Diastereoselective Synthesis of β-Aryl Cyclic Sulfoximines

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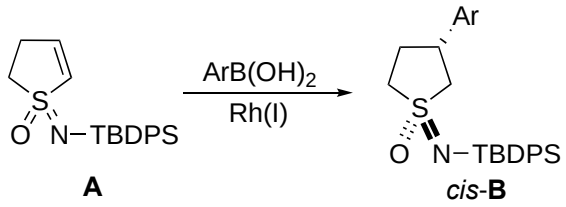
Abstract

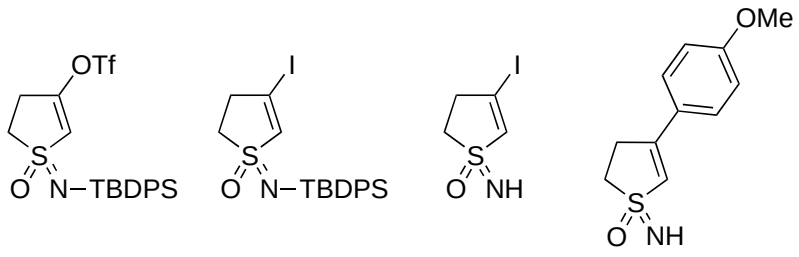
This thesis describes the diastereoselective synthesis of a β-functionalised 5-membered ring *N*-TBDPS sulfoximine *via* a novel Rh-catalysed conjugate addition reaction. The developments of synthetic methodology to a *N*-TBDPS sulfoximine enol triflate and a *N*-TBDPS iodo vinyl sulfoximine for use in a Suzuki-Miyaura cross-coupling-hydrogenation approach to β-aryl sulfoximines are also described.

Section 2.1 covers the relevant literature background for the Rh-catalysed β-arylation reactions of electron-deficient alkenes. The attempted synthesis of cyclic vinyl sulfoximine **A**, proceeding *via* a halocyclisation route, are outlined in Section 2.2. In Section 2.3, an alternative approach for the formation of vinyl sulfoximine **A** *via* elimination of a leaving group in the β-position is presented. Section 2.4 covers the successful synthesis of vinyl sulfoximine **A** and the subsequent Rh-catalysed conjugate addition of arylboronic acids to vinyl sulfoximine **A** to form β-aryl *N*-TBDPS sulfoximines *cis*-**B**.



A *cis*-**B**

Section 3.1 gives an overview of the relevant literature for the formation and Suzuki-Miyaura cross-coupling of enol triflates bearing an electron-withdrawing group in the β-position. Section 3.2 outlines the attempted synthesis of *N*-TBDPS sulfoximine enol triflate **C** using a ketal protecting group strategy. In Section 3.3, an iodo cyclisation approach for the synthesis of *N*-TBDPS iodo vinyl sulfoximine **D** is explored. The synthesis of NH iodo vinyl sulfoximine **E** and a β-aryl NH vinyl sulfoximine **F** were achieved. However, their subsequent *N*-TBDPS protection was unsuccessful.



C **D** **E** **F**

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Author's Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Hannah Smith

Abbreviations

acac	acetylacetone
Ad	adamantyl
ATR	ataxia telangiectasia and Rad3-related
(*R*,*R*)-Chiraphos	(2*R*,3*R*)-(+)-*bis*(diphenylphosphino)butane
(*S*,*S*)-Chiraphos	(2*S*,3*S*)-(-)-*bis*(diphenylphosphino)butane
cod	1,5-cyclooctadiene
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binapthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
d	doublet
dd	doublet of doublets
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dppb	1,4-*bis*(diphenylphosphino)butane
dppf	1,1'-ferrocenediyl-*bis*(diphenylphosphine)
dr	diastereomeric ratio
E	electrophile
eq.	equivalent
Et	ethyl
EWG	electron-withdrawing group
h	hour
Hz	Hertz
IR	infra-red
J	coupling constant in Hz

m	multiplet
M	molar
M^+	molecular ion
Me	methyl
min	minute
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
Ph	phenyl
Pin	2,3-dimethylbutane-2,3-diol
Pr	propyl
PIDA	(diacetoxyiodo)benzene
q	quartet
rt	room temperature
s	singlet
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
Tol	tolyl
Ts	tosyl
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

1. Introduction

1.1 Introduction to sulfoximines

Until recently, the sulfoximine functional group has been relatively underexplored despite its discovery in the form of methionine sulfoximine in the 1950s.[1] Subsequent to this, sulfoximines have been an area of focus in synthetic chemistry due to their application in agrochemical agents[2] and their potential uses in medicinal chemistry.[3] Sulfoximines are versatile: they possess a nucleophilic and basic nitrogen atom, as well as a sulfur atom that is stereogenic if $R^1 \neq R^2$ (Figure 1.1). This has allowed sulfoximines to be used as chiral auxiliaries in asymmetric synthesis.[4] Moreover, the electron-withdrawing nature of the sulfoximine functional group[5] results in acidic α-protons which can be a route to α-functionalisation.

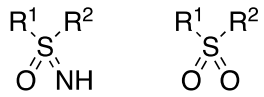
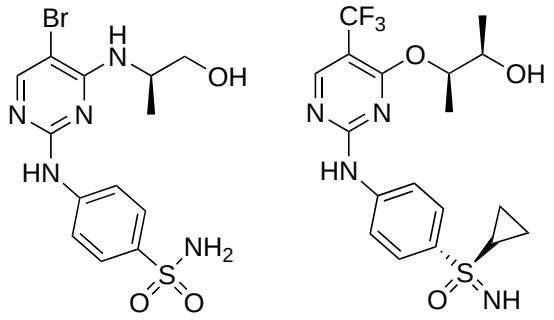


Figure 1.1 Sulfoximine and sulfone functional groups

Sulfoximines are isoelectronic to the sulfone functional group (Figure 1.1). It is important to note the diversity in reactivity and functionality that sulfoximines have over sulfones due to the replacement of an oxygen atom with a nitrogen atom. Sulfoximines exhibit a range of properties including hydrogen-bonding ability,[5] and in contrast to sulfones, sulfoximines have increased polarity[6] and improved water solubility.[7] This exemplifies the advantageous drug-like properties that sulfoximines possess. In a study by Frings *et al.*,[8] most sulfoximine derivatives tested were found to have high microsomal stability in human liver microsomes showing that the sulfoximine moiety is intrinsically metabolically stable.

With growing interest in sulfoximines, the motif has featured in some recent drug discoveries. This is best illustrated by BAY 1000394, an enantiopure pan-CDK inhibitor (Figure 1.2), developed by Bayer Pharma.[9] BAY 1000394 reached phase II clinical trials[10] in patients with advanced solid tumors.[11] Initially, sulfonamide-containing ZK 304709 was investigated but development was terminated due to its low thermodynamic solubility in water (8 mg L^{-1}) and high dose required for administration.[12] Following this, the need for improved physicochemical, pharmacological and pharmacokinetic properties were addressed in the identification of BAY 1000394, a sulfoximine-containing drug. It was

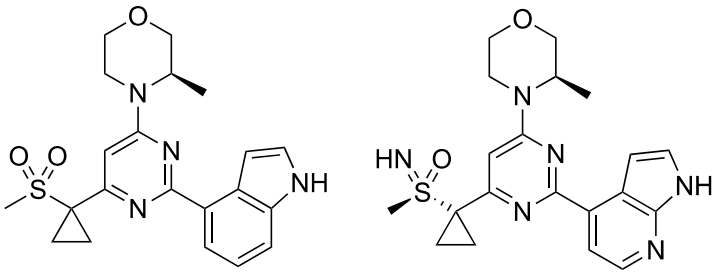
reported that BAY 1000394 overcame the limitations of ZK 304709 as it permitted higher water solubility (182 mg L^{-1}) and allowed Bayer Pharma to overcome dose limitations whilst still maintaining antitumor properties.[12]



ZK 304709 BAY 1000394

Figure 1.2 Sulfonamide and sulfoximine-containing drugs developed by Bayer Pharma

A second sulfoximine-containing drug to note is AZD6738, an ATR kinase inhibitor developed by AstraZeneca (Figure 1.3).[13] AZD6738 is currently undergoing phase II clinical trials[13] following previous development and termination of sulfone derivative AZ20. It was reported that AZD6738 exhibited higher aqueous solubility than sulfone analogue AZ20 and eliminated the high risk of drug-drug interactions that resulted from time-dependent CYP3A4 inhibition.[13] Low aqueous solubility observed in AZ20 would have limited the drug's maximum absorbable dose (D_{abs}), which is the maximum amount of an orally administered drug that can be absorbed in the gastrointestinal tract.[14] It was important to maintain high ATR potency whilst simultaneously eliminating CYP3A4 inhibition and achieving higher aqueous solubility and AZD6738 achieved this.



AZ20 AZD6738

Figure 1.3 Sulfone and sulfoximine-containing drugs developed by AstraZeneca

Unlike sulfones, sulfoximines possess a third position of diversification at the nitrogen, which means that they are amenable to synthetic modifications.[15] Due to the mild basicity

of the nitrogen atom, different *N*-functionality can be introduced onto it, leading to a range of protected or functionalised sulfoximines. Common examples of functionalised sulfoximines include aryl (*N*-Ar), alkyl (*N*-R), silyl (*N*-SiR_3) and cyano (*N*-CN). The electronic properties of the sulfoximine can be influenced by the group that is attached to the nitrogen. If an electron-withdrawing substituent is attached to the nitrogen, this will increase the overall polarity of the sulfoximine. In contrast, if an electron-donating substituent is attached, this will decrease the polarity of the sulfoximine.[16] Free NH sulfoximines are often observed in medicinal chemistry but the ability to protect the free amine group allows for alternative functionality to be exploited. Installation of different groups at the nitrogen gives way to a range of applications. For example, *N*-CN sulfoximines such as Sulfoxaflor are used as insecticides (Figure 1.4).

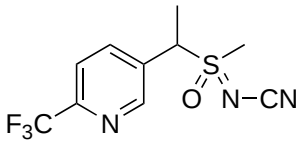


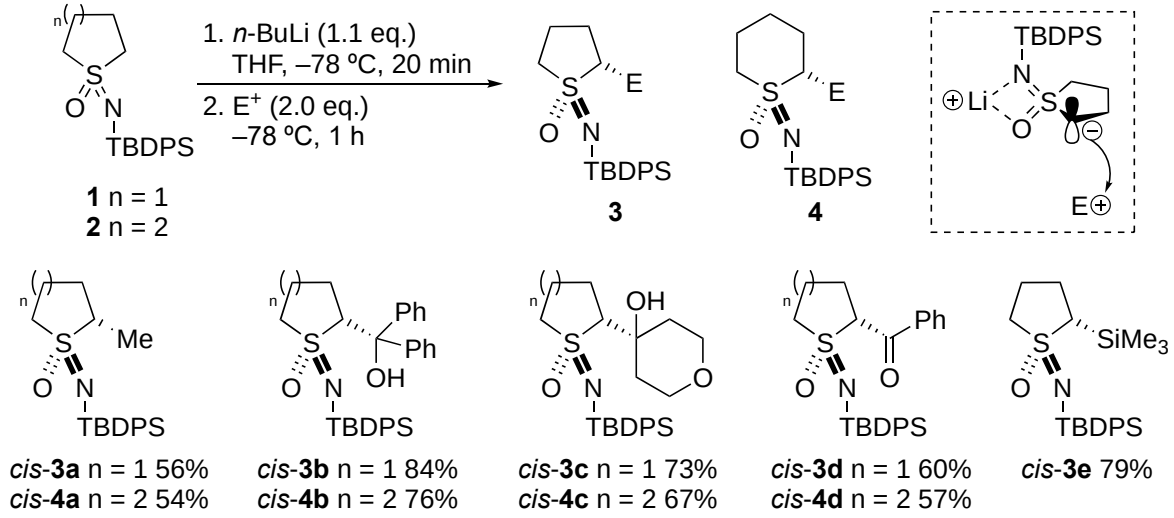
Figure 1.4 Sulfoximine-containing insecticide, Sulfoxaflor

The neonicotinoids are a class of insecticides that are chemically related to nicotine. However, insects have become increasingly resistant to neonicotinoids,[17] resulting in a demand for new insecticides such as those including the sulfoximine functionality. Sulfoxaflor was the first sulfoximine-containing insecticide to undergo commercial development and is effective against sap-feeding insects. Sulfoxaflor has a unique set of structural activity relationships (SAR) compared to neonicotinoids but sulfoxaflor still acts on the insect nicotinic receptors (nAChR). The difference in SAR is because neonicotinoids possess at least one sp^3 hybridised nitrogen. During the development of Sulfoxaflor, a nitro (NO_2) group was used as the *N*-substituent of the sulfoximine. Replacement of NO_2 with a cyano (CN) group was found to improve insecticidal activity.[17] Since then, the synthesis of sulfoximine insecticides bearing a cyano substituent has been widely explored.

1.2 α-Functionalisation of sulfoximines by lithiation-trapping and Negishi cross-coupling – previous work within the O'Brien group

The α-functionalisation of *N*-substituted sulfoximines *via* lithiation-trapping has been a focus of recent work in the O'Brien group. The α-functionalisation of cyclic sulfoximines was explored by Giordaina Hartley,[18,19] with attention paid to 5- and 6-membered ring sulfoximines as this has been relatively underexplored previously. Further work by Alexandra Hindle investigated the α-functionalisation of *N*-substituted acyclic sulfoximines.[20] The synthesis and deprotection of TBDPS-protected sulfoximines proved to be straightforward. In addition, the steric bulk of the *N*-TBDPS group resulted in highly diastereoselective reactions. Therefore, there has been particular focus on *N*-TBDPS sulfoximines within the O'Brien group, compared to the use of other *N*-protecting groups.

For example, high α-diastereoselectivity in the lithiation-trapping of 5- and 6-membered ring sulfoximines was observed.[18] Using a procedure reported for the lithiation of dimethyl sulfoximine,[21] 5- and 6-membered ring *N*-TBDPS sulfoximines **1** and **2** were lithiated using *n*-BuLi in THF at –78 °C for 20 min and then trapped using various electrophiles (methyl iodide, ketones, a Weinreb amide and Me_3SiCl) at –78 °C for 1 h. This gave α-substituted *N*-TBDPS sulfoximines *cis*-**3a-e** and *cis*-**4a-d** in high yields (Scheme 1.1).

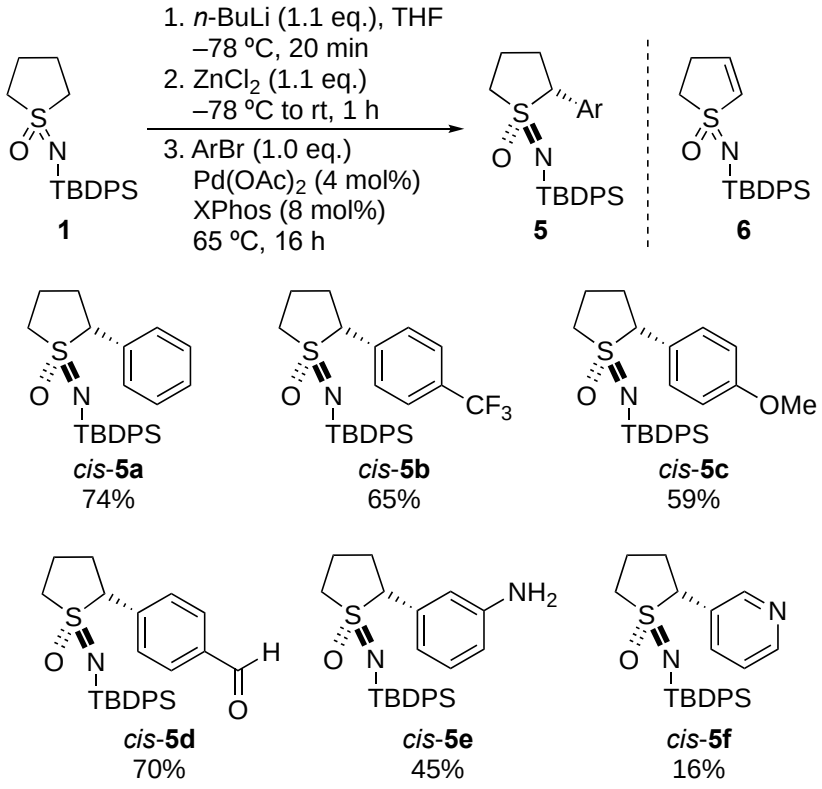


Scheme 1.1

The *cis*-stereochemistry of sulfoximines **3b** and **4b** was determined by X-ray crystallography. Using 5-membered ring *N*-TBDPS sulfoximine **1**, the proposed stereochemical model that explains the high diastereoselectivity of this methodology is

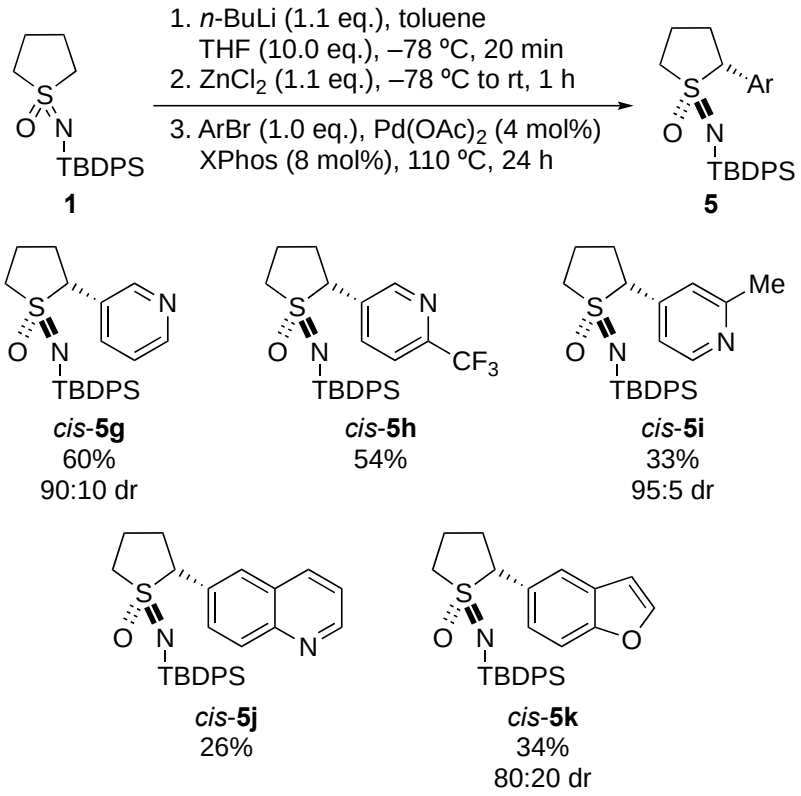
shown in the box in Scheme 1.1. The sterically bulky TBDPS group blocks one face of the lithiated sulfoximine from electrophilic attack of the carbanion and consequently, the attack occurs *cis* to the oxygen of the sulfoximine.

Further work on α-functionalisation in the group involved the development of α-arylation of *N*-TBDPS sulfoximine **1** using a Pd-catalysed Negishi cross-coupling reaction.[19] Using conditions adapted from the literature for the Pd-catalysed Negishi α-arylation of a range of sulfones,[22] lithiation of *N*-TBDPS sulfoximine **1** was carried out using standard lithiation conditions of *n*-BuLi in THF at –78 °C for 20 min. Then, anhydrous $ZnCl_2$ in THF was added and the solution was stirred at rt for 1 h before the addition of various aryl bromides and a solution of $Pd(OAc)_2$ and XPhos in THF. The resulting solution was heated at 65 °C for 16 h to give α-aryl sulfoximines *cis*-**5a-e** in 45-74% yields as single diastereomers (Scheme 1.2). In each case, it was reported that a small amount of vinyl sulfoximine **6** was obtained and, for the lower yielding reactions, a large amount of starting sulfoximine **1** was recovered. The reaction tolerated both electron-withdrawing and electron-donating substituents on the aryl bromides. However, a lower 16% yield of α-aryl sulfoximine *cis*-**5f** was obtained when cross-coupling with 3-bromopyridine was carried out.



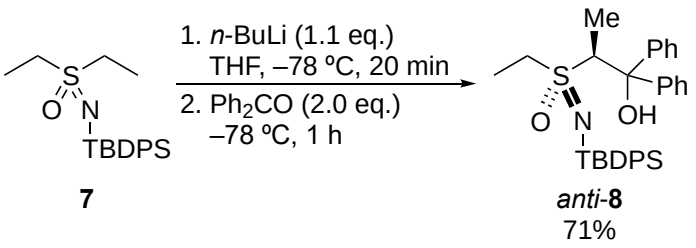
Scheme 1.2

The scope of the Pd-catalysed Negishi α-arylation of *N*-TBDPS sulfoximines was expanded when the reaction conditions were optimised to improve the yields with heteroaromatic bromides. Thus, *N*-TBDPS sulfoximine **1** was treated with *n*-BuLi in toluene/THF (10 eq.) at –78 °C for 20 min. Then, $ZnCl_2$ in THF was added and stirred at rt for 1 h before the addition of various heteroaromatic bromides and $Pd(OAc)_2$/XPhos. Since the bulk solvent was toluene, the resulting solution could be heated at a higher temperature of 110 °C. Using a reaction time of 24 h at 110 °C, a range of heteroaromatic α-aryl sulfoximines *cis*-**5g-k** were obtained in 26-60% yields with good *cis*-diastereoselectivity (Scheme 1.3).



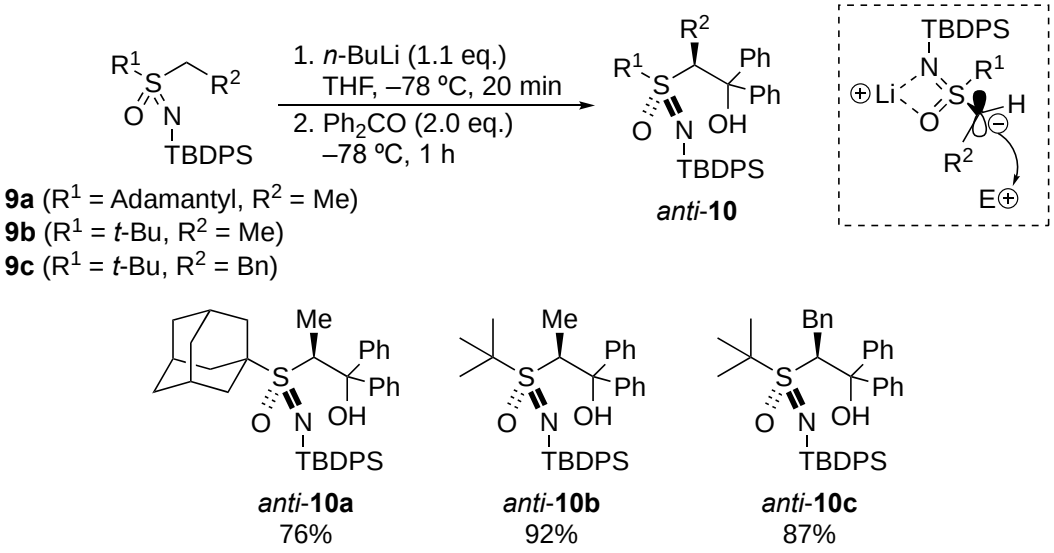
Scheme 1.3

As the TBDPS group displayed good diastereomeric control in the α-functionalisation of cyclic sulfoximines, further work in the group[20] investigated the α-functionalisation of acyclic sulfoximines *via* lithiation-trapping. For example, diethyl *N*-TBDPS sulfoximine **7** was lithiated with *n*-BuLi and then trapped with benzophenone to form α-substituted *N*-TBDPS sulfoximine *anti*-**8** in 71% yield (Scheme 1.4). The stereochemistry of *anti*-**8** was assigned *via* independent synthesis from a compound of known stereochemistry.



Scheme 1.4

Following this promising result, a variety of acyclic *N*-TBDPS sulfoximines were explored to test the scope of the reaction and three representative examples are shown in Scheme 1.5. Thus, adamantyl ethyl sulfoximine **9a** was lithiated using *n*-BuLi at –78 °C for 20 min and subsequently trapped with benzophenone at –78 °C for 1 h to give single diastereomeric alcohol *anti*-**10a** in 76% yield. Similarly, *tert*-butyl ethyl sulfoximine **9b** and *tert*-butyl benzyl sulfoximine **9c** were lithiated and trapped using benzophenone to give *anti*-**10b** (92% yield) and *anti*-**10c** (87% yield) respectively. A model to account for the observed *anti*-diastereoselectivity is shown in the box in Scheme 1.5. The steric bulk of the TBDPS group blocks one face of the lithiated sulfoximine from electrophilic attack on the carbanion in which the R^1 and R^2 groups adopt a conformation where they are held apart. Consequently, attack occurs *cis* to the oxygen of the sulfoximine.



Scheme 1.5

To summarise, a wide range of α-functionalised cyclic and acyclic *N*-TBDPS sulfoximines have been synthesised *via* lithiation-trapping methodology in high yields and diastereoselectivity. The major product was the *cis*-diastereomer for cyclic sulfoximines and

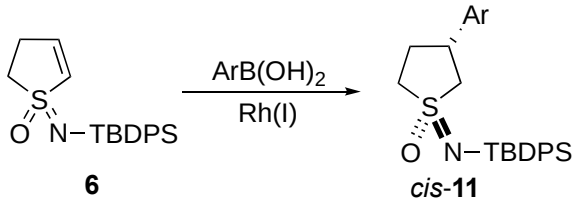
the *anti*-diastereomer for acyclic sulfoximines. Stereochemical models were proposed in both cases. Furthermore, Pd-catalysed Negishi cross-coupling of cyclic *N*-TBDPS sulfoximines with various aryl bromides expanded the scope for the α-functionalisation of cyclic sulfoximines and gave products in high yield and excellent diastereoselectivity.

1.3 Project outline

Over recent years, sulfoximines have attracted increasing attention for their use as potential medicinal compounds and agrochemical agents due to a variety of desirable properties. The development of synthetic routes for the installation and functionalisation of sulfoximines is therefore of importance. Previous work in the group[19] on the Pd-catalysed Negishi cross-coupling reaction (see Schemes 1.2 and 1.3) had provided a diastereoselective route to *cis*-α-aryl sulfoximines such as *cis*-**5a-k**. In order to broaden the scope of the synthesis of arylated cyclic sulfoximines, it was proposed to investigate the diastereoselective synthesis of β-aryl cyclic sulfoximines and this is the subject of this thesis.

Previous work within the O'Brien group (see Section 1.2) had recognised TBDPS as a versatile protecting group due to its facile protection and deprotection reactions of sulfoximine-containing compounds. The sterically bulky TBDPS group led to highly diastereoselective outcomes and it was hoped that this rationale could be applied to the diastereoselective synthesis of β-aryl cyclic sulfoximines. Therefore, the work described in this thesis has focused mainly on the use of *N*-TBDPS sulfoximines.

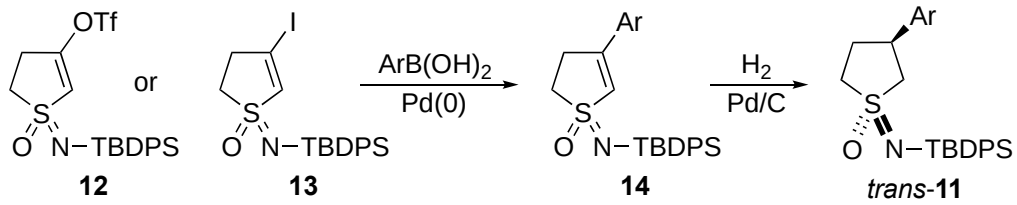
The proposed route for the synthesis of β-aryl 5-membered ring sulfoximines *cis*-**11** is shown in Scheme 1.6. The key step would be the Rh-catalysed conjugate addition of arylboronic acids to *N*-TBDPS vinyl sulfoximine **6**, based on work by Hayashi and Lim[23] on the corresponding vinyl sulfone, which was envisaged to give β-aryl *N*-TBDPS sulfoximines *cis*-**11**. It was proposed that the steric bulk of the TBDPS group would block one face of the alkene in **6** so that arylation would be directed to the opposite face. The results of our efforts on the synthesis and Rh-catalysed arylation of *N*-TBDPS vinyl sulfoximine **6** are described in Chapter 2.



Scheme 1.6

A complementary route to the diastereomeric β-aryl cyclic sulfoximines *trans*-**11** was also devised (Scheme 1.7). Starting from either sulfoximine enol triflate **12** or iodo vinyl sulfoximine **13**, Suzuki-Miyaura cross-coupling should give β-aryl vinyl sulfoximines **14**.

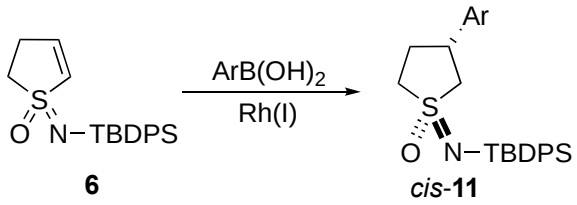
Subsequent diastereoselective hydrogenation should deliver β-aryl cyclic sulfoximines *trans*-**11** since it was predicted that hydrogenation of the alkene would occur on the opposite face to the TBDPS group. The results on this approach are described in Chapter 3.



Scheme 1.7

2. Rh-Catalysed β-Arylation of Cyclic Vinyl Sulfoximines

In this Chapter, the exploration of different synthetic routes to access *N*-TBDPS vinyl sulfoximine **6** is described, along with the subsequent study of the Rh-catalysed conjugate addition of arylboronic acids to vinyl sulfoximine **6**. The plan was that this would provide a route to β-aryl *N*-TBDPS sulfoximines *cis*-**11** since it was expected that the steric bulk of the TBDPS group would direct the arylation to the opposite face (Scheme 2.1).

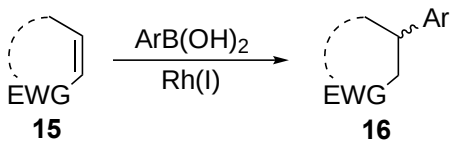


Scheme 2.1

Section 2.1 presents an overview of the relevant literature background for the racemic and asymmetric Rh-catalysed β-arylation reactions of electron-deficient alkenes, with particular focus on enones and vinyl sulfones. In Section 2.2, the attempted synthesis of *N*-TBDPS vinyl sulfoximine **6** *via* a halocyclisation route is outlined. Section 2.3 covers an alternative approach for the synthesis of *N*-TBDPS vinyl sulfoximine **6** *via* the elimination of a β-mesylate or β-acetoxy group. Finally, in Section 2.4 a successful route for the synthesis of *N*-TBDPS vinyl sulfoximine **6** is presented, together with some preliminary work on the Rh-catalysed β-arylation reaction to give β-aryl sulfoximine *cis*-**11**.

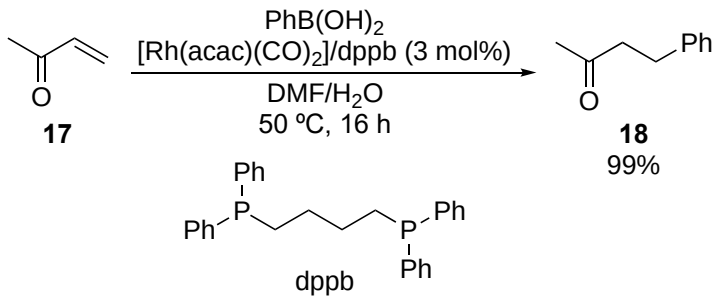
2.1 Rh-catalysed arylation of electron-deficient alkenes

Rh-catalysed arylation of electron-deficient alkenes such as **15** using arylboronic acids is a powerful synthetic tool for β-functionalisation to give arylated products **16** (Scheme 2.2). In particular, enantioselective arylation reactions have been widely studied.[24] The first example of a Rh-catalysed conjugate addition of an arylboronic acid to an enone was reported by Miyaura and co-workers in 1997.[25] Since then, this method of β-arylation has been widely used probably due to the neutral reaction conditions in the presence of water and tolerance of a wide range of functional groups in the organoboron reagents.[26] There have been many examples of β-functionalisation of α,β-unsaturated ketones[24] but comparatively fewer examples with α,β-unsaturated sulfones. In contrast, to the best of our knowledge, there are no examples of the Rh-catalysed arylation of vinyl sulfoximines. In this section, a selection of representative examples of Rh-catalysed conjugate additions to electron-deficient alkenes will be presented; as this is a large topic, there is a focus on enones and vinyl sulfones.



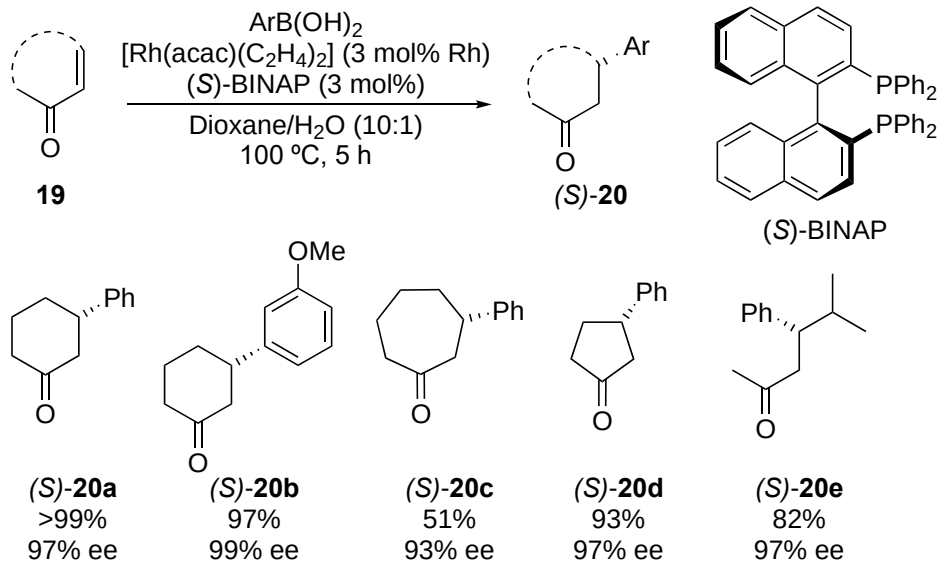
Scheme 2.2

In 1997, Miyaura and co-workers[25] reported the Rh-catalysed arylation of cyclic and linear α,β-unsaturated ketones using arylboronic acids. In their study, [Rh(acac)(CO)$_2$] was used with diphosphine ligand, dppb, in a range of different aqueous solvents. For example, methyl vinyl ketone **17** was converted into β-phenyl ketone **18** in 99% yield by reaction with [Rh(acac)(CO)$_2$]/dppb and phenylboronic acid in DMF/H$_2$O at 50 °C for 16 h (Scheme 2.3).



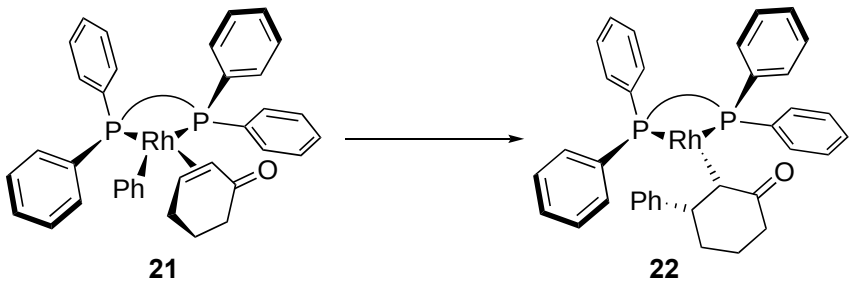
Scheme 2.3

Expanding on this discovery, Miyaura and Hayashi[27] went on to report the Rh-catalysed asymmetric arylation of α,β-unsaturated ketones using a wide range of arylboronic acids. The optimised reactions conditions utilised [Rh(acac)(C_2H_4)$_2$] with *(S)*-BINAP in dioxane/H_2O at 100 °C for 5 h. Under these conditions, it was possible for aryl groups with both electron-donating and electron-withdrawing substituents to be successfully conjugated at the β-position. A range of α,β-unsaturated ketones **19** were reacted to give β-aryl ketones (*S*)-**20a-e** in high yields and excellent enantioselectivities (Scheme 2.4).



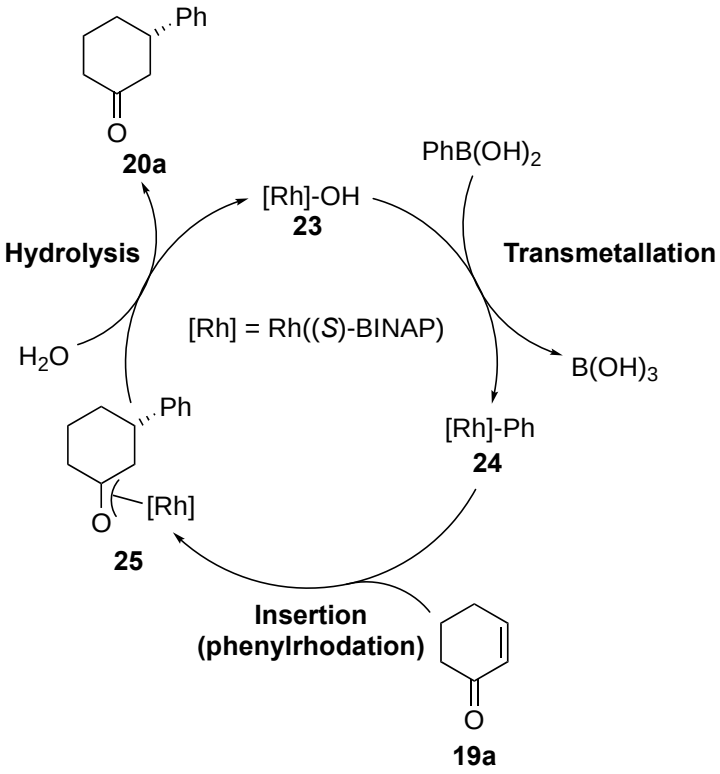
Scheme 2.4

In order to explain the sense of induction imparted by (*S*)-BINAP, the model outlined in Scheme 2.5 was proposed. Firstly, coordination of (*S*)-BINAP to the [Rh]-Ph complex results in intermediate complex **21**. The upper face of complex **21** is blocked by a phenyl ring of the (*S*)-BINAP ligand and, consequently, there is a vacant site at the lower face. The *si*-face of the alkene in 2-cyclohexenone **19a** coordinates to Rh and then undergoes migratory insertion to form the new stereogenic centre, as shown in complex **22**.



Scheme 2.5

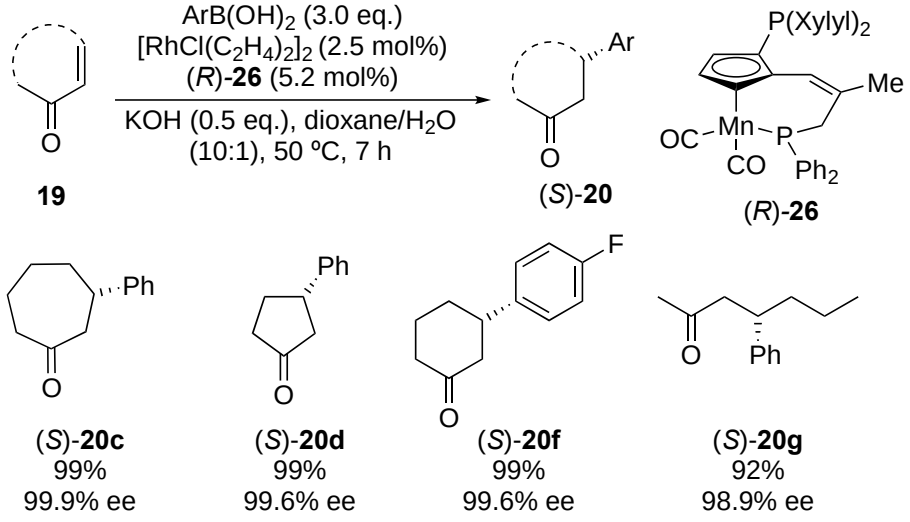
An overview of the mechanism for the Rh-catalysed arylation of 2-cyclohexenone **19a** using phenylboronic acid to give **20a** was reported by Hayashi *et al.*[28] in 2002 (Scheme 2.6). Firstly, transmetallation of the phenyl group in phenylboronic acid to [Rh]-OH complex **23** gives [Rh]-Ph complex **24**. Then, 2-cyclohexenone **19a** inserts into the Rh-Ph bond of [Rh]-Ph complex **24** to generate π-allyl Rh complex **25**. π-Allyl Rh complex **25** is readily hydrolysed in the presence of water to give β-arylated product **20a** and the regeneration of [Rh]-OH **23**. Rh remains at the +1 oxidation state throughout the catalytic cycle.



Scheme 2.6

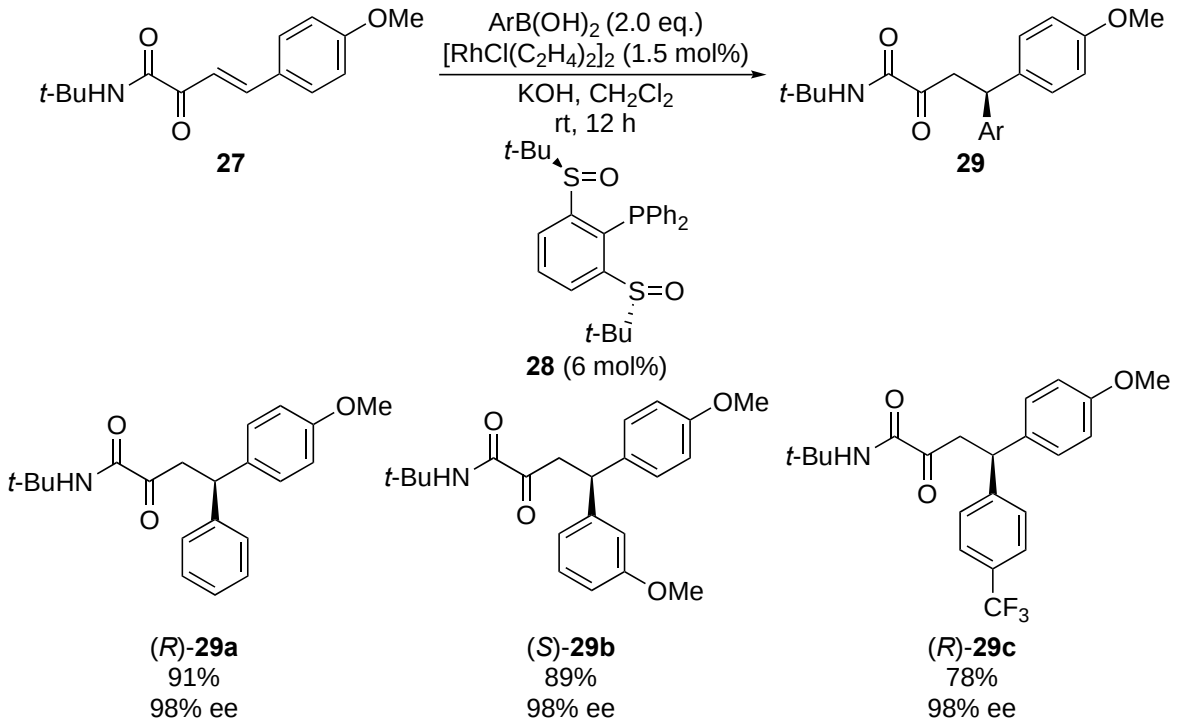
Following Miyaura's breakthrough, increased attention has been paid to the Rh(I) catalyst, ligands and reaction conditions in the Rh-catalysed asymmetric arylation of electron-deficient alkenes. For example, initial development of a chiral Cr-based phosphine-alkene ligand by Ogasawara, Kamikawa and co-workers[29] showed high enantioselectivity and promising reactivity in Rh-catalysed 1,4-addition of phenylboronic acid to cyclohexenone. However, it was found that the phosphine-alkene ligand was unstable to air-oxidation and did not work efficiently with acyclic enones. Investigations to improve these issues led to the discovery of chiral Mn-based planar-chiral phosphine-alkene ligand (*R*)-**26**. Mn-based ligand (*R*)-**26** was stable to air-oxidation and showed good reactivity and enantioselectivity in reactions with acyclic enones. Some examples are shown in Scheme 2.7. Various cyclic

and acyclic enones **19** were reacted with a range of arylboronic acids using $[RhCl(C_2H_4)_2]_2$/(*R*)-**26** and KOH in dioxane/H_2O (10:1) at 50 °C for 7 h to give β-arylated products (*S*)-**20c-d** and (*S*)-**20f-g** in excellent yields and enantioselectivities (Scheme 2.7).



