere®) represented a novel class of antineoplastic drugs. Paclitaxel was isolated from the bark of the Pacific Yew, *Taxus brevifolia.* It is a cytoskeletal drug that interacts with tubulin. Unlike other tubulin-targeted drugs, paclitaxel stabilises microtubule polymer and prevent mitosis instead of inhibiting microtubule assembly.

The unique structure of taxol has attracted organic chemists for decades. Seven independent total syntheses have been reported by Holton[22], Nicolaou[23], Danishefsky[24], Wender[25], Kuwajima[26], Mukaiyama[27] and Takahashi[28] respectively. Wender described the shortest synthesis of taxol (37 steps) in a linear manner with ring construction in the order of A, B, C, and D (Figure 8).[29] The overall yield was only 0.4% and clearly has no commercial value.

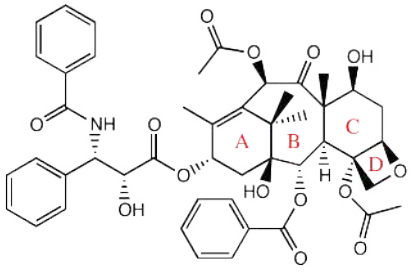
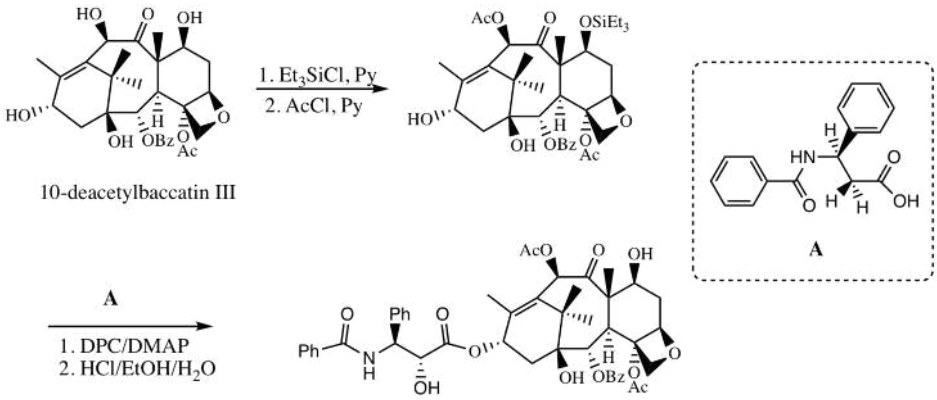


Figure 8. Paclitaxel

Commercial semi-synthesis of paclitaxel starts from the related yew metabolite, 10-deacetylbaccatin III. Taxol is produced through selectively protection of the hydroxyl on carbon 7, esterification of hydroxyl on carbon 10, side-chain addition and deprotection (Scheme 1).



Scheme 1. Semi-synthesis of taxol

The low water solubility (0.03 mg/ml) of paclitaxel limits its clinical use. The synthesis of natural compounds analogues could improve efficacy and reduce toxicity.[30] Docetaxel (Figure 9), an analogue of paclitaxel, was synthesized from extracts of the needles of the European yew tree. Two positions differ from paclitaxel, a hydroxyl group on C-10 and an ester group on the phenylpropionate side chain. The changing of the carbon 10 functional group leads to better water solubility of docetaxel. In clinical practice, docetaxel was proven to have greater benefits than paclitaxel in terms of survival and time to disease progression in the treatment of metastatic breast cancer.[31]

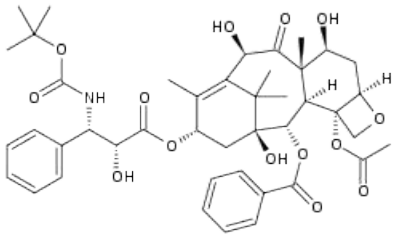


Figure 9. Structure of docetaxel

At an early stage of anticancer drug discovery, the conventional method is to scan thousands of compounds from natural sources that could represent the target. This approach is time-consuming and of low productivity. With the gradual understanding of the fundamental biochemistry of cancer cells, rational drug design approaches have been developed. It is relatively easy to find the structure of the target and then design a lead compound to fit this. Based on drug-receptor or drug-enzyme interactions, rational drug design begins with a hypothesis that a specific designed target may have

therapeutic value. The specific target should be a drug-like compound and the information of the therapeutic value may come from the disease linkage studies. Incorporation of gene expression technology and bioinformatics tools would be indispensable in the structure based drug design. Moreover, affinity for the target can be predicted before it is synthesized.

One successful example of rational drug design is the development of Imatinib (Glivec®), which is a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukemia (CML). A series of 2-phenylaminopyrimidines was identified as lead compounds by testing compound libraries *in vitro* (Figure 10). Structure-activity relationship (SAR) studies showed that the methyl substitution of the aniline-phenyl ring at C-6 position led to potent bioactivity, and the introduction of an *N*-methyl group to the piperazine improved the absorption, distribution, metabolism and excretion properties.[32]

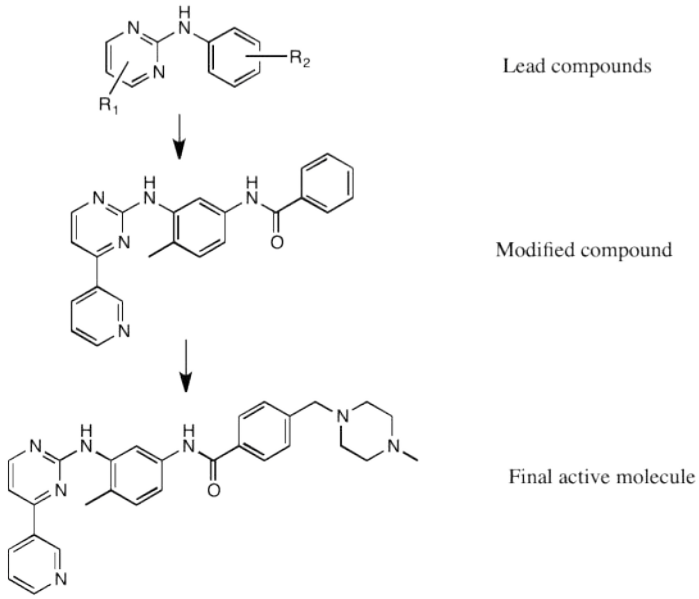


Figure 10. Discovery of imatinib.

Biological targets of currently used drugs may not be fully identified when the drug was originally developed. Drug repositioning is an attractive form of drug discovery. There are approximately 30% of newly approved drugs and vaccines resulted from drug repositioning. In order to get the maximum both clinical and commercial benefits from current available drugs, a comprehensive understanding of biological and pharmaceutical knowledge and certain mechanism-of-action of drugs is required.

Artemisinin (Figure 11), also known as Qinghaosu, is an example of drug repositioning. It was originally used as a standard treatment worldwide against *Plasmodium falciparum* malaria. The outstanding characteristics of artemisinin and its derivatives include rapid action, less significant side effects and less drug resistance. In addition to its antimalarial properties, artemisinin and its analogs have been found to be potentially inexpensive and effective cancer agents.[33] Hundreds of papers have reported this anticancer activity since 1992. Due to the different amount of intracellular free ions in cancer cells and normal cells, artemisinin and its analogs can selectively cause apoptosis in many cancer cell lines.[34] Moreover, artemisinin compounds have been found to have anti-angiogenic, anti-inflammatory, anti-metastasis and growth inhibition effects.[35] Other successful drug repositioning for anticancer applications include Itraconazole, Nelfinavir, Digoxin, Nitroxoline, Riluzole, Mycophenolic acid and Disulfiram.

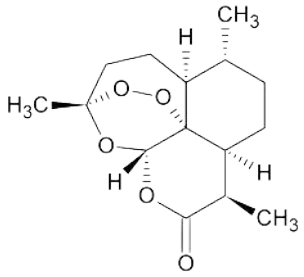
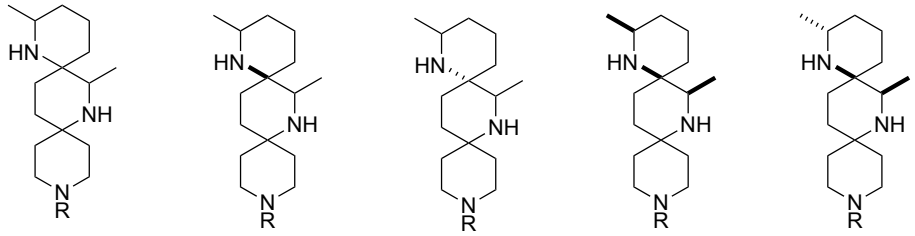


Figure 11. Artemisinin

Monoclonal antibodies play an important role in modern cancer treatment. About 40% of the best-selling anti-cancer drugs are monoclonal antibodies, which were discovered by basic research into the mechanism of generation of antibody diversity.[36] The greatest advantage of monoclonal antibodies is these molecules can be used equally in research, diagnose and the treatment of cancer.[37] The first approved monoclonal antibody treatment for cancer was Rituxan. It has been approved to treat a number of cancers including non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL) and rheumatoid arthritis (RA). The life saving drug Bevacizumab (Avastin) is the first clinically used angiogenesis inhibitor that slows the growth of new blood vessels by inhibiting vascular endothelial growth factor A (VEGF-A).

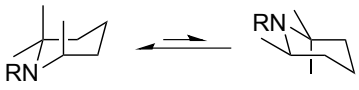
1.4 Background of current project

This project originates from a computer study carried out at Cancer Research UK, which was part of an extensive search aimed at identifying novel and previously untested structures that could become lead compounds in future efforts to obtain new treatments for cancers of any type using such small molecule therapy. The overall aim was to try to occupy previously unexplored areas of molecular space. This was achieved by taking known binding sites present in various cancer cells consisting of proteins with established structures and using the computer to generate molecules that bind reasonably strongly to such structures. In this way, the rather unusual *tris*-piperidine structure **1** was generated. Having two *spiro*-centres and three stereogenic carbons and hence eight possible stereoisomers, this satisfies exactly the aim of this computational study in thus proposing a completely novel structure.



1 **2** **3** **4** **5**

As yet, this structure or any derivatives have not been published; the compound came to the attention of Professor David Knight when he attended a lecture given by Professor Keith Jones, the Director of compound discovery at Cancer Research UK. Clearly, compound **1** presents a significant synthetic challenge; in addition, once the basic skeleton has been formed, the stereo-chemical aspects will have to be considered as well, as illustrated in structures **2-5.** An additional complication is that 2-substituted-piperidines tend to exist in conformations wherein such a group is positioned axially rather than the expected equatorial position, when the adjacent nitrogen is substituted as illustrated by the perhaps surprising equilibrium between structures **6** and **7** (scheme 2).



6 **7**

Scheme 2. Proposal equilibrium of substituted-piperidines

Section 2: Known methods for *spiro*-cyclic compound synthesis

Spiro compounds are molecules containing two rings connected with one shared atom (the *spiro* atom). Spirocyclic frameworks are characterized by a unique special arrangement of their rings. By adding functional groups in one or two rings, a broad diversity of structures can be achieved.

Azaspirocycles are nitrogen-containing spirocyclic compounds that mainly exist in naturally occurring compounds and pharmaceutical products (Figure 12). The 1-azaspiro[4.5]decane skeleton is found in cylindricines, lepadiformines, TAN1251 derivatives and lapidilectine B.[38] The 1-azaspiro[4.4]nonane skeleton was considered as a key intermediate for the total synthesis of (±)-cephalotaxine.[39] histrionicotoxin and nitraria alkaloids contain azaspiro[5.5]undecane skeletons and present valuable biological effects in drug discovery.

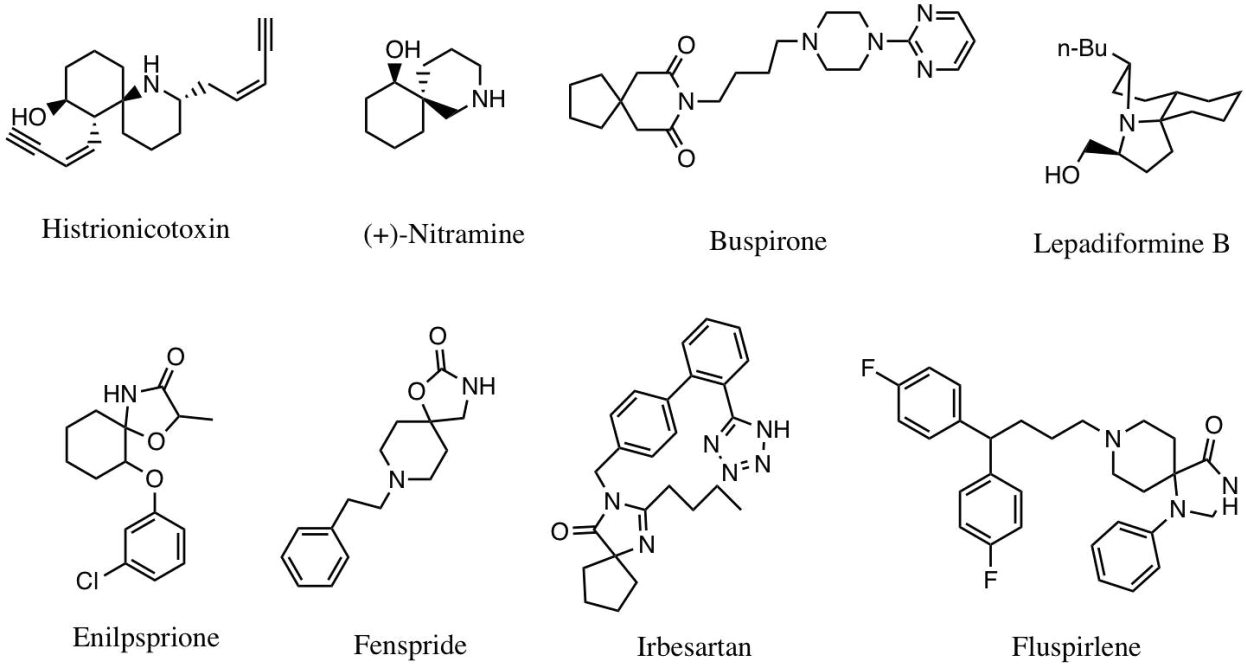


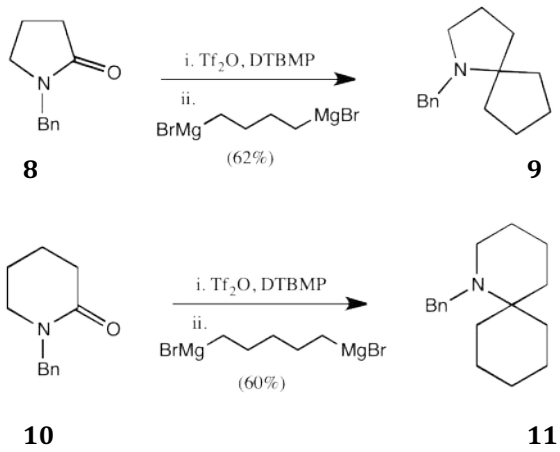
Figure 12. Natural occurring products containing azaspirocyclic skeleton

The main challenges for the preparation of spirocyclic motif include the region-controlled and stereo-controlled generation of quaternary carbon centers,[40] functional group incompatibilities and the addition of useful functionality into the newly formed ring system for further synthetic manipulation.[41] A number of synthetic methods have been described for the construction of spirocyclic ring systems. The common synthetic methodologies involve alkylation, rearrangement

reactions, ring expansion, metal catalysed cyclisation, radical cyclisation, cycloaddition, ring-closing metathesis and the cleavage of bridged ring systems.

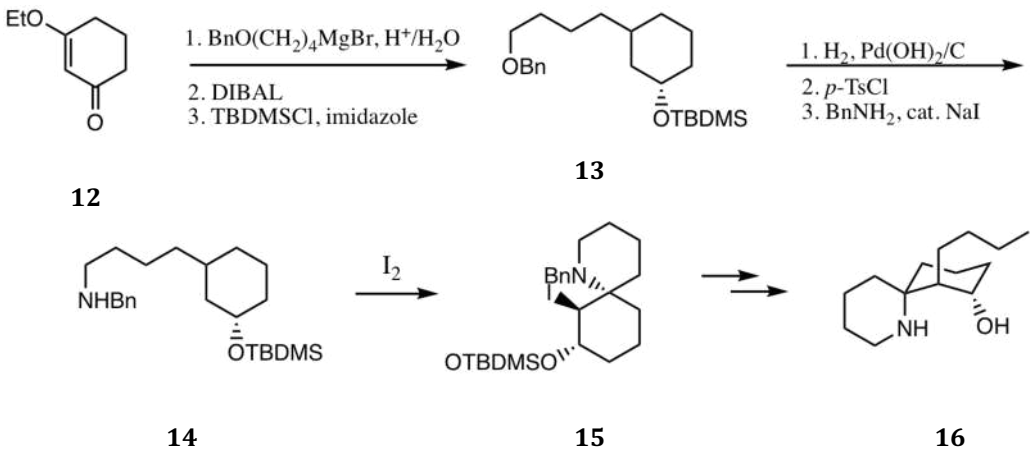
2.1 Alkylation and cyclisation

Alkylation provides an efficient way to form carbon-carbon bonds. Intramolecular alkylation to form the quaternary carbon is the most common method in the preparation of spirocyclic compounds. Alkylating agents can displace halide substituents (substitution reaction) or undergo Michael additions (1,4-addition) on a tertiary carbon to form a cycle. Xiao's group reported a one-pot reductive *bis*-alkylation of readily available lactams by organometallic reagents.[42] *Bis*-alkylation of lactam **8** with a double Grignard reagent afforded spirocyclic compound **9** in good yield (Scheme 3). This was also efficient for the formation of the larger ring system **11.**



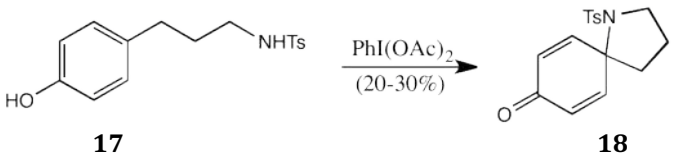
Scheme 3. Bi-alkylation approach to give 1-spirocycles

Iodocyclisation plays an important role in the synthesis of alicyclic and nitrogen-heterocyclic compounds, and can be conducted to give high levels of regio- and stereo-selective control. In a recent synthesis of the histrionicotoxin analogue **16,** the reaction of cyclisation precursor **14**, which was relatively easily prepared from cyclohexane-1,3-dione in around six steps, with excess iodine gave the spirocyclic framework **15** as a single diastereomer (Scheme 4). [43,44] This iodo-derivative could then be taken through to the target **16**.

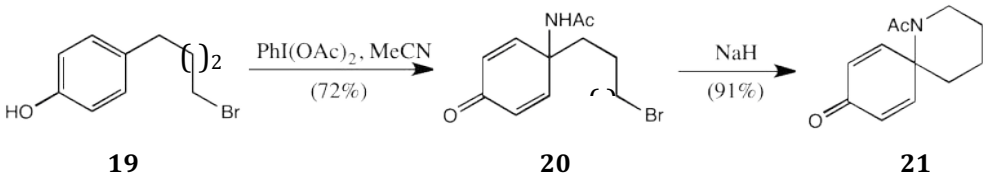


Scheme 4. Iodocyslisation in the synthesis of histrionicotoxin analogue

The oxidative spirocyclisation of phenolic primary amines[45] and secondary amines[46] with $PhI(OAc)_2$ (DIB) holds considerable potential in the synthesis of spirocyclic natural products such as cylindricine C. The DIB-mediated process was developed in the synthesis of spirocyclic compound **18** (Scheme 5). The major limitation of this approach was the poor yields obtained for azaspiro-[5.5]-undecanes.[47] This problem could be solved by further research. Cyclisation product **21** was obtained by bimolecular oxidative amidation of phenol **19,** which then underwent base-promoted cyclisation to give azaspiro- [5.5]-undecane **21** in 91% yield (Scheme 6).



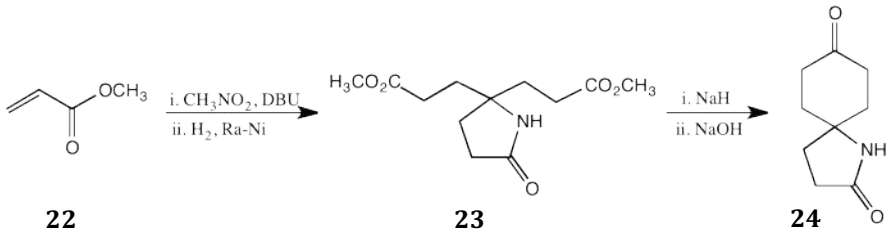
Scheme 5. Oxidative spirocyclisation



Scheme 6. 1-azaspiro-[5.5]-undecane synthesis

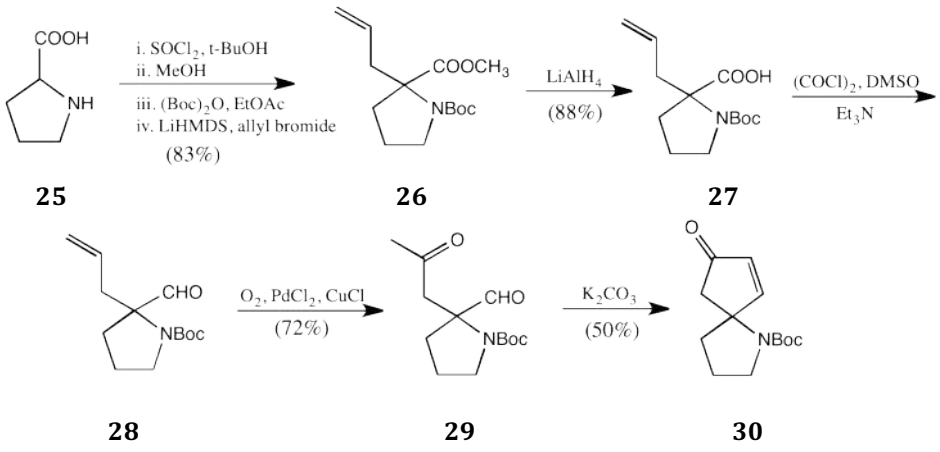
2.2 Condensation reaction

Intramolecular reactions such as Dieckmann and aldol condensations are useful in the formation of five- and six-membered rings. As shown in Scheme 7**,** *spiro*-lactam **24** was obtained by a triple 1,4-addition of nitromethane to methyl acrylate **22** in presence of excess DBU.[48] Reduction and ester-amide exchange proceeded smoothly to give reduced diester **23.** Dieckmann condensation of **23,** followed by basic hydrolysis and decarboxylation then gave the *spiro*-lactam **24** as an intermediate towards a synthesis of the potent immunosuppressant FR-901483(1).



