University of HUDDERSFIELD

1. **[1,2]-SIGMATROPIC REARRANGEMENT OF BENZYLIC AMMONIUM YLIDS**

2. **CATALYTIC SP^3-SP^3 FUNCTIONALISATION OF SULFONAMIDES**

3. **ANNULATION OF ARYNES IN THE SYNTHESIS OF SULTAMS**

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Abstract

The first chapter in this thesis describes research on the asymmetric [1,2]-sigmatropic rearrangement of benzylic ammonium ylids. Our group previousely developed method showing that DMSO as solvent, and BTPP as base, in the presence of 5Å molecular sieves, dramatically improves the yield of the reaction. Hence, we applied the developed the method using 8-(–)-phenylmenthol and (2*S*)- camphorsultam as chiral auxiliaries.

In the second chapter, a new application of Pd-catalysed allylation is reported. This enabled the synthesis of (30) of branched sp^3-functionalised sulfonamides, a compound class for which few reported methods exist. By reacting benzyl sulfonamides with allylic acetates in the presence of Pd^0 catalysts and a base, at room temperature, direct allylation was efficiently performed, yielding products that are analogues of structural motifs seen in biologically active small molecules. The reaction was performed under mild conditions and could be applied to nanomolar sigma-receptor binders, thus enabling a late-stage functionalisation and efficient expansion of drug-like chemical space.

The third chapter described a synthesis of benzosultam without recourse to transition-metal catalysis, or stoichiometric amounts of organometallic building blocks. Iodomethane sulfonylamide adds to benzyne (generated using fluoride sources), and then the formed intermediate undergos an intramolecular cyclisation to afford sultam. Using this method that procceds under simple reaction conditions, (11) benzosultams were synthesised in modest yield.

Contents

List of abbreviation

Ac	acetyl
acac	acetylacetonate
AIBN	2,2-azo-*bis*-isobutyonitrile
app	apparent
aq.	aqueous
Ar	aromatic
BMIM	1-butyl-3-methylimizadolium
Bn	benzyl
BTPP	P1-*t*-Bu-tris-(tetramethylene)
br	broad
CS	camphorsultam
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMA	dimethylacetamide
DMAP	*N,N*-dimethyaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*'-dimethylformamide

DMSO	dimethylsulfoxide
de	diastereoisomeric excess
dr	diastereoisomeric ratio
ee	enantiomeric excess
Et	ethyl
equiv	equivalents
HMPA	hexamethylphosphoramide
LDA	lithium di*iso*propylamide
LHMDS	lithium hexamethyldisilazide
m	*meta*
m	multiplet
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mp	melting point
MS	molecular sieves
NBS	*N*-bromosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance

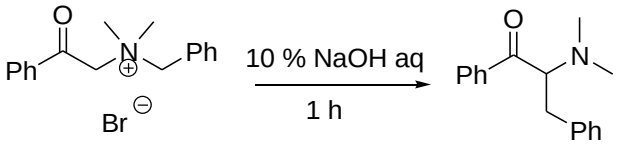
o	*ortho*
p	*para*
PE	petroleum ether
PMB	*para*-methoxybenzyl
Rf	retention factor
rt	room temperature
s	singlet
SM	starting material
t	triplet
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBAF	tetrabutylammonium fluoride
TBDMSCl	tert-Butyl dimethylchlorosilane
TBDPSCl	tert-Butyl(chloro)diphenylsilane
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THAB	tetrahexylammonium bromide
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
tmp·ZnCl·LiCl	tmp: 2,2,6,6-tetramethylpiperidine

TMSCl	trimethylsilyl chloride

Chapter 1: [1,2]-Sigmatropic rearrangement of benzylic ammonium ylids

1.1 Introduction

In 1928, Stevens *et al*. published that benzyl ammonium salts underwent [1,2]-sigmatropic rearrangement with migration of the benzyl group from the nitrogen to the adjacent carbon. Treatment of phenacylbenzyldimethylammonium bromide **1** with sodium hydroxide solution yielded **2** in high yield (Scheme 1).[1]



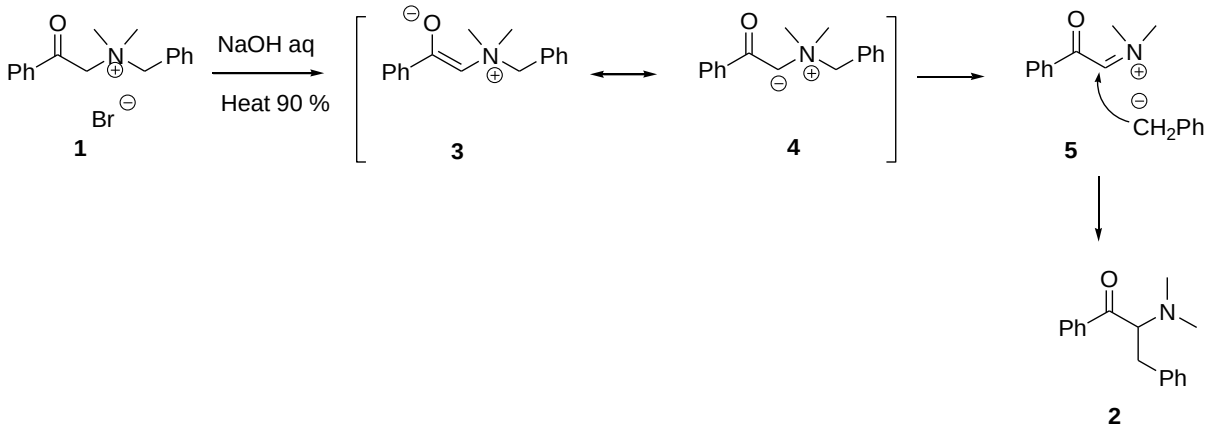
1 **2**
90 %

Scheme 1

This type of reaction, now commonly known as the [1,2]-Stevens rearrangement, has been used to produce many different types of nitrogen containing compounds. Since its discovery, this rearrangement has been widely studied for its interesting mechanism and for its synthetic utility.[2] Examples of such a rearrangement have been chosen to illustrate the wide use of this reaction for the synthesis of biologically active compounds.

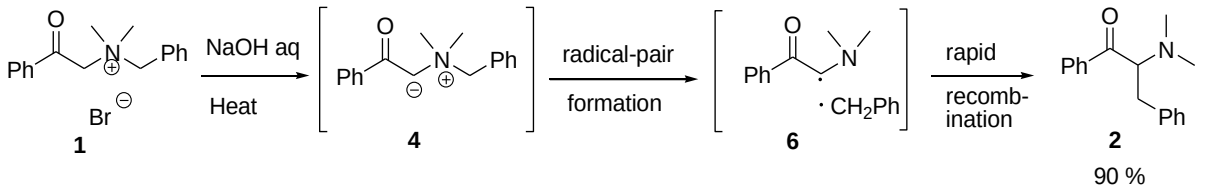
1.2 Mechanism of the Steven's rearrangement

There are two accepted mechanisms proposed for the Stevens rearrangement; ion pair and radical pair. In his early studies, Stevens revealed the intramolecular character of this reaction by mixing phenacyl-*m*-bromo-benzyl-dimethyl-ammonium and *p*-bromophenacylbenzyldimethyl-ammonium-bromide with alkaline solution and the mixture yielded only the rearrangement products corresponding to the individual salts. The mechanism of reaction proceeded by first formation of a zwitterionic intermediate (**3-4)** and then by an ion pair **5** (Scheme 2).[3]



Scheme 2

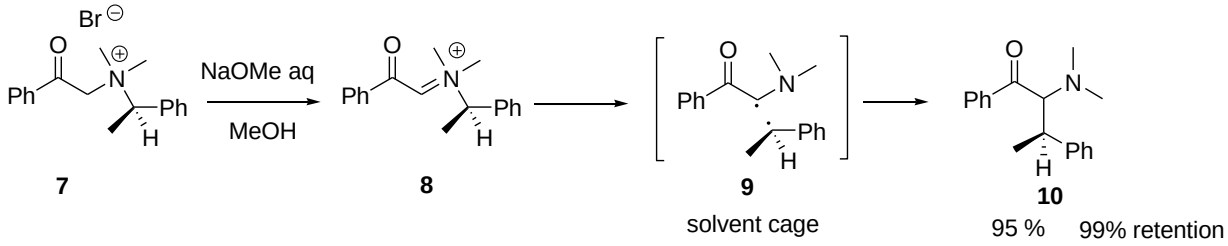
In 1932, Stevens and Thomson studied an alternative mechanism involving a radical pathway,[4] evidence for this was found later.[5,6] The mechanism proceeds via homolytic cleavage of the C-N bond to generate a stable radical (using benzyldimethylallylammonium bromide). The radical pair, which is held tightly together within the solvent cage, rapidly, recombines to form the rearranged product **2**.[7]



Scheme 3

In 1983, Ollis studied the rearrangement of α-chiral ammonium ylids in cross-over experiments that were followed by NMR using chemically induced dynamic nuclear polarisation (CIDNP).[8] Based on CIDNP spectra, it seemed reasonable that the products were formed directly from a radical pair precursor in which the radicals do not drift apart in a solvent cage.[5,8] The high enantiomeric excess and retention of configuration observed, along with the results provided by the CIDNP technique, allowed them to establish that the [1,2]-sigmatropic rearrangement of ammonium salts involved the formation of radical pair **5**. When treated with base, the salt is deprotonated to form ylid **4**. After homolytic scission of the C-N bond, formation of radical **6** occurs which then recombines within the solvent cage to yield product **2** (Scheme 3).[8]

Ollis and co-workers also reported higher levels of diastereoselectivity when the viscosity of the solvent increased. The high viscosity of the solvent seemed to favour the solvent cage effect and to lessen intermolecular interactions.[5,8,9]



Scheme 4

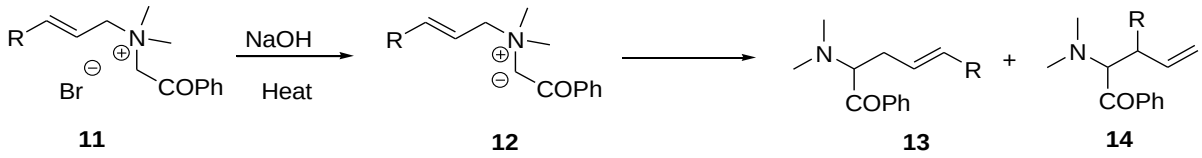
Nowadays this mechanism, involving the recombination of a radical pair within the solvent cage, is widely accepted as being the correct mechanism for the [1,2]-Stevens rearrangement for benzyl salts.

1.3 Competing reactions

The Stevens rearrangement is often beset by competing reactions and other problems. Issues with salt synthesis, ylid formation and Hoffman elimination are three of the most often observed setbacks.

1.3.1 [2,3]-sigmatropic rearrangement

Certain substrates allow more than one type of sigmatropic rearrangement to occur. In the 1960s, during mechanistic studies on the Stevens rearrangement of allylic ammonium salts, a competing reaction to the [1,2]-sigmatropic rearrangement was encountered (Scheme 5).[6] The competing reaction followed a [2,3]-sigmatropic pathway and often predominated over the [1,2]-reaction. Studying the base-promoted rearrangement of the cinnamyl ammonium salt (R=Ph, Scheme 5) Stevens and co-workers obtained a mixture of [1,2]- and [2,3]-rearranged products, while the crotyl derivative (R=Me, Scheme 5) yielded only the [2,3]-rearranged products **14**.[6]



R= Ph or Me

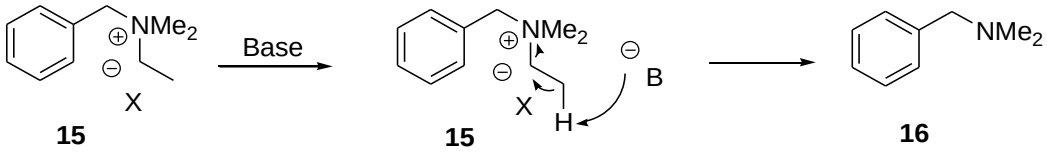
Scheme 5

The [2,3]-sigmatropic rearrangement, generally known as [2,3]-Stevens rearrangement is a

symmetry allowed reaction and believed to proceed via a concerted mechanism with a lower activation energy than the [1,2]-reaction,[11,12] thus making it possible to obtain the [2,3]-rearrangement products by carefully controlling the reaction conditions.[12]

1.3.2 Hoffmann elimination

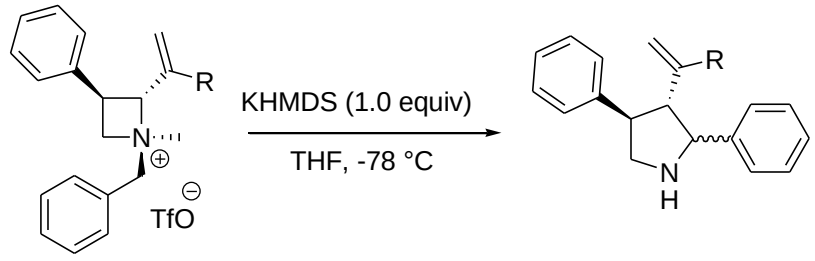
In addition to [2,3]- and [1,2]-rearrangements, the other major reaction pathway for decomposition of ylides is β-elimination. Ammonium salt **15** is prone to give β-elimination product **16** (Scheme 6) by deprotonation β- to the heteroatom.



Scheme 6

1.4 Generation of the ylid species

Traditionally, the ylid precursor to the rearrangement can be formed by treatment of corresponding ammonium or sulfonium salts with a base. Using this method, Couty*et al.* published the generation of pyrrolidines **17** from enantiomerically pure 2-alkenyl azetidines **18** via a base-promoted [1,2]-sigmatropic rearrangement.[10] Although the reaction proceeded with good regioselectivity, low diastereoselectivity at C2 in product **37** was observed due to a non-selective deprotonation (Scheme 7).

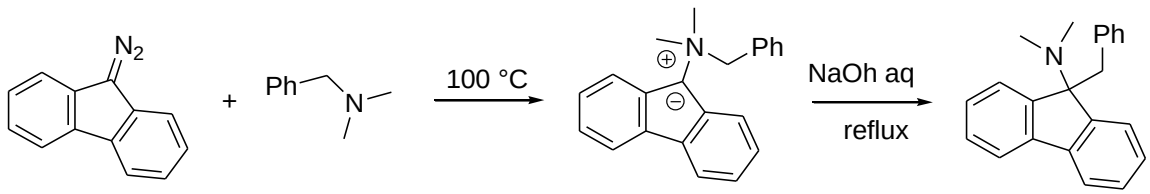


17 **18**

R= H, dr (54:56), 39%
Ph, dr (53:47), 83%

Scheme 7

This base-promoted method can be inconvenient since the base can also induce side reactions. In 1952 Stevens *et al.* reported the synthesis of α-tertiary amine **22** by heating diazofluorene **19** in the presence of *N,N*-dimethylbenzylamine **20**. [11]

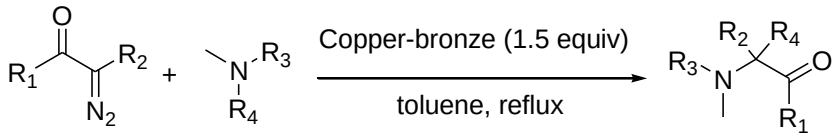


19 **20** **21** **22**

30 %

Scheme 8

The introduction of a copper catalyst allowed for the generation of metal-carbenes leading to a cleaner reaction and better yields. West *et al.* used copper-bronze catalysis to generate ammonium ylids *in situ* by decomposition of diazocarbonyl compounds **23**(**a-g**).[12] They obtained a range of α-amino esters and ketones **25**(**a-g**) in good to excellent yield.



23 (a-g) **24 (a-g)** **25 (a-g)**

R_1 = OEt, R_2 = H, R_3 = Me, R_4 = CH_2Ph	63 %
R_1 = OEt, R_2 = H, R_3 = Me, R_4 = CH_2	35 %
R_1 = OEt, R_2 = CO_2Et, R_3 = Me, R_4 = CH_2Ph	97 %
R_1 = OEt, R_2 = CO_2Et, R_3 = CH_2CO_2Et , R_4 = CH_2Ph	92 %
R_1 = Ph, R_2 = H, R_3 = Me, R_4 = CH_2Ph	70 %
R_1 = Ph, R_2 = H, R_3 = Me, R_4 = CH_2CO_2Et	26 %
R_1 = Ph, R_2 = H, R_3 = CH_2CO_2Et, R_4 = CH_2Ph	70 %

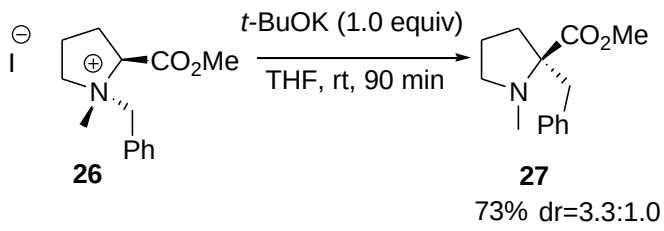
Scheme 9

Additionally, the metal-catalysed decomposition of diazo compound **23** (**a-g**) and trapping of the resulting carbenes by tertiary amines **24** (**a-g**) has successfully been used to rapidly access ylids and hence [1,2]-rearrangement products. This method gave better regioselectivities and less side reactions, and therefore became a viable alternative to the base promoted rearrangement. It is also shown that the use of copper species facilating the reaction in good to excellent yields, was superior to the use of rhodium complexes as a catalyst, which was unsuccessful whe napplied in the same reaction conditions. This was attributed to competitive coordination of the amines **24**(**a-g**) to the empty axial sites on the rhodium catalyst.[12] The ease and stability of metal-catalysed carbene generation reinvigorated research towards the Stevens rearrangement, making the reaction a powerful synthetic approach.

1.5 Asymmetric rearrangements

There have been few approaches towards asymmetric synthesis of amino acids via the Stevens rearrangement. Most efforts towards amino acids synthesis focus on the asymmetric [2,3] sigmatropic rearrangement.[2,26,27,28]

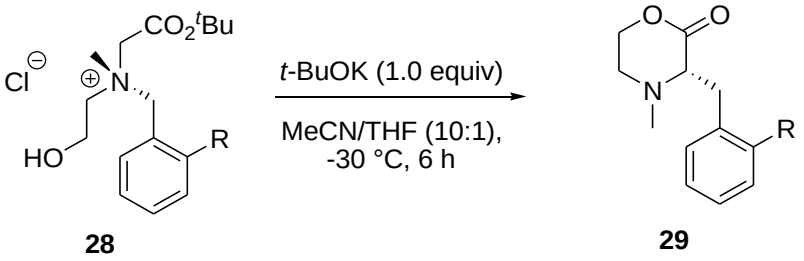
A few years later West *et al*., in another attempt to perform an asymmetric Stevens rearrangement, reacted L-proline derivative **26** under basic conditions, to afford α-quaternary amino acid **27** in good yield with moderate diastereoselectivity (Scheme 10).[14] [1,2]-rearrangement **27** was obtained with retention of configuration. However, given the modest levels of diastereoselectivity obtained, it was suggested that recombination of the radicals from the same face was competing with recombination from the opposite face or from outside the solvent cage.



Scheme 10

Similarly, Tayama *et al.* employed an N-to-C [1,2]-Stevens rearrangement approach

towards the synthesis of optically active 3-substituted morpholine-2-ones **29**.[15] Treating *N*-chiral amino acid derivatives quaternary salts **28** with base at low temperature produced 3-substituted morpholine-2-one derivatives **29** in moderate to good yield and modest enantioselectivities, with no linear amine products observed.



28 **29**

R= H, dr (3.5:1.0), 39%
Me, dr (2.6:1.0), 76%
OMe, dr (3.3:1.0), 53%

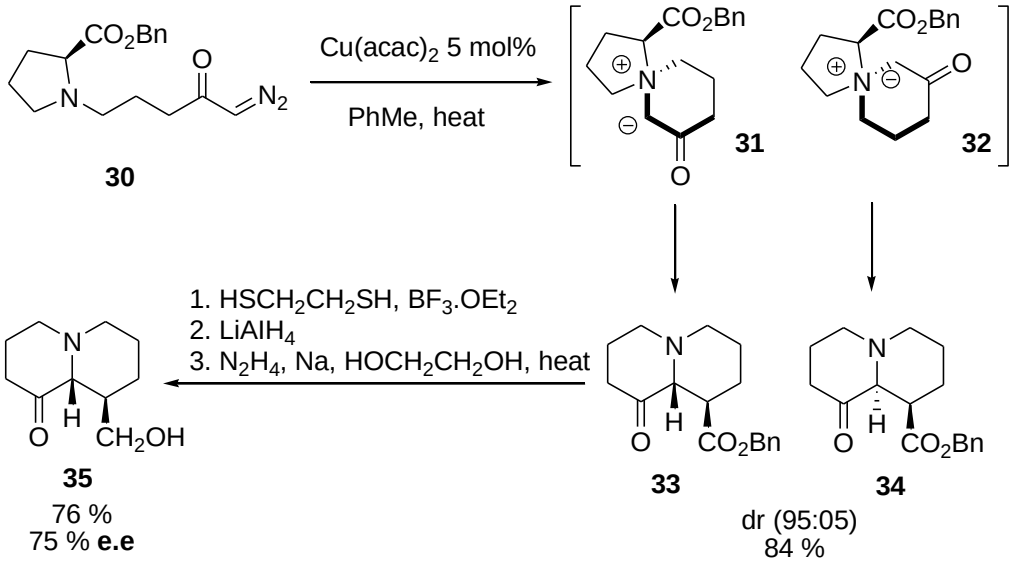
Scheme 11

1.6 Ring expansion methodology

The Stevens rearrangement has also been used as a method towards ring expansion. The potential to access many different alkaloid natural product ring systems is an appealing aspect of the Stevens rearrangement of ammonium ylids. Efficient access to a variety of amine natural product bicyclic ring systems can be achieved through formation of a spirocyclic ylid and subsequent Stevens rearrangement to afford the ring expanded products.

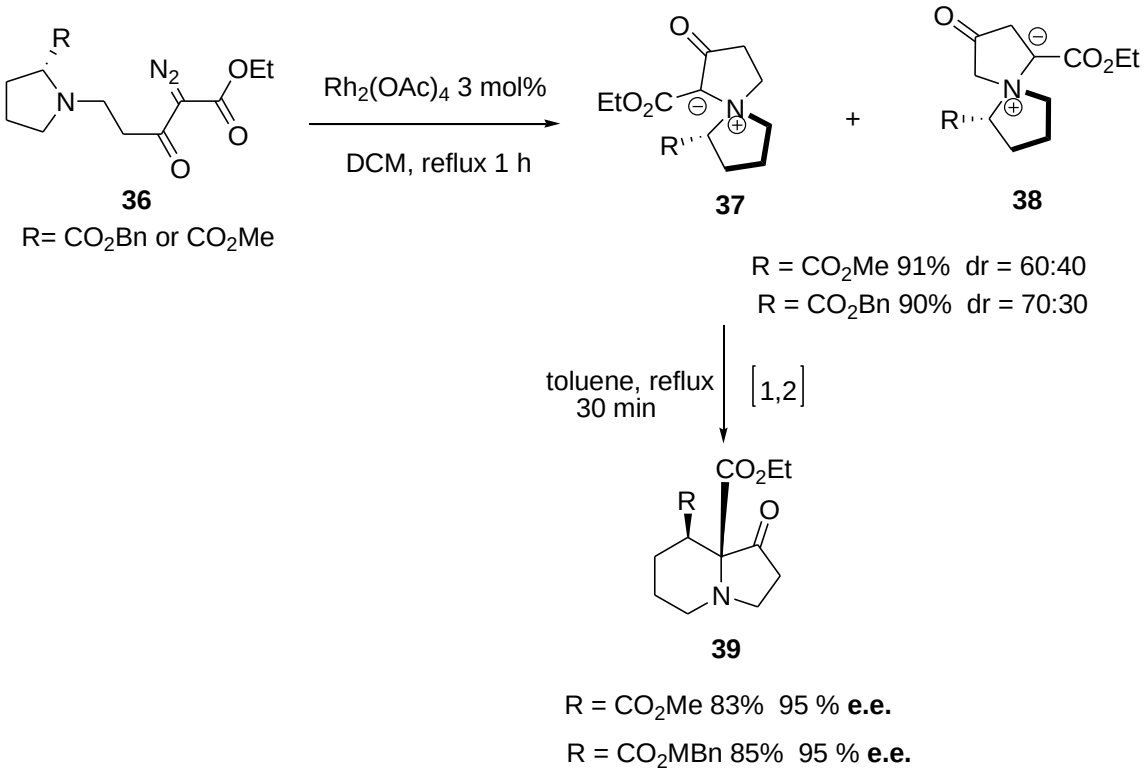
West and Naidu[16,17] applied this Stevens ring-expansion methodology, in an efficient total synthesis of quinolizidine alkaloid **35**. As described previously, diazoketone **30** available in two-steps from *L*-proline benzyl ester, was treated with copper catalysts give the diastereomeric spirocyclic ylid mixture **31** and **32**. A [1,2]-Stevens rearrangement provided the desiredquinolizidine ring system **33** and **34**, in high yield (84%) and with excellent diastereoselectivity (95:5). This level of stereochemical retention suggests that the high diastereoselectivity observed derives predominantly from preferential formation of ylid diastereomer **31** with stereospecific [1,2]-shift to give **33**. Having achieved high levels of diastereoselectivity, the authors examined the enantiomeric excess of this major

diastereomer. NMR chiral-solvating reagent (BNNPA) showed that quinolizidine **35** was obtained 75% ee.



Scheme 12

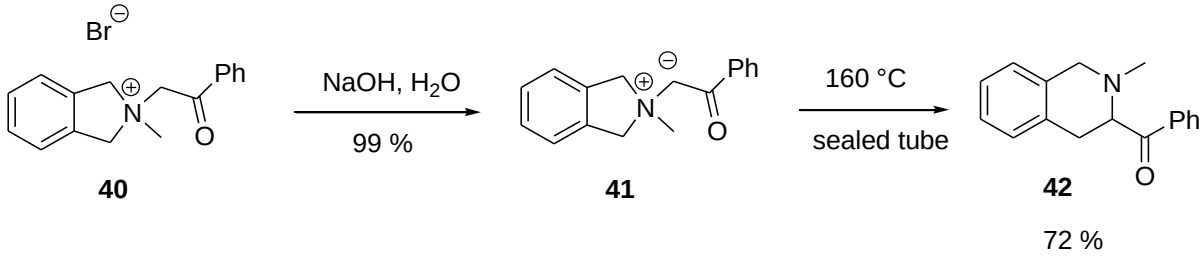
Saba and co-workers utilised the same tandem metallocarbenoid/ammonium ylid/[1,2]-Stevens rearrangement in their approach to swansonine analogues which belong to an important class of biologically active natural and unnatural chiral polyhydroxylated alkaloids.[18,19] *L*-Proline derived substrates **36** with an α-diazoketoester chain, were converted into stable isolable [5,5]-spirocyclic ammonium ylide **37** in very good yields (91-90%, respectively) but with moderate diastereoselectivity, using two transition metal catalysts and various reaction conditions. The thermal reaction for ylid **37** afforded indolizidines **39** as pure diastereomers, in good yields (83-85%) and high enantiomeric excess (95%).



Scheme 13

1.7 Rearrangement of heterocyclic benzylic ammoniumsalts

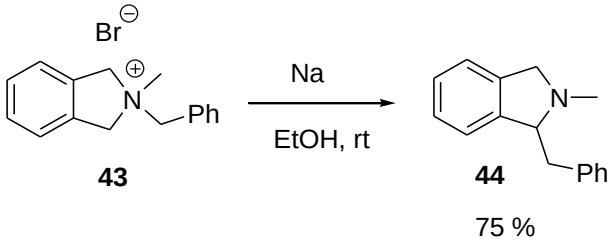
Ollis *et al.* were among the first investigate the Stevens rearrangement of heterocyclic benzylic ammonium salts. They prepared cyclic ylid **41** by deprotonation of corresponding salt **40** using sodium hydroxide.[20] However ylid **41** did not spontaneously rearrange but instead proved to be rather stable and only underwent [1,2]-sigmatropic rearrangement when heated at a high temperature (Scheme 14).



Scheme 14

Wittig and co-workers investigated the rearrangement of similar ammonium ylids, however the outcome of the rearrangement proved to be very different.[21] When they rearranged heterocyclic ammonium salt **43**, they obtained the Stevens rearranged products **44** but ring

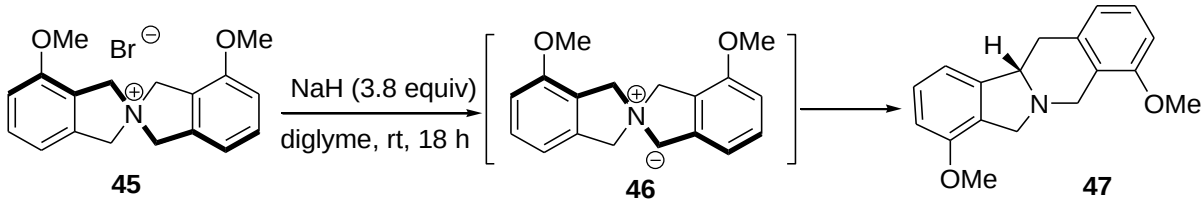
expanded product was not observed, possibly due to the deprotonation of the other benzylic position (Scheme 15).



43 **44** 75 %

Scheme 15

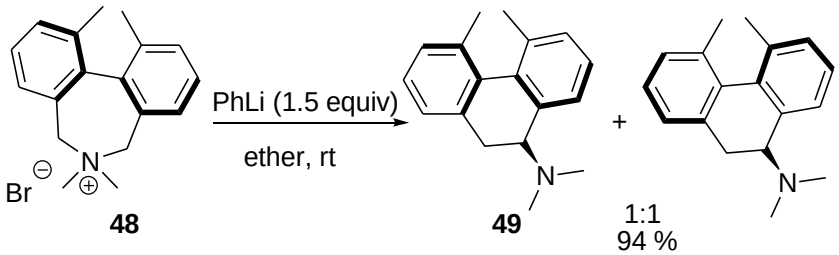
Later, Brewster and co-workers[22] established that spiro quaternary ammonium salt **45** (Scheme 16) when treated with a base, underwent a [1,2]-Stevens rearrangement to provide optically-active tertiary amine **47** with an (*S*) configuration. Bond-breaking and bond-making phases of Stevens rearrangement have happened on the two different rings of the spiro system, with a transfer of chirality from the stereogenic centre on the nitrogen to the newly-formed stereogenic carbon atom.



45 **46** **47** 11 %

Scheme 16

Another example of transfer of chirality has been reported by Padwa and co-workers, who synthesized (*S*) configured product **49** with excellent (ee) by rearrangement of diazepinium salt **48** (Scheme 17).[23]

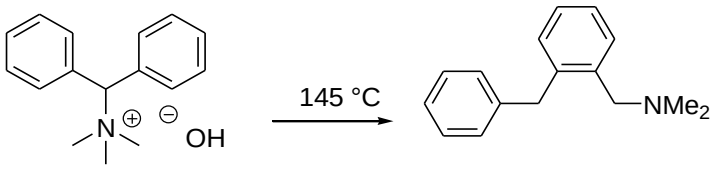


48 **49** 1:1 94 % 100 % **e.e**

Scheme 17

1.8 Sommelet-Hauser Rearrangement.

In 1937, Sommelet observed that decomposition of quaternary ammonium salt **50** leads to formation of rearranged amine **51** when kept in a desssicator over P_2O_5. The same result was achived when the salt was heated to 145 °C (Scheme 18).[24]

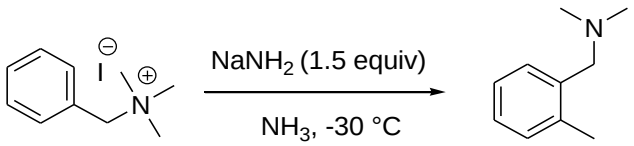


50 **51**

Scheme 18

In 1957, Hauser investigated the rearrangement of benzyltrimethylammonium ion **53**.[25] Hauser also proposed a possible mechanism for this rearrangement involving the deprotonation of quaternary ammonium salt followed by [2,3]-sigmatropic rearrangement (Scheme 19).[28]

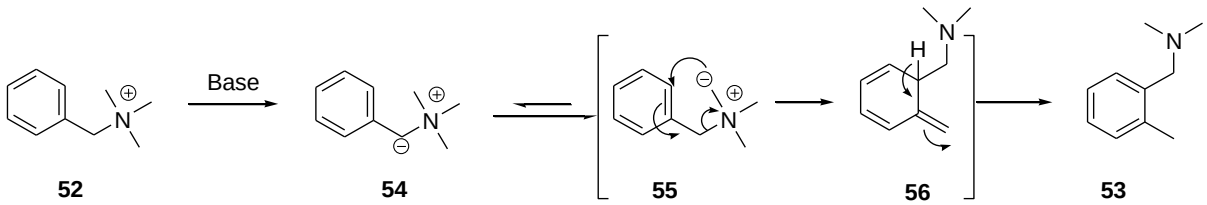
Treatment of the ammonium salt **52** with base initially generates ylid **54**, which in turn is in equilibrium with yilde **55**. Formation of yild **55** allows rearrangement via a concerted, symmetry allowed [2,3]-rearrangement to yield **53** through **56** (Scheme 20).



52 **53**

96 %

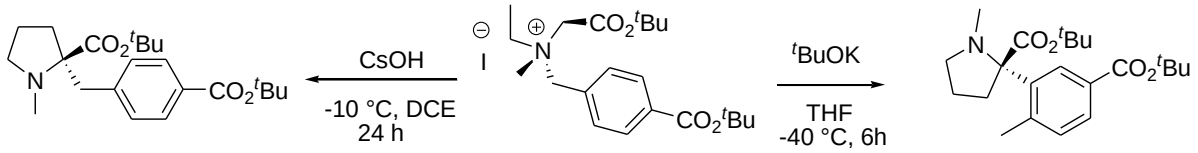
Scheme 19



52 **54** **55** **56** **53**

Scheme 20

Following their work on the Stevens rearrangement, Tayama and co-workers reported a unique example of the Sommelet-Hauser rearrangement that showed no competing [1,2] Stevens rearrangement (Scheme 21).[26] Treatment of ammonium salt **57** with solid caesium hydroxide in DCE at -10 °C leads to formation of rearranged product **58** via a [1,2] Stevens rearrangement. Treatment of salt **57** with potassium *tert*-butoxide at -40 °C in THF leads to α-aryl proline derivative **59** via a Sommelet-Hauser rearrangement.



58

42%
99% **e.e.**

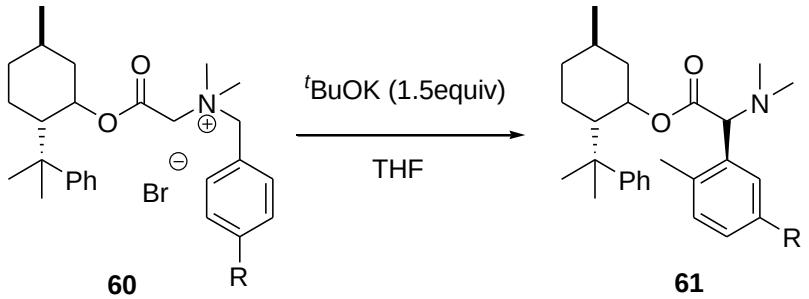
57

59

96%
99% **e.e.**

Scheme 21

Tayama also reported an asymmetric version of the Sommelet-Hauser rearrangement using the above methodology. Various *para*-substituted *N*-benzyl ammonium bromide salts **60** (Scheme 22) were treated with *t*-BuOK to generate α- tertiary amine **61** in moderate to excellent yields with a high level of diastereoselectivity. They also applied these conditions to *ortho*- and *meta*- substituted *N*-benzyl ammonium salts, yielding products in good yield and high diastereoselectivity.[27]



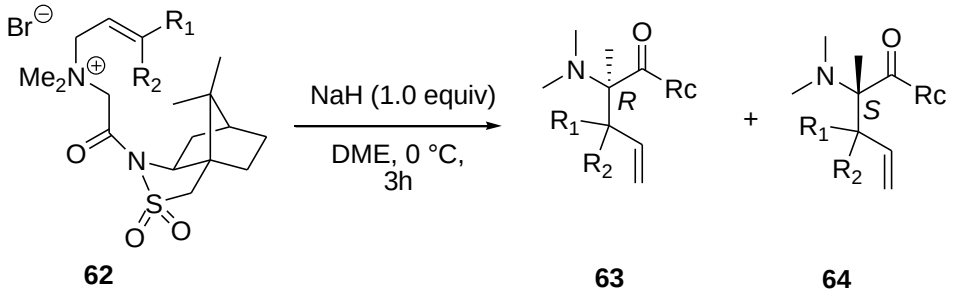
60

61

R = $CO_2{}^t$Bu, -40 °C , 4 h, 95 %, d.r (98:2)
R = CN, -40 °C, 4 h, 84 %, d.r (87:13)
R = CN, -60 °C, 8 h, 82 %, d.r (97:3)
R = CO_2Me, -60 °C, 8 h, 85 %, d.r (98:2)
R = COPh, -60 °C, 8 h, 82 %, d.r (98:2)
R = CF_3, -60 °C, 15 h, 93 %, d.r (98:2)
R = H, -60 °C, 15 h, 46 %, d.r (98:2)

Scheme 22

The most notable asymmetric [2,3]-sigmatropic rearrangement of acyclic ammonium yilds was accomplished recently by Sweeney and co-workers. They elegantly utilized various *N*-allyl glycine salts **62** bearing a camphorsultam auxiliary to obtain α-allylic glycines **63** in high yields with high diastereoselectivity (Scheme 23).[28]



62 **63** **64**

Rc= (2*R*)- or (2*S*)- Camphorsultam

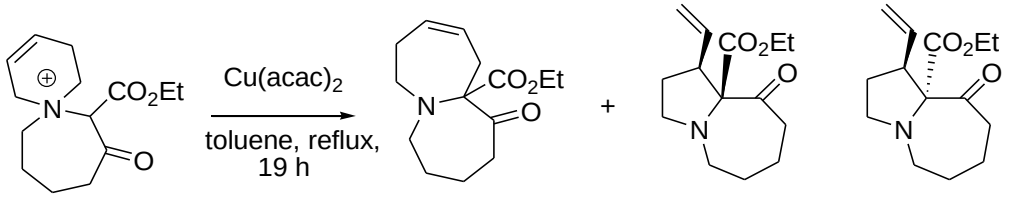
R_1 = Me, R_2 = H, 86 %, dr (96:4)

R_1 = Me, R_2 = Me, 70 %, dr (97:3)

R_1 = MeO_2C, R_2 = H, 64 %, dr (99:1)

Scheme 23

Sweeney and co-workers also developed the first example of a [2,3]-endocyclic rearrangement of spirocyclic ammonium ylid **64**.[29] They reported a facial introduction of the quaternary centre of the ring junction of the pyrroloazepine structures, and subsequent rearrangement involving the endocyclic alkenes unit furnished the desired bicycle **66** and **67** in good yields.



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

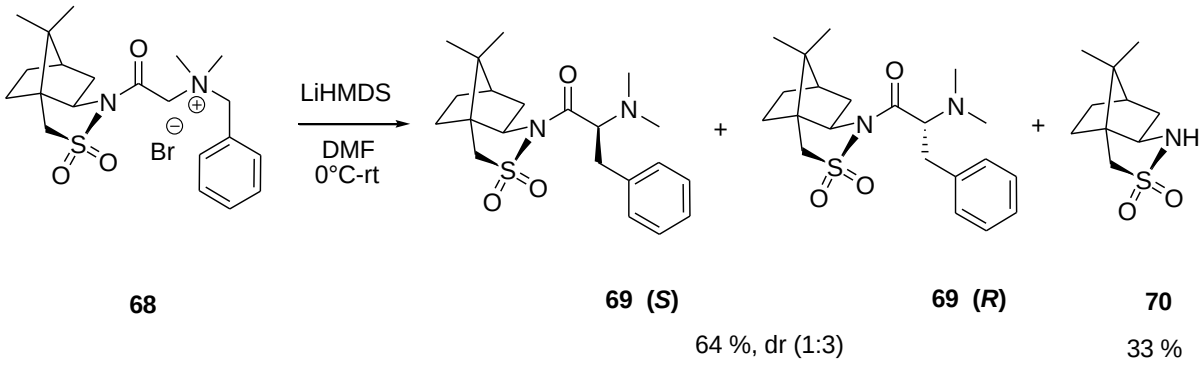
8 % 43 % 21 %

[1,2] [2,3],

Scheme 24

2.1 Previous work

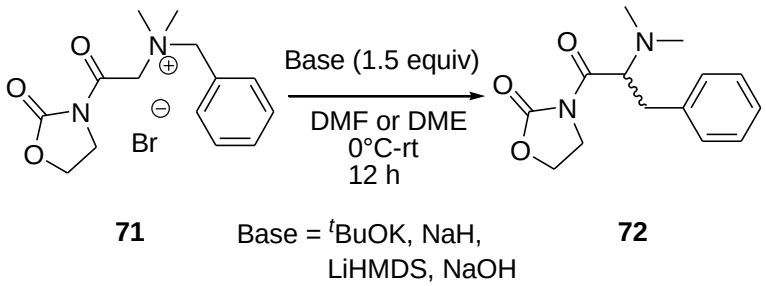
Previous work in the group developed new methodology for the [1,2]-rearrangement of *N*-benzylic ammonium salts **68** and used LiHMDS in DMF at 0°C.[33] Initial investigations indicated successful rearrangement in moderate yield, but upon introduction of a substituent on the benzyl group, yields decreased (Scheme 25). Significant amounts of cleaved chiral auxiliary **70** were recovered in many reactions.



Scheme 25

An initial diastereomeric ratio of 75:25 was promising, but cleavage of the auxiliary needed to be addressed. An obvious way to suppress the cleavage was to investigate different auxiliaries, using commercially available oxazolidinone, menthol derivatives and camphene.

The replacement of the sulfonamide linker present in camphorsultam by the carbamoyl linker present in oxazolidinones might be expected to reduce the cleavage of the chiral auxiliary, as a radical intermediate would be less stabilised, and increase yields of the rearrangement. Investigation of rearrangement of salt **71** under a range of conditions proved mainly unsuccessful (Scheme 26).[31,32]

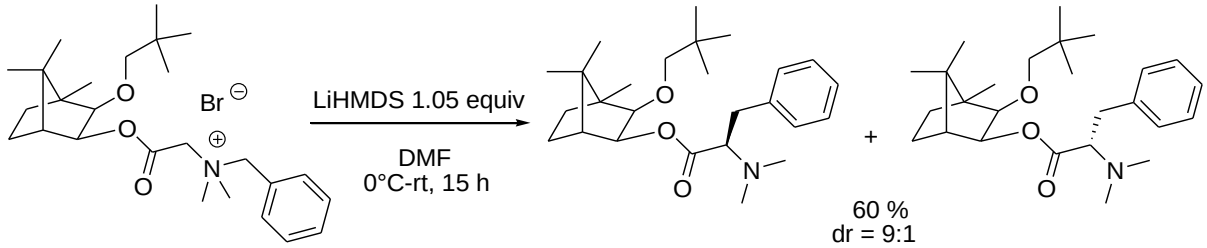


Scheme 26

Many of the reactions carried out led to decomposition of starting material **71**. it was believed that water present in the reaction would react *in situ* with the base to generate

hydroxide ions, which might cleave the oxazolidinone species.[31] When molecular sieves were used, ^{1}H NMR analysis of the crude mixture showed some impure rearranged product **72**. However, purification of **72** failed. Using oxazolidinone derivatives was therefore abandoned and from these results, it appeared necessary to examine different chiral auxiliaries.

Due to the result obtained when camphorsultam was used as the chiral auxiliary, it seemed appropriate to investigate an auxiliary with a similar core structure. A similar structure found in nature is camphene (Scheme 27). Salt **73** was rearranged upon treatment with base to give desired products **74*(R)*** and **74*(S).***



73 **74 (*R*)** **74 (*S*)**

Scheme 27

Both products **74*(R)*** and **74*(S)*** were isolated as oils, therefore the stereochemistry of both diastereoisomers was proposed by analogy: the radical pair would preferentially recombine from the least hindered face of the molecule (fig 1).[31]

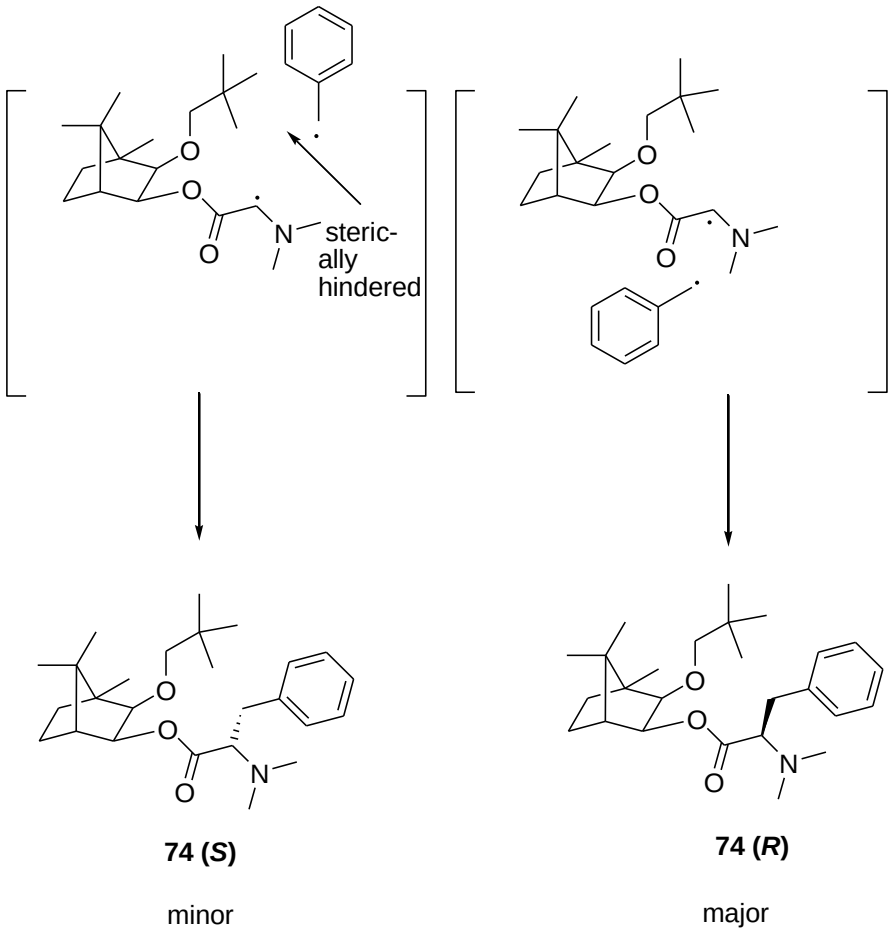
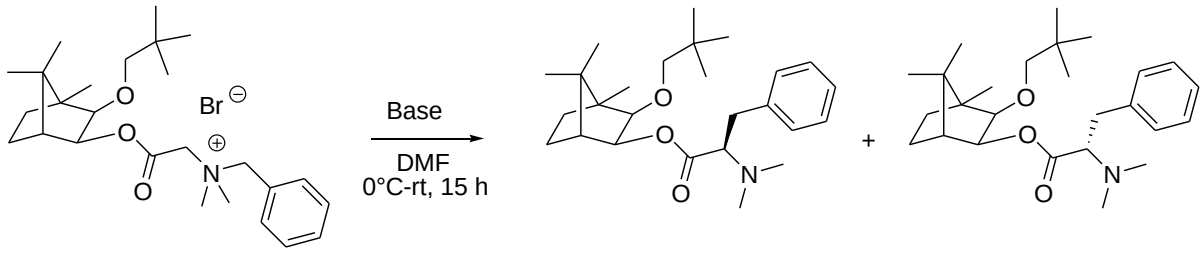


Fig 1

A base screen was first performed (Table 1) and the best result was obtained with BTPP (entries 3 and 6).



73 **74 (*R*)** **74 (*S*)**

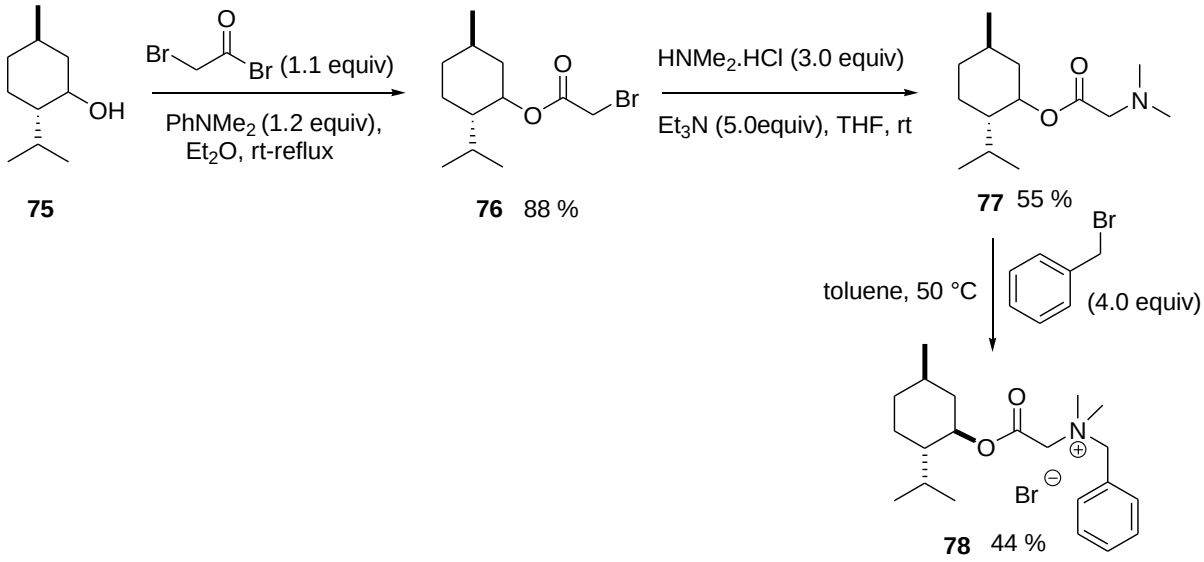
Entry	Base (equiv)	*(2R+2S)* %	dr (*2R:2S)*	Cleaved (%)
1	LiHMDS (1.05)	60	9:1	6
2	BTPP (1.05)	38	19:1	13
3	BTPP (2.00)	66	8:1	Trace
4	BTPP (2.00)	44	5:1	10

5	BTPP (2.00)	22	10:1	22
6	BTPP (1.75)	64	12:1	46

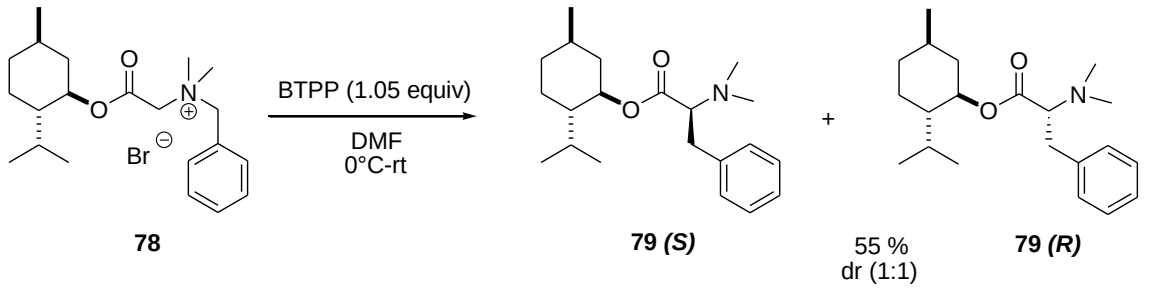
Table 1

However, the reaction was capricious, with three identical reactions giving large differences in yield (Entries 3, 4 and 5), diastereomeric ratio and auxiliary cleavage.[31] Therefore, camphene was disregarded as a suitable auxiliary replacement.

After abandoning oxazolidinone and camphene options, menthol derivatives[31] were chosen as auxiliary. Salt **78** was prepared in three steps from menthol. The bromoacetylation step was carried out using a weak base (*N*,*N*-dimethylaniline), to afford **76** in high yield.[31] The subsequent steps proceeded smoothly to give the benzyl salt **78** in 44 % overall yield. The newly formed salt was rearranged with a base to afforded desired product in good yield with a minimal amount of chiral auxiliary returned. The major problem was isolation of the product **79** as a 1:1 mixture of diastereoisomers. After purification of crude mixtures by extraction and flash column chromatography, an inseparable mixture of the two diastereoisomers was obtained.



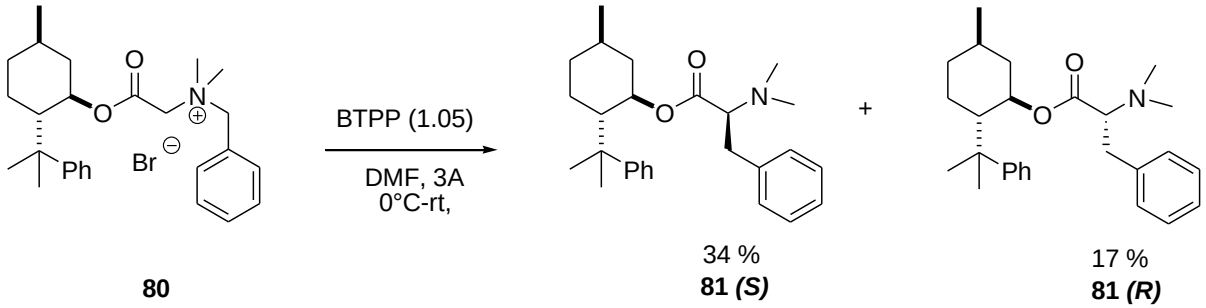
Scheme: 28



Scheme: 29

In addition, the diastereoselectivity diminished compared to reactions with camphorsultam, perhaps indicating the isopropyl group was not bulky enough to shield either face of the molecule. This could be remedied by using a morehindered group in this position leading to use of auxiliary (-)-8-phenylmenthol.

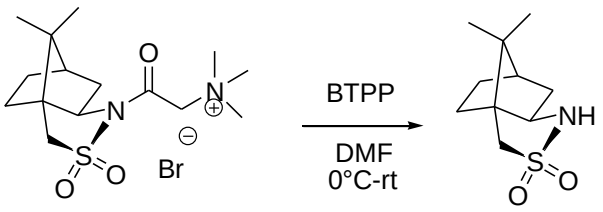
Salt **80** was treated with base to afford the desired rearrangement products **81 (*S*)** and **81 (*R*)** with only a trace amount of cleaved auxiliary. However, the reaction yields for the rearrangement were lower than the ones obtained with (-)-menthol. Both products **81 (*S*)** and **81 (*R*)** were isolated and weighed to determine the reaction diastereoselectivity (dr 2:1).



Scheme: 30

However, since the distereoselectivity observed was inferior to that using the sultam auxiliary, further investigation of the rearrangement using 8-(-)-phenylmenthol as the chiral auxiliary was dismissed.

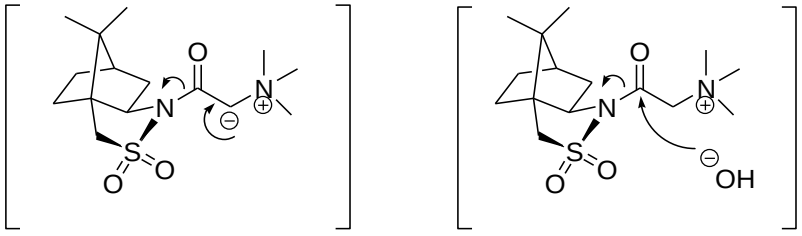
As changing auxiliaries gave poor yields and diastereoselectivities, further studies were undertaken to understand the mechanism behind the cleavage of camphorsultam auxiliary. Attempted rearrangement of camphorsultam n-trimethylammonium salt **82** yielded only cleaved camphorsultam in good yield (Scheme 31).



82 **70**

Scheme: 31

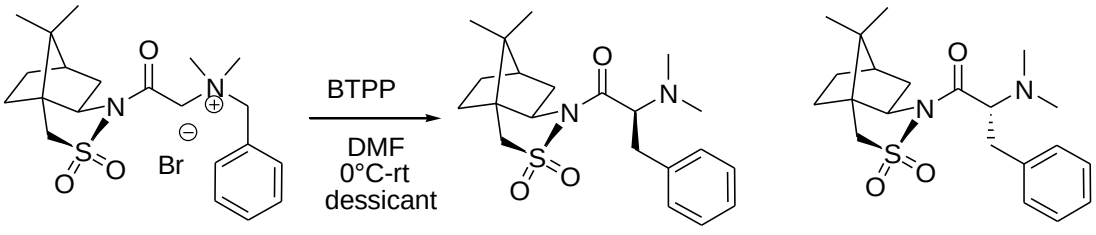
This discovery was a strong evidence to support either a hydrolysis mechanism or an anionic cleavage (Fig 2). If there were water present in the reaction medium, then the base could potentially react with it to form hydroxide anions would then hydrolyse the starting material **82**.



Anionic pathway Hydrolysis pathway

Fig 2

Ranges of desiccants were assessed (Table 2), yielding positive results. The best results were obtained using molecular sieves, and as the cavity size increased, the yield of the reaction as the diastereoselectivity increased as well. Most notably 5Å molecular sieves provided highest yield and diastereoselectivity.

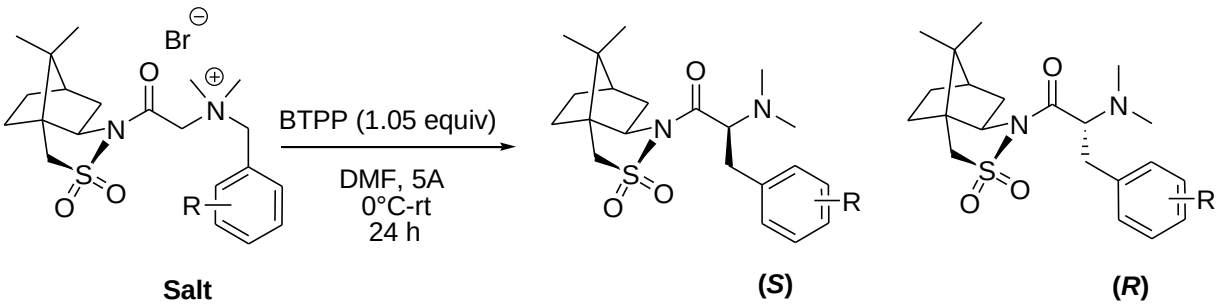


68 **69 (*S*)** **69 (*R*)**

Entry	Desiccant	*2R+2S* (%)	dr(*R:S*)	Cleaved Aux (%)
1	None	41	3:1	22
2	3 Å M.S	50	5:1	8
3	4 Å M.S	53	4:1	5
4	5 ÅM.S	65	5.5:1	10
5	Na_2SO_4	55	4:1	12

Table 2

With the use of molecular sieves, the reaction proved to be reproducible, giving a minimum amount of cleaved camphorsultam and the diastereoselectivity of the reaction increased slightly as well. Therefore, a substrate investigation was undertaken to assess the scope of asymmetric [1,2]-Stevens rearrangement as shown in (Table 3).



Salt **(*S*)** **(*R*)**

Entry	R	Substrates	*2R+2S* (%)	dr (*R:S*)	Cleaved Aux (%)
1	H	**69**	51	3:1	24
2	4-NO_2	**83**	65	5.5:1	10
3	4-CN	**84**	52	2:1	18
4	4-CF_3	**85**	54	4:1	11
5	4-$COCF_3$	**86**	41	7.2:1	18
6	2,5-F	**87**	58	3.6:1	7
7	2-NO_2	**88**	60	6.5:1	16
8	4-OMe	**89**	21	6:1	31

Table 3

The substrate of scope the asymmetric [1,2]-Stevens rearrangement was quite broad and gave the desired products in good yield and diastereoselectivity. This was the first successful

development of the asymmetric [1,2]-Stevens rearrangement of *N*-benzylic ammonium salts.