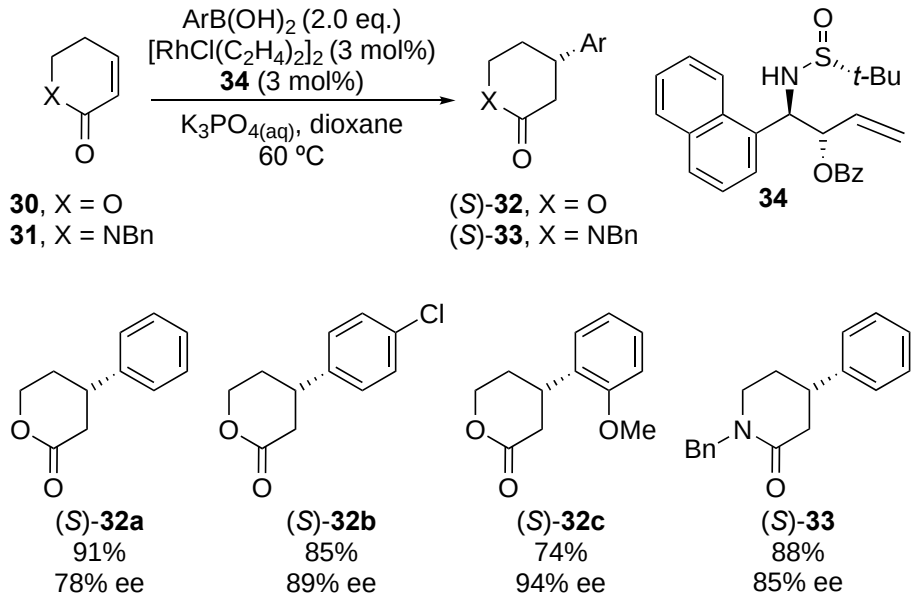
Scheme 2.7

The regio- and enantioselective Rh-catalysed asymmetric conjugate addition of various arylboronic acids to β,γ-unsaturated α-ketoamides using a chiral sulfinylphosphine ligand was reported by Liao and co-workers.[30] These Rh-catalysed β-arylation reactions were used in the synthesis of chiral γ,γ-diarylated carbonyl compounds and applied to the synthesis of the antidepressant sertraline. Having determined optimum conditions, β,γ-unsaturated α-ketoamide **27** was reacted with various arylboronic acids in the presence of $[RhCl(C_2H_4)_2]_2$, ligand **28** and KOH in CH_2Cl_2 at 20 °C for 12 h to give β-arylated products (*R*)-**29a**, (*S*)-**29b** and (*R*)-**29c** in very high yields and enantioselectivities (Scheme 2.8). With other examples, it was found that the stereoelectronic properties of the γ-aryl group did not affect the overall efficiency and selectivity of this reaction.



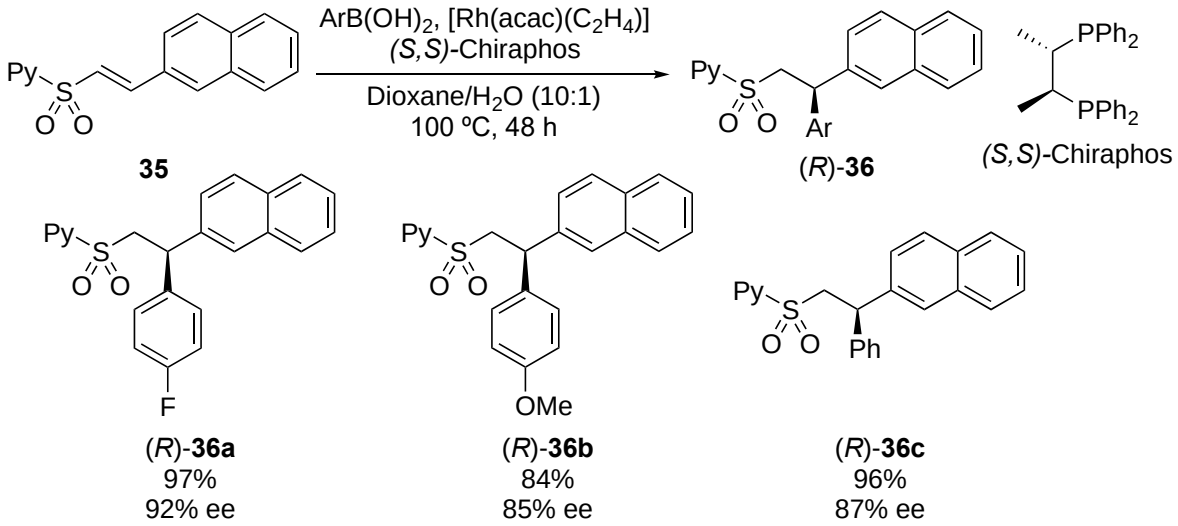
Scheme 2.8

The asymmetric Rh-catalysed 1,4-addition of arylboronic acids to α,β-unsaturated cyclic lactones and lactams was reported by Xu and co-workers.[31] For this work, a new sulfinamide-alkene ligand **34** was developed and this was in fact the first example of the use of a chiral sulfur-alkene ligand in Rh-catalysed asymmetric reactions. Thus, α,β-unsaturated cyclic carbonyl compounds **30** and **31** were reacted with various arylboronic acids in the presence of $[RhCl(C_2H_4)_2]_2$/**34** and K_3PO_4 in dioxane at 60 °C to give β-arylated products (*S*)-**32a-c** and (*S*)-**33** respectively in high yields and good enantioselectivity (Scheme 2.9).



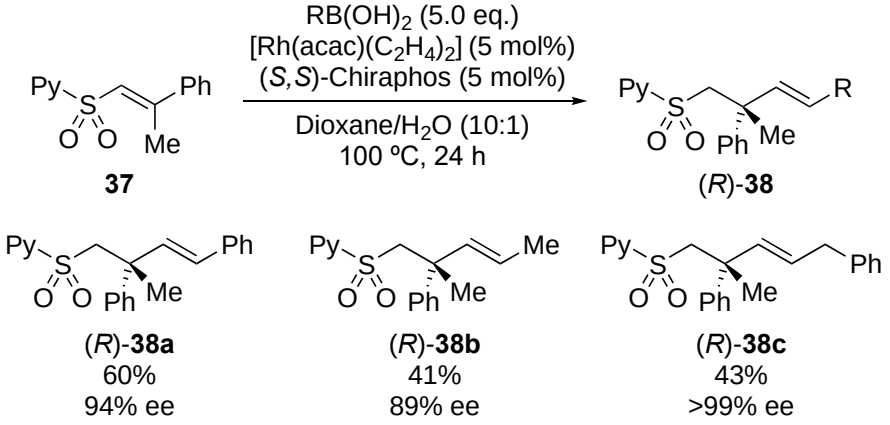
Scheme 2.9

In 2004, Carretero and Mauleón[32] showed that the Rh-catalysed arylation reaction could be extended to vinyl sulfones. In particular, a general method for the enantioselective Rh-catalysed (*S*,*S*)-Chiraphos-mediated conjugate addition of arylboronic acids to acyclic α,β-unsaturated sulfones was reported. For example, α,β-unsaturated 2-pyridyl sulfone **35** was reacted with various arylboronic acids in the presence of [Rh(acac)(C_2H_4)] and (*S*,*S*)-Chiraphos in dioxane/H_2O at 100 °C for 48 h. These reactions gave β-arylated sulfones (*R*)-**36a-c** in high yields and good enantioselectivities (Scheme 2.10). The 2-pridyl group on the sulfone was used as β-arylated sulfones (*R*)-**36a-c** were subsequently used in Julia-Kocienski reactions to form (*E*)-alkenes.



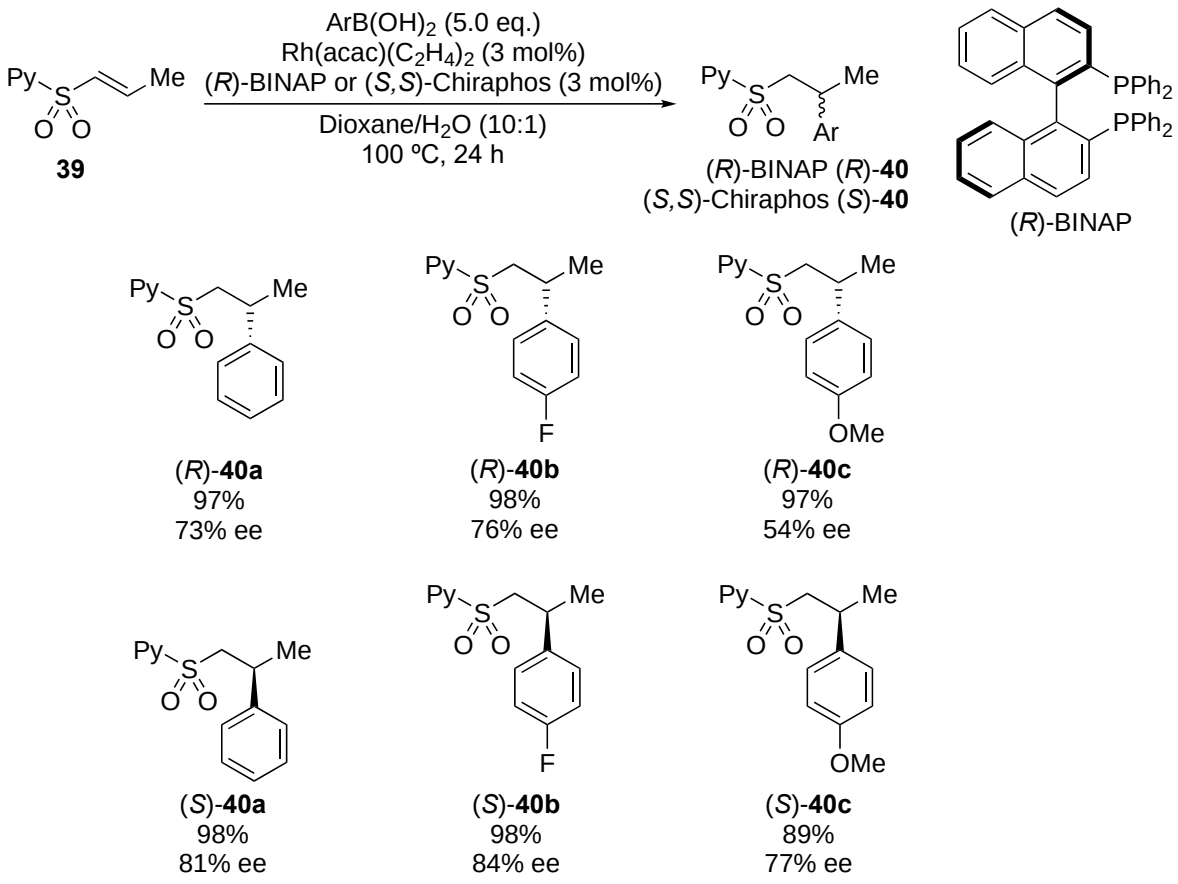
Scheme 2.10

Further studies by Carretero *et al.*[33] developed the scope of the Rh-catalysed conjugate addition to include the (*S*,*S*)-Chiraphos-mediated addition of alkenylboronic acids to α,β-unsaturated sulfones for the enantioselective synthesis of stereogenic quaternary carbons. Following on from previous results,[32] it was proposed that the incorporation of the 2-pyridyl group, α to the sulfone group, may facilitate coordination to the Rh. This occurs as the 2-pyridyl group coordinates to the Rh centre to form a stable 5-membered ring intermediate. In addition, nucleophiles with low steric bulk, such as alkenylboronic acids, were employed to overcome the otherwise difficult intermolecular conjugate addition of the disubstituted alkene. Thus, β-aryl β-alkyl α,β-unsaturated 2-pyridylsulfone **37** was treated with various alkenylboronic acids in the presence of [Rh(acac)(C_2H_4)$_2$] and (*S*,*S*)-Chiraphos in dioxane/H_2O (10:1) at 100 °C for 24 h to give β-trisubstituted 2-pyridylsulfones (*R*)-**38a-c** in moderate yields and high enantioselectivities (Scheme 2.11).



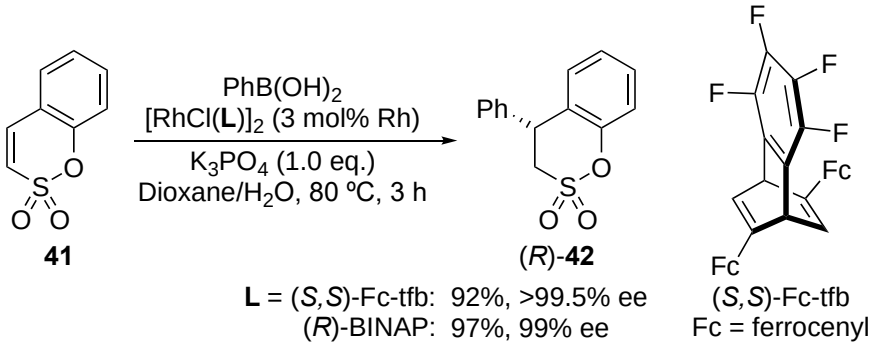
Scheme 2.11

In 2007, Carretero and co-workers[34] extended their work on Rh-catalysed conjugate addition reactions to include the addition of arylboronic acids to β-methyl vinyl 2-pyridylsulfone **39**. In their study, β-methyl vinyl 2-pyridylsulfone **39** was reacted with various arylboronic acids in the presence of [Rh(acac)(C_2H_4)$_2$] and (*R*)-BINAP in dioxane/H_2O (10:1) at 100 °C for 24 h. These reactions gave (*R*)-**40a-c** in excellent yields and moderate enantioselectivity. In contrast, the use of (*S*,*S*)-Chiraphos under the same conditions gave (*S*)-**40a-c** in excellent yields and good enantioselectivities (Scheme 2.12).



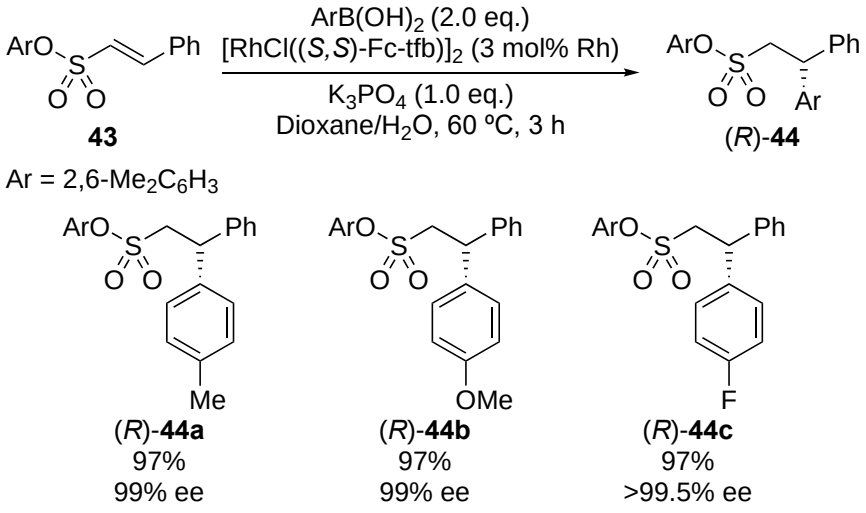
Scheme 2.12

Investigations into Rh-catalysed conjugate addition reactions of electron-deficient alkenes over the years[35] led to the discovery of chiral Rh(I)-diene catalysts which enabled certain vinyl sulfones to undergo highly successful arylation reactions. In 2012, Hayashi and co-workers[36] explored the effect of chiral diene ligands in asymmetric Rh-catalysed arylation of α,β-unsaturated sulfone-containing compounds in the absence of coordinating groups. In one example, cyclic sulfonate **41** was reacted with phenylboronic acid in the presence of [RhCl((*S*,*S*)-Fc-tfb)]$_2$ and K_3PO_4 in dioxane/H_2O at 80 °C for 3 h to give β-phenyl cyclic sulfonate (*R*)-**42** in 92% yield and >99.5% ee. Substitution of the (*S*,*S*)-Fc-tfb ligand for (*R*)-BINAP resulted in the formation of β-phenyl cyclic sulfonate (*R*)-**42** in 97% yield and 99% ee (Scheme 2.13).



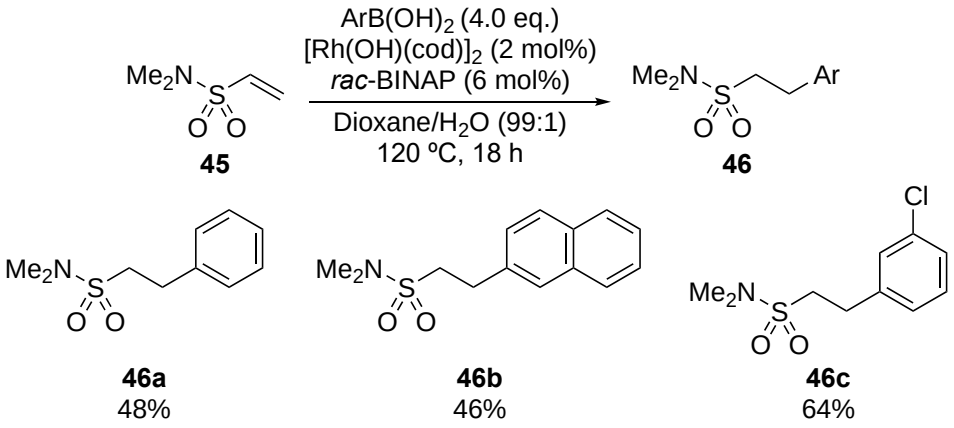
Scheme 2.13

Furthermore, Hayashi *et al.*[36] expanded the scope of their study to include the Rh-catalysed asymmetric addition reaction of arylboronic acids to alkenyl sulfonates. Reaction of alkenyl sulfonate **43** with various arylboronic acids and K_3PO_4 catalysed by [RhCl((*S*,*S*)-Fc-tfb)]$_2$ in dioxane/H_2O at 60 °C for 3 h afforded β-aryl sulfonates (*R*)-**44a-c** in excellent yields and enantioselectivity (Scheme 2.14).



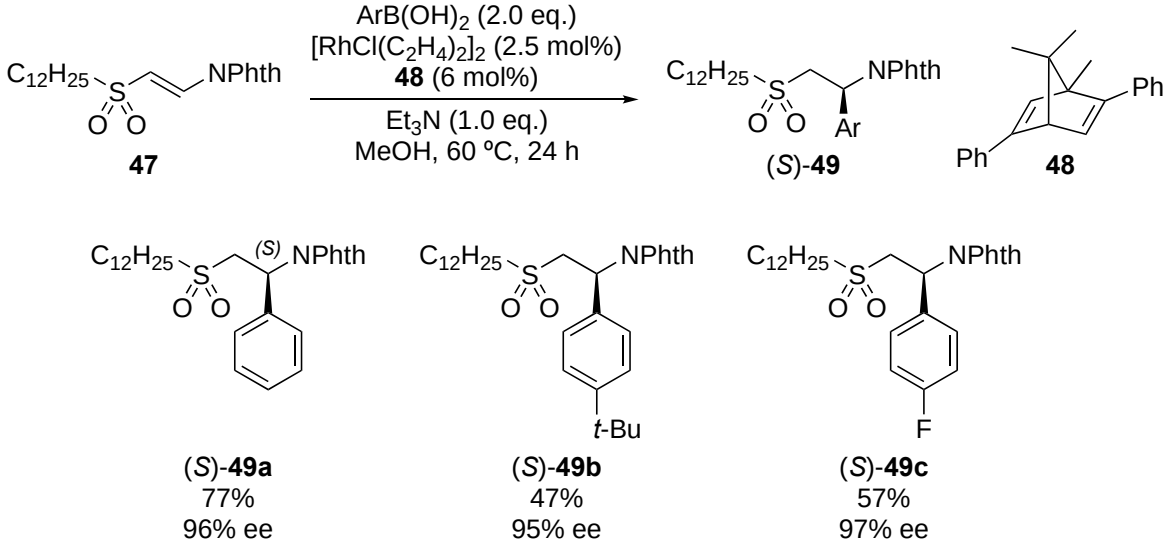
Scheme 2.14

In 2011, Van den Hoogenband and co-workers[37] detailed the synthesis of 2-arylethanesulfonamides which are of interest in medicinal chemistry. In the synthetic approach, the Rh-catalysed conjugate addition of arylboronic acids to ethenesulfonamides was described. Ethenesulfonamide **45** was arylated with various arylboronic acids in the presence of [Rh(OH)(cod)]$_2$ and racemic BINAP in dioxane/H_2O (99:1) at 120 °C for 18 h. These reactions gave β-arylated sulfonamides **46a-c** in moderate yields (Scheme 2.15).



Scheme 2.15

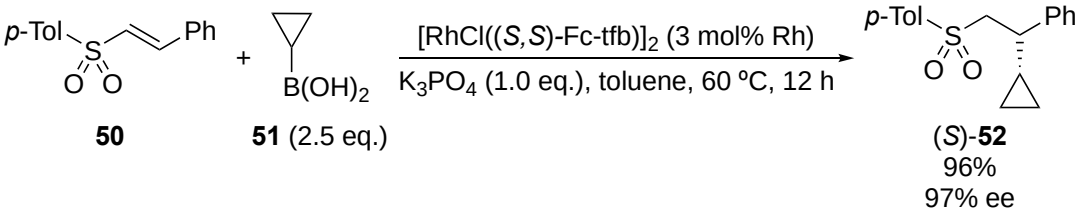
Wu and co-workers[38] described the Rh-catalysed asymmetric arylation of β-imido vinyl sulfones for use as part of a route to apremilast which is used in the treatment of psoriasis and psoriatic arthritis.[39] Various β-aryl β-phthalimido sulfones (*S*)-**49a-c** were synthesised in good yields and high enantioselectivity from the reaction of β-phthalimido vinyl sulfone **47** with arylboronic acids and Et_3N catalysed by $[RhCl(C_2H_4)_2]_2$/diene ligand **48** in MeOH at 60 °C for 24 h (Scheme 2.16).



Scheme 2.16

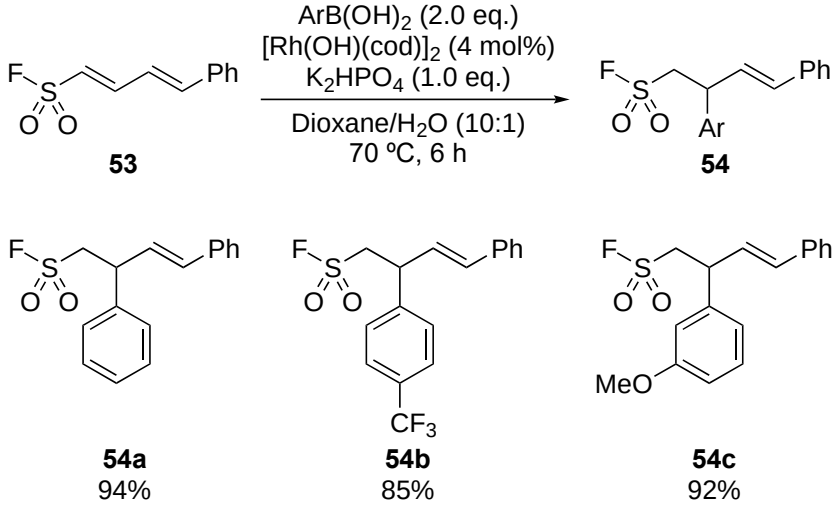
Nishimura and Takechi[40] reported the Rh-catalysed conjugate addition of cyclopropylboronic acids to electron-deficient alkenes such as alkenyl sulfones, enones, enoates and nitroalkenes. In one example with alkenyl sulfone **50** as the starting material, the highly enantioselective synthesis of β-cyclopropyl sulfone (*S*)-**52** was achieved using

chiral diene ligand (*S*,*S*)-Fc-tfb. Thus, alkenyl sulfone **50** was reacted with cyclopropylboronic acid **51**, K_3PO_4 and $[RhCl((S,S)\text{-Fc-tfb})]_2$ in toluene at 60 °C for 12 h to give β-cyclopropyl sulfone (*S*)-**52** in 96% yield and 97% ee.



Scheme 2.17

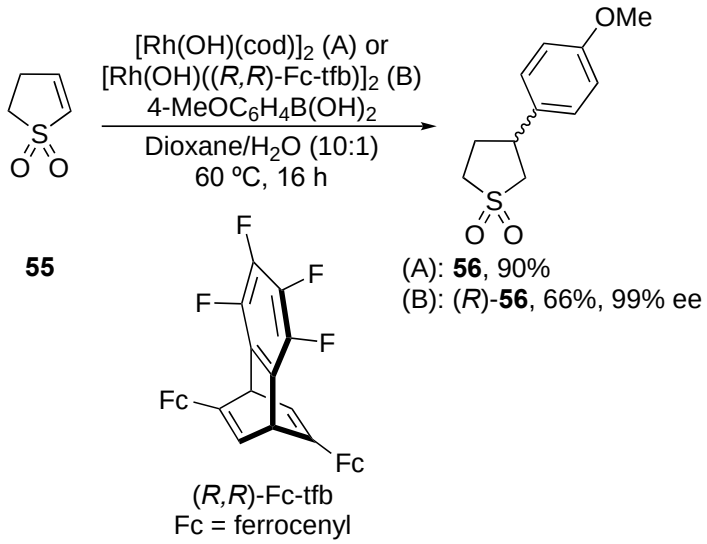
Qin and co-workers[41] reported the regioselective Rh-catalysed addition of arylboronic acids to 1,3-dienylsulfonyl fluorides. After optimisation of the catalyst, temperature and base, β-aryl sulfonyl fluorides **54a-c** were obtained in excellent yields from the treatment of 1,3-dienylsulfonyl fluoride **53** with various arylboronic acids in the presence of $[Rh(OH)(cod)]_2$ and K_2HPO_4 in dioxane/H_2O (10:1) at 70 °C for 6 h (Scheme 2.18). This reaction was exclusively regioselective for the α,β-double bond and was successful across a wide range of arylboronic acids bearing electron-donating and electron-withdrawing groups.



Scheme 2.18

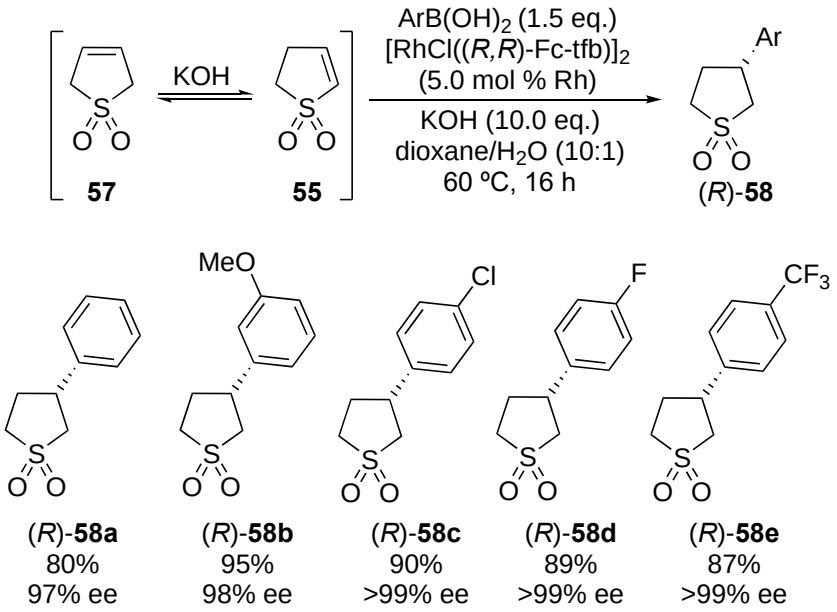
In 2015, Hayashi and Lim described the Rh-catalysed racemic and asymmetric arylation of cyclic vinyl sulfone **55** and explored the effect of the ligand on the yield and enantioselectivity.[23] In one example, racemic β-aryl sulfone **56** was obtained in 90% yield by reaction of vinyl sulfone **55** with 4-methoxyphenylboronic acid using $[Rh(OH)(cod)]_2$ in dioxane/H_2O at 60 °C for 16 h. Using the chiral Rh(I) catalyst $[Rh(OH)((R,R)\text{-Fc-tfb})]_2$,

vinyl sulfone **55** was reacted under the same conditions to give β-aryl sulfone (*R*)-**56** in 66% yield and 99% ee (Scheme 2.19).



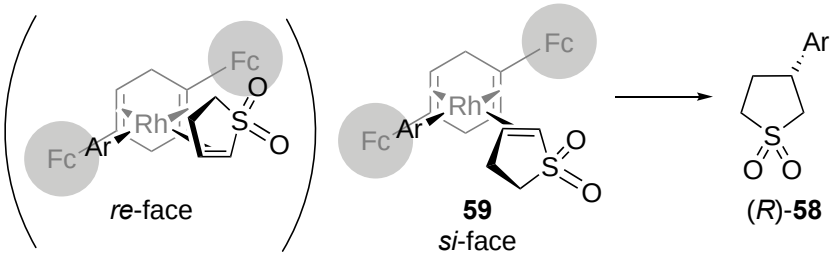
Scheme 2.19

After having explored various chiral diene and BINAP ligands, [RhCl((*R*,*R*)-Fc-tfb)]$_2$ was selected. It was known that the isomerisation of 3-sulfolene **57** into vinyl sulfone **55** takes place in the presence of a base[42] and with 3-sulfolene **57** as a readily available starting material, Hayashi and Lim explored the possibility of the addition of a base in the reaction to facilitate the *in situ* isomerisation of 3-sulfolene **57** into vinyl sulfone **55**. It was shown that arylation of vinyl sulfone **55** was much faster than that of 3-sulfolene **57**, especially with diene ligands. Thus, if the isomerisation of 3-sulfolene **57** into vinyl sulfone **55** was much faster than the arylation of 3-sulfolene **57**, it was proposed that the formation of β-aryl sulfone **58** may be achieved in high yield and enantioselectivity. Basic conditions were investigated by changing the amount of KOH in the reaction and it was found that 10 equivalents of KOH was optimal. Under the optimised conditions, 3-sulfolene **57** was isomerised *in situ* to vinyl sulfone **55** and underwent asymmetric β-arylation of vinyl sulfone **55** with arylboronic acids in the presence of [RhCl((*R*,*R*)-Fc-tfb)]$_2$ in dioxane/H_2O (10:1) at 60 °C for 16 h to give β-aryl sulfones (*R*)-**58a-e** in high yields and enantioselectivity (Scheme 2.20).



Scheme 2.20

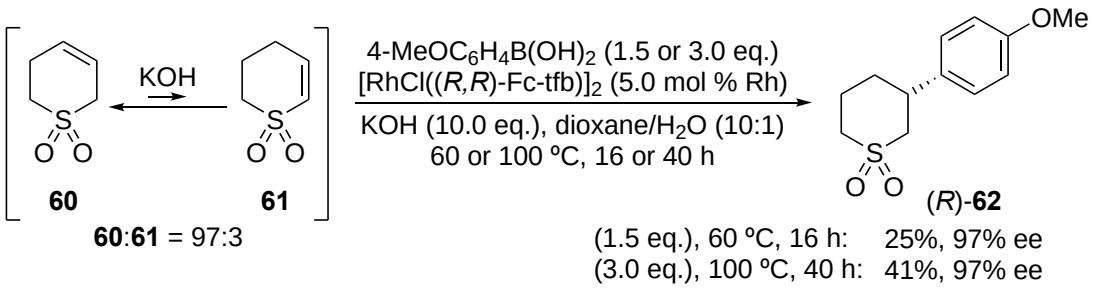
Using the (*R*,*R*)-Fc-tfb ligand, a stereochemical model was proposed (Scheme 2.21). Coordination of (*R*,*R*)-Fc-tfb ligand to Rh results in intermediate complex **59**. The upper face of complex **59** is blocked by the ferrocenyl group of (*R*,*R*)-Fc-tfb and there is thus a vacant site at the lower face. The *si*-face of the alkene in vinyl sulfone **55** coordinates to Rh and then undergoes migratory insertion to form the (*R*) stereogenic centre. In contrast, reaction *via* the *re*-face would result in significant steric clash between vinyl sulfone **55** and the ferrocenyl group.



Scheme 2.21

The methodology was expanded to the β-arylation of 6-membered ring vinyl sulfone **61**. Using [RhCl((*R*,*R*)-Fc-tfb)]$_2$, 6-membered ring vinyl sulfone **61** was reacted with 1.5 equivalents of 4-methoxyphenylboronic acid and KOH in dioxane/H_2O (10:1) at 60 °C for 16 h to give β-aryl sulfone (*R*)-**62** in 25% yield and 97% ee. In contrast, 3 equivalents of 4-methoxyphenyl boronic acid was used at a higher temperature of 100 °C for 40 h to give β-

aryl sulfone (*R*)-**62** in a higher yield of 41% and 97% ee (Scheme 2.22). For 6-membered ring allyl sulfone **60**, arylation under isomerisation conditions is more difficult than for the corresponding 5-membered ring sulfone because the equilibrium lies heavily on the side of allyl sulfone **60** (97:3 ratio of **60**:**61**).



Scheme 2.22

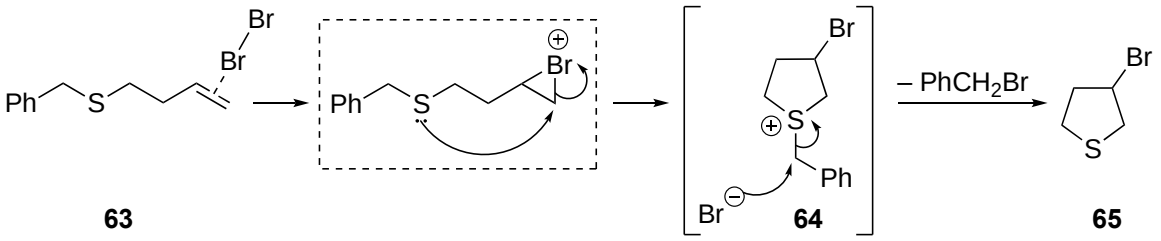
To summarise, there have been significant developments since Miyaura *et al.*'s[25] seminal report in 1997 on Rh-catalysed arylations of electron-deficient alkenes and various asymmetric reactions have been introduced. There are many examples of Rh-catalysed asymmetric arylation of α,β-unsaturated ketones. Work by Carretero and Mauleón[32] in 2004 paved the way for the asymmetric β-arylation of acyclic sulfone-containing compounds. Since then, numerous Rh-catalysed conjugate addition reactions of alkenyl and arylboronic acids to cyclic and acyclic vinyl sulfones have been reported. More recently, chiral diene and BINAP ligands have been used to avoid the need to include a Rh-coordinating group such as a pyridine in the compound. In 2015, Hayashi and Lim[23] showed that these Rh-catalysed asymmetric arylations using chiral diene and BINAP ligands could be expanded to 5- and 6-membered cyclic vinyl sulfones. A range of arylboronic acids were used and the corresponding 5-membered ring β-aryl sulfones were synthesised in excellent yields and enantioselectivity.

2.2 Attempted synthesis of a cyclic vinyl sulfoximine *via* a cyclisation route

In order to study its Rh-catalysed arylation, the initial plan was to synthesise *N*-TBDPS protected 5-membered ring vinyl sulfoximine **6** (Figure 2.1). As there were no previous reports on the synthesis of such cyclic vinyl sulfoximines, a synthetic route to the corresponding vinyl sulfone **55** (Figure 2.1) that had been reported by Ren *et al.*[43] was attractive since it should be amenable to modification to enable the synthesis of *N*-TBDPS vinyl sulfoximine **6**.

Figure 2.1 *N*-TBDPS vinyl sulfoximine **6** and vinyl sulfone **55**

Ren *et al.*[43] studied halocyclisation reactions of unsaturated benzyl sulfides as a way of synthesising β-halo cyclic sulfides. In the study, the tether length, degree of carbon-carbon unsaturation (alkene or alkyne), substituents and halogenating reagents were all varied in order to investigate the regio- and stereochemistry of the halocyclisation reactions. The mechanistic pathway for a typical example is shown in Scheme 2.23. First, coordination of Br_2 to the alkene in alkene sulfide **66** results in the formation of π-complex **63**. Then, bromonium ion formation and subsequent attack of the sulfur lone pair results in 5-membered ring benzylsulfonium ion **64**. Finally, attack of bromide at the activated benzylic position gives bromo sulfide **65** and benzyl bromide.

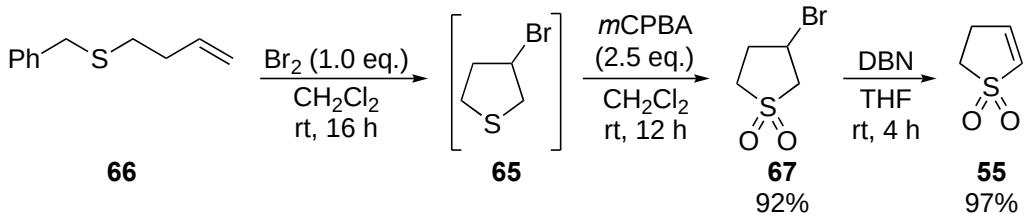


Scheme 2.23

Alkene sulfides were found to undergo 5-*endo-trig* halocyclisation in the presence of Br_2 or I_2 to give 5-membered ring halogenated sulfur-containing cycloadducts. The preferred 5-*endo* cyclisation pathway of alkenyl sulfides can be explained by the greater thermodynamic stability of the *S*-dealkylated 5-membered ring adduct **65** as opposed to the highly strained

4-membered ring which would have formed *via* 4-exo cyclisation, assuming a reversible reaction.[43]

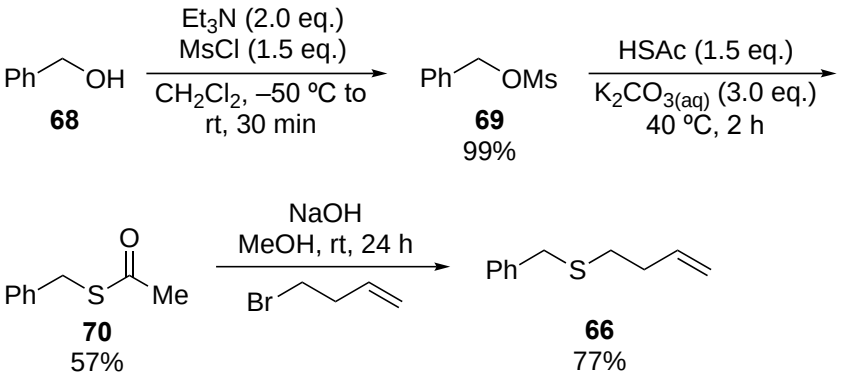
As part of their study, the synthesis of cyclic vinyl sulfone **55** was described (Scheme 2.24). Treatment of alkene sulfide **66** with Br_2 in CH_2Cl_2 at rt for 16 h gave bromo sulfide **65** as an intermediate. Then, *m*CPBA was added to the same flask and reacted over 12 h which gave bromo sulfone **67** in 92% yield. It was reported that the analogous iodocyclisation gave an iodo sulfone that was susceptible to alkene formation by spontaneous elimination of HI, *via* an $E1_{cb}$ mechanism, during work-up and purification. However, bromo sulfone **67** was more stable and required reaction with DBN in THF at rt for 4 h in order to convert it into vinyl sulfone **55** which was isolated in 97% yield (Scheme 2.24).



Scheme 2.24

We proposed to carry out a similar synthetic sequence by replacing the sulfide to sulfone oxidation step with a known sulfoximine-forming reaction.[44] Subsequent elimination and *N*-TBDPS protection should give the desired vinyl sulfoximine **6**. The synthesis of the key starting material to explore this route, alkene sulfide **66**, is summarised in Scheme 2.25. To start, benzyl mesylate **69** was prepared using a method reported by Borgati *et al.*[45] Thus, benzyl alcohol **68** was reacted with MsCl and Et_3N in CH_2Cl_2 at –50 °C for 30 min. After work-up, crude benzyl mesylate **69** was obtained in 99% yield and was of sufficient purity for use in the next step. The nucleophilic substitution reaction of benzyl mesylate **69** with thioacetic acid was reported by Olivito and co-workers.[46] Using their procedure, benzyl mesylate **69** was reacted with thioacetic acid in aqueous K_2CO_3 solution at 40 °C for 2 h. This reaction gave crude benzyl thioacetate **70** in 57% yield. In some cases, it was necessary to purify the crude product by chromatography. Finally, using a method reported by Ren *et al.*,[43] benzyl thioacetate **70** was reacted with NaOH in MeOH and 4-bromo-1-butene in MeOH at rt for 24 h which gave alkene sulfide **66** in 77% yield after purification by chromatography (Scheme 2.25). Treatment of benzyl thioacetate with NaOH would generate benzyl thiol *in situ* and subsequent nucleophilic substitution forms alkene sulfide **66**. This

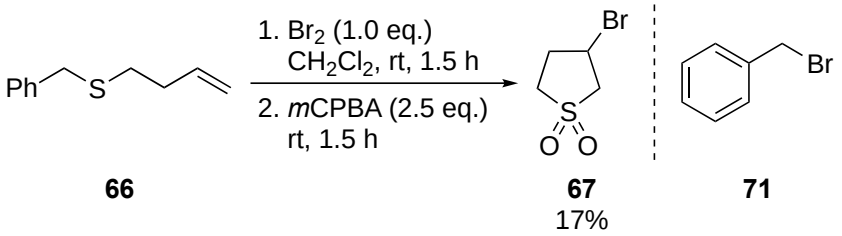
route to alkene sulfide **66** proved to be scalable and it was easy to bring through material on a multi-gram-scale.



68 **69** 99% **70** 57% **66** 77%

Scheme 2.25

Next, the plan was to repeat the synthesis of bromo sulfone **67** reported in the literature (see Scheme 2.24)[43] in order to verify that the procedure was reproducible in our hands. Treatment of alkene sulfide **66** with Br_2 in CH_2Cl_2 at rt for 1.5 h presumably gave the proposed intermediate bromo sulfide **65**. Then, *m*CPBA was added into the same flask and left to react at rt for 1.5 h. After work-up, the crude product contained a 55:45 mixture of bromo sulfone **67** and benzyl bromide **71** (by ^{1}H NMR spectroscopy). Purification by chromatography gave bromo sulfone **67** in only 17% yield (Scheme 2.26). The NMR spectroscopic data for this compound were consistent with literature values,[43] but the yield was significantly lower than the 92% yield reported.[43]

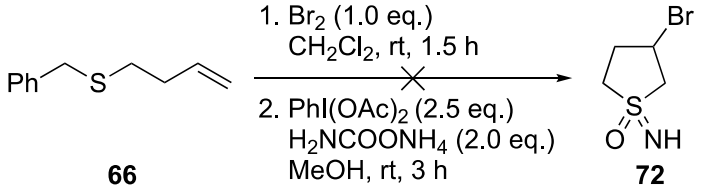


66 **67** 17% **71**

Scheme 2.26

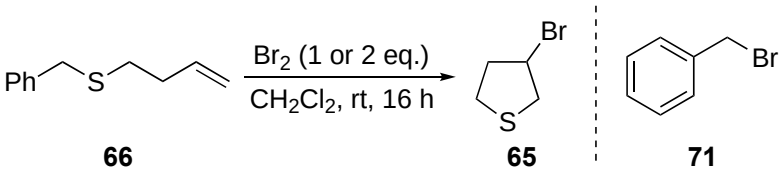
Although the yield of bromo sulfone **67** was low, we decided to attempt the synthesis of bromo sulfoximine **72** and invest our time in optimising the sulfoximine synthetic route, rather than the sulfone synthesis. For the sulfoximine-forming reaction, it was planned to use a reaction reported by Bull and Luisi[44] that has been used extensively in the O'Brien group.[18,20] This method is a one-pot synthesis of NH sulfoximines from their corresponding

sulfides using PIDA as the oxidising agent and ammonium carbamate as the amino source in MeOH. Thus, alkene sulfide **66** was reacted with Br_2 in CH_2Cl_2 at rt for 1.5 h as usual and then PIDA and ammonium carbamate in MeOH were added and reacted at rt for 3 h. Evaporation of the crude reaction mixture gave a complex mixture of products and, disappointingly, there was no evidence for the formation of bromo sulfoximines **72** (by ^{1}H NMR spectroscopy) (Scheme 2.27).



