α-Functionalisation of Cyclic Sulfoximines *via* Lithiation-Trapping

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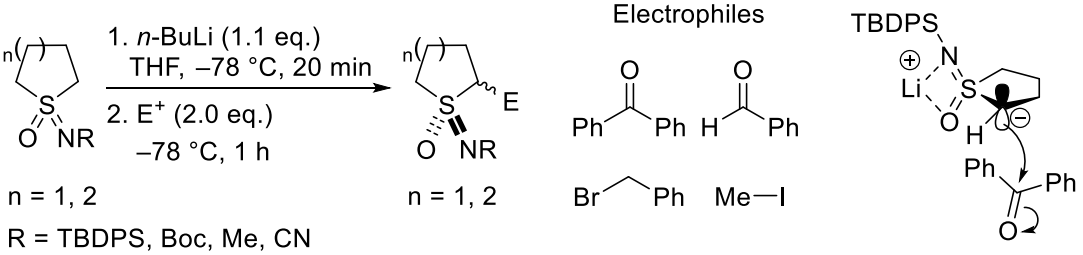
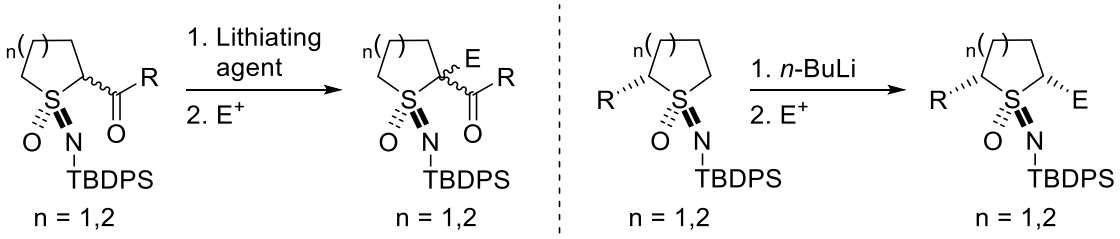
Abstract

This thesis describes the development of a general synthetic approach for the diastereoselective synthesis of a wide range of α-functionalised sulfoximines *via* lithiation-trapping reactions. In addition, studies for the synthesis of 2,2- and 2,5/2,6-disubstituted cyclic sulfoximines are reported.

The synthesis of cyclic and acyclic sulfoximines with different *N*-substituents is described in Chapter 2.1. Chapter 2.2 explores the scope and diastereoselectivity of lithiation-trapping reactions of 5- and 6-membered ring sulfoximines with a range of electrophiles (including benzophenone, benzaldehyde, benzyl bromide and methyl iodide) and *N*-substituents (TBDPS, Boc, Me and CN). Our results show high α-diastereoselectivity with the *N*-TBDPS group, giving mostly *cis* diastereomers in high yields. Good yields and diastereoselectivity were also observed for the lithiation-trapping reactions of *N*-Boc, *N*-Me and *N*-CN sulfoximines. It is proposed that the sterically bulky TBDPS group is able to block one face of the sulfoximine preventing electrophilic attack on one side. Therefore, the trapped sulfoximine adopts a configuration where the new α-substituent is *cis* to the sulfoximine oxygen.



In Chapter 2.3, the synthesis of disubstituted sulfoximines is reported. The two routes detail the diastereoselective synthesis of 2,2- and 2,5/2,6-disubstituted sulfoximines. The approach to 2,2-disubstituted sulfoximines was far less successful than that to the 2,5/2,6-disubstituted sulfoximines.



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Author's Declaration

The research presented in this thesis is, to the best of my knowledge, original except where due reference has been made to other authors. This work has not previously been presented for an award at this, or any other, University.

Giordaina Hartley

1. Introduction

1.1 Introduction to Sulfoximines

There is growing interest in synthetic chemistry using sulfoximines **1** (Figure 1.1) due to recent developments in the use of sulfoximines in both the pharmaceutical[1] and agrochemical[2] industries. The first example of the characterisation of a sulfoximine was reported in 1950.[3] With reference to synthetic chemistry, sulfoximines **1** are much less studied than their corresponding sulfones **2** and sulfoxides **3** (Figure 1.1). Commonly referred to as the mono-aza analogues of sulfones, sulfoximines **1** have a nitrogen in place of one of the oxygen atoms in sulfones **2** but share many of the properties of both sulfones and sulfoxides.

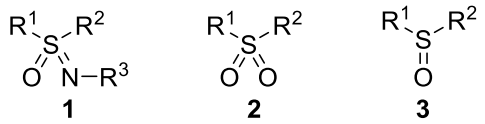
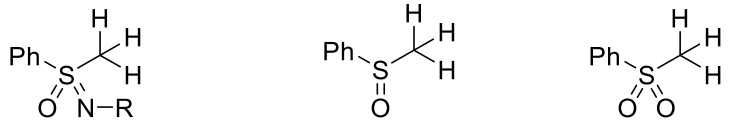


Figure 1.1 Structure of sulfoximines **1**, sulfones **2** and sulfoxides **3**

Due to the presence of a nitrogen atom in sulfoximines **1**, a range of different types of sulfoximines are possible, depending on the structure of the R^3 group. The main classes of sulfoximines contain NH, *N*-alkyl, *N*-aryl, *N*-SiR_3, *N*-SO_2R and *N*-CN groups.[4] Electron withdrawing groups such as *N*-SO_2R and *N*-CN increase the polarity of the sulfoximine unit, whilst electron donating groups such as *N*-alkyl, *N*-aryl and *N*-SiR_3 decrease the polarity. In a similar way to sulfoxides **3**, the sulfur atom in sulfoximines **1** is a stereogenic centre providing its two substituents are not identical ($R^1 \neq R^2$).

The sulfoximine unit is electron withdrawing and, as a result, the proton on nitrogen in NH sulfoximines and the α-protons on carbon of *N*-substituted sulfoximines can be deprotonated by bases. Bordwell has carried out measurements of pK_a values (DMSO, 25 °C) for numerous functional groups including the α-protons of *N*-substituted sulfoximines, sulfones and sulfoxides.[5] Some example pK_a values are shown in Figure 1.2. For sulfoximines, the *N*-substituent has a large impact on the pK_a value of the α-protons. For example, sulfoximine **4** has a methyl group on nitrogen and a pK_a of 33 but replacing the methyl with the electron withdrawing tosyl group in sulfoximine **5** results in a lower pK_a of 24.5. In contrast, the α-protons of sulfoxide **6** have a pK_a of 33 whilst

the corresponding sulfone **7** has a lower pK_a of 29, presumably due to the electron withdrawing ability of the additional oxygen atom bonded to sulfur.



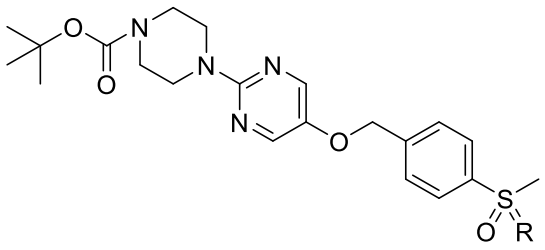
4 R = Me, pK_a = 33
5 R = Ts, pK_a = 24.5

6
pK_a = 33

7
pK_a = 29

Figure 1.2 pK_as of α-protons of sulfoximines **4** and **5**, sulfoxide **6** and sulfone **7**

Interestingly, a number of pharmaceutical companies have begun to include the sulfoximine functional group in their drug development programmes. Potential pharmaceuticals bearing the sulfoximine functional group often benefit from increased polarity and solubility in comparison to their sulfone analogues. A comparison of aqueous solubility and logD at pH 7.4 between sulfone **8** and two sulfoximines **9** and **10** is shown in Table 1.1.[6] Sulfone **8** showed a low solubility of <0.2 μM and a high logD of 3.2. Using small molecule X-ray crystallography, the insolubility of the sulfone was shown to be a result of intermolecular interactions of the sulfone group stabilising the solid-state.[7] In comparison, the corresponding NH sulfoximine **9** displayed a significantly higher solubility (7.0 μM) and was less lipophilic (logD of 2.5). The analogous *N*-Me sulfoximine **10** also displayed high solubility (5.0 μM) when compared to sulfone **8** despite having almost the same lipophilicity (logD of 3.3). High solubility and low lipophilicity are beneficial features when developing potential pharmaceuticals as they make the compounds more likely to pass through the earlier stages of clinical testing.



Entry	Compound	R	LogD	Aqueous Solubility/μM
1	**8**	O	3.2	0.2
2	**9**	NH	2.5	7.0
3	**10**	NMe	3.3	5.0

Table 1.1 Log D and aqueous solubility of sulfone **8** and sulfoximines **9** and **10**

Bayer investigated sulfonamide ZK 304709 as a potential CDK inhibitor.[8] ZK 304709 was found to have low lipophilicity (logD of 0.3 at pH 7.5) and low thermodynamic solubility in water (19 mM). During phase 1 studies of the sulfonamide, the low solubility proved to be an issue and the studies were terminated. As a result, a sulfoximine analogue was synthesised and this led to the development of enantiopure nanomolar pan-CDK inhibitor BAY 1000394 (Figure 1.3).[9] This compound displayed high thermodynamic solubility in water (423 μM) which was significantly greater than that of sulfonamide ZK 304709. The solubility of the sulfoximine was also shown to increase in organic solvents and at a low pH. Another sulfoximine compound which has shown promise as a potential cancer treatment is the enantiopure ATR inhibitor AZD6738[10,11] developed by AstraZeneca (Figure 1.3). Clinical trials have shown it to be effective at treating gastric cancer cells,[12] although research is still ongoing. In addition, the racemic sulfoximine Sudexanox[13,14] (Figure 1.3) underwent clinical trials as an oral antiasthmatic drug, with promising results.

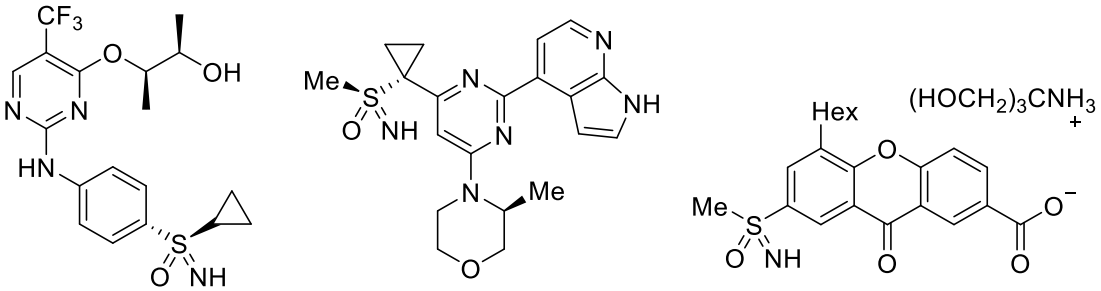


Figure 1.3 Clinical candidates bearing the sulfoximine functional group

Sulfoximines have also been utilised in agrochemistry as insecticides.[2] The mixture of diastereomeric *N*-CN sulfoximines, commonly known as Sulfoxaflor,[15] and other related sulfoximines **11**[16] and **12**[17] (Figure 1.4) have proved to be more efficient than traditional insecticides.[18] Use of a cyano group as the *N*-substituent was found to give increased insecticidal activity when compared to the corresponding nitro sulfoximines. As a result, there has been a significant effort to synthesise sulfoximines for this purpose, especially those bearing the CN functionality.

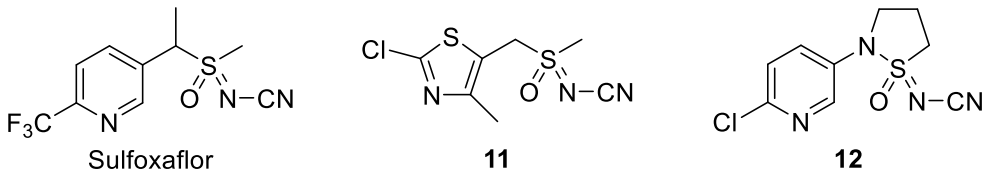
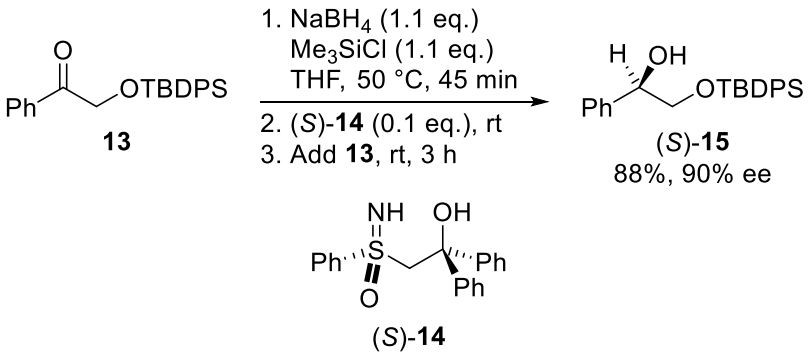


Figure 1.4 Potential insecticides bearing the sulfoximine functional group

Sulfoximines have also been used as chiral resolving agents and as chiral ligands in asymmetric catalysis.[4] For example, Johnson developed a method using an α-lithiated sulfoximine to resolve chiral ketones.[19] Work by Bolm[20] demonstrated the catalytic asymmetric reduction of ketones such as **13** using 0.1 eq. of enantiopure β-hydroxysulfoximine (*S*)-**14**. Alcohol (*S*)-**15** was isolated in 88% yield and 90% ee (Scheme 1.1). Using this method, a range of ketones were reduced in high % ee. Chiral enantiopure sulfoximines have also been utilised as ligands in palladium-catalysed asymmetric allylic substitution reactions.[21]

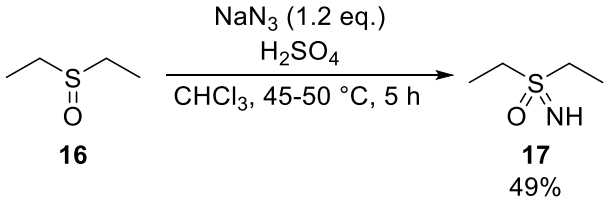


Scheme 1.1

1.2 Synthesis of Sulfoximines

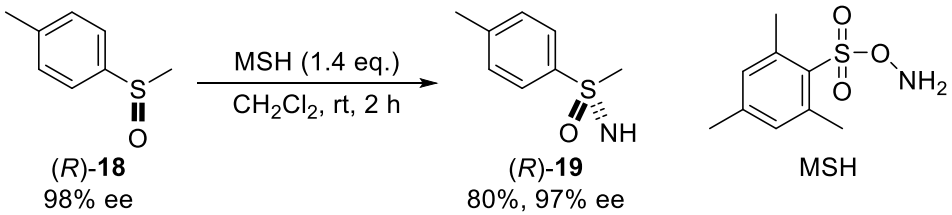
1.2.1 Synthesis of NH sulfoximines

A range of methods have been reported for the synthesis of NH sulfoximines. Routes to NH sulfoximines are of interest as the free nitrogen atom enables further functionalisation of this position. The first reported approach to an NH sulfoximine **17** started from sulfoxide **16** and involved reaction with sodium azide and sulfuric acid (Scheme 1.2). Under these conditions, it is likely that highly toxic and explosive HN_3 is generated so this is not a desirable method. In addition, partial racemisation of enantioenriched sulfoximines can occur during the imination process.[22]



Scheme 1.2

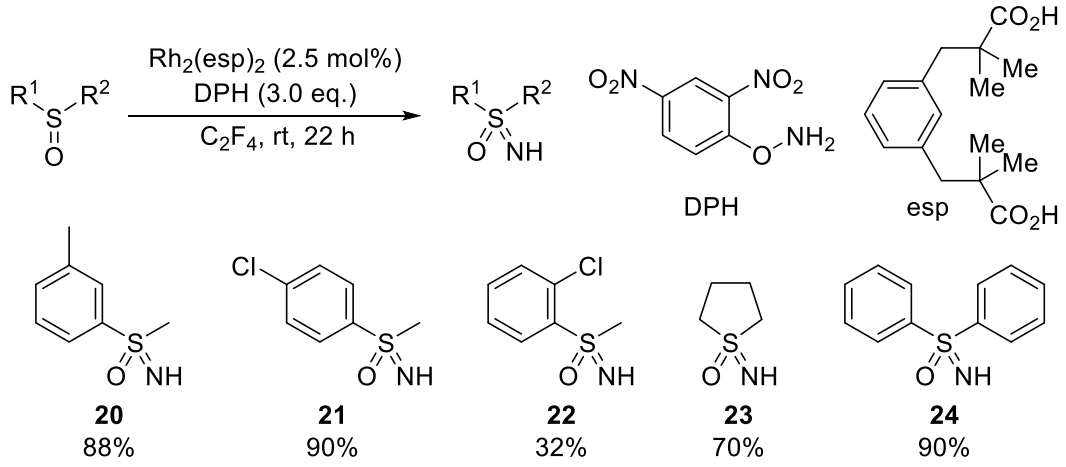
An alternate route to NH sulfoximines from sulfoxides uses *O*-mesitylsulfonylhydroxylamine (MSH) as an electrophilic source of the amino group. It was found that reaction of enantioenriched sulfoxides with MSH proceeded with retention of configuration to give the corresponding enantioenriched sulfoximines. As an example, sulfoxide (*R*)-**18** of 98% ee was converted into sulfoximine (*R*)-**19** of 97% ee in 80% yield (Scheme 1.3).[23] Altering the substituents on the sulfoxide gave sulfoximines in high yields with high % ees in most cases.



Scheme 1.3

An efficient route to arylated and cyclic sulfoximines **20-24** from the corresponding sulfoxides was reported using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) in tetrafluoroethylene (Scheme 1.4).[24] The reaction was catalysed by $Rh_2(esp)_2$ and proceeded *via* a rhodium nitrene intermediate. Good yields were obtained for the majority

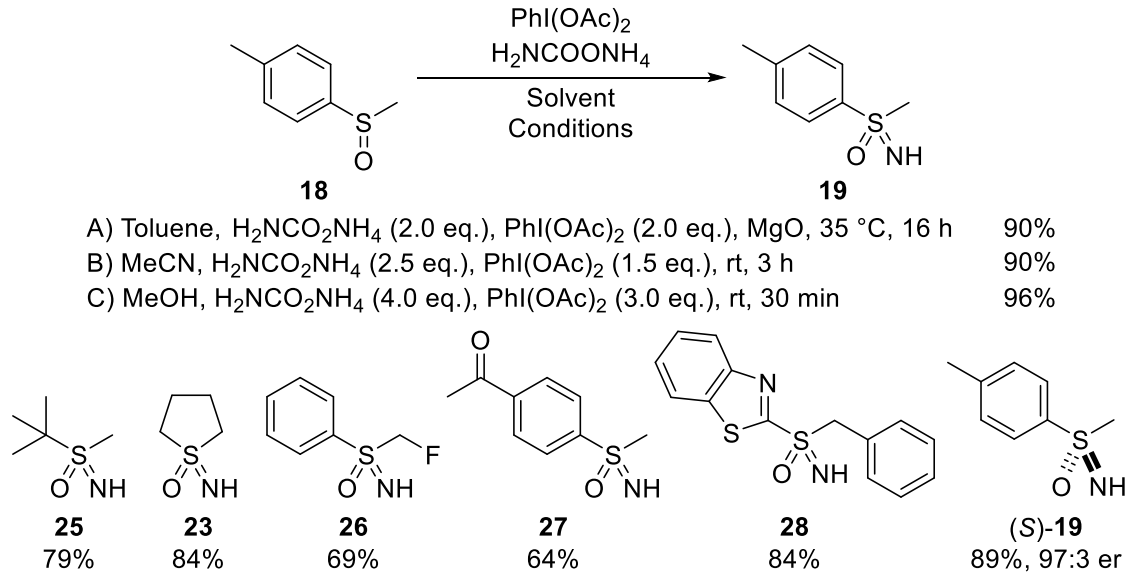
of substrates tested, including those substituted at the *meta* position (**20**, 88%) or *para* position (**21**, 90%). In contrast, substrates substituted at the *ortho* position were synthesised in poor yields (**22**, 32%) presumably due to steric hindrance. Cyclic sulfoximine **23** and diphenyl sulfoximine **24** were also synthesised in high yields. This method provides an easy route to a wide range of sulfoximines in good yields using mild conditions but involves the use of an expensive rhodium catalyst.



Scheme 1.4

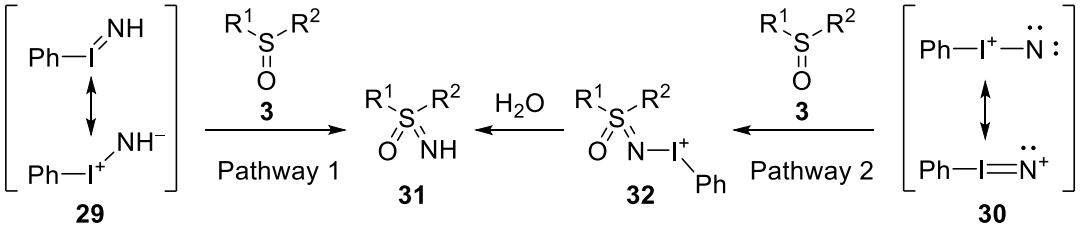
The majority of methods for the direct transfer of an imino group to sulfoxides use harsh reaction conditions or expensive reagents and exhibit some limitations as a result. Work by Luisi, Bull and co-workers detailed a simple way of converting sulfoxides into sulfoximines using mild conditions.[25] Three sets of reaction conditions were investigated using inexpensive ammonium carbamate as a source of ammonia and (diacetoxyiodo)benzene (PIDA) as an oxidising agent (Scheme 1.5). Using reaction conditions A, sulfoxide **18** was converted into sulfoximine **19** in 90% yield. A limitation of the reaction was the insolubility of ammonium carbamate in toluene and, in order to overcome this, the reaction was heated at 35 °C for 16 h. It was found that ammonium carbamate readily dissolved when the reaction was performed at rt in acetonitrile (conditions B) or methanol (conditions C) due to the increased polarity of these solvents in comparison to toluene. Reaction conditions C were preferred as the reaction only took 30 min and sulfoximine **19** was synthesised in 96% yield. The scope of the reaction was investigated using conditions C, giving a diverse range of sulfoximines **25**-**28**, **23** and (*S*)-**19** in high yields (Scheme 1.5). In addition, the reaction was shown to proceed with retention of stereochemistry when performed on an enantioenriched sulfoxide. For

example, sulfoximine (*S*)-**19** was synthesised with a 97:3 er in 89% yield from the corresponding sulfoxide of 97:3 er.



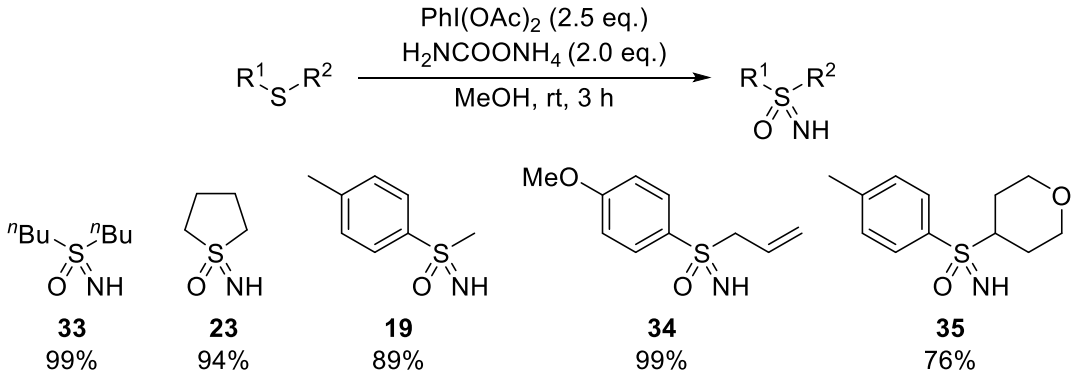
Scheme 1.5

A mechanistic investigation on this formation of sulfoximines from sulfoxides was carried out by Luisi, Bull and co-workers. Analysis of the reaction by mass spectrometry under flow conditions briefly detected intermediates **29** and **30** and, as a result, two possible pathways were proposed (Scheme 1.6). In pathway 1, the sulfur lone pair of sulfoxide **3** attacks the nitrogen atom of intermediate **29** and subsequent elimination of iodobenzene would form sulfoximine **31**. Alternatively, sulfoxide **3** could attack the iodine of intermediate **29** and then form sulfoximine **31** through a reductive elimination sequence. In pathway 2, attack on the nitrogen atom of a different cationic intermediate (**30**) by the sulfur lone pair of sulfoxide **3** would result in iodonium species **32** which forms sulfoximine **31** on work-up. Unfortunately, it was not possible to distinguish between pathways 1 and 2. Poorer yields for the reaction were observed when R^1 or R^2 in the sulfoxide was an electron-withdrawing group, showing that the nucleophilicity of the sulfoxide was important for the success of this reaction.



Scheme 1.6

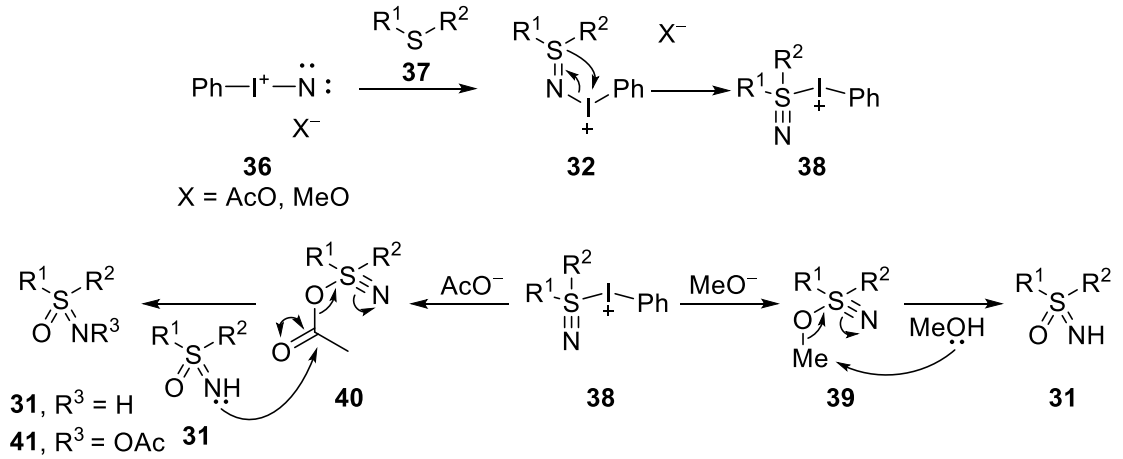
Following on from this work, Bull and Luisi investigated the direct conversion of sulfides into sulfoximines.[26] PIDA was used as the oxidising agent whilst ammonium carbamate, ammonium acetate and ammonia in methanol solution were used as sources of ammonia. The conversion of sulfides into sulfoximines was performed in toluene, acetonitrile and methanol. Methanol was the preferred solvent as the reaction time was the shortest and the yield was the highest (Scheme 1.7). It was discovered by varying the equivalents of PIDA that a minimum of two equivalents were required for complete reaction. Based on previous mechanistic studies, it is believed that one equivalent of PIDA promoted oxygen transfer whilst the second generated the key intermediates **29** or **30** (see Scheme 1.6). In addition, decreasing the amount of ammonium carbamate from four equivalents to one had no effect on the yield. The reaction conditions shown in Scheme 1.7 were selected and the scope of the reaction was investigated. Using the one-pot synthesis, a wide range of sulfoximines **33-35**, **23** and **19** bearing alkyl and aryl groups, as well cyclic sulfoximines were synthesised in high yields.



Scheme 1.7

Recently, Reboul investigated the mechanism for this metal-free preparation of sulfoximines from sulfides (Scheme 1.8).[27] First, it was shown that methanol underwent a fast ligand exchange reaction with PIDA to produce acetic acid which accelerated the decomposition of ammonium carbamate to ammonia. It is thought that ammonia attacked the iodine atom of PIDA, replacing the acetoxy groups to give iodonitrene intermediate **36**. Then, imination of sulfide **37** by iodonitrene **36**, leads to the corresponding iodonium sulfilimine **32**. It is believed that **32** rearranged to give **38** which can then proceed to sulfoximine **31** by two main pathways. Nucleophilic attack of **38** by methoxide or acetate and loss of iodobenzene would give methoxy and acetoxy sulfanenitrile intermediates **39** and **40** respectively. Intermediates **39** and **40** were characterised by ^{1}H, ^{13}C and ^{15}N NMR spectroscopic and HRMS analysis. Nucleophilic attack on methoxy sulfane nitrile **39** by

methanol would give sulfoximine **31**. It was proposed that acetoxy sulfanenitrile **40** could undergo nucleophilic attack by methanol or sulfoximine **31**. If intermediate **40** was attacked by sulfoximine **31**, NH sulfoximine **31** and *N*-acetyl sulfoximine **41** would be formed. The acetyl group of intermediate **40** could also be attacked by methanol to give sulfoximine **31** and methyl acetate. Ultimately, from the mechanistic work, it was concluded that conversion of iodonitrene **36** into sulfoximine **31** could proceed by all three of the pathways discussed.

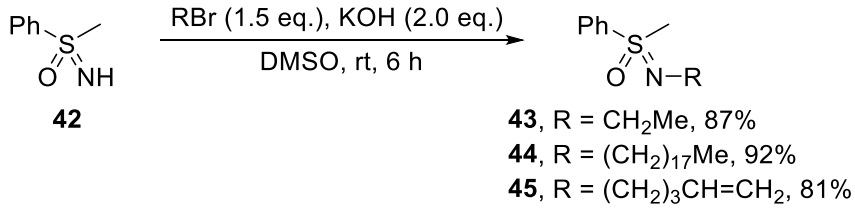


Scheme 1.8

1.2.2 Synthesis of *N*-functionalised sulfoximines

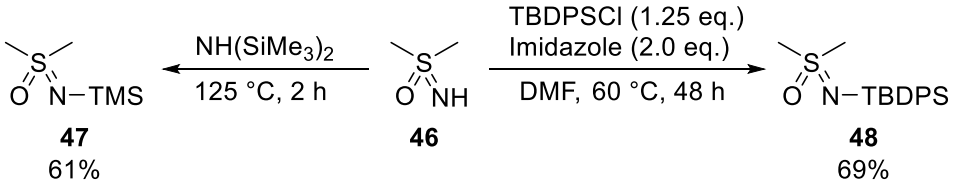
There are two main approaches to *N*-functionalised sulfoximines. One approach involves synthesis of NH sulfoximines and then different methods are used to introduce the *N*-functionality. Alternatively, the *N*-functionalised amine can be introduced directly starting from a sulfoxide or sulfide.

Sulfoximines containing *N*-alkyl groups can be easily prepared from NH sulfoximines using an alkylation reaction. A common method for alkylating NH sulfoximines using mild conditions is shown in Scheme 1.9. Reaction of sulfoximine **42** with potassium hydroxide and an alkyl bromide (rt, 6 h) gave *N*-alkyl substituted sulfoximines **43**, **44** and **45** in 81–92% yields.[28]



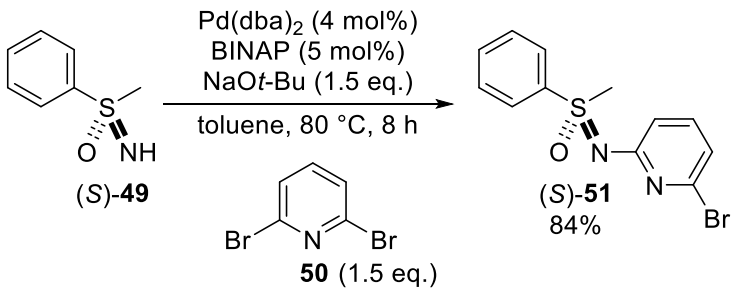
Scheme 1.9

It is currently not possible to directly introduce a *N*-SiR_3 group to a sulfoxide or sulfide. Instead, it is necessary to go *via* the NH sulfoximine. For example, the imino group of dimethyl sulfoximine **46** was readily *N*-silylated (Scheme 1.10).[29] Treatment of sulfoximine **46** with HMDS (125 °C, 2 h) gave *N*-TMS sulfoximine **47** in 61% yield. Alternatively, silylation of sulfoximine **46** using imidazole and TBDPSCl (60 °C, 48 h) gave *N*-TBDPS sulfoximine **48** in 69% yield.



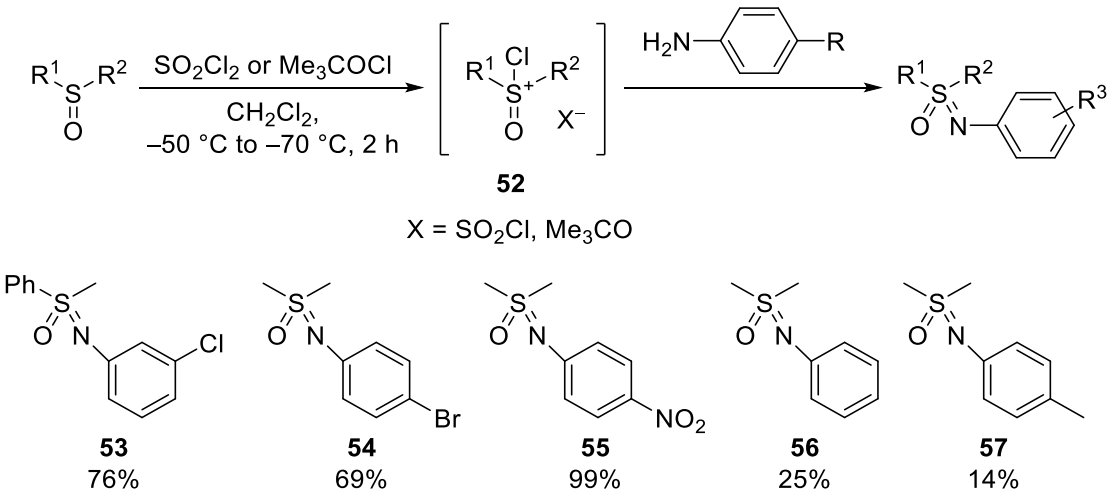
Scheme 1.10

N-Aryl sulfoximines can be directly synthesised from the NH sulfoximine. Bolm investigated palladium-catalysed cross-coupling reactions as routes to *N*-aryl sulfoximines from NH sulfoximines.[30] $Pd(dba)_2$ and BINAP were used to give a Pd(0)/BINAP complex which was able to catalyse the reaction of sulfoximine (*S*)-**49** with aryl bromide **50** (Scheme 1.11). The reaction was heated to 80 °C for 8 h resulting in *N*-aryl sulfoximine (*S*)-**51** in 84% yield, a process which proceeded with retention of stereochemistry.



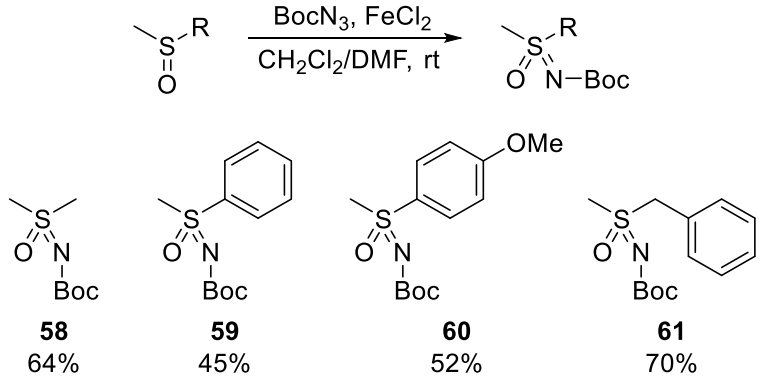
Scheme 1.11

The alternative approach to *N*-functionalised sulfoximines is synthesis directly from the corresponding sulfide or sulfoxide. For example, reaction of sulfoxides with either *t*-butyl hypochlorite or sulfuryl chloride followed by reaction with anilines gave *N*-aryl sulfoximines (Scheme 1.12).[31] The imination reaction was believed to proceed *via* chloro intermediate **52**. Both alkyl and aryl substituted sulfoxides were reacted with a range of substituted anilines giving sulfoximines **53**–**57** generally in high yields. Anilines substituted with an electron withdrawing group gave sulfoximines with significantly higher yields than those substituted with an electron donating group or with no substitution.



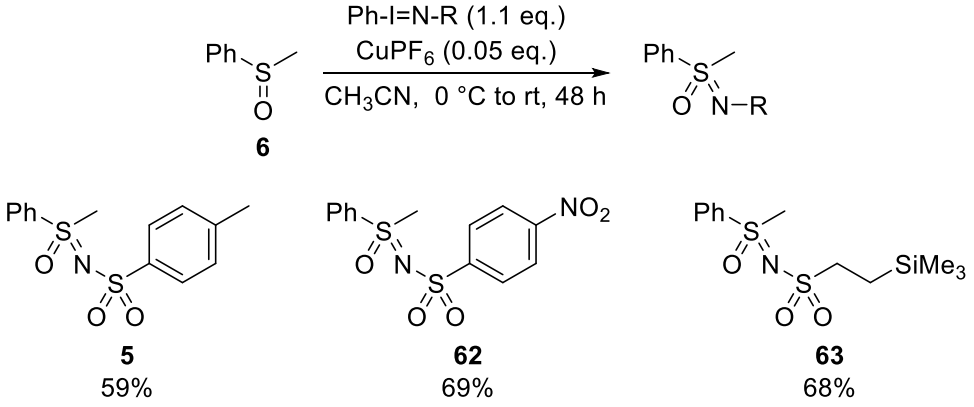
Scheme 1.12

Imination of sulfoxides with substituted azides enables the transfer of an NR group, such as *N*-Boc or *N*-SO_2R, to give *N*-functionalised sulfoximines. Reaction of sulfoximines with *t*-butyloxycarbonyl azide, promoted by a substoichiometric amount of iron(II) chloride, gave *N*-Boc sulfoximines **58**–**61** in 45–70% yields (Scheme 1.13).[32]



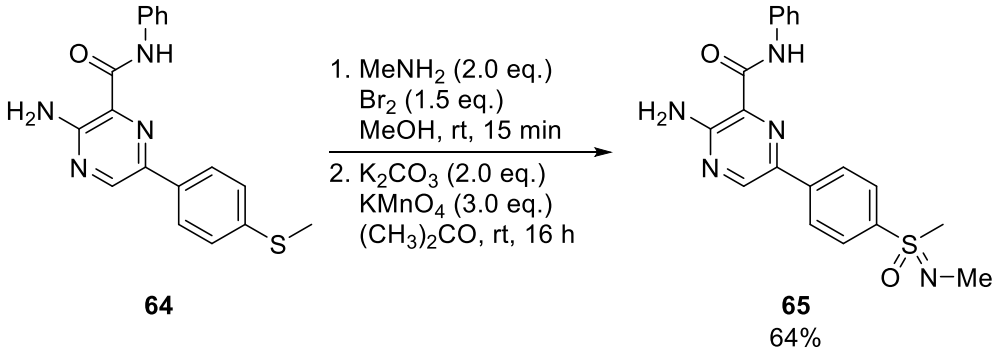
Scheme 1.13

One method for synthesising *N*-SO_2R sulfoximines, reported by Tye,[33] used copper-catalyzed imination of sulfoxides with iminoiodane reagents. As an example, sulfoxide **6** was iminated with PhINTs, PhINNs and PhINSES to give *N*-Ts, *N*-Ns and *N*-SES sulfoximines **5**, **62** and **63** in 59%, 69% and 68% yields respectively (Scheme 1.14). It is possible to remove the Ns and SES group from sulfoximines **62** and **63** to give the NH sulfoximines in good yields.



Scheme 1.14

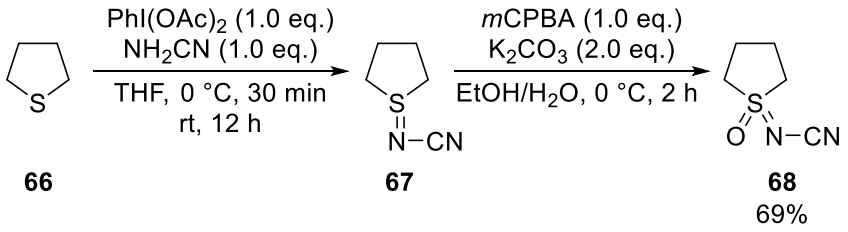
N-Me sulfoximines can be synthesised directly from the corresponding sulfide using a one-pot reaction. An interesting example of this is shown in the synthesis of the potential ATR inhibitor **65**. Imination of sulfide **64** with methylamine and bromine, followed by oxidation using potassium carbonate and potassium permanganate gave *N*-Me sulfoximine **65** in 64% yield (Scheme 1.15).[34]



Scheme 1.15

Routes to *N*-CN sulfoximines are of interest due to the potential insecticidal applications of sulfoximines bearing the cyano group. Reaction of sulfide **66** with PIDA and cyanimide gave imine **67**, and subsequent oxidation using *m*CPBA and potassium carbonate gave *N*-CN sulfoximine **68** in 69% yield over two steps (Scheme 1.16).[35] Other

commonly used conditions for the imination step substitute PIDA for a halogen source such as NCS, NBS or iodine and potassium *tert*-butoxide.[36] Both approaches provide an easy route to *N*-CN sulfoximines in good yields.



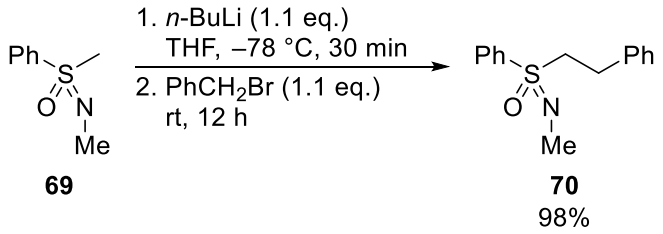
Scheme 1.16

Thus, there are currently a wide range of synthetic methods available for the synthesis of sulfoximines. Due to the mild reaction conditions and the opportunity to convert NH sulfoximines into their *N*-substituted analogues, the methods to NH sulfoximines described by Luisi and Bull appear to be the current best approach.

1.3 α-Functionalisation of Sulfoximines by Lithiation-Trapping

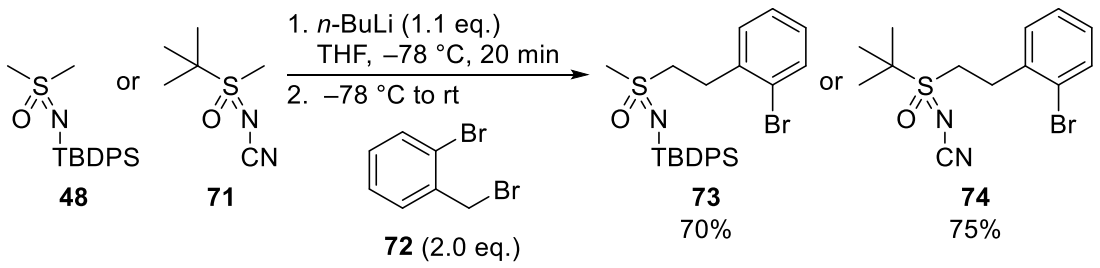
The electron-withdrawing ability of the sulfoximine unit enables the removal of a proton on the α-carbon of *N*-substituted sulfoximines using strong bases. As described in Chapter 1.1, measurements of pK_a values of the α-protons of *N*-substituted sulfoximines were carried out by Bordwell (DMSO, 25 °C).[5] The *N*-substituent of sulfoximines has a large impact on the pK_a value of the α-protons. For example, the α-protons of *N*-Me sulfoximine **4** have a pK_a of 33 whilst the α-protons of *N*-Ts sulfoximine **5** have a pK_a of 24.5 (see Figure 1.2). Given this α-proton pK_a range of 24-33 pK_a units, strong bases such as *n*-BuLi and LDA are typically used. The lithiation-trapping reactions of acyclic sulfoximines have been well explored and there is a wide range of examples. In this chapter, a selection of results are presented to show the scope and limitations of the lithiation-trapping of sulfoximines.

Lithiation-trapping reactions of sulfoximines are most commonly achieved using *n*-BuLi in THF at –78 °C for the deprotonation step, followed by trapping with an electrophile. A representative example is shown in Scheme 1.17. *N*-Me sulfoximine **69** was lithiated using *n*-BuLi in THF at –78 °C for 30 min. Trapping with benzyl bromide gave α-benzylated sulfoximine **70** in 98% yield.[37]



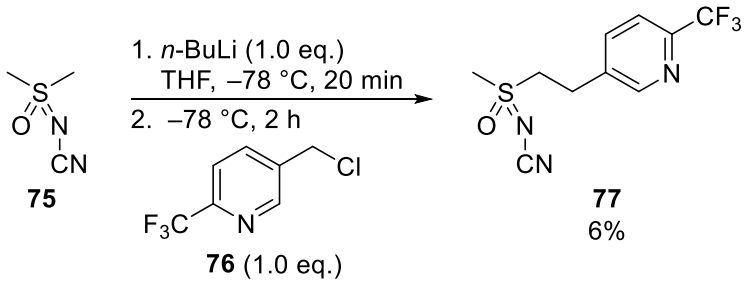
Scheme 1.17

In related reactions, *n*-BuLi at –78 °C was used to lithiate at the α-position of *N*-TBDPS sulfoximine **48** and *N*-CN sulfoximine **71**. Subsequent trapping with benzyl bromide **72** gave *N*-TBDPS sulfoximine **73** in 70% yield and *N*-CN sulfoximine **74** in 75% yield (Scheme 1.18).[38] In these examples, the *N*-substituent did not affect the yield of the products. This is a rare case of a high yielding lithiation-trapping reaction of an *N*-CN sulfoximine.



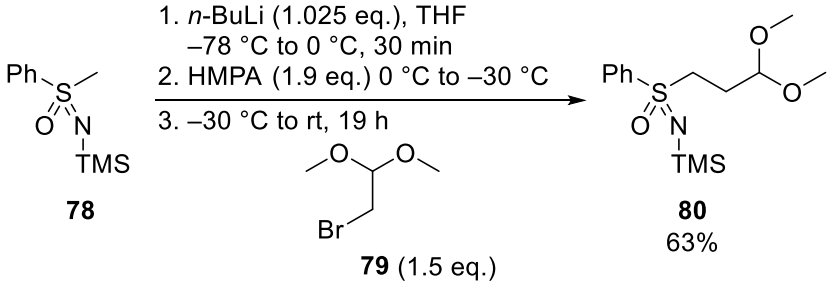
Scheme 1.18

A review of the literature showed that α-functionalised *N*-CN sulfoximines are often obtained in low yields when synthesised by lithiation-trapping reactions.[35,39] A typical example is shown in Scheme 1.19. *N*-CN sulfoximine **75** underwent lithiation by *n*-BuLi at –78 °C in THF for 20 min followed by trapping with electrophile **76** to give sulfoximine **77** in only 6% yield.[39]



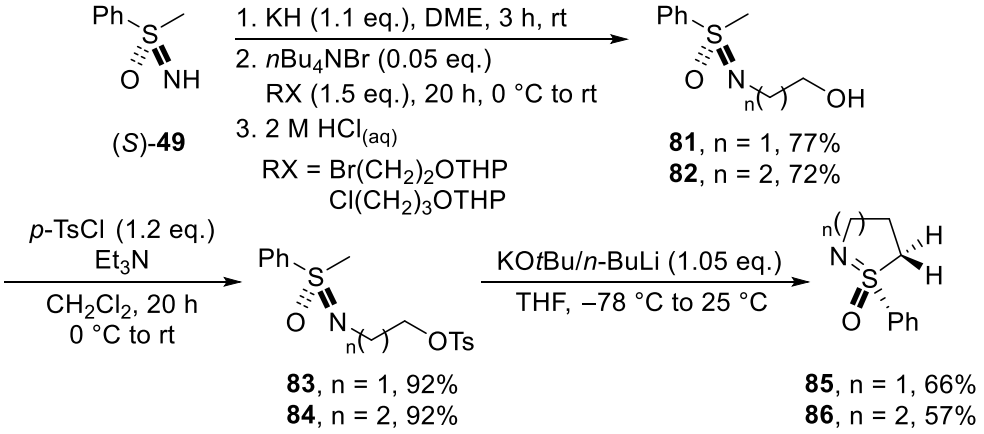
Scheme 1.19

Alkyl halides are one of the most commonly used electrophiles in lithiation-trapping reactions of sulfoximines. For example, *N*-TMS sulfoximine **78** was lithiated at –78 °C in THF using *n*-BuLi. Then, addition of HMPA followed by reaction with alkyl bromide **79** gave sulfoximine **80** in 63% yield (Scheme 1.20).[40] In this reaction, HMPA was presumably used to deaggregate oligomers of the lithiated sulfoximine and improve reactivity. Use of HMPA may have been necessary to achieve a good yield of sulfoximine **80** since alkyl halide **79** is a less activated electrophile than benzyl bromide (see Schemes 1.17 and 1.18).



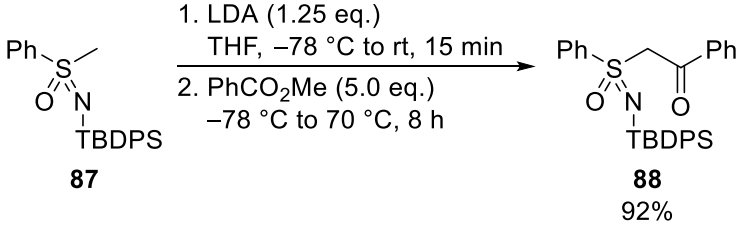
Scheme 1.20

An interesting type of cyclic sulfoximine are those in which the sulfoximine nitrogen atom is incorporated into the ring. For example, 5- and 6-membered ring sulfoximines **85** and **86** can be synthesised from enantiomerically enriched acyclic sulfoximine (*S*)-**49** by a three-step procedure (Scheme 1.21).[41] Deprotonation of the nitrogen of sulfoximine (*S*)-**49** was performed using potassium hydride in DME. Treatment with tetrabutylammonium bromide and THP-protected bromoethanol or chloropropanol gave *N*-alkylated acetals. Then, cleavage using 2 M $HCl_{(aq)}$ gave *N*-functionalised sulfoximines **81** and **82** in 77% yield and 72% yield respectively. Addition of a tosyl group to sulfoximines **81** and **82** was achieved by treatment with Et_3N and *p*-toluenesulfonyl chloride in CH_2Cl_2 to give sulfoximine tosylates **83** and **84** in 92% yield. In the final step, deprotonation at the α-position of sulfoximines **83** and **84** using potassium *tert*-butoxide and *n*-BuLi in THF allowed cyclisation to give 5- and 6-membered ring sulfoximines **85** and **86**.



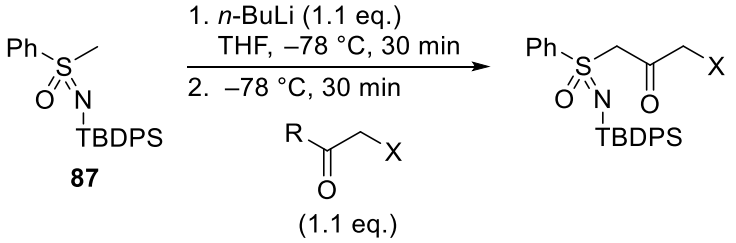
Scheme 1.21

LDA has also been used to deprotonate the α-position of sulfoximines and an example is shown in Scheme 1.22. *N*-TBDPS sulfoximine **87** was deprotonated at the α-position using LDA and subsequent trapping with methyl benzoate gave sulfoximine **88** in 92% yield.[42] Unusually, after addition of the ester the reaction mixture was heated at reflux for 8 h, although the authors did not comment on this aspect of the reaction conditions.



Scheme 1.22

β-Keto sulfoximines can also be synthesised in good yields by lithiation-trapping reactions with Weinreb amides and esters (Table 1.2). For example, lithiation of *N*-TBDPS sulfoximine **87** using *n*-BuLi in THF at –78 °C and subsequent trapping with bromo-substituted Weinreb amide **89** gave sulfoximine **90** in 84% yield (entry 1).[43] Sulfoximine **90** could also be synthesised in a slightly higher yield of 92% by trapping with ethyl ester **91** under the same conditions (entry 3). Chloro-substituted Weinreb amide **92** and ethyl ester **93** were compatible with this reaction giving sulfoximine **94** in high yields (entries 2 and 4), although trapping with iodo-substituted ethyl ester **95** was not successful and gave no sulfoximine **96** (entry 5).

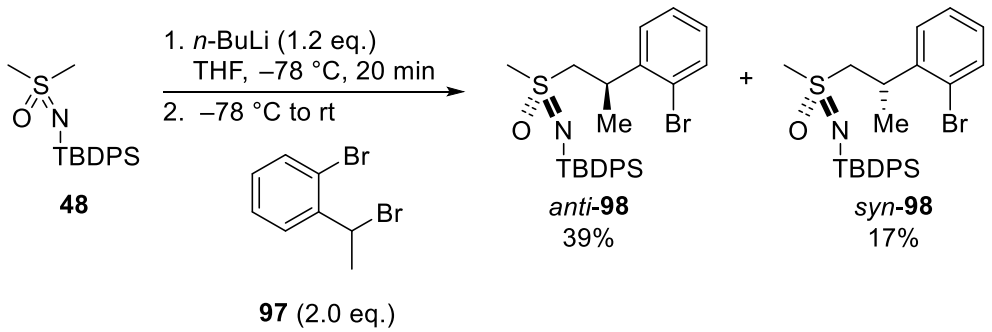


Entry	Electrophile	R	X	Product	Yield (%)[a]
1	**89**	N(OMe)Me	Br	**90**	84
2	**92**	N(OMe)Me	Cl	**94**	82
3	**91**	OEt	Br	**90**	92
4	**93**	OEt	Cl	**94**	89
5	**95**	OEt	I	**96**	0

[a] % yield after purification by chromatography.