3.1 Aim of the project

[1,2]-Sigmatropic rearrangements of ammonium salts proceed in good yields and create new carbon-carbon bonds with good diastereoselectivities. As the reaction exhibits interesting and valuable characteristics, it is peculiar that it has received such little attention, especially in total synthesis. One reason might be that the rearrangement product is a tertiary amine and is competing to [2,3]-rearrangement unless appropriate conditions are employed. The aim of this project was to develop new methodology towards the synthesis of α- and β-amino acid derivatives via [1,2]-sigmatropic rearrangements of ammonium ylids. The subsequently formed ammonium salt would then be deprotonated to form an ammonium ylide, which is expected to [1,2]-rearrange up on treatment with our new conditions. The choice of condition is of special interest, as it most likely influences the reactivity of the intermediate ylid towards the [1,2]-rearrangement. First, we selected camphorsultam auxiliary for this type of reaction, as previously, it has been reported that ammonium salts bearing camphorsultam auxiliaries underwent [1,2]-sigmatropic rearrangement in moderate yield, although cleavage of the chiral auxiliary was observed. Our attention turned to apply our new conditions towards an asymmetric [1,2]-Stevens rearrangement of *N*-benzylic ammonium salts to gain access to desired products in better yield and diastereoselectivity, and minimised cleavage by-product.

Our second goal is to investigate into alternative auxiliaries such as phenyl menthol. Tayama and co-workers successfully applied phenylmenthol as auxiliary towards [2,3]-sigmatropic rearrangement. Therefore, this can be investigated to test whether phenylmenthol auxiliary suitably provides [1,2]-shift when used in our conditions, the effect of the phenyl menthol auxiliary on yields and diseteroselectivity will be assessed.

4.0 Result and Discussion

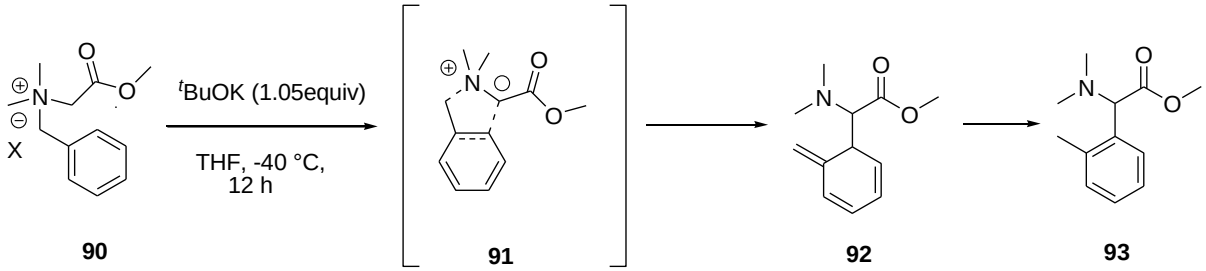
4.1 Understanding competition between [1,2]-Stevens and [2,3]-Sommelet-Hauser rearrangement

Investigation towards the understanding of the [1,2]-Stevens and [2,3]-Sommelet-Hauser rearrangements identified a number of variables. Between the two asymmetric methodologies, there are three factors: base, solvent and benzyl substitution. In fact, for the reactions developed by Sweeney and Tayama, it is surprising that the temperature is the only variable that is discounted as having any controlling factor between the rearrangements, particularly when previous reports have expressed temperature as a key criterion for rearrangement control.

Individually, all three factors do not control rearrangement, but utilising a combination of the factors can introduce a level of selectivity and the balance between [1,2]- and [2,3]-rearrangements.

4.2 Base

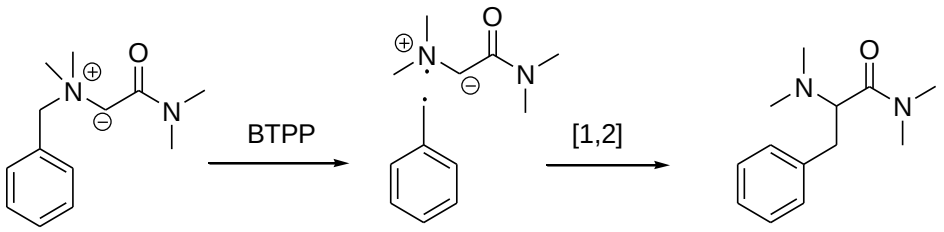
Adopting a weak base favours [2,3]-Sommelet-Hauser rearrangement, as shown in (Scheme 32). A weaker base is key for [2,3]-Sommelet-Hauser rearrangement as it allows for the partial deprotonation of the α-proton, which promotes the formation of the five-membered transition state **91** (Scheme 32).



Scheme 32

In contrast to weak bases which yielded the [2,3]-rearrangement, stronger bases promote [1,2]-rearrangement. The deprotonation caused by utilising a strong base, does not allow for formation of the five-membered transition state that promotes [2,3]-rearrangement.

Instead formation of the yilde is followed by homolysis of the benzyl carbon-nitrogen bond and gives the [1,2]-rearrangement adduct (Scheme 33).[35]



90 **94** **95**

Scheme 33

4.3 Benzyl substitution

Stevens and co-workers investigated the influence of substitution on the consequence of the [1,2]-rearrangement reaction. [3b,3c] In fact they postulated that after deprotonation of the salt and formation of the corresponding ylid, the velocity of the rearrangement depended on the cleavage of the benzylic bond. Therefore, the driving force of the reaction lay in the instability of the anionic charge and could be related to the measurement of the ylids' dissociation constant. A range of substituted salts were prepared and rearranged, the reaction rates were recorded. The authors supposed that the reaction velocity was linked to the anionic charge instability; therefore, if the acidity of the ylid diminished, then the instability of the anionic charge would increase as well as the reaction velocity.[3c]

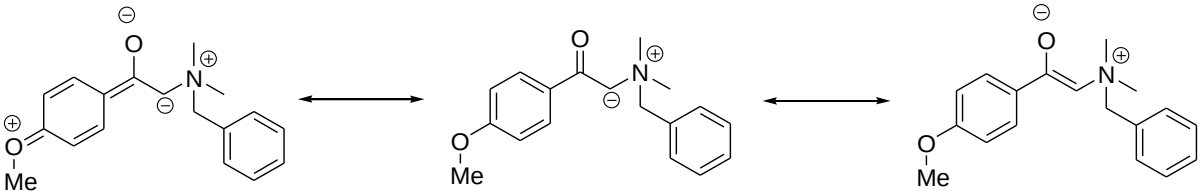


Fig 3

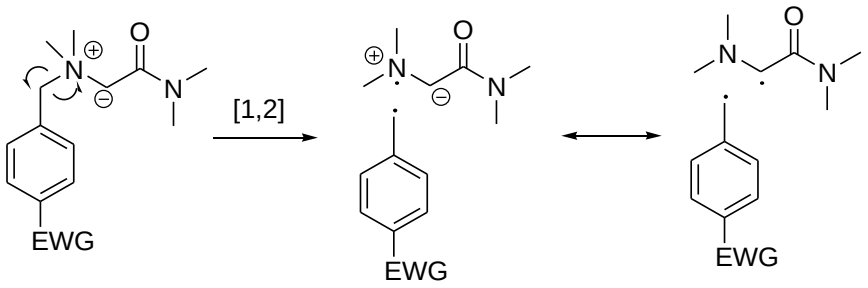


Fig 4

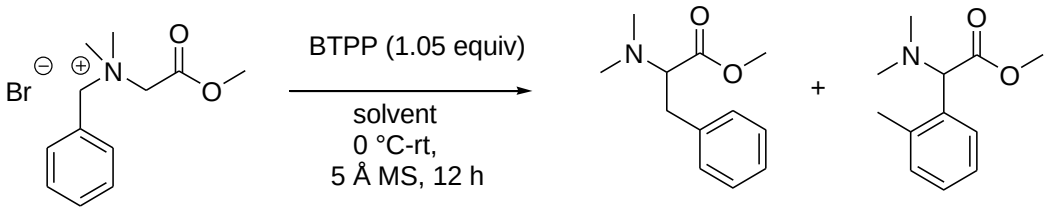
Subsequent studies of the effect of substituents on the phenyl ring of the benzyl group have demonstrated that an electron donating benzyl substituent undergo [1,2]-shift poorly due to inhibits [1,2]-rearrangement by destabilisation of the yild (Figure 3). The conclusion is that an electron withdrawing group favoured the reaction (Figure 4) whereas an electron donating group disfavoured it. The following order of reactivity was determined: NO_2> Hal > Me >OMe. The substituent most favourable to the reaction was shown to be the nitro group, which particularly accelerates the reaction compared to the other electron withdrawing substituents. This can be explained by the radical-stabilising nature of a NO_2-substituted benzyl species. Formation of the radical pair is a key attribute in the [1,2]-Stevens mechanism, hence the preference of NO_2-substituted benzyl species towards the [1,2]-shift product.[11]

4.4 Solvent

A solvent is a predictable factor that effects both [1,2]- and [2,3]-rearrangement competition, as the mechanism requires a suitable solvent to allow an adequate solvent cage for radical pair recombination. As previously discussed Ollis and co-workers[5] reported higher levels of diastereoselectivity when the viscosity of the solvent increased. The high viscosity of the solvent seemed to favour the solvent cage effect and to lessen intermolecular interactions. This solvent would also account for the high degree of intramolecularity and stereoselectivity observed in this rearrangement. Radical escape provided achiral free radicals that combined to give racemic by-products, their random recombination leading to the loss of stereochemical information (Scheme 4, Page 12).

4.5 Improving the [1,2]-Stevens rearrangement methodology

With further understanding of the behaviour of benzyl ammonium salts during the [1,2]-Stevens an attempt for improving the yield was iundertaken. Previous investigation had explored the base extensively, so in our group Mark Forester was focused towards the choice of the reaction solvent. Hence, a solvent screen (Table 4) was undertaken to indicate any improvement on the isolated yield.[32]

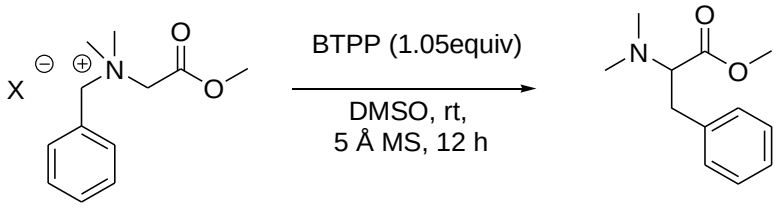


96 **95** **93**

Entry	Solvent	95 (%)	93 (%)
1	DMF	38	0
2	THF	0	Trace
3	DME	15	0
4	MeCN	22	0
5	PhMe	0	0
6	Dioxane	Trace	0
7	**DMSO**	60	0

Table 4

The solvent screening was undertaken and indicated an improvement when using DMSO. All solvents gave poor yield, with some solvents achieving no rearrangement with only starting material recovered. DMSO was used along with DMF with a variation of counter-ion in an attempt to improve yield (Table 5).[32]



90 **95**

Entry	X	DMF *95* (%)	DMSO *95* (%)
1	Br	36	55
2	Cl	33	57
3	I	31	54
4	BPh_4	24	43

Table 5

As anticipated, DMSO as a solvent improves the [1,2]-rearrangement yield. None of [2,3]-rearrangement products were observed. To understand this, the electronic distribution between DMF and DMSO must be studied.[33,34]

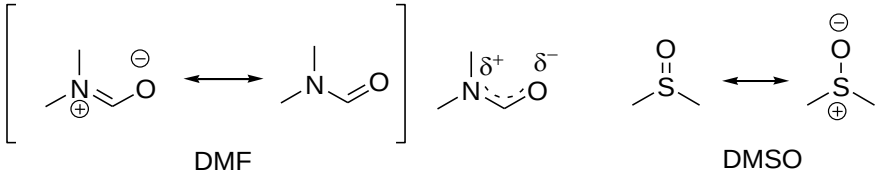
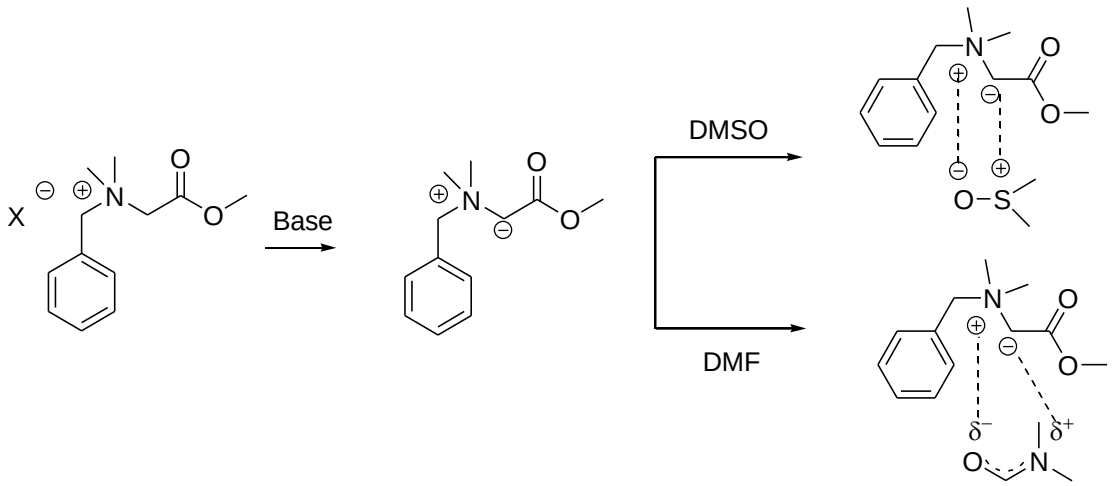


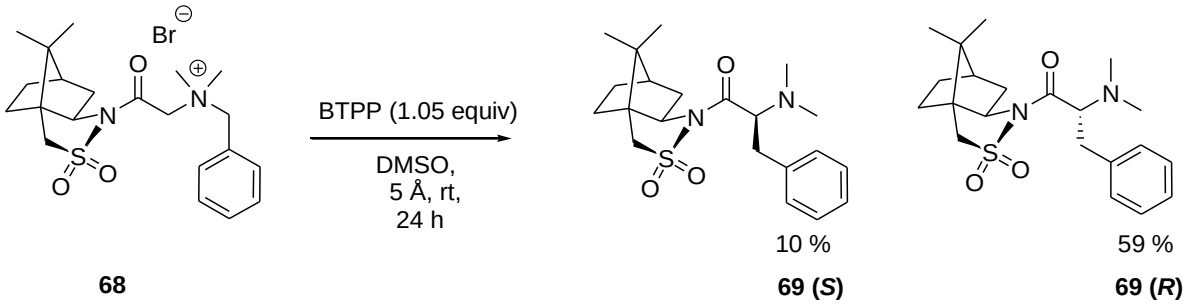
Fig 5

DMSO exists with charges on its oxygen and sulfur, whereas DMF exists with partial charges on its oxygen and nitrogen. The improved charge upon the oxygen and sulfur atoms of DMSO can interact better, which allows the reagents to overcome the energy barrier easier and decrease the energy of the transition state. In comparison, the partial charge of DMF has a decreased interaction with the forming anion, hence a reduction in yield compared to DMSO.



Scheme 35

Now with a significant improvement of the [1,2]-rearrangement reaction by using BTPP as base and DMSO as a solvent, the reaction scope could be investigated with these condition.



68 **69 (*S*)** **69 (*R*)**

Scheme 36

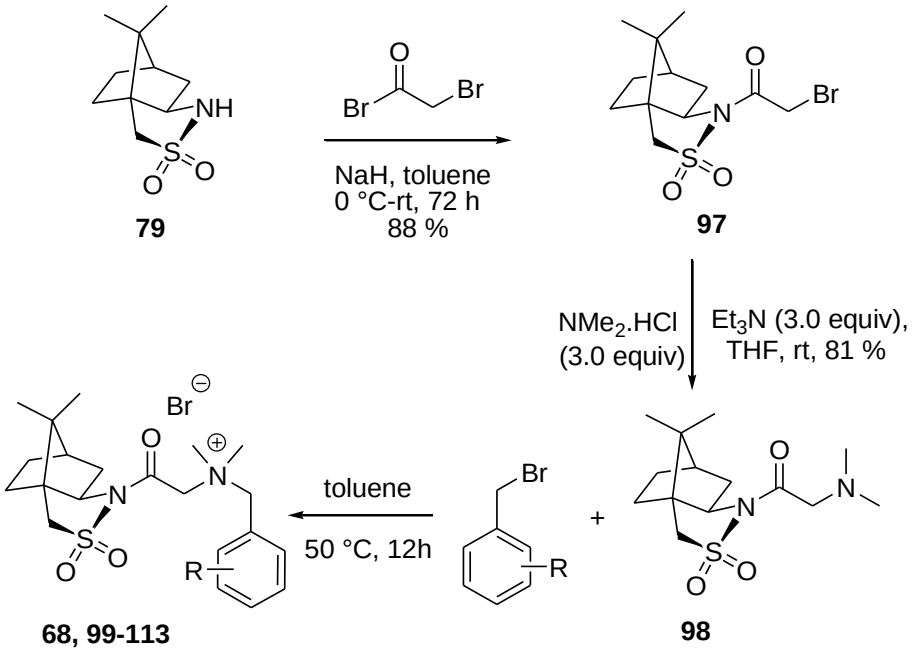
Despite the fact that some variations in diastereomeric ration were observed, using DMSO as a reaction solvent successfully improved the [1,2]-rearrangement yield and would be utilised for the future asymmetric system.

4.6 Salt Synthesis

4.6.1 Camphorsultam

Focusing on the effect of substituting benzyl group and the auxiliary behaviour, synthesis and subsequent rearrangement of salts was planned. Access to salts was achieved through reported methods.[28] First camphorsultam **70** was reacted with bromoacetylbromide using sodium hydride in toluene and formed **97** in good yield, followed by the nucleophilic

substitution of the bromide **97** with dimethylamine to furnish the tertiary amine **98** in excellent yield. Finally, the amine **98** was heated with (4.0 equiv) of bromide at 50°C in toluene to give salts in good to excellent yield (Table 6).



79 **97** **98** **68, 99-113**

Entry	R	Substrates	Yield (%)
1	H	**68**	7[a]
2	4-OMe	**99**	74[a]
3	4-COMe	**100**	89[a]
4	2,5-diF	**101**	93[a]
5	4-COPh	**102**	96[a]
6	4-COOMe	**103**	74[a]
7	2,4-diF	**104**	90[a]
8	3,5-diF	**105**	88[a]
9	2,4,6-diF	**106**	89[a]
10	3-F	**107**	91[a]
11	4-Ph	**108**	86[a]
12	2-CN	**109**	89[a]
13	2-CF_3	**110**	46[a]

14	4-CN	**111**	96
15	4-CF_3	**112**	95
16	4-NO_2	**113**	91

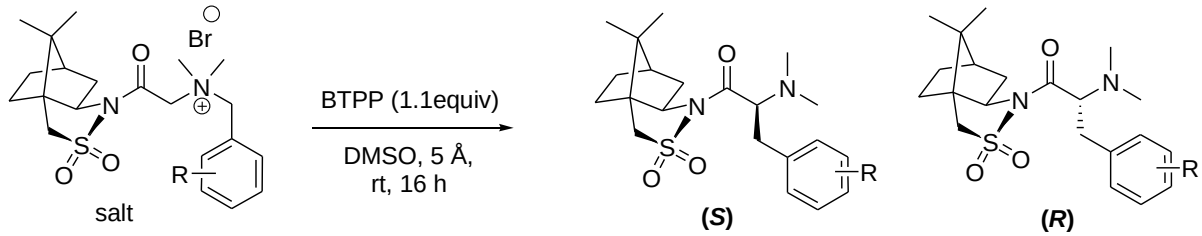
[a] These salts was prepared by H-Akriem in our group

Table 6

Formation of salts (entry 1-16) proceeded in good to excellent yield in general. Salt **110** which is substituted in the *ortho*-position, gave a lower yield (Entry 13), presumably due to the steric hindrance adjacent to the reacting centre. With the successful synthesis of all salts, interest was turned to their behaviour during rearrangement with our new conditions.

4.7 Steven's rearrangement of the benzylic ammonium salts

The ammonium salts (**68, 99-113)** were subjected to the optimised reaction conditions to give the desired products in good yields (Table 7). Most of salts delivered [1,2]-rearrangement products exclusively.



Entry	R	Substrate	(*2R+2S*)	dr(*R:S*) NMR
1	H	**69**	65%	80:20 [a]
2	4-NO_2	**83**	70%	79:21
3	4-CN	**84**	86%	80:20
4	4-CF_3	**85**	84%	79:21
5	2,5-diF	**87**	89%	78:22 [a]
6	4-OMe	**89**	65%	79:21 [a]
7	4-COMe	**114**	68%	77:23 [a]
8	2,4-diF	**115**	61%	80:20 [a]
9	4-COPh	**116**	60%	62:38 [a]

10	4-COOMe	**117**	53%	78:22 [a]
11	3,5-diF	**118**	82%	80:20 [a]
12	2,4,6-triF	**119**	65%	85:15 [a]
13	3-F	**120**	88%	71:29 [a]
14	4-Ph	**121**	73%	80:20 [a]
15	2-CN	**122**	82%	69:18:**16**[2,3]a,b
16	2-CF_3	**123**	77%	68:21:**11**[2,3] a,b

[a] prepared by H. Akriem.

[b] (2*S*)-[1,2]-product and [2,3]-product as an inseparable mixture.

Table 7

The absolute stereochemistry of the major isomer of **69** ***(S)*** was assigned from an X-ray crystal structure obtained within our group (Figure 6).

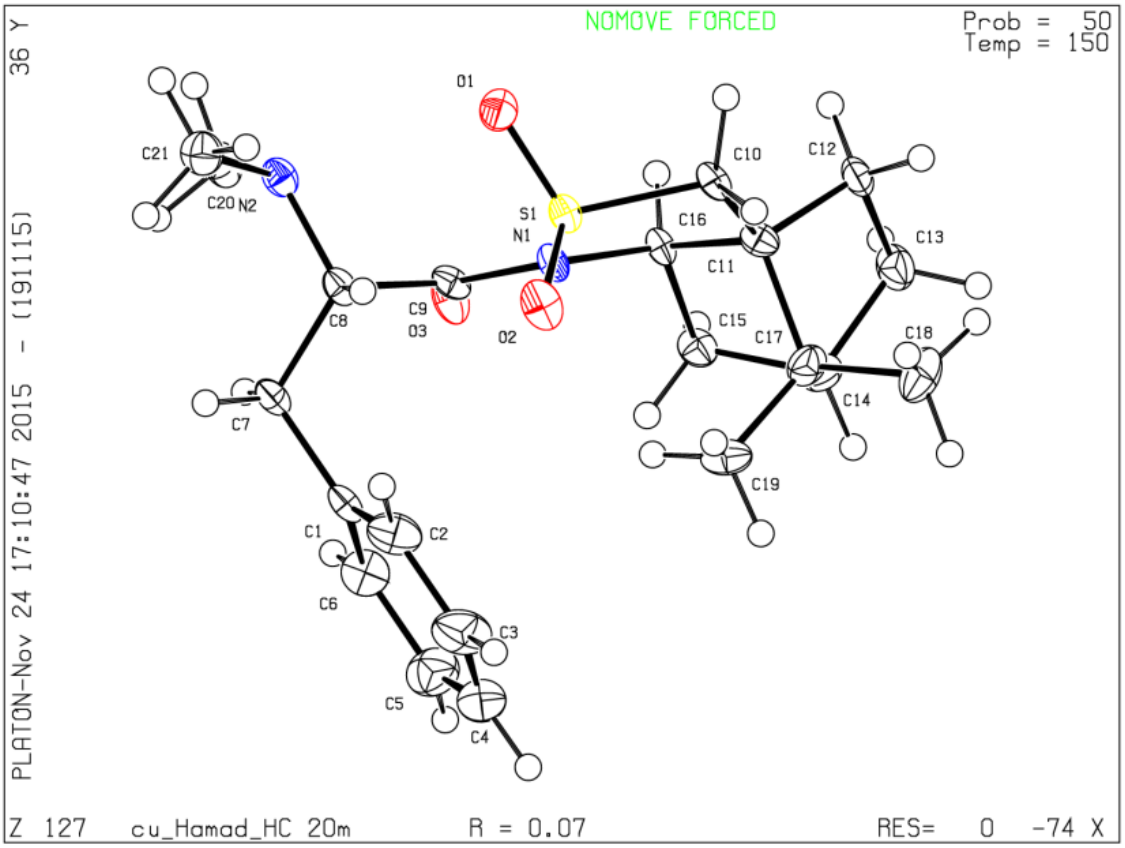


Fig 6

The spectroscopic data we obtained for **69** ***(S)*** matched the spectroscopic data obtained previously within our group. We established a comparison between the ^{1}H NMR spectra of

the minor (**69**, **83-89, 111-123**) and of the major (**69**, **83-89, 111-123**) diastereoisomers for each substituent. A trend was observed: for every major diastereoisomer the splitting pattern of the CH_2SO_2 group resonance is an apparent singlet, whereas for every minor diastereoisomer it is two doublets. Therefore, we have a diagnostic signal allowing us to assign the diastereoselectivity for each diastereoisomer. When comparing the chemical shifts and splitting patterns of respectively $CHCH_2Ar$ and $CHCH_2Ar$ resonances for both diastereoisomers, no significant trend was found. Different regioisomers of the fluorobenzyl products **87, 115** and **118 (*S*)** and **87, 115** and **118 (*R*)** were obtained in good yield and diastereoselectivity; the position of the fluorine atoms on the ring was of little influence on the reaction yield or on the diastereoselectivity (Entries 5, 8 and 11). Perhaps the most surprising observation was the absence of competing [2,3]-rearrangement from the reaction mixtures, apart from two salts: the 2-cyanobenzyl salt **122**, the 2- trifluoromethylbenzyl salt **123** (Entries 15 and 16), where minor amounts of [2,3]-products were isolated together with [1,2]- (*2S*) product.

We decided to investigate the stereochemistry of salts (**109**, **110**). Hence the absolute stereochemistry of the [2,3]-product **122** and **123** were proposed based on the study of the two possible transition states (Figure 7).

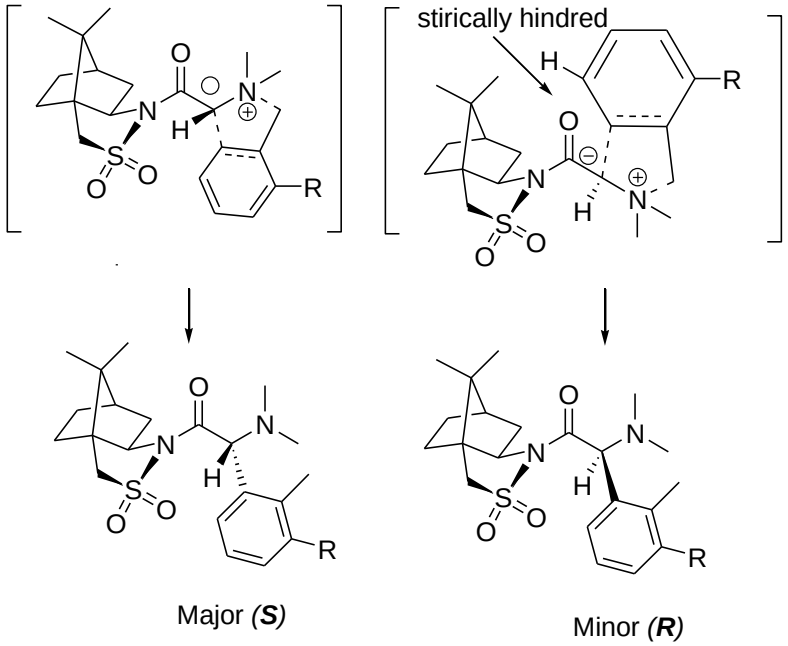


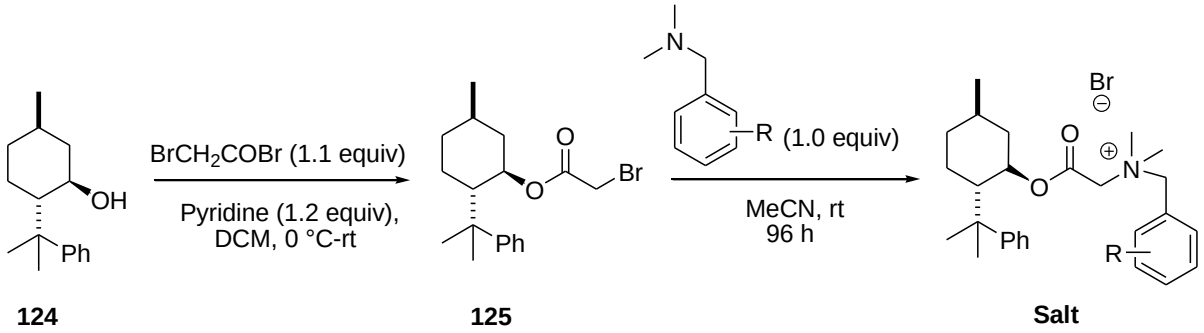
Fig 7

The [2,3]-sigmatropic rearrangement of **122** and **123** proceeds via a concerted mechanism. Approach from the bottom face, with Hα-to the nitrogen pointing up, is favoured, leading to the proposed stereochemistry for ***(S)*** products.

4.8 Phenyl menthol as auxiliary

With investigation into benzyl and acyl substituent variation having an impact upon the balance between rearrangement pathways, attention was turned to the original asymmetric reactions of Sweeney and Tayama. Utilising phenylmenthol auxiliary, investigation was undertaken with our new reaction conditions to determine whether phenylmenthol would yield [1,2]-rearrangement product as Tayama *el al.* were only able to isolate [2,3]-shift products.

The synthesis of ylid precursors, using 8-(-)-phenylmenthol as the chiral auxiliary, was carried out starting from the commercially available 8-(-)-phenylmenthol **124**. All salts were obtained in two nucleophilic substitution-benzylation sequences in good overall yield (Table 8) via the reported method.[26, 31]



124 **125** **Salt**

Entry	R	Salts	Yield (%)
1	H	**80**	91
2	2-CF_3	**126**	64
3	3-CF_3	**127**	90
4	3-CN	**128**	93

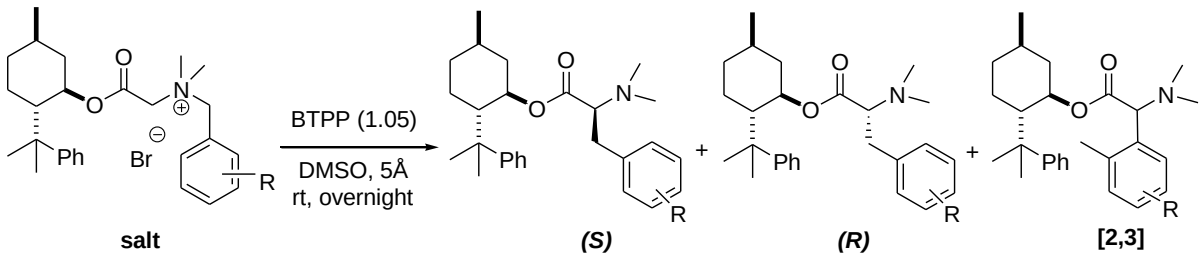
5	4-CN	**129**	96
6	4-NO_2	**130**	94
7	4-OMe	**131**	90
8	2,5-diF	**132**	94
9	4-COPh	**133**	89
10	4-COOMe	**134**	90
11	4-COMe	**135**	92

Table 8

Formation of salts (**80, 126-135)** proceeded in very good to excellent yield in general. Salt (**126)** which is substituted in the *ortho*-position, gave a lower yield (Entry 2), presumably due to the steric hindrance adjacent to the reacting centre.

4.9 Stevens' rearrangement of the benzylic ammonium salts

Using our new optimised conditions, the newly formed salts were converted in to the desired rearranged products (Table 9). Only trace amount of cleavage products was observed. Despite an increased yield of [1,2]-rearrangement products, the d.r. remained modest. The increased yield of products could be attributed to the change in solvent to DMSO. Along with [1,2]-rearrangement products, minimal amount of [2,3]-rearrangement was also observed from ^{1}H NMR of crude mixture, but no [2,3]-rearrangement products were isolated after purification by flash chromatography. Therefore, in all cases [1,2]-rearrangement were major products. The rearrangement of **140** and **144** identified less than 10 % of [2,3]-rearrangement products, and suggested that the electron withdrawing (carbonyl) *p*-substituent accelerates the Sommelet–Hauser rearrangement.



salt ***(S)*** ***(R)*** **[2,3]**

Entry	R	Substrates	Yield *S* (%)	Yield *R* (%)	dr*(S:R)*[a]	[2,3][b]
1	H	**81**	47	24	1:2	< 5 %
2	2-CF_3	**136**	62	12	1:2.5	< 5 %
3	3,5-diF	**137**	55	20	1:2.5	< 5 %
4	3-CN	**138**	49	19	1:2	< 5 %
5	3-CF_3	**139**	52	18	1:2.4	< 5 %
6	4-COOMe	**140**	44	16	1:2.3	< 10 %
7	4-OMe	**141**	33	12	1:2	Trace
8	4-NO_2	**142**	63	12	1:4.2	Trace
9	4-CN	**143**	58	-	1:2.2	< 5 %
10	4-COPh	**144**	46	18	1:1.9	< 10 %

[a] dr determined from NMR of crude mixture.

[b] amount of [2,3]-rearrangement determined from NMR of crude mixture

Table 9

Both products ***(S)*** and ***(R)*** were isolated to determine the reaction diastereoselectivity. A ^{1}H NMR analysis of the crude reaction mixture (after aqueous work-up) was obtained and the diastereoisomeric ratio was determined by integration of the *N,N*-dimethyl resonances, matching ones after isolation of both diastereoisomers.

The best results were obtained with benzyl moieties bearing electron withdrawing substituents, especially 4-nitrobenzyl product **142** (Entry 8) which afforded the highest yield and highest diastereoselectivity. This can be explained by radical stabilising nature of a 4-nitro-substituted benzyl species, hence the preference of nitro-substituted benzyl species towards [1,2]-shift product. Surprisingly, Tayama and co-workers[25] did not investigate 4-

nitrobenzyl ammonium salts, so it was unknown whether [1,2]- or [2,3]- rearrangement is favoured in the Tayama [2,3]-rearrangement conditions. A lower yield was obtained with the benzyl groups bearing the electron-donating substituents, 4-methoxy, compound **141** (entry 7). We have previously mentioned the work from Stevens and co-workers about the effect of substitution on the rearrangement velocity,[3] indicating a lower reaction rate when the salt was substituted by an electron donating group, such as 4-methoxybenzyl salt. Although it is not clear why 4-methoxybenzyl products **141** were afforded in low yield (entry 8), we hypothesise that the 4-methoxybenzyl salt **131** rearranges presumably with preventing its full delocalisation/resonance (Figure 3), as shown by Stevens *et al.*[3]

4.10 Determination of the relative stereochemistry of diastereoisomers

Products **81** ***(S)*** and **81** ***(R)*** were afforded as oils and we were not able to crystallise them. The stereochemistry was predicted based on the aforementioned mechanism of the reaction and the absolute stereochemistry predicted for both (2*R*)-camphorsultam containing diastereoisomers.

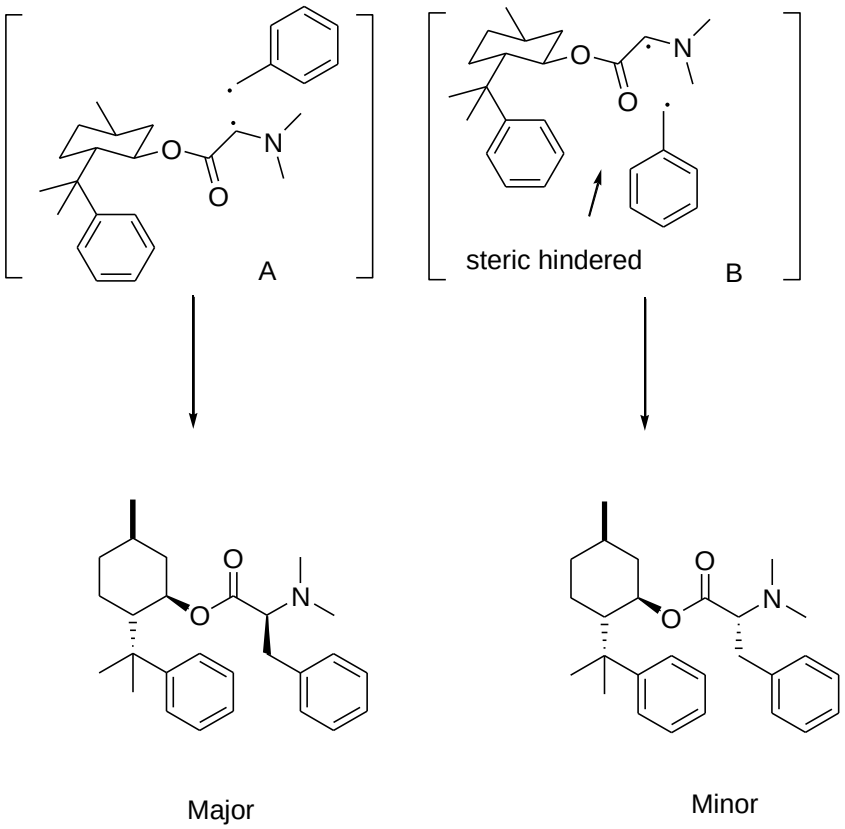


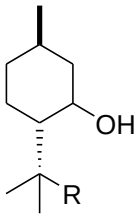
Fig 6

We proposed that the stereochemistry was a result of the recombination of the radical pair preferentially from the least hindered face of the molecule. The radical intermediate could adopt two conformations **A** and **B** (Figure 6). All the substituents are in equatorial positions, where interactions are minimised. The 1,1-dimethylbenzyl group being very bulky acts as a conformation anchor and leading this particular conformation. From this favoured conformation the benzyl radical could recombine from the top or the bottom face (Figure 6). Approach of the radical from the bottom face is sterically hindered by the large 1,1-dimethylbenzyl group (**B**); the benzyl radical would preferentially recombine from the top face leading to the major product **(A)**. The level of stereoselectivity observed was in line with reported[31,32] diastereoselectivity of [1,2]-rearrangement, but there was an increase in the reaction diastereoselectivity compared to the reactions with (-)-menthol as auxiliary, this shows that a bulky group here is necessary.

5.0 Conclusion

We have demonstrated that the [1,2]-sigmatropic rearrangement of benzylic ammonium ylids can proceed in good yield and diastereoselectivity. By using the phosphazene base BTPP and 5Å molecular sieves, we made this reaction more reliable with low return of auxiliary.

We have also demonstrated that there is competition for some examples between the Stevens and the Sommelet-Hauser rearrangements, further investigations are needed in order to identify and understand the influence of the reaction conditions, such as the choice of the chiral auxiliary, of the base or of the solvent. We have also shown that the reaction can tolerate substitution at 2-, 3-, and 4-benzyl substituents to participate in this chemistry, with electron donating group giving lower yield, due to inhibition of [1,2]-rearrangement by destabilisation of the ylid. For the phenyl menthol as auxiliary, the hindered phenyl group on menthol led to better diastereoselectivity compared to methyl group on menthol, perhaps indicating the isopropyl group was not bulky enough to shield either face of the molecule. Hence, preparing phenyl menthol with bulkier group such as **142** may lead to better diastereoselectivity.



142
R = 2,6-Di-tert-butyl phenyl

Fig 7

In this report, the best diastereoselectivity was obtained when camphorsultam was used as the chiral auxiliary. Due to its ability to form derivatives through its nitrogen atom and the structural rigidity of its chirality which allow a reaction to proceed with very specific stereoselectivity The advantage of phenyl menthol as chiral auxillary was observed to give a minimum amount of cleaved product, since an oxygen radical, higher in energy, is much less favoured than a nitrogen radical, and thus may an avoid the formation of cleaved product.

6.0 Experimental

General Method

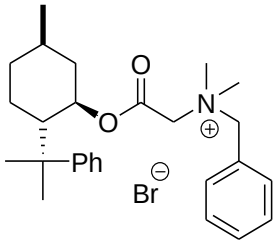
Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent in accordance with the procedures of Perrin and Armarego. Toluene and THF were distilled from sodium benzophenoneketyl radical while dichloromethane and acetonitrile were distilled from calcium hydride. DMSO anhydrous was used as obtained fromSigma-Aldrich.Thin layer chromatography (TLC) was carried out using silica gel 60 F254 aluminium sheets. Spots were visualised by quenching UV irradiation at 254 nm, and by staining with 2% $KMnO_4$ (w/v) in 20% K_2CO_3 (w/v) solution, 15% phosphomolybdic acid (w/v) in EtOH. Flash column chromatography was carried out using silica gel 60 A, 70-230 mesh, 63-200 µm obtained

from Sigma–Aldrich. The HPLC analysis was conducted on a Chiralpack IB-3 column (Dimensions: 4.6mm×250mm; particle size: 3µm). The UV detection was at wavelengths of 200, 220 and 230. Two solvents were employed; hexane, 2-propanol (1:1) and flow rate of 1mL/min. Nuclear magnetic resonance (NMR) spectroscopy was performed on a BrukerAvance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in ^{13}C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (J) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz. Mass spectrometry was performed using a BrukerMicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}.

General procedure for salt synthesis

Following previously described method,[31] salts were prepared. A round-bottomed flask was charged with (1.0 equiv), (–)-8-phenylmenthol (1.0 equiv) andbromoacetylbromid*e* (1.1 equiv) and pyridine (1.2 equiv) was added at 0 °C, after the addition the reaction was stirred at rt overnight. The resulting mixture was washed with saturated aqueous sodium hydrogen carbonate and water. The organic layer was dried over sodium sulfate. Evaporation of the solvent gave bromoacetic acid (–)-8-phenylmenthol ester in quantative yield. The crude product was used in next step without purification. A solution of bromoacetic acid (–)-8-phenyl menthol ester (1.1 equiv) and amines derivatives (1.0 equiv) in acetonitrile (0.2 M) was stirred for 3 days at room temperature. The resulting mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (dichloromethane/methanol = 10:1 as eluent) to obtain quaternary ammonium salt.[26]

***N*-Benzyl-*N*,*N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]ammonium bromide (80):** 91 % yield; colourless solid; mp 196–198 °C;



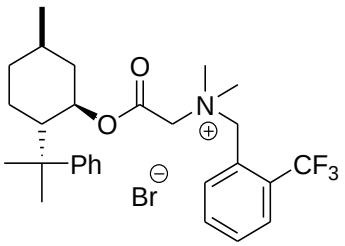
^{1}H NMR (400MHz, $CDCl_3$): δ 7.56-7.54 (m, 3H, ArC<u>H</u>), 7.51-7.42 (m, 2H, ArC<u>H</u>), 7.26-7.24 (m, 2H, ArC<u>H</u>), 7.14 (t, *J* 8.0, 2H, ArC<u>H</u>), 6.83 (t, *J* 7.2, 1H, ArC<u>H</u>), 5.20 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 4.97 (d, *J* 12.8, 1H,NC<u>H</u>$_2$Ar), 4.92 (td, *J* 10.8, 4.8, 1H, CH_2C<u>H</u>O), 4.20 (d, *J* 17.2, 1H, COC<u>H</u>$_2$N), 3.42 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.26 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.38 (d, *J* 17.2, 1H, COC<u>H</u>$_2$N), 2.16 (td, *J* 10.8, 3.6, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.03-1.99 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.87-1.82 (m, 1H, CHC<u>H</u>$_2$CHO), 1.78- 1.73 (m, 1H, CH$_2$C<u>H</u>$_2$CHCH$_3$), 1.53-1.43 (m, 1H, CH$_2$CH$_2$C<u>H</u>CH$_3$), 1.28 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.29-1.19 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(<u>C</u>H$_3$)$_2$), 1.11-0.96 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.92 (d, *J* 6.4, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9 (<u>C</u>O), 152.3 (Ar-<u>C</u>), 133.8 (2 x ArCH), 131.5 (Ar-<u>C</u>), 129.8 (2 x Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 127.1 (Ar<u>C</u>H), 125.8 (2 x Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 76.9 (CH_2<u>C</u>HO), 68.8 (N<u>C</u>H$_2$Ar), 59.9 (<u>C</u>OCH$_2$N), 51.0 (<u>C</u>HCPh(CH$_3$)$_2$), 50.5 (N(<u>C</u>H$_3$)$_2$), 49.7 (N(<u>C</u>H$_3$)$_2$), 41.7 (CH<u>C</u>H$_2$CHO), 39.7 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.5 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.7 (CPh(<u>C</u>H$_3$)$_2$), 31.4 (<u>C</u>HCH$_3$), 26.3 (CPh(<u>C</u>H$_3$)$_2$), 22.1 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.9 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2942 (CH), 1738 (CO);

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{38}NO_2$ [M-Br]$^+$ 408.2902; found 408.2908

***N,N*-Dimethyl-N-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N* (2'trifluoromethylbenzyl) -ammonium bromide, monohydrate (124)**: 64 % yield; colourless solid; mp 76–78 °C;



^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (d, *J* 7.2 Hz, 1H, ArC<u>H</u>), 7.82 (d, *J* 7.2 Hz, 1H, ArC<u>H</u>), 7.72-7.69 (m, 2H, ArC<u>H</u>), 7.39-7.21 (m, 4H, ArC<u>H</u>), 6.91 (t, *J* 7.2 Hz, 1H, ArC<u>H</u>), 5.40 (d, *J* 12.8, 1H,

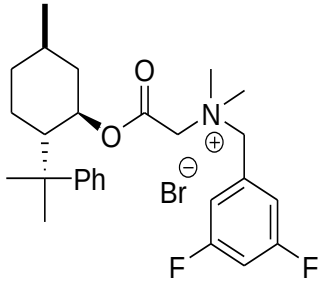
NC$\underline{H}_2$Ar), 5.18 (d, *J* 12.8 Hz, 1H,NC$\underline{H}_2$Ar), 4.92 (td, *J* 10.8, 4.8, 1H, $CH_2\underline{C}HO$), 4.45 (d, *J* 17.2 Hz, 1H, COC$\underline{H}_2$N), 3.44 (s, 3H, N(C$\underline{H}_3$)$_2$), 3.28 (s, 3H, N(C$\underline{H}_3$)$_2$), 2.48 (d, *J* 17.2 Hz, 1H, COC$\underline{H}_2$N), 2.16-2.14 (m, 1H, C$\underline{H}$CPh(CH$_3$)$_2$), 2.03-1.99 (m, 1H, C$\underline{H}_2CH_2CHCH_3$), 1.87-1.78 (m, 1H, CHC$\underline{H}_2$CHO), 1.78- 1.72 (m, 1H, $CH_2\underline{C}H_2CHCH_3$), 1.53-1.43 (m, 1H, $CH_2CH_2\underline{C}HCH_3$), 1.30 (s, 3H, CPh(C$\underline{H}_3$)$_2$), 1.32-1.19 (m, 1H, CHC$\underline{H}_2$CHO), 1.13 (s, 3H, CPh(C$\underline{H}_3$)$_2$), 1.11-0.97 (m, 2H, C$\underline{H}_2C\underline{H}_2$CHCH$_3$), 0.88 (d, *J* 6.4 Hz, 3H, CHC$\underline{H}_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 ($\underline{C}$O), 151.6 (Ar-$\underline{C}$), 133.5 (Ar$\underline{C}$H), 131.7 (q, *J* 29 Hz, Ar-$\underline{C}$), 130.8 (Ar$\underline{C}$H), 129.5 (q, *J* 6Hz, Ar$\underline{C}$H),128.4 (2 x Ar$\underline{C}$H), 127.1 (Ar$\underline{C}$H), 125.8 (2 x Ar$\underline{C}$H), 125.4 (d, *J* 1 Hz, Ar$\underline{C}$H), 123.17 (d, *J* 273 Hz, CF_3), 76.6 ($CH_2\underline{C}HO$), 68.4 (N$\underline{C}H_2$Ar), 60.2 (CO$\underline{C}H_2$N), 50.0 ($\underline{C}$HCPh(CH$_3$)$_2$), 46.5 (N($\underline{C}$H$_3$)$_2$), 49.7 (N($\underline{C}$H$_3$)$_2$), 41.7 (CH$\underline{C}H_2$CHO), 39.7 (CH$\underline{C}$Ph(CH$_3$)$_2$), 34.5 ($CH_2\underline{C}H_2CHCH_3$), 31.7 (CPh($\underline{C}H_3$)$_2$), 31.4 ($\underline{C}HCH_3$), 25.3 (CPh($\underline{C}H_3$)$_2$), 22.4 ($\underline{C}H_2CH_2CHCH_3$), 21.6 (CH$\underline{C}H_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2952 (CH), 1742 (CO), 1178 (C-F);

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}F_3NO_2$ [M-Br]$^+$ 476.2776, found 476.2736.

***N,N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*-(3,5 difluoromethyl benzyl) -ammonium bromide, monohydrate (130):** 94 % yield; colourless solid; mp 72–74 °C;



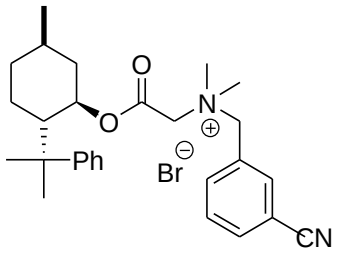
^{1}H NMR (400MHz, $CDCl_3$): δ 8.10 (d, *J* 7.2 Hz, 1H, ArC$\underline{H}$), 7.82 (d, *J* 7.2 Hz, 1H, ArC$\underline{H}$), 7.72-7.69 (m, 2H, ArC$\underline{H}$), 7.39-7.21 (m, 2H, ArC$\underline{H}$), 6.91 (t, *J* 7.2 Hz, 1H, ArC$\underline{H}$), 6.89-6.86 (m, 1H, ArC$\underline{H}$) 5.44 (d, *J* 12.8, 1H, NC$\underline{H}_2$Ar), 5.24 (d, *J* 12.8 Hz, 1H,NC$\underline{H}_2$Ar), 4.96 (td, *J* 10.8, 4.8, 1H, $CH_2\underline{C}HO$), 4.51 (d, *J* 17.2 Hz, 1H, COC$\underline{H}_2$N), 3.48 (s, 3H, N(C$\underline{H}_3$)$_2$), 3.32 (s, 3H, N(C$\underline{H}_3$)$_2$), 2.52 (d, *J* 17.2 Hz, 1H, COC$\underline{H}_2$N), 2.22-2.17 (m, 1H, C$\underline{H}$CPh(CH$_3$)$_2$), 2.06-2.01 (m, 1H, C$\underline{H}_2CH_2CHCH_3$), 1.91-1.83 (m, 1H, CHC$\underline{H}_2$CHO), 1.80- 1.76 (m, 1H, $CH_2\underline{C}H_2CHCH_3$), 1.59-1.51 (m, 1H, $CH_2CH_2\underline{C}HCH_3$), 1.32 (s, 3H, CPh(C$\underline{H}_3$)$_2$), 1.35-1.26 (m, 1H, CHC$\underline{H}_2$CHO), 1.15 (s, 3H, CPh(C$\underline{H}_3$)$_2$), 1.12-0.99 (m, 2H, C$\underline{H}_2C\underline{H}_2$CHCH$_3$), 0.90 (d, *J* 6.4 Hz, 3H, CHC$\underline{H}_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4 (C=O), 162.2 (dd, *J* 35.5, 23.1 Hz, CF), 160.3 (dd, *J* 20.0, 12.6 Hz, CF), 150.8 (Ar-C), 131.7 (Ar-C), 129.5 (ArCH),128.4 (2 x ArCH), 125.8 (2 x ArCH), 118.1 (2 x ArCH), 112.3 (ArCH), 76.4 (CH_2CHO), 68.2 (NCH_2Ar), 60.4 ($COCH_2N$), 50.0 ($CHCPh(CH_3)_2$), 46.6 ($N(CH_3)_2$), 49.8 ($N(CH_3)_2$), 41.6 ($CHCH_2CHO$), 39.9 ($CHCPh(CH_3)_2$), 34.3 ($CH_2CH_2CHCH_3$), 31.5 ($CPh(CH_3)_2$), 31.1 ($CHCH_3$), 25.5 ($CPh(CH_3)_2$), 22.4 ($CH_2CH_2CHCH_3$), 21.3 ($CHCH_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2947 (CH), 1736 (CO), 1465 (CC), 1423 (C-F);

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}F_2NO_2$ $[M\text{-}Br]^+$ 444.2714; found 444.2741.

***N*-(3'-Cyanobenzyl)-*N,N*-dimethyl-*N*-[(–phenylmenthoyloxycarbonylmethyl]ammonium bromide, monohydrate (126)**: 93 % yield; colourless solid; mp 102–105 °C;



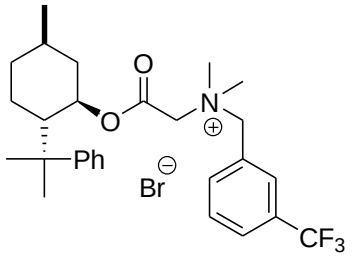
^{1}H NMR (400MHz, $CDCl_3$): δ 8.14 (d, *J* 7.2 Hz, 1H, ArCH), 7.84 (d, *J* 7.2 Hz, 1H, ArCH), 7.72-7.69 (m, 2H, ArCH), 7.29-7.10 (m, 4H, ArCH), 6.84 (t, *J* 7.2 Hz, 1H, ArCH), 5.46 (d, *J* 12.8, 1H, NCH_2Ar), 5.22 (d, *J* 12.8 Hz, 1H,NCH_2Ar), 4.92 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH_2CHO), 4.45 (d, *J* 17.2 Hz, 1H, $COCH_2N$), 3.42 (s, 3H, $N(CH_3)_2$), 3.25 (s, 3H, $N(CH_3)_2$), 2.42 (d, *J* 17.2 Hz, 1H, $COCH_2N$), 2.15-2.14 (m, 1H, $CHCPh(CH_3)_2$), 2.01-1.97 (m, 1H, $CH_2CH_2CHCH_3$), 1.89-1.80 (m, 1H, $CHCH_2CHO$), 1.78- 1.74 (m, 1H, $CH_2CH_2CHCH_3$), 1.55-1.47 (m, 1H, $CH_2CH_2CHCH_3$), 1.30 (s, 3H, $CPh(CH_3)_2$), 1.34-1.22 (m, 1H, $CHCH_2CHO$), 1.15 (s, 3H, $CPh(CH_3)_2$), 1.12-0.97 (m, 2H, $CH_2CH_2CHCH_3$), 0.89 (d, *J* 6.4 Hz, 3H, $CHCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4 (C=O), 152.6 (Ar-C), 138.5 (ArCH), 136.7 (Ar-C), 133.8 (ArCH), 129.5 (ArCH), 128.8 (2 x ArCH), 127.9 (ArCH), 125.8 (2 x ArCH), 125.4 (ArCH), 117.1 (Ar-CN), 113.2 (ArCH), 76.8 (CH_2CHO), 66.6 (NCH_2Ar), 59.4 ($COCH_2N$), 50.4 ($CHCPh(CH_3)_2$), 49.9 ($N(CH_3)_2$), 49.7 ($N(CH_3)_2$), 41.7 ($CHCH_2CHO$), 39.5 ($CHCPh(CH_3)_2$), 34.4 ($CH_2CH_2CHCH_3$), 31.4 ($CPh(CH_3)_2$), 31.2 ($CHCH_3$), 25.1 ($CPh(CH_3)_2$), 22.8 ($CH_2CH_2CHCH_3$), 21.3 ($CHCH_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2968 (CN), 1738 (CO), 2219 (C-N);

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}N_2O_2$ [M-Br]$^+$ 433.2855; found 433.2821.

***N,N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*(4'-trifluoromethylbenzyl) ammonium bromide (125)**: 90 % yield; colourless solid; mp 114–116 °C;



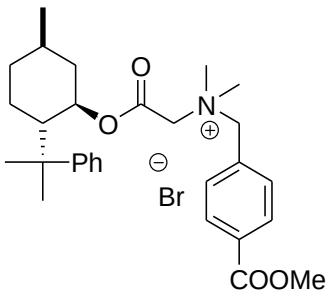
^{1}H NMR (400MHz, $CDCl_3$): δ 7.84 (2H, d, *J* 8.0 Hz, ArC<u>H</u>), 7.72 (2H, d, *J* 8.0 Hz, ArC<u>H</u>), 7.21 (2H, d, *J* 7.6 Hz, ArC<u>H</u>), 7.07 (2H, t, *J* 7.6 Hz, ArC<u>H</u>), 6.64 (1H, t, *J*7.6 Hz, ArC<u>H</u>),5.46 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 5.30 (d, *J* 12.8 Hz, 1H,NC<u>H</u>$_2$Ar), 4.90 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH_2<u>C</u>HO), 4.25 (d, *J* 17.0 Hz, 1H, COC<u>H</u>$_2$N), 3.49 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.42 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.44 (d, *J* 17.2 Hz, 1H, COC<u>H</u>$_2$N), 2.20-2.16 (m, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.05-2.01 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.90-1.81 (m, 1H, CHC<u>H</u>$_2$CHO), 1.79- 1.76 (m, 1H, CH$_2$C<u>H</u>$_2$CHCH$_3$), 1.59-1.52 (m, 1H, CH$_2$CH$_2$C<u>H</u>CH$_3$), 1.32 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.33-1.24 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.14-0.99 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.88 (d, *J* 6.4 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (<u>C</u>O), 152.1 (Ar-<u>C</u>), 135.7 (Ar-<u>C</u>), 133.8 (q, *J* 33 Hz, Ar<u>C</u>H),130.2 (ArCH), 129.2 (2 x Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 127.9(q, *J* 3 Hz, Ar<u>C</u>H), 125.8 (2 x Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 124.8 (ArCH), 123.8 (q, *J* 272 Hz, <u>C</u>F$_3$), 76.8 (CH$_2$<u>C</u>HO), 67.4 (N<u>C</u>H$_2$Ar), 59.4 (CO<u>C</u>H$_2$N), 50.1 (<u>C</u>HCPh(CH$_3$)$_2$), 49.9 (N(<u>C</u>H$_3$)$_2$), 49.4 (N(<u>C</u>H$_3$)$_2$), 41.7 (CH<u>C</u>H$_2$CHO), 39.5 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.4 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.2 (CPh(<u>C</u>H$_3$)$_2$), 30.9 (<u>C</u>HCH$_3$), 25.2 (CPh(<u>C</u>H$_3$)$_2$), 23.8 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.3 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2977 (CN), 1731 (CO), 1170 (C-F);

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}F_3NO_2$ [M-Br]$^+$ 476.2776, found 476.2778.

***N*-(4'-Cyanobenzyl)-*N,N*-dimethyl-*N*-[(–8-phenylmenthoyloxycarbonylmethyl] ammonium bromide (132):** 90 % yield; colourless; mp 176–180 °C;



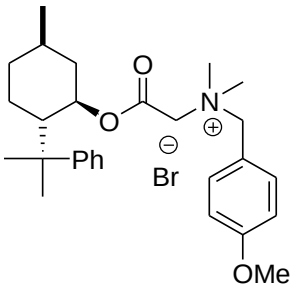
^{1}H NMR (400MHz, $CDCl_3$): δ 7.88 (2H, d, *J* 8.4 Hz, ArC<u>H</u>), 7.78 (2H,d, *J* 8.4 Hz, ArC<u>H</u>), 7.26 (2H, d, *J* 7.0 Hz, ArC<u>H</u>), 7.16 (2H, t, *J* 7.0 Hz, ArC<u>H</u>), 6.83 (1H, t, *J* 7.0 Hz, ArC<u>H</u>),5.48 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 5.38 (d, *J* 12.8 Hz, 1H,NC<u>H</u>$_2$Ar), 4.92 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH_2C<u>H</u>O), 4.25 (d, *J* 17.0 Hz, 1H, COC<u>H</u>$_2$N), 3.46 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.29 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.43 (d, *J* 17.2 Hz, 1H, COC<u>H</u>$_2$N), 2.22-2.18 (m, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.03-1.98 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.89-1.81 (m, 1H, CHC<u>H</u>$_2$CHO), 1.78- 1.75 (m, 1H, CH$_2$C<u>H</u>$_2$CHCH$_3$), 1.57-1.49 (m, 1H, CH$_2$CH$_2$C<u>H</u>CH$_3$), 1.30 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.33-1.25 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.09-0.98 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.88 (d, *J* 6.4 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (<u>C</u>O), 162.8 (<u>C</u>OMe)152.1 (Ar-<u>C</u>), 135.7 (Ar-<u>C</u>), 133.8 (Ar<u>C</u>H), 131.9 (Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 121.0 (Ar<u>C</u>H), 117.5 (Ar<u>C</u>H), 115.3 (Ar<u>C</u>H), 76.8 (CH$_2$<u>C</u>HO), 67.4 (N<u>C</u>H$_2$Ar), 59.4 (CO<u>C</u>H$_2$N), 50.1 (<u>C</u>HCPh(CH$_3$)$_2$), 49.9 (N(<u>C</u>H$_3$)$_2$), 49.4 (N(<u>C</u>H$_3$)$_2$), 41.7 (CH<u>C</u>H$_2$CHO), 39.5 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.4 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.2 (CPh(<u>C</u>H$_3$)$_2$), 30.9 (<u>C</u>HCH$_3$), 25.2 (CPh(<u>C</u>H$_3$)$_2$), 23.8 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.3 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2941 (CH), 1750 (CO), 1474 (CC);

MS*m/z* (ESI$^+$) calculated for $C_{29}H_{40}NO_4$ [M-Br]$^+$ 466.2963; found 466.2958.