Scheme 2.27

Limited success with this initial attempt at the synthesis of bromo sulfoximines **72** led us to explore whether the problem was the bromocyclisation step or whether the presence of benzyl bromide in the reaction mixture may interfere in the sulfoximine-forming step. Therefore, we decided to explore the bromocyclisation step in more detail by monitoring the conversion by ^{1}H NMR spectroscopy of the crude product after reaction with Br_2. Thus, alkene sulfide **66** was treated with 1 equivalent of Br_2 in CH_2Cl_2 at rt for 16 h. The solvent was evaporated and the ^{1}H NMR spectrum of the crude product showed a 60:20:20 mixture of alkene sulfide **66**, bromo sulfide **65** and benzyl bromide **71** (Figure 2.2). As not all of alkene sulfide **66** had reacted, the amount of Br_2 was increased to 2 equivalents which resulted in a 0:50:50 mixture of alkene sulfide **66**, bromo sulfide **65** and benzyl bromide **71** (by ^{1}H NMR spectroscopy) (Figure 2.3). However, the crude product also contained a significant amount of an unidentified product. Analysis of the ^{1}H NMR spectra of these reactions indicated that the bromocyclisation reaction was temperamental in our hands. The bromocyclisations did not always go to completion and other by-products formed with 2 equivalents of Br_2. These results were consistent with the low yield of bromo sulfone **67** (17% yield) obtained after *m*CPBA oxidation. However, it would have been expected that some bromo sulfoximines **72** would have formed in the reaction shown in Scheme 2.27. Since bromo sulfoximines **72** were not formed, we speculate that benzyl bromide **71**, formed in the bromocyclisation step, may interfere in the sulfoximine-forming step.



1 eq. Br_2: ratio of **66**:**65**:**71** = 60:20:20
2 eq. Br_2: ratio of **66**:**65**:**71** = 0:50:50

Scheme 2.28

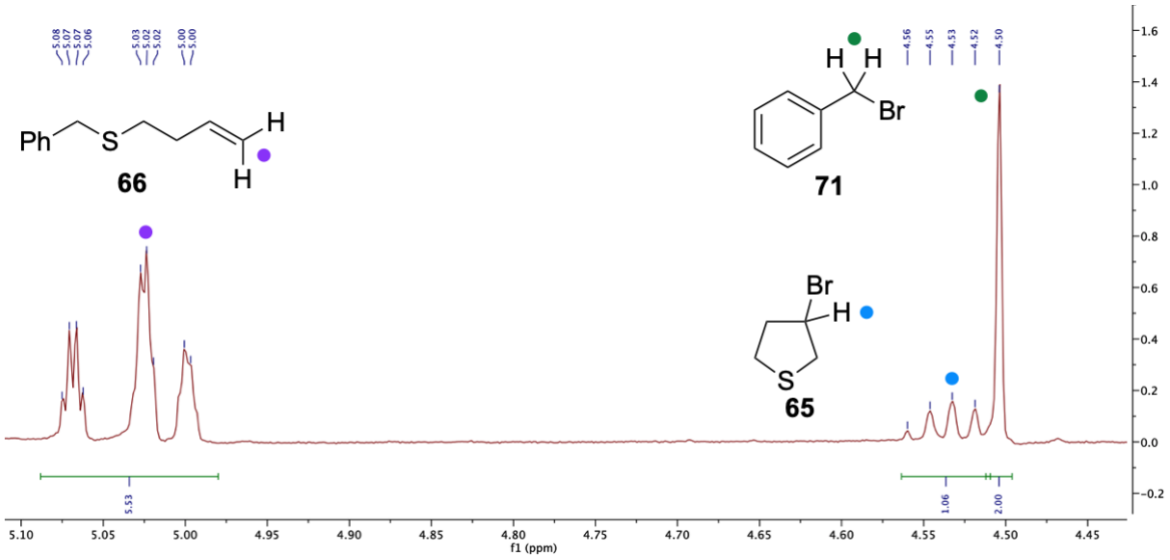


Figure 2.2 ^{1}H NMR spectrum of the 60:20:20 mixture of alkene sulfide **66** (purple), bromo sulfide **65** (blue) and benzyl bromide **71** (green) obtained from the bromocyclisation reaction

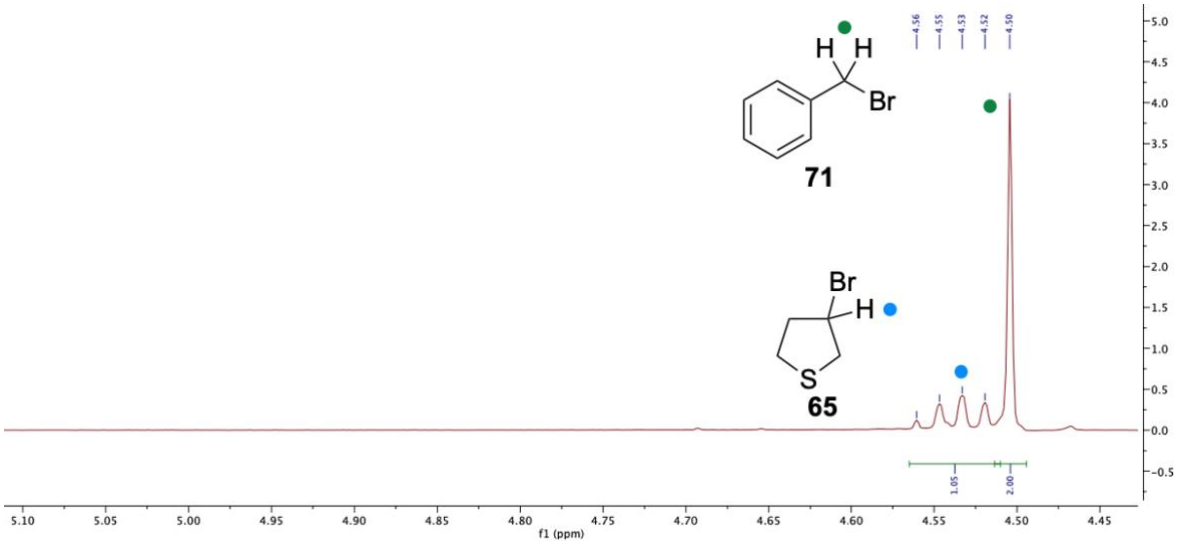
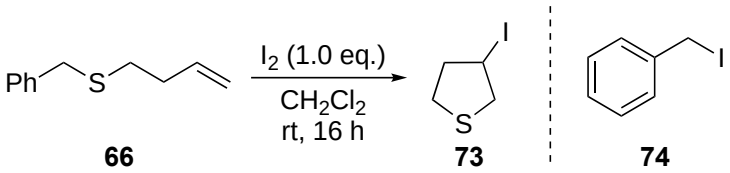


Figure 2.3 ^{1}H NMR spectrum of the 0:50:50 mixture of alkene sulfide **66**, bromo sulfide **65** (blue) and benzyl bromide **71** (green) obtained from the bromocyclisation reaction

In order to try and improve the halocyclisation step, we turned our attention to the corresponding iodocyclisation that had also been reported by Ren and co-workers.[43] Reaction of alkene sulfide **66** with I_2 in CH_2Cl_2 at rt for 16 h gave the crude product which contained a 10:45:45 mixture of alkene sulfide **66**, iodo sulfide **73** and benzyl iodide **74** (by ^{1}H NMR spectroscopy) (Scheme 2.29). After chromatography, an inseparable 10:45:45 mixture of alkene sulfide **66**, iodo sulfide **73** and benzyl iodide **74** (by ^{1}H NMR spectroscopy) was obtained. In this mixture, there was only a 10% yield of iodo sulfide **73**. Although there was almost complete conversion of alkene sulfide **66**, the yield of iodo sulfide **73** was very low and we were unable to isolate it pure. In this case, sulfoximine formation was not attempted.

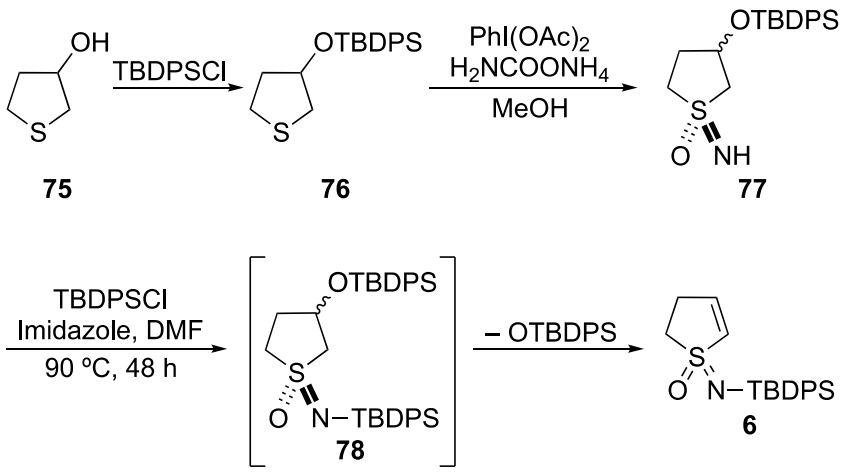


Scheme 2.29

To summarise, alkene sulfide **66** was synthesised in 43% yield over three steps which allowed us to attempt the synthesis of *N*-TBDPS vinyl sulfoximine **6**. Despite being able to synthesise bromo sulfone **67**, we were unable to reproduce the 92% yield reported in the literature.[43] Due to limited success in synthesising bromo sulfoximines **72**, we investigated the crude product of the bromocyclisation step by ^{1}H NMR spectroscopy and we were able to synthesise, but not isolate, bromo sulfide **65**. Efforts to improve the halocyclisation step, using I_2, gave a mixture of iodo sulfide **73** and benzyl iodide **74**. Since the benzyl bromide/iodide is inseparable from the halo sulfide formed, it appears that the benzyl halide interferes in the sulfoximine-forming step as shown by our failure to form sulfoximines **72** from the mixture of bromo sulfide **65** and benzyl bromide **71** (see Scheme 2.28).

2.3 Synthesis of a cyclic vinyl sulfoximine *via* an elimination route

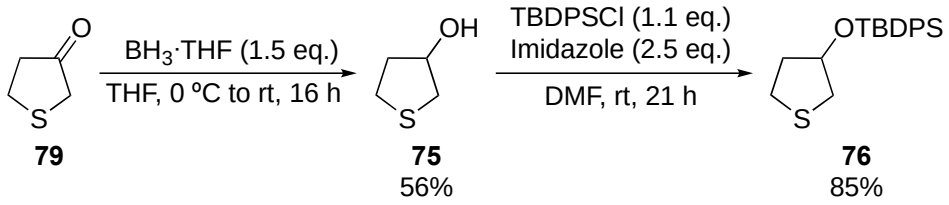
After having no success in synthesising *N*-TBDPS vinyl sulfoximine **6** *via* the halocyclisation route, an alternative approach that would proceed *via* an elimination reaction of an *O*-substituent was devised. As outlined in Scheme 2.30, it was envisioned that known hydroxy sulfide **75**[47] would be converted into TBDPSO-sulfoximines **76** in two steps *via* TBDPS protection and use of Bull and Luisi's sulfoximine-forming conditions.[44] Then, treatment of TBDPSO-sulfoximines **77** with TBDPSCl and imidazole in DMF at 90 °C for 48 h, standard silylation conditions for the *N*-TBDPS protection of sulfoximines,[48] should form disilyl sulfoximines **78**. We speculated that the harsh TBDPS protection conditions could lead to the deprotonation α to the sulfoximine and elimination of the β-OTBDPS group, *via* an $E1_{cb}$ mechanism, to form the desired *N*-TBDPS vinyl sulfoximine **6**. If elimination did not occur under these protection conditions, other bases would be explored to drive the formation of *N*-TBDPS vinyl sulfoximine **6**.



Scheme 2.30

The synthesis of hydroxy sulfide **75** has been previously reported by Konuki and Nagai.[47] Using their procedure, commercially available β-keto sulfide **79** was reacted with BH_3·THF in THF at 0 °C and then at rt for 16 h to give hydroxy sulfide **75** in 56% yield after chromatography. In some cases, crude hydroxy sulfide **75** was sufficiently pure and it was not necessary to purify the crude product by chromatography. Analysis of the ^{1}H NMR spectrum of hydroxy sulfide **75** showed a 1H broad multiplet at δ_H 4.65-4.61 which was assigned to HOC*H*. This indicated the successful reduction of β-keto sulfide **79**. Next, TBDPSO-sulfide **76** was synthesised by reaction of hydroxy sulfide **75** with TBDPSCl and

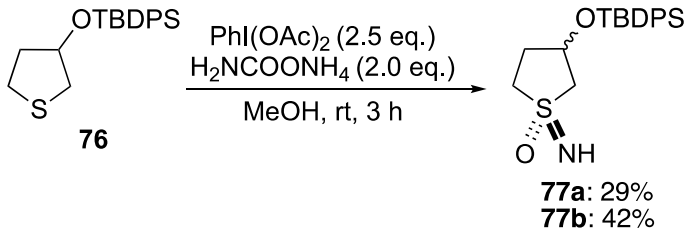
imidazole in DMF at rt for 21 h. Work-up and purification by chromatography gave TBDPSO-sulfide **76** in 85% yield (Scheme 2.31).



79 **75** 56% **76** 85%

Scheme 2.31

The next step in our proposed route was the conversion of TBDPSO-sulfide **76** into TBDPSO-sulfoximines **77**. Using Bull and Luisi's sulfoximine-forming conditions,[44] diastereomeric TBDPSO-sulfoximines **77a** and **77b** were isolated in 29% and 42% yield, respectively, after purification by chromatography (Scheme 2.32). Some of the signals in the ^{1}H NMR spectra of **77a** and **77b** are shown in Figure 2.4. Analysis of the ^{1}H NMR spectrum of **77a** showed the signal for the OCH proton to be a 1H dddd of equal coupling constants: δ_H 4.63 (dddd, J = 5.0, 5.0, 5.0, 5.0 Hz) (blue, Figure 2.4). The 1H ddd at δ_H 3.43 (ddd, J = 13.0, 8.0, 8.0 Hz) and the 3H multiplet at δ_H 3.19-3.04 were assigned to the SCH protons (green, Figure 2.4). In the ^{1}H NMR spectrum of **77b**, the signal for the OCH proton was a 1H dddd of equal J values: δ_H 4.61 (dddd, J = 4.5, 4.5, 4.5, 4.5 Hz) (red, Figure 2.4). The 1H multiplet at δ_H 3.53-3.46 and the 3H multiplet at δ_H 3.17-3.07 were assigned to the SCH protons (orange, Figure 2.4). Based on the isolated yields, sulfoximine formation was slightly diastereoselective in favour of **77b**. However, no attempt was made to assign the *cis*/*trans* stereochemistry of diastereoisomeric sulfoximines **77a** and **77b** since it was of no consequence as we planned to eliminate the β-OTBDPS group.



76

77a: 29%
77b: 42%

Scheme 2.32

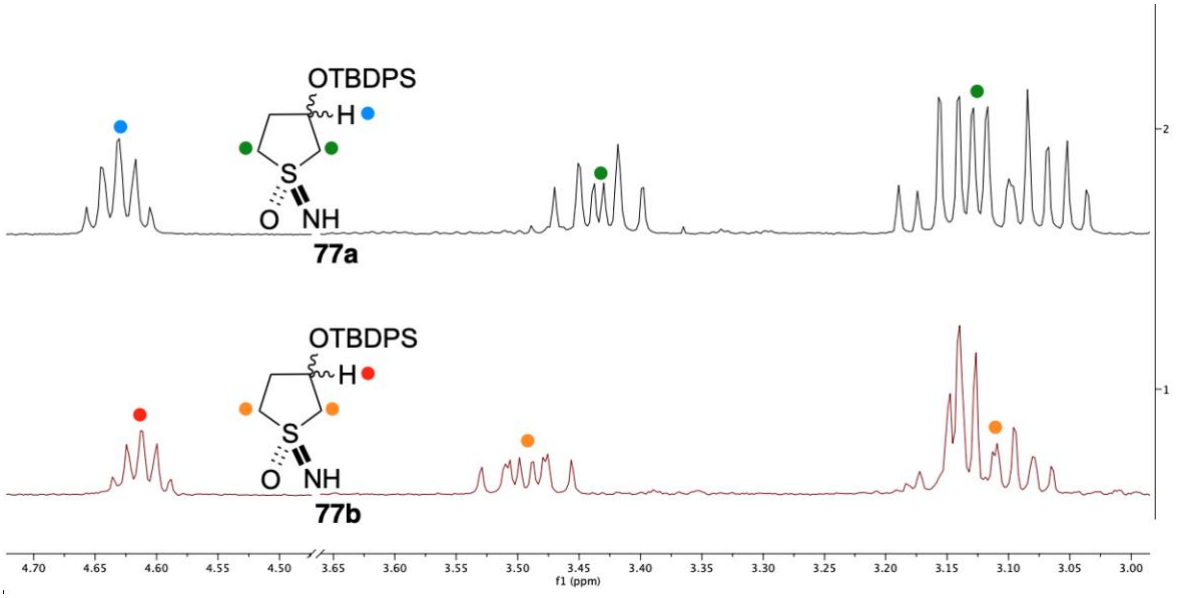
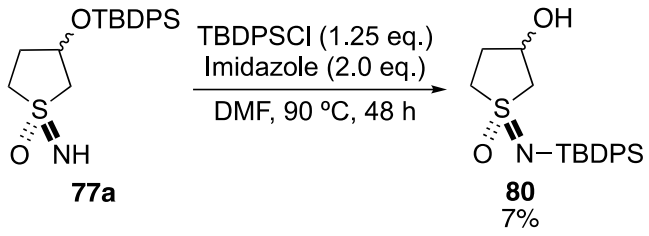


Figure 2.4 Comparison of the key signals in the ^{1}H NMR spectra of **77a** and **77b**

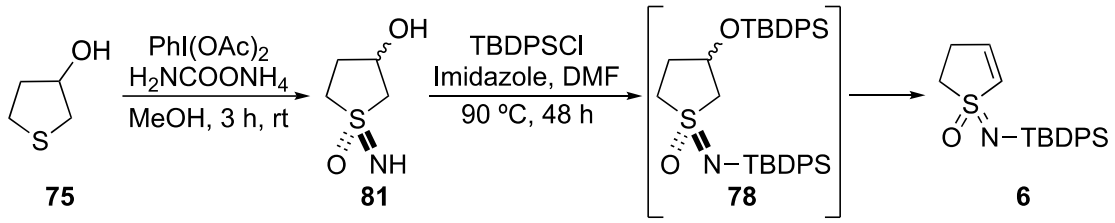
For the next step, we hoped that the *N*-TBDPS protection conditions may lead to both *N*-TBDPS protection and elimination to form *N*-TBDPS vinyl sulfoximine **6**. Thus, one of the diastereomeric TBDPSO-sulfoximines, **77a**, was reacted with TBDPSCl and imidazole in DMF at 90 °C for 48 h. This reaction was not very successful. After chromatography, only two compounds were isolated and characterised: hydroxy sulfoximines **80** (7% yield) and recovered starting sulfoximine **77a** (16% yield) (Scheme 2.33). There was no evidence for the formation of *N*-TBDPS vinyl sulfoximine **6** or disilyl sulfoximine **78** by ^{1}H NMR spectroscopy. The formation of hydroxy sulfoximines **80** was unexpected but can be rationalised to occur as a result of the TBDPS group migrating from the oxygen to the free amino group of the sulfoximine.



Scheme 2.33

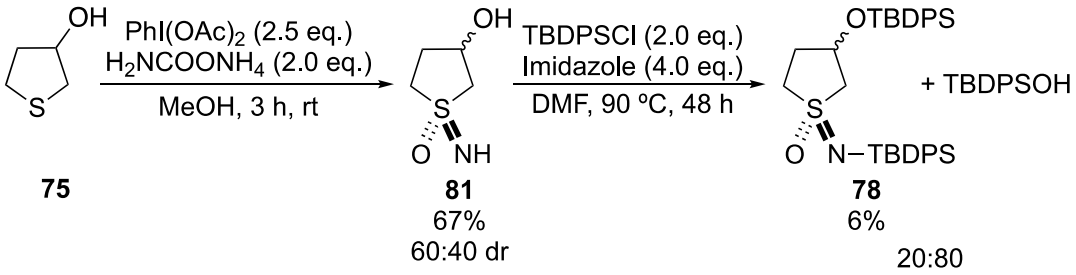
Due to this lack of success, we decided to explore an alternative elimination approach that proceeded in fewer steps (Scheme 2.34). Initially, hydroxy sulfide **75** would be converted into hydroxy sulfoximines **81**. Then, double TBDPS protection would be explored to give

disilyl sulfoximines **78** in the hope that elimination would occur to form *N*-TBDPS vinyl sulfoximine **6**.



Scheme 2.34

Hydroxy sulfide **75** was reacted with PIDA and ammonium carbamate in MeOH at rt for 3 h which gave a 60:40 mixture of inseparable diastereomeric hydroxy sulfoximines **81** in 67% yield after chromatography. This 60:40 mixture of hydroxy sulfoximines **81** was then reacted with TBDPSCl and imidazole in DMF at 90 °C for 48 h. After work-up, analysis of the ^{1}H NMR spectrum of the crude product showed no evidence for the vinylic signal of *N*-TBDPS vinyl sulfoximine **6** that was expected in the δ_H 7.0-6.0 region. After purification by chromatography, the only characterisable fraction was an inseparable 80:20 mixture of TBDPSOH and a single unidentified diastereomeric disilyl sulfoximine **78**. From this, it was calculated that disilyl sulfoximine **78** had been formed in only 6% yield (Scheme 2.35). The ^{1}H NMR spectrum showing the diagnostic signals for disilyl sulfoximine **78** is shown in Figure 2.5. A 1H signal at δ_H 4.39 (dddd, J = 5.0, 5.0, 5.0, 5.0 Hz) was assigned to the OCH proton and the four 1H signals further upfield were assigned as the SCH protons. The integrations of the *t*-butyl and phenyl signals clearly pointed to disilylation.



Scheme 2.35

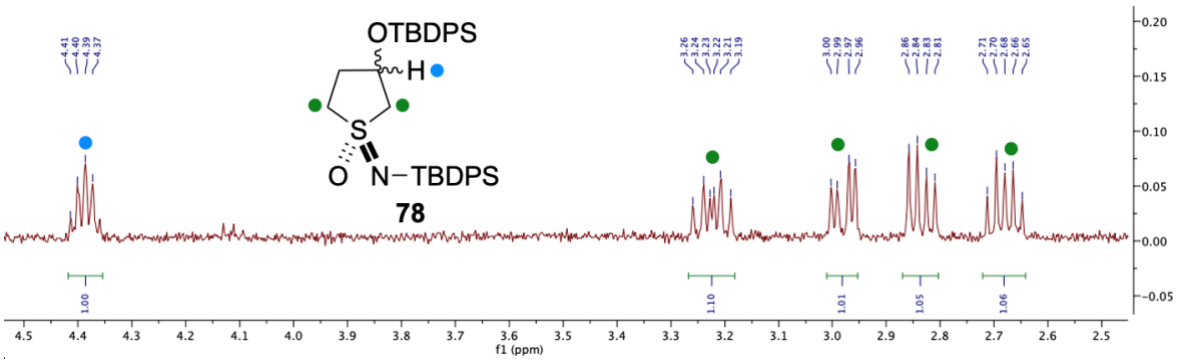
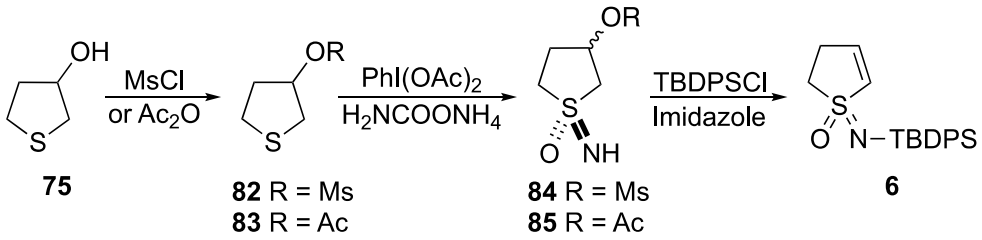


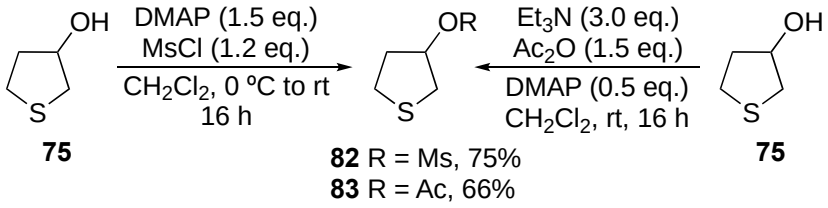
Figure 2.5 ^{1}H NMR spectrum of the diagnostic signals of disilyl sulfoximine **78**

The combination of the very low yield of disilyl sulfoximine **78** and co-elution with TBDPSOH led us to change our approach for the synthesis of *N*-TBDPS vinyl sulfoximine **6** (Scheme 2.36). In this new route, we envisaged the conversion of hydroxy sulfide **75** into mesylate sulfide **82** which would then be transformed into mesylate sulfoximines **84**. Since mesylate is a better leaving group than TBDPSO, we expected that treatment of sulfoximines **84** with TBDPSCl and imidazole in DMF at 90 °C should both protect the NH sulfoximine and eliminate the mesylate group to give *N*-TBDPS vinyl sulfoximine **6**. We also planned to explore an acetoxy leaving group in this general strategy towards vinyl *N*-TBDPS sulfoximine **6**.



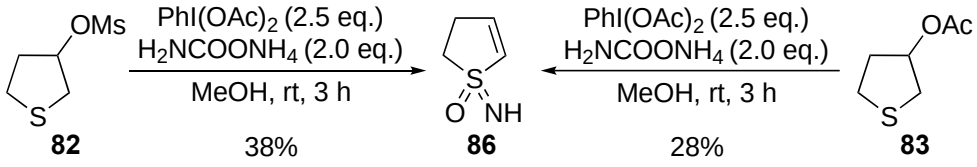
Scheme 2.36

Using a method reported by Konuki and Nagai,[47] hydroxy sulfide **75** was converted into mesylate sulfide **82**. Thus, hydroxy sulfide **75** was reacted with DMAP and MsCl in CH_2Cl_2 at 0 °C and reacted at rt for 16 h to give mesylate sulfide **82** in 75% yield after chromatography. Acetoxy sulfide **83** was also synthesised from the reaction of hydroxy sulfide **75** with Et_3N, acetic anhydride and DMAP in CH_2Cl_2 at rt for 16 h. Acetoxy sulfide **83** was obtained in 66% yield after chromatography (Scheme 2.37).



Scheme 2.37

Next, mesylate sulfide **82** was treated under the standard sulfoximine-forming conditions (PIDA, ammonium carbamate, MeOH, rt 3 h). Instead of simply forming the expected sulfoximines **84**, elimination of the mesylate also occurred to form NH vinyl sulfoximine **86**. This was isolated in 38% yield after purification by chromatography (Scheme 2.38). This was a fortuitous outcome as we are now only one step away from the desired *N*-TBDPS vinyl sulfoximine **6**. A similar outcome was observed when acetoxy sulfide **83** was also reacted under the same sulfoximine-forming conditions. After purification by chromatography, slightly impure vinyl sulfoximine **86** was isolated in 28% yield (Scheme 2.38). Analysis of the ^{1}H NMR spectra of **86** synthesised from each reaction showed the characteristic vinylic signals at δ_H 6.66 (ddd, J = 6.5, 2.0, 2.0 Hz, 1H) and 6.60 (ddd, J = 6.5, 3.0, 3.0 Hz, 1H) (Figure 2.6). The ^{3}J and ^{4}J coupling constants of the vinylic protons were surprisingly similar in magnitude and thus, we were unable to distinguish between them.



Scheme 2.38

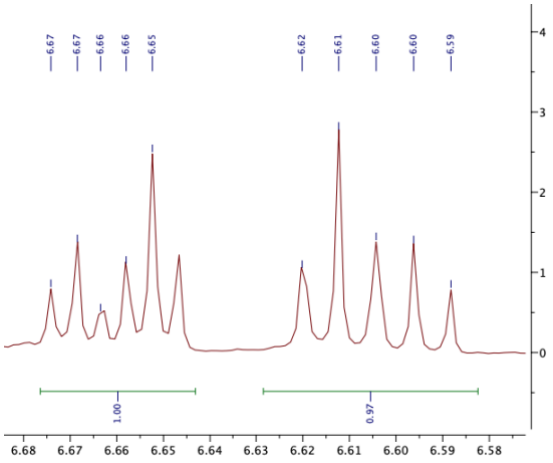
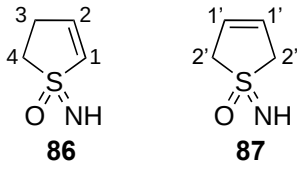


Figure 2.6 The alkene region in the ^{1}H NMR spectrum of vinyl sulfoximine **86**

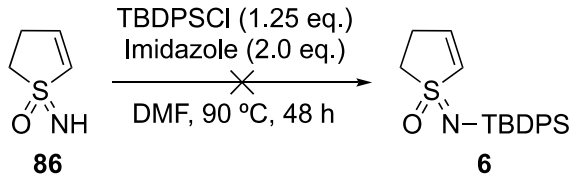
Analysis of the ^{13}C NMR spectrum of vinyl sulfoximine **86** showed two signals at δ_C 136.8 and 135.1 which were assigned to the vinylic carbons. A signal at δ_C 51.8 was assigned to the SCH_2 group and a signal at δ_C 27.6 was assigned to the CH_2 group. In our analysis, we considered that the other isomer of vinyl sulfoximine **86**, allyl sulfoximine **87**, could have formed. Since allyl sulfoximine **87** is symmetrical, only two signals would have been present in its ^{13}C NMR spectrum and so we concluded that vinyl sulfoximine **86** had indeed been synthesised.



86 **87**

Figure 2.7 Vinyl sulfoximine **86** and allyl sulfoximine **87**

With vinyl sulfoximine **86** in hand, the conversion into *N*-TBDPS vinyl sulfoximine **6** was investigated. Treatment of vinyl sulfoximine **86** with TBDPSCl and imidazole in DMF at 90 °C for 48 h gave no evidence for the formation of the desired *N*-TBDPS vinyl sulfoximine **6** by ^1H NMR spectroscopy (Scheme 2.39). The ^1H NMR spectrum of the crude product was complicated and difficult to interpret. It is not entirely clear why this reaction was unsuccessful as a range of *N*-TBDPS cyclic and acyclic sulfoximines have been prepared in the O'Brien group using this procedure.[18,20] However, due to the electrophilicity of vinyl sulfoximines, it is possible that conjugate addition of imidazole or *in situ*-generated chloride could have occurred.



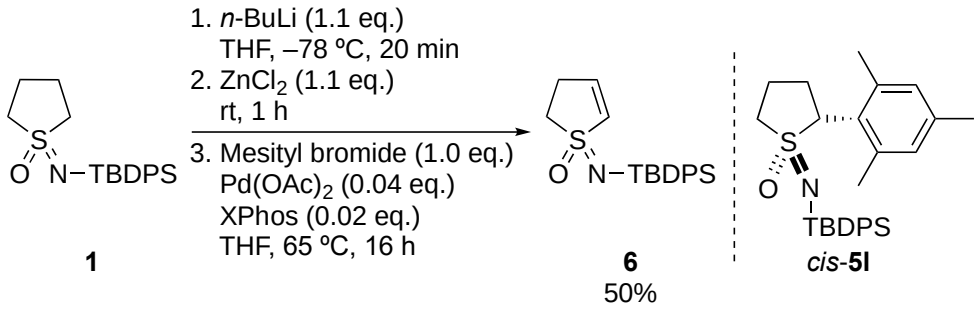
86 **6**

Scheme 2.39

To summarise, efforts to synthesise *N*-TBDPS vinyl sulfoximine **6** *via* disilyl sulfoximine **78** proved to be challenging. In contrast, vinyl sulfoximine **86** was synthesised in 38% yield from mesylate sulfide **82** *via* sulfoximine formation and elimination of the mesylate group in the β-position. With an acetoxy group, slightly impure vinyl sulfoximine **86** was formed and hence, it was concluded that the mesylate route was preferable. Unfortunately, the TBDPS protection of vinyl sulfoximine **86** was investigated with no success. However, future work using an alternative *N*-substituent may allow for the successful protection of vinyl sulfoximine **86**.

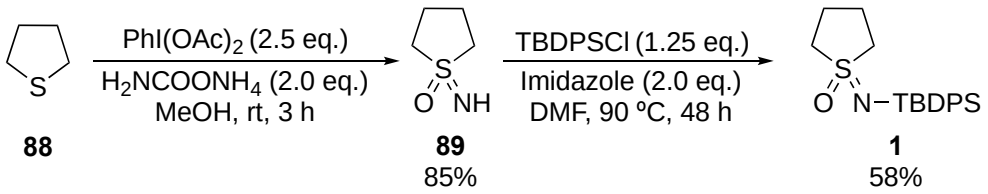
2.4 Synthesis and Rh-catalysed β-arylation of a *N*-TBDPS vinyl sulfoximine

Our efforts at preparing *N*-TBDPS vinyl sulfoximine **6** had so far proved unsuccessful. However, whilst we were exploring the routes outlined in Sections 2.2 and 2.3, a co-worker in the O'Brien group, Giordaina Hartley, unexpectedly discovered a method for preparing the targeted sulfoximine. As outlined in the Introduction (see Section 1.2), a method for the α-arylation of *N*-TBDPS sulfoximine **1** using lithiation, transmetallation to an organozinc reagent and subsequent Negishi cross-coupling had been developed in the group. However, when using sterically hindered mesityl bromide in the Negishi-cross-coupling step, it was found that the expected α-aryl sulfoximine *cis*-**5l** did not form. Instead, *N*-TBDPS vinyl sulfoximine **6** was formed (Scheme 2.40).[19] Lithiation of sulfoximine **1** with *n*-BuLi was followed by transmetallation to give the organozinc intermediate. Then, attempted Negishi cross-coupling with mesityl bromide using $Pd(OAc)_2$ and XPhos at 65 °C gave *N*-TBDPS vinyl sulfoximine **6** in 50% yield. Presumably, β-hydride elimination of the organopalladium intermediate occurred in preference to the arylation because of the use of the sterically hindered mesityl bromide. This effectively solved our quest to synthesise *N*-TBDPS vinyl sulfoximine **6** and so we set about repeating this synthesis.



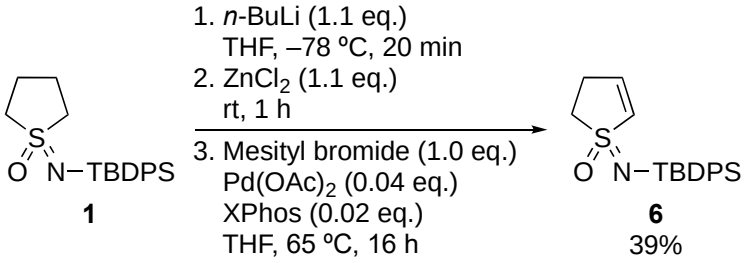
Scheme 2.40

In order to synthesise *N*-TBDPS vinyl sulfoximine **6** following the procedure outlined in Scheme 2.40, *N*-TBDPS sulfoximine **1** needed to be synthesised. Therefore, sulfide **88** was subjected to the standard sulfoximine-forming reaction[44] to give NH sulfoximine **89** in 85% yield after purification by chromatography. The NMR spectroscopic data matched those reported in the literature.[44] Then, reaction of NH sulfoximine **89** with TBDPSCl and imidazole in DMF at 90 °C for 48 h gave *N*-TBDPS sulfoximine **1** in 58% yield after chromatography (Scheme 2.41). Analysis of the ^{1}H NMR spectrum of *N*-TBDPS sulfoximine **1** showed a 9H singlet at δ_H 1.07 which indicated the successful *N*-TBDPS protection of sulfoximine **89**.



Scheme 2.41

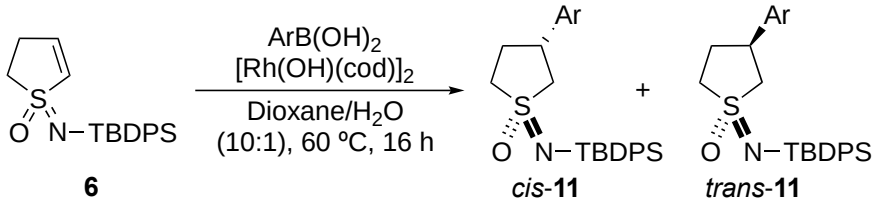
With *N*-TBDPS sulfoximine **1** in hand, the direct conversion into *N*-TBDPS vinyl sulfoximine **6** was attempted using the conditions developed in the group. This involved formation of the lithiated sulfoximine (by deprotonation of *N*-TBDPS sulfoximine **1** using *n*-BuLi) and subsequent transmetallation to an organozinc reagent with $ZnCl_2$ before the Pd-catalysed β-hydride elimination step. Treatment of *N*-TBDPS sulfoximine **1** with *n*-BuLi in THF at –78 °C for 20 min and subsequent addition of $ZnCl_2$ at rt for 1 h presumably formed the organozinc intermediate. Finally, reaction with mesityl bromide, $Pd(OAc)_2$ and XPhos in THF at 65 °C for 16 h gave *N*-TBDPS vinyl sulfoximine **6** in 39% yield after chromatography (Scheme 2.42). Analysis of the ^{1}H NMR spectrum of *N*-TBDPS vinyl sulfoximine **6** showed a 2H singlet at δ_H 6.36 which indicated the successful β-hydride elimination. This reaction was repeated a few times to bring through more material. The yields of vinyl sulfoximine **6** ranged from 20-39% for no obvious reasons and it was not possible to replicate the 50% yield previously obtained in the O'Brien group.[19] Despite these reproducibility issues, this method was suitable for the synthesis of *N*-TBDPS vinyl sulfoximine **6** and an 800 mg batch of **6** was prepared in this way which allowed us to explore the planned Rh-catalysed β-arylation. Interestingly, in the absence of mesityl bromide, *N*-TBDPS vinyl sulfoximine **6** was isolated in only 10% yield with a large amount of *N*-TBDPS sulfoximine **1** being recovered.[19]



Scheme 2.42

Based on the precedent with the analogous vinyl sulfone **55** (see Scheme 2.20), we envisaged that Rh-catalysed addition of arylboronic acids to *N*-TBDPS vinyl sulfoximine **6** would form

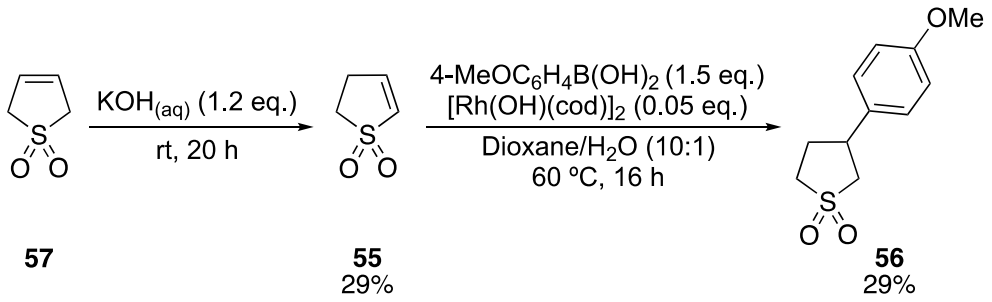
N-TBDPS β-aryl sulfoximines *cis*-**11** and *trans*-**11** (Scheme 2.43). In order to avoid complications due to kinetic resolution and to explore the diastereoselectivity of these addition reactions, the achiral catalyst, $[Rh(OH)(cod)]_2$ (which was also used with vinyl sulfone **55**) would be used. It was predicted that the steric bulk of the TBDPS group would block one face of the alkene in sulfoximine **6** so that the Rh, and hence the arylation, would be directed to the opposite face. This should result in the aryl group being *cis* to the oxygen and we expected that aryl sulfoximines *cis*-**11** would be the major products of these reactions.



Scheme 2.43

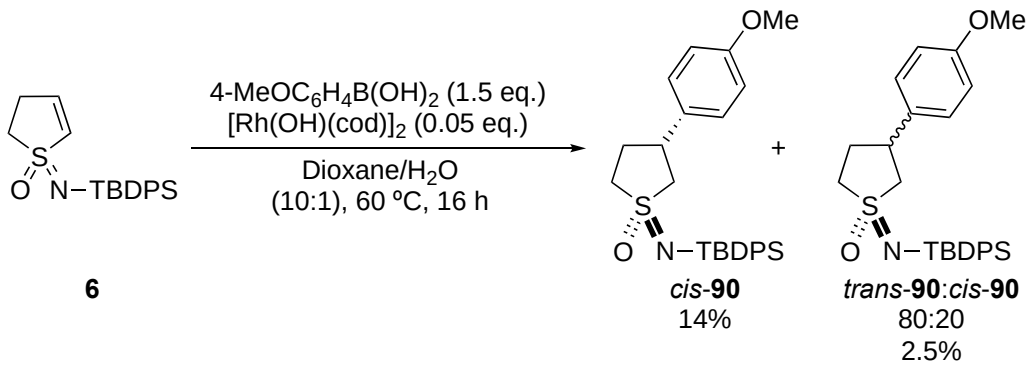
As the Rh-catalysed arylation of electron-deficient alkenes was a new reaction to the group, we began by carrying out the Rh-catalysed arylation of vinyl sulfone **55** to give β-aryl sulfone **56** as reported by Hayashi *et al.*[23] This would allow us to prove that the procedure was reproducible in our hands. For this, vinyl sulfone **55** was synthesised from 3-sulfolene **57** using a method that involved base-mediated alkene isomerisation.[23] Thus, vinyl sulfone **55** was prepared by the reaction of 3-sulfolene **57** with $KOH_{(aq)}$ at rt for 20 h. It was necessary to purify the crude product as it contained a 50:50 mixture of vinyl sulfone **55** and 3-sulfolene **57** (by ^{1}H NMR spectroscopy). After chromatography, vinyl sulfone **55** was isolated in 29% yield and 20% of the starting material, 3-sulfolene **57**, was recovered (Scheme 2.44). Next, vinyl sulfone **55**, 1.5 equivalents of 4-methoxyphenylboronic acid and $[Rh(OH)(cod)]_2$ (5 mol%) were placed in a pressure tube which was evacuated and refilled with Ar three times. Then, water and dioxane were added and the pressure tube was evacuated and refilled with Ar three times. The mixture was then heated in an oil bath at 60 °C for 16 h. After work-up and purification by chromatography, β-aryl sulfone **56** was isolated in 29% yield but was of ~90% purity due to contamination with ~10% of an impurity that appeared to be derived from the 4-methoxyphenylboronic acid. We considered that the impurity was 4-methoxyphenylboronic acid or its protodeborylated derivative but the signals in the ^{1}H NMR spectrum did not support this. It is possible that the boronic acid may have trimerised to form the 6-membered ring boroxine. In addition, 11% of the starting material, vinyl sulfone **55**,

was recovered. The NMR spectroscopic data for vinyl sulfone **55** and β-aryl sulfone **56** were consistent with those reported in the literature. However, the yield was significantly lower than the 90% yield reported.[23]



Scheme 2.44

Although the yield of β-aryl sulfone **56** was low, it was decided to focus our efforts on the investigation into the Rh-catalysed β-arylation of *N*-TBDPS vinyl sulfoximine **6**. Using the same conditions as for the arylation of vinyl sulfone **55**, *N*-TBDPS vinyl sulfoximine **6** was reacted with 4-methoxyphenylboronic acid in the presence of $[Rh(OH)(cod)]_2$ (5 mol%) in dioxane/H_2O at 60 °C for 16 h. On inspection of the ^1H NMR spectrum of the crude product, it was not immediately obvious whether the reaction had worked. However, after purification by chromatography, two fractions were isolated. The first fraction contained a single diastereomeric β-aryl *N*-TBDPS sulfoximine *cis*-**90** (14% yield). In the second fraction, there appeared to be an 80:20 mixture of diastereomeric β-aryl *N*-TBDPS sulfoximines *trans*-**90** and *cis*-**90** (2% yield of *trans*-**90** and 0.5% yield of *cis*-**90**) (by ^1H NMR spectroscopy) (Scheme 2.45). The relative stereochemistry was assigned based on recent work in the group where the major product, β-aryl *N*-TBDPS sulfoximine *cis*-**90**, was converted into its *N*-tosyl analogue (*via* TBDPS removal and tosylation) and analysed by X-ray crystallography. Unfortunately, the X-ray crystal structure is of low quality so the assignment of the relative stereochemistry shown in Scheme 2.45 should be treated as tentative. Reassuringly, this fits with our expected outcome for this reaction namely that the arylation would occur opposite the *N*-TBDPS group.



