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"Novel methods for the synthesis and functionalisation of sulfoximines and sulfonimidamides"

New pharmacophores for the medicinal chemist's toolbox

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Abbreviations List

Å	Ångström
Ac	acetyl
acac	acetylacetonate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
Ar	argon
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad (NMR signal)
BSO	buthionine sulfoximine
Bu	butyl
Bz	benzoyl
°C	centigrade
cat.	catalyst
COD	1,5-cyclooctadiene
conc.	concentrated
CPME	cyclopentyl methyl ether
Cbz	benzyloxycarbonyl
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL-H	di*iso*butylaluminium hydride
dioxane	1,4-dioxane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DPH	*o*-(2,4-dinitrophenyl)-hydroxylamine

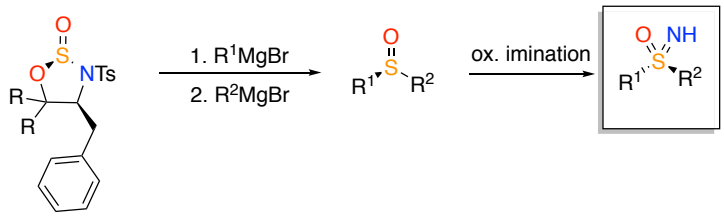
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
equiv	equivalent
es	enantioselectivity
ESI	electronic spray ionization
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropanoate
Et	ethyl
EWG	electron withdrawing group
FDA	food and drug administration
Het	heteroatom
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
i-Pr	*iso*propyl
J	coupling constant
L	ligand
LDA	lithium di*iso*propylamide
HMDS	bis(trimethylsilyl)amide
M	metal
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	2-mesityl
mol	mole
MOM	methoxymethyl acetal
Ms	methanesulfonyl
MS	molecular sieves
MSH	*o*-mesitylenesulfonylhydroxylamine
MSO	methionine sulfoximine
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NH_2CM	(-)-menthylcarbamate
Ns	4-nitrobenzenesulfonyl
Nta	*N*-(1,8-naphthoyl)-alanine

Nttl	2-(1,3-dioxobenzo[de]isoquinolin-2-yl)-3,3-dimethylbutanoic acid
Nu	nucleophile
Pc	phthalocyanine
Pg	protecting group
Ph	phenyl
1,10-Phen	phenantroline
Pht	phthalimide
PMB	*para*-methoxybenzyl
PPI	proton pump inhibitor
PTC	phase transfer
p-Tol	*para*-tolyl
RT	room temperature
SA	sulfonamide
sat.	saturated
Ses	2-trimethylsilylethanesulfonyl
SET	single electron transfer
SIA	sulfonimidamide
TBAF	tetra-*n*-butylammonium fluoride
TBS	tert-butyldimethylsilyl ether
t-Bu	*tert*-butyl
TC	thiophene-2-carboxylate
TEA	triethyl amine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoro ethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
Tol	tolyl
Tp^{*Br}	hydrotris(4-bromo-3,5-dimethyl)pyrazolyl borate
Bu_3*t*py	butyl-2,2'',6',2''-terpyridine
TrNSO	(triphenylmethyl)thionyl imide
Ts	*para*-toluenesulfonyl
δ	chemical shift

Abstract

Sulfoximines, the monoaza analogues of sulfones, have recently gained considerable recognition as a new and versatile structural motif in the life sciences.[1] Therefore our group, in collaboration with Bayer AG (Berlin), is investigating a simple scalable and efficient methodology to make valuable chiral sulfoximines with control of stereochemistry.

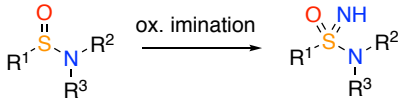
In the first chapter of this report we describe a novel synthetic route towards sulfoximine synthesis. Two types of key precursors are investigated: sulfoxides and phenylalanine templates. With these substrates in hand, we investigated their use in S(O)=N transfer chemistry to obtain enantioenrieched sulfoximines (Scheme 1).



Scheme 1. Proposed route towards synthesis of chiral sulfoximines

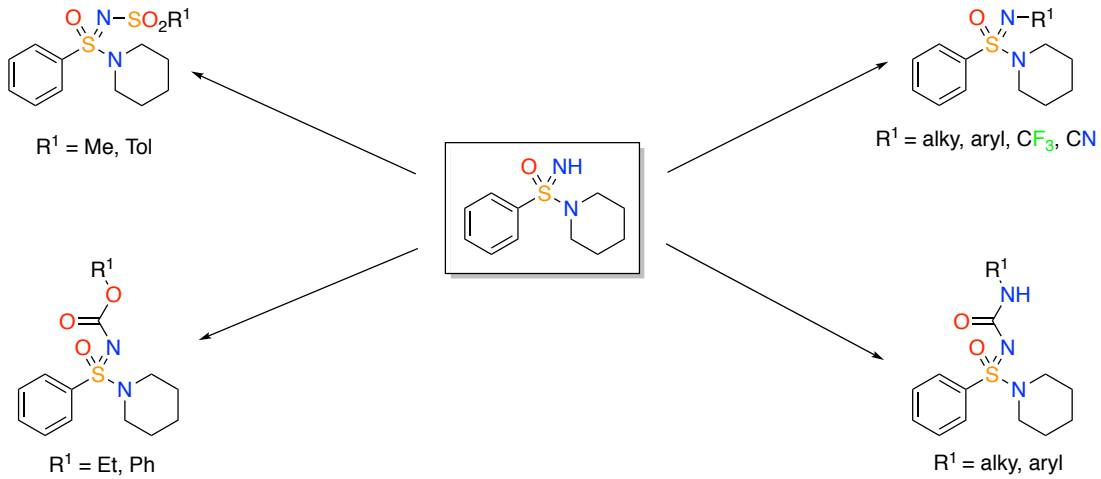
Synthetic methodology for sulfoximine preparation has progressed significantly over the last decade.[2] In contrast, sulfonimidamides, the monoaza-analogues of sulfonamides have been neglected in the life sciences so far, even though they seem to offer very interesting properties.[3] It can be speculated that the use of sulfonimidamides in the life sciences has been hampered substantially by the lack of commercial availability and limited synthetic methods.[4] In this context, we also investigated a facile synthesis of NH sulfonimidamides by NH transfer to tertiary sulfinamides. Racemic NH sulfonimidamides have been prepared in yields from good to excellent in a one-pot transformation.

Given the limited availability of synthetic methods to produce enantioenrieched sulfonimidamides, we expanded our work towards the synthesis of tertiary enantiopure sulfinamides, which will be used as starting material for sulfonimidamide synthesis (Scheme 2).



Scheme 2. Proposed synthesis of sulfonimidamides

Sulfonimidamides, like sulfoximines, offer an additional point for substitution, the =NH group. We have now developed new methods for the functionalisation of this NH group by arylation, alkylation, trifluoromethylation, cyanation, sulfonylation, alkoxycarbonylation, and aminocarbonylation (Scheme 3).



Scheme 1. Proposed transformations for the =NH position of sulfonimidamides

Finally, to gain further insight into the medicinal relevant properties of sulfonimidamides, a variety of structurally diverse sulfonimidamides were analysed in the same *in vitro* panel.

Chapter 1: Introduction

1.1 Pharmacophore: Definition

The medicinal chemistry approach towards drug design is based on four general strategies:

- **Analogue design**: modification of structural features of existing active molecule to make an improved drug
- **Serendipitous observations** of unexpected biological activities
- **Rational design** of drugs inspired from the knowledge of the interaction between target/molecule and the disease activity
- **Selective optimisation of side activities** of known drugs on new pharmacological targets

In addition to these pre-existing tactics, pharmacophore approaches have become one of the main resources in drug discovery. A pharmacophore model can be defined both in a ligand-based manner, by superimposing active molecules and understanding common chemical features essential for the bioactivity, or in a structure based manner, by understanding the interaction between the molecular target and ligands.[1]

Ehrlich was the first to introduce the idea of pharmacophore in 1909.[2] He described it as "a molecular framework that carries the essential features responsible for a drug's biological activity". According to IUPAC, it is "an ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response".[3]

In this work we will analyse and discuss the possibility to use sulfoximines and sulfonimidamides as new pharmacophores in drug discovery.

1.2 Sulfur atom

1.2.1 Introduction

Sulfur is a chemical element belonging to the p-block, group VI, with atomic number 16 and symbol S. The atom name derives from Latin *sulpur*, which means literally "burning stone." It has, in fact, been known since ancient times in China, India and Greece, where drugs containing elemental sulfur were used as balm and to treat parasites.[4]

In its natural forms, sulfur is present in metal/sulfur clusters and its elemental crystalline structure of S_8 molecule.[5] In nature sulfur can be found in many natural gases, such as H_2S also highly toxic (cause of unpleasant smell), SO_2 (a highly toxic gas) and in many inorganic compounds.[6] Magnesium sulfate, for instance, was the first sulfur containing compound to be approved by the FDA (Food and Drug Administration).[7] It also plays key roles in living systems and it is present in many drugs, such as antibacterial sulfonamides, β-lactam antibiotics (penicillins, monolactams etc.) but also in aminoacids[6] like cysteine and methionine (Figure 1. 1). The latter is responsible for the initiation of the synthesis in the eukaryotic proteins while the former plays key role in the protein structure and folding-pathways.[8] Disulfide bonds (S-S) formed between cysteines in peptides chains are fundamental in protein structure and formation.[9] Furthermore, sulfur plays an important role as key component of coenzyme A.[9]



Figure 1. 1 Sulfur containing aminoacids

Sulfur's electronic configuration is $1s^2 2s^2 2p^6 3s^2 3p^4$ (Figure 1. 2) and it has the same electronegativity as carbon (2.5) and less than oxygen (3.5). Because of its position in the periodic table, it can form bonds with elements that don't react otherwise with oxygen.

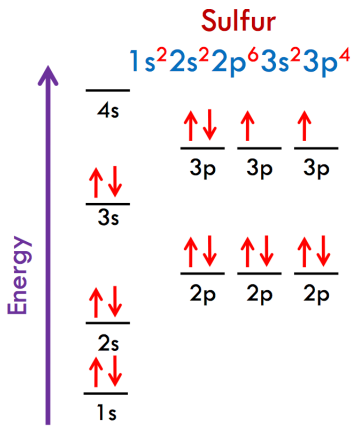


Figure 1. 2 Sulfur orbital diagram

The chemical element exists in five different oxidation states going from -2 to 6 (-2, 0, 2, 4 and 6). Some examples of sulfur(II), (IV) and (VI) are given by sulfides, sulfoxides, and sulfones. Sulfides have two lone pairs available, while the sulfoxide just one (Figure 1. 3). Sulfones on the other hand have all its electrons involved in bonding (Figure 1. 3). The 3p orbitals on the sulfur atom are too diffuse to overlap exactly with the 2p orbitals on the oxygen or carbon and because of this the pi character of the S=O bond is reduced (Figure 1. 3).

When the sulfone reacts with a strong base on the methyl group in the α-position, the negative charge can be stabilised by delocalising it in a p orbital aligned between the oxygen and the sulfur.[10,11]

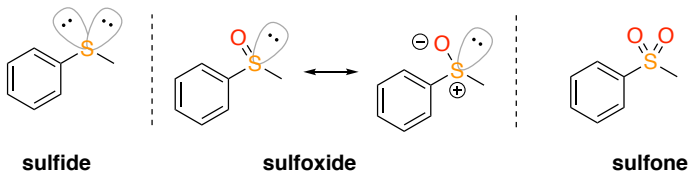


Figure 1. 3 Sulfur compounds in different oxidation states

While sulfur(II) compounds are achiral, sulfur(IV) and sulfur(VI) can be chiral when appropriately substituted, having the four bonds pointing to the corners of a tetrahedron. Moreover, these sulfur-organo compounds are widely employed in chemistry reactions such as Corey-Chaycovsky[12], Swern oxidation,[13] Ramberg-Bäcklund,[1] Mislow-Evans[14] and Pummerer rearrangement (Figure 1. 4).[15,16]

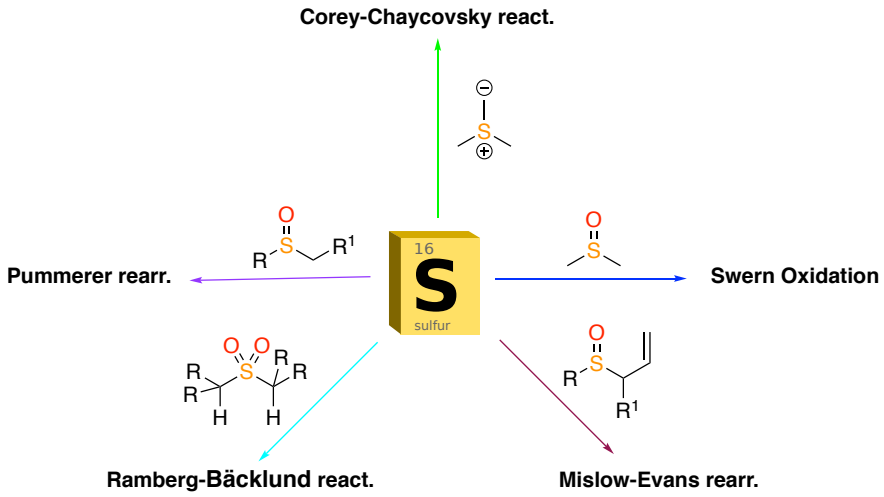


Figure 1. 4 Organo-sulfur compounds in classical chemistry

In this chapter the synthesis of racemic and enantiopure S(IV) (sulfoxides and sulfinamides) and S(VI) imino compounds (sulfoximines and sulfonimidamides) will be described in detail.