***N,N*-Dimethyl-*N*-(4'-methoxybenzyl)-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl] ammonium (129):** 90 % yield; colourless solid; mp 90–94 °C;



^{1}H NMR (400MHz, $CDCl_3$): δ 7.46 (2H, d, *J* 8.5 Hz, ArC<u>H</u>), 7.30-7.23 (2H, m, ArC<u>H</u>), 7.15 (2H, t, *J* 7.4 Hz, ArC<u>H</u>), 6.99 (2H, d, *J* 8.5 Hz, ArC<u>H</u>), 6.81 (1H, t, J 7.4 Hz, ArC<u>H</u>), 5.12 (d, J 12.8,

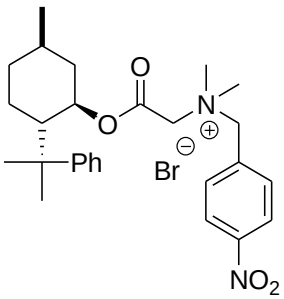
1H, NHC$_2$Ar), 4.98 (d, J 12.8 Hz, 1H, NCH$_2$Ar), 4.92-4.93 (m, 1H, CH$_2$CHO), 4.19 (d, *J* 17.0 Hz, 1H, COCH$_2$N), 3.82 (s, 3H, OCH$_3$), 3.46 (s, 3H, N(CH$_3$)$_2$), 3.29 (s, 3H, N(CH$_3$)$_2$), 2.43 (d, *J* 17.2 Hz, 1H, COCH$_2$N), 2.24-2.18 (m, 1H, CHCPh(CH$_3$)$_2$), 2.02-1.96 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.86-1.78 (m, 1H, CHCH$_2$CHO), 1.74- 1.69 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.52-1.44 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.30 (s, 3H, CPh(CH$_3$)$_2$), 1.30-1.19 (m, 1H, CHCH$_2$CHO), 1.12 (s, 3H, CPh(CH$_3$)$_2$), 1.1-0.98 (m, 2H, CH$_2$CH$_2$CHCH$_3$), 0.86 (d, *J* 6.4 Hz, 3H, CHCH$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (CO), 161.8 (COMe), 153.1 (ArC), 135.7 (ArC), 128.4 (2 x ArCH), 125.6 (2 x ArCH), 121.0 (ArCH), 118.4 (ArCH), 114.3 (ArCH), 76.5 (CH$_2$CHO), 67.5 (NCH$_2$Ar), 59.6 (COCH$_2$N), 50.1 (CHCPh(CH$_3$)$_2$), 49.9 (N(CH$_3$)$_2$), 49.1 (N(CH$_3$)$_2$), 41.4 (CHCH$_2$CHO), 39.2 (CHCPh(CH$_3$)$_2$), 34.6 (CH$_2$CH$_2$CHCH$_3$), 31.1 (CPh(CH$_3$)$_2$), 30.6 (CHCH$_3$), 26.6 (Ar-OCH$_3$), 25.3 (CPh(CH$_3$)$_2$), 23.5 (CH$_2$CH$_2$CHCH$_3$), 21.1 (CHCH$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2962 (CN), 1766 (CO), 1479 (CC), 1224 (C-O);

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{40}NO_3$ [M-Br]$^+$ 438.3008; found 438.3002.

***N,N*-Dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl]-*N*(4'-nitromethylbenzyl) ammonium bromide (128)**: 94% yield; colourless solid; mp 92–94 °C;



^{1}H NMR (400MHz, $CDCl_3$): δ 8.14 (d, *J* 7.2 Hz, 1H, ArCH), 7.86 (d, *J* 7.2 Hz, 1H, ArCH), 7.72-7.69 (m, 2H, ArCH), 7.30-7.12 (m, 4H, ArCH), 6.89 (t, *J* 7.2 Hz, 1H, ArCH), 5.48 (d, *J* 12.8, 1H, NCH$_2$Ar), 5.32 (d, *J* 12.8 Hz, 1H,NCH$_2$Ar), 4.90 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH$_2$CHO), 4.48 (d, *J* 17.2 Hz, 1H, COCH$_2$N), 3.44 (s, 3H, N(CH$_3$)$_2$), 3.28 (s, 3H, N(CH$_3$)$_2$), 2.46 (d, *J* 17.2 Hz, 1H, COCH$_2$N), 2.16-2.12 (m, 1H, CHCPh(CH$_3$)$_2$), 2.02-1.99 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.89-1.82 (m, 1H, CHCH$_2$CHO), 1.76- 1.71 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.56-1.46 (m, 1H, CH$_2$CH$_2$CHCH$_3$), 1.32 (s, 3H, CPh(CH$_3$)$_2$), 1.35-1.25 (m, 1H, CHCH$_2$CHO), 1.16 (s, 3H, CPh(CH$_3$)$_2$), 1.11-0.99 (m, 2H, CH$_2$CH$_2$CHCH$_3$), 0.89 (d, *J* 6.4 Hz, 3H, CHCH$_3$);

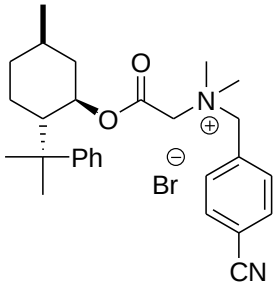
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (CO), 151.6 (Ar-C), 148.5 (Ar-C), 135.8 (ArCH), 129.5 (ArCH), 128.8 (2 x ArCH), 125.8 (2 x ArCH), 125.4 (ArCH), 122.1 (ArCH), 76.8 (CH$_2$CHO), 66.8

(N<u>C</u>H$_2$Ar), 59.1 (CO<u>C</u>H$_2$N), 50.2 (<u>C</u>HCPh(CH$_3$)$_2$), 49.9 (N(<u>C</u>H$_3$)$_2$), 49.2 (N(<u>C</u>H$_3$)$_2$), 41.5 (CH<u>C</u>H$_2$CHO), 39.3 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.1 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.2 (CPh(<u>C</u>H$_3$)$_2$), 31.4 (<u>C</u>HCH$_3$), 25.1 (CPh(<u>C</u>H$_3$)$_2$), 22.8 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.3 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2938 (CN), 1744 (CO), 1535 (NO_2);

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{37}N_2O_4$ [M-Br]$^+$ 453.2753; found 453.2741.

***N,N*-Dimethyl-*N*-(4'-metoxycarbonylbenzyl)-*N*-[(–)-8-phenylmenthoyloxy carbonylmethyl] (127):** 96% yield; colourless solid; mp 166–170 °C;



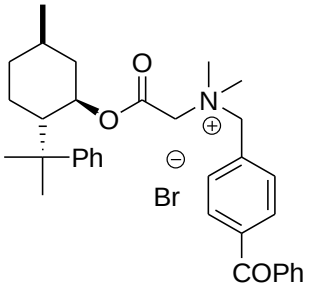
^{1}H NMR (400MHz, $CDCl_3$): δ 8.10 (2H, d, *J* 8.2 Hz, ArC<u>H</u>), 7.72 (2H, d, *J* 8.2 Hz, ArC<u>H</u>), 7.24 (2H, d, *J* 7.3 Hz, ArC<u>H</u>), 7.11 (2H, t, *J* 7.3 Hz, ArC<u>H</u>), 6.79 (1H, t, *J* 7.3 Hz, ArC<u>H</u>), 5.38 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 5.30 (d, *J* 12.8 Hz, 1H,NC<u>H</u>$_2$Ar), 4.90 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH$_2$C<u>H</u>O), 4.45 (d, *J* 17.0 Hz, 1H, COC<u>H</u>$_2$N), 3.49 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.29 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.42 (d, *J* 17.2 Hz, 1H, COC<u>H</u>$_2$N), 2.20-2.18 (m, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.04-2.00 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.88-1.78 (m, 1H, CHC<u>H</u>$_2$CHO), 1.76- 1.71 (m, 1H, CH$_2$C<u>H</u>$_2$CHCH$_3$), 1.55-1.51 (m, 1H, CH$_2$CH$_2$C<u>H</u>CH$_3$), 1.32 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.30-1.24 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.11-0.99 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.88 (d, *J* 6.4 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (<u>C</u>O), 152.1 (Ar-<u>C</u>), 135.7 (Ar-<u>C</u>), 133.8 (2 x Ar<u>C</u>H), 129.5 (Ar<u>C</u>H), 128.4 (2 x Ar<u>C</u>H), 126.2 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 115.1 (<u>C</u>N), 110.2 (Ar-<u>C</u>), 76.8 (CH$_2$<u>C</u>HO), 67.4 (N<u>C</u>H$_2$Ar), 59.4 (CO<u>C</u>H$_2$N), 50.1 (<u>C</u>HCPh(CH$_3$)$_2$), 50.0 (N(<u>C</u>H$_3$)$_2$), 49.5 (N(<u>C</u>H$_3$)$_2$), 41.7 (CH<u>C</u>H$_2$CHO), 39.5 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.4 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.2 (CPh(<u>C</u>H$_3$)$_2$), 30.9 (<u>C</u>HCH$_3$), 25.1 (CPh(<u>C</u>H$_3$)$_2$), 22.8 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.2 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2955 (CH), 2239 (CN), 1766 (CO);

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}N_2O_2$ [M-Br]$^+$ 433.2861; found 433.2858.

***N*-(4'-Benzoylbenzyl)-*N,N*-dimethyl-*N*-[(–)-8-phenylmenthoyloxycarbonylmethyl] ammonium (131):** 89% yield; colourless solid; mp 122–126 °C;



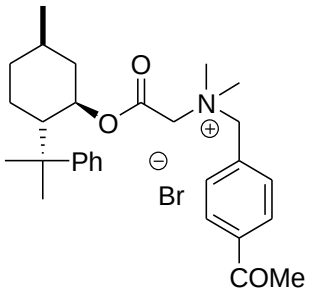
1H NMR ($CDCl_3$, 400 MHz) δ 7.91-7.73 (6H, m, ArC<u>H</u>), 7.65 (1H, t, *J* = 7.3 Hz, ArC<u>H</u>), 7.52 (2H, t, *J* = 7.3 Hz, ArC<u>H</u>), 7.30-7.22 (2H, m, ArC<u>H</u>), 7.18 (2H, t, *J* = 7.3 Hz, ArC<u>H</u>), 6.87 (1H, t, *J* = 7.3 Hz, ArC<u>H</u>), 5.42 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 5.31 (d, *J* 12.8 Hz, 1H, NC<u>H</u>$_2$Ar), 4.93 (ddd, *J* 11.0, 11.0, 4.8, 1H, CH_2C<u>H</u>O), 4.15 (d, *J* 17.0 Hz, 1H, COC<u>H</u>$_2$N), 3.47 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.33 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.47 (d, *J* 17.2 Hz, 1H, COC<u>H</u>$_2$N), 2.24-2.22 (m, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.06-2.00 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.92-1.84 (m, 1H, CHC<u>H</u>$_2$CHO), 1.78- 1.72 (m, 1H, CH_2C<u>H</u>$_2$CHCH$_3$), 1.55-1.51 (m, 1H, CH_2CH_2C<u>H</u>CH$_3$), 1.34 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.32-1.27 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.11-0.97 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.86 (d, *J* 6.4 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9 (C=O), 163.4 (<u>C</u>O), 152.1 (Ar-<u>C</u>), 139.2 (Ar-<u>C</u>), 135.7 (Ar-<u>C</u>), 133.8 (Ar-<u>C</u>), 133.1 (Ar<u>C</u>H), 130.7 (2 x Ar<u>C</u>H), 130.1 (2 x Ar<u>C</u>H), 126.7 (2 x Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 125.4 (2 x Ar<u>C</u>H), 125.2 (2 x Ar<u>C</u>H), 76.8 (CH_2<u>C</u>HO), 67.4 (N<u>C</u>H$_2$Ar), 59.4 (CO<u>C</u>H$_2$N), 50.6 (<u>C</u>HCPh(CH$_3$)$_2$), 50.0 (N(<u>C</u>H$_3$)$_2$), 49.2 (N(<u>C</u>H$_3$)$_2$), 41.3 (CH<u>C</u>H$_2$CHO), 39.2 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.0 (CH_2<u>C</u>H$_2$CHCH$_3$), 31.2 (CPh(<u>C</u>H$_3$)$_2$), 30.7 (<u>C</u>HCH$_3$), 25.9 (CPh(<u>C</u>H$_3$)$_2$), 22.1 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.3 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}): 2960 (CH), 1781 (CO), 1669 (CO);

MS*m/z* (ESI$^+$) calculated for $C_{34}H_{42}NO_3$ [M-Br]$^+$ 512.3165; found 512.3163.

***N*-(4'-Cyanobenzyl)-*N,N*-dimethyl-*N*-[(–8-phenylmenthoyloxycarbonylmethyl] ammonium bromide (133):** 90 % yield; colourless solid; mp 174–178 °C;



^{1}H NMR (400MHz, $CDCl_3$): δ 7.82 (2H, d, *J* 8.4 Hz, ArC<u>H</u>), 7.75 (2H,d, *J* 8.4 Hz, ArC<u>H</u>), 7.22 (2H, d, *J* 7.0 Hz, ArC<u>H</u>), 7.10 (2H, t, *J* 7.0 Hz, ArC<u>H</u>), 6.80 (1H, t, *J* 7.0 Hz, ArC<u>H</u>), 5.38 (d, *J* 12.8, 1H, NC<u>H</u>$_2$Ar), 5.32 (d, *J* 12.8 Hz, 1H,NC<u>H</u>$_2$Ar), 4.89 (ddd, *J* 10.5, 10.5, 4.4, 1H, CH_2<u>C</u>HO), 4.22 (d, *J* 17.0 Hz, 1H, COC<u>H</u>$_2$N), 3.65 (s, 3H, ArCO<u>C</u>H$_3$), 3.46 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.26 (s, 3H, N(C<u>H</u>$_3$)$_2$), 2.41 (d, *J* 17.2 Hz, 1H, COC<u>H</u>$_2$N), 2.20-2.116 (m, 1H, C<u>H</u>CPh(CH$_3$)$_2$), 2.01-1.98 (m, 1H, C<u>H</u>$_2$CH$_2$CHCH$_3$), 1.87-1.78 (m, 1H, CHC<u>H</u>$_2$CHO), 1.76- 1.72 (m, 1H, CH$_2$C<u>H</u>$_2$CHCH$_3$), 1.55-1.48 (m, 1H, CH$_2$CH$_2$C<u>H</u>CH$_3$), 1.30 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.32-1.26 (m, 1H, CHC<u>H</u>$_2$CHO), 1.15 (s, 3H, CPh(C<u>H</u>$_3$)$_2$), 1.10-0.99 (m, 2H, C<u>H</u>$_2$C<u>H</u>$_2$CHCH$_3$), 0.88 (d, *J* 6.4 Hz, 3H, CHC<u>H</u>$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (<u>C</u>O), 158.8 (<u>C</u>OMe), 152.3 (Ar-<u>C</u>), 136.6 (Ar-<u>C</u>), 133.4 (Ar<u>C</u>H), 131.6 (Ar<u>C</u>H), 128.2 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 121.1 (Ar<u>C</u>H), 118.1 (Ar<u>C</u>H), 115.1 (Ar<u>C</u>H), 76.6 (CH$_2$<u>C</u>HO), 67.2 (N<u>C</u>H$_2$Ar), 59.6 (CO<u>C</u>H$_2$N), 50.1 (<u>C</u>HCPh(CH$_3$)$_2$), 49.9 (N(<u>C</u>H$_3$)$_2$), 49.2 (N(<u>C</u>H$_3$)$_2$), 41.6 (CH<u>C</u>H$_2$CHO), 39.5 (CH<u>C</u>Ph(CH$_3$)$_2$), 34.4 (CH$_2$<u>C</u>H$_2$CHCH$_3$), 31.3 (CPh(<u>C</u>H$_3$)$_2$), 30.8 (<u>C</u>HCH$_3$), 26.8 (ArCO<u>C</u>H$_3$), 25.1 (CPh(<u>C</u>H$_3$)$_2$), 23.9 (<u>C</u>H$_2$CH$_2$CHCH$_3$), 21.5 (CH<u>C</u>H$_3$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2958 (CH), 1777 (CO), 1666 (CO);

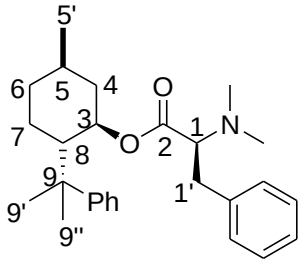
MS*m/z* (ESI$^+$) calculated for $C_{29}H_{40}NO_3$ requires [M-Br]$^+$ 450.3008; found 450.3002.

General procedure for [1,2]-Stevens rearrangement.

To an oven dried round-bottomed flask, flushed with nitrogen, ammonium bromide salt (100 mg, 1 equiv) in DMSO (5 mL) at room temperature with 5Å molecular sieves, was added dropwise BTPP (1.05 equiv). The reaction mixture was allowed to stir overnight. The crude mixture was filtered through a small pad of Celite and washed with Et_2O. The filtrate was partitioned with water (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the crude rearranged product, which was analysed by HPLC and then purified by flash chromatography on silica gel.

(*1R,2S,5R*)-5-methyl-2-(1-methyl-1-phenylethyl) cyclohexyl 2-(dimethylamino)-3-)phenyl)propanoate (81).

The benzylic ammonium bromide salt (100 mg, 0.18 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (39.0 mg, 47 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



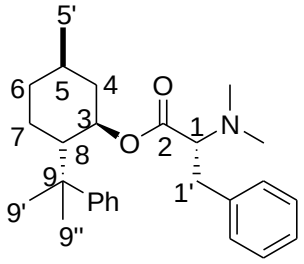
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* 7.9 Hz, 1H, ArC<u>H</u>), 7.41-7.45 (m, 1H, ArC<u>H</u>), 7.24-7.32 (m, 6H, ArC<u>H</u>), 7.10-7.15 (m, 1H, ArC<u>H</u>), 4.73 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.12-3.18 (m, 1H, 1-<u>H</u>), 3.07-3.10 (m, 1H, 1'-<u>H</u>), 2.69 (dd, *J* 14.3, 7.4 Hz, 1H, 1'-<u>H</u>), 2.37 (s, 6H, N(C<u>H</u>$_3$)$_2$),2.22 (d, *J* 5.7 Hz, 1H, 8-<u>H</u>), 1.78-1.89 (m, 1H, 4-<u>H</u>), 1.67-1.77 (m, 1H, 5-<u>H</u>), 1.48-1.57 (m, 1H, 6-<u>H</u>), 1.37-1.46 (m, 2H, 4-<u>H</u> and 7-<u>H</u>), 1.31 (s, 3H, 9'-<u>H</u>$_3$), 1.20 (s, 3H, 9''-<u>H</u>$_3$), 0.84-1.03 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.80 (d, *J* 6.5 Hz, 3H, 5'-<u>H</u>$_3$), 0.66-0.76 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (2-<u>C</u>O), 151.1 (Ar-<u>C</u>), 131.8 (Ar-<u>C</u>), 131.4 (2 x Ar<u>C</u>H), 128.0 (2 x Ar<u>C</u>H), 126.4 (Ar<u>C</u>H), 126.0 (2 x Ar<u>C</u>H), 125.6 (Ar<u>C</u>H), 125.1 (2 x Ar<u>C</u>H), 75.3 (1-<u>C</u>), 67.0 (3-<u>C</u>), 50.1 (8-<u>C</u>), 41.5 (N(<u>C</u>H$_3$)$_2$), 41.44 (1'-<u>C</u>), 39.9 (9-<u>C</u>), 34.4 (4-<u>C</u>), 31.2 (5-<u>C</u>), 27.5 (6-<u>C</u>), 26.9 (7-<u>C</u>), 25.9 (9'-<u>C</u> and 9''-<u>C</u>), 21.7 (5'-<u>C</u>).

ν_{max} (neat, cm^{-1}); 2980 (C-H), 1722 (C=O), 1214 (C-O).

MS*m/z* (ESI^+) calculated for $[M+H]^+$ $C_{27}H_{38}NO_2$ 408.2899; found 408.2897.

HPLC t_R 3.55 min.



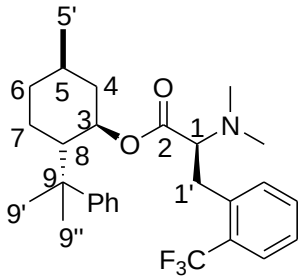
Isolated impure (20.0 mg, 24 %). Partial characterisation was only possible, as the product was not isolated pure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.21 (m, 10H, ArC<u>H</u>), 4.65 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.18-3.12 (m, 1H, 1-<u>H</u>), 3.07-2.98 (m, 1H, 1'-<u>H</u>), 2.59 (dd, *J* 14.3, 7.4 Hz, 1H, 1'-<u>H</u>), 2..19 (s, 6H, N(C<u>H</u>$_3$)$_2$), 2.01 (d, *J* 5.7 Hz, 1H, 8-<u>H</u>), 1.73-1.69 (m, 1H, 4-<u>H</u>), 1.57-1.67 (m, 1H, 5-<u>H</u>), 1.38-

1.31 (m, 1H, 6-H), 1.27-1.21 (m, 2H, 4-H and 7-H), 1.18-1.12 (m, 2H, 6-H and 7-H), 1.11 (s, 3H, 9′-H_3), 1.03 (s, 3H, 9′′-H_3), 0.83 (s, 3H, 5′-H_3), 0.59-0.55 (m, 1H, 7-H).

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(dimethylamino)-3-(2-(trifuoromethyl)phenyl)propanoate (134).

The benzylic ammonium bromide salt (100 mg, 0.18 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (53.0 mg, 62 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



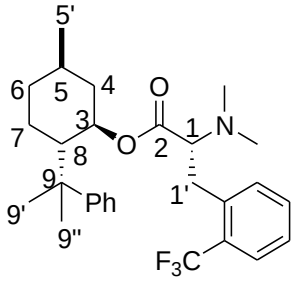
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* 7.4 Hz, 1H, ArCH), 7.41-7.45 (m, 1H, ArCH), 7.27-7.40 (m, 5H, ArCH), 7.01-7.20 (m, 2H, ArCH), 4.73 (td, *J* 10.7, 4.2 Hz, 1H, 3-H), 3.06-3.18 (m, 2H, 1-H and 1′-H), 2.96 (dd, *J* 14.0, 7.5 Hz, 1H, 1’-H), 2.42 (s, 6H, N(CH_3)$_2$), 2.17-2.25 (m, 1H, 8-H), 1.80-1.89 (m, 1H, 4-H), 1.69-1.76 (m, 1H, 5-H), 1.49-1.56 (m, 1H, 6-H), 1.37-1.46 (m, 2H, 4-H and 7-H), 1.31 (s, 3H, 9′-H_3), 1.20 (s, 3H, 9′′-H_3), 0.9-1.05 (m, 2H, 6-H and 7-H), 0.80 (dd, *J* 6.5 Hz, 1H, 5‘-H), 0.68-0.75 (m, 1H, 7-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (2-CO), 151.1 (Ar-C), 136.9 (Ar-C), 131.8 (ArCH), 131.4 (2 x ArCH), 128.6 (Ar-C-CF_3), 128.0 (ArCH), 126.4 (ArCH), 126.0 (d, ArCH), 125.6 (2 x ArCH), 125.1 (ArCH), 123.2 (Ar-CF_3), 75.2 (1-C), 67.0 (3-C), 50.2 (8-C), 41.5 (N(CH_3)$_2$), 41.4 (1'-C), 39.9 (9-C), 34.4 (4-C), 31.2 (5-C), 27.5 (6-C), 26.9 (7-C), 25.9 (9’-C and 9’’-C), 21.7 (5′-C).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1730 (C=O), 1214 (C-O), 1153 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}F_3NO_2$ $[M+H]^+$ 476.2771; found 476.2770.

HPLC t_R 4.11 min.



Isolated as a pale yellow oil (10.0 mg, 12 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* 7.4 Hz, 1H, ArC<u>H</u>),7.43-7.22 (m, 7H, ArC<u>H</u>), 4.51 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.13-3.01 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.84 (dd, *J* 14.0, 7.5 Hz, 1H, 1'-<u>H</u>), 2.22 (s, 6H, N($C\underline{H}_3$)$_2$), 1.99-1.95 (m, 1H, 8-<u>H</u>), 1.88-1.80 (m, 1H, 4-<u>H</u>), 1.75-1.67 (m, 1H, 5-<u>H</u>), 1.58-1.51 (m, 1H, 6-<u>H</u>), 1.49-1.36 (m, 2H, 4-<u>H</u> and 7-<u>H</u>), 1.10-1.25 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.06 (s, 3H, 9′-$\underline{H}_3$), 0.99 (s, 3H, 9″-$\underline{H}_3$), 0.80 (dd, *J* 6.5 Hz, 1H, 5'-<u>H</u>), 0.68-0.57 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5 (2-<u>C</u>O), 150.1 (Ar-<u>C</u>), 133.9 (Ar-<u>C</u>), 132.3 (Ar-<u>C</u>H), 130.1 (2 x Ar-<u>C</u>H), 128.2 (Ar-<u>C</u>F_3), 127.7 (Ar-<u>C</u>H), 126.1 (Ar-<u>C</u>H), 125.8 (Ar-<u>C</u>H), 125.2 (2 x Ar<u>C</u>H), 124.9 (Ar-<u>C</u>H), 123.0 (Ar-<u>C</u>F_3), 76.2 (1-<u>C</u>), 67.3 (3-<u>C</u>), 50.2 (8-<u>C</u>), 42.5 (N($\underline{C}H_3$)$_2$), 41.1 (1'-<u>C</u>), 39.7 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.3 (5-<u>C</u>), 27.5 (6-<u>C</u>), 26.4 (7-<u>C</u>), 25.5 (9'-<u>C</u>and 9''-<u>C</u>), 20.2 (5′-<u>C</u>).

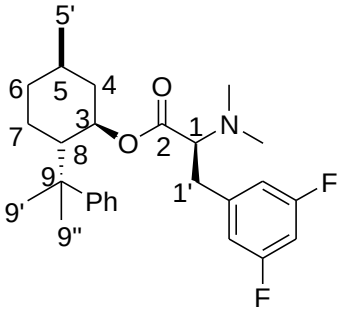
ν_{max} (neat, cm^{-1}): 2988 (C-H), 1735 (C=O), 1221 (C-O), 1159 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{37}F_3NO_2$ $[M+H]^+$ 476.2771; found 476.2766.

HPLC t_R 3.96 min.

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl2-(dimethylamino)-3-(3,5-difuorophenyl)propanoate (135).

The benzylic ammonium bromide salt (100 mg, 0.19 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (46.6 mg, 55 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



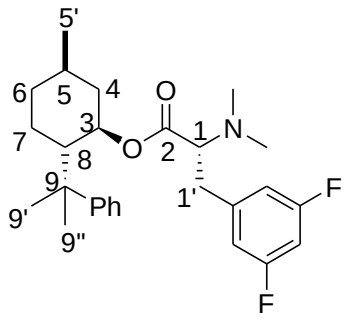
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02-7.29 (m, 5H, ArC<u>H</u>), 6.73-6.80 (m, 3H, ArC<u>H</u>), 4.73 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 2.98-3.02 (m, 1H, 1-<u>H</u>), 2.85 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.67 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.39 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.83-1.95 (m, 1H, 8-<u>H</u>), 1.65-1.74 (m, 1H, 4-<u>H</u>), 1.37-1.59 (m, 3H, 4-<u>H</u>, 5-<u>H</u>and 6-<u>H</u>), 1.30 (s, 3H, 9′-<u>H</u>$_3$), 1.14 (s, 3H, 9′′-<u>H</u>$_3$), 0.84-1.04 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.85 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.70-0.79 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (2-<u>C</u>O), 162.7 (Ar-<u>C</u>-F), 162.2 (Ar-<u>C</u>-F), 151.3 (Ar-<u>C</u>), 132.0 (Ar-<u>C</u>), 128.0 (2 x Ar<u>C</u>H), 125.5 (2 x Ar<u>C</u>H), 121.2 (Ar<u>C</u>H), 110.9 (2 x Ar<u>C</u>H), 103.5 (Ar<u>C</u>H), 75.1 (1-<u>C</u>), 66.6 (3-<u>C</u>), 50.0 (8-<u>C</u>), 41.5 (N(<u>C</u>H$_3$)$_2$), 41.5(1'-<u>C</u>), 39.8 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.2 (5-<u>C</u>), 28.3 (6-<u>C</u>), 26.8 (7-<u>C</u>), 26.6 (9'-<u>C</u> and 9''-<u>C</u>), 21.7 (5′-<u>C</u>).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1722 (C=O), 1152 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}F_2NO_2$ $[M+H]^+$ 444.2709; found 444.2710.

HPLC t_R 3.06 min.



Isolated as a pale yellow oil (17.0 mg, 20 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-6.99 (m, 8H, ArC<u>H</u>), 4.53 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.00-29.8 (m, 1H, 1-<u>H</u>), 2.67 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.55 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.21 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.83-1.69 (m, 1H, 8-<u>H</u>), 1.62-1.54 (m, 1H, 4-<u>H</u>), 1.47-1.38 (m, 3H, 4-<u>H</u>, 5-<u>H</u> and 6-<u>H</u>), 1.21-1.14 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.13 (s, 3H, 9′-<u>H</u>$_3$), 1.01 (s, 3H, 9′′-<u>H</u>$_3$), 0.85 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.70-0.79 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (2-<u>C</u>O), 160.1 (Ar-<u>C</u>-F), 159.8 (Ar-<u>C</u>-F), 151.1 (Ar-<u>C</u>), 132.0 (Ar-<u>C</u>), 128.5 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 122.2 (Ar-<u>C</u>H), 113.4 (2 x Ar<u>C</u>H), 105.5 (Ar<u>C</u>H), 75.4 (1-<u>C</u>), 66.9 (3-<u>C</u>), 50.1 (8-<u>C</u>), 42.3 (N(<u>C</u>H$_3$)$_2$), 41.5(1'-<u>C</u>), 39.8 (9-<u>C</u>), 35.2 (4-<u>C</u>), 32.1 (5-<u>C</u>), 28.8 (6-<u>C</u>), 27.1 (7-<u>C</u>), 26.5 (9'-<u>C</u> and 9''-<u>C</u>), 21.9 (5′-<u>C</u>).

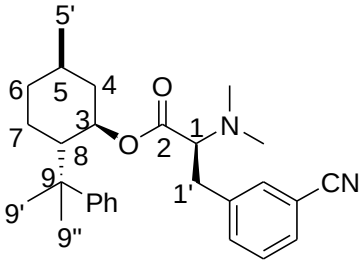
ν_{max} (neat, cm^{-1}): 2980 (C-H), 1717 (C=O), 1142 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}F_2NO_2$ $[M+H]^+$ 444.2709; found 444.2721.

HPLC t_R 2.94 min.

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl3-(3-cyanophenyl)-2-dimethylamino)propanoate (136).

The benzylic ammonium bromide salt (100 mg, 0.195 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (41.3 mg, 49 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



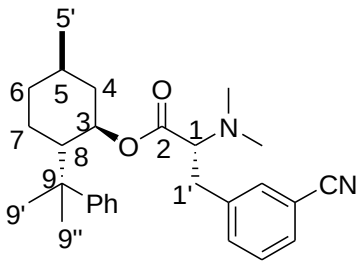
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.50 (m, 1H, ArC<u>H</u>), 7.10-7.41 (m, 8H, ArC<u>H</u>), 4.71 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 2.73-2.80 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.63 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.36 (s, 6H, N(C<u>H</u>$_3$)$_2$),1.90-1.97 (m, 1H, 8-<u>H</u>), 1.61-1.70 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.40-1.49 (m, 1H, 6-<u>H</u>), 1.29 (s, 3H, 9′-<u>H</u>$_3$), 1.16 (s, 3H, 9′′-<u>H</u>$_3$), 0.92-1.00 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.86 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.75-0.80 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (2-<u>C</u>O), 151.8 (Ar-<u>C</u>), 140.0 (Ar-<u>C</u>), 133.7 (Ar<u>C</u>H), 132.7 (Ar<u>C</u>H), 130.0 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.0 (2 x Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 125.1 (2 x Ar<u>C</u>H), 119.0 (Ar-<u>C</u>-N), 112.2 (Ar-<u>C</u>), 75.1 (1-<u>C</u>), 67.2 (3-<u>C</u>), 49.9 (8-<u>C</u>), 41.6 (N(<u>C</u>H$_3$)$_2$), 41.3 (1'-<u>C</u>), 39.6 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.2 (5-<u>C</u>), 28.1 (6-<u>C</u>), 26.6 (7-<u>C</u>), 24.9 (9'-<u>C</u> and 9''-<u>C</u>), 21.7 (5′-<u>C</u>).

ν_{max} (neat, cm^{-1}); *m/z* (ESI$^+$) 2980 (C-H), 2227 (CN), 1722 (C=O), 1214 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{36}N_2O_2$ $[M+NH]^+$ 433.2855; found 433.2850.

HPLC t_R 3.56 min.



Isolated as yellow oil (16 mg, 19 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.13 (m, 9H, ArC<u>H</u>), 4.69 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 2.76-2.70 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.56 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.23 (s, 6H, N($C\underline{H}_3$)$_2$),1.97-1.92 (m, 1H, 8-<u>H</u>), 1.66-1.50 (m, 3H, 4-$\underline{H}_2$ and 5-<u>H</u>), 1.40-1.28 (m, 1H, 6-<u>H</u>), 1.22-1.17 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.14 (s, 3H, 9′-$\underline{H}_3$), 1.06 (s, 3H, 9′′-$\underline{H}_3$), 0.81 (d, *J* 6.5 Hz, 3H, 5′-$\underline{H}_3$), 0.72-0.55 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100MHz, $CDCl_3$): δ171.1 (2-<u>C</u>O), 151.6 (Ar-<u>C</u>), 139.8 (Ar-<u>C</u>), 133.2 (Ar<u>C</u>H), 132.1 (Ar<u>C</u>H), 1295 (Ar<u>C</u>H), 128.3 (Ar<u>C</u>H), 127.7 (2 x Ar<u>C</u>H), 125.6 (Ar<u>C</u>H), 125.1 (2 x ArCH), 118.1 (Ar-<u>C</u>-N), 113.2 (Ar-<u>C</u>), 75.1 (1-<u>C</u>), 66.4 (3-<u>C</u>), 50.1 (8-<u>C</u>), 41.8 (N($\underline{C}H_3$)$_2$), 41.2 (1′-<u>C</u>), 39.2 (9-<u>C</u>), 34.1 (4-<u>C</u>), 31.1 (5-<u>C</u>), 27.4 (6-<u>C</u>), 26.2 (7-<u>C</u>), 24.3 (9′-<u>C</u> and 9′′-<u>C</u>), 21.7 (5′-<u>C</u>).

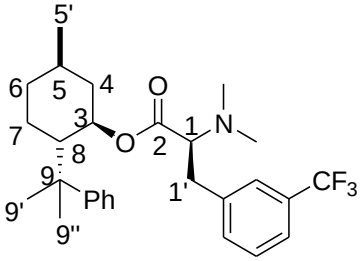
ν_{max} (neat, cm^{-1}); *m/z* (ESI$^+$) 2980 (C-H), 2222 (CN), 1732 (C=O), 1221 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{36}N_2O_2$ $[M+NH]^+$ 433.2855; found 433.2858.

HPLC t_R 3.41 min.

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(dimethylamino)-3-(4-(trifuoromethyl)phenyl)propanoate (137).

The benzylic ammonium bromide salt (100 mg, 0.18 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement productas a yellow oil (44.4 mg, 52 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* 8.0 Hz 1H, ArC<u>H</u>), 7.30-7.39 (m, 7H, ArC<u>H</u>), 7.13-7.19 (m, 1H, ArC<u>H</u>), 4.01 (td, *J* 10.2, 4.2 Hz, 1H, 3-<u>H</u>), 2.80-2.86 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.70 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.38 (s, 6H, N($C\underline{H}_3$)$_2$), 1.87-1.94 (m, 1H, 8-<u>H</u>), 1.57-1.67 (m, 3H, 4-$\underline{H}_2$ and 5-<u>H</u>), 1.32-1.44 (m, 1H, 6-<u>H</u>), 1.29 (s, 3H, 9′-$\underline{H}_3$), 1.16 (s, 3H, 9′′-$\underline{H}_3$), 0.85-1.01 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.72-0.84 (d, *J* 6.5 Hz, 3H, 5′-$\underline{H}_3$), 0.71-0.76 (m, 1H, 7-<u>H</u>).

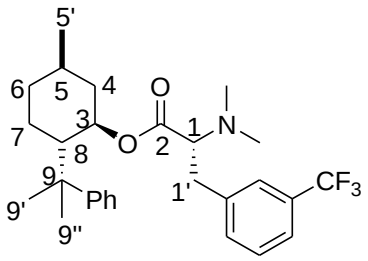
^{13}C NMR (100MHz, $CDCl_3$): δ171.5 (2-<u>C</u>O), 151.7 (Ar-<u>C</u>), 139.4 (Ar-<u>C</u>), 132.7 (Ar<u>C</u>H), 130.4 (Ar-<u>C</u>), 128.3 (2 x Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 125.9 (Ar-<u>C</u>-CF_3), 125.5 (Ar<u>C</u>H), 125.1 (2 x Ar<u>C</u>H), 123.1

(Ar-<u>C</u>F_3), 122.9 (Ar-<u>C</u>H), 75.0 (1-<u>C</u>), 67.4 (3-<u>C</u>), 49.9 (8-<u>C</u>), 41.4 (N(<u>C</u>H_3)$_2$), 41.3 (1'-<u>C</u>), 39.6 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.2 (5-<u>C</u>), 27.8 (6-<u>C</u>), 26.6 (7-<u>C</u>), 25.3 (9'-<u>C</u> and 9''-<u>C</u>), 21.6 (5′-<u>C</u>).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1724 (C=O), 1214 (C-O), 1129 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{36}F_3NO_2$ $[M+H]^+$ 476.2776; found 476.2772.

HPLC t_R 3.00 min.



Isolated as yellow oil (15 mg, 18 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.15 (m, 9H, ArC<u>H</u>), 3.98 (td, *J* 10.2, 4.2 Hz, 1H, 3-<u>H</u>), 2.79-2.71 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.65 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.21 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.92-1.84 (m, 1H, 8-<u>H</u>), 1.67-1.57 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.42-1.34 (m, 1H, 6-<u>H</u>), 119-1.14 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.09 (s, 3H, 9′-<u>H</u>$_3$), 1.02 (s, 3H, 9′′-<u>H</u>$_3$), 0.86 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.71-0.66 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (2-<u>C</u>O), 151.3 (Ar-<u>C</u>), 139.1 (Ar-<u>C</u>), 133.5 (Ar<u>C</u>H), 130.4 (Ar-<u>C</u>), 128.6 (2 x Ar<u>C</u>H), 127.6 (ArCH), 125.1 (Ar-<u>C</u>), 124.8 (Ar-<u>C</u>-CF_3), 124.1 (2 x Ar<u>C</u>H), 123.6 (Ar-<u>C</u>F_3), 122.6 (Ar-<u>C</u>H), 75.0 (1-<u>C</u>), 67.6 (3-<u>C</u>), 50.0 (8-<u>C</u>), 41.7 (N(<u>C</u>H_3)$_2$), 41.1 (1'-<u>C</u>), 39.4 (9-<u>C</u>), 34.3 (4-<u>C</u>), 31.0 (5-<u>C</u>), 27.7 (6-<u>C</u>), 26.2 (7-<u>C</u>), 25.1 (9'-<u>C</u> and 9''-<u>C</u>), 21.3 (5′-<u>C</u>).

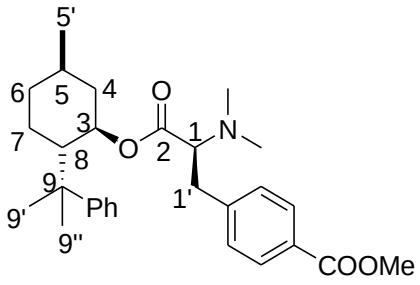
ν_{max} (neat, cm^{-1}): 2980 (C-H), 1710 (C=O), 1224 (C-O), 1125 (C-F).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{36}F_3NO_2$ $[M+H]^+$ 476.2776; found 476.2752.

HPLC t_R 2.90 min.

Methyl4-(2-(dimethylamino)-3-(((*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl)oxy)-3-oxopropyl)benzoate (138).

The benzylic ammonium bromide salt (100 mg, 0.183 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (37.5 mg, 44 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



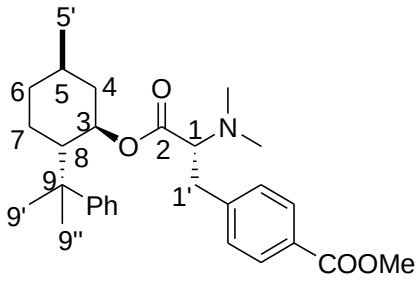
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.98 (m, 2H, ArC<u>H</u>), 7.21-7.30 (m, 4H, ArC<u>H</u>), 7.13-7.17 (m, 3H, ArC<u>H</u>), 4.73 (td, *J* 10.7 Hz, 4.2 Hz, 1H, 3-<u>H</u>), 3.90 (s, 3H, OC<u>H</u>$_3$), 2.92-3.00 (m, 1H, 1-<u>H</u>), 2.84 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.70 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.37 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.87-1.99 (m, 1H, 8-<u>H</u>),1.52-1.67 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.35-1.45 (m, 1H, 6-<u>H</u>), 1.29 (s, 3H, 9′-<u>H</u>$_3$), 1.17 (s, 3H, 9′′-<u>H</u>$_3$), 0.84-1.1 (m, 2H, 6-<u>H</u> and 7-<u>H</u>$_2$), 0.80 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.71-0.80 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (2-<u>C</u>O), 167.1 (<u>C</u>OOCH$_3$), 151.5 (Ar-<u>C</u>), 144.0 (Ar-<u>C</u>),129.5 (2 x Ar<u>C</u>H), 129.2 (2 x Ar<u>C</u>H), 128.1 (2 x Ar<u>C</u>H), 125.4 (Ar<u>C</u>H), 125.2 (2 x Ar<u>C</u>H), 75.0 (1-<u>C</u>), 67.6 (3-<u>C</u>), 52.0 (COO<u>C</u>H$_3$), 49.9 (8-<u>C</u>), 41.5 (N(<u>C</u>H$_3$)$_2$), 41.5 (1'-<u>C</u>), 39.7 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.2 (5-<u>C</u>), 27.2 (6-<u>C</u>), 26.7 (7-<u>C</u>), 25.9 (9'-<u>C</u> and 9''-<u>C</u>), 21.7 (5′-<u>C</u>).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1727 (C=O), 1656 (C=O), 1151 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{29}H_{40}NO_4$ $[M+H]^+$ 466.2957; found 466.2952.

HPLC t_R 3.81 min.

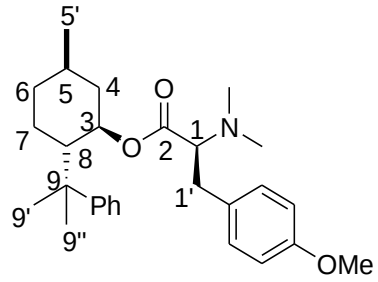


Isolated impure. Partial characterisation was only possible, as the product was not isolated pure.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.14 (m, 9H, ArC<u>H</u>), 4.69 (td, *J* 10.7 Hz, 4.2 Hz, 1H, 3-<u>H</u>), 3.83 (s, 3H, OC<u>H</u>$_3$), 3.03-2.91 (m, 1H, 1-<u>H</u>), 2.79 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.61 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.23 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.98-1.91 (m, 1H, 8-<u>H</u>),1.69-1.59 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.41-1.38 (m, 1H, 6-<u>H</u>), 1.22-1.16 (m, 2H, 6-<u>H</u> and 7-<u>H</u>$_2$), 1.10 (s, 3H, 9′-<u>H</u>$_3$), 1.02 (s, 3H, 9′′-<u>H</u>$_3$), 0.81 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.66-0.59 (m, 1H, 7-<u>H</u>).

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(dimethylamino)-3-(4-methoxyphenyl)propanoate (139).

The benzylic ammonium bromide salt (100 mg, 0.193 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted fllowing the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (28 mg, 33 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



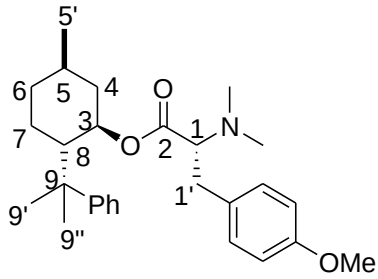
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.31 (m, 4H, ArC<u>H</u>), 7.13-7.18 (m, 1H, ArC<u>H</u>), 7.01-7.03 (m, 2H, ArC<u>H</u>), 6.78-6.81 (m, 2H, ArC<u>H</u>), 4.72 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.81 (s, 3H, OC<u>H</u>$_3$), 2.96-3.00 (m, 1H, 1-<u>H</u>), 2.80 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.72 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.39 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.85-1.91 (m, 1H, 8-<u>H</u>), 1.62-1.67 (m, 1H, 4-<u>H</u>), 1.44-1.56 (m, 2H, 4-<u>H</u> and 5-<u>H</u>), 1.31-1.39 (m, 1H, 6-<u>H</u>), 1.31 (s, 3H, 9′-<u>H</u>$_3$), 1.19 (s, 3H, 9′′-<u>H</u>$_3$), 0.86-1.00 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.78 (d, *J* 6.5 Hz, 3H,5′-<u>H</u>$_3$), 0.68-0.77 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3 (2-<u>C</u>O), 158.1 (<u>C</u>OCH$_3$), 151.4 (Ar-<u>C</u>), 130.1 (Ar-<u>C</u>), 128.7 (2 x Ar<u>C</u>H), 128.0 (2 x Ar<u>C</u>H), 125.5 (Ar<u>C</u>H), 125.2 (2 x Ar<u>C</u>H), 113.6 (2 x Ar<u>C</u>H), 75.0 (1-<u>C</u>), 68.3 (3-<u>C</u>), 55.2 (CO<u>C</u>H$_3$), 50.0 (8-<u>C</u>), 41.7 (N(<u>C</u>H$_3$)$_2$), 41.3 (1′-<u>C</u>), 39.8 (9-<u>C</u>), 34.5 (4-<u>C</u>), 31.2 (5-<u>C</u>), 26.9 (9′-<u>C</u> and 9′′-<u>C</u>), 26.8 (6-<u>C</u>), 26.4 (7-<u>C</u>), 21.7 (5′-<u>C</u>).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1717 (C=O), 1214 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{39}NO_3$ $[M+H]^+$ 438.3003; found 438.3021.

HPLC t_R 4.28 min.



Isolated as yellow oil (10 mg, 12 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19--6.81 (m, 9H, ArC<u>H</u>), 4.65 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 3.73 (s, 3H, OC<u>H</u>$_3$), 2.99-2.4 (m, 1H, 1-<u>H</u>), 2.75 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.64 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.21 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.91-1.99 (m, 1H, 8-<u>H</u>), 1.61-1.60 (m, 1H, 4-<u>H</u>), 1.46-1.51 (m, 2H, 4-<u>H</u> and 5-<u>H</u>), 1.29-1.22 (m, 1H, 6-<u>H</u>), 1.17-1.10 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.04 (s, 3H, 9′-<u>H</u>$_3$), 0.97 (s, 3H, 9′′-<u>H</u>$_3$), 0.75 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.69-0.57 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100MHz, $CDCl_3$): δ170.3 (2-<u>C</u>O), 156.5 (<u>C</u>OCH$_3$), 150.4 (Ar-<u>C</u>), 130.2 (Ar-<u>C</u>), 128.6 (2 x Ar<u>C</u>H), 128.0 (2 x Ar<u>C</u>H), 125.6 (Ar<u>C</u>H), 125.1 (2 x Ar<u>C</u>H), 112.8 (2 x Ar<u>C</u>H), 76.2 (1-<u>C</u>), 68.2 (3-<u>C</u>), 54.4 (CO<u>C</u>H$_3$), 50.0 (8-<u>C</u>), 41.7 (N(<u>C</u>H$_3$)$_2$), 41.1 (1′-<u>C</u>), 39.9 (9-<u>C</u>), 34.3 (4-<u>C</u>), 31.6 (5-<u>C</u>), 27.2 (9′-<u>C</u>and 9′′-<u>C</u>), 26.2 (6-<u>C</u>), 25.5 (7-<u>C</u>), 21.3 (5′-<u>C</u>).

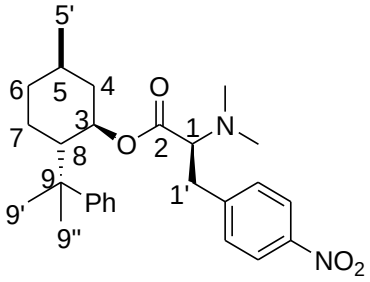
ν_{max} (neat, cm^{-1}): 2980 (C-H), 1727 (C=O), 1219 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{28}H_{39}NO_3$ [M+H]$^+$ 438.3003; found 438.2992.

HPLC t_R 4.12 min.

(*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl 2-(dimethylamino)-3-(4-nitrophenyl)propanoate (140).

The benzylic ammonium bromide salt (100 mg, 0.187 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement productas a yellow oil (53.4 mg, 63 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



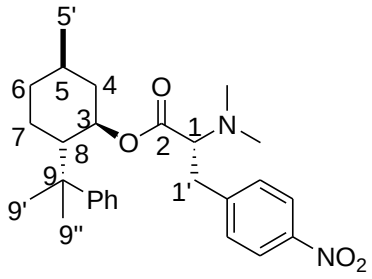
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* 8.4 Hz, 1H, ArC<u>H</u>),7.46-7.52 (m, 1H, ArC<u>H</u>), 7.34-7.39 (m, 2H, ArC<u>H</u>), 7.28-7.29 (m, 1H, ArC<u>H</u>), 7.23-7.25 (m, 4H, ArC<u>H</u>), 7.01-7.13 (m, 1H, ArC<u>H</u>), 4.73 (td, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.85 (dd, *J* 14.0 Hz, 7.5 Hz, 1H, 1′-<u>H</u>), 2.38 (s, 6H, N(C<u>H</u>$_3$)$_2$), 1.83-1.89 (m, 1H, 8-<u>H</u>), 1.57-1.67 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.37-1.50 (m, 1H, 6-<u>H</u>), 1.32-1.44 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 1.29 (s, 3H, 9′-<u>H</u>$_3$), 1.18 (s, 3H, 9′′-<u>H</u>$_3$), 0.78 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.7-0.77 (m, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1 (2-CO), 151.2 (Ar-C), 149.8 (C-NO_2), 133.7 (Ar-C), 132.9 (2 x ArCH), 128.0 (2 x ArCH), 127.4 (ArCH), 125.3 (2 x ArCH), 124.7 (2 x ArCH), 75.3 (1-C), 66.9 (3-C), 49.9 (8-C), 41.6 (2 x N(CH_3)$_2$), 41.5 (1'-C), 39.8 (9-C), 34.4 (4-C), 31.2 (5-C), 29.7 (6-C), 26.8 (7-C), 26.5 (9'-C and 9''-C), 21.7 (5'-C).

ν_{max} (neat, cm^{-1}): 2980 (C-H), 1657 (C=O), 1221 (C-O), 1599 and 1381 (NO_2).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}N_2O_4$ $[M+H]^+$ 453.2753; found 453.2748.

HPLC t_R 5.62 min.



Isolated as pale yellow (10 mg, 12%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* 8.4 Hz, 1H, ArCH), 7.50-7.54 (m, 1H, ArCH), 7.34-7.40 (m, 2H, ArCH), 7.01-7.15 (m, 5H, ArCH),4.62 (td, *J* 10.7, 4.2 Hz, 1H, 3-H), 3.41-3.39 (m, 1H, 1-H), 2.86 (dd, *J* 14.0, 7.5 Hz, 1H, 1'-H), 2.75 (dd, *J* 14.0 Hz, 7.5 Hz, 1H, 1'-H), 2.13 (s, 6H, N(CH_3)$_2$), 1.99-1.91 (m, 1H, 8-H), 1.65-1.57 (m, 3H, 4-H_2 and 5-H), 1.49-1.39 (m, 1H, 6-H), 1.32-1.22 (m, 2H, 6-H and 7-H), 1.18 (s, 3H, 9'-H_3), 1.05 (s, 3H, 9''-H_3), 0.79 (d, *J* 6.5 Hz, 3H, 5'-H_3), 0.67-0.57 (m, 1H, 7-H).

^{13}C NMR (100MHz, $CDCl_3$): δ 171.1 (2-CO), 151.2 (Ar-C), 149.8 (C-NO_2), 133.7 (Ar-C), 132.9 (2 x ArCH), 128.0 (2 x ArCH), 127.4 (ArCH), 125.3 (2 x ArCH), 124.7 (2 x ArCH), 75.3 (1-C), 66.9 (3-C), 49.9 (8-C), 41.6 (2 x N(CH_3)$_2$), 41.5 (1'-C), 39.8 (9-C), 4.4 (4-C), 31.2 (5-C), 29.7 (6-C), 26.8 (7-C), 26.5 (9'-C and 9''-C), 21.7 (5'-C).

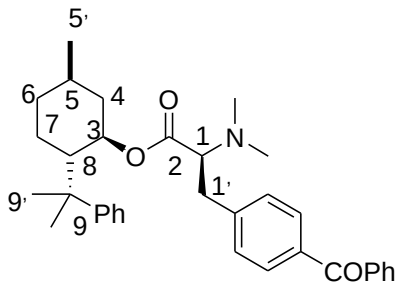
ν_{max} (neat, cm^{-1}): 2980 (C-H), 1665 (C=O), 1203 (C-O), 1608 and 1389 (NO_2).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}N_2O_4$ $[M+H]^+$ 453.2753; found 453.274860.

HPLC t_R 5.43 min.

Methyl4-(2-(dimethylamino)-3-(((*1R,2S,5R*)-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl)oxy)-3-oxopropyl)benzoate (142).

The benzylic ammonium bromide salt (100 mg, 0.169 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (40.0 mg, 48 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



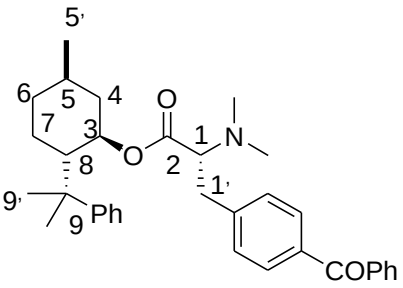
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* 8.8 Hz, 2H, ArC<u>H</u>), δ7.73 (d, *J* 8.8 Hz, 2H, ArC<u>H</u>), 7.62-7.51 (m, 5H, ArC<u>H</u>), 731-7.21 (m, 5H, ArC<u>H</u>), 7.18-7.13 (m, 3H, ArC<u>H</u>), 4.75 (td, *J* 10.7 Hz, 4.2 Hz, 1H, 3-<u>H</u>), 3.04-2.99 (m, 1H, 1-<u>H</u>), 2.91-2.82 (dd, *J* 14.0 Hz, 7.5 Hz, 1H, 1'-<u>H</u>), 2.66 (dd, *J* 14.0 Hz, 7.5 Hz, 1H, 1'-<u>H</u>), 2.41 (s, 6H, 2 x N(C<u>H</u>$_3$)$_2$), 201-1.89 (m, 1H, 8-<u>H</u>), 1.74-1.68 (m, 1H, 4-<u>H</u>), 1.62-1.57 (m, 2H, 4-<u>H</u> and 5-<u>H</u>), 1.44-1.40 (m, 1H, 6-<u>H</u>), 1.26 (s, 3H, 9'-<u>H</u>$_3$), 1.15 (s, 3H, 9'-<u>H</u>$_3$), 0.93-1.03 (m, 2H, 6 <u>H</u> and 7-<u>H</u>), 0.89-0.74 (d, *J* 6.5 Hz, 3H, 5'-<u>H</u>$_3$), 0.62-0.55 (dd, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ 1.96.6 (<u>C</u>OPH), 172.3 (2-<u>C</u>O), 151.2 (Ar-<u>C</u>), 143.5 (Ar-<u>C</u>), 136.6 (Ar-<u>C</u>), 133.5 (Ar<u>C</u>H), 129.3 (Ar<u>C</u>H), 128.8 (Ar-<u>C</u>), 128.2 (2 x Ar<u>C</u>H) 127.7 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 125.3 (2 x Ar<u>C</u>H), 125.0 (Ar-<u>C</u>), 75.2 (1-<u>C</u>), 67.3 (3-<u>C</u>), 51.6 (COO<u>C</u>H$_3$), 49.9 (8-<u>C</u>), 41.7 (2 x N(<u>C</u>H$_3$)$_2$), 39.3 (9-<u>C</u>), 35.4 (4-<u>C</u>), 34.0 (1'-<u>C</u>), 31.1 (5-<u>C</u>), 26.9 (9'-<u>C</u>), 26.1 (6-<u>C</u>), 25.3 (7-<u>C</u>), 21.7 (5'-<u>C</u>).

ν_{max} (neat, cm^{-1}): 2978 (C-H), 1655 (C=O), 1219 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}N_2O_4$ $[M+H]^+$ 512.3165; found 512.3127.

HPLC t_R 5.48 min.



Isolated as pale yellow (16 mg, 18 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* 8.4 Hz, 2H, ArC<u>H</u>), 7.67 (d, *J* 8.4 Hz, 2H, ArC<u>H</u>), 7.13-7.58 (m, 10H, ArC<u>H</u>), 4.71 (td, J 10.7 Hz, 4.2 Hz, 1H, 3-<u>H</u>), 2.92-3.00 (m, 1H, 1-<u>H</u>), 2.81-2.87 (dd, J 14.0 Hz, 7.5 Hz, 1H, 1′-<u>H</u>), 2.65-2.74 (dd, J 14.0 Hz, 7.5 Hz, 1H, 1′-<u>H</u>), 2.22 (s, 6H, 2 x N(C<u>H</u>$_3$)$_2$), 1.87-1.99 (m, 1H, 8-<u>H</u>), 1.64-1.67 (m, 1H, 4-<u>H</u>), 1.52-1.57 (m, 2H, 4-<u>H</u> and 5-<u>H</u>), 1.35-1.45 (m, 1H, 6-<u>H</u>), 1.29 (s, 3H, 9′-<u>H</u>$_3$), 1.17 (s, 3H, 9′-<u>H</u>$_3$), 0.87-1.03 (m, 2H, 6 and 7-<u>H</u>), 0.76-0.84 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.48-0.60 (dd, 1H, 7-<u>H</u>).

^{13}C NMR (100 MHz, $CDCl_3$): δ): δ 196.4 (<u>C</u>OPH), 171.2 (2-<u>C</u>O), 152.2 (Ar-<u>C</u>), 143.1 (Ar-<u>C</u>), 136.6 (Ar-<u>C</u>), 133.5 (Ar<u>C</u>H), 129.0 (Ar<u>C</u>H), 128.5(Ar-<u>C</u>), 128.1 (2 x Ar<u>C</u>H) 127.6 (2 x Ar<u>C</u>H), 125.6 (2 x Ar<u>C</u>H), 125.3 (2 x Ar<u>C</u>H), 125.0 (Ar-<u>C</u>), 75.2 (1-<u>C</u>), 67.3 (3-<u>C</u>), 51.6 (COO<u>C</u>H$_3$), 49.9 (8-<u>C</u>), 41.7 (2 x N(<u>C</u>H$_3$)$_2$), 39.3 (9-<u>C</u>), 35.4 (4-<u>C</u>), 34.0 (1′-<u>C</u>), 31.1 (5-<u>C</u>), 26.9 (9′-<u>C</u>), 26.1 (6-<u>C</u>), 25.3 (7-<u>C</u>), 21.7 (5′-<u>C</u>).

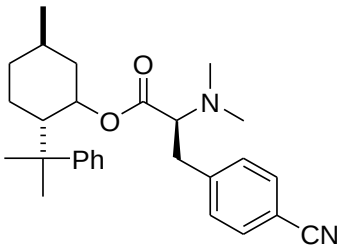
ν_{max} (neat, cm^{-1}): 2978 (C-H), 1665 (C=O), 1222 (C-O).

MS*m/z* (ESI$^+$) calculated for $C_{27}H_{36}N_2O_4$ $[M+H]^+$ 512.3165; found 512.3170.

HPLC t_R 5.29 min.

(*1R,2S,5R)*-5-methyl-2-(2-phenylpropan-2-yl) cyclohexyl3-(4-cyanophenyl)-2-dimethylamino)propanoate (141).