Scheme 2.45

Analysis of the ^{1}H NMR spectrum of β-aryl *N*-TBDPS sulfoximine *cis*-**90** (Figure 2.8) showed two 2H signals at δ_H 7.07 (d, J = 8.5 Hz) and δ_H 6.84 (d, J = 8.5 Hz) corresponding to the protons on the methoxyphenyl ring (light blue). The 3H singlet at δ_H 3.78 was assigned to the methoxy CH_3 protons (dark blue). The 1H signal at δ_H 3.35-3.28 was assigned to the ArCH proton (dark green). The 2H signals at δ_H 3.26-3.17 and δ_H 3.02-2.90 were assigned to the four SCH protons (orange). The 1H multiplets at δ_H 2.36-2.28 and δ_H 2.26-2.15 were assigned to the CH_2 group (light green).

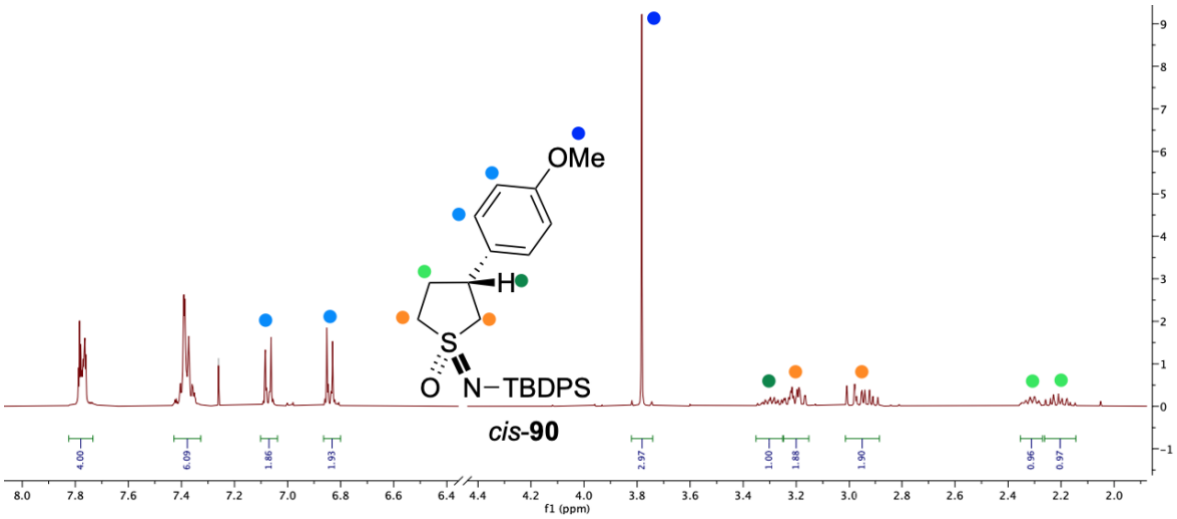


Figure 2.8 The key signals in the ^{1}H NMR spectrum of β-aryl sulfoximine *cis*-**90**

Analysis of the ^{1}H NMR spectrum of the second fraction confirmed that the other diastereomer had been isolated. On comparison of the ^{1}H NMR spectrum of *cis*-**90** with the ^{1}H NMR spectrum of the 80:20 mixture of *cis*-**90** and *trans*-**90** (Figure 2.9), the key signals for *trans*-**90** were as follows: the ArCH proton was assigned to the 1H signal at δ_H 3.56-3.47 (dark green) and the SCH protons (blue) were assigned to the 1H signal at δ_H 3.29-3.22, the 2H signal at δ_H 3.12-3.08 and the 1H signal at δ_H 2.80 (dd, J = 12.5, 12.5 Hz).

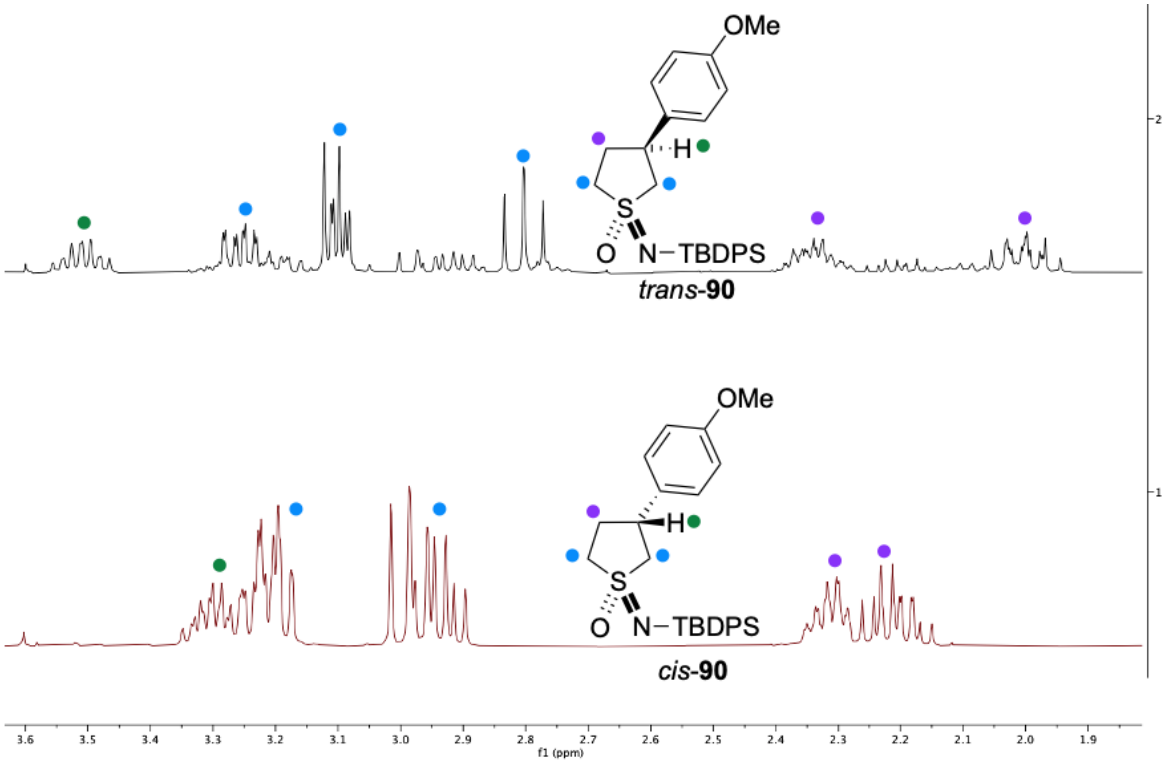
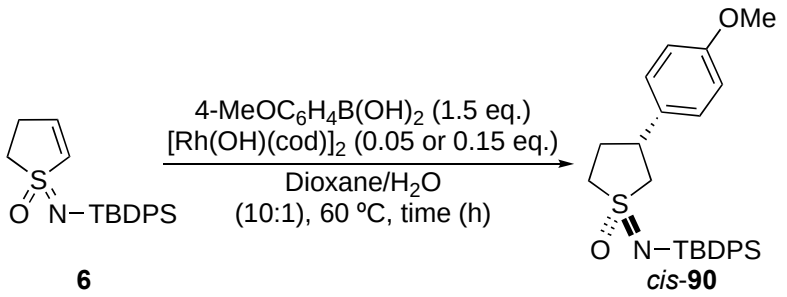


Figure 2.9 Comparison of the key signals in the ^{1}H NMR spectra of *cis*-**90** and the 80:20 mixture of *trans*-**90** and *cis*-**90**

In an effort to improve the yield of β-aryl *N*-TBDPS sulfoximines **90**, two other reaction conditions were explored (Table 2.1). First, the reaction time with $[Rh(OH)(cod)]_2$ (5 mol%) was increased from 16 h to 48 h. Interestingly, this gave β-aryl *N*-TBDPS sulfoximine *cis*-**90** as a single diastereomer in 15% yield after chromatography (Entry 2). There was no evidence of the formation of any of the minor diastereomeric sulfoximine *trans*-**90**. As the yield was essentially the same as the 16 h reaction, the loading of $[Rh(OH)(cod)]_2$ was increased to 15 mol% with a reaction time of 16 h. Under these conditions, β-aryl *N*-TBDPS sulfoximine *cis*-**90** was isolated as a single diastereomer in 28% yield after chromatography (Entry 3).

Table 2.1 Exploration of the Rh-catalysed β-arylation of *N*-TBDPS vinyl sulfoximine **6**



6 *cis*-**90**

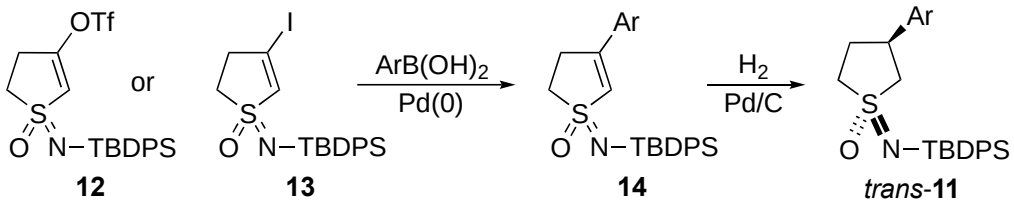
Entry	Rh-catalyst (mol%)	Time (h)	Yield of *cis*-**90** (%)[a]
1	5	16	14.5[b]
2	5	48	15
3	15	16	28

[a]% yield after purification by chromatography, [b]2% yield of sulfoximine *trans*-**90** also isolated.

To summarise, the synthesis of saturated *N*-TBDPS sulfoximine **1** was achieved in 49% yield over two steps. Negishi cross-coupling conditions using a sterically bulky aryl bromide led to β-hydride elimination to form the desired *N*-TBDPS vinyl sulfoximine **6** in 39% yield (19% yield over three steps). The synthesis of β-aryl *N*-TBDPS sulfoximine *cis*-**90** was initially achieved in 14.5% yield and it was found that varying reaction time had no effect on the yield. However, increasing the amount of Rh-catalyst to 15 mol% improved the yield to give β-aryl *N*-TBDPS sulfoximine *cis*-**90** in 28% yield. Prior to the initial optimisation reactions for the Rh-catalysed arylation of *N*-TBDPS vinyl sulfoximine **6**, efforts exploring routes to the diastereomeric *trans*-β-aryl sulfoximines were under way, the results of which are covered in Chapter 3. We had planned to expand the scope of our initial promising result from the Rh-catalysed β-arylation of *N*-TBDPS vinyl sulfoximine **6**. However, unfortunately, due to laboratory time lost during the COVID-19 pandemic, there was insufficient time to return to the Rh-catalysed arylation route.

3. Investigation of a Suzuki-Miyaura Cross-Coupling-Hydrogenation Route to β-Aryl Cyclic Sulfoximines

In this Chapter, the development of methodology in order to access β-aryl *N*-TBDPS sulfoximines *trans*-**11** is described. The proposed routes are summarised in Scheme 3.1. Thus, the plan was to prepare either sulfoximine enol triflate **12** or iodo vinyl sulfoximine **13** which would each be converted into β-aryl vinyl sulfoximines **14** using Suzuki-Miyaura cross-coupling. Finally, diastereoselective hydrogenation should enable β-aryl cyclic sulfoximines *trans*-**11** to be formed as hydrogenation of the alkene should occur on the opposite face to the TBDPS group.

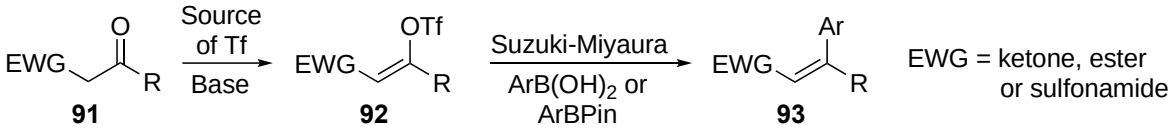


Scheme 3.1

Section 3.1 presents an overview of the relevant literature background for the formation and Suzuki-Miyaura cross-coupling of enol triflates bearing an electron-withdrawing group in the β-position (analogous to sulfoximine enol triflate **12**). Particular focus was paid to substrates containing lactones, coumarins, ketones and a sulfonamide as there are no sulfoximine examples. Section 3.2 outlines the attempted synthesis of sulfoximine enol triflate **12** starting from the corresponding cyclic keto sulfide, including the use of different ketal protecting groups. In Section 3.3, the attempted synthesis of iodo vinyl sulfoximine **13** for the preparation of the β-functionalised cyclic sulfoximines is presented. The key step involved an iodocyclisation reaction.

3.1 Suzuki-Miyaura cross-coupling of enol triflates with a β-electron-withdrawing group

Transition metal-mediated cross-coupling reactions have revolutionised the way C–C bonds are formed in synthesis. In particular, Suzuki-Miyaura cross-coupling reactions have been extensively explored for the formation of aryl-aryl bonds.[49] In addition, Suzuki-Miyaura cross-coupling reactions of enol triflates with electron withdrawing groups at the β-position have been widely used in total syntheses of complex natural products,[50] as well as for the preparation of potential drug molecules in the pharmaceutical industry due to their scalability and cost-effectiveness.[51] In general, a Pd-catalysed Suzuki-Miyaura cross-coupling reaction involves the coupling of a vinyl or aryl organoboron derivative with an organic halide or triflate in the presence of an aqueous base. Basic conditions are required to activate the organoboron species.[52] The general scheme for a Suzuki-Miyaura reaction between an arylboronic acid or boronate and an enol triflate **92** with a β-electron-withdrawing group (prepared from precursor carbonyl compound **91**) to give arylated alkene **93** is summarised in Scheme 3.2.

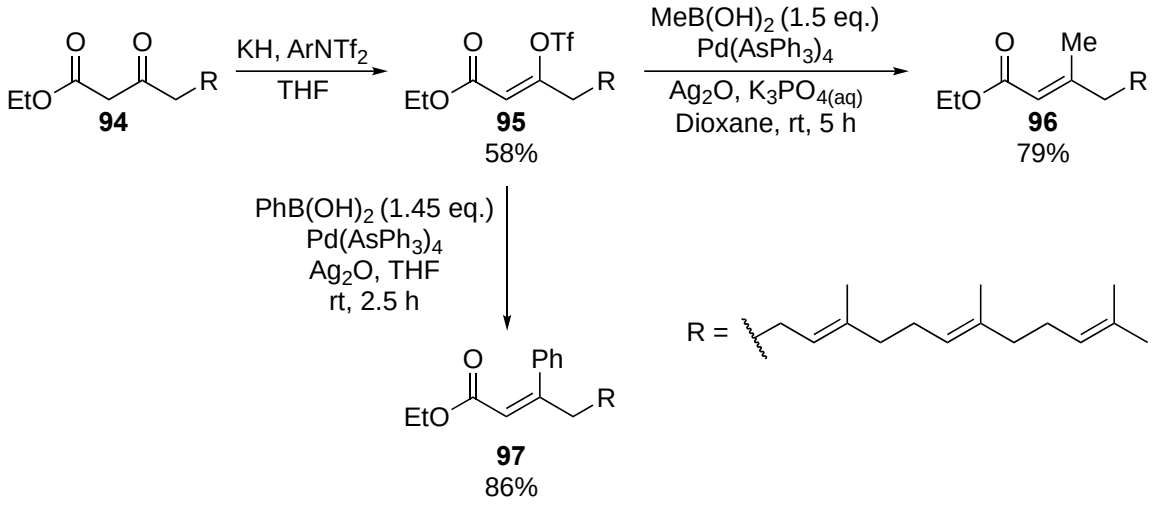


Scheme 3.2

In this section, a selection of key examples of Suzuki-Miyaura cross-coupling reactions of enol triflates bearing an electron-withdrawing group at the β-position, with a focus on substrates containing lactones, coumarins, ketones and a sulfonamide, will be presented. In each case, the method used to prepare the enol triflate and the conditions for the Suzuki-Miyaura cross-coupling reaction will be highlighted.

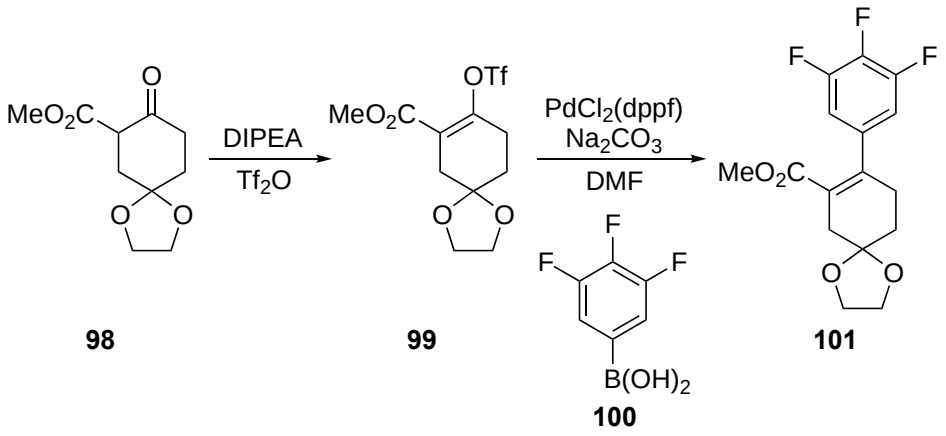
Suzuki-Miyaura cross-coupling reactions of isoprenoid triflates with methyl and phenylboronic acids were reported by Gibbs and Mu[53] for the preparation of potential PGGTase I inhibitors. PGGTase I inhibitors are of importance for their potent anticancer activity as well as their potential advantages in the treatment of cardiovascular diseases and osteoporosis. In their study, enol triflate **95** was prepared by reaction of β-keto ester **94** with KH and $ArNTf_2$ in THF. Then, Suzuki-Miyaura cross-coupling of enol triflate **95** with methylboronic acid using $Pd(AsPh_3)_4$, Ag_2O and $K_3PO_{4(aq)}$ in dioxane at rt for 5 h gave β-

methyl ester **96** in 79% yield. In addition, the phenyl analogue was prepared by reaction of enol triflate **95** with phenylboronic acid using $Pd(AsPh_3)_4$ and Ag_2O in THF at rt for 2.5 h. This gave β-phenyl ester **97** in 86% yield (Scheme 3.3).



Scheme 3.3

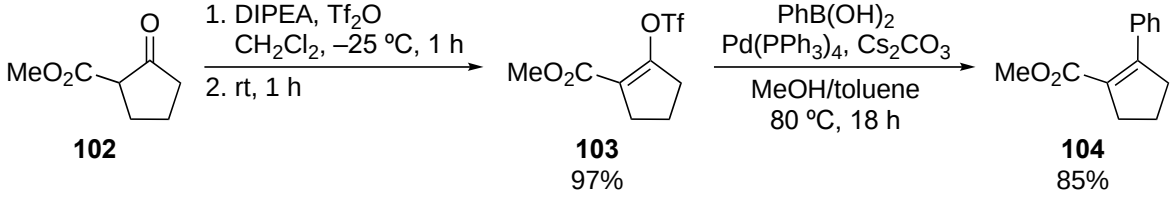
Biftu and co-workers[54] reported the synthesis of a novel cyclohexylamine DPP-4 inhibitor *via* a route that involved a Suzuki-Miyaura cross-coupling reaction of an enol triflate with a boronic acid. Thus, reaction of β-ketoester **98** with DIPEA and Tf_2O gave enol triflate **99**. Subsequent Suzuki-Miyaura reaction of enol triflate **99** with boronic acid **100** using $PdCl_2(dppf)$ and $Na_2CO_{3(aq)}$ in DMF gave cross-coupled product **101** (yields not reported) (Scheme 3.4).



Scheme 3.4

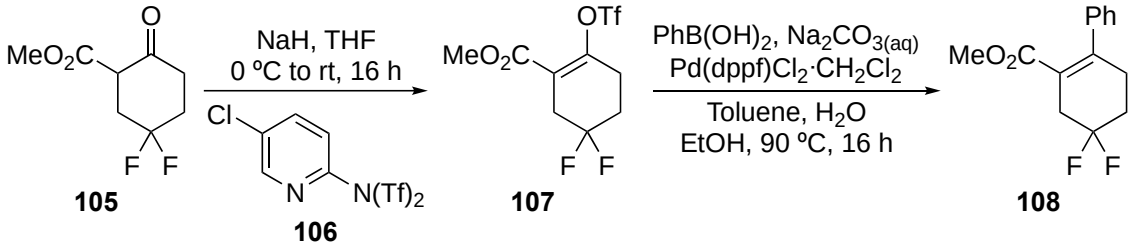
An example of the conversion of a 5-membered ring β-ketoester into a β-ester enol triflate for use in a Suzuki-Miyaura cross-coupling reaction was reported in a patent by Zhang *et*

al.[55] for the synthesis of pyrimidone derivatives for use in the treatment of a viral disease. Thus, reaction of β-ketoester **102** with DIPEA and Tf_2O gave enol triflate **103** in 97% yield. Subsequent Suzuki-Miyaura reaction of enol triflate **103** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in MeOH/toluene at 80 °C for 18 h gave disubstituted cyclopentene **104** in 85% yield (Scheme 3.5).



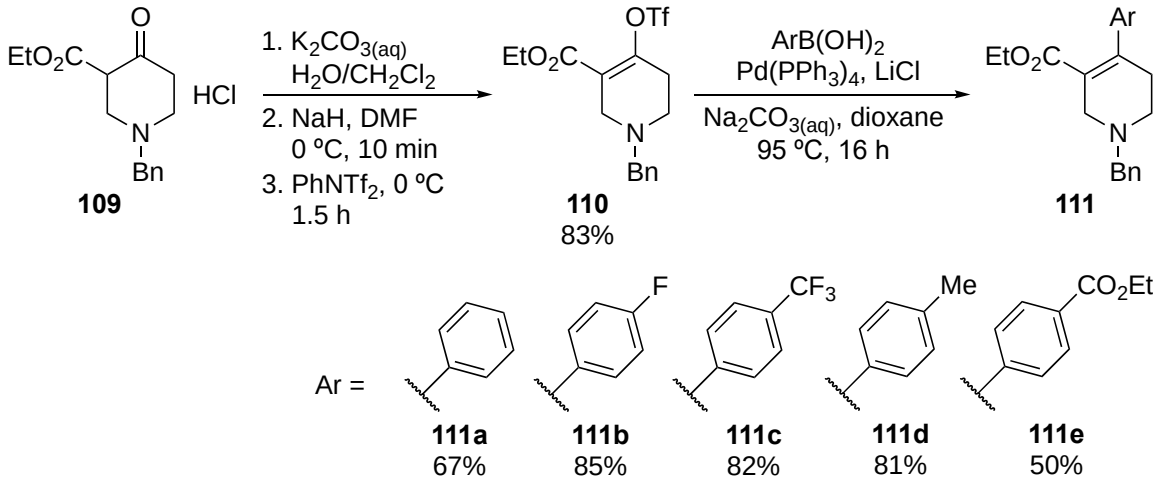
Scheme 3.5

In 2018, Seefeld *et al.*[56] reported the synthesis of novel K_v7 ion channel openers for the treatment of epilepsy using Suzuki-Miyaura cross-coupling of a β-ester enol triflate. β-Ester enol triflate **107** was prepared by the reaction of β-ketoester **105** with NaH and Comins' reagent **106**. Then, a Suzuki-Miyaura reaction of β-ester enol triflate **107** with phenylboronic acid using $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ and $Na_2CO_{3(aq)}$ in toluene, H_2O and EtOH at 90 °C for 16 h gave cross-coupled product **108** (yields not reported) (Scheme 3.6).



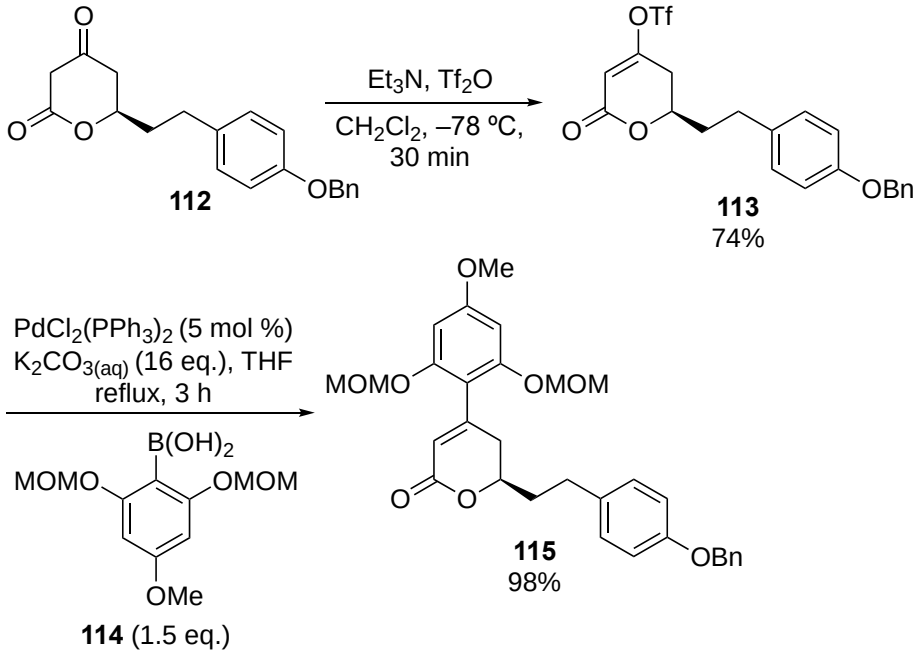
Scheme 3.6

Provencher *et al.*[57] described the synthesis of arylpiperidinylquinazolines as potential inhibitors of human vesicular monoamine transporter 2 for the treatment of methamphetamine addiction. In the synthetic route, β-ketoester **109** was converted into enol triflate **110** in 83% yield using NaH in DMF followed by the addition of $PhNTf_2$. Then, Suzuki-Miyaura cross-coupling of enol triflate **110** with various arylboronic acids in the presence of $Pd(PPh_3)_4$, LiCl and $Na_2CO_{3(aq)}$ in dioxane at 95 °C for 16 h gave cross-coupled products **111a-e** in high yields (Scheme 3.7).



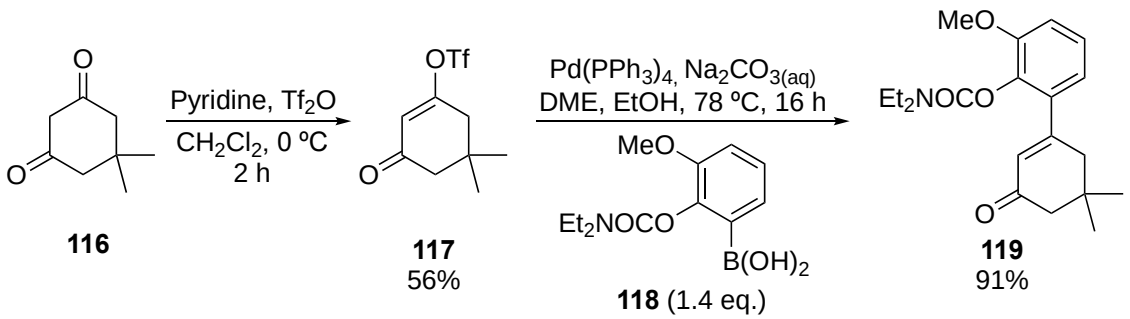
Scheme 3.7

The Suzuki-Miyaura cross-coupling of 2,4,6-trialkoxyphenylboronic acids and enol triflates was utilised by Cakir and Mead[58] for the synthesis of lactones which were precursors to several calyxin analogues. Thus, reaction of β-keto ester **112** with Et_3N and Tf_2O gave lactone enol triflate **113** in 74% yield. Then, reaction of enol triflate **113** with arylboronic acid **114** in the presence of $PdCl_2(PPh_3)_2$ and $K_2CO_{3(aq)}$ in THF at reflux for 3 h gave arylated lactone **115** in 98% yield (Scheme 3.8). In contrast, the analogous enol tosylate did not give not give any of the desired arylated lactone **115**.



Scheme 3.8

Quesnelle and Snieckus[59] described the Suzuki-Miyaura cross-coupling reactions of enol triflates with boronic acids bearing a directing metalation group in the *ortho* position. For example, dimedone **116** was converted into enol triflate **117** in 56% yield using pyridine and Tf_2O. Then, enol triflate **117** underwent a Suzuki-Miyaura cross-coupling reaction with boronic acid **118** using $Pd(PPh_3)_4$ and $Na_2CO_{3(aq)}$ in DME/EtOH at 78 °C for 16 h to give cross-coupled product **119** in 91% yield (Scheme 3.9).



116

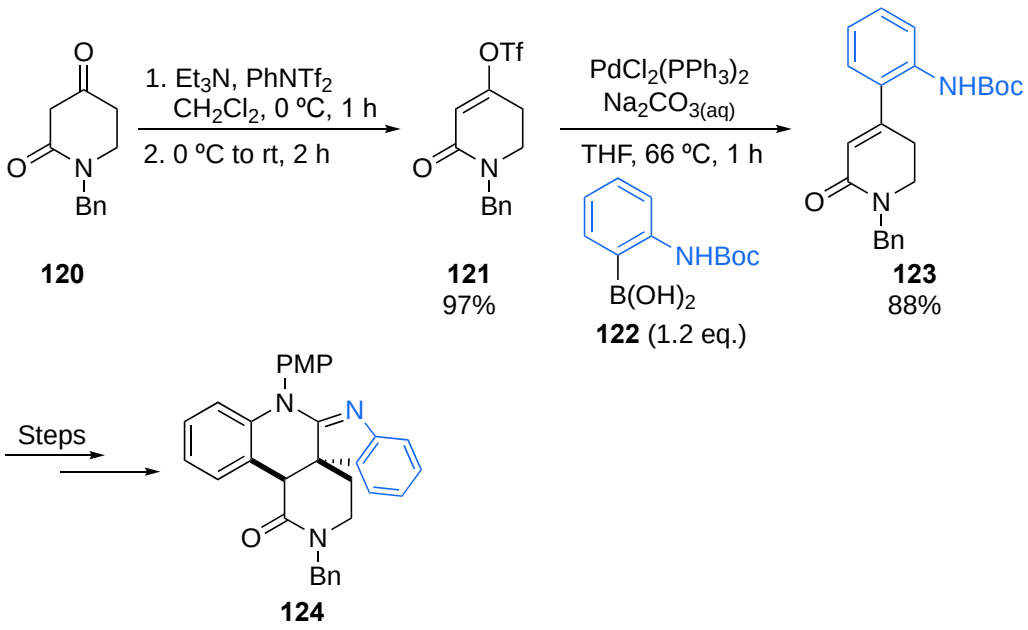
117
56%

118 (1.4 eq.)

119
91%

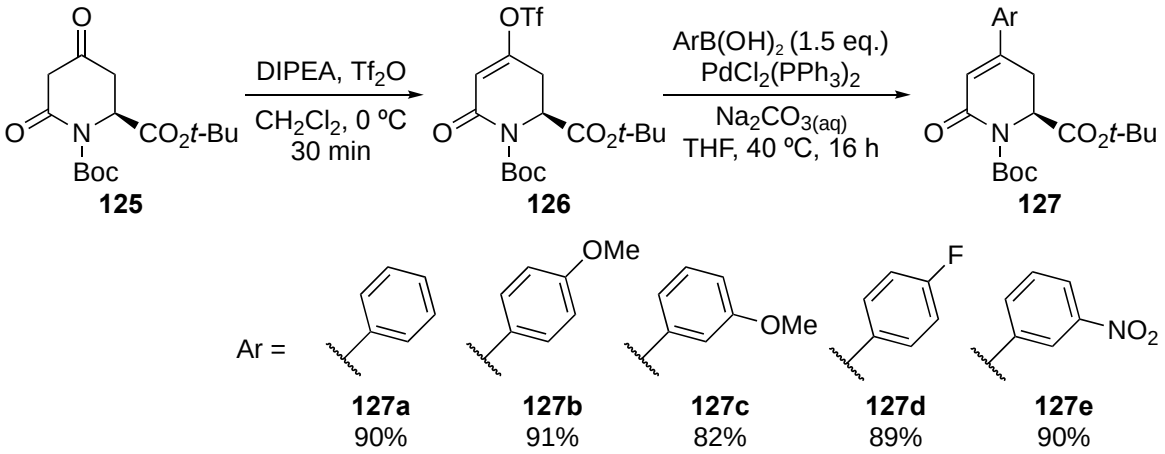
Scheme 3.9

The importance of Suzuki-Miyaura cross-coupling reactions in natural product syntheses was shown by Ishida and Takemoto[60] in the synthesis of the pentacyclic core of perophoramidine *via* a 3,3-disubstituted 2-iminoindoline. Indole derivatives containing a nitrogen at the 2-position, such as 3,3-disubstituted 2-iminoindolines, are frequently found in natural products and exhibit various biological activities.[60] In the reported synthesis, diketo benzylpiperidinone **120** was reacted with Et_3N and $PhNTf_2$ to give enol triflate **121** in 97% yield. The Suzuki-Miyaura cross-coupling reaction of enol triflate **121** with boronic acid **122** in the presence of $PdCl_2(PPh_3)_2$ and $Na_2CO_{3(aq)}$ in THF at reflux for 1 h gave Boc-protected aniline **123** in 88% yield (Scheme 3.10). Subsequently, Boc-protected aniline **123** was carried forward in the synthesis of pentacyclic core **124**.



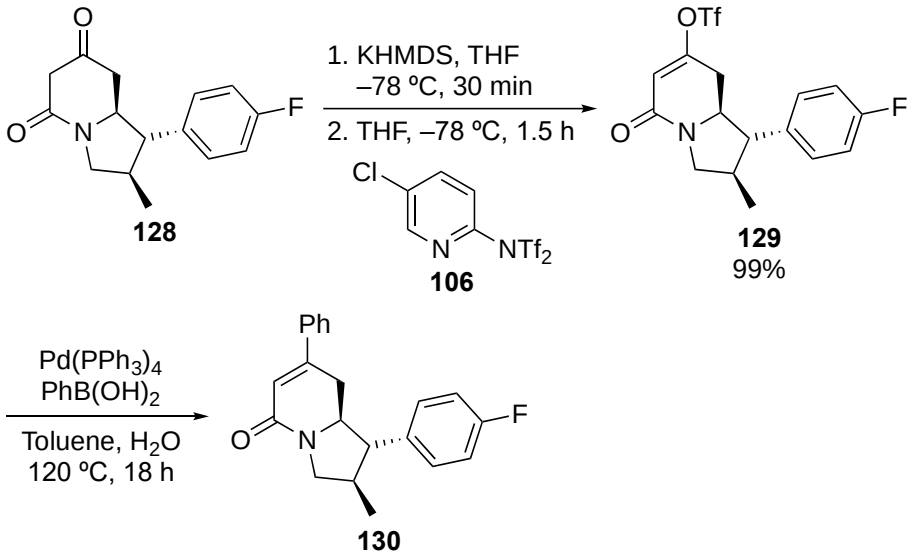
Scheme 3.10

Similarly, using an *N*-protected piperidinone enol triflate, Hanessian and co-workers[61] reported the diastereoselective synthesis of functionally diverse substituted pipecolic acids in which the key step was a Suzuki-Miyaura cross-coupling reaction. Substituted pipecolic acid intermediates are a way of accessing more complex monocyclic and polycyclic compounds that are of interest in medicinal chemistry and natural product synthesis.[62,63] In this study, diketo piperidine **125** was treated with DIPEA and Tf_2O to give piperidine enol triflate **126** (no yield reported). Next, piperidine enol triflate **126** underwent a Suzuki-Miyaura reaction with phenylboronic acid using $PdCl_2(PPh_3)_2$ and $Na_2CO_{3(aq)}$, in THF at 40 °C for 16 h to give cross-coupled product **127a** in 90% yield. Various arylboronic acids were coupled to enol triflate **126** to give aryl products **127b-e** in moderate to high yields (Scheme 3.11).



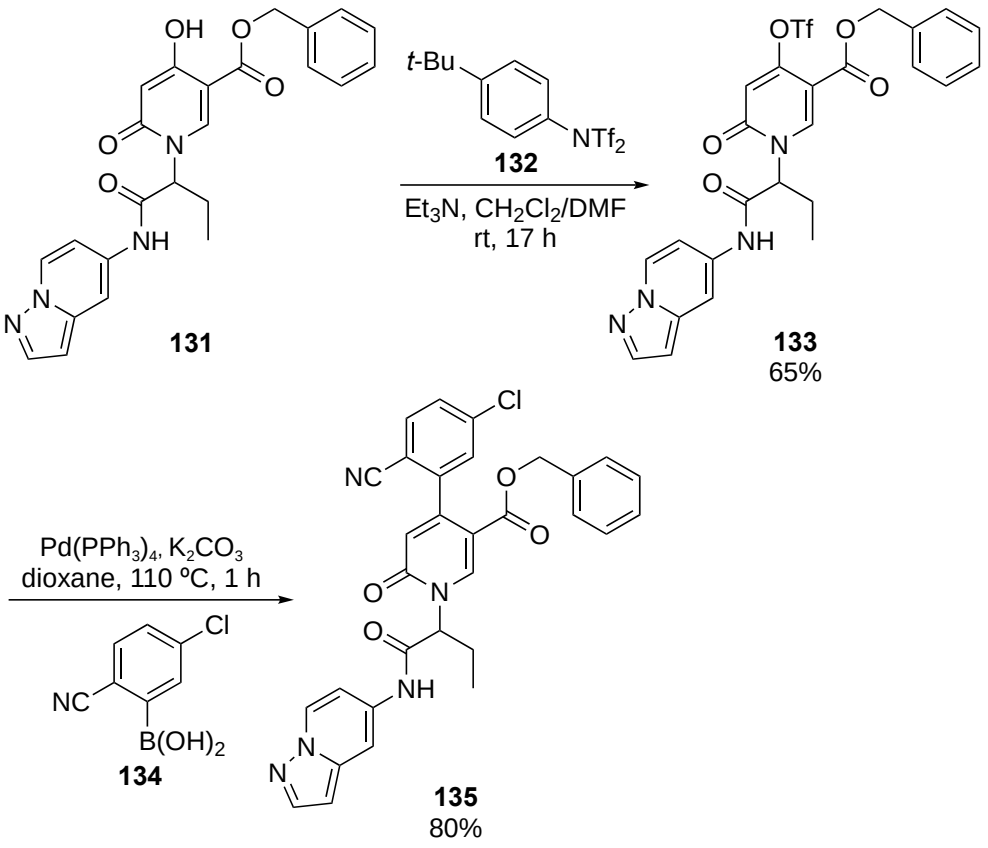
Scheme 3.11

In 2010, the synthesis of novel tetrahydroindolizinone NK_1 receptor antagonists was reported by Bao *et al.*[64] NK_1 receptor antagonists possess antidepressant, anxiolytic and antiemetic properties for use in medicines. They also play a key role in nausea and vomiting prevention for patients undergoing cancer chemotherapy.[65] The key step in the synthesis of the tetrahydroindolizinone NK_1 receptor antagonist was β-functionalisation of a lactam. This functionality was achieved *via* a Suzuki-Miyaura cross-coupling reaction between phenylboronic acid and lactam enol triflate **129**. Thus, lactam enol triflate **129** was prepared in 99% yield by reaction of β-keto lactam **128** with KHMDS and then Comins' reagent **106**. Next, enol triflate **129** was reacted with phenylboronic acid in the presence of $Pd(PPh_3)_4$ in toluene and water at 120 °C for 18 h to give cross-coupled product **130** (no yield reported) (Scheme 3.12). A range of aryl groups were successfully coupled using these Suzuki-Miyaura cross-coupling conditions.



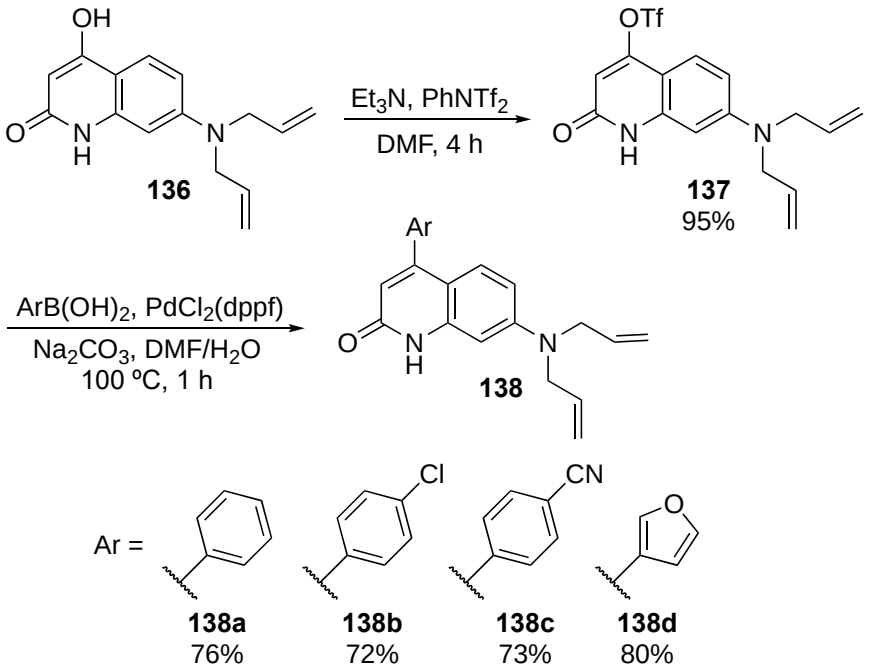
Scheme 3.12

The synthesis of substituted oxopyridine derivatives for use in the treatment of cardiovascular disorders was reported in a patent.[66] Triflation of hydroxypyridone **131** was carried out using triflimide **132** to give triflate **133** in 65% yield. Subsequent Suzuki-Miyaura cross-coupling of enol triflate **133** with boronic acid **134** using $Pd(PPh_3)_4$ and K_2CO_3 in dioxane at 110 °C for 1 h yielded cross-coupled product **135** in 80% yield (Scheme 3.13).