1.3 S(IV) compounds

1.3.1 Sulfoxides

In the last few decades, organosulfur compounds have acquired increased importance as their application in asymmetric synthesis and the pharmaceutical industry kept growing. Chiral sulfoxides have been studied since 1926,[8] and particularly in the last forty years many research groups have been involved in the design and study of new synthetic methods for generation of enantiopure sulfoxides.[9]

Sulfoxides play an important role in a large number of medicinal targets. Currently this class of compounds has 11 FDA approved drugs on the market, in both racemic and enantiopure forms. Sulfinylpyrazone, in particular, was the first one to be commercialised given its high antiplatelet activity. Then, a whole class of proton pump inhibitors (PPI) bearing the sulfoxide functionality were developed. Omeoprazole was the first to be synthesised and sold as a racemate. Interestingly esomeprazole is the only molecule sold in its enantiopure form from this class of compounds. It is structurally identical to omeoprazole, but only the (*S*)-enantiomer is used (Figure 1. 5). Another interesting example of drug containing a sulfoxide moiety is fulvestrantor; a unique molecule which has a steroid core derived from 17β-estradiol and five fluorine atoms. Fulvestrantor is used to treat breast cancer (Figure 1. 5).[7]

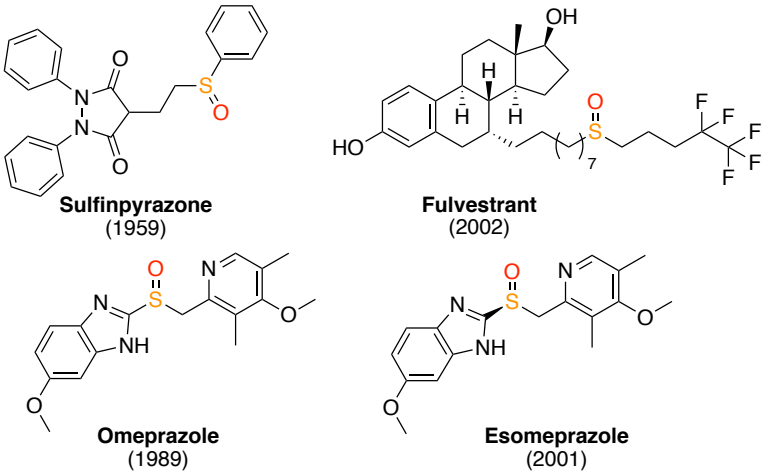
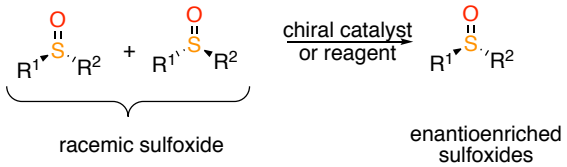


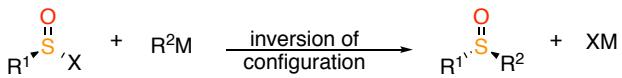
Figure 1. 5 Sulfoxides containing drugs

Furthermore sulfoxides are often employed as chiral auxiliaries for asymmetric C-C bond formation and as ligand for metals in catalytic asymmetric synthesis.[17] Because of their important properties and applications it is fundamental to find practical and mild methods for their asymmetric synthesis. In the scheme below some strategies are described.[6]

1) Kinetic resolution of racemic mixture

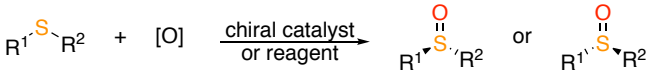


2) Transformation of diasteomerically pure sulfinate

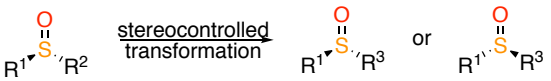


X = chiral nucleofuge
R^2M = organometallics

3) Enantioselective oxidation of sulfide



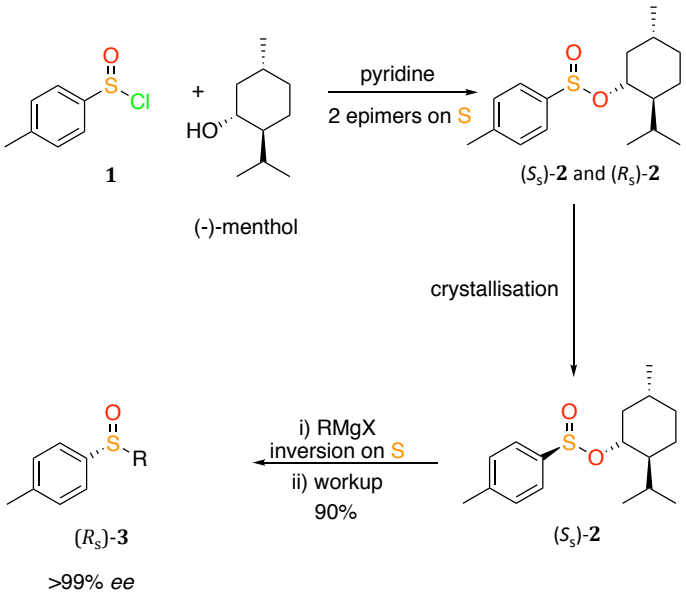
4) Modification of the structure of chiral sulfoxide



Scheme 1. 1 Main routes towards chiral sulfoxide synthesis

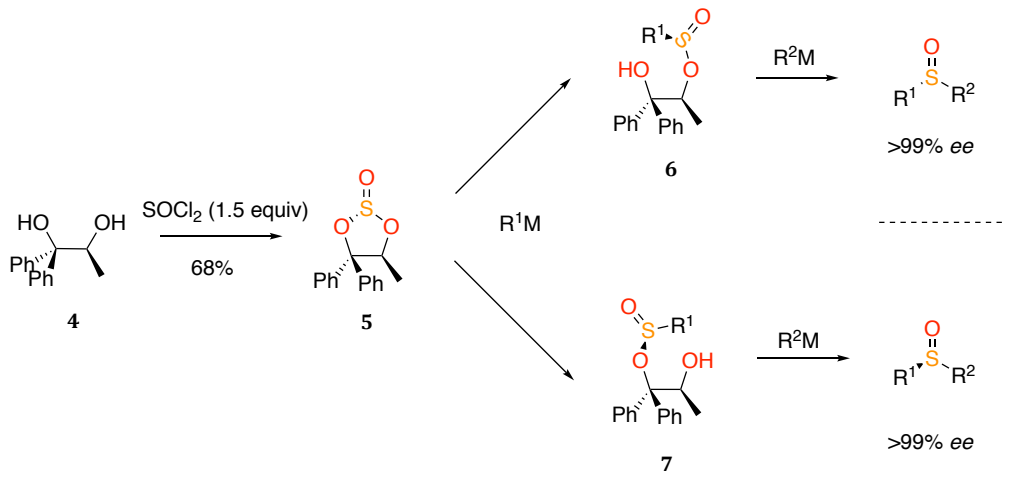
Until now the synthesis of sulfoxides could be achieved either through asymmetric oxidation of prochiral sulfides,[18] (Scheme 1. 1, 3) or organometallic addition to electrophilic sulfinic-acid derivatives.[19] In this paragraph, we are going to focus mainly on the latter method (Scheme 1. 1, 2).

In 1926, Gilman suggested the first optically active sulfoxide synthesis,[20] while in 1962 Andersen obtained chiral sulfoxides by employing a sulfinate diastereoisomer separation, derived from a reaction between sulfinyl chloride **1** and (-)-menthol. Subsequently addition of nuclephiles, such as Grignard reagents, to **2** produced the sulfoxide in high *ee* and inversion of configuration (Scheme 1. 2). [21,22]



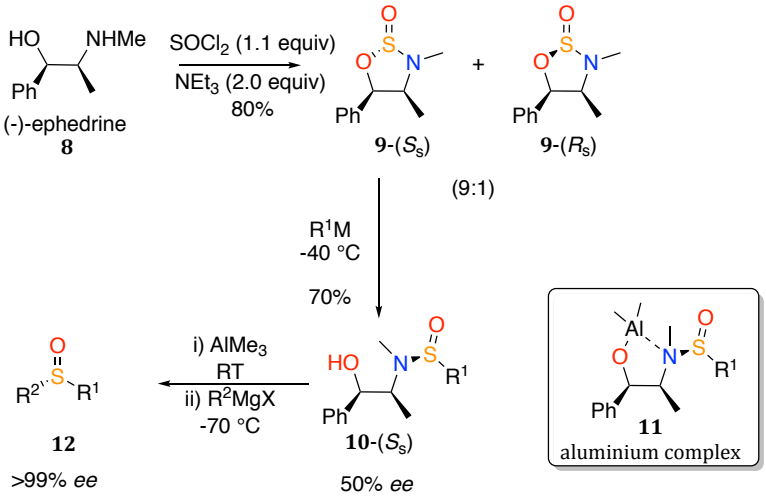
Scheme 1. 2 Anderson's route for enantioenrieched sulfoxides

In 1991 Kagan and co-workers investigated on the regioselectivity of *dissymmetrical* sulfites when reacted with 1 equivalent of organometallic reagent (Scheme 1. 3). [23] It was observed that the regiochemistry of the sulfinates (**7** or **6**) depends on the nature of Grignard reagents added, for example PhMgBr and BnMgBr did not show any stereochemical preference in ring opening, while MesMgBr or *tert*-BuMgBr gave preferentially S_s sulfinate **6** (**6**:**7** = 88:12 and 95:5 respectively). Furthermore every substitution on the sulfite gave an inversion of configuration at the stereogenic center (S_N2) (Scheme 1. 3).



Scheme 1. 3 From chiral sulfite to chiral sulfoxides

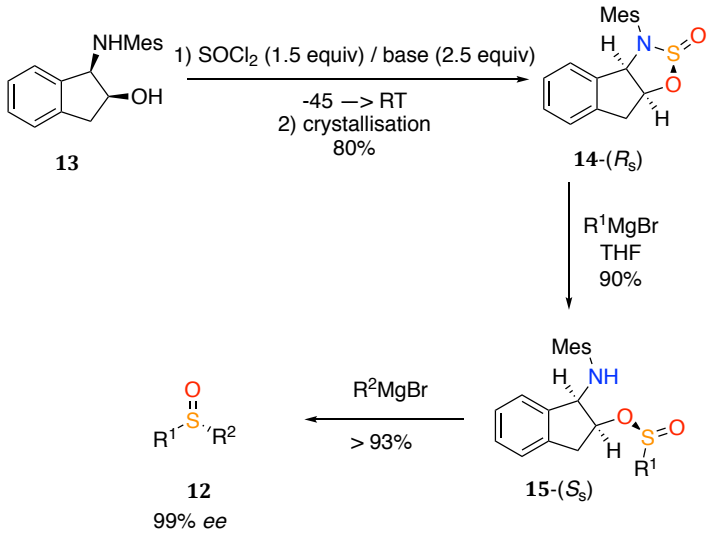
In the past years the synthesis of sulfoxides starting from sulfinamides has been achieved.[24] The first pioneers were Wudl and Lee, who used commercially available (-)-ephedrine **8** as a starting material and reacted it with $SOCl_2/NEt_3$, to make 1,2,3-oxathiazolidine-2-oxide in a good yield (80%) as a mixture of diastereomers (72:28) (Scheme 1. 4). Further studies showed how the use of HCl-catalysed equilibration and crystallisation could drive the reaction to the formation of pure **9**-(S_s) in 65% yield (see Scheme 1. 4).[25] The ring opening of the cyclic sulfite happens regioselectively. The addition of R^1MgX gives the intermediate sulfinamide **10** in good yield (70%), but poor enantioselectivity of only 50% *ee*. In 1991, the same reaction was reinvestigated by Snyder and Benson who managed to improve the chemical yield to 95-99%.[26] The authors modified the reaction introducing $AlMe_3$, before the second Grignard reagent. The noteworthy exception in this approach is the production of sterically hindered sulfoxides such as *tert*-butyl sulfoxide which gave low yields.[26] A great improvement in *ee* (> 99%) which was explained by the possible formation of an aluminium complex **11** (see Scheme 1. 4) which would help the achievement of a variety of chiral sulfoxides **12**.