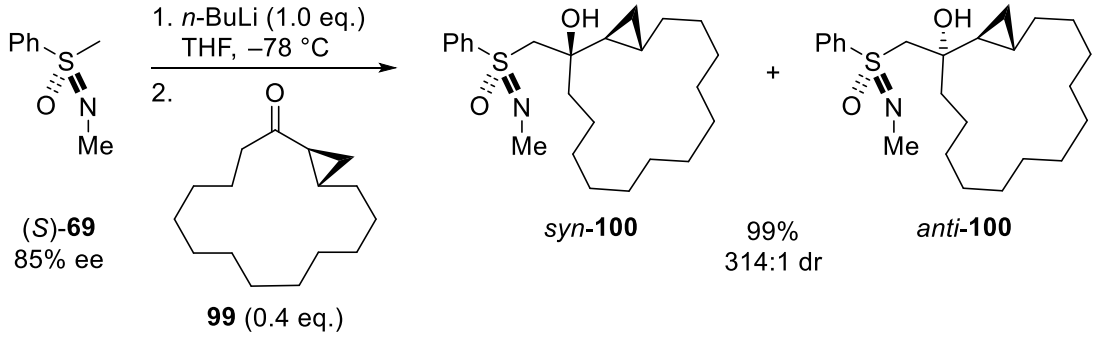
Table 1.2 Lithiation-trapping of sulfoximine **87** with α-halogenated Weinreb amides and esters

Trapping of sulfoximines with secondary alkyl halides can result in a second stereocentre at the β-position (Scheme 1.23). Deprotonation of *N*-TBDPS sulfoximine **48** at the α-position was carried out using *n*-BuLi in THF at –78 °C and subsequent trapping with alkyl bromide **97** gave α-alkylated sulfoximines *anti*-**98** (39% yield) and *syn*-**98** (17% yield).[38] The moderate diastereoselectivity in this reaction arises from match/mismatch effects in the trapping with this chiral electrophile. Sulfoximines *syn*-**98** and *anti*-**98** were converted into known compounds and a comparison of the ^{1}H NMR spectra of these products with those reported in the literature enabled assignment of the relative stereochemistry.[44]



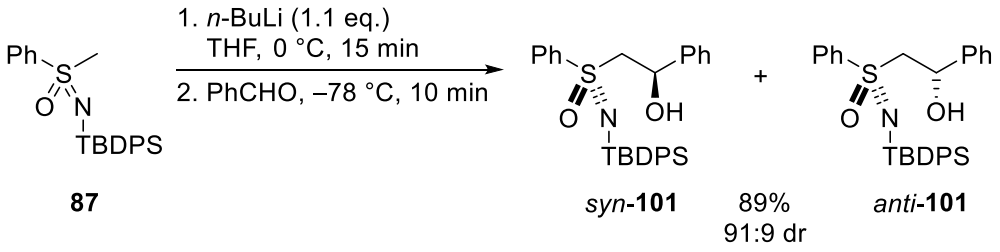
Scheme 1.23

Lithiation-trapping reactions of sulfoximines with a variety of ketones, such as benzophenone, have been explored.[45] Structurally more complex ketones such as **99** containing a macrocycle have also been explored. For example, *N*-Me sulfoximine (*S*)-**69** of 85% ee was lithiated using *n*-BuLi and trapped with enantiomerically enriched macrocyclic ketone **99** (Scheme 1.24).[46] The reaction proceeded with a high level of stereocontrol giving a 314:1 ratio of hydroxy sulfoximines *syn*-**100** and *anti*-**100** in 99% yield with respect to ketone **99**. An investigation of lithiation-trapping reactions with ring sizes from 6-16 showed that reactions with 7-membered rings and larger proceeded with high yields and good stereoselectivity.



Scheme 1.24

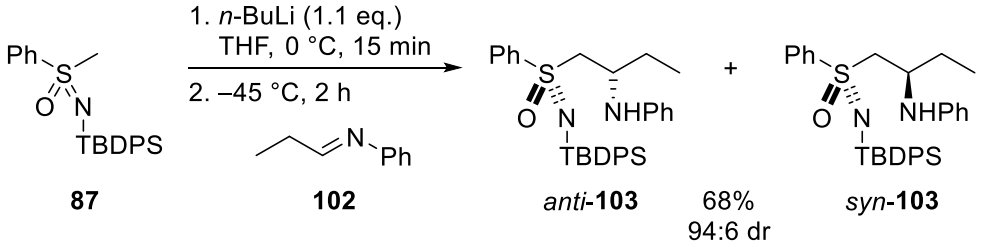
The trapping of lithiated sulfoximines with aldehydes has also been reported. In certain cases, good stereocontrol for the introduction of a stereocentre at the β-position was observed. For example, lithiation of *N*-TBDPS sulfoximine **87** using *n*-BuLi in THF at 0 °C and trapping with benzaldehyde at –78 °C gave a 91:9 mixture of alcohols *syn*-**101** and *anti*-**101** (Scheme 1.25). The stereocontrol at the β-position is high and use of the sterically bulky TBDPS group as the *N*-substituent is necessary. When smaller silyl *N*-substituents such as TMS were used in lithiation-trapping reactions with aldehydes, lower diastereoselectivity was observed.[47]



87 *syn*-**101** 89% 91:9 dr *anti*-**101**

Scheme 1.25

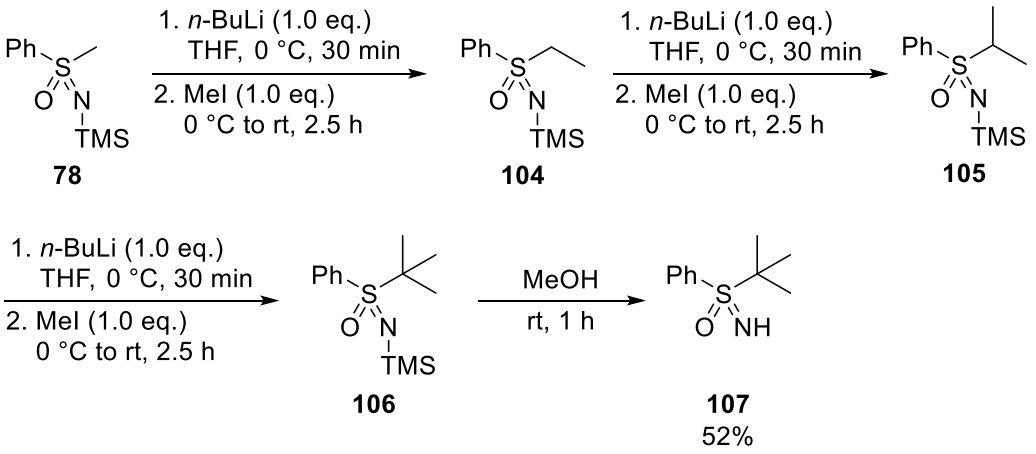
Diastereoselectivity at the β-position is not limited to trapping with aldehydes as imines can also be successfully used. As an example, lithiation of *N*-TBDPS sulfoximine **87** using *n*-BuLi in THF at 0 °C and subsequent trapping with imine **102** at –45 °C gave a 94:6 mixture of amines *anti*-**103** and *syn*-**103** in 68% yield (Scheme 1.26).[48] This reaction proceeded with high diastereoselectivity but much lower diastereoselectivity was observed with an *N*-Me substituent.



87 **102** *anti*-**103** 68% 94:6 dr *syn*-**103**

Scheme 1.26

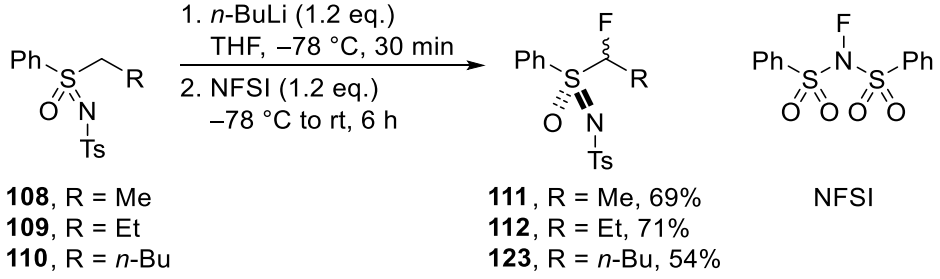
The use of sequential lithiation-trapping has been reported for the synthesis of a trisubstituted sulfoximine **107**. Thus, *N*-TMS sulfoximine **78** was lithiated using *n*-BuLi and trapped with methyl iodide to give sulfoximine **104**. Subsequent repetition of this reaction gave first disubstituted sulfoximine **105** then trisubstituted sulfoximine **106**, which was deprotected using methanol to give NH sulfoximine **107** in 52% overall yield (Scheme 1.27).[49] This reaction demonstrates that di- and trisubstituted sulfoximines can be synthesised with ease in high yields using lithiation-trapping reactions. The reactions were performed at 0 °C which is unusually high as a lower temperature of –78 °C is often used for lithiation-trapping reactions. Previous literature shows that the first methylation would have been successful at –78 °C,[50] although a higher temperature is likely to be necessary for the second and third lithiations.



Scheme 1.27

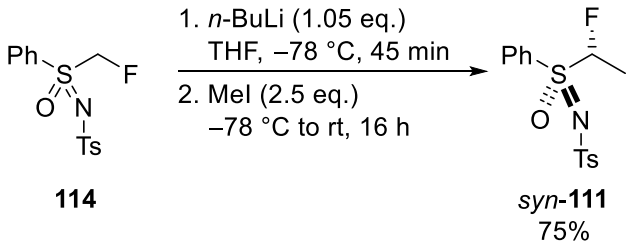
There has been a significant amount of work on the lithiation-trappings of *N*-substituted methyl sulfoximines and the previous examples in this chapter provide a representative sample. However, exploration of more complex sulfoximines remains somewhat neglected. A comprehensive set of examples is provided in the following schemes.

The α-fluorination of *N*-Ts alkyl sulfoximines **108**–**110** has been investigated. Lithiation using *n*-BuLi and trapping with NFSI gave fluorinated sulfoximines **111**–**113** as mixtures of diastereomers in yields of 54-71% (Scheme 1.28).[51] Unfortunately, there was no comment by the authors on the ratio of the diastereomers in these reactions.



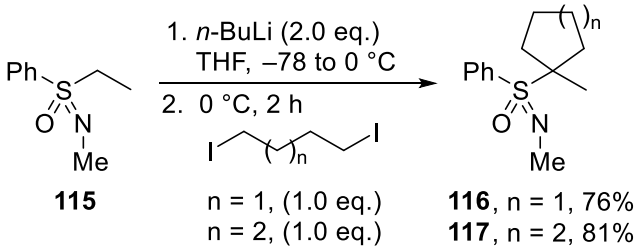
Scheme 1.28

α-Fluorinated sulfoximines are able to undergo lithiation-trapping reactions to further functionalise the α-position. For example, α-fluoro *N*-Ts sulfoximine **114** was lithiated using *n*-BuLi in THF at –78 °C and trapped with methyl iodide to give sulfoximine *syn*-**111** (Scheme 1.29).[52] Sulfoximine *syn*-**111** was isolated in 75% yield as a single diastereomer after recrystallisation.



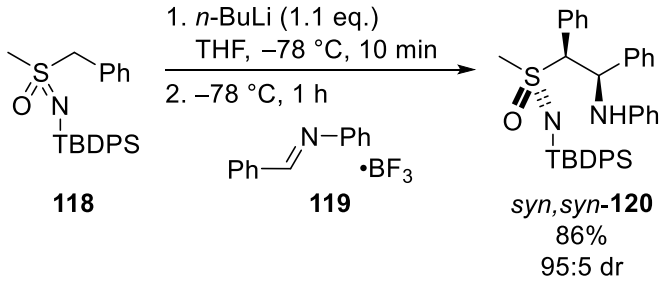
Scheme 1.29

Double trapping at the α-position of sulfoximines such as *N*-Me sulfoximine **115** has also been reported. In this case, *N*-Me sulfoximine **115** was lithiated using two equivalents of *n*-BuLi (THF, –78 °C). The authors propose that a dianion is formed. Then, trapping with 1,4-diiodobutane and 1,5-diiodopentane resulted in cyclisation to give sulfoximines **116** and **117** in 76% and 81% yield respectively (Scheme 1.30).[53] Trapping with shorter chain haloalkanes resulted in lower yields of the cyclisation products presumably due to increased strain in the small ring systems.



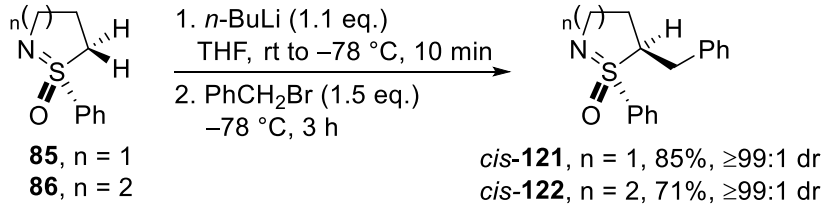
Scheme 1.30

The lithiation of sulfoximines and trapping with imines can be diastereoselective at both the α- and β-position. For example, *N*-TBDPS sulfoximine **118** was lithiated with *n*-BuLi in THF at –78 °C and subsequently trapped with imine **119**.[54] Preferential lithiation at the benzylic position gave sulfoximine *syn,syn*-**120** in 86% yield with a 95:5 dr (Scheme 1.31). The reaction displayed high diastereoselectivity when the imine was precomplexed with boron trifluoride-diethyl ether. When the reaction was performed without BF_3•Et_2O, sulfoximine *syn,syn*-**120** was obtained in 60% yield with a 79:21 dr.



Scheme 1.31

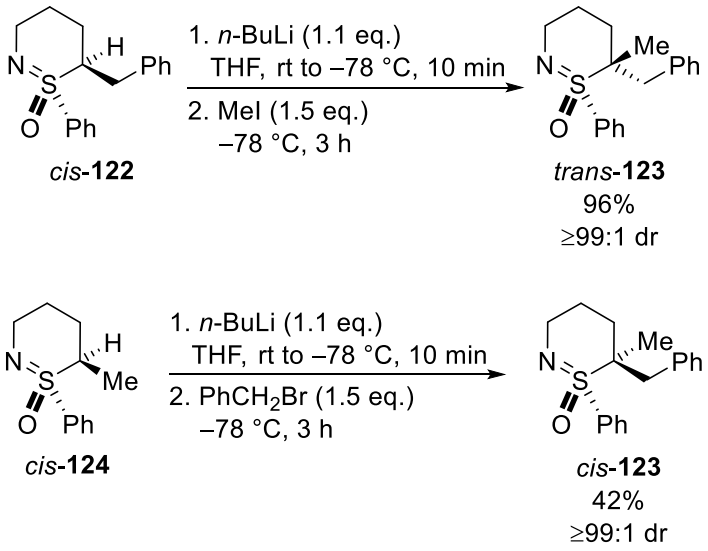
The lithiation-trapping of some cyclic sulfoximines has been explored using a range of alkyl halides. An example is the lithiation of 5-membered ring sulfoximine **85** using *n*-BuLi in THF and subsequent trapping with benzyl bromide to give sulfoximine *cis*-**121** as a single diastereomer in 85% yield (Scheme 1.32).[41] Similarly, the lithiation-trapping of 6-membered ring sulfoximine **86** with benzyl bromide gave sulfoximine *cis*-**122** as a single diastereomer in 71% yield. Additional lithiation-trappings of 6-membered ring sulfoximine **86** were performed with methyl iodide, isopropyl iodide and 2,4,6-trimethylbenzyl chloride giving α-substituted sulfoximines in good to high yields with high diastereoselectivity. It is proposed that the fixed conformation of the sulfoximine ring and a pyramidalised α-carbon allow the bulky phenyl group to block one face of the sulfoximine. This results in attack of the electrophile from the opposite face giving sulfoximines with the α-functional group *cis* to the sulfoximine oxygen.



Scheme 1.32

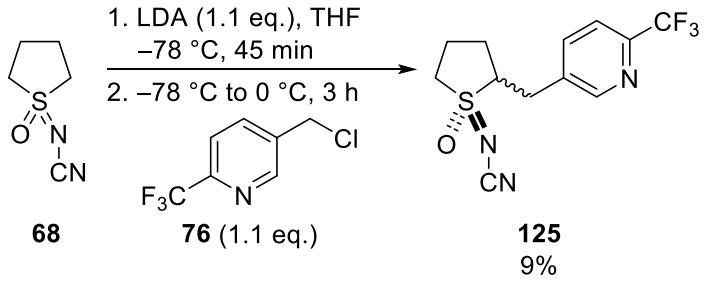
The effect of a second lithiation-trapping reaction at the α-position of cyclic sulfoximine *cis*-**122** was then investigated (Scheme 1.33). Treatment of sulfoximine *cis*-**122** with *n*-BuLi in THF followed by trapping with methyl iodide resulted in stereoselective addition of the methyl group at the α-position *trans* to the phenyl group. Disubstituted sulfoximine *trans*-**123** was synthesised as a single diastereomer in 96% yield. The opposite diastereomer, sulfoximine *cis*-**123**, was obtained using the same methodology. Thus, lithiation-trapping of sulfoximine *cis*-**124** with benzyl bromide gave disubstituted sulfoximine *cis*-**123** as a single diastereomer in 42% yield. These reactions demonstrate

that multiple substitutions can occur at the α-position of cyclic sulfoximines by a lithiation-trapping sequence. In addition, they proceed with full diastereoselectivity and offer a way of isolating both diastereomers of sulfoximine **123**.



Scheme 1.33

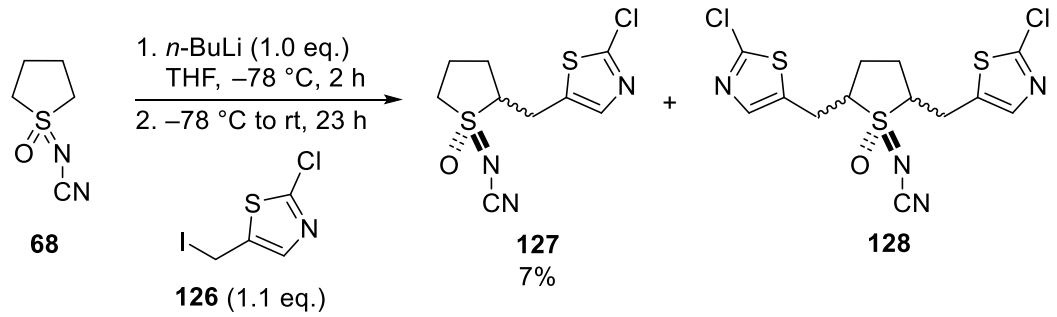
There are a few examples of the lithiation-trapping reactions of cyclic *N*-CN sulfoximines since the α-functionalised products have potential applications as insecticides. Lithiation of *N*-CN sulfoximine **68** with LDA and trapping with electrophile **76** gave sulfoximine **125** as a mixture of diastereomers in only 9% yield (Scheme 1.34).[35] The authors did not comment on the diastereoselectivity or the low yield of the reaction.



Scheme 1.34

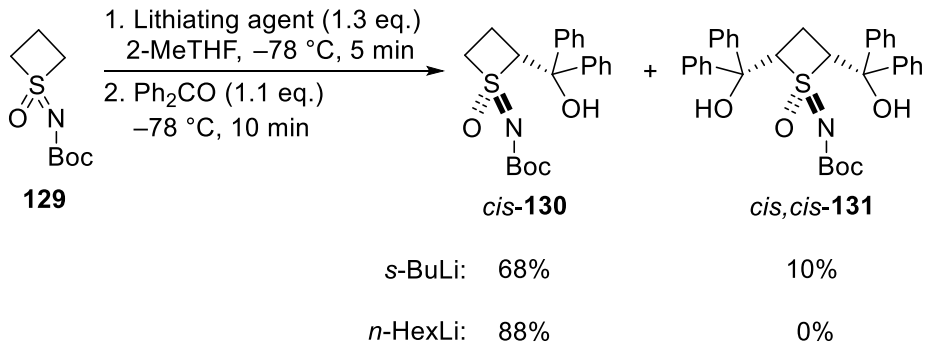
In another reaction, *N*-CN sulfoximine **68** was lithiated using *n*-BuLi and trapped with electrophile **126** to give monosubstituted sulfoximine **127** in 7.3% yield (Scheme 1.35).[2] In addition to this, a large quantity of unwanted disubstituted sulfoximine **128** was formed but no yield was given. The unintentional synthesis of disubstituted sulfoximines is of

particular interest as this was not observed in the previous reactions discussed. There was no comment on the diastereoselectivity of these reactions.



Scheme 1.35

Work by Degennaro describes a comprehensive study on the diastereoselectivity of lithiation of 4-membered ring *N*-Boc sulfoximine **129** and trapping with a range of electrophiles (Scheme 1.36).[55] Optimisation of the reactions found organolithiums LDA and LHMDS were ineffective at deprotonation of the sulfoximine at the α-position, whilst use of stronger bases such as *n*-BuLi, *n*-HexLi and *s*-BuLi were successful. For example, lithiation of *N*-Boc sulfoximine **129** with *s*-BuLi in 2-MeTHF at –78 °C and trapping with benzophenone gave sulfoximine *cis*-**130** in 68% yield. In addition, 2,4-disubstituted sulfoximine *cis,cis*-**131** was obtained in 10% yield. The reaction was repeated using *n*-HexLi as the lithiating agent in place of *s*-BuLi, obtaining exclusively sulfoximine *cis*-**130** in 88% yield. A possible explanation for the synthesis of disubstituted sulfoximine *cis,cis*-**131** is *via* the formation of a dianion. This is likely due to the excess 0.3 equivalents of *s*-BuLi used and the fact that it is a stronger base than *n*-HexLi. *n*-HexLi was used for future reactions as it gave the highest yield of sulfoximine *cis*-**130** and no disubstituted sulfoximine *cis,cis*-**131**. The diastereoselectivity of the reactions was impressive, showing full *cis* stereocontrol at the α-position



Scheme 1.36

Using the *n*-HexLi conditions in Scheme 1.36, a range of electrophiles were reacted successfully at the α-position of *N*-Boc sulfoximine **129** to give products with low to excellent yields (Figure 1.6). Of the electrophiles tested, benzyl bromide, phenyl isocyanate, methyl iodide and cyclopentanone all gave sulfoximines *cis*-**132**-**135** with the α-substituent in a *cis* relationship to the oxygen with >95:5 dr in yields of 30-83% (Figure 1.6). Trapping with cyclopentanone gave sulfoximine *cis*-**135** in a relatively low yield of 30%, which may be due to the competing α-deprotonation of cyclopentanone by the lithiated sulfoximine to form the enolate.

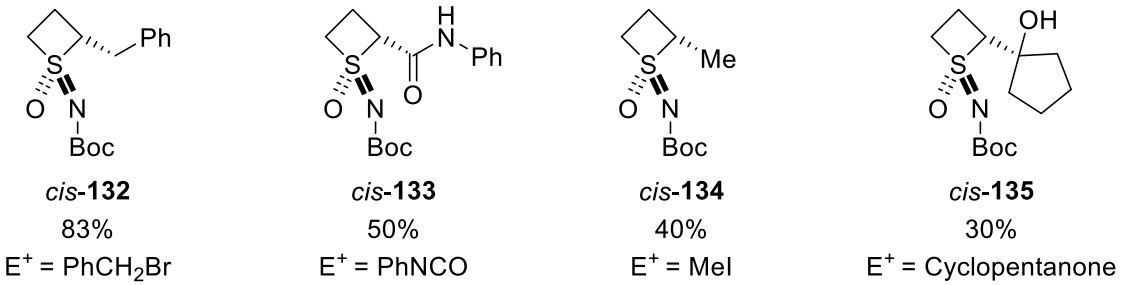
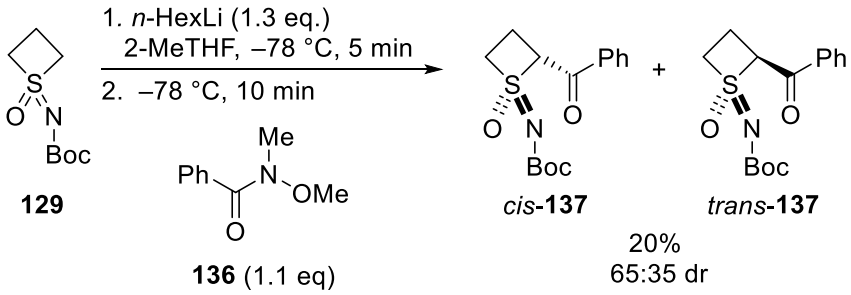


Figure 1.6 α-Functionalised products of lithiation-trapping reactions of *N*-Boc sulfoximine **129**

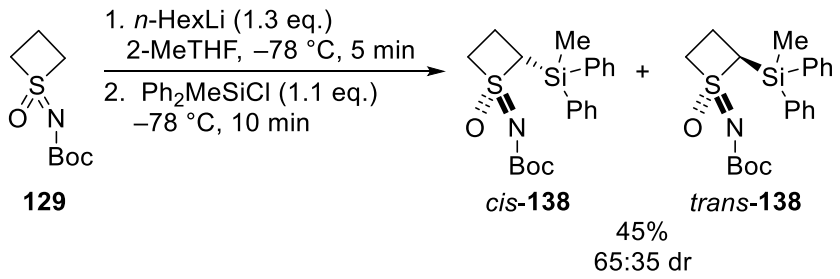
When *N*-Boc sulfoximine **129** was lithiated using *n*-HexLi and trapped with Weinreb amide **136**, a 65:35 mixture of keto-sulfoximines *cis*-**137** and *trans*-**137** was obtained in only 20% yield (Scheme 1.37). We suggest that a likely explanation for the poor diastereoselectivity of this reaction is that the acidic α-proton of the β-keto sulfoximine leads to epimerisation during the work-up. The low yield of this reaction was unexpected as Weinreb amides typically give good yields for lithiation-trapping reactions.



Scheme 1.37

As a final example, lithiation of *N*-Boc sulfoximine **129** using *n*-HexLi and trapping with $Ph_2MeSiCl$ gave a 65:35 mixture of sulfoximines *cis*-**138** and *trans*-**138** in 45% yield (Scheme 1.38). In this case, it is unlikely that sulfoximines *cis*-**138** and *trans*-**138** can

undergo epimerisation in the work-up so the reason for the poor diastereoselectivity is unknown.

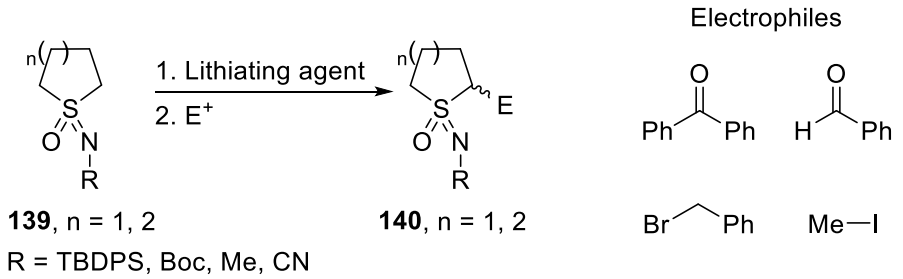


Scheme 1.38

In summary, the lithiation-trapping of acyclic sulfoximines using a range of *N*-alkyl groups and electrophiles is well established. However, there are comparatively fewer examples with cyclic sulfoximines. With both acyclic and cyclic sulfoximines, there are isolated examples of α-diastereoselectivity but, apart from Degennaro's results with *N*-Boc 4-membered ring sulfoximine **129**, there are no systematic studies of α-diastereoselectivity with different electrophiles.

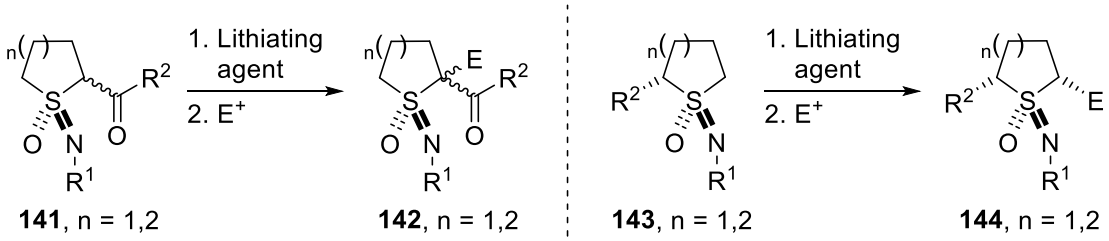
1.4 Project Outline

There is increased interest in the use of the sulfoximine functional group in medicinal chemistry and agrochemistry. In terms of lithiation-trapping reactions, the current literature focuses on acyclic sulfoximines. Therefore, in order to broaden the synthetic scope of the methodology, we planned to investigate the lithiation-trapping of 5- and 6-membered cyclic sulfoximines **139** to obtain α-substituted cyclic sulfoximines **140** (Scheme 1.39). Functionalisation of the α-position with a range of electrophiles would allow us to investigate the diastereoselectivity of the reaction. We also planned to use a number of substituents on the nitrogen atom such as TBDPS, Boc, Me and CN to add further diversification to the molecule and to investigate their effect on the diastereoselectivity of the reaction. The results of these studies are discussed in Chapter 2.1.



Scheme 1.39

Using the conditions of the initial studies set out in Scheme 1.39, we next planned to further functionalise α-substituted sulfoximines **141** and **143** to give 2,2-disubstituted products **142** as well as 2,5- and 2,6-disubstituted products **144** (Scheme 1.40). To access the 2,2-disubstituted products **142**, lithiation at the most acidic position α to the ketone would be used to control the regiochemistry. Thus, lithiation of sulfoximine **141** should give sulfoximine **142**. Lithiation-trapping of sulfoximines **143** should give disubstituted products **144** with regioselectivity controlled by steric factors. The results of our studies in both of these reactions are described in Chapter 2.2

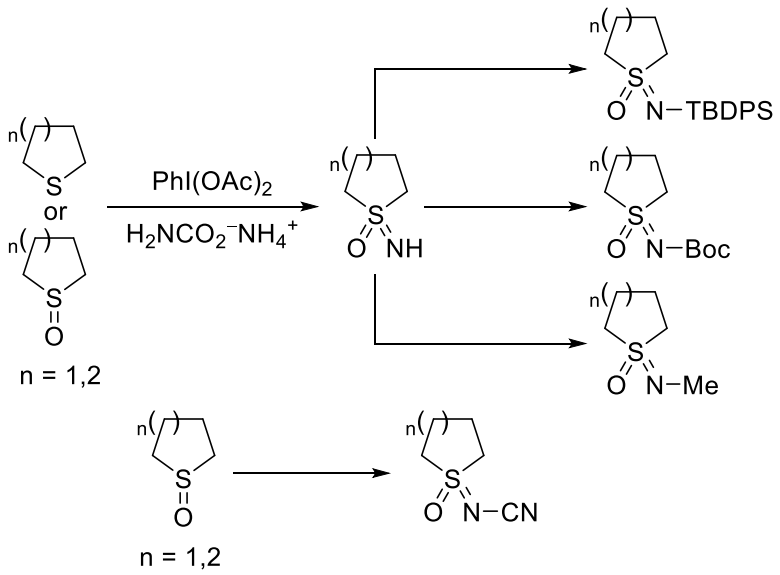


Scheme 1.40

2. Results and Discussion

2.1 Synthesis of Sulfoximines

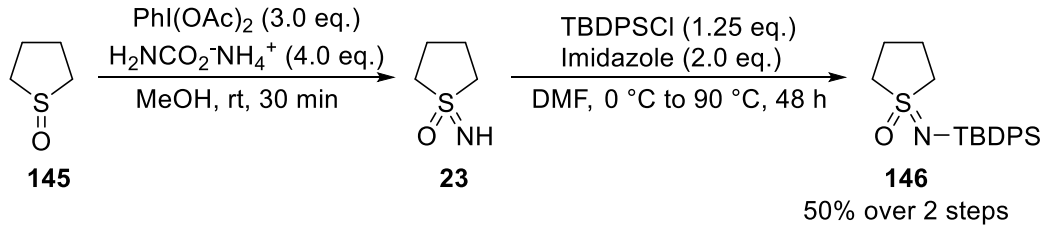
For our planned lithiation-trapping studies, it was decided to synthesise cyclic sulfoximines with different *N*-substituents such as *N*-TBDPS, *N*-Boc, *N*-Me and *N*-CN. Based on the literature presented in Chapter 1.2, the methods by Luisi, Bull and co-workers for direct synthesis of NH sulfoximines from sulfides[26] and sulfoxides[25] were selected as the key step in the planned route to the *N*-TBDPS, *N*-Boc and *N*-Me sulfoximines (Scheme 2.1). These methods were preferable as they were metal-free, did not require potentially explosive reagents such as azides and were performed under mild conditions. The NH sulfoximine could then be easily functionalised with different substituents to give the *N*-TBDPS, *N*-Boc and *N*-Me sulfoximines. In contrast, we planned to synthesise the *N*-CN sulfoximines by a one-pot procedure directly from the sulfoxides as this avoided the use of particularly toxic cyanogen bromide.[56]



Scheme 2.1

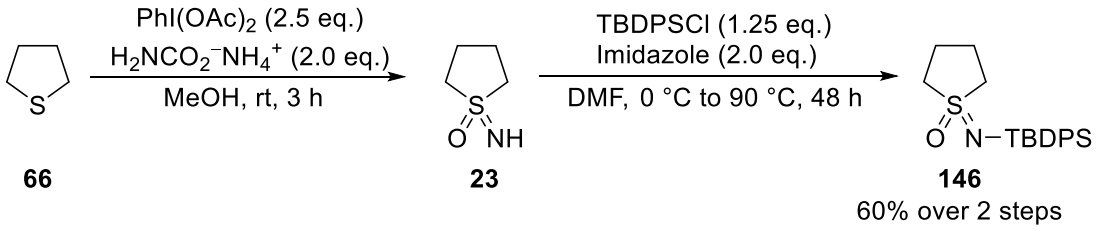
To start, 5-membered ring *N*-TBDPS cyclic sulfoximine **146** was synthesised. The first route explored used Luisi and Bull's original method.[25] Treatment of sulfoxide **145** with PIDA (3.0 eq.) and ammonium carbamate (4.0 eq.) at rt for 30 min gave NH sulfoximine **23** (Scheme 2.2). The crude product was reasonably pure by ^{1}H NMR spectroscopy, with the signals matching those stated in the literature.[25] For the introduction of the TBDPS group, a method that was reported for an acyclic sulfoximine was selected. Thus, reaction

of NH sulfoximine **23** with TBDPSCl (1.25 eq.) and imidazole (2.0 eq.) in DMF at 90 °C gave novel *N*-TBDPS sulfoximine **146** in 50% overall yield after chromatography. Analysis of the ^{1}H NMR spectrum of *N*-TBDPS sulfoximine **146** showed a 9H singlet at δ_H 1.08 which indicated the successful addition of the TBDPS group.



Scheme 2.2

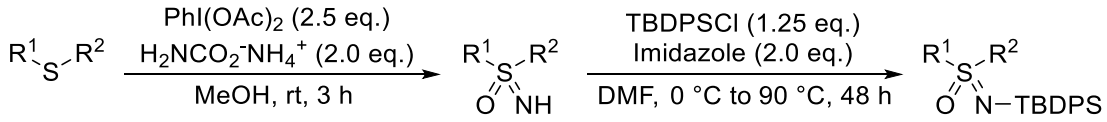
An alternative route to 5-membered ring *N*-TBDPS sulfoximine **146** was explored using Luisi and Bull's method starting from the corresponding sulfide.[26] Treatment of sulfide **66** with PIDA (2.5 eq.) and ammonium carbamate (2.0 eq.) at rt for 3 h gave crude NH sulfoximine **23** which was sufficiently pure for use in the next step. Subsequent TBDPS protection using the same method as used previously gave *N*-TBDPS sulfoximine **146** in 60% overall yield (Scheme 2.3). A comparison of the two routes to *N*-TBDPS sulfoximine **146** showed that less equivalents of PIDA and ammonium carbamate were required when starting from the sulfide compared to the sulfoxide and that a longer reaction time of 3 h was needed for the sulfide route. Sulfide **66** was significantly cheaper to purchase than sulfoxide **23** and therefore it was preferable to synthesise the NH sulfoximine from the sulfide and this method was selected for all the other examples.



Scheme 2.3

The syntheses of five *N*-TBDPS protected sulfoximines using this two-step approach are summarised in Table 2.1. The best yields were obtained for the 5- and 6-membered ring *N*-TBDPS sulfoximines **146** and **147** (entries 2 and 3). Unexpectedly, the 4-membered ring *N*-TBDPS sulfoximine **148** was obtained in a low 19% yield (entry 1). Intermediate yields were observed for the acyclic diethyl and phenylethyl *N*-TBDPS sulfoximines **149**

and **150** (entries 4 and 5). The NMR spectroscopic data of all NH sulfoximines matched the literature in each case.[26,57,58,59] All *N*-TBDPS sulfoximines **146**–**150** were not previously reported in the literature and analysis of their ^{1}H NMR spectra showed a 9H singlet around δ_H 1.0-1.2 which indicated the successful addition of the TBDPS group.

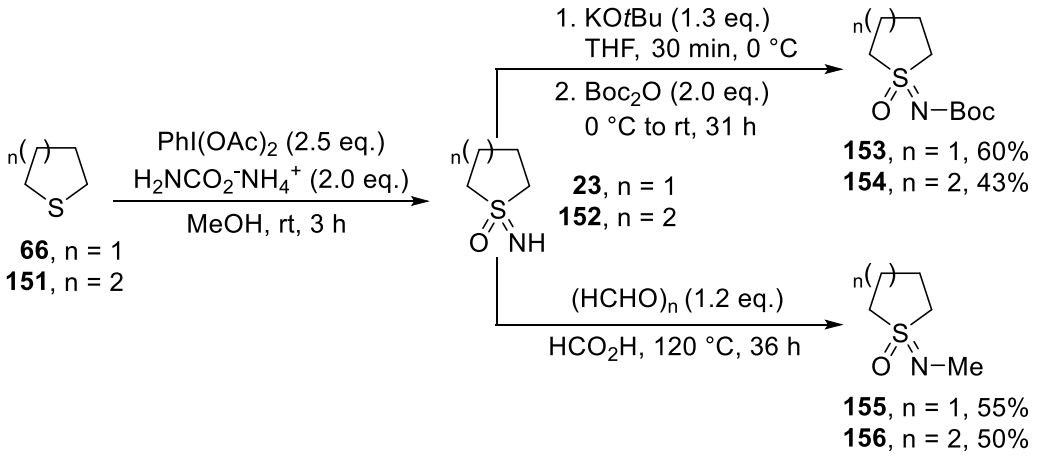


Entry	R^1	R^2	Compound	Yield/%[a]
1	-$(CH_2)_3$-		**148**	19
2	-$(CH_2)_4$-		**146**	60
3	-$(CH_2)_5$-		**147**	53
4	Et	Et	**149**	32
5	Ph	Et	**150**	38

[a] % yield after purification by chromatography.

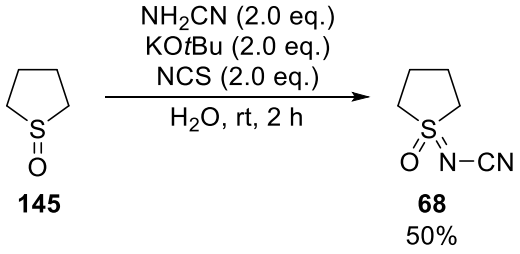
Table 2.1 Synthesis of *N*-TBDPS sulfoximines **146**–**150**

The synthesis of *N*-Boc sulfoximines was explored using our standard procedure to form the 5-membered ring NH sulfoximine **23** from sulfide **66**, and a procedure for the addition of a Boc group to an acyclic sulfoximine (Scheme 2.4).[60] Addition of potassium *tert*-butoxide and Boc_2O to NH sulfoximine **23** gave 5-membered ring *N*-Boc sulfoximine **153** in 60% yield over two steps. The spectroscopic data for this compound was consistent with those reported in the literature.[57] The same method was applied to the 6-membered ring sulfide **152** resulting in a 43% yield of *N*-Boc sulfoximine **154**, a compound that has not been reported previously in the literature. For the synthesis of *N*-Me sulfoximines, our standard procedure was used to afford NH sulfoximines **23** and **152**. We then opted to use Eschweiler-Clarke conditions for the *N*-methylation due to literature precedent.[37] Treatment of NH sulfoximines **23** and **152** with paraformaldehyde and formic acid gave *N*-Me sulfoximines **155** and **156** in 55% and 50% yield respectively (Scheme 2.4). The spectroscopic data for *N*-Me sulfoximine **155** was consistent with those reported in the literature[37] whilst *N*-Me sulfoximine **156** has not been previously reported.



Scheme 2.4

N-CN sulfoximines can be synthesised from NH sulfoximines but methods typically require toxic reagents such as cyanogen bromide.[61] In order to avoid this, we followed a procedure by Dannenberg which used relatively mild conditions to synthesise *N*-CN 5-membered ring sulfoximine **68** directly from sulfoxide **145**.[56] Treatment of sulfoxide **145** with cyanamide, potassium *tert*-butoxide and *N*-chlorosuccinimide in water resulted in *N*-CN sulfoximine **68** in 50% yield (Scheme 2.5). The NMR spectroscopic data for this compound were consistent with literature values.[56]



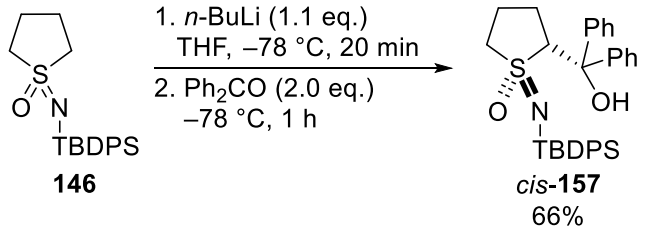
Scheme 2.5

2.2 α-Lithiation and Trapping of Sulfoximines

With a range of *N*-substituted cyclic and acylic sulfoximines in hand, the α-lithiation-trapping reactions were investigated. The plan was to explore the effect of different ring sizes, different *N*-substituents and different electrophiles on the yield and diastereoselectivity of the lithiation-trapping reactions.

2.2.1 α-Lithiation and Trapping of *N*-TBDPS Sulfoximines

To begin with, we explored the lithiation-trapping of 5-membered ring *N*-TBDPS sulfoximine **146**. It was decided to use *n*-BuLi as the lithiating agent, THF as the solvent and a temperature of –78 °C for the reaction based on related literature examples (see Chapter 1.3). Benzophenone was selected as the first electrophile as it should undergo fast trapping and reaction of the lithiated sulfoximine would introduce only one additional stereocentre. Based on a procedure reported for dimethyl sulfoximine **48**,[38] *N*-TBDPS sulfoximine **146** was lithiated using *n*-BuLi in THF at –78 °C for 20 min and trapped with benzophenone to give *N*-TBDPS sulfoximine *cis*-**157** in 66% yield after purification by column chromatography (Scheme 2.6).



Scheme 2.6

Analysis by ^{1}H NMR spectroscopy of both the crude and purified product showed that only one diastereomer of the sulfoximine was obtained. Diagnostic signals in the ^{1}H NMR spectrum of *N*-TBDPS sulfoximine *cis*-**157** are shown in Figure 2.1. A 1H signal at δ_H 4.32 (dd, J = 16.5, 7.5 Hz) was assigned to the α-proton adjacent to the benzyl alcohol. This signal was significantly further downfield than the 2H multiplet at δ_H 2.67-2.51 due to the other two α-protons. A 1H singlet at δ_H 5.11 was assigned to the OH group.

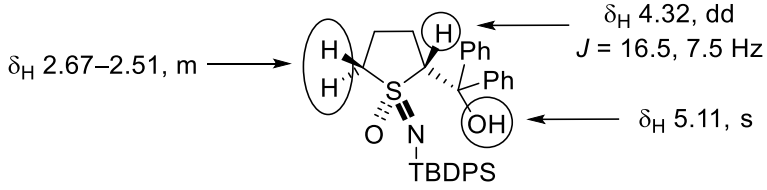
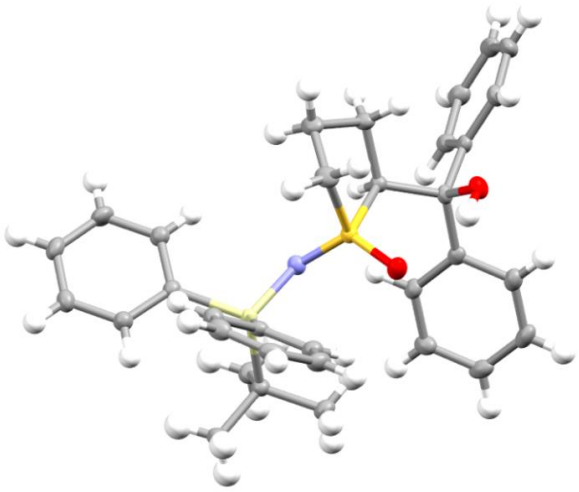
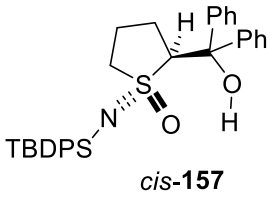


Figure 2.1 ^{1}H NMR spectroscopic data for *N*-TBDPS sulfoximine *cis*-**157**

The *cis*-stereochemistry of sulfoximine *cis*-**157** was determined by X-ray crystallography (Figure 2.2). The X-ray structure clearly showed that the oxygen bonded to sulfur is *cis* to the α-substituent, with the nitrogen in a *trans* orientation. The proximity of the sulfoximine oxygen to the OH group indicates the presence of an intramolecular hydrogen bond.

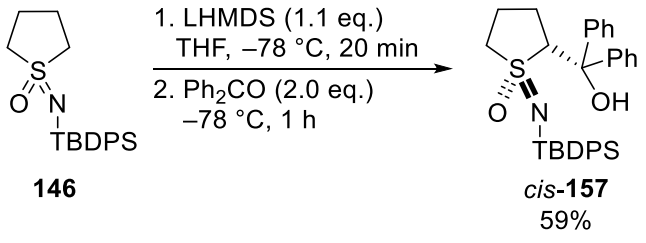




cis-**157**

Figure 2.2 X-ray structure of *N*-TBDPS 5-membered ring sulfoximine *cis*-**157**

In an effort to improve the yield of sulfoximine *cis*-**157**, we followed a procedure for the lithiation-trapping of an acyclic sulfoximine which used LHMDS for the deprotonation step.[60] Sulfoximine **146** was lithiated using LHMDS in THF at –78 °C for 20 min and subsequent trapping with benzophenone gave sulfoximine *cis*-**157** in 59% yield (Scheme 2.7). In an attempt to improve the yield, the lithiation time was increased from 20 min to 1 h. However, this had little effect as sulfoximine *cis*-**157** was formed in 53% yield with a 1 h lithiation time.



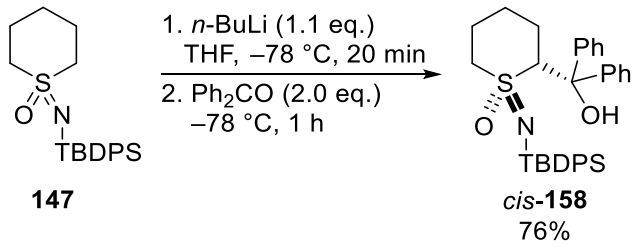
146 *cis*-**157**
59%

Scheme 2.7

It was then realised that sulfoximine **146** appeared to be rather hygroscopic. Therefore, extra steps were taken for drying the compound, including removing the water by azeotroping with toluene and drying on the high vacuum immediately before use. With

these precautions in place, the reaction with *n*-BuLi shown in Scheme 2.7 was repeated and this gave sulfoximine *cis*-**157** in 84% yield. The extra drying steps led to a higher yield of sulfoximine *cis*-**157** and this method was therefore preferred and used for all subsequent lithiation-trapping reactions. Lithiation-trapping reactions were typically performed on a 0.5 or 1.0 mmol scale.

For comparison, the lithiation-trapping of 6-membered ring *N*-TBDPS sulfoximine **147** using *n*-BuLi and benzophenone was carried out. In this case, sulfoximine *cis*-**158** was obtained in 76% yield after chromatography (Scheme 2.8). Analysis by ^{1}H NMR spectroscopy of both the crude and purified product showed that only one diastereomer was formed in this reaction.



Scheme 2.8

The stereochemistry of sulfoximine *cis*-**158** was confirmed by X-ray crystallography (Figure 2.3). In the chair conformation of the 6-membered ring, the oxygen of the sulfoximine is axial and the adjacent α-substituent is equatorial confirming their *cis* relationship. In this case, there is an intramolecular hydrogen bond between the sulfoximine nitrogen and the OH group, contrasting with the 5-membered ring sulfoximine *cis*-**157** (see Figure 2.2).

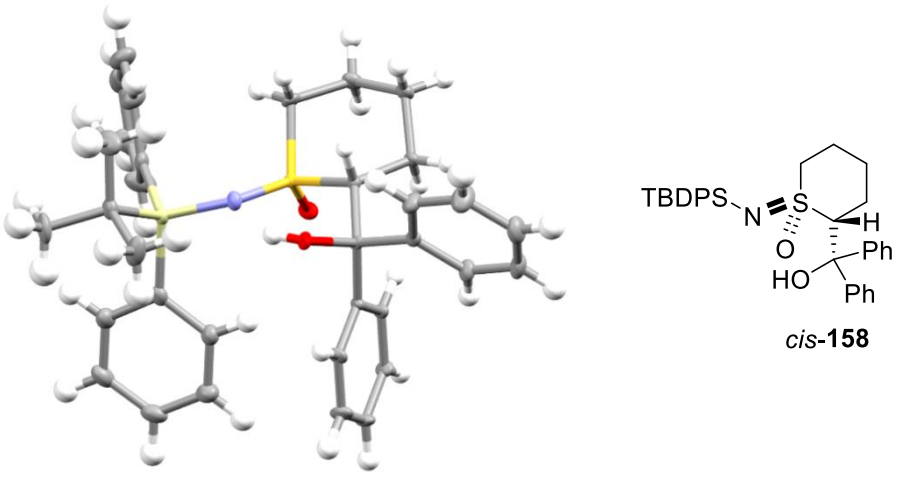
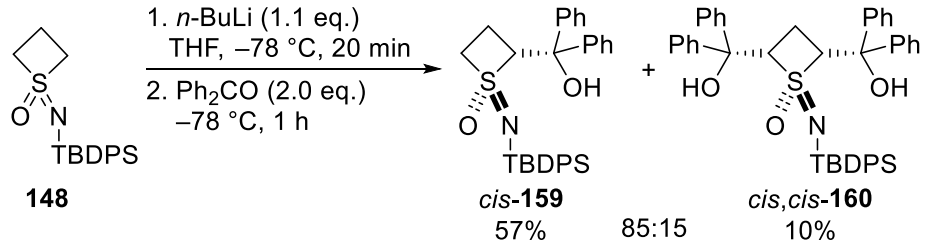


Figure 2.3 X-ray structure of *N*-TBDPS 6-membered ring sulfoximine *cis*-**158**

To explore whether the observed *cis*-diastereoselectivity in the trapping applied to other ring sizes, we investigated the diastereoselectivity of the lithiation-trapping of 4-membered ring *N*-TBDPS sulfoximine **148**. This would also provide an interesting comparison with the related 4-membered ring *N*-Boc sulfoximine **129** which displayed a high level of *cis*-diastereoselectivity across a range of electrophiles (see Chapter 1.3).[55] Thus, *N*-TBDPS sulfoximine **148** was lithiated with *n*-BuLi and trapped with benzophenone to give an 85:15 mixture of sulfoximine *cis*-**159** and the unexpected double-trapped sulfoximine *cis,cis*-**160** (by ^{1}H NMR spectroscopy). After chromatography, the two products were obtained as an inseparable 85:15 mixture of sulfoximines *cis*-**159** (57% yield) and *cis,cis*-**160** (10% yield) (Scheme 2.9). The stereochemistry of sulfoximine *cis*-**159** was assigned by analogy with the previously described 5- and 6-membered ring results. For the double-trapped sulfoximine *cis,cis*-**160**, the symmetrical features in the ^{1}H and ^{13}C NMR spectra and the fact it would likely come from sulfoximine *cis*-**159** led us to propose the assigned stereochemistry.



Scheme 2.9

Diagnostic signals in the ^{1}H NMR spectrum of *N*-TBDPS sulfoximine *cis,cis*-**160** are shown in Figure 2.4. A 2H signal at δ_H 5.15 (dd, J = 10.0, 10.0 Hz) was assigned to the α-protons adjacent to the benzyl alcohol. A 1H signal at δ_H 2.92 (dt, J = 12.5, 10.0 Hz) was assigned to one of the two diastereotopic protons in the ring. The 2H singlet at δ_H 4.82 was assigned to the two OH groups.

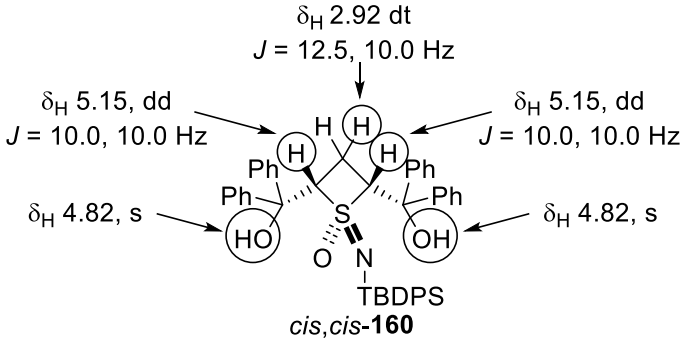
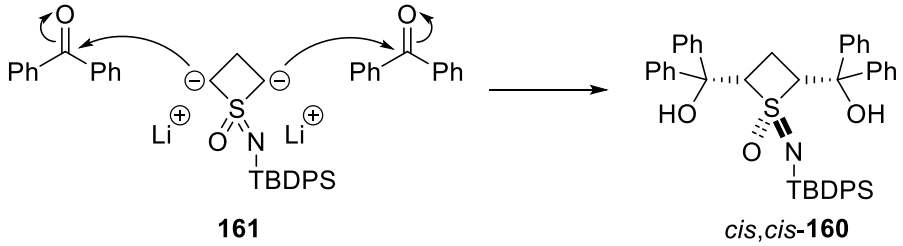


Figure 2.4 ^{1}H NMR spectroscopic data for *N*-TBDPS sulfoximine *cis,cis*-**160**

Analysis of the ^{13}C NMR spectrum of monosubstituted sulfoximine *cis*-**159** showed a signal at δ_C 86.4 which was assigned to the SCH group. The signal at δ_C 65.8 was assigned to the SCH_2 group and the signal at δ_C 10.2 was assigned to the CH_2 in the ring. The ^{13}C NMR spectrum of double-trapped sulfoximine *cis,cis*-**160** had one signal at δ_C 83.7 assigned to the two equivalent SCH groups. There was no signal indicating an SCH_2 group and the signal at δ_C 13.9 was assigned to the CH_2 in the ring. A comparison of these two signals gave further evidence that sulfoximine *cis,cis*-**160** was disubstituted and had a plane of symmetry. This plane of symmetry means that the sulfoximine could have either *cis,cis*- or *trans,trans*-stereochemistry. However, we believe that benzophenone adds *trans* to the *N*-TBDPS group as this was the case for both the 5- and 6-membered ring sulfoximines *cis*-**157** and *cis*-**158**.

In order to explain the formation of the disubstituted sulfoximine *cis,cis*-**160**, we propose that the 4-membered ring *N*-TBDPS sulfoximine **148** forms a small amount of dianion **161** during lithiation which is then double-trapped with benzophenone (Scheme 2.10). The formation of a dianion from sulfoximines is known (see Scheme 1.30, sulfoximine **115**) although, this was achieved by using 2 equivalents of *n*-BuLi at a high temperature of 0 °C. Since no disubstituted product was observed when 5- and 6-membered ring *N*-TBDPS sulfoximines **146** and **147** underwent lithiation-trapping with benzophenone, it appears that the 4-membered ring sulfoximine **148** is more susceptible to dianion formation. Presumably, the 0.1 equivalents excess of *n*-BuLi in the reaction mixture is thought to contribute to the formation of the dianion.