The benzylic ammonium bromide salt (100 mg, 0.195 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow oil (48 mg, 58 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0).



^{1}H NMR (400 MHz, $CDCl_3$):δ 7.46 (d, *J* 7.4 Hz, 1H, ArC<u>H</u>), 7.31 (d, *J* 7.4 Hz, 1H, ArC<u>H</u>),7.10-7.28 (m, 6H, ArC<u>H</u>), 4.61 (td, *J* 10.7, 4.2 Hz, 1H, 3-<u>H</u>), 2.98-3.02 (m, 2H, 1-<u>H</u> and 1′-<u>H</u>), 2.83 (dd, *J* 14.0, 7.5 Hz, 1H, 1′-<u>H</u>), 2.36 (s, 6H, N(C<u>H</u>$_3$)$_2$),1.92-1.99 (m, 1H, 8-<u>H</u>), 1.61-1.69 (m, 3H, 4-<u>H</u>$_2$ and 5-<u>H</u>), 1.44-1.52 (m, 1H, 6-<u>H</u>), 1.33 (s, 3H, 9′-<u>H</u>$_3$), 1.19 (s, 3H, 9′′-<u>H</u>$_3$), 0.99-1.07 (m, 2H, 6-<u>H</u> and 7-<u>H</u>), 0.85 (d, *J* 6.5 Hz, 3H, 5′-<u>H</u>$_3$), 0.75-0.80 (m, 1H, 7-<u>H</u>).

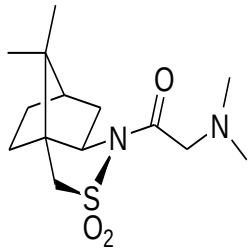
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3 (2-CO), 151.8 (Ar-C), 142.2 (Ar-C), 133.7 (ArCH), 132.7 (ArCH), 130.0 (ArCH), 128.6 (2 x ArCH), 125.1 (2 x ArCH), 115.0 (Ar-C-N), 111.2 (Ar-C), 75.4 (1-C), 67.5 (3-C), 49.9 (8-C), 41.4 ($N(CH_3)_2$), 41.3 (1'-C), 39.6 (9-C), 34.3 (4-C), 31.1 (5-C), 28.1 (6-C), 26.3 (7-C), 24.9 (9'-C and 9''-C), 21.7 (5'-C).

ν_{max} (neat, cm^{-1}); 2980 (C-H), 2227 (CN), 1722 (C=O), 1214 (C-O).

MS*m/z* (ESI^+) calculated for $C_{28}H_{36}N_2O_2$ $[M+H]^+$ 433.2855; found 433.2855.

HPLC t_R 3.56 min.

2-(Dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo [5.2.1.01,5] dec-4-yl]ethanone (98)



To a solution of 2-bromo-1-[(1*S*,5*R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5] dec-4-yl]ethanone(1.0 g, 3.00 mmol, 1 equiv) and dimethylamine hydrochloride salt (734 mg, 9.00 mmol, 3 equiv.) in THF (15 mL) at 0°C under a nitrogen atmosphere, was added dropwise Et_3N (2.1 mL, 15.00 mmol, 5 equiv). The reaction mixture was allowed to warm to r t, stirred for two days, filtered through Celite® and then concentrated *in vacuo* to afford the productas an orange /brown solid (730 mg, 81%).

m.p. = 124-127°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (t, *J* 7.1, 1H, NCH), 3.75 (s, 2H, NCH_2CO), 3.51 (d, *J* 13.8, 1H, CH_2SO_2), 3.42 (d, *J* 13.8, 1H, CH_2SO_2), 2.37 (s, 6H, 2 x $N(CH_3)_2$), 2.17-1.87 (m, 5H, $CH_2C(R)HCH_2CH_2$), 1.45-1.26 (m, 2H, $C(R)_2HCH_2CH_2$), 1.15 (s, 3H, $(CH_3)_2CR_2$), 0.97 (s, 3H, $(CH_3)_2CR_2$);

^{13}C NMR (62.5MHz, CDCl3): δ 169.7 (CO), 65.6 (NCH), 61.6 (NCH_2CO), 53.3 (CH_2SO_2), 49.2 (CCH_2SO_2), 48.2 ($C(CH_3)_2$), 45.9 (2 x $N(CH_3)_2$), 45.0 ($CH_2CH_2CHCH_2$), 38.9 ($CR_2HCH_2C(R)HN$), 33.7 ($CR_2HCH_2CH_2CR_3$), 26.8 ($CR_2HCH_2CH_2CR_3$), 21.2 ($(CH_3)_2CR_2$), 20.3 ($(CH_3)_2CR_2$),

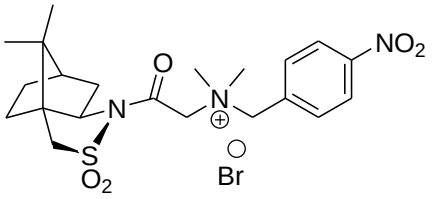
νmax/cm-1 ($CHCl_3$): 1706 (CO), 1334, 1165 (SO_2);

MS*m/z* (ESI^+) calculated for $C_{14}H_{25}N_2O_3S$ 301.1586; found 301.1582.

General procedure for salt synthesis

A solution of 2-(dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5] dec-4-yl]ethanone(200 mg, 0.666 mmol, 1 equiv) and aryl bromide (0.142 mL, 1.996 mmol, 4 equiv) in toluene (10 mL) was heated to 50°C under a nitrogen atmosphere for 75 hours. The precipitate was collected over a glass sinter and washed with pentane (15 mL). Then the solid was dissolved with DCM (20 mL) and concentrated *in vacuo*to afford the product.

2-[(*1S,5R*)-10,10-Dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5]dec-4-yl]-*N,N*-dimethyl- *N*-(4-nitrobenzyl)-2-oxoethylammonium bromide (113).



Following the method above, the product was isolated as a pale yellow solid (313 mg, 91%,) **m.p.** = 184-192°C;

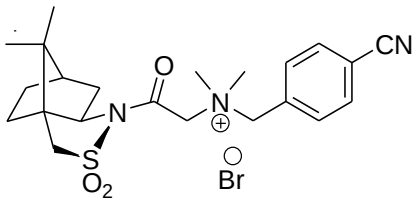
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J*8.6, 2H, ArC<u>H</u>), 8.01 (d, *J* 8.6, 2H, ArC<u>H</u>$_2$), 5.68 (d, *J* 12.7, 1H, COC<u>H</u>$_2$N), 5.63 (d, *J* 12.7, 1H, COC<u>H</u>$_2$N), 5.13-4.90 (br m, 1H, NC<u>H</u>$_2$Ar), 4.67 (d, *J* 16.7, 1H, NC<u>H</u>$_2$Ar), 4.15-3.99 (br m, 1H, NC<u>H</u>), 3.69 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.62 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.57 (d, *J* 14.0, 1H, C<u>H</u>$_2$SO$_2$), 3.54 (d, *J* 14.0, 1H, C<u>H</u>$_2$SO$_2$), 2.18-1.94 (m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 1.54-1.36 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 0.98 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.94 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0 (<u>C</u>O), 149.2 (Ar-<u>C</u>), 134.9 (Ar-<u>C</u>), 134.0 (Ar<u>C</u>H), 133.6 (Ar<u>C</u>H), 124.1 (2 x Ar<u>C</u>H), 66.5 (CO<u>C</u>H$_2$N), 64.9 (N<u>C</u>H), 61.2 (N<u>C</u>H$_2$Ar), 52.7 (<u>C</u>H$_2$SO$_2$), 51.7 (N(<u>C</u>H$_3$)$_2$), 51.2 (N(<u>C</u>H$_3$)$_2$), 49.5 (<u>C</u>CH$_2$SO$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 44.8 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 38.2(CR$_2$H<u>C</u>H$_2$C(R)HN), 32.8 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 26.2 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$);

νmax/cm^{-1} (CHCl3): 3020 (CH), 1678 (CO), 1531 (NO2), 1350, 1119 (SO2);

MS*m/z* (ESI$^+$) calculated for $C_{21}H_{30}N_3O_5S$ [M-Br]$^+$ 436.1901; found 436.1904.

***N*-(4-Cyanobenzyl)-2-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo [5.2.1.01,5] dec-4-yl]-*N,N*-dimethyl-2-oxoethylammonium bromide (111).**



Following method above, the product was isolated as a beige solid (256 mg,77%).

m.p. = 165-167°C;

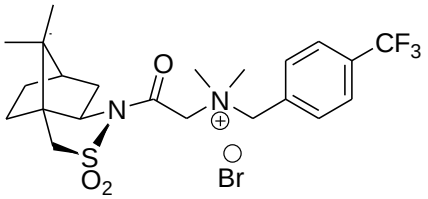
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* 7.5, 2H, ArC<u>H</u>), 7.77 (d, *J* 7.5, 2H, ArC<u>H</u>), 5.63 (d, *J* 12.5, 1H, COC<u>H</u>$_2$N), 5.51 (d, *J* 12.5, 1H, COC<u>H</u>$_2$N), 5.20-4.95 (br m, 1H, NC<u>H</u>$_2$Ar), 4.60 (d, *J* 15.0, 1H, NC<u>H</u>$_2$Ar), 4.14-4.01 (br m, 1H, NC<u>H</u>), 3.68 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.59 (s, 3H, N(C<u>H</u>$_3$)$_2$), 3.57 (d, *J* 12.5, 1H, C<u>H</u>$_2$SO$_2$), 3.54 (d, *J* 12.5, 1H, C<u>H</u>$_2$SO$_2$), 2.18-2.16 and 1.94 (m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 1.50-1.41 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.11 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.99 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (<u>C</u>O), 134.3 (2 x Ar<u>C</u>H), 132.9 (2 x Ar<u>C</u>H), 132.6 (Ar-<u>C</u>), 117.8 (Ar-<u>C</u>-CN), 114.7 (Ar-<u>C</u>N), 66.8 (CO<u>C</u>H$_2$N), 64.8 (N<u>C</u>H), 61.1 (N<u>C</u>H$_2$Ar), 52.7 (<u>C</u>H$_2$SO$_2$), 51.3 (N(<u>C</u>H$_3$)$_2$), 50.9 (N(<u>C</u>H$_3$)$_2$), 49.5 (<u>C</u>CH$_2$SO$_2$), 48.0 (<u>C</u>(CH$_3$)$_2$), 44.8 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 38.2(CR$_2$H<u>C</u>H$_2$C(R)HN), 32.8 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 26.2 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$),19.8 ((<u>C</u>H$_3$)$_2$CR$_2$);

νmax/cm^{-1} ($CHCl_3$): 2958 (CH), 2234 (CN), 1699 (CO), 1350, 1119 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{22}H_{30}N_3O_3S$ [M-Br]$^+$ 416.2002; found 416.1985.

2-[(*1S,5R*)-10,10-Dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5]dec-4-yl]-2-oxo-N-[4-(trifluoromethyl)benzyl]ethylammonium bromide (112).



Following method, the product was isolated as a beige solid (151 mg, 84%). **m.p.** = 180-183°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* 7.5, 2H, ArC<u>H</u>), 7.69 (d, *J* 7.5, 2H, ArC<u>H</u>), 5.53 (d, *J* 12.5, 1H, COC<u>H</u>$_2$N), 5.47 (d, *J* 12.5, 1H, COC<u>H</u>$_2$N), 5.31-5.08 (br m, 1H, NC<u>H</u>$_2$Ar), 4.85 (d, *J* 15.0, 1H, NC<u>H</u>$_2$Ar), 4.29-4.07 (br m, 1H, NC<u>H</u>), 3.64-3.56 (m, 8H, 2 x N(C<u>H</u>$_3$)$_2$ and C<u>H</u>$_2$SO$_2$), 2.21 and 2.00-1.91 (br m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 1.54-1.35 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.10 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.97 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$);

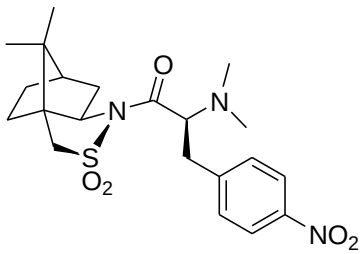
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (<u>C</u>O), 134.0 (2 x Ar<u>C</u>H), 132.8 (q, *J* 32.2 Hz, Ar-<u>C</u>F3), 131.1 (Ar-C), 126.1 (2 x Ar<u>C</u>H), 123.5 (q, *J* 273 Hz, Ar-<u>C</u>-CF3), 66.9 (N<u>C</u>H$_2$CON), 64.8 (N<u>C</u>H), 61.2 (N<u>C</u>H$_2$Ar), 52.7 (<u>C</u>H$_2$SO$_2$), 51.2 (N(<u>C</u>H$_3$)$_2$), 50.8 (N(<u>C</u>H$_3$)$_2$), 49.8 (<u>C</u>CH$_2$SO$_2$), 48.1 (<u>C</u>(CH$_3$)$_2$), 44.9 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 38.2 (CR$_2$H<u>C</u>H$_2$C(R)HN), 32.8 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 26.1 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 21.0 ((<u>C</u>H$_3$)$_2$CR$_2$), 19.8 ((<u>C</u>H$_3$)$_2$CR$_2$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2957 (CH), 1696 (CO), 1324, 1137 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{22}H_{30}F_3N_3O_5S$ $[M\text{-}Br]^+$ 459.1924; found 459.1924.

(*2S*)-2-(Dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo [5.2.1.01,5]dec-4-yl]-3-(4-nitrophenyl)propan-1-oneand (*2R*)-2-(dimethylamino)-1-[(1S,5R)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5]dec-4-yl]-3-(4-nitro phenyl)propan-1-one (83).

The ammonium bromide salt (100 mg, 0.187 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a yellow solid (10 mg, 15 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0); **m.p.** = 147-149°C;

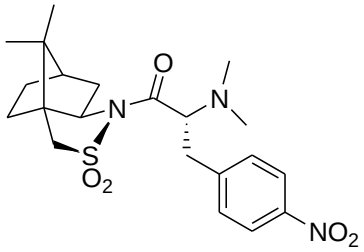


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* 7.5, 2H, ArC<u>H</u>), 7.40 (d, *J* 7.5, 2H, ArC<u>H</u>), 4.19 (t, *J* 7.5, 1H, C<u>H</u>CH$_2$Ar), 3.88 (dd, *J* 7.5, 5.0, 1H, NC<u>H</u>camphor), 3.50 (d, *J* 15.0, 1H, C<u>H</u>$_2$SO$_2$), 3.38 (d, *J* 15.0, 1H, C<u>H</u>$_2$SO$_2$), 3.12 (dd, *J* 12.5, 7.5, 1H, NCHC<u>H</u>$_2$), 2.98 (dd, *J* 12.5, 7.5, 1H, NCHC<u>H</u>$_2$), 2.39 (s, 6H, 2 x N(C<u>H</u>$_3$)$_2$), 2.18-1.88 (m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 1.44-1.25 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 1.19 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.98 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8 (CO), 146.6 (ArC), 146.3 (ArC), 130.3 (2 x ArCH), 123.5 (2 x ArCH), 66.9 ($NCHCH_2Ar$), 65.4 (NCH camphor), 53.2 (CH_2SO_2), 48.2 (CCH_2SO_2), 47.8 ($C(CH_3)_2$), 44.9 ($CH_2CH_2CHCH_2$), 41.3 (2 x $N(CH_3)_2$), 39.1 ($CR_2HCH_2C(R)HN$), 33.3 (CH_2Ar), 33.0 ($CR_2HCH_2CH_2CR_3$), 26.4 ($CR_2HCH_2CH_2CR_3$), 21.0 ($(CH_3)_2CR_2$), 19.9 ($(CH_3)_2CR_2$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 1686 (CO), 1521 (NO2), 1346, 1131 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{21}H_{30}N_3O_5S$ $[M+H]^+$ 436.1901; found 436.1908.



Isolated as white solid (46 mg, 55 %) **m.p.** = 145-153°C;

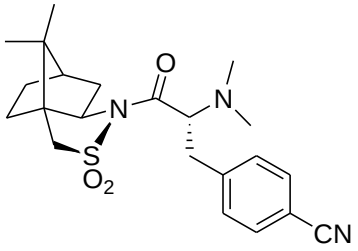
^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (d, *J* 8.0, 2H, ArCH), 7.44 (d, *J* 8.0, 2H, ArCH), 4.21 (t, *J* 8.0, 1H, $CHCH_2Ar$), 3.86 (dd, *J* 8.0, 4.0, 1H, NCH camphor), 3.41 (s, 2H, CH_2SO_2), 3.17 (dd, *J* 12.0, 8.0, 1H, $NCHCH_2$), 3.06 (dd, *J* 12.0, 8.0, 1H, $NCHCH_2$), 2.54 (s, 6H, 2 x $N(CH_3)_2$), 2.06-2.00 and 1.88-1.77 (m, 5H, $CH_2C(R)HCH_2CH_2$), 1.39-1.31 (m, 2H, $C(R)_2HCH_2CH_2$), 0.89 (s, 3H, $(CH_3)_2CR_2$), 0.67 (s, 3H, $(CH_3)_2CR_2$);

^{13}CNMR (100 MHz, $CDCl_3$): δ 171.9 (CO), 147.2 (Ar-C), 145.9 (Ar-C), 130.8 (2 x ArCH), 123.9 (2 x ArCH), 67.1 ($NCHCH_2Ar$), 65.5 (NCH camphor), 53.4 (CH_2SO_2), 48.6 (CCH_2SO_2), 48.0 ($C(CH_3)_2$), 44.8 ($CH_2CH_2CHCH_2$), 41.9 (2 x $N(CH_3)_2$), 38.6 ($CR_2HCH_2C(R)HN$), 34.5 (CH_2Ar), 33.2 ($CR_2HCH_2CH_2CR_3$), 26.7 ($CR_2HCH_2CH_2CR_3$), 20.6 ($(CH_3)_2CR_2$), 20.1($(CH_3)_2CR_2$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2925 (CH), 1690 (CO), 1522 (NO_2), 1348, 1135 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{21}H_{30}N_3O_5S$ $[M+H]^+$ 436.1901; found 436.1906.

(*2S*)-2-(Dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo [5.2.1.01,5] dec-4-yl]-3-(4-cyanophenyl)propan-1-one and (*2R*)-2-(dimethylamino)- 1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4 azatricyclo [5.2.1.01,5]dec-4-yl]-3-(4-cyano phenyl)propan-1-one (84).



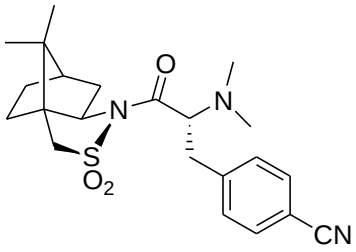
The ammonium bromide salt (100 mg, 0.187 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a white solid (51 mg, 51 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0); **m.p.** = 147-149°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* 8.4, 2H, ArC<u>H</u>), 7.37 (d, *J* 8.4, 2H, ArC<u>H</u>), 4.18 (t, *J* 7.5, 1H, <u>C</u>HCH$_2$Ar), 3.88-3.83 (m, 1H, NC<u>H</u> camphor), 3.41 (s, 2H, C<u>H</u>$_2$SO$_2$), 3.12 (dd, *J* 13.4, 7.5, 1H, NCHC<u>H</u>$_2$), 3.01 (dd, *J* 13.4, 7.5, 1H, NCHC<u>H</u>$_2$), 2.49 (s, 6H, 2 x N(C<u>H</u>$_3$)$_2$), 2.06-1.98 and 1.89-1.79 (m, 5H, C<u>H</u>$_2$C(R)<u>H</u>C<u>H</u>$_2$C<u>H</u>$_2$), 1.40-1.34 (m, 2H, C(R)$_2$HC<u>H</u>$_2$C<u>H</u>$_2$), 0.87 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$), 0.68 (s, 3H, (C<u>H</u>$_3$)$_2$CR$_2$);

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8 (<u>C</u>O), 143.7 (Ar-<u>C</u>), 132.5 (2 x Ar<u>C</u>H), 130.8 (2 x Ar<u>C</u>H), 119.4 (Ar-<u>C</u>-CN), 110.8 (Ar-<u>C</u>N), 67.1 (N<u>C</u>HCH$_2$Ar), 65.6 (N<u>C</u>H camphor), 53.4 (<u>C</u>H$_2$SO$_2$), 48.6 (<u>C</u>CH$_2$SO$_2$), 48.0 (<u>C</u>(CH$_3$)$_2$), 44.8 (CH$_2$CH$_2$<u>C</u>HCH$_2$), 41.9 (2 x N(<u>C</u>H$_3$)$_2$), 38.6 (CR$_2$H<u>C</u>H$_2$C(R)HN), 34.7 (NCH<u>C</u>H$_2$), 33.2 (CR$_2$HCH$_2$<u>C</u>H$_2$CR$_3$), 26.8 (CR$_2$H<u>C</u>H$_2$CH$_2$CR$_3$), 20.7 ((<u>C</u>H$_3$)$_2$CR$_2$), 20.1 ((<u>C</u>H$_3$)$_2$CR$_2$);

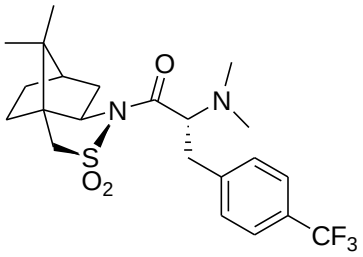
ν_{max} (neat, cm^{-1}) ($CHCl_3$): 2927 (CH), 2398 (CN), 1698 (CO), 1334, 1134 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{22}H_{30}N_3O_3S$ $[M+H]^+$ 416.2002; found 416.2010.



The product was not isolated pure.

(*2S*)-2-(Dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo [5.2.1.01,5]dec-4-yl]-3-[4-(trifluoromethyl)phenyl]propan-1-one and (*2R*)-2-(dimethylamino)-1-[(*1S,5R*)-10,10-dimethyl-3,3-dioxido-3-thia-4-azatricyclo[5.2.1.01,5] dec-4-yl]-3-[4-(trifluoromethyl)phenyl]propan-1-one (85).



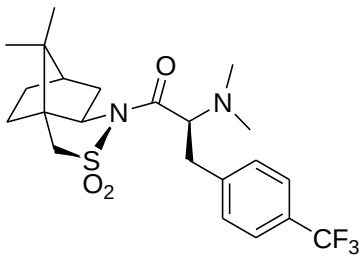
The ammonium bromide salt (100 mg, 0.187 mmol, 1.0 equiv) and BTTP (0.067 mL, 1.05 equiv) were reacted following the general procedure to yield the desired [1,2] rearrangement product as a white solid (51 mg, 51 %). Purified by flash chromatography Pet.ether:EtOAc (3.0:1.0); **m.p**. = 155-157°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* 8.1, 2H, ArC<u>H</u>), 7.36 (d, *J* 8.1, 2H, ArC<u>H</u>), 4.20 (t, *J* 7.1, 1H, C<u>H</u>CH_2Ar), 3.85-3.80 (br m, 1H, NC<u>H</u> camphor), 3.38 (s, 2H, C<u>H_2</u>SO_2), 3.10 (dd, *J* 13.2, 7.1, 1H, NCHC<u>H_2</u>), 3.00 (dd, *J* 13.2, 7.1, 1H, NCHC<u>H_2</u>), 2.50 (s, 6H, 2 x N(C<u>H_3</u>)$_2$), 2.04-1.75 (m, 5H, C<u>H_2</u>C(R)<u>H</u>C<u>H_2</u>C<u>H_2</u>), 1.35-1.13 (m, 2H, C(R)$_2$HC<u>H_2</u>C<u>H_2</u>), 0.87 (s, 3H, (C<u>H_3</u>)$_2$CR_2), 0.59 (s, 3H, (C<u>H_3</u>)$_2$CR_2);

^{13}C NMR (100 MHz, CDCl3): δ 171.9 (<u>C</u>O), 141.9 (Ar<u>C</u>), 130.3 (2 x Ar<u>C</u>H), 129.1 (q, J 32.2 Hz, Ar<u>C</u>CF_3), 128.0 (q, *J* 290 Hz, ArC<u>C</u>F_3), 125.6 (2 x Ar<u>C</u>H), 67.2 (N<u>C</u>HCH_2Ar), 65.5 (N<u>C</u>H camphor), 53.4 (<u>C</u>H_2SO_2), 48.4 (<u>C</u>CH_2SO_2), 47.9 (<u>C</u>$(CH_3)_2$), 44.9 (CH_2CH_2<u>C</u>HCH_2), 42.0 (2 x N(<u>C</u>H_3)$_2$), 38.6 (CR_2H<u>C</u>H_2C(R)HN), 34.3 (NCH<u>C</u>H_2Ar), 33.3 (CR_2HCH_2<u>C</u>H_2CR_3), 26.8 (CR_2H<u>C</u>$H_2CH_2CR_3$), 20.5 ((<u>C</u>H_3)$_2$CR_2), 19.8 ((<u>C</u>H_3)$_2$CR_2);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 1690 (CO), 1326, 1133 (SO_2);

MS*m/z* (ESI$^+$) calculated for $C_{22}H_{30}F_3N_2O_3S$ $[M+H]^+$ 459.1922; found 459.1930.



Isolated as pale yellow solid **m.p**. = 123-126°C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* 8.1, 2H, ArC<u>H</u>), 7.37 (d, *J* 8.1, 2H, ArC<u>H</u>), 4.18 (t, *J* 8.2, 1H, C<u>H</u>CH_2Ar), 3.90 (dd, *J* 7.1,5.2, 1H, NC<u>H</u> camphor), 3.49 (d, *J* 13.7, 1H, C<u>H_2</u>SO_2), 3.39 (d, *J* 13.7, 1H, C<u>H_2</u>SO_2), 3.03(dd, *J* 14.3, 8.2, 1H, NCHC<u>H_2</u>), 2.97 (dd, *J* 14.3, 8.2, 1H, NHCHC<u>H_2</u>), 2.39 (s, 6H, 2 x N(C<u>H_3</u>)$_2$), 2.11-1.87 (m, 5H, C<u>H_2</u>C(R)<u>H</u>C<u>H_2</u>C<u>H_2</u>), 1.43-1.11 (m, 2H, C(R)$_2$HC<u>H_2</u>C<u>H_2</u>), 0.92 (s, 3H, (C<u>H_3</u>)$_2$CR_2), 0.85 (s, 3H, (C<u>H_3</u>)$_2$CR_2);

^{13}C NMR (100 MHz, CDCl3): δ 171.6 (<u>C</u>O), 142.9 (Ar<u>C</u>), 130.1 (2 x Ar<u>C</u>H), 128.6 (q, *J* 44.6 Hz, Ar<u>C</u>CF_3), 127.8 (d, *J* 281. Hz, ArC<u>C</u>F_3), 125.5 (2 x Ar<u>C</u>H), 67.3 (N<u>C</u>HCH_2Ar), 65.8 (N<u>C</u>H camphor), 53.6 (<u>C</u>H_2SO_2), 48.6 (<u>C</u>CH_2SO_2), 48.1(<u>C</u>$(CH_3)_2$), 45.3 (CH_2CH_2<u>C</u>HCH_2), 41.6 (2 x

N($\underline{C}H_3)_2$), 39.5 ($CR_2H\underline{C}H_2C(R)HN$), 33.4 ($CR_2HCH_2\underline{C}H_2CR_3$), 30.1 ($NCH\underline{C}H_2Ar$), 26.8 ($CR_2H\underline{C}H_2CH_2CR_3$), 21.4 (($\underline{C}H_3)_2CR_2$), 20.3 (($\underline{C}H_3)_2CR_2$);

ν_{max} (neat, cm^{-1}) ($CHCl_3$): 1690 (CO), 1326, 1133 (SO_2);

MS*m/z* (ESI^+) calculated for $C_{22}H_{30}F_3N_2O_3S$ $[M+H]^+$ 459.1922; found 459.1930.

7.0 References

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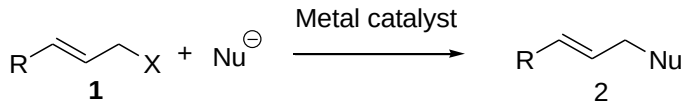
Chapter 2: Catalytic sp^3–sp^3 Functionalisation of Sulfonamides

1. Introduction

1.1 Metal-Catalysed allylic alkylation

The allylic alkylation reaction can be described as a nucleophilic displacement on a cyclic or acyclic allylic electrophile, via a metal-allyl complex or a SN2-type allylic substitution. The most common leaving groups are halides and acetate.[1]



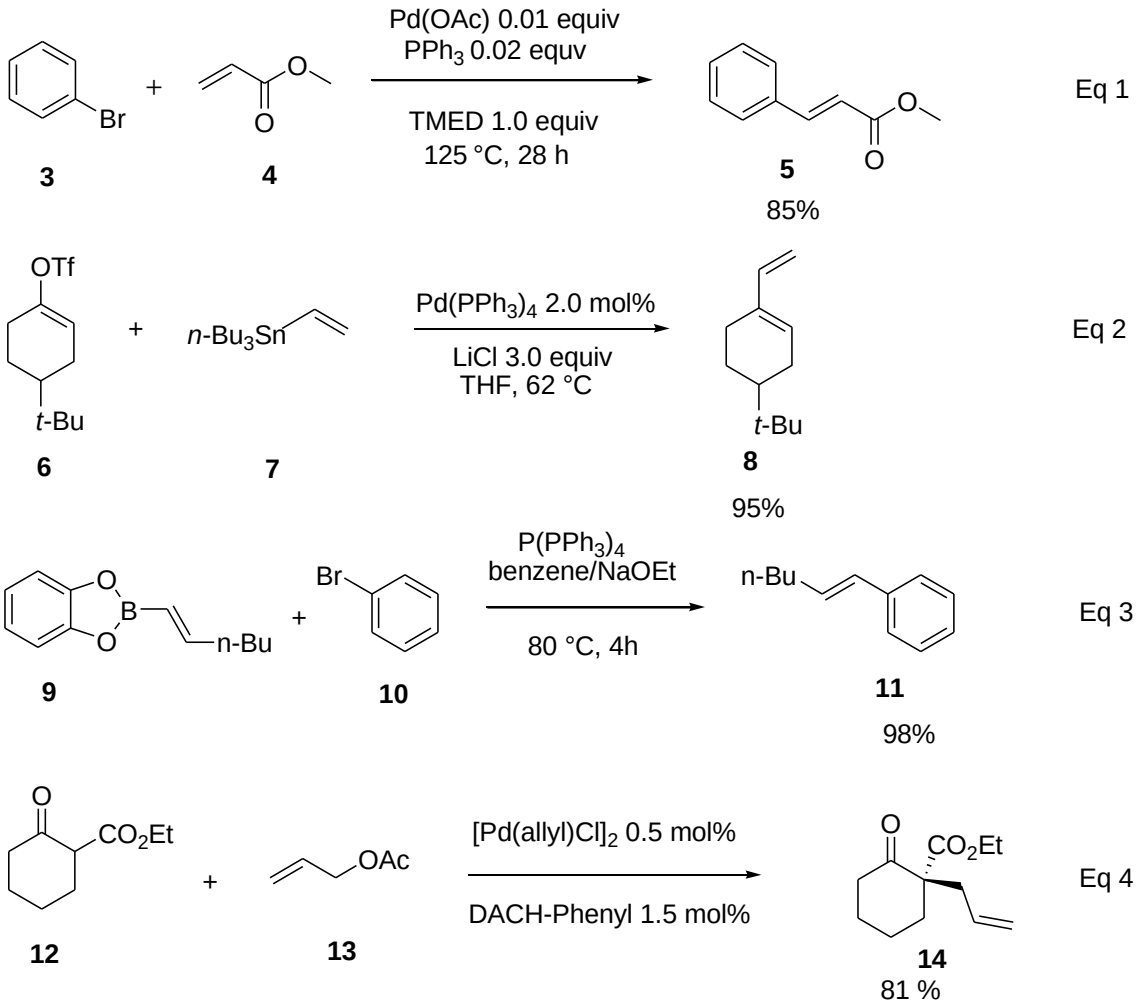
X= halide, alcohol, acetate.
Nu= nucleophile

Scheme 1

This reaction has been extensively studied with various classes of substrates (cyclic and acyclic), nucleophiles[8], metals and ligands[2b]. It has been applied successfully in both medicinal chemistry and in the synthesis of natural products.[2] Other advantages of this method are its high level of asymmetric induction when used with chiral ligands and flexibility in the type of bonds that can be created-besides C-C bonds, this includes C-N, C-P and C-S bonds.[3] Nowadays several classes of ligands are available for this purpose and many different metals catalyse the reaction including palladium[4], platinum,[1] gold,[5]rhodium,[6]ruthenium.[7] At present, chiral palladium complexes have proven to be the most versatile and have the broadest scope.

Palladium has shown to be a feature in many of different reactions such as the Heck,[9] Stille,[10] Suzuki,[11] and the Tsuji-Trost[12] (allylic alkylation) reaction (Scheme 2, eq 1-4). An advantage with palladium catalyzed reactions is that they often proceed under mild conditions affording excellent yields with high chemo-, regio-, and diastereoselectivities.[12] Most commonly, these reactions occur at sp^2-hybridized carbon atoms (Scheme 2, eq 1-3) on the electrophiles. However, in the allylic alkylation reaction the substitution occurs on a sp^3-hybridized carbon atom (Scheme 2, eq 4) via an (η^3-allyl)Pd complex. Another difference of Tsuji-Trost reaction is that the nucleophile in the allylic reaction is not necessarily an

organometallic compound like in (Stille (Sn) and Suzuk (B)) where organometallic compounds participate in the reaction via a transmetallation to palladium (the products are formed after reductive eliminations).



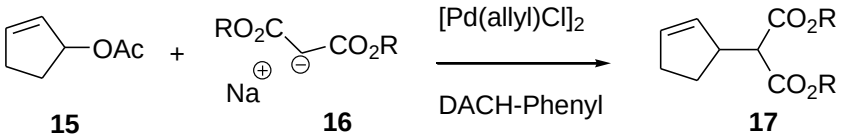
Scheme 2

1.2 The Tsuji-Trost reaction

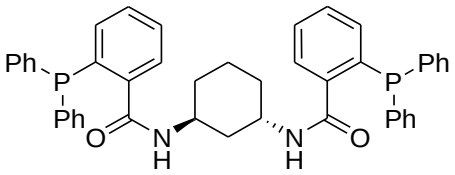
The Tsuji-Trost reaction is referred to as the alkylation of allylic substrates by stabilized carbanions, such as malonates (Scheme 3). The reaction was first reported by Tsuji *et al.* in 1965 using pre-formed (η^3-allyl)Pd complexes.[13] Thereafter, the reaction was further developed by Trost *et al.* by introduction of phosphine ligands[14] leading to improved reactivity and numerous asymmetric allylic alkylation strategies.[15]

The allylic alkylation can be performed under mild conditions at ambient temperature. The most commonly used substrates are allyl acetates, but a wide range of leaving groups can be

utilized to form the π allylpalladium complex, for example benzoates, carbonates, carbamates and halides.[16] A variety of nucleophiles can be applied in the reaction, but the most commonly used are soft stabilized carbon nucleophiles, *e.g.*malonates.[16]



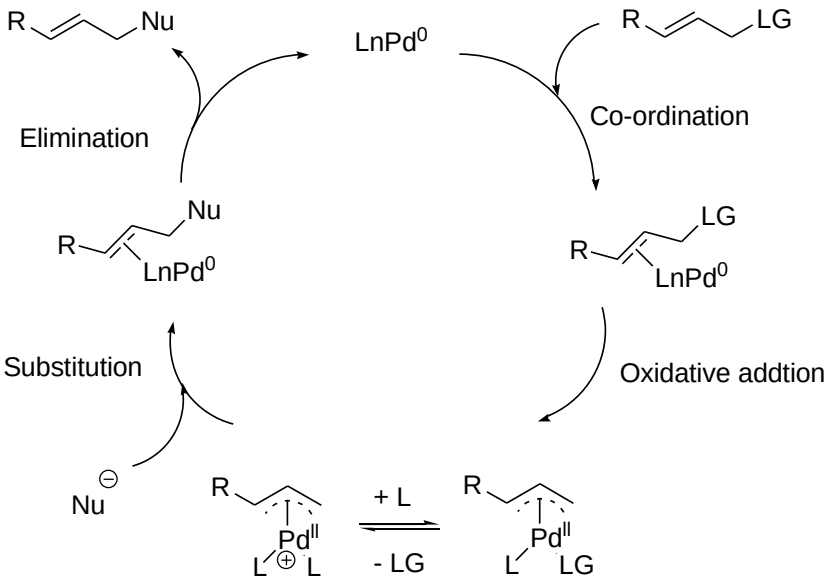
15 **16** **17**



DACH-Phenyl

Scheme 3

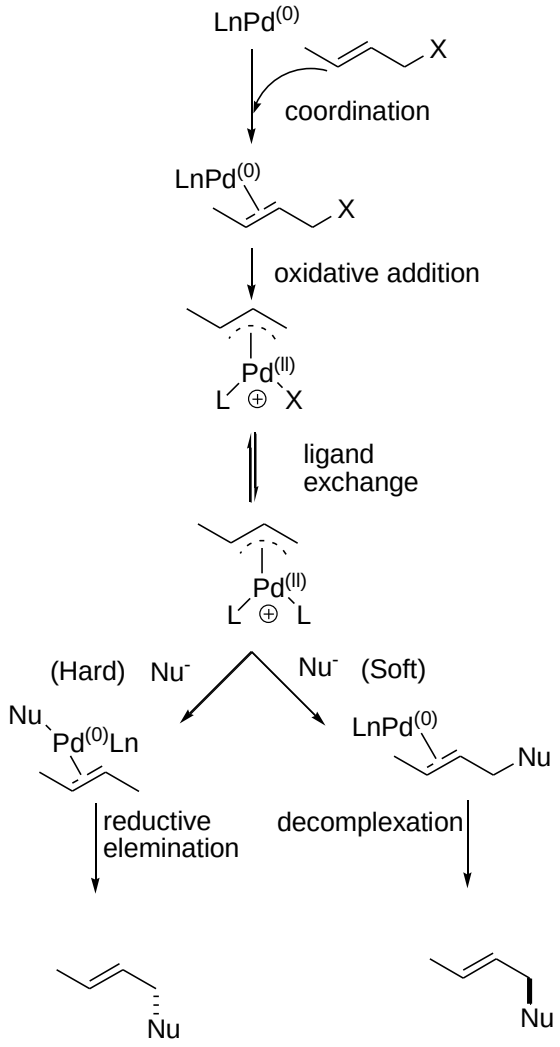
The allylic alkylation reaction has been the object of numerous investigations, from the scope of the reaction to its mechanism.[17,18] The catalytic cycle of the allylic alkylation reaction starts by co-ordination of the palladium (0) species to the alkene forming a η^2-complex (Scheme 4). The next step is oxidative addition, forming a (η^3-allyl)Pd complex with the leaving group as a counter ion. The resulting (η^3-allyl)Pd complex reacts with the nucleophile, yielding a η^2-complex between Pd^0 and the product. At the completion of the reaction, the product is decomplexed from the Pd^0 catalyst.



Ligand exchane

Scheme 4

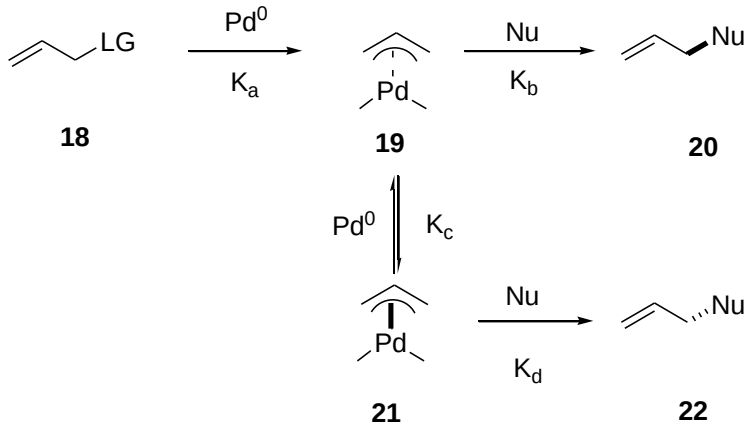
The mechanism of the reaction determines that the ionisation step occurs with inversion of configuration in the case of soft nucleophiles, the attack of nucleophile leads to second inversion which ultimately leads to forming the final product with an overall retention (Scheme 4). Hard unstabilized carbon nucleophiles react with the η^3-allyl complex by another mechanism: at the beginning a trans-metalation to Pd occurs and then transfer to anallylic carbon atom by reductive elimination, thus forming the final product with an overall inversion (Scheme 5). One valuable difference between these two classes of nucleophiles is the distinct mechanistic pathways through which each undergoes transition metal-catalyzed allylic substitution reactions: “soft” nucleophiles leads to outer-sphere nucleophile attack to directly afford the product, while “hard” nucleophiles internally attack the metal to form a neutral complex that expels the product by reductive elimination.[8]



Scheme 5

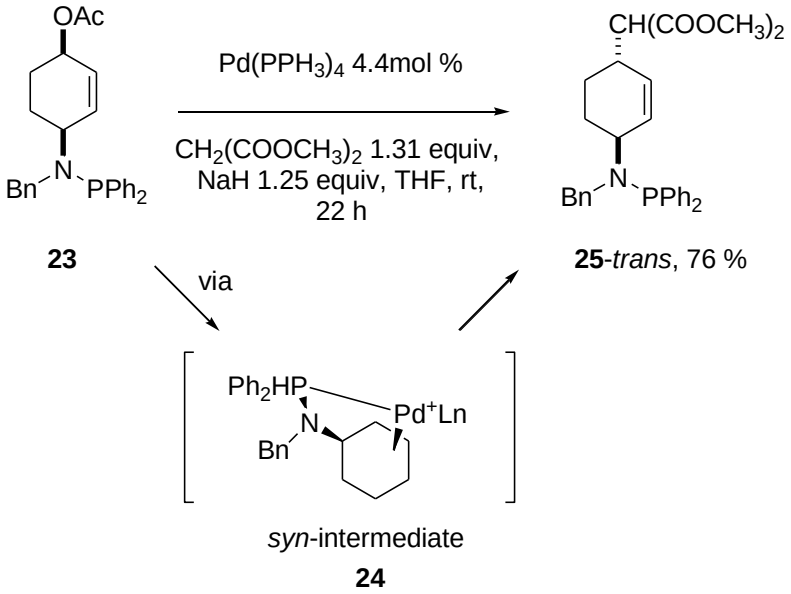
1.3 Factors effecting mechanism

The first step in the catalytic cycle after co-ordination involves an oxidative addition of Pd^0 in to the C-leaving group leading to the formation of the Pd^{II}-intermediate. The π-allyl-palladium^{II} complexes can react with another incoming zero valent palladium through an SN2-type pathway, leading to stereo-inversion of the intermediate (Scheme 6). As the equilibration rate (Kc) between **19** and **21** is faster than the nucleophilic attack, a mixture of the diastereomeric products **20** and **22** will be achived. The role of the concentration of the catalyst in the reaction was also significant. If the amount of catalyst increases, often results in reduced stereo-specificity.[19,20,21]



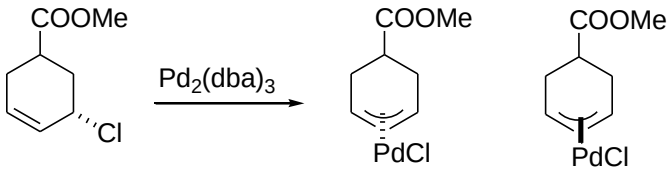
Scheme 6

Kočovský and Farthing showed the steric course of the first step of Pd^0-catalyzed allylic substitution with stabilized C-nucleophiles can be completely reversed by a suitably positioned co-ordinating Ph_2P group, resulting in inversion of stereochemistry, as opposed to the normally observed retention.[22] Therefore, in the presence of a PPh_2 group on the amine, the reaction was completely reversed resulting in *trans*-product **25**. They also observed the formation of the same *syn-η3*-intermediate regardless of the stereochemistry of the starting allylic acetate when treating **23** with a stoichiometric amount of $Pd(PPh_3)_4$ in the absence of the nucleophile. Hence, these results strongly support the participation of *η3*-chelate **24** in the formation of the *trans*-product **25** (Scheme 7). This work showed how the presence of a coordinating group can affect the mechanism of the reaction.[22]



Scheme 7

The Kurosawa group investigated the effect of solvent on the stereochemistry of oxidative addition to allylic chlorides. They showed solvent polarity had significant impact on the intermediate stereochemistry (Scheme 8). As they predicted, the formation of **27**-*trans* in the reaction was obtained in less polar solvents (benzene, DCM, THF), whereas **27**-*cis*- was favoured by polar solvents such as MeCN and DMSO.[23]

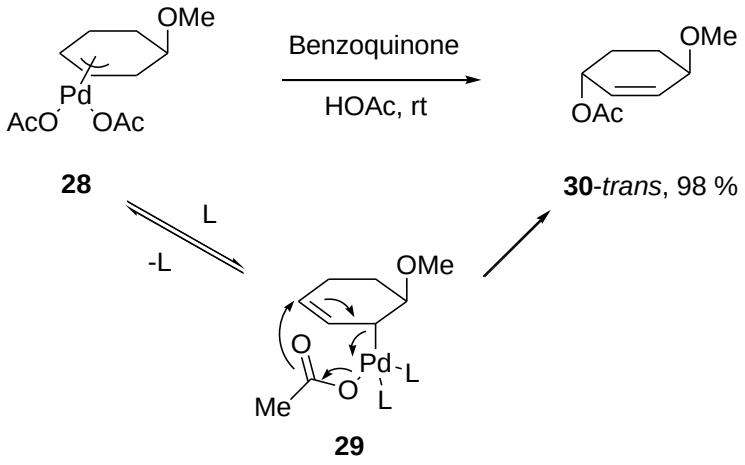


26 **27**-*trans* **27**-*cis*

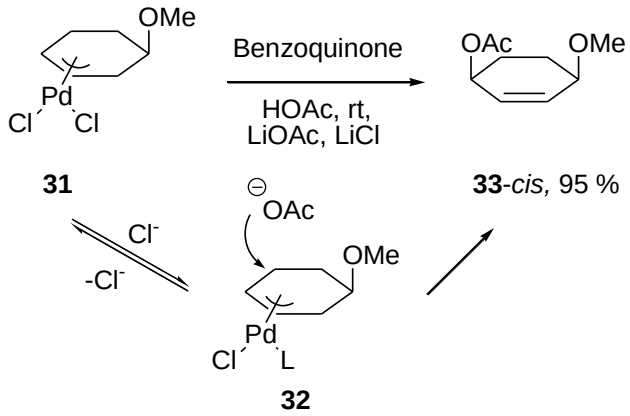
solvent	ratio (%)	
benzen	100	0
DCM	94	6
THF	95	5
acetone	75	25
DMF	29	71
MeCN	5	95
DMSO	3	97

Scheme 8

Bäckvall *et al.* investigated the effect of an acetate anion on the stereochemical outcome of the reaction. The reaction of complex **28** in the presences of benzoquinone at room temperature gave a *cis* attack by a concerted mechanism to yield only *trans*-product (>98%) (Scheme 9). When they performed the same reaction in the same condition with complex **31** in the presence lithium acetate and lithium chloride pure *cis*-**33** was obtained (>95%) (Scheme 10). The reason behind this is chlorine atom obstructs the lower face of the molecule. (Scheme 9) shows c*is* migration seems to occur via σ-allyl palladium complex **29** in the presence of benzoquinone as ligand.[24,25]

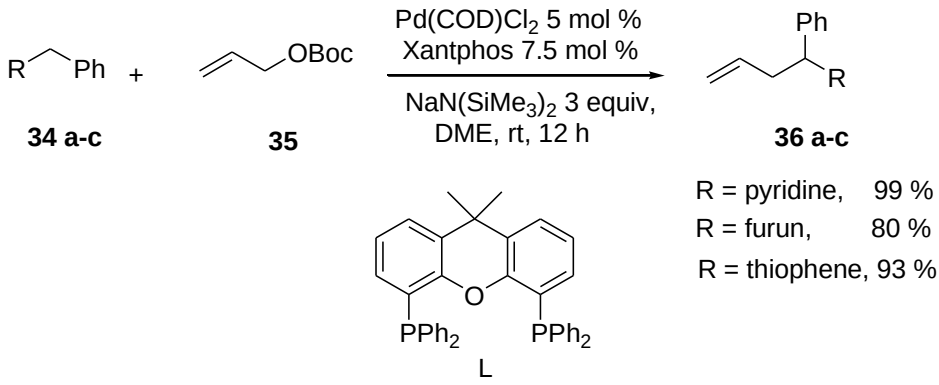


Scheme 9



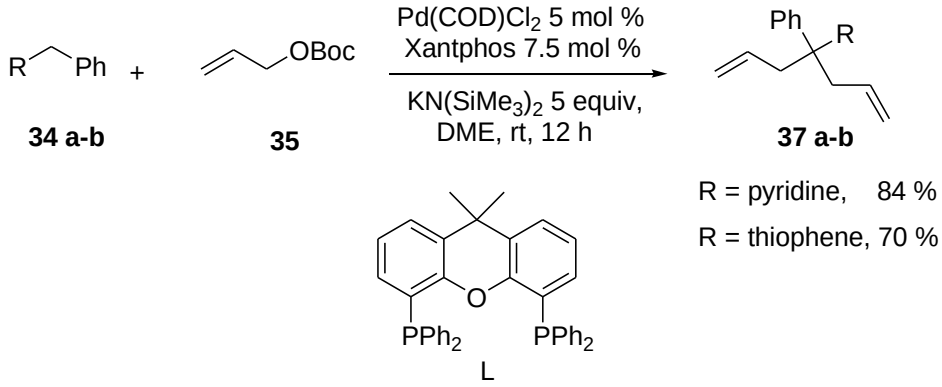
Scheme 10

Due to the importance of this reaction in organic chemistry, it has been extensively studied with various classes of nucleophiles, electrophiles, and ligands. Walsh *et al.* applied Pd-catalysed allylic substitution with diarylmethane and heterocyclic derivatives. [8] The synthetic significance of this method was that the scope of soft nucleophiles would be expanded to some pronucleophiles that have much higher pK_a than (25). Some of the nucleophiles have reported pK_a ranging all the way to (32). These reactions were undertaken by employing strong bases at ambient temperature and with van Leeumen's Xantphos ligand.[8]



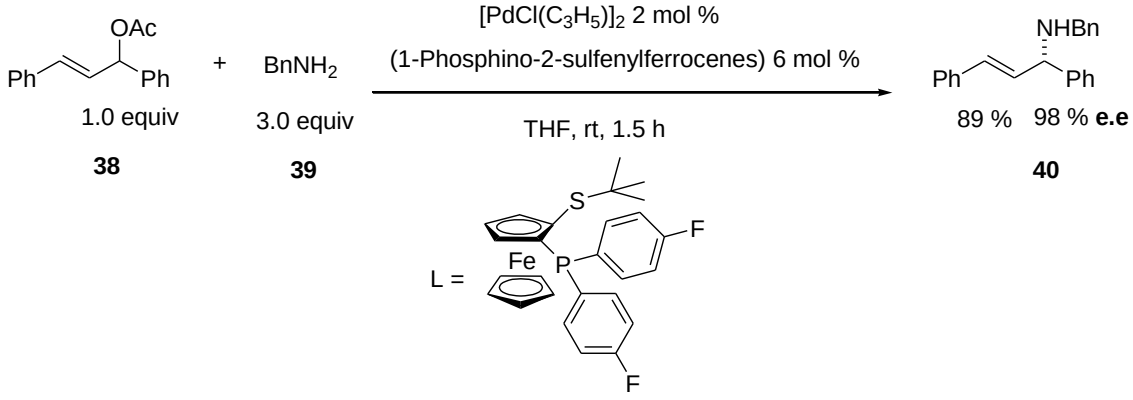
Scheme 11

Diallylation of diarylmethanes was optimised under similar reaction conditions. Products **37** (**a-b**) were obtained by one pot reaction protocol in very good yield.[8]



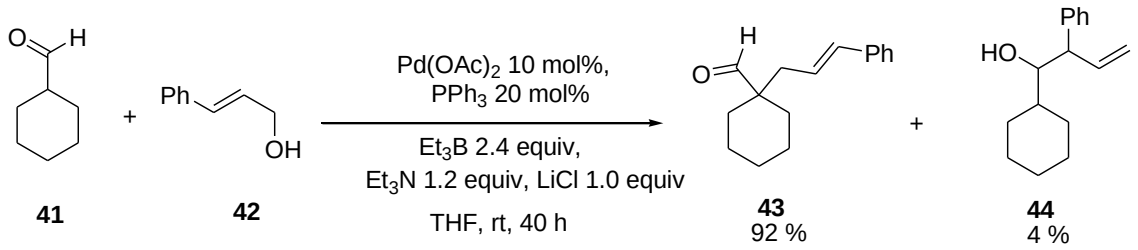
Scheme 12

Carretero *et al.* reported the allylic substitution of 1,3-diphenyl-2-propenyl acetate **38** with benzyl amine **39** as nucleophile, yielding desired product **40** in high yield and excellent ee.[26]



Scheme 13

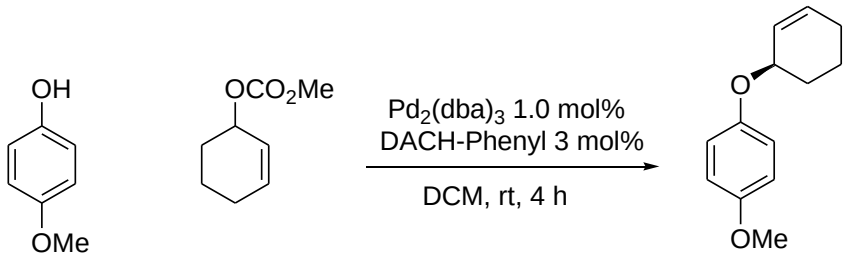
In 2001, Tamaru *et al* published the first example of direct α-allylic alkylation of aldehydes with allyl alcohols in the presence of palladium (10 mol %) and stoichiometric amounts of Et_3B, Et_3N, and LiCl at room temperature. They observed that the reaction did not take place in the absence of triethylamine, due to formation of $PdCl_2$ and its subsequent de-coordination being difficult, and remain intact. They hypothesised that in the presence of triethylamine, $PdCl_2$ might be reduced to a Pd^0 to allow the formation of product (Scheme 14).[27]



41 **42** **43** 92 % **44** 4 %

Scheme 14

Asymmetric allylation of an alcohol as the nucleophile was first reported by Trost and Toste in 1998. They showed that oxygen nucleophiles could be allylated using palladium catalyst (0) witha phosphoamidite ligand. The allylation of phenol **45** proceeded under mild conditions giving product **47** in excellent yield and high ee (Scheme 15).[28]

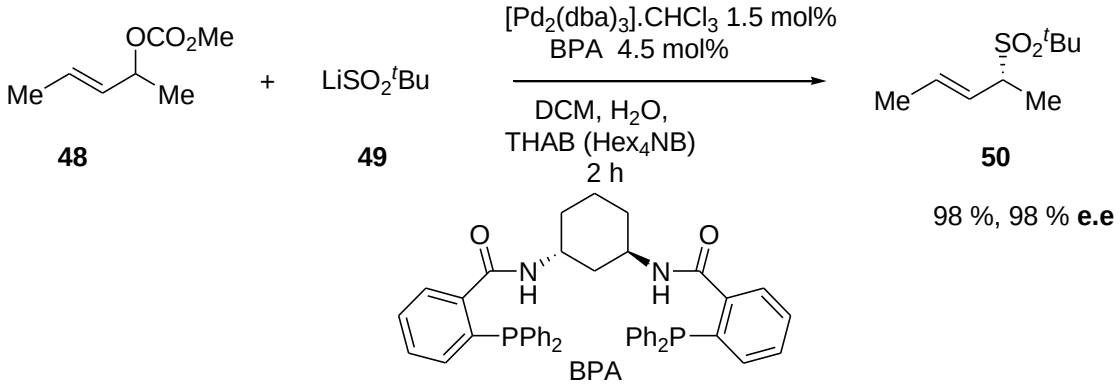


45 **46** **47**

88 %, 97 % **e.e**

Scheme 15

In 2003, Gais and co-workers reported the asymmetric allylation of sulfonates. Using $Pd_2(dba)_3$, acetate **48** was reacted with sulfinate salt **49** to yield sulfone **50** in excellent yields and high ee (Scheme 16).[29]



Scheme 16

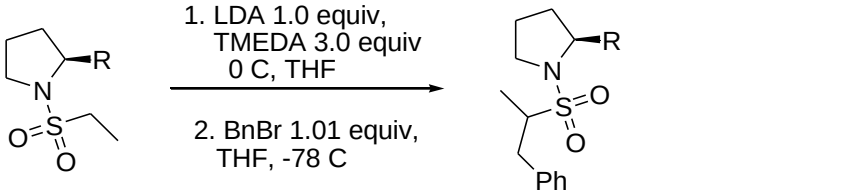
1.4 Sulfonamides

Sulfonamides have been a leading constituent in new drugs since their first appearance in a drug the 1930s.[30] The impact of the development of sulfur therapeutics is instrumental to the evolution of the pharmaceutical industry.[31,32] Sulfonamide drugs were the first antibiotics[33] to be used systemically, and paved the way for the new antibiotic revolution in medicine. However, antibiotics are not the only use of of sulfonamides, they are widely used in numerous applications example as an anticancer agent,[34] as an antiviral HIV protease inhibitor [35] and in central nervous system disease such as (Stroke and trauma).[36]

1.5 Direct α-functionalisation of sulfonamides

Within the traditional chemical space of drug-like molecules, the sulfonamide motif is a frequently seen subunit of synthetic biologically active molecules. The motif is a robust, pharmacologically reliable unit that appears in both drug substances and drug-like molecules. [37] α-Substitution with alkyl groups can improve the binding properties; [38] however, despite the wide interest in the exploitation of sulfonamides, many of the compounds reported bear sparse substitution patterns adjacent to the sulfonyl moiety. In the context of the drive for late-stage molecular functionalisation, there has been a recent interest in the development of new methods for direct α-functionalisation of sulfonamides.[38,42,43]

Enders and co-workers developed an efficient chiral auxiliary that would allow, for the first time, asymmetric α-alkylation of sulfonamides. They lithiated sulfonamides **51a-c** with lithium diisopropylamide (LDA) and allowed reaction with benzyl bromide at -78 °C to afford the sustituted sulfonamides **52a-c** with good yield but poor diastereoselectivity. They determined that unsatisfactory diastereoselectivities (de) were due to the lower steric demand of the side chain at the pyrrolidine ring.[39]

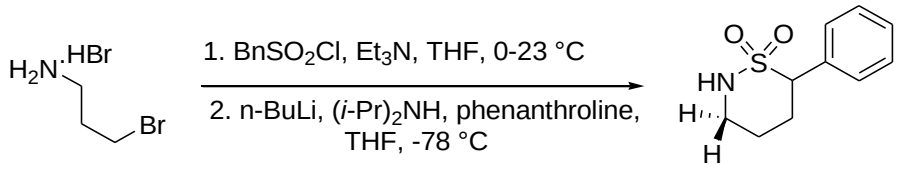


51 a-c **52 a-c**

R = $MeOCH_2OCH_2$ 85 %, 4% **d.e**
R = $MeOCH_2$ 94 %, 11 % **d.e**
R = $MeOC(Me)_2$ 78 %, 27% **d.e**

Scheme 17

Considerable efforts have been directed towards the discovery of selective RORc (retinoic acid receptor-related orphan receptor) inverse agonists as potential treatments of inflammatory diseases by Fauber and co-workers.[38] They prepared sultam **54** by reacting compound **53** with phenylmethanesulfonyl chloride and triethylamine to yield the secondary sulfonamide, followed by treatment with two equivalents of base to facilitate cyclization to sultam **54**.[38]