Scheme 1. 4 Use of 1,2,3-oxathioazolidine-2-oxide for asymmetric synthesis of chiral sulfoxides

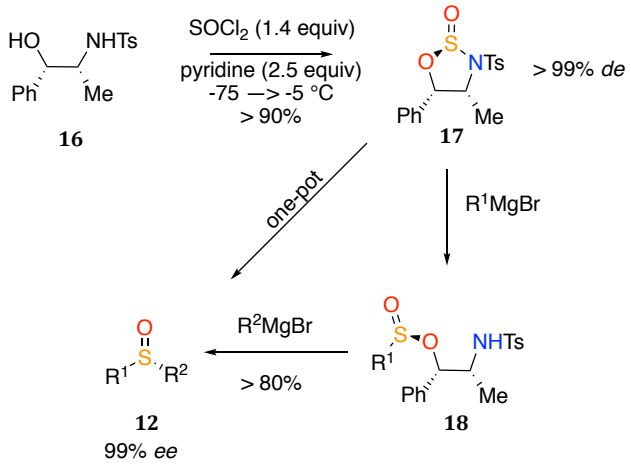
Later, Alcudia and co-workers reported a method to form both enantiomers of sulfoxides through dynamic kinetic resolution using a chiral controller (diacetone D-glucose).[27]

The possibility of using chiral sulfonyl group, with two different leaving groups, in a one-pot reaction sequence with two nucleophiles, to produce chiral sulfoxides **12** raised the interest of many research groups. In this light, Senanayake and Han studied a selective, asymmetric route towards 1,2,3-oxathiazolidine-2-oxide **14** system starting from an aminoalcohol **13** and thionyl chloride (Scheme 1. 5) to give chiral product **14** in 80% yield on a kilogram scale.[28] The presence of the electron-withdrawing group on the nitrogen directs cleavage of the S-N bond exclusively. If the nitrogen is bearing an electron-donating group the result would be exactly the opposite, with S-O bond breaking predominating. As a result, an intermediate **15** with inversion of configuration is formed in excellent yield and used as a building block for enantiopure sulfinamides or sulfoxides **12** (Scheme 1. 5).



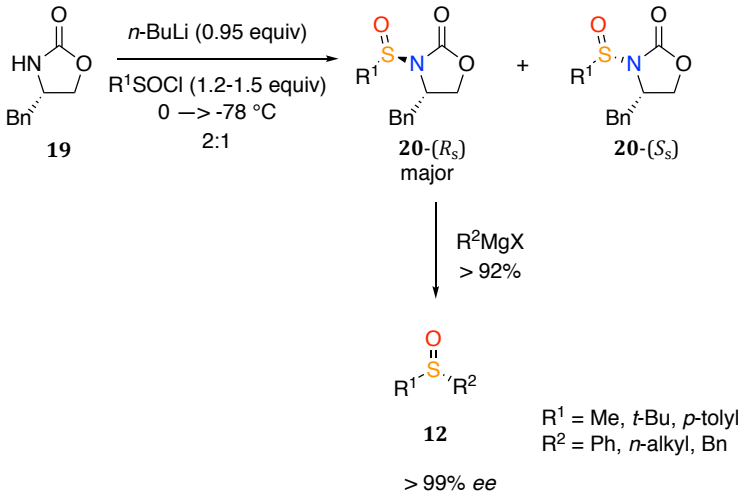
Scheme 1. 5 Use of 1,2,3-oxathioazolidine-2-oxide **14** for asymmetric synthesis of chiral sulfoxides

Senanayake and co-workers employed the less bulky norephedrine template to form the cyclic oxathiazolidine (Scheme 1. 6).[29,30] After R^1MgBr addition to the template **17**, the formation of the intermediate **18** is achieved in good yield and excellent *ee*. The S-N bond is chemoselectively cleaved followed by the displacement of the S-O bond with the second organometallic (R^2MgBr) which leads to the chiral sulfoxides **12**. The configuration of the sulfoxide **12** depends on the order and nature of the two Grignard reagents reacted with the template. Furthermore, once the product **12** is formed, chiral auxiliary **16** is released and it can be isolated and recycled. Perhaps the most interesting part of these discoveries was the possibility of performing the reaction sequence step-wise or a one-pot procedure. The obvious advantages of this procedure made it highly desirable to use for the production of valuable chiral sulfoxides **12** in excellent yields and enantiopurity.



Scheme 1. 6 Norephedrine template derivative for asymmetric sulfoxides synthesis

Another example of chiral sulfoxide synthesis was reported in 1992, by Evans. The synthesis began with the formation of the reactive *N*-sulfinyloxazolidinone (Scheme 1. 7) to give a mixture of sulfinamides which are easy to isolate by silica gel chromatography.[31] The nucleophilic addition of R^2MgX to **20** generated the desired sulfoxide **12** in excellent enantiopurity (>99% *ee*) (Scheme 1. 7).

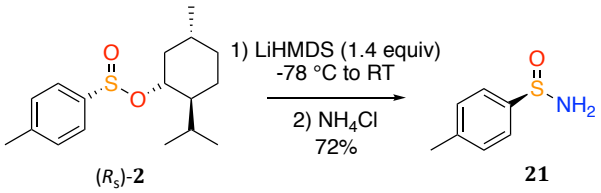


Scheme 1. 7 Use of Evans' auxiliary for chiral sulfoxide formation

Oxazolidinone **19** is a commercially available reagent, preferable to Senanayake's sulfur template **17** because of its reduced cost (£ 78.70 for 5g on Sigma Aldrich). However, the R^1SOCl reagent limits the substrate scope for Evan's reaction. Infact, in order to obtain sulfoxides with different R^1 groups, prior synthesis of sulfinyl chlorides is necessary.

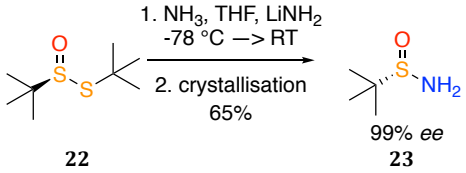
1.3.2 Sulfinamides

Sulfinamides are useful and efficient chiral auxiliaries for synthesis of chiral amines, [32] α- and δ-amino acids,[33] amino alcohols,[34] and aziridines[35]. Despite the importance of sulfinamides in asymmetric chemistry, few methods have been developed for their synthesis. In the early 1970s, Davis and co-workers were the first to highlight the importance of sulfinamide chemistry due to their studies on *p*-toluenesulfinimines,[36] and twenty years later they successfully prepared the first enantiomerically pure *p*-toluenesulfinamide **21** (*p*-TSA) from Anderson reagent (Scheme 1. 8).[37,38]



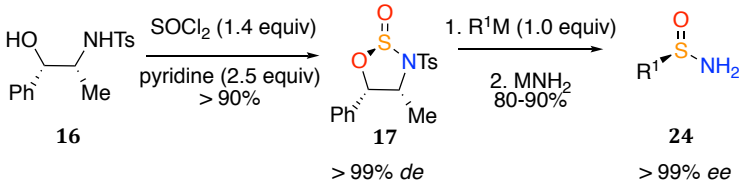
Scheme 1. 8 Asymmetric synthesis of *para*-toluenesulfinamide

Later, Ellman and co-workers developed a method for the sythesis of *tert*-butanesulfinamide (*tert*-BSA) **23** *via* displacement of *tert*-butylthiolate with lithium amide. Enantiomerically pure sulfinamide **23** was obtained (99% *ee*, 65% overall yield) (Scheme 1. 9).[32]



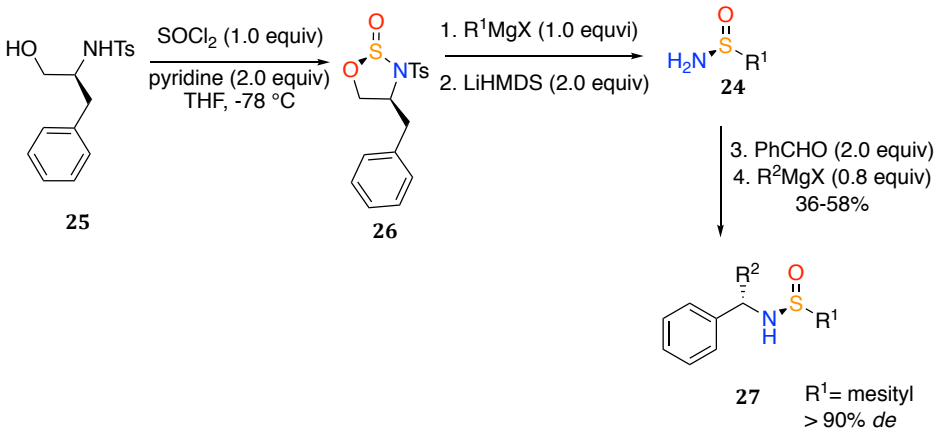
Scheme 1. 9 Asymmetric synthesis of *tert*-butanesulfinamide

Furthermore, the synthesis of chiral sulfinamides was possible using Senanayake's adaptation of Wudl's sulfoxide synthesis (see Scheme 1. 4) or by catalytic asymmetric oxidation of di-*tert*-butyldisulfide followed by ammonolysis in liquid ammonia and sodium amide (Scheme 1. 10).[28–30,39–41]



Scheme 1. 10 Modular asymmetric synthesis of enantiopure sulfinamides

The major disadvantage deriving from Senanayake's method was the relatively high cost of the template. The Stockman group, inspired by Sananayake's work, has achieved a convenient synthesis of chiral non racemic sulfinamides based on his norephedrine-template (Scheme 1. 11).[42,43] Template (**26**) (analogous to Senanayake's norephedrine template) was synthesised starting from L-phenylalanine, an inexpensive and readily available chiral starting material.



Scheme 1. 11 Five component synthesis of sulfinamides

A range of mesityl sulfinamides (R^1 = mesityl) where produced in 36-58% yield and excellent diastereoselectivity (>90 *de*). The process involves the formation of four new bonds and two stereogenic centers in a single-pot synthesis.

Thanks to the work reported so far, synthesis of primary and secondary chiral sulfinamides in excellent yields and *ee* is now possible. However, a simple, scalable methodology to produce tertiary sulfinamides is yet to be disclosed.

1.4 S(VI) compounds

1.4.1 Sulfoximines: History

Sulfoximines are the aza-analogue of a sulfone, and as such belong to the highly oxidised S(VI) group. When R^1 and R^2 are different from each other the sulfur molecule becomes chiral. Other members of this group are sulfondiimines and sulfonimidamides (Figure 1. 6).

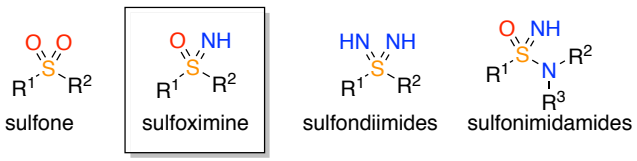
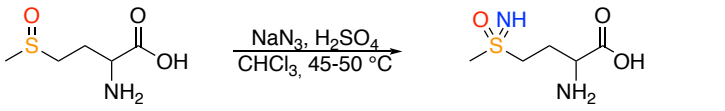


Figure 1. 6 Sulfur(VI) compounds

In 1946 Bentley and Whitehead isolated the first sulfoximine molecule. The authors were curious about the unusual effects of some dogs fed with a diet rich in agenized flour due to the high rates of epileptiform fits and eventual death.[44,45] The cause of the toxicity was identified as methionine sulfoximine (**MSO**) (Scheme 1. 12). Further

studies showed infact the capability of the molecule to inhibit both glutamine synthetase[46] and γ-glutamylcysteine synthetase.[47]



Scheme 1. 12 Synthesis of **MSO**

Since the 1940's, due to their unusual structure and interesting bioactivity, sulfoximines have attracted the attention of the synthetic and medicinal chemists alike.[48] Recently the buthionine sulfoximine (**BSO**), structurally very similar to **MSO** was cited in many articles and a variety of research groups are evaluating its use in the treatment of cancer (Figure 1. 7).[49] Furthermore, **BSO** was found to be a specific inhibitor of γ-glutamylcysteine synthetase.[50]

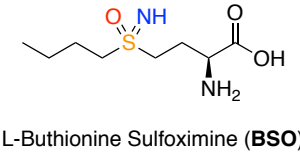


Figure 1. 7 Chemical structure of **BSO**

The sulfoximine structure provides this class of molecule with several properties such as metal ion coordination (given the basicity of the nitrogen),[51] formation of salts with mineral acids and dual role of donor or acceptor of protons (free sulfoximines).[49,52] Furthermore, what makes these compounds of great importance in both the pharmaceutical and medical fields is the high solubility of sulfoximines in protic solvents (Figure 1. 8).[48]