161 *cis,cis*-**160**

Scheme 2.10

In order to explain the preferred formation of the *cis*-sulfoximines *cis*-**157**, *cis*-**158** and *cis*-**159**, we surveyed the literature for information on the structure of the lithiated sulfoximine from either X-ray crystallography or solution NMR spectroscopic studies. Work by Gais and co-workers reported the characterisation of lithiated allyl *N*-TMS sulfoximine **161** by X-ray crystallography (Figure 2.5).[62] The angle between the sulfur-

α-carbon bond and the α-carbon-β-carbon bond was 124.3° which is close to the value expected for an sp^2 hybridised carbanion. Additional bond angle calculations showed that the α-carbon is in an essentially planar environment. The structure of related lithiated *N*-TMS sulfoximine **162** (Figure 2.5) was determined by X-ray crystallography and solution NMR spectroscopic studies in THF.[63] In the proton-coupled ^{13}C NMR spectrum, the α-carbon signal appeared as a doublet at δ_C 40.6 with a J_{CH} coupling of 15.0 Hz. This indicated that lithiated sulfoximine **162** is highly solvated by THF with some planarity around the α-carbon atom and little or no C–Li contact.

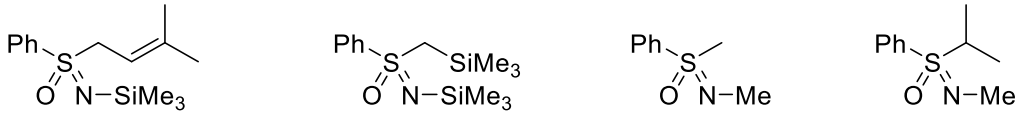


Figure 2.5 Lithiated sulfoximines **161–163** and **69**

Analysis of lithiated *N*-Me sulfoximine **69** (Figure 2.5) by X-ray crystallography showed that the α-carbon-sulfur bond displayed double bond character as it was shorter than that expected for a single bond.[64] It was suspected that the α-carbon-sulfur bond of lithiated *N*-Me sulfoximine **163** (Figure 2.5) also displayed similar double bond character. Variable temperature ^{13}C NMR spectroscopic studies of lithiated sulfoximine **163** showed a rapid exchange of the diastereotopic methyl groups at temperatures down to –103 °C. Therefore, if the two methyl groups in sulfoximine **163** were replaced with non-identical groups, the resultant lithiated sulfoximine would be configurationally unstable at the anionic carbon atom. This configurational instability also suggests that there is no C–Li bond.

Putting all of this structural information on lithiated sulfoximines together, we suggest that the model shown in Figure 2.6 can explain the diastereoselectivity of the lithiation-trapping reactions of cyclic *N*-TBDPS sulfoximines. It is proposed that electrophilic trapping occurs from an sp^2 hybridised carbanion with no C–Li contact. The sterically bulky TBDPS group is able to block one face of the sulfoximine preventing electrophilic attack on one side. As a result, the trapped sulfoximine adopts a configuration where the new α-substituent is *cis* to the sulfoximine oxygen.

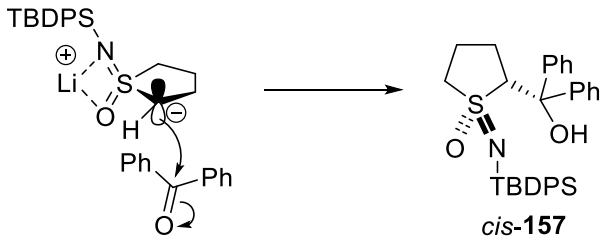
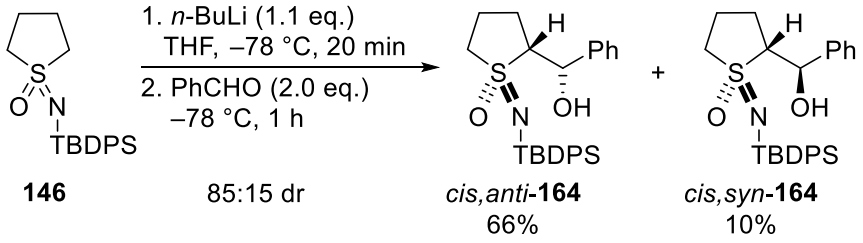


Figure 2.6 Model for electrophilic trapping

Due to the high yields and diastereoselectivity, the lithiation-trapping reactions of 5-membered ring and 6-membered ring *N*-TBDPS sulfoximines **146** and **147** were then explored using a range of electrophiles. Lithiation-trapping of 5-membered ring sulfoximine **146** with benzaldehyde gave a crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis,anti*-**164** and *cis,syn*-**164**. After purification by chromatography, sulfoximines *cis,anti*-**164** and *cis,syn*-**164** were isolated in 66% and 10% yield respectively (Scheme 2.11). Analysis of the minor product *cis,syn*-**164** by X-ray crystallography identified its stereochemistry (Figure 2.7). The oxygen bonded to sulfur is *cis* to the α-substituent whilst the nitrogen is in a *trans* orientation. Both the sulfoximine oxygen and the alcohol oxygen are held closely together due to intramolecular hydrogen bonding between the two. Given that other electrophile trappings occur *trans* to the *N*-TBDPS group, the major product was believed to be *cis,anti*-**164** and was assigned by analogy.



Scheme 2.11

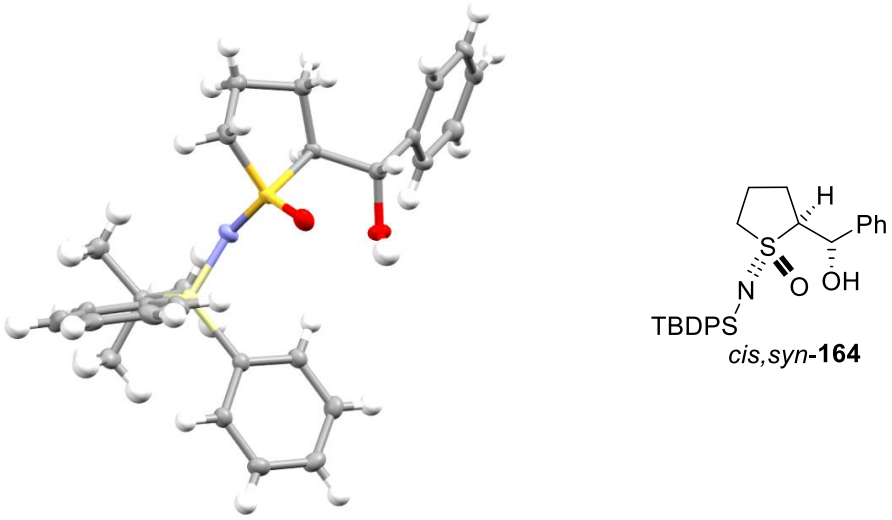
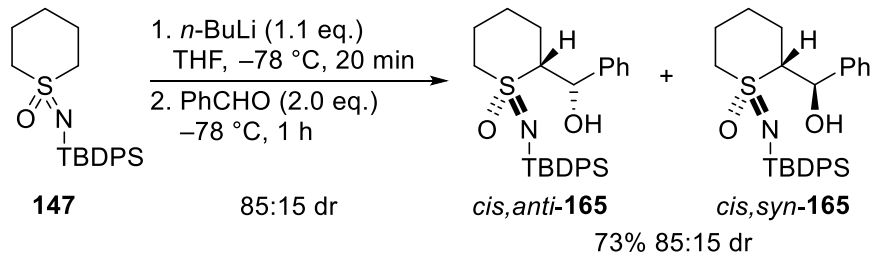


Figure 2.7 X-ray structure of *N*-TBDPS sulfoximine *cis,syn*-**164**

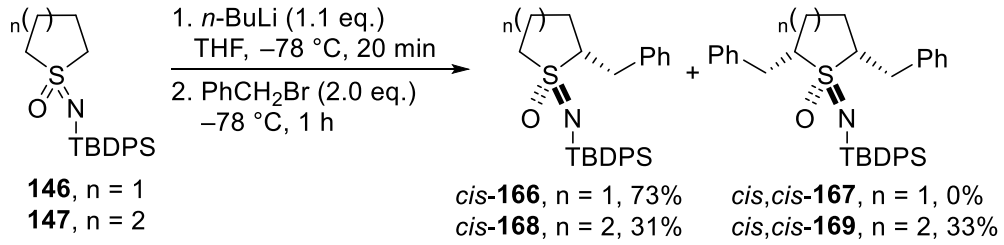
In the ^{1}H NMR spectrum of *cis,anti*-**164**, the PhC*H* signal appeared as a 1H singlet at δ_H 5.12 as any coupling to the SCH was too small to be resolved, whereas the ^{1}H NMR spectrum of *cis,syn*-**164** displayed the PhC*H* signal as a 1H doublet at δ_H 4.89 (J = 9.5 Hz). The ^{13}C NMR spectra of both products showed signals at similar δ_C values. For example, *cis,syn*-**164** had signals at δ_C 70.1 for SCH, δ_C 68.6 for Ph*C*H and δ_C 57.3 for SCH_2 whereas *cis,anti*-**164** had signals at δ_C 70.5 for SCH, δ_C 75.5 for Ph*C*H and δ_C 56.2 for SCH_2.

The lithiation-trapping of 6-membered ring sulfoximine **147** with benzaldehyde gave a similar result. An 85:15 mixture of sulfoximines *cis,anti*-**165** and *cis,syn*-**165** was formed (from the ^{1}H NMR spectrum of the crude product). In this case, the diastereomers were not separable and an 85:15 mixture was isolated in 73% yield after chromatography (Scheme 2.12). The stereochemistry of the products was assigned by analogy with 5-membered ring sulfoximines *cis,anti*-**164** and *cis,syn*-**164**. The stereochemical assignment was supported by the fact that the ^{1}H NMR spectra of sulfoximines *cis,anti*-**165** and *cis,syn*-**165** displayed key similarities with those of sulfoximines *cis,anti*-**164** and *cis,syn*-**164**. The PhC*H* signal of *cis,anti*-**165** appeared as a 1H singlet at δ_H 5.89 and the PhC*H* signal of *cis,syn*-**165** appeared as a 1H doublet at δ_H 5.34 (J = 9.0 Hz). Hence, the PhC*H* signals of *cis,syn*-**165** and *cis,syn*-**164** appear as 1H doublets with similar J values (9.0, 9.5 Hz) and are slightly further upfield than the 1H singlets for the PhC*H* signals of *cis,anti*-**165** and *cis,anti*-**164**.



Scheme 2.12

At this stage, we decided to explore alkylating reagents for the trapping of the lithiated sulfoximines. Lithiation-trapping of 5-membered ring sulfoximine **146** with benzyl bromide gave sulfoximine *cis*-**166** as a single diastereomer in 73% yield (Scheme 2.13). The stereochemistry of *cis*-**166** was assigned by analogy with sulfoximine *cis*-**157**. Analysis of sulfoximine *cis*-**166** by ^{1}H and ^{13}C NMR spectroscopy showed no additional signals indicating that only one diastereomer was obtained and no disubstituted sulfoximine *cis,cis*-**167** was synthesised. In contrast, trapping of 6-membered ring sulfoximine **147** with benzyl bromide gave the disubstituted sulfoximine *cis,cis*-**169** in 33% yield in addition to sulfoximine *cis*-**168** in 31% yield (Scheme 2.13).



Scheme 2.13

Analysis of sulfoximine *cis,cis*-**169** by ^{1}H NMR spectroscopy showed that the compound is symmetrical. There were two 2H dd signals at δ_H 3.42 (J = 13.5, 2.5 Hz) and δ_H 2.51 (J = 12.5, 12.5 Hz) due to the four PhC*H*$_2$ protons. The 2H multiplet signal at δ_H 2.96-2.83 showed that there were two α-protons. Additional evidence came from the ^{13}C NMR spectrum where only one CH signal and three CH_2 signals were observed (Figure 2.8). The CH signal was significantly downfield at δ_C 67.6 and corresponded to the two SCH carbons. One CH_2 signal at δ_C 31.6 was assigned to the two Ph*C*H$_2$ carbons whilst the two remaining CH_2 signals at δ_C 29.0 and δ_C 24.8 were assigned to the three CH_2 groups in the ring. If the sulfoximine was not symmetrical, we would have observed three additional signals, one for SCH, one for Ph*C*H$_2$ and one for a CH_2 in the ring. As the data proved that the sulfoximine is symmetrical, we knew that the stereochemistry had to be either

cis,cis or *trans,trans*. The stereochemistry of both sulfoximines *cis*-**157** and *cis*-**158** were proven by X-ray crystallography and therefore we reasoned that benzyl bromide would add to sulfoximine **147** *trans* to the *N*-TBDPS group to give sulfoximine *cis,cis*-**169**.

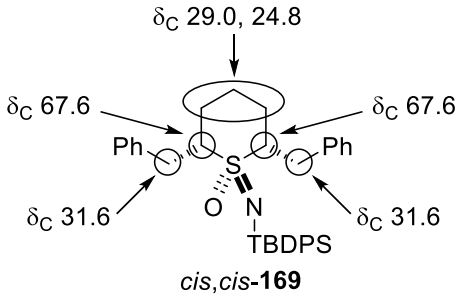
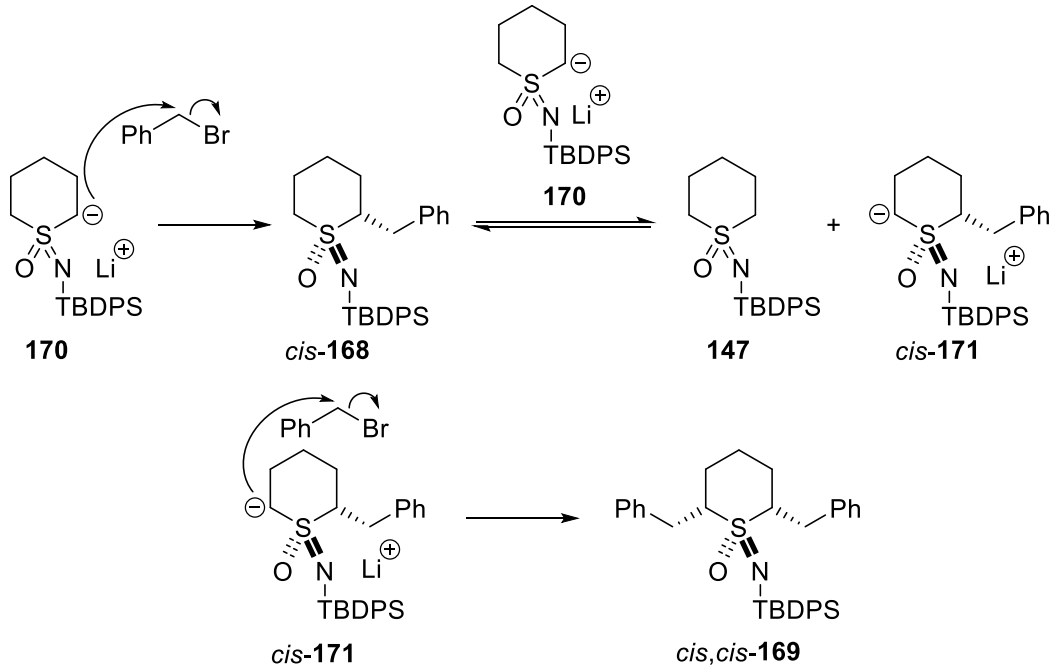


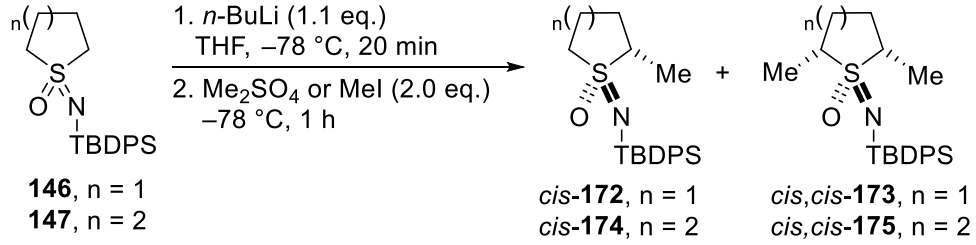
Figure 2.8 ^{13}C NMR spectroscopic data for *N*-TBDPS sulfoximine *cis,cis*-**169**

Our proposed pathway for the formation of the disubstituted product *cis,cis*-**169** is shown in Scheme 2.14. Initially, we believe that the desired reaction occurs i.e. the carbanion of deprotonated sulfoximine **170** attacks benzyl bromide to form *cis*-**168**. If benzyl bromide was slow to trap then it is likely that there would be deprotonated sulfoximine **170** still present. This could deprotonate sulfoximine *cis*-**168** at the other α-position to give *cis*-**171** and regenerate the starting material **147**. The carbanion of deprotonated sulfoximine *cis*-**171** could then trap a second benzyl bromide to form *cis,cis*-**169**. We believe dianion formation, as proposed in Scheme 2.10 with the 4-membered ring sulfoximine **148**, is less likely as formation of the disubstituted product would be dependent on the initial lithiation step. We observed no disubstituted product when these same conditions were used in the lithiation-trapping of 5- and 6-membered ring sulfoximines **146** and **147** with benzophenone (Scheme 2.14). Analysis of the ^{1}H NMR spectrum of the crude product showed that a small amount of starting material was present although the exact amount could not be calculated due to overlapping signals. The presence of this starting material supports our proposed pathway.



Scheme 2.14

The synthesis of disubstituted sulfoximine *cis,cis*-**169** led us to investigate whether disubstituted products would result after trapping sulfoximines with other alkylating agents. We therefore investigated the lithiation-trapping of sulfoximines **146** and **147** with methyl iodide and dimethyl sulfate. The results are summarised in Table 2.2.

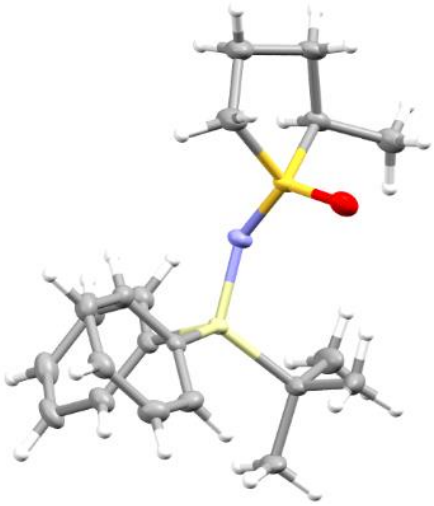


Entry	n	Starting material	Electrophile	Mono-product (%)[a]	Di-product (%)[a]
1[b]	1	**146**	MeI	*cis*-**172**, 56	*cis,cis*-**173**, 0
2[d]	1	**146**	MeI	*cis*-**172**, 45	*cis,cis*-**173**, 3
3[b]	2	**147**	MeI	*cis*-**174**, 47	*cis,cis*-**175**, 12
4[c]	1	**146**	Me_2SO_4	*cis*-**172**, 45	*cis,cis*-**173**, 7
5[b]	2	**147**	Me_2SO_4	*cis*-**174**, 52	*cis,cis*-**174**, 9

[a] % yield after purification by chromatography. [b] 0.5 mmol scale. [c] 1.0 mmol scale. [d] 5.0 mmol scale.

Table 2.2 Results of lithiation-trapping reactions with methylating agents

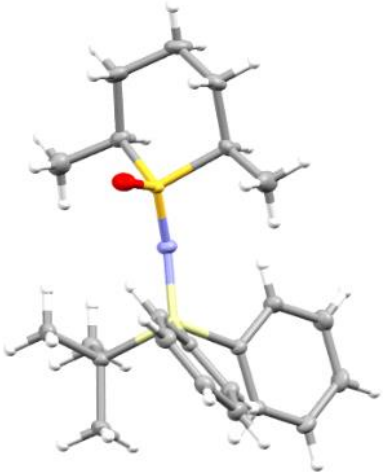
The relative configuration of 5-membered ring sulfoximine *cis*-**172** was confirmed by X-ray crystallography (Figure 2.9) and the relative configuration of 5-membered ring sulfoximine *cis,cis*-**173** was assigned by analogy. The X-ray crystal structure of sulfoximine *cis*-**172** showed that the oxygen bonded to sulfur is *cis* to the α-substituent, with the nitrogen in a *trans* orientation.



cis-**172**

Figure 2.9 X-ray structure of *N*-TBDPS sulfoximine *cis*-**172**

The relative configuration of 6-membered ring sulfoximine *cis,cis*-**175** was confirmed by X-ray crystallography (Figure 2.10) and the relative configuration of 6-membered ring sulfoximine *cis*-**174** was assigned by analogy. The X-ray crystal structure of sulfoximine *cis,cis*-**175** showed that both α-substituents are *cis* to the oxygen bonded to sulfur, with the nitrogen in a *trans* orientation. The 6-membered ring adopts a chair conformation where *N*-TBDPS and the two α-methyl groups sit in equatorial positions whereas the oxygen bonded to sulfur is axial.



cis,*cis*-**175**

Figure 2.10 X-ray structure of *N*-TBDPS sulfoximine *cis,cis*-**175**

Analysis of the ^{1}H NMR spectrum of disubstituted *cis,cis*-**173** showed a 6H doublet at δ_H 1.09 (J = 7.0 Hz) showing that there were two equivalent methyl groups. The ^{13}C NMR spectrum showed that there was only one signal at δ_C 59.3 for the two SCH carbons, one signal at δ_C 28.1 for the two CH_2 carbons in the ring and one signal at δ_C 12.7 for the two α-methyl groups. Therefore, the sulfoximine must be symmetrical. The ^{1}H and ^{13}C NMR spectra of *cis,cis*-**175** also displayed the same evidence of symmetry.

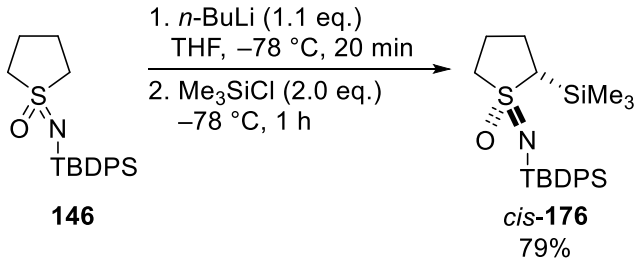
The lithiation-trapping of 5-membered ring sulfoximine **146** with methyl iodide gave exclusively 5-membered ring sulfoximine *cis*-**172** in 56% yield (Table 2.2, entry 1). However, when this reaction was repeated on a 5 mmol scale, we obtained sulfoximine *cis*-**172** in 45% yield and disubstituted sulfoximine *cis,cis*-**173** in 3% yield (entry 2). It is likely a small amount of the disubstituted product formed in the small-scale reaction although it was not visible by ^{1}H NMR spectroscopy and we were unable to isolate it. Lithiation-trapping of 6-membered ring sulfoximine **147** with methyl iodide gave the monosubstituted sulfoximine *cis*-**174** in 47% yield and disubstituted sulfoximine *cis,cis*-**175** in 12% yield (entry 3).

The use of dimethyl sulfate was also explored. Lithiation-trapping of 5-membered ring sulfoximine **146** with dimethyl sulfate gave mono-substituted methyl sulfoximine *cis*-**172** in 45% yield and disubstituted sulfoximine *cis,cis*-**173** in 7% yield (entry 4). It was found that lithiation-trapping of 6-membered ring sulfoximine **147** with dimethyl sulfate also gave the disubstituted sulfoximine *cis,cis*-**175** (9% yield) together with monosubstituted sulfoximine *cis*-**174** (52% yield) (entry 5).

By comparing all of the results in Table 2.2, it is clear that use of either methyl iodide or dimethyl sulfate gave similar yields of both monosubstituted and disubstituted sulfoximines. A comparison of the 5- and 6-membered ring systems showed that 6-membered ring disubstituted sulfoximine *cis,cis*-**175** was synthesised in a slightly higher yield than 5-membered ring disubstituted sulfoximine *cis,cis*-**173** when either methylating reagent was used. The structural similarity of the methylating reagents and benzyl bromide suggests that they are likely to behave in the same way in lithiation-trapping reactions. As a result, we propose that disubstituted sulfoximines *cis,cis*-**173** and *cis,cis*-**175** are synthesised *via* the mechanism shown in Scheme 2.14. The moderate yields of the methylation reactions and formation of disubstituted sulfoximines is expected to be a result of slow trapping by the methylating reagents at low temperatures

(–78 °C).[65] To establish this, we plan to monitor the reactions using *in situ* ReactIR™ in the future.

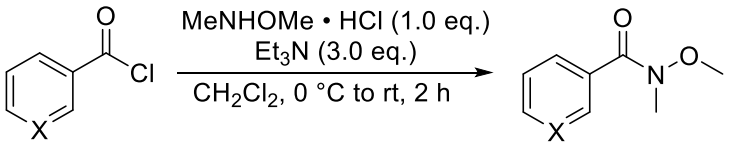
The lithiation-trapping of 5-membered ring sulfoximine **146** with trimethylsilyl chloride was also explored and we found that it gave exclusively silyl sulfoximine *cis*-**176** in 79% yield (Scheme 2.15). We assigned the stereochemistry of sulfoximine *cis*-**176** by analogy with the other examples studied thus far. The ^{1}H NMR spectrum showed a 2H multiplet at δ_H 2.60-2.53 for two SCH protons and the other SCH proton was a 1H dd (J = 12.0, 7.5 Hz) slightly further upfield at δ_H 2.42. In our previous lithiation-trapping reactions, the α-substituent was electron withdrawing resulting in a large downfield shift of the remaining α-proton in the ^{1}H NMR spectrum and a large downfield shift of the SCH signal in the ^{13}C NMR spectrum. In this case, silicon is electron donating and these shifts are not observed. For example, the ^{13}C NMR spectrum of *cis*-**176** showed a signal δ_C 57.1 for SCH and a signal at δ_C 56.5ppm for SCH_2.



146 *cis*-**176** 79%

Scheme 2.15

Sulfoximines with a ketone functionality, β-keto sulfoximines, can be synthesised by lithiation-trapping reactions with either esters or Weinreb amides (Table 1.2 and Scheme 1.37). As disubstitution is possible when trapping with esters, we started with Weinreb amides. Following a literature procedure,[66] phenyl and pyridine Weinreb amides **136** and **179** were synthesised from benzoyl chloride **177** and nicotinoyl chloride hydrochloride **178** using *N*,*O*-dimethyl hydroxylamine hydrochloride and Et_3N. Phenyl and pyridine Weinreb amides **136** and **179** were obtained in 74% and 57% yield respectively (Scheme 2.16).

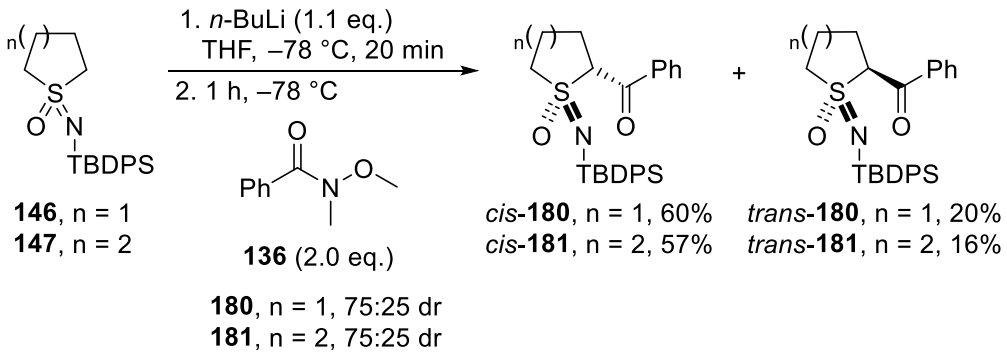


177, X = CH
178, X = N

136, X = CH, 74%
179, X = N, 57%

Scheme 2.16

Lithiation-trapping of 5-membered ring sulfoximine **146** with phenyl Weinreb amide **136** gave a 75:25 ratio of diastereomeric ketones *cis*-**180** and *trans*-**180** (by ^{1}H NMR spectroscopy of the crude product). The sulfoximines were separated by chromatography to give ketones *cis*-**180** and *trans*-**180** in 60% and 20% yield respectively (Scheme 2.17). In this case, the stereochemistry of the two products is assumed to be as depicted. We found that the diastereomeric ratio changed each time that the reaction was performed, giving a 55:45 mixture in one instance and a 65:35 mixture in another. A similar outcome was observed with 6-membered ring sulfoximine **147**. Thus, lithiation-trapping of sulfoximine **147** gave the crude product which contained a 75:25 mixture of ketones *cis*-**181** and *trans*-**181** (by ^{1}H NMR spectroscopy). After chromatography, sulfoximines *cis*-**181** and *trans*-**181** were isolated in 57% and 16% yield respectively (Scheme 2.17).

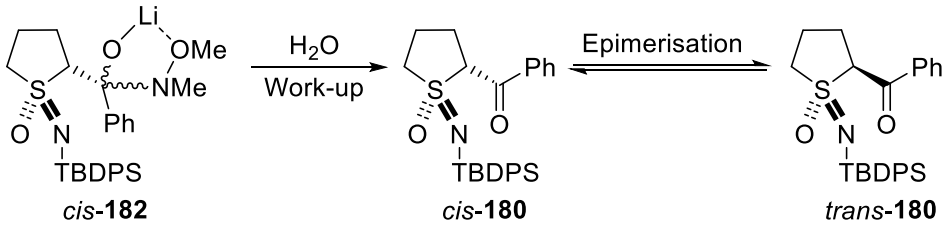


Scheme 2.17

The stereochemistry of the β-keto sulfoximines were assigned by assuming that the major products had *cis* configurations. Analysis of 5-membered ring sulfoximines *cis*-**180** and *trans*-**180** by ^{1}H NMR spectroscopy showed their spectra to have 1H dd signals for *cis*-**180** and *trans*-**180** at δ_H 4.73 (J = 8.0, 6.0 Hz) and δ_H 4.97 (J = 7.5, 7.5 Hz) respectively. These were significantly further downfield than the other protons on the ring (δ_H 2.00-3.00) due to the introduction of the ketone functionality. Analysis of 6-membered ring sulfoximines *cis*-**181** and *trans*-**181** by ^{1}H NMR spectroscopy showed that their spectra contained 1H multiplet signals for *cis*-**181** and *trans*-**181** at δ_H 4.55-4.50 and δ_H 4.85-4.78 respectively, which are similar shifts to those of the 5-membered ring sulfoximines.

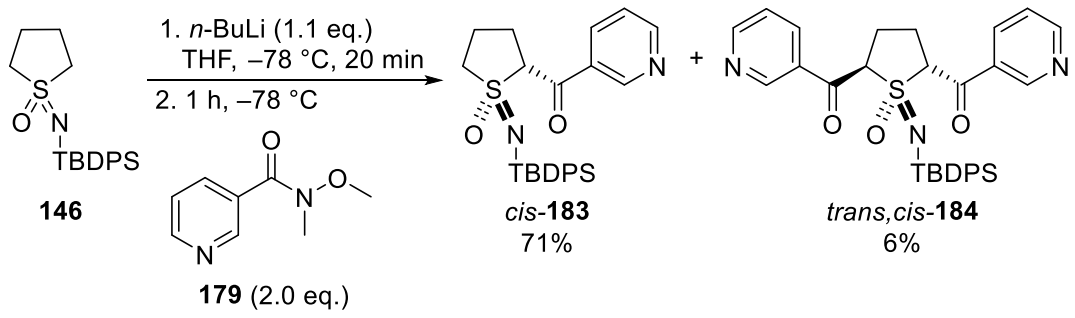
At this time, phenyl Weinreb amide **136** was the only electrophile to demonstrate poor α-diastereoselectivity. To explain this outcome, we suggest that tetrahedral intermediate *cis*-**182** forms and, upon quenching, this gives β-keto sulfoximine *cis*-**180** (Scheme 2.18). However, due to the acidity of the α-proton, epimerisation readily occurs *via* enolisation

to give the observed ratio of β-keto sulfoximines *cis*-**180** and *trans*-**180**. Epimerisation could occur to different amounts to explain the different ratios obtained.



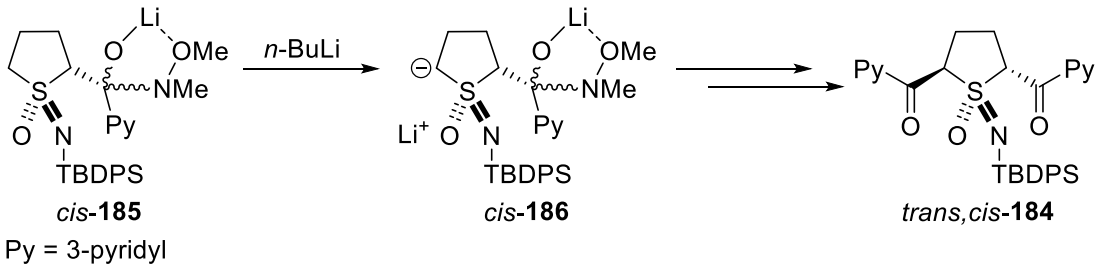
Scheme 2.18

Following on from this work, the lithiation-trapping of 5-membered ring sulfoximine **146** with pyridine Weinreb amide **179** was explored. This gave an 85:15 ratio of β-keto sulfoximine *cis*-**183** and double-trapped β-keto sulfoximine *trans,cis*-**184** (by ^{1}H NMR spectroscopy). The sulfoximines were separated by column chromatography to give sulfoximines *cis*-**183** and *trans,cis*-**184** in 71% and 6% yield respectively (Scheme 2.19). The stereochemistry of sulfoximine *cis*-**183** was assumed based on the previous examples. Analysis of sulfoximine *cis*-**183** by ^{1}H NMR spectroscopy showed a 1H dd at δ 4.92 (J = 7.5, 7.5 Hz) for the α-proton which had shifted significantly downfield due to the addition of the ketone. No additional signals were present in the ^{1}H or ^{13}C NMR spectra indicating that the *trans* diastereomer was not formed. It is not clear why epimerisation did not occur in this case. The 2,5-disubstituted sulfoximine was assigned as *trans,cis*-**184** as the ^{1}H NMR spectrum showed two 1H dd signals for the α-protons at δ_H 5.10 (J = 8.0, 8.0 Hz) and δ_H 4.54 (J = 8.0, 3.5 Hz). Additional evidence came from the ^{13}C NMR spectrum. Two signals at 69.4 ppm and 68.9 ppm were observed for the two SCH groups and two signals at 23.6 ppm and 23.3 ppm were seen for the two CH groups in the ring. Therefore, the sulfoximine was not symmetrical.



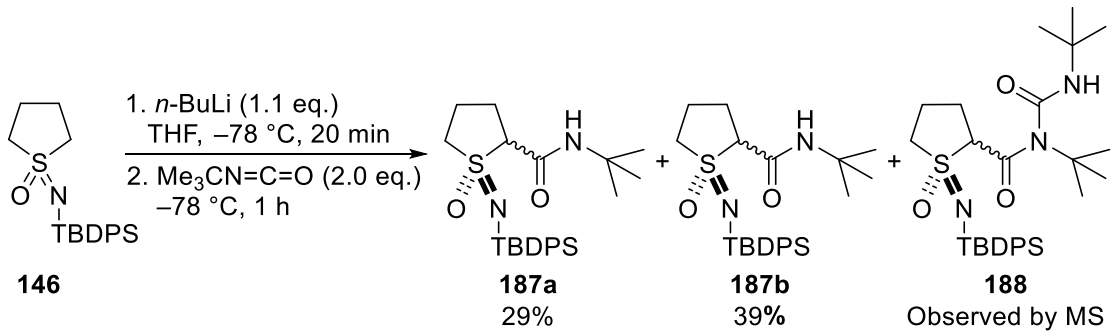
Scheme 2.19

The formation of the disubstituted sulfoximine was surprising and we propose two possible routes for its synthesis. Sulfoximine **146** could form a dianion due to the 0.1 equivalents excess of *n*-BuLi however, there is currently no evidence for this as our previous reactions with sulfoximine **146** have shown disubstitution to occur only with alkylating agents. An alternative route is shown in Scheme 2.20. Reaction of the lithiated sulfoximine with Weinreb amide **179** would give sulfoximine *cis*-**185**. It is then possible that the excess *n*-BuLi could lithiate sulfoximine *cis*-**185** to give carbanion *cis*-**186** which could be trapped a second time with Weinreb amide **179**. It may be expected that diketone *cis,cis*-**184** should form but it is possible that epimerisation occurs to give the observed *trans,cis*-**184**.



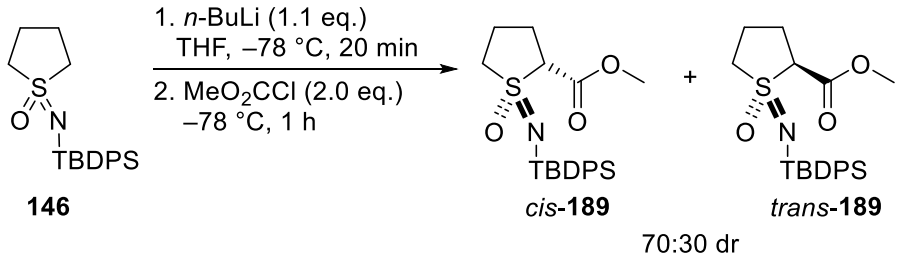
Scheme 2.20

As the addition of the pyridine Weinreb amide **179** to sulfoximine **146** gave exclusively β-keto sulfoximine *cis*-**183**, we wondered if high stereoselectivity would prevail with other carbonyl additions. However, lithiation-trapping of 5-membered ring sulfoximine **146** with *tert*-butyl isocyanate gave amido sulfoximines **187a** and **187b** as a 55:45 mixture of diastereomers (by ^{1}H NMR spectroscopy). Amido sulfoximine **187a** was isolated in 29% yield, whilst amido sulfoximine **187b** was isolated in 39% yield (Scheme 2.21). Presumably, epimerisation in the work-up of the amido sulfoximines **187a** and **187b** could account for such poor diastereoselectivity. A small quantity of by-product **188** was detected by mass spectrometry. This was thought to form from reaction of the initially formed amido anion with a second equivalent of electrophile.



Scheme 2.21

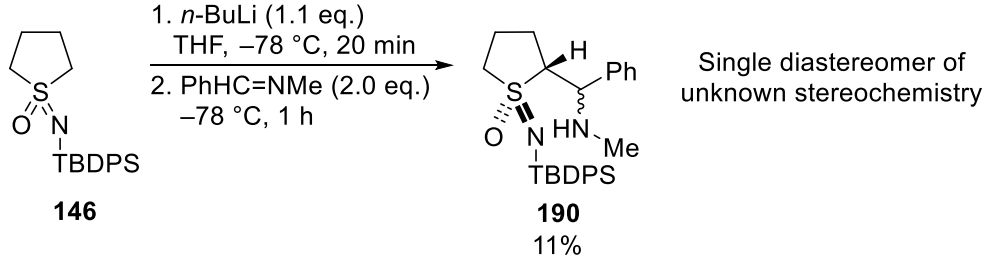
Use of methyl chloroformate as the electrophile also led to poor α-diastereoselectivity. Trapping 5-membered ring sulfoximine **146** with methyl chloroformate gave a 70:30 mixture of ester sulfoximines *cis*-**189** and *trans*-**189** (by ^{1}H NMR spectroscopy) (Scheme 2.22). It is assumed that the major product was *cis*-**189**. The formation of the products was confirmed by mass spectrometry and ^{1}H NMR spectroscopy. However, a significant amount of starting material remained which was not quantifiable. After several attempts at purification by chromatography, the products were not isolated cleanly.



Scheme 2.22

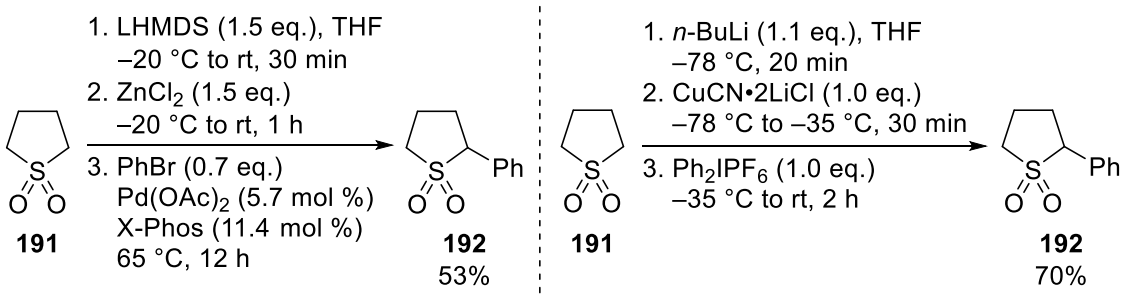
In terms of yield, lithiation and trapping with an imine was not very successful. When the lithiation-trapping of 5-membered ring sulfoximine **146** with *N*-benzylidene methylamine was attempted, a single unassigned diastereomeric amino sulfoximine **190** was obtained in only 11% yield (Scheme 2.23). In addition, 66% of the starting material **146** was recovered. Repetition of the reaction did not increase the yield of amino sulfoximine **190**. Analysis of the ^{1}H NMR spectrum of amino sulfoximine **190** showed the signal for the α-proton to be a 1H multiplet at δ_H 3.22–3.13 and the signal for PhC*H* to be a 1H doublet at δ_H 3.88 (J = 10.0 Hz). The ^{13}C NMR spectrum showed only one set of signals, indicating that amino sulfoximine **190** was isolated as a single diastereomer. Based on other examples in this chapter, it is likely that the α-substituent is *cis* to the sulfoximine oxygen but we were unable to assign the configuration at the amino stereocentre. The low

yield may be caused by the lithiated sulfoximine acting as a base and deprotonating the *N*-methyl protons on the imine.



Scheme 2.23

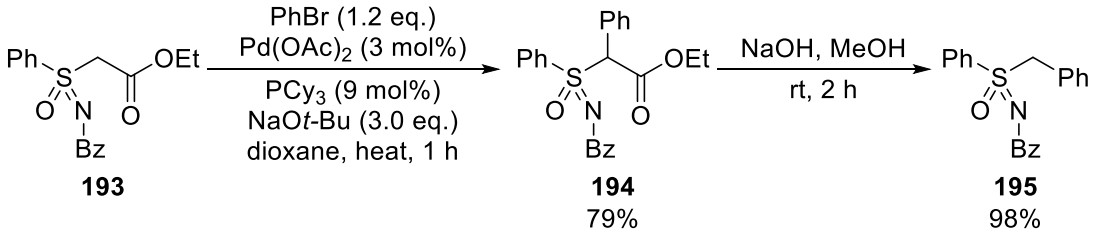
In order to widen the electrophile scope, we considered whether it would be possible to introduce an aromatic group at the α-position of sulfoximines. There is some literature precedent for the α-arylation of sulfones and sulfoximines using different approaches. For example, Zhou reported the palladium-catalysed Negishi α-arylation of cyclic sulfones with aryl bromides which gave α-arylated sulfones in moderate to high yields. Lithiation of 5-membered ring cyclic sulfone **191** with LHMDS in THF was followed by transmetallation with zinc(II) chloride. Then, Negishi coupling with bromobenzene using palladium(II) acetate and X-Phos gave arylated sulfone **192** in 53% yield (Scheme 2.24).[67] An alternate route to arylated sulfone **192** using organocopper chemistry was reported by Luisi. Sulfone **191** was lithiated with *n*-BuLi in THF and transmetallated to an organocuprate using CuCN·2LiCl. Subsequent reaction with the iodonium salt Ph_2IPF_6 gave arylated sulfone **192** in 70% yield (Scheme 2.24).[68] Luisi's route is higher yielding and does not require an expensive palladium catalyst but many more aryl bromides are available compared to iodonium salts.



Scheme 2.24

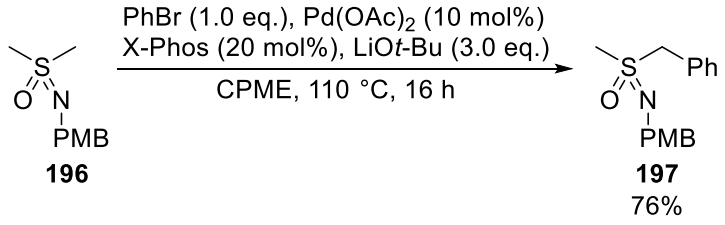
The palladium-catalysed α-arylation of acyclic sulfoximines has been explored. The first reported example showed that aryl groups could be added to sulfoximines in good yields

by first introducing an ester functional group, followed by cross-coupling with an aryl bromide and removal of the ester. For example, cross-coupling of *N*-benzamide sulfoximine **193** with bromobenzene was achieved using palladium(II) acetate, tricyclohexylphosphine and sodium *tert*-butoxide.[69] Heating the mixture at reflux for 1 h gave arylated sulfoximine **194** in 79% yield (Scheme 2.25). Hydrolysis of sulfoximine **194** with sodium hydroxide in methanol removed the ester group to give α-arylated sulfoximine **195** in 98% yield.



Scheme 2.25

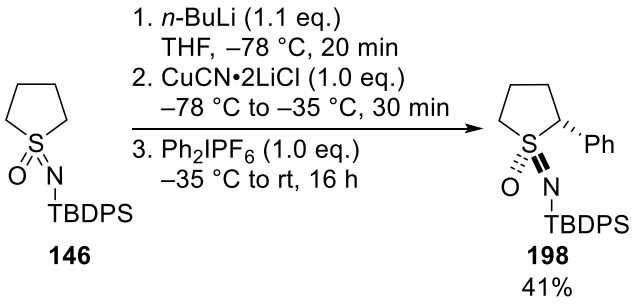
Following on from this work, a one-pot reaction was reported to give α-arylated sulfoximines in good yields without the need for addition and removal of an ester. Reaction of *N*-PMB protected dimethyl sulfoximine **196** with bromobenzene, palladium(II) acetate, X-Phos and lithium *tert*-butoxide in cyclopentyl methyl ether gave α-arylated sulfoximine **197** in 76% yield (Scheme 2.26).[70] The use of other *N*-protecting groups (e.g. TBDPS, Bz and Ts) was much less successful.



Scheme 2.26

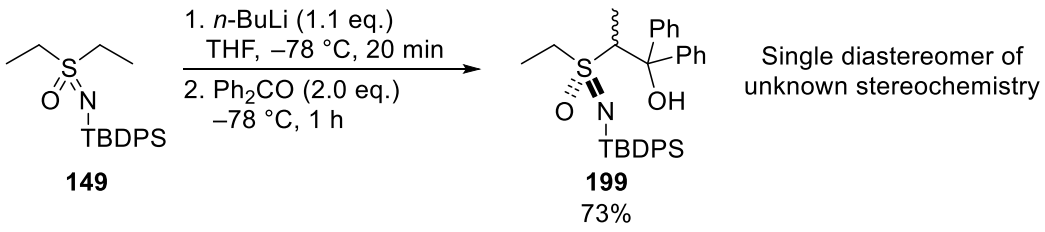
As a first attempt, we decided to explore whether Luisi's organocuprate method would be suitable for the α-arylation of cyclic sulfoximines. Lithiation of 5-membered ring sulfoximine **146** with *n*-BuLi in THF was followed by addition of 1.0 equivalent of CuCN·2LiCl. After stirring at –35 °C for 30 min, Ph_2IPF_6 was added. The mixture was stirred at rt for 16 h and, after chromatography, phenyl sulfoximine **198** was isolated as a single diastereomer in 41% yield (Scheme 2.27). Analysis of phenyl sulfoximine **198** by ^{1}H NMR spectroscopy showed a 1H dd signal at δ_H 4.04 (J = 12.0, 7.5 Hz) for the α-

proton adjacent to the phenyl group. The remaining two α-protons appeared as a 2H multiplet further upfield at δ_H 3.09-2.93. The relative stereochemistry of phenyl sulfoximine **198** was determined by X-ray crystallography. This method for α-arylation is promising as it shows full α-diastereoselectivity.



Scheme 2.27

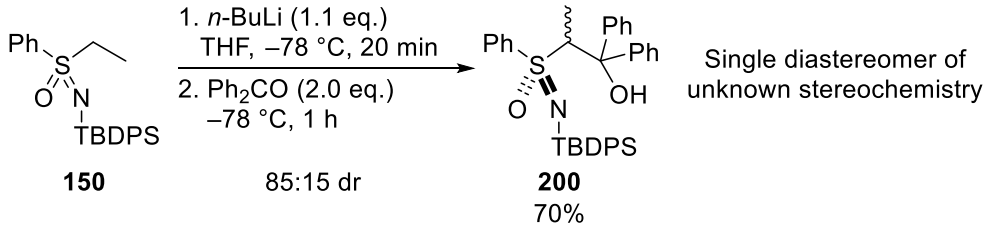
As the 5- and 6-membered ring *N*-TBDPS sulfoximines **146** and **147** displayed such good diastereoselectivity when undergoing lithiation-trapping reactions, we considered whether high diastereoselectivity would be possible with acyclic *N*-TBDPS sulfoximines. In this context, there were some examples in Chapter 1.3 showing good α-diastereoselectivity (see Schemes 1.29 and 1.31). Diethyl sulfoximine **149** was selected to undergo lithiation-trapping with benzophenone. Using our standard reaction conditions, α-substituted sulfoximine **199** was synthesised as a single diastereomer which was isolated in 73% yield after chromatography (Scheme 2.28). Both the ^{1}H and ^{13}C NMR spectra showed only one set of signals, indicating that a single diastereomer was formed. Key signals in the ^{1}H NMR spectrum showed a 1H quartet at δ_H 4.18 (J = 7.0 Hz) assigned to the α-proton adjacent to the benzyl alcohol and a 3H doublet at δ_H 1.45 (J = 7.0 Hz) assigned to the methyl group adjacent to the substituted α-carbon atom. The relative stereochemistry of α-substituted sulfoximine **199** has not been determined.



Scheme 2.28

The lithiation-trapping of phenyl ethyl sulfoximine **150** using benzophenone was also investigated. In this case, α-substituted sulfoximine **200** was synthesised as an 85:15 mixture of diastereomers (by ^{1}H NMR spectroscopy of the crude product). After

chromatography, only the major diastereomer was isolated in 70% yield (Scheme 2.29). It is possible that the minor diastereomer was not isolated due to degradation on the column. Analysis of the ^{1}H NMR spectrum of the crude product showed two 1H quartets at δ_H 4.44 (J = 7.0 Hz) and δ_H 4.23 (J = 7.0 Hz) for the α-protons adjacent to the alcohol of the major and minor diastereomers respectively. In addition, two 3H doublets were observed at δ_H 1.43 (J = 7.0 Hz) and δ_H 1.47 (J = 7.0 Hz) for the methyl group of the major and minor diastereomers respectively. Analysis of the ^{1}H NMR spectrum of the purified sulfoximine showed only signals for the major diastereomer.



Scheme 2.29

To explain the high diastereoselectivity in the lithiation-trapping of acyclic sulfoximines **149** and **150**, it is proposed that one of the two pathways shown in Figure 2.11 is the major one. Both pathways proceed *via* a sp^2 hybridised α-carbon as proposed for the cyclic sulfoximines (see Figure 2.6). Reaction with benzophenone from conformation **A** would occur opposite the bulky TBDPS group to give sulfoximine *syn*-**201**. Alternatively, reaction from conformation **B** would give sulfoximine *anti*-**201**. In order to distinguish between these two options, the stereochemistry of the major diastereomeric products would need to be established.

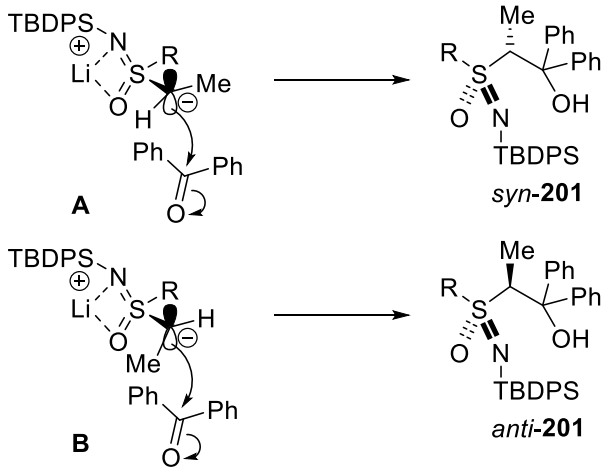


Figure 2.11 Models for electrophilic trapping

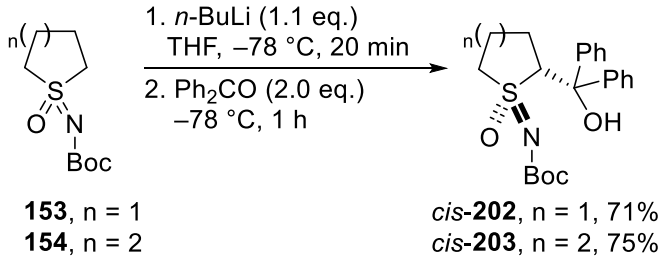
Overall, focusing on the results with 5- and 6-membered ring *N*-TBDPS cyclic sulfoximines **146** and **147**, we have observed high levels of *cis* α-diastereoselectivity with a wide range of electrophiles. This includes benzophenone, benzaldehyde, benzyl bromide, methyl iodide, dimethyl sulfate and trimethylsilyl chloride. In some cases, lower diastereoselectivity was observed with products containing an α-carbonyl group, which we propose is due to epimerisation of the β-keto sulfoximine products. Our brief exploration of *N*-TBDPS acyclic sulfoximines **149** and **150** also displayed a high level of α-diastereoselectivity with benzophenone although, at this time, we do not know the stereochemistry of the major diastereomers. The α-substituted cyclic and acyclic sulfoximines were isolated in moderate to high yields, with the exception of ester sulfoximine **189** and amino sulfoximine **187**. In addition, reactions of cyclic sulfoximines with benzyl bromide, methyl iodide and dimethyl sulfate gave varying amounts of disubstituted products which lowered the overall yield of the desired α-substituted products.

2.2.2 α-Lithiation and Trapping of *N*-Boc Sulfoximines

Given the success of the lithiation-trapping of *N*-TBDPS cyclic sulfoximines **146** and **147**, we decided to explore the corresponding *N*-Boc 5- and 6-membered ring sulfoximines **153** and **154**. Investigating the lithiation-trapping reactions of these sulfoximines would provide a direct comparison between the *N*-Boc and *N*-TBDPS groups. In addition, our results could be compared with those from Degennaro's study on *N*-Boc 4-membered ring sulfoximine **129** (see Chapter 1.3). For our own planned studies, four different electrophiles were chosen. Benzophenone, benzyl bromide and methyl iodide were selected as they were used in both our work on *N*-TBDPS cyclic sulfoximines **146** and **147** and in Degennaro's study on 4-membered ring *N*-Boc sulfoximine **129**. Benzaldehyde was also tested to establish the effect of the *N*-Boc group on the diastereoselectivity at the hydroxy stereocentre.