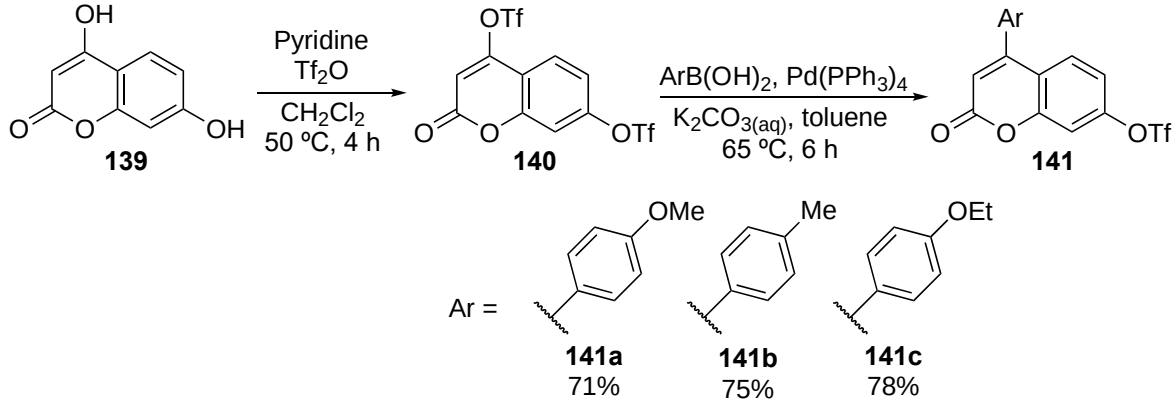
Scheme 3.13

Sames *et al.*[67] reported the design of ratiometric optical probes where the synthetic work relied upon Suzuki-Miyaura cross-couplings of an enol triflate derived from a carbostyril. The photon antenna of the probe, which sensitises the luminescence, may be functionally-adapted by the different aryl groups containing electron withdrawing groups in the β-position. In order to develop a general, divergent path to functionalised carbostyrils, triflate **137** was synthesised. Reaction of phenol **136** with Et_3N and $PhNTf_2$ gave triflate **137** in 95% yield. Various aryl groups were successfully coupled to triflate **137** with arylboronic acids in the presence of $PdCl_2$(dppf) catalyst and Na_2CO_3 in DMF/H_2O at 100 °C for 1 h and gave the corresponding aryl products **138a-d** in high yields (Scheme 3.14).



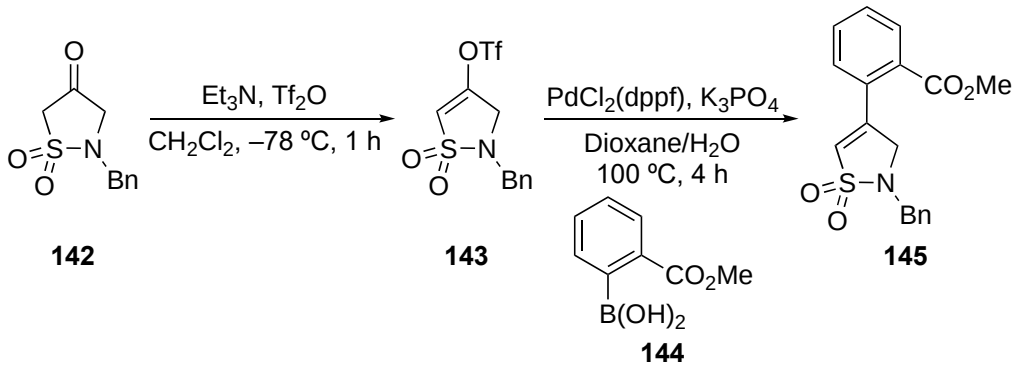
Scheme 3.14

The regioselective synthesis of 4-aryl coumarins *via* Suzuki-Miyaura cross-coupling reactions of a β-lactone enol triflate was reported by Langer *et al.*[68] 4-Aryl coumarins have various pharmacological activities including anticancer, antibacterial and antiviral activity. In Langer's synthetic route, bis triflate **140** was prepared by reaction of coumarin **139** with pyridine and Tf_2O. Then, a completely regioselective Suzuki-Miyaura reaction of bis triflate **140** at the more activated enol triflate β to the lactone carbonyl group occurred. Thus, reaction with arylboronic acids in the presence of $Pd(PPh_3)_4$ and $K_2CO_{3(aq)}$ in toluene at 65 °C for 6 h gave cross-coupled products **141a-c** in high yields, with complete regioselectivity (Scheme 3.15). The remaining aryl triflate was then available for other subsequent cross-coupling reactions.



Scheme 3.15

Developments in the Suzuki-Miyaura cross-coupling reactions of enol triflates has led to the preparation and cross-coupling of a sulfonamide enol triflate in a route towards a compound for the treatment of hepatitis B.[69] Thus, sulfonamide enol triflate **143** was prepared by reaction of β-keto sulfonamide **142** with Et_3N and Tf_2O. Then, cross-coupling of sulfonamide enol triflate **143** with boronic acid **144** in the presence of $PdCl_2$(dppf) and K_3PO_4 in dioxane/H_2O at 100 °C for 4 h gave cross-coupled product **145** (Scheme 3.16). Unfortunately, yields were not reported throughout this patent.

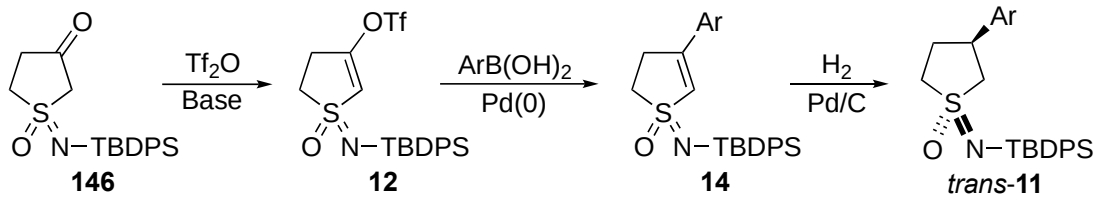


Scheme 3.16

To summarise, there is a wide range of precedent for the Suzuki-Miyaura cross-coupling of enol triflates bearing a β-electron-withdrawing group, particularly lactones, coumarins and ketones. Many of these cross-coupling reactions have been utilised to access various drug molecules and as part of synthetic routes towards complex natural products. There are no examples of Suzuki-Miyaura cross-couplings of sulfoximine or sulfone enol triflates. The closest example to the reaction we proposed to study was the Suzuki-Miyaura cross-coupling reaction of sulfonamide enol triflate **143** (see Scheme 3.16).

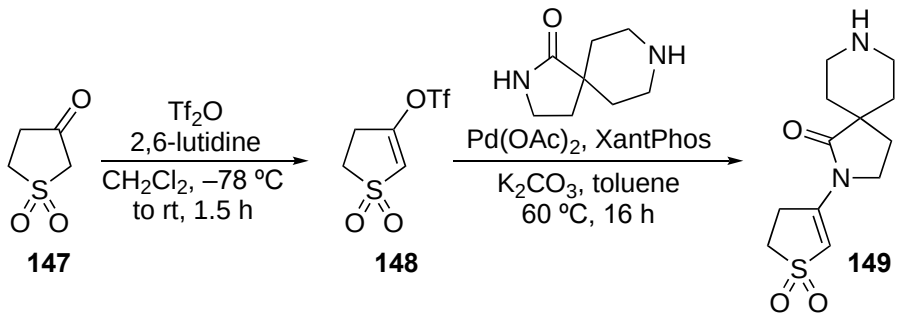
3.2 Attempted synthesis of β-aryl sulfoximines *via* an enol triflate

The aim for this part of the project was to develop a diastereoselective synthesis of β-aryl sulfoximine *trans*-**11** *via* sulfoximine enol triflate **12** (Scheme 3.17). In our proposed route, β-keto *N*-TBDPS sulfoximine **146** would be regioselectively converted into sulfoximine enol triflate **12** upon treatment with Tf_2O and a base. Then, a Suzuki-Miyaura cross-coupling reaction using an arylboronic acid and Pd(0) would be used to convert sulfoximine enol triflate **12** into β-aryl vinyl sulfoximines **14**. It was anticipated that subsequent hydrogenation using H_2 and Pd/C would result in the diastereoselective formation of β-aryl sulfoximines *trans*-**11**. Due to the steric bulk of the TBDPS group, we expected that hydrogenation of the alkene in β-aryl vinyl sulfoximines **14** would occur on the opposite face to the TBDPS group. If successful, this approach would allow access to the other diastereomeric series to that obtained from the Rh-catalysed arylation described in Section 2.4.



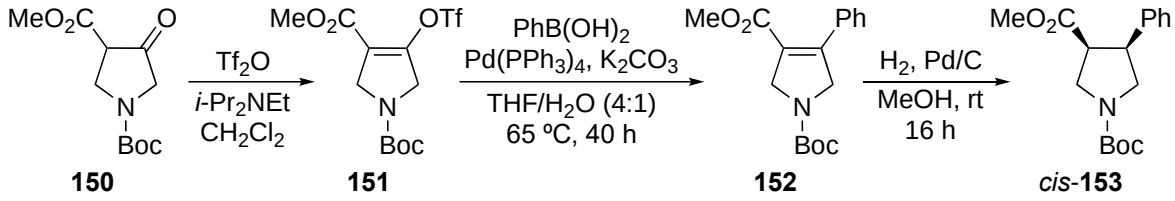
Scheme 3.17

As far as we are aware, there are no examples of the synthesis and cross-coupling of sulfoximine enol triflates such as **12**. The closest example is a Buchwald-Hartwig amination of sulfone enol triflate **148** from the patent literature.[70] In their example, β-keto sulfone **147** was treated with Tf_2O and 2,6-lutidine to give sulfone enol triflate **148** which underwent Buchwald-Hartwig amination using a piperidine lactam, $Pd(OAc)_2$ and XantPhos to give sulfone enamide **149** (Scheme 3.18). Unfortunately, yields were not reported.



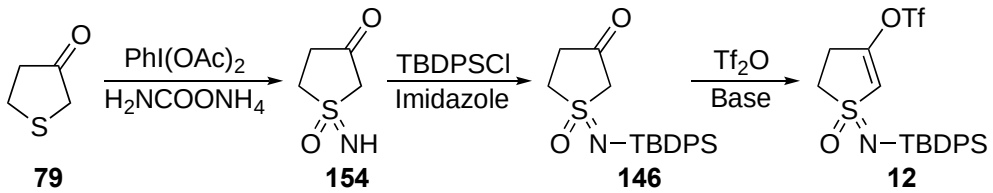
Scheme 3.18

Previous work in the O'Brien group[71] had investigated Suzuki-Miyaura cross-coupling reactions of 5-membered ring β-keto esters. In one example, β-keto ester **150** was converted into enol triflate **151** using *i*-Pr_2NEt and Tf_2O. Then, a Suzuki-Miyaura cross-coupling reaction using phenylboronic acid and $Pd(PPh_3)_4$ afforded dihydropyrrole **152** in 83% yield. Hydrogenation of the alkene in dihydropyrrole **152** with H_2 and Pd/C gave pyrrolidine *cis*-**153** as a single diastereomer in 97% yield (Scheme 3.19).



Scheme 3.19

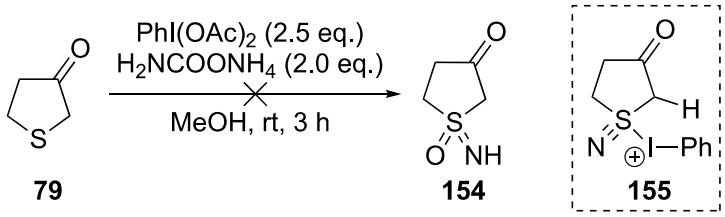
Our proposed route for the synthesis of the key starting material to explore the enol triflate route, sulfoximine enol triflate **12**, is summarised in Scheme 3.20. We envisaged that Bull and Luisi's sulfoximine-forming conditions (PIDA, ammonium carbamate, MeOH)[44] would convert β-keto sulfide **79** into β-keto sulfoximine **154**. Using TBDPS protection conditions, β-keto sulfoximine **154** would be converted into β-keto *N*-TBDPS sulfoximine **146**. Addition of Tf_2O and a base to β-keto *N*-TBDPS sulfoximine **146** would then be used to synthesise *N*-TBDPS sulfoximine enol triflate **12**.



Scheme 3.20

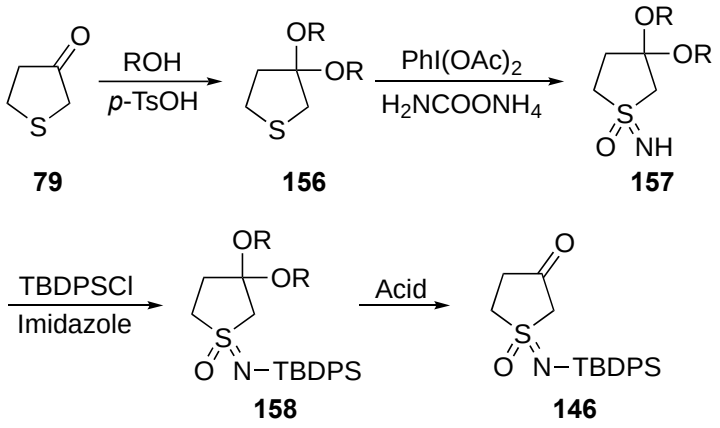
To begin with, using the commercially available β-keto sulfide **79**, a direct sulfoximine synthesis was attempted using Bull and Luisi's method.[44] Reaction of β-keto sulfide **79** with PIDA and ammonium carbamate in MeOH at rt for 3 h returned starting material, β-keto sulfide **79**, as the main product, along with a complex mixture of unidentifiable products (Scheme 3.21). A mechanism proposed by Reboul[72] for sulfoximine formation under these conditions led us to hypothesise why the direct sulfoximine synthesis was unsuccessful. A key intermediate in the mechanism is **155**. Due to the electron-withdrawing properties of the

ketone in the β-position, the α-proton highlighted in **155** may be deprotonated by the methoxy or acetate anion instead of undergoing the productive next step of the mechanism. To support this idea, as shown in Scheme 2.41 (see Section 2.4), the corresponding reaction with tetrahydrothiophene proceeded with no issues and gave sulfoximine **89** in 85% yield.



Scheme 3.21

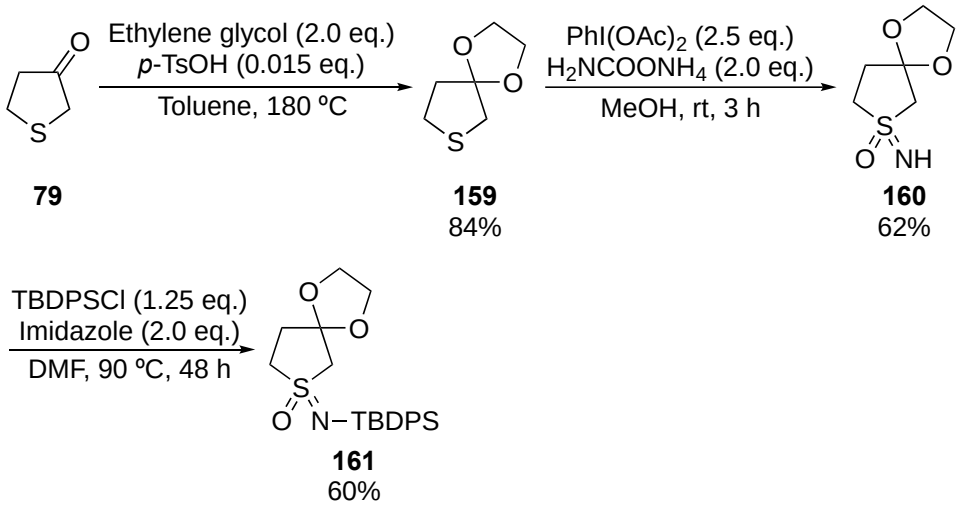
Due to the lack of success with the direct synthesis of β-keto sulfoximine **79** and our concern that the ketone functionality was the source of the problem, we decided to explore whether it would be possible to synthesise β-keto *N*-TBDPS sulfoximine **146** using a ketal protecting group strategy (Scheme 3.22). Protecting the ketone should allow the *N*-TBDPS sulfoximine **146** functionality to be formed *via* ketal sulfoximine **157**. We then planned to deprotect to reform the ketone allowing us to complete the synthesis of sulfoximine enol triflate **12**.



Scheme 3.22

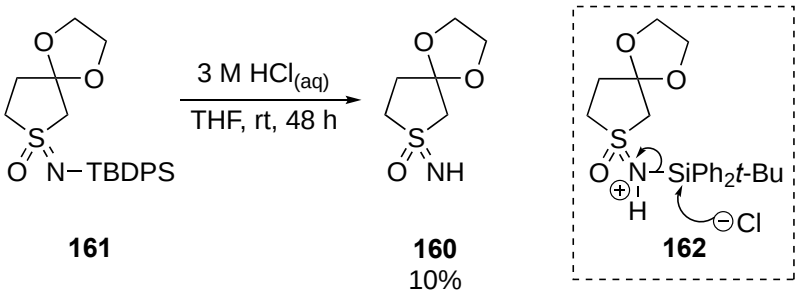
A cyclic ketal was initially explored (Scheme 3.23). Using general conditions from the literature,[73] β-keto sulfide **79** was reacted with ethylene glycol and *p*-toluenesulfonic acid in toluene at 180 °C with a Dean-Stark water separator attached for 16 h. After work-up, crude β-ketal sulfide **159** was obtained in 84% yield without the need for further purification by chromatography. Analysis by ^{1}H NMR spectroscopy showed a 4H multiplet in the ^{1}H NMR spectrum at δ_H 4.01-3.97 which was assigned to the OCH_2 protons of the ketal. Analysis of

the ^{13}C NMR spectrum showed a signal at δ_C 118.1 which was assigned to the ketal OCO carbon. These signals, along with the absence of the C=O peak in the IR spectrum, indicated the successful protection of the ketone. Treatment of crude β-ketal sulfide **159** with PIDA and ammonium carbamate in MeOH at rt for 3 h afforded β-ketal sulfoximine **160** in 62% yield after purification by chromatography. Thus, the ketal protecting group allowed for the successful sulfoximine formation. β-Ketal sulfoximine **160** was then converted into β-ketal *N*-TBDPS sulfoximine **161** using standard TBDPS protection conditions to give β-ketal *N*-TBDPS sulfoximine **161** in 60% yield after purification by chromatography. Analysis of the ^1H NMR spectrum of β-ketal *N*-TBDPS sulfoximine **161** showed a 9H singlet at δ_H 1.05 signifying that the TBDPS protection had been successful. This synthetic route was reliable and a 1.5 g batch of β-ketal *N*-TBDPS sulfoximine **161** was prepared in this way.



Scheme 3.23

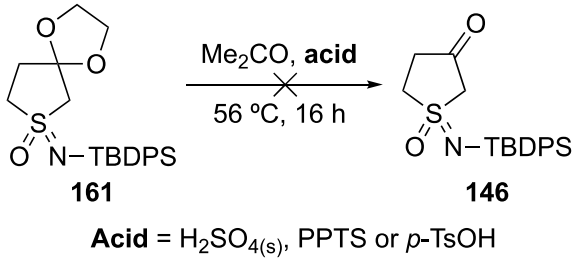
Following this, we set out to explore deprotection conditions for the formation of β-keto *N*-TBDPS sulfoximine **146**. Acid-catalysed deprotection of β-ketal *N*-TBDPS sulfoximine **161** was attempted using 3 M $HCl_{(aq)}$ in THF at rt for 48 h. On analysis of the ^1H NMR spectrum, it was apparent that key TBDPS signals were absent, suggesting the loss of the TBDPS group. Backed up by mass spectrometry evidence, we hypothesised that the TBDPS group was selectively cleaved over the ketal group to give β-ketal NH sulfoximine **160** (10% yield after chromatography) (Scheme 3.24) as the main product with no conversion to β-keto sulfoximine **146**. It was proposed that since sulfoximines are known to be basic, due to the nitrogen lone pair, protonation by the acid is likely to occur at the nitrogen. The chloride anion could then attack the silyl group to remove it, as shown in intermediate **162**.



161 **160** 10% **162**

Scheme 3.24

In light of this, alternative acids that did not contain potentially nucleophilic anions were explored to avoid the cleavage of the TBDPS group. Using a method reported by Greene,[74] acid-catalysed ketal exchange conditions were investigated. Thus, sulfuric acid, pyridinium tosylate (PPTS) and *p*-toluenesulfonic acid (*p*-TsOH) were used in three separate reactions with acetone as the solvent. It was proposed that an excess of acetone would help to drive the deprotection of β-ketal *N*-TBDPS sulfoximine **161** by protecting acetone's ketone functionality. For these reactions, β-ketal *N*-TBDPS sulfoximine **161** was reacted with a source of acid in acetone at 56 °C for 16 h. In each case, starting material was recovered as the main product and the TBDPS group remained intact. Unfortunately, there was no evidence for the formation of β-keto *N*-TBDPS sulfoximine **146** (by ^{1}H NMR spectroscopy) (Scheme 3.25).

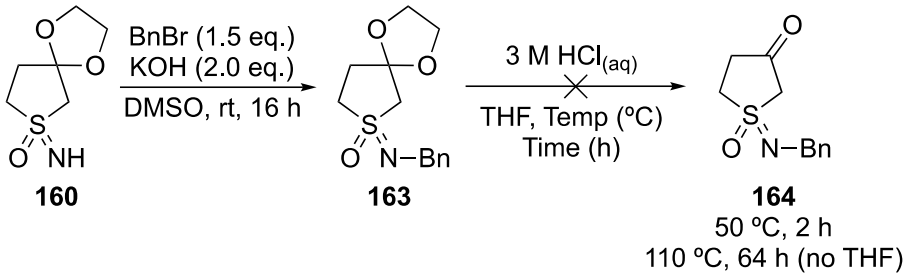


161 **146**

Scheme 3.25

In order to attempt the deprotection of the ketal group using harsher conditions, it was decided to explore some different *N*-substituents. Aware of potential complications during the planned hydrogenation of the Suzuki-Miyaura cross-coupled products in the latter part of our proposed synthetic route, we first explored a *N*-benzyl group. This is because the *N*-benzyl group should be stable to acidic deprotection conditions. Using literature conditions for *N*-benzylation,[75] β-ketal sulfoximine **160** was reacted with benzyl bromide and KOH in DMSO at rt for 16 h to give β-ketal *N*-Bn sulfoximine **163** in only 13% yield after

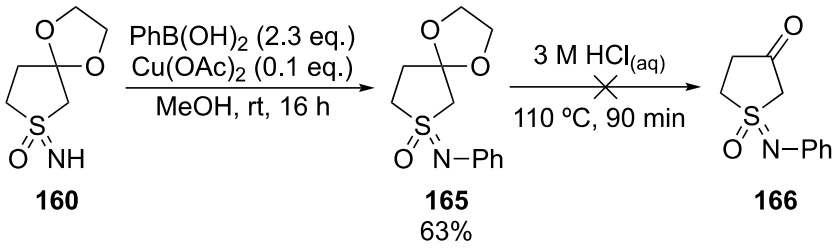
purification by chromatography (Scheme 3.26). Analysis of the ^{1}H NMR spectrum showed two 1H doublets at δ_H 4.32 (d, J = 14.5 Hz) and δ_H 4.29 (d, J = 14.5 Hz) which were assigned to the diastereotopic benzylic NCH_2 protons. Despite the low yield, β-ketal *N*-Bn sulfoximine **163** was subjected to conditions of 3 M $HCl_{(aq)}$ in THF at 50 °C for 2 h to attempt to remove the ketal group. Unfortunately, there was no conversion into β-keto *N*-Bn sulfoximine **164** and the main product recovered was starting β-ketal *N*-Bn sulfoximine **163**. With the aim of creating harsher deprotection conditions, we proposed the following modifications: increasing the temperature, increasing the reaction time and undertaking the reaction neat. Thus, treatment of β-ketal sulfoximine **163** with 3 M $HCl_{(aq)}$ at 110 °C for 64 h led to a complex mixture of products with no evidence for the formation of β-keto *N*-Bn sulfoximine **164** (by ^{1}H NMR spectroscopy) (Scheme 3.26). It was hypothesised that under acidic conditions, the amine group of β-ketal sulfoximine **163** will be protonated and because of this, it may be unfavourable for protonation of the ketal oxygen to occur. This is a mechanistic requirement for ketal hydrolysis and it may also explain why the ketal deprotection of β-ketal *N*-TBDPS sulfoximine **161** terminated at the NH sulfoximine.



Scheme 3.26

In 2005, Moessner and Bolm reported that the copper salt-catalysed *N*-arylation of sulfoximines.[76] In this chemistry, $Cu(OAc)_2$ activated arylboronic acids for the reaction with NH sulfoximines, without the need for a base or heating. Therefore, in order to explore another *N*-substituent, the procedure reported by Moessner and Bolm was followed with the aim of attempting a ketal deprotection reaction subsequently. First, β-ketal sulfoximine **160** was reacted with phenylboronic acid and $Cu(OAc)_2$ in MeOH and was stirred in a 100 mL round-bottomed flask capped with a $CaCl_2$-drying tube at rt for 16 h (as reported in the literature procedure). After work-up and purification, β-ketal *N*-Ph sulfoximine **165** was obtained in 63% yield. Next, β-ketal *N*-Ph sulfoximine **165** was reacted with 3 M $HCl_{(aq)}$ at

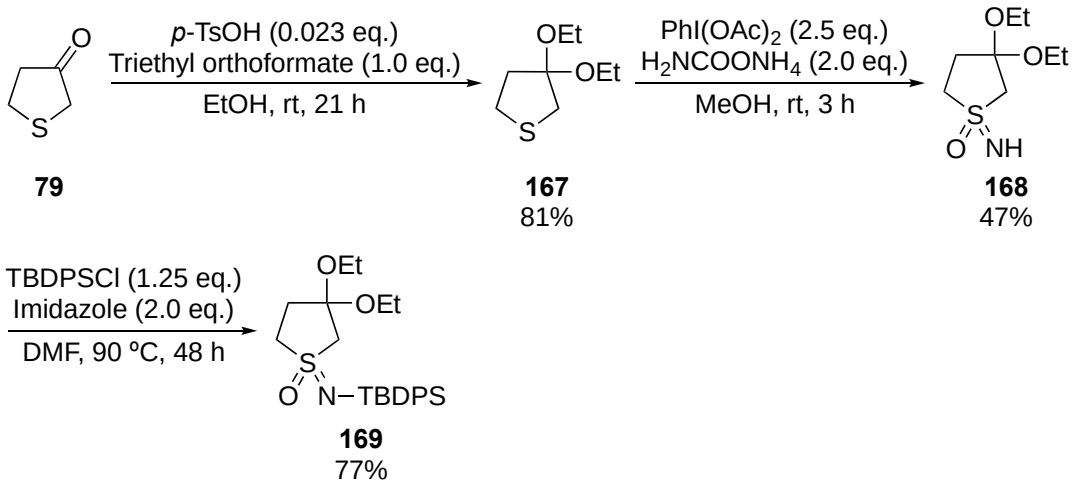
110 °C for 90 min. After work-up, only starting material **165** was recovered and there was no evidence of β-keto *N*-Ph sulfoximine **166** (by ^{1}H NMR spectroscopy) (Scheme 3.27).



160 **165** 63% **166**

Scheme 3.27

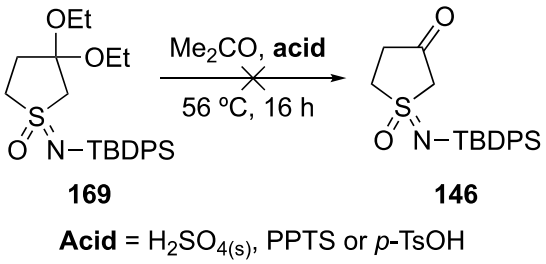
With numerous unsuccessful attempts at deprotecting the cyclic ketal in different β-ketal sulfoximines, we decided to use an alternative protecting group that may be more easily deprotected – a diethoxy ketal. The synthesis of β-diethoxy sulfide **167** has been previously reported[77] and this procedure was followed. Thus, β-keto sulfide **79** was converted into β-diethoxy sulfide **167** using *p*-TsOH and triethyl orthoformate in EtOH at rt for 21 h. After work-up, crude β-diethoxy sulfide **167** was obtained in 81% yield. Analysis of the ^{1}H NMR spectrum showed a 4H multiplet at δ_H 3.59-3.48 which was assigned to the OCH_2 group and a 6H triplet at δ_H 1.21 which was assigned to the Me groups of the ketal. Reaction of crude β-diethoxy sulfide **167** under the standard sulfoximine-forming conditions proceeded uneventfully and gave β-diethoxy sulfoximine **168** in 47% yield after purification by chromatography. Finally, β-diethoxy sulfoximine **168** was reacted with TBDPSCl and imidazole in DMF at 90 °C for 48 h to give β-diethoxy *N*-TBDPS sulfoximine **169** in 77% yield after chromatography (Scheme 3.28).



79 **167** 81% **168** 47% **169** 77%

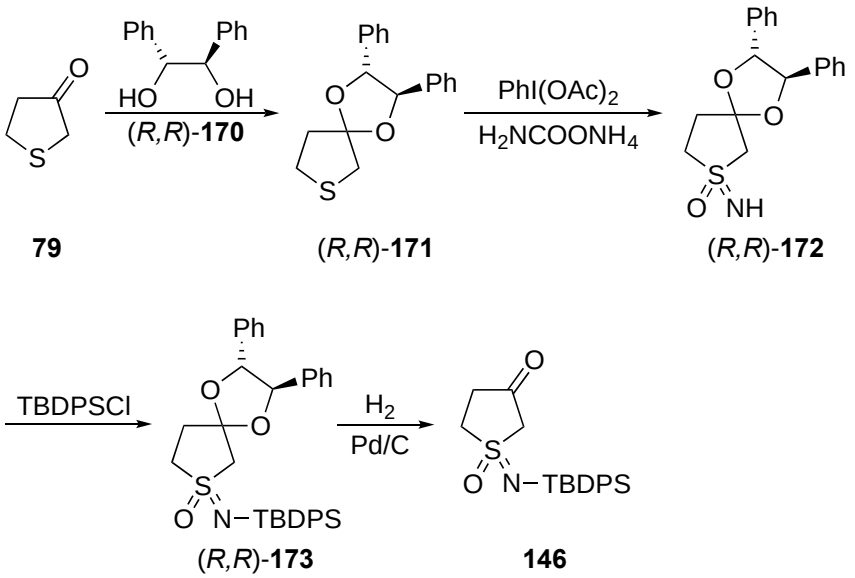
Scheme 3.28

With β-diethoxy *N*-TBDPS sulfoximine **169** in hand, the deprotection to give β-keto *N*-TBDPS sulfoximine **146** was explored. Due to previous problems when using $HCl_{(aq)}$, the acid-catalysed ketal exchange conditions were used. Three reactions were performed using sulfuric acid, PPTS or *p*-TsOH in acetone at 56 °C for 16 h. Disappointingly, each of the reactions returned starting material **169** and there was no evidence for the formation of β-keto *N*-TBDPS sulfoximine **146** (Scheme 3.29).



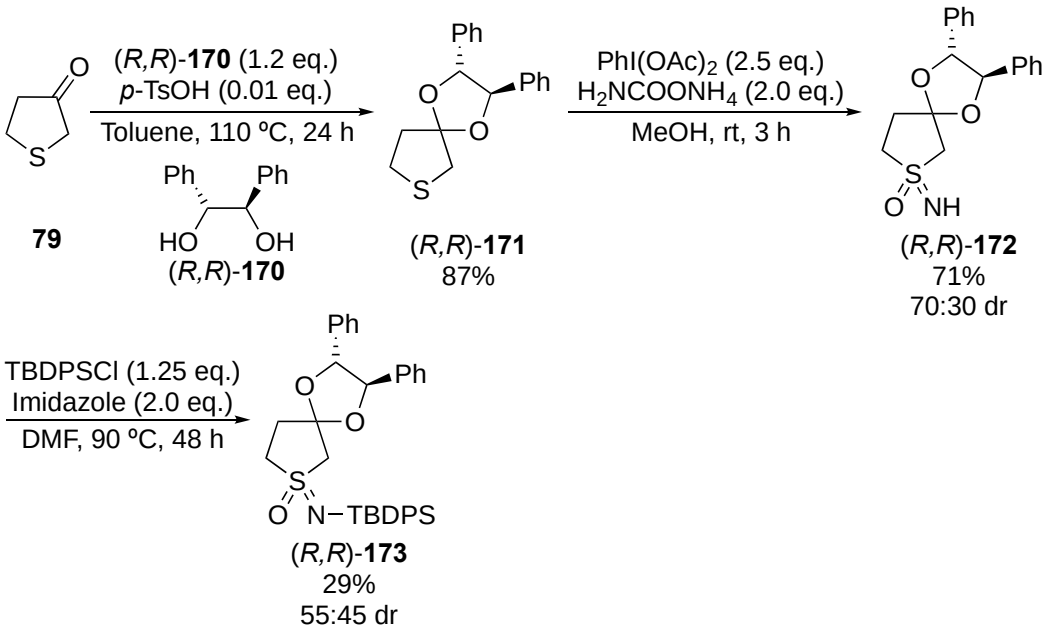
Scheme 3.29

Due to limited success in the acid-catalysed deprotection of the cyclic and diethoxy ketals, we were interested in using a different ketal protecting group that could be cleaved under non-acidic conditions. Our attention was drawn to a ketal derived from diphenylethan-1,2-diol **170** as the deprotection typically uses Pd-catalysed hydrogenolysis conditions.[78–81] Diphenylethan-1,2-diol **170** is commercially available in either its (*R*,*R*) or (*S*,*S*) forms. Our proposed route, using diol (*R*,*R*)-**170**, is shown in Scheme 3.30. Thus, we envisaged that the protection of β-keto sulfide **79** using diol (*R*,*R*)-**170** would give β-ketal sulfide (*R*,*R*)-**171**. Next, using sulfoximine-forming conditions, β-ketal sulfide (*R*,*R*)-**171** would be converted into diastereomeric β-ketal sulfoximines (*R*,*R*)-**172**. There is potential for some diastereoselectivity in the sulfoximine-forming reaction. Then, using the standard TBDPS protection conditions, β-ketal sulfoximines (*R*,*R*)-**172** would be converted into β-ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173**. Finally, using literature conditions,[81] treatment of β-ketal *N*-TBDPS sulfoximine (*R*,*R*)-**173** with H_2 and Pd/C should give β-keto *N*-TBDPS sulfoximine **146**.



Scheme 3.30

A report by Myles and Akhoon described the protection of 2-alkylcinnamaldehydes using diol (*R*,*R*)-**170** in toluene at reflux in the presence of catalytic *p*-TsOH.[79] Using this procedure, β-keto sulfide **79** was reacted with diol (*R*,*R*)-**170** and *p*-TsOH in toluene at 110 °C with a Dean-Stark water separator attached for 24 h. After purification by chromatography, β-ketal sulfide (*R*,*R*)-**171** was obtained in 87% yield. Analysis of the ^{1}H NMR spectrum showed two 1H doublets at δ_H 4.80 (d, J = 8.5 Hz) and δ_H 4.77 (d, J = 8.5 Hz) that were assigned to the OCH protons of the ketal group. Treatment of β-ketal sulfide (*R*,*R*)-**171** with PIDA and ammonium carbamate in MeOH at rt for 3 h gave a 70:30 mixture of diastereomeric β-ketal sulfoximines (*R*,*R*)-**172** (by ^{1}H NMR spectroscopy) in 71% yield after chromatography. In the ^{1}H NMR spectrum, a 1H doublet at δ_H 4.85 (d, J = 8.5 Hz) was assigned to one of the OCH protons in one of the two diastereomeric sulfoximines. The overlapping signals at δ_H 4.78 (d, J = 8.5 Hz) and δ_H 4.77 (d, J = 8.5 Hz) integrated for 0.7H and 0.3H respectively. These signals are shown in green in Figure 3.1. The 70:30 mixture of diastereomeric β-ketal sulfoximines (*R*,*R*)-**172** was subjected to TBDPS protection conditions to give a 55:45 mixture of diastereomeric β-ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173** (by ^{1}H NMR spectroscopy) in 29% yield after purification by chromatography. In this case, the two OCH doublets were not overlapping in the ^{1}H NMR spectrum for β-ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173** (blue, Figure 3.1).



Scheme 3.31

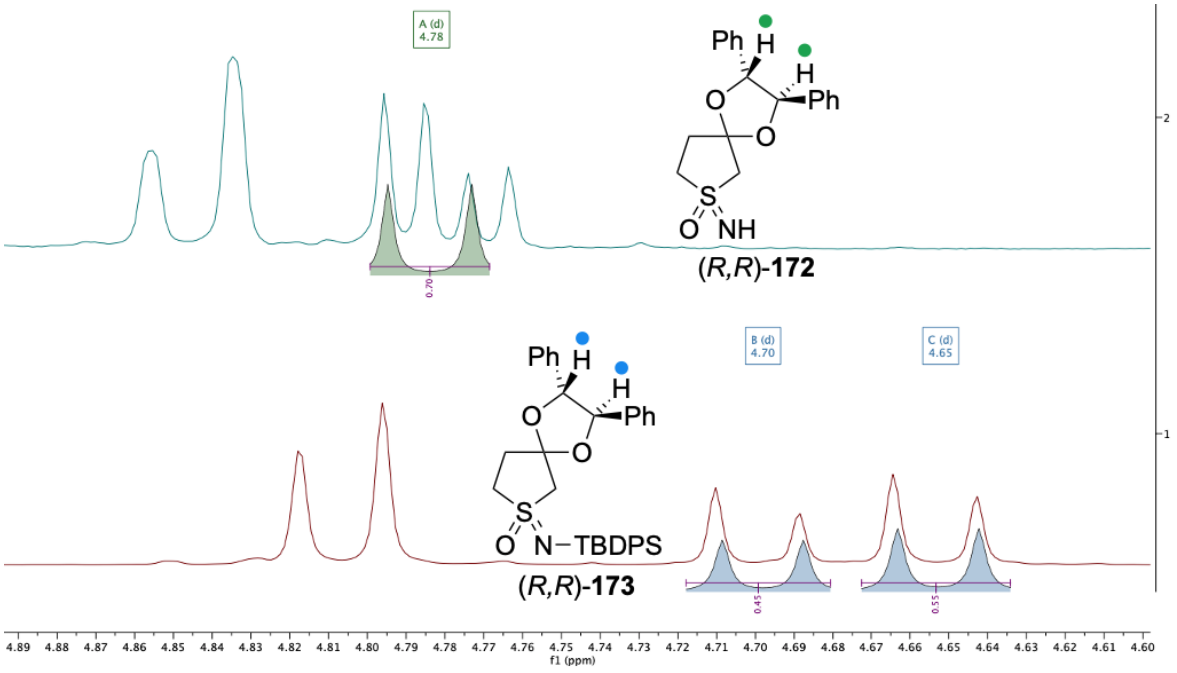
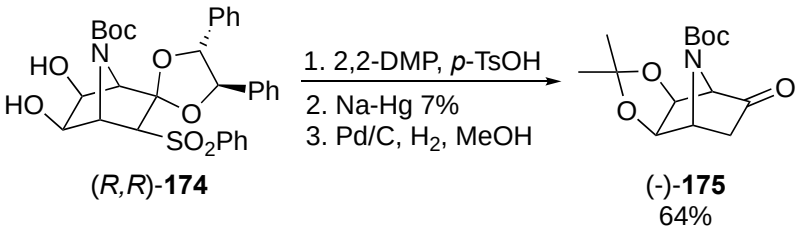


Figure 3.1 The OCH signals in the ^{1}H NMR spectrum for β-ketal sulfoximines (*R*,*R*)-**172** (green) and β-ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173** (blue)

With β-ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173** in hand, the diphenyl ketal deprotection conditions were explored. In 2011, Pandey and Rajender[81] reported hydrogenolysis conditions for the removal of a diphenyl ketal. In their three-step synthesis, 7-azabicylic system (*R*,*R*)-**174** was firstly treated with 2,2-dimethoxypropane and *p*-TsOH to protect the

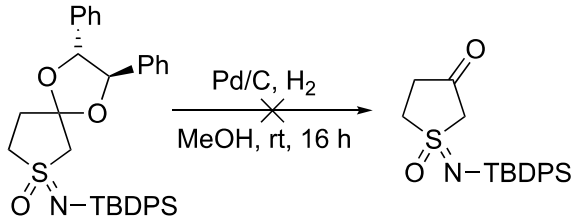
diol. Subsequent reductive removal of the sulfone group was achieved on addition of Na-Hg. Finally, cleavage of the benzylic C–O bonds by hydrogenolysis, using Pd/C and H_2 in MeOH, formed ketone (-)-**175** in 64% yield over the three steps (Scheme 3.32).



(*R,R*)-**174** (-)-**175** 64%

Scheme 3.32

Using the method reported by Pandey and Rajender, the 55:45 mixture of diastereomeric β-ketal *N*-TBDPS sulfoximines (*R,R*)-**173** was treated with Pd/C and H_2 in MeOH at rt for 16 h. Unfortunately, this gave a complex mixture of products and there was no evidence for the formation of β-keto *N*-TBDPS sulfoximine **146** (by ^{1}H NMR spectroscopy) (Scheme 3.33).



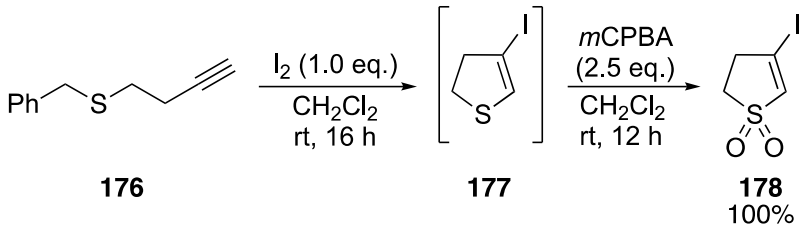
(*R,R*)-**173** **146**

Scheme 3.33

To summarise, a reliable synthetic route to β-ketal *N*-TBDPS sulfoximine **161** was developed and it was easy to bring through material on a multi-gram scale. Discovery of the selective cleavage of the TBDPS group in the presence of chloride led us to explore acid-catalysed ketal exchange conditions to no avail. Alternative sulfoximine *N*-substituents were investigated for the HCl-catalysed deprotection but the cyclic ketal proved to be too stable. β-Diethoxy *N*-TBDPS sulfoximine **169** was synthesised with the aim of this ketal being easier to deprotect. However, exploration of the acid-catalysed ketal exchange conditions was unsuccessful. A modified route to sulfoximine enol triflate **12** was explored where deprotection of the ketal involved hydrogenolysis in lieu of acid-catalysed conditions. Disappointingly, this hydrogenolysis route also failed in the ketal deprotection step.