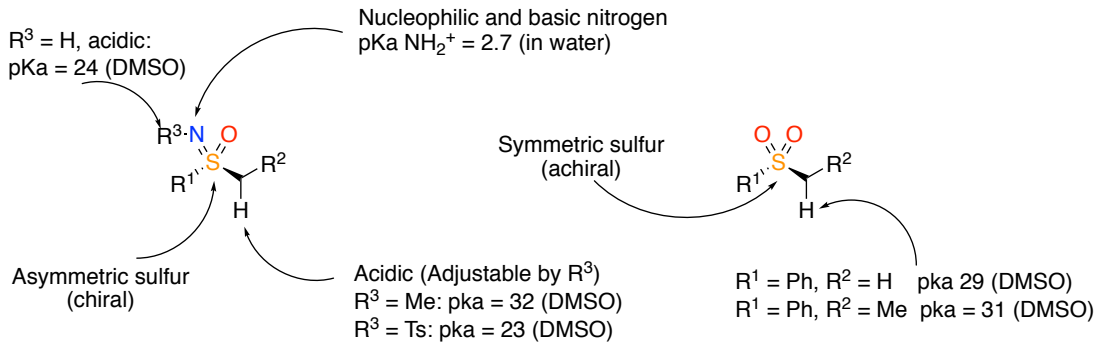


Figure 1. 8 Sulfoximines[53] and sulfones properties

In drug discovery we can find several examples where the sulfoximine group has been employed. For instance Satzinger and Stoss pioneered its use developing an antiasthmatic and polyvalent spasmolytic agent called suloxifen containing the sulfur(VI) functionality.[53,54] High spasmolytic activities were also recorded for an analogue drug **HE-HK 52** synthesised by scientists at Heumann Pharma (Figure 1. 9).[55]

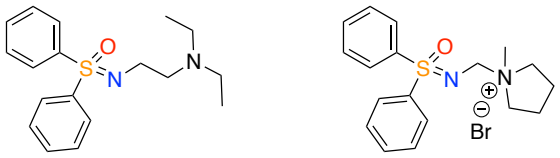


Figure 1. 9 Structure of spasmolytic agents containing S(VI)

Subsequently, chemists at Bayer Pharma AG investigated, for the first time, the sulfoximine as a pharmacophore, leading to development of **BAY 1000394** as a CDK inhibitor. CDKs (cyclin-dependent kinases) are strong candidates for the treatment of cancer (Figure 1. 10).[56–58] Later, AstraZeneca developed an ATR-inhibitor, **AZD6738**, containing the sulfoximine moiety which is currently under clinical trials for cancer treatment (Figure 1. 10).[59,60]

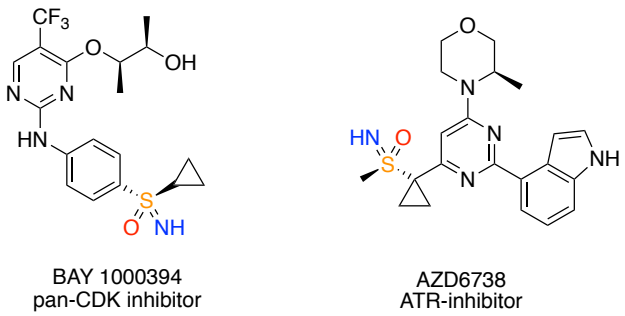


Figure 1. 10 Clinical pan-CDK inhibitor and ATR-inhibitor

The use of sulfoximines has been explored not only in medicinal but also in agricultural science. Applications in crop protection have been reported by Dow Agroscience[61,62] and Syngenta[63–65] for the molecules in Figure 1. 11.

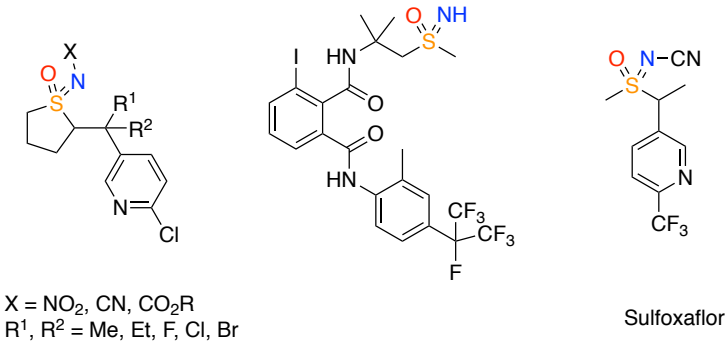
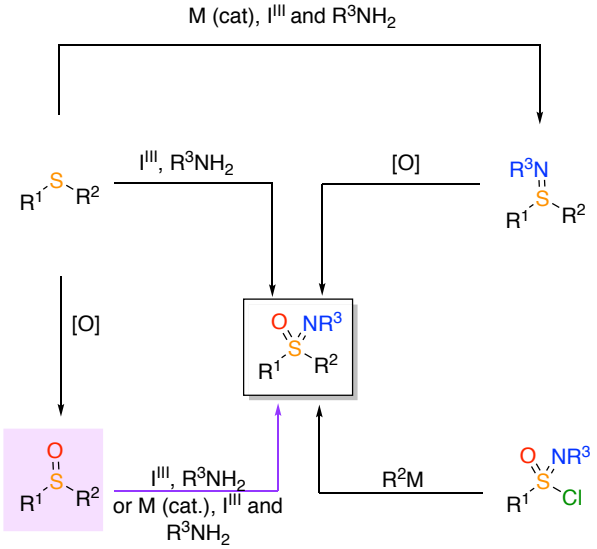


Figure 1. 11 Sulfoximine containing molecules with insecticidal activity

1.4.2 Sulfoximines: Synthesis

In 1965 the first synthesis of an enantiopure sulfoximine was reported,[66] and since that time many others followed.[49,67] Given the presence of an amphoteric nitrogen and stereogenic sulfur atom, they have been widely used in asymmetric synthesis as building blocks and chiral ligands. Formally, sulfoximines are the monoaza analogue of sulfones;[49] instead of two oxygens the sulfur is bonded to one oxygen and one nitrogen. The possibility to modify the N-H bond on sulfoximines represents a binding point not present in sulfones.

Several strategies for the preparation of sulfoximines have been developed over the past decades.[68] Currently, there are three established ways to obtain them (Scheme 1. 13). However, the most direct and largely exploited is the oxidative imination of sulfoxides.

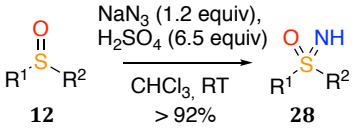


Scheme 1. 13 Main routes towards sulfoximines

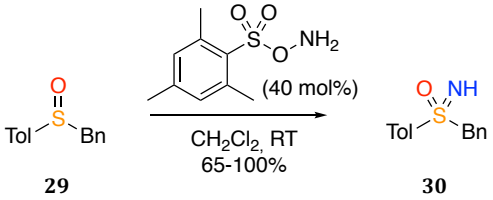
1.4.2.1 Non-catalytic methods

In the past, the most commonly used method for oxidative imination, utilised a mixture of sodium azide and sulfuric acid (Scheme 1. 14 **A**).[69–72] Given the toxicity and the harsh conditions of the azide method, Ikeda and co-workers developed a reaction which involved the use of *o*-mesitylenesulfonyl hydroxylamine (MSH) (Scheme 1. 14 **B**). The configuration of the sulfur atom is retained during the course of the reaction enabling the conversion of optically active sulfoxides into the corresponding sulfoximines.[73,74]

A[69–72]

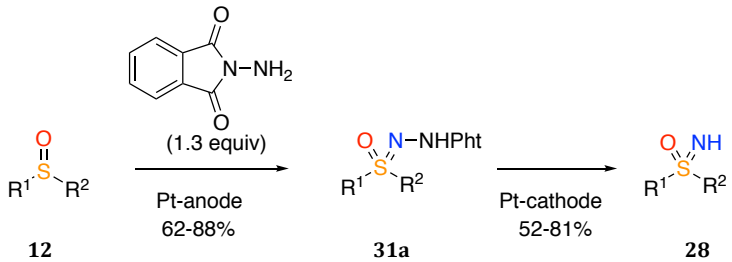


B[73,74]



Scheme 1. 14 A and **B** procedures for sulfoximines synthesis

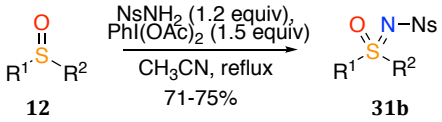
In 2002 Yudin developed an electrochemical oxidation to form sulfoximines (Scheme 1. 15).[75] He started by imination of chiral sulfoxides to produce *N*-phthalimide, which was easily cleaved under the electrochemical conditions, to yield the valuable sulfoximine with an unprotected NH group.



Scheme 1. 15 Yudin's synthesis of sulfoximine

In 2005 Bolm and co-workers reported a metal free *in situ* formation of a nitrogen transfer agent by mixing nosyl amide with diacetoxyiodobenzene (Scheme 1. 16). Although the method didn't require toxic reagents, and the nosyl protecting group is

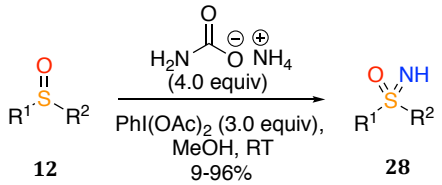
easy to remove, studies showed that the reaction led to partial racemisation, possibly due to the high reaction temperatures.[76]



Scheme 1. 16 Metal-free synthesis of sulfoximines using $NsNH_2$

Sulfoximines are often prepared by transfer of protected nitrogen group on the sulfoxides.[77] The direct transfer of NH group has frequently involved undesirable or harsh reaction conditions and explosive reagents (see Scheme 1. 14).[70] Recently, a scalable synthesis of NH sulfoximine in flow was reported by Kappe and co-workers using trimethylsilyl azide and fuming sulfuric acid to transfer an NH group directly upon the sulfoxide intermediate of **AZD6738**, but racemization of the chiral sulfur occurred.[78]

In 2016, Lusi, Bull and co-workers reported a novel process based on commercially available and inexpensive reagents for the stereospecific synthesis of NH sulfoximines **28** from sulfoxides **12**, using ammonium carbamate, as the NH source, and diacetoxyiodobenzene (Scheme 1. 17).



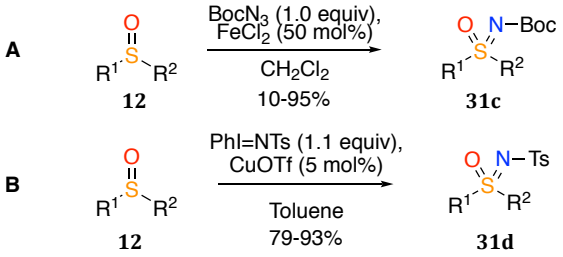
Scheme 1. 17 Synthesis of sulfoximines using ammonium carbamate

A large number of substituents were tested (R^1 and R^2), obtaining sulfoximines from moderate to high yields (54-96%), nevertheless employing a sulfoxide bearing an electron-withdrawing trifluoromethyl group appeared to be at the limit of the reactivity for this methodology (9% yield).[79] The scalability of the reaction was demonstrated performing the reaction on 10 mmol (91% yield). However, no example of a large-scale reaction employing enantiopure sulfoxides was reported by the authors.

1.4.2.2 Metal-catalysed methods

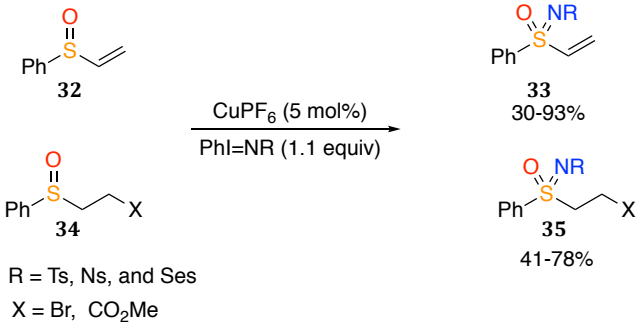
More than 30 years ago two research groups reported, almost in parallel, transition metal catalyst mediated oxidative imination protocols of sulfoxides, which showed

major methodological improvements in comparison to the early, metal free, routes for sulfoximines synthesis (Scheme 1. 18).[80] Bach and co-workers described the first metal mediated imination of sulfoxides **28** with $BocN_3$ catalysed by $FeCl_2$; even if the efficiency of this catalyst wasn't excessively high (up to 2.2 turnovers) the Boc (*tert*-butoxy carbonyl) protecting group could be easily cleaved to provide the free NH group, which is a great advantage over previous methods (Scheme 1. 18 **A**). [81,82] Muller on the other hand, reported a similar reaction mediated by CuOTf and using PhI=NTs as the imine source. The [(arenesulfonyl)imino]phenyliodinanes have been used as efficient nitrene source for many transformations.[83–85] The same cannot be said for the [(alkylsulfonyl)imino]phenyliodinanes analogues which are possibly explosive and unstable.[86] The downside, though, was given by the difficult transformation of the tosyl group into their synthetically useful NH counterparts (Scheme 1. 18 **B**).[87]



Scheme 1. 18 Metal catalysed procedures for sulfoximine synthesis

A few years later, Tye and co-workers found out that $CuPF_6$ was also an efficient catalyst to produce a range of sulfoximines on substrates which did not react in the presence of MSH (Scheme 1. 19). [88] Sulfoxides **32** and **34** were reacted together with different amido-iodanes (PhI=NR), which had on the nitrogen an R group easy to cleave. The corresponding NH sulfoximines were obtained in good to high yields. These findings were an important step forward for sulfoximine synthesis.