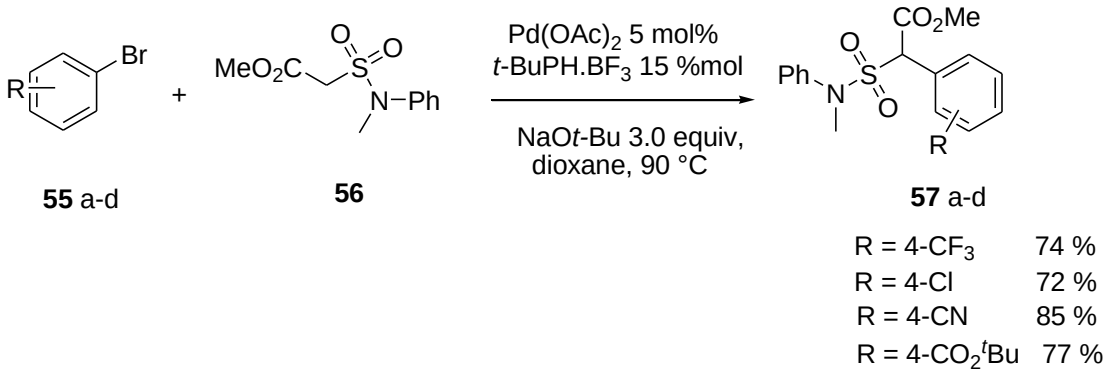
53 **54**
42 % over 2 steps

Scheme 18

As shown above, traditional methods (Scheme 17-18) for direct alkylation of sulfonamides require strong bases, reactive electrophiles, low temperatures and the use of stoichiometric

amounts of polar additives such as tetramethylethylenediamine (TMEDA),[40] hexamethylphosphoramide (HMPA),[41] and phenanthroline.[38] With a demand for functional group tolerance milder condition were needed, therefore, several recent reports have described metal-catalysed α-arylation of alkyl sulfonamides.[43]

Northrup *et al.* described the reaction of α-methanesulfonamide **56** with aryl bromide **55**(**a-d**) using palladium catalysis and a bulky electron rich trialkylphosphine ligand in the precence of sodium-tert-butoxide at high temperature. Authors believed that the bulky trialkylphosphine ligand led to increased conversions by reducing homocoupling and hydrodehalogenation reaction pathways.[42]

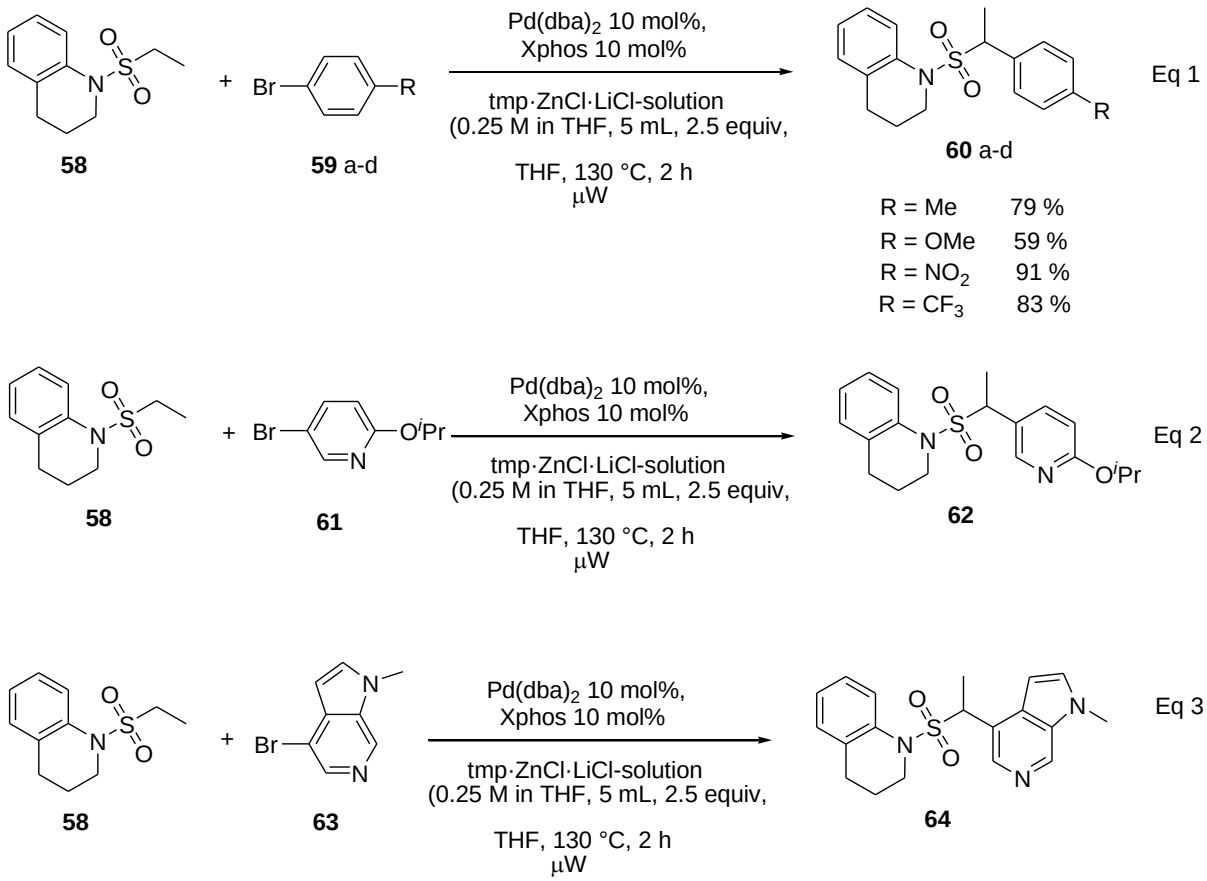


55 a-d **56** **57** a-d

R = 4-CF_3	74 %
R = 4-Cl	72 %
R = 4-CN	85 %
R = 4-$CO_2{}^t$Bu	77 %

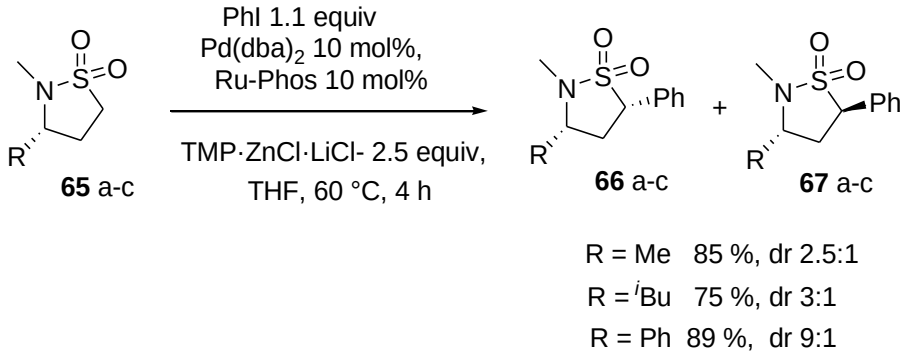
Scheme 19

In 2016, Knauber and Tucker developed a palladium catalyzed Negishi-type α-arylation of sulfones and sulfonamides with a broad range of aryl bromides. In *situ* sulfonamide selectively reacts with tmp·ZnCl·LiCl base (tmp: 2,2,6,6-tetramethylpiperidine) and undergoes transmetalation with arylpallaium species. They also successfully coupled a board range of electron-deficient, electron-rich, and heterocyclic aryl bromides with sensitive functional groups well tolerated. Aryl bromides were converted within 2 h at 130 °C in a microwave reactor. The desired monoarylated α-branched benzyl sulfones and sulfonamides were obtained in good yields, and diarylation was not observed. [43a]



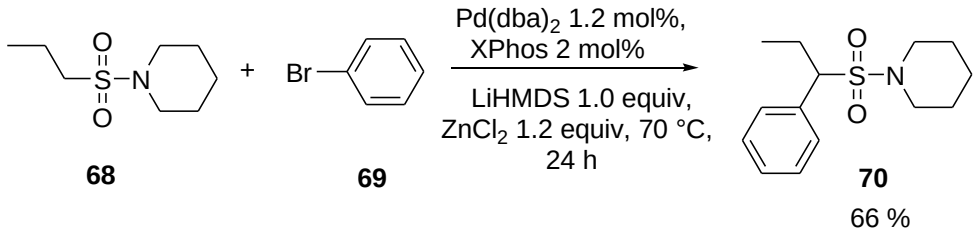
Scheme 20

Yajima and co-workers published Palladium$^{(0)}$-catalyzed conditions for the α-arylation of sultams with iodobenzene (Scheme 21).[43c] Product **66–a** was isolated in very good yield 85% and good diastereoselectivity (2.5:1). The slightly more sterically demanding *iso*-butyl-containing sultam **65-b** also proved to be a suitable coupling partner and gave rise to arylated product **66–b** in 75% yield, with a slight improved 3:1 dr in favour of the *cis* product. Furthermore, the bulkier phenyl substituted **65–a** yielded product **66–c** in 89% isolated yield and 9:1 dr. Overall, it appears that the steric demand of the C3 substituent significantly contributes to the diastereomeric outcome of the reaction, with the bulkier substituent giving rise to the thermodynamically preferred *cis* product.[43c]



Scheme 21

Zhou *et al* reported a single example of branched sulfonamide synthesis. When they reacted bromobenzene **69** with sulfonamide **68** in the presence of a palladium (0) catalyst and strong base at 70°C obtained product **70** in good yield.[43d]



Scheme 22

2. Aim of the project

A palladium catalyzed α-allylation of benzyl sulfonamides with a broad range of ally acetates has been presented. At the beginning, we hypothesized that anions derived from benzyl sulfonamides would be amenable to Pd-catalysed allylation (Figure 2); however, there are relatively few reports of the use of nucleophiles other than carbonyl-stabilised carbanions in such reactions,[49] and fewer examples still of the use of non-carbonyl abranched anions.[8] Hence, sulfonamides were deprotonated with NaH base *in situ* and cross-coupled in the presence of a Pd catalyst and ligand at room temperature. Several allyl acetate derivatives have been successfully cross-coupled, and sigma-receptor binders were tolerated. The desired monoallylated α-branched sulfonamides were obtained in good yields. This method would be suitable for late stage functionalization in medicinal chemistry.

In addition, the pk_a of sulfonamide-derived anions are not definitively established; direct deprotonation even of benzyl sulfonamides often requires strong base,[50] suggesting that the anions thus obtained might be considered to be (hard) and therefore likely to lead to products of inversion upon reaction with π-allylpalladium species. Nevertheless, mechanistic studies of Pd-catalysed allylation indicated direct attack at the carbon rather than Pd, this confirms that the anions derived from benzylsulfonamides can be considered to be (soft) reagents.

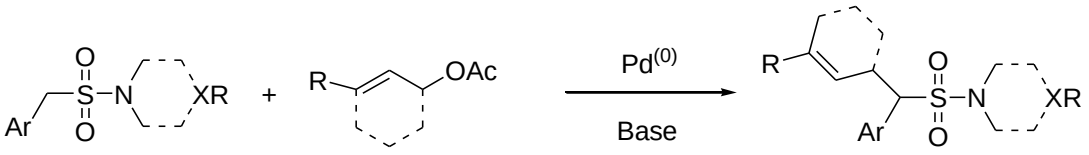


Fig 2

3. Result and Discussion

The difficulties in accessing non-planar "hard-to-make" chemical matter for incorporation into drug molecules have been well-enumerated,[44] and in some therapeutic areas these difficulties have significant consequences. There has been a drive to deliver new small molecules with enhanced biological relevance, and a concomitant call for late-stage functionalisation[45] to enable improvements in pharmacological properties. Since the discovery of the antibacterial activity of streptozone and sulfachrysoidine by Domagk,[46] sulfonamides have found widespread application in the development of new antibiotics. Numerous examples of α- substituted sulfonamides of the general type **71** displayed potent pharmacological activity. The racemic α-substituted sulfonylmethanesulfonamide derivatives **72** and **73** are reported to be inhibitors of carbonic anhydrase (CA).[47] In particular, fluorosulfonamide **72** was determined as the most potent inhibitor among the compounds of this type examined. The small improvements in binding affinity observed upon introducing a methyl group have been attributed to desolvation effects.[48] Increased methylation reduces the free energy of desolvation required to strip a ligand of solvated water molecules when it transfers from an aqueous environment to the greasy cavity of a protein.[48]

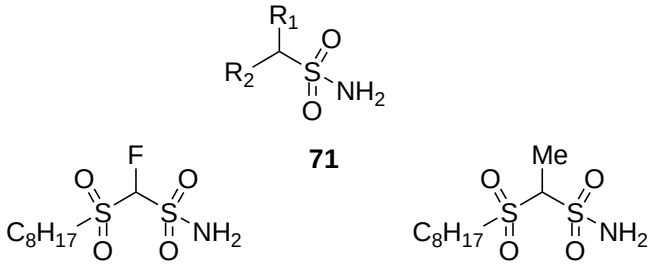
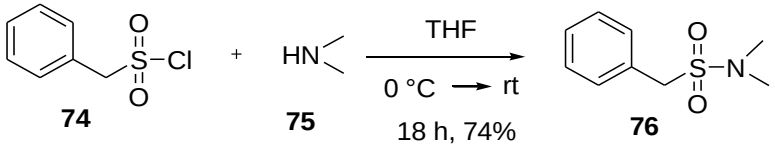


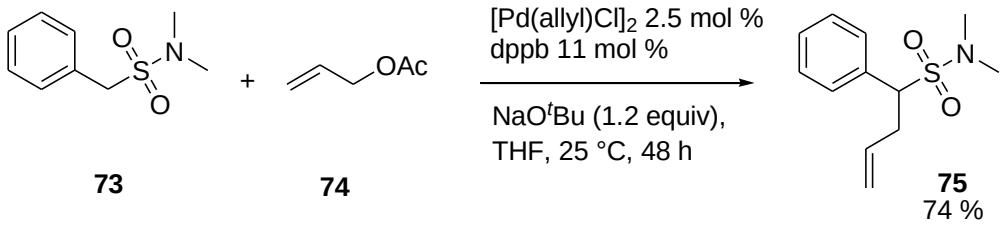
Fig 1

Given these important applications, we set out to introduce diarylmethane derived nucleophiles for the Pd-catalyzed allylic substitution. Sulfonamide **76** was readily prepared in multi-gram scale in 86% yield from phenylsulfonyl chloride **74** and stoichiometric amount of methylamine solution **75** in chloroform using a known procedure.



Scheme 23

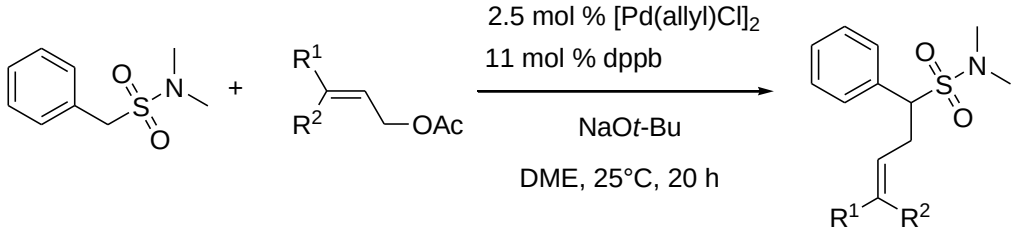
We commenced our study with an examination of the reaction of dimethylsulfonamide **73** with allyl acetate **74** under Pd-catalysed allylation conditions. Given that the transformation was previously unreported, we were gratified to observe that the reaction afforded the desired *sp*^{3}-functionalised allylated product **75** in moderate yield (Scheme 24).



Scheme 24

A screening of several organic solvents was initiated and all reactions were monitored by TLC analysis of crude mixtures. A solvent screen was undertaken with the Pd-allylation reaction using same conditions as mentioned above. When $CHCl_3$ was applied as a solvent only starting material was recovered. It was found that DME solvent gave the best results. The reaction also readily went to work in DMF, THF, NMP, DCM and Benzene with low yields to DME. For reactions performed in MeCN and Dioxane were observed a significant amount of starting material in the NMRs, therefore the yields quoted are with impurities.

As shown in (Scheme 24), this study was initially evaluated in the reaction of sulfonamide with allyl acetate in the presence of allyl palladium catalyst and dppb ligand. Gratifyingly, under influence of 1.2 equiv sodium *tert*-butoxide base at a room temperature, the reaction produced allyl sulfonamide **75** in 74 % yields in DME. Having recognised the significant reaction conditions, we set out to examine a series of allyl acetate derivatives with our new conditions.

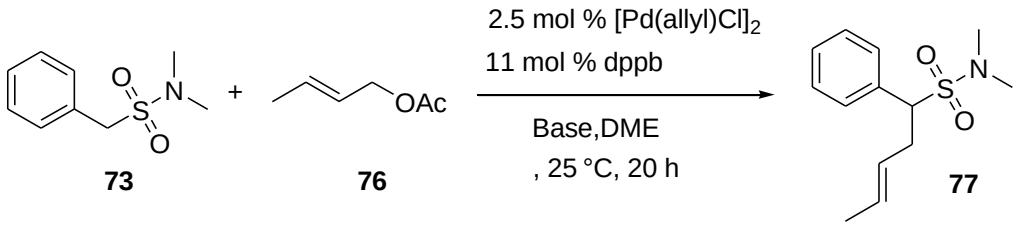


Entry	R1	R2	Base (equiv)	Yield (%)
1	Ph	H	(1.2, 3.0, 5.0)	-
2	CH_3	H	5.0	24 %
3	CH_3	CH_3	(1.2, 3.0, 5.0)	-
4	CH_2- CH_2- CH_3	H	1.2	63 %

Table 1

Unfortunately, most of the hindered allyl acetate derivatives (prenyl acetate and cinnamyl acetate) provide to be fruitless under the same reaction condition. It was thought that to increase the conversion of starting material, more bases would necessary. Unfortunately, no reaction was observed when 3.0 equiv of sodium *tert*-butoxide was used. But when 5.0 equiv of the base was used the desired product was obtained in 24% yield (Table 1, entry 2). Potassium *tert*- butoxide (Pk_a of conjugate acid around 17 similar to sodium-*tert*-butoxide) (1.2, 3.0, 5.0 equiv) failed to give any observable product and only starting materials were

recovered. We, therefore, believe that reaction conditions play a critical role in this transformation. We hypothesized that generation of deprotonated sulfonamide was problematic, and that the variation of base would significantly impact the conversion (Table 2).



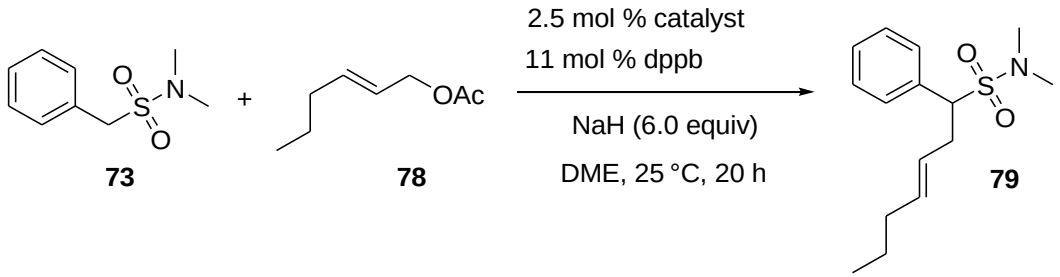
Entry	Base	Amount (equiv)	Yield (%)
1	LiHMDS	1.5	0
2	LiHMDS	3	0
3	LiHMDS	4	8
4	LiHMDS	5	11
5	KHMDS	5	0
6	NaHMDS	5	0
7	BTPP	5	0
8	NaH	1.0	0
9	NaH	3.0	Trace
10	NaH	6.0	94 %

Table 2

Based on the assumption that NaO^{t}Bu was a weak base to deprotonate the α-C adjacent to sulfonamide group, a stronger base was needed. Walsh and co-workers[8] actually obtained good yield of the desired allylated product with strong anionic bases. Hence, **73** and **76** were treated with NaHMDS, LiHMDS and KHMDS under the same reaction conditions. Several approaches were tried and some selected results are presented in (Table 2). Unfortunately, low or no yield of the rearranged product **77** was obtained and starting material **73** was recovered in various amounts. To test if a base with lower Pk_a value could increase the conversion of the allylated product, NaH was probed. Treating a mixture of **73** and **76** with NaH (1.0 equiv) at room temperature yielded no product, but at elevated base (3.0 equiv) some conversion could be observed by ^{1}H NMR. Finally, using NaH (6.0 equiv) **76** was

converted to product **77** in 94% yield. Hence, sodium hydride was chosen and compared to the allylation promoted by NaO^tBu, this base gave a best result.

We believed that one of the main aspects of the reaction that required significant optimisation was the source of palladium. A catalyst screen was performed to investigate the effect of the catalyst on the reaction. In addition, hexenyl acetate was chosen as it gave the highest yield with the optimised condition (Table 4, entry 5). (Table 3, entry 1, 2, 3 and 4) summarizes the result. As shown, $PdCl_2(MeCN)_2$ gave the good results. $Pd(OAc)_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$did give a moderate conversion to the desired product **79** but with low yields. Indeed, there wasa highest yield achieved when $Pd(allyl)Cl_2$ used as catalysts.



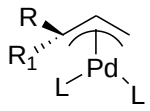
73 **78** **79**

Entry	Catalyst	Yield (%)
1	$Pd(OAc)_2$	21
2	$Pd_2(dba)_3$	30
3	$Pd(PPh_3)_4$	43
4	$PdCl_2(MeCN)_2$	90
5	$Pd(allyl)Cl_2$	96

Table 3

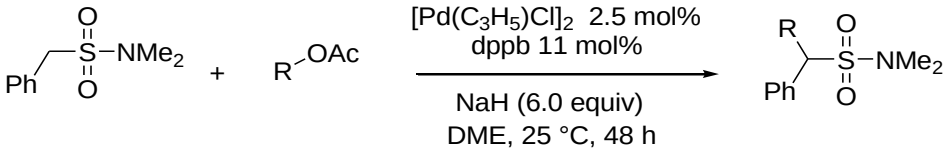
Armed with these initial data, we proceeded next to probe the scope of the reaction with regard to the allyl component (Table 4), using a range of commercial or easily prepared substrates. It quickly transpired that the catalytic allylation reaction proceeded in generally good yield under mild conditions with a diverse range of allyl donors to afford α-substituted sulfonamides. Both acyclic and cyclic acetates delivered the corresponding C-allylated sulfonamides efficiently, and, if present, alkene stereochemistry was generally retained (**75, 77, 79-86**). For compound **77** a mixture of *E/Z* product was observed. It appeared to us that a rigid bidentate ligand should interfere more sterically with a *syn* substituent, leading to a preference for the *anti* configuration. Provided isomerisation is sufficiently fast, this offers

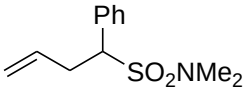
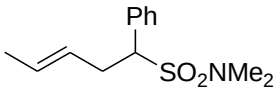
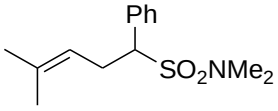
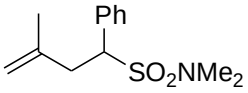
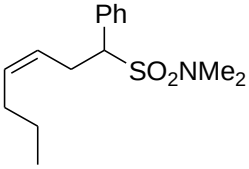
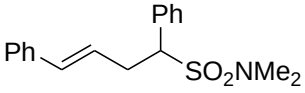
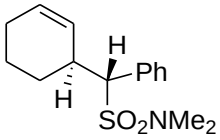
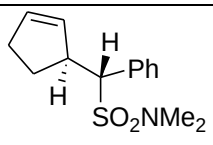
the possibility of obtaining *Z*-products in palladium-promoted reactions of allylic substrates, irrespective of the configuration of the starting material (Fig 5). [51]

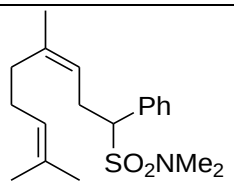
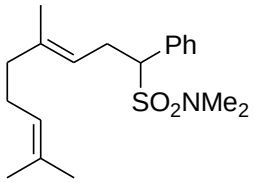


(*anti*) R = H, R = Me
(*syn*) R = Me, R = H

Fig 5



Entry	R	Compound	Product	Yield (%)
1	Allyl	**75**		79
2	Crotyl	**77**	 *E/Z* 67:33	82, 94[b]
3	Prenyl	**80**		86[f]
4	2-Methyl-2-propenyl	**81**		82[f]
5	Hexenyl	**79**		96
6	Cinnamyl	**82**		79[c]
8	Cyclohexenyl	**83**	 dr = 60:40	74[d]
9	Cyclopentenyl	**84**	 dr = 50:50	79[d]

10	Neryl	**85**		83, 68[b]
11	Geranyl	**86**		84[c,f]

[a] yields are quoted for isolated compounds.

[b] 1,2-bis(diphenylphosphino)ethane (dppe) used as ligand.

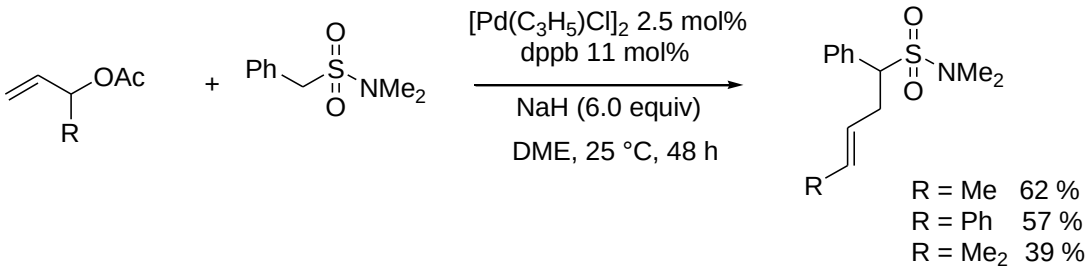
[c] 1,1'-bis(diphenylphosphino)ferrocene (dppf) used as ligand.

[d] d.r. refers to the relative configuration at the exocyclic stereogenic centre.

[f] Prepared by S. Walton

Table 4

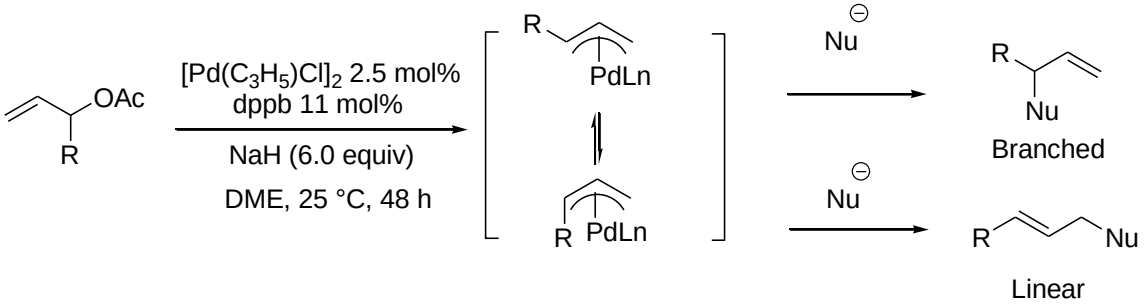
In all cases in which isomerism was possible, linear products were exclusively favoured over branched isomers, affording compounds **87-89** (Scheme 25).



Scheme 25

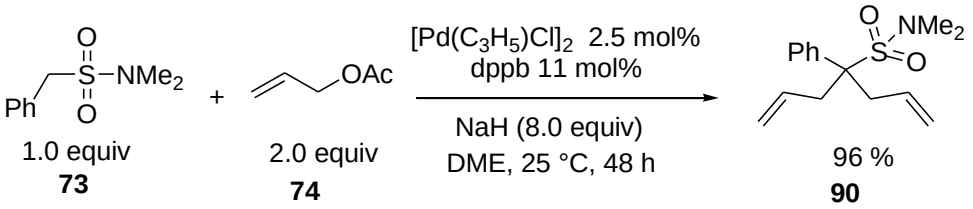
The regioisomeric ratio of products is influenced by several factors, including the nature of the R-group, the ability of the intermediate to *syn-anti* isomerize, and the ligands used. [52] When applying a monosubstituted allylic substrate, terminal attack of the nucleophile at π-allyl specie swas the preferred result. The allylic carbon atoms in the *syn*- and *anti*-isomers of the η3-allyl-palladium complex possess different reactivity. In monosubstituted allylic substrates the resulting *anti*-isomer has a moderate preference for internal nucleophilic substitution whereas the *syn* isomer has a strong preference for terminal nucleophilic attack.[52b] The *syn*-isomer is usually more stable than the *anti*-isomer and, as a result, the

major product in palladium catalyzed allylic alkylation reactions is the product of attack on the least substituted carbon linear product (Scheme 25).

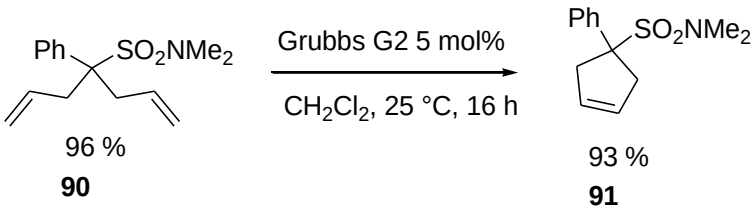


Scheme 26

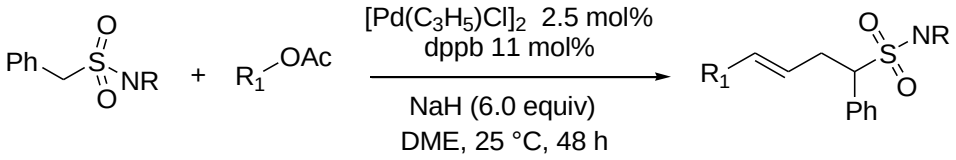
The allylated products still have an acidic α-proton, the possibility exists for a second functionalisation. Thus, when reacted with excess allyl acetate, sulfonamide **73** was directly converted to diallylated product **90** (96% yield), which could be converted by ring-closing metathesis (RCM)[53] in high yield into previously unreported tertiary sulfonamide **91**.



Scheme 27



Scheme 28

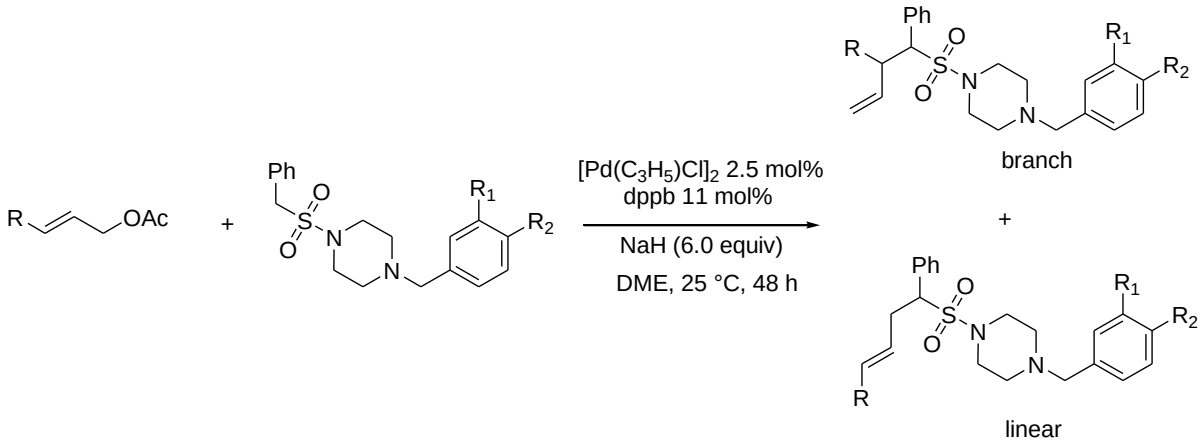


Entry	R	R_1	Compound	Yield (%)
1	Boc-piperazinyl	Allyl	**92**	71
2	Boc-piperazinyl	Hexenyl	**93**	52
3	Boc-piperazinyl	Nerayl	**94**	52
4	Boc-piperazinyl	Crotyl	**95**	59
5	Boc-piperazinyl	Prenyl	**96**	52
6	Morpholinyl	Allyl	**97**	52[a]
7	Morpholinyl	Hexenyl	**98**	79[a]
8	Morpholinyl	Nerayl	**99**	45[a]
9	Piperidinyl	Allyl	**100**	77
10	Pyrrolidinyl	Allyl	**101**	61
11	Tetrahydropyridinyl	Allyl	**102**	82[a]

[a] prepared by S. Walton

Table 5

After we had conclusively demonstrated the feasibility of the sulfonamide allylation reaction, our attention turned to an examination of the scope in the nitrogen sub-unit: again we observed generally efficient reaction of sulfonamides under the catalytic allylation conditions, leading to new sulfonamides **92-102** (Table 5). In contrast, the Boc-piperizene derivatives **92-96**[58] resulted in modest 52-59% yields (Entry 1-5). The lower yield is likely due to attack of nucleophile on the *tert*-butyl ester carbonyl. When crotyl acetate (entry 4) reacted with the anion of nucleophile, only *E*-product **95** could be detected, confirming a higher relative reactivity at the *anti* substituted carbon.[51]



Entry	R	R_1	R_2	Compound	Yield (%)	Linear:Branched
1	H	H	H	**103**	76	10:0 [a]
2	H	F	H	**104**	67	10:0
3	H	Me	H	**105**	53	10:0
4	$CH_3CH_2CH_2$	H	H	**106**	58	10:0
5	CH_3	H	Br	**107**	63	10:0 [a]
6	H	H	OMe	**108**	37	10:0 [a]
7	Ph	Cl	H	**109**	62	3:2

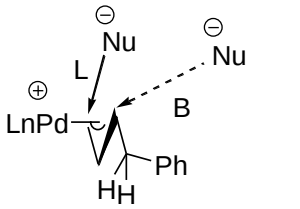
[a] Prepared by S. Walton

Table 6

To probe the suitability of the reaction as a late-stage functionalisation tool, we next examined nanomolar receptor ligands as substrates. Thus, sigma-receptor binding sulfonamides[57] reacted smoothly under the reaction conditions to afford new α-functionalised products **103-107** and **109** in good yield (Table 6). Compounds containing halogens substituted are important because of their bioactivities and uses in material science.[54] Therefore, the reaction was interesting with 3-fluoro sigma receptor binding sulfonamide (Entry 2) as nucleophile afforded the desired product **104** in 67% yield (Entry 2). We then applied our reaction conditions to 4-bromo and 3-chloro sigma receptor binding sulfonamides (Entry 5 and 7). A potential problem with these substrates lies in the competing oxidative addition of C−X (X = Cl, Br) bonds to the active Pd(0) species. We were pleased to find that Pd-catalyzed allylic substitution afforded the allylated products **107** and **109** in 63 and 62% yield, respectively. These results suggest that generation of the π-allyl palladium intermediate is significantly faster than the oxidative addition of C−X bonds to the Pd(0) species under our reaction conditions. As might be anticipated, nucleophiles with electron donating groups are less acidic and, therefore, more difficult to deprotonate. We found that 3-methyl sigma receptor binding sulfonamide (Entry 3) underwent substitution to give **105** in 53% yield. Surprisingly, 4-methoxy sigma receptor binding sulfonamide (Entry 6) reacted to provide **108** in 37% yield under our reaction conditions as Walsh *et al* failed to gain a desired product with 4-methoxy substitutent.[8]

Notably, reaction with cinnamyl acetate afforded both linear and branched products (**109**, respectively, 3:2 ratio), whereas reactions with hexenyl and crotyl acetates afforded only linear products **106**, **107** and **108**. The reduced regioselectivity in this case, relative to cases with less basic nucleophiles, is likely a manifestation of the high reactivity of the 3-

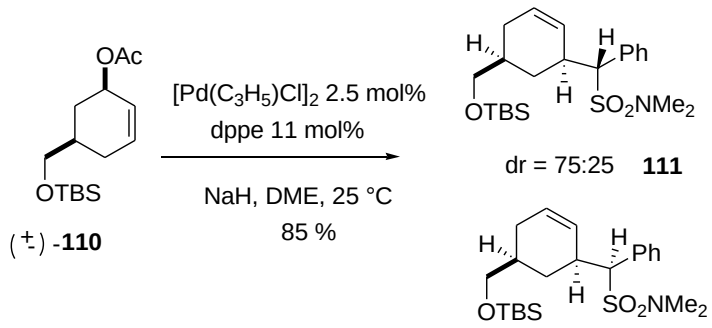
chlorobenzylpyparizen phenyl sulfonamide nucleophile. The additional substituent (Ph) on the *η3*-allyl in the phenyl causes this group to adopt a conformation positioning it *anti* to the bulky (legend)Pd center (Figure 6). The substituent partially blocks the nucleophilic attack at the more substituted terminus, resulting in a modification of the regioselectivity toward the less substituted carbon of the allyl.[8] The mildness of the method is emphasised by the fact that, if present, halogen substituents were tolerated, allowing for subsequent synthetic development.



L = linear, B = branched

Fig 6

In our group, the structure of the product was confirmed by X-ray crystallography. The mechanism of Pd-catalysed allylation is well-predicated to occur by one of two pathways, depending on the polarisation of the nucleophile component.[55] If the allylation reaction was performed with *cis*-cyclohexenyl acetate **110**,[56] *cis* products **111** were obtained exclusively (as confirmed by X-ray (Fig 7) analysis of a single crystal of a *p*-bromobenzoyl derivative, **111**, of the major product, Scheme 29). The *cis*-configured product indicates direct attack at the carbon rather than Pd, this confirms that the anions derived from benzylsulfonamides can be considered to be "soft" reagents, at least in the context of Pd catalysis.



Scheme 29

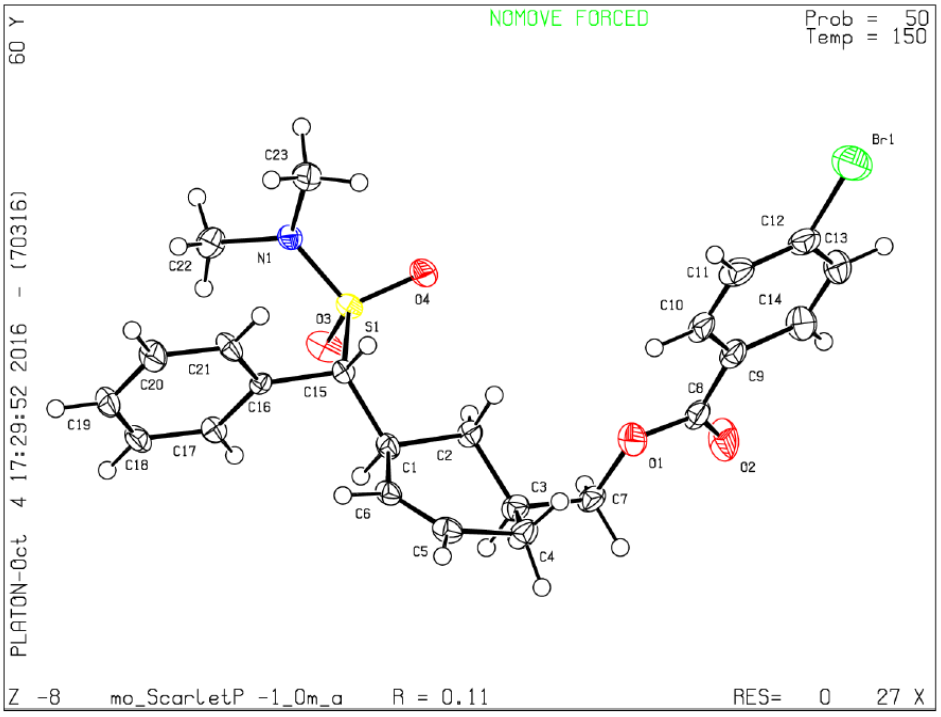


Fig 7

4. Conclusion

In summary, we have developed a new application of Pd catalysed allylation for direct sp^3-sp^3 coupling of sulfonamides and demonstrated that the reaction is applicable to bioactive small molecules. The transformation occurs at ambient temperature, is tolerant to sensitive functional groups and provides ready access to new compounds in good yields. Mechanistic studies have shown that benzyl sulfonamide derivatives behave as (soft) or stabilized nucleophiles. The nucleophile derived from benzyl sulfonamide undergoes external attack on π-allyl palladium species under our reaction conditions. The use of asymmetric protocols in this process has proved non-productive, delivering allylated products in variable yields and with no discernible enantioselectivity.

5. Experimental

General methods

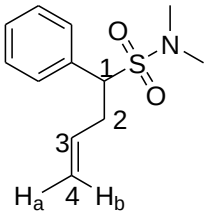
Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent in accordance with the procedures of Perrin and Armarego. Dimethoxyethane and THF were distilled from sodium benzophenone ketyl radical while DCM was distilled from calcium hydride. Thin layer chromatography was performed on aluminium sheets coated with Merck silica gel 60 F254 with visualisation using potassium permanganate solution, phosphomolybdic acid and/or scrutinised under 254 nm UV light. Column chromatography was performed using Silica 60 (35-70 microns) supplied by Fisher unless otherwise stated. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker Avance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in ^{13}C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz. Mass spectrometry was performed using a Bruker MicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}.

General Procedure for the Palladium-catalysed sulfonamide allylation

To an oven dried round-bottomed flask, flushed with nitrogen, sodium hydride 60 % in mineral oil (120 mg, 3.0 mmol) was added, and was immediately washed with petrol. To this, palladium chloride dimer (4.7 mg, 0.0125 mmol), 1,4-bis(diphenylphosphino)butane (dppb, 23 mg, 0.055 mmol) in DME (1 mL) was added and stirred for one hour at 25 °C. To this mixture, sulfonamide (0.50 mmol) and allylic acetate (0.55 mmol) in DME (1 mL) was

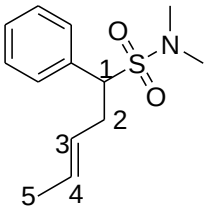
added and stirred for 48 hours at 25 °C. After this time the reaction was quenched with water (0.5 mL) and purified by flash column chromatography to yield the title compound.

***N,N*-Dimethyl-1-phenylbut-3-en-1-sulfonamide (75)**



N,N-Diphenylmethanesulfonamide (100 mg, 0.50 mmol) and allyl acetate (0.06 mL, 0.55 mmol) were reacted following the general procedure to yield *N,N*-dimethyl-1-phenylbut-3-en-1-sulfonamide (98 mg, 82 %) as a colourless solid; R_f= 0.5 (95:5 toluene: EtOAc); mp: 91–92 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ7.34-7.42 (5H, m, Ar-H); 5.57 (1H, ddt,*J* 7.0 Hz 10.1 Hz 17.1 Hz, 3-H); 5.06 (1H, dd, *J* 1.4 Hz 17.0 Hz,4-H_b); 4.99 (1H, dd, *J* 0.8 Hz 10.1 Hz, 4-H_a); 4.15 (1H, dd, *J* 4.2 Hz11.3 Hz 1-H); 3.00-3.10 (2H, m, 2-H_2); **^{13}C NMR** (100 MHz) δ_C133.3 (3-CH); 129.6 (Ar-CH); 128.9 (Ar-CH); 128.7 (Ar-CH); 118.2 (4-CH_2); 37.6 (N-(CH_3)$_2$); 34.3 (2-CH_2); ν_{max} (solid, cm^{-1}) 1137 & 1310 (sulfonamide S-N); 969 (CH=CH); ***m/z***(ESI$^+$) calculated for $C_{12}H_{17}NO_2S$ $[M+Na]^+$; 262.0872, found 262.0869.

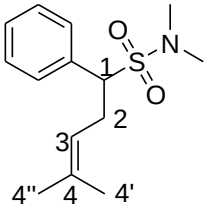
***(E)*-*N,N*-Dimethyl-1-phenylpent-3-ene-1-sulfonamide (77)**



N,N-Dimethyl-1-phenylmethanesulfonamide (92mg, 0.5 mmol) and *E*-2-butenyl acetate (95 % *E*) (0.07 ml, 0.55 mmol) was reacted following the general method, to yield (*E*)-*N,N*-dimethyl-1-phenylpent-3-ene-1-sulfonamide (*E:Z* 67:33) (103 mg, 82% or 119 mg, 94 % with dppe) as a colourless solid*;* R_f= 0.52 (95:5 toluene:EtOAc); mp: 92 – 94 °C; Data for *trans* isomer **^{1}H NMR** ($CDCl_3$ 400 MHz) δ 7.34-7.42 (m, 5H, Ar-H); 5.44-5.54 (1H, m, 3-H); 5.11-5.19 (1H, m, 4-H); 4.11 (1H, dd, *J* 4.1 Hz 11.2 Hz, 1-H); 2.8-3.0 (2H, m, 2-H_2); 2.50 (6H, s, N-(CH_3)$_2$); 1.5 (3H, dd, *J* 0.8 Hz 6.5 Hz, 5-H_3); **^{13}C NMR** (100 MHz) δ_C 133.4 (Ar-C); 129.6 (Ar-CH); 128.9 (Ar-CH); 128.8 (3-CH); 125.6 (4-CH); 67.6 (1-CH); 37.6 (N-(CH_3)$_2$); 33.2 (2-CH_2); 17.8 (5-CH_3);

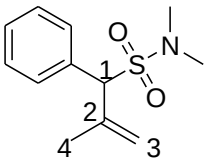
ν_{max} (solid, cm^{-1}) 1137 & 1319 (sulfonamide S-N); ***m/z*** (ESI^+) calculated for $C_{13}H_{19}NO_2S$ $[M+Na]^+$; 267.1029, found 276.1025.

***N,N*-4-Trimethyl-1-phenylpent-3-ene-1-sulfonamide (80)**



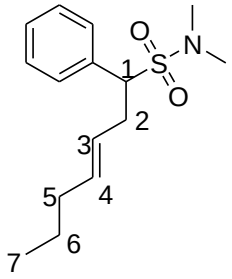
N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol) and prenyl acetate (0.075 mL, 0.55 mmol) was reacted following the general method to yield *N,N*-4-trimethyl-1-phenylpent-3-ene-1-sulfonamide (115 mg, 86 % or 0.99 mg, 74 % with dppe) as a colourless solid; R_f= 0.58 (95:5 toluene:EtOAc); mp 90–92°C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ 7.34-7.42 (5H, m, Ar-H); 4.87 (1H, ddt, *J* 1.4 Hz 3.0 Hz 7.3 Hz, 3-H); 4.07 (1H, dd, *J* 4.0 Hz 11.3 Hz, 1-H); 3.05-2.84 (2H, m, 2-H_2); 2.50 (6H, s, N-(CH_3)$_2$); 1.56 (6H, s, 4''-CH_3, 4'-CH_3; **^{13}C NMR** (100 MHz) δ 134.9 (Ar-C); 133.6 (4-C); 129.6 (Ar-CH); 128.7 (Ar-CH); 128.6 (Ar-CH); 118.9 (3-CH); 67.4 (1-CH); 37.6 (N-(CH_3)$_2$); 28.8 (2-CH_2); 25.6 (4''-CH_3); 17.9 (4'-CH_3); ν_{max} (solid, cm^{-1}) 1133 & 1304 (sulfonamide S-N); ***m/z*** (ESI^+) calculated for $C_{14}H_{21}NO_2S$ $[M+H]^+$; 268.1366, found 268.1366.

***N,N*-3-Trimethyl-1-phenylbut-3-ene-1-sulfonamide (81)**



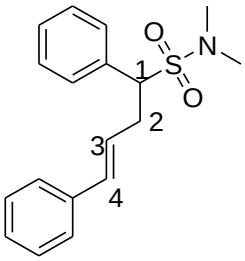
N,N-Dimethyl-1-phenylmethanesulfonamide (97 mg, 0.49 mmol) and 2-methylallyl acetate (72 mg, mmol) was reacted following the general method to yield *N,N*-3-trimethyl-1-phenylbut-3-ene-1-sulfonamide (102 mg, 82 %) as a colourless solid; R_f= 0.50 (95:5 toluene:EtOAc); m.p: 127 – 128 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ7.35-7.42 (5H, m, Ar-H); 4.67 (1H, bs, 3'-H); 4.61 (1H, bs, 3'-H); 4.30 (1H, dd, *J* 3.7 Hz 11.6 Hz, 1-H); 2.88-3.06 (2H, m, 2-H); 2.54 (6H, s, N-(CH_3)$_2$); 1.61 (3H, 4-H_3); **^{13}C NMR** (100 MHz) δ140.3 (3-C); 133.3 (Ar-C); 129.6 (Ar-CH); 128.9 (Ar-CH); 114.1 (3'-CH_2); 66.0 (N-(CH_3)$_2$); 37.7 (N-(CH_3)$_2$); 22.3 (4-CH_3); ν_{max} (solid, cm^{-1}) 1132 & 1323 (sulfonamide S-N); 895 (geminal alkene); ***m/z*** (ESI^+) calculated for $C_{13}H_{19}NO_2S$ $[M+Na]^+$; 276.1029, found 276.1030.

***(E)-N,N*-Dimethyl-1-phenylhept-3-ene-1-sulfonamide (79)**



N,N-Dimethyl-1-phenylmethanesulfonamide (0.099 g, 0.5 mmol) and *E*-2-hexenyl acetate (0.09 mL, 0.55 mmol) was reacted following the general method to yield (E)-*N,N*-dimethyl-1-phenylhept-3-ene-1-sulfonamide (137 mg, 96%) as a colourless solid; R_f= 0.60 (95:5 toluene:EtOAc); mp: 65 – 67 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ 7.34-7.41 (5H, m, Ar-H); 5.38-5.47 (1H, m, 4-H); 5.08-5.17 (1H, m, 3-H); 4.10 (1H, dd *J* 4.2 Hz 11.1 Hz, 1-H); 2.81-3.04 (2H, m, 2-H_2); 2.54 (6H, s, N-(CH_3)$_2$); 1.76-1.88 (2H, m, 5-H_2); 1.19-1.26 (2H, m, 6-H_2); 0.72 (3H, t, *J* 7.1 Hz, 7-H); **^{13}C NMR** (100 MHz) δ134.5 (4-CH); 133.4 (Ar-C); 129.7 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 124.5 (3-CH); 67.6 (1-CH); 37.6 (N-(CH_3)$_2$); 34.4 (2-CH_2); 33.2 (5-CH_2); 22.3 (6-CH_2); 13.4 (7-CH_3); ν_{max} (solid, cm^{-1}) 1137 & 1320 (sulfonamide S-N); 964 (*E*-alkene);***m/z*** (ESI^+) calculated for $C_{15}H_{23}NO_2S$ $[M+K]^+$; 320.1081, found 320.1083.

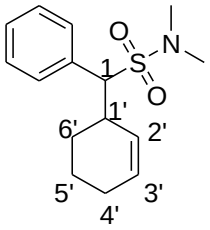
(*E*)-*N,N*-Dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (81)



N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, mmol) and cinnamyl acetate (0.097 g, mmol) was reacted following the general method, replacing dppb with1,1'-bis(diphenylphosphino)ferrocene as the ligand, to yield (*E*)-*N,N*-dimethyl-1,4-diphenylbut-3-ene-1-sulfonamide (125 mg, 79 %) as a colourless solid; R_f= 0.5 (95:5 toluene:EtOAc); mp: 88–90 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ7.36-7.46 (5H, m, Ar-H); 7.17 (5H, m, Ar-H); 6.43 (1H, d, *J* 15.6, 4-H); 5.93 (1H, dt, *J* 7.2, 15.7, 3-H); 4.22 (1H, dd, *J* 4.2, 10.8, 1-H); 3.25 (1H, dddd, *J* 1.0 Hz 4.2 Hz 7.6 Hz 14.2 Hz, 2-H); 3.08 (1H, dddd, *J* 1.1 Hz 6.8 Hz 10.9 Hz 14.2 Hz, 2-H); 2.55 (6H, s, N-(CH_3)$_2$); **^{13}C NMR** (100 MHz) δ_C 136.9 (Ar-C); 133.2 (Ar-C); 133.1 (4-CH); 129.6 (Ar-CH); 129.0 (Ar-CH); 128.8 (Ar-CH); 128.5 (Ar-CH); 127.4 (Ar-CH); 126.2 (Ar-CH); 124.8 (3-CH); 67.3

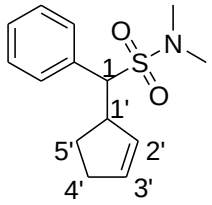
(1-C̲H); 37.6 ((N-C̲H$_3$)$_2$); 33.7 (2-C̲H$_2$); ν_{max} (solid, cm^{-1}) 1135.6 & 1317 (sulfonamide S-N); 926 (*E*-alkene); ***m/z*** (ESI$^+$) calculated forC$_{18}$H$_{21}$NO$_2$S [M+Na]$^+$; 338.1185, found 338.1184.

1-(Cyclohex-2-en-1-yl)-*N,N*-dimethyl-1-phenylmethanesulfonamide (83)



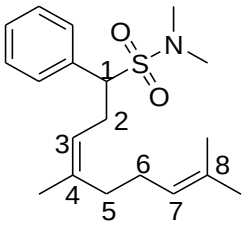
N,N-Dimethyl-1-phenylmethanesulfonamide (98 mg, 0.5 mmol) and cyclohex-2-en—yl acetate (77 mg, mmol) was reacted following the general method to yield 1-(cyclohex-2-en-1-yl)-*N,N*-dimethyl-1-phenylmethanesulfonamide (dr (59:41 determined by ^{1}H NMR) (105 mg, 74 %) as a colourless solid; R$_f$= 0.42 (95:5 toluene:EtOAc); m.p:119–121 °C; data for diastereomer **A**: **^{1}H NMR** (CDCl$_3$ 400 MHz) δ7.36-7.43 (5H, m, Ar-H̲); 5.69-5.72(1H, m, 3'-H̲); 5.46 (1H, bd, *J* 10.2 Hz, 2'-H̲); 3.99 (1H, d *J* 8.5 Hz, 1-H̲); 3.19-3.22 (1H, m, 1'-H̲); 2.44 (6H, s, (N-CH̲$_3$)$_2$); 2.13 (1H, dt *J* 6.3 Hz 11.0 Hz, 6'-H̲); 1.88-1.97 (2H, m, 4'H̲); 1.58-1.63 (2H, m, 1-H, 6'-H̲); **^{13}C NMR** (100 MHz) δ133.4 (Ar-C̲); 130.1 (Ar-C̲H); 129.7 (3'-C̲H); 128.8 (Ar-C̲H); 128.6 (Ar-C̲H); 127.0 (2'-C̲H); 71.8 (1-C̲H); 37.5 (N-C̲H$_3$)$_2$); 37.4 (1'-C̲H); 28.0 (6'-C̲H); 24.9 (4'-C̲H); 21.2 (5'-C̲H); data for diastereomer **B**: **^{1}H NMR**(CDCl$_3$ 400 MHz) δ7.36-7.43 (5H, m, Ar-H̲); 6.22 (1H, dd *J* 2.3 Hz 10.5 Hz, 2'-H̲); 5.78-5.83 (1H, m, 3'-H̲); 4.07 (1H, d *J* 9.9 Hz, 1-H̲); 3.12-3.17 (1H, m, 1'-H̲); 2.42 (6H, s, N-(CH̲$_2$)$_2$); 1.92-1.97 (2H, m, 4'-H̲$_2$); 1.52-1.63 (3H, 5'-H̲$_2$, 6'-H̲); 1.09-1.16 (1H, m, 6'-H̲); **^{13}C NMR** (100 MHz) δ133.6 (Ar-C̲); 130.0 (Ar-C̲H); 128.7 (3'-C̲H$_2$, 4 x Ar-C̲H); 128.6 (2'-C̲H); 72.6(1-C̲H); 36.5 (N-(C̲H$_3$)$_2$); 30.9 (1'-C̲H); 26.7 (6'-C̲H$_2$); 25.0 (4'-C̲H$_2$); 20.6 (5'-C̲H$_2$); ν_{max} (solid, cm^{-1}) 1319 & 1136 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for C$_{15}$H$_{21}$NO$_2$S [M+Na]$^+$;302.1185, found 302.1180.

1-(Cyclopent-2-en-1-yl)-*N,N*-dimethyl-1-phenylmethanesulfonamide (84)



N,N-Dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol) and cyclopent-2-en-1-yl acetate (70 mg, 0.55 mmol) was reacted following the general method to yield 1-(cyclopent-2-en-1-yl)-*N,N*-dimethyl-1-phenylmethanesulfonamide (d.r 50:50) (114 mg, 79 %) as a colourless solid; R_f=0.45 (95:5 toluene:EtOAc); m.p 88–91 °C; data for diastereomer **A**: **^{1}H NMR** (400 MHz $CDCl_3$) δ7.35-7.37 (5H, m, Ar-H); 5.77 (1H, dd *J* 2.3 Hz 5.6 Hz, 2'-H); 5.42 (1H, dd *J* 1.7 Hz 5.5 Hz, 3'-H); 3.98 (2H, d *J* 8.8 Hz, 1-H); 3.72-3.79 (1H, m, 1'-H); 2.47 (6H, s, N-(CH_3)$_2$); 2.31-2.36 (1H, m, 5'-H); 2.27-2.29 (2H, m, 4'-H_2); 1.88-1.93 (1H, m, 5'-H); ^{13}C NMR (100 MHz) δ_C 134.2 (Ar-C); 133.3 (2'-CH); 131.1 (3'-CH); 128.7 (Ar-CH); 128.6 (Ar-CH); 128.5 (Ar-CH); 71.6 (1-CH); 46.7 (1'-CH); 37.5 (N-CH_3)$_2$); 32.3 (5'-CH); 29.2 (4'-CH); data for diastereomer **B**: ^{1}H NMR (400 MHz $CDCl_3$) δ_H7.38-7.43 (5H, m, Ar-H); 6.27 (1H, dd *J* 2.2 Hz 5.7 Hz, 2'-H); 5.86 (1H, dd *J* 2.4 Hz 5.6 Hz, 3'-H); 3.98 (1H, d *J* 10.4 Hz, 1-H); 3.66-3.70 (1H, m 1'-H); 2.45 (6H, s, N-(CH_3)$_2$); 2.19-2.26 (2H, 4'-H_2);1.83-1.86 (1H, m, 5'-H); 1.22-1.32 (1H, m, 5'-H); ^{13}C NMR (100 MHz) δ_C133.7 (Ar-C); 132.9 (2'-CH); 132.2 (3'-CH); 130.0 (Ar-CH); 129.7 (Ar-CH); 128.7 (Ar-CH); 72.4 (1-CH); 46.9 (1'-CH); 37.4 (N-(CH_3)$_2$); 30.9 (4'-CH_2); 29.0 (5'-CH);ν_{max} (solid, cm^{-1}) 1316 & 1131 (sulfonamide S-N);*m/z* (ESI^+) calculated for $C_{14}H_{19}NO_2S$ $[M+Na]^+$; 288.1029, found 288.1028.

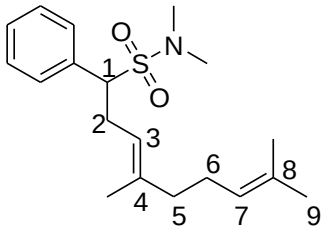
***(Z)-N,N,*4,8-Tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (85)**



N,N-Dimethyl-1-phenylmethanesulfonamide (108 mg, 0.5 mmol) and neryl acetate (119 mg, 0.55 mmol) was reacted following the general method to yield (*Z*)-*N,N,*4,8-tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide(140 mg, 83 % or 114 mg, 68 % with dppe) as a yellow oil; R_f= 0.62 (95:5 toluene:EtOAc); **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 7.35-7.42 (5H, m, Ar-H); 5.07-5.09 (1H, m, 3-H); 4.83-4.87 (1H, t, *J* 7.2, 7-H); 4.05 (1H, dd, *J*3.9 Hz 11.2 Hz, 1-H); 3.02-3.09 (1H, m, 2-H); 2.79-2.88 (1H, m, 2-H); 2.54 (6H, s, (CH_3)$_2$); 2.00-2.03 (2H, m, 5-CH_2); 1.70 (2H,

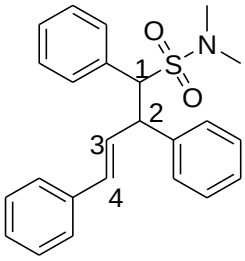
bs, 6-C$\underline{H}_2$); 1.60 (3H, s, 8-C$\underline{H}_3$); 1.57 (3H, s, 8-C$\underline{H}_3$); 1.53 (3H, s, 4-C$\underline{H}_3$). **^{13}C NMR** (100 MHz) δ 138.6 (4-$\underline{C}$); 133.6 (Ar-$\underline{C}$); 131.8 (8-$\underline{C}$); 129.6 (Ar-$\underline{C}$H); 128.8 (Ar-$\underline{C}$H); 128.6 (Ar-$\underline{C}$H); 123.9 (7-$\underline{C}$H); 119.5 (3-$\underline{C}$H); 67.6 (1-$\underline{C}$H); 37.6 (N-($\underline{C}H_3$)$_2$); 32.0(5-$\underline{C}H_2$); 28.4 (2-$\underline{C}H_2$); 26.3 (6-$\underline{C}H_2$); 25.8 (8-$\underline{C}H_3$); 23.8 (8-$\underline{C}H_3$) 17.6 (4-$\underline{C}H_3$); 16.2 (4-$\underline{C}H_3$);ν_{max} (solid, cm^{-1}) 1136 & 1329 (sulfonamide S-N); 700 (*cis* alkene); ***m/z*** (ESI$^+$) calculated for $C_{19}H_{29}NO_2S$ [M+Na]$^+$; 358.1811, found 358.1805.