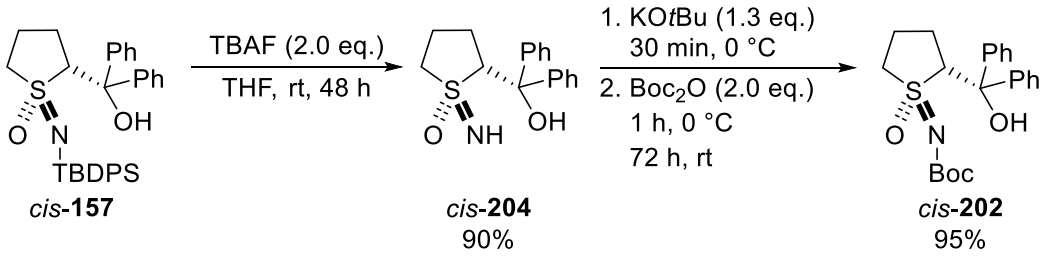
The first electrophile to be investigated was benzophenone. We decided to use our standard lithiation conditions of *n*-BuLi at −78 °C for 20 min for comparison reasons and because they are very similar to Degennaro's conditions (see Scheme 1.36). Lithiation of 5-membered ring *N*-Boc sulfoximine **153** with *n*-BuLi and trapping with benzophenone gave sulfoximine *cis*-**202** in 71% yield (Scheme 2.30). The relative stereochemistry of

sulfoximine *cis*-**202** was assigned by its separate synthesis from *N*-TBDPS sulfoximine *cis*-**157** of known configuration, as described below. Analysis by ^{1}H NMR spectroscopy showed a 1H signal at δ_H 4.74 (dd, J = 9.0, 9.0 Hz) which was assigned to the α-proton adjacent to the benzyl alcohol. A 1H singlet at δ_H 4.11 was assigned to the OH group. 6-Membered ring sulfoximine **154** behaved in the same way. Lithiation of 6-membered ring sulfoximine **154** with *n*-BuLi and trapping with benzophenone gave sulfoximine *cis*-**203** in 75% yield (Scheme 2.30). The relative stereochemistry of sulfoximine *cis*-**203** was assumed by analogy with 5-membered ring sulfoximine *cis*-**202**. Analysis by ^{1}H NMR spectroscopy showed a 1H signal at δ_H 4.81 (dd, J = 9.5, 3.5 Hz) which was assigned to the α-proton adjacent to the benzyl alcohol. A 1H singlet at δ_H 5.05 was assigned to the OH group. The high yields and diastereoselectivity of these reactions were promising results, as changing the *N*-substituent appeared to have no effect on the reaction.



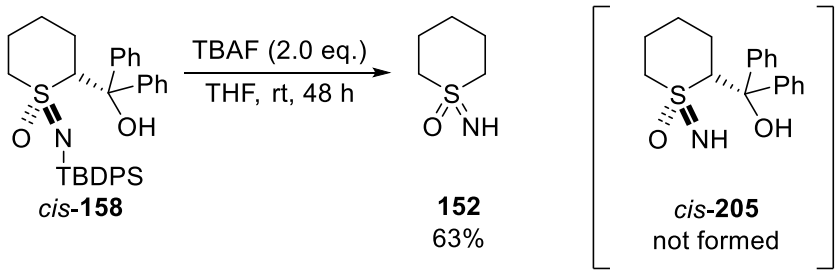
Scheme 2.30

The relative stereochemistry of 5-membered ring *N*-Boc sulfoximine *cis*-**202** was proven as shown in Scheme 2.31. Deprotection of 5-membered ring *N*-TBDPS sulfoximine *cis*-**157**, whose stereochemistry was established by X-ray crystallography (see Figure 2.2), was achieved using TBAF to give NH sulfoximine *cis*-**204** in 90% yield. Subsequent protection of NH sulfoximine *cis*-**204** using potassium *tert*-butoxide and Boc_2O gave *N*-Boc sulfoximine *cis*-**202** in 95% yield. A comparison of the ^{1}H and ^{13}C NMR spectra of sulfoximine *cis*-**202** synthesised by lithiation-trapping and *via* the route shown in Scheme 2.31 showed that their spectra were identical, enabling the stereochemistry assignment.



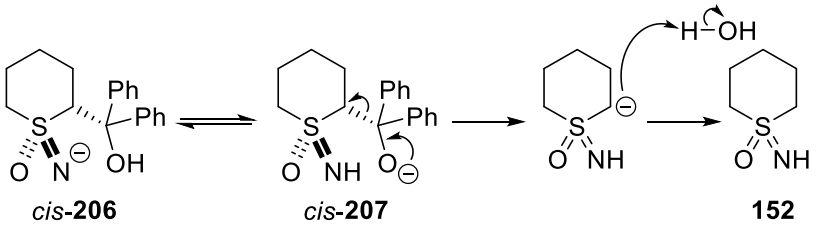
Scheme 2.31

Attempts to prove the relative stereochemistry of 6-membered ring *N*-Boc sulfoximine *cis*-**203** in a similar way were unsuccessful. An initial attempt at deprotection of sulfoximine *cis*-**158** using TBAF at rt for 48 h did not give any NH sulfoximine *cis*-**205**. Instead, this reaction returned unfunctionalised sulfoximine **152** in 63% yield (Scheme 2.32). The reaction was repeated with a decreased reaction time of 24 h but unfunctionalised sulfoximine **152** was once again the only product (60% yield).



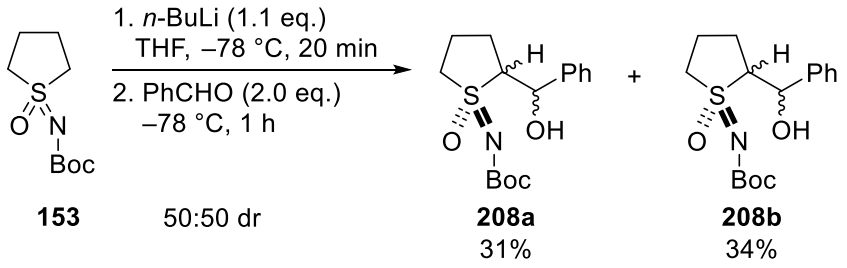
Scheme 2.32

Our mechanistic proposal for the formation of NH sulfoximine **152** is shown in Scheme 2.33. It is thought that the TBDPS deprotection proceeds as expected to give deprotonated NH sulfoximine *cis*-**206** which could be in equilibrium with alkoxide *cis*-**207**. Then, a retro-aldol-type process could occur from alkoxide *cis*-**207** to ultimately give NH sulfoximine **152** after protonation, probably from some water in the TBAF solution. It is not clear why the 6-membered ring sulfoximine *cis*-**158** is more susceptible to this fragmentation than 5-membered ring sulfoximine *cis*-**157**.



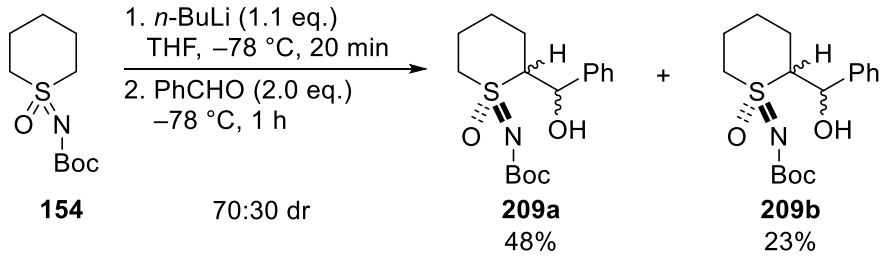
Scheme 2.33

The diastereoselectivity of lithiation-trapping reactions of *N*-Boc sulfoximines **153** and **154** with benzaldehyde was then explored. Lithiation-trapping of 5-membered ring sulfoximine **153** with benzaldehyde gave a 50:50 mixture of sulfoximines **208a** and **208b** (from the ^{1}H NMR spectrum of the crude product). After chromatography, sulfoximines **208a** and **208b** were isolated in 31% and 34% yield respectively (Scheme 2.34). Analysis of the ^{1}H NMR spectra of the sulfoximines showed a broad 1H singlet at δ_H 5.59 for the PhC*H* signal of **208a** and a 1H doublet at δ_H 5.84 (J = 3.0 Hz) for the PhC*H* signal of **208b**. The relative stereochemistry of sulfoximines **208a** and **208b** is currently unknown.



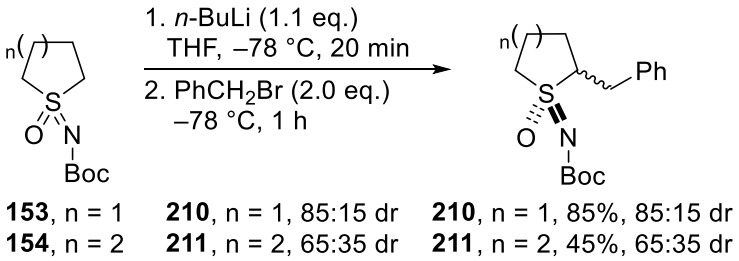
Scheme 2.34

The lithiation-trapping of 6-membered ring sulfoximine **154** with benzaldehyde gave a crude product which contained a 70:30 mixture of sulfoximines **209a** and **209b** (by ^{1}H NMR spectroscopy). After chromatography, sulfoximines **209a** and **209b** were isolated in 48% and 23% yield respectively (Scheme 2.35). Analysis of the ^{1}H NMR spectra of the sulfoximines showed a 1H singlet at δ_H 5.81 for the PhC*H* signal of **209a** and a 1H singlet at δ_H 5.91 for the PhC*H* signal of **209b**. The relative stereochemistry of sulfoximines **209a** and **209b** is currently unknown.



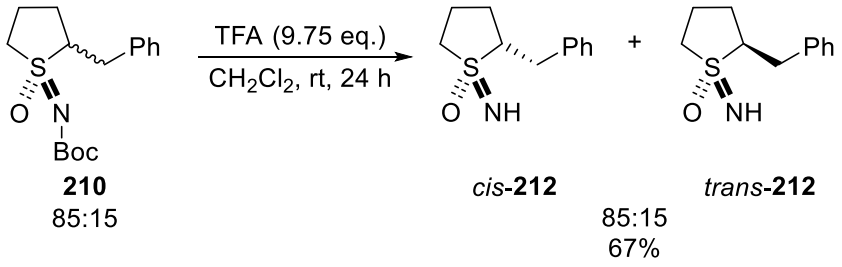
Scheme 2.35

Lithiation-trapping of 5-membered ring *N*-Boc sulfoximine **153** with benzyl bromide gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**210** and *trans*-**210** in the crude product. In this case, the diastereomers were not separable and an 85:15 mixture of sulfoximines *cis*-**210** and *trans*-**210** was isolated in 85% yield after chromatography (Scheme 2.36). The relative configuration of the diastereomers was assigned by a separate synthesis of *N*-Boc sulfoximine *cis*-**210** from *N*-TBDPS sulfoximine *cis*-**166**, although the stereochemistry of each of these compounds is not proven unequivocally. Lithiation-trapping of 6-membered ring sulfoximine **154** displayed a lower level of α-diastereoselectivity, giving a 65:35 mixture of sulfoximines **211a** and **211b** (from the ^{1}H NMR spectrum of the crude product). After chromatography, a 65:35 mixture of sulfoximines **211a** and **211b** was isolated in 45% yield (Scheme 2.36).



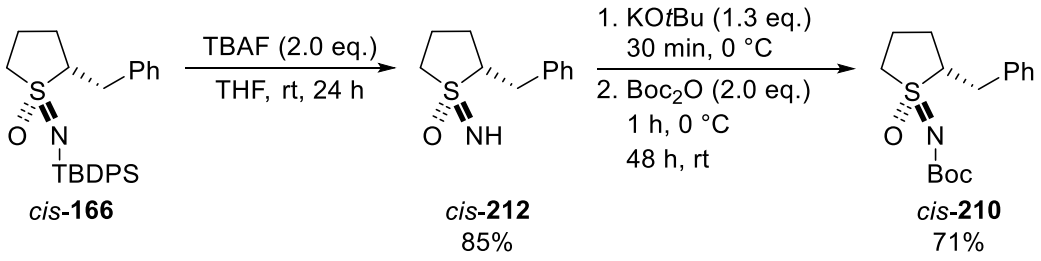
Scheme 2.36

We were surprised that these two reactions did not give high α-stereocontrol. However, we initially wondered whether the two sets of signals could have been due to *N*-Boc rotamers. Therefore, in order to prove that the 5-membered ring *N*-Boc sulfoximines **210** were diastereomers and not rotamers, the Boc group was removed. Deprotection of the 85:15 mixture of 5-membered ring *N*-Boc sulfoximines **210** was achieved using TFA to give an 85:15 mixture of NH sulfoximines *cis*-**212** and *trans*-**212** in 67% yield (Scheme 2.37). This proved that the sulfoximines were indeed diastereomers. Analysis by ^{1}H NMR spectroscopy showed a 0.85H multiplet at δ_H 1.96-1.84 which was assigned to a CH signal and a 0.15H multiplet at δ_H 1.84-1.73 also assigned to a CH signal.



Scheme 2.37

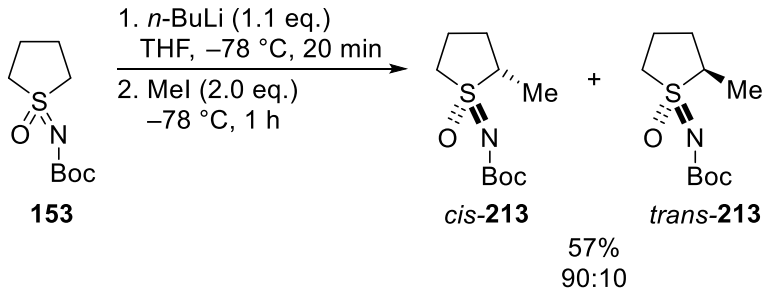
The reactions shown in Scheme 2.38 were used to prove that the major diastereomer from lithiation and benzylation of *N*-Boc sulfoximine **153** and *N*-TBDPS sulfoximine **146** were the same. As described in Chapter 2.2.1, we have assigned the stereochemistry in *N*-TBDPS sulfoximine *cis*-**166** by analogy with other examples although it is not proven. Reaction of *N*-TBDPS 5-membered ring sulfoximine *cis*-**166** with TBAF gave NH sulfoximine *cis*-**212** in 85% yield. Subsequent reprotection of NH sulfoximine *cis*-**212** using potassium *tert*-butoxide and Boc_2O, gave *N*-Boc sulfoximine *cis*-**210** in 71% yield (Scheme 2.38). A comparison of the ^{1}H NMR spectra of sulfoximine *cis*-**210** and the 85:15 mixture of sulfoximines *cis*-**210** and *trans*-**210** showed that the major diastereomer has *cis* stereochemistry.



cis-**166** *cis*-**212** 85% *cis*-**210** 71%

Scheme 2.38

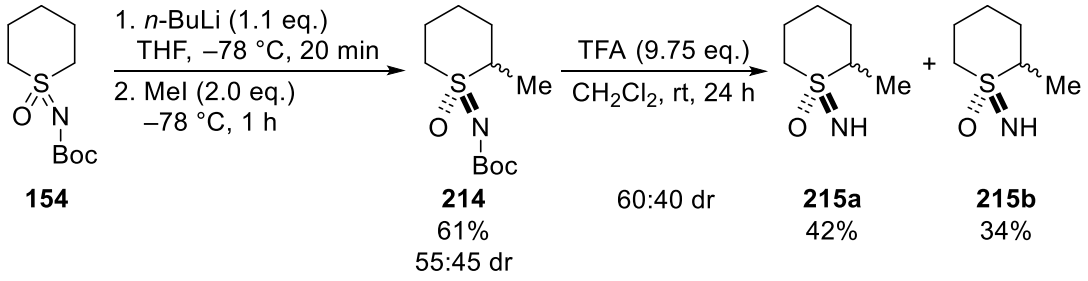
The lithiation-trapping of 5-membered ring sulfoximine **153** with methyl iodide gave a crude product which appeared to show the presence of two diastereomers. However, the ratio of diastereomers could not be calculated from the ^{1}H NMR spectrum due to overlapping peaks. After purification by chromatography, sulfoximines *cis*-**213** and *trans*-**213** were isolated in 57% yield but the ratio of diastereomers still could not be calculated from the ^{1}H NMR spectrum. However, the ^{13}C NMR spectrum showed two sets of signals in a ratio of 90:10 (Scheme 2.39). We therefore assumed that a 90:10 mixture of sulfoximines *cis*-**213** and *trans*-**213** were formed, and the stereochemistry was assigned by analogy with the benzyl bromide result.



153 *cis*-**213** *trans*-**213** 57% 90:10

Scheme 2.39

Lithiation-trapping of 6-membered ring sulfoximine **154** with methyl iodide gave, after purification by chromatography, sulfoximine **214** in 61% yield. Due to overlapping peaks in the ^{1}H NMR spectrum, the ratio of the two diastereomers could not be calculated. It was hoped that removal of the Boc group would shift the signals in the ^{1}H NMR spectrum enough to enable calculation of the ratio. Treatment of sulfoximine **214** with TFA for 24 h gave a 60:40 mixture (by ^{1}H NMR spectroscopy) of NH sulfoximines **215a** and **215b**. After purification by chromatography, sulfoximines **215a** and **215b** were isolated in 42% and 34% yield respectively (Scheme 2.40).



Scheme 2.40

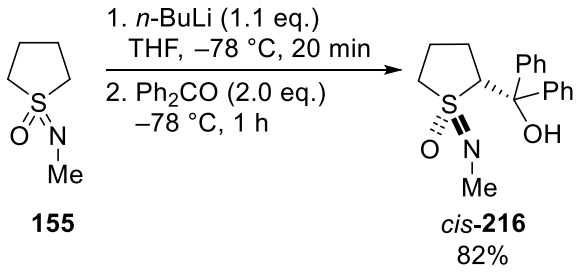
Overall, the α-diastereoselectivity observed with *N*-Boc sulfoximines **153** and **154** was more variable than with *N*-TBDPS sulfoximines **146** and **147**. A comparison of the 5- and 6-membered ring *N*-Boc sulfoximines showed them both to have high diastereoselectivity with benzophenone, as observed with the analogous *N*-TBDPS sulfoximines **146** and **147**. However, with benzaldehyde, benzyl bromide and methyl iodide the α-diastereoselectivity was lower than the *N*-TBDPS sulfoximines. It is of interest that, for the *N*-Boc sulfoximines **146** and **147**, no disubstituted products were formed with benzyl bromide and methyl iodide. In addition, the 5-membered ring *N*-Boc sulfoximine **153** displayed higher diastereoselectivity than the 6-membered ring *N*-Boc sulfoximine **154**. Our results can also be compared with Degennaro's results on 4-membered ring *N*-Boc sulfoximine **129**. Since the 4-membered ring sulfoximine **129** showed full α-diastereoselectivity with benzophenone, benzyl bromide and methyl iodide, it appears that increasing the ring size decreases the diastereoselectivity of the reactions.

2.2.3 α-Lithiation and Trapping of *N*-Me Sulfoximines

An exploration of the lithiation-trapping reactions of *N*-Me 5- and 6-membered ring sulfoximines **155** and **156** would enable a direct comparison of the *N*-Me, *N*-Boc and *N*-TBDPS groups. Therefore, we could determine the effect of the sterically less hindered *N*-Me substituent on the diastereoselectivity of the reactions. The electrophiles selected were benzophenone, benzyl bromide, methyl iodide and benzaldehyde due to their use with *N*-TBDPS sulfoximines **146** and **147** and *N*-Boc sulfoximines **153** and **154**.

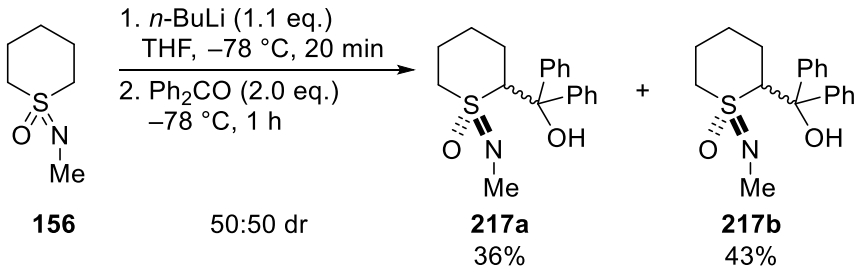
Using benzophenone, we used our standard lithiation conditions of *n*-BuLi at −78 °C for 20 min for direct comparison with the *N*-TBDPS and *N*-Boc results. Thus, 5-membered ring *N*-Me sulfoximine **155** was lithiated and trapped with benzophenone to give sulfoximine *cis*-**216** in 82% yield (Scheme 2.41). The relative stereochemistry of

sulfoximine *cis*-**216** was assigned by analogy with *N*-TBDPS sulfoximine *cis*-**157**. Analysis by ^{1}H NMR spectroscopy displayed key diagnostic signals. For example, a 1H signal at δ_H 4.33 (dd, J = 9.5, 8.5 Hz) was assigned to the α-proton adjacent to the benzyl alcohol and a 1H singlet at δ_H 5.06 was assigned to the OH group.



Scheme 2.41

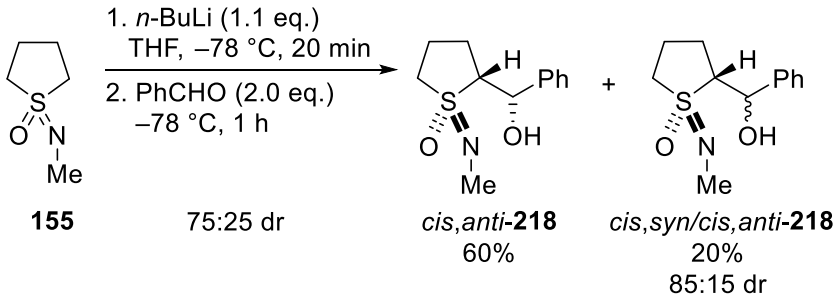
In contrast, the lithiation and trapping of 6-membered ring *N*-Me sulfoximine **156** with benzophenone gave the crude product which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of sulfoximines **217a** and **217b** (Scheme 2.42). After purification by chromatography, sulfoximine **217a** was isolated in 36% yield and sulfoximine **217b** was isolated in 43% yield. The ^{1}H NMR spectra of these sulfoximines displayed the usual diagnostic signals. Sulfoximine **217a** showed a 1H signal at δ_H 3.95 (dd, J = 12.0, 3.0 Hz) which was assigned to the α-proton and a 1H singlet at δ_H 7.74 for the OH group. Sulfoximine **217b** had a 1H signal at δ_H 3.99 (dd, J = 12.0, 2.0 Hz) which was assigned to the α-proton, although the signal for the OH group was not visible. For the reactions with benzophenone, 5-membered ring sulfoximine **155** displayed full α-diastereocontrol whilst the 6-membered ring sulfoximine **156** showed no α-diastereoselectivity. At this time, we cannot offer an explanation for this result.



Scheme 2.42

Surprisingly, the trend in α-diastereoselectivity was not observed with benzaldehyde. Lithiation-trapping of 5-membered ring sulfoximine **155** with benzaldehyde gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis,anti*-**218** and *cis,syn*-**218**. After

purification by chromatography, sulfoximine *cis,anti*-**218** (60% yield) and an 85:15 mixture of sulfoximines *cis,syn*-**218** and *cis,anti*-**218** (20% yield) were isolated (Scheme 2.43). Analysis of the major diastereomer *cis,anti*-**218** by X-ray crystallography identified its stereochemistry (Figure 2.12). The oxygen bonded to sulfur is *cis* to the α-substituent whilst the nitrogen is in a *trans* orientation. Given that other electrophile trappings occur *trans* to the *N*-substituent, the minor product was believed to be *cis,syn*-**218**.



Scheme 2.43

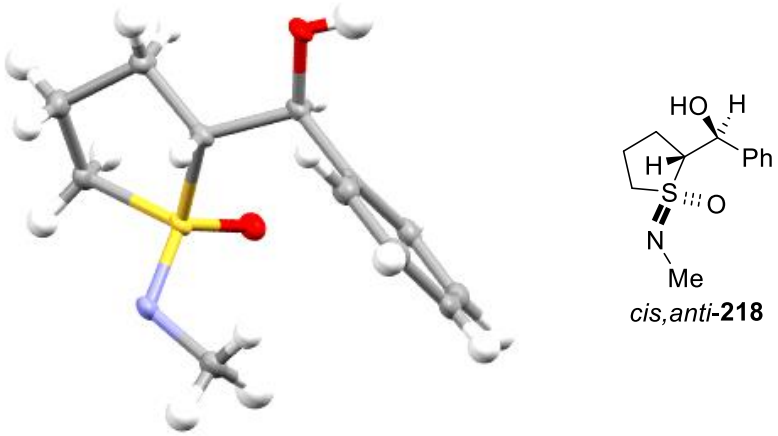
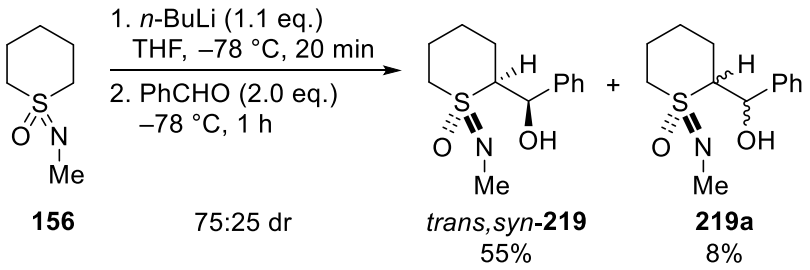


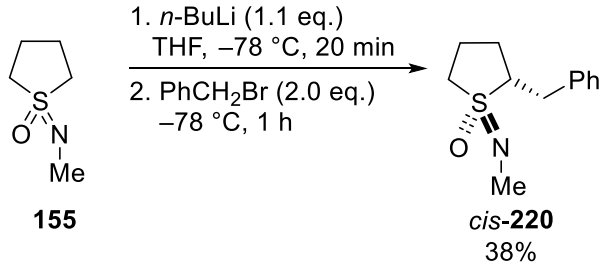
Figure 2.12 X-ray structure of *N*-Me sulfoximine *cis,anti*-**218**

The lithiation and trapping of 6-membered ring sulfoximine **156** with benzaldehyde gave a 75:25 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *trans,syn*-**219** and **219a**. Purification by chromatography gave sulfoximine *trans,syn*-**219** in 55% yield and sulfoximine **219a** in 8% yield (Scheme 2.44). The relative stereochemistry of sulfoximine *trans,syn*-**219** was determined by X-ray crystallography. It is interesting that lithiation-trapping of 6-membered ring sulfoximine **156** with benzaldehyde showed a degree of diastereoselectivity, giving only two out of four possible diastereomers, whilst the reaction with benzophenone (see Scheme 2.42) was not diastereoselective.



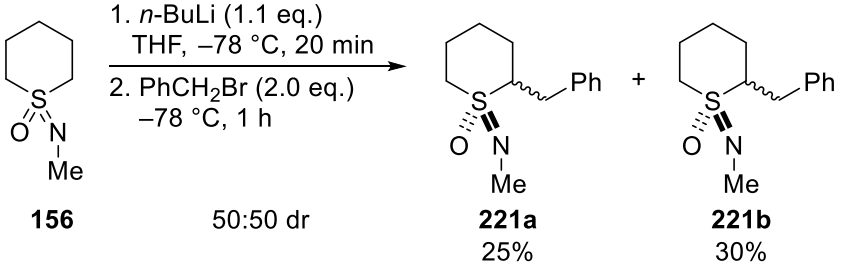
Scheme 2.44

The reactions of *N*-Me sulfoximines **155** and **156** with alkylating agents was also studied. The lithiation and trapping of 5-membered ring sulfoximine **155** with benzyl bromide gave sulfoximine *cis*-**220** in 38% yield (Scheme 2.45). The relative stereochemistry of sulfoximine *cis*-**220** was assigned by analogy with *N*-TBDPS sulfoximine *cis*-**166**. It is unknown why the yield of this reaction is low in comparison to the other lithiation-trapping examples with benzyl bromide.



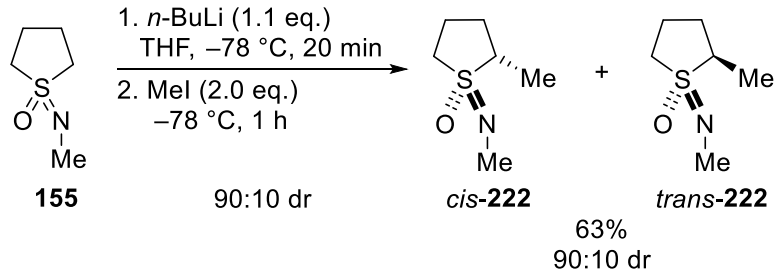
Scheme 2.45

Next, 6-membered ring sulfoximine **156** was lithiated and trapped with benzyl bromide to give a 50:50 mixture (by ^{1}H NMR spectroscopy) of sulfoximines **221a** and **221b**. After purification by chromatography, sulfoximine **221a** was isolated in 30% yield and sulfoximine **221b** was isolated in 25% yield (Scheme 2.46). With benzyl bromide, 5-membered ring *N*-Me sulfoximine **155** showed complete α-diastereoselectivity whereas 6-membered ring *N*-Me sulfoximine **156** showed no diastereoselectivity.



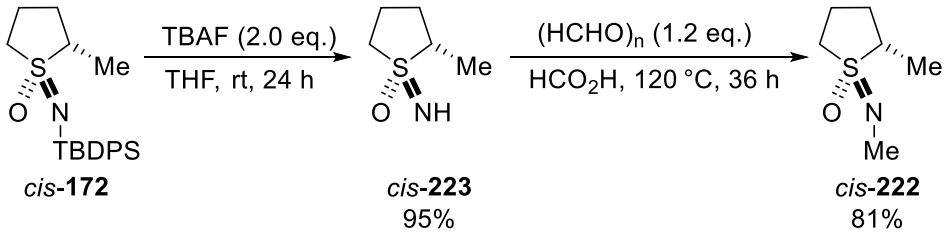
Scheme 2.46

Finally, we tested the lithiation-trapping reactions of *N*-Me sulfoximines **155** and **156** with methyl iodide. Lithiation-trapping of 5-membered ring sulfoximine **155** with methyl iodide gave the crude product which contained a 90:10 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**222** and *trans*-**222**. After purification by chromatography, the sulfoximines were isolated as a 90:10 mixture of *cis*-**222** and *trans*-**222** in 63% yield (Scheme 2.47). The relative stereochemistry of sulfoximine *cis*-**222** was assigned by its separate synthesis from *N*-TBDPS sulfoximine *cis*-**172** of known configuration. This was the only case where reaction of 5-membered ring sulfoximine **155** gave some of the *trans*-diastereomer. Key diagnostic signals in the ^{1}H NMR spectrum showed a 3H doublet at δ_H 1.33 (J = 7.0 Hz) for the α-Me group of sulfoximine *cis*-**222** and a 3H doublet at δ_H 1.31 (J = 7.0 Hz) for the α-Me group of sulfoximine *trans*-**222**.



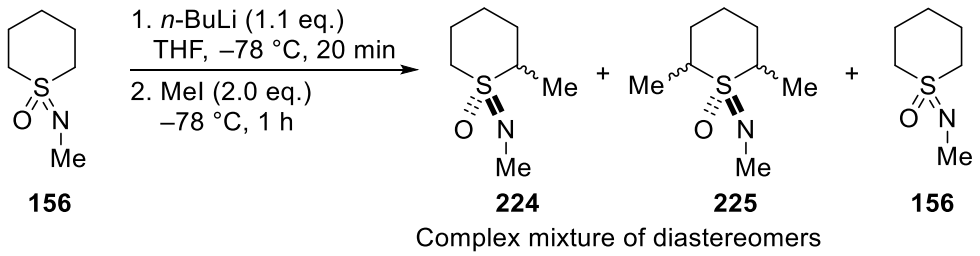
Scheme 2.47

The relative stereochemistry of 5-membered ring *N*-Me sulfoximine *cis*-**222** was proven as shown in Scheme 2.48. TBAF was used to deprotect *N*-TBDPS sulfoximine *cis*-**172**, (stereochemistry proven by X-ray crystallography, see Figure 2.9) to give NH sulfoximine *cis*-**223** in 95% yield. Subsequent reaction of NH sulfoximine *cis*-**223** with paraformaldehyde in formic acid gave *N*-Me sulfoximine *cis*-**222** in 81% yield (Scheme 2.48). A comparison of the ^{1}H and ^{13}C NMR spectra of sulfoximine *cis*-**222** synthesised *via* the route shown in Scheme 2.47 and the 90:10 mixture of sulfoximines *cis*-**222** and *trans*-**222** synthesised by lithiation-trapping showed that the major diastereomer in the mixture was sulfoximine *cis*-**222**.



Scheme 2.48

The lithiation of 6-membered ring *N*-Me sulfoximine **156** and trapping with methyl iodide was also investigated (Scheme 2.49). The ^{1}H NMR spectrum of the crude product showed a complex mixture of starting material **156**, a diastereomeric mixture of monosubstituted sulfoximines **224** and a diastereomeric mixture of disubstituted sulfoximines **225**. Purification by chromatography proved unsuccessful, returning an inseparable mixture. Due to overlapping peaks in the ^{1}H NMR spectrum, the amount and diastereomeric ratio of the products could not be obtained.



Scheme 2.49

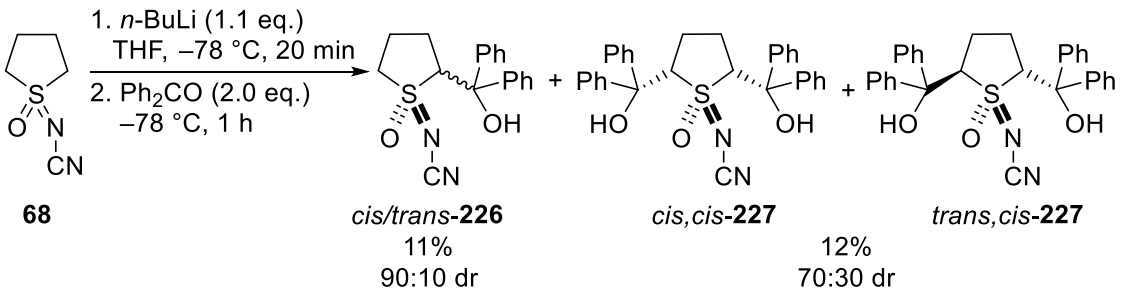
Overall, 5-membered ring *N*-Me sulfoximine **155** displayed a high level of α-diastereoselectivity with all four electrophiles. This was slightly better α-diastereoselectivity than 5-membered ring *N*-Boc sulfoximine **153** and similar to 5-membered ring *N*-TBDPS sulfoximine **146** apart from the reaction with methyl iodide. Conversely, 6-membered ring *N*-Me sulfoximine **156** only showed high α-diastereoselectivity with benzaldehyde; mixtures of diastereomers were obtained when trapping with benzophenone, benzyl bromide and methyl iodide.

2.2.4 α-Lithiation and Trapping of *N*-CN Sulfoximines

As a final study of cyclic sulfoximines, we chose to study the lithiation-trapping of 5-membered ring *N*-CN sulfoximine **68** using our standard four electrophiles (benzophenone, benzaldehyde, benzyl bromide and methyl iodide). As discussed in the Introduction (see Chapter 1.3), the lithiation-trapping reactions of a range of acyclic and some cyclic *N*-CN sulfoximines often result in low yields. In addition, it is possible that lower levels of α-diastereoselectivity would be observed with the smaller *N*-CN substituent.

Benzophenone was explored first using the standard lithiation conditions (*n*-BuLi, −78 °C, 20 min). The lithiation and trapping of *N*-CN 5-membered ring sulfoximine **68** with

benzophenone gave a crude product which contained diastereomeric mixtures of monosubstituted sulfoximines **226** and disubstituted sulfoximines **227**. The ratio of products could not be calculated from the ^{1}H NMR spectrum of the crude product due to overlapping signals. Purification by chromatography gave a 90:10 mixture (by ^{1}H NMR spectroscopy) of monosubstituted sulfoximines *cis*-**226** and *trans*-**226** (11% yield). In addition, a 70:30 mixture of disubstituted sulfoximines *cis,cis*-**227** and *trans,cis*-**227** was isolated in 12% yield (Scheme 2.50).



Scheme 2.50

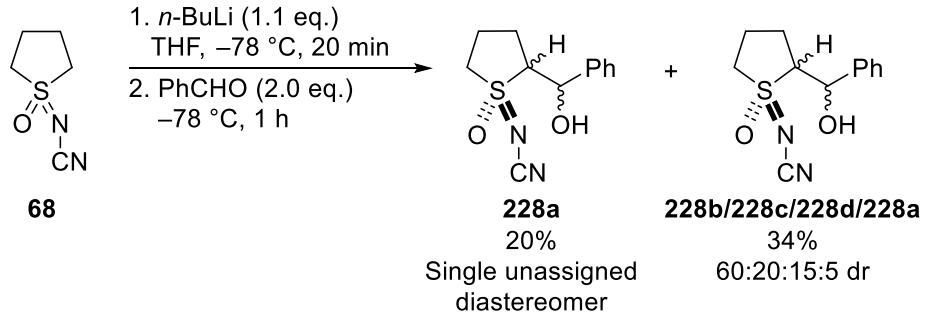
Diagnostic signals in the ^{1}H NMR spectrum of *N*-CN sulfoximines *cis*-**226** and *trans*-**226** were a 1H signal at δ_H 4.69 (dd, J = 10.0, 8.0 Hz) which was assigned to the α-proton adjacent to the benzyl alcohol in sulfoximine *cis*-**226** and a 1H signal at δ_H 4.50 (dd, J = 10.0, 8.0 Hz) which was assigned to the analogous proton in sulfoximine *trans*-**226**. Analysis of the ^{13}C NMR spectrum of the 90:10 mixture of sulfoximines *cis*-**226** and *trans*-**226** showed a major and minor set of peaks. The stereochemistry of these sulfoximines was assumed by analogy with our other lithiation-trapping reactions.

The determination of the ratio of disubstituted sulfoximines *cis,cis*-**227** and *trans,cis*-**227** was not straightforward due to overlapping signals and required a combined analysis of the ^{1}H and ^{13}C NMR spectra. Analysis of the ^{13}C NMR spectrum of the mixture of disubstituted sulfoximines **227** showed a major and minor set of peaks corresponding to two diastereomers. The major diastereomer appeared to be a symmetrical compound and the minor one appeared to be unsymmetrical. Sulfoximine *cis,cis*-**227**, had a signal at δ_C 79.8 which we assigned to the two COH groups, a signal at δ_C 72.1 which was assigned to the two SCH groups and a signal at δ_C 25.6 which was assigned to the two CH_2 groups. Sulfoximine *trans,cis*-**227**, had two signals at δ_C 78.6 and 77.6 which were assigned to the two COH groups, two signals at δ_C 73.5 and 72.7 which were assigned to the two SCH groups and two signals at δ_C 23.7 and 22.9 which were assigned to the two CH_2 groups.

Having established that the major disubstituted sulfoximine was *cis,cis*-**227** and the minor one was *trans,cis*-**227**, analysis of the ^{1}H NMR spectrum enabled the ratio to be determined. For sulfoximine *trans,cis*-**227**, the two 1H singlets at δ_H 4.91 and 3.87 were assigned to the two OH groups and the 1H signal at δ_H 4.37 (dd, J = 12.0, 6.0 Hz) was assigned to an SCH proton. The ^{1}H NMR spectrum also showed a multiplet at δ_H 4.89-4.82 which contained two SCH protons from sulfoximine *cis,cis*-**227** and one SCH proton from sulfoximine *trans,cis*-**227**. Analysis of these signals gave a 70:30 ratio of *cis,cis*-**227** and *trans,cis*-**227**. The stereochemical assignments of the sulfoximines are an assumption based on the results from other lithiation-trapping reactions.

Overall, the result of our initial reaction of *N*-CN sulfoximine **68** with benzophenone showed it to be low yielding for both the monosubstituted and disubstituted sulfoximines. We believe that the disubstituted sulfoximines were synthesised *via* the dianion route presented in Scheme 2.10 for 4-membered ring *N*-TBDPS sulfoximine **148**.

A slightly different reaction profile was obtained using benzaldehyde. The crude product showed a complex mixture of diastereomers. After purification by chromatography, a single unassigned diastereomer **228a** was isolated in 20% yield. In addition, a 60:20:15:5 mixture of sulfoximines **228b**, **228c**, **228d** and **228a** was isolated in 34% yield (Scheme 2.51). No disubstituted products were detected. The overall yield of this reaction was an encouraging 54%. On the other hand, the diastereoselectivity of the reaction appeared poor and was further complicated by the additional hydroxyl stereocentre.

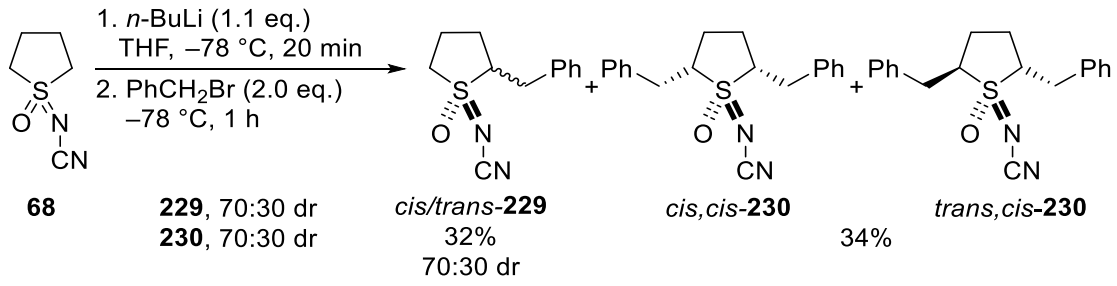


Scheme 2.51

Analysis of sulfoximine **228a** by ^{1}H NMR spectroscopy showed a 1H signal at δ_H 5.54 (dd, J = 4.0, 2.0 Hz) which was assigned to the PhC*H* group, a 1H signal at δ_H 3.28 (ddd, J = 13.0, 10.5, 8.0 Hz) which was assigned to an α-proton and a 1H signal at δ_H 3.19 (d, J = 4.0 Hz) which was assigned to the OH group. Analysis of the mixture of diastereomers showed four signals which were assigned to the PhC*H* group and, from the integrations,

we were able to calculate the ratio of the diastereomers. The signal at δ_H 4.98 (dd, *J* = 10.0, 4.0 Hz) was assigned to sulfoximine **228b**, the signal at δ_H 5.10 (dd, *J* = 10.0, 4.0 Hz) was assigned to sulfoximine **228c**, the signal at δ_H 5.55 (dd, *J* = 3.5, 2.5 Hz) was assigned to sulfoximine **228d** and the signal at δ_H 5.52 (dd, *J* = 4.0, 2.0 Hz) was assigned to sulfoximine **228a**.

Lithiation-trapping with benzyl bromide gave a crude product a mixture of diastereomers of monosubstituted sulfoximines **229** and disubstituted sulfoximines **230**. The ratio could not be calculated from the ^{1}H NMR spectrum of the crude product due to overlapping signals. Purification by chromatography gave a 70:30 mixture (by ^{1}H NMR spectroscopy) of monosubstituted sulfoximines *cis*-**229** and *trans*-**229** in 32% yield. An unknown ratio (due to overlapping signals in the ^{1}H NMR spectrum) of disubstituted sulfoximines *cis,cis*-**230** and *trans,cis*-**230** was isolated in 34% yield (Scheme 2.52). The overall yield of α-trapped products was 66%.

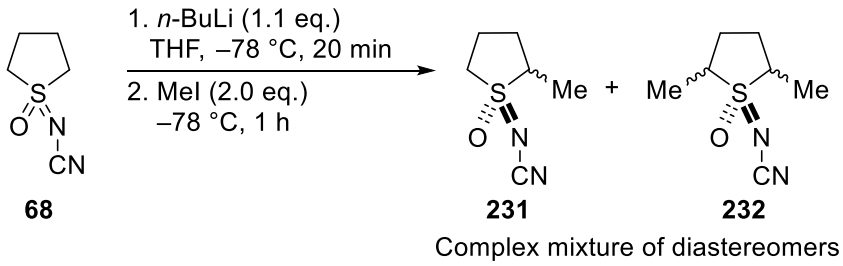


Scheme 2.52

The ^{1}H NMR spectrum of the mixture of monosubstituted sulfoximines **229** had a minor signal at δ_H 2.90 (dd, *J* = 15.0, 11.0 Hz) and a major signal at δ_H 2.80 (dd, *J* = 14.0, 10.0 Hz), which were each assigned to one of the PhC*H* protons. From this, we were able to calculate a 70:30 ratio of sulfoximines *cis*-**229** and *trans*-**229**. The stereochemistry of sulfoximines *cis*-**229** and *trans*-**229** was assumed by analogy with our previous results. The ratio of disubstituted sulfoximines *cis,cis*-**230** and *trans,cis*-**230** could not be calculated from the ^{1}H NMR spectrum due to overlapping signals. Analysis of the ^{13}C NMR spectrum showed a major set of signals. A signal at δ_C 64.9 was assigned to the two SCH carbons, a signal at δ_C 33.8 was assigned to two Ph*C*H$_2$ carbons and a signal at δ_C 26.5 was assigned to the two CH_2 groups in the ring. The ^{13}C NMR spectrum showed symmetry and therefore we believe these signals to be due to sulfoximine *cis,cis*-**230**. In addition, there was a minor set of signals: signals at δ_C 68.2 and 65.1 were each assigned

to an SCH carbon, signals at δ_C 34.6 and 34.0 were each assigned to a Ph*C*H_2 carbon and signals at δ_C 28.0 and 27.8 were each assigned to the CH_2 groups in the ring. These results indicated that the sulfoximine was not symmetrical and it therefore was assumed to be sulfoximine *trans,cis*-**230**. The ratio of the two disubstituted sulfoximines could not be determined from the ^{13}C NMR spectrum. The stereochemical assignment of these sulfoximines was assumed from our previous results and whether the sulfoximine was symmetrical.

Lastly, sulfoximine **68** was lithiated and trapped with methyl iodide. This reaction gave a complex mixture of monosubstituted sulfoximines **231** and disubstituted sulfoximines **232** (Scheme 2.53). Even after purification by chromatography, the ratio of the sulfoximines could not be calculated from the ^1H NMR spectrum due to overlapping signals and therefore a yield could not be calculated. The formation of the monosubstituted and disubstituted sulfoximines **231** and **232** was confirmed by mass spectrometry.

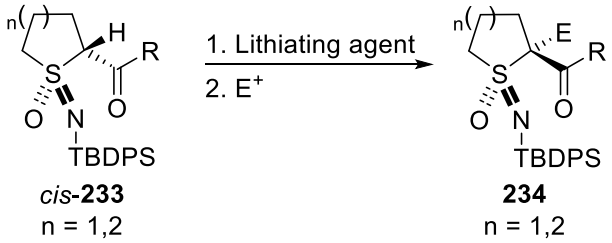


Scheme 2.53

To conclude, the reactions with *N*-CN sulfoximine **68** have demonstrated CN to be a poor choice of *N*-substituent when compared to *N*-TBDPS, *N*-Boc and *N*-Me groups. The *N*-CN group offers varying levels of diastereoselectivity and the products were obtained in low to moderate yields. In addition, disubstituted sulfoximines were synthesised in the reactions with benzophenone, benzyl bromide and methyl iodide, further complicating the reactions.

2.3 Synthesis of Disubstituted Sulfoximines

The lithiation and trapping reactions of 5- and 6-membered ring *N*-TBDPS sulfoximines **146** and **147** showed promise, proceeding with high yields and high diastereoselectivity with the majority of electrophiles tested. As a result, we wanted to utilise these products in further reactions and decided to explore whether a second lithiation-trapping reaction of an α-functionalised sulfoximine could be used to add a second substituent at either of the two α-carbon atoms. Two possible routes were proposed for the regioselective functionalisation of α-substituted sulfoximines. In the first approach, we hoped to develop a route for the synthesis of 2,2-disubstituted sulfoximines **234** starting from β-keto sulfoximines *cis*-**233** (Scheme 2.54). In order to achieve deprotonation at the 2-position, the acidity of the α-proton on the 2-position would need to be higher than the α-protons at the 5/6-position. This would be achieved by the presence of the carbonyl group at the α-position in β-keto sulfoximines *cis*-**233** and would allow regioselective enolate formation and addition of the substituent to generate the 2,2-disubstituted products **234**. In our previous reactions, electrophiles typically add to sulfoximines *trans* to the bulky *N*-TBDPS group and, therefore, we believe that the second electrophile would add to give disubstituted sulfoximine **234** with the stereochemistry indicated in Scheme 2.54.



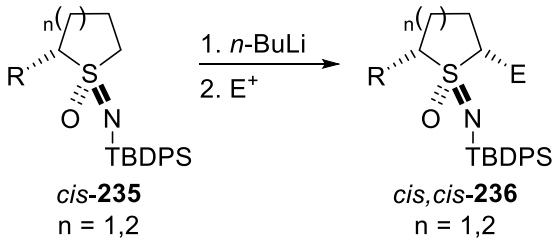
cis-**233**
n = 1,2

234
n = 1,2

Scheme 2.54

The second approach to be investigated would provide a route to introduce a substituent in the 5/6-position depending on whether we started with the 5- or 6-membered ring α-substituted sulfoximine. We propose to start with an α-substituted sulfoximine *cis*-**235** (e.g. R = Me) and predict that lithiation-trapping using *n*-BuLi should give 2,5/2,6-disubstituted sulfoximines *cis,cis*-**236** (Scheme 2.55). This is because lithiation at the 2-position will be sterically hindered. Thus, lithiation will occur at the more accessible 5/6-position. In our previous lithiation-trapping reactions of 5- and 6-membered ring *N*-TBDPS sulfoximines (see Chapter 2.2.1), the electrophile typically adds *trans* to the sterically bulky *N*-TBDPS group. We expect a similar effect with the addition of a second

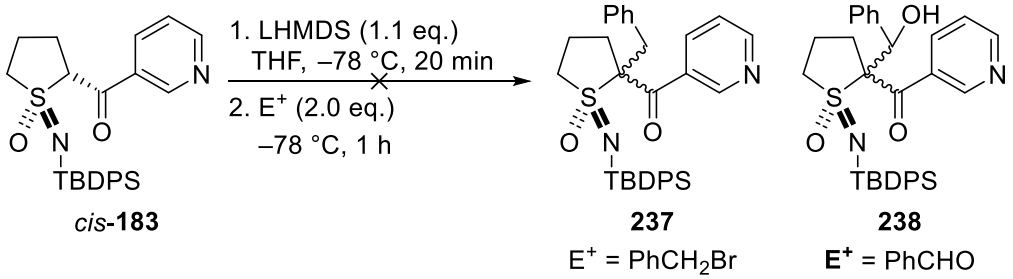
electrophile to give 2,5- and 2,6-disubstituted sulfoximines *cis,cis*-**236**. It was important to select an α-substituted sulfoximine starting material with minimal functionality (e.g. R = Me in *cis*-**235**) for the disubstitution reaction in order to prevent unwanted side reactions. The next two chapters summarise our results with each of these two proposed approaches to disubstituted sulfoximines.



Scheme 2.55

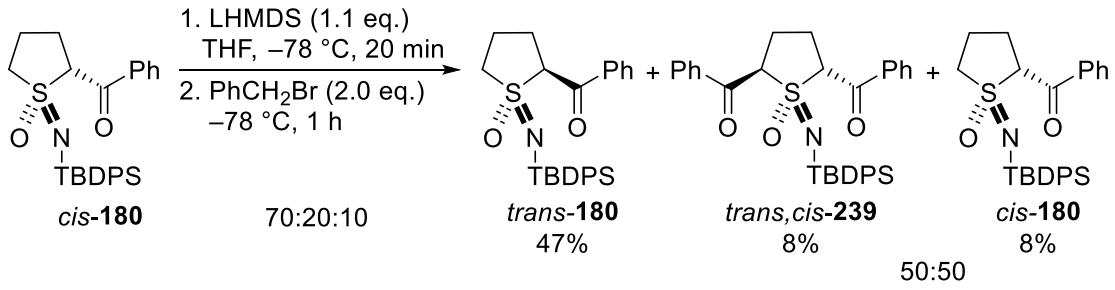
2.3.1 Synthesis of 2,2-Disubstituted Sulfoximines

We first investigated enolate formation and trapping with pyridine-containing β-keto sulfoximine *cis*-**183**. In order to prevent nucleophilic attack on the ketone by the lithiating agent, a more sterically hindered base than *n*-BuLi was used. LHMDS was selected and we expected it to deprotonate sulfoximine *cis*-**183** at the 2-position to form the enolate. Deprotonation of sulfoximine *cis*-**183** using LHMDS and trapping with benzyl bromide did not give any sulfoximine **237** and none of the starting sulfoximine *cis*-**183** was recovered (Scheme 2.56). We were unsure why the reaction was unsuccessful so decided to repeat the reaction with benzaldehyde as the electrophile. Deprotonation of sulfoximine *cis*-**183** with LHMDS and trapping with benzaldehyde did not give any of sulfoximine **238** (Scheme 2.56). However, we found that the LHMDS had partially epimerised the starting material *cis*-**183** giving a 75:25 mixture (from the ^{1}H NMR spectrum of the crude product) of sulfoximines *cis*-**183** and *trans*-**183**. This suggested that at least some enolate formation had occurred.



Scheme 2.56

We decided to investigate a different substrate for the 2,2-disubstitution reactions and selected keto sulfoximines *cis*-**180** and *trans*-**180**. Benzyl bromide was chosen as the first electrophile for direct comparison with the reactions of keto sulfoximine *cis*-**183 (**see Scheme 2.56). Deprotonation of sulfoximine *cis*-**180** using LHMDS and trapping with benzyl bromide gave a crude product which contained a 70:20:10 mixture (by ^{1}H NMR spectroscopy) of monosubstituted sulfoximine *trans*-**180**, disubstituted sulfoximine *trans,cis*-**239** and monosubstituted sulfoximine *cis*-**180**. Purification by chromatography gave sulfoximine *trans*-**180** in 47% yield and a 50:50 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**180** (8% yield) and *trans,cis*-**239** (8% yield) (Scheme 2.57). None of the desired 2,2-disubstituted sulfoximine was formed.

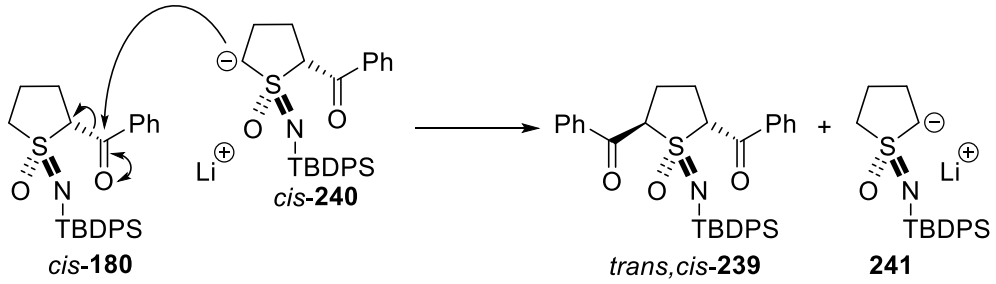


Scheme 2.57

Analysis of the ^{1}H NMR spectrum of sulfoximine *trans,cis*-**239** showed two signals at δ_H 5.16 (dd, J = 8.0, 8.0 Hz) and 4.62 (dd, J = 8.0, 3.5 Hz) which were assigned to the two SCH protons. There was also a 9H singlet at δ_H 0.80 which was assigned to the CMe_3 group. Analysis by ^{13}C NMR spectroscopy showed two sets of signals at δ_C 69.0 and 68.7 which were assigned to the SCH groups and two sets of signals at δ_C 24.0 and 23.7 which were assigned to the CH_2 groups. In addition, one signal at δ_C 26.2 was assigned to the C*Me*$_3$ carbons and one signal at δ_C 19.3 was assigned to the *C*Me$_3$ carbon. This evidence proves that an unsymmetrical sulfoximine was synthesised and supports our stereochemical assignment of as *trans,cis*-**239**.