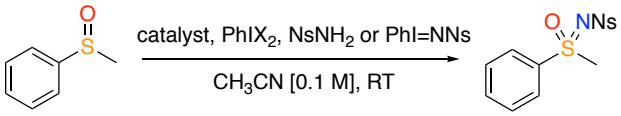


Scheme 1. 19 Tye's studies of sulfoximines

Recently Bolm and co-workers reported a comparative study, which investigated the effect a series of catalysts, imination agents, and reaction conditions for the imination

of a number of sulfur compounds (sulfides and sulfoxides; Table 1. 1).[89] Silver, iron, copper and rhodium proved to be excellent metal catalysts providing excellent yields, reasonable reaction times and relatively low costs (apart from the latter, which limited large scale synthesis). In **Method A** the nitrene source was made *in situ* from PhI=O or $PhI(OAc)_2$ and Ns-NH_2, while **Method B**, in order to reduce the reaction times, involved the use of the pre-formed intermediate PhI=NNs. Both the protocols were carried out at room temperature using mild conditions.

Table 1. 1 Reaction conditions for the metal catalysed imination of phenyl methylsulfoxide **36a**



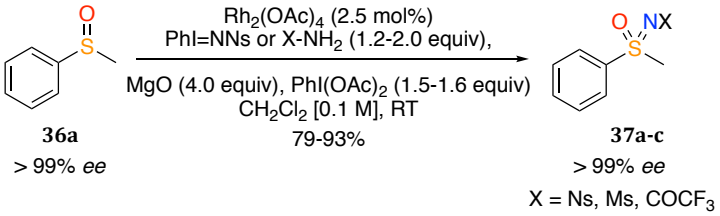
36a **37a**

Catalyst (mol%)	Method	$Ph(X)_2$	t (h)	Yield (%)
$Rh_2(OAc)_4$(2.5)	A	$PhI(OAc)_2$	6	86
$AgNO_3$/*t*Bu_3tpy	A	$PhI(OAc)_2$	16	83
$Fe(acac)_3$(10)	A	$PhI(OAc)_2$	3	90
$Fe(acac)_3$(10)	A	PhI=O	0.5	97
$Cu(OTf)_2$(10)	A	$PhI(OAc)_2$	16	28
$Co(ClO_4)_2$(10)	A	$PhI(OAc)_2$	72	25
$Co(acac)_3$(10)	A	$PhI(OAc)_2$	24	/
$Mn(acac)_3$(10)	A	$PhI(OAc)_2$	24	/
$Rh_2(OAc)_4$(2.5)	B	PhI=NNs	1	93
$AgNO_3$/*t*Bu_3tpy	B	PhI=NNs	8	85
$Fe(acac)_3$(10)	B	PhI=NNs	1	8
$Cu(OTf)_2$(10)	B	PhI=NNs	16	81
$Co(ClO_4)_2$(10)	B	PhI=NNs	72	28
$Co(acac)_3$(10)	B	PhI=NNs	24	/
$Mn(acac)_3$(10)	B	PhI=NNs	24	/

Method A : $NsNH_2$ (1.2-2.0 equiv) and $PhI(OAc)_2$ or PhI=O (1.5-1.6 equiv). **Method B** : PhI=NNs (1.5 equiv)

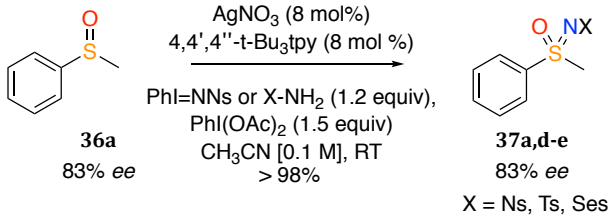
Bolm first focused his attention on $Rh_2(OAc)_4$, which was found to be an efficient catalyst. Sulfoxides and sulfides were reacted with 2.5 mol% of the Rh catalyst,

together with trifluoroacetamide or sulfonamides in combination with iodobenzene diacetate and magnesium oxide (Scheme 1. 20).[90] Iodobenzene diacetate is known for being a mild oxidant and less dangerous than MSH or the azido derivatives.[74] Amongst the different amides used (Ms-NH_2, Ns-NH_2, etc.) in the imination step trifluoroacetamide was the most valuable one; because of the easy deprotection step to achieve the synthetically useful N-H sulfoximines. This procedure presented undoubted advantages, since it did not require the use of inert atmosphere or anhydrous solvents. The reaction times were short (1-24 h) and the yield of the sulfoximines high (79-93%) (Scheme 1. 20). Furthermore, the imination step was stereospecific, and it lead to optically active products.[90] The only drawback of this synthetic protocol is the prohibitive cost of the rhodium catalyst (£758 per gram).[90]



Scheme 1. 20 Rhodium oxidative imination

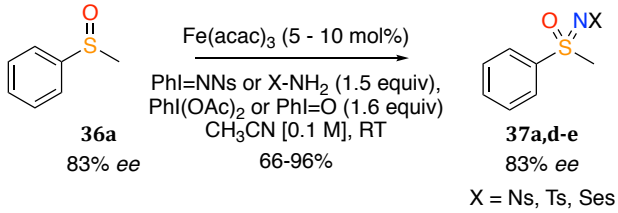
The effect of several silver salts and ligands was, then explored.[91] It was observed that $AgNO_3$ and 4,4',4''-*tert*-Bu_3tpy (4,4',4''-tri-*tert*-butyl-2,2',6',2''-terpyridine) formed a catalyst able to perform the oxidative imination on different substrates, under mild conditions (Scheme 1. 21). Most of the iminating agents (Ts-NH_2, Ns-NH_2, Ses-NH_2) gave the corresponding sulfoximines in moderate to excellent yield (up to 98%). Unfortunately, all attempts to use trifluoroacetamide, as nitrogen source, to gain the corresponding sulfoximine **37c** were unsuccessful. The overall process proceeds with retention of configuration on the stereogenic sulfur atom, in analogy to the reported rhodium catalysed procedure (Scheme 1. 21).



Scheme 1. 21 Silver oxidative imination

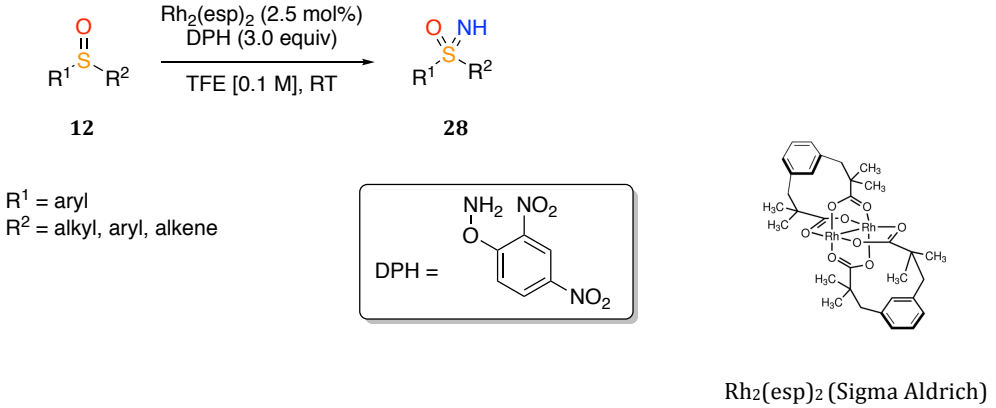
In order to improve further the reaction conditions, and find a cheaper catalyst Bolm decided to investigate iron(III) salts as catalyst. A number of iron salts showed excellent reactivity giving sulfoximines in good yields (66-88%). Optimal results were

reported when iodosylbenzene was used, instead of (diacetoxy)iodobenzene as oxidising agent. Iron catalysed imination proceeded well at room temperature with different nitrogen sources ($TsNH_2$, $NsNH_2$, $SesNH_2$ etc.). The amount of iron catalyst used (from 5 to 10 mol%) didn't change significantly the conversion of the starting material. This reaction protocol represents an alternative route toward enantiopure sulfoximines (Scheme 1. 22).[92]



Scheme 1. 22 Iron oxidative imination

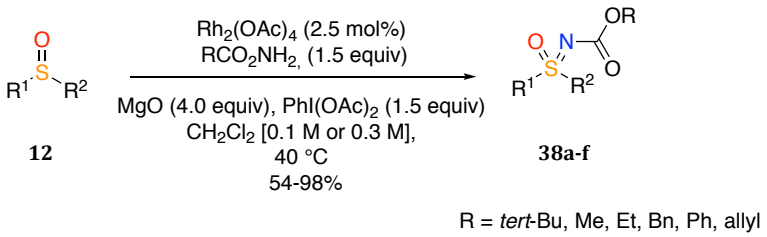
Recently, inspired by Kürti's report, regarding the rhodium catalysed route to unprotected N-H-aziridines using *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH),[93] Richards performed the first direct metal-catalysed synthesis of free N-H-sulfoximines. Amongst the large variety of solvent tested trifluoroethanol (TFE) was found optimal to use together with $Rh_2(esp)_2$ (esp = α,α,α',α'-tetramethyl-1,3-benzenedipropanoate) catalyst (Scheme 1. 23). The methodology was applied to the imination on different sulfoxides. Functional groups such as halogens, alkyl or acyl groups on the phenyl ring gave good to excellent yields (56-94%), while *para*-acyl or *ortho* substituted sulfoxides gave lower yield.[94]



Scheme 1. 23 Richards' direct sulfoximine synthesis

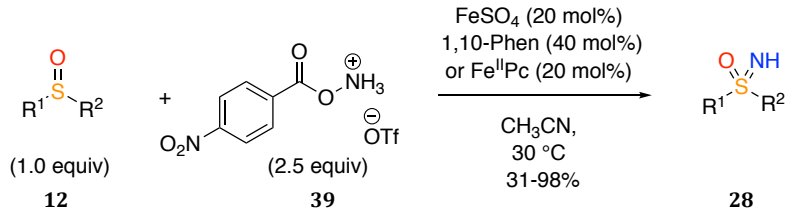
Soon after this work had been published, Bull and Luisi, adapting Bolm's rhodium catalysis,[90] achieved the direct formation of *N*-Boc sulfoximines using *tert*-butyl carbamate as the nitrenoid species (i.e. BocN=Rh).[95] The scope of the reaction was explored, and several sulfoximines were obtained in high yields (54-98%).

Interestingly, the desired sulfoximines **33a-f** were also obtained when different carbamates, other than Boc carbamates, were reacted with **12** (Scheme 1. 24). The usefulness of this method was demonstrated by the easy deprotection of the Boc and Cbz protecting groups.



Scheme 1. 24 Examples of Rh-catalysed imination

Recently, Bolm and co-workers looked into an iron-catalysed direct synthesis of free NH sulfoximine formation.[96] As previously seen, the only precedent for such a reaction was rhodium catalysed, and because of the cost of the reagent, the scale up can be challenging. For this reason iron can be an appealing alternative. The authors employed two types of iron catalysts. $FeSO_4$ in combination with 1,10-phenanthroline was suitable when R^1 was an aryl ring providing different sulfoximines **28** in modest to high yields (31-98%), but ineffective when R^1 was bearing a heteroatom on the aromatic ring. Fe^{II} phthalocyanine, on the other hand, proved to be an excellent catalyst for iminating these types of sulfoxides (**12**). Aroylhydroxylamine triflic acid **39** was used in both methods as NH source (Scheme 1. 25).

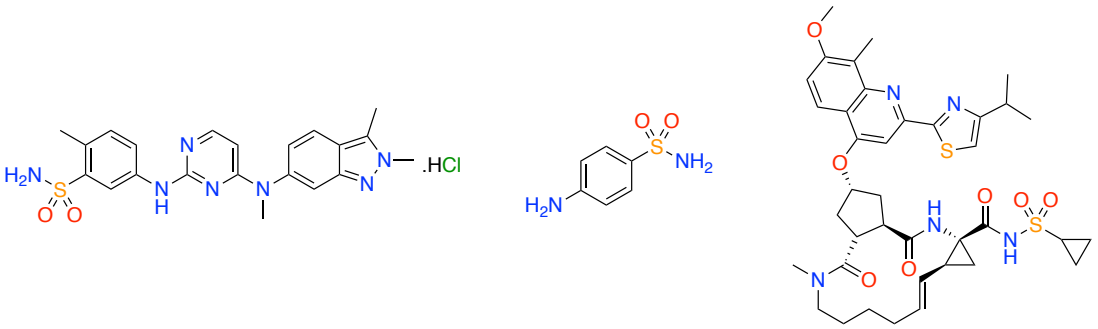


Scheme 1. 25 Iron-catalysed imidation of sulfoxides

Since their discovery a variety of methods for the synthesis of sulfoximines have been explored. Several strategies have been reported so far, both metal-free and metal catalysed, to achieve racemic and chiral sulfoximines. However, the most recent papers by Bull and Luisi[79] is the one that, above all the previously mentioned synthetic approaches, offers an easy and fast access to free NH-sulfoximines.