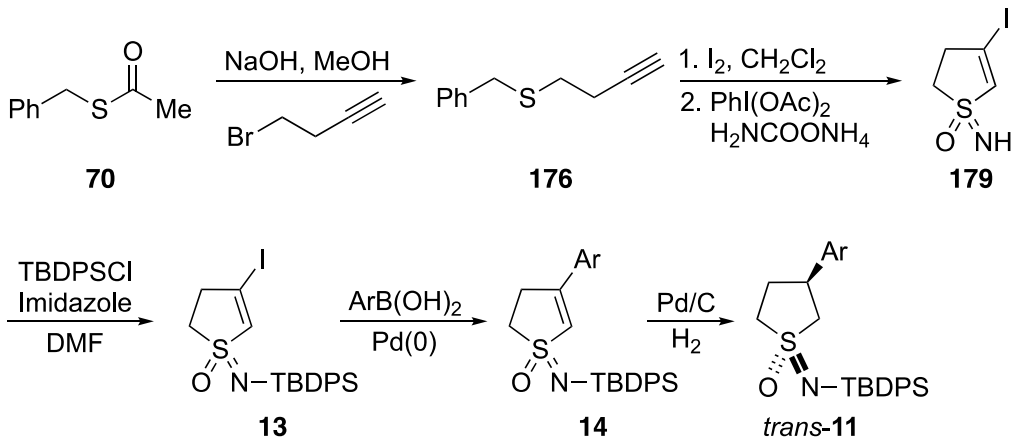
3.3 Attempted synthesis of β-aryl sulfoximines *via* a cyclisation route

Our efforts at synthesising β-keto *N*-TBDPS sulfoximine **146** *via* ketal protecting groups proved unsuccessful. An alternative approach that would follow a similar synthetic route to that described in Section 2.2 was devised. Ren and co-workers[43] reported the synthesis of iodo vinyl sulfone **178**, as outlined in Scheme 3.35, which proceeded *via* an iodocyclisation reaction, similar to that of alkene sulfide **66** (see Scheme 2.29). As part of their studies, alkyne sulfide **176** was reacted with I_2 in CH_2Cl_2 at rt for 16 h to give intermediate iodo vinyl sulfide **177**. Then, 2.5 equivalents of *m*CPBA in CH_2Cl_2 was added to the same flask and stirred at rt for 12 h to afford iodo vinyl sulfone **178** in 100% yield (Scheme 3.35).



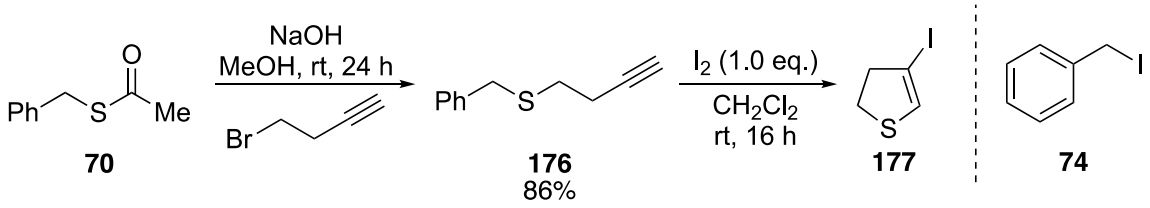
Scheme 3.35

It was envisaged that replacing the sulfone oxidation step with a sulfoximine-forming step would allow access to iodo vinyl sulfoximine **179**. Incorporation of the iodo functionality in the β-position would enable the Suzuki-Miyaura cross-coupling reactions to be attempted. The initial proposed plan is detailed in Scheme 3.36. Benzyl thioacetate **70** would be reacted with NaOH and 4-bromo-1-butyne to give alkyne sulfide **176**. Then, alkyne sulfide **176** would be reacted with I_2 in CH_2Cl_2 followed by reaction with PIDA and ammonium carbamate to give iodo vinyl sulfoximine **179**. Subsequent *N*-TBDPS protection of iodo vinyl sulfoximine **179** would give iodo vinyl *N*-TBDPS sulfoximine **13**. Suzuki-Miyaura cross-coupling reactions using an arylboronic acids and Pd(0) would convert iodo vinyl *N*-TBDPS sulfoximine **13** into β-aryl vinyl *N*-TBDPS sulfoximines **14**. Diastereoselective hydrogenation using H_2 and Pd/C should result in β-aryl *N*-TBDPS sulfoximines *trans*-**11** as it is proposed that hydrogenation of the alkene in **14** should occur on the opposite face to the TBDPS group.



Scheme 3.36

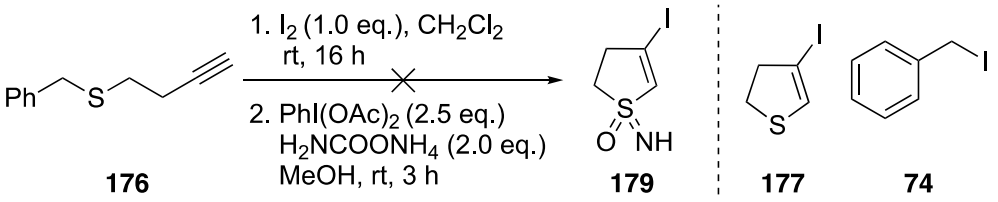
To start, using the procedure reported by Ren *et al.*,[43] the conversion of benzyl thioacetate **70** into alkyne sulfide **176** was achieved by reaction in the presence of NaOH and 4-bromo-1-butyne in MeOH at rt for 24 h. This gave alkyne sulfide **176** in 86% yield after purification by chromatography. The NMR spectroscopic data for this compound were consistent with literature values[43] and we were able to replicate the high yield reported. Mechanistically, alkyne sulfide **176** was formed by nucleophilic substitution using *in situ* generated benzyl thiol (formed from the reaction of benzyl thioacetate **70** and NaOH in MeOH). Alkyne sulfide **176** was then reacted with I_2 in CH_2Cl_2 at rt for 16 h. Evaporation of the crude product gave an inseparable 50:50 mixture of iodo vinyl sulfide **177** and benzyl iodide **74** in high yield (by ^{1}H NMR spectroscopy) (Scheme 3.37). Analysis of the ^{1}H NMR spectrum of iodo vinyl sulfide **177** showed a 1H triplet at δ_H 6.34 (t, J = 2.0 Hz), indicative of the vinylic proton. A triplet was observed due to ^4J coupling of the vinylic proton to the CH_2 protons.



Scheme 3.37

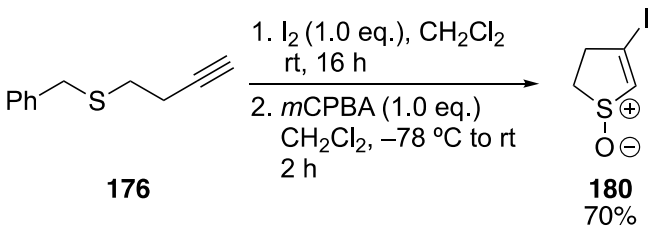
Since iodo vinyl sulfide **177** was formed in high yield, the synthesis of iodo vinyl sulfoximine **179** was attempted. Due to the co-elution of benzyl iodide **74** with iodo vinyl sulfide **177**, the formation of iodo vinyl sulfoximine **179** would be carried out in a one-pot synthesis. Thus, alkyne sulfide **176** was reacted with I_2 in CH_2Cl_2 at rt for 16 h and then

PIDA and ammonium carbamate in MeOH were added to the same flask and stirred at rt for 3 h. Purification by chromatography gave an inseparable 60:40 mixture of benzyl iodide **74** (56% recovered) and iodo vinyl sulfide **177** (28% recovered) with no evidence for the formation of iodo vinyl sulfoximine **179** (by ^{1}H NMR spectroscopy) (Scheme 3.38).



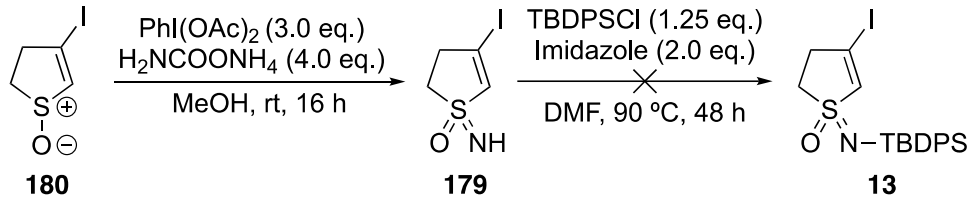
Scheme 3.38

Supported by the previous work in Section 2.2, where benzyl bromide **71** was inseparable from bromo sulfide **65** and the subsequent sulfoximine-forming reaction was unsuccessful, it is hypothesised that benzyl iodide **74** behaves similarly in the sulfoximine-forming step shown in Scheme 3.38. Therefore, we proposed to initially form iodo vinyl sulfoxide **180** by the partial oxidation of iodo vinyl sulfide **177** using 1 equivalent of *m*CPBA. It was hoped that a sulfoximine-forming reaction reported by Bull and Luisi[6] could be used to convert iodo vinyl sulfoxide **180** into iodo vinyl sulfoximine **179**. To start, alkyne sulfide **176** was reacted with I_2 in CH_2Cl_2 at rt for 16 h. Then, using a method for the oxidation of a vinyl sulfide to a vinyl sulfoxide reported by Vidal-Ferran and co-workers,[82] *m*CPBA was added to the same flask in CH_2Cl_2 at –78 °C and the reaction mixture was stirred at –78 °C for 1 h and then stirred at rt for 1 h. After purification by chromatography, iodo vinyl sulfoxide **180** was isolated in 70% yield. Analysis of the ^{1}H NMR spectrum of iodo vinyl sulfoxide **180** showed a 1H signal at δ_H 7.08 (dd, J = 2.0, 2.0 Hz) indicating the presence of the vinylic proton. This 1H signal at δ_H 7.08 is further downfield in the ^{1}H NMR spectrum in contrast to the 1H triplet of iodo vinyl sulfide **177** (δ_H 6.34).



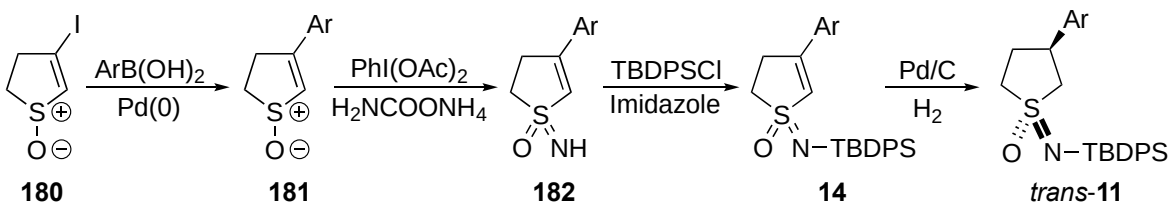
Scheme 3.39

Having successfully isolated iodo vinyl sulfoxide **180**, a procedure used for the conversion of sulfoxides to sulfoximines reported by Bull and Luisi[6] was adapted for the formation of iodo vinyl sulfoximine **179**. Thus, iodo vinyl sulfoxide **180** was treated with PIDA and ammonium carbamate in MeOH at rt for 16 h. Purification by chromatography gave an inseparable 80:20 mixture of iodo vinyl sulfoximine **179** (52% yield) and iodo vinyl sulfoxide **180** (13% recovered) (by ^{1}H NMR spectroscopy). Next, we planned to TBDPS protect iodo vinyl NH sulfoximine **179** as it was predicted that the TBDPS would decrease the polarity and consequently, it should be possible to separate iodo vinyl sulfoxide **180** from iodo vinyl *N*-TBDPS sulfoximine **13** by chromatography. Thus, the 80:20 mixture of iodo vinyl sulfoximine **179** and iodo vinyl sulfoxide **180** was treated with TBDPSCl and imidazole in DMF at 90 °C for 60 h (Scheme 3.40). After work-up, the crude product contained a complex mixture of products and there was no evidence for the formation of iodo vinyl *N*-TBDPS sulfoximine **13** (by ^{1}H NMR spectroscopy).



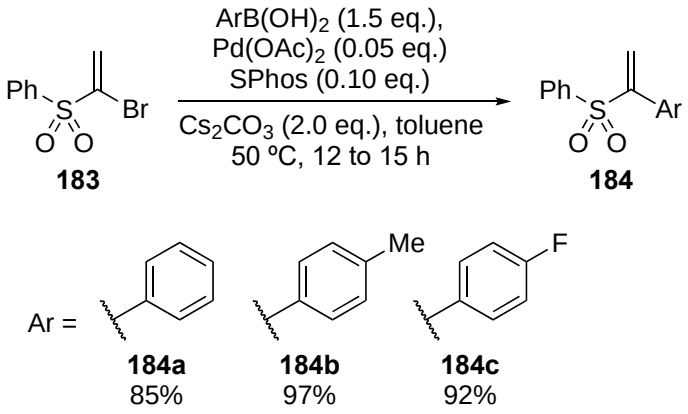
Scheme 3.40

Due to limited success in the formation of iodo vinyl *N*-TBDPS sulfoximine **13**, an alternative route to β-aryl *N*-TBDPS sulfoximine *trans*-**11** was devised. It was proposed that the Suzuki-Miyaura cross-coupling reaction of iodo vinyl sulfoxide **180** with an arylboronic acid in the presence of Pd(0) would form β-aryl vinyl sulfoxide **181**. Then, it was hoped that the sulfoximine-forming reaction of β-aryl vinyl sulfoxide **181** would result in the formation of β-aryl vinyl sulfoximine **182**. Subsequent *N*-TBDPS protection would result in β-aryl vinyl *N*-TBDPS sulfoximine **14**. Diastereoselective hydrogenation of β-aryl vinyl *N*-TBDPS sulfoximine **14** would form β-aryl *N*-TBDPS sulfoximines *trans*-**11** (Scheme 3.41).



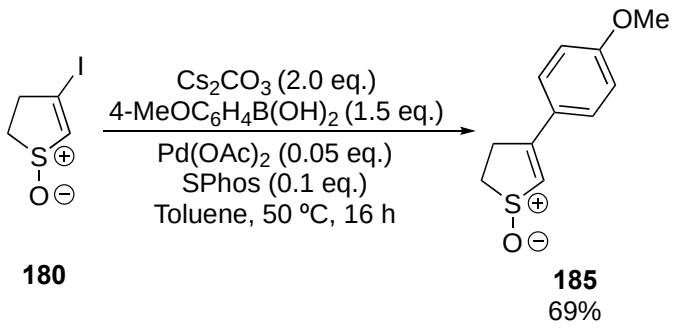
Scheme 3.41

In 2016, Fang *et al.* developed a method for the α-arylation of alkenylsulfones under Suzuki-Miyaura conditions.[83] Suzuki-Miyaura cross-coupling of α-bromo alkenylsulfones and boronic acids occurred in the presence of $Pd(OAc)_2$ and SPhos under mild conditions. In one example, α-bromo phenylsulfone **183** was reacted with various arylboronic acids and Cs_2CO_3 in the presence of $Pd(OAc)_2$ and SPhos in toluene at 50 °C for 12-15 h to give α-aryl vinyl sulfones **184a-c** in excellent yields (Scheme 3.42).



Scheme 3.42

Using the procedure reported by Fang *et al.*,[83] iodo vinyl sulfoxide **180** was treated with 4-methoxyphenylboronic acid and Cs_2CO_3 in the presence of $Pd(OAc)_2$ and SPhos in toluene at 50 °C for 16 h. This gave β-aryl vinyl sulfoxide **185** in 69% yield after purification by chromatography (Scheme 3.43). Analysis of the ^{1}H NMR spectrum of β-aryl vinyl sulfoxide **185** showed a 1H signal at δ_H 6.86 (dd, J = 2.0, 2.0 Hz) which was assigned to the vinylic proton. As shown in Figure 3.2, two 1H signals at δ_H 3.69 (dddd, J = 17.0, 8.0, 6.0, 2.0 Hz) and δ_H 3.18 (dddd, J = 17.0, 8.0, 3.0, 2.0 Hz) were assigned to the diastereotopic allylic CH_2 protons which each exhibited ^4J allylic coupling to the vinylic proton. The two 1H signals at δ_H 3.47 (ddd, J = 14.0, 8.0, 6.0 Hz) and δ_H 3.09 (ddd, J = 14.0, 8.0, 3.0 Hz) were assigned to the diastereotopic SCH_2 protons. The key signals in the ^{13}C NMR spectrum at δ_C 161.4 and δ_C 114.4 were assigned to the =*C*Ar and C=*C*H carbons respectively.



Scheme 3.43

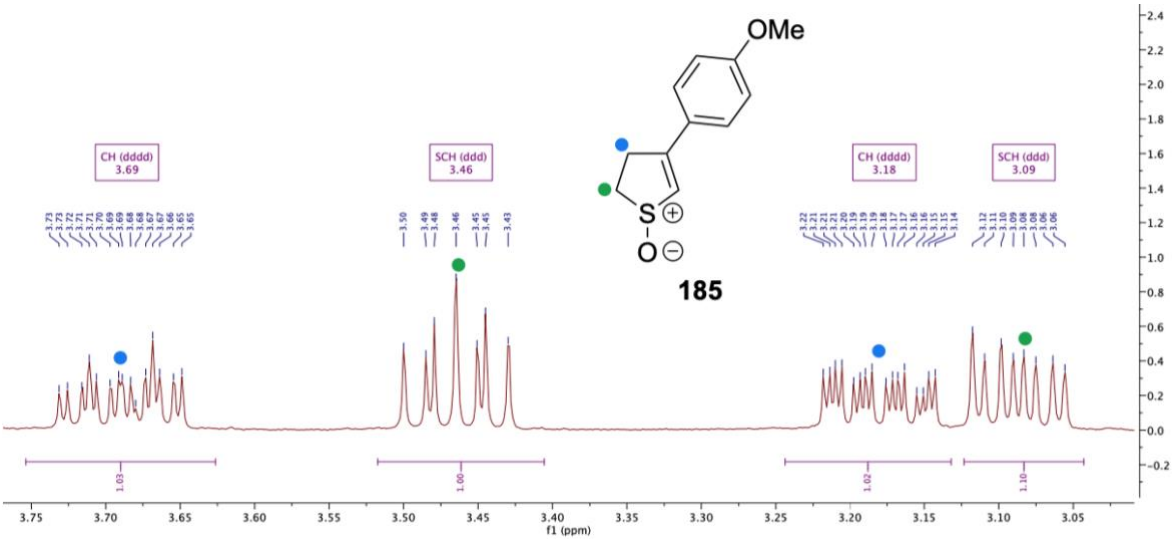
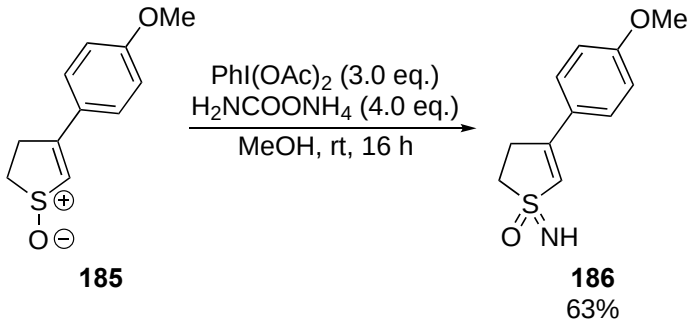


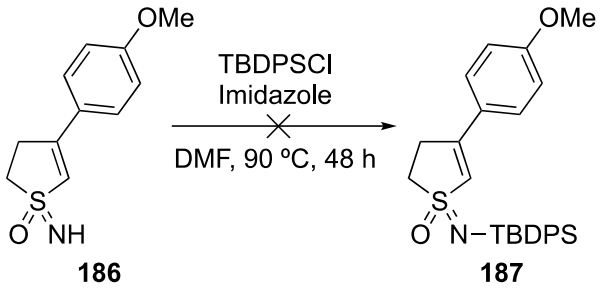
Figure 3.2 The CH signals in the ^{1}H NMR spectrum of β-aryl vinyl sulfoxide **181**

Next, β-aryl vinyl sulfoxide **185** was successfully converted into β-aryl vinyl sulfoximine **186** in 63% yield, after chromatography, following reaction with PIDA and ammonium carbamate in MeOH at rt for 16 h (Scheme 3.44). The ^{13}C NMR spectrum of β-aryl vinyl sulfoximine **186** showed a signal at δ_C 161.7 which was assigned to the =*C*Ar carbon and a signal at δ_C 125.3 which was assigned to the C=*C*H carbon.



Scheme 3.44

Due to time limitations, the *N*-TBDPS protection of β-aryl vinyl sulfoximine **186** was attempted by a member of the O'Brien group. However, using the standard TBDPS protection conditions, this reaction was unsuccessful as there was no evidence for the formation of β-aryl vinyl *N*-TBDPS sulfoximine **187** (by ^{1}H NMR spectroscopy) (Scheme 3.45).



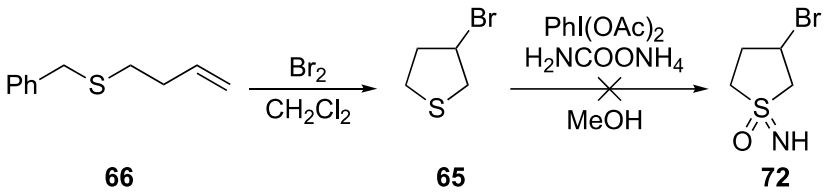
186 **187**

Scheme 3.45

In summary, different approaches for the synthesis of iodo vinyl *N*-TBDPS sulfoximine **13** were explored without success. Iodo cyclisation of alkyne sulfide **176** into iodo vinyl sulfide **177** worked but the subsequent sulfoximine formation failed due to likely interference from the inseparable benzyl iodide **74** that was present as a by-product of the cyclisation step. An alternative route to iodo vinyl *N*-TBDPS sulfoximine **13** *via* iodo vinyl sulfoxide **180** was explored and iodo vinyl sulfoxide **180** was synthesised in 70% yield. Although its conversion into iodo vinyl sulfoximine **179** worked, the subsequent *N*-TBDPS protection was unsuccessful. Thus, iodo vinyl sulfoxide **180** was arylated first using a Suzuki-Miyaura cross-coupling step and then subjected to the sulfoximine-forming reaction. This proved to be successful and β-aryl vinyl sulfoximine **186** was synthesised in 43% yield over two steps. However, the *N*-TBDPS formation was unsuccessful. Indeed, we have been unable to *N*-TBDPS protect any vinyl sulfoximines (see Schemes 2.39, 3.40 and 3.45) which highlights a limitation in our proposed synthetic approach. Due to time constraints, we were unable to explore alternative *N*-substituents which may have allowed us to access *N*-protected vinyl sulfoximines. Nevertheless, using iodo vinyl sulfoxide **180**, it was pleasing to demonstrate that Suzuki-Miyaura arylation is a viable approach for β-arylation.

4. Conclusions and Future Work

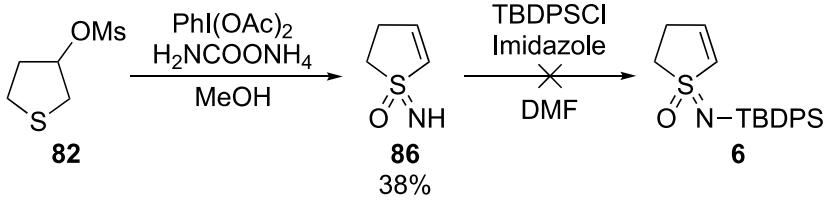
To conclude, we have achieved the β-functionalisation of a cyclic *N*-TBDPS sulfoximine *via* Rh-catalysed conjugate addition methodology. The synthetic route towards the formation of *N*-TBDPS vinyl sulfoximine **6** was explored throughout Chapter 2 for use as the starting material in Rh-catalysed β-arylation reactions. In Section 2.2, a halocyclisation route was investigated but, despite the formation of bromo sulfide **65**, it was not possible to prepare bromo sulfoximine **72** (Scheme 4.1). It was hypothesised that the by-product of the bromocyclisation, benzyl bromide, interferes in the sulfoximine-forming step by reacting with any nucleophilic species in the mixture.



66 **65** **72**

Scheme 4.1

In Section 2.3, our efforts to synthesise *N*-TBDPS vinyl sulfoximine **6** *via* disilyl sulfoximines were unsuccessful and so attention turned to the elimination of a leaving group in the β-position. Synthesis of mesylate sulfide **82** allowed us to perform standard sulfoximine-forming conditions which gave vinyl sulfoximine **86** in 38% yield. This meant that *N*-TBDPS vinyl sulfoximine **6** was only one step away. Unfortunately, however, TBDPS protection of vinyl sulfoximine **86** to give *N*-TBDPS vinyl sulfoximine **6** was unsuccessful (Scheme 4.2).

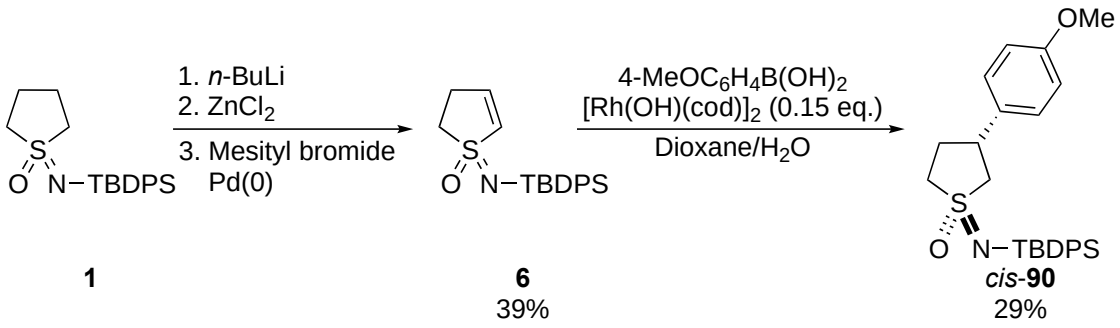


82 **86** 38% **6**

Scheme 4.2

Using a procedure discovered in the group,[19] *N*-TBDPS vinyl sulfoximine **6** was finally synthesised in 39% yield *via* β-hydride elimination of the intermediate organopalladium species in a Pd-catalysed Negishi cross-coupling reaction of *N*-TBDPS sulfoximine **1** with mesityl bromide. Consequently, Rh-catalysed conjugate addition was explored using 4-

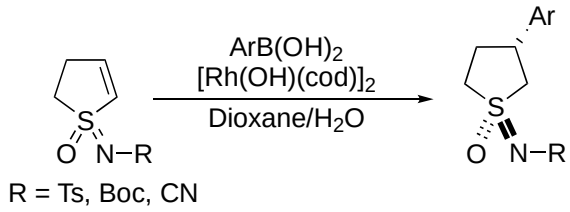
methoxyphenylboronic acid and $[Rh(OH)(cod)]_2$ (15 mol%) in dioxane/H_2O. This delivered β-aryl *N*-TBDPS sulfoximine *cis*-**90** as a single diastereomer in 29% yield (Scheme 4.3) (Section 2.4). This is the first example of such a reaction with sulfoximines and, pleasingly, it proceeded with high diastereoselectivity. The relative stereochemistry of *cis*-**90** was assigned based on recent work in the O'Brien group where *cis*-**90** was converted into the *N*-Ts analogue for analysis by X-ray crystallography. We propose that the *cis*-stereochemistry can be explained due to the steric bulk of the TBDPS group which directs arylation on the same face as the oxygen of the sulfoximine.



1 → **6** 39% → *cis*-**90** 29%

Scheme 4.3

As limited time was spent optimising the reaction conditions for the Rh-catalysed β-arylation of *N*-TBDPS vinyl sulfoximine **6** with 4-methoxyphenylboronic acid, future work would involve further optimisation to improve the yield of this reaction. Different catalysts and ligands could be explored, including the use of chiral catalysts in which a kinetic resolution reaction could be investigated. As attempts to *N*-TBDPS protect various vinyl sulfoximines proved to be a limitation in our synthetic route, other protecting groups should be explored. It is possible that more electron-withdrawing *N*-substituents on the sulfoximine could improve the efficiency of the reaction and therefore *N*-Ts, *N*-Boc, *N*-CN substituents should be explored both in terms of reactivity and also diastereoselectivity (Scheme 4.4). Following this, expansion of the scope of the Rh-catalysed conjugate addition reaction to include a wide range of medicinally-relevant arylboronic acids bearing electron-withdrawing and electron-donating groups should be investigated.



R = Ts, Boc, CN

Scheme 4.4

As described in Chapter 3, it proved to be challenging to develop methodology for the synthesis of β-aryl *N*-TBDPS sulfoximines *trans*-**11** and various routes to the desired sulfoximine enol triflate and vinyl iodide were explored. As described in Section 3.2, a ketone protection route was explored. Five ketal sulfoximines were synthesised with the final aim to deprotect the ketal: cyclic ketal *N*-TBDPS sulfoximine **161**, cyclic ketal *N*-Bn sulfoximine **163,** cyclic ketal *N*-Ph sulfoximine **165**, diethoxy ketal *N*-TBDPS sulfoximine **169** and ketal *N*-TBDPS sulfoximines (*R,R*)-**173** (Figure 4.1). The synthetic routes towards ketal *N*-TBDPS sulfoximines **161** and **169** were scalable and reliable. Acid deprotection conditions were explored for ketals **161**, **163**, **165** and **169** but, disappointingly, we were unable to deprotect the ketal groups. It was proposed that, under acidic conditions, the amine group of the sulfoximines will be protonated making it unfavourable for protonation of the ketal oxygen to occur. Similarly, ketal *N*-TBDPS sulfoximines (*R,R*)-**173** could not be deprotected under hydrogenolysis conditions. However, there was only time and material for one set of hydrogenolysis conditions to be studied and future work could investigate other catalysts and reaction conditions.[78,79]

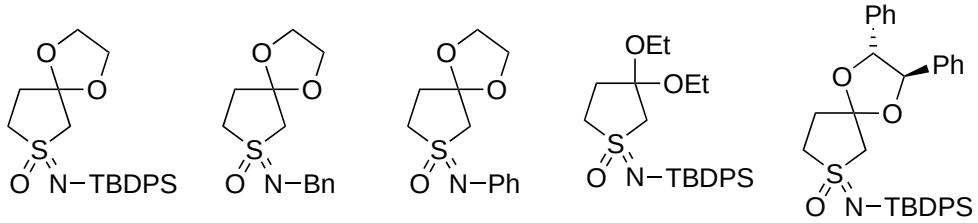
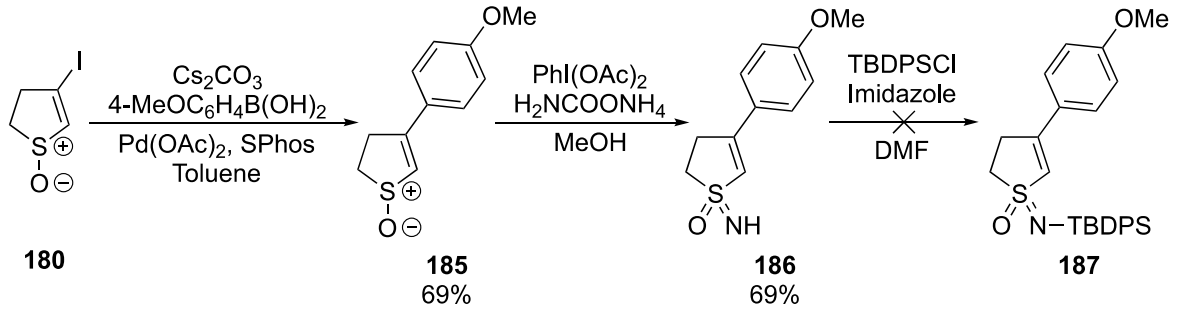


Figure 4.1 Ketal sulfoximines with different *N*-substituents

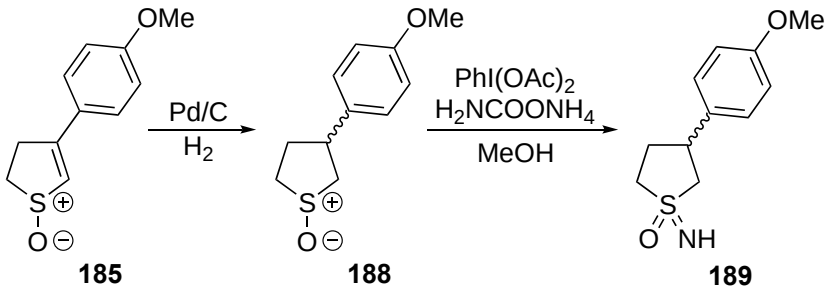
An alternative route towards an iodo vinyl sulfoximine *via* a halocyclisation was explored (Section 3.3). Similar issues involving co-elution of benzyl iodide that were experienced in Section 2.2 were also observed in the attempted formation of iodo vinyl sulfoximine **179**. To get around this issue, iodo vinyl sulfoxide **180** was synthesised in 70% yield and subsequent sulfoximine-formation gave iodo vinyl sulfoximine **179**. As we were unable to TBDPS protect iodo vinyl sulfoximine **179**, a different strategy was explored in which iodo vinyl sulfoxide **180** would undergo Suzuki-Miyaura cross-coupling prior to the sulfoximine-forming reaction. Thus, β-aryl vinyl sulfoxide **185** was synthesised in 69% yield and converted into β-aryl vinyl sulfoximine **186** in 63% yield. Unfortunately, synthesis of iodo vinyl *N*-TBDPS sulfoximine **187** was unsuccessful (Scheme 4.6). The inability to *N*-TBDPS protect **186** and two other vinyl sulfoximines (see Schemes 2.39 and 3.40) was believed to

be due to the electrophilicity of vinyl sulfoximines in which conjugate addition of imidazole or *in situ*-generated chloride could have occurred which would terminate the reaction. It would be interesting to investigate whether other *N*-substituents such as *N*-Boc or *N*-Ts could be introduced and the subsequent hydrogenation could then be investigated.



Scheme 4.5

To avoid *N*-TBDPS protection of a vinyl sulfoximine, future work could involve the hydrogenation of β-aryl vinyl sulfoxide **185** to form β-aryl sulfoxides **188**. Treatment of **188** under sulfoximine-formation conditions would form β-aryl sulfoximines **189** which could be of interest for use in medicinal chemistry (Scheme 4.6). In this sequence, it would be interesting to explore the diastereoselectivity of the hydrogenation of sulfoxide **185** under different conditions. In this context, diastereoselective oxygen-directed Rh-catalysed hydrogenation of vinyl sulfoxides has been reported.[82–84]



Scheme 4.6

5. Experimental

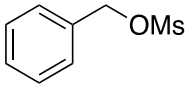
5.1 General methods

All-non aqueous reactions were carried out under oxygen−free Ar using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[85] Other reagents from commercial suppliers were used without purification. Brine refers to a saturated $NaCl_{(aq)}$ 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 and 2D NMR experiments (HMQC and COSY). 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.

5.2 Experimental procedures and characterisation data

Benzyl methanesulfonate 69

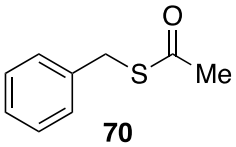


69

Methanesulfonyl chloride (3.48 mL, 45.0 mmol, 1.5 eq.) was added dropwise to a stirred solution of benzyl alcohol (3.12 mL, 30.0 mmol, 1.0 eq.) and Et_3N (8.36 mL, 60.0 mmol, 2.0 eq.) in CH_2Cl_2 (120 mL) at –50 °C under Ar. The resulting solution stirred at –50 °C for 30 min. Then, the solution was washed with 1% $HCl_{(aq)}$ (30 mL) and sat. $NaHCO_{3(aq)}$ (30 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give benzyl mesylate **69** (5.52 g, 99%) as a yellow oil, R_F (8:2 hexane-EtOAc) 0.62; IR (ATR) 1498, 1347, 1168, 912, 696, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.39 (m, 5H, Ph), 5.24 (s, 2H, OCH_2), 2.90 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 133.5 (*ipso*-Ph), 129.5 (Ph), 128.99 (Ph), 128.95 (Ph), 71.7 (OCH_2), 38.4 (Me); MS (ESI) *m/z* 209 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_8H_{10}O_3S$ $(M + Na)^+$ 209.0243, found 209.0243 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[43,86]

Lab book reference: **HS-2-2**

1-(Benzylsulfanyl)ethan-1-one 70



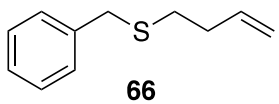
70

Thioacetic acid (1.97 mL, 27.6 mmol, 1.5 eq.) was added dropwise to a stirred solution of benzyl mesylate **69** (3.422 g, 18.4 mmol, 1.0 eq.) in 0.4 M $K_2CO_{3(aq)}$ (137.5 mL, 55.0 mmol, 3.0 eq.) at rt. The resulting solution was stirred and heated at 40 °C for 2 h. After being allowed to cool to rt, Et_2O (30 mL) was added. The two layers were separated and the organic layer was washed with water (3 × 30 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give benzyl thioacetate **70** (1.74 g, 57%) as a yellow oil, R_F (7:3 hexane-EtOAc) 0.43; IR (ATR) 1689 (C=O), 1496, 1454, 1132, 958, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H, Ph), 7.25-7.22 (m, 1H, Ph), 4.12 (s, 2H, SCH_2), 2.35 (s, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.3 (C=O), 137.7 (*ipso*-Ph), 128.9 (Ph), 128.7 (Ph), 127.4 (Ph), 33.5 (SCH_2), 30.4 (Me); MS (APCI) *m/z* 167 $(M + H)^+$;

HRMS (APCI) *m/z* calcd for $C_9H_{10}OS$ $(M + H)^+$ 167.0525, found 167.0522 (+2.1 ppm error). Spectroscopic data consistent with those reported in the literature.[87]

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

[(But-3-en-1-ylsulfanyl)methyl]benzene 66

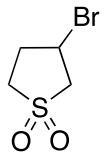


66

A 0.5 M NaOH solution in MeOH (20 mL) was added dropwise to a stirred solution of 4-bromo-1-butene (1.03 mL, 10.1 mmol, 1.0 eq.) in MeOH (50 mL) at 0 °C under Ar. Then, a solution of benzyl thioacetate **70** (1.70 g, 10.2 mmol, 1.01 eq.) in MeOH (20 mL) was added. The resulting solution was stirred at rt for 24 h. Water (20 mL) was added and the mixture 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 9:1 hexane-EtOAc as eluent gave alkene sulfide **66** (1.38 g, 77%) as a colourless oil, R_F (95:5 hexane-EtOAc) 0.37; IR (ATR) 2917, 1640, 1494, 1453, 914, 699, 564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H, Ph), 5.80 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, =CH), 5.08-5.01 (m, 2H, $=CH_2$), 3.73 (s, 2H, SCH_2), 2.50 (t, J = 7.5 Hz, 2H, SCH_2), 2.32 (br td, J = 7.5, 7.0 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.6 (*ipso*-Ph), 136.9 ($HC=CH_2$), 129.0 (Ph), 128.6 (Ph), 127.1 (Ph), 116.0 ($CH=CH_2$), 36.4 (SCH_2Ph), 33.7 (CH_2), 30.8 (SCH_2); MS (APCI) *m/z* 179 $(M + H)^+$; HRMS (APCI) *m/z* calcd for $C_{11}H_{14}S$ $(M + H)^+$ 179.0889, found 179.0884 (–2.5 ppm error). Spectroscopic data consistent with those reported in the literature.[43,88]

Lab book reference: **HS-1-91**

3-Bromo-1λ^6-thiolane-1,1-dione 67

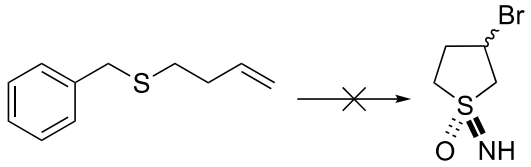


67

Bromine (30 μL, 0.6 mmol, 1.01 eq.) was added dropwise to a stirred solution of alkene sulfide **66** (100 mg, 0.56 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 1.5 h. Then, *m*CPBA (480 mg of 50-60% purity *m*-CPBA, approx. 1.4 mmol, 2.5 eq.) was added and the resulting solution was stirred at rt for 1.5 h. Sat. $Na_2S_2O_{5(aq)}$ (20 mL) was added and the mixture was stirred for 30 min. The two layers were separated. Then, the organic layer was washed with sat. $NaHCO_{3(aq)}$ (10 mL) and 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 which contained a 55:45 mixture of bromo sulfone **67** and benzyl bromide (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 8:2 and then 6:4 hexane-EtOAc as eluent gave bromo sulfone **67** (19 mg, 17%) as a colourless oil, R_F (6:4 hexane-EtOAc) 0.26; IR (ATR) 1409, 1308, 1270, 1123, 853 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (dddd, J = 7.0, 7.0, 7.0, 5.0 Hz, 1H, BrCH), 3.62 (dd, J = 14.0, 7.0 Hz, 1H, SCH), 3.45-3.38 (m, 2H, SCH), 3.15 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H, SCH), 2.79 (dddd, J = 14.5, 7.0, 7.0, 5.0 Hz, 1H, CH), 2.60 (dddd, J = 14.5, 7.0, 7.0, 7.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 60.3 (SCH_2), 51.1 (SCH_2), 39.7 (BrCH), 34.2 (CH_2); MS (APCI) *m/z* 199 (M(^{79}Br) + H)$^+$; HRMS (APCI) *m/z* calcd for $C_4H_7{}^{79}BrO_2S$ (M(^{79}Br) + H)$^+$ 198.9423, found 198.9414 (+4.4 ppm error). Spectroscopic data consistent with those reported in the literature.[43]

Lab book reference: **HS-1-95**

Attempted synthesis of 3-bromo-1-imino-1λ^6-thiolan-1-one 72

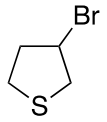


66 **72**

Bromine (44 μL, 0.85 mmol, 1.01 eq.) was added dropwise to a stirred solution of alkene sulfide **66** (150 mg, 0.84 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 1.5 h. Then, a solution of (diacetoxyiodo)benzene (680 mg, 2.1 mmol, 2.5 eq.) and ammonium carbamate (132 mg, 1.68 mmol, 2.0 eq.) in MeOH (2 mL) was added and the resulting solution was stirred at rt for 3 h. Water (20 mL) was added and the mixture 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 none of the desired sulfoximines **72** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-92**

3-Bromothiolane 65



65

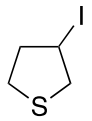
Bromine (30 μL, 0.6 mmol, 1.01 eq.) was added dropwise to a stirred solution of alkene sulfide **66** (100 mg, 0.56 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product (120 mg) as an orange oil which contained a 60:20:20 mixture of alkene sulfide **66**, bromo sulfide **65** and benzyl bromide (by ^{1}H NMR spectroscopy). Diagnostic signals for bromo sulfide **65**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dddd, J = 5.0, 5.0, 5.0, 5.0 Hz, 1H, BrCH), 3.35 (dd, J = 12.0, 5.0 Hz, 1H, SCH), 3.15-3.05 (m, 2H, CH), 2.97-2.89 (m, 1H, CH), 2.71-2.64 (m, 1H, CH), 2.58-2.53 (m, 1H, CH); diagnostic signal for benzyl bromide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2H, $BrCH_2$).

Lab book reference: **HS-1-99**

Bromine (60 μL, 1.1 mmol, 2.0 eq.) was added dropwise to a stirred solution of alkene sulfide **66** (100 mg, 0.56 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product (100 mg) as an orange oil which contained a 0:50:50 mixture of alkene sulfide **66**, bromo sulfide **65** and benzyl bromide (by ^{1}H NMR spectroscopy).

Lab book reference: **HS-1-100**

3-Iodothiolane 73

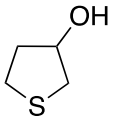


73

Iodine (73 mg, 0.41 mmol, 1.0 eq.) was added to a solution of alkene sulfide **66** (100 mg, 0.41 mmol, 1.0 eq.) in CH_2Cl_2 (2.2 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product which contained a 10:45:45 mixture of alkene sulfide **66**, iodo sulfide **73** and benzyl iodide (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave a 10:45:45 mixture of alkene sulfide **66**, iodo sulfide **73** and benzyl iodide (17 mg, i.e. 9 mg (10%) of iodo sulfide **73**) (by ^{1}H NMR spectroscopy) as a brown oil. Diagnostic signals for iodo sulfide **73**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (dddd, J = 8.0, 8.0, 5.5, 5.5 Hz, 1H, ICH), 3.33 (dd, J = 11.0, 5.5 Hz, 1H, SCH), 3.13 (dd, J = 11.0, 8.0 Hz, 1H, SCH), 2.96 (ddd, J = 10.5, 7.5, 5.0 Hz, 1H, SCH), 2.87 (ddd, J = 10.5, 7.5, 7.5 Hz, 1H, SCH), 2.52-2.37 (m, 1H, CH), 2.34-2.20 (m, 1H, CH); diagnostic signal for benzyl iodide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H, ICH_2).