Scheme 7. Dieckmann condensation

The intramolecular aldol condensation was worked in a similar way. The condensation of **29** in the presence of potassium carbonate afforded 1-azaspiro[4.4]non-8-en-7-one **30** in 50% yield (Scheme 8).[49]

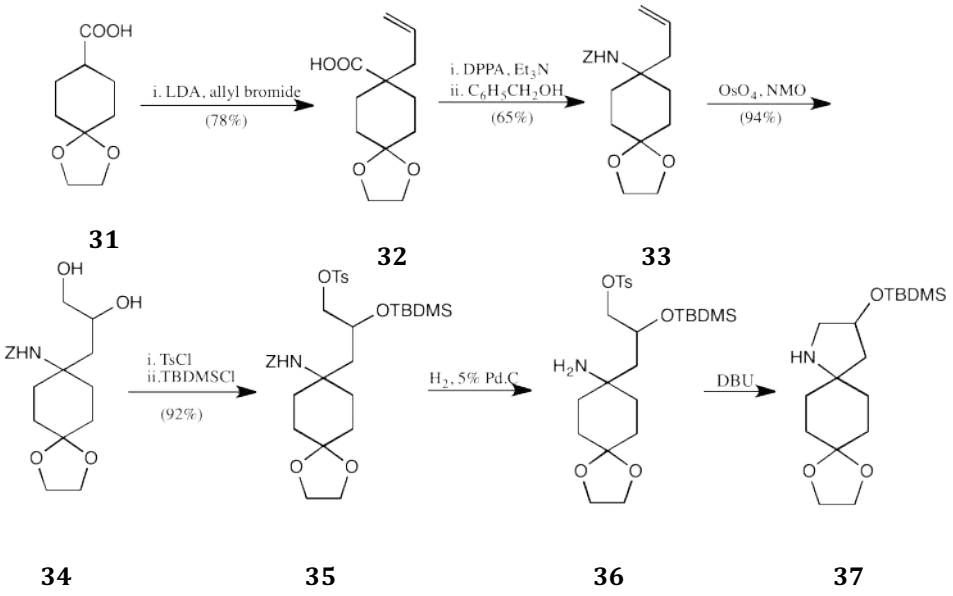


Scheme 8. intramolecular aldol condensation

2.3 Rearrangement reaction

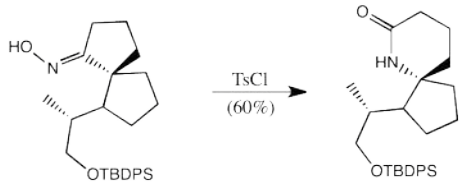
The rearrangement of the carbon skeleton of a molecular can be used to form a structural isomer of the original molecular. Beckmann, Curtius, Claisen, Piancatelli, sigmatropic and Schmidt rearrangements have been used in the preparation of azaspirocycles.

The Curtius rearrangement is a classic method of establishing a 3° stereocentre attached to an amine-derived functional group.[50] In Nagumo's route, the rearrangement of carboxylic acid **31** and N-alkylation were the key steps in the formation of 1-azaspirocyclic compound **37** (Scheme 9).[51] The amine group was expected to be more suitable carbamate than for cyclisation. The synthesis from cyclohexyl aldehyde was carried out using similar procedures by Liebowitz.[52]



Scheme 9. Curtius rearrangement and N-lkylation in the synthesis of 1-azaspirocycles.

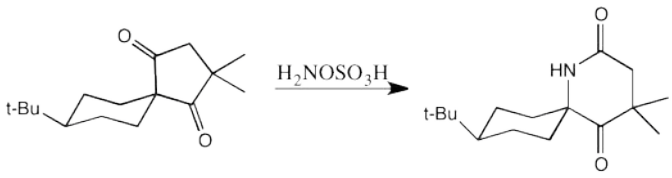
The acid-induced Beckmann rearrangement of oximes **38** to give *spiro*-bicyclic lactam **39** was reported by Pilli and de Sousa.[53] Due to the competitive fragmentation process, the rearrangement was proven to be best carried out by treatment of the oxime with tosyl chloride in pyridine at 0°C to make the oxime hydroxyl group into a good leaving group (Scheme 10).



38 **39**

Scheme 10. Beckmann rearrangement

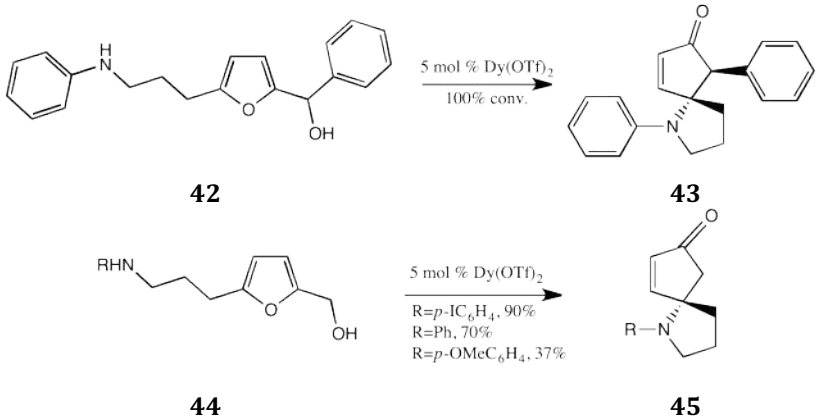
Another example of a Beckmann rearrangement was reported by Burnell. *Spiro*-lactam **41** was formed by treatment of carbocyclic *spiro*-ketone **40** with hydroxylamine-*O*-sulfonic acid in the presence of formic acid (Scheme 11).[54]



40 **41**

Scheme 11. Beckmann rearrangement

The intramolecular aza-Piancatelli rearrangement provided an efficient pathway to construct the tertiary carbon center bearing a nitrogen atom and formation of the spirocyclic ring in a single operation. Dysprosium(III) triflate-catalysed aza-Piancatelli rearrangement provided a method for the preparation of 1-azaspirocycles (Scheme 12).[55] Increasing the size of the R group increased the reaction time and resulted in a lower yield of the desired products.

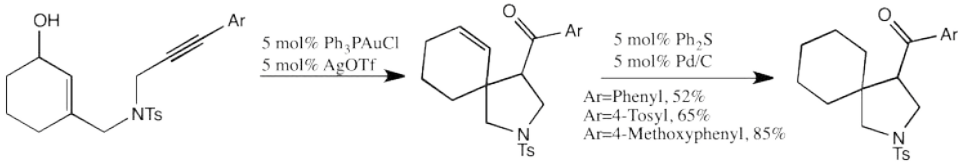


42 **43**

44 **45**

Scheme 12. The intramolecular aza-Piancatelli rearrangement

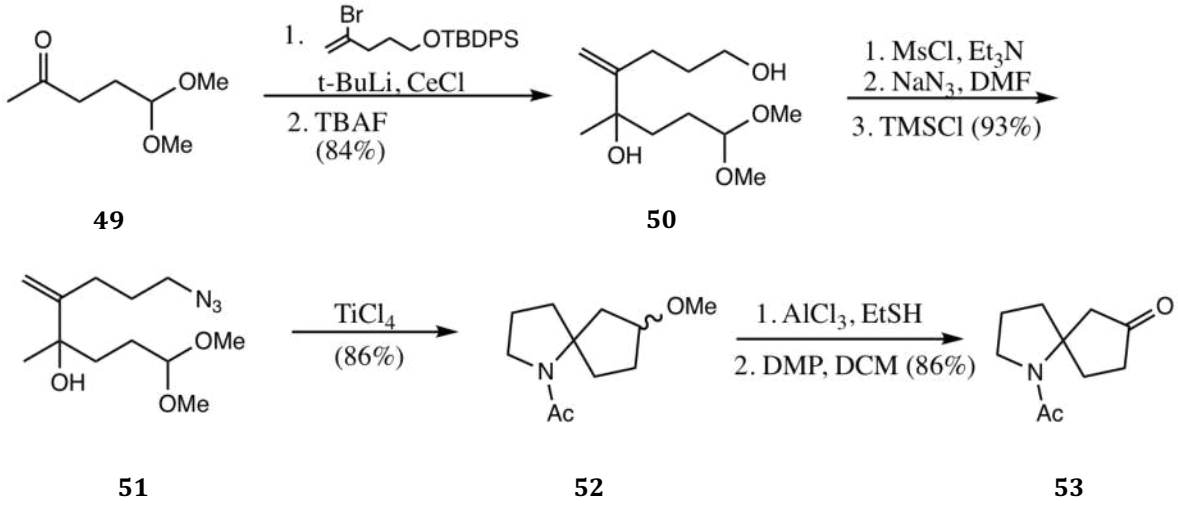
A [3.3]-sigmatropic rearrangement is an aliphatic Claisen rearrangement that can generate two stereogenic centers and a carbon-carbon double bond. The Yeh group reported a facile synthesis of spirocyclic ketones via a cationic allylic vinyl ether gold intermediate.[56] The hydroxyl group first attacked the gold-activated alkyne and was followed by Claisen rearrangement to give azaspirocycle **47** (Scheme 13). Due to the difficulty in separating the 1:1 diastereomeric mixture of **47,** saturated azaspirocycle **48** was obtained by hydrogenation.



46 **47** **48**

Scheme 13. [3.3] Sigmatropic rearrangement

A Prins-Pinacol rearrangement reaction was used as a key step for the construction of azaspiro[4.4]nonane (Scheme 14).[57]



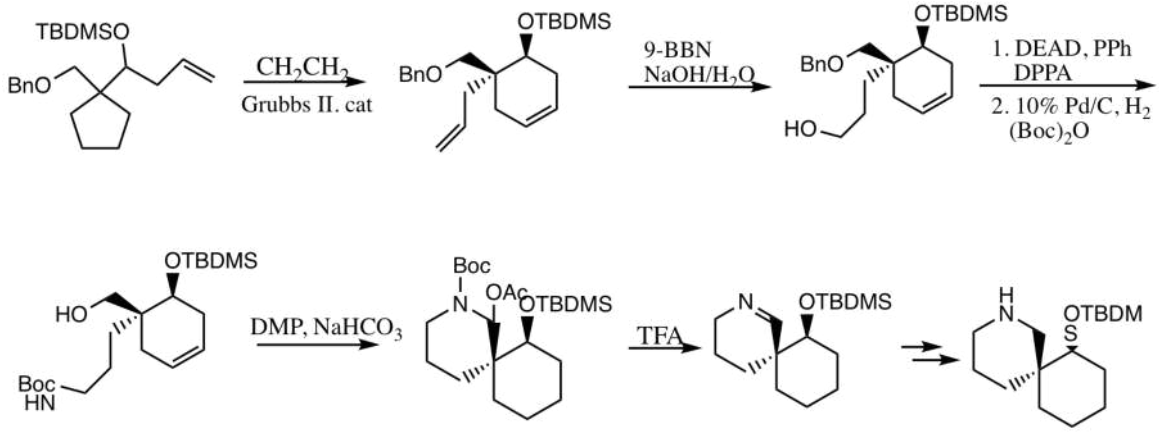
49 **50**

51 **52** **53**

Scheme 14. Prins-Pinacol rearrangement.

Ring-rearrangement metathesis (RRM) has been reported in the synthesis of cyclohexene derivatives. The conversion of a cyclic structure into a new cyclic product involves ring-closing and ring-opening steps. For the synthesis of nitramine, the major challenge is construction of the quaternary carbon center with the correct stereochemistry. In a total synthesis of (±)-nitramine **60**,

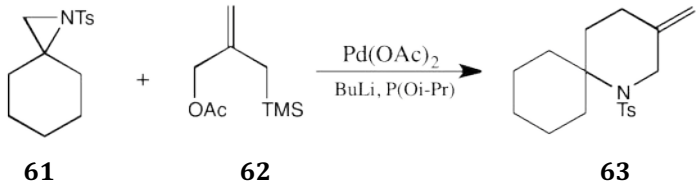
RRM can be an attractive approach to form two contiguous stereogenic centres in one step (Scheme 15).[58]



Scheme 15. Ring-rearrangement metathesis

2.4 Cycloaddition

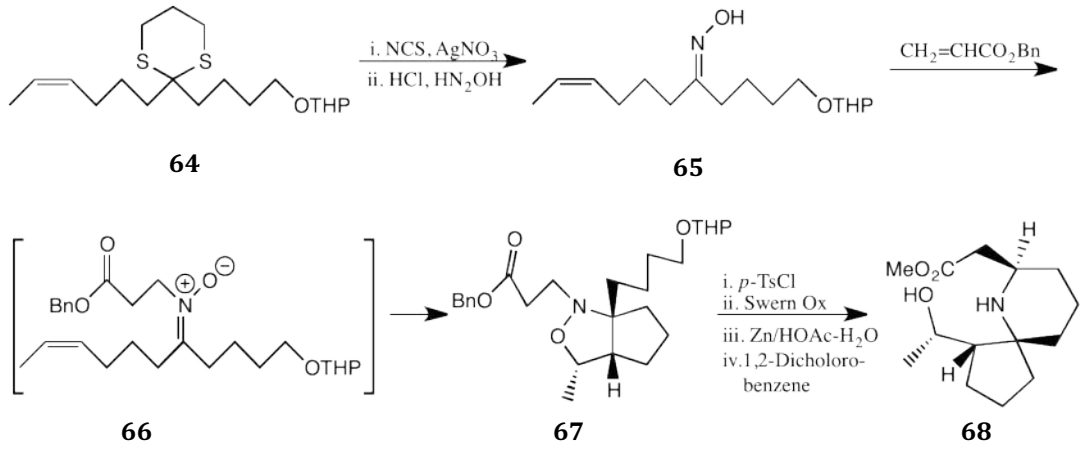
A few examples of cycloaddition have been used in the synthesis of azaspirocycles. A [3+3]-dipolar cycloaddition has been used in a formal total synthesis of 12*H*-HTX (Scheme 16).[59]



Scheme 16. Dipolar cycloaddition in the synthesis of 12*H*-HTX.

Based on studies by Grigg and co-workers of a series of inter- and intramolecular aza[3+2] cycloadditions,[60] Lee and Zhao used a similar cycloaddition reaction to set up the azaspiro core in pinnaic acid and halichorine.64 The addition of an oxime **64** to an alkene gave nitrone **65,** and then intramolecular cycloaddition of the nitrone afforded bicyclic compound **67** (Scheme 17). Spirocycle **68** was finally obtained via intramolecular Michael addition in overall 40% yield. The

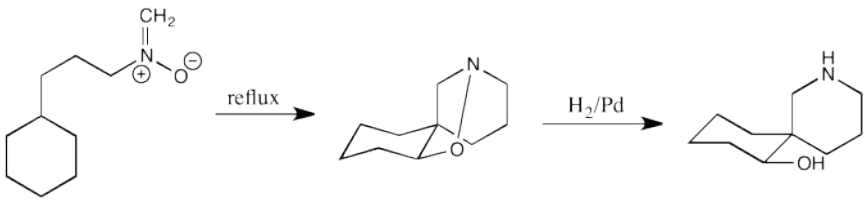
stereochemistry can be controlled in this step by the different olefin geometry.



64 **65** **66** **67** **68**

Scheme 17. Intramolecular aza[3+2] cycloadditions

Ketenes were reactive in various cycloaddtions. Snider and Cartaya-Marin demonstrated the utility of ketene in the preparation of (±)-nitramine, which was the first alkaloid identified to possess the 2-azaspiro[5.5]undecane skeleton. In the intramolecular cycloaddition of the nitrone **69**, a six-membered ring was favoured due to the entropic effects of C-C bond formation (Scheme 18).[61] (±)-Nitramine **60** was prepared by hydrogenolysis of **70** with hydrogen over Pd.



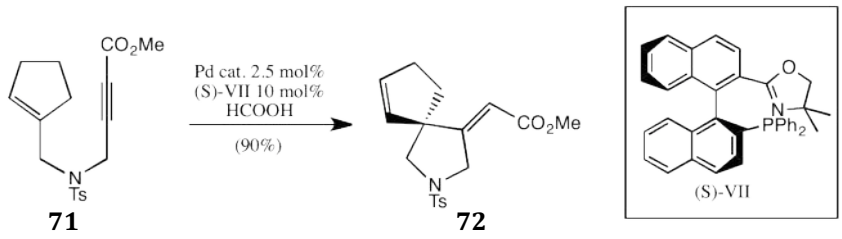
69 **70** **60**

Scheme 18. Intramolecular cycloaddition of ketenes.

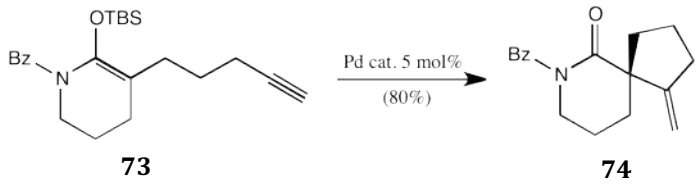
2.5 Metal-catalysed reactions

Palladium plays an important role in modern chemistry. A large number of reactions in organic chemistry can be facilitated by catalysis with palladium compounds.[62] Intramolecular ene-type cyclisation catalysed by cationic Pd(II) complex was described by Hatano and Mikami in 2003.[63] Spirocycles **72** were prepared in good yield and excellent enantioselectivities (Scheme 19). A

similar methodology was reported later (2007) by Corkey and Toste (Scheme 20).[64] Pd-catalysed reactions highlighted have several drawbacks including the use of an expensive catalyst, the need for complex starting materials and poor structural diversity.[65]

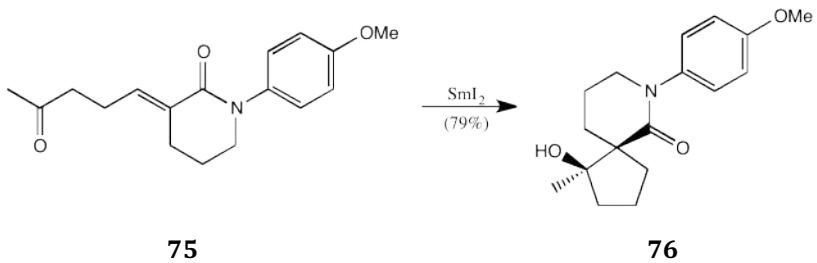


Scheme 19. Pd-catalysed synthesis of spirocycles by Hatano and Mikami.



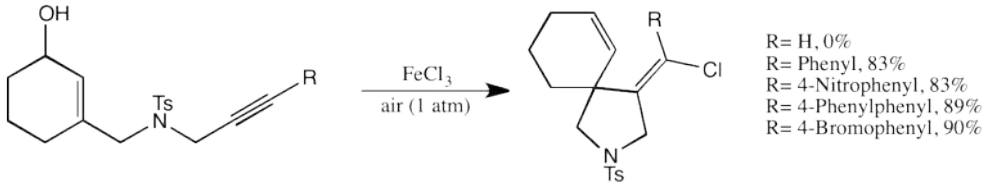
Scheme 20. Pd-catalysed spirocyclisation by Corey and Toste

Samarium(II)-mediated cyclisation of unsaturated keto-lactams to give spirocyclic pyrrolidines and piperidines was studied by the Procter group (Scheme 21).[66] The substituent on nitrogen in the cyclisation substrates had a significant effect on the reaction. The electron-withdrawing group on nitrogen was essential for the formation of five-membered rings. Moreover, six-membered substrates were more efficiently formed by this approach than the analogous five-membered examples.



Scheme 21. Samarium(II)-mediated cyclisation

Iron complexes are inexpensive and low-toxicity substitutes for the previous metals. $FeCl_3$-promoted intramolecular cyclisations have been developed.[67] At the alkyne terminus of starting material **77,** both electro-neutral and electro-deficient arenes were found to be good substrates to give (Z)-4-(arylchloromethlene)-substituted azaspirocycles **78** in excellent yields (Scheme 22). The main advantage of this approach is that reaction is instantaneous, only one minute was required for the reaction.



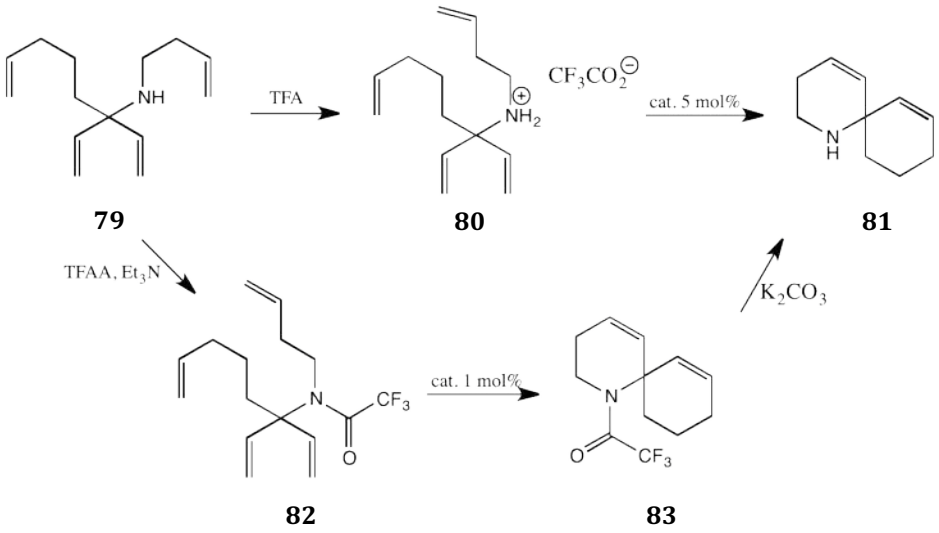
77 **78**

Scheme 22. $FeCl_3$-promoted cyclisation.