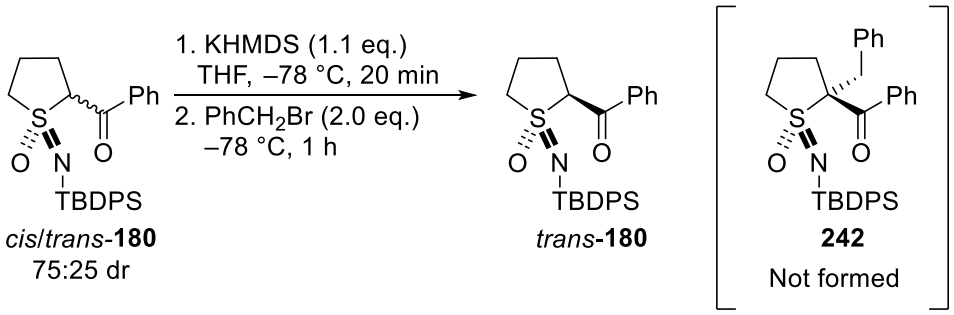
The synthesis of 2,5-disubstituted sulfoximine *trans,cis*-**239** as a by-product of this reaction was surprising. A proposed route for its synthesis is shown in Scheme 2.58. Although this does not fit with the likely pK_a values, we propose that some of sulfoximine *cis*-**180** could be lithiated at the 5-position to give carbanion *cis*-**240**. This may be possible because the proton at the 2-position is sterically hindered and LHMDS is a sterically hindered base. Then, carbanion *cis*-**240** could subsequently attack the carbonyl of keto

sulfoximine *cis*-**180** with carbanion **241** as a leaving group. Finally, epimerisation may occur to give diketone *trans,cis*-**239**.



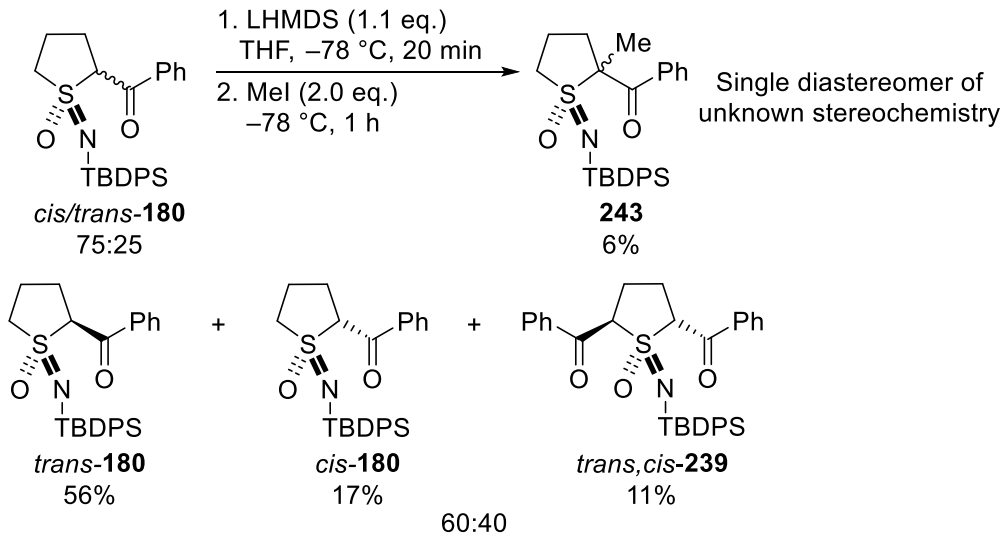
Scheme 2.58

At this point, we were unsure whether the issue was enolate formation or whether the enolate did form but was unreactive in the reaction with benzyl bromide. Therefore KHMDS was explored. Deprotonation of a 75:25 mixture of sulfoximines *cis*-**180** and *trans*-**180** using KHMDS and trapping with benzyl bromide gave none of the 2,2-disubstituted sulfoximine **242** (Scheme 2.59) By ^{1}H NMR spectroscopy of the crude product, the starting material was returned as sulfoximine *trans*-**180**. This is an interesting result and clearly establishes that the enolate must have formed. The stereochemistry could be explained as follows. Deprotonation occurred to give the enolate and stereoselective protonation in the work-up, with the proton adding opposite the *N*-TBDPS group, would then give keto sulfoximine *trans*-**180**.



Scheme 2.59

We therefore moved on to explore a different electrophile, methyl iodide, starting with LHMDS as the base. Deprotonation of a 75:25 mixture of sulfoximines *cis*-**180** and *trans*-**180** and trapping with methyl iodide gave 2,2-disubstituted sulfoximine **243** as a single diastereomer of unknown stereochemistry in only 6% yield. Starting sulfoximine *trans*-**180** was isolated in 56% yield. In addition, a 60:40 mixture of starting sulfoximine *cis*-**180** (17% yield) and 2,5-disubstituted sulfoximine *trans,cis*-**239** (11% yield) and was obtained (Scheme 2.60).

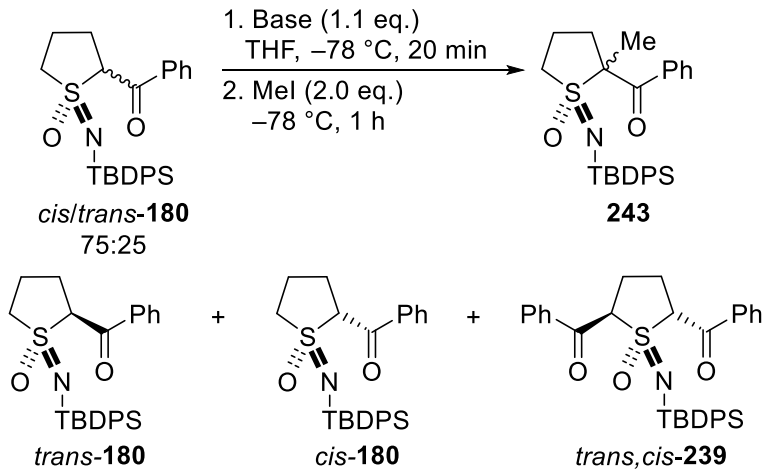


Scheme 2.60

The ^{1}H NMR spectrum of 2,2-disubstituted sulfoximine **243** showed two 1H multiplets at δ_H 3.24-3.14 and 2.92-2.82 which were each assigned to an SCH proton. A 3H singlet at δ_H 1.74 was assigned to the methyl group. The ^{13}C NMR DEPT spectrum showed a signal at δ_C 74.1 which was assigned to S*C*Me. In addition, a signal at δ_C 57.8 was assigned to the SCH_2 carbon and a signal at δ_C 36.6 was assigned to the methyl group. Analysis of both the ^{1}H and ^{13}C NMR spectra of 2,2-disubstituted sulfoximine **243** showed that the methyl group had added at the 2-position and not the 5-position. Diketone *trans,cis*-**239** was presumably formed *via* the process shown in Scheme 2.58. The formation of 2,2-disubstituted sulfoximine **243** and a significant amount of keto sulfoximine *trans*-**180** suggested that enolate formation was occurring successfully.

In order to fully explore the 2,2-disubstitution reaction, we investigated a range of bases: LHMDS, KHMDS, NaHMDS, NaH and LDA. The results are summarised in Table 2.3. LHMDS was the most successful base, giving disubstituted sulfoximine **243** as a single diastereomer in 6% yield (entry 1). We tested the reaction with KHMDS which gave 2,2-disubstituted sulfoximine **243** in a slightly lower yield of 5%. A 70:30 mixture (by ^{1}H NMR spectroscopy) of starting sulfoximine *cis*-**180** (20% yield) and 2,5-disubstiuted sulfoximine *trans,cis*-**239** (8% yield) was also obtained. Starting sulfoximine *trans*-**180** was isolated in 58% yield (entry 2). Reaction with NaHMDS was poor and gave 2,2-disubstituted sulfoximine **243** in only 1% yield. In addition, a 65:25:10 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *trans*-**180** (52% yield), *cis*-**180** (20% yield) and *trans,cis*-**239** (8%) was isolated (entry 3). Deprotonation with NaH gave 2,2-disubstituted

sulfoximine **243** in 4% yield as well as a 65:25:10 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *trans*-**180** (55% yield), *cis*-**180** (21% yield) and *trans,cis*-**239** (8%) (entry 4). With LDA, no disubstituted sulfoximines were observed and the staring material was returned as an 85:15 mixture (by ^{1}H NMR spectroscopy of the crude product) of sulfoximines *trans*-**180** and *cis*-**180** (entry 5).



Entry	Base	**243**/%[a]	*trans*-**180**/%[a]	*cis*-**180**/%[a]	*trans,cis*-**239**/%[a]
1	LHMDS	6	56	17[b]	11[b]
2	KHMDS	5	58	20[c]	8[c]
3	NaHMDS	1	52[d]	20[d]	8[d]
4	NaH	4	55[d]	21[d]	8[d]
5[e]	LDA	0	-	-	0

[a] % yield after purification by chromatography. [b] Isolated as a 60:40 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**180** and *trans,cis*-**239**. [c] Isolated as a 70:30 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**180** and *trans,cis*-**239**. [d] Isolated as a 65:25:10 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *trans*-**180**, *cis*-**180**, and *trans,cis*-**239**. [e] Products not purified as no sulfoximine **243** was synthesised, 85:15 mixture of sulfoximines *trans*-**180** and *cis*-**180** observed (by ^{1}H NMR spectroscopy).

Table 2.3 Effect of different bases on the 2,2-disubstituion of sulfoximine *cis*/*trans*-**180**

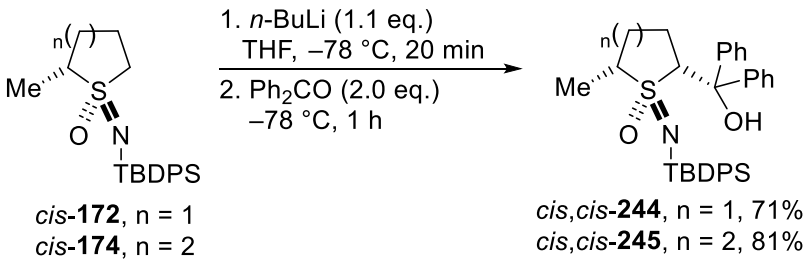
With all bases except LDA, a small amount of 2,5-disubstituted sulfoximine *trans,cis*-**239** and a large quantity of starting sulfoximines *cis*-**180** and *trans*-**180** were isolated. LHMDS proved to be the most effective base giving 2,2-disubstituted sulfoximine **243** in 6% yield, although there was little variance in the results when different bases were used. We have yet to confirm the stereochemistry of the product, although the results of our

other lithiation-trapping reactions support the proposal that the methyl group is *cis* to the oxygen of the sulfoximine.

Overall, our results showed that deprotonation of sulfoximines *cis/trans*-**180** occurred to give the enolate. Therefore, the main issue of the reaction must be in the trapping step. Future work could focus on investigating different α-substituents and electrophiles.

2.3.2 Synthesis of 2,5- and 2,6-Disubstituted Sulfoximines

Finally, we explored the synthesis of 2,5- and 2,6-disubstituted sulfoximines. A methyl group was chosen as the α-substituent, as its lack of functionality decreases the chances of side reactions occurring. Thus, methylated 5-membered ring *N*-TBDPS sulfoximine *cis*-**172** was lithiated using *n*-BuLi (–78 °C, 20 min) and trapped with benzophenone to give sulfoximine *cis,cis*-**244** in 71% yield (Scheme 2.61). Evidence from both the ^{1}H and ^{13}C NMR spectra showed that benzophenone addition had occurred at the 5-position. Key signals in the ^{1}H NMR spectrum were two 1H signals at δ_H 4.43 (dd, J = 8.5, 8.5 Hz) and δ_H 2.78-2.66 (m) assigned to the two SCH protons as well as a 3H doublet at δ_H 0.95 (J = 7.0 Hz) assigned to the methyl group. The ^{13}C NMR spectrum showed two signals at δ_C 71.7 and 62.3 which were assigned to the two SCH carbons. A signal at δ_C 78.5 was assigned to the COH and a signal at δ_C 13.5 was assigned to the methyl group. These data showed that both the benzyl alcohol and the methyl group were attached to different α-carbon atoms.

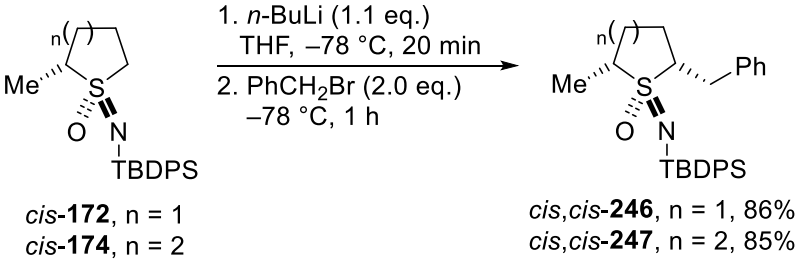


Scheme 2.61

In a similar way, lithiation-trapping of methylated 6-membered ring *N*-TBDPS sulfoximine *cis*-**174** with benzophenone gave sulfoximine c*is,cis*-**245** in 81% yield (Scheme 2.61). The ^{1}H and ^{13}C NMR spectra displayed the key diagnostic signals observed with 5-membered ring sulfoximine *cis,cis*-**244**. Analysis of the ^{1}H NMR spectrum of 6-membered ring sulfoximine *cis,cis*-**245** showed two 1H signals at δ_H 3.88

(dd, J = 12.0, 1.5 Hz) and δ_H 2.94-2.82 (multiplet) for the two SCH protons and a 3H doublet at δ_H 0.49 (J = 7.0 Hz) assigned to the methyl group. Key signals in the ^{13}C NMR spectrum included two signals at δ_C 74.7 and 64.4 which were assigned to the two SCH carbons. A signal at δ_C 82.2 was assigned to the COH and a signal at δ_C 12.7 was assigned to the methyl group. The stereochemistry of 5- and 6-membered ring sulfoximines c*is,cis*-**244** and c*is,cis*-**245** was assigned by analogy with lithiation-trappings of other *N*-TBDPS sulfoximines. Both reactions proceeded with high diastereoselectivity and regioselectivity giving each product as a single diastereomer in high yields.

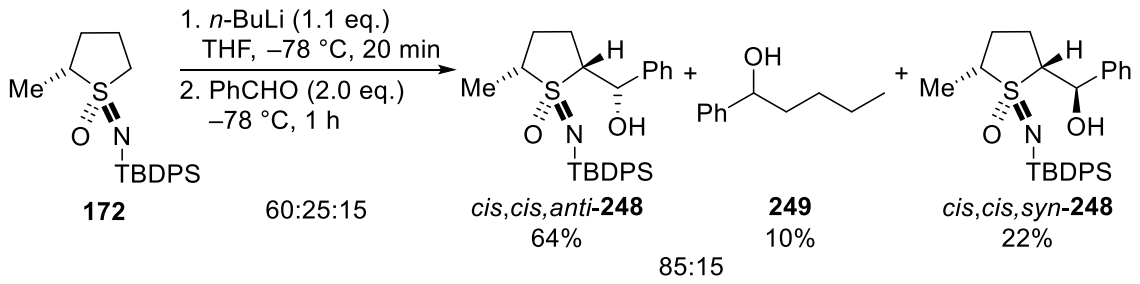
The diastereoselectivity of the reaction with benzyl bromide was explored next. Lithiation-trapping of 5-membered ring methylated sulfoximine *cis*-**172** with benzyl bromide gave sulfoximine *cis,cis*-**246** in 86% yield. Similarly, 6-membered ring methylated sulfoximine *cis*-**174** gave sulfoximine *cis,cis*-**247** in 85% yield (Scheme 2.62). The stereochemistry of the sulfoximines was assigned by analogy with lithiation-trappings of other *N*-TBDPS sulfoximines. Both reactions were diastereoselective and sulfoximines *cis,cis*-**246** and *cis,cis*-**247** were synthesised in high yields. In a previous reaction, disubstitution of 6-membered ring *N*-TBDPS sulfoximine **147** was observed when trapping with benzyl bromide (see Scheme 2.13). However, when starting with methyl sulfoximines *cis*-**172** and *cis*-**174**, there was no evidence of further lithiation-trapping with benzyl bromide. Presumably, this is because 6-membered ring sulfoximine *cis*-**174** is more sterically hindered at the 2-position due to the methyl substituent.



Scheme 2.62

Lastly, trapping with benzaldehyde was investigated. Lithiation-trapping of 5-membered ring methyl sulfoximine *cis*-**172** with benzaldehyde gave a crude product which contained a 60:25:15 mixture (from the ^1H NMR spectrum) of sulfoximines *cis,cis,anti*-**248**, *cis,cis,syn*-**248** and 1-phenyl-1-pentanol **249** (resulting from *n*-BuLi reacting with benzaldehyde). After purification by chromatography, an inseparable 85:15 mixture of

sulfoximine *cis,cis,anti*-**248** (64% yield) and 1-phenyl-1-pentanol **249** (10% yield) was isolated; sulfoximine *cis,cis,syn*-**248** was also isolated in 22% yield (Scheme 2.63).



Scheme 2.63

The stereochemistry of sulfoximines *cis,cis,anti*-**248** and *cis,cis,syn*-**248** was assigned by analogy with *N*-TBDPS sulfoximine *cis,syn*-**164** (stereochemistry assigned by X-ray crystallography, see Figure 2.7). Analysis of the ^{1}H NMR spectra showed that sulfoximine *cis,cis,anti*-**248** had a 1H broad singlet at δ_H 5.07 which was assigned to the PhC*H*OH proton and sulfoximine *cis,anti*-**164** also had a 1H singlet at δ_H 5.12 which was assigned to the PhC*H*OH (Figure 2.13). Similarly, the ^{1}H NMR spectrum of sulfoximine *cis,cis,syn*-**248** displayed a 1H signal at δ_H 4.83 (dd, J = 9.5, 3.0 Hz) which was assigned to the PhC*H*OH proton, whilst sulfoximine *cis,anti*-**165** had a 1H doublet at δ_H 4.89 (d, J = 9.5 Hz) which was assigned to the PhC*H*OH proton (Figure 2.13). The similarities in the chemical shifts of the peaks assigned to the PhC*H*OH proton support our stereochemical assignment of sulfoximines *cis,cis,anti*-**248** and *cis,cis,syn*-**248**. Overall, the reaction proceeded with high diastereoselectivity and the products were synthesised in high yields.

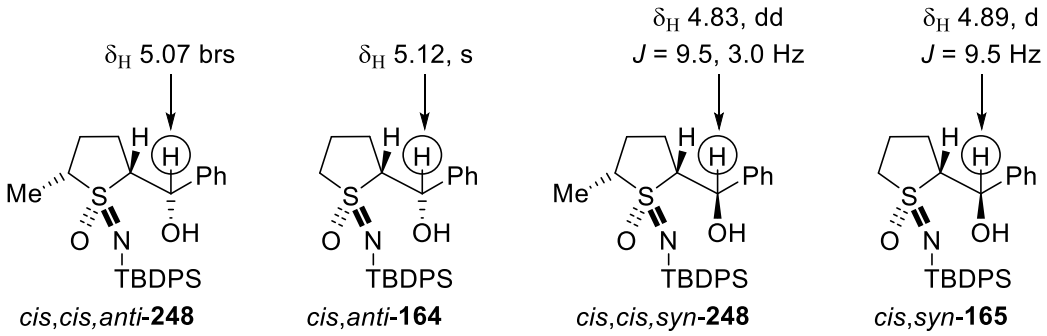


Figure 2.13 Diagnostic signals in the ^{1}H NMR spectra of *anti*- and *syn*-hydroxy sulfoximines

Thus, a regioselective and diastereoselective route to 2,5- and 2,6-disubstituted sulfoximines has been successfully developed. In particular, we have developed a simple two-step approach allowing two different substituents to be attached.

3. Conclusions and Future Work

In summary, we have developed a highly diastereoselective route to α-functionalised cyclic sulfoximines *via* lithiation-trapping reactions. The reactions are straightforward and proceed *via* lithiation using *n*-BuLi (–78 °C, 20 min) and subsequent trapping with an electrophile. Using the *N*-TBDPS group, we were able to synthesise a range of α-functionalised cyclic and acyclic sulfoximines as single diastereomers in high yields. A lower level of diastereoselectivity was observed in three reactions which contained an α-carbonyl group, presumably as these groups allowed epimerisation to occur. However, diastereomerically pure sulfoximines could still be isolated in high yields. A selection of our best results are shown in Figure 3.1.

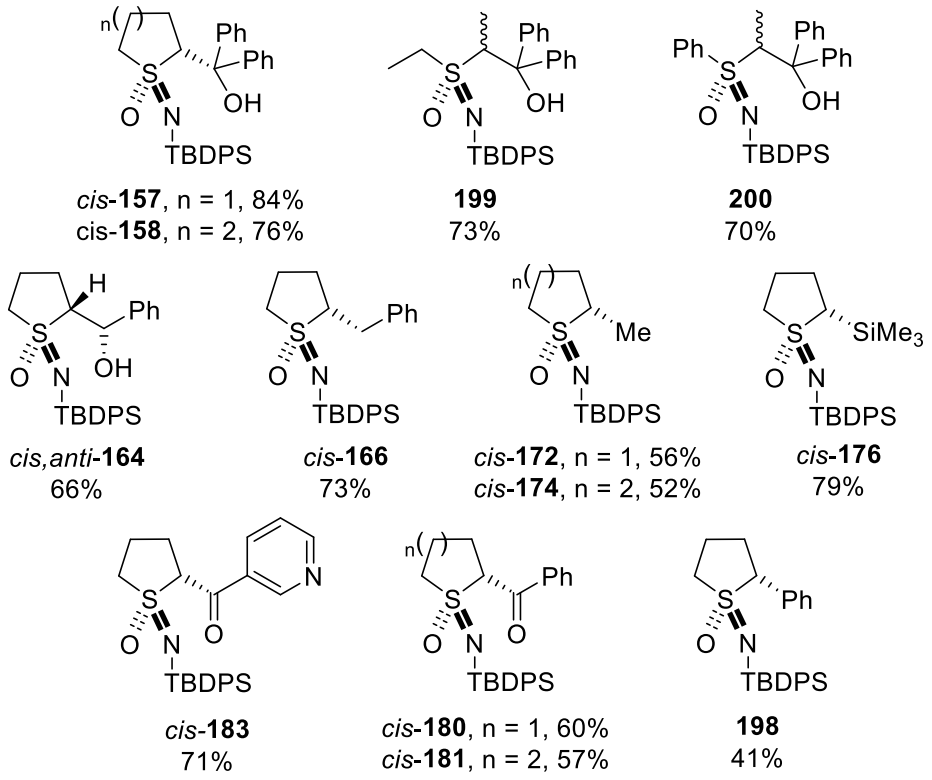


Figure 3.1 Products of lithiation-trapping reactions of *N*-TBDPS sulfoximines

An exploration of the reactions of *N*-Boc, *N*-Me and *N*-CN 5- and 6-membered ring sulfoximines with four electrophiles (benzophenone, benzyl bromide, benzaldehyde and methyl iodide) was also carried out. These reactions generally gave sulfoximines with high diastereoselectivity and good yields. Of the sulfoximines tested, it was observed that reactions with 6-membered ring *N*-Me sulfoximine **156** and 5-membered ring *N*-CN

sulfoximine **68** gave products with a lower level of diastereoselectivity, but good yields were still obtained with some electrophiles. The key finds are summarised in Figure 3.2.

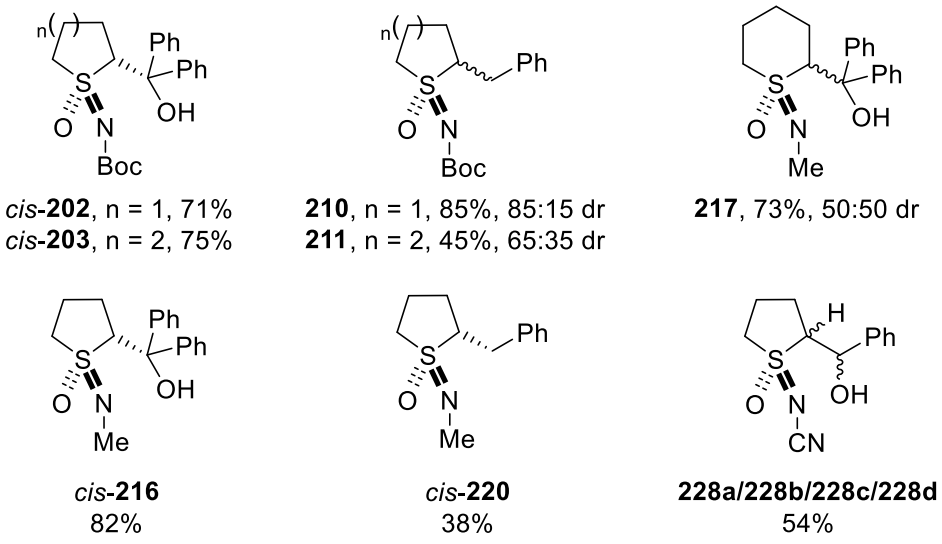


Figure 3.2 Products of lithiation-trapping reactions of *N*-Boc, *N*-Me and *N*-CN sulfoximines

Our attempts at the synthesis of 2,2-disubstituted sulfoximines for the synthesis of 2,2-disubstituted sulfoximines were not successful, as the highest yield achieved was 6%. Further optimisation of this chemistry will be required. In contrast, the synthesis of 2,5- and 2,6-disubstituted sulfoximines was highly successful as we were able to control the regiochemistry and stereochemistry of the reaction to give *cis,cis*-sulfoximines in high yields (Figure 3.3).

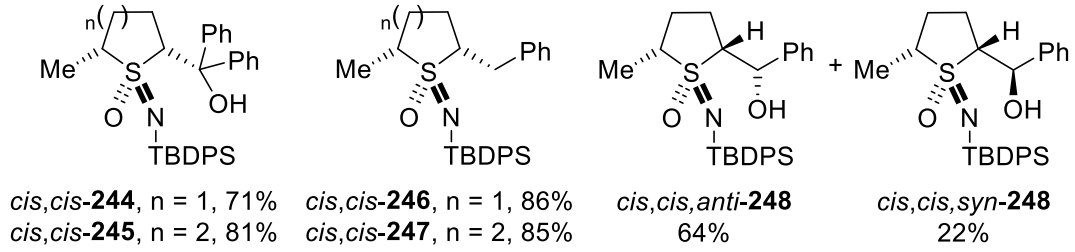
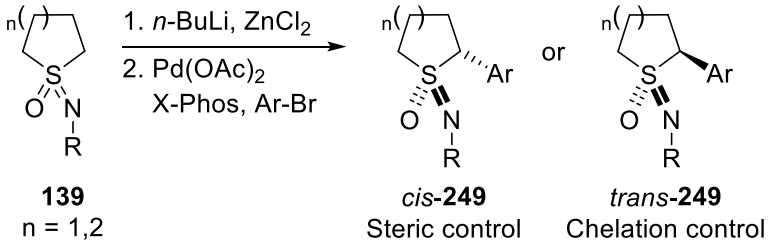


Figure 3.3 Results of 2,5- and 2,6-disubstitution reactions

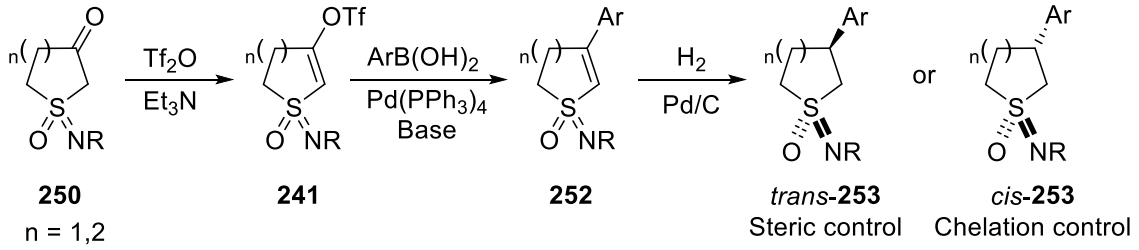
In future work, we want to confirm our proposed stereochemical assignments for some more of the sulfoximines. This will be achieved by either X-ray crystallography or their separate synthesis from sulfoximines of known configuration. We also plan to expand the scope of our work to include 4–7 membered cyclic sulfoximines. We also envisage exploring the use of Negishi cross-coupling reactions in the diastereoselective arylation

of sulfoximines at the α-position. Using Negishi conditions (*n*-BuLi, $ZnCl_2$ and $Pd(OAc)_2$), the α-arylation reactions are likely to be sterically controlled by the bulky NR group, forcing the α-substituent *trans* to the NR group to give sulfoximine *cis*-**249** (Scheme 3.1). It may also be possible to override the steric control by putting a Pd-chelating group on the nitrogen of sulfoximine **139**. As a result, Pd-mediated arylation may proceed *via* chelation control to give sulfoximine *trans*-**249**.



Scheme 3.1

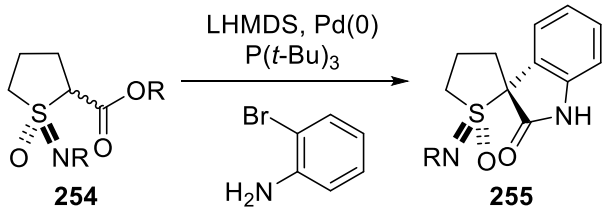
These methods of steric and chelation control could also be utilised in the synthesis of β-arylated sulfoximines and a proposed method for their synthesis is shown in Scheme 3.2. β-keto sulfoximines **250** can be readily converted into enol triflates **251** and subsequently arylated using Suzuki-Miyaura cross-coupling to give β-arylated unsaturated sulfoximines **252**. Hydrogenation proceeding *via* steric control will add the hydrogen *trans* to the sterically bulky NR group resulting in sulfoximine *trans*-**253**. Hydrogen addition *via* chelation control will likely be delivered *cis* to the NR group, giving sulfoximine *cis*-**253**.



Scheme 3.2

Other future plans could include the synthesis of bicyclic and spirocyclic sulfoximines which can be achieved by a number of different routes. An example of spirocycle synthesis is shown in Scheme 3.3. Using LHMDS, Pd(0) and tri-*tert*-butylphosphine arylation of sulfoximine **254** would occur at the α-position. Subsequent attack of the carbonyl by the aryl amine would give spirocyclic sulfoximine **255**. The stereochemistry

of sulfoximine **255** is assumed to be as depicted, based on the results presented in this thesis.



Scheme 3.3

4. Experimental

4.1 General Information

All-non aqueous reactions were carried out under oxygen free Ar or N_2 using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use. Electrophiles (dimethyl sulfate, methyl iodide and benzaldehyde) used in lithiation reactions were distilled over CaH_2 before use. Electrophiles (benzophenone, benzyl bromide, TMSCl, Weinreb amide **136**, Weinreb amide **179**, *tert*-butyl isocyanate, methyl chloroformate and *N*-benzylidene methylamine) were used without further purification. Brine refers to a saturated solution. Water is distilled water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium backed silica plates. Proton (400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

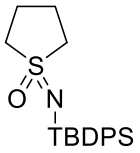
4.2 General Procedure

General Procedure A: Lithiation-trapping of cyclic sulfoximines using *n*-BuLi at –78 °C

n-BuLi (2.5 M solution in hexanes, 1.1 eq.) was added dropwise to a stirred solution of the sulfoximine (0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, the electrophile (1.0 mmol, 2.0 eq.) (as a solution in THF for benzophenone) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

4.3 Experimental Procedures and Characterisation Data

1-[(*tert*-Butyldiphenylsilyl)imino]-1λ⁶-thiolan-1-one 146



146

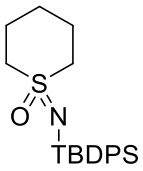
A solution of tetramethylene sulfide **66** (1.76 mL, 20.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (16.1 g, 50.0 mmol, 2.5 eq.) and ammonium carbamate (3.1 g, 40.0 mmol, 2.0 eq.) in MeOH (40 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave impure sulfoximine **23** (2.0 g) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17–3.10 (m, 4H, SCH) 2.31–2.18 (m, 4H CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 55.5 (SCH_2), 24.1 (CH_2). TBDPSCl (5.6 mL, 21.5 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure sulfoximine **23** (2.0 g, 17.2 mmol assumed, 1.0 eq.) and imidazole (2.3 g, 34.3 mmol, 2.0 eq.) in DMF (7.65 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. The solution was allowed to cool to rt and then water (10 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 and then 7:3 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **146** (4.4 g, 60% over 2 steps) as a white solid, mp 74–76 °C; R_F (7:3 hexane-EtOAc) 0.30; IR (ATR) 3069, 2930, 2855, 1290, 1253, 1153, 1129, 1106, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 4H, Ph), 7.42–7.33 (m, 6H, Ph), 2.95–2.86 (m, 2H, SCH), 2.81–2.73 (m, 2H, SCH), 2.16–1.96 (m, 4H, CH), 1.08 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.4 (*ipso*-Ph), 135.7 (Ph), 129.2 (Ph), 127.6 (Ph), 55.8 (SCH_2), 27.2 (CMe_3), 23.2 (SCH_2CH_2), 19.3 (CMe_3); MS (ESI) *m/z* 358 (M + H)$^+$; MS (ESI) *m/z* 358 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NOSSi$ (M + H)$^+$ 358.1655, found 358.1657 (–0.5 ppm error). This product appears to be hygroscopic and it is sometimes necessary to remove water by azeotroping with toluene.

Lab book reference: **GH-1-80**

A solution of tetrahydrothiophene 1-oxide **145** (0.9 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (9.66 g, 30.0 mmol, 3.0 eq.) and ammonium carbamate (3.12 g, 40.0 mmol, 4.0 eq.) in MeOH (20 mL) was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 and then 9:1 CH_2Cl_2-MeOH gave impure sulfoximine **23** (1.19 g) as a yellow oil. TBDPSCl (3.25 mL, 12.5 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure sulfoximine **23** (1.19 g, 10.0 mmol assumed, 1.0 eq.) and imidazole (1.36 g, 20.0 mmol, 2.0 eq.) in DMF (4.5 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. The solution was allowed to cool to rt and then water (10 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 and then 7:3 hexane-EtOAc as eluent gave the *N*-TBDPS sulfoximine **146** (1.79 g, 50% over 2 steps) as a white solid.

Lab book reference: **GH-1-30**

1-[(*tert*-Butyldiphenylsilyl)imino]-1λ⁶-thian-1-one 147



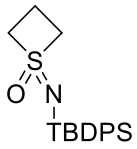
147

A solution of pentamethylene sulfide **151** (0.42 mL, 4.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (3.22 g, 10.0 mmol, 2.5 eq.) and ammonium carbamate (625 mg, 8.0 mmol, 2.0 eq.) in MeOH (8 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 95:5 EtOAc-MeOH as eluent gave impure sulfoximine **152** (416 mg) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.24; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09–3.03 (m, 4H, SCH), 2.12–2.02 (m, 4H, CH), 1.68–1.59 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.5 (SCH_2), 24.3 (CH_2), 24.2 (CH_2). TBDPSCl (1.02 mL, 3.91 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure

sulfoximine **152** (416 mg, 3.13 mmol assumed, 1.0 eq.) and imidazole (426 mg, 6.25 mmol, 2.0 eq.) in DMF (1.39 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 63 h. The solution was allowed to cool to rt and then water (5 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 and then 7:3 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **147** (892 mg, 60% over 2 steps) as a white solid, mp 82–84 °C; R_F (7:3 hexane-EtOAc) 0.29; IR (ATR) 3073, 2929, 2855, 1323, 1289, 1145, 1107, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.5, 1.5 Hz, 4H, Ph), 7.40–7.31 (m, 6H, Ph), 2.87–2.78 (m, 2H, SCH), 2.77–2.68 (m, 2H, SCH), 1.99–1.90 (m, 4H, CH), 1.57–1.44 (m, 2H, CH), 1.07 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.9 (*ipso*-Ph), 135.7 (Ph), 129.1 (Ph), 127.5 (Ph), 56.3 (SCH_2), 27.3 (CMe_3), 24.7 (CH_2), 24.4 (CH_2), 19.4 (CMe_3); MS (ESI) *m/z* 372 $(M + H)^+$ HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NOSSi$ $(M + H)^+$ 372.1812, found 372.1814 (–0.4 ppm error). This product appears to be hygroscopic and it is sometimes necessary to remove water by azeotroping with toluene.

Lab book reference: **GH-1-20**

1-[(*tert*-Butyldiphenylsilyl)imino]-1λ⁶-thietan-1-one 148



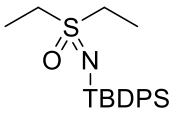
148

A solution of trimethylene sulfide (0.72 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH gave the impure sulfoximine (900 mg) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (m, 4H, SCH_2), 2.31–2.17 (m, 2H, SCH_2CH_2), 2.08 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 66.6 (SCH_2), 7.7 (SCH_2CH_2). TBDPSCl (2.79 mL, 10.72 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure sulfoximine (900 mg, 8.58 mmol assumed,

1.0 eq.) and imidazole (1.17 g, 17.16 mmol, 2.0 eq.) in DMF (5 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. The solution was allowed to cool to rt and then water (10 mL) was added to the solution. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (5 × 60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **148** (663 mg, 19% over 2 steps) as a white solid, mp 50–52 °C, R_F (6:4 hexane-EtOAc) 0.47; IR (ATR) 3069, 2957, 2855, 1306, 1214, 1145, 1104, 821, 739, 700, 606, 552, 501, 489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 4H, Ph), 7.43–7.34 (m, 6H, Ph), 4.03–3.92 (m, 2H, SCH), 3.84–3.73 (m, 2H, SCH), 2.12–1.87 (m, 2H, SCH_2CH_2), 1.09 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.8 (*ipso*-Ph), 135.5 (Ph), 129.4 (Ph), 127.7 (Ph), 68.6 (SCH_2), 27.1 (CMe_3), 19.2 (CMe_3), 7.3 (SCH_2CH_2); MS (ESI) *m/z* 344 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{19}H_{25}NOSSi$ $(M + H)^+$ 344.1499, found 344.1497 (+0.5 ppm error).

Lab book reference: **GH-2-55**

[(*tert*-Butyldiphenylsilyl)imino]diethyl-λ⁶-sulfanone 149



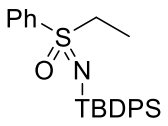
149

A solution of ethyl sulfide (1.08 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH gave the impure sulfoximine (0.70 g) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.17; ^1H NMR (400 MHz, $CDCl_3$) δ 3.06 (q, J = 7.5 Hz, 4H, SCH_2), 2.07 (s, 1H, NH), 1.41 (t, J = 7.5 Hz, 6H, SCH_2Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 48.4 (SCH_2), 7.1 (SCH_2Me). TBDPSCl (1.89 mL, 7.25 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure sulfoximine (0.70 g, 5.8 mmol assumed, 1.0 eq.) and imidazole (0.79 g, 11.6 mmol, 2.0 eq.) in DMF (3 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. The solution

was allowed to cool to rt and then water (5 mL) was added to the solution. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (5 x 60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **149** (1.15 g, 32% over 2 steps) as a clear oil, R_F (6:4 hexane-EtOAc) 0.64; IR (ATR) 3069, 2930, 2855, 2888, 1307, 1281, 1261, 1145, 1106, 821, 783, 737, 699, 624, 613, 587, 495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71 (m, 4H, Ph), 7.40–7.31 (m, 6H, Ph), 2.89–2.73 (m, 4H, SCH), 1.24 (t, *J* = 7.5 Hz, 6H, SCH_2*Me*), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.9 (*ipso*-Ph), 135.7 (Ph), 129.1 (Ph), 127.5 (Ph), 49.7 (SCH_2), 27.3 (C*Me*$_3$), 19.5 (*C*Me_3), 7.9 (SCH_2*Me*); MS (ESI) *m/z* 360 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}NOSSi$ $(M + H)^+$ 360.1812, found 360.1809 (+0.8 ppm error).

Lab book reference: **GH-2-54**

(*tert*-Butyldiphenylsilyl)[ethyl(oxo)phenyl-λ⁶-sulfanylidene]amine 150



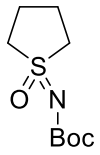
150

A solution of ethyl phenyl sulfide (1.35 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH gave the impure sulfoximine (1.09 g) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98–7.93 (m, 2H, Ph), 7.64–7.58 (m, 1H, Ph), 7.57–7.50 (m, 2H, Ph), 3.18 (q, *J* = 7.5 Hz, 2H, SCH_2), 2.08 (s, 1H, NH), 1.25 (t, *J* = 7.5 Hz, 3H, SCH_2*Me*). TBDPSCl (2.2 mL, 8.01 mmol, 1.25 eq.) was added dropwise to a stirred solution of the impure sulfoximine (1.09 g, 6.4 mmol assumed, 1.0 eq.) and imidazole (0.87 g, 12.8 mmol, 2.0 eq.) in DMF (4 mL) at 0 °C under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. The solution was allowed to cool to rt and then water (5 mL) was added to the solution. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined

organic layers were washed with brine (5 × 60 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **150** (1.54 g, 38% over 2 steps) as a clear oil, R_F (6:4 hexane-EtOAc) 0.56; IR (ATR) 3069, 2930, 2855, 1427, 1323, 1298, 1156, 1108, 740, 720, 702, 690, 499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98–7.91 (m, 2H, Ph), 7.89–7.77 (m, 4H, Ph), 7.58–7.50 (m, 1H, Ph), 7.50–7.33 (m, 8H, Ph), 3.17–2.91 (m, 2H, SCH_2), 1.22–1.14 (m, 12H, C*Me*$_3$,SCH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.1 (*ipso*-Ph), 136.56 (*ipso*-Ph), 136.49 (*ipso*-Ph), 135.67 (Ph), 135.63 (Ph), 132.2 (Ph), 129.00 (Ph), 128.96 (Ph), 128.7 (Ph), 127.9 (Ph), 127.40 (Ph), 127.36 (Ph), 54.7 (SCH_2), 27.3 (C*Me*$_3$), 19.5 (*C*Me$_3$), 8.4 (SCH_2*Me*); MS (ESI) *m/z* 408 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{24}H_{29}NOSSi$ $(M + H)^+$ 408.1812, found 408.1794 (+4.3 ppm error).

Lab book reference: **GH-2-66**

tert-Butyl _N_-(1-oxo-1λ⁶-thiolan-1-ylidene)carbamate 153



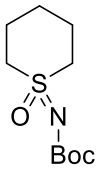
153

A solution of tetramethylene sulfide **66** (0.88 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 and then 9:1 CH_2Cl_2-MeOH gave impure sulfoximine **23** (824 mg) as a yellow oil. A solution of potassium *tert*-butoxide (1.01 g. 9.0 mmol, 1.3 eq.) in THF (18 mL) was added to a stirred solution of impure sulfoximine **23** (824 mg, 6.9 mmol assumed, 1.0 eq.) in THF (21 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a solution of Boc_2O (3.01 g, 13.8 mmol, 2.0 eq.) in THF (32 mL) was added and the resulting solution was stirred at 0 °C for 1 h. The solution was allowed to warm to rt and stirred at rt for 30 h. Saturated $NH_4Cl_{(aq)}$ (35 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated

under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc and then 1:4 hexane-EtOAc as eluent gave *N*-Boc sulfoximine **153** (1.32 g, 60%) as a yellow oil, R_F (1:4 hexane-EtOAc) 0.24; IR (ATR) 2975, 1654 (C=O), 1289, 1252, 1218, 1159, 913, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64–3.55 (m, 2H, SCH), 3.32–3.22 (m, 2H SCH), 2.38–2.19 (m, 4H, CH), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.4 (C=O), 80.9 (*C*Me_3), 53.0 (SCH_2), 28.3 (C*Me*$_3$), 23.7 (CH_2); MS (ESI) *m/z* 242 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_9H_{17}NO_3S$ $(M + Na)^+$ 242.0821, found 242.0819 (+0.9 ppm error).

Lab book reference: **GH-1-57**

tert-Butyl *N*-(1-oxo-1λ⁶-thian-1-ylidene)carbamate 154



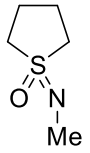
154

A solution of pentamethylene sulfide **151** (1.04 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 95:5 EtOAc-MeOH as eluent gave impure sulfoximine **152** (944 mg) as a yellow oil. A solution of potassium *tert*-butoxide (1.03 g. 9.2 mmol, 1.3 eq.) in THF (18 mL) was added to a stirred solution of the impure sulfoximine **152** (940 mg, 7.0 mmol assumed, 1.0 eq.) in THF (22 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a solution of Boc_2O (3.09 g, 14.2 mmol, 2.0 eq.) in THF (33 mL) was added and the solution was stirred at 0 °C for 1 h. The solution was allowed to warm to rt and stirred for 30 h. Saturated $NH_4Cl_{(aq)}$ (35 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc and then 1:4 hexane-EtOAc as eluent gave *N*-Boc sulfoximine **154** (1.01 g, 43% over 2 steps) as a white solid, mp 78–80 °C;

R_F (1:4 hexane-EtOAc) 0.34; IR (ATR) 2978, 2931, 2872, 1658 (C=O), 1281, 1246, 1158, 960, 893, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.57–3.49 (m, 2H, SCH), 3.31–3.20 (m, 2H, SCH), 2.17–2.02 (m, 4H, SCH_2CH_2), 1.74–1.60 (m, 2H, CH_2), 1.49 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (C=O), 80.5 (CMe_3), 51.1 (SCH_2), 28.3 (CMe_3), 23.8 (CH_2), 23.4 (CH_2); MS (ESI) *m/z* 256 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NO_3S$ $(M + Na)^+$ 256.0978, found 256.0979 (–0.5 ppm error).

Lab book reference: **GH-1-59**

1-(Methylimino)-1λ⁶-thiolan-1-one 155



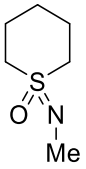
155

A solution of tetramethylene sulfide **66** (0.88 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 30 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2 and then 9:1 CH_2Cl_2-MeOH gave impure sulfoximine **23** (871 mg) as a yellow oil. A solution of paraformaldehyde (263 mg, 8.8 mmol, 1.2 eq.) and impure sulfoximine **23** (871 mg, 7.3 mmol assumed, 1.0 eq.) in formic acid (10.95 mL) was stirred and heated at 120 °C for 36 h. The solution was allowed to cool to rt and the solvent evaporated under reduced pressure. The residue was dissolved in 2 M $H_2SO_{4(aq)}$ (51.1 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The aqueous layer was basified by the addition of 2 M $NaOH_{(aq)}$ until pH 12 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave *N*-Me sulfoximine **155** (754 mg, 57%) as an amber oil, R_F (9:1 EtOAc-MeOH) 0.15; IR (ATR) 3398, 2944, 2802, 1224, 1147, 1100, 1074, 905, 847 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 3.24–3.13 (m, 2H, SCH), 3.02–2.93 (m, 2H, SCH), 2.83 (s, 3H, NMe), 2.30–2.10 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 51.4

(SCH_2), 30.8 (CH_3), 23.8 (CH_2); MS (ESI) *m/z* 134 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_5H_{11}NOS$ $(M + H)^+$ 134.0634, found 134.0631 (+2.6 ppm error).

Lab book reference: **GH-1-65**

1-(Methylimino)-1λ⁶-thian-1-one 156

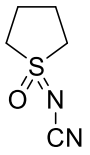


156

A solution of pentamethylene sulfide **151** (1.04 mL, 10.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (8.05 g, 25.0 mmol, 2.5 eq.) and ammonium carbamate (1.56 g, 20.0 mmol, 2.0 eq.) in MeOH (20 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 190:9:1 EtOAc-MeOH-$NH_4OH_{(aq)}$ as eluent gave impure sulfoximine **152** (1.11 g) as a yellow oil. A solution of paraformaldehyde (301 mg, 10.0 mmol, 1.2 eq.) and the impure sulfoximine **152** (1.11 g, 8.4 mmol assumed, 1.0 eq.) in formic acid (12.5 mL) was stirred and heated at 120 °C for 36 h. The solution was allowed to cool to rt and the solvent evaporated under reduced pressure. The residue was dissolved in 2 M $H_2SO_{4(aq)}$ (59 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The aqueous layer was basified by the addition of 2 M $NaOH_{(aq)}$ until pH 12 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave *N*-Me sulfoximine **156** (741 mg, 50%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.17; IR (ATR) 2929, 2876, 2804, 1230, 1136, 1106, 867 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 3.15–3.06 (m, 2H, SCH), 3.04–2.96 (m, 2H, SCH), 2.80 (s, 3H, NMe), 2.08–1.93 (m, 4H, SCH_2CH_2), 1.72–1.54 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 50.5 (SCH_2), 28.6 (Me), 24.5 (CH_2), 24.1 (CH_2); MS (ESI) *m/z* 148 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{13}NOS$ $(M + H)^+$ 148.0791, found 148.0792 (–0.6 ppm error).

Lab book reference: **GH-1-75-2**

[(1-oxo-1λ⁶-thiolan-1-ylidene)amino]formonitrile 68

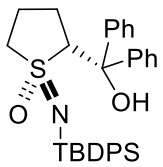


68

Potassium *tert*-butoxide (2.24 g, 20 mmol, 2.0 eq.) and cyanamide (840 mg, 20 mmol, 2.0 eq.) were added sequentially to a stirred solution of tetrahydrothiophene 1-oxide **145** (0.90 mL, 10 mmol, 1.0 eq.) in water (100 mL) at rt. The resulting solution was stirred at rt for 10 min. *N*-chlorosuccinimide (2.67 g, 20 mmol, 2.0 eq.) was added and the resulting solution was stirred at rt for 2 h. CH_2Cl_2 (100 mL) and 20% $NaOH_{(aq)}$ (50 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc and then 9:1 EtOAc-hexane as eluent gave *N*-CN sulfoximine **68** (716 mg, 50%) as a white solid, mp 78–80 °C (lit.[36] 78–79 °C); R_F (EtOAc) 0.30; IR (ATR) 3004, 2948, 2184 (C≡N), 1448, 1408, 1280, 1228, 1176, 1091, 900, 817, 733, 600, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59–3.49 (m, 2H, SCH), 3.35–3.23 (m, 2H, SCH), 2.45–2.26 (m, 4H, SCH_2CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 112.5 (C≡N), 53.0 (SCH_2), 23.6 (SCH_2CH_2); MS (ESI) *m/z* 145 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_5H_8N_2OS$ $(M + H)^+$ 145.0430, found 145.0430 (0.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[56]

Lab book reference: **GH-1-86-2**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(hydroxydiphenylmethyl)-1λ⁶-thiolan-1-one *cis*-157



***cis*-157**

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with hexane to 95:5 hexane-EtOAc as eluent gave alcohol *cis*-**157** (228 mg, 84%) as a white solid, mp 109–111 °C; R_F (8:2 hexane-EtOAc) 0.47; IR (ATR) 3437 (OH), 3072, 2930, 2855, 1299, 1109, 734, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.74 (m, 2H, Ph), 7.73–7.69 (m, 2H, Ph), 7.55–7.51 (m, 2H, Ph), 7.43–7.32 (m, 6H, Ph), 7.29–7.17 (m, 7H, Ph), 7.17–7.12 (m, 1H, Ph), 5.11 (s, 1H, COH), 4.32 (dd, J = 16.5, 7.5 Hz, 1H, SCH), 2.67–2.51 (m, 2H, SCH), 2.22–2.11 (m, 1H, CH), 2.01–1.91 (m, 1H, CH), 1.91–1.72 (m, 2H, CH), 1.04 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.6 (*ipso*-Ph), 145.4 (*ipso*-Ph), 136.1 (*ipso*-Ph), 135.83 (*ipso*-Ph), 135.77 (Ph), 135.74 (Ph), 129.4 (Ph), 129.3 (Ph), 128.42 (Ph), 128.38 (Ph), 127.8 (Ph), 127.6 (Ph), 127.3 (Ph), 126.8 (Ph), 126.5 (Ph), 125.1 (Ph), 78.6 (COH), 70.9 (SCH), 57.8 (SCH_2), 27.1 (CMe_3), 27.0 (CH_2), 21.3 (CH_2), 19.3 (CMe_3); MS (ESI) *m/z* 540 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{33}H_{37}NO_2SSi$ $(M + H)^+$ 540.2387, found 540.2399 (–0.2 ppm error). The stereochemistry of *cis*-**157** was assigned by X-ray crystallography.

Crystal structure determination of *cis*-**157**

$C_{33}H_{37}NO_2SSi$, M = 539.78, monoclinic, a = 10.37330(10), b = 17.0824(2), c = 16.0625(2) Å, β = 90.9500(10)°, U = 2845.90(6) $Å^3$, T = 110.05(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 1.646 mm^{-1}, 21242 reflection measured, 5437 unique (R_{int} = 0.0246) which were used in calculation. The final R1 was 0.0317 (I≥2σ) and wR2 was 0.0850 (all data).

Lab book reference: **GH-1-33**

LHMDS (0.55 mL of a 1 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and then water (5 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were

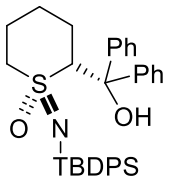
dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane and then 95:5 hexane-EtOAc as eluent gave the alcohol *cis*-**157** (158 mg, 59%) as a white solid.

Lab book reference **GH-1-26**

LHMDS (0.55 mL of a 1 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) was added dropwise and the resulting solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and then water (5 mL) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with hexane to 97:3 hexane-EtOAc as eluent gave the alcohol *cis*-**157** (143 mg, 53%) as a white solid.

Lab book reference: **GH-1-28**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(hydroxydiphenylmethyl)-1λ⁶-thian-1-one *cis*-158



cis-**158**

Using general procedure A, *N*-TBDPS sulfoximine **147** (186 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc and then 9:1 hexane-EtOAc as eluent gave alcohol *cis*-**158** (209 mg, 76%) as a white solid, mp 96–98 °C, R_F (8:2 hexane-EtOAc) 0.30; IR (ATR) 3274 (OH), 3065, 2931, 2857, 1255, 1139, 729, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.70 (m, 2H, Ph),

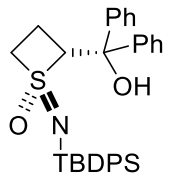
7.69–7.66 (m, 2H, Ph), 7.50–7.46 (m, 2H, Ph), 7.43–7.34 (m, 8H, Ph), 7.33–7.20 (m, 6H, Ph), 7.12 (s, 1H, COH), 3.90 (dd, J = 12.0, 2.0 Hz, 1H, SCH), 2.58–2.47 (m, 1H, SCH), 2.26–2.11 (m, 2H, CH), 1.90–1.61 (m, 4H, CH), 1.33–1.22 (m, 1H, CH), 1.00 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.8 (*ipso*-Ph), 142.1 (*ipso*-Ph), 136.3 (*ipso*-Ph), 136.1 (Ph), 135.8 (Ph), 135.6 (*ipso*-Ph), 129.5 (Ph), 129.3 (Ph), 128.4 (Ph), 128.2 (Ph), 127.8 (Ph), 127.69 (Ph), 127.67 (Ph), 127.6 (Ph), 127.5 (Ph), 127.2 (Ph), 81.5 (COH), 72.9 (SCH), 57.9 (SCH_2), 28.1 (CH_2), 27.2 (CMe_3), 25.9 (CH_2), 24.0 (CH_2), 19.2 (CMe_3); MS (ESI) *m/z* 554 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{34}H_{39}NO_2SSi$ $(M + H)^+$ 554.2544, found 554.2556 (–2.2 ppm error). The stereochemistry of *cis*-**158** was assigned by X-ray crystallography.