1.4.3 Sulfonimidamides: History

The sulfonamide (SAs) functional group **43**, is an important pharmacophore which can be found in more than 200 drugs currently on the market.[7,97] In 1932, a series of antibacterial drugs containing a sulfonamide functionality (such as Sulfanilamide **41**) were discovered and since then sulfonamides have been widely used in drug discovery. Molecules featuring a sulfonamide have been used for treatment in a wide variety of illness, such as high blood pressure, diabetes, bacterial infections and HIV (Figure 1. 12).[1,2]



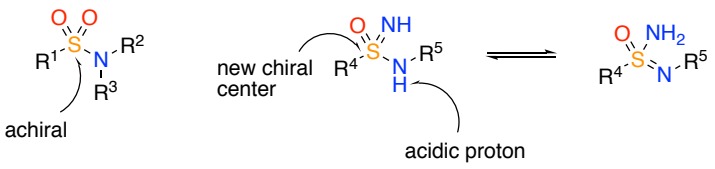
Pazopanib hydrochloride 40
Inhibitor of multiple protein tyrosine kinases

Sulfanilamide 41
Antibacterial

Simeprevir (Olysio®) 42
For hepatitis C treatment

Figure 1. 12 Examples of marketed drugs featuring a sulfonamide

Sulfonimidamides **44** (SIAs), the aza variant of a sulfonamide **43** (Figure 1. 13), have, on the other hand, found little application in drug discovery to date. This is quite surprising given the novel geometry of the functional group and its interesting chemical properties. These include increased stability, multiple hydrogen bond acceptor/donor functionalities and favourable physicochemical properties.[6,98–101] Replacing an oxygen for a nitrogen, not only generates a stereogenic centre at the sulfur atom, but also offers the possibility to further functionalise the nitrogen, allowing for additional structural diversification of the sulfonimidamides **44** (Figure 1. 13).[101]



Sulfonamide (43) **Sulfonimidamide (44)**

Figure 1. 13 General structure of sulfonamide and sulfonimidamide

Additionally, primary and secondary sulfonimidamides can exist as tautomers due to the proton exchange between the amide and the imide group. These tautomeric ratios are influenced by electronic effects of the substituent (R^5).[102]

It could be argued that the reason these molecules have been neglected in drug discovery is due to limited synthetic methodology and commercial availability.[103,104] From this point of view SIAs state-of-the-art resembles the one of sulfoximines 15 years ago (Figure 1. 14).

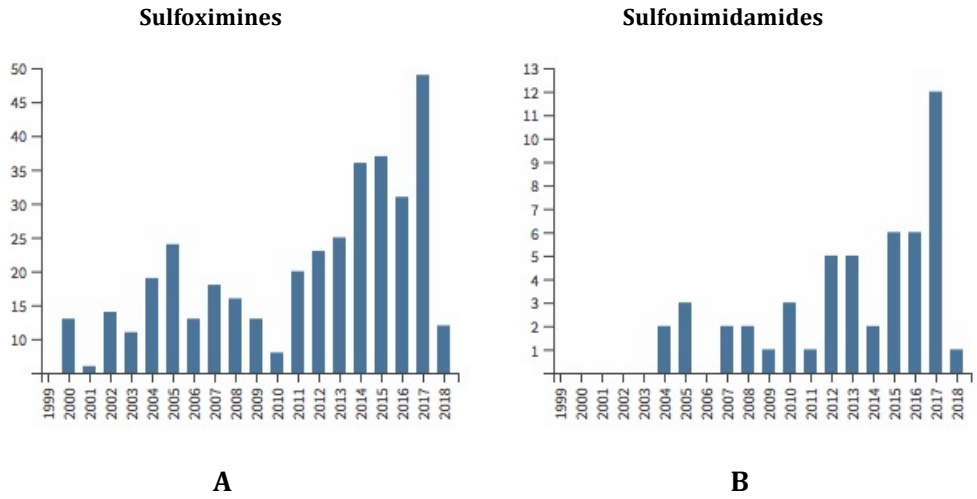
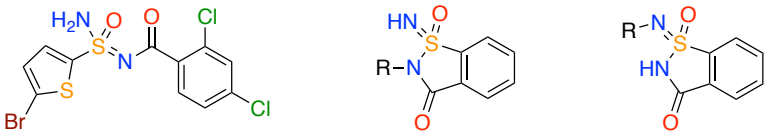


Figure 1. 14 Comparison of total publications by year of sulfoximines A and sulfonimidamides B (graph generated using Web of Science data)

As previously stated (see paragraph 1.4.1), interest in sulfoximines increased significantly over the last several years as evidenced by current compounds under clinical evaluation.[104] For SIAs, a clinical candidate is yet to be evaluated, however, several examples of compounds featuring sulfonimidamides have been reported (Figure 1. 15).[101,102] The most interesting one is the sulfonimidamide analogue of Tasisulam, an anti-cancer agent, which has been shown to have comparable inhibitor and antiproliferative properties *in vitro*.[3, 6, 7] However, further *in vitro* studies will be necessary to establish whether it could be a safer and more efficient alternative to Tasisulam (**45**).[105]



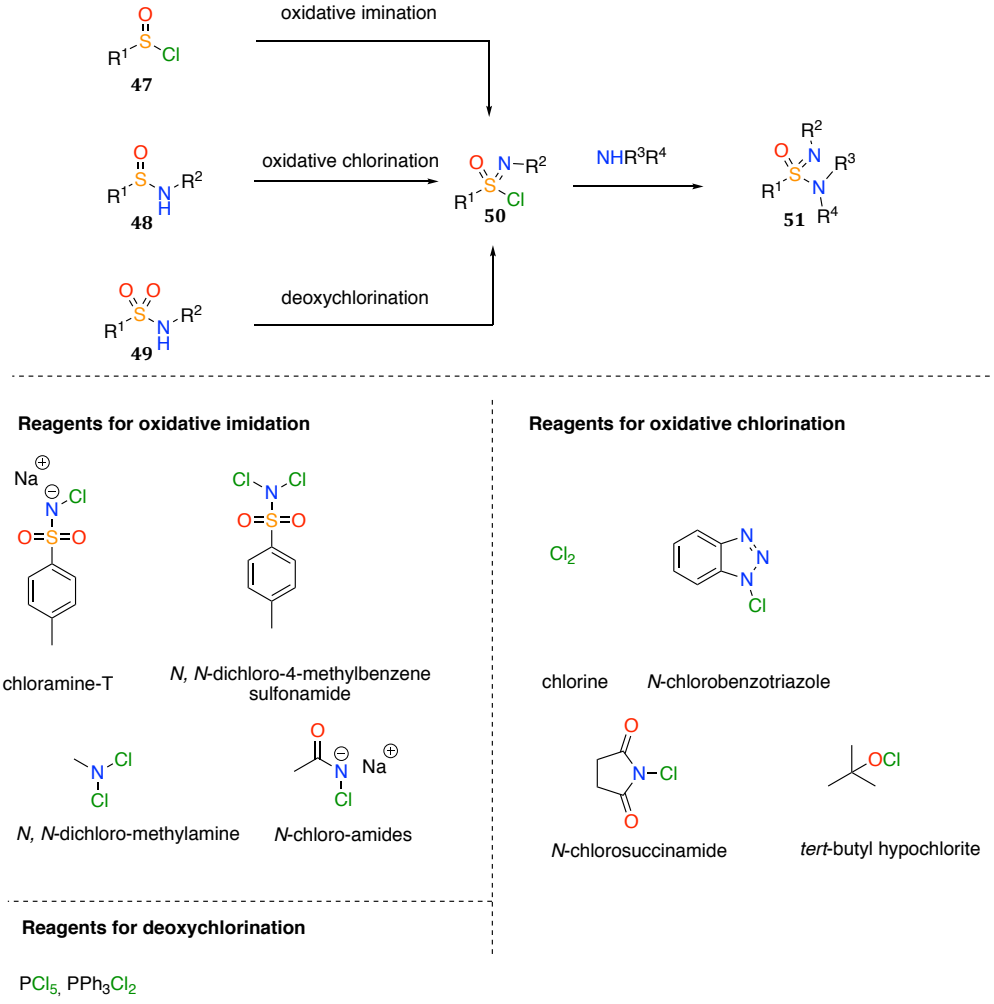
tasisulam analogue (45) **saccharin analogue I (46a)** **saccharin analogue II (46b)**

Figure 1. 15 SIAs analogues to anticancer agent tasisulam and novel saccharin azabioisosteres

1.4.4 Sulfonimidamides: Synthesis

1.4.4.1 Racemic sulfonimidamides

Levchenko and co-workers reported the first synthesis of sulfonimidamides in the 1960s.[107] Formation of SIA **51**, was accomplished *via* an oxidative imination of sulfinyl chloride **47** using a variety of different imidating reagents (chloramine-T, *N, N*-dichloro-methylamine, etc.), followed by nucleophilic addition of an amine (Scheme 1. 26).[102,107]

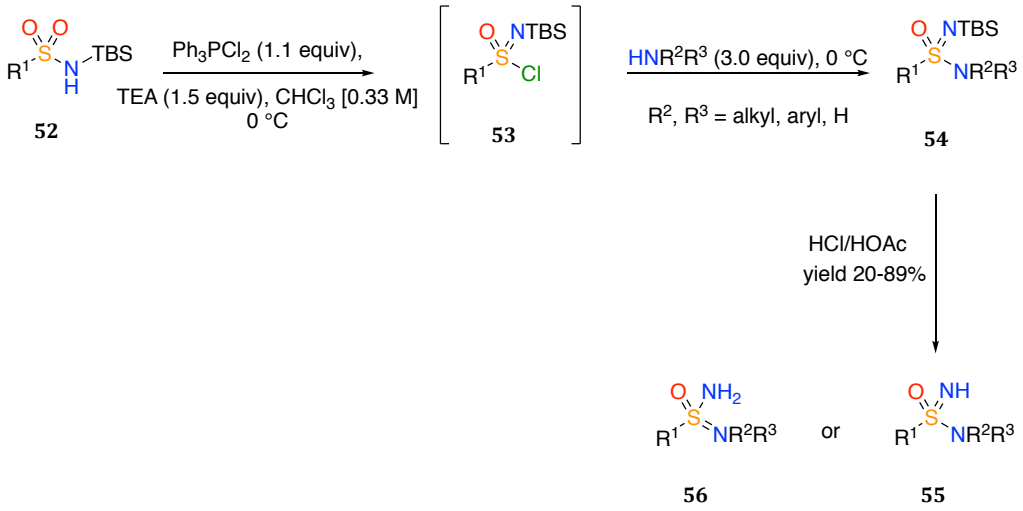


Scheme 1. 26 Previous methods and reagents for synthesis of SIA **51** *via* sulfonimidoyl chloride **50**

Since this first route for SIAs synthesis, few others followed, but formation of sulfonimidoyl chloride **50** intermediate was required in all the cases (see Scheme 1. 26). Sulfinamide **48,** for example, can also undergo oxidative chlorination to form sulfonimidoyl chloride **50** using chlorinating agents such as chlorine, *N*-chlorobenzotriazole, *tert*-butylhypochlorite and NCS.[102,108–110]

However, these methods have some limitations, like accessibility and stability of sulfinamides and sulfinyl chlorides, which are poor when compared to S(VI) compounds. Furthermore, chloramine-T and *tert*-butylhypochlorite reagents can be unstable and explosive, so they have to be handled with extra care.[110,111]

Later, Levchenko and co-workers reported the synthesis of sulfonimidoyl chloride **50** from readily available sulfonamides **49** using PCl_5 as chlorinating agent.[112,113] In 1993, Roy developed a new chlorinating agent, Ph_3PCl_2, which is more stable than PCl_5 and gave better results.[111] Recently, Chen and Gibson achieved a one-pot synthesis of SIAs converting silyl-protected sulfonamides **52** to sulfonimidamides **54** under mild reaction conditions using Roy's reagent Ph_3PCl_2 (Scheme 1. 27).[103]

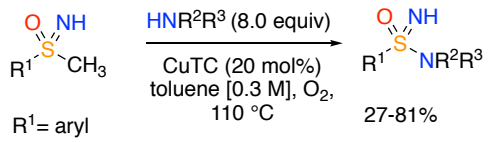


52 53 54 56 55

Scheme 1. 27 Deoxichlorination of silyl protected sulfonamide **52** via Ph_3PCl_2 reagent

However, all the previously reported protocols have limited substrate scope, require protecting groups, and resulting deprotection of the NH group may be challenging.[104]

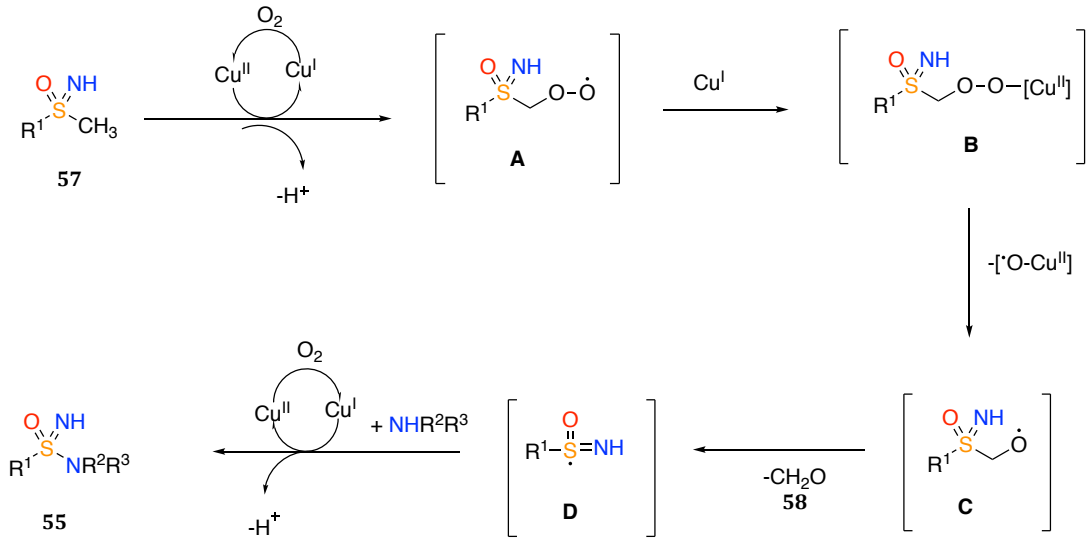
In 2016, Bolm and co-workers developed the first protecting group free synthesis of SIAs **55**. The reaction was copper-catalysed and lead to an unprecedented redox-neutral S-C to S-N bond exchange, which allowed the conversion of sulfoximines **57** to sulfonimidamides **55** (Scheme 1. 28).