Other metals such as titanium, platinum(II), ytterbium and zirconium have all been used as catalyst components for the synthesis of spirocyclic compounds. Ramanathan and Odom described titanium-mediated amine allyation of cyclohexylamine by allyl alcohol to prepare the 1-azaspiro[5.5]undecane.[68] $Ti(OiPr)_4$ was used in the intramolecular spirocyclisation of pyridine substrates to construct 3,9-diazaspiro[5.5]undecane derivatives.[69]

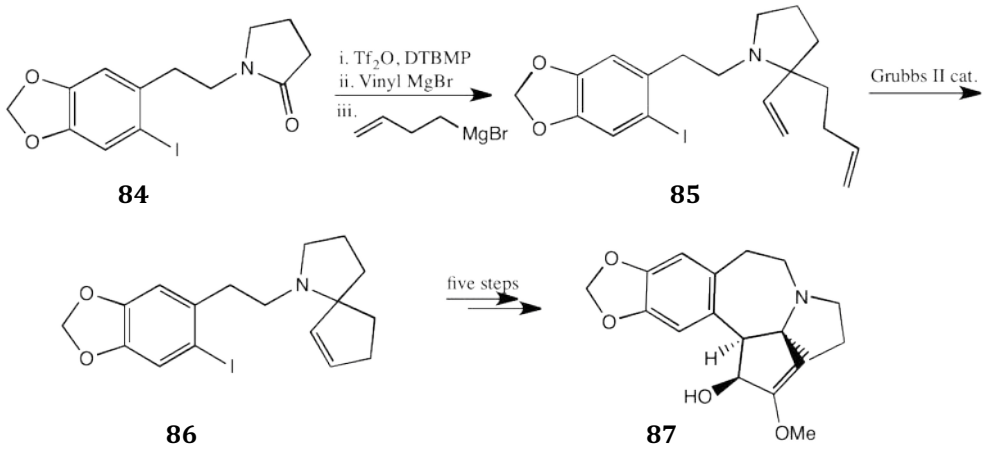
2.6 Ring Closing Metathesis

Ring closing metathesis (RCM) was widely used to make various spirocyclic systems with an additional double bond in such products to enable further synthetic manipulation. The Edwards research group has focused on using tandem RCM reactions of polyolefins to give azaspirocyclic compounds in good yield (Scheme 23).[70] There were two pathways to form spiropiperidine **81**: conversion of amine **79** into ammonium triflate **80** or trifluoroacetamide **82**. Although conversion of ammonium triflate **80** into **81** required more catalyst and a longer time, the procedure was convenient with no need for hydrogenation. Selective epoxidation reaction was used in the next step to prepare histrionicotoxin analogues.



Scheme 23. RCM for histrionicotoxin analogue synthesis

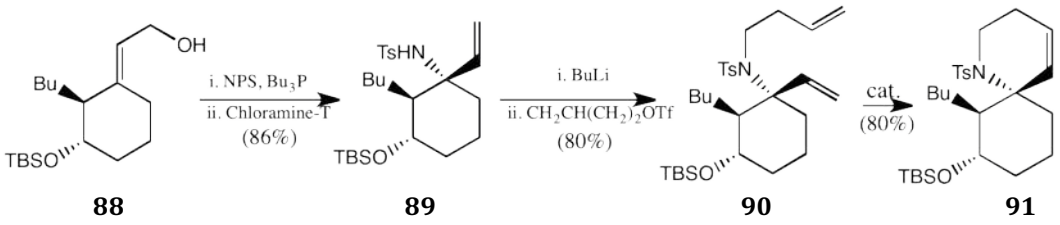
The introduction of two olefinic side chains into lactam **84** would afford various spirocycles by means of ring-closing metathesis (RCM). The two-step approach is more flexible than the one-step approach. Various *spiro-cyclic* alkenes could be formed with different ring sizes by addition of two different alkenyl groups, and the carbon-carbon double bond could be built in different positions for further synthetic manipulation. This approach was used in the synthesis of racemic cephalotaxine **87** (Scheme 24).[71,72]



Scheme 24. The synthesis of (±)-cephalotaxine

The combination of sigmatropic rearrangement and RCM provided a short and efficient route to the synthesis of spirocyclic alkaloids such as (±)-perhydrohistrionicotoxin.[73] The rearrangement product **89** was formed by treatment of the allylic alcohol **88** with N-(phenylseleno)phthalimide

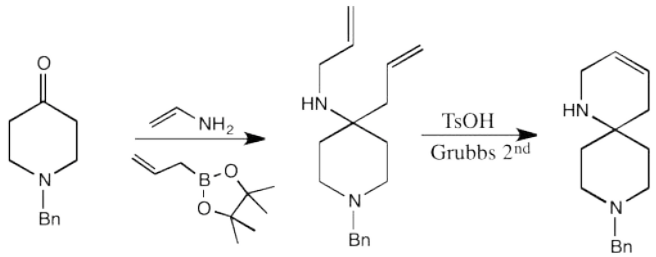
(NPS) and tributylphosphine (Bu_3P), followed by exposure to chloramine-T (Scheme 25)**.** The alkylation of **89** afforded cyclisation precursor **90** in good yield.



88 **89** **90** **91**

Scheme 25. The combination of sigmatropic rearrangement and RCM approach

A one-pot multicomponent reaction between *N*-Boc-3-piperidine **92,** allylamine, and a boronic ester led to cyclisation precursor **93** in toluene at 80°C (Scheme 26). The RCM reaction was processed under a standard procedure to form spirocyclic compound **94**.[74] The addition of *p*-TsOH was essential in the RCM reaction due to the influence of the nucleophilic amino group on Grubbs catalyst. This approach was limited to the five-membered ring system.

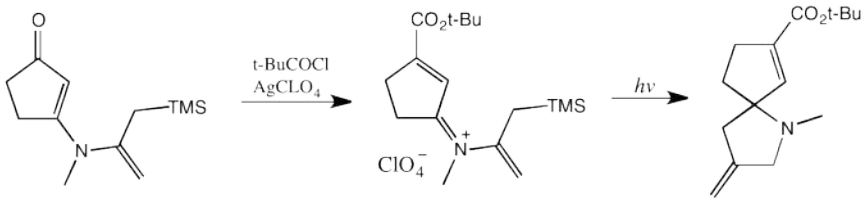


92 **93** **94**

Scheme 26. One-pot multicomponent reaction.

2.7 Other reactions

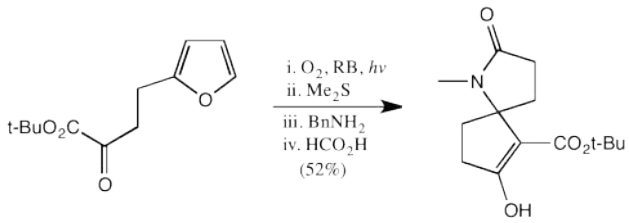
Mariano *et al.* discovered a single electron transfer (SET)-promoted photocyclisation to form the spirocyclic amine **97** (Scheme 27).[75] Silylarene- iminium salt **96** was the key precursor for the cyclisation and was prepared from β-aminoketone **95.**



95 **96** **97**

Scheme 27. Single electron transfer (SET)-promoted photocyclisation

An interesting synthetic approach for the elaboration of 1-azaspiro frameworks was reported by Kalaitzakis *et al.*[76] This one-pot process was initiated by singlet oxygen-mediated oxidation of the 2-substituted furan. The target spirocycle **99** was obtained through an aza-Prins cyclisation (Scheme 28).



98 **99**

Scheme 28. One-pot synthesis of 1-azaspirocycles by photooxidationof 2-substitued furan

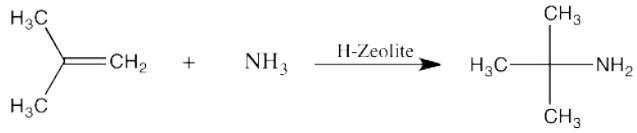
Preparation of spirocyclic derivatives aiming for low-toxic drugs and new drugs *via* organic synthesis has become common practice. Moreover, the efficient routes for the formation of spirocyclic structures are highly desired in the development of synthetic methodology. The use of such flexible synthetic routes using simple reagents under mild conditions is of great importance.

Section 3: Application of acid-catalysed cyclisation in the Knight group

3.1 Introduction to acid-catalysed cyclisation

Amines are important chemical intermediates in terms of the synthesis of polymers, pharmaceuticals and surfactants, along with many other chemicals. Among the methods used for the formation of carbon-nitrogen bonds, hydroamination is one of the most attractive pathways to various nitrogen-containing molecules by the addition of amines to alkenes or alkynes. It provides both potentially atom-efficient and thermodynamically feasible pathways.[77]

The hydroamination of alkenes is difficult because of the lower reactivity and electron density of carbon-carbon double bonds. For example, in the reaction of 2-methylpropene **100** and ammonia **101** (Scheme 29), the thermodynamic equilibrium is shifted to the starting materials, and the yield decreases with increasing reaction temperature.[78] Therefore, a catalyst is required.



100 **101** **102**

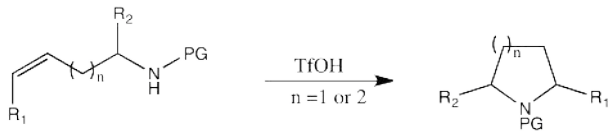
Scheme 29.The amination of 2-methylpropene

Many efforts have been put into the development of efficient and eco-friendly catalysts. Various examples are known to be efficient for both inter- and intra-molecular hydroamination of alkenes. Metal catalysts play an important role in these reactions. In early studies, hydroaminations were mostly triggered by transition-metal catalysts. Compared with late transition metals, early transition-metal catalysts such as titanium complexes showed excellent functional group tolerance. Gold as a catalyst in hydroamination reactions could work with unactivated olefins to give Markovnikov products.[79] However, gold cannot be used in reactions of alkylamines or anilines. Due to the excellent stereoselectivity obtained using organolanthanide catalysts,[80] these have been used as highly efficient catalysts for inter- and intramolecular hydroamination and could be used for the synthesis of naturally occurring alkaloids. However, lanthanide complexes were limited by lack of

compatibility with a number of important functional groups. In order to find a cheap and green metal catalyst, the scope of the catalyst was expanded by using main-group metals such as Ca[81], Bi[82], Zn[83] as catalysts.

The disadvantages of metal catalysts include reagent cost, toxicity (Hg, Pd), high air- and moisture-sensitivity (lanthanides), high electropositivity (main-group metals) and low functional-group tolerance.[84] To overcome these problems, it is important to find alternatives to such reactions.

In 2002, Schlummer and Hartwig first described the triflic acid-catalysed intramolecular hydroamination of tosyl-protected amino olefins in the preparation of pyrrolidines and piperidines (Scheme 30). After screening various acids (TfOH, Tf_2O, H_2SO_4, AcOH), they found that an acid with a $pK_a \leq 10$ was sufficiently acidic to act as catalyst.[85] When using concentrated sulfuric acid as catalyst, longer reaction times were required.

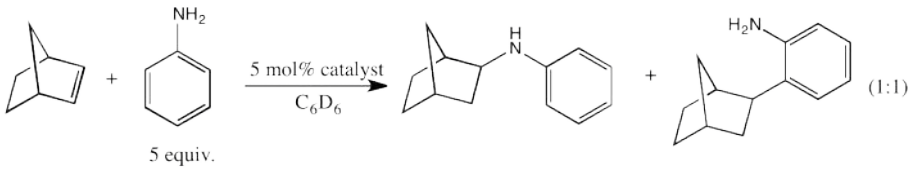


103 **104**

Scheme 30. Intramolecular hydroamination by Hartwig et al.

In 2005, Bergman *et al.* reported proton-catalysed hydroamination and hydroarylation reactions of aniline and norbornene (Table 1). Both anilinium salts and strong acids were tested in order to find an optimal catalyst. Results from experiments suggested that decreasing anion coordination ability lead to increase in catalytic efficacy; the coordinating anion NTf^{2-} is stronger than OTf^-.[86]

Table 1. Acid-catalysed hydroamination and hydroarylation of aniline and norbornene

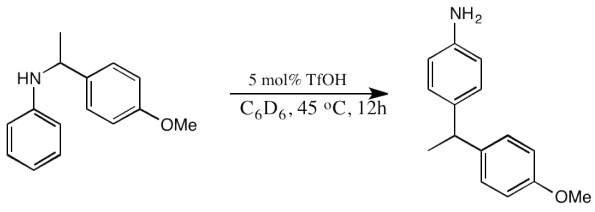


105 **106** **107** **108**

Catalyst	T (^{o}C)	t (h)	% yield[a]
$PhNH_3B(C_6H_5)_4.Et_2O$	135	27	60
$HNTf_2$	135	27	35
$HNTf_2$	135	48	84
HOTf	135	27	13

a. Combined yield of **107** and **108**.

Bergman *et al.* also found that the generation of either kinetic or thermodynamic products depended on both reaction time and temperature. Products from N-H addition mainly occurred at short reaction times, while longer times and higher temperatures are required fro Ar-H addition. It was notable that products from hydroamination can be transferred to hydroarylation products in the presence of 5-mol% of catalyst (Scheme 31).



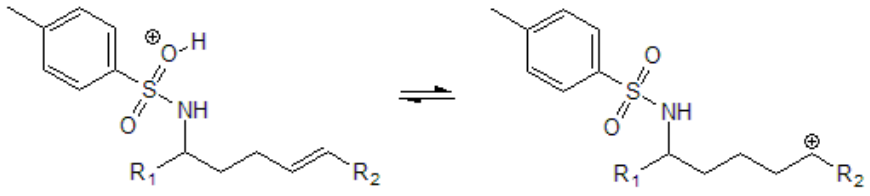
109 **110**

Scheme 31. Conversion of hyrdroamination products to hydroacylation products

In 2006, it was reported that intermolecular additions of phenols and protected amines to the unactivated olefins could be catalysed by 1-5% triflic acid in toluene.[87] This is an alternative method to metal-catalysed reaction to form carbon-oxygen and carbon-nitrogen bonds. In contrast to the addition to phenols, hydroamination required a higher reaction temperature (80-85^{o}C). If the

concentration of the Brønsted acid and the reaction temperature can be controlled appropriately, the intolerance of functional groups could be avoided. The pKa of triflic acid is -15, which places it in the super acid class. Experiments shown above indicate that triflic acid can be an effective catalyst in hydroamination reactions of alkenes. Optimization of reaction conditions may improve the efficiency of using TfOH.

In acid-catalysed hydroamination cyclizations, the mechanism of intramolecular cyclisation probably involves protonation of the tosylamine group and formation of a carbocation by intramolecular proton transfer. The resulting carbocation then reacts with the lone pair electron on nitrogen to form a ring (Scheme 32). According to Baldwin's rule, the transformation is an overall unfavorable 5-*endo*-trig cyclisation, but as it involves a carbocation, this is not strictly a mechanism to which these rules apply. The basicity of the reacting amine impacts on the reaction rate: more basic amines lead to lower reaction rates.[88]

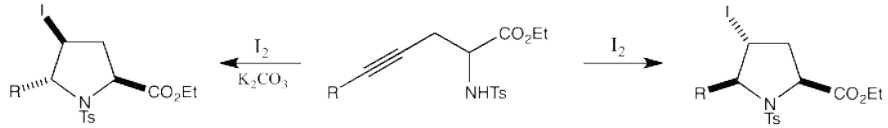


111 **112**

Scheme 32. Intramolecular proton transfer.

3.2 Application of acid-catalysed hydroamination in the Knight group

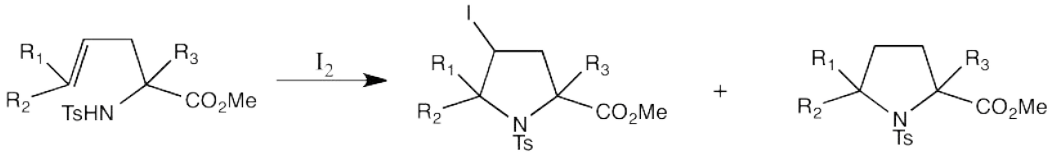
Triflic acid-catalysed hydroamination has been a major focus of research in the Knight group and has become a straightforward approach for the synthesis of nitrogen-contain heterocycles. The very familiar iodocyclisation has been used as a smooth and efficient synthetic method for the preparation of pyrrolidines (Scheme 33).[89] Haskins in the Knight group found that the overall 5-*endo*-trig iodocyclisation of **114** gave only the 2,5-*cis* isomers **115** when the base was omitted.



113 **114** **115**

Scheme 33. Iodocyclisation

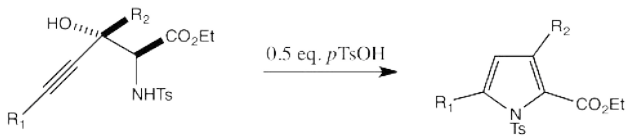
The same phenomenon was observed in the synthesis of highly substituted pyrrolidines. In the absence of base, however, small amounts of de-iodopyrrolidines **118** were obtained during the iodocyclisation process (Scheme 34). The generation of **118** indicated that a direct acid-catalyzed cyclisation might be a strategy for this kind of reaction.



116 **117** **118**

Scheme 34. Iodocyclisation

Acids such as *p*-toluenesulfonic acid (tosic acid), acetic acid, trifluoroacetic acid, trifluoromethanesulfonic acid (triflic acid) were used in initial trials of this acid-catalysed hydroamination. Treatment of cyclisation precursor **119** with 0.5 equivalents of tosic acid resulted in expected cyclized product **120** (Scheme 35). It indicated that an independent proton source induced the same reaction as iodocyclisation.[90]



119 **120**

Scheme 35. Acid-catalysed cyclisation

When using acetic or trifluoroacetic acids as catalyst, none of the product was obtained. Due to the high temperature (70^{o}C) that was essential for tosic acid to work, triflic acid was the reagent of

choice for subsequent intramolecular hydroaminations. The standard protocol was to use 0.4 equivalents of triflic acid in chloroform or dichloromethane at 0^{o}C for around 15 minutes.

Triflic acid-catalyzed cyclisations were developed as a valuable method for the synthesis of many substituted pyrrolidines in Knight group (Figure 13).[91] Furthermore, the methodology was extended to the synthesis of *spiro*-pyrrolidines.

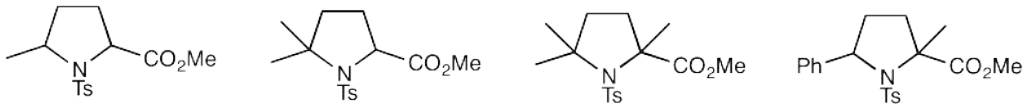
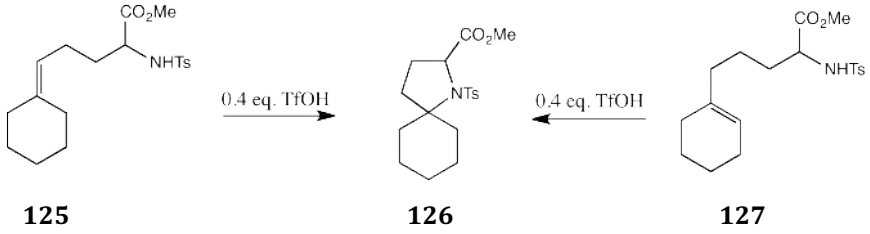


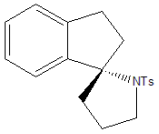
Figure 13. Synthesis of substituted pyrrolidines *via* acid-catalyzed hydroamination

Spiro-pyrrolidine **126** was prepared by treatment of cyclohexane derivative **125** with 0.4 equivalents of triflic acid in chloroform at 0 ^{o}C (Scheme 36).[92] Cyclisation of cyclohexene derivative **127** gave the same *spiro*-cycle **126** under similar conditions. In Haskin's research, the functionalized amino-ester group was found necessary for the acid-catalysed hydroamination to occur. Although the *N*-Ts protecting group was suitable in this approach, detosylation was not efficient.



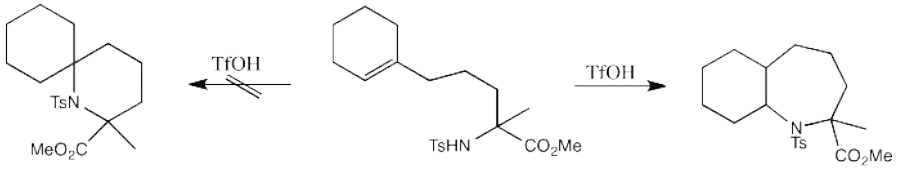
Scheme 36. TfOH-catalysed cyclisation in spirocycles synthesis

Subsequent work by Henderson in the Knight group tested the ester adjacent to the sulfonamide to determine if it was needed for acid-catalysed hydroamination to occur in the synthesis of indene-derived *spiro*-cycles. However, sulfonamides were not successfully cyclized to give the desired *spiro*-cycles; all efforts to preparer *spiro*-pyrrolidine **128** failed. The sulfonamide was considered to be too hindered and might be replaced by a smaller N-protecting group with benefit. Moreover, the functionalized amino-ester group might indeed be needed for the formation of five-membered ring system.



128

For the formation of six-membered ring systems, treatment of cyclohexene derivative **129** with triflic acid gave the 6/7 ring system **131** rather than the desired *spiro*-piperidine **130** (Scheme 37). Even though a tertiary carbocation is considered more stable than secondary one, the 7-*endo*-trig cyclisation occurred instead of the expected 6-*exo*-trig process.