Crystal structure determination of *cis*-**158**

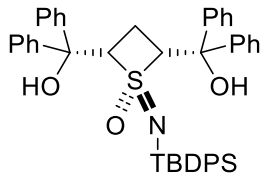
$C_{34}H_{39}NO_2SSi$, M = 553.81, monoclinic, a = 20.0762(3), b = 10.90514(18), c = 81.5001(12) Å, β = 93.6761(13)°, U = 17806.4(5) $Å^3$, T = 110.05(10) K, space group $P2_1$, Z = 24, μ(Mo-Kα) = 1.591 mm^{-1}, 117774 reflection measured, 31743 unique (R_{int} = 0.0496) which were used in calculation. The final R1 was 0.0729 (I≥2σ) and wR2 was 0.2085 (all data).

Lab book reference: **GH-1-36**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(hydroxydiphenylmethyl)-1λ⁶-thietan-1-one *cis*-159 and 1-[(*tert*-Butyldiphenylsilyl)imino]-2,4-bis(hydroxydiphenylmethyl)-1λ⁶-thietan-1-one *cis,cis*-160



cis-**159**



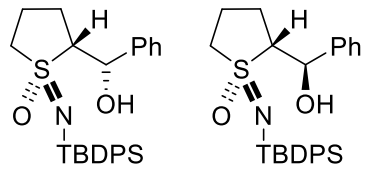
cis,cis-**160**

Using general procedure A, *N*-TBDPS sulfoximine **148** (172 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an 85:15 mixture (by ^1H NMR spectroscopy) of sulfoximines *cis*-**159** and *cis,cis*-**160**. Purification by flash column chromatography on silica with 95:5

hexane-EtOAc as eluent gave an 85:15 mixture of sulfoximines *cis*-**159** and *cis,cis*-**160** (185 mg, 149 mg (57%) of *cis*-**159** and 36 mg (10%) of *cis,cis*-**160**) as a white solid, R_F (8:2 hexane-EtOAc) 0.46; IR (ATR) 3459 (OH), 3068, 2930, 2856, 1449, 1427, 1333, 1186, 1153, 1110, 740, 700, 508, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.68 (m, 3H, Ph), 7.68–7.59 (m, 2H, Ph), 7.52–7.14 (m, 14H, Ph), 7.08–6.93 (m, 1H, Ph), 5.25 (dd, *J* = 9.0, 9.0 Hz, 0.85H, SCH), 5.15 (dd, *J* = 10.0, 10.0 Hz, 0.3H, SCH), 5.03 (s, 0.85H, COH), 4.82 (s, 0.3H, COH), 3.88–3.66 (m, 0.85H, SCH), 3.67 (ddd, *J* = 12.5, 10.5, 8.5 Hz, 0.85H, SCH), 2.92 (dt, *J* = 12.5, 9.5 Hz, 0.15H, CH) 2.48–2.34 (m, 0.85H, SCHC*H*), 1.84–1.70 (m, 1H, SCHC*H*), 1.11 (s, 7.65H, C*Me*$_3$), 0.93 (s, 1.35H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.4 (*ipso*-Ph), 145.0 (*ipso*-Ph), 143.95 (*ipso*-Ph), 143.85 (*ipso*-Ph), 135.53 (Ph), 135.51 (Ph), 135.46 (Ph), 135.44 (Ph), 129.5 (Ph), 128.5 (Ph), 128.4 (Ph), 127.78 (Ph), 127.73 (Ph), 127.2 (Ph), 126.6 (Ph), 126.0 (Ph), 125.56 (Ph), 125.45 (Ph), 86.4 (SCH, *cis*-**159**), 83.7 (SCH, *cis,cis*-**160**), 78.7 (COH, *cis,cis*-**160**), 78.3 (COH, *cis*-**159**), 65.8 (SCH_2, *cis*-**159**), 27.0 (C*Me*$_3$, *cis*-**159**), 26.7 (C*Me*$_3$, *cis,cis*-**160**), 19.32 (*C*Me$_3$, *cis,cis*-**160**), 19.29 (*C*Me$_3$, *cis*-**159**), 13.9 (CH_2, *cis,cis*-**160**), 10.2 (CH_2, *cis*-**159**) (some Ph resonances not resolved); MS (ESI) *m/z* 526 $(M + H)^+$ HRMS (ESI) *m/z* calcd for $C_{32}H_{35}NO_2SSi$ $(M + H)^+$ 526.2231, found 526.2223 (+1.5 ppm error), MS (ESI) *m/z* 730 $(M + H)^+$ HRMS (ESI) *m/z* calcd for $C_{45}H_{45}NO_3SSi$ $(M + H)^+$ 730.2782, found 730.2793 (–1.6 ppm error). The stereochemistry of *cis*-**159** and *cis,cis*-**160** was assigned by analogy with related examples.

Lab book reference: **GH-2-59**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-[hydroxy(phenyl)methyl]-1λ⁶-thiolan-1-one *cis,anti*-164 and *cis,syn*-164



cis,anti-**164** *cis,syn*-**164**

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an

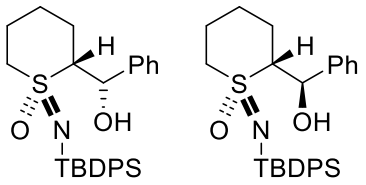
85:15 mixture (by ^{1}H NMR spectroscopy) of alcohols *cis,anti*-**164** and *cis,syn*-**164**. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave alcohol *cis,anti*-**164** (154 mg, 66%) as a white solid and alcohol *cis,syn*-**164** (23 mg, 10%) as a white solid, mp 86–88 °C; R_F (8:2 hexane-EtOAc) 0.27; IR (ATR) 3479 (OH), 3069, 2930, 2855, 1299, 1108, 731, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.80–7.73 (m, 4H, Ph), 7.43–7.34 (m, 6H, Ph), 7.28–7.16 (m, 3H, Ph), 7.00 (d, *J* = 7.0 Hz, 2H, Ph), 5.12 (s, 1H, PhC*H*OH), 3.98 (s, 1H, PhCHO*H*), 3.01–2.88 (m, 3H, SCH), 2.30–2.18 (m, 1H, CH), 2.13–2.02 (m, 1H, CH), 1.93–1.80 (m, 1H, CH), 1.74–1.65 (m, 1H, CH), 1.11 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 140.5 (*ipso*-Ph), 136.19 (*ipso*-Ph), 136.15 (*ipso*-Ph), 135.70 (Ph), 135.66 (Ph), 129.51 (Ph), 129.46 (Ph), 128.4 (Ph), 127.81 (Ph), 127.78 (Ph), 127.4 (Ph), 125.6 (Ph), 70.1 (SCH), 68.6 (Ph*C*HOH), 57.3 (SCH_2), 27.2 (C*Me*$_3$), 22.3 (CH_2), 20.9 (CH_2), 19.3 (*C*Me$_3$); MS (ESI) *m/z* 464 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NO_2SSi$ $(M + H)^+$ 464.2074, found 464.2079 (–1.2 ppm error), mp 82–84 °C; R_F (8:2 hexane-EtOAc) 0.20; IR (ATR) 3468 (OH), 3068, 2930, 2855, 1304, 1108, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 4H, Ph), 7.46–7.35 (m, 6H, Ph), 7.35–7.29 (m, 3H, Ph), 7.29–7.25 (m, 2H, Ph), 4.89 (d, *J* = 9.5 Hz, 1H, Ph*CH*OH), 4.07 (s, 1H, PhCHO*H*), 3.19 (ddd, *J* = 9.5, 9.5, 9.5 Hz, 1H, SCH), 2.95–2.77 (m, 2H, SCH), 2.07–1.94 (m, 1H, CH), 1.92–1.79 (m, 1H, CH), 1.78–1.68 (m, 1H, CH), 1.68–1.55 (m, 1H, CH), 1.11 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.3 (*ipso*-Ph), 136.04 (*ipso*-Ph), 136.01 (*ipso*-Ph), 135.8 (Ph), 129.4 (Ph), 128.7 (Ph), 128.4 (Ph), 127.8 (Ph), 127.7 (Ph), 127.1 (Ph), 75.5 (Ph*C*HOH), 70.5 (SCH), 56.2 (SCH_2), 27.2 (C*Me*$_3$), 27.0 (CH_2), 20.9 (CH_2), 19.3 (*C*Me$_3$) (two Ph resonances not resolved); MS (ESI) *m/z* 464 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NO_2SSi$ $(M + H)^+$ 464.2074, found 464.2070 (+0.9 ppm error). The stereochemistry of *cis,syn*-**164** was assigned by X-ray crystallography and that of *cis,anti*-**164** was assigned by analogy.

Crystal structure determination of *cis,syn*-**164**

$C_{27}H_{33}NO_2SiS$, *M* = 463.69, monoclinic, *a* = 14.6428(2), *b* = 11.09222(10), *c* = 16.4498(2) Å, *β* = 113.4106(16)°, *U* = 2451.85(6) Å^3, *T* = 110.05(10) K, space group $P2_1$, Z = 4, *μ*(Mo-Kα) = 1.822 mm^{-1}, 18079 reflection measured, 4375 unique (R_{int} = 0.0274) which were used in calculation. The final R1 was 0.0327 (I≥2σ) and wR2 was 0.0893 (all data).

Lab book reference **GH-1-35**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-[hydroxy(phenyl)methyl]-1λ⁶-thian-1-one *cis,anti*-165 and *cis,syn*-165

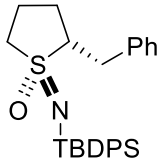


cis,anti-**165** *cis,syn*-**165**

Using general procedure A, *N*-TBDPS sulfoximine **147** (186 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of alcohols *cis,anti*-**165** and *cis,syn*-**165**. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave an 85:15 mixture of diastereomeric alcohols *cis,anti*-**165** and *cis,syn*-**165** (174 mg, 73%) as a white solid, R_F (8:2 hexane-EtOAc) 0.31; IR (ATR) 3488 (OH), 3069, 2929, 2856, 1324, 1284, 1259, 1134, 1107, 732, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.78 (m, 4H, Ph), 7.42–7.30 (m, 9H, Ph), 7.26–7.30 (m, 2H, Ph), 5.89 (s, 0.85H, PhC*H*OH), 5.34 (d, *J* = 9.0 Hz, 0.15H, PhC*H*OH), 3.55 (s, 1H, PhCH*OH*), 3.12–3.06 (m, 0.15H, SCH), 2.86–2.77 (m, 1.7H, SCH), 2.78–2.67 (m, 0.85H, SCH), 2.58–2.50 (m, 0.15H, SCH), 2.43–2.39 (m, 0.15H, SCH), 2.20–2.06 (m, 1H, CH), 2.05–1.91 (m, 1H, CH), 1.90–1.72 (m, 2H, CH), 1.74–1.65 (m, 1H, CH), 1.22–1.16 (m, 1H, CH), 1.13 (s, 7.65H, CMe_3) 1.11 (s, 1.35H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *cis,anti*-**165** δ 140.4 (*ipso*-Ph), 136.47 (*ipso*-Ph), 136.46 (*ipso*-Ph), 135.69 (Ph), 135.62 (Ph), 129.4 (Ph), 128.4 (Ph), 127.73 (Ph), 127.70 (Ph), 127.48 (Ph), 125.90 (Ph), 70.2 (SCH), 67.8 (Ph*C*HOH), 57.6 (SCH_2), 27.3 (C*Me*$_3$), 24.4 (CH_2), 24.2 (CH_2), 21.9 (CH_2), 19.5 (*C*Me_3) (one Ph resonance not resolved); MS (ESI) *m/z* 478 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}NO_2SSi$ $(M + H)^+$ 478.2231, found 478.2238 (–1.6 ppm error). Diagnostic signals for *cis,syn*-**165** δ 73.1 (SCH), 69.1 (Ph*C*HOH), 55.6 (SCH_2), 27.5 (C*Me*$_3$), 27.2 (CH_2), 24.03 (CH_2), 23.95 (CH_2), 19.2 (*C*Me_3). The stereochemistry of *cis,syn*-**165** and *cis,anti*-**165** was assigned by analogy with related examples.

Lab book reference: **GH-1-37**

2-Benzyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thiolan-1-one *cis*-166

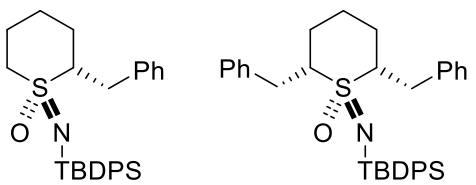


cis-**166**

Using general procedure A, *N*-TBDPS sulfoximine **146** (358 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.44 mL of a 2.5 M solution in *n*-hexane, 1.1 mmol, 1.1 eq.) and benzyl bromide (0.24 mL, 2.0 mmol, 2.0 eq.) in THF (10 mL) gave the crude product. Purification by flash column chromatography on silica with hexane and then 95:5 hexane-EtOAc as eluent gave benzyl sulfoximine *cis*-**166** (328 mg, 73%) as a white semi-solid, R_F (9:1 hexane-EtOAc) 0.24; IR (ATR) 3073, 2929, 2855, 1307, 1153, 1108, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 4H, Ph), 7.43–7.32 (m, 6H, Ph), 7.28–7.17 (m, 3H, Ph), 7.00 (d, *J* = 7.0 Hz, 2H, Ph), 3.12 (dd, *J* = 14.0, 4.5 Hz, 1H, PhCH), 3.02–2.83 (m, 3H, SCH), 2.61 (dd, *J* = 14.0, 10.5 Hz, 1H, PhCH), 2.08–1.92 (m, 2H, CH), 1.88–1.67 (m, 2H, CH), 1.08 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3 (*ipso*-Ph), 136.56 (*ipso*-Ph), 136.54 (*ipso*-Ph), 135.7 (Ph), 129.3 (Ph), 129.1 (Ph), 128.7 (Ph), 127.7 (Ph), 126.7 (Ph), 66.2 (SCH), 55.8 (SCH_2), 33.8 ($PhCH_2$), 28.9 (CH_2), 27.2 (CMe_3), 20.5 (CH_2), 19.3 (CMe_3) (three Ph resonances not resolved); MS (ESI) *m/z* 448 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NOSSi$ $(M + H)^+$ 448.2125, found 448.2126 (–0.3 ppm error). The stereochemistry of *cis*-**166** was assigned by analogy with related examples.

Lab book reference: **GH-1-18**

2-Benzyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thian-1-one *cis*-168 and 2,6-Dibenzyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thian-1-one *cis,cis*-169

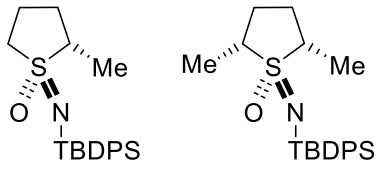


cis-**168** *cis,cis*-**169**

Using general procedure A, *N*-TBDPS sulfoximine **147** (72 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 55:45 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**168** and *cis,cis*-**169**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave dibenzyl sulfoximine *cis,cis*-**169** (91 mg, 33%) as a clear oil, R_F (8:2 hexane-EtOAc) 0.56; IR (ATR) 3027, 2930, 2855, 1358, 1346, 1320, 1268, 1156, 1106, 759, 739, 699, 614, 601, 491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.87 (m, 4H, Ph), 7.43–7.34 (m, 6H, Ph), 7.23–7.11 (m, 6H, Ph), 6.85–6.78 (m, 4H, Ph), 3.42 (dd, *J* = 13.0, 2.5 Hz, 2H, PhCH), 2.96–2.83 (m, 2H, SCH), 2.51 (dd, *J* = 13.0, 12.0 Hz, 2H, PhCH), 1.76–1.59 (m, 5H, CH), 1.19–1.08 (m, 1H, CH), 1.12 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ; 137.7 (*ipso*-Ph), 136.6 (*ipso*-Ph), 135.8 (Ph), 129.5 (Ph), 129.2 (Ph), 128.6 (Ph), 127.7 (Ph), 126.6 (Ph), 67.6 (SCH), 31.6 (CH_2), 29.0 (CH_2), 27.2 (C*Me*$_3$), 24.8 (CH_2), 20.0 (*C*Me$_3$); MS (ESI) *m/z* 552 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{35}H_{41}NOSSi$ $(M + H)^+$ 552.2751, found 552.2750 (+0.2 ppm error) and benzyl sulfoximine *cis*-**168** (72 mg, 31%) as a clear oil, R_F (8:2 hexane-EtOAc) 0.51; IR (ATR) 3068, 2929, 2855, 1321, 1281, 1259, 1167, 1141, 1106, 820, 733, 698, 656, 602, 495, 462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 4H, Ph), 7.43–7.33 (m, 6H, Ph), 7.32–7.17 (m, 3H, Ph), 7.05 (d, *J* = 7.0 Hz, 2H, Ph), 3.60 (dd, *J* = 13.5, 2.5 Hz, 1H, PhCH), 2.95–2.75 (m, 2H, SCH), 2.75–2.54 (m, 1H, SCH), 2.55 (dd, *J* = 13.5, 11.5 Hz, PhCH), 2.04–1.90 (m, 1H, CH), 1.90–1.77 (m, 2H, CH), 1.77–1.62 (m, 2H, CH), 1.28–1.14 (m, 1H, CH), 1.11 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9 (*ipso*-Ph), 136.92 (*ipso*-Ph), 136.90 (*ipso*-Ph), 135.75 (Ph), 135.72 (Ph), 129.5 (Ph), 129.2 (Ph), 128.7 (Ph), 127.6 (Ph), 126.7 (Ph), 66.7 (SCH), 56.4 (SCH_2), 31.2 ($PhCH_2$), 28.5 (CH_2), 27.3 (C*Me*$_3$), 24.6 (CH_2), 24.5 (CH_2), 19.5 (*C*Me$_3$) (two Ph resonances not resolved); MS (ESI) *m/z* 462 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}NOSSi$ $(M + H)^+$ 462.2281, found 462.2282 (–0.1 ppm error). The stereochemistry of *cis*-**168** and *cis,cis*-**169** was assigned by analogy with related examples.

Lab book reference: **GH-1-96**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-methyl-1λ⁶-thiolan-1-one *cis*-172 and 1-[(*tert*-Butyldiphenylsilyl)imino]-2,5-dimethyl-1λ⁶-thiolan-1-one *cis,cis*-173



cis-**172** *cis,cis*-**173**

Using general procedure A, *N*-TBDPS sulfoximine **146** (358 mg, 1.0 mmol, 1.0 eq.), *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol, 1.1 eq.) and dimethyl sulfate (0.19 mL, 2.0 mmol, 2.0 eq.) in THF (10 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**172** and *cis,cis*-**173**. Purification by flash column chromatography on silica with hexane and then 9:1 hexane-EtOAc as eluent gave dimethyl sulfoximine *cis,cis*-**173** (28 mg, 7%) as a white solid, mp 49–51 °C; R_F (9:1 hexane-EtOAc) 0.5; IR (ATR) 3069, 2930, 2854, 1313, 1248, 1145, 1106, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.71 (m, 4H, Ph), 7.38–7.29 (m, 6H, Ph), 2.93–2.81 (m, 2H, SCH), 2.08–1.98 (m, 2H, CH), 1.65–1.55 (m, 2H, CH), 1.09 (d, *J* = 7.0 Hz, 6H, CH*Me*), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.6 (Ph), 136.9 (*ipso*-Ph), 135.7 (Ph), 130.4 (Ph), 129.1 (Ph), 127.5 (Ph), 59.3 (SCH), 28.1 (CH_2), 27.2 (C*Me*$_3$), 19.4 (*C*Me$_3$), 12.7 (CH*Me*) (two Ph resonances not resolved); MS (ESI) *m/z* 386 (M + H)$^+$ HRMS (ESI) *m/z* calcd for $C_{22}H_{31}NOSSi$ (M + H)$^+$ 386.1968, found 386.1968 (+0.1 ppm error) and methyl sulfoximine *cis*-**172** (166 mg, 45%) as a white solid, mp 64–66 °C; R_F (9:1 hexane-EtOAc) 0.38; IR (ATR) 3069, 2930, 2855, 1305, 1250, 1147, 1107, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71 (m, 4H, Ph), 7.41–7.32 (m, 6H, Ph), 2.90–2.76 (m, 3H, SCH), 2.21–2.11 (m, 1H, CH), 2.08–1.97 (m, 1H, CH), 1.92–1.79 (m, 1H, CH), 1.73–1.61 (m, 1H, CH), 1.18 (d, *J* = 7.0 Hz, 3H, CH*Me*), 1.07 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.67 (*ipso*-Ph), 136.62 (*ipso*-Ph), 135.70 (Ph), 135.68 (Ph), 129.2 (Ph), 127.57 (Ph), 127.55 (Ph), 60.3 (SCH), 54.9 (SCH_2), 30.9 (CH_2), 27.2 (C*Me*$_3$), 20.5 (CH_2), 19.3 (*C*Me$_3$), 12.3 (CH*Me*) (one Ph resonance not resolved); MS (ESI) *m/z* 372 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}NOSSi$ (M + H)$^+$ 372.1812 found, 372.1819 (–1.8 ppm error). The stereochemistry of *cis*-**172** was assigned by X-ray crystallography and that of *cis,cis*-**173** was assigned by analogy.

Crystal structure determination of *cis*-**172**

$C_{21}H_{29}NOSSi$, M = 371.60, monoclinic, a = 11.22483(13), b = 11.01708(15), c = 16.9162(2) Å, β = 103.5456(13)°, U = 2033.75(5) Å^3, T = 110.05(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 2.031 mm^{-1}, 11190 reflection measured, 3640 unique (R_{int} = 0.0186)

which were used in calculation. The final R1 was 0.0294 ($I \geq 2\sigma$) and wR2 was 0.0796 (all data).

Lab book reference: **GH-1-15**

Using general procedure A, *N*-TBDPS sulfoximine **146** (1.79 g, 5 mmol, 1.0 eq.), *n*-BuLi (2.4 mL of a 2.3 M solution in hexanes, 5.5 mmol, 1.1 eq.) and methyl iodide (0.62 mL, 10 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with hexane and then 9:1 hexane-EtOAc as eluent gave dimethyl sulfoximine *cis,cis*-**173** (52 mg, 3%) as a white solid and methyl sulfoximine *cis*-**172** (834 mg, 45%) as a white solid.

Lab book reference: **GH-1-82**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-methyl-1λ⁶-thiolan-1-one *cis*-172

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with hexane and then 9:1 hexane-EtOAc as eluent gave methyl sulfoximine *cis*-**172** (109 mg, 56%) as a white solid.

Lab book reference: **GH-1-46**

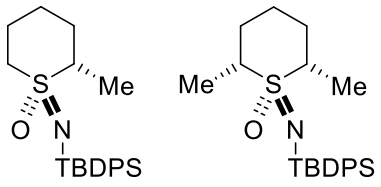
1-[(*tert*-Butyldiphenylsilyl)imino]-2,5-dimethyl-1λ⁶-thiolan-1-one *cis,cis*-173

n-BuLi (0.54 mL of a 2.3 M solution in hexanes, 1.25 mmol, 2.5 eq.) was added dropwise to a stirred solution of the *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.12 mL, 2.0 mmol, 4.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with

95:5 hexane-EtOAc as eluent gave dimethyl sulfoximine *cis,cis*-**173** (148 mg, 74%) as a white solid, R_F (8:2 hexane-EtOAc) 0.40.

Lab book reference: **GH-2-43**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-methyl-1λ⁶-thian-1-one *cis*-174 and 1-[(*tert*-Butyldiphenylsilyl)imino]-2,6-dimethyl-1λ⁶-thian-1-one *cis,cis*-175



cis-**174** *cis,cis*-**175**

Using general procedure A, *N*-TBDPS sulfoximine **147** (186 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an 80:20 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**174** and *cis,cis*-**175**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave dimethyl sulfoximine *cis,cis*-**175** (24 mg, 12%) as a white solid, mp 164–166 °C; R_F (8:2 hexane-EtOAc) 0.53; IR (ATR) 3069, 2931, 2855, 1329, 1280, 1107, 1181, 1154, 702 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.80–7.74 (m, 4H, Ph), 7.39–7.30 (m, 6H, Ph), 2.87–2.73 (m, 2H, SCH), 1.87–1.69 (m, 5H, CH), 1.49–1.37 (m, 1H, CH), 1.10 (d, *J* = 7.0 Hz, 6H, CH*Me*), 1.04 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.9 (*ipso*-Ph), 135.8 (Ph) 129.0 (Ph), 127.4 (Ph), 61.2 (SCH), 32.9 (CH_2), 27.3 (C*Me*$_3$), 25.3 (CH_2), 19.8 (*C*Me$_3$), 12.1 (CH*Me*); MS (ESI) *m/z* 400 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{23}H_{33}NOSSi$ $(M + H)^+$ 400.2131 found 400.2131 (+0.1 ppm error) and methyl sulfoximine *cis*-**174** (90 mg, 47%) as a white solid, mp 158–160 °C; R_F (8:2 hexane-EtOAc) 0.44; IR (ATR) 3069, 2931, 2855, 1329, 1280, 1107, 1181, 1154, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.71 (m, 4H, Ph), 7.40–7.30 (m, 6H, Ph), 2.89–2.71 (m, 2H, SCH), 2.68–2.58 (m, 1H, SCH), 2.01–1.70 (m, 5H, CH), 1.41–1.30 (m, 1H, CH), 1.28 (d, *J* = 7.0 Hz, 3H, CH*Me*), 1.06 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.1 (*ipso*-Ph), 137.0 (*ipso*-Ph), 135.74 (Ph), 135.70 (Ph), 129.08 (Ph), 129.06 (Ph), 127.50 (Ph), 127.48 (Ph), 60.5 (SCH), 55.9 (SCH_2), 32.2 (CH_2), 27.3 (C*Me*$_3$), 24.8 (CH_2), 24.6 (CH_2), 19.5 (*C*Me$_3$), 11.8 (CH*Me*); MS (ESI) *m/z* 386 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{31}NOSSi$ $(M + H)^+$ 386.1968, found 386.1975 (–1.6 ppm error). The

stereochemistry of *cis,cis*-**175** was assigned by X-ray crystallography and that of *cis*-**174** was assigned by analogy.

Crystal structure determination of *cis,cis*-**175**

$C_{23}H_{33}NOSSi$, M = 399.65, monoclinic, a = 12.32310(10), b = 10.67430(10), c = 16.70490(10) Å, β = 98.4940(10)°, U = 2173.27(3) Å^3, T = 110.00(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 1.934 mm^{-1}, 20529 reflection measured, 4167 unique (R_{int} = 0.0166) which were used in calculation. The final R1 was 0.0374 (I≥2σ) and wR2 was 0.0973 (all data).

Lab book reference: **GH-1-55**

Using general procedure A, *N*-TBDPS sulfoximine **147** (186 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and dimethyl sulfate (0.1 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis*-**174** and *cis,cis*-**175**. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave dimethyl sulfoximine *cis,cis*-**175** (18 mg, 9%) as a white solid and methyl sulfoximine *cis*-**174** (101 mg, 52%) as a white solid.

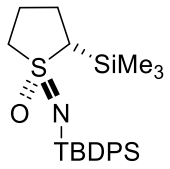
Lab book reference: **GH-1-24**

n-BuLi (0.54 mL of a 2.3 M solution in hexanes, 1.25 mmol, 2.5 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine **147** (186 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.12 mL, 2.0 mmol, 4.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of sulfoximines *cis,cis*-**175** and *cis*-**174**. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave dimethyl sulfoximine

cis,cis-**175** (108 mg, 54%) as a white solid and methyl sulfoximine *cis*-**174** (21 mg, 11%) as a white solid.

Lab book reference: **GH-2-44**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(trimethylsilyl)-1λ⁶-thiolan-1-one *cis*-176

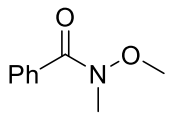


cis-**176**

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and TMSCl (0.13 mL, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 and then 8:2 hexane-EtOAc as eluent gave silyl sulfoximine *cis*-**176** (170 mg, 79%) as a clear oil, R_F (9:1 hexane-EtOAc) 0.50; IR (ATR) 3069, 3048, 2955, 2893, 2855, 1427, 1300, 1248, 1140, 1108, 845, 821, 738, 702, 605, 500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.71 (m, 4H, Ph), 7.41–7.31 (m, 6H, Ph), 2.60–2.53 (m, 2H, SCH), 2.42 (dd, *J* = 12.0, 7.5 Hz, 1H, SCH), 2.16–2.02 (m, 2H, CH), 2.00–1.78 (m, 2H, CH), 1.07 (s, 9H, CMe_3), 0.22 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.8 (*ipso*-Ph), 136.5 (*ipso*-Ph), 135.9 (Ph), 135.8 (Ph), 129.16 (Ph), 129.11 (Ph), 127.58 (Ph), 127.55 (Ph), 57.1 (SCH), 56.5 (SCH_2), 27.2 (C*Me*$_3$), 26.1 (CH_2), 24.8 (CH_2), 19.4 (*C*Me_3), –1.9 ($SiMe_3$); MS (ESI) *m/z* 430 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{23}H_{35}NOSSi_2$ $(M + H)^+$ 430.2051, found 430.2052 (–0.3 ppm error). The stereochemistry of silyl sulfoximine *cis*-**176** was assigned by analogy with related examples.

Lab book reference: **GH-2-25**

***N*-Methoxy-*N*-methylbenzamide 136**

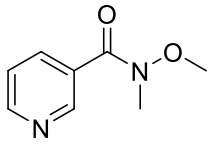


136

Et_3N (3 mL, 21.3 mmol, 1.0 eq.) was added to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (694 mg, 7.11 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) at rt under Ar. The resulting solution was cooled to 0 °C. Then, benzoyl chloride **177** (0.83 mL, 7.11 mmol, 1.0 eq.) was added. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. Saturated $NH_4Cl_{(aq)}$ (20 mL) and saturated $NaHCO_{3(aq)}$ (20 mL) were added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 4:1 and then 1:1 hexane-EtOAc as eluent gave Weinreb amide **136** (869 mg, 74%) as a yellow oil, R_F (4:1 hexane-EtOAc) 0.21; IR (ATR) 2970, 2936, 1636 (C=O), 1447, 1413, 1377, 977, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H, Ph), 7.48–7.37 (m, 3H, Ph), 3.55 (s, 3H, OMe), 3.36 (s, 3H, NMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1 (C=O), 134.2 (*ipso*-Ph), 130.7 (Ph), 128.3 (Ph), 128.1 (Ph), 61.2 (OMe), 33.3 (NMe); MS (ESI) *m/z* 166 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_9H_{11}NO_2$ $(M + H)^+$ 166.0863, found 166.0862 (+0.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[66]

Lab book reference: **GH-1-1**

N-Methoxy-*N*-methylpyridine-3-carboxamide 179



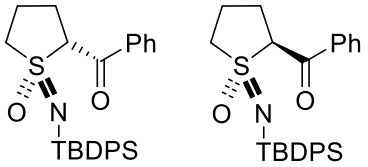
179

Et_3N (6.27 mL, 45 mmol, 3.0 eq.) was added to a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.46 g, 15.0 mmol, 1.0 eq.) in CH_2Cl_2 (20 mL) at rt under Ar. The resulting solution was cooled to 0 °C. Then, nicotinoyl chloride hydrochloride **178** (2.67 g, 15.0 mmol, 1.0 eq.) was added. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (40 mL) and saturated $NaHCO_{3(aq)}$ (40 mL) were added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave Weinreb amide **179**

(1.42 g, 57%) as a clear oil, R_F (EtOAc) 0.19; IR (ATR) 2934, 1642 (C=O), 1590, 1414, 1383, 979, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.0 Hz, 1H, Ar), 8.69 (dd, *J* = 1.5, 5.0 Hz, 1H, Ar), 8.05–8.00 (m, 1H, Ar), 7.36 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 3.56 (s, 3H, OMe), 3.40 (s, 3H, NMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.6 (C=O), 151.6 (Ar), 149.5 (Ar), 136.3 (Ar), 130.0 (Ar), 123.1 (Ar), 61.4 (OMe), 33.3 (NMe); MS (ESI) *m/z* 167 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_8H_{10}N_2O_2$ $(M + H)^+$ 167.0815, found 167.0820 (–2.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[71]

Lab book reference: **GH-1-78-2**

2-Benzoyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thiolan-1-one *cis*-180 and *trans*-180



cis-**180** *trans*-**180**

Using general procedure A, *N*-TBDPS sulfoximine **146** (1.86 g, 5.2 mmol, 1.0 eq.), *n*-BuLi (2.49 mL of a 2.3 M solution in hexanes, 5.72 mmol, 1.1 eq.) and Weinreb amide **136** (1.03 mL, 6.76 mmol, 1.3 eq.) in THF (50 mL) gave the crude product which contained a 75:25 mixture (by ^1H NMR spectroscopy) of keto-sulfoximines *cis*-**180** and *trans*-**180**. Purification by flash column chromatography on silica with 97:3 and then 9:1 hexane-EtOAc as eluent gave keto-sulfoximine *cis*-**180** (1.43 g, 60%) as a white solid, mp 120–122 °C, R_F (6:4 hexane-EtOAc) 0.60; IR (ATR) 3068, 2929, 2855, 1683 (C=O), 1299, 1153, 1108, 734, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94–7.90 (m, 2H, Ph), 7.80–7.76 (m, 2H, Ph), 7.74–7.70 (m, 2H, Ph), 7.56–7.50 (m, 1H, Ph), 7.46–7.32 (m, 8H, Ph), 4.73 (dd, *J* = 8.0, 6.0 Hz, 1H, SCH), 3.01–2.92 (m, 1H, CH), 2.87–2.79 (m, 1H, CH), 2.76–2.65 (m, 1H, CH), 2.36–2.25 (m, 1H, CH), 2.22–2.05 (m, 2H, CH), 1.08 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 191.9 (C=O), 136.9 (*ipso*-Ph), 135.9 (*ipso*-Ph), 135.8 (Ph), 135.7 (Ph), 133.7 (Ph), 129.5 (Ph), 129.4 (Ph), 128.7 (Ph), 127.81 (Ph), 127.77 (Ph), 69.1 (SCH), 56.5 (SCH_2), 27.2 (CMe_3), 26.0 (CH_2), 21.5 (CH_2), 19.5 (CMe_3) (two Ph resonances not resolved); MS (ESI) *m/z* 462 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{31}NO_2SSi$ $(M + H)^{+;}$ 462.1918, found 462.1924 (–1.4 ppm error) and keto-sulfoximine *trans*-**180** (470 mg, 20%) as a white solid, mp 112–114 °C, R_F (6:4 hexane-

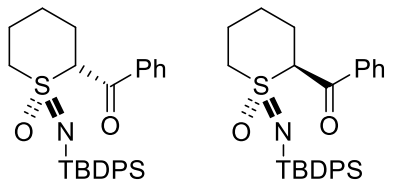
EtOAc) 0.53; IR (ATR) 3069, 2955, 2930, 1684 (C=O), 1307, 1255, 1217, 1175, 1157, 1109, 702, 690, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19–8.15 (m, 2H, Ph), 7.62–7.56 (m, 1H, Ph), 7.52–7.44 (m, 6H, Ph), 7.37–7.22 (m, 6H, Ph), 4.97 (dd, *J* = 7.5, 7.5 Hz, 1H, SCH), 2.83–2.73 (m, 1H, CH), 2.73–2.65 (m, 1H, CH), 2.55 (ddd, *J* = 12.5, 10.0, 7.0 Hz, 1H, SCH), 2.33–2.17 (m, 2H, CH), 2.17–2.06 (m, 1H, CH), 0.75 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 191.6 (C=O), 137.2 (*ipso*-Ph), 135.70 (*ipso*-Ph), 135.63 (Ph), 135.59 (Ph), 133.8 (Ph), 129.6 (Ph), 129.2 (Ph), 128.8 (Ph), 127.53 (Ph), 127.46 (Ph), 68.6 (SCH), 56.4 (SCH_2), 26.8 (C*Me*$_3$), 25.8 (CH_2), 21.9 (CH_2), 19.1 (*C*Me$_3$) (two Ph resonances not resolved); MS (ESI) *m/z* 462 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{31}NO_2SSi$ $(M + H)^+$ 462.1918, found 462.1923 (–1.2 ppm error). The stereochemistry of keto-sulfoximines *cis*-**180** and *trans*-**180** was assigned by analogy with related examples.

Lab book reference: **GH-2-31**

Using general procedure A, *N*-TBDPS sulfoximine **146** (326 mg, 0.91 mmol, 1.0 eq.), *n*-BuLi (0.40 mL of a 2.5 M solution in hexanes, 1.0 mmol, 1.1 eq.) and Weinreb amide **136** (0.28 mL, 1.82 mmol, 2.0 eq) in THF (10 mL) gave the crude product which contained a 55:45 mixture (by ^1H NMR spectroscopy) of keto-sulfoximines *cis*-**180** and *trans*-**180**. Purification by flash column chromatography on silica with hexane and then 9:1 hexane-EtOAc as eluent gave keto-sulfoximine *cis*-**180** (185 mg, 40%) as a white solid and keto-sulfoximine *trans*-**180** (147 mg, 32%) as a white solid.

Lab book reference: **GH-1-12**

2-Benzoyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thian-1-one *cis*-181 and *trans*-181



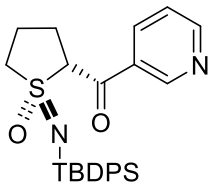
cis-**181** *trans*-**181**

Using general procedure A, *N*-TBDPS sulfoximine **147** (2.02 g, 5.44 mmol, 1.0 eq.), *n*-BuLi (2.60 mL of a 2.3 M solution in hexanes, 5.99 mmol, 1.1 eq.) and Weinreb amide **136** (1.08 mL, 7.07 mmol, 1.3 eq.) in THF (50 mL) gave the crude product which contained a 75:25 mixture (by ^1H NMR spectroscopy) of keto sulfoximines *cis*-**181** and

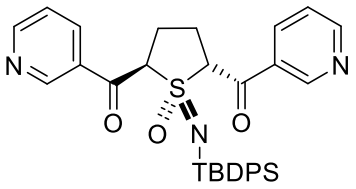
trans-**181**. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave keto-sulfoximine *cis*-**181** (1.48 g, 57%) as a white solid, mp 140–142 °C, R_F (6:4 hexane-EtOAc) 0.63; IR (ATR) 3069, 2929, 2855, 1677 (C=O), 1448, 1427, 1283, 1142, 1108, 909, 821, 729, 699, 685, 601, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.73 (m, 4H, Ph), 7.58–7.54 (m, 2H, Ph), 7.54–7.49 (m, 1H, Ph), 7.46–7.31 (m, 8H, Ph), 4.55–4.50 (m, 1H, SCH), 3.50–3.39 (m, 1H, SCH), 2.92–2.82 (m, 1H, SCH), 2.32–2.05 (m, 4H, CH), 2.05–1.91 (m, 1H, CH), 1.62–1.51 (m, 1H, CH), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 194.3 (C=O), 136.74 (*ipso*-Ph), 136.71 (*ipso*-Ph), 136.53 (*ipso*-Ph), 135.87 (Ph), 135.83 (Ph), 133.6 (Ph), 129.3 (Ph), 128.9 (Ph), 128.6 (Ph), 127.7 (Ph), 66.4 (SCH), 54.7 (SCH_2), 28.3 (CH_2), 27.3 (C*Me*$_3$), 25.0 (CH_2), 20.5 (CH_2), 19.3 (*C*Me_3) (two Ph resonances not resolved); MS (ESI) *m/z* 476 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{33}NO_2SSi$ $(M + H)^+$ 476.2074, found 476.2080 (–1.2 ppm error) and keto-sulfoximine *trans*-**181** (423 mg, 16%) as a white solid, 136–138 °C, R_F (6:4 hexane-EtOAc) 0.55; IR (ATR) 3069, 2929, 2855, 1679 (C=O), 1321, 1304, 1288, 1141, 1108, 821, 731, 701, 603, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H, Ph), 7.62 (d, *J* = 7.0 Hz, 2H, Ph), 7.59–7.53 (m, 3H, Ph), 7.46–7.39 (m, 2H, Ph), 7.35–7.29 (m, 2H, Ph), 7.28–7.23 (m, 4H, Ph), 4.85–4.78 (m, 1H, SCH), 3.32 (ddd, *J* = 13.5, 8.5, 5.0 Hz, 1H, SCH), 2.80–2.69 (m, 1H, SCH), 2.42–2.21 (m, 2H, CH), 2.03–1.84 (m, 3H, CH), 1.59–1.48 (m, 1H, CH), 0.93 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.7 (C=O), 136.8 (*ipso*-Ph), 136.6 (*ipso*-Ph), 136.3 (*ipso*-Ph), 135.70 (Ph), 135.67 (Ph), 133.7 (Ph), 129.2 (Ph), 129.05 (Ph), 129.02 (Ph), 128.7 (Ph), 127.4 (Ph), 67.6 (SCH), 55.1 (SCH_2), 28.2 (CH_2), 27.1 (C*Me*$_3$), 24.4 (CH_2), 20.4 (CH_2), 19.3 (*C*Me_3) (one Ph resonance not resolved); MS (ESI) *m/z* 476 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{33}NO_2SSi$ $(M + H)^+$ 476.2074, found 476.2083 (–1.9 ppm error). The stereochemistry of keto-sulfoximines *cis*-**181** and *trans*-**181** was assigned by analogy with related examples.

Lab book reference: **GH-2-46**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(pyridine-3-carbonyl)-1λ⁶-thiolan-1-one *cis*-183 and 1-[(*tert*-Butyldiphenylsilyl)imino]-2-[1-(pyridin-3-yl)ethenyl]-5-(pyridine-3-carbonyl)-1λ⁶-thiolan-1-one *trans,cis*-184



cis-**183**



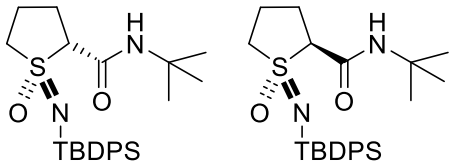
trans,cis-**184**

Using general procedure A, *N*-TBDPS sulfoximine **146** (1.00 g, 2.80 mmol, 1.0 eq.), *n*-BuLi (1.34 mL of a 2.3 M solution in hexanes, 3.08 mmol, 1.1 eq.) and Weinreb amide **179** (0.85 mL, 5.60 mmol, 2.0 eq.) in THF (28 mL) gave the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of keto-sulfoximines *cis*-**183** and *trans,cis*-**184**. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave keto-sulfoximine *cis*-**183** (920 mg, 71%) as a white solid, mp 128–130 °C; R_F (1:1 hexane-EtOAc) 0.29; IR (ATR) 2930, 2856, 1688 (C=O), 1586, 1427, 1298, 1255, 1172, 1158, 1108, 869, 729, 700, 604, 500, 488 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (d, *J* = 2.0 Hz, 1H, Ar), 8.77 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 8.39 (ddd, *J* = 8.0, 2.0, 2.0 Hz, 1H, Ar), 7.53–7.49 (m, 2H, Ar), 7.49–7.44 (m, 2H, Ar), 7.41–7.32 (m, 3H, Ar), 7.32–7.25 (m, 4H, Ar), 4.92 (dd, *J* = 7.5, 7.5 Hz, 1H, SCH), 2.85–2.67 (m, 2H, SCH, CH), 2.59 (ddd, *J* = 12.5, 10.0, 7.0 Hz, 1H, SCH), 2.37–2.07 (m, 3H, CH), 0.77 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 190.9 (C=O), 153.9 (Ar), 150.7 (Ar), 136.6 (Ar), 135.5 (Ar), 135.4 (Ar), 135.34 (*ipso*-Ar), 135.28 (*ipso*-Ar), 132.4 (*ipso*-Ar), 129.32 (Ar), 129.29 (Ar), 127.56 (Ar), 127.53 (Ar), 123.6 (Ar), 69.0 (SCH), 56.5 (SCH_2), 26.7 (CMe_3), 25.5 (CH_2), 21.8 (CH_2), 19.1 (CMe_3); MS (ESI) *m/z* 463 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_2O_2SSi$ $(M + H)^+$ 463.1870, found 463.1876 (–1.3 ppm error) and keto-sulfoximine *trans,cis*-**184** (96 mg, 6%) as a white solid, mp 122–124 °C; R_F (1:1 hexane-EtOAc) 0.17; IR (ATR) 2961, 2857, 1683 (C=O), 1585, 1420, 1317, 1236, 1164, 1109, 909, 820, 729, 698, 500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, *J* = 2.0 Hz, 1H, Ar), 8.81 (dd, *J* = 4.5, 1.0 Hz, 1H, Ar), 8.71 (d, *J* = 2.0 Hz, 1H, Ar), 8.68–8.64 (m, 1H, Ar), 8.39–8.35 (m, 1H, Ar), 7.67–7.62 (m, 2H, Ar), 7.54 (d, *J* = 7.0 Hz, 2H, Ar), 7.46–7.35 (m, 6H, Ar), 7.30–7.24 (m, 2H, Ar), 7.08 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 5.10 (dd, *J* = 8.0, 8.0 Hz, 1H, SCH), 4.54 (dd, *J* = 8.0, 3.5 Hz, 1H, SCH), 3.10–2.98 (m, 1H, CH), 2.71–2.55 (m, 2H, CH), 2.46–2.35 (m, 1H, CH), 0.81 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.2 (C=O), 189.2 (C=O), 154.2 (Ar), 153.8 (Ar), 150.8 (Ar), 150.1 (Ar), 136.9 (Ar), 136.2 (Ar), 135.61 (Ar), 135.52 (Ar), 135.1 (*ipso*-Ar), 134.4 (*ipso*-Ar), 131.7 (*ipso*-Ar), 129.86 (Ar), 129.76 (Ar), 127.95 (Ar), 127.87 (Ar), 123.6 (Ar), 123.4 (Ar), 69.4 (SCH), 68.9 (SCH), 26.7 (CMe_3), 23.6 (CH_2), 23.3 (CH_2), 19.3 (CMe_3)

(one *ipso*-Ar resonance not resolved); MS (ESI) *m/z* 568 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{32}H_{34}N_3O_3SSi$ $(M + H)^+$ 568.2085, found 568.2096 (–2.1 ppm error). The stereochemistry of keto-sulfoximines *cis*-**183** and *trans,cis*-**184** was assigned by analogy with related examples.

Lab book reference: **GH-2-10**

N-*tert*-Butyl-1-[(*tert*-butyldiphenylsilyl)imino]-1-oxo-1λ⁶-thiolane-2-carboxamide *cis*-187 and *trans*-187



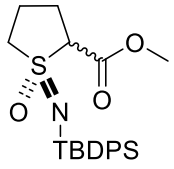
cis-**187** *trans*-**187**

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and *tert*-butyl isocyanate (0.11 mL, 1.0 mmol, 2.0 eq) gave the crude product which contained a 45:55 mixture (by ^{1}H NMR spectroscopy) of diastereomeric amido sulfoximines *cis*-**187** and *trans*-**187**. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave amido sulfoximine **187a** (65 mg, 29%) as a clear oil, R_F (1:1 hexane-EtOAc) 0.60; IR (ATR) 3355 (NH), 3070, 2962, 2856, 1685 (C=O), 1518, 1454, 1427, 1390, 1362, 1302, 1225, 1159, 1109, 821, 737, 702, 805, 502 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 4H, Ph), 7.43–7.34 (m, 6H, Ph), 5.87 (s, 1H, NH), 3.29 (dd, *J* = 8.0, 8.0 Hz, 1H, SCH), 2.96–2.79 (m, 2H, SCH), 2.45–2.33 (m, 1H, CH), 2.24–2.10 (m, 2H, CH), 2.02–1.89 (m, 1H, CH), 1.28 (s, 9H, $NCMe_3$), 1.08 (s, 9H, $SiCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9 (C=O), 135.85 (*ipso*-Ph), 135.83 (*ipso*-Ph), 135.69 (Ph), 135.68 (Ph), 129.6 (Ph), 127.8 (Ph), 68.6 (SCH), 55.3 (SCH_2), 52.0 (N*C*Me$_3$), 28.7 (NC*Me*$_3$), 27.2 (SiC*Me*$_3$), 25.5 (CH_2), 20.2 (CH_2), 19.3 (Si*C*Me$_3$) (two Ph signals not resolved); MS (ESI) *m/z* 457 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{25}H_{36}N_2O_2SSi$ $(M + H)^+$ 457.2340, found 457.2343 (–0.8 ppm error) and amido sulfoximine **187b** (90 mg, 39%) as a clear oil, R_F (1:1 hexane-EtOAc) 0.43; IR (ATR) 3348 (NH), 2962, 2931, 2856, 1678 (C=O), 1545, 1360, 1298, 1253, 1104, 821, 732, 702, 604, 501, 489 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 4H, Ph), 7.41–7.31 (m, 6H, Ph), 6.09 (s, 1H, NH), 3.60–3.50 (m, 1H, SCH), 2.77–2.66 (m, 2H, SCH), 2.53–2.41

(m, 1H, CH), 2.35–2.23 (m, 1H, CH), 2.16–1.92 (m, 2H, CH), 1.19 (s, 9H, $NCMe_3$), 1.08 (s, 9H, $SiCMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1 (C=O), 135.90 (*ipso*-Ph), 135.85 (Ph), 135.74 (Ph), 135.68 (*ipso*-Ph), 129.4 (Ph), 129.3 (Ph), 127.7 (Ph), 69.0 (SCH), 54.4 (SCH_2), 52.0 ($NCMe_3$), 28.7 ($NCMe_3$), 27.3 ($SiCMe_3$), 25.7 (CH_2), 20.4 (CH_2), 19.5 ($SiCMe_3$) (one Ph resonance not resolved); MS (ESI) *m/z* 457 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{25}H_{36}N_2O_2SSi$ $(M + H)^+$ 457.2340, found 457.2338 (+0.3 ppm error).

Lab book reference: **GH-2-27**

Methyl 1-[(*tert*-butyldiphenylsilyl)imino]-1-oxo-1λ⁶-thiolane-2-carboxylate 189

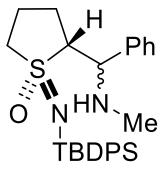


189

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl chloroformate (0.077 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with hexane and then 9:1 hexane-EtOAc as eluent gave a 70:30 mixture (by ^1H NMR spectroscopy) of diastereomeric sulfoximines **189**, MS (ESI) *m/z* 416 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_3SSi$ $(M + H)^+$ 416.1710, found 416.1710 (–1.4 ppm error). Diagnostic signals: ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (dd, *J* = 7.5, 5.5 Hz, 1H, SCH), 3.93 (dd, *J* = 7.5, 5.5 Hz, SCH).

Lab book reference: **GH-1-49-3**

1-{[Diphenyl(trimethylsilyl)methyl]imino}-2-[(methylamino)(phenyl)methyl]-1λ⁶-thiolan-1-one 190



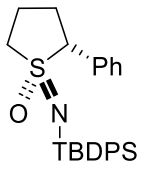
190

Using general procedure A, *N*-TBDPS sulfoximine **146** (179 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and *N*-benzylidene

methylamine (0.12 mL, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 95:5 and then 8:2 hexane-EtOAc as eluent gave a single diastereomeric amino sulfoximine **190** (26 mg, 11%) as a yellow oil, R_F (1:1 hexane-EtOAc) 0.40; IR (ATR) 3068, 2930, 2854, 1288, 1251, 1153, 1127, 1106, 820, 736, 699, 650, 602, 558, 532, 500, 487 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.78 (m, 4H, Ph), 7.43–7.37 (m, 6H, Ph), 7.35–7.31 (m, 4H, Ph), 7.31–7.26 (m, 1H, Ph), 3.88 (d, *J* = 10.0 Hz, 1H, PhC*H*NH), 3.22–3.13 (m, 1H, SCH), 2.85–2.76 (m, 1H, SCH), 2.59–2.49 (m, 1H, SCH), 2.23 (s, 1H, NH), 2.07 (s, 3H, HN*Me*), 1.86–1.76 (m, 2H, CH), 1.59–1.41 (m, 2H, CH), 1.15 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.5 (*ipso*-Ph), 136.4 (*ipso*-Ph), 136.1 (*ipso*-Ph), 135.9 (Ph), 135.6 (Ph), 129.4 (Ph), 128.7 (Ph), 128.4 (Ph), 128.0 (Ph), 127.74 (Ph), 127.70 (Ph), 70.1 (SCH), 65.5 (Ph*C*HNH), 55.9 (SCH_2), 34.2 (HNMe), 28.3 (CH_2), 27.3 (C*Me*$_3$), 20.7 (CH_2), 19.5 (*C*Me_3) (one Ph resonance not resolved); MS (ESI) *m/z* 477 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}NOSSi_2$ $(M + H)^+$ 477.2390, found 477.2393 (–0.6 ppm error).

Lab book reference: **GH-2-24**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-phenyl-1λ⁶-thiolan-1-one *cis*-198



cis-**198**

Preparation of a solution of CuCN•2LiCl in THF: THF (2 mL) was added to dry LiCl (85 mg, 2.0 mmol, 4.0 eq.) at rt under Ar and the resulting solution was stirred at rt for 30 min. CuCN (90 mg, 1.0 mmol, 2.0 eq.) was added to the solution and the resulting solution was stirred at rt for 30 min to give a 0.5 M solution of CuCN•2LiCl in THF.

n-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine **146** (179 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min and then CuCN·2LiCl (1 mL of the freshly prepared 0.5 M solution in THF, 0.5 mmol, 1.0 eq) was added. The resulting solution was allowed to warm to –35 °C and stirred at –35 °C for 15 min. Then, Ph_2IPF_6 (213 mg, 0.5 mmol, 1.0 eq.) was added. The resulting solution was stirred at –35 °C for 15 min and then allowed to warm to rt and stirred at rt for 16 h. Then,

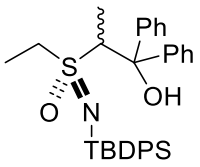
saturated $NH_4Cl_{(aq)}$ (2 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 95:5 as eluent gave a single diastereomeric phenyl sulfoximine *cis*-**198** (88 mg, 41%) as a white solid, mp 88–90 °C, R_F (8:2 hexane-EtOAc) 0.32; IR (ATR) 3068, 2929, 2854, 1427, 1302, 1262, 1238, 1156, 1103, 821, 736, 696, 602, 498 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H, Ph), 7.41–7.28 (m, 11H, Ph), 4.04 (dd, *J* = 12.0, 7.5 Hz, 1H, SCH), 3.09–2.93 (m, 2H, SCH), 2.49–2.32 (m, 2H, CH), 2.29–2.17 (m, 1H, CH), 2.12–1.97 (m, 1H, CH), 1.00 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.55 (*ipso*-Ph), 136.49 (*ipso*-Ph), 135.63 (Ph), 135.62 (Ph), 131.7 (*ipso*-Ph), 129.8 (Ph), 129.1 (Ph), 128.6 (Ph), 128.5 (Ph), 127.5 (Ph), 70.6 (SCH), 54.8 (SCH_2), 28.7 (CH_2), 27.1 (CMe_3), 20.2 (CH_2), 19.3 (CMe_3) (two Ph resonances not resolved); MS (ESI) *m/z* 434 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{31}NOSSi$ $(M + H)^+$ 434.1968, found 434.1956 (+2.9 ppm error).