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

Thiolan-3-ol 75



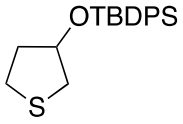
75

BH_3·THF (30 mL of a 1.0 M solution in THF, 30 mmol, 1.5 eq.) was added dropwise to a stirred solution of tetrahydrothiophene-3-one **79** (1.7 mL, 20 mmol, 1.0 eq.) in THF (20 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. The solution was then cooled to 0 °C and MeOH (2 mL) was added dropwise. Then, EtOAc (20 mL) and a 25% aqueous solution of Rochelle salt (sodium potassium tartrate) (20 mL) were added and the resulting solution was stirred vigorously at rt for 30 min. The two layers were separated and the aqueous layer was extracted with EtOAc (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 7:3 hexane-EtOAc as eluent gave hydroxy

sulfide **75** (1.2 g, 56%) as a yellow oil, R_F (6:4 hexane-EtOAc) 0.28; IR (ATR) 3353 (OH), 2934, 1427, 1332, 1195, 1025, 952, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65-4.61 (br m, 1H, HOC*H*), 3.03-2.80 (m, 4H, SCH), 2.20-2.12 (m, 1H, CH), 1.91-1.81 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 74.7 (OCH), 40.0 (CH_2), 38.1 (CH_2), 28.2 (CH_2); MS (ESI) *m/z* 105 $(M + H)^+$; HRMS (ESI) *m/z* calcd for C_4H_8OS $(M + H)^+$ 105.0369, found 105.0366 (+2.5 ppm error). Spectroscopic data consistent with those reported in the literature.[89]

Lab book reference: **HS-2-11**

***tert*-Butyldiphenyl(thiolan-3-yloxy)silane 76**

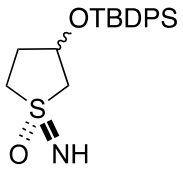


76

TBDPSCl (0.60 mL, 2.4 mmol, 1.1 eq.) was added dropwise to a stirred solution of hydroxy sulfide **75** (227 mg, 2.17 mmol, 1.0 eq.) and imidazole (370 mg, 5.40 mmol, 2.5 eq.) in DMF (7 mL) at rt under Ar. The resulting solution was stirred at rt for 21 h. Sat. $NaHCO_{3(aq)}$ (6 mL) and Et_2O (6 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (4 × 6 mL) and the combined organic layers were washed with brine (4 × 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 95:5 hexane-EtOAc as eluent gave TBDPSO-sulfide **76** (630 mg, 85%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.49; IR (ATR) 2931, 2856, 1427, 1059, 699, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H, Ph), 7.44-7.37 (m, 6H, Ph), 4.54 (dddd, *J* = 4.0, 4.0, 4.0, 4.0 Hz, 1H, OCH), 3.05 (ddd, *J* = 9.5, 9.5, 6.0 Hz, 1H, SCH), 2.82-2.75 (m, 3H, SCH), 2.10-2.03 (m, 1H, CH), 1.77-1.69 (m, 1H, CH), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.9 (Ph), 134.0 (*ipso*-Ph), 133.9 (*ipso*-Ph), 129.9 (Ph), 127.8 (Ph), 76.1 (OCH), 39.1 (CH_2), 38.8 (CH_2), 28.6 (CH_2), 27.0 (C*Me*$_3$), 19.3 (*C*Me_3) (three Ph resonances not resolved); MS (ESI) *m/z* 343 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}OSSi$ $(M + H)^+$ 343.1546, found 343.1546 (+0.1 ppm error).

Lab book reference: **HS-1-66**

3-[(*tert*-Butyldiphenylsilyl)oxy]-1-imino-1λ^6-thiolan-1-ones 77

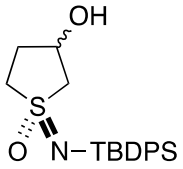


77

A solution of TBDPSO-sulfide **76** (593 mg, 1.73 mmol, 1.0 eq.), (diacetoxyiodo)benzene (1.39 g, 4.32 mmol, 2.5 eq.) and ammonium carbamate (272 mg, 3.46 mmol, 2.0 eq.) in MeOH (6 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 TBDPSO-sulfoximine **77a** (190 mg, 29%) as a yellow oil, R_F (EtOAc) 0.48; IR (ATR) 3277 (NH), 2932, 2857, 1428, 1225, 1108, 703, 607, 507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 4H, Ph), 7.48-7.38 (m, 6H, Ph), 4.63 (dddd, J = 5.0, 5.0, 5.0, 5.0 Hz, 1H, OCH), 3.43 (ddd, J = 13.0, 8.0, 8.0 Hz, 1H, SCH), 3.19-3.04 (m, 3H, SCH), 2.32-2.26 (m, 2H, CH), 1.07 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.8 (Ph), 132.8 (*ipso*-Ph), 130.3 (Ph), 128.1 (Ph), 70.8 (OCH), 63.5 (SCH_2), 53.9 (SCH_2), 33.4 (CH_2), 26.9 (CMe_3), 19.2 (CMe_3); MS (ESI) *m/z* 374 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{28}NO_2SSi$ $(M + H)^+$ 374.1605, found 374.1609 (–1.2 ppm error) and TBDPSO-sulfoximine **77b** (269 mg, 42%) as a yellow oil, R_F (EtOAc) 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 4H, Ph), 7.47-7.38 (m, 6H, Ph), 4.61 (dddd, J = 4.5, 4.5, 4.5, 4.5 Hz, 1H, OCH), 3.53-3.46 (m, 1H, SCH), 3.17-3.07 (m, 3H, SCH), 2.30-2.24 (m, 2H, CH), 1.08 (s, 9H, CMe_3); MS (ESI) *m/z* 374 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NO_2SSi$ $(M + H)^+$ 374.1605, found 374.1609 (–1.2 ppm error).

Lab book reference: **HS-1-67**

1-[(*tert*-Butyldiphenylsilyl)imino]-3-hydroxy-1λ^6-thiolan-1-one 80

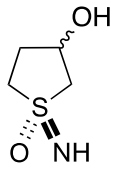


80

TBDPSCl (0.16 mL, 0.63 mmol, 1.25 eq.) was added dropwise to a stirred solution of TBDPSO-sulfoximine **77a** (190 mg, 0.50 mmol, 1.0 eq.) and imidazole (68 mg, 1.0 mmol, 2.0 eq.) in DMF (1 mL) at rt under Ar. The resulting solution was stirred and heated at 90 ºC for 48 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 6:4 hexane-EtOAc and then EtOAc as eluent gave hydroxy *N*-TBDPS sulfoximine **80** (20 mg, 7%) as an orange oil, R_F (1:1 hexane-EtOAc) 0.39; IR (ATR) 2923, 2855, 1628, 1460, 1107, 736, 704, 506 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 4H, Ph), 7.50-7.39 (m, 6H, Ph), 4.76-4.72 (m, 1H, HOC*H*), 3.77 (ddd, *J* = 14.0, 9.0, 9.0 Hz, 1H, SCH), 3.70 (dd, *J* = 14.0, 3.0 Hz, 1H, SCH), 3.40 (ddd, *J* = 14.0, 6.0, 6.0 Hz, 1H, SCH), 3.27 (dd, *J* = 14.0, 6.0 Hz, 1H, SCH), 2.34-2.29 (m, 2H, CH), 1.06 (s, 9H, CMe_3) and TBDPSO-sulfoximine **77a** (48 mg, 26% recovered) as an orange oil.

Lab book reference: **HS-1-70**

3-Hydroxy-1-imino- 1λ⁶-thiolan-1-ones 81

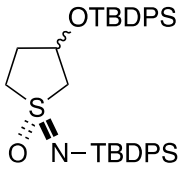


81

A solution of hydroxy sulfide **75** (210 mg, 2.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (1.61 g, 5.00 mmol, 2.5 eq.) and ammonium carbamate (315 mg, 4.00 mmol, 2.0 eq.) in MeOH (4 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 (dry loading) with EtOAc and then 9:1 EtOAc-MeOH as eluent gave a 60:40 mixture of diastereomeric hydroxy sulfoximines **81** (180 mg, 67%) as a brown oil, R_F (95:5 EtOAc-MeOH) 0.11; IR (ATR) 3268 (OH/NH), 1437, 1241, 1214, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.75-4.72 (m, 0.4H, HOC*H*), 4.70-4.66 (m, 0.6H, HOC*H*), 3.47-3.34 (m, 2.4H, SCH), 3.30 (s, 1H, NH), 3.27-3.18 (m, 1.6H, SCH), 2.57-2.37 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 69.4 (OCH), 68.5 (OCH), 62.9 (SCH_2), 62.0 (SCH_2), 53.6 (SCH_2), 53.0 (SCH_2), 33.2 (CH_2), 33.0 (CH_2); MS (ESI) *m/z* 158 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_4H_9NO_2S$ $(M + Na)^+$ 158.0246, found 158.0243 (+2.2 ppm error).

Lab book reference: **HS-1-68**

1-[(*tert*-Butyldiphenylsilyl)imino]-3-[(*tert*-butyldiphenylsilyl)oxy]-1λ⁶-thiolan-1-one 78



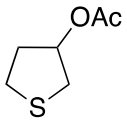
78

TBDPSCl (1.60 mL, 6.3 mmol, 2.0 eq.) was added dropwise to a stirred solution of a 60:40 mixture of diastereomeric hydroxy sulfoximines **81** (427 mg, 3.15 mmol, 1.0 eq.) and imidazole (860 mg, 12.6 mmol, 4.0 eq.) in DMF (4 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. After being allowed to cool to rt, water (20 mL) and Et_2O (10 mL) were added. 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 × 20 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 an 80:20 mixture of TBDPSOH and a single unidentified diastereomeric diprotected sulfoximine **78** (390 mg, i.e. 110 mg (6%) of **78**) (by ^{1}H NMR spectroscopy) as a colourless oil. Diagnostic signals for diprotected sulfoximine **78**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31-4.36 (m, 1H, OCH), 3.22 (ddd, J = 13.0, 8.0, 5.0 Hz, 1H, SCH), 2.98 (dd, J = 13.0, 5.0 Hz, 1H, SCH), 2.83 (dd, J = 13.0, 6.5 Hz, 1H, SCH), 2.68 (ddd, J = 13.0, 6.5, 6.5 Hz, 1H, SCH), 2.15-2.02 (m, 2H, CH), 1.03 (s, 9H, CMe_3), 1.00 (s, 9H, CMe_3); MS (ESI) *m/z* 612 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{36}H_{45}NO_2SSi_2$ $(M + H)^+$ 612.2782, found 612.2798 (–2.5 ppm error); diagnostic signals for TBDPSOH: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.71 (m, 4H, Ph), 7.41-7.36 (m, 6H, Ph), 1.07 (s, 9H, CMe_3).

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

Thiolan-3-yl acetate 83

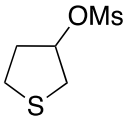


83

A solution of hydroxy sulfide **75** (73 mg, 7.0 mmol, 1.0 eq.), Et_3N (2.91 mL, 20.9 mmol, 3.0 eq.), acetic anhydride (1.00 mL, 10.5 mmol, 1.5 eq.) and DMAP (43 mg, 3.5 mmol, 0.5 eq.) in CH_2Cl_2 (25 mL) was stirred at rt for 16 h. Then, CH_2Cl_2 (20 mL) was added and the solution was washed with 1 M $HCl_{(aq)}$ (20 mL), sat. $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane-EtOAc as eluent gave acetoxy sulfide **83** (670 mg, 66%) as a yellow oil, R_F (1:1 hexane-EtOAc) 0.60; IR (ATR) 2939, 1732 (C=O), 1430, 1372, 1236, 1186, 1022, 980, 605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49-5.46 (br m, 1H, OCH), 3.12 (dd, J = 12.0, 5.0 Hz, 1H, SCH), 3.00-2.88 (m, 3H, SCH), 2.29-2.20 (m, 1H, CH), 2.05 (s, 3H, Me), 2.01-1.92 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7 (C=O), 77.0 (OCH), 36.7 (CH_2), 36.0 (CH_2), 29.0 (CH_2), 21.4 (Me); MS (ESI) *m/z* 147 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{10}O_2S$ $(M + H)^+$ 147.0474, found 147.0475 (–0.7 ppm error).

Lab book reference: **HS-1-61**

Thiolan-3-yl methanesulfonate 82

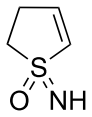


82

DMAP (352 mg, 2.88 mmol, 1.5 eq.) and methanesulfonyl chloride (0.18 mL, 2.3 mmol, 1.2 eq.) were added to a stirred solution of hydroxy sulfide **75** (200 mg, 1.92 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 5 °C under Ar. The resulting solution was stirred at rt for 16 h. Then, 1 M $HCl_{(aq)}$ (10 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 6:4 hexane-EtOAc as eluent gave mesylate sulfide **82** (260 mg, 75%) as a colourless oil, R_F (7:3 hexane-EtOAc) 0.33; IR (ATR) 1329, 1165, 882, 523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.44 (dddd, J = 4.0, 4.0, 3.5, 3.5 Hz, 1H, OCH), 3.23-3.09 (m, 2H, SCH), 3.05 (s, 3H, Me), 3.04-2.93 (m, 2H, SCH), 2.51-2.44 (m, 1H, CH), 2.11-2.02 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 83.0 (OCH), 38.8 (Me), 37.0 (CH_2), 36.9 (CH_2), 28.2 (CH_2); MS (ESI) *m/z* 205 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_5H_{10}O_3S_2$ $(M + Na)^+$ 204.9964, found 204.9968 (–2.3 ppm error). ^1H NMR spectroscopic data consistent with those reported in the literature.[47]

Lab book reference: **HS-2-21**

1-Imino-2,3-dihydro-1λ⁶-thiophen-1-one 86



86

A solution of mesylate sulfide **82** (205 mg, 1.12 mmol, 1.0 eq.), (diacetoxyiodo)benzene (905 mg, 2.81 mmol, 2.5 eq.) and ammonium carbamate (176 mg, 2.24 mmol, 2.0 eq.) in MeOH (2.5 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 9:1 EtOAc-MeOH gave vinyl sulfoximine **86** (50 mg, 38%) as a brown oil, R_F (8:2 EtOAc-MeOH) 0.23; IR (ATR) 3346 (NH), 1319, 1122, 701, 643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (ddd, J = 6.5, 2.0, 2.0 Hz, 1H, =CH), 6.60 (ddd, J = 6.5, 3.0, 3.0 Hz, 1H, =CH), 3.36-3.31 (m, 2H, SCH), 2.98-2.93 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.8 (=CH),

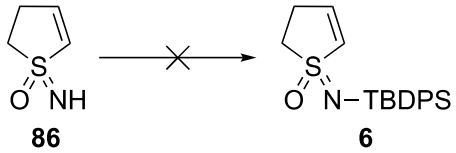
135.1 (=CH), 51.8 (SCH_2), 27.6 (CH_2); MS (ESI) *m/z* 118 $(M + H)^+$; HRMS (ESI) *m/z* calcd for C_4H_7NOS $(M + H)^+$ 118.0321, found 118.0317 (+3.2 ppm error).

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

A solution of acetoxy sulfide **83** (73 mg, 0.50 mmol, 1.0 eq.), (diacetoxyiodo)benzene (403 mg, 1.25 mmol, 2.5 eq.) and ammonium carbamate (78.7 mg, 1.00 mmol, 2.0 eq.) in MeOH (1 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 1% Et_3N in EtOAc and then 9:1 EtOAc-MeOH as eluent gave slightly impure vinyl sulfoximine **86** (25 mg, 28%) as a yellow oil.

Lab book reference **HS-1-63**

Attempted synthesis of 1-[(*tert*-butyldiphenylsilyl)imino]-2,3-dihydro-1λ⁶-thiophen-1-one 6

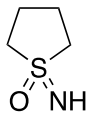


86 **6**

TBDPSCl (0.15 mL, 0.60 mmol, 1.25 eq.) was added dropwise to a stirred solution of vinyl sulfoximine **86** (56 mg, 0.48 mmol, 1.0 eq.) and imidazole (65 mg, 0.96 mmol, 2.0 eq.) in DMF (0.5 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 60 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added. 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 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired *N*-TBDPS sulfoximine **6** (by ^{1}H NMR spectroscopy and mass spectrometry).

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

1-Imino-1λ⁶-thiolan-1-one 89

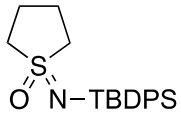


89

A solution of tetrahydrothiophene (1.32 g, 15.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (12.1 g, 37.5 mmol, 2.5 eq.) and ammonium carbamate (2.36 g, 30.0 mmol, 2.0 eq.) in MeOH (30 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 95:5 and then 9:1 EtOAc-MeOH as eluent gave sulfoximine **89** (1.52 g, 85%) as a yellow oil, R_F (95:5 EtOAc-MeOH) 0.20; IR (ATR) 3260 (NH), 2949, 1196, 988, 718, 540 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (br s, 1H, NH), 3.17-3.10 (m, 4H, SCH), 2.29-2.21 (m, 4H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.5 (SCH_2), 23.5 (CH_2); MS (ESI) *m/z* 120 $(M + H)^+$; MS (ESI) *m/z* 120 $(M + H)^+$; HRMS (ESI) *m/z* calcd for C_4H_9NOS $(M + H)^+$ 120.0478, found 120.0479 (–1.5 ppm error). Spectroscopic data consistent with those reported in the literature.[6]

Lab book reference: **HS-1-51**

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

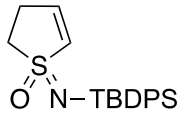


1

TBDPSCl (3.53 mL, 14.1 mmol, 1.25 eq.) was added dropwise to a stirred solution of sulfoximine **89** (1.34 g, 11.2 mmol, 1.0 eq.) and imidazole (1.53 g, 22.5 mmol, 2.0 eq.) in DMF (6 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (5 × 20 mL), 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 **1** (2.31 g, 58%) as a white solid, mp 68-70 °C, R_F (7:3 hexane-EtOAc) 0.34; IR (ATR) 2857, 1321, 1254, 1151, 1068, 702, 494 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.72 (m, 4H, Ph), 7.39-7.32 (m, 6H, Ph), 2.90 (ddd, J = 12.5, 6.5, 6.5 Hz, 2H, SCH), 2.76 (ddd, J = 12.5, 6.5, 6.5 Hz, 2H, SCH), 2.16-1.96 (m, 4H, CH), 1.07 (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), 27.1 (CMe_3), 23.3 (CH_2), 19.3 (CMe_3); MS (ESI) *m/z* 358 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{27}NOSSi$ $(M + H)^+$ 358.1655, found 358.1641 (+4.0 ppm error).

Lab book reference: **HS-1-49**

1-[(*tert*-Butyldiphenylsilyl)imino]-2,3-dihydro-1λ⁶-thiophen-1-one 6



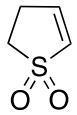
6

n-BuLi (2.55 mL of a 2.08 M solution in hexanes, 6.20 mmol, 1.1 eq.) was added dropwise to a stirred solution of *N*-TBDPS sulfoximine **1** (2.02 g, 5.65 mmol, 1.0 eq.) in THF (30 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, $ZnCl_2$ (8.9 mL of a 0.70 M solution in THF, 6.2 mmol, 1.1 eq.) was added. The resulting solution was allowed to warm slowly to rt and stirred at rt for 1 h. Then, mesityl bromide (0.86 mL, 5.7 mmol, 1.0 eq.) was added, followed by the addition of a solution of $Pd(OAc)_2$ (51 mg,

0.23 mmol, 0.04 eq.) and XPhos (220 mg, 0.45 mmol, 0.08 eq.) in THF (3 mL). The resulting solution was stirred and heated at 65 °C for 16 h. After being allowed to cool to rt, sat. $NH_4Cl_{(aq)}$ (10 mL) and 1 M $HCl_{(aq)}$ (5 mL) were added. The two layers were separated and 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 85:15 hexane-EtOAc as eluent gave *N*-TBDPS vinyl sulfoximine **6** (780 mg, 39%) as a yellow solid, mp 66-68 °C, R_F (7:3 hexane-EtOAc) 0.35; IR (ATR) 2920, 2838, 1295, 1156, 1107, 702, 503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 4H, Ph), 7.39-7.32 (m, 6H, Ph), 6.36 (s, 2H, =CH), 3.10 (ddd, J = 13.5, 9.0, 4.5 Hz, 1H, SCH), 2.94 (ddd, J = 13.5, 9.0, 4.5 Hz, 1H, SCH), 2.80-2.72 (m, 1H, CH), 2.65-2.55 (m, 1H, CH), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.27 (*ipso*-Ph), 136.23 (*ipso*-Ph), 135.7 (Ph), 134.6 (=CH), 129.3 (Ph), 127.65 (Ph), 127.62 (Ph), 52.6 (SCH_2), 27.1 (CMe_3), 27.0 (CH_2), 19.3 (CMe_3) (one =CH and two Ph resonances not resolved); MS (ESI) *m/z* 356 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}NOSSi$ $(M + H)^+$ 356.1499, found 356.1502 (–0.8 ppm error).

Lab book reference: **HS-1-54**

2,3-Dihydro-1λ^6-thiophene-1,1-dione 55

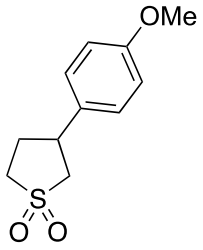


55

A solution of 3-sulfolene (500 mg, 4.2 mmol, 1.0 eq.) and KOH (280 mg, 5.0 mmol, 1.2 eq.) in water (10 mL) was stirred at rt for 20 h. Then, 0.5 M $HCl_{(aq)}$ was added and the resulting mixture 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 8:2 Et_2O-hexane as eluent gave 3-sulfolene **57** (100 mg, 20%) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (s, 2H, =CH), 3.76 (s, 4H, CH_2) and vinyl sulfone **55** (140 mg, 29%) as a white solid, mp 46-48 °C (lit.,[90] 48-49 °C); IR (ATR) 3084, 1289, 1137, 1088, 703, 648, 589 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dt, J = 6.5, 3.0 Hz, 1H, =CH), 6.67 (dt, J = 6.5, 2.5 Hz, 1H, =CH), 3.24 (t, J = 6.5 Hz, 2H, SCH_2), 2.94-2.87 (m, 2H, CH_2); MS (ESI) *m/z* 140 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_4H_6O_2S$ $(M + Na)^+$ 140.9981, found 140.9979 (+0.9 ppm error). ^{1}H NMR spectroscopic data for **55** and **57** consistent with those reported in the literature.[23,91]

Lab book reference: **HS-2-1**

3-(4-Methoxyphenyl)tetrahydrothiophene-1,1-dioxide 56



56

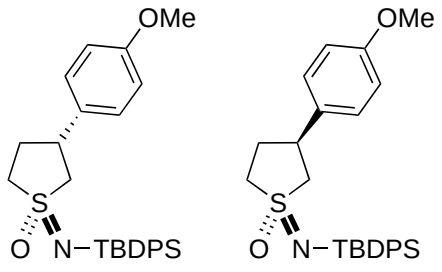
Vinyl sulfone **55** (75 mg, 0.63 mmol, 1.0 eq.), 4-methoxyphenylboronic acid (140 mg, 0.95 mmol, 1.5 eq.) and $[Rh(OH)(cod)]_2$ (15 mg, 0.032 mmol, 0.05 eq.) were placed in a 25 mL pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, water (0.42 mL) and dioxane (4.2 mL) were added and the pressure tube was evacuated and refilled with Ar three times. The pressure tube was placed in a pre-heated oil bath at 60 °C and the mixture was stirred and heated at 60 °C under Ar for 16 h. After being allowed to cool to rt, the mixture was passed through a short pad of silica with EtOAc (100 mL) as the

eluent. The solution was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 EtOAc-MeOH as eluent gave β-aryl sulfone **56** (42 mg, 29%*) as a white solid, mp 84-86 °C; R_F (9:1 EtOAc-MeOH) 0.63; IR (ATR) 2917, 1609, 1514, 1181, 1030, 830, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H, Ar), 6.89 (d, J = 8.5 Hz, 2H, Ar), 3.80 (s, 3H, OMe), 3.58 (dddd, J = 12.0, 12.0, 7.5, 5.5 Hz, 1H, ArCH), 3.48-3.41 (m, 1H, SCH), 3.36 (ddd, J = 13.0, 8.0, 2.0 Hz, 1H, SCH), 3.17 (ddd, J = 13.0, 12.0, 8.0 Hz, 1H, SCH), 3.08 (dd, J = 12.0, 12.0 Hz, 1H, SCH), 2.52 (dddd, J = 13.5, 7.5, 4.0, 2.0 Hz, 1H, CH), 2.27 (dddd, J = 13.5, 12.0, 12.0, 8.0 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.2 (*ipso*-Ar), 131.5 (*ipso*-Ar), 127.9 (Ar), 114.6 (Ar), 57.9 (SCH_2), 55.4 (OMe), 53.0 (SCH_2), 41.3 (*C*HAr), 31.1 (CH_2); MS (ESI) *m/z* 225 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_3S$ $(M + H)^+$ 225.0580, found 225.0583 (–1.2 ppm error) and vinyl sulfone **55** (9 mg, 11% recovered) as a white solid. Spectroscopic data for β-aryl sulfone **56** consistent with those reported in the literature.[23]

*β-Aryl sulfone **56** was ~90% pure – it is contaminated with ~10% of an impurity that appears to be derived from the 4-methoxyphenylboronic acid.

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

1-[(*tert*-Butyldiphenylsilyl)imino]-3-(4-methoxyphenyl)-1λ^6-thiolan-1-ones *cis*-90 and *trans*-90



N-TBDPS vinyl sulfoximine **6** (250 mg, 0.70 mmol, 1.0 eq.), 4-methoxyphenylboronic acid (161 mg, 1.05 mmol, 1.5 eq.) and $[Rh(OH)(cod)]_2$ (48 mg, 0.11 mmol, 0.15 eq.) were placed in a 25 mL pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, water (0.47 mL) and dioxane (4.7 mL) were added and the pressure tube was evacuated and refilled with Ar three times. The pressure tube was placed in a pre-heated oil bath at 60 °C and the mixture was stirred and heated at 60 °C under Ar for 16 h. After being allowed to cool to rt, the mixture was passed through a short pad of silica with EtOAc

(100 mL) as the eluent. The solution was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 and then 8:2 hexane-EtOAc as eluent gave β-aryl sulfoximine *cis*-**90** (91 mg, 28%) as a colourless oil, R_F (7:3 hexane-EtOAc) 0.48; IR (ATR) 2956, 2855, 1514, 1248, 1139, 1106, 702, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (m, 4H, Ph), 7.43-7.35 (m, 6H, Ph), 7.07 (d, J = 8.5 Hz, 2H, Ar), 6.84 (d, J = 8.5 Hz, 2H, Ar), 3.78 (s, 3H, OMe), 3.35-3.28 (m, 1H, ArCH), 3.26-3.17 (m, 2H, SCH), 3.02-2.90 (m, 2H, SCH), 2.36-2.28 (m, 1H, CH), 2.26-2.15 (m, 1H, CH), 1.11 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.9 (*ipso*-Ar), 136.4 (*ipso*-Ar), 136.3 (*ipso*-Ar), 135.7 (Ar), 132.7 (*ipso*-Ar), 129.3 (Ar), 128.0 (Ar), 127.7 (Ar), 114.3 (Ar), 62.5 (SCH_2), 57.8 (SCH_2), 55.4 (OMe), 41.9 (*C*HAr), 31.6 (CH_2), 27.2 (C*Me*$_3$), 19.3 (*C*Me_3) (three Ar resonances not resolved); MS (ESI) *m/z* 486 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NO_2SSi$ $(M + Na)^+$ 486.1893, found 486.1899 (–1.1 ppm error).

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

N-TBDPS vinyl sulfoximine **6** (250 mg, 0.70 mmol, 1.0 eq.), 4-methoxyphenylboronic acid (161 mg, 1.05 mmol, 1.5 eq.) and $[Rh(OH)(cod)]_2$ (16 mg, 0.035 mmol, 0.05 eq.) were placed in a 25 mL pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, water (0.47 mL) and dioxane (4.7 mL) were added and the pressure tube was evacuated and refilled with Ar three times. The pressure tube was placed in a pre-heated oil bath at 60 °C and the mixture was stirred and heated at 60 °C under Ar for 48 h. After being allowed to cool to rt, the mixture was passed through a short pad of silica with EtOAc (100 mL) as the eluent. The solution was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 and then 8:2 hexane-EtOAc as eluent gave β-aryl sulfoximine *cis*-**90** (48 mg, 15%) as a colourless oil.

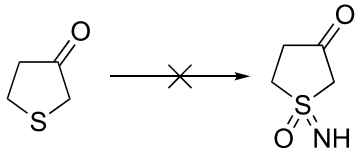
Lab book reference: **HS-2-49**

N-TBDPS vinyl sulfoximine **6** (250 mg, 0.70 mmol, 1.0 eq.), 4-methoxyphenylboronic acid (161 mg, 1.05 mmol, 1.5 eq.) and $[Rh(OH)(cod)]_2$ (16 mg, 0.035 mmol, 0.05 eq.) were placed in a 25 mL pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, water (0.47 mL) and dioxane (4.7 mL) were added and the pressure tube was evacuated and refilled with Ar three times. The pressure tube was placed in a pre-heated oil bath at 60 °C and the mixture was stirred and heated at 60 °C under Ar for 16 h. After being allowed to cool to rt, the mixture was passed through a short pad of silica with EtOAc

(100 mL) as the eluent. The solution was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc and then 8:2 hexane-EtOAc as eluent gave β-aryl sulfoximine *cis*-**90** (44 mg, 14%) as a colourless oil and an 80:20 mixture of diastereomeric β-aryl sulfoximines *trans*-**90** and *cis*-**90** (8 mg, i.e. 6 mg (2%) of *trans*-**90** and 2 mg (0.5%) of *cis*-**90**) (by ^{1}H NMR spectroscopy) as a colourless oil. Diagnostic signals for *trans*-**90**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.5 Hz, 2H, Ar), 6.81 (d, J = 8.5 Hz, 2H, Ar), 3.78 (s, 3H, OMe), 3.56-3.47 (m, 1H, ArCH), 3.29-3.22 (m, 1H, SCH), 3.12-3.08 (m, 2H, SCH), 2.80 (dd, J = 12.5, 12.5 Hz, 1H, SCH), 2.39-2.32 (m, 1H, CH), 2.05-1.94 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.8 (*ipso*-Ar), 136.3 (*ipso*-Ar), 135.7 (Ar), 132.5 (*ipso*-Ar), 129.4 (Ar), 127.9 (Ar), 127.7 (Ar), 114.3 (Ar), 62.3 (SCH_2), 57.6 (SCH_2), 55.5 (OMe), 41.5 (*C*HAr), 31.6 (CH_2), 27.2 (C*Me*$_3$), 19.3 (*C*Me$_3$) (one *ipso*-Ar and three Ar resonances not resolved); IR (ATR) 2931, 2855, 1514, 1301, 1145, 1106, 731, 501 cm^{-1}; MS (ESI) *m/z* 464 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{27}H_{33}NO_2SSi$ $(M + H)^+$ 464.2074, found 464.2074 (0.0 ppm error).

Lab book reference: **HS-2-30**

Attempted synthesis of 1-imino-1λ⁶-thiolane-1,3-dione 154

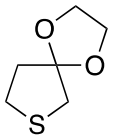


79 **154**

A solution of tetrahydrothiophen-3-one **79** (0.43 mL, 5.0 mmol, 1.0 eq.), (diacetoxyiodo)benzene (4.03 g, 12.5 mmol, 2.5 eq.) and ammonium carbamate (785 mg, 10.0 mmol, 2.0 eq.) in MeOH (10 mL) was stirred at rt for 3 h. The solvent was evaporated under reduced pressure to give the crude product which contained starting β-keto sulfide **79** and none of the desired keto sulfoximine **154** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-1**

1,4-Dioxa-6-thiaspiro[4.4]nonane 159

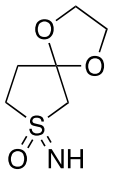


159

A solution of tetrahydrothiophen-3-one **79** (4.29 mL, 50.0 mmol, 1.0 eq.), ethylene glycol (5.60 mL, 100 mmol, 2.0 eq.) and *p*-toluenesulfonic acid (130 mg, 0.75 mmol, 0.015 eq.) in toluene (50 mL) was stirred and heated at 180 °C with a Dean-Stark water separator attached for 16 h. The solution was allowed to cool to rt and washed with 2 M $NaOH_{(aq)}$ (50 mL) and water (50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give ketal sulfide **159** (6.17 g, 84%) as a brown oil, IR (ATR) 2937, 2884, 1317, 1225, 1099, 947, 921 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01-3.97 (m, 4H, OCH_2), 2.88-2.86 (m, 4H, SCH_2), 2.07 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 118.1 (OCO), 65.1 (OCH_2), 37.5 (CH_2), 36.9 (CH_2), 27.0 (CH_2); MS (ESI) *m/z* 145 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{10}O_2S$ $(M + H)^+$ 145.0319, found 145.0318 (–0.5 ppm error).

Lab book reference: **HS-1-31**

7-Imino-1,4-dioxa-7λ^6-thiaspiro[4.4]nonane 7-oxide 160



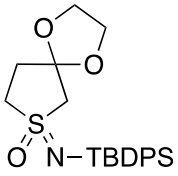
160

A solution of ketal sulfide **159** (4.95 g, 33.9 mmol, 1.0 eq.), (diacetoxyiodo)benzene (27.3 g, 84.8 mmol, 2.5 eq.) and ammonium carbamate (5.34 g, 67.8 mmol, 2.0 eq.) in MeOH (70 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 ketal sulfoximine **160** (3.75 g, 62%) as a yellow solid, mp 84-86 °C, R_F (95:5 EtOAc-MeOH) 0.20; IR (ATR) 3270 (NH), 2954, 2897, 1398, 1320, 1215, 1084, 999, 745, 672, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05-3.96 (m, 4H, OCH), 3.40-3.26 (m, 4H, SCH), 2.46 (t, J = 7.5 Hz, 2H, CH_2), 1.60 (br s, 1H, NH); ^{13}C

NMR (100.6 MHz, $CDCl_3$) δ 111.5 (OCO), 65.4 (OCH_2), 65.3 (OCH_2), 63.2 (SCH_2), 55.8 (SCH_2), 35.0 (CH_2); MS (ESI) *m/z* 178 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_6H_{11}NO_3S$ $(M + H)^+$ 178.0532, found 178.0533 (–0.6 ppm error).

Lab book reference **HS-1-5**

7-[(*tert*-Butyldiphenylsilyl)imino]-1,4-dioxa-7λ⁶-thiaspiro[4.4]nonan-7-one 161

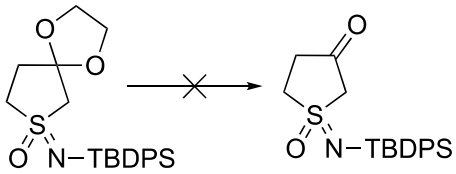


161

TBDPSCl (1.83 mL, 7.10 mmol, 1.25 eq.) was added dropwise to a stirred solution of ketal sulfoximine **160** (1.00 g, 5.60 mmol, 1.0 eq.) and imidazole (770 mg, 11.3 mmol, 2.0 eq.) in DMF (2.5 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added. 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 × 20 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, 9:1 hexane-EtOAc and then 7:3 hexane-EtOAc as eluent gave *N*-TBDPS sulfoximine **161** (1.41 g, 60%) as a yellow oil, R_F (7:3 hexane-EtOAc) 0.28; IR (ATR) 2956, 2856, 1473, 1428, 1316, 1102, 1010, 702, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.73 (m, 4H, Ph), 7.41-7.33 (m, 6H, Ph), 3.98-3.91 (m, 2H, OCH), 3.90-3.80 (m, 2H, OCH), 3.23-3.05 (m, 2H, SCH), 3.11 (d, *J* = 13.5 Hz, 1H, SCH), 2.99 (d, *J* = 13.5 Hz, 1H, SCH), 2.36 (ddd, *J* = 13.5, 8.0, 8.0 Hz, 1H, CH), 2.26 (ddd, *J* = 13.5, 7.0, 7.0 Hz, 1H, CH), 1.05 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.1 (*ipso*-Ph), 135.7 (Ph), 129.3 (Ph), 127.6 (Ph), 111.2 (OCO), 65.1 (OCH_2), 64.8 (OCH_2), 63.6 (SCH_2), 57.0 (SCH_2), 34.5 (CH_2), 27.1 (CMe_3), 19.3 (CMe_3); MS (ESI) *m/z* 416 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{22}H_{29}NO_3SSi$ $(M + H)^+$ 416.1709, found 416.1710 (+0.3 ppm error).

Lab book reference: **HS-1-13**

Attempted synthesis of 1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thiolane-1,3-dione 146



161 **146**

A solution of ketal *N*-TBDPS sulfoximine **161** (210 mg, 0.50 mmol, 1.0 eq.) and 3 M $HCl_{(aq)}$ (1.25 mL) in THF (1.25 mL) under Ar was stirred at rt for 48 h. Sat. $NaHCO_{3(aq)}$ (5 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 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 ketal sulfoximine **160** (9 mg, 10%) as a yellow oil.

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

A solution of *N*-TBDPS sulfoximine **161** (210 mg, 0.50 mmol, 1.0 eq.) and H_2SO_4 (2 mg, 0.02 mmol, 0.04 eq.) in acetone (5 mL) was stirred and heated at 56 °C for 10 min. After being allowed to cool to rt, sat. $Na_2CO_{3(aq)}$ (20 mL) was added and the solids were removed by filtration. EtOAc (30 mL) was added and the two layers of the filtrate were separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **161** and none of the desired keto sulfoximine **146** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-14**

A solution of *N*-TBDPS sulfoximine **161** (210 mg, 0.50 mmol, 1.0 eq.) and pyridinium *p*-toulenesulfonate (38 mg, 0.15 mmol, 0.3 eq.) in acetone (5 mL) was stirred and heated at 56 °C for 2 h. After being allowed to cool to rt, Et_2O (30 mL) was added and the solution was washed with sat. $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **161** and none of the desired keto sulfoximine **146** (by ^1H NMR spectroscopy and mass spectrometry).

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

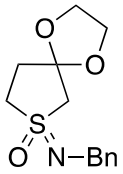
A solution of *N*-TBDPS sulfoximine **161** (210 mg, 0.50 mmol, 1.0 eq.) and H_2SO_4 (2 mg, 0.02 mmol, 0.04 eq.) in acetone (5 mL) was stirred and heated at 56 °C for 1 h. After being allowed to cool to rt, sat. $Na_2CO_{3(aq)}$ (20 mL) was added and the solids were removed by filtration. EtOAc (30 mL) was added and the two layers of the filtrate were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **161** and none of the desired keto sulfoximine **146** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-16**

A solution of *N*-TBDPS sulfoximine **161** (210 mg, 0.50 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (21 mg, 0.12 mmol, 0.24 eq.) in acetone (6 mL) was stirred at rt for 12 h. Water (5 mL) and EtOAc (5 mL) were added and the two layers were separated. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **161** and none of the desired keto sulfoximine **146** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-17**

7-(Benzylimino)-1,4-dioxa-7λ⁶-thiaspiro[4.4]nonan-7-one 163

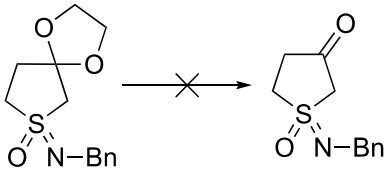


163

Benzyl bromide (1.0 mL, 8.5 mmol, 1.5 eq.) was added to a stirred solution of ketal sulfoximine **160** (1.00 g, 5.60 mmol, 1.0 eq.) and KOH (630 mg, 11.3 mmol, 2.0 eq.) in DMSO (7 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were 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 4:1 hexane-EtOAc as eluent gave an 80:20 mixture of ketal *N*-Bn ketal sulfoximine **163** and DMSO (200 mg, i.e.190 mg (13%) of **163**) as a yellow oil, R_F (8:2 hexane-EtOAc) 0.53; IR (ATR) 2895, 1224, 1094, 944, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.5 Hz, 2H, Ph), 7.32 (dd, J = 7.5, 7.5 Hz, 2H, Ph), 7.23 (t, J = 7.5 Hz, 1H, Ph), 4.32 (d, J = 14.5 Hz, 1H, NCH), 4.29 (d, J = 14.5 Hz, 1H, NCH), 4.05-3.87 (m, 4H, OCH), 3.39-3.31 (m, 1H, SCH), 3.26-3.20 (m, 1H, SCH), 3.19 (d, J = 13.0 Hz, 1H, SCH), 3.13 (d, J = 13.0 Hz, 1H, SCH), 2.40-2.31 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.8 (*ipso*-Ph), 128.6 (Ph), 128.0 (Ph), 127.0 (Ph), 111.4 (OCO), 65.2 (OCH_2), 65.1 (OCH_2), 59.9 (SCH_2), 53.4 (SCH_2), 48.1 (NCH_2), 34.3 (CH_2); MS (ESI) *m/z* 268 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{13}H_{17}NO_3S$ $(M + H)^+$ 268.1003, found 268.1002 (–0.3 ppm error).

Lab book reference: **HS-1-19**

Attempted synthesis of 1-(benzylimino)-1λ⁶-thiolane-1,3-dione 164



163 **164**

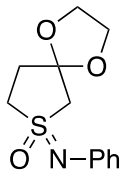
A solution of *N*-Bn sulfoximine **163** (38 mg, 0.14 mmol, 1.0 eq.) and 3 M $HCl_{(aq)}$ (0.5 mL) in THF (0.5 mL) was stirred under Ar at 50 °C for 2 h. After being allowed to cool to rt, sat. $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the two layers were separated. The aqueous layer 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 which contained only starting *N*-Bn sulfoximine **163** and none of the desired keto sulfoximine **164** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-23**

A solution of *N*-Bn sulfoximine **163** (170 mg, 0.64 mmol, 1.0 eq.) in 3 M $HCl_{(aq)}$ (6.5 mL) was stirred at rt for 64 h. Then, sat. $Na_2CO_{3(aq)}$ (15 mL) and CH_2Cl_2 (15 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (3 x 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired keto sulfoximine **164** (by ^{1}H NMR spectroscopy and mass spectrometry).

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

7-(Phenylimino)-1,4-dioxa-7λ⁶-thiaspiro[4.4]nonan-7-one 165

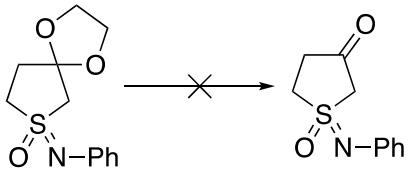


165

A solution of ketal sulfoximine **160** (180 mg, 1.0 mmol, 1.0 eq.), phenylboronic acid (281 mg, 2.30 mmol, 2.3 eq.) and $Cu(OAc)_2$ (18 mg, 0.10 mmol, 0.1 eq.) in MeOH (3.3 mL) in a 100 mL round-bottomed flask capped with a $CaCl_2$-drying tube was stirred at rt for 16 h. CH_2Cl_2 (5 mL) was added and the mixture was washed with water (5 mL), sat. $NaHCO_{3(aq)}$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 1:1 and then 7:3 EtOAc-hexane as eluent gave *N*-Ph ketal sulfoximine **165** (120 mg, 63%) as an orange oil, R_F (7:3 EtOAc-hexane) 0.37; IR (ATR) 2926, 1444, 1397, 1278, 1119, 987, 820, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 7.5, 7.5 Hz, 2H, Ph), 7.06 (d, J = 7.5 Hz, 2H, Ph), 6.98 (t, J = 7.5 Hz, 1H, Ph), 4.08-3.93 (m, 4H, OCH), 3.66 (ddd, J = 13.0, 6.5, 6.5 Hz, 1H, SCH), 3.51 (d, J = 13.5 Hz, 1H, SCH), 3.43-3.38 (m, 1H, SCH), 3.35 (d, J = 13.5 Hz, 1H, SCH), 2.48-2.42 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.4 (*ipso*-Ph), 129.4 (Ph), 123.0 (Ph), 122.3 (Ph), 111.5 (OCO), 65.4 (OCH_2), 65.2 (OCH_2), 59.4 (SCH_2), 53.2 (SCH_2), 34.6 (CH_2); MS (ESI) *m/z* 254 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NO_3S$ $(M + H)^+$ 254.0845, found 254.0843 (+1.1 ppm error).