130 **129** **131**

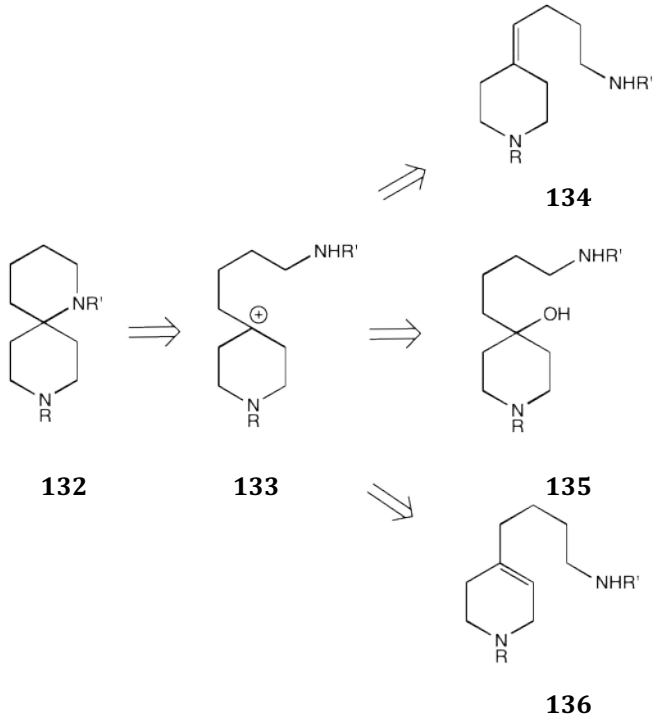
Scheme 37. TfOH-catalysed cyclisation for the formation of 6-membered ring system

Acid-catalyzed hydroamination for the formation of cyclic compounds is of great convenience and can be very efficient. However, only a relatively limited range of compounds has been successfully synthesized using this method. The preparation of azaspiro[4.5]decane and azaspiro[5.5]undecane skeletons by acid-catalysed hydroamination needs to be further investigated. Moreover, the preference of the direction of ring closing is not as predictable as in previous experiments. Further research is needed.

Section 4: Acid-catalysed cyclisation in targeted synthesis

4.1 Synthetic hypothesis

The synthetic plan for the present project was based purely on identifying ways in which a *spiro*-piperidine could be synthesized using our recently discovered acid-catalysed methodology for the synthesis of saturated *N*-heterocycles. Given this idea, then the initial aims can be summarized by the following Scheme:

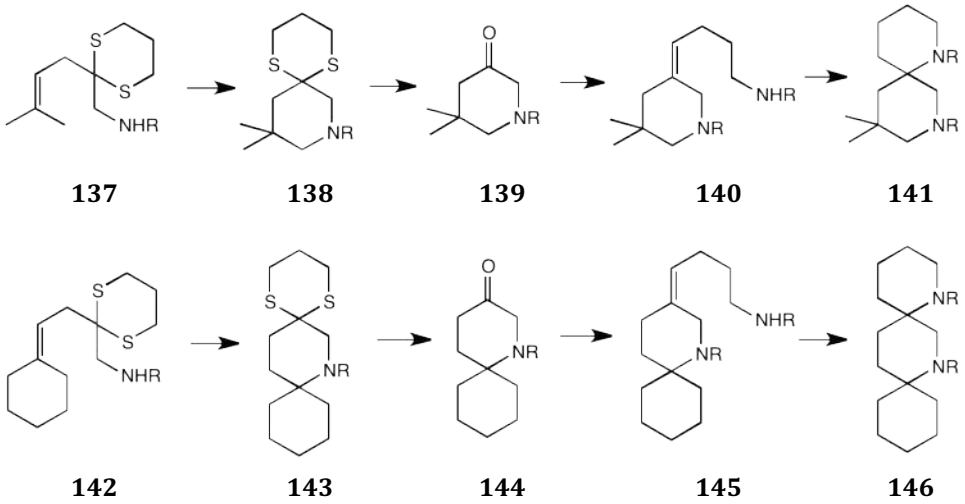


Scheme 38. Synthetic plan for *spiro*-cyclic compound synthesis

Based on our reported findings concerning such cyclisations, the initial target, the *spiro*-piperidine **132** should be generated by trapping of the carbenium ion **133** by the pendant protected amino group in the side chain. In principle, there are three suitable precursors to this carbenium ion: the *exo*-alkene **134**, the tertiary alcohol **135**, and the *endo*-alkene **136**, by exposure to strongly acidic conditions.

The polarity inversion of a carbonyl group was thought to be an efficient way to form spirocyclic compounds containing a functional carbonyl group. 2-Substitutied-1,3-dithianes (**137** and **142**) will be formed under known procedures by reaction of carbamates and 1,3-propanedithiol followed by alkylation. If the preparation of ketones (**139** and **144**) is successful, combined with experimented

successful synthetic pathways shown on Scheme 37, the formation of bis-*spiro*-cyclic compound **141** and tris-*spiro*-cyclic compound **146** could be possible (Scheme 39).



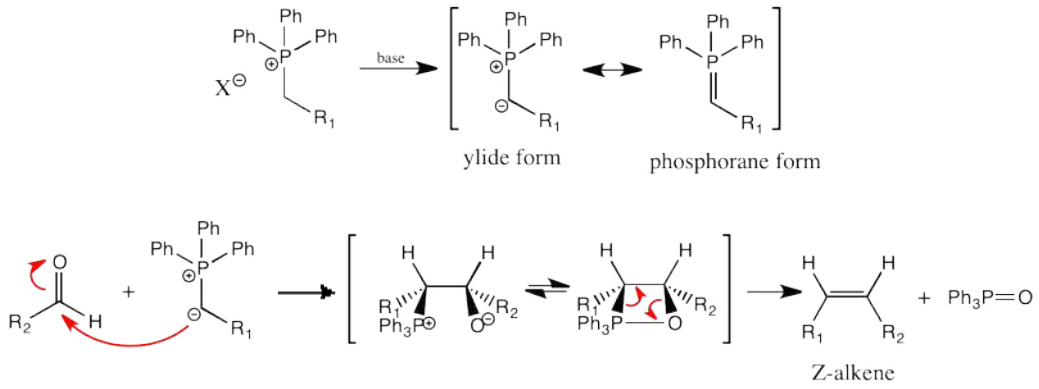
Scheme 39. Initial routes for *spiro*-cyclic compound synthesis

4.2 Results and discussion

4.2.1 Preparation of 1,9-diazaspiro[5,5]undecane

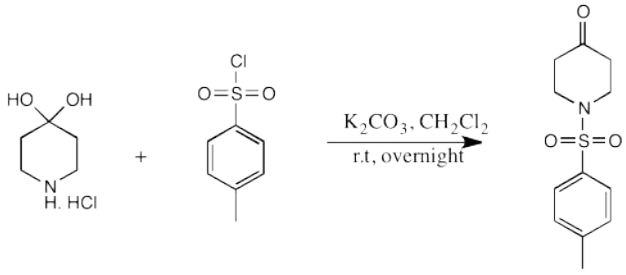
4.2.1.1 Wittig reaction

The Wittig reaction is widely used in organic synthesis for the preparation of alkenes and commonly used to couple aldehydes or ketones to singly substituted phosphine ylides. Generally, the geometry of the resulting alkene depends on the ylide: simple phosphoranes are unstable and very reactive and tend to lead to (*Z*)-alkenes, while (*E*)-alkenes will usually be formed from stabilized ylides (Scheme 40).



Scheme 40. Wittig reaction mechanism

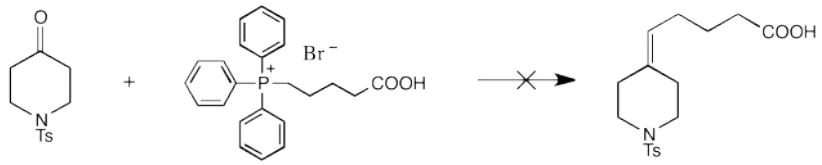
An initial attempt was made to prepare the 1,9-azaspiro[5.5]undecane skeleton using such a Wittig reaction (Scheme 41). Nitrogen-protected 4-piperdione **149** was prepared using a reported method[93] and expected to be reactive due to its wide use as an important intermediate in the chemical and pharmaceutical industry. For example, *N*-benzyl-4-piperidone is used to make Pimozide and Benperidol, and *N*-methyl-4-piperidone was used to make Dorastine.



147 **148** **149**

Scheme 41. Synthesis of 1-tosylpiperidin-4-one

The Wittig addition of 1-tosylpiperidin-4-one **149** to the ylide derived from phosphonium salt **150** was carried out using the previously reported procedure (Scheme 42).[94] The ylide was generated by adding a solution of phosphonium salt **150** to 2.2 equivalents of potassium bis(trimethylsilyl)amide (KHMDS). After 15 minutes at room temperature, a solution of the ketone **149** was added to the resulting bright red solution and the mixture was stirred at room temperature. After 3 hours, the reaction was quenched with water. The water layer was extracted with ether and acidified with 10% HCl to pH 2 and re-extracted.

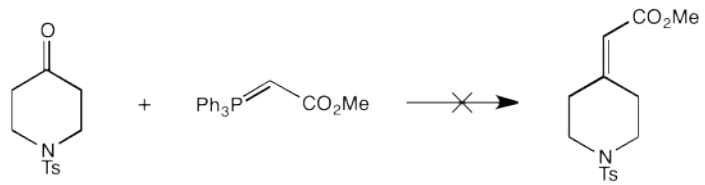


149 **150** **151**

Scheme 42. *Reagents and conditions*: KHMDS, THF, r.t, 3h.

NMR analysis of the crude product showed the product was mainly unreacted 1-tosylpiperidin-4-one **149**. Only a trace of alkene product could be seen from the NMR spectrum, which was present around 5.0-5.3 ppm. Leaving the reaction mixture overnight also resulted in none of expected compound being obtained. However, later repeats of this reaction (Scheme 58) did indeed produce the desired acid.

The stablized ylide **152** is easy to prepare, but obviously is less reactive than an unstablised ylide. The Wittig reaction of methyl (triphenylphosphoranylidene) acetate **152** and piperidone **149** was tried under similar reaction conditions (Scheme 43). Unfortunately, none of the desired product **153** was obtained.

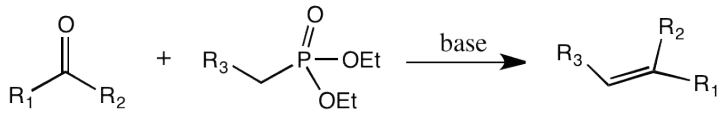


149 **152** **153**

Scheme 43. *Reagents and conditions*: THF, r.t, 3h.

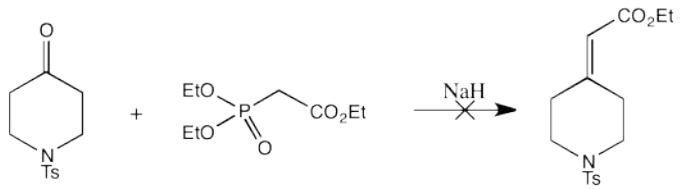
The unstable and quite reactive zwitterionic intermediate ylide might be a reason for the unsuccessful Wittig reaction. The active zwitterion could instead act as a base, hence preventing condensation as the ketone would be enolized.

A slightly different approach to the Wittig reaction, a Horner-Wadsworth-Emmons (HWE) reaction is another phosphorus-mediated reaction to form alkenes. Compared with phosphonium ylides in Wittig reactions, phosphonate-stabilized carbanions in HWE reactions are more nucleophilic and can react with a wider variety of ketones (Scheme 44).[95]



Scheme 44. *Horner-Wadsworth-Emmons (HWE) Olefination*

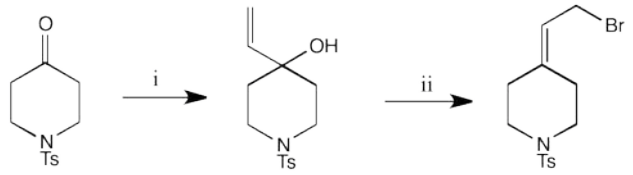
The HWE reaction could be an alternative method for the failed Wittig reaction in our case. Sodium hydride (60% dispersion in mineral oil) was used to form an α-metalated phosphonate. Nucleophilic addition of deprotonated **154** onto the 4-piperidone **149** (Scheme 45) did not give the desired *exo*-alkene **155**.



149 **154** **155**

Scheme 45. *Reagents and conditions*: NaH, THF, r.t, 3h

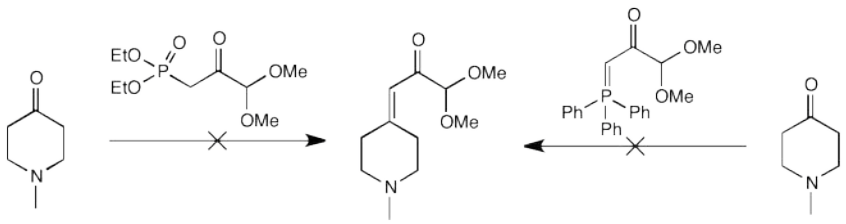
Alternatively, another approach to effect such a homologation could be by treatment of 4-piperidone **149** with Grignard reagents, which was attempted. The addition of 1.5 equivalents of vinylmagnesium bromide to 1 equivalent 4-piperdidone led to alcohol **156** in moderate yield (Scheme 46). Increasing reaction temperature to 25-30^{o}C, the product yield was improved and the crude product can be used directly to next step without any purification. However, only trace amounts of the desired bromide **157** were detected after bromination with PBr_3.



149 **156** **157**

Scheme 46. *Reagents and conditions*: i. $CH_2CHMgBr$, 25°C, 16h; ii. PBr_3, r.t, 16h.

The unreactive properties of the 4-piperidone were in good agreement with the observations made by Reddy who found that either Wittig reaction and HWE reactions of *N*-subtituded-4-piperidone **158** did not provide the expected product **159** under a diverse range of conditions (Scheme 47).[96] The decomposition of the phosphonate and Wittig reagents was found rather than the expected product. We still do not know the reason why such piperidones were not reactive in these phosphorus-mediated reactions.

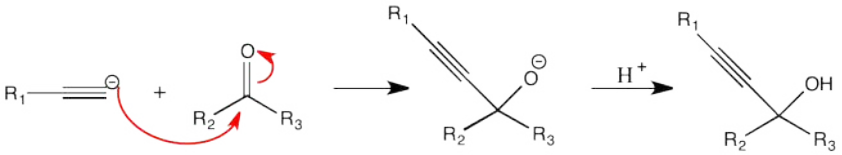


158 **159** **158**

Scheme 47. Attempted synthesis of piperidine building block under diverse conditions.

4.2.1.3 Alkynylation

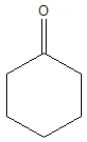
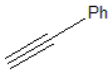
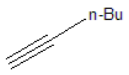
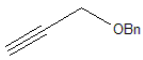
Direct addition of alkynes to carbonyl groups provides a way of C-C bond formation, which has been widely used in the preparation of propargyl alcohols. The alkoxide is first formed by nucleophilic addition of acetylides to carbonyl compounds, protonation of which gives propargyl alcohols (Scheme 48). Strong bases such as n-butyllithium (BuLi), lithium diisopropylamide (LDA), potassium hexamethyldisilylamide (KHMDS), sodium hydride (NaH), and potassium hydride (KH) are often used to remove protons from terminal alkynes.



Scheme 48. Preparation of propargyl alcohols.

An addition of a terminal alkene to a ketone would provide access to propargyl alcohols. Similar experiments have been reported in the literature. A catalysed alkynylation of various terminal alkynes and cyclohexanone was reported by Ishikawa *et al*. The reaction of diverse ketones and alkynes using benzyl trimethylammonium hydroxide as base smoothly proceeded to give the corresponding propargylic alcohols in good yields (Table 2).[97] Hence, such an addition of an alkyne to a ketone can be a useful way to introduce an alkyl group. The reaction of 1-hexyne with cyclohexanone required a longer reaction time (20h) to result in a low yield of product (43%), in contrast to the reaction of alkynes containing benzyl ether group. Aromatic alkynes may be more suitable in these reactions.

Table 2. Examples of addition of alkynes to aliphatic ketones

Entry	Ketone	Alkyne	Method[a]	Time / hrs	Yield / %
1			A	2	95
2			A	20	43
3			A	12	84

[a] Method A: To a solution of alkyne (5.0 mmol) and ketone (1.2 eq.) in DMSO (2.5 mL) was added a solution of catalyst (10 mol %) in DMSO (2.5 mL) over 10 min at r.t;

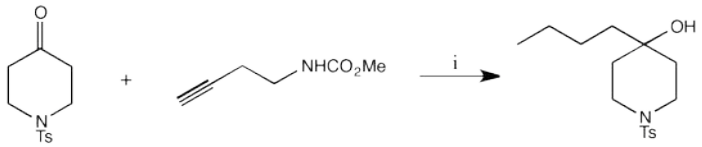
In absence of catalysts, a nucleophilic addition of 4-(tosyloxy)but-1-yne and carbonyl compounds was reported by Mukai *et al.*.[98] The yields of propargylic alcohols were quite low, especially when a symmetrical ketone was used (Table 3).

Table 3. Nucleophilic addition of terminal alkynes to ketones

R_1	R_2	Yield (%)
H	Me	54
H	Bu	48
Me	Me	44

Direct addition of terminal alkynes to 4-piperidone could therefore be an attractive method to prepare the 1,9-diazasoiro[5.5]undecane skeleton. The alkyne is first deprotonated followed by addition of the resulting nucleophiles to the carbonyl group give the propargyl alcohol, then hydrogenation and cyclisation could produce the desired *spiro*-piperidine. If this approach is successful, it will be an efficient way to produce *spiro*-piperidines.

A co-solvent such as DMPU might be necessary to this kind of reaction to promote the solubility of reagents and accelerate the reaction rate. Treatment of 4-piperidone **149** with the terminal alkyne **160** in the absence of DMPU afforded the unexpected product **161** (Scheme 49). Evidently, NMR analysis of the crude product showed no terminal alkyne protons around 2 ppm. Butyl lithium (BuLi) had attacked the ketone faster than the alkyne at room temperature and resulted in the formation of undesired alkylation product.

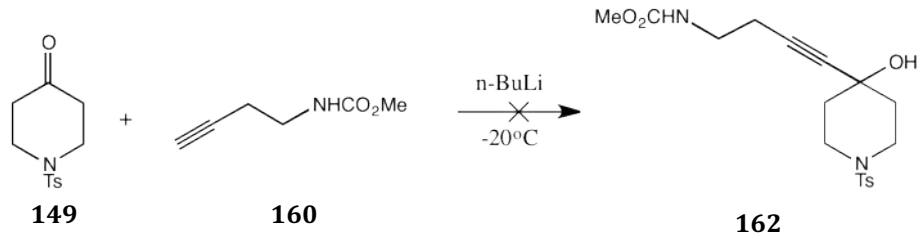


149 **160** **161**

Scheme 49. *Reagents and conditions*: i, BuLi, THF, 0 ^oC – -78 ^oC – r.t; 15.8%

A solution of 2.1 equivalents of BuLi and 1.1 equivalents of alkyne **160** in THF was stirred at -40^oC for 2h then cooled down to -78^oC. 4 equivalents of DMPU were added dropwise and the resulting solution was stirred for a further 1h. Piperidone **149** in THF was then added dropwise. The reaction

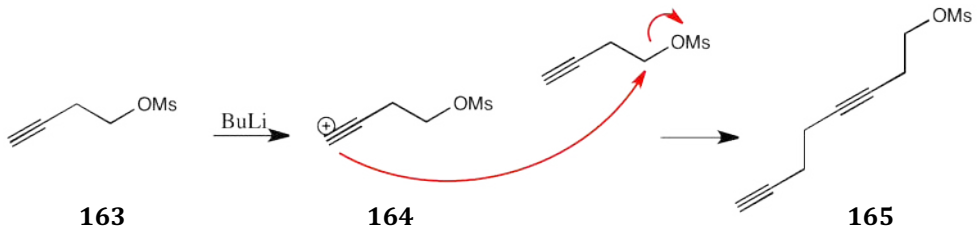
mixture was stirred at -78°C for 4h, followed by warming slowing to -20°C and stirring overnight. Aqueous ammonium chloride was added to quench the reaction, which was then extracted. ^{1}H NMR data showed that none of the desired new product was formed (Scheme 50).



149 **160** **162**

Scheme 50. *Reagents and conditions*: i, n-BuLi, DMPU, THF, -20 °C, overnight.

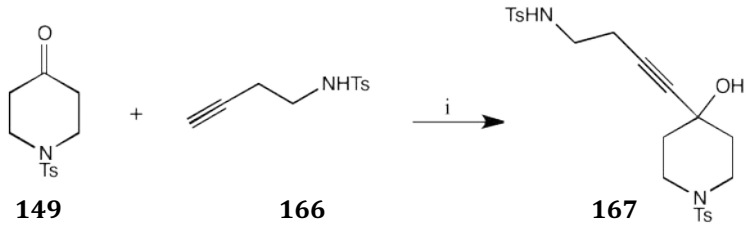
The *O*-tosyl protected alkyne was also tried. Considering the possible deprotonation of the mesyl group in mesylated alkene with BuLi, the alternative base, LDA, was used. Unfortunately, no reaction occurred even after leaving the reaction for 48h. Mesylate is a good leaving group; it is possible to form a compound containing two triple bonds, which might be hard to identify from the ^{1}H NMR spectrum of crude product (Scheme 51).



163 **164** **165**

Scheme 51. Possibility of formation of **165**.

An addition of the *N*-tosylated alkyne to piperidone gave a small amount of expected product (Scheme 52). ^{1}H NMR analysis of the product isolated from silica gel column chromatography showed that no starting ketone was presented, and new peaks at 2.0, 2.4 and 3.3 ppm for the piperidone were found. Moreover, two different shifts for the tosyl group could be seen between 7.2-7.8 ppm. Increasing amount of DMPU, increasing reaction temperature, changing solvent had no positive effect on the reaction, and mainly starting materials were present.



149 166 167

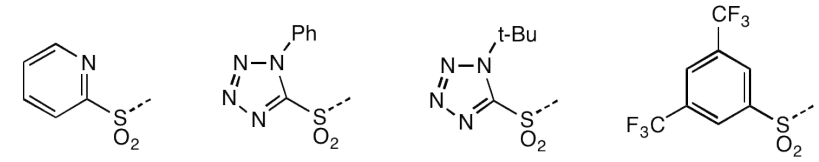
Scheme 52. *Reagents and conditions*: i. n-BuLi, DMPU, THF, -20 ^{o}C, overnight.