***(E)-N,N*,4,8-Tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (86)**



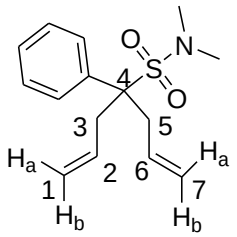
N,N-Dimethyl-1-phenylmethanesulfonamide (101 mg, mmol) and geranyl acetate (108 mg, mmol) was reacted following the general method, using dppf ligand (30 mg, 0.055 mmol) to yield (*E*)-*N,N,*4,8-tetramethyl-1-phenylnona-3,7-diene-1-sulfonamide (140 mg, 84 %) as a colourless solid; R_f= 0.6 (95:5 toluene:EtOAc); m.p: 52 – 53 °C ; **^{1}H NMR** (400 MHz) δ7.34-7.42 (5H, m, Ar-C$\underline{H}$); 4.87-4.9 (1H, m, 7-$\underline{H}$); 4.83-4.85 (1H, m, 3-$\underline{H}$); 4.07 (1H, dd *J* 3.8 Hz 11.3 Hz, 1-$\underline{H}$); 3.00-3.07 (1H, m, 2-$\underline{H}$); 2.82-2.89 (1H, m, 2-$\underline{H}$); 2.54 (6H, s, N-C$\underline{H}_3$)$_2$); 1.90-1.94 (2H, m, 6-$\underline{H}_2$); 1.83-1.89 (2H, m, 5-$\underline{H}_2$); 1.61 (3H, s, 8-C$\underline{H}_3$); 1.56 (3H, s, 4-C$\underline{H}_3$); 1.51 (3H, s, 9-C$\underline{H}_3$); **^{13}C NMR** (100 MHz) δ_C138.5 (4-$\underline{C}$); 133.6 (Ar-$\underline{C}$); 131.4 (8-$\underline{C}$); 129.6 (Ar-$\underline{C}$H); 128.7 (Ar-$\underline{C}$H); 123.9 (7-$\underline{C}$H); 118.9 (3-$\underline{C}$H); 67.4 (1-$\underline{C}$H); 39.5 (5-$\underline{C}H_2$); 37.7 (N-$\underline{C}H_3$)$_2$); 28.7 (2-$\underline{C}H_2$); 26.4 (6-$\underline{C}H_2$); 25.6 (8-$\underline{C}H_3$); 17.6 (9-$\underline{C}H_3$); 16.2 (4-$\underline{C}H_3$);ν_{max} (solid, cm^{-1}) 1323 & 1135 (sulfonamide S-N); 926 (*trans* alkene); ***m/z*** (ESI$^+$) calculated for $C_{19}H_{29}NO_2S$ [M+Na]$^+$; 358.1811, found 358.1815.

***(E)-N,N*-Dimethyl-1,2,4-triphenylbut-3-ene-1-sulfonamide**



N,N-Dimethyl-1-phenylmethanesulfonamide (99 mg, 0.5 mmol) and (±)-*trans*-diphenylallyl acetate (138 mg, 0.55 mmol) was reacted following the general method to yield (*E)-N,N*-dimethyl-1,2,4-triphenylbut-3-ene-1-sulfonamide (dr 80:20 determined by ^{1}H NMR) (172 mg, 87 %) as a colourless solid; R_f= 0.6 (95:5 toluene:EtOAc); m.p: 131 – 133 °C; data for diastereomer **A**: **^{1}H NMR** ($CDCl_3$ 400 MHz) δ 7.17-7.47 (15H, m, Ar-C<u>H</u>); 6.32-6.39 (2H, m, 3-<u>H</u>, 4-<u>H</u>); 4.61 (1H, t *J* 7.1 Hz, 2-<u>H</u>), 4.51 (1H, d *J*7.1 Hz, 1-<u>H</u>); 2.44 (6H, s, N-(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (100 MHz) δ 141.4 (Ar-<u>C</u>); 137.2 (Ar-<u>C</u>H); 132.6 (3/4-<u>C</u>H); 132.4 (Ar-<u>C</u>H); 130.7 (2 x Ar-<u>C</u>H); 128.9 (1 x Ar-<u>C</u>H); 128.8 (3/4-<u>C</u>H); 128.6 (2 x Ar-<u>C</u>H); 128.5 (2 x Ar-<u>C</u>H); 128.4 (2 x Ar-<u>C</u>H); 128.3 (2 x Ar-<u>C</u>H); 127.4 (1 x Ar-<u>C</u>H); 127.1 (1 x Ar-<u>C</u>H); 126.3 (2 x Ar-<u>C</u>H); 71.8 (1-<u>C</u>H); 50.2 (2-<u>C</u>H); 37.4 (N-(<u>C</u>H$_3$)$_2$); ν_{max} (solid, cm^{-1}) 1133 & 1459 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{24}H_{25}NO_2S$ $[M+K]^+$; 430.1238, found 430.1234.

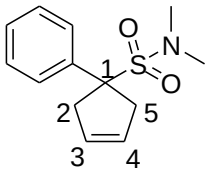
_N,N_-Dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (90)



To an oven dried round-bottomed flask flushed with nitrogen, sodium hydride 60 % in mineral oil (160 mg, 4 mmol) was added and immediately washed with petrol. To this, $Pd_2Cl_2(allyl)_2$ (4.8 mg, 0.0125 mmol) and dppb (22 mg, 0.055 mmol) was added in DME (1 mL), stirred for one hour at 25 °C. To this mixture, *N,N*-dimethyl-1-phenylmethanesulfonamide (100 mg, 0.5 mmol) and allyl acetate (250 mg, 2.5 mmol) was added in DME (1 mL) stirring at 25 °C for 48 hours. The reaction was quenched with water (0.2 mL) and purified using column chromatography to yield *N,N*-dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (131 mg, 96 %) as a colourless solid; R_f = 0.52 (95:5 toluene:EtOAc); m.p:80 – 83 °C; **^{1}H NMR** (400 MHz) δ7.59-7.61 (2H, m, Ar-C<u>H</u>); 7.35-7.42 (3H, m, Ar-C<u>H</u>); 5.86 (2H, ddt *J* 7.0 Hz 10.2 Hz 14.0 Hz, 2-C<u>H</u>, 6-C<u>H</u>); 5.19 (2H, dd *J* 1.2 Hz 17.0 Hz, 1-C<u>H</u>$_a$, 7-C<u>H</u>$_a$);

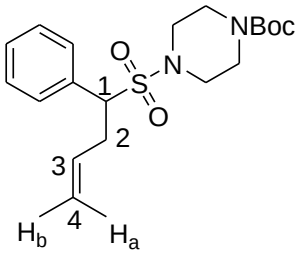
5.12 (2H, d *J* 10.3 Hz, 1-C$\underline{H}_b$, 7-C$\underline{H}_b$); 3.27 (2H, dd *J* 6.7 Hz 15.1 Hz, 3-C$\underline{H}$, 5-C$\underline{H}$); 3.01 (2H, dd *J* 7.1 Hz 15.1 Hz, 3-C$\underline{H}$, 5-C$\underline{H}$); 2.46 (6H, s, N-(C$\underline{H}_3$)$_2$); **^{13}C NMR** (100 mHz) δ 135.9 (Ar-$\underline{C}$); 132.4 (1-$\underline{C}$H, 6-$\underline{C}$H), 129.3 (Ar-$\underline{C}$H); 128.4 (Ar-$\underline{C}$H); 128.2 (Ar-$\underline{C}$H); 119.3 (1-$\underline{C}$H$_2$, 7-$\underline{C}$H$_2$); 71.7 (4-$\underline{C}$); 38.7 (N-($\underline{C}$H$_3$)$_2$); 36.7 (2-$\underline{C}$H$_2$, 7-$\underline{C}$H$_2$); ν_{max} (solid, cm^{-1}) 1312 & 1131 (sulfonamide S-N); 919 (mono-substituted alkene); ***m/z*** (ESI$^+$) calculated for $C_{15}H_{21}NO_2S$ [M+Na]$^+$; 302.1185, found 302.1190.

***N,N*-Dimethyl-1-phenylcyclopent-3-ene-1-sulfonamide (91)**



N,N-Dimethyl-4-phenylhetpa-1,6-diene-4-sulfonamide (100 mg, 0.36 mmol) and Grubbs 2nd generation catalyst (15.2 mg, 0.018 mmol) was dissolved in DCM (6 mL) and the reaction mixture was stirred at 25 °Cfor overnight. The reaction mixture was passed through a silica plug and the solvent evaporated to dryness to yield N,N-dimethyl-1-phenylcyclopent-3-ene-1-sulfonamide (84 mg, 93 %) as a grey solid; m.p: 111 – 114 °C; **^{1}H NMR** (400 MHz) δ7.50-7.52 (2H, m, Ar-C$\underline{H}$); 7.31-7.39 (3H, m, Ar-C$\underline{H}$); 5.83 (2H, s, 3-C$\underline{H}$, 4-C$\underline{H}$); 3.55 (2H, d *J* 15.7, 2/5-C$\underline{H}_2$); 3.15 (2H, d *J* 16.6, 2/5-C$\underline{H}_2$); 2.64 (6H, s, (N-(C$\underline{H}_3$)$_2$); **^{13}C NMR** (100 MHz) δ139.1 (Ar-$\underline{C}$); 129.6 (Ar-$\underline{C}$H); 128.3 (3-$\underline{C}$H, 4-$\underline{C}$H); 128.2 (Ar-$\underline{C}$H); 128.1 (Ar-$\underline{C}$H); 41.9 (2-$\underline{C}$H$_2$, 5-$\underline{C}$H$_2$); 38.9 (N-($\underline{C}$H$_3$)$_2$), ν_{max} (solid, cm^{-1}) 1312 & 1131 (sulfonamide S-N); 705 (*cis*-alkene); ***m/z*** (ESI$^+$) calculated for $C_{13}H_{17}NO_2S$ [M+Na]$^+$; 274.0872, found 274.0873.

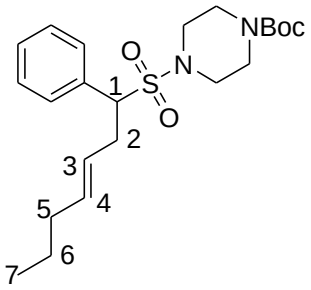
***Tert*-butyl 4-[(1-phenylbut-3-en-1-yl)sulfonyl]piperazine-1-carboxylate (92)**



Tert-butyl 4-(benzylsulfonyl)piperazine-1-carboxylate (170 mg, 0.5 mmol) and allyl acetate (57 mg, 0.55 mmol) was reacted following the general procedure to yield *tert*-butyl 4-[(1-phenylbut-3-en-1-yl)sulfonyl]piperazine-1-carboxylate (135 mg, 71 %) as a colourless solid; R_f= 0.31; (95:5 toluene:EtOAc); m.p: 88 – 91 °C; **^{1}H NMR** (400 MHz) δ_H 7.38 (5H, s, Ar-C$\underline{H}$);

5.52 (1H, ddt *J* 7.0 Hz 10.0 Hz 14.0 Hz, 3-H); 5.05 (1H, dd *J* 1.3 Hz 17.0 Hz, 4-H_a); 4.97 (1H, dd *J* 1.2 Hz 10.1 Hz, 4-H_b); 4.07 (1H, dd *J* 4.1 Hz 11.2 Hz, 1-H); 3.28 (2H, bs, N-(CH_2)$_2$); 3.17-3.23 (2H, m, N-(CH_2)$_2$); 3.06-3.12 (1H, m, 2-H); 2.96-3.02 (2H, m, N-(CH_2)$_2$); 2.85-2.98 (1H, m, 2-CH); 2.72-2.77 (2H, m, N-(CH_2)$_2$); 1.42 (9H, s, (CH_3)$_3$); **^{13}C NMR** (100 MHz) δ_C 154.3 (C=O); 133.1 (3-CH); 132.7 (Ar-C); 129.7 (Ar-CH); 129.2 (Ar-CH); 128.9 (Ar-CH); 118.4 (4-CH_2); 80.3 ((CH_3)$_3$); 68.2 (1-CH); 45.9 (N-(CH_2)$_2$); 34.4 (2-CH_2); 21.5 (N-(CH_2)$_2$); ν_{max} (solid, cm^{-1}) 1692 (C=O); 1131 & 1321 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{19}H_{28}N_2O_4S$ [M+Na]$^+$; 403.1662, found 403.1671.

***Tert*-butyl (*E*)-4-([1-phenylhept-3-en-1-yl]sulfonyl)piperazine-1-carboxylate (93)**



Tert-butyl 4-(benzylsulfonyl)piperazine-1-carboxylate (174 mg, 0.5 mmol) and *E*-2-hexenyl acetate (78mg, 0.55 mmol) was reacted following the general procedure to yield t*ert*-butyl (*E*)-4-[(1-phenylhept-3-en-1-yl)sulfonyl]piperazine-1-carboxylate (110 mg, 52 %) as a yellow oil; R_f= 0.29; (95:5 toluene:EtOAc); **^{1}H NMR** (400 MHz) δ_H 7.35 (5H, s, Ar-H); 5.41 (1H, dt *J* 6.9 Hz 15.2 Hz, 4-H); 5.07 (1H, dt *J* 7.0 Hz 15.0 Hz, 3-H); 4.07 (1H, dd *J* 4.1 Hz 11.2 Hz, 1-H); 3.18-3.22 (2H, m, N-(CH_2)$_2$); 3.15-3.21 (2H, m, N-(CH_2)$_2$); 2.95-3.04 (3H, m, 2-CH, N-CH_2); 2.66-3.04 (3H, m, 2-CH, N-CH_2); 1.77-1.84 (2H, m, 5-CH_2); 1.39 (9H, s, (C-CH_3)$_3$); 1.13-1.24 (2H, m, 6-H_2); 0.69 (3H, t *J* 7.5, 7-H_3); **^{13}C NMR** (100 MHz) δ_C 154.4 (C=O); 134.6 (4-CH); 132.9 (Ar-C); 129.7 (Ar-CH); 129.0 (Ar-CH); 128.7 (Ar-CH); 124.3 (3-CH); 80.3 (C-(CH$_3$)$_3$); 68.6 (1-CH); 45.8 (N-(CH_2)$_4$); 34.4 (5-CH_2); 33.3 (2-CH_2); 28.3 ((CH_3)$_3$); 22.3 (6-CH_2); 13.4 (7-CH_3); ν_{max} (solid, cm^{-1}) 1693 (C=O); 1145 & 1338 (S=O); ***m/z*** (ESI$^+$) calculated for $C_{22}H_{34}N_2O_2S$ [M+Na]$^+$; 445.2131, found 445.2132.

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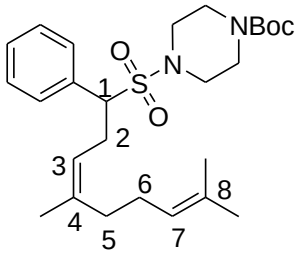
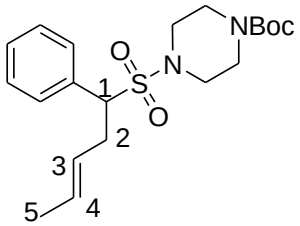
***Tert*-butyl (*Z*)-4-([4,8-dimethyl-1-phenylnona-3,7-dien-1-yl]sulfonyl)piperazine-1-carboxylate (94)**



Tert-butyl 4-(benzylsulfonyl)piperazine-1-carboxylate (175 mg, 0.5 mmol) and neryl acetate (109 mg, 0.55 mmol) was reacted following the general procedure to yield Tert-butyl (*Z*)-4-([4,8-dimethyl-1-phenylnona-3,7-dien-1-yl]sulfonyl)piperazine-1-carboxylate (127 mg, 52 %) as a yellow oil; R_f = 0.23; (95:5 toluene:EtOAc); **^{1}H NMR** (400 MHz); δ7.37 (s, 5H, Ar-H); 5.04-5.12 (1H, m 7-H); 4.80-4.87 (1H, t *J* 6.76 Hz 11.24 Hz, 3-H); 3.97 (1H, dd *J* 4.0 Hz 11.4 Hz, 1-H); 3.14-3.42 (4H, m, N-(CH_2)$_2$); 2.60-3.10 (6H, m, 2-H_2, N-(CH_2)$_2$); 1.81-2.10 (4H, m, 5-H_2, 6-H_2); 1.70 (3H, s, C-H_3); 1.60 (3H, s, C-H_3); 1.57 (3H, s, C-H_3); 1.42 (9H, s, ((CH_3)$_3$); **^{13}C NMR** (100 MHz) δ154.3 (C=O); 138.8 (4-C); 133.2 (Ar-C); 131.9 (8-C); 126.7 (Ar-CH); 129.0 (Ar-CH); 128.7 (Ar-CH); 123.9 (7-CH); 119.3 (3-CH); 80.3 (C(-CH_3)$_3$); 68.7 (1-CH); 45.8 (N-(CH_2)$_2$); 32.0 (5-CH); 28.3 ((CH_3)$_3$); 26.3 (6-CH); 25.8 (4-CH_3); 23.3 (2-CH_2); 17.7 (8-CH_3); 16.2 (8-CH)$_3$); ν_{max} (oil, cm^{-1}) 1694 (C=O); 1281 & 1134 (sulfonamide S-N); 702 (*cis*-alkene); ***m/z*** (ESI$^+$) calculated for $C_{26}H_{40}N_2O_2S$ [M+Na]$^+$; 499.2601, found 499.2587.

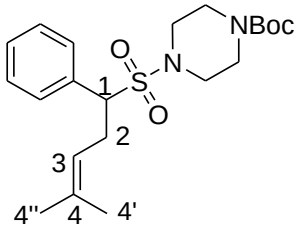
Tert-butyl (_E_)-4-([1-phenylpent-3-en-1-yl]sulfonyl)piperazine-1-carboxylate (95)



Tert-butyl 4-(benzylsulfonyl)piperazine-1-carboxylate (174mg, 0.5 mmol) and crotyl acetate (62mg, 0.55 mmol) was reacted following the general procedure to yield*tert*-butyl (*E*)-4-([1-phenylpent-3-en-1-yl]sulfonyl)piperazine-1-carboxylate (116 mg, 59 %) as a colourless solid; R_f = 0.28; m.p: 84 – 85 °C; **^{1}H NMR** (400 MHz) δ7.42-7.46 (2H, m, Ar-H); 7.34-7.39 (3H, m, Ar-H); 5.34-5.52 (1H, m, 4-H); 5.05-5.18 (1H, m, 3-H); 4.01 (1H, dd *J* 4.0 Hz 11.1 Hz, 1-H); 3.05-3.20 (4H, m, N-(CH_2)$_2$); 2.69-3.04 (6H, m, 2-H_2, N-(CH_2)$_2$); 1.51 (3H, d *J* 6.4 Hz, 5-H_3); 1.40 (9H, s, C-(CH_3)$_3$); **^{13}C NMR** (100 MHz) δ154.4 (C=O); 133.0 (Ar-C); 130.2 (Ar-CH); 129.7 (4-CH); 129.1 (Ar-CH); 128.8 (Ar-CH); 125.4 (3-CH); 80.3 (C(CH_3)$_3$); 68.6 (1-CH); 45.8 (N-CH_2); 33.2 (2-

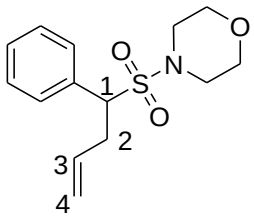
$\underline{C}H_2$); 28.4 (C-($\underline{C}H_3)_3$);17.9 (5-$\underline{C}H_3$); ν_{max} (solid, cm^{-1}) 1684 (C=O); 1337 & 1148 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{20}H_{30}N_2O_4S$ $[M+Na]^+$; 417.1818, found 417.1821.

Tert-butyl-4-([4-methyl-1-phenylpent-3-en-1-yl]sulfonyl)piperazine-1-carboxylate (96)



Tert-butyl 4-(benzylsulfonyl)piperazine-1-carboxylate (174 mg, 0.5 mmol) and prenyl acetate (70 mg, 0.55 mmol) was reacted following the general procedure to yield*tert*-butyl-4-([4-methyl-1-phenylpent-3-en-1-yl]sulfonyl)piperazine-1-carboxylate (104 mg, 52 %) as acolourless solid; R_f = 0.3; m.p: 93 – 96 °C; **^{1}H NMR** (400 MHz) δ7.44-7.48 (2H, m, Ar-$\underline{H}$); 7.36-7.41 (3H, m, Ar-$\underline{H}$); 4.84-4.90 (1H, m, 3-$\underline{H}$); 3.98 (1H, dd *J* 4.0 Hz 11.2 Hz, 1-$\underline{H}$); 3.1-3.34 (4H, m, N-($\underline{C}H_2)_2$); 2.65-3.01 (6H, m, 2-$\underline{H}_2$, N-($\underline{C}H_2)_2$); 1.55 (3H, s, 4''-$\underline{H}_3$); 1.53 (3H, s, 4'-$\underline{H}_3$); 1.38 (9H, s, C-($\underline{C}H_3)_3$); **^{13}C NMR** (100 MHz) δ154.4 (C=O); 133.5 (Ar-$\underline{C}$); 133.2 (4-$\underline{C}$); 129.7 (Ar-$\underline{C}$H); 129.0 (Ar-$\underline{C}$H); 128.7 (Ar-$\underline{C}$H); 118.0 (3-$\underline{C}$H); 80.3 ($\underline{C}$(-$CH_3)_3$); 68.2 (1-$\underline{C}H_2$); 45.8 (N-($\underline{C}H_2)_2$); 28.9 (4''-$\underline{C}H_3$); 28.3 (C-($\underline{C}H_3)_3$); 25.7 (2-$\underline{C}H_2$); 17.9 (4'-$\underline{C}H_3$); ν_{max} (solid, cm^{-1}) 1687 (C=O); 1337 & 1140 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{21}H_{32}N_2O_4S$ $[M+K]^+$; 447.1714, found 447.1738.

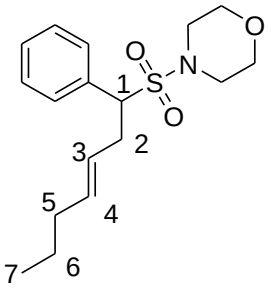
4-([1-Phenylbut-3-en-1-yl]sulfonyl)morpholine (97)



4-(Benzylsulfonyl)morpholine (120 mg, 0.5 mmol) and allyl acetate (60 mg, mmol) was reacted following the general method, to yield 4-[(1-phenylbut-3-en-1-yl)sulfonyl]morpholine (274 mg, 98 %) as a colourless solid; R_f = 0.25 (95:5 Toluene:EtOAc);m.p: 84 – 87 °C; **^{1}H NMR** (400 MHz) δ7.36-7.40 (5H, m, Ar-C$\underline{H}$); 5.52 (1H, ddt *J* 7.0 Hz 10.0 Hz 17.0 Hz, 3-$\underline{H}$); 5.04 (1H, dd *J* 1.2 Hz 17.0 Hz, 4-$\underline{H}$); 4.96 (1H, d *J* 10.1 Hz, 4-$\underline{H}$); 4.09 (2H, dd *J* 4.1 Hz 11.2 Hz, 1-$\underline{H}$); 3.53 (2H, ddd *J* 3.0 Hz 6.3 Hz 11.5 Hz, O-C$\underline{H}_2$); 3.44 (2H, ddd *J* 3.0 Hz 6.2 Hz 11.2 Hz, O-C$\underline{H}_2$); 3.08-3.13 (1H, m, 2-$\underline{H}$); 2.89 (1H, ddd *J* 6.8 Hz 11.2 Hz

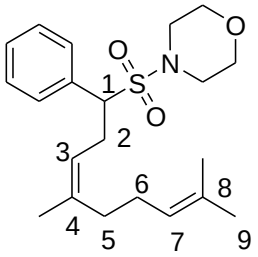
14.0 Hz, 2-H); 3.02-3.07 (2H, m, N-CH_2); 2.76 (2H, bs, N-CH_2); **^{13}C NMR** (100 MHz) δ 133.0 (3-CH); 132.8 (Ar-C); 129.7 (Ar-CH); 129.2 (Ar-CH); 128.9 (Ar-CH); 118.4 (4-CH_2); 67.9 (1-CH); 66.8 (N-(CH_2)$_2$); 46.1 (O-(CH_2)$_2$); 34.4 (2-CH_2); ν_{max} (solid, cm^{-1}) 1335 & 1125 (sulfonamide S-N); 1110 (mono-substituted alkene); ***m/z*** (ESI$^+$) calculated for $C_{14}H_{19}NO_3S$ $[M+Na]^+$; 304.0978, found 304.0978.

(*E*)- 4-([1-Phenylhept-3-en-1-yl]sulfonyl)morpholine (98)



4-(Benzylsulfonyl)morpholine (124 mg, 0.5 mmol) and *trans*-2-hexenyl acetate (82 mg, 0.55 mmol) was reacted following the general method, to yield (*E*)- 4-([1-phenylhept-3-en-1-yl]sulfonyl)morpholine (102 mg, 79 %) as a colourless solid; R_f = 0.25 (95:5 Toluene:EtOAc); m.p: 69 – 71 °C; **^{1}H NMR** (400 MHz) δ7.36-7.38 (5H, m, Ar-CH); 5.43 (1H, dt *J* 6.9 Hz 14.3 Hz, 4-H); 5.09 (1H, dt *J* 6.9 Hz 14.5 Hz, 3-H); 4.04 (1H, dd *J* 4.0 Hz 11.2 Hz, 1-H); 3.54 (2H, ddd *J* 2.8 Hz 6.3 Hz 11.2 Hz, O-CH_2); 3.45 (2H, ddd *J* 2.9 Hz 6.3 Hz 9.2 Hz, O-CH_2); 2.99-3.07 (3H, m, N-CH_2, 2-H); 2.78 (3H, m, N-CH_2, 2-H); 1.77-1.87 (2H, m, 5-H_2); 1.16-.25 (2H, m, 6-H_2); 0.71 (3H, t *J* 7.4, 7-H_3); **^{13}C NMR** (100 MHz) δ134.6 (4-CH); 132.9 (Ar-C); 129.8 (Ar-CH); 128.9 (Ar-CH); 128.7 (Ar-CH); 124.3 (3-CH); 68.4 (1-CH); 66.8 (N-(CH_2)$_2$); 46.1 (O-(CH_2)$_2$); 34.4 (5-CH_2); 33.4 (2-CH_2); 22.3 (6-CH_2); 13.4 (7-CH_3); ν_{max} (solid, cm^{-1}) 1106& 1322 (sulfonamide S-N); 952 (*trans* alkene); ***m/z*** (ESI$^+$) calculated for $C_{17}H_{25}NO_2S$ $[M+Na]^+$; 346.1447, found 346.1446.

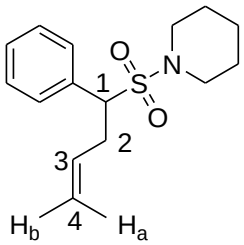
(Z)-4-([4,8-Dimethyl-1-phenylnona-3,7-dien-1-yl]sulfonyl)morpholine (99)



4-(Benzylsulfonyl)morpholine (120 mg, 0.5 mmol) and neryl acetate (118 mg, 0.55 mmol) was reacted following the general method, to yield (*Z*)-4-((4,8-dimethyl-1-phenylnona-3,7-

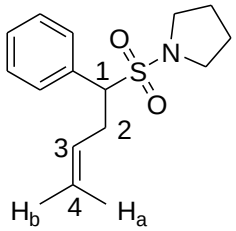
dien-1-yl)sulfonyl)morpholine (83 mg, 45 %) as a yellow oil; R_f= 0.30 (95:5 Toluene:EtOAc); **^{1}H NMR** (400 MHz) δ7.36-7.41 (5H, m, Ar-H); 5.06-5.07 (1H, m, 7-H); 4.84 (1H, t *J* 7.1, 3-H); 3.98 (1H, dd *J* 3.8 Hz 11.2 Hz, 1-H); 3.54 (3H, ddd *J* 2.9 Hz 6.4 Hz 11.5 Hz, O-CH_2)$_2$); 3.45 (2H, ddd *J* 2.9 Hz 6.3 Hz 9.1 Hz, O-(CH_2)$_2$); 3.01-3.10 (3H, m, 2-H, N-(CH_2)$_2$); 2.77-2.85 (2H, m, 2-H, N-(CH_2)$_2$); 1.98-2.14 (4H, m, 6-H_2, 5-H_2); 1.69 (3H, s); 1.59 (3H, s); 1.57 (3H, s, 4-CH_3); **^{13}C NMR** (100 MHz) δ 138.8 (4-C); 133.2 (Ar-C); 131.9 (8-C); 129.7 (Ar-CH); 129.0 (Ar-CH); 128.8 (Ar-CH); 123.9 (7-CH); 119.2 (3-CH); 68.4 (1-CH); 66.8 (N-(CH_2)$_2$); 46.1 (O-(CH_2)$_2$); 32.0 (5-CH_2); 28.6 (2-CH_2); 26.3 (6-CH_2); 25.7 (-CH_3); 23.3 (-CH_3); 17.7 (4-CH_3); ν_{max} (oil, cm^{-1}) 1339 & 1112 (sulfonamide S-N); 702 (*cis* alkene); ***m/z*** (ESI$^+$) calculated for $C_{21}H_{31}NO_3S$ [M+Na]$^+$; 400.1917, found 400.1919.

1-([1-Phenylbut-3-en-1-yl]sulfonyl)piperidine (100)



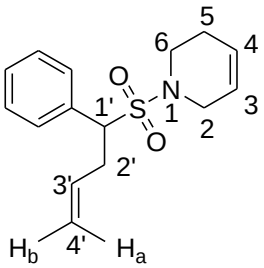
1-(Benzylsulfonyl)piperidine (119 mg, 0.5 mmol) and allyl acetate (57 mg, 0.55 mmol) was reacted following the general method, to yield 1-([1-phenylbut-3-en-1-yl]sulfonyl)piperidine (107 mg, 77 %);R_f=0.42(95:5 Toluene:EtOAc); m.p: 78–80 °C; **^{1}H NMR** (400 MHz) δ7.34-7.41 (5H, m, Ar-H); 5.53 (1H, ddt, *J* 6.9 Hz 10.0 Hz 13.9 Hz, 3-H); 5.0 (1H, dd *J* 1.4 Hz17.0 Hz, 4-H_a); 4.95 (1H, d *J* 10.0 Hz, 4-H_b); 4.05 (1H, dd *J* 3.9 Hz 11.2 Hz, 1-H); 3.06-3.12 (1H, m, 2-H); 2.97-3.03 (2H, m, N-CH_2); 2.85-2.93 (1H, m, 2-H); 2.76 (2H, bs, N-CH_2); 1.39-1.44 (6H, m, (-CH_2)$_3$); **^{13}C NMR** (100 MHz) δ133.4 (3-CH); 133.3 (Ar-C); 129.7 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 118.1 (4-CH_2); 67.7 (1-CH); 46.9 (N-(CH_2)$_2$); 34.5 (2-CH_2); 25.9 (C-(CH_2)$_2$); 23.7 (C-CH_2);ν_{max} (solid, cm^{-1}) 1132 & 1276 (sulfonamide S-N); 937 (mono-substituted alkene); ***m/z*** (ESI$^+$) calculated for $C_{15}H_{21}NO_2S$ [M+K]$^+$; 318.0925, found 318.0926.

1-([1-Phenylbut-3-en-1-yl]sulfonyl)pyrrolidine (101)



1-(Benzylsulfonyl)pyrrolidine (112 mg, 0.5 mmol) and acetate (57 mg, mmol) was reacted following the general method, to yield 1-([1-phenylbut-3-en-1-yl]sulfonyl)pyrrolidine (109 mg, 83 %) as a colourless solid; R_f= 0.48 (95:5 Toluene:EtOAc);m.p: 84 – 86 °C; **^{1}H NMR** (400 MHz) δ 7.35-7.41 (5H, Ar-H); 5.56 (1H, ddt *J* 7.0 Hz 10.0 Hz 14.0 Hz, 3-H); 5.06 (1H, dd *J* 1.3 Hz 17.0 Hz, 4-H_a); 4.97 (1H, dd *J* 9.9 Hz, 4-H_b); 4.18 (1H, dd *J* 4.0 Hz 11.2 Hz, 1-H); 3.14-3.23 (2H, m, N-CH_2); 3.10 (1H, ddd *J* 4.2 Hz 5.5 Hz 7.0 Hz, 2-H); 2.94 (1H, ddd *J* 6.9 Hz 11.2 Hz 14.3 Hz 2-H); 2.79-2.84 (2H, m, N-CH_2); 1.62-1.73 (4H, m,N-(CH_2)$_2$); **^{13}C NMR** (100 MHz) δ 133.5 (3-CH); 133.4 (Ar-C); 129.7 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 118.1 (4-CH_2); 67.1 (1-CH); 48.1 (N-(CH_2)$_2$); 34.0 (2-CH_2); 25.8 (N-(CH_2)$_2$; ν_{max} (solid, cm^{-1}) 1107 & 1334 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{14}H_{19}NO_2S$ [M+K]$^+$; 304.0768, found 304.0769

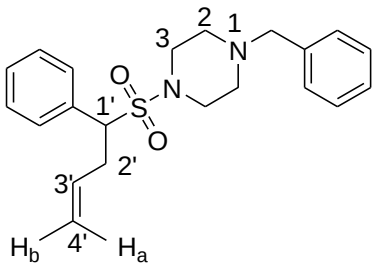
1-([1-Phenylbut-3-en-1-yl]sulfonyl)-1,2,5,6-tetrahydropyridine (102)



1-(Benzylsulfonyl)-1,2,5,6-tetrahydropyridine (116 mg, 0.5 mmol) and allyl acetate (63 mg, 0.55 mmol) was reacted following the general method, to yield 1-([1-phenylbut-3-en-1-yl]sulfonyl)-1,2,3,6-tetrahydropyridine (113 mg, 82 %) as an orange oil; R_f= 0.50 (95:5 Toluene:EtOAc); **^{1}H NMR** (400 MHz) δ7.34-7.41 (5H, Ar-H); 5.68-5.71 (1H, m, 4-H); 5.52-5.58 (1H, m, 3'-H); 5.47-5.51 (1H, m, 5-H); 5.04 (1H, dd *J* 1.1 Hz 17.0 Hz, 4'-H_a); 4.95 (1H, d *J* 10.0 Hz, 4'-H_b); 4.11 (1H, dd *J* 4.1 Hz 11.0 Hz, 1'-H); 3.61 (1H, dt *J* 2.5 Hz 5.1 Hz, 6-H);3.35-3.36 (1H, m, 6-H); 3.06-3.14 (2H, m, 2'-H, 3-H); 2.87-2.95 (2H, m, 2'-H, 3-H); 2.04-2.00 (1H, m, 2-H); 1.84-1.88 (1H, m, 2-H); **^{13}C NMR** (100 MHz) δ 133.3 (3'-CH); 133.1 (Ar-C); 129.7 (Ar-CH); 128.8 (Ar-CH); 128.7 (Ar-CH); 125.2 (5-CH); 123.3 (4-CH); 118.2 (4'-CH_2);67.8 (1'-CH); 44.7 (6-CH_2); 42.7 (3-CH_2); 34.3 (2'-CH_2); 25.6 (2-CH_2); ν_{max} (oil, cm^{-1}) 1144 & 1309 (sulfonamide S-

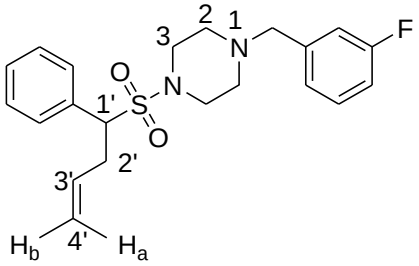
N); 920 (mono-substituted alkene); ***m/z*** (ESI$^+$) calculated for $C_{15}H_{19}NO_2S$ [M+Na]$^+$; 300.1029, found 300.1029.

1-Benzyl-4-([1-phenylbut-3-en-1-yl]sulfonyl)piperazine (103)



1-Benzyl-4-(benzylsulfonyl)piperazine (165 mg, 0.5 mmol) and allyl acetate (57 mg, 0.55 mmol) was reacted following the general method, to yield 1-benzyl-4-((1-phenylbut-3-en-1-yl)sulfonyl)piperazine (141 mg, 76 %) as a colourless solid; R_f=; m.p: 74 – 78 °C; **^{1}H NMR** (400 MHz) δ7.36-7.39 (5H, m, Ar-H); 7.23-7.31 (5H, m, Ar-H); 5.53 (1H, ddt *J* 7.0 Hz 10.0 Hz 14.0 Hz, 3'-H); 5.02 (1H, d *J* 10.2 Hz, 4'-H_a); 4.96 (1H, d *J* 10.2 Hz, 4'-H_b); 4.07 (1H, dd *J* 4.0 Hz 11.2 Hz, 1'-H); 3.44 (2H, bs, 1-H_2); 3.05-3.13 (3H, m, 2'-H,3-H_2); 2.85-2.94 (3H, m, 2'-H,3-H_2); 2.22-2.36 (4H, m, 2-H_2); **^{13}C NMR** (100 MHz) δ137.4 (Ar-C); 133.2 (3'-CH); 132.9 (Ar-C); 129.8 (Ar-CH); 129.1 (Ar-CH); 128.9 (Ar-CH); 128.7 (Ar-CH); 128.3 (Ar-CH); 127.3 (Ar-CH); 118.2 (4'-CH_2); 68.0 (1'-CH); 62.7 (1-CH_2); 52.9 (2-CH_2); 46.0 (3-CH_2); 34.5 (2'-CH_2); ν_{max} (solid, cm^{-1}) 1147 & 1340 (sulfonamide S-N); 959 (mono-substituted alkene); ***m/z*** (ESI$^+$) calculated for $C_{21}H_{26}N_2O_2S$ [M+H]$^+$; 371.1788, found 371.1799.

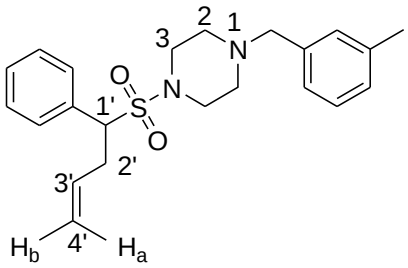
1-(3-Fluorobenzyl)-4-([1-phenylbut-3-en-1-yl]sulfonyl)piperazine (104)



1-(Benzylsulfonyl)-4-(3-fluorobenzyl)piperazine (174 mg, 0.5 mmol) and allyl acetate (60 mg, 0.55 mmol) was reacted following the general method to yield 1-(3-fluorobenzyl)-4-([1-phenylbut-3-en-1-yl]sulfonyl)piperazine (130mg, 67 %) as an orange oil; R_f= 0.20 (95:5 toluene:EtOAc); **^{1}H NMR** (400 MHz) δ7.38-7.39m (5H, m, Ph-H); 7.17-7.27 (1H, m, Ar-H); 6.91-7.00 (3H, m, Ar-H); 5.54 (1H, ddt *J* 7.0 Hz 9.9 Hz 17.0 Hz 3'-H); 5.0 (1H, d *J* 17 Hz, 4'-H_a);

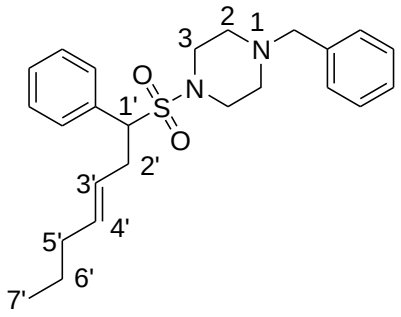
4.96 (1H, d *J* 10.0 Hz, 4'-$\underline{H}_b$); 4.08 (1H, dd *J* 3.9 Hz 11.0 Hz, 1'-$\underline{H}_2$); 3.47 (2H, s, 1-$\underline{H}_2$); 3.06-3.16 (3H, m, 2'-$\underline{H}$, N-C$\underline{H}_2$); 2.86-2.94 (2H, m, 2'-C$\underline{H}$, N-C$\underline{H}_2$); 2.22-2.40 (4H, m, N-(C$\underline{H}_2$)$_2$); **^{13}C NMR** (100 MHz) δ_C164.1 (Ar-$\underline{C}$); 161.7 (Ph-$\underline{C}$); 140.3 (Ar-$\underline{C}$F, d J_{CF} 6.7); 133.2 (Ph-$\underline{C}$H); 130.8 (Ph-$\underline{C}$H); 129.7 (Ar-$\underline{C}$H); 128.7 (Ph-$\underline{C}$H); 124.5 (Ar-$\underline{C}$H); 118.3 (4'-$\underline{C}$H$_2$); 115.7 (Ar-$\underline{C}$H, d J_{CF} 21.2); 114.3 (Ar-$\underline{C}$H, d J_{CF} 21.2); 68.1 (1'-$\underline{C}$H); 62.1 (1-$\underline{C}$H); 52.9 (N-($\underline{C}$H$_2$)$_2$); 45.9 (N-($\underline{C}$H$_2$)$_2$); 34.2 (2'-$\underline{C}$H$_2$)); ν_{max} (oil, cm^{-1}) 1486 (C-F); 1340 & 1140 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{21}H_{25}FN_2O_2S$ [M+H]$^+$; 389.1694, found 389.1695.

1-(3-Methylbenzyl)-4-([1-phenylbut-3-en-1-yl]sulfonyl)piperazine (105)



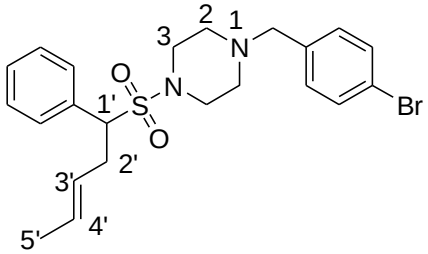
1-(Benzylsulfonyl)-4-(3-methylbenzyl)piperazine (174 mg, 0.5 mmol) and allyl acetate (60 mg, 0.55 mmol) was reacted following the general method to yield 1-(3-methylbenzyl)4-([1-phenylbut-3-en-1-yl]sulfonyl)piperazine (100 mg, 53 %) as an orange oil; R_f = 0.35 (CH_2Cl_2:EtOAc 95:5); **^{1}H NMR** (400 MHz) δ7.36-7.39 (5H, m, Ar-$\underline{H}$); 5.54 (1H, ddt *J* 7.0 Hz 10.0 Hz 13.9 Hz, 3'-$\underline{H}$); 5.05 (1H, dd *J* 1.2 Hz 17.0 Hz, 4'-$\underline{H}_a$); 4.96 (1H, bd *J* 10.5 Hz, 4'-$\underline{H}_b$); 4.07 (1H, dd *J* 3.9 Hz 11.2 Hz, 1'-$\underline{H}$); 3.40 (2H, s, 1-H_2); 3.05-3.12 (3H, m, 2'-$\underline{H}$, N-$\underline{H}_2$); 2.85-2.93 (3H, m, 2-$\underline{H}$, N-$\underline{H}_2$); 2.32-2.35 (5H, s, Ar-C$\underline{H}_3$, N-$\underline{H}_2$); 2.23-2.28 (2H, m, N-$\underline{H}_2$); **^{13}C NMR** (100 MHz) δ 137.9 (Ar-$\underline{C}$); 137.2 (Ar-$\underline{C}$); 133.2 (3-$\underline{C}$H); 129.9 (Ar-$\underline{C}$H); 129.7 (Ph-$\underline{C}$H); 128.9 (Ph-$\underline{C}$H); 128.7 (Ph-$\underline{C}$H); 128.1 (Ar-$\underline{C}$H); 128.0 (Ar-$\underline{C}$H); 126.3 (Ar-$\underline{C}$H); 118.2 (4-$\underline{C}$H$_2$); 68.1 (1-$\underline{C}$H); 62.7 (Ar-$\underline{C}$H$_2$); 52.9 (N-($\underline{C}$H$_2$)$_2$); 45.9 (N-($\underline{C}$H$_2$)$_2$); 34.4 (2-$\underline{C}$H$_2$); 21.4 (Ar-$\underline{C}$H$_3$); ν_{max} (oil, cm^{-1}) 1341 & 1145 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{22}H_{28}N_2O_2S$ [M+H]$^+$; 385.1944, found 385.1943.

(*E*)-1-Benzyl-4-([1-phenylhept-3-en-1-yl]sulfonyl)piperazine (106)



1-Benzyl-4-(benzylsulfonyl)piperazine (165 mg, 0.5 mmol) and *E*-2-hexenyl acetate acetate (60 mg, 0.55 mmol) was reacted following the general method, to yield (*E*)-1-Benzyl-4-([1-phenylhept-3-en-1-yl]sulfonyl)piperazine (120 mg, 58 %) as a colourless solid; R_f = 0.22 (toluene:EtOAC); **^{1}H NMR** (400 MHz) δ7.34 (5H, m, Ar-H); 7.22-7.31 (5H, m, Ar-H); 5.38 -5.45 (1H, m, 4'-H); 5.05-5.13 (1H, m, 3'-H); 4.00 (1H, dd *J* 3.9 Hz 11.2 Hz, 1'-H); 3.42 (2H, s, 1-H_2); 2.99-3.08 (3H, m, 2'-H, N-CH_2); 2.79-2.85 (3H,m, 2'H, N-CH_2); 2.22-2.32 (N-(CH_2)$_2$); 1.20 (2H, ddd *J* 2.4 Hz 7.4 Hz 9.8 Hz, 6'-H_2); 0.74 (3H, t *J* 7'-H_3); **^{13}C NMR** (100 MHz) δ137.5 (Ar-C); 134.5 (4'-CH); 133.2 (Ar-CH); 129.8 (Ar-CH); 129.1 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 128.3 (Ar-CH); 127.2 (Ar-CH); 124.5 (3'-CH); 68.5 (1'-CH); 62.7 (1-CH_2); 52.9 (N-(CH_2)$_2$); 46.0 (N-(CH_2)$_2$); 34.4 (5'-CH_2); 33.4 (2'-CH_2); 22.3 (6'-CH_2); 13.4 (7'-CH_2); ν_{max} (solid, cm^{-1}) 1147& 1340 (sulfonamide S-N); ***m/z*** (ESI$^+$) calculated for $C_{24}H_{32}N_2O_2S$ $[M+H]^+$; 413.2257, found 413.2257.

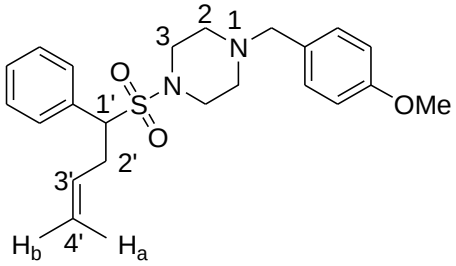
(*E*)-1-(4-Bromobenzyl)-4-([1-phenylpent-3-en-1-yl]sulfonyl)piperazine (107)



1-(Benzylsulfonyl)-4-(3-bromobenzyl) piperazine (100 mg, 0.244 mmol) and allyl acetate (36.4 mg, 0.0.29 mmol) was reacted following the general method to yield(0.71 g, 63 %) as an orange oil R_f = 0.27 (95:5 toluene:EtOAc); 1-(4-bromobenzyl)-4-([1,4diphenylpent-3-en-1-yl]sulfonyl)piperazine. R_f = 0.27 (toluene:EtOAc 95:5); m.p: 88 – 90 °C;**^{1}H NMR** (400 MHz) δ7.3-7.42 (7H, m, Ar-H); 7.14-7.29 (2H, m, Ph-H);5.43-5.54 (1H, m, 3'-H); 5.06-5.16 (1H, m, 4'-H); 4.00 (1H, dd *J* 3.9 Hz 11.1 Hz, 1'-H); 3.36 (2H, s, 1-H_2); 2.98-3.07 (3H, m, 2'-H, N-(CH_2); 2.76-2.84 (3H, m, N-CH_2); 2.20-2.30 (4H, m,N-(CH_2)$_2$); 1.52 (3H, d *J* 6.3 Hz, 5'-H_3); **^{13}C**

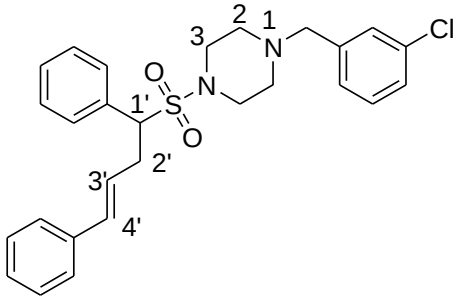
NMR (100 MHz) δ_C 136.6 (Ph-C); 133.1 (Ar-C); 134.4 (Ar-CH); 130.7 (Ph-CH); 129.8 (3'-CH); 128.9, 128.8, 128.7, 128.6, 128.4 (Ar-CH, Ph-CH); 125.5 (4'-CH); 121.1 (C-Br); 68.5 (1'-CH); 61.9 (1-CH_2); 52.8 (N-(CH_2)$_2$); 45.9 (N-(CH_2)$_2$); 33.4 (2'-CH_2); 17.9 (5'-CH_3);ν_{max} (solid, cm^{-1}) 1148 & 1340 (sulfonamide S-N); 960 (mono-substituted alkene); 704-730 (C-Br); ***m/z*** (ESI^+) calculated for $C_{22}H_{27}BrN_2O_2S$ $[M+H]^+$; 463.1049, found 463.1049.

1-(4-Methoxybenzyl)-4-([1-phenylbut-3-en-1yl]sulfonyl)piperazine (108)



1-(Benzylsulfonyl)-4-(4-methoxybenzyl) piperazine (180 mg, 0.5 mmol) and allyl acetate (58 mg, 0.55 mmol) was reacted following the general method to yield 1-(4-Methoxybenzyl)-4-([1-phenylbut-3-en-1yl]sulfonyl)piperazine (71 mg, 37 %) as an orange oil; R_f = 0.25 (DCM:MeOH 98:2); **^{1}H NMR** (400 MHz) δ7.34-7.43 (5H, m, Ph-H); 7.13 (2H, d *J*8.6 Hz, Ar-H); 6.83 (2H, dd *J* 1.9 Hz 6.7 Hz, Ar-H); 5.52 (1H, ddt *J* 7.1Hz 10.0 Hz 13.9 Hz, 3'-H); 5.02 (1H, dd *J* 1.7 Hz 17.1 Hz, 4-H_a); 4.96 (1H, dd *J* 1.2 Hz 10.4 Hz, 4-H_b); 3.78 (3H, s, -OCH_3); 3.36 (2H, s, 1-H_2); 3.03-3.14 (2H, m, 2'-H, 3-H); 2.84-2.92 (2H, m, 2'-H, 3-H); 2.19-2.32 (4H, m, 2-(H_2)$_2$); **^{13}C NMR** (100 MHz) δ158.8 (C-OMe); 133.2 (3'-CH); 132.9 (Ph-C); 130.3 (Ar-CH); 129.7 (Ph-CH); 129.4 (Ar-C); 128.9 (Ph-CH); 128.7 (Ph-CH); 118.2 (4'-CH_2); 113.5 (Ar-CH); 68.0 (1'-CH); 62.1 (1-CH_2); 55.3 (-OCH_3); 52.7 (2-(CH_2)$_2$); 46.0 (2-(CH_2)$_2$); 34.5 (2'-CH_2); ν_{max} (oil, cm^{-1})

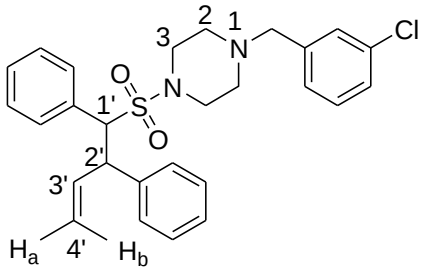
(*E*)-1-(3-Chlorobenzyl)-4-([1,4-diphenylbut-3-en-1-yl]sulfonyl)piperazine (109-linear)



1-(Benzylsulfonyl)-4-(3-chlorobenzyl) piperazine (100 mg, 0.27 mmol) and allyl acetate (50 mg, 0.30 mmol) was reacted following the general method to yield 1-(4-chlorobenzyl)-4-((1,4diphenylbut-3-en-1-yl)sulfonyl)piperazine as a mixture of linear:branched compound

(49 mg, 37 % linear, 33 mg, 25 %, branched) as an orange oil; Data for linear isomer: R_f = 0.26 (95:5 toluene:EtOAc); m.p: 102 – 104 °C; **^{1}H NMR** (400 MHz) δ7.37-7.45 (5H, m, Ph-H); 7.15-7.26 (9H, m, Ph-H, Ar-H); 7.09-7.11 (1H, m, Ar-H); 6.42 (1H, d *J* 6.42 Hz, 4'-H); 5.91 (1H, dt *J* 7.5, 14.8, 3'-H); 4.12 (1H, dd *J* 3.9 Hz 11.0 Hz, 1'H); 3.40 (2H, s, 1-H_2); 3.00-3.11 (3H, m, 2'-H, N-CH_2); 2.86 (2H, bs, 2'-H, N-CH_2); 2.31-2.36 (2H, m, N-CH_2); 2.22-2.27 (N-CH_2); **^{13}C NMR** (100 MHz) δ136.9 (Ar-C); 134.2 (Ph-C-Cl); 133.3 (4'-CH); 132.9 (Ph-C); 129.7 (Ar-CH); 129.8 (Ph-CH); 129.1 (Ar-CH); 129.0 (Ar-CH); 128.9 (Ar-CH); 128.8 (Ar-CH); 128.5 (Ar-CH); 127.5 (Ar-CH); 127.4 (Ph-CH); 127.1 (Ar-CH); 126.2 (Ph-CH); 124.8 (3'-CH); 68.3 (1'-CH); 62.1 (1-CH_2); 52.9 (N-(CH_2)$_2$); 45.9 (N-CH_2)$_2$); 33.9 (2'-CH_2); υ_{max} (solid, cm^{-1}) 1149 & 1341 (sulfonamide S-N); 960 (mono-substituted alkene); 567-690 (C-Cl); ***m/z*** (ESI$^+$) calculated for $C_{27}H_{29}ClN_2O_2S$ $[M+H]^+$; 481.1711, found 481.1712.

1-(4-Chlorobenzyl)-4-([1,2-diphenylbut-3-en-2-yl]sulfonyl)piperazine (109-branched)



Data for branched isomer: (dr 1:0.8 **A:B**) R_f = 0.21 (95:5 toluene:EtOAc); m.p: 96 – 98 °C;data for diastereomer **A**; **^{1}H NMR** (400 MHz $CDCl_3$) δ6.98-7.38 (14 H, m, Ar-H, Ph-H); 6.34 (1H, ddd *J* 8.9, 10.0, 17.0, 3'-H); 5.22 (1H, d *J* 16.8 Hz,4'-H_b); 5.17 (1H, d *J* 10.0 Hz, 4'-H_a); 4.26-4.33 (2H, m, 1'-H,2'-H);3.35 (2H, s, 1-H_2); 2.92-3.02 (2H, m, N-(CH_2)$_2$); 2.69 (2H, bs, N-(CH_2)$_2$); 2.12-2.24 (4H, m, N-(CH_2)$_2$); **^{13}C NMR** (100 MHz) δ141.1, 140.5, 139.8 (Ar-C); 138.9 (3'-CH); 134.2 (Ar-C); 130.7, 129.9, 129.5, 128.9, 128.5, 128.4, 128.3, 128.2, 127.4, 127.0, 126.5 (Ar-CH); 116.3 (4'-CH_2); 72.9 (1'-CH); 62.0 (1-CH_2); 52.8 (2'-CH); 52.7 (N-CH_2)$_2$); 45.7 (N-CH_2); data for diastereomer**B**:**^{1}H NMR** (400 MHz) δ6.98-7.38 (14H, m Ar-H, Ph-H); 5.95 (1H, ddd *J* 8.4 Hz 10.2 Hz 16.9 Hz, 3'-H); 5.01 (1H, d *J* 10.0 Hz, 4'H_a); 4.99 (1H, d *J* 17.0 Hz, 4-H_b); 4.38-4.45 (2H, m, 1'-H, 2'-H); 3.33 (2H, s, 1-H_2); 2.92-3.02 (2H, m, N-(CH_2)$_2$); 2.69 (2H, bs, N-(CH_2)$_2$); 2.12-2.24 (4H, m, N-(CH_2)$_2$);**^{13}C NMR** (100 MHz) δ137.0 (3'-CH); 133.1 (Ar-C); 132.4 (Ar-C);130.7, 129.9, 129.5, 128.9, 128.5, 128.4, 128.3, 128.2, 127.4, 127.0, 126.5 (Ar-CH); 117.7 (4'-CH_2); 73.5 (1'-CH); 51.2 (2'-CH); 45.7 (N-(CH_2)$_2$); 29.7 (N-(CH_2)$_2$); ν_{max} (solid, cm^{-1})

1152 & 1335 (sulfonamide S-N); 960 (mono-substituted alkene); 597-695 (C-Cl); ***m/z*** (ESI^+) calculated for $C_{27}H_{29}ClN_2O_2S$ $[M+H]^+$; 481.1711, found 481.1711.

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Chapter 3: Transition-Metal-Free Coupling/Intramolecular Annulation of Arynes in the synthesis of sultams

1. Introduction

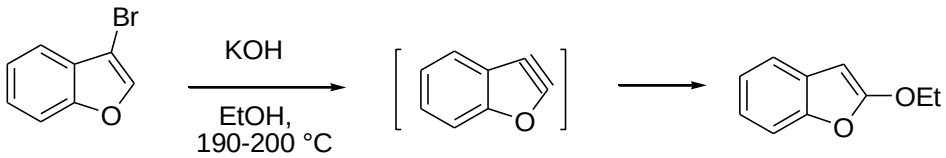
1.1 Benzene generation

Benzyne **1** is a highly reactive species formed by removal of two *ortho*-hydrogen substituents from the system.[1] Arynes are usually described as having a strained triple bond; however, they possess some biradical[2] or zwitteric ion[3] character as well. The discovery of benzyne led to rapid developments in synthetic methodologies to make this highly reactive intermediate useful for organic synthesis. Varieties of natural products have been prepared using arynes as intermediates. The exploitation of these reactive species have been extensively studied over the past seven decades.

1

Fig 1

Stoermer and Kahlert published the first indication of aryne in 1902.[4] The reaction was undertaken by treating 3-bromobenzofuran (**2**) (Scheme 1) with bases in absolute ethanol and generated 2-ethoxybenzofuran (**4**). This product was unexpected as the desired reaction was the formation of the 3-ethoxy-derivative. This was the first example of benzyne chemistry.



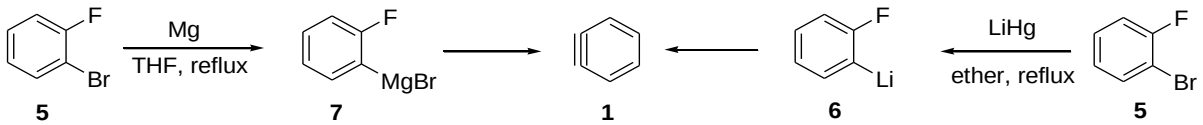
2 **3** **4**

Scheme 1

Over the year's numerous new methods were developed to generate benzyne. Some of the more popular methods for generating arynes are detailed below.

In 1955, Wittig and Pohmer[5,6] generated benzyne by treating 2-bromofluorobenzene with organometallic bases. Treatment of 2-bromofluorobenzene **5** with a metal (either lithium or magnesium) generated a metallated intermediate **6** or **7**, (Scheme 2) which then underwent

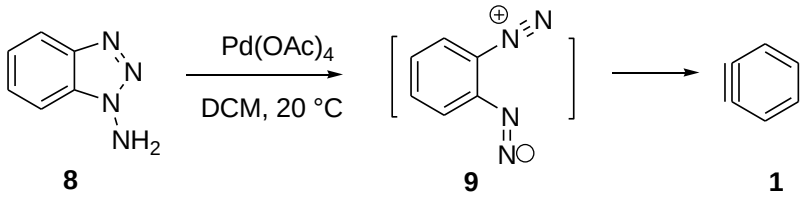
elimination to form benzyne **1**. This procedure has a remarkable advantage over the mono-halogenated method, as regiocontrol of aryne formation is viable.



5 **7** **1** **6** **5**

Scheme 2

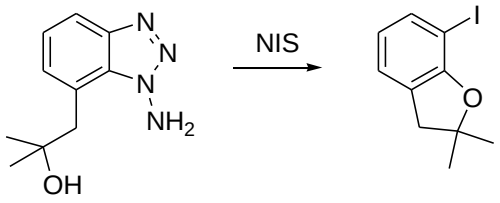
The formation of aryne from aminobenzotriazole **8** was first reported by Rees and co-workers in 1969.[7] The procedure includes an oxidation of triazole **8** producing nitrene intermediate **9**, which then fractures into two molecule of nitrogen and benzyne (Scheme 3).