57 **55**

Scheme 1. 28 Redox-neutral S-C to S-N bond exchange reaction converting a sulfoximine **57** into the free NH sulfonimidamide **55**

On the basis of these results and previous reports in the literature,[114–116] the authors describe a process, which is initiated by the interaction of copper salts (copper(I)-thiophene-2-carboxylate, CuTC) with the sulfoximines **57** (Scheme 1. 29).



57 **A** **B** **C** **D** **55**

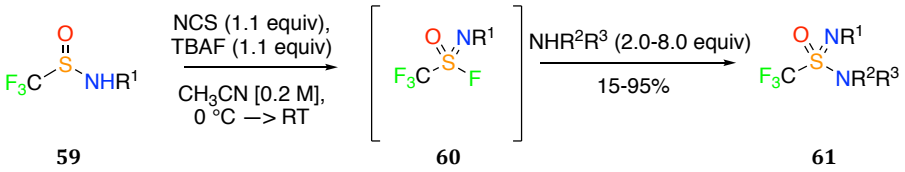
Scheme 1. 29 Proposed mechanism of Bolm's reaction

The reaction proceeds through a sequential deprotonation of **57** followed by a single electron transfer (SET) to give the corresponding radical adduct. Subsequent propagation with dioxygen generates radical intermediate **A**. At this point, copper(I) coordinates to peroxy intermediate **A** to give **B**, which then loses an oxygen and generates species **C**. When **C** eliminates formaldehyde **58**, sulfur-centered radical **D** is obtained, which further reacts with copper(I) and an amine to give SIA **55** as the product (Scheme 1. 29).

Even if Bolm's method is superior to the previously described, it has two major drawbacks: dioxygen atmosphere and prior synthesis of sulfoximines **57**, which may be challenging according to the R^1 group.[104]

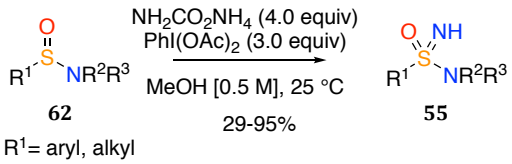
Just last year, four significant papers on synthesis of sulfonimidamides have been published in a rapid sequence. First, Oehlrich, Trabanco and co-workers described a

synthetic path towards trifluoromethyl SIAs **61** using trifluoro sulfinamide **60**, which had previously been unsuccessfully attempted by Bolm and co-workers *via* oxidative chlorination on sulfinamide **59**.[117] Fluorine incorporation is a useful strategy in Medicinal Chemistry as it can improve physicochemical properties in drug molecules.[118] For this reason 20% of the pharmaceutical contain at least one fluorine atom.[119] The Janssen scientists believed that sulfonimidoyl fluoride **60** would have been more electronically favoured and stable for the reaction. Therefore, reacting **59** with NCS and TBAF, **60** was generated, and subsequent addition of different amines gave the targeted SIAs **61**. The scientists at Janssen pharmaceutical hypothesised that the formation of **60** proceeded through the highly unstable sulfonimidoyl chloride, which then undergoes rapid *in situ trans*-halogenation to form intermediate **60** (Scheme 1. 30). [120]



Scheme 1. 30 Synthesis of trifluoromethylated SIAs **61**

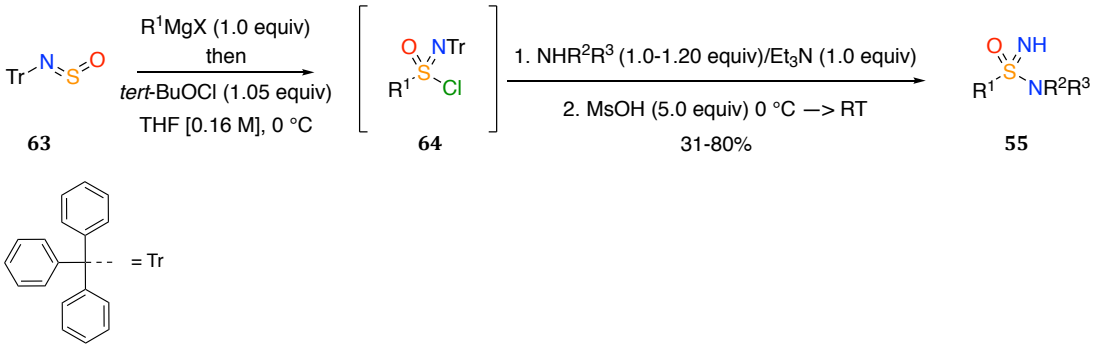
Then, Stockman and co-workers described the synthesis of unprotected tertiary sulfonimidamides **55** from sulfinamides **62** (Scheme 1. 31).[104] Inspired by Bull and Luisi's work on sulfoximines (see Scheme 1. 17),[79] various tertiary sulfinamides **62**, in the presence of diacetoxyiodobenzene and ammonium carbamate in methanol, gave the desired SIAs **55** in moderate to excellent yields (Scheme 1. 31). Most importantly, the reaction proceeds under open air (CO_2 evolution observed), at room temperature, and all the reagents are commercially available.[104] Although limited to tertiary sulfonimidamides, this approach provides a protecting group free route to unsubstituted NH SIAs.[102]



Scheme 1. 31 Direct transfer of NH into sulfinamides **62** to gain deprotected tertiary SIAs **55**

Then, Willis and co-workers disclosed a novel three component route to access sulfonimidamides using a bench stable sulfinylamine reagent **63**, readily synthesised in one step from commercial materials (Scheme 1. 32).[121] The resulting synthesis would

proceed combining TrNSO **63** with the selected organometallic, followed by fast addition of *tert*-butylhypochlorite to generate the sulfonimidoyl chloride **64**, which then undergoes nucleophilic displacement with a variety of amines to give the trityl protected sulfonimidamides. Finally, using methanesulfonic acid to remove the trityl protecting group the free NH sulfonimidamides **55** are obtained. (Hetero)aryl and alkyl organometallic reagents were well tolerated, and a wide range of primary and secondary amines were successfully employed to provide a wide reaction scope and sulfonimidamides in moderate to excellent yields (Scheme 1. 32).



Scheme 1. 32 Willis and co-workers three component synthesis of SIAs **55**

Furthermore, to verify the applicability of this new reaction for the synthesis of complex drug molecules, Willis and co-workers investigated the preparation of the sulfonimidamide analogue of the non-steroidal anti-inflammatory Celecoxib (Figure 1. 16).

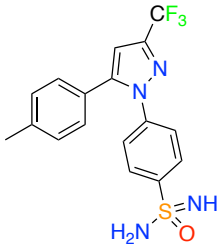
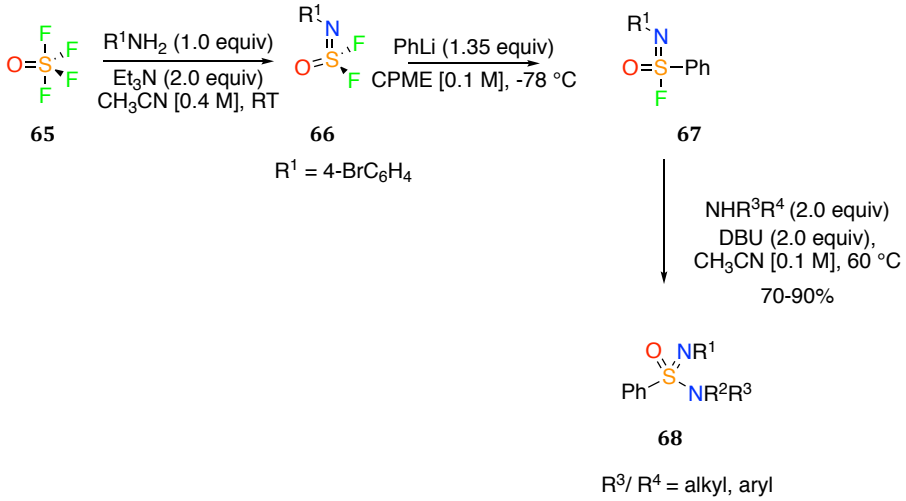


Figure 1. 16 Sulfonimidamide analogue to celecoxib drug molecule

Although sulfonimidamide analogue of celecoxib (Figure 1. 16) shows weaker inhibition of COX-2, the metabolic stability (especially the one measured in human liver microsomes) and liphophilicity are increased significantly.[121]

This year, Sharpless and co-workers expanded the scope of sulfur fluoride exchange (SuFEx) click chemistry. First, the thionyl tetrafluoride **65** was synthesised, and

combined with an amine to give **66**, which was further reacted, under optimised conditions, with phenyllithium. The monosubstitution of the fluorine atom generates the stable intermediate sulfonimidoyl fluoride **67**, which upon treatment with amines produced sulfonimidamides **68** (Scheme 1. 33).[122]

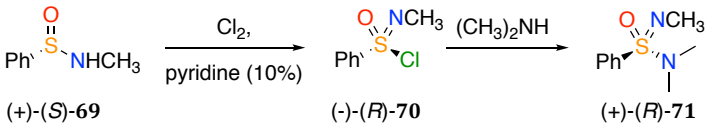


Scheme 1. 33 SuFEX chemistry for sulfonimidamides **68** synthesis

The previously described procedure is a versatile and fast approach to complex sulfonimidamides, however, this is limited by the initial formation of thionyl tetrafluoride **65**. For the compound synthesis, specific equipment (autoclave) is required and the process is associated with a risk of explosion given the nature of the gas involved (NO_2, O_2, SF_4).

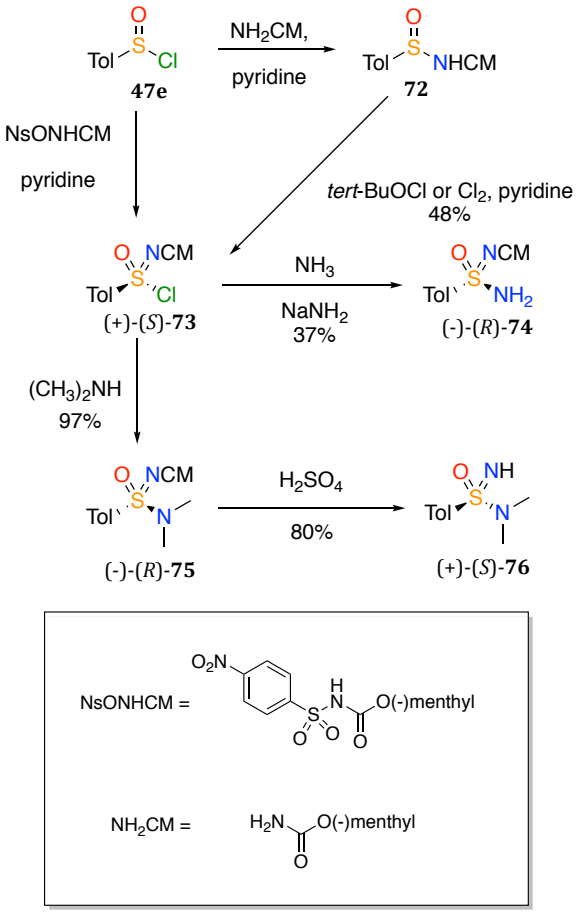
1.4.4.2 Chiral sulfonimidamides

To date, there are few procedures to synthesise enantioenriched sulfonimidamides. Johnson and co-workers were the first to report a synthesis of chiral sulfonimidamides in 1971.[123] Enantiopure sulfinamide **69** was reacted together with Cl_2 gas in the presence of pyridine to give sulfonimidoyl chloride with retention of configuration, addition of pyridine prevented racemisation of the starting material. Treatment of **70** with dimethylamine gave sulfonimidamide **71** as the opposite enantiomer and in excellent *ee* (Scheme 1. 34).