4.2.2 Preparation of 1-azaspiro[5.5]undecane

4.2.2.1 Modified-Julia Olefination

The classic Julia olefination comprises of the addition of a lithiated sulfone to a carbonyl group, with the formation of a β-hydroxy or derived acyloxy sulfone and elimination. The disadvantages of the classic Julia olefination include low tolerance of reducible functional groups and reversible processes in the reaction between the sulfone anion and the ketone.[99]

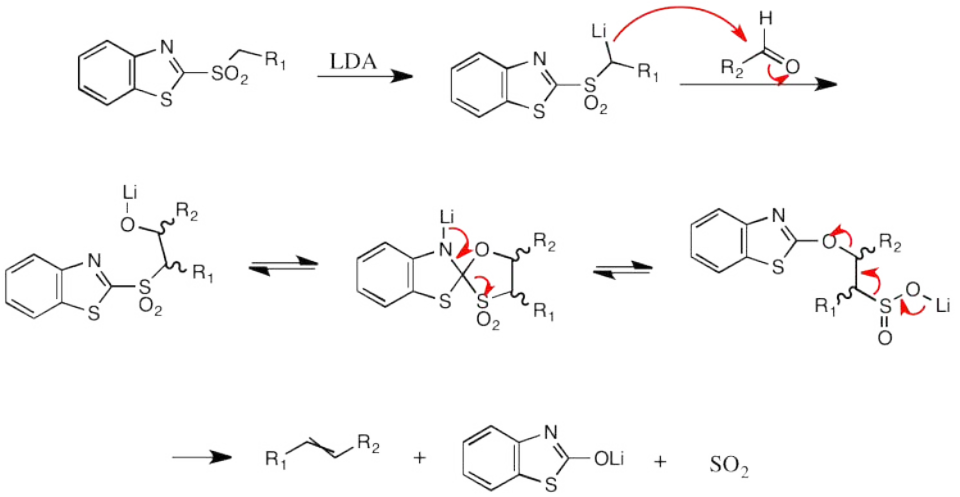
The modified Julia olefination gives the olefin directly by replacement of phenylsulfone with heteroaryl sulfones. Benzothiazolyl (BT) sulfone is widely used, comparing with other heteroaryl sulfones such as pyridin-2-yl (PYR), 1-phenyl-1*H*-tetrazol-5-yl (PT), 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) or 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfone (Figure 14). However, for sterically unencumbered sulfones such as methyl BT-sulfone, self-condensation cannot be avoided due to its donor-acceptor nature.[100] Self-condensation of BT-sulfone has been improved by using Barbier conditions.[101]



PYR-sulfones PT-sulfones TBT-sulfones BTFP-sulfones

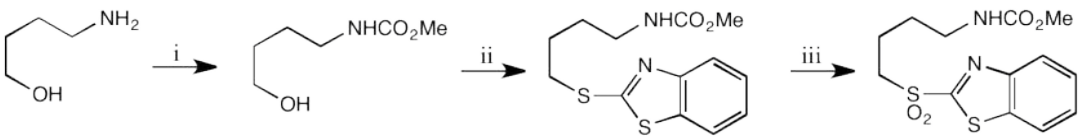
Figure 14. Heteroaryl sulfones for the modified Julia olefination

The first step of modified Julia olefination is the same as in its original form and involves the addition of metalated BT-sulfone to a carbonyl group (Scheme 53). The resulting β-alkoxysulfone experiences a facile rearrangement and results in formation of a sulfinate salt. Alkenes will be produced directly by spontaneous elimination of sulfur dioxide and lithium benzothiazolone.



Scheme 53. Mechanism of modified Julia olefination.

A preparation of the desired BT-sulfone **172** for the modified Julia olefination was first tried starting from 4-amino-1 butanol, in three steps (Scheme 54). The commercially available 4-amino-1-butanol **168** was first protected as the corresponding carbamate **169** by using 1.1 equivalents of methyl chloroformate in the presence of triethylamine (Et_3N). The resulting carbamate was found to be water-soluble and its isolation resulted in a low yield. The work-up procedure could be optimized by evaporating the reaction solvent straight away and eluting the subsequent chromatography column with 2% methanol in dichloromethane, after the reaction was completed.

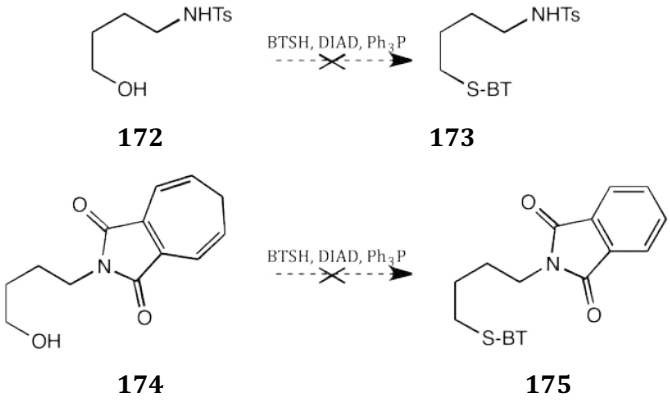


168 **169** **170** **171**

Scheme 54. *Reagents and conditions*: i, $ClCO_2Me$, DCM, 0°C→r.t., 4h; ii, BTSH, DIAD, Ph_3P, THF, 0°C→r.t., 24h; iii, $Na_2WO_4.2H_2O$-H_2O_2.

The Mitsunobu reaction allows for facile change of functionality of the hydroxyl group to thioether via a nucleophilic displacement. Azodicarboxylic acid esters such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) are used as oxidants of triphenylphosphine to triphenylphosphine oxide. 1.5 Equivalents of DIAD were added slowly to a solution of alcohol **169**, triphenylphosphine and BTSH at 0^{o}C. After 4h, none of desired thioether product was obtained. Increasing the amount of BTSH to 2.2 equivalents and increasing the reaction temperature to 40^{o}C, gave only 3% desired BT-sulfide **170**. The combination of sodium tungstate dihydrate and 30% aqueous hydrogen peroxide was used as oxidant in preparation of the Julia olefination precursor BT-sulfone**171**. Less than 2% of the expected product was generated after purification.

Considering the possible influence of the carbamate on the Mitsunobu reaction, tosylated amine **172**, and phthalimide **174** were tried under the same conditions. Unfortunately, none of the desired products were obtained (Scheme 55).

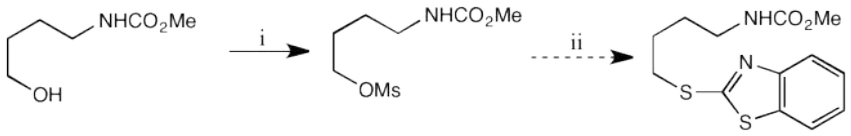


Scheme 55. Failed Mitsunobu reactions

The Ph_3P-DIAD system is generally useful for acidic nucleophiles with pKa < 11.[102] In our case, more active coupling agents may be needed. Moreover, Mitsunobu reactions may be more suitable for secondary alcohols than primary alcohols in these examples.

Alternatively, BT-sulfones can be prepared using standard substitution procedures (Scheme 56). Using an excess amount of triethylamine was effective for the mesylation: 5 equivalents of triethylamine produced a higher yield of the mesylated product **176** than using 2.3 equivalents; the

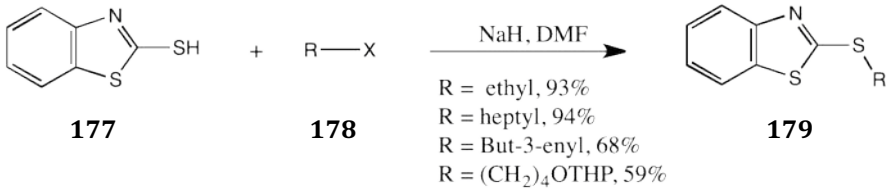
yields were 98% and 70% respectively. The substitution of carbamate with BTSH proceeded in dichloromethane in the presence of triethylamine as base. The desired BT-sulfide **170** was produced in very low yield and the ^{1}H NMR spectrum showed that the products were mainly unreacted starting material BTSH. The reaction was tried using different combinations of base and solvents but all attempts to improve the yields of the substituted products were ineffective.



169 **176** **170**

Scheme 56. *Reagents and conditions*: i, MsCl, Et_3N, DCM, 0^{o}C, 1h; ii, BTSH, Et_3N, DCM, r.t., overnight.

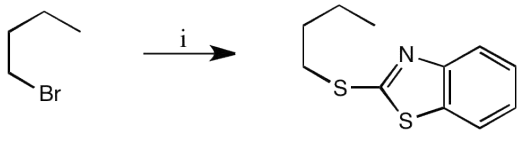
In the preparation of BT-sulfone derivatives using reported literature methods (Scheme 57),[103,104] the reaction was found not to be affected by an increase of the size of the alkyl chains of substrates. However, the alkyl chains terminated by polar functional groups had a deleterious influence on the substitution.



177 **178** **179**

Scheme 57. preparation of BT-sulfone derivatives

The influence of terminal functional groups existed in our case. In the absence of the protected amine group, the reaction of bromide **180** proceeded smoothly with two equivalents of triethylamine and produced the BT-sulfone **181**in 76% yield (Scheme 58).



180 **181**

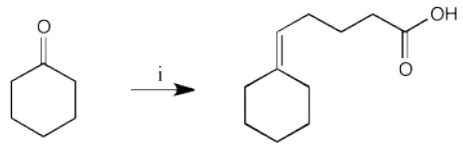
Scheme 58. *Reagents and conditions*: i, BTSH, Et_3N, DCM, r.t., overnight.

The synthesis of the required BT-sulfone intermediates was not achieved. The reaction time for *S*-alkylation and *S*-oxidation was long and the yields were very low. Oxidation of the thioether resulted in isolation of a residue that was deemed beyond purification. The synthetic route outlined above (Schemes 53 and 55) could possibly be successful if the amine group could be introduced in a later step or by starting from a secondary alcohol.

The selectivity for BT-sulfones was highly dependent on the choice of base and the exact reaction conditions. Chatterjee *et al*. reported the Julia-Kocienski olefination afforded the highest yield (68%) by using KHMD as base and Et_2O as solvent at -78^{o}C, while no product was produced in presence of NaHMD in THF at -78^{o}C.[105] Considering the relatively low yield in the preparation of trisubstituted olefines (29%-33%) in the reported literature.[106] we returned to the use of Wittig reactions to construct the required trisubstituted olefins, but using cyclohexanone as a simpler model ketone.

4.2.2.2 Wittig Olefination

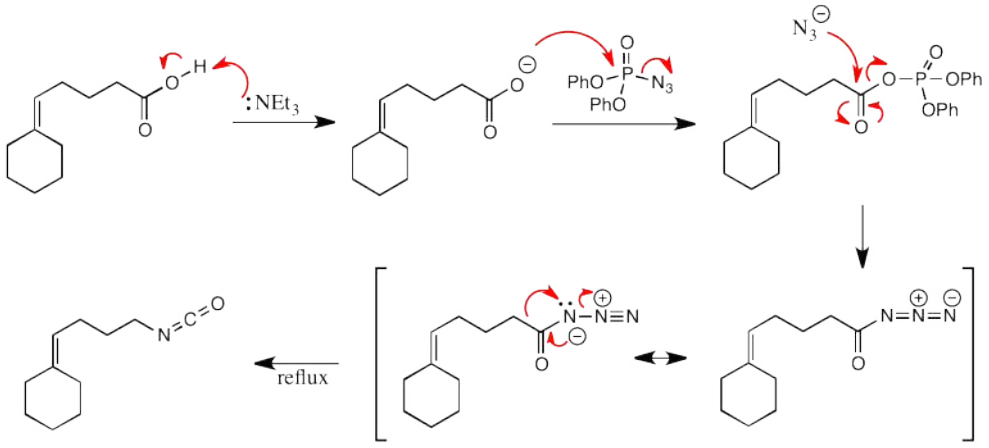
The Wittig reagent 4-carboxybutyltriphenylphosphonium bromide is commercially available. The Wittig reaction proceeded smoothly with potassium bis(trimethylsilyl)amide in anhydrous THF (Scheme 59). In our case, only one isomer could be obtained via a Wittig reaction. The NMR spectrum of the crude product shown peaks for the alkene proton at around 5 ppm.



182 **183**

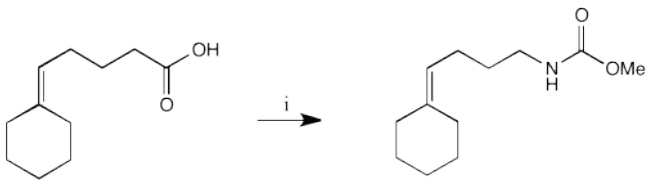
Scheme 59. *Reagents and conditions*: i. KHMDS, THF, r.t, 3h;

The carboxylic acid **184** could be easily converted into the corresponding carbamate *via* a Curtius rearrangement. The mechanism of Curtius rearrangement is a concerted mechanism with the formation of an acyl nitrene and isocyanate happening together (Scheme 60). The formed isocyanate can be used to react with alcohols to generate a carbamate, or be hydrolysed to give a primary amine, or react with amines to form urea derivatives.



Scheme 60. Mechanism of Curtius rearrangement.

In our case, carbamate was prepared by the adding of methanol to introduce the methoxy group. Zinc chloride ($ZnCl_2$) was expected to work better than copper(II) chloride ($CuCl_2$) as the latter is a weak Lewis acid (Scheme 61). However, results from our experiments showed that both $ZnCl_2$ and $CuCl_2$ are not efficient catalysts.



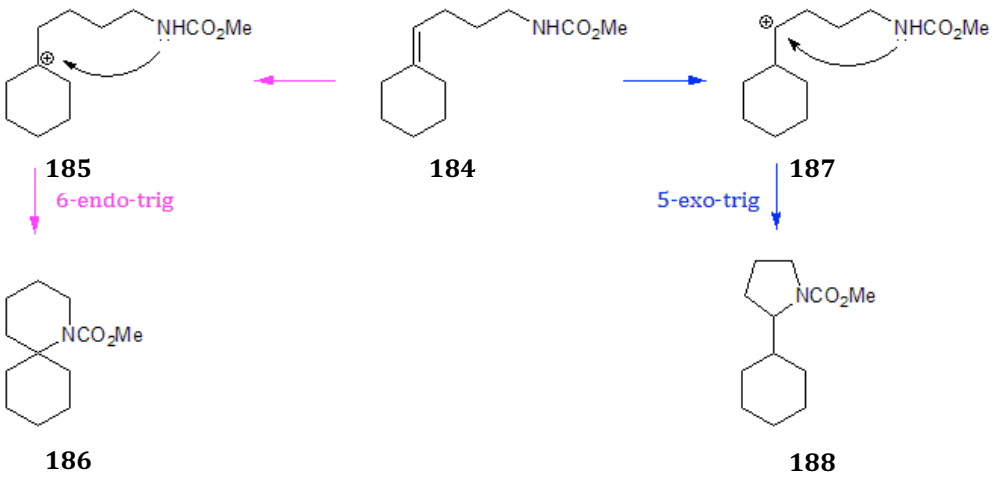
183 **184**

Scheme 61. *Reagents and conditions*: i. DPPA, Et_3N, $CuCl_2$, CH_3OH, toluene, reflex, 2h.

*4.2.2.*3 Cyclisation

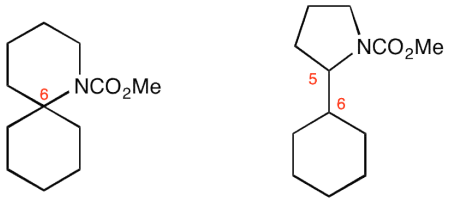
A brand new bottle of triflic acid was used as catalyst in the attempted intramolecular hydroamination of the amino-alkene. Following some standard procedures for acid-catalyzed hydroamination, treatment of the amino-alkene with 0.5 equivalent of triflic acid in dichloromethane at room temperature could give cyclised product.

There are two possibilities to form a carbenium ion by protonation: a secondary carbenium ion and tertiary carbenium ion (Scheme 62). If the secondary carbenium ion **187** were formed, cyclisation would occur though an overall 5-*exo*-trig process leading to the unwanted pyrrolidine **188**. As was expected, if the tertiary carbenium ion **185** were to be formed, the desired *spiro*-piperidine **186** would be obtained via an overall 6-*endo* cyclisation.



Scheme 62. Two pathways to form carbenium ion and cyclisation

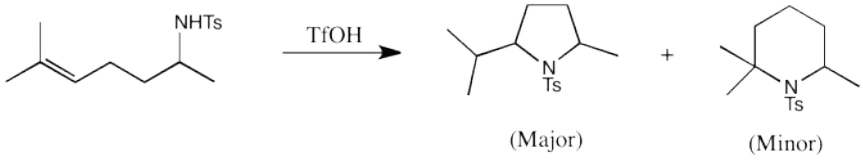
Compound **186** would most likely form carbenium ion **185** as this would be more stable than secondary carbocation **187**. The cyclisation of **184** was carried out at room temperature for 30 minutes and showed formation of the product **188** rather than of **186**. The most obvious distinction of these two compounds would be visible in their ^{1}H spectra. A poorly resolved quartet was present around 3.1 ppm, which could be attributable to the proton on C-5. A notable peak was present at 2.5 ppm (C-6) as a doublet of triplets. Those two notable peaks should belong to new compound **188**. This was further confirmed by ^{13}C spectroscopy. The quaternary carbon expected for the *spiro*-piperidine **186** was not present. Instead, two CH signals in pyrrolidine **188** were present at 41 ppm (C-6) and 58.9 ppm (C-5).



186 **188**

Although both 5-*exo*-trig and 6-*endo*-trig processes are favored, the secondary carbocation was more challenging to form than the tertiary one. It was therefore very surprising that pyrrolidine **188** was formed instead of the expected *spiro*-piperidine **186**. Maybe the stabilization afforded by the cyclohexyl group was insufficient to enable formation of the tertiary carbenium ion **185**, resulting in the formation of pyrrolidine **188**. More likely, however, is the influence of some steric factors, which make the hoped-for *spiro*-piperidine more difficult to access.

Studies into intramolecular acid-catalysed hydroamination of amino-alkenes in the Knight group, conducted by Haskins and Henderson, showed that the formation of the five-membered ring products was favoured, which were highly sterically crowded. The overall 6-*endo*-trig process was favoured kinetically to give the piperidine **191** in the cyclisations of this and related hydroxylamines, but this then rapidly isomerized to the more stable pyrrolidine **190**. Only small amounts of the piperidine **191** were ever isolated from such cyclisations (Scheme 63).[107]



189 **190** **191**

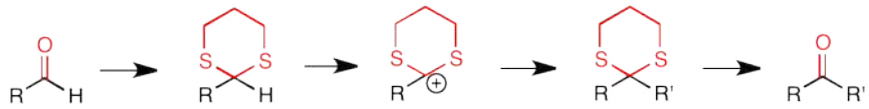
Scheme 63. Acid-catalyzed cyclization of amino-alkene

The failure to synthesize *spiro*-piperidine **186** from carbamate **185** suggests that further investigation of this acid-catalysed hydroamination via a 6-*endo*-trig process is required. According to Baldwin's rules in cyclisation, both 5-*exo*-trig and 6-*endo*-trig processes are favored. Results from previous experiments suggested that 5-*exo*-trig is more favored in our acid-catalyzed cyclisation system.

Moreover, a small amount of product from the 6-*endo*-trig process can be isolated from cyclisation, which indicated ring opening and ring closing processes may exist. Reaction conditions may be optimized to prevent these ring opening and ring closing processes in future work.

4.2.3 Preparation of 2-substituted-1,3-dithiane derivatives

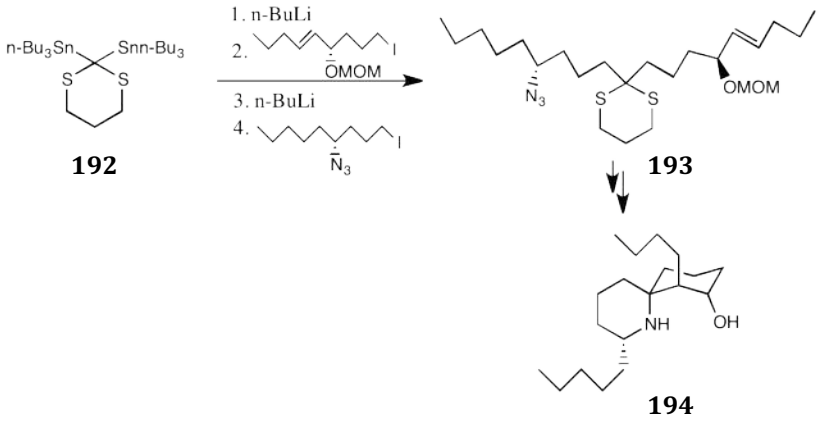
The controlled formation of carbon-carbon bonds is a critical step in organic synthesis. Organosulfur carbanions have been proven to be useful in C-C bond formation. As a temporary reversal of the functional group polarity, 1, 3-dithiane derivatives have been widely used in the total synthesis of natural products. 2-Substituted-1,3-dithiane derivatives can be easily prepared by deprotonation with alkyl lithiums of the corresponding dithiane (Scheme 64). The corresponding ketone will be obtained by reaction with an electrophile.



Scheme 64. Polarity inversion of a carbonyl group.

2-Lithio-1,3-dithiane derivatives were considered to be amongst the most successful sulfur-stabalised acyl anions due to the effect of the sulfur atoms on the adjacent carbanions by electron back-donation into vacant sulfur *d*-orbitals.[108,109] Due to the highly nucleophilic nature of dithiane anions, many electrophiles react smoothly with them, although obviously sites where reactions are not required need protection.

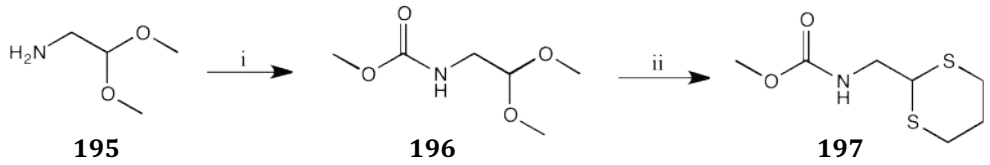
In the synthesis of compound **194**, it was found that trans-metalation at the 2-position of the dithiane **193** occurred rapidly at low temperature and this process is faster than direct metalation, allowing for the smooth introduction of the two substituent chains (Scheme 65).[110]



192 **193** **194**

Scheme 65. Transmetalation of 2-substitutied-1, 3-dithiane

Preparation of the desired 2-substitutied-1,3-dithiane **197** followed the standard procedure: treatment of carbamate **196** with 1,3-propanedithiol and boron trifluoride diethyl etherate gave **197** in an excellent yield (Scheme 66).[112]

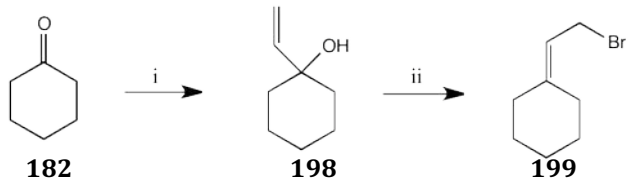


195 **196** **197**

Scheme 66. *Reagents and conditions*: i. Et_3N, $ClCO_2CH_3$, DCM, r.t, overnight; ii. $HS(CH_2)_3SH$, $BF_3.O(C_2H_5)_2$, 0°C, 6h.