8 **9** **1**

Scheme 3

Despite the formation of benzyne in excellent yield in a short time, the use of stoichiometric amounts of toxic metals such as lead has strictly limited the use of this method in synthesis. The application of oxidative conditions would probably also prove problematic with some sensitive substrates. This process has also been shown to occur with *N*-iodosuccinimide (NIS), however iodine integration into the final product **11** has been shown to occur (Scheme 4).[8]

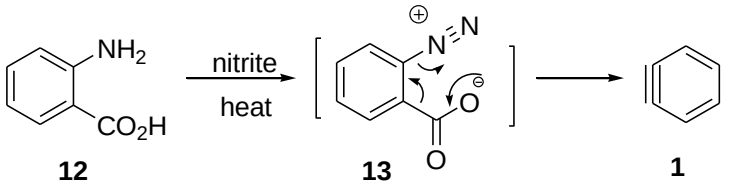


10 **11**
95 %

Scheme 4

In 1963, Friedman *et al*. reported the generation of arynes by treating anthranilic acid **10** with sodium nitrite. Formation of the zwitterionic intermediate **13** was first observed, then

intermediate **13** decomposes on heating to produce benzyne, CO_2 and nitrogen (Scheme 5).[9] Although, this strategy is a clean and efficient procedure for the formation of aryne, the zwitterionic intermediate **13**, is highly unstable and extremely explosive.[10,11,12]

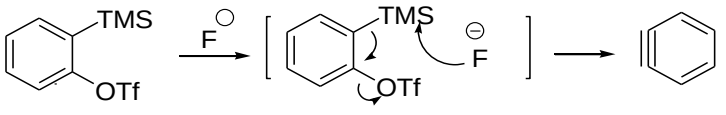


12 **13** **1**

Scheme 5

All of the methods described above have major drawbacks, which have restricted the development of aryne chemistry. The requirement of strong bases,[5,6] oxidants,[7] metallic reagents,[5,6] high temperatures[4] or explosive intermediates[9] (extreme caution during preparation) limited the compatibility of aryne chemistry in use.

In 1983, Kobayashi reported a novel method showing that 2- (trimethylsilyl)phenyl trifluoromethanesulfonate **14** would successfully desilylate and eliminate triflate to generate benzyne **1** in high yield under extremely mild conditions when treated with a suitable fluoride source.[13] Advantages are that this methodology tolerates several motifs which may be incompatible with previously described conditions, as reactions could be performed at room temperature, without need for harsh reagents. Moreover, the reaction carried out smoothly with a range of fluoride sources (cesium fluoride, TBAF, TBAT, and potassium fluoride with 18-crown-6)[16-25] in variouse solvents (DME, toluene, THF, MeCN). [16-25]



14 **15** **1**

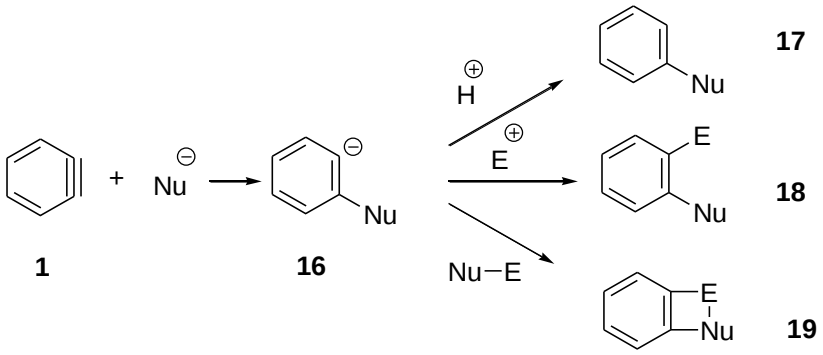
Scheme 6

1.2 Arynes reactivity

1.2.1 Nucleophile addition

Benzyne is an excellent electrophile that will react with many nucleophiles. Reaction of benzyne with nucleophile results in the formation of a mono-substituted arene **17**. When an

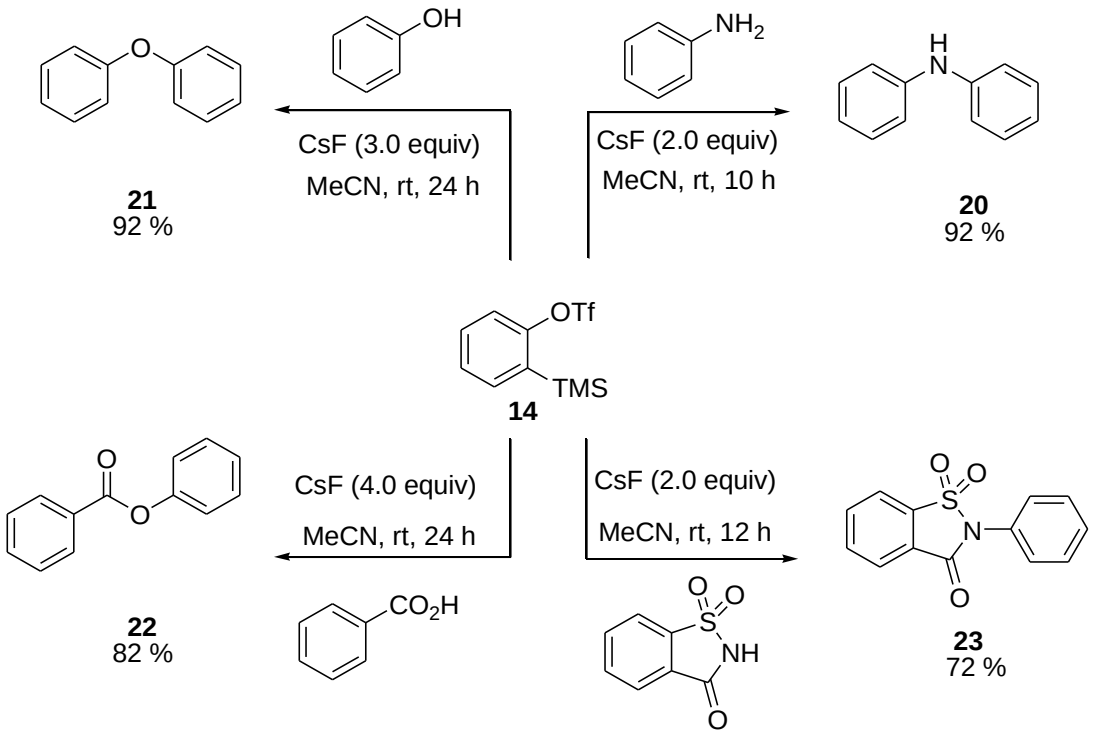
electrophile introduced in the reaction (three-component coupling) *ortho*-disubstituted arenes **18** are formed. Alternatively, both nucleophile and electrophile parts can be on the same compound resulting in cyclised products **19** (Scheme 7).[14]



Scheme 7

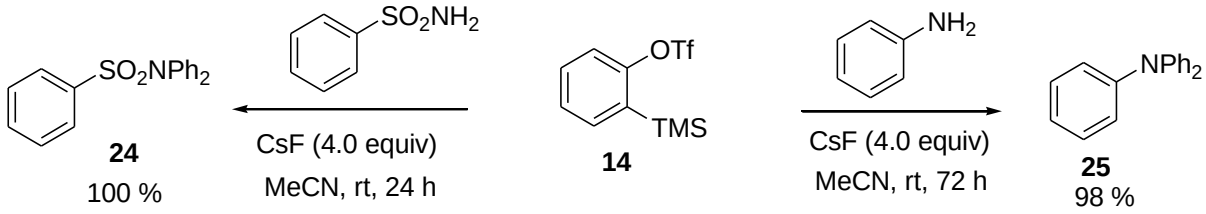
The simple addition of nucleophilic species to benzyne has been extensively studied over the last century and numerous examples of each of these processes have been reported.

In 2006, Liu and Larock employed many classes of nucleophiles with 2-(trimethylsilyl) phenyl triflate **14** as the benzyne precursor; which gave products in good to excellent yields (Scheme 8).[15]



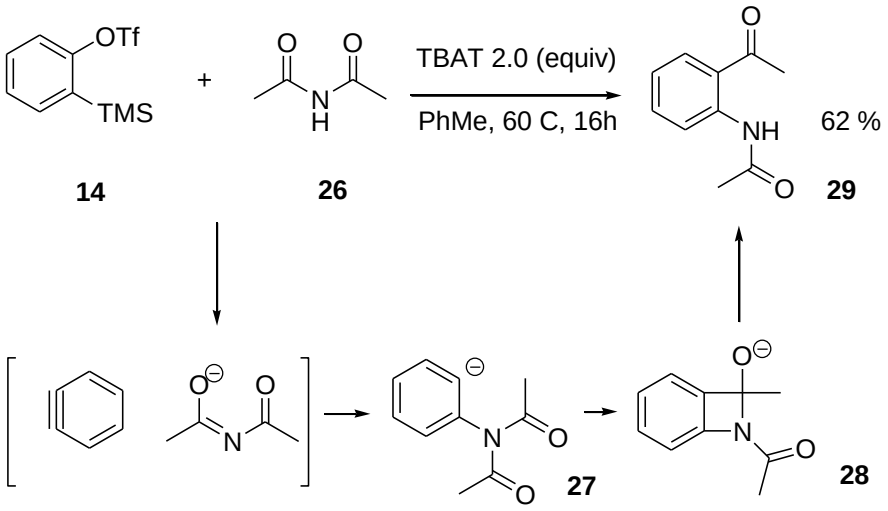
Scheme 8

Double arylation occurred with some species; using primary sulfonamides and an excess of silylaryltriflate, one obtains the corresponding diarylation product in high yield in a fairly short reaction time compared with the times required for the *N*-arylation of amines (Scheme 9).[15]



Scheme 9

In 2016, Stoltz *et al.* reported the insertion of arynes into acetylacetamide **26** (Scheme 10), using arynes which generated *insitu* from **14** under mild reaction conditions. The reaction proceeds by deprotonation of the acetylacetamide in the presence of a fluoride, resulting **27** attacks the benzyne generating **28**. Strained **28** ring opens forming ketoamide **29**.[16]

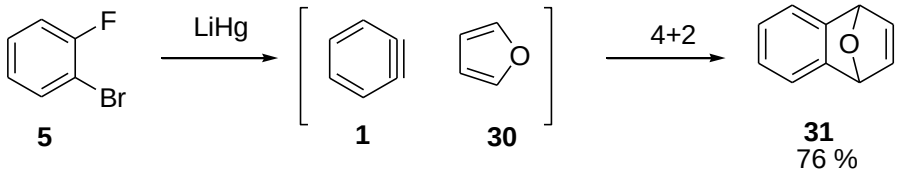


Scheme 10

1.2.2 Peri-cyclic reactions

A common way to verify wether arynes are formed efficiently is to subject them to cycloaddition (Diels-Alder) condition using furan. This reaction was initially reported by

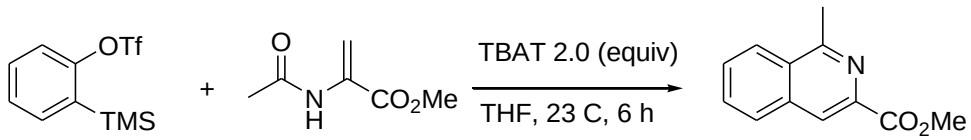
Wittig and Pohmer in 1955 (Scheme 11).[5] They used 2-bromofluorobenzene **5** as the benzyne precursors and reacted it with furan to yield cycloaddition product **31** in 76% yield.



5 **1** **30** **31** 76 %

Scheme 11

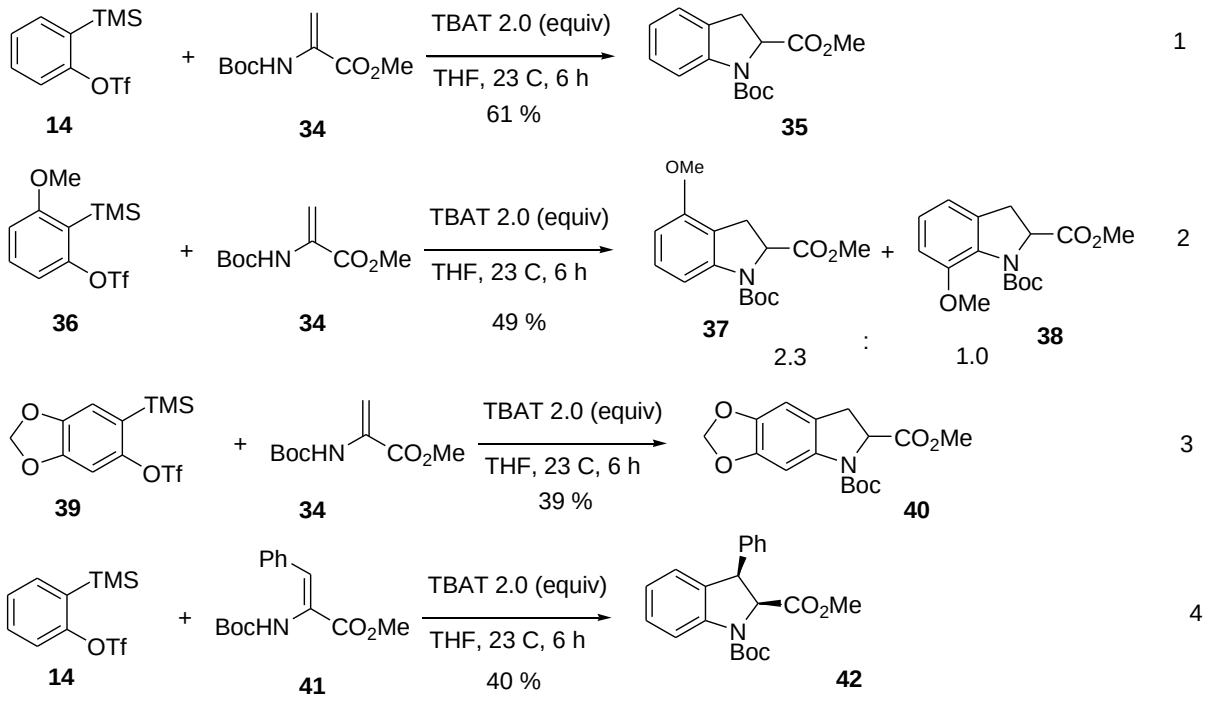
In the past, several examples of [4 + 2] cycloadditions with benzynes have been published in the literature. The diene substrate sphere is widely enlarging, and currently includes several dienes containing sulfur, nitrogen and oxygen,[7,17,39] as well as some aromatic structures.[18] In addition, aryne cyclisations have proved to be an exceptional method for gaining metal-free access to heterocyclic molecules.[19] In 2008 Stoltz and co-workers reported the synthesis of isoquinoline **33** via aryne annulations. **33** arises from a Diels-Alder reaction between the *N*-acyl enamine **32** and aryne **14** followed by dehydrative aromatization. Under optimized conditions (TBAT, THF, 23 °C, 6 h), reaction of benzyne and *N*-acetyl dehydroalanine ester gave **33** in excellent yield (Scheme 12).[20]



14 **32** **33** 87 %

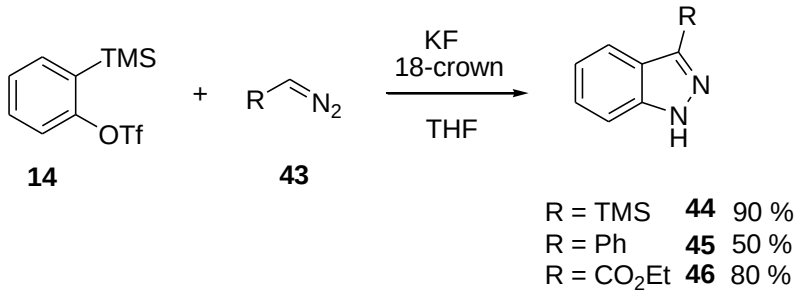
Scheme 12

In the same report, Stoltz *et al.* predicted the formation of indolines via [2+3] cycloaddition from *N*-carbamoyl dehydroalanine esters (Scheme 13). These substrates, when reacted with silyl aryl triflate **14** in the presence of TBAT, in THF, under mild condition, produced an indoline adduct arising from a formal [3+2] cycloaddition (eq 1-3). Moreover, dehydrophenylalanine derivative afforded the corresponding 1,2,3-trisubstituted indoline as a single isolated diastereoisomer (eq 4). Interestingly, an unexpected *cis* stereochemical relationship is observed, they believed the reason behind this is that protonation occurs from the less-hindered face of the enolate adduct, *anti* to the bulky α-substituent.[20]



Scheme 13

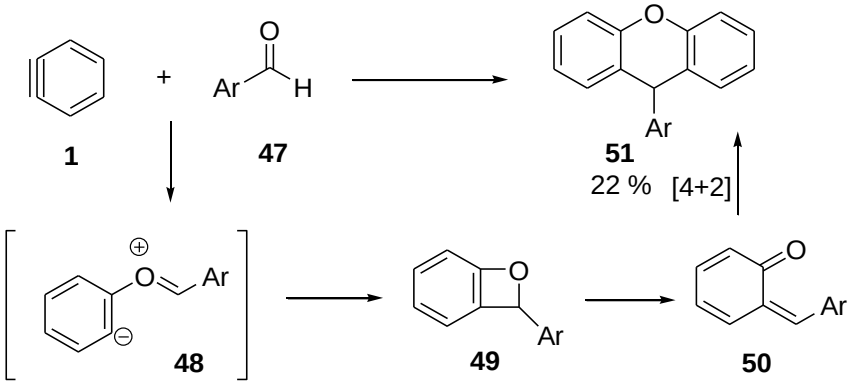
In the same year, Yamamoto and Jin reported a [3+2] cycloaddition between substituted derivatives of diazomethane **43** and affording 1*H*-indazoles in good to excellent yields and regioselectivities (Scheme 14).[21]



Scheme 14

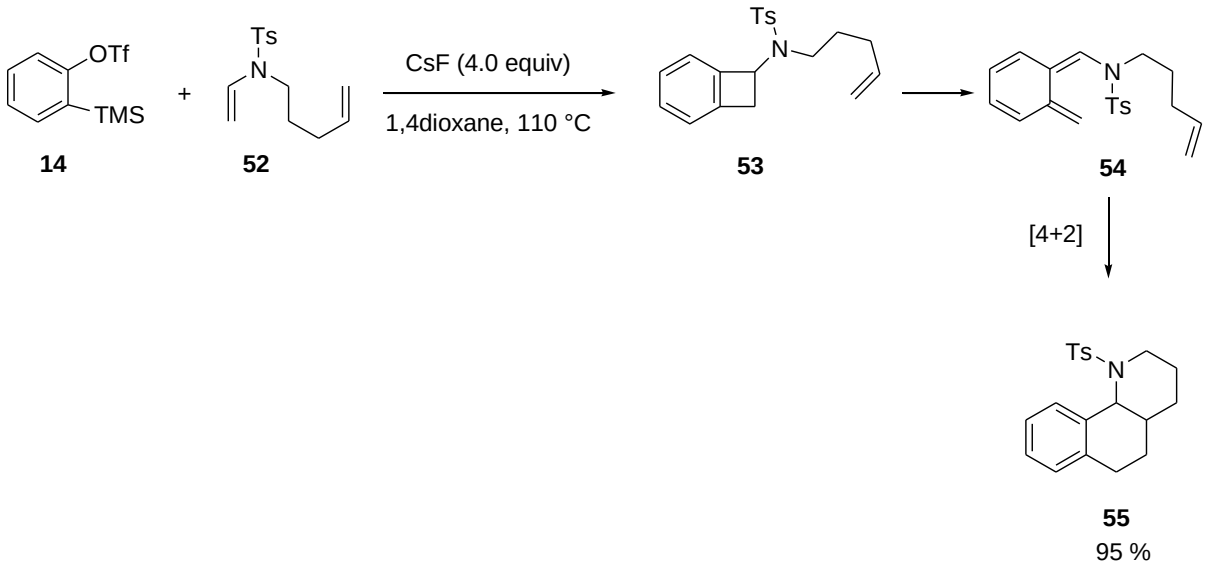
Arynes are also undergoing [2+2] processes including dimerisation to biphenylene in the absence of nucleophile species in *situ*,[22] and there are many reactions of benzyne with olefins.[23] For example, Kunai and co-workers obtained 9-arylxanthene derivative product **51** upon treatment of aryl aldehyde **47** with benzyne (Scheme 15). The mechanism was thought to proceed *via* a zwitterionic intermediate. First, a nucleophilic attack of a carbonyl oxygen atom on benzyne gives zwitterion **48**, which then undergoes intramolecular cyclization to

afford benzoxete **49**. Subsequent isomerization to *o*-quinonemethide **50**, followed by [4 + 2] cycloaddition with another molecule of aryne provides **51**.[24]



Scheme 15

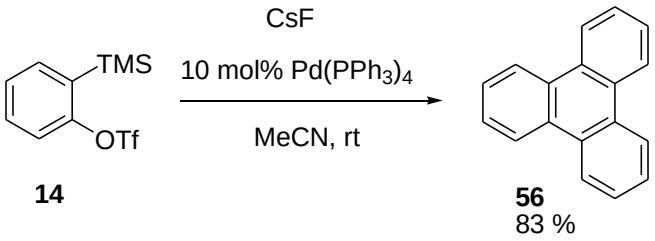
Hsung and co-workers developed an enamide-benzyne [2 + 2] cycloaddition using benzyne precursor **14** and enamide **52** in the presence of CsF in 1,4 dioxane at 110 °C. Aza-tricycle **55** as a single diastereomer was achieved by using enamide **52** tethered with an olefin. The formation of **55** involves four-bond formation through benzocyclobutane [2 + 2] cycloaddition in tandem with the ring opening to *o*-quinonedimethide **54** which undergoes *N*-tethered intramolecular [4 + 2] cycloaddition.[25]



Scheme 16

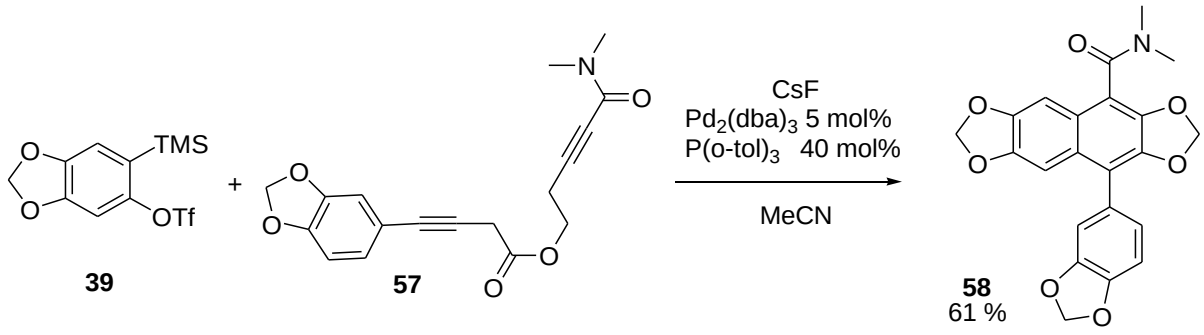
1.2.3 Transition Metal-Catalyzed Aryne Annulation

Catalytic transformation of arynes have been of major interest over the last three decades, since Guitián and co-workers reported the first palladium-catalysed reaction of arynes to synthesis triphenylene derivatives **56** by palladiuum-catalysed [2+2+2] cyclotrimerisation of benzyne.[26]



Scheme 17

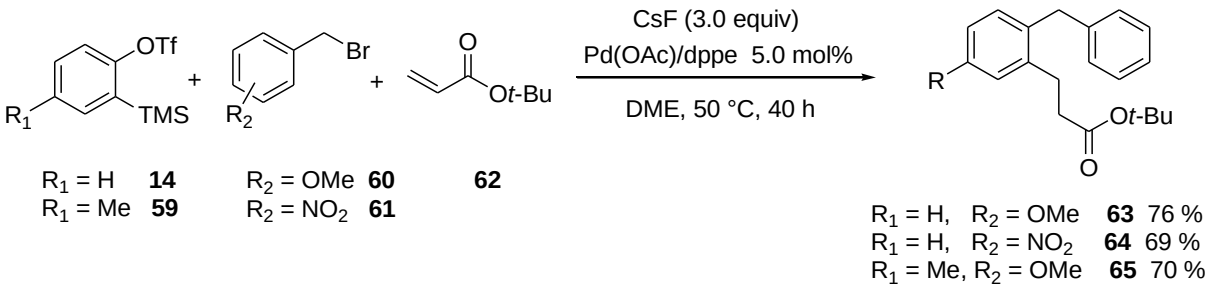
This methodology has since been extended to include co-cyclisation reactions, particularly with other electron-deficient species, as well as intramolecular [2+2+2] reactions for the preparation of fused polycycles. For examples, Mori and co-workers obtained tetracycle **58** (an intermediate for the synthesis of taiwanins C and E) from the palladium-catalysed co-cyclisation of benzyne obtained from benzyne precursor **39** with **57**. [27]



Scheme 18

Greaney and co-workers have also developed a three-component coupling (TCC) of benzyl bromides, benzyne, and tert-butyl acrylate using 5 mol % of $Pd(OAc)_2$/dppe as a catalyst. This methodology presents alternatives to simple allylchlorides as the initial carbopalladation electrophile, introduces the Heck reaction to benzyne TCC, and provides

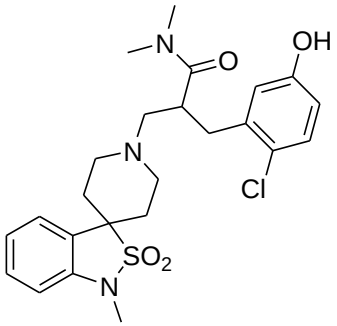
rapid and efficient access to diverse 1,2-functionalized arenes. The use of benzyl bromides as coupling partners is notable, providing a quick and easy route to various benzylphenyl compounds.[28]



Scheme 19

1.3 Sultams

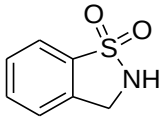
Benzosultams are important targets for drug discovery because of their potent biological activities. These motifs are present in the substructures of many pharmaceutical agents. The potent bioactivities include phosphotyrosine phosphatase 1B (PTP1B) inhibitors for treatment of type I and II diabetes, progesterone receptor antagonist and opioid receptor-like 1 (ORL1) antagonist.[29,30]



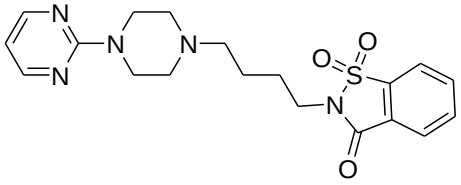
ORL 1 antagonist

Recently, there has been a sharp increase in the number of publications concerning the synthesis and use of sultams as cyclic analogs of sulfonamides. This is related to the absence of general methods for their synthesis, despite numerous skinds of sultams being already well established in clinical practice as anticonvulsant, [31] β1-adrenoblocking [32] and diuretic [33] agents. One of the important example of this family is 1,2-benzisothiazoline 2,2-dioxide, which has got numerous potential applications. The total synthesis of saccharine-based cyclic sulfonamide derivatives,[51] the core structure of spiropyrrolidinyl-benzoisothiazoline

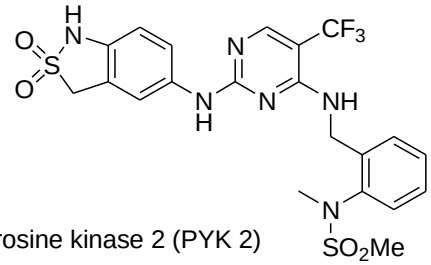
derivatives[29,30] and a novel potent inhibitors of proline-rich tyrosine kinase 2 (PYK 2) are example of theses system.[35]



1,2-benzisothiazoline 2,2-dioxide

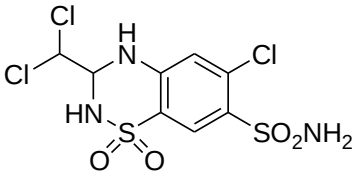


Ipsapirone



Proline-rich tyrosine kinase 2 (PYK 2) inhibitor

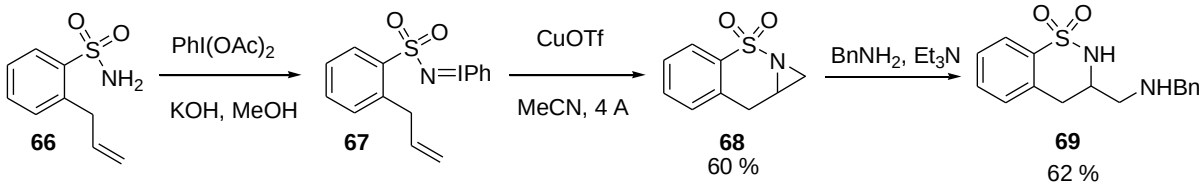
Other benzosultams have also shown their importance in pharmaceutical and medicinal chemistry because they are widely used as benzothiazine diuretics, such as trichloromethiazide, chlorthalidone, indapamide, and furosemide.[36] They also significantly inhibit carbonic anhydrases (CAs) and the X-ray crystal structures of their CA adducts exhibit a different behavior as compared to classical inhibitors, e.g., acetazolamide, methazolamide, and ethoxyzolamide. The newly found binding modes of these diuretics may be exploited for designing better CA II inhibitors as well as compounds with selectivity/affinity for various isoforms with medicinal applications. Because of the important biological activities of sultams, many efforts have been devoted to develop simple novel methods to generate them.[37]



Trichlormethiazide

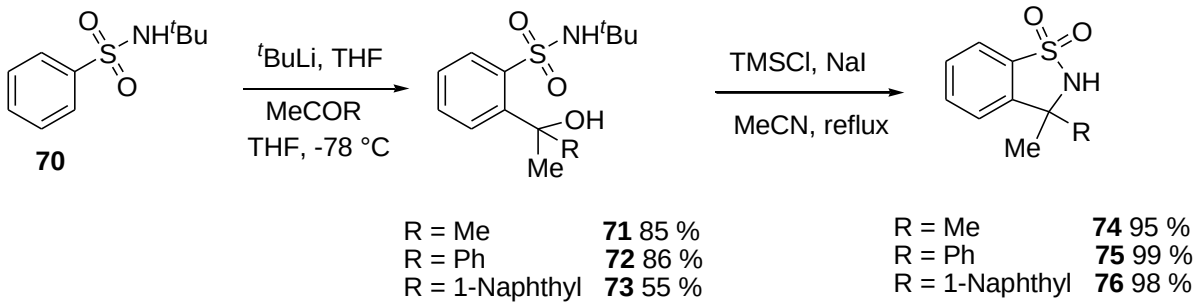
In 2000, Dauban and Dodd described a new methodology for the preparation of benzosultams based on copper- or bromine catalyzed aziridination.[38] Olefinic primary sulfonamide **66** was treated with iodobenzene diacetate and potassium hydroxide in

methanol to give intermediate iminoiodinane **67**, which was immediately treated with a catalytic amount of copper triflate to yield the aziridine **68.** Aziridine **68** was ring opened with various nucleophiles for example with benzylamine to give corresponding sultam **69.**



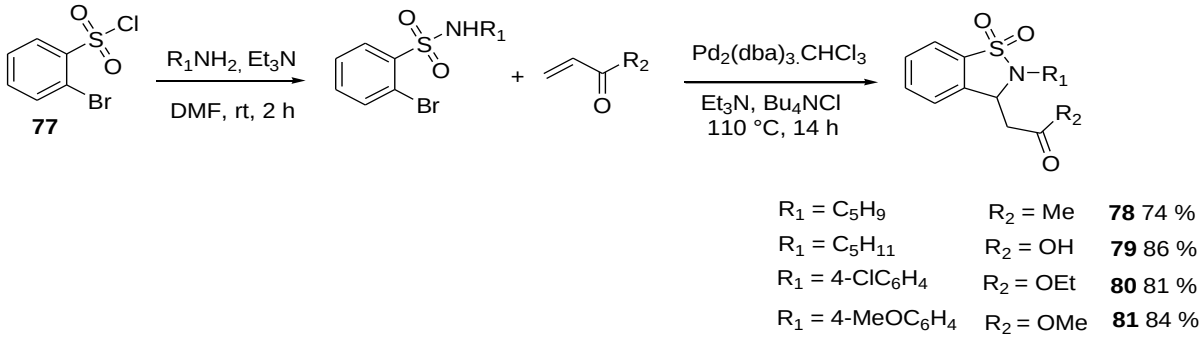
Scheme 20

In 2000, Takeuchi and co-workres reported the synthesis of 3,3-disubstituted benzosultams **74-76** by *o*-lithiation of *N*-tertbutylbenzenesulfonamide **70** and subsequent reaction with ketones followed by TMSCl-NaI mediated cyclization in refluxing acetonitrile.[40]



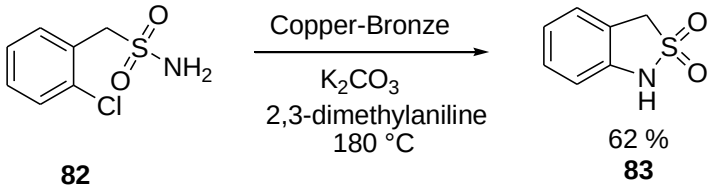
Scheme 21

Hanson and co-workers reported a new approach for the preparation of benzosultam using a domino process where a classical Heck reaction was coupled to an aza-Michael reaction, ultimately resulting in a one-pot protocol for a three-component reaction of α-bromobenzenesulfonylhalide, amines, and Michael acceptors (Scheme 22).[41] Several examples of benzosultams were prepared using this one-pot protocol (Scheme 22). First, α-bromobenzenesulfonyl chlorides **77** were coupled with a range of aromatic, cyclic, andalkylamines to yield the intermediate sulfonamides. After 2 h, Et_3N, Bu_4NCl, $Pd_2(dba)_3$, $CHCl_3$, and the appropriate Michael acceptor were added to the reaction, which was subsequently heated at 110 °C for 14 h to afford the desired sultams **78-81** in high yield.



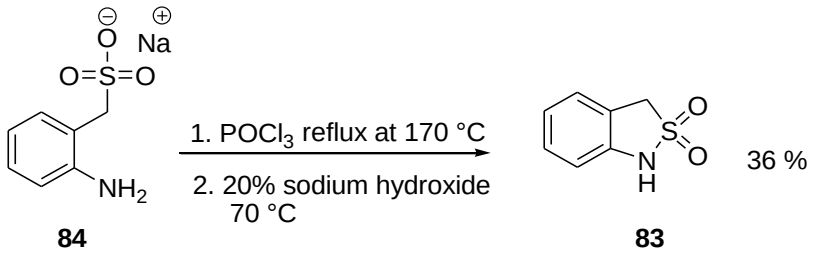
Scheme 22

In 1986, Chiarino and Contri obtained 1,2-benzisothiazoline 2,2-dioxide **83** and derivatives by heating a mixture of **82,** potassium carbonate and copper-bronze powder in 2,3-dimethylaniline as the solvent to give the corresponding substituted derivatives of sultam **83**.[42]



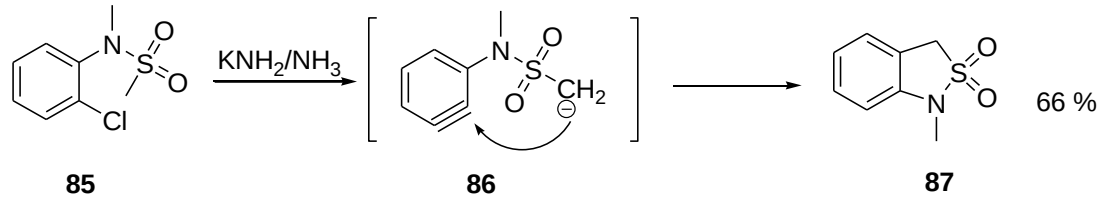
Scheme 23

In the same report, they worked with an alternative route for the formation of sultam **83**. For this purpose, 2-aminobenzylsulfonic acid sodium salt **84** was refluxed with phosphorus oxychloride (Scheme 24). After cooled down the mixture treated with sodium hydroxide in water, heated at 70 °C for a short time then work up to afford the sultam in a lower 36 % yiled.[42]



Scheme 24

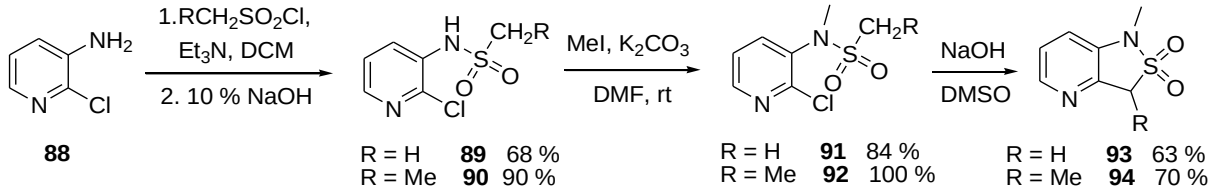
In 1974, Skorcz *et al*. reported an aryne-mediated intramolecular substitution in 2- chloro-*N*-methyl-*N*-methanesulfonylaniline **85** which results in benzosultam **87** via **86**.[43]



85 **86** **87**

Scheme 25

Pyridosultams **93**-**94** were synthesized from 3-amino-2-chloropyridine **88**.[44] Aminopyridine was reacted to yield monosulfonylated products **89-90** in high yields. The products were subsequently *N*-alkylated with a methyl iodide in the presence of K_2CO_3 in dimethylformamide. Cyclization of the *N*-alkylsulfonamides **91-92** by SNAr with solid NaOH in dimethylsulfoxide (DMSO) gave pyridosultams **93-94** in good yields.



88

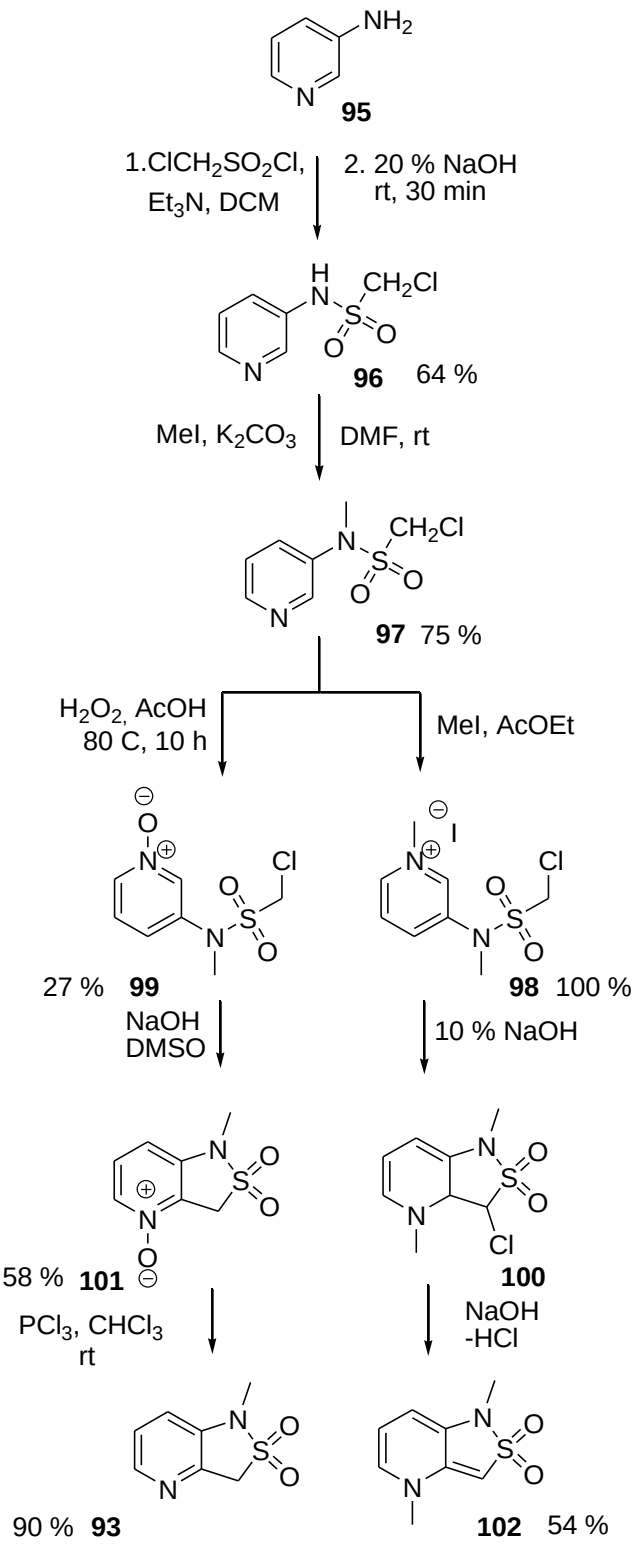
R = H **89** 68 %
R = Me **90** 90 %

R = H **91** 84 %
R = Me **92** 100 %

R = H **93** 63 %
R = Me **94** 70 %

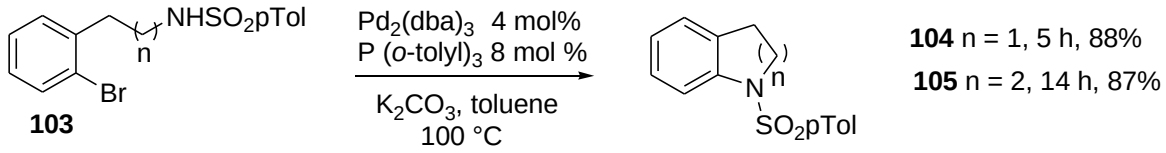
Scheme 26

The same group reported the application of vicarious nucleophilic substitution (VNS) for the synthesis of pyrido- and quinolinosultams.[45] However, attempted cyclization of **97** by intramolecular VNS under standard conditions (powdered NaOH in DMSO or *t*-BuOK in DMF) for thesynthesis of sultams failed. This is probably due to the lack of reactivity toward nucleophilic substitution of the pyridine ring. The electrophilicity of the pyridine ring was enhanced by either *N*-oxidation (using 30% hydrogen peroxide in acetic acid) or by quaternization of the nitrogen atom (using MeI) to give more reactive **98** and **99** respectively. *N*-oxide **99** in the presence of NaOH in DMSO and salt **98** in the presence of 10% aqueous NaOH underwent fast intramolecular VNS reactions to afford the corresponding sultams **93** and **102** (Scheme 27). [45]



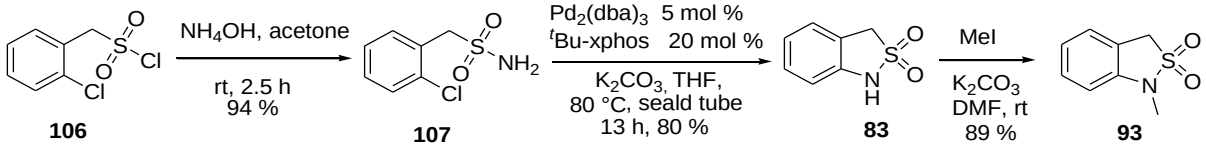
Scheme 27

In 1996, Buchwald and co-workers developed reaction conditions for intramolecular amide cyclizations, as well as cyclizations of sulfonamides. Reactions proceeded optimally for five-membered rings **104** and six membered rings **105**.[46]



Scheme 28

Recently, Blagg and co-workersobtained sultam **93** from 2-chlorobenzylsulfonyl chloride in three steps.[34] Treatment of 2-chlorobenzylsulfonyl chloride **106** with ammonium hydroxide solution in acetone at rt, gave (2-chlorophenyl) methanesulfonamide **107** in excellent yield. Intramolecular-coupling of (2-chlorophenyl) methanesulfonamide followed by reaction with methyl iodide, gave 1-methyl-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide **93** in good yields.



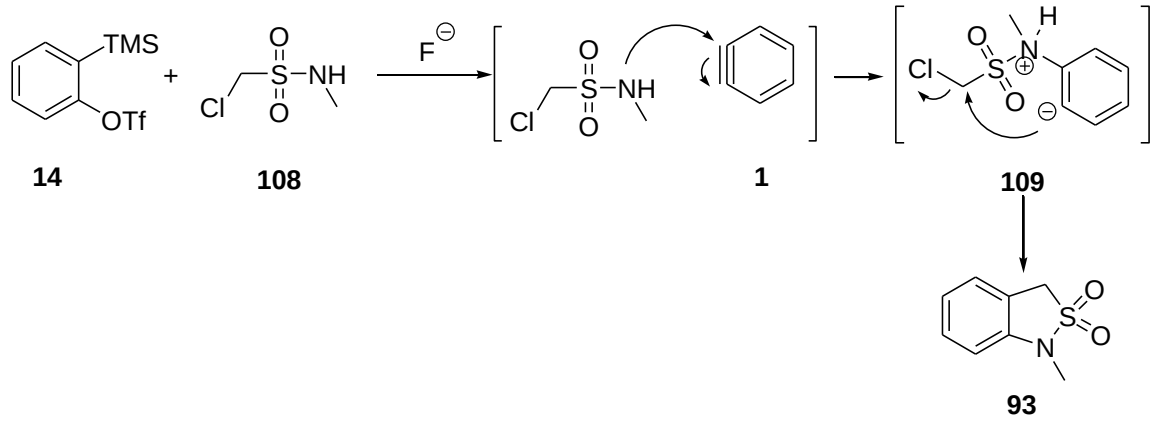
Scheme 29

2. Aim of the project

Our research group focused on the synthesis of sultam. Traditional methods for preparation of sultams required strong bases, costly reagents and high temperatures.

Initial investigation began with studying methods to employ benzyne precursors in the preparation of sultams. Over ten decades, arynes have gained a powerful role in a chemistry methodology and been shown to serve as electrophiles towards nucleophiles such as nitrogen.[16,21,22,26] Therefore, we visualised a novel pathway for the synthesis of sultam **93** from arynes and sulfonyl amide species **108** (Scheme 30). Specifically, we expected benzyne to undergo nucleophilic addition of sulfonamide **108** to form phenyl anion **109**, which would then add to α-carbon next to sulfonyl group with an elimination of chloride to form the five-membered ring, giving sultam **93**. Up to this point, we were positive that the addition of the nitrogen to benzyne would be competent, but there was no lead for the interamolecular

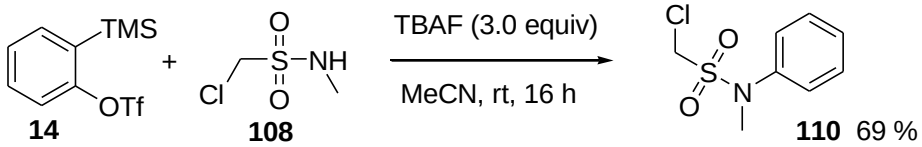
cyclisation step. We therefore tried to undestand whether this may be a feasible approach for the synthesis of sultams. The successful development of a one-pot reaction method for sultam synthesis from simply preparable materials would unlock a new direction toward bioactive products and hence, become an improvement in the organic chemistry and medicinal chemistry areas.[39]



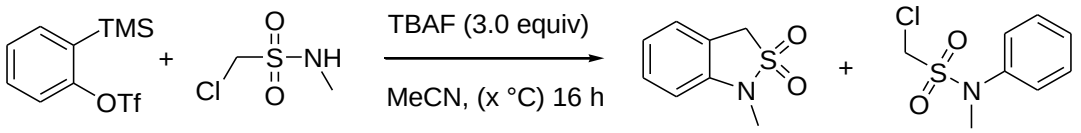
Scheme 30

3. Result and discussion

The initial design focused on substrates derived from 2-chloromethane sulfonyl chloride, particularly 2-chloromethane sulfonyl amide which was prepared by treating 2-chloromethane sulfonyl chloride with methylamine solution in chloroform at 0 °C for 4 h,[61] yielding the desired product in high yield. Treating this reagent **108** with Kobayashi's benzyne precuorse **14,** we undertook a reaction by applying conditions formerly used to boost aryne acyl-alkylation using acetonitrile as a solvent and TBAF as a fluoride source.[47] Unfortunately, this initial attempt failed to give the desired product and instead produced uncyclised product **110** in good yield (Scheme 31). In an attempt to gain cyclised sulfonamide, we were examining our hypothesis by screening reaction conditions (Table 1).



Scheme 31

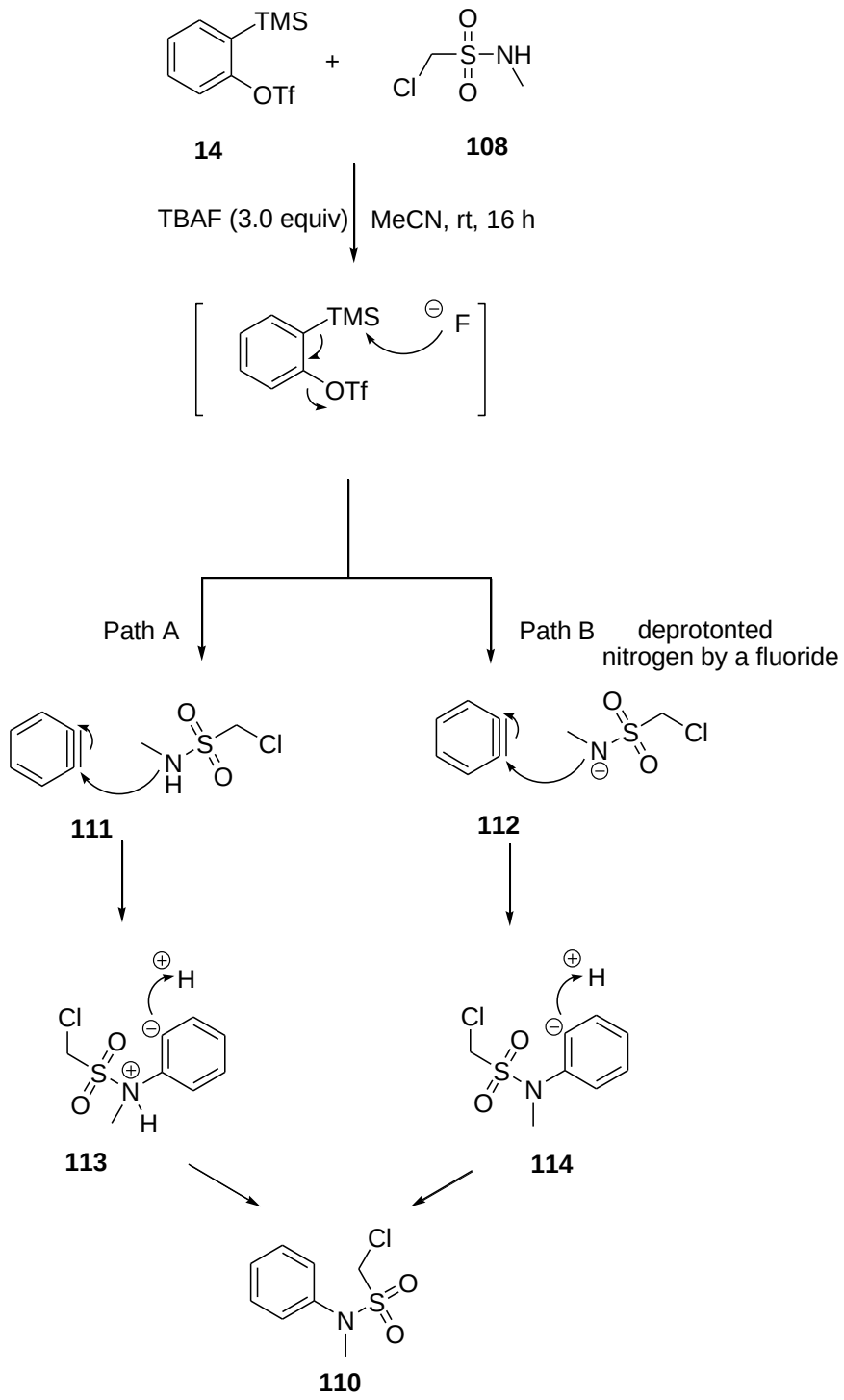


14 **108** **93** **110**

Entry	14 (eq)	108 (eq)	Temperature (°C)	Time (h)	93 (%)	110 (%)
1	1.0	1.0	Rt	16	0	69
2	1.0	1.0	60	16	0	72
3	1.0	1.0	80	16	0	79
4	1.0	1.0	80	8	0	79
5	1.0	1.0	80	4	0	80
6	1.2	1.0	80	4	0	77
7	1.5	1.0	80	4	0	75
8	2.0	1.0	80	4	0	70
9	1.0	1.2	80	4	0	68
10	1.0	1.5	80	4	0	70
11	1.0	2.0	80	4	0	66

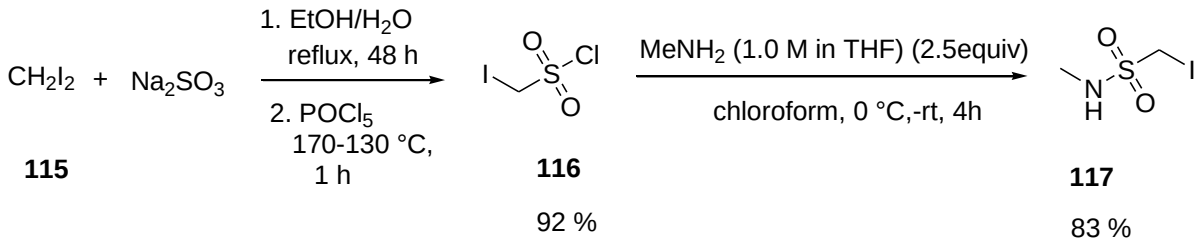
Table 1, Scheme 32

Initial screening did not show any trace of desired cyclysed products. Although in all cases benzyne precursors were undergoing *N*-arylation reactions (Table 1, Scheme 32), which showed that the nitrogen atom of sulfonylamide was nucleophilic enough to add to benzyne. However, it also suggested that either zwitterionic **113** or anionic species **114** created *in situ* was not able to attack the α-carbon next to sulfonyl group and underwent rapid proton abstraction in the reaction. The lack of success with these reactions was discouraging and it was decided to approach the reaction from a different angle.



Scheme 33

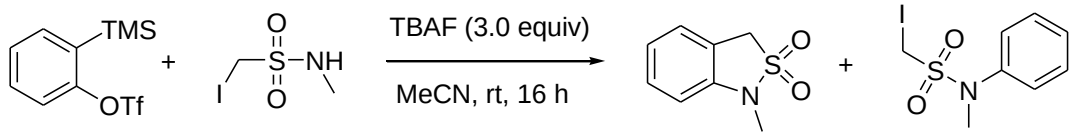
To rule out the last hypothesis, it was decided to use a better leaving group. As chloride is a poor leaving group compared to iodide and bromide, the chlorine was replaced with an iodine. 2-Iodosulfonyl amide **117** was generated in two steps from the commercially available starting material di-iodomethane **115**.[62]



115 **116** 92 % **117** 83 %

Scheme 34

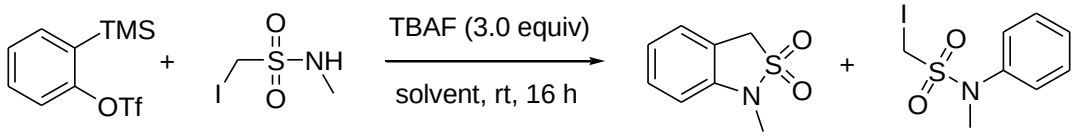
We began by testing our conditions to promote phenyl anion intermolecular addition (Scheme 35). To our delight, desired sultam **93** was produced in 15% yield along with uncyclised product **118** in 68%.



14 **117** **93** 15 % **118** 68 %

Scheme 35

Successful generation of **93** by this protocol was encouraging. Next was the attempted optimisation of the reaction to give the desired sultam as a major product. First a solvent screen was performed to investigate the effect of solvents on the reaction (Table 2). As expected, the generation of sultam with THF gave the best yield. DMA, DME and toluene all failed to give any observable product, but when DMF was adopted as a solvent; trace amount of benzene triple bond and significant amount of benzyne precursors was generated. From the results shown in (Table 2), THF was an ideal solvent to use in further optimasation.



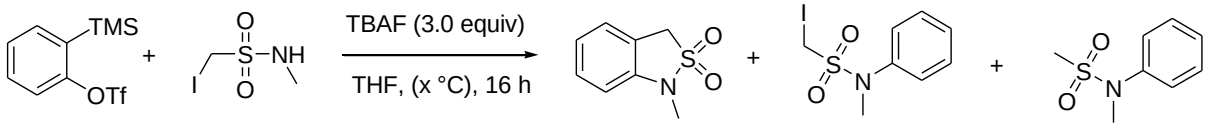
14 **117** **93** **118**

Entry	Solvent	93 (%)	118 (%)
1	THF	18	62
2	MeCN	15	68

3	DMA	0	0
4	DME	0	0
5	Toluene	0	0
6	DMF	0	0

Table 2, Scheme 36

Following the discovery of the reaction of benzyne with 2-iodosulfonyl amide in THF to generate sultam (Table 2, entry 1), it was important to carry out more optimisation for reaction which could then be applied in the generation of the desired product in a better yield. A range of conditions were investigated (Table 3). It was found when increasing the reaction time, there was no significant increase in isolated yield. The temperature of the reaction was decreased to 0 °C, -10 °C and -40 °C in order to slow down the generation of benzyne and allow better control of the reaction, but this decreased the yield of desired product. However, due to the low yield of cyclised product, the temperature of the reaction had to be increased for the intramolecular nucleophilic aromatic substitution to happen efficiently. Surprisingly, when the reaction was carried out at high temperatures a new by-product **119** was isolated. From these results, it should be noted that there was a relationship between uncyclised compound and cleaved compound, when amount of uncyclised product increased, amount of cleaved product decreased. Also the mechanism of the compound **119** was not possible to determine within the time limitation of the project.



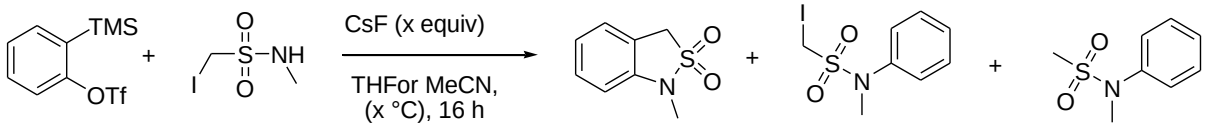
14 **117** **93** **118** **119**

Entry	Temperature (°C)	Time (h)	NMR (93 : 118 : 119)
1	Rt	16	1 : 3.4 : trace
2	Rt	48	1: 3.5 : trace
3	Rt	72	1 : 3.4 : trace

4	0	16	1:4:0
5	-10	16	1:7:0
6	-40	16	1:10:0
7	60	16	1:2.9:1
8	80	16	1:2.4:1.8
9	100	16	1:1.5:2.5

Table 3, Scheme 37

Although we could not explain the mechanism of formation of compound **119**, the yields obtained for **93** were promising and this encouraged us to further optimise the conditions to obtain a higher yield of sultam. The next variable for optimising was the fluoride source. Reactions involving CsF (3.0, 4.0 and 5.0 equiv) as the fluoride source failed to provide any expected product. When the reaction was carried out at 80 °C, trace amounts of *N*-arylation product could be detected but starting materials were mainly recovered at the end of the reaction. Hence, THF was replaced by MeCN which is an ideal solvent for CsF, this also failed to give any desired product and we recovered starting material.



14 **117** **93** **118** **119**

Scheme 38

We then decided to use the tetrabutylammoniumtriphenylsilyldifluoro silicate salt known as TBAT (Figure 2) as the fluoride source instead of TBAF or CsF.