Lab book reference: **HS-1-27**

Attempted synthesis of 1-(phenylimino)-1λ⁶-thiolane-1,3-dione 166



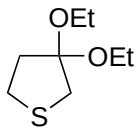
165 **166**

A solution of *N*-Ph sulfoximine **165** (81 mg, 0.32 mmol, 1.0 eq.) in 3 M $HCl_{(aq)}$ (3.2 mL) was stirred at 110 °C for 90 min. After being allowed to cool to rt, sat. $Na_2CO_{3(aq)}$ was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to the

crude product which contained only starting *N*-Ph sulfoximine **165** and none of the desired keto sulfoximine **166** (by ^{1}H NMR spectroscopy and mass spectrometry).

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

3,3-Diethoxythiolane 167

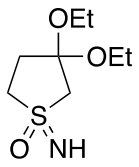


167

A solution of tetrahydrothiophen-3-one **79** (510 mg, 5.0 mmol, 1.0 eq.), triethyl orthoformate (740 mg, 5.0 mmol, 1.0 eq.) and *p*-toluenesulfonic acid (20 mg, 0.58 mmol, 0.023 eq.) in EtOH (10 mL) was stirred at rt for 21 h. The solvent was evaporated and Et_2O (20 mL) and $NaHCO_{3(aq)}$ (20 mL) were added. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give diethoxy ketal sulfide **167** (710 mg, 81%) as a yellow oil, IR (ATR) 2974, 2933, 2383, 1442, 1315, 1220, 1051, 953, 755, 685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59-3.48 (m, 4H, OCH_2), 2.92 (s, 2H, CH_2), 2.84-2.79 (m, 2H, CH_2), 2.16-2.12 (m, 2H, CH_2), 1.21 (t, J = 7.0 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 111.1 (OCO), 57.8 (OCH_2), 36.8 (CH_2), 36.4 (CH_2), 27.3 (CH_2), 15.6 (Me); HRMS (ESI) *m/z* unsuccessful.

Lab book reference: **HS-1-34**

3,3-Diethoxy-1-imino-1λ⁶-thiolan-1-one 168



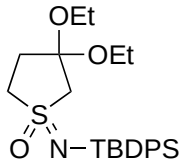
168

A solution of diethoxy ketal sulfide **167** (120 mg, 0.68 mmol, 1.0 eq.), (diacetoxyiodo)benzene (548 mg, 1.70 mmol, 2.5 eq.) and ammonium carbamate (107 mg, 1.36 mmol, 2.0 eq.) in MeOH (1.5 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 diethoxy ketal sulfoximine **168** (67 mg, 47%) as a yellow oil, R_F (95:5 EtOAc-MeOH) 0.51; IR (ATR)

3271 (NH), 2977, 1446, 1408, 1213, 1047, 994, 877, 771, 529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54-3.44 (m, 4H, OCH), 3.42 (d, J = 13.0 Hz, 1H, SCH), 3.33 (d, J = 13.0 Hz, 1H, SCH), 3.31-3.25 (m, 2H, SCH), 2.54-2.37 (m, 2H, CH), 1.22-1.18 (m, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 104.9 (OCO), 63.5 (SCH_2), 57.8 (OCH_2), 57.6 (OCH_2), 55.1 (SCH_2), 32.6 (CH_2), 15.2 (Me); MS (ESI) *m/z* 208 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_8H_{17}NO_3S$ $(M + H)^+$ 208.0999, found 208.1002 (+1.4 ppm error).

Lab book reference: **HS-1-29**

1-[(*tert*-Butyldiphenylsilyl)imino]-3,3-diethoxy-1λ⁶-thiolan-1-one 169

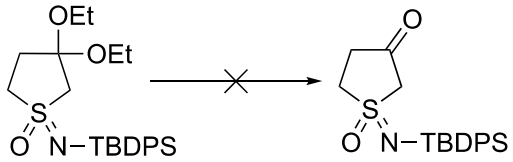


169

TBDPSCl (0.31 mL, 1.2 mmol, 1.25 eq.) was added dropwise to a stirred solution of diethoxy ketal sulfoximine **168** (200 mg, 0.96 mmol, 1.0 eq.) and imidazole (131 mg, 1.92 mmol, 2.0 eq.) in DMF (1.5 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 48 h. After being allowed to cool to rt, water (10 mL) and Et_2O (10 mL) were added. 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 × 20 mL), 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 *N*-TBDPS sulfoximine **169** (330 mg, 77%) as a colourless oil, R_F (7:3 hexane-EtOAc) 0.58; IR (ATR) 1316, 1109, 703, 501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.70 (m, 4H, Ph), 7.40-7.32 (m, 6H, Ph), 3.52-3.31 (m, 4H, OCH), 3.17 (d, J = 13.0 Hz, 1H, SCH), 3.11 (d, J = 13.0 Hz, 1H, SCH), 3.11-2.95 (m, 2H, SCH), 2.37-2.26 (m, 2H, CH), 1.16 (t, J = 7.0 Hz, 6H, Me), 1.06 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.3 (*ipso*-Ph), 135.7 (Ph), 129.3 (Ph), 127.6 (Ph), 104.5 (OCO), 64.3 (SCH_2), 57.7 (OCH_2), 57.2 (OCH_2), 56.3 (SCH_2), 32.2 (CH_2), 27.2 (CMe_3), 19.3 (CMe_3), 15.3 (Me); MS (ESI) *m/z* 446 $(M + H)^+$; HRMS (ESI) m/z calcd for $C_{24}H_{35}NO_3SSi$ $(M + H)^+$ 446.2180, found 446.2185 (–1.1 ppm error).

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

Attempted synthesis of 1-[(*tert*-butyldiphenylsilyl)imino]- 1λ⁶-thiolane-1,3-dione 146



169 **146**

A solution of *N*-TBDPS sulfoximine **169** (110 mg, 0.24 mmol, 1.0 eq.) and conc. $H_2SO_{4(aq)}$ (0.01 mL, 0.2 mmol, 0.78 eq.) in acetone (2.5 mL) was stirred and heated at 56 °C for 1 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure and CH_2Cl_2 (10 mL) and sat. $NaHCO_{3(aq)}$ (10 mL) were added. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **169** and none of the desired keto sulfoximine **146** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-43**

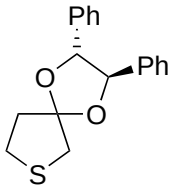
A solution of *N*-TBDPS sulfoximine **169** (110 mg, 0.24 mmol, 1.0 eq.) and pyridinium *p*-toluenesulfonate (20 mg, 0.08 mmol, 0.33 eq.) in acetone (2.5 mL) was stirred and heated at 56 °C for 3 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure and CH_2Cl_2 (10 mL) and sat. $NaHCO_{3(aq)}$ (10 mL) were added. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **169** and none of the desired keto sulfoximine **146** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-44**

A solution of *N*-TBDPS sulfoximine **169** (110 mg, 0.24 mmol, 1.0 eq.) and *p*-toluenesulfonic acid (10 mg, 0.06 mmol, 0.24 eq.) in acetone (2.5 mL) was stirred at rt for 16 h. The solvent was evaporated under reduced pressure and CH_2Cl_2 (10 mL) and sat. $NaHCO_{3(aq)}$ (10 mL) were added. The two layers were separated and the organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained starting *N*-TBDPS sulfoximine **169** and none of the desired keto sulfoximine **146** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **HS-1-45**

(*2R,3R*)-2,3-Diphenyl-1,4-dioxa-7-thiaspiro[4.4]nonane (*R,R*)-171

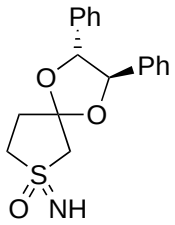


(*R,R*)-**171**

A solution of tetrahydrothiophen-3-one **79** (0.30 mL, 3.5 mmol, 1.0 eq.), diol (*R,R*)-**170** (900 mg, 4.20 mmol, 1.2 eq.) and *p*-toluenesulfonic acid (9 mg, 0.04 mmol, 0.01 eq.) in toluene (80 mL) was stirred and heated at 110 °C with a Dean-Stark water separator attached for 24 h. The solution was allowed to cool to rt and washed with sat. $NaHCO_{3(aq)}$ (40 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (40 mL), 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 6:4 hexane-EtOAc as eluent gave ketal sulfide (*R,R*)-**171** (800 mg, 87%) as a white solid, mp 74-76 °C, R_F (9:1 hexane-EtOAc) 0.56; $[\alpha]^{25}_D$ = –65.8 (*c* 1.0, CH_2Cl_2); IR (ATR) 1454, 1233, 1109, 1019, 753, 534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 6H, Ph), 7.23-7.21 (m, 4H, Ph), 4.80 (d, *J* = 8.5 Hz, 1H, OCH), 4.77 (d, *J* = 8.5 Hz, 1H, OCH), 3.25 (d, *J* = 11.0 Hz, 1H, SCH), 3.16 (d, *J* = 11.0 Hz, 1H, SCH), 3.06-2.96 (m, 2H, SCH), 2.45-2.32 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.26 (*ipso*-Ph), 136.18 (*ipso*-Ph), 128.67 (Ph), 128.64 (Ph), 126.82 (Ph), 126.74 (Ph), 118.7 (OCO), 86.1 (OCH), 85.8 (OCH), 38.9 (CH_2), 38.1 (CH_2), 27.1 (CH_2) (two Ph resonances not resolved); MS (ESI) *m/z* 321 $(M + Na)^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}O_2S$ $(M + Na)^+$ 321.0920, found 321.0915 (+1.4 ppm error).

Lab book reference: **HS-2-40**

(*2R,3R*)-7-Imino-2,3-diphenyl-1,4-dioxa-7λ^6-thiaspiro[4.4]nonan-7-ones 172

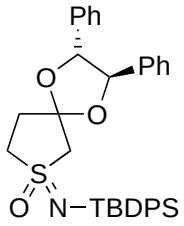


(*R,R*)-**172**

A solution of ketal sulfide (*R,R*)-**171** (170 mg, 0.58 mmol, 1.0 eq.), (diacetoxyiodo)benzene (461 mg, 1.43 mmol, 2.5 eq.) and ammonium carbamate (91 mg, 1.2 mmol, 2.0 eq.) in MeOH (1.8 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 9:1 EtOAc-MeOH as eluent gave a 70:30 mixture of diastereomeric ketal sulfoximines (*R,R*)-**172** (140 mg, 71%) as a white oil, R_F (9:1 EtOAc-MeOH) 0.63; IR (ATR) 3034 (NH), 1496, 1455, 1320, 1282, 1230, 1107, 764, 534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 6H, Ph), 7.23-7.16 (m, 4H, Ph), 4.85 (d, J = 8.5 Hz, 1H, OCH), 4.78 (d, J = 8.5 Hz, 0.7H, OCH), 4.77 (d, J = 8.5 Hz, 0.3H, OCH), 3.75-3.58 (m, 2H, SCH), 3.52-3.47 (m, 2H, SCH), 2.82-2.70 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.3 (*ipso*-Ph), 135.2 (*ipso*-Ph), 135.12 (*ipso*-Ph), 135.06 (*ipso*-Ph), 129.0 (Ph), 128.9 (Ph), 128.82 (Ph), 128.79 (Ph), 126.9 (Ph), 126.6 (Ph), 112.0 (OCO), 111.9 (OCO), 86.1 (OCH), 86.0 (OCH), 85.87 (OCH), 85.85 (OCH), 64.4 (SCH_2), 55.7 (SCH_2), 55.6 (SCH_2), 36.2 (CH_2) (two Ph resonances, one SCH_2 and one CH_2 resonances not resolved); MS (ESI) *m/z* 330 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3S$ $(M + H)^+$ 330.1158, found 330.1165 (–2.0 ppm error).

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

(*2R,3R*)-7-[(*tert*-Butyldiphenylsilyl)imino]-2,3-diphenyl-1,4-dioxa-7λ^6-thiaspiro[4.4]nonan-7-ones 173

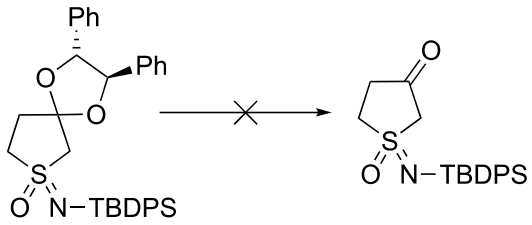


(*R,R*)-**173**

TBDPSCl (0.30 mL, 0.32 mmol, 1.25 eq.) was added dropwise to a stirred solution of a 70:30 mixture of diastereomeric ketal sulfoximines (*R,R*)-**172** (310 mg, 0.94 mmol, 1.0 eq.) and imidazole (128 mg, 1.88 mmol, 2.0 eq.) in DMF (1 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 60 h. The solution was allowed to cool to rt and then water (10 mL) and Et_2O (10 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1, 8:2 and then 7:3 hexane-EtOAc as eluent gave a 55:45 mixture of diastereomeric *N*-TBDPS ketal sulfoximines (*R,R*)-**173** (160 mg, 29%) as a white oil, R_F (7:3 hexane-EtOAc) 0.54; IR (ATR) 3069, 2930, 1315, 1101, 908, 730, 697, 499 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.75 (m, 4H, Ph), 7.44-7.30 (m, 12H, Ph), 7.25-7.20 (m, 2H, Ph), 7.16-7.13 (m, 2H, Ph), 4.81 (d, J = 8.5 Hz, 1H, OCH), 4.70 (d, J = 8.5 Hz, 0.45H, OCH), 4.65 (d, J = 8.5 Hz, 0.55H, OCH), 3.53-3.21 (m, 4H, SCH), 2.75-2.55 (m, 2H, CH), 1.15 (s, 4H, CMe_3), 1.12 (s, 5H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 136.05 (*ipso*-Ph), 136.02 (*ipso*-Ph), 135.99 (*ipso*-Ph), 135.94 (*ipso*-Ph), 135.69 (Ph), 135.64 (Ph), 135.45 (*ipso*-Ph), 135.40 (*ipso*-Ph), 135.31 (*ipso*-Ph), 135.29 (*ipso*-Ph), 134.91 (Ph), 129.70 (Ph), 129.30 (Ph), 129.27 (Ph), 128.91 (Ph), 128.88 (Ph), 128.79 (Ph), 128.72 (Ph), 128.70 (Ph), 128.64 (Ph), 127.80 (Ph), 127.68 (Ph), 127.64 (Ph), 126.81 (Ph), 126.75 (Ph), 126.63 (Ph), 126.55 (Ph), 111.71 (OCO), 111.62 (OCO), 86.04 (OCH), 85.66 (OCH), 85.63 (OCH), 64.99 (SCH_2), 64.50 (SCH_2), 56.92 (SCH_2), 56.85 (SCH_2), 35.76 (CH_2), 35.70 (CH_2), 27.16 (C*Me*$_3$), 27.12 (C*Me*$_3$), 26.67, 19.31 (*C*Me$_3$), 19.28 (*C*Me$_3$) (five Ph resonances and one OCH resonance not resolved); MS (ESI) *m/z* 568 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{34}H_{37}NO_3SSi$ $(M + H)^+$ 568.2336, found 568.2346 (–1.8 ppm error).

Lab book reference: **HS-2-45**

Attempted synthesis of 1-[(*tert*-butyldiphenylsilyl)imino]-1λ⁶-thiolane-1,3-dione 146

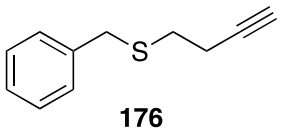


(*R*,*R*)-**173** **146**

10% Pd/C (100 mg, 0.09 mmol) was added to a stirred solution of a 55:45 mixture of diastereomeric ketal *N*-TBDPS sulfoximines (*R*,*R*)-**173** (130 mg, 0.22 mmol, 1.0 eq.) in MeOH (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The resulting mixture was stirred under a balloon of H_2 for 16 h. The solids were removed by filtration through Celite and washed with MeOH (2 × 30 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained some starting sulfoximines (*R*,*R*)-**173** (by ^{1}H NMR spectroscopy). Then, 10% Pd/C (100 mg, 0.09 mmol) was added to a stirred solution of the crude product in MeOH (2 mL) at rt under Ar. The reaction flask was evacuated under reduced pressure and back-filled with Ar three times and then with H_2 three times. The resulting mixture was stirred under a balloon of H_2 for 16 h. The solids were removed by filtration through Celite and washed with MeOH (2 × 30 mL). The filtrate was evaporated under reduced pressure to give the crude product which contained none of the desired keto sulfoximine **146** (by ^{1}H NMR spectroscopy).

Lab book reference: **HS-2-50**

[(But-3-yn-1-ylsulfanyl)methyl]benzene 176



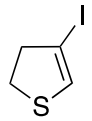
176

A 0.5 M NaOH solution in MeOH (24 mL) was added dropwise to a stirred solution of 4-bromo-1-butyne (1.15 mL, 12.3 mmol, 1.0 eq.) in MeOH (62 mL) at 0 °C. Then, a solution of benzyl thioacetate **70** (2.08 g, 12.4 mmol, 1.01 eq.) in MeOH (24 mL) was added. The resulting solution was stirred at rt for 24 h. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to the crude product. Purification by flash column

chromatography on silica with 9:1 hexane-EtOAc as eluent gave alkyne sulfide **176** (1.85 g, 86%) as a colourless oil, R_F (9:1 hexane-EtOAc) 0.53; IR (ATR) 3292 (≡CH), 2921, 1494, 1286, 700, 641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H, Ph), 3.77 (s, 2H, SCH_2), 2.59 (t, J = 7.0 Hz, 2H, SCH_2), 2.43 (td, J = 7.0, 2.5 Hz, 2H, CH_2), 2.02 (t, J = 2.5 Hz, 1H, ≡CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.2 (*ipso*-Ph), 129.0 (Ph), 128.7 (Ph), 127.2 (Ph), 82.8 (*C*≡CH), 69.6 (C≡*C*H), 36.4 (S*C*H_2Ph), 30.0 (SCH_2), 19.7 (CH_2); MS (APCI) *m/z* 177 $(M + H)^+$; HRMS (APCI) *m/z* calcd for $C_{11}H_{12}S$ $(M + H)^+$ 177.0732, found 177.0738 (+3.0 ppm error). Spectroscopic data consistent with those reported in the literature.[43]

Lab book reference: **HS-2-34**

4-Iodo-2,3-dihydrothiophene 177

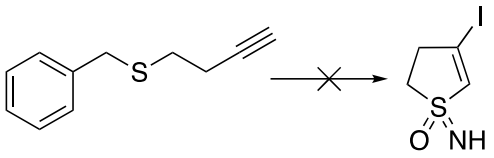


177

Iodine (279 mg, 1.10 mmol, 1.0 eq.) was added to a stirred solution of alkyne sulfide **176** (195 mg, 1.10 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solvent was evaporated under reduced pressure to give the crude product (252 mg) as a brown oil which contained a 50:50 mixture of iodo vinyl sulfide **177** and benzyl iodide (by ^1H NMR spectroscopy). Diagnostic signals for iodo vinyl sulfide **177**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (t, J = 2.0 Hz, 1H, =CH), 3.27 (t, J = 8.5 Hz, 2H, SCH_2), 2.93 (td, J = 8.5, 2.0 Hz, 2H, CH_2); R_F (7:3 hexane-EtOAc) 0.38; IR (ATR) 2926, 2859, 1728, 906, 730 cm^{-1}; diagnostic signal for benzyl iodide: ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H, ICH_2).

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

Attempted synthesis of 1-imino-4-iodo-2,3-dihydro-1λ⁶-thiophen-1-one 179

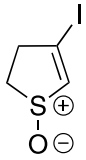


176 **179**

Iodine (279 mg, 1.10 mmol, 1.0 eq.) was added to a stirred solution of alkyne sulfide **176** (195 mg, 1.10 mmol, 1.0 eq.) in CH_2Cl_2 (6 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, a solution of (diacetoxyiodo)benzene (886 mg, 2.75 mmol, 2.5 eq.) and ammonium carbamate (173 mg, 2.20 mmol, 2.0 eq.) in MeOH (2.2 mL) was added and the resulting solution 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 7:3 hexane-CH_2Cl_2 as eluent gave a 60:40 mixture of benzyl iodide and iodo vinyl sulfide **177** (101 mg, i.e. 33 mg (28%) of iodo vinyl sulfide **177** and 68 mg (56%) of benzyl iodide) (by ^{1}H NMR spectroscopy) as a colourless oil. There was no evidence of formation of the desired sulfoximine **179** (by ^{1}H NMR spectroscopy and mass spectrometry).

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

4-Iodo-2,3-dihydro-1λ⁴-thiophen-1-one 180



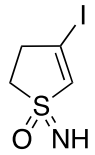
180

Iodine (432 mg, 1.70 mmol, 1.0 eq.) was added to a stirred solution of alkyne sulfide **176** (300 mg, 1.70 mmol, 1.0 eq.) in CH_2Cl_2 (9 mL) at rt under Ar. The resulting solution was stirred at rt for 16 h. Then, the solution was cooled to –78 °C and a solution of *m*CPBA (381 mg of ≥77% purity *m*CPBA, approx. 1.70 mmol, 1.0 eq.) in CH_2Cl_2 (5 mL) was added dropwise at –78 °C. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. Sat. $Na_2S_2O_{3(aq)}$ (20 mL) was added and the mixture was stirred for 15 min. The two layers were separated and the organic layer was washed with sat. $NaHCO_{3(aq)}$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and 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 iodo vinyl sulfoxide **180** (140 mg, 70%) as a brown oil, R_F (8:2 EtOAc-MeOH) 0.47; IR (ATR) 1573, 1429, 1300, 1029, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, J = 2.0, 2.0 Hz, 1H, =CH), 3.62 (dddd, J = 18.0, 8.0, 6.0, 2.0 Hz, 1H, CH), 3.33 (ddd, J = 14.0, 8.5, 6.0 Hz, 1H, SCH), 3.09 (dddd, J = 18.0, 8.5, 3.0, 2.0 Hz, 1H, CH), 2.92 (ddd, J = 14.0, 8.0, 3.0 Hz, 1H, SCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.0 (C=*C*H), 110.3 (I*C*=C), 52.7 (CH_2), 45.1 (CH_2); MS (ESI) *m/z* 228 $(M + H)^+$; HRMS (ESI) *m/z* calcd for C_4H_5IOS $(M + H)^+$ 228.9179, found 228.9175 (+1.5 ppm error).

Lab book reference: **HS-2-41**

1-Imino-4-iodo-2,3-dihydro-1λ^6-thiophen-1-one 179

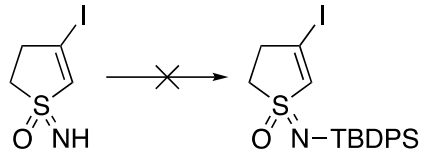


179

A solution of iodo vinyl sulfoxide **180** (130 mg, 0.58 mmol, 1.0 eq.), (diacetoxyiodo)benzene (564 mg, 1.75 mmol, 3.0 eq.) and ammonium carbamate (183 mg, 2.33 mmol, 4.0 eq.) in MeOH (4 mL) was stirred at rt under Ar for 18 h. 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 an 80:20 mixture of iodo vinyl sulfoximine **179** and iodo vinyl sulfoxide **180** (89 mg, i.e. 73 mg (52%) of iodo vinyl sulfoximine **179** and 17 mg (13% recovered) of iodo vinyl sulfoxide **180**) (by ^1H NMR spectroscopy) as a brown oil. Diagnostic signals for iodo vinyl sulfoximine **179**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, J = 2.0, 2.0 Hz, 1H, =CH), 3.49-3.34 (m, 2H, SCH), 3.29-3.25 (m, 2H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 141.6 (C=*C*H), 127.6 (I*C*=C), 54.3 (SCH_2), 39.8 (CH_2); R_F (9:1 CH_2Cl_2-MeOH) 0.34; IR (ATR) 3348 (NH), 2871, 1380, 1128, 950, 908 cm^{-1}; MS (ESI) *m/z* 243 $(M + H)^+$; HRMS (ESI) *m/z* calcd for C_4H_6INOS $(M + H)^+$ 243.9288, found 243.9288 (–0.4 ppm error).

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

Attempted synthesis of 1-[(*tert*-butyldiphenylsilyl)imino]-4-iodo-2,3-dihydro-1λ^6-thiophen-1-one 13

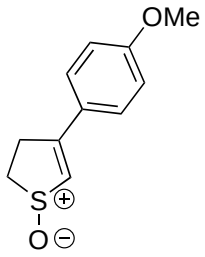


179 **13**

TBDPSCl (0.12 mL, 0.46 mmol, 1.5 eq.) was added dropwise to a stirred solution of an 80:20 mixture of iodo vinyl sulfoximine **179** and iodo vinyl sulfoxide **180** (89 mg, i.e. 73 mg of iodo vinyl sulfoximine **179**, 0.30 mmol, 1.0 eq.) and imidazole (50 mg, 0.73 mmol, 2.4 eq.) in DMF (0.5 mL) at rt under Ar. The resulting solution was stirred and heated at 90 °C for 60 h. The solution was allowed to cool to rt and then water (10 mL) and Et_2O (10 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (5 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a complex mixture of products which contained none of the desired *N*-TBDPS sulfoximine **13** (by ^{1}H NMR spectroscopy and mass spectrometry).

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

4-(4-Methoxyphenyl)-2,3-dihydro-1λ^4-thiophen-1-one 185



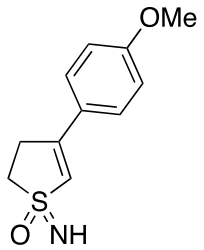
185

Iodo vinyl sulfoxide **180** (250 mg, 1.10 mmol, 1.0 eq.), Cs_2CO_3 (717 mg, 2.20 mmol, 2.0 eq.), 4-methoxyphenylboronic acid (249 mg, 1.64 mmol, 1.5 eq.), $Pd(OAc)_2$ (12 mg, 0.055 mmol, 0.05 eq.) and SPhos (45 mg, 0.11 mmol, 0.1 eq.) were added to a flask. The flask was evacuated and refilled with Ar. Then, toluene (8.8 mL) was added and the resulting solution was stirred and heated at 50 °C under Ar for 16 h. After being allowed to cool to rt, water (15 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (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 9:1 EtOAc-MeOH as eluent gave β-aryl sulfoxide **185** (160 mg, 69%) as a yellow solid, mp 106-108 °C, R_F (8:2 EtOAc-MeOH) 0.55; IR (ATR) 2927, 1606, 1512, 1256, 1025, 904, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 9.0 Hz, 2H, Ar), 6.93 (d, J = 9.0 Hz, 2H, Ar), 6.86 (dd, J = 2.0, 2.0 Hz, 1H, =CH), 3.85 (s, 3H, OMe), 3.69 (dddd, J = 17.0, 8.0, 6.0, 2.0 1H, CH), 3.47 (ddd, J = 14.0, 8.0, 6.0 Hz, 1H, SCH), 3.18 (dddd, J = 17.0, 8.0, 3.0, 2.0, 1H, CH), 3.09 (ddd, J = 14.0, 8.0, 3.0 Hz, 1H, SCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.4 (=*C*Ar), 154.5 (*ipso*-Ar), 129.0 (Ar), 125.8 (Ar), 125.2 (Ar), 114.4 (C=*C*H), 55.5 (OMe), 51.2 (SCH_2), 33.7 (CH_2); MS (ESI) *m/z* 209 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{11}H_{12}O_2S$ $(M + H)^+$ 209.0631, found 209.0627 (+1.6 ppm error).

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

1-Imino-4-(4-methoxyphenyl)-2,3-dihydro-1λ^6-thiophen-1-one 186



186

A solution of β-aryl sulfoxide **185** (140 mg, 0.67 mmol, 1.0 eq.), (diacetoxyiodo)benzene (650 mg, 2.0 mmol, 3.0 eq.) and ammonium carbamate (211 mg, 2.68 mmol, 4.0 eq.) in MeOH (4.6 mL) was stirred at rt for 16 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 β-aryl sulfoximine **186** (95 mg, 63%) as a colourless oil, R_F (8:2 EtOAc-MeOH) 0.47; IR (ATR) 3267 (NH), 3072, 2937, 1605, 1513, 1254, 1182, 1000, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 9.0 Hz, 2H, Ar), 6.93 (d, J = 9.0 Hz, 2H, Ar), 6.78 (dd, J = 2.0, 2.0 Hz, 1H, =CH), 3.84 (s, 3H, OMe), 3.58-3.49 (m, 2H, SCH), 3.28-3.23 (m, 2H, SCH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.7 (=*C*Ar), 147.9 (*ipso*-Ar), 128.2 (Ar), 125.3 (C=*C*H), 125.2 (Ar), 114.5 (Ar), 55.6 (OMe), 53.5 (SCH_2), 28.3 (CH_2); MS (ESI) *m/z* 224 $(M + H)^+$; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO_2S$ $(M + H)^+$ 224.0740, found 224.0740 (–0.2 ppm error).

Lab book reference: **HS-2-53**

6. References

(1) Bentley, H. R. *R. Soc. London Ser. B* **1951**, *138*, 265.

(2) Zhu, Y.; Loso, M. R.; Watson, G. B.; Sparks, T. C.; Rogers, R. B.; Huang, J. X.; Gerwick, B. C.; Babcock, J. M.; Kelley, D.; Hegde, V. B.; Nugent, B. M.; Renga, J. M.; Denholm, I.; Gorman, K.; Deboer, G. J.; Hasler, J.; Meade, T.; Thomas, J. D. *J. Agric. Food Chem.* **2011**, *59*, 2950–2957.

(3) Lücking, U. *Angew. Chem., Int. Ed.* **2013**, *52*, 9399–9408.

(4) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341–347.

(5) Wang, M.; Jiang, X. *Sulfur–Sulfur Bond Construction* in Topics in Current Chemistry 2018, Vol. 376.

(6) Zenzola, M.; Doran, R.; Degennaro, L.; Luisi, R.; Bull, J. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 7203–7207.

(7) Goldberg, F. W.; Kettle, J. G.; Xiong, J.; Lin, D. *Tetrahedron* **2014**, *70*, 6613–6622.

(8) Frings, M.; Bolm, C.; Blum, A.; Gnamm, C. *Eur. J. Med. Chem.* **2017**, *126*, 225–245.

(9) Siemeister, G.; Lücking, U.; Wengner, A. M.; Lienau, P.; Steinke, W.; Schatz, C.; Mumberg, D.; Ziegelbauer, K. *Mol. Cancer Ther.* **2012**, *11*, 2265–2273.

(10) Reck, M.; Horn, L.; Novello, S.; Barlesi, F.; Albert, I.; Juhász, E.; Kowalski, D.; Robinet, G.; Cadranel, J.; Bidoli, P.; Chung, J.; Fritsch, A.; Drews, U.; Wagner, A.; Govindan, R. *J. Thorac. Oncol.* **2019**, *14*, 701–711.

(11) Bahleda, R.; Gazzah, A.; Varga, A.; Rajagopalan, P.; Henderson, D. A.; Kornacker, M. *J. Clin. Oncol.* **2012**, *30*, 3012.

(12) Lücking, U.; Jautelat, R.; Krüger, M.; Brumby, T.; Lienau, P.; Schäfer, M.; Briem, H.; Schulze, J.; Hillisch, A.; Reichel, A.; Wengner, A. M.; Siemeister, G. *ChemMedChem* **2013**, *8*, 1067–1085.

(13) Foote, K. M.; Nissink, J. W. M.; McGuire, T.; Turner, P.; Guichard, S.; Yates, J. W. T.; Lau, A.; Blades, K.; Heathcote, D.; Odedra, R.; Wilkinson, G.; Wilson, Z.; Wood, C. M.; Jewsbury, P. J. *J. Med. Chem.* **2018**, *61*, 9889–9907.

(14) Ding, X.; Rose, J. P.; Van Gelder, J. *Int. J. Pharm.* **2012**, *427*, 260–269.

(15) Mutai, P.; Breuzard, G.; Pagano, A.; Allegro, D.; Peyrot, V.; Chibale, K. *Bioorg. Med. Chem.* **2017**, *25*, 1652–1665.

(16) Reggelin, M.; Zur, C. *Synthesis.* **2000**, 1–64.

(17) Sparks, T. C.; Watson, G. B.; Loso, M. R.; Geng, C.; Babcock, J. M.; Thomas, J. D. *Pestic. Biochem. Physiol.* **2013**, *107*, 1–7.

(18) Hartley, G. *α-Functionalisation of Cyclic Sulfoximines via Lithiation-Trapping*; MSc Thesis, University of York, 2018.

(19) Hartley, G. *Unpublished Results*; University of York, 2019.

(20) Hindle, A. *Lithiation and Trapping of Acyclic Sulfoximines: Scope and Diastereoselectivity*; MSc Thesis, University of York, 2019.

(21) Pandey, A. G.; McGrath, M. J.; Mancheño, O. G.; Bolm, C. *Synthesis.* **2011**, 3827–3838.

(22) Zhou, G.; Ting, P. C.; Aslanian, R. G. *Tetrahedron Lett.* **2010**, *51*, 939–941.

(23) Lim, K.; Hayashi, T. *J. Am. Chem. Soc.* **2015**, *137*, 3201–3204.

(24) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093–2105.

(25) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4230.

(26) Tian, P.; Dong, H. Q.; Lin, G. Q. *ACS Catal.* **2012**, *2*, 95–119.

(27) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.

(28) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058.

(29) Kamikawa, K.; Tseng, Y.-Y.; Jian, J.-H.; Takahashi, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2017**, *139*, 2020.

(30) Wang, J.; Wang, M.; Cao, P.; Jiang, L.; Chen, G.; Liao, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6673–6677.

(31) Jin, S. S.; Wang, H.; Xu, M. H. *Chem. Commun.* **2011**, *47*, 7230–7232.

(32) Mauleón, P.; Carretero, J. C. *Org. Lett.* **2004**, *6*, 3195–3198.

(33) Mauleón, P.; Carretero, J. C. *Chem. Commun.* **2005**, 4961–4963.

(34) Mauleón, P.; Alonso, I.; Rivero, M. R.; Carretero, J. C. *J. Org. Chem.* **2007**, *72*, 9924–9935.

(35) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.

(36) Nishimura, T.; Takiguchi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 9086–9089.

(37) Zilaout, H.; Van Den Hoogenband, A.; De Vries, J.; Lange, J. H. M.; Terpstra, J. W. *Tetrahedron Lett.* **2011**, *52*, 5934–5939.

(38) Syu, J.-F.; Gopula, B.; Jian, J.-H.; Li, W.-S.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Hsieh, M.-C.; Tsai, M.-K.; Wu, H.-L. *Org. Lett.* **2019**, *21*, 4614–4618.

(39) Zerilli, T.; Ocheretyaner, E. *P&T* **2015**, *40*, 495–500.

(40) Takechi, R.; Nishimura, T. *Chem. Commun.* **2015**, *51*, 8528–8531.

(41) Moku, B.; Fang, W.-Y.; Leng, J.; Assen, E.; Kantchev, B.; Qin, H.-L. *ACS Catal.* **2019**, *9*, 10477–10488.

(42) Kuhn, H. J.; Defoin, R.; Gollnick, K.; Y, C. K.; Liu, H. T. L.; Beizb, P. *Tetrahedron* **1989**, *45*, 1667–1677.

(43) Ren, X. F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468–6483.

(44) Tota, A.; Zenzola, M.; Chawner, S. J.; St John-Campbell, S.; Carlucci, C.; Romanazzi, G.; Leonardo Degennaro, C.; Bull, J. A.; Luisi, R. *Chem. Commun.* **2017**, *53*, 348.

(45) Borgati, T. F.; Alves, R. B.; Teixeira, R. R.; De Freitas, R. P.; Perdigão, T. G.; Da Silva, S. F.; Aparecida, A.; Santos, D.; De, A.; Bastidas, J. O. *Artic. J. Braz. Chem. Soc.* **2013**, *24*, 953–961.

(46) Olivito, F.; Costanzo, P.; Di Gioia, M. L.; Nardi, M.; Oliverio, M.; Procopio, A. *Org. Biomol. Chem.* **2018**, *16*, 7753–7759.

(47) Konuki, K.; Nagai, H. *Tetrahedron Asymmetry* **2014**, *25*, 1581–1589.

(48) McGrath, M.; Bolm, C. *Beilstein J. Org. Chem.* **2007**, *3*.

(49) Martin, R.; Buchwald, S. L. *Acc Chem Res.* **2008**, *41*, 1461–1473.

(50) Vyvyan, J. R.; Peterson, E. A.; Stephan, M. L. *Tetrahedron Lett.* **1999**, *40*, 4947–4949.

(51) Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 49–58.

(52) Lima, C. F. R. A. C.; Rodrigues, A. S. M. C.; Silva, V. L. M.; Silva, A. M. S.; Santos, L. M. N. B. F. *ChemCatChem* **2014**, *6*, 1291–1302.

(53) Mu, Y. Q.; Eubanks, L. M.; Poulter, C. D.; Gibbs, R. A. *Bioorg. Med. Chem.* **2002**, *10*, 1207–1219.

(54) Biftu, T.; Scapin, G.; Singh, S.; Feng, D.; Becker, J. W.; Eiermann, G.; He, H.; Lyons, K.; Patel, S.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Wu, J.; Zhang, X.; Doss, G. A.; Thornberry, N. A.; Weber, A. E. *Bioorg. Med. Chem.* **2007**, *17*, 3384–3387.

(55) Zhang, Z.; Wolkerstorfer, A.; Szolar, O.; Handler, N.; Buschmann, H.; Cusack, S.; Smith, M.; So, S.-S.; Hawley, R. C.; Sidduri, A. US2014/194431A1, **2014**.

(56) Seefeld, M. A.; Lin, H.; Holenz, J.; Downie, D.; Donovan, B.; Fu, T.; Pasikanti, K.; Zhen, W.; Cato, M.; Chaudhary, K. W.; Brady, P.; Bakshi, T.; Morrow, D.; Rajagopal, S.; Samanta, S. K.; Madhyastha, N.; Kuppusamy, B. M.; Dougherty, R. W.; Bhamidipati, R.; Mohd, Z.; Higgins, G. A.; Chapman, M.; Rouget, C.; Lluel, P.; Matsuoka, Y. *Bioorg. Med. Chem.* **2018**, *28*, 3793–3797.

(57) Provencher, B. A.; Eshleman, A. J.; Johnson, R. A.; Shi, X.; Kryatova, O.; Nelson, J.; Tian, J.; Gonzalez, M.; Meltzer, P. C.; Janowsky, A. *J. Med. Chem.* **2018**, *61*, 9121–9131.

(58) Cakir, S. P.; Mead, K. T. *Tetrahedron Lett.* **2006**, *47*, 2451–2454.

(59) Quesnelle, C. A.; Snieckus, V. *Synthesis.* **2018**, *50*, 4413–4428.

(60) Ishida, T.; Takemoto, Y. *Tetrahedron* **2013**, *69*, 4517–4523.

(61) Hanessian, S.; Riber, L.; Marin, J. *Synlett* **2009**, *1*, 71–74.

(62) Hanessian, S.; Papeo, G.; Angiolini, M.; Fettis, K.; Beretta, M.; Munro, A. *J. Org.*

Chem. **2002**, *68*, 7204.

(63) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070.

(64) Bao, J.; Lu, H.; Morriello, G. J.; Carlson, E. J.; Wheeldon, A.; Chicchi, G. G.; Kurtz, M. M.; Tsao, K. L. C.; Zheng, S.; Tong, X.; Mills, S. G.; DeVita, R. J. *Bioorg. Med. Chem.* **2010**, *20*, 2354–2358.

(65) Hesketh, P. J. *Support Care Cancer* **2004**, *12*, 550–554.

(66) Rohrig, S.; Hillisch, A.; Strassburger, J.; Heitmeier, S.; Schmidt, M.; Schlemmer, K.-H.; Tersteegen, A.; Buchmuller, A.; Gerdes, C.; Schafer, M.; Teller, H.; Jimenez Nunez, E.; Schirok, H.; Klar, J. US2016/272637A1, **2016**.

(67) Tremblay, M. S.; Halim, M.; Sames, D. *J. Am. Chem. Soc.* **2007**, *129*, 7570–7577.

(68) Khaddour, Z.; Akrawi, O. A.; Suleiman, A. S.; Patonay, T.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2014**, *55*, 4421–4423.

(69) Han, X.; Lin, X.; Shen, H.; Hu, T. WO2018/011163A1, **2018**.

(70) Dejesus, R. K.; Fu, Q.; Jiang, J.; Tang, H. WO2016/122994A1, **2016**.

(71) Downes, T. *Design and Synthesis of a 3-D Fragment Library*; PhD Thesis, University of York, 2019.

(72) Lohier, J. F.; Glachet, T.; Marzag, H.; Gaumont, A. C.; Reboul, V. *Chem. Commun.* **2017**, *53*, 2064–2067.

(73) Rosenkranz, G.; Velasco, M.; Sondheimer, F. *J. Am. Chem. Soc.* **1954**, *76*, 5024–5025.

(74) Greene, T.; Wuts, G. M. P. *Protective Groups in Organic Chemistry*, John Wiley and Sons, 2006, 431-532.

(75) Izzo, F.; Schäfer, M.; Lienau, P.; Ganzer, U.; Stockman, R.; Lücking, U. *Chem. Eur. J.* **2018**, *24*, 9295–9304.

(76) Moessner, C.; Bolm, C. *Org. Lett.* **2005**, *7*, 2667–2669.

(77) Altenbach, R. J.; Kalvoda, L.; Carroll, W. A. *Synth. Commun.* **2004**, *34*, 567–570.

(78) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1995**, *36*, 4193–4196.

(79) Akhoon, K. M.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6041–6045.

(80) Hamilton, J. Y.; Morandi, B.; Carreira, E. M. *Synthesis.* **2013**, 1857–1862.

(81) Pandey, G.; Rajender, S. *Chem. Eur. J.* **2011**, *17*, 6304–6308.

(82) Fernández-Pérez, H.; Lao, J. R.; Grabulosa, A.; Vidal-Ferran, A. *Eur. J. Org. Chem.* **2020**, 4331–4338.

(83) Fang, Y.; Yuan, M.; Zhang, J.; Zhang, L.; Jin, X.; Li, R.; Li, J. *Tetrahedron Lett.* **2016**, *57*, 1460–1463.

(84) Ando, D.; Bevan, C.; Brown, J. M.; Price, D. W. *Eur. J. Org. Chem.* **1992**, 592–594.

(85) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281–283.

(86) Cao, J.; Ma, C.; Zang, J.; Gao, S.; Gao, Q.; Kong, X.; Yan, Y.; Liang, X.; Ding, G.; Zhao, C.; Wang, B.; Xu, W.; Zhang, Y. *Bioorg. Med. Chem.* **2018**, *26*, 3145–3157.

(87) Hu, X.; Yu, J.; Jiang, S.; Gao, Y.; Sun, F. *Bioorg. Med. Chem.* **2020**.

(88) Lin, Y. A.; Chalker, J. M.; Floyd, N.; Bernardes, G. J. L.; Davis, B. G. *J. Am. Chem. Soc.* **2008**, *130*, 9642–9643.

(89) Duguet, N.; Petit, S. M.; Marchand, P.; Harrison-Marchand, A.; Maddaluno, J. *J. Org. Chem.* **2008**, *73*, 5397–5409.

(90) Mukhamedova, L. A.; Kursheva, L. I.; Nechaeva, M. A. *Chem. Heterocycl. Compd.* **1982**, *18*, 361.

(91) Kotha, S.; Khedkar, P.; Kumar Ghosh, A. *Eur. J. Org. Chem.* **2005**, 3581–3585.