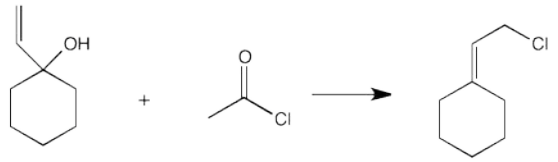
In our targeted synthesis, 1,3-dithiane derivatives can potentially be used to form cyclisation precursors by such substitutions. The resulting 2-substituted-1,3-dithiane derivatives could then undergo acid-catalysed hydroaminations to arrive at the targeted spirocyclic compounds having a 1, 3-dithiane group, which could subsequently be hydrolysed to reveal the corresponding ketone group.

In a model study, Grignard reagent addition of vinylmagnesium chloride to cyclohexanone gave the product **198** (Scheme 67), which was directly used in the next step without purification. Treatment of alcohol **198** with PBr_3 yielded only 23% of the bromide **199**. Both the Grignard and bromination products turned out to be highly sensitive compounds. Alternatively, chlorination of alcohol **198** with 1.5 equivalents of acetyl chloride **200** gave the more stable chloride **201** in excellent yield (Scheme 68).



182 **198** **199**

Scheme 67. *Reagents and conditions*: i. $CH_2CHMgBr$, THF, r.t., 12h; ii. PBr_3

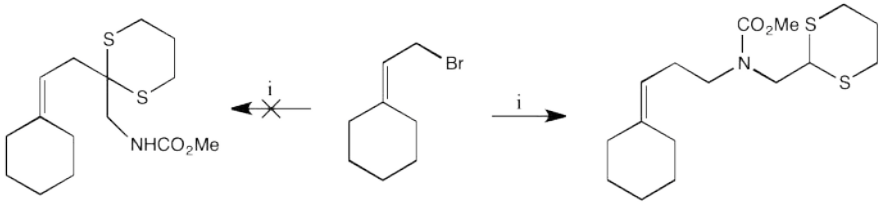


198 **200** **201**

S**cheme 68.** *Reagents and conditions*: i. 1.5 AcCl, CH_3OH, CH_2Cl_2, r.t., 2h.

Generally, 1,3-dithianes can be metallated with n-BuLi (pKa ≥ 45) and the resulting anions are sufficiently stable and reactive to serve as nucleophiles in carbon-carbon bond formation. The pKa of carbamate is approximately 17, whereas the pKa of 1,3-dithianes ranges from 30 to 35. n-BuLi is therefore a suitable choice of base in the next step.

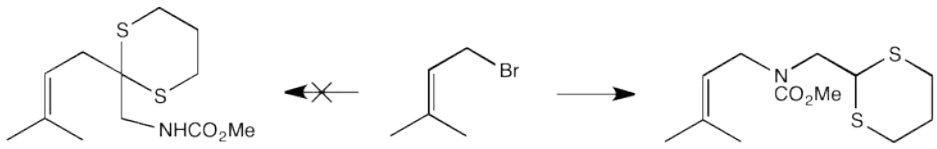
The substitution reaction of the bromide **199** and 1,3-dithiane derivatives **197** provided the product **202** instead of the expected product **142** (Scheme 69): the substitution reaction of the allylic bromide with **199** occurred on the amine, which was both surprising and disappointing. From the ^{1}H NMR spectrum of **202**, a notable triplet at 4.0 ppm indicated that substitution did not occur on the dithiane. A board singlet peak for NH was not visible. An alkene proton was observed around 5.0 ppm.



142 **199** **202**

Scheme 69. *Reagents and conditions*: i. n-BuLi, dithiane X, DMPU, -78^{o}C to -20^{o}C, overnight in freezer.

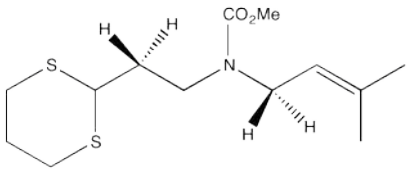
The substitution of 1,3-dithiane **197** with simple bromide **203** was tried under the same reaction conditions. Unfortunately, none of desired compound **137** was obtained but rather compound **204** (Scheme 70).



137 **203** **204**

Scheme 70. i. n-BuLi, dithiane X, DMPU, -78°C to -20°C, overnight in freezer.

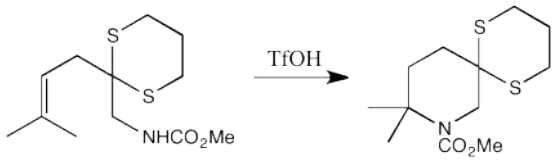
From ^{1}H NMR analysis of compound **204**, which was similar to compound **202**, a singlet peak at 5.1 ppm was assigned to the alkene. Moreover, a triplet at 4.0 ppm showed that the 1,3-dithiane starting material had not been substituted. It is notable that there are two double doublets between 3.5-4.0 ppm, which could correspond to the two protons adjacent to a nitrogen (Figure 15). The two methyl groups appear as just one singlet peak at 1.7 ppm. The product might therefore be **204**.



204

Figure 15. Two protons beside nitrogen in compound **204**

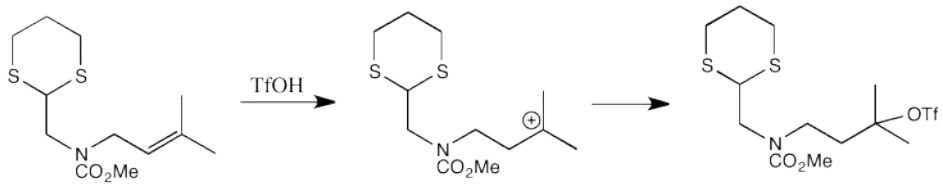
The compound generated from substitution of 1,3-dithiane was treated with triflic acid to prove the proposed structure. If building block **137** had been successfully prepared, and the foregoing conclusion incorrect, cyclisation of **137** with triflic acid should give the piperidine **138** (Scheme 71).



137 **138**

Scheme 71. Cyclisation

If carbamate **204** was formed from substitution of 1,3-dithianes, as we think is the case, a tertiary carbocation **205** will be formed when treated with triflic acid. To our surprise, the tertiary triflate **206** was isolated, thereby confirming the foregoing assignments (Scheme 72).

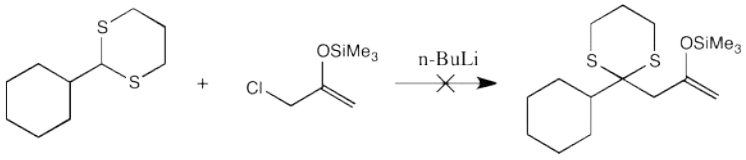


204 **205** **206**

Scheme 72. Cyclisation

The formation of compound **206** could be confirmed by ^{1}H NMR spectroscopy. First of all, a clear triplet presenting at 2.7 ppm indicated the alkene had been converted into an alkane. Secondly, a characteristic resonance of a trifluoromethyl group of **205** can be found in the carbon NMR spectrum, with four resonances appearing around 120 ppm. According to the Aldrich NMR library database, the ^{13}C NMR resonances for a trifluoromethyl group are present at 125 ppm, 121 ppm, 117 ppm and 112 ppm. Thirdly, one quaternary carbon for C-OTf in **205** was visible at 91 ppm.

A similar experimental procedure was found in a reported literature. All attempts to carry out the reaction of lithiated dithiane **207** with 3-chloro-2-(trimethylsiloxy)-1-propene **208** were unsuccessful.[111] The authors concluded that more reactive electrophiles might be required for the condensation of the lithiated dithiane (Scheme 73).



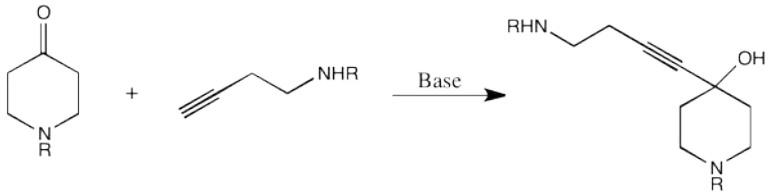
207 **208** **209**

Scheme 73. Reaction of lithiated dithiane with 3-chloro-2-(trimethylsiloxy)-1-propene

4.3 Conclusions and future work

An initial attempt was made to apply acid-hydroamination in synthesis of *bis*-piperidone failed. A large amount of time was dedicated to form the *exo*-alkene starting from *N*-tosylated piperidone. After the failed synthesis of BT-sulfones using the modified Julia olefination to generate the amino-alkene, alternative Wittig reaction and HWE reaction were also tried but only starting material could be recovered. The starting material *N*-tosylated piperidone was surprising unreactive.

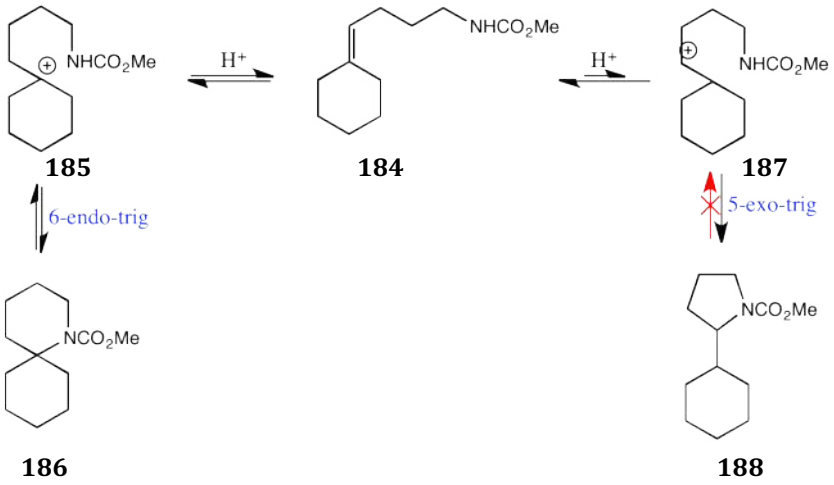
In the preparation of propargylic alcohols (Scheme 74), even though a disappearance of starting material was observed during attempted alkynylation, only a small amount of desired compound was isolated. Various terminal alkynes were tried but failed to give any of the expected products. Different bases and solvents need to be tried in future work to promote such additions of alkynes.



Scheme 74. Preparation of propargylic alcohols

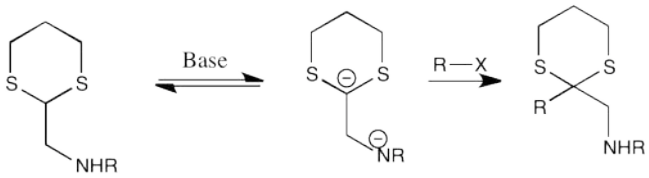
Cyclohexanone was used to replace 4-piperidone to investigate acid-catalysed hydroamination in *spiro*-cyclic compound synthesis. The carboxylic acid was prepared by a Wittig reaction in high yield, but conversion of the carboxylic acid to a carbamate via Curtius arrangement only afford less than 10% isolated product. DPPA is known to be unstable and it was difficult to purify the target product from the phosphorus residues. Sodium azide may be worth investigating in further experiments, and Lewis acids such as $Zn(OTf)_2$, $ZnCl_2$, $CuCl_2$, and AgOTf could also be effective.

In the cyclisations of the *exo*-alkene **184**, we have discovered that although the tertiary carbocation was more stable than the secondary carbocation, it was more challenging to obtain. It is proposed that triflic acid might process ring opening and ring-closing via equilibrating carbenium ions in the presence of strong acid to form the pyrrolidine **188** instead of *spiro*-piperidine **186** (Scheme 75). This problem was encountered in previous research in the Knight group.



Scheme 75. Equilibrating carbenium ions of amino-alkene

In studies into the substituition reaction of bromides and 2-substitued 1,3-dithianes, a lot of effort was dedicated towards identifying the product from the substitution reaction. Metalation of 1,3-dithianes with n-BuLi may not be complete (Scheme 76). Further investigation into the synthesis of 1,3-dithianes bearing different protecting groups is needed.



Scheme 76. Metallation of 1,3-dithianes with base

Section 5: Experimental Section

5.1 General Details

All non-aqueous reactions were performed using oven-dried glassware and under an atmosphere of dry nitrogen. Unless otherwise stated, reactions were stirred magnetically. Heated reactions were conducted in a stirred oil bath heated on a hotplate. Reactions conducted at "0°C" were cooled using an ice-water bath. Reactions conducted at "-20°C" were cooled using an ice-sodium chloride bath. Reactions conducted at "-78°C" were cooled using an acetone-solid carbon dioxide bath. "Evaporated" refers to solvent removal using a Buchi rotary evaporator with water pump vacuum and water bath at ambient temperature.

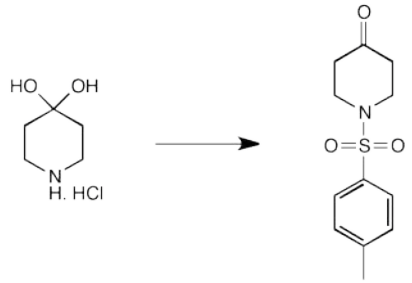
Dry tetrahydrofuran (THF) was obtained by fresh distillation from sodium wire and benzophenone. Dry dichloromethane (DCM) was obtained by fresh distillation from calcium hydride. All other dry solvents were obtained commercially from Fisher Scientific Ltd.

Silica gel chromatography and filtration were performed using Matrex Silica (35-70 μm). All reactions were monitored by TLC, using Merck silica gel 60 F254 pre-coated aluminium-backed plates and were visualised using ultraviolet light and potassium permanganate. All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infrared Spectrometer, as a solution in dichloromethane (DCM). NMR spectra were recorded on a Bruker DPX 400 instrument with proton (^{1}H) NMR spectra recorded at 400 MHz. ^{13}C spectra recorded at 125 MHz were obtained using a Bruker DPX500 instrument. Unless otherwise stated, spectra were obtained from dilute solutions in deuteriochloroform (Chloroform d; $CDCl_3$) and at 298 K. Abbreviations used for the multiplicities are: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), septet (sept.), unresolved multiplet (m). Apparent (app.) refers to overlapping peaks appearing to display a given multiplicity. Mass spectra were recorded on a Fisons VG Platform II Mass Spectrometer using atmosphere pressure chemical ionization [APCI].

As this was planned to be an extended model study, many of the products have only been characterized by proton NMR data.

5.2 Experimental data

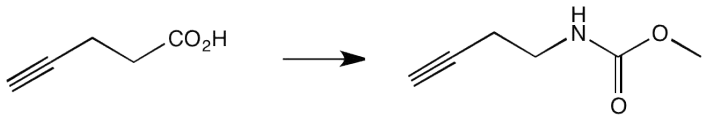
1-Tosylpiperidin-4-one 149



147 **149**

p-Toluenesulfonyl chloride (7.53 g, 39 mmol) was added to a slurry of potassium carbonate (8.90 g, 64 mmol) and 4-piperidone monohydrate hydrochloride **147** (3.80 g, 25 mmol) in water (30 mL) and CH_2Cl_2 (30 mL). The reaction mixture was vigorously stirred overnight at room temperature. Saturated aqueous sodium bicarbonate solution was added to quench the reaction. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give the *title compound* **149** as a colourless solid (8.25 g; 84%). The crude material was purified by recrystallization from petrol/DCM (10:2) and showed m.p. 280-283^oC. ^1H NMR (400 MHz / $CDCl_3$) δ: 7.2-7.6 (m, 4H, TsCH), 3.2 (t, 4H, *J* = 6.2 Hz, 2 x CH_2N), 2.40 (app. t, 4H, *J* = 6.2 Hz, 2 x $COCH_2$) and 2.30 (s, 3H, Ts CH_3). LRMS m/z calcd. for $C_{12}H_{15}NO_3S$ [M]+ = 253; found: 253.

N-(Methoxycarbonyl)-3-butynylamine 160

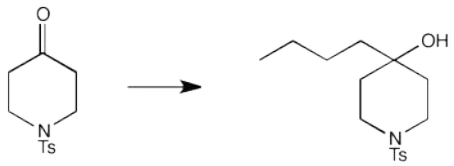


160

To a stirred mixture of 4-pentynoic acid (1.04 g, 10.6 mmol), toluene (15 mL) and triethylamine (1.48 mL, 1.08 g, 10.6 mmol). Diphenylphosphoryl azide (2.28 mL, 2.92 g, 10.6 mmol) was added *via* syringe over 2 min, and the resulting solution heated at 80^oC for 2h until bubbling ceased. The oil bath was cooled to 50^oC and methanol (4.4 mL, 102 mmol) was added. The resulting reaction

mixture was stirred at 50°C for 14h and then allowed to cool down to room temperature. The toluene and methanol was removed by rotary evaporation at room temperature. The resulting yellow oily residue was diluted with 20 mL of Et_2O, 10 mL of water and 2 mL of saturated aqueous sodium carbonate. The aqueous layer was separated and extracted with ten 10-mL portions of Et_2O, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered and concentrated to give the *title compound* **160** as a yellow oil. The crude compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 10:1) to afford the pure product as a pale yellow oil, ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.46 (app. br s, 1H, N*H*), 3.60 (s, 3H, CO_2CH_3), 3.21 (app q, 2H, J = 6.4 Hz, $NHCH_2$), 2.40 (dt, 2H, J = 2.6, 9.1Hz, 3-CH_2) and 2.00 (t, 1H, J = 2.6 Hz, alkyne-C*H*).

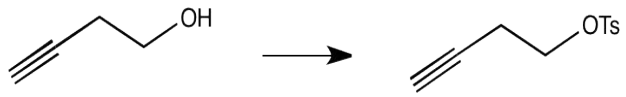
4-Butyl-1-tosylpiperidin-4-ol 161



149 **161**

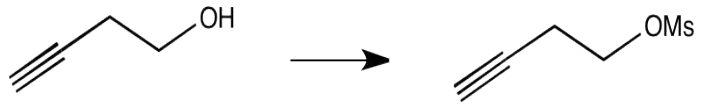
The carbamate **160** (0.267 g, 2.1 mmol, 1.0 eq.) was dissolved in dry THF (5 ml) under N_2 and the solution cooled to 0°C for 5 minutes. BuLi (2.5M in hexane, 0.15 ml, 2.02 mmol, 2.1 eq.) was then added dropwise then the temperature was maintained at 0 °C for 30 minutes, then cooled down to -78°C. Piperidone **149** (0.243 g, 0.96 mmol, 1.0 eq.) in THF (5 ml) was then added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous ammonium chloride (1 ml) was added into the reaction mixture, which was then evaporated. The residue was partitioned between water (10 ml) and dichloromethane (20 ml) and the separated organic layer dried over $MgSO_4$, filtered and evaporated to give the *title compound* **161** as a light yellow oil (0.053 g, 16%); ^{1}H NMR (400 MHz / $CDCl_3$) δ: 7.2-7.6 (m, 4H, Ts C*H*), 3.5 (d, 2H, J = 11.4 Hz, CH_2), 2.6 (td, 2H, J = 13.5, 4.7 Hz, CH_2), 1.5 (d, 2H, J = 12.5 Hz, CH_2), 1.4 (d, 2H, J = 7.2 Hz, CH_2), and 1.2 (m, 4H).

But-3-yn-1-yl 4-methylbenzenesulfonate



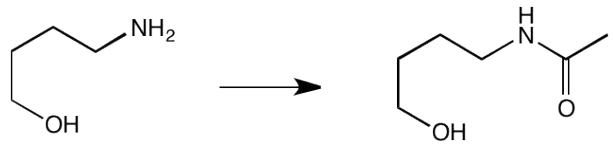
3-Butyn-1-ol (1 ml, 13.2 mmol, 1.0 eq.) was stirred in dichloromethane (12 ml) and the solution cooled to 0 °C. *p*-Toluenesulfonyl chloride (3.8 g, 20 mmol, 1.5 eq.) was added, followed by pyridine (2.2 ml, 28.4 mmol, 2.16 eq.). The resulting reaction mixture was stirred at 0°C for 3h and then was diluted with ether (35 ml) and the solution washed consecutively with water (2 x 30 ml), 1M HCl (2 x 30 ml), 2M aqueous NaOH (2 x 30 ml) and brine (30 ml), and then dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography, eluting with 30% petrol in DCM, to give the pure *title compound* (1.86 g, 77%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 7.9 (d, 2H, Ts C*H*), 7.4 (d, 2H, Ts C*H*), 4.2 (t, 2H, CH_2), 2.6 (dt, 2H, CH_2), 2.4 (s, 3H, Ts CH_3), and 2.0 (t, 1H, C*H*).

But-3-yn-1 methanesulfonate



But-3-yn-1-ol (1.08 ml, 14.2 mmol) was dissolved in dichloromethane (10 ml) and the solution cooled to 0°C. Triethylamine (9.94 ml, 71 mmol, 5 eq.) was added, followed by methanesulfonyl chloride (1.33ml, 17.0 mmol, 1.2 eq.). The reaction mixture was stirred at 0 °C for 1h and then was diluted with water (10 ml) and extracted with dichloromethane (3 × 10 ml). The combined organic layers were washed with water (2 x 10 ml) and brine (2 x 10 ml) then dried over $MgSO_4$, filtered and evaporated to give the *title compound* as a colourless oil (1.90 g, 90%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 4.3 (t, 2H, J = 6.6 Hz, CH_2), 3.0 (s, 3H, Ms CH_3), 2.6 (dt, 2H, J = 2.6, 9.3 Hz, CH_2), 2.0 (t, 1H, J = 2.6 Hz, C*H*).