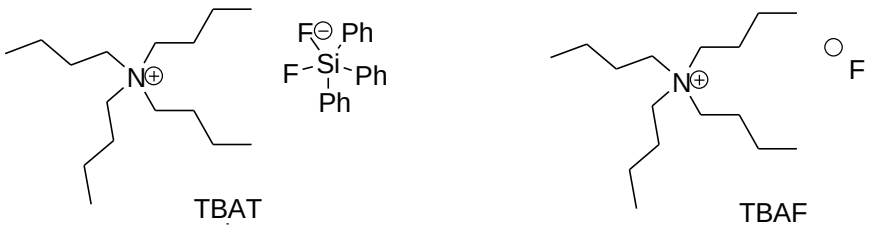
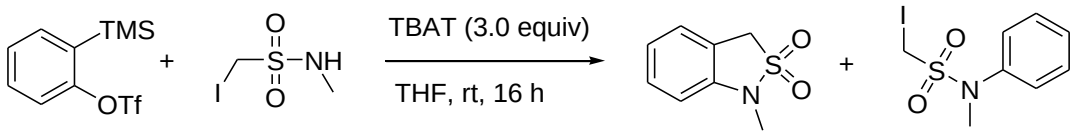


Fig 2

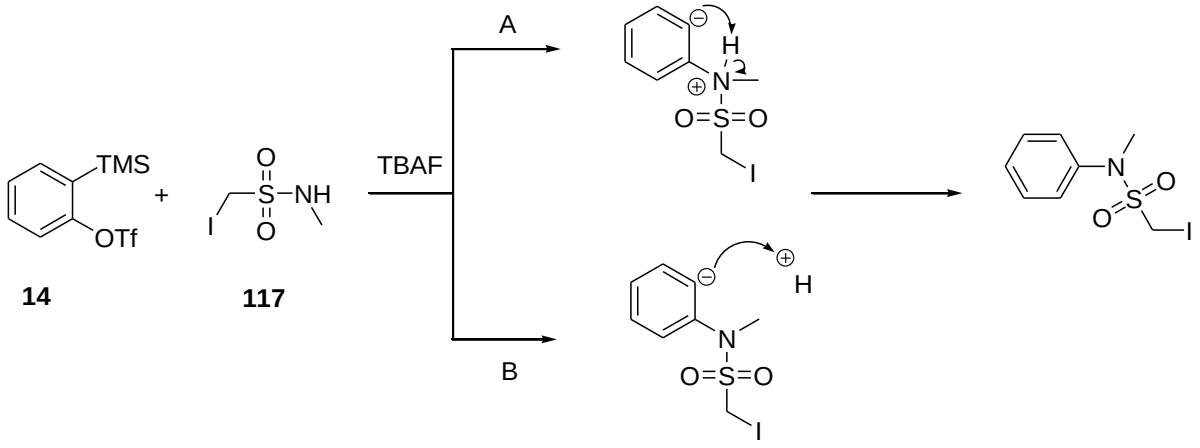
TBAT is a non-hygroscopic fluoride source that proved to be efficient in some reactions when other fluoride sources such as CsF or TBAF were not.[48,49,50] The observed reactivity of TBAT was very different compare to TBAF. Reactions performed in both MeCN and THF gave complex reaction mixtures with more than six visible spots on TLC whereas reactions using TBAF in same solvents gave two to three visible spot. Once again, THF used in the reaction provided cyclised and uncyclised products (12 % and 25 % isolated yield), with no sign of compound **119**.



14 **117** **93** 12 % **118** 25 %

Scheme 39

Given these results, we can hypothesise that the nucleophilic attack of the nitrogen occurs first and that the failure to cyclise may be due to an intramolecular proton abstraction from the zwitterions or proton from the fluoride source (Scheme 40).

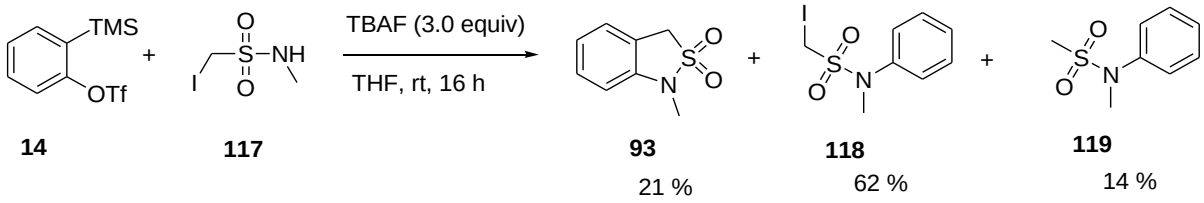


14 **117**

Scheme 40

From this point our investigation was focused on tetrabutylammonium fluoride (TBAF) as a fluoride source. Vaghefi and co-workers[63] published the desilylation rates of the ribosyl purine and the ribosyl pyrimidine nucleosides by using dry TBAF. They examined the ability of TBAF reagents dried with molecular sieves to deprotect an oligo ribonucleotide. Following Vaghefi's work, TBAF was dried over molecular sieves (3 A) for a week at rt.[63] The reaction was run with the dried TBAF applied. Gratifyingly, when dried TBAF was used, cyclised

products could be obtained in a higher yield. Indeed, compound **93** was isolated with 21% yield. However, both of uncyclised and by-product compounds were isolated as a majority (76 %) of the reaction.

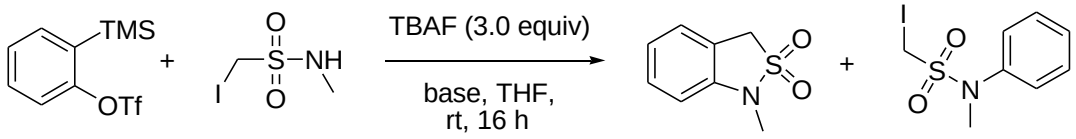


14 **117** **93** **118** **119**

21 % 62 % 14 %

Scheme 41

In an attempt to reduce further uncyclised product and thus increasing the desired product, we examined removal of proton source from the reaction by using a range of common bases (Scheme 42) (Table 4).



14 **117** **93** **118**

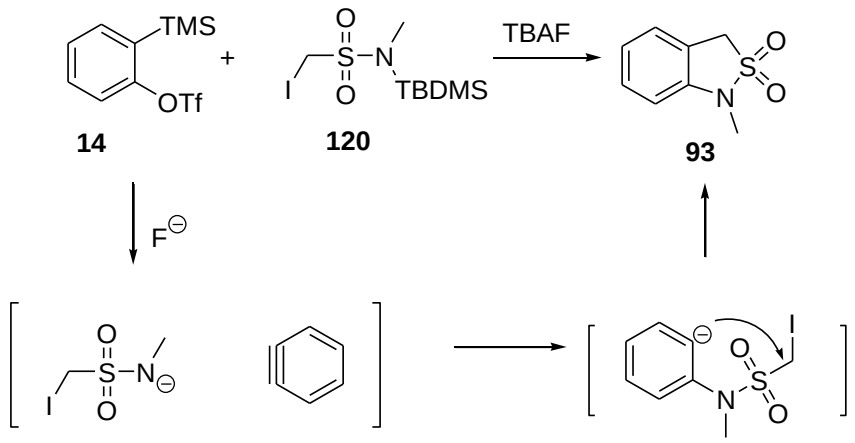
Entry	Base	Yield (%)	NMR (93:118)
1	K_2CO_3	84	1:2.6
2	K_2CO_3	85[a]	1:2.6[a]
3	Triethyl amine	78	1:3.8
4	Cs_2CO_3	71	1:5.0
5	Hünig's base	86	1:2.9
6	$NaHCO_3$	80	1:5.2

a) 2.0 equiv of base used

Table 4, Scheme 42

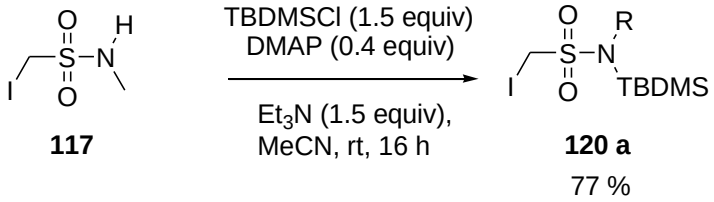
When bases were tested in our reaction, it slightly improved the amount of cyclised product (determined by ^{1}H NMR). Employing Hünig's base with tetrabutylammonium fluoride (TBAF) improved the yield observed (Entry 5). The use of one equivalent of K_2CO_3 gave the best result (based on ^{1}HNMR spectroscopy, Table 4, entry 1). Increasing by an equivalent of base

did not effect the yield of the reaction (Entry 2). Use of other bases like $NaHCO_3$, caesium carbonate and tri-ethylamine lowered the yield of **93** (Entries 3-6). Being encouraged by these preliminary results, we protected the secondary amine with a TBDMS group. It was proposed that the fluoride source could deprotect both silyl-groups in the reaction. By doing this it was believed that the amount of proton in the reaction would be reduced, resulting in a reduction in side reactions.



Scheme 43

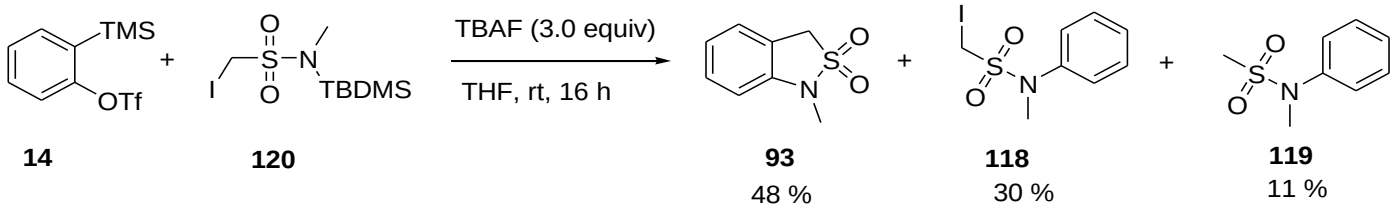
The best silyl-protecting group was found to be TBDMS, as the TMS-group was too sensitive and upon contact with air underwent hydrolysis. Following a modified procedure, the secondary amine **117** was protected with TBDMS-Cl in the presence of DMAP and tri-ethylamine in MeCN to give the desired protected compound **120** in good yield 77 %.



Scheme 44

The reaction also had the advantage of going to completion in a far better yield than the TBDPSCl (21% yield obtained for protecting amine). Examining the crude mixture (Scheme 44) by TLC only the spot of new product was observed. Upon purification of this crude by columun chromatography compound **120 a** was isolated in good yield. Compound **120 a** was subsequently applied to our reaction conditions. Interestingly, the yield of desired cyclised product was increased dramatically, the ratio between cyclised and uncyclised products was

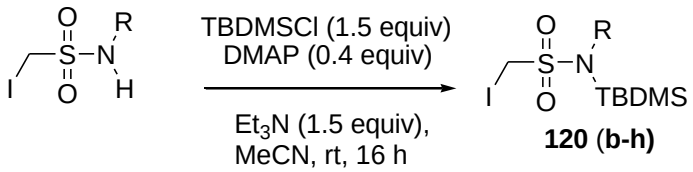
(1.5:1.0 respectively) determined by NMR. Unfortunately, the amount of by-product **119** was also increased compare to pervious reaction conditions (Scheme 45).



14 **120** **93** 48 % **118** 30 % **119** 11 %

Scheme 45

Following the success with protected *N*-methylsulfonyliodide, a variety of amine derivatives were therefore synthesized to investigate inthe reaction. Making the TBDMS-amines was straight forward, and gave the desired products **120 (b-i)** by yields of 64-81% (Scheme 46 and Table 5).

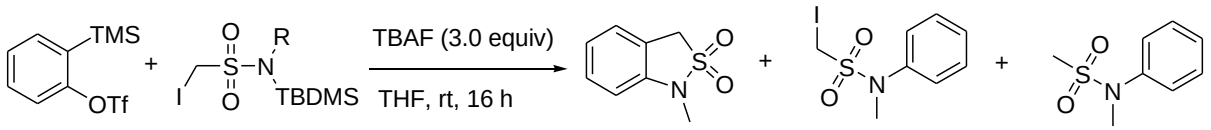


120 (**b-h)**

Entry	R	Substrate	Yield (%)
1	Ethyl	**120-b**	78
2	Iso-propyl	**120-c**	74
3	Iso-butyl	**120-d**	68
4	Amyl	**120-e**	81
5	Cyclohexyl	**120-f**	64
6	Tert-butyl	**120-g**	73
7	Propyl	**120-h**	80

Table 5, Scheme 46

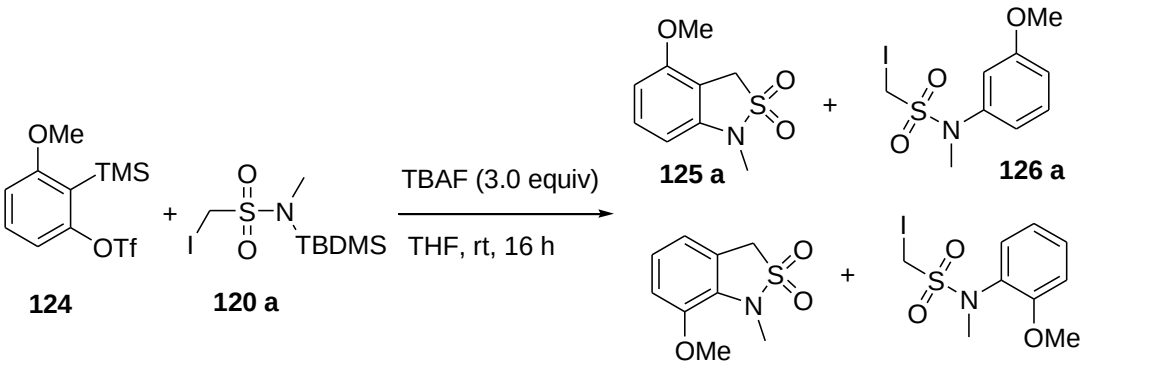
Once products **120 (b-i)** had been isolated, reactions were investigated with them. The newly developed conditions were used with dried TBAF as fluoride source. The reaction was applied to a variety of sulfonamide drivatives, yielding the cyclic products in modest yields (37-51 %) (Scheme 47, Table 6).



Entry	R	121 b-h (%)	122 b-h (%)	123 b-h (%)
1	Ethyl	51	33	13
2	Iso-propyl	46	31	22
3	Iso-butyl	44	35	18
4	Amyl	48	33	15
5	Cyclohexyl	38	29	12
6	Tert-butyl	46	37	13
7	Propyl	49	33	17

Table 6, Scheme 47

All compounds delivered the desired cyclised products as the major compound. We can see from this selection of compounds that amides with less hindrance gave better yields than those with hindered substituent. The low yields are thought to be due to steric hindrance during both the nucleophilic addition and the cyclisation steps. Having a better understanding of the substrate range suitable for the reaction, we adopted substituted aryne precursors to study the reactivity associated with electronic and steric effects (Scheme 48). However, in the case of unsymmetrical benzynes two regioisomers could be formed.



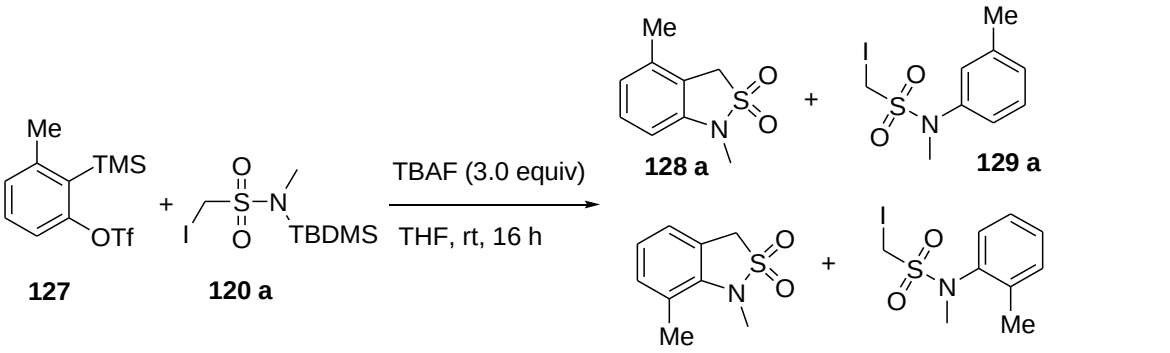
124 **120 a**

125 a **126 a**

125 b **126 b**

Ratio = **125 a** 4:1 **125 b** Ratio = **126 a** 4:1 **126 b**

44 % yield 34 % yield



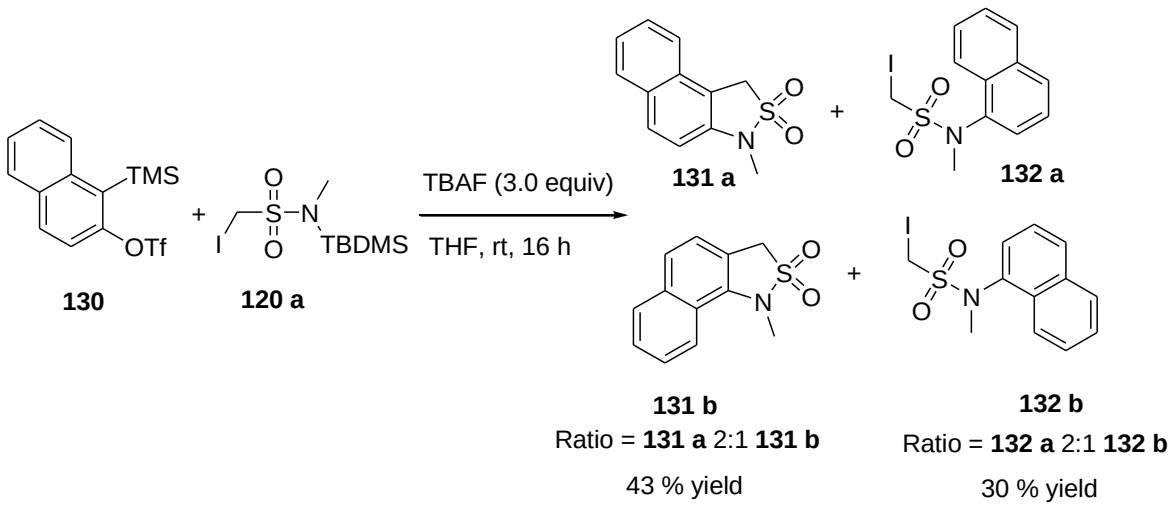
127 **120 a**

128 a **129 a**

128 b **129 b**

Ratio = **128 a** 1.2:1 **128 b** Ratio = **129 a** 1.2:1 **129 b**

49 % yield 30 % yield



Scheme 48

For example, the addition of 3-methoxybenzyne **124**, occurs with high regioselectivity at C1. This can be explained by a combination of the steric repulsion by the methoxy-substituent and the inductive electron donating nature of the methoxy- substituent. Bulky 3-substituted benzynes, such as naphthalene **130**, favour addition at the least hindered position; this is C1 for the benzyne due to repulsion from the *peri*-hydrogen. In the case of a meta methyl aryne **127**, the product was observed as a 1.2:1 mixture of isomers. The slight regioselectivity for C2 of 3-methylbenzyne (Fig 3), however, may be due to the electron-donating nature of the methyl substituent making C1 comparatively electron-rich, thus favouring **128a** over **128b**.[60]

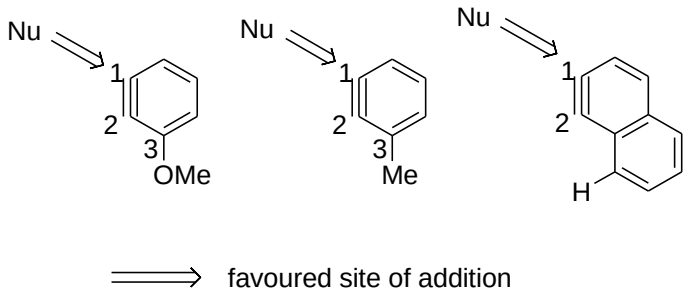


Fig 3

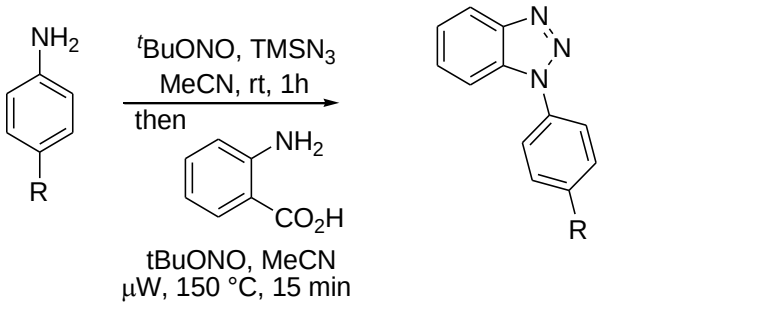
3.1 Microwave Methodology

Microwave technology has been applied in organic chemistry since the late 1980s when the microwave cavity was redesigned thus improving the heating characteristics.[52,54] The

progress of this technology for organic chemistry has been rather slow compared to computational and inorganic chemistry fields.[54] This initial slow progress in this field has been ascribed to lack of controability, reproducibility, microwave dielectric heating, system control for ample temperature and pressure.[53] Nevertheless, the number of publications associated to this area has dramatically increased since the late-1990s.[53,54] The main rationales for this remarkable growth is because of development of solvent free reaction, shorter reaction times from days to hours or minutes and the availability of microwave equipment.[53,54,59]

Furthermore, microwave dielectric heating possesses certain advantages over traditional methods due to energy rate that cannot reproduced by refluxing as in a classical heating method insufficient energy is transferred to the system. Other advantages are higher yield, reduced side reaction and shorter time with microwave reactor method. In addition, in pressurized system,[52,54,59] it is possible to increase the temperature far above the boiling point of the solvent, therefore solvents with lower boiling point could be employed and can be easily removed in the reaction mixture during work up or purification.[52]

In 2009, Mosses and Zhang[56] published the preparation of aromatic azides formed by addition of the corresponding anthranilic acid, benzyne precursor and t-BuONO in a microwave reactor and irradiating for 15 min at 150 °C. These conditions favoured electron-rich azides **134a**, whereas lower yields were observed with electron-poor substrates **134b-c**.

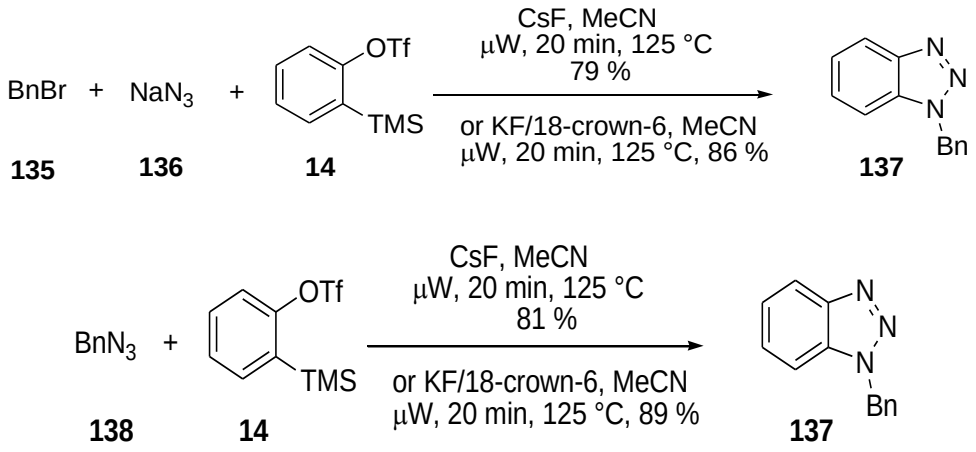


R = OMe **133a**
R = NO_2 **133b**
R = CN **133c**

R = OMe **134a** 86 %
R = NO_2 **134b** 29 %
R = CN **134c** 42%

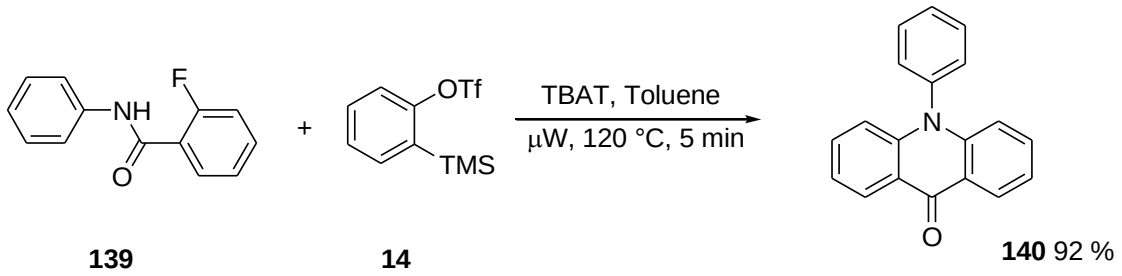
Scheme 49

In the same year, Ankati and Biehl[57]applied the microwave click chemistry to prepare 1H-benzo[d]triazoles in good to excellent yields, with two-component and three-component substrates. They ran reactions with two different conditions as detailed below (Scheme 50).



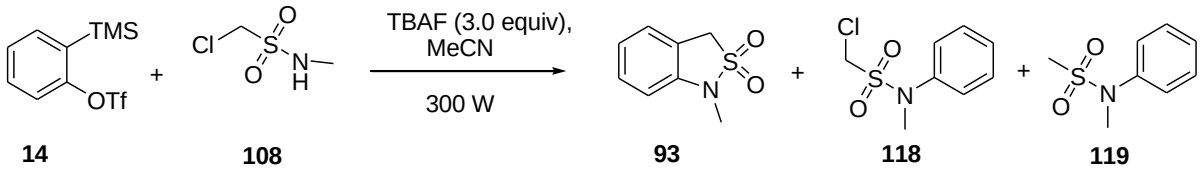
Scheme 50

Greaney's group developed a single-step method to synthesies acridones in high yield from aryl amides using just 5 min of microwave irradiation at 120 °C in the presence of TBAT (Scheme 51).[58]



Scheme 51

The compatibility of precursor **14** with microwave heating has recently been remarked[56,57,58] upon and is testament to its superb versatility in aryne chemistry, therefore we decided to apply this methodology with our reaction conditions using acetonitrile as a solvent as it is known to be an ideal microwave solvent, and 2-chloro-sulfonyl amide **108** was chosen to avoid formation of cleaved product **119** (Table 7).



14 **108** **93** **118** **119**

Entry	Temperature (°C)	Time (min)	93 (%)	118 (%)	119 (%)
1	Rt	60	0	24	0
2	60	60	0	50	0
3	80	60	14	74	0
4	100	60	53	5	0
5	100	20	0	0	0
6	100	30	0	0	0
7	100	120	5	64	22
8	100	180	5	56	31
9	120	60	5	20	44

Table 7, Scheme 52

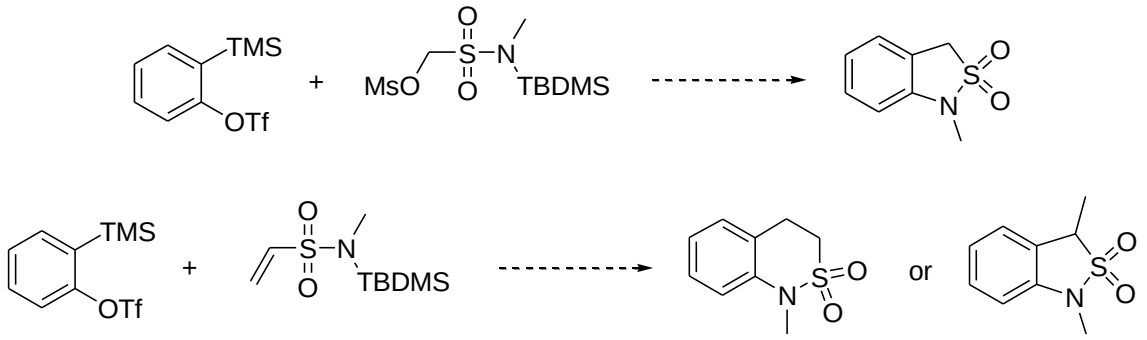
Successful generation of **93** by this protocol was encouraging. Direct analysis of the results shows a clear trend in the isolated yields when increasing the temperature to 100 °C (entry 4). Unfortunately, we were unable to reproduce the result when the same conditions were applied again. Attempts to further analyse the extent of this trend by increasing the reaction temperature to 120 °C produced cleaved product **119** as a major product and trace amount of **93**. It is important to note that entries 5 and 6 did not reach full conversion after 20 and 30 minutes, as **14** was still present. Furthermore, the analogous process using non-microwave methodology would take up to 16 hours to reach completion. With this in mind a screening of reaction run-times was performed to achieve a full conversion of **14** at an ideally lower reaction temperature. In addition, we increased the run-time of the highest yielding reaction temperature (entry 7 and 8) to see if this would increase the isolated yield, but only a trace of cyclised product was observed.

4. Conclusion and Future Work

A new optimised route to the synthesis of sultams is described; our method is a simple and two step procedure in one pot of reaction. The reaction includes the addition of nitrogen nucleophile to phenyl anion following ring closure through intermolecular elimination. In fact, the previous publications in aryne methodology concentrated on addition reactions

between phenyl halide and sulfonamide. We initially studied this area with the belief that phenyl anions endured cyclisation to furnish a variety of annulated rings. In our conditions, easily accessible substrates 2-iodomethane sulfonylamide and *ortho*-silyl aryl triflates generate uncyclised product in good yield when TBAF used as the fluoride source. Nevertheless, the formation of a mixture of cyclic and acyclic products leads us to consider the mechanism entailing second nucleophilic attack to α-C next to sulfonyl group. In an attempt to increase the amount of the cyclised product in the reaction, we therefore began investigating *N*-protected sulfonyl-2-iodides as alternative substrates. This compound produced cyclised product in moderate yield. Based on this result, a series of *N*-protected sulfonyl amine derivatives were shown to form sultams. In addition, it has been shown that there is some hope for preparation of sultams by using our conditions in a microwave system.

Future work would include more investigations into the mechanism of the reaction, further experimentation is expected to increase yield of cyclised product, for example, by preparing anhydous TBAF, using different benzyne precursors or by replacing the iodine group with altenative leaving group such as tosyl and mesyl. Stoltz[16] previously described ring closure via intermolecular conjugate addition; this in turn can be further functionalised to the six or five membered ring sultams (Scheme 53).



Scheme 53

5. Experimental

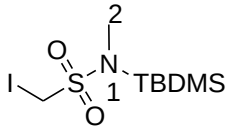
General methods

Unless otherwise stated, all reactions were carried out under an inert atmosphere of dried nitrogen, in glassware which had been oven-dried. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fisher Scientific, TCI UK or Lancaster Research Chemicals and were not purified except where stated. Solvents were purchased anhydrous and stored over molecular sieves, or distilled under nitrogen from an appropriate drying agent in accordance with the procedures of Perrin and Armarego. Toluene and THF were distilled from sodium benzophenoneketyl radical while dichloromethane and acetonitrile were distilled from calcium hydride. DMSO anhydrous was used as obtained fromSigma-Aldrich.Thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} aluminium sheets. Spots were visualised by quenching UV irradiation at 254 nm, and by staining with 2% $KMnO_4$ (w/v) in 20% K_2CO_3 (w/v) solution, 15% phosphomolybdic acid (w/v) in EtOH. Flash column chromatography was carried out using silica gel 60 A, 70-230 mesh, 63-200 µm obtained from Sigma–Aldrich. Nuclear magnetic resonance (NMR) spectroscopy was performed on a BrukerAvance 400 NMR spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) with the appropriate deuterated solvent. Chemical shifts in ^{1}H NMR spectra are expressed as ppm downfield from TMS and in ^{13}C NMR, are relative to internal standard, and reported as singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). Coupling constants (*J*) are quoted in Hz and are averaged between coupling partners and rounded to the nearest 0.2 Hz. Mass spectrometry was performed using a BrukerMicroTOF-Q instrument with electrospray ionisation in the positive mode. FT-IR data was acquired using Thermo Electron Corporation Nicolet 380 FTIR with Smart Orbit diamond window instrument with wavenumbers being reported in cm^{-1}.

General procedure for protecting amine

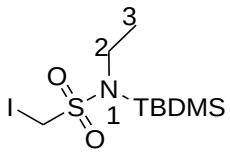
To an oven dried round-bottomed flask, flushed with nitrogen, 2-iodomethanesulfonyl amide derivatives (1.0 g) was added, and was taken up with MeCN (20 mL). To this triethylamine (1.5 equiv) and TBDMSCl (1.5 equiv) was added and stirred for 16 hours at 25 °C. After this time the mixture was concentrated under reduce pressure and purified by flash column chromatography to yield the title compound.

N-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-methylamine



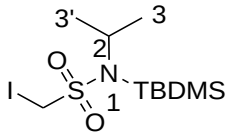
Prepared following the general procedure to yield **120a** (1.14 g, 77 %) as a colourless solid; mp: 128-130 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.38 (s, 2H, I-C$\underline{H}_2$), 2.58 (s, 3H, 2-CH_3), 0.9 (s, 9H-(($C\underline{H}_3$)$_3$C-Si(CH_2)$_2$), 0.08 (s, 6 H, (CH_3)$_3$C-Si($C\underline{H}_3$)$_2$); **^{13}C NMR** (100MHz, $CDCl_3$): δ_C 30.9 (I-$\underline{C}H_2$), 26.4 (($\underline{C}H_3$)$_3$C-Si(CH_3)$_2$), 25.2 (2-CH_3), 14.3 ((CH_3)$_3\underline{C}$-Si(CH_3)$_2$), -8 ((CH_3)$_3$C-Si($\underline{C}H_3$)$_2$); ν_{max} (solid, cm^{-1}); 1335, 1152 (SO_2), 1027 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_8H_{20}INO_2SSi$ 349.0030 $[M+H]^+$; found 349.0033.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-ethylamine**



Prepared following the general procedureto yield **120b** (1.13 g, 78 %) obtained as a colourless solid; mp : 136-138 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.39 (s, 2H, I-C$\underline{H}_2$), 2.68 (t, *J* 6.4 Hz, 2H, 2-CH_2), 1.4 (s, 3H, 3-CH_3), 1.1 (s, 9H (($C\underline{H}_3$)$_3$C-Si(CH_2)$_2$), 0.08 (s, 6H, (CH_3)$_3$C-Si($C\underline{H}_3$)$_2$); **^{13}C NMR** (100MHz, $CDCl_3$): δ_C 32.1 (2-$\underline{C}H_2$), 31.9 (I-$\underline{C}H_2$), 26.8 (($\underline{C}H_3$)$_3$C-Si(CH_3)$_2$), 15.2 (3-$\underline{C}H_3$), 14.5 ((CH_3)$_3\underline{C}$-Si(CH_3)$_2$), -9.5 ((CH_3)$_3$C-Si($\underline{C}H_3$)$_2$); ν_{max} (solid, cm^{-1}); 1331, 1150 (SO_2), 1055 (N-C) ; **MS***m/z* (ESI$^+$) calculated for $C_9H_{22}INO_2SSi$ 363.0185 $[M+H]^+$; found 363.0192.

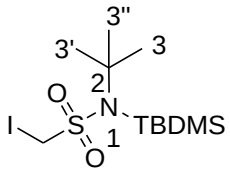
***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-isopropylamine**



Prepared following the general procedureto yield **120c** (1.05 g, 74 %) as a colourless solid; mp : 156-158 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.39 (s, 2H, I-C$\underline{H}_2$), 3.15-3.10 (m, 1H, 2-C$\underline{H}$), 1.15 (s, 6H, 3-C$\underline{H}_3$ and 3'-C$\underline{H}_3$), 1.05 (s, 9H, ($C\underline{H}_3$)$_3$C-Si(CH_2)$_2$), 0.09 (s, 6H, (CH_3)$_3$C-Si($C\underline{H}_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 36.6 (2-$\underline{C}$H), 32.2 (I-$\underline{C}$), 26.9 (($\underline{C}H_3$)$_3$C-Si(CH_3)$_2$), 15.2 (3-$\underline{C}H_3$ and

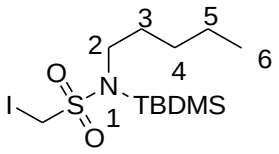
3'-$\underline{C}H_3$), 14.6 ($(CH_3)_3\underline{C}$-Si$(CH_3)_2$), -9.0 ($(CH_3)_3$C-Si($\underline{C}H_3)_2$); ν_{max} (solid, cm^{-1}); 1333, 1149 (SO_2), 1045 (C-N); **MS***m/z* (ESI$^+$) calculated for $C_{10}H_{24}INO_2SSi$ 377.0342 $[M+H]^+$; found 377.0339.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-tertbutylamine**



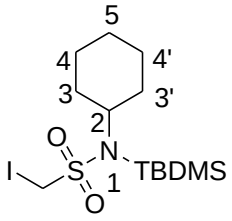
Prepared following the general procedureto yield **120g** (0.96 g, 68 %) as a colourless solid; mp : 168-172 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.39 (s, 2H, I-C$\underline{H}_2$), 1.42 (s, 9H, 3-C$\underline{H}_3$, 3'-C$\underline{H}_3$ and 3''-C$\underline{H}_3$), 1.05 (s, 9H, (C$\underline{H}_3)_3$C-Si$(CH_2)_2$), 0.08 (s, 6H, $(CH_3)_3$C-Si(C$\underline{H}_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 39.4 (2-$\underline{C}$H), 33.2 (I-$\underline{C}H_2$), 30.8 (3-$\underline{C}H_3$, 3'-$\underline{C}H_3$ and 3''-$\underline{C}H_3$), 25.9 (($\underline{C}H_3)_3$C-Si$(CH_3)_2$), 15.1 ($(CH_3)_3\underline{C}$-Si$(CH_3)_2$), -8.7 ($(CH_3)_3$C-Si($\underline{C}H_3)_2$); ν_{max} (solid, cm^{-1}); 1337, 1148 (SO_2), 1029 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{11}H_{26}INO_2SSi$ 391.0500 $[M+H]^+$; found 391.0057.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-amylamine**



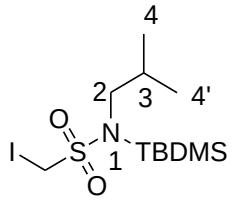
Prepared following the general procedure to yield **120e** (1.124 g, 81 %) as a colourless solid; mp : 152-156 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.38 (s, 2H, I-C$\underline{H}_2$), 2.65 (t, *J* 6.5 Hz, 2H, 2-C$\underline{H}_2$), 1.50-1.55 (m, 2H, 3-C$\underline{H}_2$), 1.29-1.37 (m, 4H, 4-C$\underline{H}_2$ and 5-C$\underline{H}_2$), 1.03 (s, 9H, (C$\underline{H}_3)_3$C-Si$(CH_3)_2$), 0.96 (t, *J* 7.0 Hz, 3H, 6-C$\underline{H}_3$), 0.08 (s, 6H, ($(CH_3)_3$C-Si(C$\underline{H}_3)_2$); **^{13}C NMR** (100MHz, $CDCl_3$): δ_C 40.3 (2-$\underline{C}H_2$), 33.2 (I-$\underline{C}H_2$), 30.8 (3-$\underline{C}H_2$), 29.5 (4-$\underline{C}H_2$), 27.1 (($\underline{C}H_3)_3$C-Si$(CH_3)_2$), 24.6 (5-$\underline{C}H_2$), 15.1 $(CH_3)_3\underline{C}$-Si$(CH_3)_2$), 14.6 (C-6), -8.7 ($(CH_3)_3$C-Si($\underline{C}H_3)_2$); ν_{max} (solid, cm^{-1}); 1337, 1148 (SO_2), 1032 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{12}H_{28}INO_2SSi$ 405.0655 $[M+H]^+$; found 405.0653.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-cyclohexylamine**



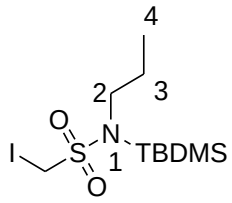
Prepared following the general procedure to yield **120f** (0.88 g, 64 %) as a colourless solid; mp : 172-176 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.40 (s, 2H, I-C$\underline{H}_2$), 2.79-2.75 (m, 1H, 2-CH), 2.57-1.72 (m, 4H, 3-C$\underline{H}_2$ and 3'-C$\underline{H}_2$),1.58-1.43 (m, 6H, 4-C$\underline{H}_2$,, 4'-C$\underline{H}_2$ and 5-C$\underline{H}_2$), 0.98 (s, 9H, (C$\underline{H}_3$)$_3$C-Si(CH$_3$)$_2$), 0.07 (s, 6H, (CH$_3$)$_3$C-Si(C$\underline{H}_3$)$_2$); **^{13}C NMR**(100MHz, $CDCl_3$): δ_C 39.9 (2-$\underline{C}$H), 33.2 (3-CH$_3$ and 3'-CH$_3$), 32.9 (I-CH$_2$), 30.8 (5-CH$_3$), 25.9 ((C$\underline{H}_3$)$_3$C-Si(CH$_3$)$_2$), 22.3 (4-CH$_3$ and 4'-CH$_3$), 15.1 ((CH$_3$)$_3$$\underline{C}$-Si(CH$_3$)$_2$), -8.7 ((CH$_3$)$_3$C-Si($\underline{C}H_3$)$_2$); ν_{max} (solid, cm^{-1}); 1337, 1148 (SO_2), 1055 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{13}H_{28}INO_2SSi$ 417.0657 $[M+H]^+$; found 417.0655.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-isobutylamine**



Prepared following the general procedureto yield **120d** (1.03 g, 73 %) obtained as a colourless solid; mp : 168-172 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.38 (s, 2H, I-C$\underline{H}_2$), 2.62 (t, *J* 6.4 Hz, 1H, 2-C$\underline{H}_2$), 2.09-2.06 (m, 1H, 3-C$\underline{H}$), 0.95 (d, *J* 6.5 Hz, 6H, 4-C$\underline{H}_3$ and 4'-C$\underline{H}_3$), 1.03 (s, 9H, (C$\underline{H}_3$)$_3$C-Si(CH$_3$)$_2$), 0.09 (s, 6H, CH$_3$)$_3$C-Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 49.9.4 (2-$\underline{C}$H$_2$), 32.2 (I-$\underline{C}$H$_2$), 29.8 (3-$\underline{C}$H), 26.4 ($\underline{C}$H$_3$)$_3$C-Si(CH$_3$)$_2$), 20.5 (4-$\underline{C}$H$_2$ and 4'-$\underline{C}$H$_2$), 14.3 (CH$_3$)$_3$$\underline{C}$-Si(CH$_3$)$_2$), -9.1 (CH$_3$)$_3$C-Si($\underline{C}H_3$)$_2$); ν_{max} (solid, cm^{-1}); 1337, 1148 (SO_2), 1019 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{11}H_{26}INO_2SSi$ 391.0498 $[M+H]^+$; found 391.0493.

***N*-(tert-butyldimethylsilyl)(iodomethylsulfonyl)-*N*-propylamine**

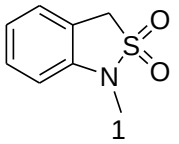


Prepared following the general procedureto yield **120h** (1.15 g, 80 %) obtained as a colourless solid; mp : 136-138 °C; **^{1}H NMR** ($CDCl_3$ 400 MHz) δ_H 4.39 (s, 2H, I-C$\underline{H}_2$), 2.69 (t, *J* 6.6 Hz, 2H, 2-C$\underline{H}_2$),1.61-1.59 (m, 2H, 3-C$\underline{H}_2$), 0.96 (t, *J* 7.5 Hz 3H, 4-C$\underline{H}_3$), 1.0 (s, 9H, ($\underline{C}H_3)_3$C-Si$(CH_3)_2$), 0.08 (s, 6H, $(CH_3)_3$C-Si($C\underline{H}_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C32.1 (2-$\underline{C}H_2$), 31.9 (I-$\underline{C}H_2$), 26.8 (($\underline{C}H_3)_3$C-Si$(CH_3)_2$), 25.2 (3-$\underline{C}H_2$), 15.2 $(CH_3)_3\underline{C}$-Si$(CH_3)_2$), 14.5 (4-$\underline{C}H_3$), -9.5 $(CH_3)_3$C-Si($\underline{C}H_3)_2$); ν_{max} (solid, cm^{-1}); 1331, 1150 (SO_2), 1024 (N-C); **MS***m/z* (ESI^+) calculated for $C_{10}H_{24}INO_2SSi$ 377.0342 $[M+H]^+$; found 377.0341.

General method for synthesis of sultams

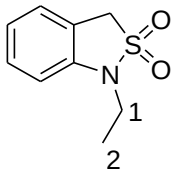
To an oven dried microwave vial, flushed with nitrogen, iodomethanesulfonyl-protected amine derivatives (100 mg) was added followed by dry THF (2.0 mL). To this, benzyne precursor (1.0 equiv) was added and stirred overnight at 25 °C. After this time solvent was removed and the mixture was purified by flash column chromatography to yield the title compound.

1-methyl-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (121a)



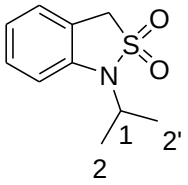
N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-methylamine (100 mg, 0.29 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.97 mg, 0.29 mmol) was reacted following the general method to yield 1-methyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (28 mg, 53 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 1H, Ar-C$\underline{H}$), 7.24−7.19 (m, 1H, Ar-C$\underline{H}$), 7.02 (td, *J* 7.6, 1.0 Hz, 1H, Ar-C$\underline{H}$), 6.78 (d, *J* 8.0 Hz, 1H, Ar-C$\underline{H}$), 4.33 (s, 2H, SO_2-C$\underline{H}_2$), 3.12 (s, 3H, 1-C$\underline{H}_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.3 (Ar-$\underline{C}$), 129.8 (Ar-$\underline{C}$H), 126.8 (Ar-$\underline{C}$H), 121.9 (Ar-$\underline{C}$), 118.5 (Ar-$\underline{C}$H), 112.6 (Ar-$\underline{C}$H), 54.7 (SO_2-$\underline{C}H_2$), 31.3 (1-$\underline{C}$); ν_{max} (solid, cm^{-1}); 1333, 1144 (SO_2), 1321 (N-C); **MS***m/z* (ESI^+) calculated for $C_8H_9NSO_2$ 183.0354 $[M+H]^+$; found 183.0359.

1-ethyl-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (121b)



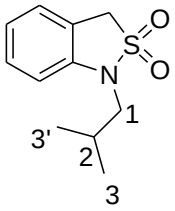
N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-ethylamine (100 mg, 0.28 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.82 mg, 0.28 mmol) was reacted following the general method to yield 1-ethyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (28 mg, 51 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 1H, Ar-C<u>H</u>), 7.29−7.25 (m, 1H, Ar-C<u>H</u>), 7.03 (td, *J* 7.5, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.84 (d, *J* 8.0 Hz, 1H, Ar-C<u>H</u>), 4.32 (s, 2H, SO_2-C<u>H</u>$_2$), 3.14 (t, *J* 14.4 Hz, 2H, 1-C<u>H</u>$_2$), 1.41 (t, *J* 7.0 Hz, 3H, 2-C<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.3 (Ar-<u>C</u>), 132.3 (Ar-<u>C</u>H), 128.5 (Ar-<u>C</u>H), 118.5 (Ar-<u>C</u>), 114.8 (Ar-<u>C</u>H), 112.9 (Ar-<u>C</u>H), 55.2 (SO_2-<u>C</u>H_2), 41.3 (1-<u>C</u>H_2), 9.9 (2-<u>C</u>H_3); ν_{max} (solid, cm^{-1}); 1343, 1145 (SO_2), 1315 (N-C); **MS***m/z* (ESI^+) calculated for $C_9H_{11}NSO_2$ 197.0510 $[M+H]^+$; found 197.0511.

1-i*so*propyll-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121c)



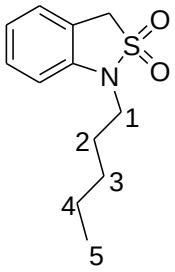
N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-i*so*propylamine (100 mg, 0.27 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.79 mg, 0.27 mmol) was reacted following the general method to yield 1-*iso*propyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (26 mg, 46 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36−7.32 (m, 1H, Ar-C<u>H</u>), 7.27−7.23 (m, 1H, Ar-C<u>H</u>), 6.99 (td, *J* 7.5, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.68 (d, *J* 8.0 Hz, 1H, Ar-C<u>H</u>), 4.32 (s, 2H, SO_2-<u>C</u>H_2), 4.29 (m, 1H, 1-C<u>H</u>), 1.51 (m, 6H, 2-C<u>H</u>$_3$ and 2'-C<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.1 (Ar-<u>C</u>), 130.2 (Ar-<u>C</u>H), 127.9 (Ar-<u>C</u>H), 117.6 (Ar-<u>C</u>), 113.8 (Ar-<u>C</u>H), 112.5 (Ar-<u>C</u>H), 55.0 (SO_2-<u>C</u>H_2), 44.4 (1-<u>C</u>H), 20.1 (2-<u>C</u>H_3 and 2'-<u>C</u>H_3); ν_{max} (solid, cm^{-1}); 1335, 1144 (SO_2), 1317 (N-C); **MS***m/z* (ESI^+) calculated for $C_{10}H_{13}NSO_2$ 211.0667 $[M+H]^+$; found 211.0661.

1-*iso*butyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121d)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-is*o*butylamine (100 mg, 0.26 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.76 mg, 0.26 mmol) was reacted following the general method to yield 1-*iso*butyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (26 mg, 44 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 1H, Ar-C<u>H</u>), 7.24−7.20 (m, 1H, Ar-C<u>H</u>), 7.0 (td, *J* 7.5, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.86 (d, *J* 8.0 Hz, 1H, Ar-C<u>H</u>), 4.33 (s, 2H, SO_2-<u>C</u>H_2), 3.41-3.39 (m, 2H, 1-C<u>H</u>$_2$), 2.2-2.1 (m, 1H, 2-C<u>H</u>), 1.01 (s, 6H, 3-C<u>H</u>$_3$ and 3'-C<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8 (Ar-<u>C</u>), 131.1 (Ar-<u>C</u>H), 128.0 (Ar-<u>C</u>H), 118.2 (Ar-<u>C</u>), 113.7 (Ar-<u>C</u>H), 113.0 (Ar-<u>C</u>H), 55.9 (SO_2-<u>C</u>H_2), 54.3 (1-<u>C</u>H_2), 25.5 (2-<u>C</u>H), 19.9 (3-<u>C</u>H_3 and 3'-<u>C</u>H_3); ν_{max} (solid, cm^{-1}); 1335, 1144 (SO_2), 1329 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{11}H_{15}NSO_2$ 225.0823 $[M+H]^+$; found 225.0811.

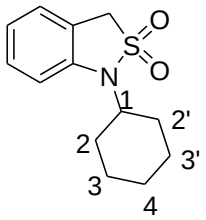
1-amyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121e)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-amylamine(100 mg, 0.25 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.74 mg, 0.25 mmol) was reacted following the general method to yield 1-amyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (29 mg, 48 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 1H, Ar-C<u>H</u>), 7.38−7.29 (m, 1H, Ar-C<u>H</u>), 7.01 (td, *J* 7.5, 1.0 Hz, 1H, Ar-C<u>H</u>), 6.79 (d, *J* 8.0 Hz, 1H, Ar-C<u>H</u>), 4.34 (s, 2H, SO_2-<u>C</u>H_2), 3.58 (t, *J* 15.0 Hz, 2H, 1-C<u>H</u>$_2$), 1.57-1.52 (m, 2H, -C<u>H</u>$_2$), 1.47-143 (m, 2H, 3-C<u>H</u>$_2$), 1.40-1.33(m, 2H, 4-C<u>H</u>$_2$), 0.97 (t, *J* 7.0 Hz, 3H, 5-C<u>H</u>$_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8 (Ar-<u>C</u>), 133.1 (Ar-<u>C</u>H), 128.8 (Ar-<u>C</u>H), 119.4 (Ar-<u>C</u>), 115.1 (Ar-<u>C</u>H), 113.1 (Ar-<u>C</u>H), 54.7 (SO_2-<u>C</u>H_2), 47.7 (1-<u>C</u>H_2),

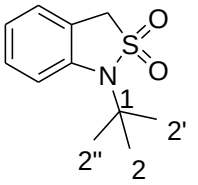
29.6 (2-$\underline{C}H_2$), 26.6 (3-$\underline{C}H_2$), 22.5 (4-$\underline{C}H_2$), 13.9 (5-$\underline{C}H_3$); ν_{max} (solid, cm^{-1}); 1343, 1145 (SO_2), 1334 (N-C); **MS***m/z* (ESI^+) calculated for $C_{12}H_{17}NSO_2$ 239.0930 $[M+H]^+$; found 239.0932

1-cyclohexyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121f)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-amylamine(100 mg, 0.24 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.71 mg, 0.24 mmol) was reacted following the general method to yield 1-cyclohexyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (23 mg, 38 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42−7.38 (m, 1H, Ar-C$\underline{H}$), 7.33−7.28 (m, 1H, Ar-C$\underline{H}$), 6.99 (td, *J* 7.5, 1.0 Hz, 1H, Ar-C$\underline{H}$), 6.84 (d, *J* 8.0 Hz, 1H, Ar-C$\underline{H}$), 4.32 (s, 2H, SO_2-$\underline{C}H_2$), 3.59-3.56 (m, 1H, 1-C$\underline{H}$), 2.19-1.97 (m, 2H, 2-C$\underline{H}$ and , 2'-C$\underline{H}$), 1.77-145 (m, 6H, 3-C$\underline{H}$, 3'-C$\underline{H}$ and , 4-C$\underline{H}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.1 (Ar-$\underline{C}$), 134.0 (Ar-$\underline{C}$H), 129.6 (Ar-$\underline{C}$H), 119.9 (Ar-$\underline{C}$), 115.2 (Ar-$\underline{C}$H), 113.6 (Ar-$\underline{C}$H), 55.1 (SO_2-$\underline{C}$), 47.3 (1-$\underline{C}$H), 30.6 (2-$\underline{C}H_2$ and 2'-$\underline{C}H_2$), 28.1 (4-CH_2), 23.5 (3-$\underline{C}H_2$ and 3'-$\underline{C}H_2$); ν_{max} (solid, cm^{-1}); 1348, 1149 (SO_2), 1331 (N-C); **MS***m/z* (ESI^+) calculated for $C_{13}H_{17}NSO_2$ 251.0980 $[M+H]^+$; found 250.0980.

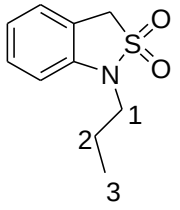
1-tertbutyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121g)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-is*o*butylamine (100 mg, 0.26 mmol) and 2-(trimethylsily)phenyltifluoromethanesulfonate (0.76 mg, 0.26 mmol) was reacted following the general method to yield 1-*tert*butyl-1, dihydrobenzo[c]isothiazole 2,2-dioxide (27 mg, 44 %) as a colourless gum.**^{1}H NMR** (400 MHz, CDCl3) δ 7.39−7.31 (m, 1H), 7.28−7.25 (m, 1H), 7.02 (td, *J* 7.5, 1.0 Hz, 1H), 6.84 (d, *J* 8.0 Hz, 1H), 4.32 (s, 2H, SO_2-$\underline{C}H_2$), 1.78 (s, 9H, 2-$\underline{C}H_3$, 2'-$\underline{C}H_3$ and 2''-$\underline{C}H_3$). **^{13}C NMR** (100 MHz, CDCl3) δ 141.5 (Ar-$\underline{C}$), 131.6 (Ar-$\underline{C}$H), 128.2 (Ar-$\underline{C}$H),

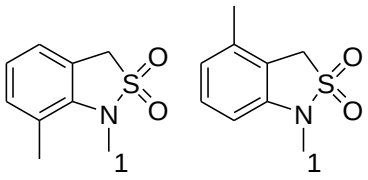
118.7 (Ar-C), 113.8 (Ar-CH), 112.9 (Ar-CH), 55.6 (SO_2-CH_2), 44.7 (1-CH), 27.3 (2-CH, 2'-CH and 2''-CH); ν_{max} (solid, cm^{-1}); 1332, 1140 (SO_2), 1320 (N-C); **MS***m/z* (ESI^+) calculated for $C_{11}H_{15}NSO_2$ 225.0823 $[M+H]^+$; found 225.0813.

1-propyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (121h)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-ethylamine(100 mg, 0.27 mmol) and 2-(trimethylsily) phenyltifluoromethanesulfonate (0.79 mg, 0.27 mmol) was reacted following the general method to yield 1-propyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (28 mg, 49 %) as a colourless gum.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 1H, Ar-CH), 7.29−7.25 (m, 1H, Ar-CH), 7.03 (td, *J* 7.5, 1.0 Hz, 1H, Ar-CH), 6.84 (d, *J* 8.0 Hz, 1H, Ar-CH), 4.32 (s, 2H, SO_2-CH_2), 3.14-3.10 (m, 2H, 1-CH_2), 1.41 (m, 2H, 2-CH_2), 0.96 (t, *J* 7.0 Hz, 3H, 3-CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.3 (Ar-C), 132.3 (Ar-CH), 128.5 (Ar-CH), 118.5 (Ar-C), 114.8 (Ar-CH), 112.9 (Ar-CH), 55.2 (SO_2-CH_2), 41.3(1-CH_2), 20.2 (2-CH_2), 9.9 (3-CH_3); ν_{max} (solid, cm^{-1}); 1343, 1145 (SO_2), 1327 (N-C); **MS***m/z* (ESI^+) calculated for $C_{10}H_{13}NSO_2$ 211.0667 $[M+H]^+$; found 211.0667.

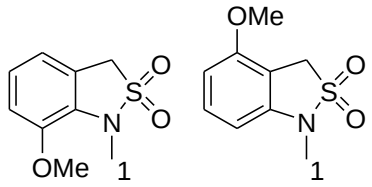
1-methyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (128a-128b)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-methylamine (100 mg, 0.29 mmol) and 2-methYL-6-(trimethylsily)phenyltifluoromethanesulfonate (0.95 mg, 0.29 mmol) was reacted following the general method to yield 1-methyl-1,dihydrobenzo[c]isothiazole 2,2-dioxide (25 mg, 44 %) as a colourless gum. Major: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27−7.24 (m, 1H, Ar-CH), 7.1-7.03 (m, 1H, Ar-CH), 6.56 (d, *J* 8.0 Hz, 1H, Ar-CH), 4.26 (s, 2H, SO_2-CH_2), 3.10 (s, 3H, Ar-C-CH_3), 2.25 (s, 3H, 1-CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.3 (Ar-C), 129.7 (Ar-C), 126.6

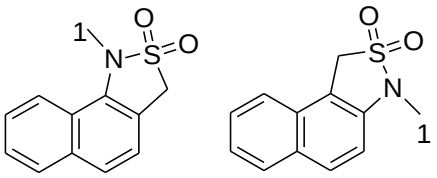
(Ar-CH), 121.9 (Ar-C), 118.5 (Ar-CH), 112.6 (Ar-CH), 52.4 (SO_2-CH_2), 30.1(1-CH_3), 17.9 (Ar-C-CH_3); ν_{max} (solid, cm^{-1}); 1333, 1144 (SO_2), 1314 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_9H_{11}NSO_2$ 197.0510 $[M+H]^+$; found 197.0513.

1-methoxy-1,dihydrobenzo[c]isothiazole 2,2-dioxide (125a-125b)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-methylamine (100 mg, 0.29 mmol) and 2-methyl-6-(trimethylsily)phenyltifluoromethanesulfonate (0.91 mg, 0.29 mmol) was reacted following the general method to yield 1-methoxy-1,dihydrobenzo[c]isothiazole 2,2-dioxide (27 mg, 48 %) as a colourless gum: Major; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29−7.26 (t, *J* 16.0 Hz, 1H, Ar-CH), 7.02-7.00 (t, *J* 16.0 Hz, 1H, Ar-CH), 6.29 (dd, *J* 8.0, 2.4 Hz, 1H, Ar-CH), 5.30 (s, 2H, O-CH_3), 4.78 (s, 2H SO_2-CH_2), 3.89 (s, 3H, O-CH_3), 2.83 (s, 3H, 1-CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6 (Ar-C-OMe), 141.2 (Ar-C), 123.4 (Ar-CH), 122.1 (Ar-C), 118.9 (Ar-CH), 113.7 (Ar-CH), 55.4 (O-CH_3), 52.4 (SO_2-CH_2), 30.1 (1-CH_3); ν_{max} (solid, cm^{-1}); 1333, 1144 (SO_2), 1308 (N-C), 1219 (C-O); **MS***m/z* (ESI$^+$) calculated for $C_9H_{11}NSO_3$ 213.0460. $[M+H]^+$; found 213.0465.

2-naphthaline-6-(Trimethylsily)phenyltifluoromethanesulfonate (131a-131b)



N-(*tert*-Butyldimethylsilyl)(iodomethylsulfonyl)-*N*-methylamine (100 mg, 0.29 mmol) and 2-naphthaline-6-(trimethylsily)phenyltifluoromethanesulfonate (101 mg, 0.29 mmol) was reacted following the general method to yield 1-methoxy-1,dihydrobenzo[c]isothiazole 2,2-dioxide (29 mg, 43 %) as a colourless gum: Major; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* 8.5 Hz, 2H, Ar-CH), 7.51-7.32 (m, 2H, Ar-CH), 7.16-7.04 (dd, *J* 8.5, 2.4 Hz, 1H, Ar-CH), 4.63 (s, 2H, SO_2-CH_2), 3.43 (s, 3H, 1-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.6 (Ar-C), 136.5 (Ar-C), 128.4 (Ar-CH), 127.1 (Ar-C), 125.8 (Ar-CH), 123.8 (Ar-CH), 123.7 (Ar-CH), 120.3 (Ar-CH), 120.1 (Ar-CH), 118.9 (Ar-C), 52.5 (SO_2-CH_2), 30.3 (1-CH_3); ν_{max} (solid, cm^{-1}); 1333, 1144 (SO_2), 1319 (N-C); **MS***m/z* (ESI$^+$) calculated for $C_{12}H_{11}NSO_2$ 233.0511 $[M+H]^+$; found 233.0513

6. References

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