Crystal structure determination of *cis*-**198**

$C_{26}H_{31}NOSSi$, *M* = 433.67, monoclinic, *a* = 11.90777(15), *b* = 21.8687(2), *c* = 9.87464(13) Å, *β* = 110.2919(15) °, *U* = 2411.84(6) $Å^3$, *T* = 110.00(10) K, space group $P2_1$, Z = 4, *μ*(Mo-Kα) = 1.787 mm^{-1}, 9179 reflection measured, 4301 unique (R_{int} = 0.0149) which were used in calculation. The final R1 was 0.0290 (I≥2σ) and wR2 was 0.0769 (all data).

Lab book reference: **GH-2-63**

[(*tert*-Butyldiphenylsilyl)imino](ethyl)(1-hydroxy-1,1-diphenylpropan-2-yl)-λ⁶-sulfanone 199



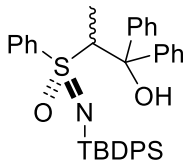
199

Using general procedure A, *N*-TBDPS sulfoximine **149** (180 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude

product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave a single diastereomeric alcohol **199** (198 mg, 73%) as a white solid, mp 54–56 °C; R_F (8:2 hexane-EtOAc) 0.45; IR (ATR) 3388 (OH), 2931, 2856, 1450, 1427, 1308, 1136, 1109, 740, 702, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.69 (m, 2H, Ph), 7.66–7.62 (m, 4H, Ph), 7.58–7.54 (m, 2H, Ph), 7.40–7.26 (m, 10H, Ph), 7.21–7.15 (m, 2H, Ph), 6.29 (s, 1H, COH), 4.18 (q, *J* = 7.0 Hz, 1H, SCH), 2.17 (dq, *J* = 14.5, 7.5 Hz, 1H, SCH), 1.67 (dq, *J* = 14.5, 7.5 Hz, 1H, SCH), 1.45 (d, *J* = 7.0 Hz, 3H, SCH*Me*), 1.04 (s, 9H, CMe_3), 0.91 (t, *J* = 7.5 Hz, 3H, SCH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.0 (*ipso*-Ph), 145.7 (*ipso*-Ph), 136.2 (*ipso*-Ph), 135.92 (*ipso*-Ph), 135.79 (Ph), 135.71 (Ph), 129.34 (Ph), 129.31 (Ph), 128.5 (Ph), 128.3 (Ph), 127.64 (Ph), 127.55 (Ph), 127.3 (Ph), 126.9 (Ph), 126.1 (Ph), 125.2 (Ph), 79.0 (COH), 63.0 (SCH), 51.8 (SCH_2), 27.3 (C*Me*$_3$), 19.6 (*C*Me_3), 11.7 (SCH*Me*), 8.9 (SCH_2*Me*); MS (ESI) *m/z* 542 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{33}H_{39}NO_2SSi$ $(M + H)^+$ 542.2544, found 542.2549 (–0.9 ppm error).

Lab book reference: **GH-2-58**

2-{[(*tert*-Butyldiphenylsilyl)imino](oxo)phenyl-λ⁶-sulfanyl}-1,1-diphenylpropan-1-ol 200



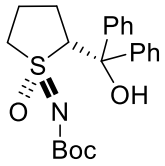
200

Using general procedure A, *N*-TBDPS sulfoximine **150** (204 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained an 85:15 mixture (by ^1H NMR spectroscopy) of diastereomeric alcohols **200a** and **200b**. Purification by flash column chromatography on silica with 99:1 and then 98:2 hexane-EtOAc as eluent gave a single diastereomeric alcohol **200a** (206 mg, 70%) as a white solid, mp 158–160 °C, R_F (8:2 hexane-EtOAc) 0.45; IR (ATR) 3408 (OH), 3068, 2930, 2856, 1448, 1261, 1141, 1108, 907, 732, 699, 646, 604, 566, 497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H, Ph), 7.52 (d, *J* = 7.5 Hz, 2H, Ph), 7.47–7.40 (m, 2H, Ph), 7.40–7.36 (m, 2H, Ph), 7.32–7.26 (m, 1H, Ph), 7.26–7.20 (m, 6H, Ph), 7.20–7.04 (m, 5H, Ph), 7.04–6.92 (m, 5H, Ph), 6.33 (s, 1H, CHO*H*), 4.44 (q, *J* = 7.0

Hz, 1H, SCH), 1.43 (d, *J* = 7.0 Hz, 3H, CH*Me*), 1.01 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 146.2 (*ipso*-Ph), 144.9 (*ipso*-Ph), 143.1 (*ipso*-Ph), 135.73 (Ph), 135.70 (Ph), 135.63 (*ipso*-Ph), 135.2 (*ipso*-Ph), 131.4 (Ph), 129.03 (Ph), 128.86 (Ph), 128.4 (Ph), 128.2 (Ph), 127.75 (Ph), 127.71 (Ph), 127.4 (Ph), 127.1 (Ph), 126.73 (Ph), 126.72 (Ph), 126.2 (Ph), 124.9 (Ph), 79.3 (COH), 67.9 (SCH), 27.2 (CMe_3), 19.4 (CMe_3), 12.5 (SCH*Me*); MS (ESI) *m/z* 590 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{37}H_{39}NO_2SSi$ $(M + H)^+$ 590.2544, found 590.2540 (+0.6 ppm error). The minor diastereomeric alcohol **200b** was not isolated. Diagnostic signals for minor diastereomeric alcohol **200b**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.0 Hz, 1H, SCH), 1.47 (d, *J* = 7.0 Hz, 3H, CH*Me*).

Lab book reference: **GH-2-67**

tert-Butyl *N*-[2-(hydroxydiphenylmethyl)-1-oxo-1λ⁶-thiolan-1-ylidene]carbamate *cis*-202



cis-**202**

Using general procedure A, *N*-Boc sulfoximine **153** (110 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc to 9:1 hexane-EtOAc as eluent gave alcohol *cis*-**202** (142 mg, 71%) as a white solid, mp 200–202 °C, R_F (1:1 hexane-EtOAc) 0.43; IR (ATR) 3497 (OH), 2978, 1659 (C=O), 1449, 1366, 1280, 1247, 1152, 909, 861, 733, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H, Ph), 7.40–7.33 (m, 4H, Ph), 7.30–7.23 (m, 3H, Ph), 7.19–7.15 (m, 1H, Ph), 4.74 (dd, *J* = 9.0, 9.0 Hz, 1H, SCH), 4.23–4.16 (m, 1H, SCH), 4.11 (s, 1H, COH), 3.16 (ddd, *J* = 13.0, 12.0, 7.5, Hz, 1H, SCH), 2.41–2.31 (m, 1H, CH), 2.31–2.20 (m, 1H, CH), 2.09–1.95 (m, 1H, CH), 1.90–1.82 (m, 1H, CH), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6MHz, $CDCl_3$) δ 158.4 (C=O), 144.7 (*ipso*-Ph), 144.4 (*ipso*-Ph), 128.7 (Ph), 128.6 (Ph), 127.9 (Ph), 127.2 (Ph), 125.9 (Ph), 125.0 (Ph), 81.0 (CMe_3), 78.9 (COH), 67.4 (SCH), 53.5 (SCH_2), 28.3 (CH_2), 26.7 (CH_2), 21.3 (CH_2); MS (ESI) *m/z* 402 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{27}NO_4S$ $(M + H)^+$ 402.1734, found 402.1727 (+1.7 ppm

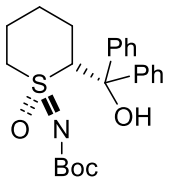
error). The stereochemistry of alcohol *cis*-**202** was assigned by synthesis from *N*-TBDPS sulfoximine *cis*-**157**.

Lab book reference: **GH-1-62-3**

TBAF (0.66 mL of a 1 M solution in THF, 0.66 mmol, 2.0 eq.) was added dropwise to a stirred solution of the *N*-TBDPS sulfoximine *cis*-**157** (178 mg, 0.33 mmol, 1.0 eq.) in THF (5 mL) at rt °C under Ar. The resulting solution was stirred at rt for 48 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave NH sulfoximine *cis*-**204** (90 mg, 90%) as a white solid, mp 180–182 °C, R_F (9:1 EtOAc-MeOH) 0.53; IR (ATR) 3429 (NH/OH), 3323 (NH/OH), 3059, 1493, 1448, 1201, 1177, 1111, 995, 962, 909, 733, 699, 657, 551, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (m, 2H, Ph), 7.51–7.45 (m, 2H, Ph), 7.41–7.35 (m, 2H, Ph), 7.32–7.24 (m, 3H, Ph), 7.21–7.15 (m, 1H, Ph), 5.13 (s, 1H, COH), 4.31 (dd, *J* = 10.5, 7.5 Hz, 1H, SCH), 3.37–3.28 (m, 1H, SCH), 3.13 (dd, *J* = 13.0, 9.5, 7.5 Hz, 1H, SCH), 2.53 (s, 1H, NH), 2.52–2.42 (m, 1H, SCH), 2.23–2.13 (m, 1H, CH), 2.13–1.97 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (*ipso*-Ph), 144.6 (*ipso*-Ph), 128.7 (Ph), 128.5 (Ph), 127.8 (Ph), 127.1 (Ph), 125.6 (Ph), 124.9 (Ph), 77.5 (COH), 71.3 (SCH), 57.1 (SCH_2), 27.5 (CH_2), 20.6 (CH_2); MS (ESI) *m/z* 302 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_2S$ $(M + H)^+$ 302.1209, found 302.1206 (+0.9 ppm error). A solution of potassium *tert*-butoxide (44 mg. 0.39 mmol, 1.3 eq.) in THF (1 mL) was added to a stirred solution of NH sulfoximine *cis*-**204** (90 mg, 0.30 mmol, 1.0 eq.) in THF (1 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a solution of Boc_2O (131 mg, 0.60 mmol, 2.0 eq.) in THF (1.5 mL) was added. The resulting solution was stirred at 0 °C for 1 h. The solution was allowed to warm to rt and stirred at rt for 72 h. Saturated $NH_4Cl_{(aq)}$ (2 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave alcohol *cis*-**202** (117 mg, 95%) as a white solid.

Lab book reference: **GH-2-20-2**

***tert*-Butyl *N*-[2-(hydroxydiphenylmethyl)-1-oxo-1λ⁶-thian-1-ylidene]carbamate *cis*-203**

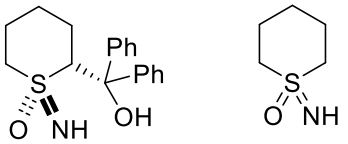


cis-**203**

Using general procedure A, *N*-Boc sulfoximine **154** (117 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc and then 9:1 hexane-EtOAc as eluent gave alcohol *cis*-**203** (156 mg, 75%) as a white solid, mp 80–82 °C, R_F (1:1 hexane-EtOAc) 0.37; IR (ATR) 3497 (OH), 3288 (OH), 2977, 1652 (C=O), 1449, 1366, 1282, 1251, 1151, 908, 861, 731, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H, Ph), 7.47–7.42 (m, 2H, Ph), 7.34–7.28 (m, 4H, Ph), 7.25–7.19 (m, 2H, Ph) 5.05 (s, 1H, OH), 4.81 (dd, *J* = 9.5, 3.5 Hz, 1H, SCH), 3.57 (ddd, *J* = 14.0, 8.5, 5.5 Hz, 1H, SCH), 3.47 (ddd, *J* = 14.0, 5.5, 5.5 Hz, 1H, SCH), 2.16–2.03 (m, 3H, CH), 1.99–1.84 (m, 2H, CH), 1.52–1.43 (m, 1H, CH) 1.41 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.9 (C=O), 145.2 (*ipso*-Ph), 143.9 (*ipso*-Ph), 128.5 (Ph), 128.4 (Ph), 127.6 (Ph), 127.3 (Ph), 126.1 (Ph), 125.9 (Ph) 80.43 (*C*Me_3/COH), 80.36 (*C*Me_3/COH), 66.0 (SCH), 53.2 (SCH_2), 28.3 (C*Me*$_3$), 26.6 (CH_2), 23.3 (CH_2), 22.8 (CH_2); MS (ESI) *m/z* 416 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{23}H_{29}NO_4S$ $(M + H)^+$ 416.1890, found 416.1894 (–1.0 ppm error). The stereochemistry of alcohol *cis*-**203** was assigned by analogy with related examples.

Lab book reference: **GH-1-61-3**

Attempted synthesis of 2-(Hydroxydiphenylmethyl)-1-imino-1λ⁶-thian-1-one *cis*-205



cis-**205** **152**

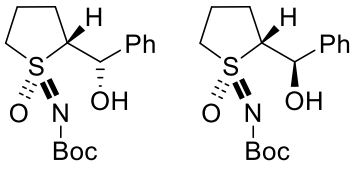
TBAF (0.24 mL of a 1 M solution in THF, 0.24 mmol, 2.0 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine *cis*-**158** (67 mg, 0.12 mmol, 1.0 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 48 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave unsubsstituted NH sulfoximine **152** (10 mg, 63%) as a yellow oil and none of the desired product *cis*-**205**.

Lab book reference: **GH-2-15**

TBAF (0.75 mL of a 1 M solution in THF, 0.75 mmol, 2.0 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine *cis*-**158** (207 mg, 0.37 mmol, 1.0 eq.) in THF (2 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave none of the desired product *cis*-**205**.

Lab book reference: **GH-2-48**

tert-Butyl _N_-{2-[hydroxy(phenyl)methyl]-1-oxo-1λ⁶-thiolan-1-ylidene}carbamate _cis,anti_-208 and _cis,syn_-208



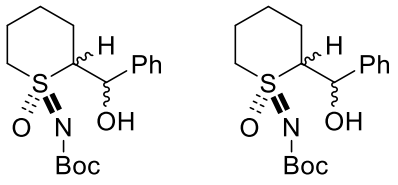
cis,anti-**208** *cis,syn*-**208**

Using general procedure A, *N*-Boc sulfoximine **153** (110 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of alcohols *cis,anti*-**208** and *cis,syn*-**208**. Purification by flash column chromatography on silica with 9:1 and then 8:2 hexane-EtOAc as eluent gave alcohol **208a** (51 mg, 31%) as a white solid, mp 126–128 °C, R_F (1:1 hexane-EtOAc) 0.36; IR (ATR) 3361 (OH), 2980, 1663 (C=O), 1453, 1392, 1367, 1291, 1250, 1213, 1153, 906, 856, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4H, Ph), 7.33–7.27 (m, 1H, Ph), 5.59 (br s, 1H, PhC*H*), 4.90 (d, *J* = 2.5 Hz, 1H, CHO*H*), 3.64–3.55 (m, 2H, SCH), 3.30–3.21 (m, 1H, SCH), 2.30–2.22 (m, 2H, CH), 2.21–2.09 (m, 1H, CH),

2.02–1.90 (m, 1H, CH), 1.50 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.7 (C=O), 140.2 (*ipso*-Ph), 128.8 (Ph), 128.1 (Ph), 125.7 (Ph), 81.4 (*C*Me_3), 70.4 (Ph*C*HOH), 67.6 (SCH), 53.8 (SCH_2), 28.3 (C*Me*$_3$), 21.8 (CH_2), 21.5 (CH_2); MS (ESI) *m/z* 348 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_4S$ $(M + Na)^+$ 348.1240, found 348.1230 (–3.0 ppm error) and alcohol **208b** (56 mg, 34%) as a white solid, mp 136–138 °C, R_F (1:1 hexane:EtOAc) 0.26; IR (ATR) 3496 (OH), 2976, 2931, 1654 (C=O), 1287, 1250, 1218, 1153, 1120, 898, 857, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.40 (m, 2H, Ph), 7.39–7.34 (m, 2H, Ph), 7.31–7.26 (m, 1H, Ph), 5.84 (d, *J* = 3.0 Hz, 1H, PhC*H*), 3.83–3.76 (m, 1H, SCH), 3.74–3.66 (m, 1H, SCH), 3.21 (d, *J* = 3.5 Hz, 1H, CHO*H*), 3.11 (ddd, *J* = 13.0, 11.0, 7.0 Hz, 1H, SCH), 2.60–2.48 (m, 1H, CH), 2.33–2.24 (m, 1H, CH), 2.03–1.89 (m, 2H, CH), 1.53 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.9 (C=O), 140.0 (*ipso*-Ph), 128.7 (Ph), 127.9 (Ph), 125.6 (Ph), 81.2 (*C*Me_3), 69.4 (Ph*C*HOH), 68.0 (SCH), 54.1 (SCH_2), 28.3 (C*Me*$_3$), 23.0 (CH_2), 21.1 (CH_2); MS (ESI) *m/z* 348 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_4S$ $(M + Na)^+$ 348.1240, found 348.1255 (+4.4 ppm error). The *cis* stereochemistry of *cis,anti*-**208** and *cis,syn*-**208** was assigned by analogy with related examples.

Lab book reference: **GH-2-3**

tert-Butyl *N*-{2-[hydroxy(phenyl)methyl]-1-oxo-1λ⁶-thian-1-ylidene}carbamate 209a and 209b



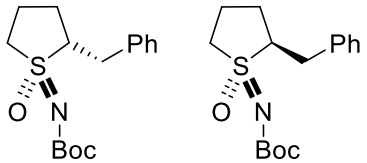
209a **209b**

Using general procedure A, *N*-Boc sulfoximine **154** (117 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 70:30 mixture (by ^1H NMR spectroscopy) of alcohols **209a** and **209b**. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave alcohol **209a** (82 mg, 48%) as a white solid, mp 194–196 °C, R_F (1:1 hexane-EtOAc) 0.47; IR (ATR) 3358 (OH), 2977, 2931, 1668 (C=O), 1452, 1367, 1283, 1242, 1197,

1152, 1098, 1065, 904, 889, 860, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.34 (m, 4H, Ph), 7.33–7.27 (m, 1H, Ph), 5.81 (s, 1H, PhC*H*), 4.96 (s, 1H, CHO*H*), 4.46 (brd, *J* = 14.0 Hz, 1H, SCH), 2.99 (ddd, *J* = 13.5, 12.0, 3.5 Hz, 1H, SCH), 2.90 (dd, *J* = 12.0, 3.0 Hz, 1H, SCH), 2.30–2.17 (m, 1H, CH), 2.15–2.06 (m, 1H, CH), 2.03–1.93 (m, 1H, CH), 1.93–1.82 (m, 2H, CH), 1.49 (s, 9H, CMe_3), 1.37–1.28 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5 (C=O), 139.9 (*ipso*-Ph), 128.6 (Ph), 127.9 (Ph), 126.1 (Ph), 81.0 (*C*Me_3), 68.3 (SCH), 67.1 (Ph*C*HOH), 51.1 (SCH), 28.3 (C*Me*$_3$), 24.4 (CH_2), 23.8 (CH_2), 22.3 (CH_2); MS (ESI) *m/z* 362 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_4S$ $(M + Na)^+$ 362.1396, found 362.1382 (+3.9 ppm error) and alcohol **209b** (39 mg, 23%) as a white solid, mp 188–190 °C, R_F (1:1 hexane-EtOAc) 0.39; IR (ATR) 3297 (OH), 2942, 1670 (C=O), 1279, 1268, 1251, 1210, 1153, 904, 856, 759, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 4H, Ph), 7.32–7.27 (m, 1H, Ph), 5.91 (s, 1H, PhC*H*), 3.71 (ddd, *J* = 14.5, 4.5, 4.5 Hz, 1H, SCH), 3.56 (dd, *J* = 10.5, 3.5 Hz, 1H, SCH), 3.38 (ddd, *J* = 14.5, 10.5, 5.5 Hz, 1H, SCH), 3.15 (s, 1H, CHO*H*), 2.26–2.17 (m, 1H, CH), 2.17–2.08 (m, 2H, CH), 1.99–1.89 (m, 1H, CH), 1.87–1.78 (m, 1H, CH), 1.51 (s, 9H, CMe_3), 1.43–1.31 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.6 (C=O), 139.6 (*ipso*-Ph), 128.6 (Ph), 127.9 (Ph), 125.9 (Ph), 80.8 (*C*Me_3), 69.0 (Ph*C*HOH), 65.0 (SCH), 51.6 (SCH_2), 28.3 (C*Me*$_3$), 23.14 (CH_2), 23.05 (CH_2), 21.2 (CH_2); MS (ESI) *m/z* 362 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_4S$ $(M + Na)^+$ 362.1396, found 362.1381 (–4.4 ppm error).

Lab book reference: **GH-2-4**

tert-Butyl _N_-(2-benzyl-1-oxo-1λ⁶-thiolan-1-ylidene)carbamate _cis_-210 and _trans_-210



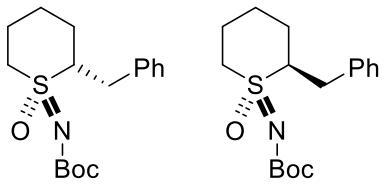
cis-**210** *trans*-**210**

Using general procedure A, *N*-Boc sulfoximine **153** (110 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained an 85:15 mixture (by ^1H NMR spectroscopy) of benzyl sulfoximines *cis*-**210** and *trans*-**210**. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave an 85:15 mixture of benzyl sulfoximines *cis*-**210** and *trans*-**210** (131 mg, 85%) as a

clear oil, R_F (1:1 hexane-EtOAc) 0.26; IR (ATR) 2975, 1653 (C=O), 1455, 1366, 1283, 1251, 1221, 1160, 895, 863, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H, Ph), 7.28–7.18 (m, 3H, Ph), 3.88–3.79 (m, 0.85H, SCH), 3.67–3.57 (m, 1.7H, SCH,CHPh), 3.72–3.36 (m, 0.6H, CH), 3.23 (ddd, *J* = 13.5, 10.0, 8.0 Hz, 0.85H, SCH), 2.80 (dd, *J* = 14.0, 11.0 Hz, 0.15H, CHPh), 2.72 (dd, *J* = 14.0, 12.0, 0.85H, CHPh), 2.32–2.12 (m, 2H, CH), 2.07–1.84 (m, 2H, CH), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.7 (C=O, *cis*-**210**), 159.3 (C=O, *trans*-**210**), 137.04 (*ipso*-Ph, *trans*-**210**), 136.99 (*ipso*-Ph, *cis*-**210**), 129.14 (Ph, *cis*-**210**), 129.05 (Ph, *trans*-**210**), 128.98 (Ph, *trans*-**210**), 128.94 (Ph, *cis*-**210**), 127.18 (Ph, *trans*-**210**), 127.14 (Ph, *cis*-**210**), 80.86 (*C*Me_3, *trans*-**210**), 80.81 (*C*Me_3, *cis*-**210**), 65.9 (SCH, *trans*-**210**), 63.8 (SCH, *cis*-**210**), 53.5 (SCH_2, *cis*-**210**), 52.4 (SCH_2, *trans*-**210**), 34.3 (Ph*C*H_2, *cis*-**210**), 33.8 (Ph*C*H_2, *trans*-**210**), 29.65 (CH_2, *cis*-**210**), 28.63 (CH_2, *trans*-**210**), 28.3 (C*Me*$_3$, *cis*-**210**, *trans*-**210**), 21.4 (CH_2, *cis*-**210**), 20.9 (CH_2, *trans*-**210**); MS (ESI) *m/z* 332 $(M + Na)^+$ HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3S$ $(M + Na)^+$ 332.1291, found 332.1294 (–1.0 ppm error). The stereochemistry of benzyl sulfoximine *cis*-**210** was assigned by synthesis from *N*-TBDPS sulfoximine *cis*-**166**.

Lab book reference: **GH-1-84-2**

tert-Butyl *N*-(2-benzyl-1-oxo-1λ⁶-thian-1-ylidene)carbamate 211a and 211b



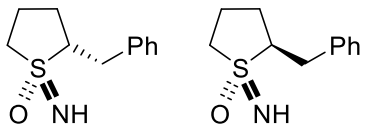
cis-**211** *trans*-**211**

Using general procedure A, *N*-Boc sulfoximine **154** (117 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 and then 8:2 hexane-EtOAc as eluent gave a 75:25 mixture of benzyl sulfoximines **211a** and **211b** (71 mg, 45%) as a white solid, R_F (1:1 hexane-EtOAc) 0.39; IR (ATR) 2933, 1655 (C=O), 1366, 1276, 1248, 1151, 907, 860, 726, 701, 646, 455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H, Ph), 7.29–7.23 (m, 1H, Ph), 7.23–7.15 (m, 2H, Ph), 3.80–3.71 (m, 0.75H, SCH), 3.66 (dd, *J* = 13.5, 3.0 Hz, 0.75H, PhC*H*), 3.62–3.50 (m, 1.25H, SCH, PhC*H*), 3.40–3.30 (m, 0.75H, SCH),

3.22–3.13 (m, 0.25H, SCH), 3.09–2.98 (m, 0.25H, SCH), 2.85 (dd, *J* = 13.5, 11.5 Hz, 0.25H, PhC*H*), 2.70 (dd, *J* = 13.5, 11.5 Hz, 0.75H, PhC*H*), 2.19–2.04 (m, 2H, CH), 2.03–1.87 (m, 1H, CH), 1.87–1.74 (m, 2H, CH), 1.53 (s, 2.25H, CMe_3), 1.51 (s, 6.75H, CMe_3), 1.47–1.35 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.1 (C=O, **211b**), 158.6 (C=O, **211a**), 136.6 (*ipso*-Ph, **211b**), 136.2 (*ipso*-Ph, **211a**), 129.51 (Ph, **211a**), 129.47 (Ph, **211b**), 128.92 (Ph, **211b**), 128.88 (Ph, **211a**), 127.12 (Ph, **211a**, **211b**), 80.48 (*C*Me_3, **211b**), 80.39 (*C*Me_3, **211a**), 64.0 (SCH, **211b**), 61.1 (SCH, **211a**), 50.1 (SCH_2, **211a**), 49.6 (SCH_2, **211b**), 31.4 (Ph*C*H_2, **211b**), 31.3 (Ph*C*H_2, **211a**), 28.34 (C*Me*$_3$, **211b**), 28.29 (C*Me*$_3$, **211a**), 26.6 (CH_2, **211a**), 24.0 (CH_2, **211b**), 23.8 (CH_2, **211b**), 23.4 (CH_2, **211b**), 23.04 (CH_2, **211a**), 22.97 (CH_2, **211a**) (one Ph resonance not resolved); MS (ESI) *m/z* 324 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}NO_3S$ $(M + H)^+$ 324.1628, found 324.1624 (+1.3 ppm error). The stereochemistry of benzyl sulfoximines **211a** and **211b** was assigned by analogy with related examples.

Lab book reference: **GH-2-12**

2-Benzyl-1-imino-1λ⁶-thiolan-1-one *cis*-212 and *trans*-212



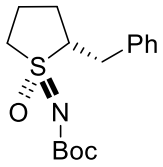
cis-**212** *trans*-**212**

TFA (0.19 mL, 2.4 mmol, 9.75 eq.) was added dropwise to a stirred solution of an 85:15 mixture of *N*-Boc sulfoximines *cis*-**210** and *trans*-**210** (79 mg, 0.25 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) at rt. The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in water (1.3 mL). Saturated $Na_2CO_{3(aq)}$ (2.6 mL) was added and the aqueous mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave an 85:15 mixture of NH sulfoximines *cis*-**212** and *trans*-**212** (35 mg, 67%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.32; IR (ATR) 3262 (NH), 3027, 2946, 1496, 1454, 1214, 1200, 1151, 1106, 994, 757, 702, 537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (m, 2H, Ph), 7.28–7.21 (m, 3H, Ph), 3.36–3.20 (m, 3H, SCH, PhC*H*), 3.19–3.07 (m, 1H, SCH), 2.83–2.70 (m, 1H, PhC*H*), 2.47 (s, 1H, NH), 2.28–2.11 (m, 2H, CH), 2.11–1.96 (m, 1H, CH),

1.96–1.84 (m, 0.85H, CH), 1.84–1.73 (m, 0.15H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.5 (*ipso*-Ph, *cis*-**212**), 137.3 (*ipso*-Ph, *trans*-**212**), 129.1 (Ph, *cis*-**212**), 128.93 (Ph, *trans*-**212**), 128.89 (Ph, *trans*-**212**), 128.86 (Ph, *cis*-**212**), 127.03 (Ph, *trans*-**212**), 127.01 (Ph, *cis*-**212**), 65.9 (SCH, *cis*-**212**), 65.1 (SCH, *trans*-**212**), 55.8 (SCH_2, *cis*-**212**), 54.6 (SCH_2, *trans*-**212**), 34.4 (Ph*C*H_2, *trans*-**212**), 34.0 (Ph*C*H_2, *cis*-**212**), 30.4 (CH_2, *trans*-**212**), 30.2 (CH_2, *cis*-**212**), 21.1 (CH_2, *cis*-**212**), 20.7 (CH_2, *trans*-**212**); MS (ESI) *m/z* 210 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{11}H_{15}NOS$ $(M + H)^+$ 210.0955, found 210.0947 (–3.6 ppm error). The stereochemistry of NH sulfoximines *cis*-**212** and *trans*-**212** was assigned by analogy with related examples.

Lab book reference: **GH-1-81-2**

tert-Butyl *N*-(2-benzyl-1-oxo-1λ⁶-thiolan-1-ylidene)carbamate *cis*-210



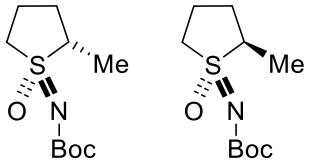
cis-**210**

TBAF (1.1 mL of a 1 M solution in THF, 1.1 mmol, 2.0 eq.) was added dropwise to a stirred solution of *N*-TBDPS benzyl sulfoximine *cis*-**166** (246 mg, 0.55 mmol, 1.0 eq.) in THF (5 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 hexane-EtOAc and then EtOAc as eluent gave NH sulfoximine *cis*-**212** (98 mg, 85%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H, Ph), 7.28–7.21 (m, 3H, Ph), 3.33–3.21 (m, 3H, SCH, PhC*H*), 3.14 (ddd, *J* = 13.0, 9.5, 8.0 Hz, 1H, SCH), 2.84–2.73 (m, 1H, PhC*H*), 2.28–2.13 (m, 2H, CH), 2.10–1.96 (m, 1H, CH), 1.96–1.84 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.6 (*ipso*-Ph), 129.1 (Ph), 128.9 (Ph), 127.1 (Ph), 66.0 (SCH), 55.8 (SCH_2), 34.1 (Ph*C*H_2), 30.3 (CH_2), 21.1 (CH_2). A solution of potassium *tert*-butoxide (68 mg. 0.60 mmol, 1.3 eq.) in THF (1 mL) was added to a stirred solution of NH sulfoximine *cis*-**210** (98 mg, 0.46 mmol, 1.0 eq.) in THF (2 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 30 min. Then, a solution of Boc_2O (200 mg, 0.92 mmol, 2.0 eq.) in THF (2 mL) was added and the resulting solution was stirred at 0 °C for 1 h.

The solution was allowed to warm to rt and stirred at rt for 48 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave *N*-Boc benzyl sulfoximine *cis*-**210** (101 mg, 71%) as a white solid, mp 100–102 °C, R_F (1:1 hexane-EtOAc) 0.49; IR (ATR) 2975, 1653 (C=O), 1455, 1366, 1283, 1251, 1221, 1160, 895, 863, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H, Ph), 7.28–7.19 (m, 3H, Ph), 3.88–3.78 (m, 1H, SCH), 3.67–3.56 (m, 2H, SCH, PhC*H*), 3.28–3.16 (m, 1H, SCH), 2.72 (dd, *J* = 14.0, 12.0 Hz, 1H, PhC*H*), 2.30–2.21 (m, 2H, CH), 2.07–1.84 (m, 2H, CH), 1.52 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.7 (C=O), 137.1 (*ipso*-Ph), 129.2 (Ph), 129.0 (Ph), 127.2 (Ph), 80.9 (*C*Me_3), 63.9 (SCH), 53.6 (SCH_2), 34.3 (Ph*C*H_2), 29.7 (CH_2), 28.3 (C*Me*$_3$), 21.5 (CH_2); MS (ESI) *m/z* 332 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_3S$ $(M + Na)^+$ 332.1291, found 332.1286 (+1.4 ppm error).

Lab book reference: **GH-2-49**

tert-Butyl *N*-(2-methyl-1-oxo-1λ⁶-thiolan-1-ylidene)carbamate *cis*-213 and *trans*-213



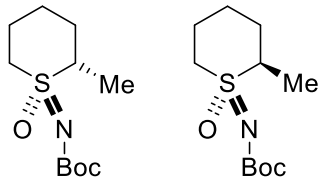
cis-**213** *trans*-**213**

Using general procedure A, *N*-Boc sulfoximine **153** (110 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 and then 4:1 EtOAc-hexane as eluent gave an approx. 90:10 mixture (by ^{13}C NMR spectroscopy) of methyl sulfoximines *cis*-**213** and *trans*-**213** (66 mg, 57%) as a clear oil, R_F (EtOAc) 0.47; IR (ATR) 2975, 2935, 1651 (C=O), 1366, 1280, 1248, 1213, 1153, 1135, 1097, 1082, 893, 862, 790, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79–3.71 (m, 1H, SCH), 3.59–3.28 (m, 1H, SCH), 3.20–3.07 (m, 1H, SCH), 2.44–2.33 (m, 1H, CH), 2.30–2.17 (m, 1H, CH), 2.11–1.97 (m, 1H, CH), 1.90–1.78 (m, 1H, CH), 1.52–1.38 (m, 12H, CMe_3,SCH*Me*); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 159.5 (C=O, *cis*-**213**), 159.1 (C=O, *trans*-**213**) 80.56 (*C*Me_3, *cis*-**213**), 60.3 (SCH, *trans*-**213**), 58.3 (SCH, *cis*-**213**), 52.8 (SCH_2, *cis*-**213**), 51.8 (SCH_2, *trans*-**213**), 31.8 (CH_2, *cis*-**213**), 31.2 (CH_2, *trans*-**213**), 28.2 (C*Me*$_3$, *cis*-**213**), 21.4 (CH_2, *cis*-**213**), 20.9 (CH_2, *trans*-**213**), 13.45 (SCH*Me*, *trans*-**213**), 13.37 (SCH*Me*, *cis*-**213**) (one *C*Me_3 and one C*Me*$_3$ resonance not resolved); MS (ESI) *m/z* 256 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{10}H_{19}NO_3S$ $(M + Na)^+$ 256.0978, found 256.0983 (–2.0 ppm error). The stereochemistry of sulfoximines *cis*-**213** and *trans*-**213** was assigned by analogy with related examples.

Lab book reference: **GH-2-7**

tert-Butyl *N*-(2-methyl-1-oxo-1λ⁶-thian-1-ylidene)carbamate *cis*-214 and *trans*-214



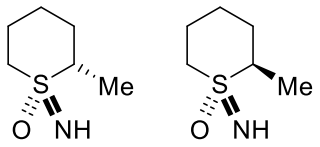
cis-**214** *trans*-**214**

Using general procedure A, *N*-Boc sulfoximine **154** (117 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 ml, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained a 55:45 mixture (by ^{1}H NMR spectroscopy) of sulfoximines. Purification by flash column chromatography on silica with 9:1 to 1:1 hexane-EtOAc as eluent gave a 55:45 mixture of methyl sulfoximines *trans*-**214** and *cis*-**214** (75 mg, 61%), R_F (1:1 hexane-EtOAc) 0.27; IR (ATR) 2981, 2935, 1656 (C=O), 1278, 1250, 1159, 894 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17–4.07 (m, 0.55H, SCH), 3.81 (ddd, *J* = 14.0, 4.5, 4.5 Hz, 0.45H, SCH), 3.44–3.34 (m, 0.45H, SCH), 3.29–3.14 (m, 1H, SCH), 3.00 (ddd, *J* = 14.0, 11.0, 3.5 Hz, 0.55H, SCH), 2.14–1.77 (m, 5H, CH), 1.65–1.58 (m, 1H, CH), 1.49 (s, 4.95H, CMe_3), 1.48 (s, 4.05H, CMe_3), 1.45 (d, *J* = 7.0 Hz, 1.65, CH*Me*), 1.43 (d, *J* = 7.0 Hz, 1.35H CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.2 (C=O, *trans*-**214**), 158.9 (C=O, *cis*-**214**), 80.4 (*C*Me_3, *trans*-**214**), 80.3 (*C*Me_3, *cis*-**214**), 55.9 (SCH), 49.7 (SCH_2, *cis*-**214**), 49.1 (SCH_2, *trans*-**214**), 31.4 (CH_2, *trans*-**214**), 30.4 (CH_2, *cis*-**214**), 28.38 (C*Me*$_3$, *trans*-**214**), 28.35 (C*Me*$_3$, *cis*-**214**), 24.0 (CH_2, *trans*-**214**), 23.2 (CH_2, *cis*-**214**), 23.1 (CH_2, *cis*-**214**), 20.4 (CH_2, *trans*-**214**), 12.3 (CH*Me*, *trans*-**214**), 12.1 (CH*Me*, *cis*-**214**) (one

SCH resonance not resolved); MS (ESI) *m/z* 270 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{11}H_{21}NO_3S$ $(M + Na)^+$ 270.1134, found 270.1134 (0.0 ppm error).

Lab book reference: **GH-1-66-2**

1-Imino-2-methyl-1λ⁶-thian-1-one *cis*-215a and *trans*-215



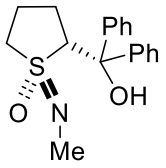
cis-**215** *trans*-**215**

TFA (0.20 ml, 2.5 mmol, 9.75 eq.) was added dropwise to a stirred solution of an unknown mixture of *N*-Boc methyl sulfoximines *cis*-**215** and *trans*-**215** (65 mg, 0.25 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL). The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure and water (1.3 mL) and saturated $Na_2CO_{3(aq)}$ (2.6 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product which contained a 60:40 mixture (by ^{1}H NMR spectroscopy) of NH sulfoximines *trans*-**215** and *cis*-**215**. Purification by flash column chromatography on silica with 95:5 and then 9:1 EtOAc-MeOH as eluent gave NH sulfoximine *trans*-**215** (16 mg, 42%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.18; IR (ATR) 3535 (NH), 3266 (NH), 2933, 2861, 1648 (C=O), 1453, 1238, 1194, 1177, 1098, 986, 722, 469 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (ddd, *J* = 14.0, 3.5, 3.5 Hz, 1H, SCH), 3.12–3.01 (m, 1H, SCH), 2.95–2.86 (m, 1H, SCH), 2.24 (br s, 1H, NH), 2.12–2.01 (m, 2H, CH), 1.99–1.89 (m, 1H, CH), 1.90–1.78 (m, 1H, CH), 1.78–1.67 (m, 1H, CH), 1.54–1.42 (m, 1H, CH), 1.32 (d, *J* = 7.0 Hz, 3H, SCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 58.8 (SCH), 53.7 (SCH_2), 32.7 (CH_2), 25.2 (CH_2), 24.6 (CH_2), 11.6 (Me); MS (ESI) *m/z* 148 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{13}NOS$ $(M + H)^+$ 148.0791, found 148.0790 (+0.3 ppm error) and NH sulfoximine *cis*-**215** (13 mg, 34%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.12; IR (ATR) 3527 (NH), 3267 (NH), 2934 , 2861, 1654 (C=O), 1454, 1233, 1202, 1173, 992, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20–3.07 (m, 1H, SCH), 3.03–2.87 (m, 2H, SCH), 2.60 (br s, 1H, NH), 2.10–2.00 (m, 2H, CH), 2.00–1.93 (m, 1H, CH), 1.90–1.74 (m, 2H, CH), 1.52–1.42 (m, 1H, CH), 1.34 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 59.1 (SCH), 53.3 (SCH_2), 31.55 (CH_2), 24.5 (CH_2), 23.7

(CH_2), 11.4 (Me); MS (ESI) *m/z* 148 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{13}NOS$ $(M + H)^+$ 148.0791, found 148.0787 (+2.4 ppm error).

Lab book reference: **GH-1-70-3**

2-(Hydroxydiphenylmethyl)-1-(methylimino)-1λ⁶-thiolan-1-one *cis*-216

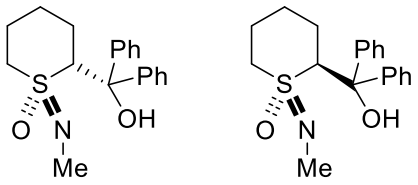


cis-**216**

Using general procedure A, *N*-Me sulfoximine **155** (67 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 9:1 and then 1:1 hexane-EtOAc as eluent gave alcohol *cis*-**216** (129 mg, 82%) as a white solid, mp 144–146 °C, R_F (1:1 hexane-EtOAc) 0.12; IR (ATR) 3428 (OH), 3064, 2942, 2871, 2802, 1493, 1449, 1253, 1224, 1091, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2H, Ph), 7.46–7.42 (m, 2H, Ph), 7.36–7.30 (m, 2H, Ph), 7.30–7.24 (m, 2H, Ph), 7.24–7.18 (m, 1H, Ph), 7.18–7.13 (m, 1H, Ph), 5.06 (s, 1H, COH) 4.33 (dd, *J* = 9.5, 8.5 Hz, 1H, SCH), 3.42–3.34 (m, 1H, SCH), 2.89 (ddd, *J* = 12.5, 11.5, 6.5 Hz, SCH), 2.49 (s, 3H, NMe), 2.37–2.25 (m, 1H, CH), 2.17–2.07 (m, 1H, CH), 2.01–1.85 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.8 (*ipso*-Ph), 145.0 (*ipso*-Ph), 128.6 (Ph), 128.5 (Ph), 127.4 (Ph), 126.9 (Ph), 126.0 (Ph), 125.1 (Ph), 78.1 (COH), 68.9 (SCH), 53.3 (SCH_2), 30.0 (NMe), 27.7 (CH_2), 20.9 (CH_2); MS (ESI) *m/z* 316 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}NO_2S$ $(M + H)^+$ 316.1366, found 316.1367 (–0.3 ppm error). The stereochemistry of alcohol *cis*-**216** was assigned by analogy with related examples.

Lab book reference: **GH-1-69-2**

2-(Hydroxydiphenylmethyl)-1-(methylimino)-1λ⁶-thian-1-one *cis*-217 and *trans*-217

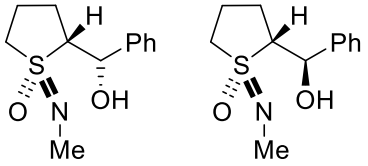


cis-**217** *trans*-**217**

Using general procedure A, *N*-Me sulfoximine **156** (74 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of alcohols *cis*-**217** and *trans*-**217**. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc and then 1:1 as eluent gave alcohol **217a** (60 mg, 36%) as a white solid, mp 148–150 °C R_F (1:1 hexane-EtOAc) 0.26; IR (ATR) 3063, 2929, 2880, 1492, 1448, 1230, 1211, 1132, 1096, 831, 750, 705, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H, COH) 7.72–7.68 (m, 2H, Ph), 7.54–7.49 (m, 2H, Ph), 7.33–7.26 (m, 4H, Ph), 7.21–7.14 (m, 2H, Ph), 3.95 (dd, *J* = 12.0, 3.0 Hz, 1H, SCH), 3.47–3.38 (m, 1H, SCH), 2.93–2.83 (m, 1H, SCH), 2.64 (s, 3H, NMe), 2.39–2.23 (m, 1H, CH), 2.01–1.73 (m, 4H, CH), 1.52–1.37 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ145.45 (*ipso*-Ph), 145.37 (*ipso*-Ph), 128.56 (Ph), 127.61 (Ph), 127.0 (Ph), 126.8 (Ph), 126.2 (Ph), 124.9 (Ph), 79.1 (SCH*C*OH), 66.5 (SCH), 50.5 (SCH_2), 27.8 (NMe), 27.6 (CH_2), 25.1 (CH_2), 24.5 (CH_2); MS (ESI) *m/z* 330 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_2S$ (M + H)$^+$ 330.1522, found 330.1515 (+2.2 ppm error) and sulfoximine **217b** (70 mg, 43%) as a white solid, mp 150–152 °C, R_F (1:1 hexane-EtOAc) 0.14; IR (ATR) 3058, 2929, 2807, 1446, 1237, 1216, 1107, 864, 730, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2H, Ph), 7.44–7.40 (m, 2H, Ph), 7.38–7.21 (m, 6H, Ph), 3.99 (dd, *J* = 12.0, 2.0 Hz, 1H, SCH), 3.28–3.19 (m, 1H, SCH), 2.88–2.77 (m, 1H, SCH), 2.53 (s, 3H, NMe), 2.26–2.14 (m, 1H, CH), 2.03–1.84 (m, 4H, CH), 1.49–1.35 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.7 (*ipso*-Ph), 142.2 (*ipso*-Ph), 128.4 (Ph), 127.6 (Ph), 127.4 (Ph), 127.1 (Ph), 80.7 (SCH*C*OH), 70.1 (SCH), 53.8 (SCH_2), 28.2 (NMe), 27.0 (CH_2), 26.0 (CH_2), 23.5 (CH_2) (two Ph resonances not resolved); MS (ESI) *m/z* 330 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}NO_2S$ (M + H)$^+$ 330.1522, found 330.1521 (+0.5 ppm error).

Lab book reference: **GH-1-76**

2-[Hydroxy(phenyl)methyl]-1-(methylimino)-1λ⁶-thiolan-1-one *cis,anti*-218 and *cis,syn*-218



cis,anti-**218** *cis,syn*-**218**

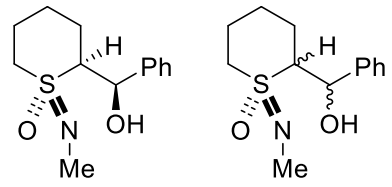
Using general procedure A, *N*-Me sulfoximine **155** (67 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.22 mL of a 2.5 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq.) in THF (5 mL) gave the crude product which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of alcohols *cis,anti*-**218** and *cis,syn*-**218**. Purification by flash column chromatography on silica with EtOAc as eluent gave alcohol *cis,anti*-**218** (68 mg, 60%) as a white solid, mp 134–136 °C, R_F (9:1 EtOAc-MeOH) 0.33; IR (ATR) 3455 (OH), 3186, 2946, 2878, 2802, 1451, 1216, 1138, 1101, 842, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.33 (m, 4H, Ph), 7.31–7.26 (m, 1H, Ph), 5.46 (s, 1H, C*H*OH), 3.87 (d, *J* = 2.5 Hz, 1H, CHO*H*), 3.42–3.30 (m, 2H, SCH,SCH_2), 2.98–2.89 (m, 1H, SCH), 2.89 (s, 3H, NMe), 2.47–2.34 (m, 1H, CH), 2.26–2.16 (m, 1H, CH), 1.95–1.80 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.3 (*ipso*-Ph), 128.7 (Ph), 127.9 (Ph), 125.7 (Ph), 70.0 (Ph*C*HOH), 66.8 (SCH), 52.2 (SCH_2), 30.5 (NMe), 22.8 (CH_2), 21.4 (CH_2); MS (ESI) *m/z* 240 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO_2S$ $(M + H)^+$ 240.1053, found 240.1053 (–0.2 ppm error) and an 85:15 mixture of alcohols *cis,syn*-**218** and *cis,anti*-**218** (24 mg, 20 mg (17%) of *cis,syn*-**218** and 4 mg (3%) of *cis,anti*-**218**) as a white solid, mp 136–138 °C, R_F (9:1 EtOAc-MeOH) 0.28; IR (ATR) 3440 (OH), 3061, 2928, 2808, 1453, 1228, 1140, 1108, 863, 841, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for *cis,syn*-**218** δ 7.40–7.32 (m, 5H, Ph), 4.83 (d, *J* = 9.5 Hz, 1H, C*H*OH), 3.91 (s, 1H, CHO*H*), 3.43–3.33 (m, 2H, SCH), 3.02 (ddd, *J* = 12.5, 10.5, 7.5 Hz, 1H, SCH), 2.84 (s, 3H, NMe), 2.16–2.06 (m, 1H, CH), 1.98–1.87 (m, 1H, CH), 1.84–1.76 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *cis,syn*-**218** δ 140.5 (*ipso*-Ph), 128.9 (Ph), 128.7 (Ph), 126.9 (Ph), 73.9 (Ph*C*HOH), 67.8 (SCH), 53.8 (SCH_2), 30.6 (NMe), 28.5 (CH_2), 21.4 (CH_2); MS (ESI) *m/z* 240 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NO_2S$ $(M + H)^+$ 240.1053, found 240.1050 (+0.9 ppm error). The stereochemistry of alcohol *cis,anti*-**218** was assigned by X-ray crystallography and that of alcohol *cis,syn*-**218** was assigned by analogy with related examples.

Crystal structure determination of *cis,anti*-**218**

$C_{12}H_{17}NO_2S$, M = 239.32, monoclinic, a = 8.7992(3), b = 18.9535(6), c = 7.1301(2) Å, β = 99.909(4)°, U = 1171.38(7) Å^3, T = 110.00(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 2.336 mm^{-1}, 3823 reflection measured, 2087 unique (R_{int} = 0.0269) which were used in calculation. The final R1 was 0.0371 (I≥2σ) and wR2 was 0.0969 (all data).

Lab book reference: **GH-1-71**

2-[Hydroxy(phenyl)methyl]-1-(methylimino)-1λ⁶-thian-1-one *trans,syn*-219 and 219a



trans,syn-**219** **219a**

Using general procedure A, *N*-Me sulfoximine **156** (74 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of alcohols *trans,syn*-**219** and **219a**. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave alcohol *trans,syn*-**219** (70 mg, 55%) as a white solid, mp 136–138 °C, R_F (EtOAc) 0.58; IR (ATR) 3245 (OH), 2925, 2860, 1452, 1240, 1227, 1213, 1166, 1137, 1098, 1063, 869, 825, 768, 713, 699, 667, 461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 4H, Ph), 7.29–7.24 (m, 1H, Ph), 5.95 (s, 1H, PhCHO*H*), 5.77 (s, 1H, PhC*H*OH), 3.63–3.54 (m, 1H, SCH), 2.88–2.78 (m, 2H, SCH), 2.78 (s, 3H, NMe), 2.27–2.13 (m, 1H, CH), 2.02–1.92 (m, 1H, CH), 1.90–1.76 (m, 2H, CH), 1.75–1.66 (m, 1H, CH), 1.31–1.16 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.3 (*ipso*-Ph), 128.5 (Ph), 127.6 (Ph), 126.2 (Ph), 67.9 (Ph*C*HOH), 67.0 (SCH), 48.4 (SCH_2), 28.0 (NMe), 24.4 (CH_2), 24.3 (CH_2), 22.6 (CH_2); MS (ESI) *m/z* 254 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_2S$ $(M + H)^+$ 254.1209, found 254.1210 (–0.1 ppm error) and alcohol **219a** (10 mg, 8%) as a white solid, mp 130–132 °C, R_F (1:1 hexane-EtOAc) 0.58; IR (ATR) 3215 (OH), 2926, 2861, 1453, 1233, 1214, 1167, 1138, 1106, 1058, 865, 769, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 5H, Ph), 5.13 (d, J = 9.0 Hz, 1H, PhC*H*OH), 3.55–3.48 (m, 1H,

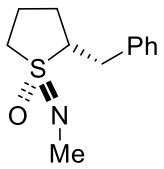
SCH), 3.17 (ddd, *J* = 9.0, 7.5, 3.0 Hz, 1H, SCH), 2.86 (s, 3H, NMe), 2.75–2.65 (m, 1H, SCH), 2.06–1.91 (m, 2H, CH), 1.80–1.70 (m, 1H, CH), 1.67–1.55 (m, 1H, CH), 1.31–1.20 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.6 (*ipso*-Ph), 128.7 (Ph), 128.5 (Ph), 127.6 (Ph), 72.7 (SCH), 65.8 (Ph*C*HOH), 50.5 (SCH_2), 28.5 (NMe), 26.0 (CH_2), 24.7 (CH_2), 23.3 (CH_2); MS (ESI) *m/z* 254 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NO_2S$ $(M + H)^+$ 254.1209, found 254.1208 (+0.5 ppm error). The stereochemistry of alcohol *trans,syn*-**219** was assigned by X-ray crystallography.

Crystal structure determination of *trans,syn*-**219**

$C_{13}H_{19}NO_2S$, *M* = 253.35, monoclinic, *a* = 15.4721(5), *b* = 5.42359(16), *c* = 30.2011(7) Å, *β* = 90 °, *U* = 2534.31(12) Å^3, *T* = 110.05(10) K, space group $P2_1$, Z = 8, *μ*(Mo-Kα) = 2.188 mm^{-1}, 4998 reflection measured, 3147 unique (R_{int} = 0.0220) which were used in calculation. The final R1 was 0.0357 (I≥2σ) and wR2 was 0.0937 (all data).

Lab book reference: **GH-2-5**

2-Benzyl-1-(methylimino)-1λ^6-thiolan-1-one *cis*-220



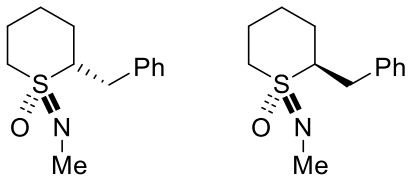
cis-**220**

Using general procedure A, *N*-Me sulfoximine **155** (67 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc and then 99:1 EtOAc-MeOH as eluent gave benzyl sulfoximine *cis*-**220** (42 mg, 38%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.37; IR (ATR) 2929, 2800, 1496, 1454, 1223, 1137, 1098, 859, 754, 726, 701, 529, 463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H, Ph), 7.26–7.21 (m, 3H, Ph), 3.40–3.25 (m, 3H, SCH, PhC*H*), 2.93 (ddd, *J* = 13.0, 10.0, 7.5 Hz, 1H, SCH), 2.79–2.71 (m, 1H, PhC*H*), 2.74 (s, 3H, NMe), 2.22–2.12 (m, 2H, CH), 1.99–1.79 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.8 (*ipso*-Ph), 129.2 (Ph), 128.9 (Ph), 127.0 (Ph), 63.5 (SCH), 51.7 (SCH_2), 35.2 (Ph*C*H_2), 30.5 (NMe), 30.3 (CH_2), 21.5 (CH_2); MS (ESI) *m/z* 224 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{17}NOS$ $(M + H)^+$ 224.1104, found 224.1103 (+0.4

ppm error). The stereochemistry of benzyl sulfoximine *cis*-**220** was assigned by analogy with related examples.