Methyl (4-hydroxybutyl)carbamate 169



168 **169**

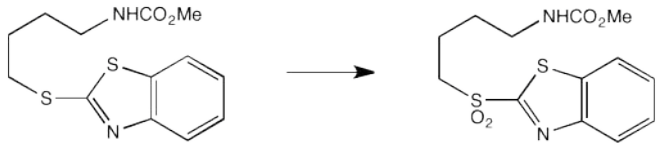
4-Amino-1-butanol (0.5 mL, 0.484 g, 5.42 mmol) was dissolved in dry DCM (5 mL) and cooled down to 0°C. Et_3N (0.83 mL, 0.604 g, 5.97 mmol) was added dropwise, followed by methyl chloroformate (0.461 mL, 0.564 g, 5.97 mmol) in DCM (5 mL). The reaction mixture was allowed to slowly warm up to room temperature and stirred for 2h. The solvent was evaporated and the residue purified by column chromatography, eluting the *carbamate* **169** (0.72g, 90%) as a colorless oil. ^{1}H NMR (400 MHz / $CDCl_3$) δ: 4.9 (br. s, 1H, N*H*), 3.6 (s, 3H, OCH_3), 3.2 (q, 2H, *J* = 7.4 Hz, CH_2N), 2.1 (br. s, 1H, O*H*), 1.6 (dt, 2H, *J* = 7.4, 3.0 Hz, CH_2), and 1.4 (t, 2H, *J* = 7.4 Hz, CH_2OH).

Methyl (4-(benzo[*d*]thiazol-2-ylthio)butyl)carbamate 170

169 **170**

To a stirred solution of the alcohol **169** (0.05g, 0.340 mmol, 1 eq.) in anhydrous THF (5ml) at room temperature under N_2 was added 2-mercapto-1,3-benzothiazole (0.068 mg, 0.41 mmol, 1.2 eq.) and triphenylphosphine (0.107g, 0.407 mmol, 1.2 eq.). The resulting solution was cooled to 0°C and diisopropyl azodicarboxylate (0.09g, 0.088 mL, 0.890 0.445 mmol, 1.3 eq.) added dropwise. The cooling bath was removed and the mixture stirred for 2h. The solvent was removed in vacuum and the residue further purified *via* column chromatography (eluting with 3% EtOAc in hexanes) to give *the titled compound* **170** as a colourless oil (0.009 g, Yield: 9%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 7.3-7.8 (m, 4H, Ts C*H*), 3.7 (s, 3H, OCH_3), 3.6 (t, 2H, *J* = 7.0 Hz, CH_2S), 3.2 (t, 2H, *J* = 6.9 Hz, CH_2N), 1.7 (dt, 2H, *J* = 3.0, 7.0 Hz, CH_2), and 1.58 (t, 2H, *J* = 7.0 Hz, CH_2OH).

Methyl (4-(benzo[*d*]thiazol-2-ylsulfonyl)butyl)carbamate 171



170 **171**

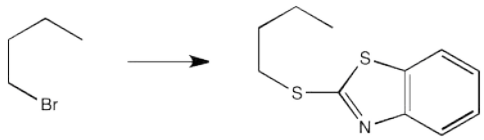
To a solution of thioether **170** (0.134 g, 0.452 mmol, 1 eq.) in methanol (10 mL) at 0°C was added sodium tungstate dihydrate (0.037 g, 0.113 mmol, 0.25 eq.) followed by 30% aqueous H_2O_2 (0.153 g, 4.52 mmol, 10 eq.). The reaction mixture was allowed to warm to room temperature and stirred for 24h. The reaction was then diluted with DCM (10 mL) and a solution of 10% aqueous $NaHSO_3$ was added. The biphasic mixture was stirred for 15 min and the layers were separated. The aqueous layer was washed with DCM (2 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated to give *the title compound* **171** as a colourless oil (0.04g, yield: 27%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 7.7-8.3 (m, 4H, Ts C*H*), 3.8 (s, 3H, OCH_3), 3.6 (t, 2H, *J* = 7.4 Hz, CH_2S), 3.2 (t, 2H, *J* = 6.9 Hz, CH_2N), 1.7 (dt, 2H, *J* = 6.9, 7.4 Hz, CH_2), and 1.6 (t, 2H, *J* = 7.4 Hz, CH_2OH).

4-((Methoxycarbonyl)amino)butyl methanesulfonate 176

169 **176**

The alcohol (200 mg, 1.36 mmol) was dissolved in dichloromethane (10 ml) and cooled to 0°C. Triethylamine (0.436 ml, 6.80 mmol) was added, followed by methanesulfonyl chloride (0.126 ml, 1.63 mmol). The reaction mixture was stirred at 0°C for 1h. The reaction mixture was extracted with water (3 x 30 ml), 2M HCl (2 x 30 ml) and 2M NaOH (2 x 30 ml), then dried over Na_2SO_4 and evaporated to give *the titled compound* **176** as a colourless oil (0.20 g, yield: 98%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 4.5 (t, 2H, *J* = 7.4 Hz, CH_2O), 3.8 (s, 3H, OCH_3), 3.2 (t, 2H, *J* = 7.4 Hz, CH_2N), 3.0 (s, 3H, Ms CH_3), 2.0 (t, 2H, *J* = 7.4 Hz, CH_2) and 1.7 (t, 2H, *J* = 7.4 Hz, CH_2).

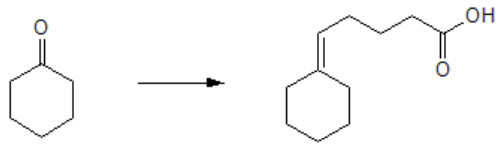
2-(Butylthio)benzo[*d*]thiazole 181



180 **181**

1-Bromobutane **180** (1 ml, 9.3 mmol) was dissolved in dichloromethane (15 ml) and 2-mercapto-1,3-benzothiazole (1.56 g, 9.3 mmol) was added. Triethylamine (2.6 ml, 18.6 mmol) was added slowly. The resulting mixture was stirred at room temperature for 19h. After the reaction was completed, the reaction mixture was washed with 2M HCl (2 x 15 ml) and saturated aqueous sodium carbonate (20 ml), then dried over Na_2SO_4, filtered and evaporated to give the *title compound* **181** as a colourless oil (1.60 g, 76%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 7.8 (t, 1H, C*H*), 7.6 (t, 1H, C*H)*, 7.4 (m, 1H, C*H*), 7.2 (m, 1H, C*H*), 3.2 (t, 2H, *J*=7.3 Hz, CH_2Br), 1.7 (m, 2H, CH_2), 1.4 (m, 2H, CH_2), and 0.83 (t, 3H, *J*=7.4 Hz, CH_3). LRMS *m/z* calcd. for $C_{12}H_{15}NO_3S$ $[M+H]^+$ = 223; found: 223.

5-Cyclohexylidenepentanoic acid 183

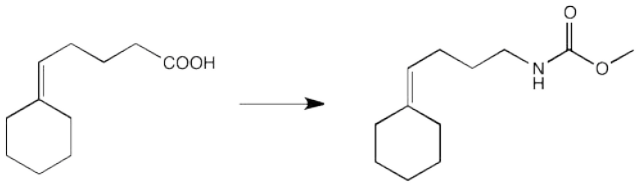


182 **183**

A solution of 4-carboxybutyltriphenylphosphonium bromide (5.43 g, 12.2 mmol) in anhydrous THF (20 ml) was treated with potassium bis(trimethylsilyl)amide (4.88 g, 24.8 mmol), and the resulting orange mixture was stirred at room temperature for 15 min. A solution of cyclohexanone (300 mg, 3.06 mmol) in anhydrous THF (10 ml) was then added and the resulting heterogeneous mixture stirred at room temperature for 3h. The reaction was quenched with water (10 ml), and the water layer was extracted with ether to remove the unreacted cyclohexanone. The water layer was then acidified with 10% HCl to pH 2, and extracted with ethyl acetate. The combined organic extracts were washed with brine and then dried with $MgSO_4$. The solvent was evaporated *in vacuo* to give the *title product* **183** as a colourless oil (0.38 g, 67%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 4.9 (t, *J* = 7.4

Hz, 1H, CH=C), 2.2 (t, *J* = 7.2 Hz, 2H, C*H*$_2$CO), 2.0-1.9 (m, 6H, C*H*$_2$), and 1.6-1.4 (m, 8H, C*H*$_2$). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 180.4(*C*OOH), 140.9 (*C*=CH), 129.6 (C=*C*H), 37.2 (*C*H$_2$), 33.4 (*C*H$_2$), 28.7 (*C*H$_2$), 28.7 (*C*H$_2$), 27.8 (*C*H$_2$), 26.9 (*C*H$_2$), 26.3 (*C*H$_2$), 25.0 (*C*H$_2$).

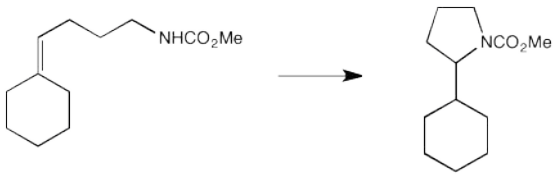
Methyl (4-cyclohexylidenebutyl)carbamate 184



183 **184**

Diphenylphosphoryl azide (0.311 ml, 1.25 mmol) and triethylamine (0.201 ml, 1.45 mmol) were added to a solution of the foregoing cyclohexylidenepentanoic acid **183** (0.24 g, 1.32 mmol) in dry toluene (7 ml). The reaction mixture was heated under reflux for 1h under N_2. Zinc chloride (0.5M in THF, 0.262 ml, 0.132 mmol) and methanol (3.2 ml) were added and the mixture was heated under reflux for 1h. After the reaction was completed, the reaction mixture was extracted, and then dried over $MgSO_4$, filtered and evaporated to give the *carbamate* **184** as a colourless oil (0.28 g, 18%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 4.94 (t, *J* = 14.6 Hz, 1H, C*H*=C), 4.80 (br s, 1H, N*H*), 3.58 (s, 3H, CO_2CH_3), 2.0 -1.9 (m, 6H, 3 x C*H*$_2$), and 1.4 - 2.0 (m, 10H, 5 x C*H*$_2$). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 157.4 (CO), 140.6 (*C*=CH), 125.4 (C=*C*H), 51.9 (OCH_3), 40.8 (CH_2N), 37.1 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 24.3 (CH_2). HRMS (EI) *m/z calcd.* For $C_{12}H_{21}NO_2$ $[M]^+$ = 2112.1651, found: 212.1660.

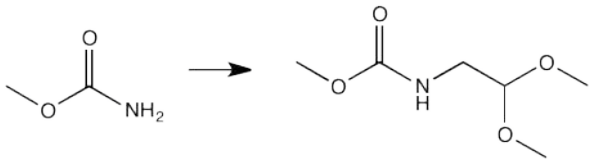
Methyl 2-cyclohexylpyrrolidine-1-carboxylate 188



184 **188**

The carbamate **184** (0.188 g, 0.558 mmol, 1 eq.) was dissolved in dichloromethane (5 ml), to which was added triflic acid (0.025ml, 0.247 mmol, 0.5 eq.) and stirred at 0°C for 30 mins. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 m) and the two layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml), the combined organic layers were dried over $MgSO_4$, filtered, and evaporated to give the *title compound* **188** as a colourless oil (0.05 mg, Yield: 42%). ^{1}H NMR (400 MHz/ $CDCl_3$) δ: 3.6 (s, 3H, OC*H*$_3$), 3.4 (t, 2H, J=6.0 Hz, NC*H*$_2$), 3.1 (app. q, C*H*N), 2.51 (dt, 2H, CHC*H*), 1.6- 1.3 (m, 14H, 7XC*H*$_2$). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 156.4 (*C*O), 58.9 (*C*H) 51.7 (O*C*H$_3$), 40.7 (*C*H), 33.4 (*C*H$_2$), 33.1 (*C*H$_2$), 31.1 (*C*H$_2$), 26.7 (*C*H$_2$), 26.4 (*C*H$_2$), 25.6 (*C*H$_2$), 23.5 (*C*H$_2$), 22.8 (*C*H$_2$). HRMS *m/z* calcd. for $C_{12}H_{21}NO_2$ $[M]^+$ = 211.1572, found: 211.1573.

Methyl 2,2-dimethoxyethyl carbamate 196

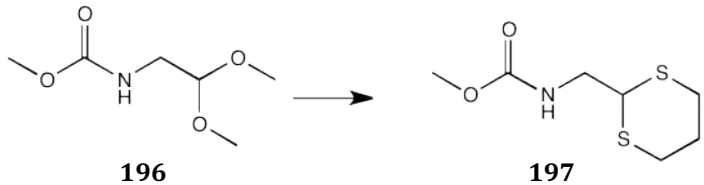


195 **196**

To a solution of amino acetaldehyde dimethyl acetal (10 ml, 89 mmol, 1.0 eq.) in dichloromethane (100 ml) at 0^{o}C triethylamine (27.3 ml, 196 mmol, 2.2 eq.) was added dropwise, followed by the dropwise addition of methyl chloroformate (8.27 ml, 107 mmol, 1.2 eq.). The resulting solution was allowed to warm to room temperature and stirred overnight. The solution was diluted by the addition of dichloromethane and washed with 0.2M hydrochloric acid (3 x 50 mL), water (4 x 50 mL) and brine (2 x 50 mL). The combined organic layers were then dried over $MgSO_4$, filtered and

evaporated to give the *title compound* **196** as an orange oil (9.87 g, 68%); ^{1}H NMR (400 MHz / CDCl3) δ: 4.9 (br s, 1H, N*H*), 4.3 (t, 1H, *J* = 5.4 Hz, C*H*(OMe)$_2$), 3.6 (s, 3H, C*H*$_3$O$_2$C), 3.4 (s, 6H, 2 x OC*H*$_3$), 3.25 (app dd, 2H, *J* = 5.4, 2.1 Hz, C*H*$_2$N)

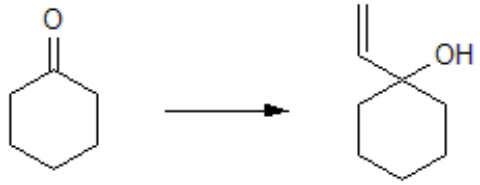
Methyl N-(1,3-dithian-2-ylmethyl)carbamate 197



196 **197**

To a solution of the carbamate **196** (4.08 g, 25.0 mmol, 1 eq.) in dichloromethane (50 ml) at 0^{o}C, 1,3-propanedithiol (2.51 mL, 25.0 mmol, 1 eq.) was added dropwise, followed by the addition of boron trifluoride diethyl etherate (8.15 mL, 50.3 mmol, 2.1 eq.). The mixture was allowed to stir for 6h at 0^{o}C before warming to room temperature. The mixture was then poured into aqueous 2M potassium hydroxide (100 mL) and the organic layer separated. This organic layer was washed with brine (3 x 25 mL), dried with $MgSO_4$, filtered and evaporated to give the *title compound* **197** as a chalky white solid (3.89 g, 90%); m.p. 75-77^{o}C. ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.49 (1H, br, s, NH), 3.95 (1H, t, *J* = 7.1 Hz, CHS_2), 3.57 (3H, s, CH_3O_2C), 3.46 (2H, t, *J* = 6.4, CH_2N), 2.81 (2H, ddd, *J* = 14.0, 7.0, 2.4 Hz, 2 x SCH_2), 2.66 (2H, td, *J* = 9.6, 2.4 Hz, 2 x SCH_2), 2.01-1.94 (1H, m, SCH_2CH_A), 1.87-1.79 (1H, m, SCH_2CH_B). ^{13}C NMR (125 MHz/$CDCl_3$) δ: 156.9 (C=O), 52.2 (CH_3O_2C), 45.4 (CHS_2), 44.3 (CH_3N), 28 (2 x CH_2), 25.6 (CH_2).[112]

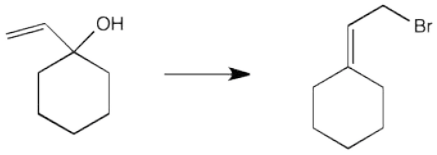
1-Vinylcyclohexanol 198



182 **198**

To a THF solution (20 mL) of cyclohexanone (1.96 g, 2.07 mL, 20 mmol, 1 equiv.) was added vinylmagnesium bromide (30 mL, 30 mmol, 1.5 equiv.). After stirring for 16h at room temperature, an aqueous solution of NH_4Cl (50 mL, 1M) was added. The organic and aqueous layers were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and the filtrate evaporated. The residue was purified by column chromatography (silica gel, petroleum ether/ether = 10:1) to give *the title compound* **198** as a colourless oil (1.94g, 77%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.8 (dd, 1H, *J* = 9.5, 16.7 Hz, C*H*), 5.2 (dd, 1H, *J* = 16.7, 1.3 Hz, C*H*), 4.9 (dd, 1H, *J* = 9.5, 1.3 Hz, C*H*), and 1.4-1.5 (m, 10H, 5 x CH_2).

***β*-Cyclohexylideneethyl bromide 199**



198 **199**

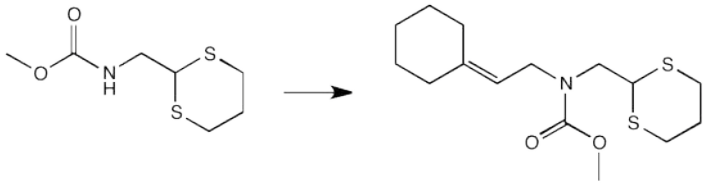
To 1-vinylcyclohexanol **198** (0.203 g, 1.61 mol) containing anhydrous pyridine (0.013 mL) in 3mL anhydrous petroleum ether (b. p. 40-60^{o}c) was added phosphorus tribromide (0.189 mL, 2.01mmol) dropwise under efficient cooling and stirring. The solution was kept for 16h at room temperature, then decomposed with ice-cold water (5 mL) and extracted with petroleum ether (5 mL). The petroleum ether extracts were washed free of acid with saturated salt solution and finally with dilute sodium bicarbonate solution, and water, dried over Na_2SO_4, and the solvent removed under vacuum and the residue distilled to give *the title compound* **199** (0.14 g, yield: 46%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.4 (td, 1H, *J* = 7.5, 1.1 Hz, C*H*) 3.9 (d, 2H, *J* = 7.5 Hz, CH_2), and 1.4 - 1.5 (m, 10H, 5 x CH_2).

***β*-Cyclohexylideneethyl chloride 201**

198 **201**

To a magnetically stirred solution of the alcohol **190** (0.316 g, 2 mmol, 1 equiv.) in DCM (10 ml) was added AcCl (0.213 ml, 3 mmol, 1.5 equiv.). The mixture was stirred at room temperature. After addition of H_2O (25 mL), the organic layer was separated and washed with aqueous $NaHCO_3$ solution (25 mL) and H_2O (25 mL) then dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the *chloride* **201** (0.341 g, yield: 94%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.3 (t, 1H, J = 8.0 Hz, C*H*), 4.1 (d, 2H, J = 8.0 Hz, CH_2Cl), and 1.6-1.9 (m, 10H, 5 x CH_2).

Methyl ((1,3-dithian-2-yl)methyl)(3-cyclohexylidenepropyl)carbamate 202

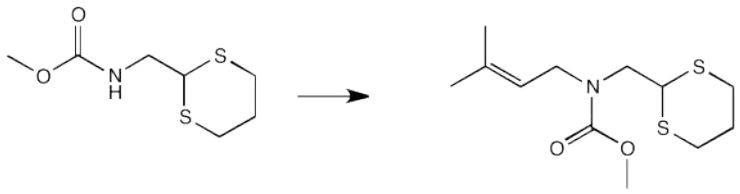


199 **202**

To a stirred solution of dithiane **196** (0.230 g, 1.11 mmol, 1.5 eq.) in THF (15 ml) at -40 °C was added a 2.5M solution of n-BuLi in hexanes (0.086 ml, 2.3 mmol, 3.1 eq.). The resulting solution was stirred for 2h at -20 °C. The solution was then cooled to -78°C and DMPU (0.57 ml, 4.44 mmol, 6 eq.) was added dropwise and the solution was stirred for a further 1h at -78°C. The solution was carefully transferred by cannula to a solution of bromide **199** (0.14 g, 0.7 mmol, 1.0 eq.) in THF (10 ml) at -78°C. The reaction mixture was stirred at -78°C for 4h followed by warming slowly to -20°C and kept in the freezer overnight. The reaction mixture was then poured into ice water (50 ml) and the aqueous layer was extracted with ether (5 x 20 ml). The combined organic layers were dried over $MgSO_4$ then filtered and evaporated to give the crude title product. The crude mixture was separated

by column chromatography using 15% ethyl acetate in hexane to give the *titled compound* **202** as a pale oil (0.19g, yield: 81%). ^{1}H NMR (400 MHz / $CDCl_3$) δ: 5.2 (app. t, 1H, *J* = 6.9 Hz, C*H*=C), 4.0 (t, 1H, *J* = 4.1 Hz, C*H*S), 3.6 (s, 3H, *O*C*H*$_3$), 3.5 (t, 2H, *J* = 6.1 Hz, C*H*$_2$N), 3.5 (t, 2H, *J* = 4.1 Hz, C*H*$_2$CH$_2$), 2.8 (ddd, 2H, *J* = 14.0, 7.0, 2.4 2 x SCH_2), 2.7 (2H, td, *J* = 9.6, 2.4 Hz, 2 x SC*H*$_2$), 2.0 – 1.9 (1H, m, SCH_2CH_a), 1.9 - 1.8 (1H, m, SCH_2CH_b) and 1.5 (m, 10H, 5 x CH_2).

Methyl ((1,3-dithian-2-yl)methyl)(3-methylbut-2-en-1-yl)carbamate 204



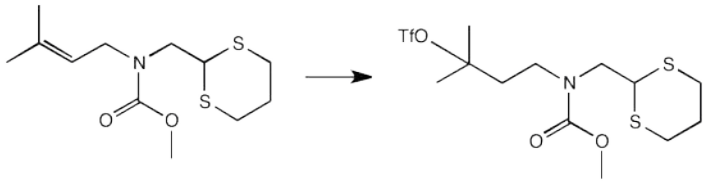
199 **204**

To a stirred solution of dithiane **199** (1.43 g, 6.9 mmol, 1.5 eq.) in THF (37.5 ml) at -40°C was added a 2.5M solution of n-BuLi in hexanes (5.7 ml, 14.28 mmol, 3.1 eq.). The resulting solution was stirred for 2h at -20°C. The solution was then cooled to -78°C and DMPU (3.38 ml, 27.7 mmol) was added dropwise and the solution was stirred for a further 1h at -78°C. The solution was carefully transferred by cannula to a solution of 1-bromo-3-methyl-2-butene (0.536 ml, 4.61 mmol, 1 eq.) in THF (20 ml) at -78°C. The reaction mixture was stirred at -78 °C for 4h followed by warming slowly to -20°C and kept in the freezer overnight. The reaction mixture was then poured into ice water (50 ml) and the aqueous layer was extracted with ether (5 x 20 ml). The combined organic layers were dried over Mg_2SO_4 then filtered and evaporated to give the crude title product. The crude mixture was separated by column chromatography using 15% ethyl acetate in hexane to give pure N-*alkylated dithiane* **204** as a light yellow oil (0.835g, 44%), as a pair of rotomers.

204a ^{1}H NMR (400 MHz/ $CDCl_3$) δ: 5.1 (br. s, 0.43H, C=C*H*), 4.1 (t, 0.43H, *J* = 7.4 Hz, SC*H*), 3.9 (d, 0.43H, *J* = 5.6 Hz, NCH_2CH), 3.6 (s, 0.43H, CO_2CH_3), 3.4 (d, 0.43H, *J* = 7.4 Hz, C=CHCH_2), 2.9-2.8 (m, 0.86H, 2 x SCH_2), 2.1-1.9 (m, 0.43H), 1.9-1.8 (m, 0.43H), and 1.6 (s, 1.29H, 2 x CH_3). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 156.9 (*C*O), 136 (C_q), 120.1 (*C*H), 52.7 (O*C*H_3), 50.0 (*C*H_2N), 45.7 (S*C*H_2), 44.4 (SCH$_2$*C*H2$_2$), 28.8 (CH*C*H_2N), 25.8 (*C*H_2), and 25.3 (*C*H_3).

204b ^{1}H NMR (400 MHz/ $CDCl_3$) δ: 5.1 (br. s, 0.57H, C=C*H*), 4.1 (t, 0.57H, *J* = 7.4 Hz, SC*H*), 3.9 (d, 0.57H, *J* = 5.6 Hz, NCH_2CH), 3.6 (s, 0.57H, CO_2CH_3), 3.4 (d, 0.57H, *J* = 7.4 Hz, C=CHCH_2), 2.9 - 2.8 (m, 1.14H, 2 x SCH_2), 2.1-1.9 (m, 0.57H), 1.9-1.8 (m, 0.57H), and 1.6 (s, 0.57H, CH_3). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 156.6 (*C*O), 135.6 (C_q), 120 (*C*H), 52.7 (O*C*H_3), 49.3 (*C*H_2N), 45.3 (S*C*H_2), 44.4 (SCH$_2$*C*H2$_2$), 28.2 (CH*C*H_2N), 25.8 (*C*H_2), and 17.9 (*C*H_3). IR (neat) ν/cm^{-1}: 2920, 1702, 1470, 1436, 1228, 1128, 942, 768. LRMS *m/z* calcd. for $C_{12}H_{21}NO_2S_2$ $[M]^+$ = 275, found: 275.

4-(((1,3-Dithian-2-yl)methyl)(methoxycarbonyl)amino)-2-methylbutan-2-yl trifluoromethanesulfonate 206



204 **206**

The dithiane **204** (135 mg, 0.49 mmol, 1 eq.) was dissolved in DCM (5 ml), to which was added triflic acid (0.021ml, 0.24mmol, 0.5 eq.) and the solution stirred at 0^{o}C for 30 mins. The reaction was quenched by the addition of saturated aqueous K_2CO_3 (15 m) and the two phases were separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml), the combined organic layers were dried over Mg_2SO_4, filtered, and evaporated to give *the title compound* **206** as a colourless oil (103 mg, 49%). ^{1}H NMR (400 MHz/ $CDCl_3$) δ: 4.2 (t, 1H, *J* = 8.0 Hz, SC*H*), 4.1 (s, 3H, OCH_3), 3.9 (d, 2H, *J* = 8.0 Hz, CH_2), 3.7 (t, 2H, *J* = 6.1 Hz, NCH_2), 2.9 - 2.8 (m, 2H, 2 x SCH_2), 2.2 (t, 2H, *J* = 6.1, CH_2C), 2.0 - 1.9 (m, 2H, CH_2), 1.5 (s, 6H, 2 x CH_3). ^{13}C NMR (125 MHz/ $CDCl_3$) δ: 157.0 (CO), 120.0 (CF_3), 91.3 (Cq), 49.9 (CH_2N), 49.3 (CH_2), 52.6 (OCH_3), 28.2 (SCH2), 28.7 (SCH_2), 25.7 (CH_2), and 17.8 (CH_3).

References:

[1] *World Cancer Report 2014,* World Health Organisation, **2014.**

[2] Baylin S. B.; Ohm J. E. *Nature Reviews Cancer,* **2006,** *6,* 107.

[3] D. E. Thurston, Chemistry and Pharmacology of Anticancer Drugs, CRC Press, UK, **2006**

[4] Pourquier P. *Bull Cancer,* **2011,** *98,* 1237.

[5] Demain A. L.; Vaishnav P. *Microbial Biotechnol.,* **2011,** *4,* 687.

[6] Goppi P. G.; Broglia C.; Merli F.; Dell'Olio M.; Stelitano C.; Lannitto E.; Federico M.; Berte R.; Luisi D.; Molica S.; Cacalli C.; Dezza L.; Ascari E. *Cancer,* **2003,** *98,* 2393.

[7] Wall M. E.; Wani M. C.; Cook C. E.; Palmer K. H.; McPhail A. I. Sim G. A. *J. Am. Chem. Soc.,* **1966,** *88,* 3888.

[8] Jang M.; Cai L.; Udeani G. O.; Slowing K. V.; Thomas C. F.; Beecher C. W. W.; Fong H. H. S.; Farmsworth N. R.; Kinghorn A. D.; Mehta R. G.; Moon R. C.; Pezzuto J. M. *Science,* **1997,** *275,* 218.

[9] Park J. W.; Choi Y. J.;Jiang M. A.; Lee Y. S.; Jun D. Y.; Suh S.; Baek W. K.; Suh M.;JinI.; Kwon T. K. *Cancer Lett.,* **2001,** *163,* 43.

[10] Longer Against Shorter (ATLAS) Collaborative Group, *The Lancet,* **2013,** *381,* 805.

[11] Cohen P. *Nature Reviews Drug Discovery,* **2002,** *1,* 309.

[12] Smith C. *Nature,* **2003,** *422,* 341.

[13] Lipinski C. A.; Lombardo F.; Dominy B. W.; Feeney P. *J. Advanced Drug Delivery Reviews,* **2001,** *46,* 3.

[14] Hughes J. P.; Rees S.; Kalindjian S. B.; Philpott K. L. *Br J Pharmacol.,* **2011,** *162,* 1239.

[15] Cheng K., Korfmacher W. A.; White R. E.; Njoroge F. G. *Perspect Medicin Chem.* **2007,** *1,* 1.

[16] Pandeya S. N.; Thakkar D. *Ind. J. Chem.*, 2005, 44B, 335.

[17] Simon R. J.; Zuckermann R. N.; Huebner V. D.; Jewell D. A.; *Proc. Natl Acad Sci USA,* **1992,** *89,* 9367.

[18] Tan D. K.; Foley M. A.; Stockwell B. R.; Shair M. D.; Schreiber S. L. *J. Am. Chem. Soc.,* **1999,** *121,* 9073.

[19] Amin A.; Gali-Mulitasib H.; Ocker M.; Schneider-Stock R. *Int. J. Biomed. Sci.,* **2009,** *5,* 1.

[20] Gordaliza M. *Clin Transl Oncol,* **2007,** *9,* 767.

[21] Cragg G. M.; Newman D. J. *Journal of Ethnopharmacology 100,* **2005,** 72.

[22] Holton R. A.; Kim H. B.; Somoza C.; Liang F.; Biediger R. J.; Boatman P. D.; Shindo M.; Smith C. C.; Kim S.; Nadizadeh H.; Suzuki Y.; Tao C.; Vu P.; Tang S.; Zhang P.; Murthi K. K.; Gentile L. N.; Liu J. H. *J. Am. Chem. Soc.,* **1994**, *116*, 1599.

[23] Nicolaou K. C.; Yang Z.; Liu J. J.; Ueno H.; Nantermet P. G.; Guy R. K.; Claiborne C. F.; Renaud J.; Couladouros E. A.; Paulcannan K.; Sorensen E. J. *Nature*, **1994**, *367*, 630.

[24] Danishefsky S. J.; Masters J. J.; Young W. B.; Link J. T.; Snyder L. B.; Magee T. V.; Jung D. K.; Isaacs R. C. A.; Bornmann W. G.; Alaimo C. A.; Coburn C. A.; Di Grandi M. J. *J. Am. Chem. Soc.,* **1996**, *118*, 2843.

[25] Wender P.A.; Badham N. F.; Conway S. P.; Floreancig P. E.; Glass T. E.; Houze J. B.; Krauss N. E.; Lee D.; Marquess D. G.; McGrane P. L.; Meng W.; Natchus M. G.; Shuker A. J.; Sutton J. C.; Taylor R. E. *J. Am. Chem. Soc.,* **1997**, *119*, 2757.

[26] Morihira K.; Hara R.; Kawahara S.; Nishimori T.; Nakamura N.; Kusama H.; Kuwajima I. *J. Am. Chem. Soc.,* **1998**, *120*, 12980.

[27] Mukaiyama T.; Shiina I.; Iwadare H.; Saitoh M.; Nishimura T.; Ohkawa N.; Sakoh H.; Nishimura K.; Tani Y.; Hasegawa M.; Yamada K.; Saitoh K. *Chem. Eur. J.* **1999**, *5*, 121.

[28] Doi T.; Fuse S.; Miyamoto S.; Nakai K.; Sasuga D.; Takahashi T. *Chem. Asian. J.*, **2006**, *1*, 370.

[29] Walji A. M.; MacMillan D. W. C. *Synlett*, **2007**, *20*, 1477.

[30] Mans D. R. A.; Jung F. A.; Schwartmann G. *J. Brazilian Assoc Advancement Sci.*, **1994**, *46*, 70.

[31] Jones S.E.; Erban J.; Overmoyer B.; Budd G. T.; Hutchins L.; Lower E.; Laufman L.; Sundaram S.; Urba W. J.; Pritchard K. I.; Mennel R.; Richards D.; Olsen S.; Meyers M. L.; Ravdin P. M. *J. Clin. Oncology.*, **2005**, *23*, 5542.

[32] Lydon N. B.; Druker B. J. *Leukemia Research 28S1*, **2004**, S29.

[33] Lai. H. C.; Singh N. P. *Anticancer Res.*, **2004**, *24*, 2277.

[34] Efferth T.; Dunstan H.; Sauerbrey A.; Miyachi H.; Chitambar C. R. *Int. J. Oncol,* **2001**, *18*, 767

[35] Lai H.; Singh N. P.; Sasaki T. *Invest New Drugs.*, **2013**, *31*, 230.

[36] Monoclonal Antibodies: Principles and Pactice, 3rd ed. Jm1996, Academic press, London.

[37] Alkan S. S.; *Nature Reviews immunology*, **2004**, *4*, 153.

[38] Pandeya S. N.; Thakkar D. *Ind. J. Chem.*, 2005, 44B, 335.

[39] Simon R. J.; Zuckermann R. N.; Huebner V. D.; Jewell D. A.; Proc. *Natl. Acad. Sci. USA*, **1992**, *89*, 9367.

[40] Tan D. K.; Foley M. A.; Stockwell B. R.; Shair M. D.; Schreiber S. L. *J. Am. Chem. Soc.*, **1999**, *121*, 9073.

[41] Diaba F.; Ricou E.; Bonjoch J., *Tetrahedron: Asymmetry*, **2006**, *17*, 1437.

[42] KuehneM. E.; Bornmann W. G.; Parsons W. H.; Spitzer T. D.; Blount J. F.; Zubieta J. *J. Org. Chem.*, **1988**, *53*, 3439.

[43] Langkoft E.; Schinzer D. *Chem. Rev.* **1995**, *95*, 1375.

[44] Rios R. *Chem. Soc. Rev.* **2012**, *41*, 1060.

[45] Canesi S.; Bouchu D.; Ciufolini M. A. *Angew. Chem. Int. Ed.,* **2004,** *43,* 4336.

[46] Canesi S.; Belmont P.; Bouchu D.; Rousset L.; Ciufolini M. A. *Tetrahedron Lett.,* **2002,** *43,* 5193.

[47] Canesi S.; Bouchu D.; Ciufolini M. A. *Org. Lett.,* **2005,** *7,* 175.

[48] Kan T.; Fujimoto T.; Leda S.; Asoh Y.; Kitaoka H.; Fukuyama T. *Org. Lett.* **2004,** *6,* 2729.

[49] Ikeda M.; Hirose K.; El Bialy S. A. A.; Sato T.; Yakura T.; Bayomi S. M. *Chem. Pharm. Bull.,* **1998,** *46,* 1084.

[50] Dake G. *Tetrahedron,* **2006,** *62,* 3467.

[51] Nagumo S.; Nishida A.; Yamazaki C.; Matoba A.; Murashige K.; Kawahara N., *Tetrahedron.,* **2002,** *58,* 4917.

[52] Liebowitz S. M.; Belair E. J.; Witiak D. T.; Ledenicer D. *Eur. J. Med. Chem. -Chim. Ther.,* **1986**, *21*, 439.

[53] Pilli R. A.; de Sousa A. L. *Org. Lett.,* **2005,** *7,* 1617.

[54] Elliott C. E.; Miller D. O.; Burnell D. J. *J. Chem. Soc, Perkin Trans,* **2002,** 217.

[55] Palmer L. I.; de Alaniz J. R. *Angew. Chem. Int. Ed.,* **2011,** *50,* 7167.

[56] Yeh M. C. P.; Pai H. F.; Hsiow C. Y.; Wang Y. R. *Organometallics,* **2010,** *29,* 160.

[57] Chen Z.; Tu Y.; Zhang S.; Zhang F. *Org. Lett.,* **2011,** *13,* 724.

[58] Li J.; Lee D. *Chem. Sci.* **2012,** *3,* 3296.

[59] Hedley S. J.; Moran W. J.; Price D. A.; Harrity J. P. A. *J. Org. Chem.,* **2003,** *68,* 4286.

[60] Grigg R.; Markandu J.; Surendrakumar S.; Thornton-Pett M.; Warnock W. J . *Tetrahedron Lett.,* **1992,** *48,* 10399.

[61] Lee S.; Zhao Z. *Org. Lett.,* **1999,** *1,* 681.

[62] El Bialy S. A. A.; Braun H.; Tietze L. F. *Synthesis.,* **2004,** *14,* 2249.

[63] Hatano M.; Mikami K. *J. Mol. Catal. A: Chem.,* **2003,** *196,* 165.

[64] Corkey B. K.; Toste F. D. *J. Am. Chem. Soc.,* **2007,** *129,* 2764.

[65] Rios R. *Chem. Soc. Rev.***2012***, 41,* 1060.

[66] Guazzelli G.; Duffy L. A.; Procter D. J. *Org. Lett.,***2008***, 10,* 4291.

[67] Yeh M. C. P.; Fang C. W.; Lin H. H. *Org. Lett.,***2012***, 14,* 1830.

[68] Ramanathan B.; Odom A. L. *J. Am. Chem. Soc.,* **2006,** *128,* 9344.

[69] Parameswarappa S.; Pigge F. C. *Tetrahedron Lett.,* **2011,** *52,* 4357.

[70] Edwards A. S.; Wybrow R. A. J.; Johnstone C.; Adams H.; Harrity J. P. A. *Chem.Commun.,* **2002,** 1542.

[71] Suga S.; Watanabe M.; Yoshida J. *J. Am. Chem. Soc.,* **2002,** *124,* 14824.

[72] Isono N.; Mori M. *J. Org. Chem.,* **1995,** *60,* 115.

[73] Tanner D.; Hagverg L.; Poulsen A. *Tetrahedron,* **1999,** *55,* 1427.

[74] Gracias V.; Gasiecki A.F.; Moore J. D.; Zanze I. A.; Djuric S.W. *Tetrahedron Lett.,* **2006,** *47,* 8977.

[75] Chiu F. T.; Ullrich J. W.; Mariano P. S. *J. Org. Chem.,* **1984,** *49,* 228.

[76] Kalatizakis D.; Antonatou E.; Vassilikogiannakis G. *Chem. Commun.,* **2014***,* 400.

[77] Cheng X.; Xia Y.; Wei H.;Xu B.; Zhang C.; Li Y.;Qian Q.; Zhang X.; Li K.; Li W. *Eur. J. Org. Chem.* **2008**, 1929.

[78] Penzien J.; Su R. Q.; Muller T. E. *J. Molecular Catatlysis A: Chemical*, **2002**, *182*, 489.

[79] Zhang J.; Yang C. He C. *J. Am. Chem. Soc.*, **2006**, *128*, 1798.

[80] Hong S.; Marks T. J. *Acc. Chem. Res.*, **2004**, *37*, 673.

[81] Crimmin M. R.; Casely I. J.; Hill M. S. *J. Am. Chem. Soc.*, **2005**, *127*, 2042.

[82] Mathia F.; Szolcsányi P. *Org. Biomol. Chem.*, **2012**, *10*, 2830.

[83] Zulys A.; Dochnahl M.; Hollmann D.; Lohnwitz K.; Herrmann J. Roseky P. W.; Blechert S.; *Angew. Chem. Int. Ed.*, **2005**, *44*, 7794,

[84] Brown A. R.; Uyeda C.; Brotherton C. A.; Jacobsen E. N. *J. Am. Chem. Soc.*, **2013**, *135*, 6747.

[85] Schlummer B.; Hartwig J. F. *Org. Lett.***2002**, *4*, 1471.

[86] Aderson L. L.;Arnold J.; Bergman R. G. *J. Am. Chem. Soc.*, **2005**, *127*, 14542.

[87] Li Z.; Zhang J.; Brouwer C.; Yang C.; Reich N. W.; He C. *Org. Lett.*, **2006**, *8*, 4175.

[88] Jimenez O.; Müller T. E.; Schwieger W.; Lercher J. A. *J. Catal.*, **2006**, *239*, 42.

[89] Knight D.W.; Jones A. D.; Hibbs D. E. *J. Chem. Soc., Perkin Trans. 1*., **2001**, 1182.

[90] Knight D. W.; Sharland C. M. *Synlett*, **2005**, 2258.

[91] Haskins C. M.; Knight D. W. *Tetrahedron*. **2010**, *66*, 4150.

[92] Haskins C. M.; Knight D. W. *Chem. Commun*. **2002**, 2724.

[93] McNally A.; Haffemayer B.; Beatrice S. L.; Mattew J. *Nature*, **2014**, *510*, 129.

[94] Avlonitis N.; Lekka E.; Detsi A.; Koufaki M.; Calogeropoulou T.; Scoulica E.; Siapi E.; Kyrikou I.; Mavromoustakos T.; Tostonos A.; Grdadolnik S. G.; Makriyannis A. *J. Med. Chem.* **2003**, *46*, 755.

[95] Wadsworth W. S; Emmons W. D. *J. Am. Chem. Soc.*, **1961**, *83*, 1733.

[96] Reddy K.R.; Lubian E.; Pavan M. P.; Kim H.; Yang E.; Holten D.; Lindsey J. S. *New. J.Chem.*, **2013**, *37*, 1157.

[97] Ishikawa T.; Mizuta T.; Hagiwar K.; Aikawa T.; Kudo T.; Saito S. *J. Org. Chem.*, **2003**, *68*, 3702.

[98] Mukai C.; Kobayashi M.; Kubota S.; Takahashi Y.; Kitagaki S. *J. Org. Chem.*, **2004**, *69*, 2128.

[99] Chatterjee .; Bera S.; Mondal D. *Tetrahedron: Asymmetry*, **2014**, *25*, 1.

[100] Baudin J. B.; Hareau G.; Julia S. A.; Lorne R.; Ruel O. *Bull. Soc. Chim. Fr.*, **1993**, *130*, 856.

[101] Blakemore P. R. *J. Chem. Perkin Trans. 1*, **2002**, 2563

[102] Swany K. C. K.; Kumar N. N. B.; Kumar K. V. P. P. *Chem. Rev.*, **2009**, *109*, 2551.

[103] Bourdon B.; Corbet M.; Fontaine P.; Goekjian P. G.; Guryrard D. *Tetrahedron letters.*, **2008**, *49*, 747.

[104] Blakemore P. R.; Ho D. K. H.; Nap W. M. Org. *Biomol. Chem.,* **2005**, *3*, 1365.

[105] Chatterjee .; Bera S.; Mondal D. *Tetrahedron: Asymmetry*, **2014**, *25*, 1.

[106] Pospíšil J.; Pospíšil T.; Marko I. E. *Org. Lett.,* **2005**, *7*, 2373.

[107] Haskins C. M.; Knight D. W. *Tetrahedron*. **2010**, *66*, 4150.

[108] Yus M.; Nájera C.; Foubelo F. *Tetrahedron*, **2013**, *59*, 6147.

[109] Page P. C. B.; Van Niel M. B.; Prodger J. C. *Tetrahedron*, **1989**, *45*, 7643.

[110] Tanner D.; Hagberg L.; *Tetrahedron*, **1998**, *54*, 7907.

[111] Fargeas V.; Baalouch M.; Metay E.; Baffreau J.; Ménard D.; Gosselin P.; Bergé J. P.; Barthomeuf C.; Lebreton J *Tetrahedron.*, **2004**, *60*, 10359.

[112] Seebach, D.; Maestro, M. A.; Sefkow, M.; Neidlein, A.; Sternferd, F.; Adam, G.; Sommerfeld, T. *Helv. Chim. Acta.* **1991**, *74*, 2112.