Lab book reference: **GH-2-16**

2-Benzyl-1-(methylimino)-1λ⁶-thian-1-one 221a and 221b



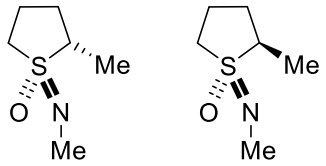
221a **221b**

Using general procedure A, *N*-Me sulfoximine **156** (74 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 50:50 mixture (by ^{1}H NMR spectroscopy) of benzyl sulfoximines **221a** and **221b**. Purification by flash column chromatography on silica with EtOAc as eluent gave benzyl sulfoximine **221a** (35 mg, 30%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.45; IR (ATR) 3027, 2923, 2872, 2801, 1454, 1443, 1239, 1224, 1131, 1098, 872, 826, 756, 699, 462 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H, Ph) 7.26–7.21 (m, 1H, Ph), 7.21–7.16 (m, 2H, Ph), 3.51 (dd, *J* = 13.5, 3.0 Hz, 1H, PhC*H*), 3.47–3.39 (m, 1H, SCH), 3.05–2.95 (m, 1H, SCH) , 2.89–2.79 (m, 1H, SCH), 2.83 (s, 3H, NMe), 2.69 (dd, *J* = 13.5, 11.5 Hz, 1H, PhC*H*), 2.02–1.84 (m, 3H, CH), 1.84–1.71 (m, 2H, CH) 1.36–1.22 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.5 (*ipso*-Ph), 129.5 (Ph), 128.8 (Ph), 126.9 (Ph), 64.5 (SCH), 48.5 (SCH_2), 31.8 (Ph*C*H_2), 29.9 (CH_2), 28.5 (NMe), 24.5 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 238 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NOS$ $(M + H)^+$ 238.1260, found 238.1263 (–1.2 ppm error) and benzyl sulfoximine **221b** (30 mg, 25%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.41; IR (ATR) 3027, 2929, 2870, 2802, 1454, 1237, 1209, 1163, 1135, 1104, 866, 755, 701, 463, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 2H, Ph) 7.25–7.20 (m, 1H, Ph), 7.20–7.16 (m, 2H, Ph), 3.61 (dd, *J* = 13.5, 3.0 Hz, 1H, PhC*H*), 3.33–3.25 (m, 1H, SCH), 3.17–3.08 (m, 1H, SCH), 2.90 (s, 3H, NMe), 2.85–2.76 (m, 1H, SCH), 2.66 (dd, *J* = 13.5, 12.0 Hz, 1H, PhC*H*), 2.06–1.85 (m, 2H, CH), 1.87–1.66 (m, 3H, CH) 1.39–1.25 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.2 (*ipso*-Ph), 129.5 (Ph), 128.8 (Ph), 126.7 (Ph), 63.0 (SCH), 50.3 (SCH_2), 32.0 (Ph*C*H_2), 29.1

(NMe), 27.4 (CH_2), 23.8 (CH_2), 23.7 (CH_2); MS (ESI) *m/z* 238 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{13}H_{19}NOS$ $(M + H)^+$ 238.1260, found 238.1259 (+0.4 ppm error).

Lab book reference: **GH-1-83**

2-Methyl-1-(methylimino)-1λ⁶-thiolan-1-one *cis*-222 and *trans*-222

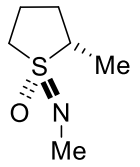


cis-**222** *trans*-**222**

Using general procedure A, *N*-Me sulfoximine **155** (67 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 90:10 mixture (by ^{1}H NMR spectroscopy) of methyl sulfoximines *cis*-**222** and *trans*-**222**. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave a 90:10 mixture of methyl sulfoximines *cis*-**222** and *trans*-**222** (46 mg, 63%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.18; IR (ATR) 2935, 2800, 1451, 1413, 1217, 1136, 1098, 1056, 1020, 867, 839, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34–3.26 (m, 1H, SCH), 3.20–3.10 (m, 1H, SCH), 2.88–2.78 (m, 1H, SCH), 2.80 (s, 3H, NMe), 2.35–2.26 (m, 1H, CH), 2.21–2.11 (m, 1H, CH), 2.02–1.88 (m, 1H, CH), 1.79–1.67 (m, 1H, CH), 1.33 (d, *J* = 7.0 Hz, 2.7H, SCH*Me*), 1.31 (d, *J* = 7.0 Hz, 0.3H, SCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 57.2 (SCH, *cis*-**222**), 56.4 (SCH, *trans*-**222**), 51.3 (SCH_2, *trans*-**222**), 50.2 (SCH_2, *cis*-**222**), 31.9 (CH_2, *cis*-**222**), 30.5 (NMe, *cis*-**222**), 29.2 (CH_2, *trans*-**222**), 28.5 (NMe, *trans*-**222**), 23.8 (CH_2, *trans*-**222**), 21.4 (CH_2, *cis*-**222**), 14.6 (SCH*Me*, *trans*-**222**), 13.8 (SCH*Me*, *cis*-**222**); MS (ESI) *m/z* 148 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{13}NOS$ $(M + H)^+$ 148.0791, found 148.0788 (+1.9 ppm error). The stereochemistry of methyl sulfoximine *cis*-**222** was assigned by synthesis from *N*-TBDPS sulfoximine *cis*-**172**.

Lab book reference: **GH-2-17**

2-Methyl-1-(methylimino)-1λ⁶-thiolan-1-one *cis*-222

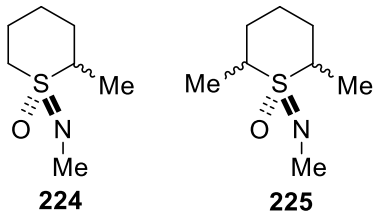


cis-**222**

TBAF (1.76 mL of a 1 M solution in THF, 1.76 mmol, 2.0 eq.) was added dropwise to a stirred solution of *N*-TBDPS methyl sulfoximine *cis*-**172** (327 mg, 0.88 mmol, 1.0 eq.) in THF (7 mL) at rt under Ar. The resulting solution was stirred at rt for 24 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 99:1 EtOAc-MeOH as eluent gave NH sulfoximine *cis*-**223** (112 mg, 95%) as a yellow oil, R_F (9:1 EtOAc-MeOH) 0.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (ddd, *J* = 12.5, 8.5, 4.0 Hz, 1H, SCH), 3.14–3.02 (m, 2H, SCH), 2.41–2.32 (m, 1H, CH) 2.23–2.12 (m, 1H, CH), 2.12–2.00 (m, 1H, CH), 1.85–1.73 (m, 1H, CH), 1.34 (d, *J* = 7.0 Hz, 3H, SCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 59.3 (SCH), 55.3 (SCH_2), 32.0 (CH_2), 21.3 (CH_2), 12.7 (SCH*Me*). A solution of paraformaldehyde (30 mg, 1.0 mmol, 1.2 eq.) and NH sulfoximine *cis*-**223** (112 mg, 0.84 mmol, 1.0 eq.) in formic acid (2 mL) was stirred and heated at 120 °C for 36 h. The solution was allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was dissolved in 2 M $H_2SO_{4(aq)}$ (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was basified by the addition of 2 M $NaOH_{(aq)}$ until pH 12 was reached. The aqueous mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc and then 9:1 EtOAc-MeOH as eluent gave methyl sulfoximine *cis*-**222** (100 mg, 81%) as a clear oil, R_F (9:1 EtOAc-MeOH) 0.18; IR (ATR) 2934, 2873, 1451, 1267, 1217, 1178, 1135, 1098, 1057, 1020, 867, 838 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34–3.26 (m, 1H, SCH), 3.20–3.10 (m, 1H, SCH), 2.88–2.78 (m, 1H, SCH), 2.80 (s, 3H, NMe), 2.35–2.26 (m, 1H, CH), 2.21–2.11 (m, 1H, CH), 2.02–1.88 (m, 1H, CH), 1.79–1.67 (m, 1H, CH), 1.33 (d, *J* = 7.0 Hz, 3H, SCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 57.2 (SCH), 50.2 (SCH_2), 31.9 (CH_2), 30.5 (NMe), 21.4 (CH_2), 13.8 (CH*Me*); MS (ESI) *m/z* 148 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_6H_{13}NOS$ (M + H)$^+$ 148.0791, found 148.0787 (+2.7 ppm error).

Lab book reference: **GH-2-52**

2-Methyl-1-(methylimino)-1λ⁶-thian-1-one 224 and 2,6-dimethyl-1-(methylimino)-1λ⁶-thian-1-one 225

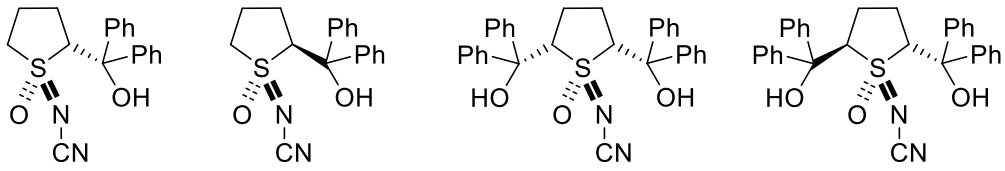


224 **225**

Using general procedure A, *N*-Me sulfoximine **156** (74 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with EtOAc then 9:1 EtOAc-MeOH as eluent gave a complex mixture of sulfoximine **156**, methyl sulfoximine **224** and dimethyl sulfoximine **225** (40 mg) as a colourless oil. It was not possible to determine the ratio from the ^{1}H NMR spectrum. Evidence for methyl sulfoximine **224** and dimethyl sulfoximine **225** was provided by MS data.

Lab book reference: **GH-2-8**

{[2-(Hydroxydiphenylmethyl)-1-oxo-1λ⁶-thiolan-1-ylidene]amino}formonitrile *cis*-226 and *trans*-226 and {[2,5-Bis(hydroxydiphenylmethyl)-1-oxo-1λ⁶-thiolan-1-ylidene]amino}formonitrile *cis,cis*-227 and *trans,cis*-227



cis-**226** *trans*-**226** *cis,cis*-**227** *trans,cis*-**227**

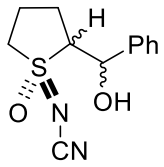
Using general procedure A, *N*-CN sulfoximine **68** (72 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc and then EtOAc as eluent gave a 70:30 mixture of disubstituted sulfoximines *cis,cis*-**227** and *trans,cis*-**227** (30 mg, 12%) as a white solid, R_F (4:1 EtOAc-hexane) 0.59; IR (ATR) 3524 (OH), 3060, 2925, 2192 (CN), 1492, 1449, 1235, 1160, 1049, 1033, 907, 729, 697, 523

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 0.6H, Ph), 7.66 (d, *J* = 7.5 Hz, 2.8H, Ph), 7.59 (d, *J* = 7.5 Hz, 0.6H, Ph), 7.49–7.40 (m, 4H, Ph), 7.40–7.15 (m, 12H, Ph), 4.91 (s, 0.3H, COH), 4.89–4.82 (m, 1.7H, SCH), 4.37 (dd, *J* = 12.0, 6.0 Hz, 0.3H, SCH), 3.87 (s, 0.3H, COH), 3.72 (s, 1.4H, COH), 2.72–2.56 (m, 1.4H, CH), 2.47–2.37 (m, 0.6H, CH), 2.05–1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 144.0 (*ipso*-Ph, *trans,cis*-**227**), 143.72 (*ipso*-Ph, *cis,cis*-**227**), 143.66 (*ipso*-Ph, *cis,cis*-**227**), 143.4 (*ipso*-Ph, *trans,cis*-**227**), 142.9 (*ipso*-Ph, *trans,cis*-**227**), 142.4 (*ipso*-Ph, *trans,cis*-**227**), 129.5 (Ph, *trans,cis*-**227**), 129.2 (Ph, *trans,cis*-**227**), 129.1 (Ph, *cis,cis*-**227**), 128.85 (Ph, *cis,cis*-**227**), 128.82 (Ph, *trans,cis*-**227**), 128.79 (Ph, *trans,cis*-**227**), 128.7 (Ph, *trans,cis*-**227**), 128.40 (Ph, *trans,cis*-**227**), 128.35 (Ph, *trans,cis*-**227**), 128.3 (Ph, *cis,cis*-**227**), 127.74 (Ph, *trans,cis*-**227**), 127.68 (Ph, *cis,cis*-**227**), 125.8 (Ph, *trans,cis*-**227**), 125.4 (Ph, *trans,cis*-**227**), 125.12 (Ph, *cis,cis*-**227**), 125.07 (Ph, *cis,cis*-**227**), 125.0 (Ph, *trans,cis*-**227**), 124.8 (Ph, *trans,cis*-**227**), 111.8 (CN, *cis,cis*-**227**), 110.3 (CN, *trans,cis*-**227**), 79.8 (COH, *cis,cis*-**227**), 78.6 (COH, *trans,cis*-**227**), 77.6 (COH, *trans,cis*-**227**), 73.5 (SCH, *trans,cis*-**227**), 72.7 (SCH, *trans,cis*-**227**), 72.1 (SCH, *cis,cis*-**227**), 25.6 (CH_2, *cis,cis*-**227**) 23.7 (CH_2, *trans,cis*-**227**), 22.9 (CH_2, *trans,cis*-**227**); MS (ESI) *m/z* 509 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{31}H_{28}N_2O_3S$ $(M + H)^+$ 509.1893, found 509.1902 (–1.7 ppm error) and a 90:10 mixture of monosubstituted sulfoximines *cis*-**226** and *trans*-**226** (18 mg, 11%) as a white solid, mp 180–182 °C, R_F (4:1 EtOAc-hexane) 0.41; IR (ATR) 3533 (OH), 2928, 2192, 1494, 1449, 1235, 1180, 1061, 1033, 908, 807, 787, 730, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.66 (m, 1.8H, Ph), 7.64–7.60 (m, 0.2H, Ph), 7.45–7.36 (m, 3.7H, Ph), 7.35–7.27 (m, 3.2H, Ph), 7.23–7.17 (m, 1.1H, Ph), 4.69 (dd, *J* = 10.0, 8.0 Hz, 0.9H, SCH), 4.50 (dd, *J* = 10.0, 8.0 Hz, 0.1H, SCH), 3.78 (dd, *J* = 13.0, 6.0 Hz, 0.9H, SCH), 3.72 (s, 0.9H, COH), 3.58–3.47 (m, 0.2H, SCH), 3.21 (ddd, *J* = 13.0, 6.5, 6.5 Hz, 0.9H, SCH), 2.54–2.40 (m, 1H, CH), 2.38–2.24 (m, 1H, CH), 2.14–1.94 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.9 (*ipso*-Ph, *cis*-**226**), 143.2 (*ipso*-Ph, *cis*-**226**), 129.21 (Ph, *cis*-**226**), 129.17 (Ph, *trans*-**226**), 129.08 (Ph, *trans*-**226**), 128.8 (Ph, *cis*-**226**), 128.4 (Ph, *cis*-**226**), 127.6 (Ph, *cis*-**226**), 125.5 (Ph, *trans*-**226**), 125.4 (Ph, *cis*-**226**), 125.0 (Ph, *cis*-**226**), 124.9 (Ph, *trans*-**226**), 112.1 (CN, *cis*-**226**) 78.54 (COH, *cis*-**226**), 71.1 (SCH, *trans*-**226**), 69.1 (SCH, *cis*-**226**), 56.6 (SCH_2, *trans*-**226**), 55.1 (SCH_2, *cis*-**226**), 27.6 (CH_2, *cis*-**226**), 27.1 (CH_2, *trans*-**226**), 20.8 (CH_2, *trans*-**226**), 20.7 (CH_2, *cis*-**226**) (two *ipso*-Ph, two Ph, one CN and one COH signal not resolved for sulfoximine *trans*-

226); MS (ESI) *m/z* 327 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_2O_2S$ $(M + H)^+$ 372.1162, found 372.1163 (–0.5 ppm error).

Lab book reference: **GH-1-90**

({2-[Hydroxy(phenyl)methyl]-1-oxo-1λ⁶-thiolan-1-ylidene}amino)formonitrile 228



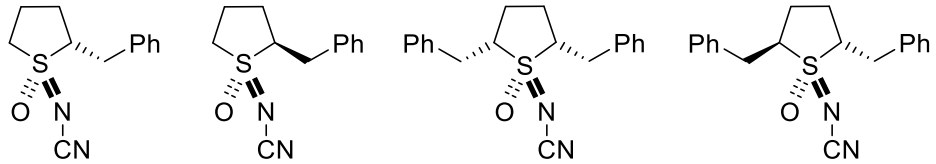
228

Using general procedure A, *N*-CN sulfoximine **68** (72 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 8:2 and then 1:1 hexane-EtOAc as eluent gave one unassigned diastereomer of sulfoximine **228a** (25 mg, 20%) as a white solid, mp 114–116 °C, R_F (EtOAc) 0.61; IR (ATR) 3350 (OH), 2952, 2188 (CN), 1240, 1186, 1067, 817, 736, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 4H, Ph), 7.35–7.30 (m, 1H, Ph), 5.54 (dd, *J* = 4.0, 2.0 Hz, 1H, PhC*H*), 3.71–3.57 (m, 2H, SCH), 3.28 (ddd, *J* = 13.0, 10.5, 8.0 Hz, 1H, SCH), 3.19 (d, *J* = 4.0 Hz, 1H, CHO*H*), 2.58–2.45 (m, 1H, CH), 2.45–2.35 (m, 1H, CH), 2.13–1.98 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.1 (*ipso*-Ph), 129.0 (Ph), 128.5 (Ph), 125.6 (Ph), 112.7 (CN), 69.1 (Ph*C*H), 67.3 (SCH), 52.7 (SCH_2), 22.0 (CH_2), 20.6 (CH_2); MS (ESI) *m/z* 273 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2O_2S$ $(M + Na)^+$ 273.0668, found 273.0669 (–0.1 ppm error) and a 60:20:15:5 mixture of sulfoximines **228b**, **228c**, **228d** and **228a** (42 mg, 34%) as a white solid, mp 116–118 °C, R_F (EtOAc) 0.53; IR (ATR) 3361 (OH), 2946, 2193 (CN), 1243, 1192, 823, 772, 730, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (m, 4H, Ph), 7.33–7.27 (m, 1H, Ph), 5.55 (dd, *J* = 3.5, 2.5 Hz, 0.15H, PhC*H*, **228d**), 5.52 (dd, *J* = 4.0, 2.0 Hz, 0.05H, PhC*H*, **228a**), 5.10 (dd, *J* = 10.0, 4.0 Hz, 0.2H, PhC*H*, **228c**), 4.98 (dd, *J* = 10.0, 4.0 Hz, 0.6H, PhC*H*, **228b**), 3.81–3.41 (m, 2.6H, SCH,CHO*H*), 3.64 (d, *J* = 4.0 Hz, 0.2H, CHO*H*), 3.52 (d, *J* = 4.0 Hz, 0.6H, CHO*H*), 3.29 (ddd, *J* = 13.5, 11.0, 7.5 Hz, 0.6H, SCH), 2.51–2.34 (m, 0.4H, CH), 2.30–1.97 (m, 1.8H, CH), 1.92–1.71 (m, 1.8H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.7 (*ipso*-Ph, **228c**, **228d**), 139.5 (*ipso*-Ph, **228c**, **228d**), 139.3 (*ipso*-Ph, **228b**), 129.3 (Ph, **228b**), 129.2 (Ph, **228b**), 128.9 (Ph, **228c**, **228d**), 128.46 (Ph,

228c, **228d**), 128.42 (Ph, **228c**, **228d**), 126.9 (Ph, **228b**), 126.7 (Ph, **228c**, **228d**), 125.8 (Ph, **228c**, **228d**), 125.7 (Ph, **228c**, **228d**), 112.9 (CN, **228c**, **228d**), 112.5 (CN, **228b**), 112.2 (CN, **228c**, **228d**), 72.9 (SCH, CHOH, **228c**, **228d**), 72.7 (SCH, CHOH, **228c**, **228d**), 72.3 (CHOH, **228b**), 71.6 (SCH, **228b**), 70.1 (SCH, **228c**, **228d**), 68.2 (CHOH, **228c**, **228d**), 54.8 (SCH_2, **228b**), 54.5 (SCH_2, **228c**, **228d**), 53.4 (SCH_2, **228c**, **228d**), 28.3 (CH_2, **228b**), 27.7 (CH_2, **228c**, **228d**), 22.4 (CH_2, **228c**, **228d**), 21.2 (CH_2, **228b**), 20.7 (CH_2, **228c**, **228d**), 20.5 (CH_2, **228c**, **228d**) (signals for **228a** not resolved); MS (ESI) *m/z* 252 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O_2S$ $(M + H)^+$ 251.0849, found 251.0850 (–0.5 ppm error).

Lab book reference: **GH-2-6**

[(2-Benzyl-1-oxo-1λ⁶-thiolan-1-ylidene)amino]formonitrile *cis*-229 and *trans*-229 and [(2,5-Dibenzyl-1-oxo-1λ⁶-thiolan-1-ylidene)amino]formonitrile *cis,cis*-230 and *trans,cis*-230



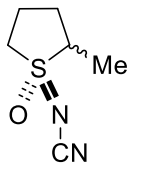
cis-**229** *trans*-**229** *cis,cis*-**230** *trans,cis*-**230**

Using general procedure A, *N*-CN sulfoximine **68** (72 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 1:1 EtOAc-hexane and then 4:1 EtOAc-hexane as eluent gave an unknown mixture of disubstituted sulfoximines *cis,cis*-**230** and *trans,cis*-**230** (55 mg, 34%) as a clear gel, R_F (4:1 EtOAc-hexane) 0.70; IR (ATR) 3037, 2930, 2188 (CN), 1496, 1455, 1233, 1177, 832, 756, 699, 540, 464 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 6H, Ph), 7.25–7.19 (m, 4H, Ph), 3.83–3.35 (m, 4H, SCH/PhC*H*), 2.90–2.60 (m, 2H, PhC*H*), 2.29–1.92 (m, 3H, CH), 1.84–1.65 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.69 (*ipso*-Ph), 135.64 (*ipso*-Ph), 135.49 (*ipso*-Ph), 135.42 (*ipso*-Ph), 129.22 (Ph), 129.18 (Ph), 129.17 (Ph), 129.12 (Ph), 129.02 (Ph), 127.69 (Ph), 127.66 (Ph), 127.61 (Ph), 112.46 (CN), 112.37 (CN), 68.18 (SCH, *trans,cis*-**230**), 65.08 (SCH, *trans,cis*-**230**), 64.86 (SCH, *cis,cis*-**230**), 34.63 (Ph*C*H_2, *trans,cis*-**230**), 33.95 (Ph*C*H_2, *trans,cis*-**230**), 33.79 (Ph*C*H_2, *cis,cis*-**230**), 28.03 (CH_2, *trans,cis*-**230**), 27.81 (CH_2,

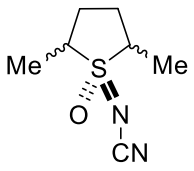
trans,cis-**230**), 26.52 (CH_2, *cis,cis*-**230**); MS (ESI) *m/z* 325 $(M + H)^+$ HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2OS$ $(M + H)^+$ 325.1369, found 325.1369 (–0.1 ppm error) and a 70:30 mixture (by ^1H NMR spectroscopy) of monosubstituted sulfoximines *cis*-**229** and *trans*-**229** (37 mg, 32%) as a clear gel, R_F (4:1 EtOAc-hexane) 0.39; IR (ATR) 2938, 2188 (CN), 1496, 1455, 1233, 1192, 819, 755, 702, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 3H, Ph), 7.25–7.20 (m, 2H, Ph), 3.76–3.68 (m, 0.7H, SCH), 3.68–3.57 (m, 1H, SCH), 3.55–3.37 (m, 1.6H, PhC*H*, SCH), 3.26 (ddd, *J* = 13.5, 10.0, 8.0 Hz, 0.7H, SCH), 2.90 (dd, *J* = 15.0, 11.0 Hz, 0.3H, PhC*H*), 2.80 (dd, *J* = 14.0, 10.0 Hz, 0.7H, PhC*H*), 2.41–2.23 (m, 2H, CH), 2.23–1.86 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.8 (*ipso*-Ph, *trans*-**229**), 135.5 (*ipso*-Ph, *cis*-**229**), 129.21 (Ph, *cis*-**229**), 129.18 (Ph, *trans*-**229**), 129.09 (Ph, *cis*-**229**), 129.01 (Ph, *trans*-**229**), 127.69 (Ph, *cis*-**229**), 127.63 (Ph, *trans*-**229**), 112.50 (CN, *trans*-**229**), 112.46 (CN, *cis*-**229**), 67.05 (SCH, *trans*-**229**), 64.76 (SCH, *cis*-**229**), 53.64 (SCH_2, *cis*-**229**), 52.42 (SCH_2, *trans*-**229**), 33.86 (Ph*C*H_2, *cis*-**229**), 33.00 (Ph*C*H_2, *trans*-**229**), 29.94 (CH_2, *cis*-**229**), 29.12 (CH_2, *trans*-**229**), 21.22 (CH_2, *cis*-**229**), 20.44 (CH_2, *trans*-**229**); MS (ESI) *m/z* 235 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}N_2OS$ $(M + H)^+$ 235.0900, found 235.0899 (+0.1 ppm error).

Lab book reference: **GH-1-89**

[(2-Methyl-1-oxo-1λ⁶-thiolan-1-ylidene)amino]formonitrile 231 and [(2,5-Dimethyl-1-oxo-1λ⁶-thiolan-1-ylidene)amino]formonitrile 232



231



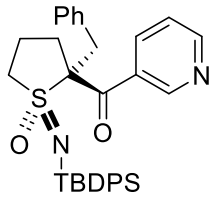
232

Using general procedure A, *N*-CN sulfoximine **68** (72 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and then methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 4:1 EtOAc-hexane and then EtOAc as eluent gave a complex mixture of diastereomeric monosubstituted sulfoximines **231** and disubstituted sulfoximines **232** (25 mg) as a clear oil, R_F (EtOAc) 0.33; IR (ATR) 2940, 2185 (CN), 1451, 1225, 1186, 817, 724, 539 cm^{-1}; MS (ESI) *m/z* 181 $[(M + Na)^+]$ HRMS (ESI) *m/z* calcd for $C_6H_{10}N_2OS$ $(M + Na)^+$ 181.0406, found 181.0410 (–2.4 ppm error); MS (ESI)

m/z 195 [(M + Na)$^+$] HRMS (ESI) *m/z* calcd for $C_7H_{12}N_2OS$ (M + Na)$^+$ 195.0568, found 195.0567 (–1.0 ppm error).

Lab book reference: **GH-1-91-7**

Attempted synthesis of 2-Benzyl-1-[(*tert*-butyldiphenylsilyl)imino]-2-(pyridine-3-carbonyl)-1λ⁶-thiolan-1-one 237

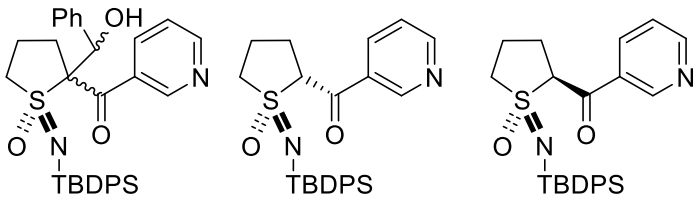


237

LHMDS (0.55 mL of a 1 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS keto-sulfoximine *cis*-**183** (231 mg, 0.5 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 and then 1:1 hexane-EtOAc as eluent gave no identifiable products and no starting material (by ^{1}H NMR spectroscopy).

Lab book reference: **GH-2-13**

Attempted synthesis of 1-[(*tert*-Butyldiphenylsilyl)imino]-2-(pyridine-3-carbonyl)-1λ⁶-thiolan-1-one 238



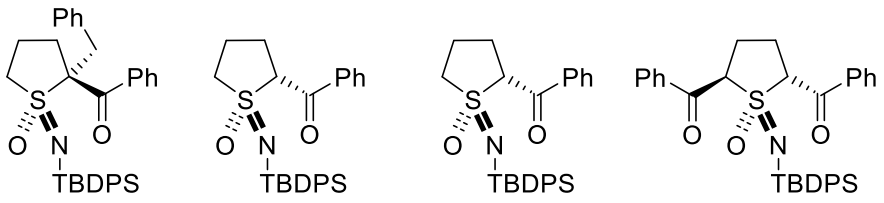
238 *cis*-**183** *trans*-**183**

LHMDS (0.55 mL of a 1.0 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS keto-sulfoximine *cis*-**183** (231 mg, 0.50 mmol,

1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture (by ^{1}H NMR spectroscopy) of keto-sulfoximines *cis*-**183** and *trans*-**183**. Purification by flash column chromatography on silica with 7:3 and then 1:1 hexane-EtOAc as eluent gave keto-sulfoximine *trans*-**183** (50 mg, 22%) as a white solid, mp 112–115 °C, R_F (1:1 hexane-EtOAc) 0.35; IR (ATR) 3070, 3049, 2930, 2891, 2856, 1687 (C=O), 1586, 1427, 1300, 1256, 1154, 1108, 998, 821, 731, 699, 603, 500, 487 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (d, *J* = 1.5 Hz, 1H, Ar), 8.75–8.70 (m, 1H, Ar), 8.11–8.04 (m, 1H, Ar), 7.78–7.67 (m, 4H, Ph), 7.43–7.34 (m, 6H, Ph), 7.23 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar), 4.64 (dd, *J* = 8.0, 5.5 Hz, 1H, SCH), 3.00–2.90 (m, 1H), 2.88–2.80 (m, 1H), 2.76–2.68 (m, 1H), 2.34–2.26 (m, 1H, CH), 2.22–2.09 (m, 2H, CH), 1.08 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 191.3 (C=O), 153.9 (Ar), 150.5 (Ar), 136.6 (Ar), 135.68 (Ar), 135.63 (Ar), 135.48 (*ipso*-Ar), 135.44 (*ipso*-Ar), 132.2 (*ipso*-Ar), 129.7 (Ar), 127.89 (Ar), 127.84 (Ar), 123.5 (Ar), 69.3 (SCH), 56.5 (SCH_2), 27.1 (CMe_3), 25.5 (CH_2), 21.4 (CH_2), 19.4 (CMe_3) (one Ar resonance not resolved); MS (ESI) *m/z* 463 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{26}H_{30}N_2O_2SSi$ $(M + H)^+$ 463.1870, found 463.1877 (–1.6 ppm error) and keto-sulfoximine *cis*-**183** (157 mg, 68%) as a white solid. The stereochemistry of keto-sulfoximines *cis*-**183** and *trans*-**183** was assigned by analogy with related examples.

Lab book reference: **GH-2-19**

Attempted synthesis of 2-benzoyl-2-benzyl-1-[(tert-butyldiphenylsilyl)imino]-1λ⁶-thiolan-1-one 242 and 2,5-dibenzoyl-1-[(tert-butyldiphenylsilyl)imino]-1λ⁶-thiolan-1-one *trans,cis*-239

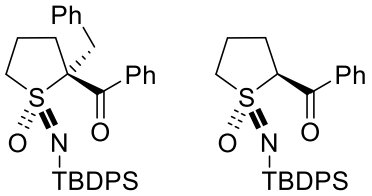


242 *trans*-**180** *cis*-**180** *trans,cis*-**239**

LHMDS (0.55 mL of a 1.0 M solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine *cis*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 70:20:10 mixture (by ^{1}H NMR spectroscopy) of monosubstituted sulfoximine *trans*-**180**, disubstituted sulfoximine *trans,cis*-**239** and monosubstituted sulfoximine *cis*-**180**. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave a 50:50 mixture of sulfoximines *cis*-**180**, and *trans,cis*-**239** (43 mg, 19 mg (8%) of *cis*-**180** and 22 mg (8%) of *trans,cis*-**239**) as a white solid, R_F (8:2 hexane-EtOAc) 0.36; IR (ATR) 3069, 2930, 2856, 1682, 1327, 1299, 1154, 1108, 728, 701, 603, 501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for *trans,cis*-**239** δ 8.17–8.10 (m, 2H, Ph), 7.69–7.64 (m, 2H, Ph), 7.63–7.29 (m, 12H, Ph), 7.25–7.14 (m, 4H, Ph), 5.16 (dd, *J* = 8.0, 8.0 Hz, 1H, SCH), 4.62 (dd, *J* = 8.0, 3.5 Hz, 1H, SCH), 3.11–3.01 (m, 1H, CH), 2.68–2.52 (m, 2H, CH), 2.46–2.35 (m, 1H, CH), 0.80 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *trans,cis*-**239** δ 193.1 (C=O), 190.1 (C=O), 136.6 (*ipso*-Ph), 136.4 (*ipso*-Ph), 135.8 (Ph), 135.7 (Ph), 134.9 (*ipso*-Ph), 134.1 (Ph), 133.6 (Ph), 129.8 (Ph), 129.6 (Ph), 129.1 (Ph), 128.8 (Ph), 128.7 (Ph), 127.8 (Ph), 127.7 (Ph), 69.0 (SCH), 68.7 (SCH), 26.2 (C*Me*$_3$), 24.0 (CH_2), 23.7 (CH_2), 19.3 (*C*Me$_3$) (two Ph resonances not resolved); MS (ESI) *m/z* 566 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{34}H_{35}NO_3SSi$ $(M + H)^+$ 566.2180, found 566.2183 (–0.7 ppm error) and sulfoximine *trans*-**180** (109 mg, 47%) as a white solid

Lab book reference: **GH-2-22**

Attempted synthesis of 2,5-Dibenzoyl-1-[(*tert*-butyldiphenylsilyl)imino]-1λ^6-thiolan-1-one 242

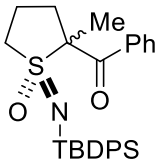


242 *trans*-**180**

KHMDS (1.1 mL of a 0.5 M solution in toluene, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180** and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained only keto-sulfoximine *trans*-**242** (by ^{1}H NMR spectroscopy).

Lab book reference: **GH-2-33**

Attempted synthesis of 2-Benzoyl-1-[(*tert*-butyldiphenylsilyl)imino]-2-methyl-1λ⁶-thiolan-1-one 243



243

LHMDS (0.55 mL of a 1.0 M solution in THF, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180** and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 98:2 and then 95:5 hexane-EtOAc as eluent gave a single unassigned diastereomeric sulfoximine **243** (14 mg, 6%)

as a white solid, R_F (8:2 hexane-EtOAc) 0.35; IR (ATR) 3069, 2956, 2928, 2855, 1680 (C=O), 1427, 1306, 1263, 1142, 1109, 737, 702, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15–8.09 (m, 2H, Ph), 7.82–7.77 (m, 3H, Ph), 7.46–7.32 (m, 10H, Ph), 3.24–3.14 (m, 1H, SCH), 2.92–2.82 (m, 1H, SCH), 2.69–2.58 (m, 1H, CH), 2.22–2.08 (m, 1H, CH), 1.97–1.85 (m, 1H, CH), 1.79–1.69 (m, 1H, CH), 1.74 (s, 3H, Me), 1.17 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.1 (C=O), 136.3 (*ipso*-Ph), 135.9 (Ph), 135.8 (Ph), 135.7 (*ipso*-Ph), 134.9 (Ph), 132.5 (Ph), 130.1 (Ph), 129.52 (Ph), 129.51 (Ph), 128.2 (Ph), 127.78 (Ph), 127.76 (Ph), 74.1 (S*C*Me), 57.8 (SCH_2), 36.6 (SC*Me*), 27.3 (CMe_3), 25.0 (CH_2), 20.1 (CH_2), 19.8 (CMe_3) (one *ipso*-Ph resonance not resolved); MS (ESI) *m/z* 476 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{33}NO_2SSi$ $(M + H)^+$ 476.2074, found 476.2083 (–1.9 ppm error), a 60:40 mixture (by ^1H NMR spectroscopy) of keto-sulfoximines *cis*-**180** and *trans*,*cis*-**239** (70 mg, 39 mg (17%) of *cis*-**180** and 31 mg (11%) of *trans*,*cis*-**239**) and keto-sulfoximine *trans*-**180** (130 mg, 56%).

Lab book reference: **GH-2-36**

KHMDS (1.1 mL of a 0.5 M solution in toluene, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180** and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 and then 95:5 hexane-EtOAc as eluent gave a single unassigned diastereomeric sulfoximine **243** (12 mg, 5%) as a white solid and a 70:30 mixture (by ^1H NMR spectroscopy) of keto-sulfoximines *cis*-**180** and *trans*,*cis*-**239** (69 mg, 45 mg (20%) of *cis*-**180** and 24 mg (8%) of *trans*,*cis*-**239**) and keto-sulfoximine *trans*-**180** (135 mg, 58%).

Lab book reference: **GH-2-37**

NaHMDS (0.28 mL of a 2.0 M solution in toluene, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180**

and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 and then 95:5 hexane-EtOAc as eluent gave a single unassigned diastereomeric sulfoximine **243** (2 mg, 1%) as a white solid, and a 65:25:10 mixture (by ^{1}H NMR spectroscopy) of keto-sulfoximines *trans*-**180**, *cis*-**180**, and *trans,cis*-**239** (189 mg, 120 mg (52%) of *trans*-**180**, 46 mg (20%) of *cis*-**180** and 22 mg (8%) of *trans,cis*-**239**).

Lab book reference: **GH-2-38**

NaH (0.022g of 60% in mineral oil, 0.55 mmol, 1.1 eq.) was added to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180** and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 97:3 and then 95:5 hexane-EtOAc as eluent gave a single unassigned diastereomeric sulfoximine **243** (10 mg, 4%) as a white solid, and a 65:25:10 mixture (by ^{1}H NMR spectroscopy) of keto-sulfoximines *trans*-**180**, *cis*-**180** and *trans,cis*-**239** (200 mg, 127 mg (55%) of *trans*-**180**, 49 mg (21%) of *cis*-**180** and 24 mg (8%) of *trans,cis*-**239**).

Lab book reference: **GH-2-39**

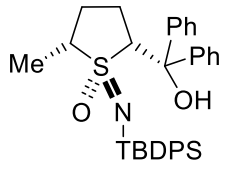
n-BuLi (0.65 mL of a 2.3 M solution in hexane, 1.5 mmol, 1.0 eq) was added dropwise to a stirred solution of diisopropylamine (0.21 mL, 1.5 mmol, 1.0 eq) in THF (1 mL) at 0

°C under Ar. The resulting solution was stirred at 0 °C for 30 min. This gave a freshly prepared solution of LDA in THF.

Freshly prepared LDA (0.68 mL of a 0.8 M solution in THF, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of a 75:25 mixture of *N*-TBDPS keto-sulfoximines *cis*-**180** and *trans*-**180** (231 mg, 0.50 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, methyl iodide (0.06 mL, 1.0 mmol, 2.0 eq) was added dropwise. The resulting solution was stirred at –78 °C for 1 h and then allowed to warm to rt. Then, water (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained an 85:15 mixture (by ^{1}H NMR spectroscopy) of keto-sulfoximines *trans*-**180** and *cis*-**180**

Lab book reference: **GH-2-60**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(hydroxydiphenylmethyl)-5-methyl-1λ⁶-thiolan-1-one *cis,cis*-244



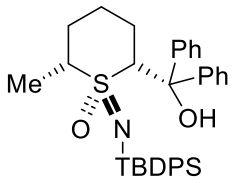
cis,cis-**244**

Using general procedure A, *N*-TBDPS sulfoximine *cis*-**172** (186 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product. Purification by flash column chromatography on silica with 98:2 hexane-EtOAc as eluent gave disubstituted sulfoximine *cis,cis*-**244** (197 mg, 71%) as a white solid, mp 58–60 °C; R_F (9:1 hexane-EtOAc) 0.5; IR (ATR) 3433 (OH), 3068, 2930, 2855, 2194, 1449, 1427, 1310, 1240, 1107, 730, 700, 644, 605, 501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.77 (m, 2H, Ph), 7.77–7.73 (m, 2H, Ph), 7.61–7.56 (m, 2H, Ph), 7.50–7.36 (m, 6H, Ph), 7.36–7.25 (m, 6H, Ph), 7.25–7.14 (m, 2H, Ph), 5.20 (s, 1H, COH), 4.43 (dd, *J* = 8.5, 8.5 Hz, 1H, SCH), 2.78–2.66 (m, 1H, SCH), 2.26–2.05 (m, 2H, CH), 1.85–1.68 (m, 2H, CH), 1.07 (s, 9H, CMe_3), 0.95 (d, *J* = 7.0 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 145.66 (*ipso*-Ph), 145.57 (*ipso*-Ph), 136.3 (*ipso*-Ph), 136.1 (*ipso*-Ph), 135.8 (Ph), 135.7 (Ph), 129.32 (Ph), 129.26 (Ph), 128.41 (Ph), 128.37 (Ph), 127.7 (Ph), 127.5 (Ph), 127.1 (Ph), 126.7 (Ph), 126.3 (Ph), 125.1 (Ph), 78.5 (COH), 71.7 (S*C*HCOH), 62.3 (S*C*HMe), 29.0 (CH_2), 27.1 (C*Me*$_3$), 24.3 (CH_2), 19.3 (*C*Me$_3$), 13.5 (SCH*Me*); MS (ESI) *m/z* 554 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{34}H_{39}NO_2SSi$ $(M + H)^+$ 554.2544, found 554.2552 (–1.6 ppm error). The stereochemistry of disubstituted sulfoximine *cis,cis*-**244** was assigned by analogy with related examples.

Lab book reference: **GH-1-87-2**

1-[(*tert*-Butyldiphenylsilyl)imino]-2-(hydroxydiphenylmethyl)-6-methyl-1λ⁶-thian-1-one *cis,cis*-245

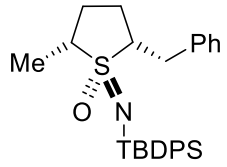


cis,cis-**245**

Using general procedure A, *N*-TBDPS methyl sulfoximine *cis*-**174** (193 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzophenone (0.25 mL of a 4 M solution in THF, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave disubstituted sulfoximine *cis,cis*-**245** (231 mg, 81%) as a white solid, mp 108–110 °C, R_F (9:1 hexane-EtOAc) 0.47; IR (ATR) 3286 (OH), 3055, 2932, 2856, 1255, 1155, 1106, 909, 729, 698, 610, 492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.69 (m, 6H, Ph), 7.45–7.22 (m, 14H, Ph), 3.88 (dd, *J* = 12.0, 1.5 Hz, 1H, SCH), 2.94–2.82 (m, 1H, SCH), 2.30–2.15 (m, 1H, CH), 1.93–1.85 (m, 1H, CH), 1.81–1.64 (m, 3H, CH), 1.41–1.28 (m, 1H, CH), 0.91 (s, 9H, CMe$_3$), 0.49 (d, *J* = 7.0 Hz, 3H, SCH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.4 (*ipso*-Ph), 142.1 (*ipso*-Ph), 136.2 (*ipso*-Ph), 136.0 (Ph), 135.7 (Ph), 135.40 (*ipso*-Ph), 129.33 (Ph), 129.25 (Ph), 128.9 (Ph), 128.3 (Ph), 127.69 (Ph), 127.66 (Ph), 127.5 (Ph), 127.4 (Ph), 127.3 (Ph), 82.2 (COH), 74.7 (SC*H*COH), 64.4 (SC*H*Me), 33.2 (CH_2), 28.6 (CH_2), 26.9 (C*Me*$_3$), 26.5 (CH_2), 19.6 (*C*Me$_3$), 12.7 (SCH*Me*) (one Ph resonance not resolved); MS (ESI) *m/z* 568 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{35}H_{41}NO_2SSi$ $(M + H)^+$ 568.2700, found 568.2687 (+2.4 ppm error).

Lab book reference: **GH-2-64-2**

2-Benzyl-1-[(*tert*-butyldiphenylsilyl)imino]-5-methyl-1λ⁶-thiolan-1-one *cis,cis*-246

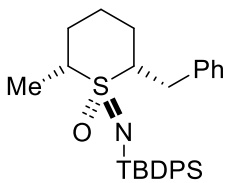


cis,cis-**246**

Using general procedure A, *N*-TBDPS sulfoximine *cis*-**172** (186 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 95:5 and then 9:1 hexane-EtOAc as eluent gave disubstituted sulfoximine *cis,cis*-**246** (198 mg, 86%) as a clear viscous oil, R_F (8:2 hexane-EtOAc) 0.63; IR (ATR) 3068, 2930, 2855, 1322, 1247, 1145, 1107, 821, 736, 701, 605, 500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.72 (m, 4H, Ph), 7.41–7.32 (m, 6H, Ph), 7.25–7.14 (m, 3H, Ph), 6.94–6.88 (m, 2H, Ph), 3.07–2.88 (m, 3H, SCH, PhC*H*), 2.57–2.47 (m, 1H, PhC*H*), 2.07–1.95 (m, 1H, CH), 1.88–1.77 (m, 1H, CH), 1.75–1.58 (m, 2H, CH), 1.17 (d, *J* = 7.0 Hz, 3H, SCH*Me*), 1.08 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.3 (*ipso*-Ph), 136.86 (*ipso*-Ph), 136.80 (*ipso*-Ph), 135.78 (Ph), 135.75 (Ph), 129.23 (Ph), 129.20 (Ph), 129.1 (Ph), 128.6 (Ph), 127.63 (Ph), 127.61 (Ph), 126.6 (Ph), 65.1 (S*C*HCH$_2$Ph), 60.0 (S*C*HMe), 33.9 (Ph*C*H$_2$), 28.0 (CH_2), 27.3 (C*Me*$_3$), 25.7 (CH_2), 19.4 (*C*Me$_3$), 12.8 (SCH*Me*); MS (ESI) *m/z* 462 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}NOSSi$ $(M + H)^+$ 462.2281, found 462.2285 (–0.7 ppm error). The stereochemistry of disubstituted sulfoximine *cis,cis*-**246** was assigned by analogy with related examples.

Lab book reference: **GH-2-28**

2-Benzyl-1-[(*tert*-butyldiphenylsilyl)imino]-6-methyl-1λ⁶-thian-1-one *cis,cis*-247

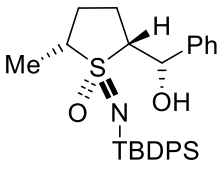


cis,cis-**247**

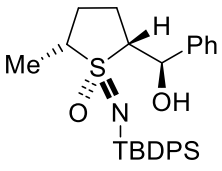
Using general procedure A, *N*-TBDPS sulfoximine *cis*-**174** (193 mg, 0.5 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzyl bromide (0.12 mL, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 95:5 hexane-EtOAc as eluent gave disubstituted sulfoximine *cis,cis*-**247** (202 mg, 85%) as a white solid, mp 110–112 °C, R_F (9:1 hexane-EtOAc) 0.39; IR (ATR) 3068, 2931, 2854, 1346, 1277, 1159, 1106, 759, 733, 701, 648, 603, 493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 4H, Ph), 7.45–7.33 (m, 6H, Ph), 7.24–7.14 (m, 3H, Ph), 6.84–6.77 (m, 2H, Ph), 3.36 (dd, *J* = 13.5, 2.5 Hz, 1H, PhC*H*), 2.94–2.79 (m, 2H, SCH), 2.46 (dd, *J* = 13.0, 12.0 Hz, 1H, PhC*H*), 1.87–1.59 (m, 5H, CH), 1.35–1.22 (m, 1H, CH), 1.18 (d, *J* = 7.0 Hz, 3H, SCH*Me*), 1.10 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.9 (*ipso*-Ph), 136.9 (*ipso*-Ph), 136.5 (*ipso*-Ph), 135.79 (Ph), 135.74 (Ph), 129.5 (Ph), 129.1 (Ph), 128.5 (Ph), 127.61 (Ph), 127.55 (Ph), 126.5 (Ph), 67.2 (SCH), 61.6 (SCH), 32.8 (CH_2), 31.5 (Ph*C*H_2), 29.0 (CH_2), 27.3 (C*Me*$_3$), 25.0 (CH_2), 19.9 (*C*Me$_3$), 12.2 (SCH*Me*) (one Ph resonance not resolved); MS (ESI) *m/z* 476 (M + H)$^+$; HRMS (ESI) *m/z* calcd for $C_{29}H_{37}NOSSi$ (M + H)$^+$ 476.2438, found 476.2428 (+2.0 ppm error). The stereochemistry of disubstituted sulfoximine *cis,cis*-**247** was assigned by analogy with related examples.

Lab book reference: **GH-2-65-2**

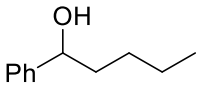
1-{[Diphenyl(trimethylsilyl)methyl]imino}-2-[hydroxy(phenyl)methyl]-5-methyl-1λ⁶-thiolan-1-one *cis,cis,anti*-248 and *cis,cis,syn*-248 and 1-phenyl-1-pentanol 249



cis,cis,anti-**248**



cis,cis,syn-**248**



249

Using general procedure A, *N*-TBDPS sulfoximine *cis*-**172** (186 mg, 0.50 mmol, 1.0 eq.), *n*-BuLi (0.24 mL of a 2.3 M solution in hexanes, 0.55 mmol, 1.1 eq.) and benzaldehyde (0.10 mL, 1.0 mmol, 2.0 eq) in THF (5 mL) gave the crude product which contained a 60:25:15 mixture (by ^1H NMR spectroscopy) of alcohols *cis,cis,anti*-**248**, *cis,cis,syn*-**248** and 1-phenyl-1-pentanol **249** i.e. a 70:30 mixture of alcohols *cis,cis,anti*-**248** and *cis,cis,syn*-**248**. Purification by flash column chromatography on silica with 97:3 and then 95:5 hexane-EtOAc as eluent gave an 85:15 mixture of alcohol *cis,cis,anti*-**248** and 1-

phenyl-1-pentanol **249** (161 mg, 152 mg (64%) of *cis,cis,anti*-**248** and 9 mg (10%) of 1-phenyl-1-pentanol **249**) as a white solid, mp 80–82 °C, R_F (9:1 hexane-EtOAc) 0.26; IR (ATR) 3479 (OH), 3068, 2930, 2855, 1451, 1427, 1313, 1244, 1132, 1103, 821, 733, 699, 607, 499 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) for *cis,cis,anti*-**248** δ 7.82–7.78 (m, 2H, Ph), 7.77–7.74 (m, 2H, Ph), 7.34–7.34 (m, 6H, Ph), 7.25–7.18 (m, 3H, Ph), 6.96–6.92 (m, 2H, Ph), 5.07 (brs, 1H, PhC*H*OH), 4.04 (d, *J* = 2.0 Hz, 1H, PhCHO*H*), 3.05–2.94 (m, 2H, SCH), 2.24–2.13 (m, 1H, CH), 2.11–2.01 (m, 1H, CH), 1.79–1.67 (m, 1H, CH), 1.64–1.53 (m, 1H, CH), 1.26 (d, *J* = 7.0 Hz, 3H, SCH*Me*), 1.11 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) for *cis,cis,anti*-**248** δ 140.5 (*ipso*-Ph), 136.34 (*ipso*-Ph), 136.31 (*ipso*-Ph), 135.68 (Ph), 135.63 (Ph), 129.46 (Ph), 129.38 (Ph), 128.3 (Ph), 127.77 (Ph), 127.71 (Ph), 127.3 (Ph), 125.5 (Ph), 69.0 (SCH), 68.5 (Ph*C*HOH), 61.1 (SCH), 28.8 (CH_2), 27.2 (C*Me*$_3$), 19.5 (CH_2), 19.3 (*C*Me_3), 11.7 (SCH*Me*); MS (ESI) *m/z* 478 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}NO_2SSi$ $(M + H)^+$ 478.2231, found 478.2237 (–1.4 ppm error) and alcohol *cis,cis,syn*-**248** (53 mg, 22%) as a white solid, mp 140–142 °C, R_F (9:1 hexane-EtOAc) 0.18; IR (ATR) 3472 (OH), 3068, 2930, 2855, 1454, 1427, 1310, 1242, 1136, 1107, 821, 767, 732, 700, 606, 500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 4H, Ph), 7.44–7.35 (m, 6H, Ph), 7.34–7.27 (m, 3H, Ph), 7.24–7.20 (m, 2H, Ph), 4.83 (dd, *J* = 9.5, 3.0 Hz, 1H, PhC*H*OH), 4.06 (d, *J* = 3.0 Hz, 1H, PhCHO*H*), 3.26–3.18 (m, 1H, SCH), 2.96–2.86 (m, 1H, SCH), 2.09–1.99 (m, 1H, CH), 1.74–1.56 (m, 3H, CH), 1.13 (d, *J* = 7.0 Hz, 3H, SCH*Me*), 1.10 (s, 9H, C*Me*$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.4 (*ipso*-Ph), 136.29 (*ipso*-Ph), 136.23 (*ipso*-Ph), 135.8 (Ph), 129.4 (Ph), 128.7 (Ph), 128.4 (Ph), 127.7 (Ph), 127.6 (Ph), 127.1 (Ph), 74.6 (Ph*C*HOH), 70.5 (SCH), 62.1 (SCH), 29.1 (CH_2), 27.2 (C*Me*$_3$), 24.7 (CH_2), 19.3 (*C*Me_3), 13.3 (SCH*Me*) (two Ph resonances not resolved); MS (ESI) *m/z* 478 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}NO_2SSi$ $(M + H)^+$ 478.2231, found 478.2234 (–0.7 ppm error). The stereochemistry of sulfoximines *cis,cis,anti*-**248** and *cis,cis,syn*-**248** was assigned by analogy with related examples.

Diagnostic signals for 1-phenyl-1-pentanol **249** ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (ddd, *J* = 7.5, 6.0, 3.5 Hz, 1H, PhC*H*OH) 0.89 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (*ipso*-Ph), 128.5 (Ph), 127.5 (Ph), 126.0 (Ph), 74.7 (PhCOH), 39.0 (PhCOH*C*H_2), 28.1 (MeCH_2*C*H_2), 22.7 (Me*C*H_2), 14.1 (Me). Spectroscopic data are consistent with those reported in the literature.[72]

Lab book reference: **GH-2-18**

Abbreviations

Ar	argon
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CPME	cyclopentyl methyl ether
d	doublet
DCE	1,2-dichloroethane
dba	Dibenzylideneacetone
DME	1,2-Dimethoxyethane
DPH	*O*-(2,4-dinitrophenyl)hydroxylamine
dr	diastereomeric ratio
E^+	electrophile
esp	α,α,α′,α′-Tetramethyl-1,3-benzenedipropionic acid
eq.	equivalent
HMDS	hexamethyldisilizane
HMPA	hexamethylphosphoramide
HOBt	hydroxybenzotriazole
Hz	Hertz
IR	infra-red
J	coupling constant in Hz
KHMDS	potassium hexamethyldisilazide
LHMDS	lithium hexamethyldisilazide
m	multiplet
M	molar
*m*CPBA	3-chloroperbenzoic acid
M^+	molecular ion
Me	methyl
min	minute
MP	melting point
MS	mass spectrometry

MSH	*O*-mesitylsulfonylhydroxylamine
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
Ns	*para*-nitrobenzenesulfonyl
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
PMB	*p*-methoxybenzyl
rt	room temperature
s	singlet
SES	trimethylsilylethylsulfonyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TFE	tetrafluoroethylene
TMS	trimethylsilyl
Ts	tosyl
X-Phos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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