Scheme 1. 34 Johnson's synthesis of chiral sulfonimidamide **71**

Later, Cram and Jones reported the preparation of two chiral arylsulfonimidoyl chlorides, which were converted into the corresponding sulfonimidamides (SIAs) **74** and **76**, going *via* two different routes (Scheme 1. 35).[100]

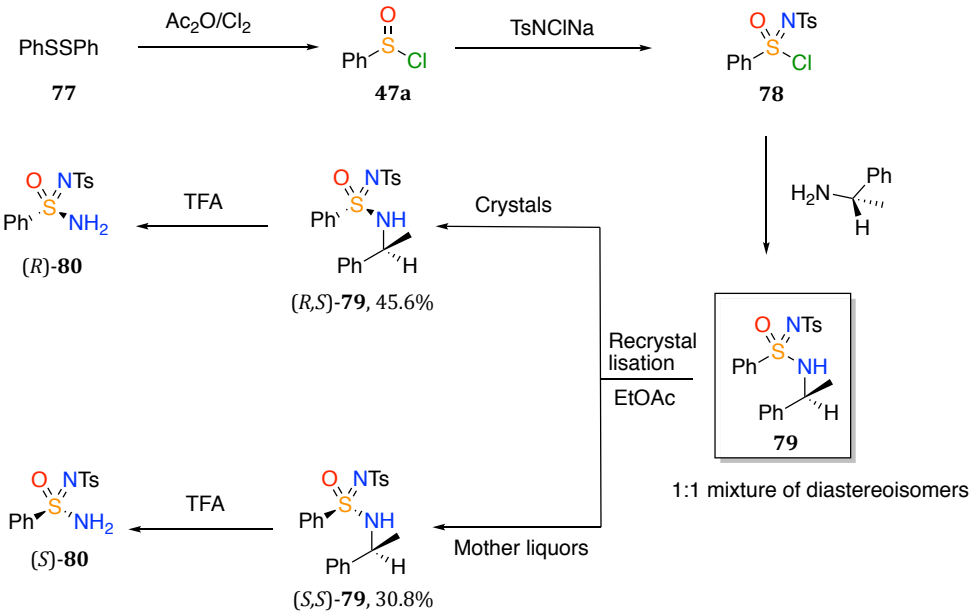


Scheme 1. 35 Two different routes towards chiral sulfonimidamides (SIAs)

In the first procedure, sulfinyl chloride **47e** was added to (-)-menthylcarbamate (NH_2CM) to give racemic sulfinamide **72**, which was chlorinated with either *tert*-BuOCl or Cl_2 to give **73** as a mixture of two diastereoisomers. After a rapid chromatography and crystallisation, only enantiopure (+)-(*S*)-**73** was isolated. Subsequent reaction with sodium amide in liquid ammonia gave optically pure SIA **74** (Scheme 1. 35). In the second approach, **47e** undergoes carbomenthoxynitreneation, catalysed by pyridine, to obtain (+)-(*S*)-**73** sulfonimidoyl chlroride. The chlorine is then replaced by dimethylamine, with inversion of configuration, to provide the optically active SIA **75.** Hydrolysis with concentrated sulfuric acid yielded the chiral sulfonimidamide (+)-(*S*)-**76** (Scheme 1. 35).[100]

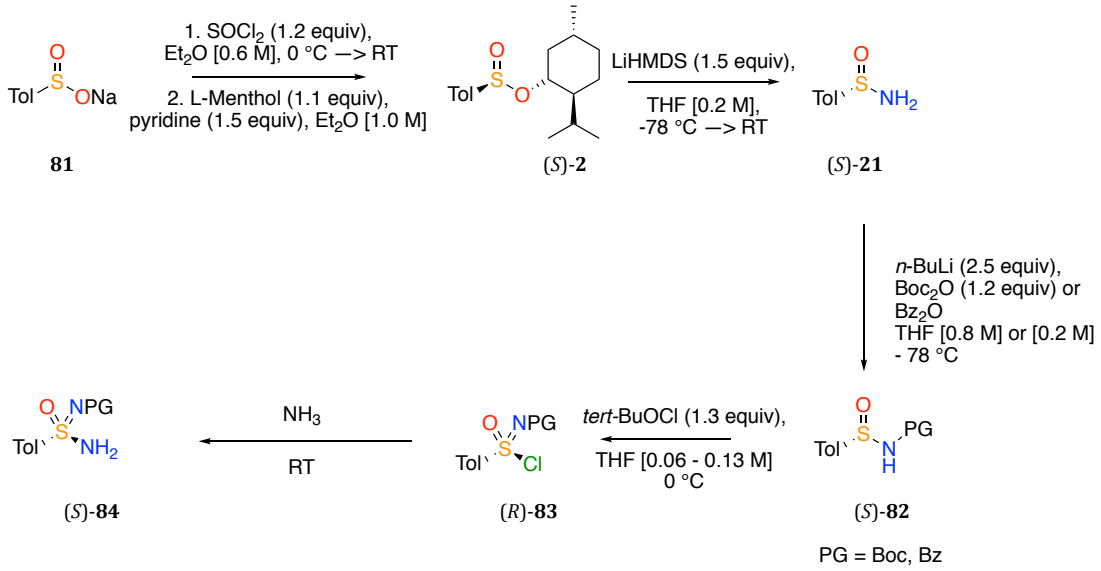
In 1989, Onami and co-workers reported a synthetic route to both diastereoisomers of *N*-(*p*-tolylsulfonyl)benezenesulfonimidamide **80**. Racemic sulfonimidoyl chloride **78**

was achieved using known literature procedures,[107,124] and then reacted with (*S*)-α-methylbenzylamine to afford the corresponding sulfonimidamide **79** as a mixture of diastereomers. Much to the author's surprise, diastereomer (*R,S*)-**79** was insoluble in ethyl acetate, therefore it was possible to isolate it as crystals, whilst the other diastereomer was completely soluble in the organic solvent. Finally, (*S*)-α-methylbenzylamine was easily cleaved using trifluoroacetic acid to give the desired sulfonimidamides **80**. Both compounds were subsequently transformed into chiral selenium diimide reagents (Scheme 1. 36).[125]



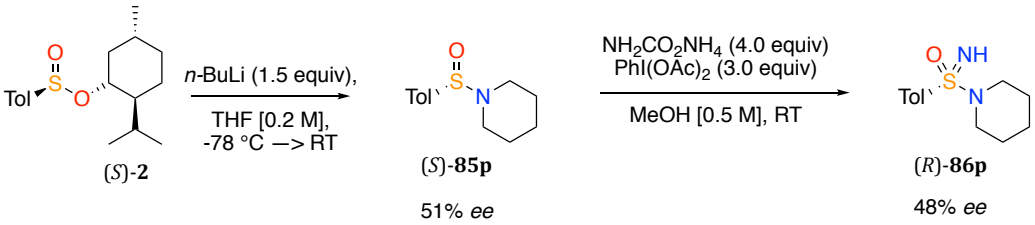
Scheme 1. 36 Synthesis of sulfonimidamides **80** *via* resolution process

In 2010, Bolm and co-workers reported the synthesis of enantiopure *N*-benzoyl and *N*-*tert*-butyloxycarbonyl-protected sulfonimidamides **84**, by a four step sequence (Scheme 1. 37). First, commercially available racemic *p*-toluenesulfinic acid salt **81** was transformed to menthyl ester **2** with >99% de. Then, LiHMDS was added and the corresponding sulfinamide **21** was formed in 99% *ee* and 87% yield after recrystallisation. Upon treatment with sulfinamide **21** with di-*tert*-butyl dicarbonate or benzoic acid anhydride, the corresponding protected sulfinamide **82** were obtained with retention of stereochemistry. Oxidative chlorination of **82** and subsequent treatment with liquid ammonia, the desired enantioenriched sulfonimidamides **84** were achieved in two steps and 99% *ee*. The absolute configuration of the chiral sulfur atom was determined by experimental and theoretical circular dichroism spectroscopy, which allowed determination of the spatial arrangement of substituents with high degree of probability. The absolute configuration assignment matched the results from a single crystal X-ray crystalography analysis of **84** (Scheme 1. 37).[126]



Scheme 1. 37 Four steps-sequence of enantiopure SIAs **84**

Finally, Lücking, Stockman and co-workers in their recent publication on the synthesis of SIAs explored the stereospecificity of their work. Using Andersen's auxiliary as starting material, the enantioenriched sulfinamide **85p** was prepared in 51% *ee*, following a previously published methodology.[127] The oxidative addition of ammonium carbamate to sulfinamide **85p,** gave SIA **86p** in 48% *ee* (Scheme 1. 38).[104]



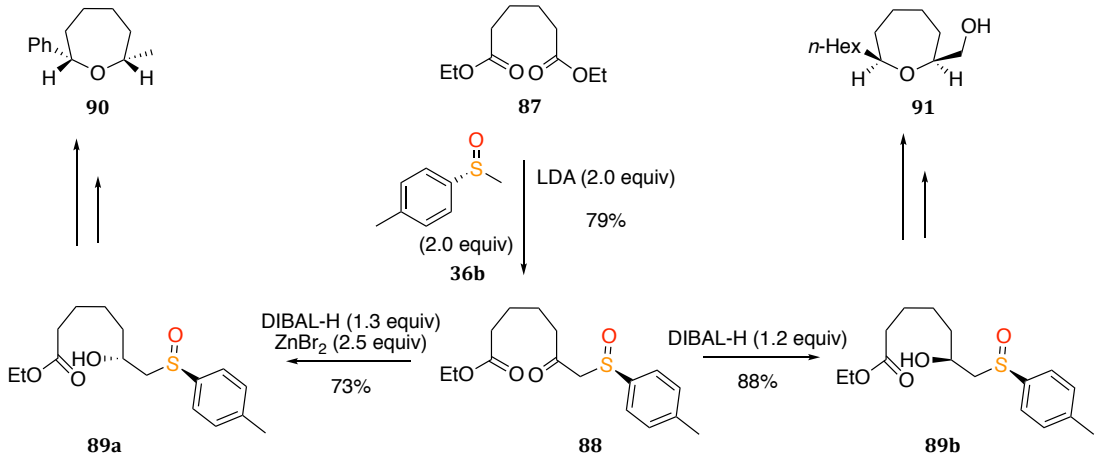
Scheme 1. 38 Synthesis of enantiopure sulfonimidamide **86p** using Lücking and Stockman reaction conditions

Even though, many efforts towards the synthesis of enantiopure sulfonimidamides have been placed so far, the methodologies still suffer from a limited reaction scope (the aryl group on the SIA is prevalently *p*-Tolyl group), and modest/good chemical yields.

1.5 Chiral sulfur(IV/VI) reagents in synthesis

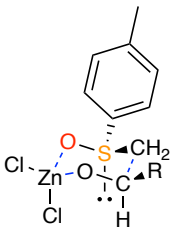
1.5.1 Chiral sulfoxides

Sulfoxides are well suited to the role of chiral transfer agent. The reasons can be found in their structure: the large steric differences between its substituents, which range from a lone pair to large alkyl and aryl groups, makes the molecule highly differentiated. Furthermore, both sulfur and oxygen have lone pairs of electrons available to coordinate to Lewis acidic functionality, often promoting highly ordered transition states. Finally, sulfur can form covalent bonds with heteroatoms and can be easily cleaved under mild conditions. Chiral auxiliary methodologies aim to produce relatively simple sulfoxides with very high enantiomeric purity. Sulfoxide auxiliaries are often employed in diastereoselective reductions of β-ketones, as exemplified by Solladié's formal synthesis of (+)-isolaurepan (Scheme 1. 39).[128]



Scheme 1. 39 Synthesis of (+)-isolaurepan

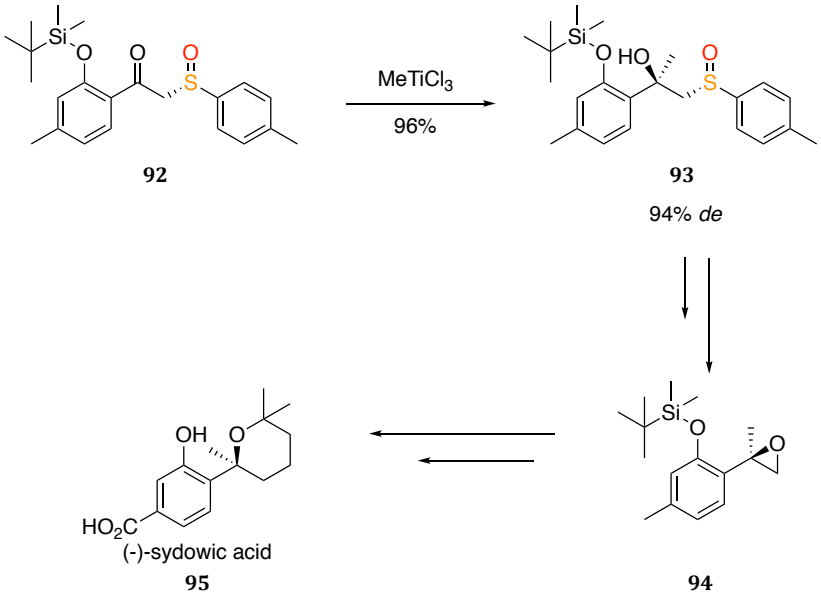
The diastereoselectivity of the reaction can be changed by addition of Lewis acids, such as $ZnBr_2$, a phenomenon readily explained by a familiar chair-like transition state (Figure 1. 17).[129]



Transition state for **89a**

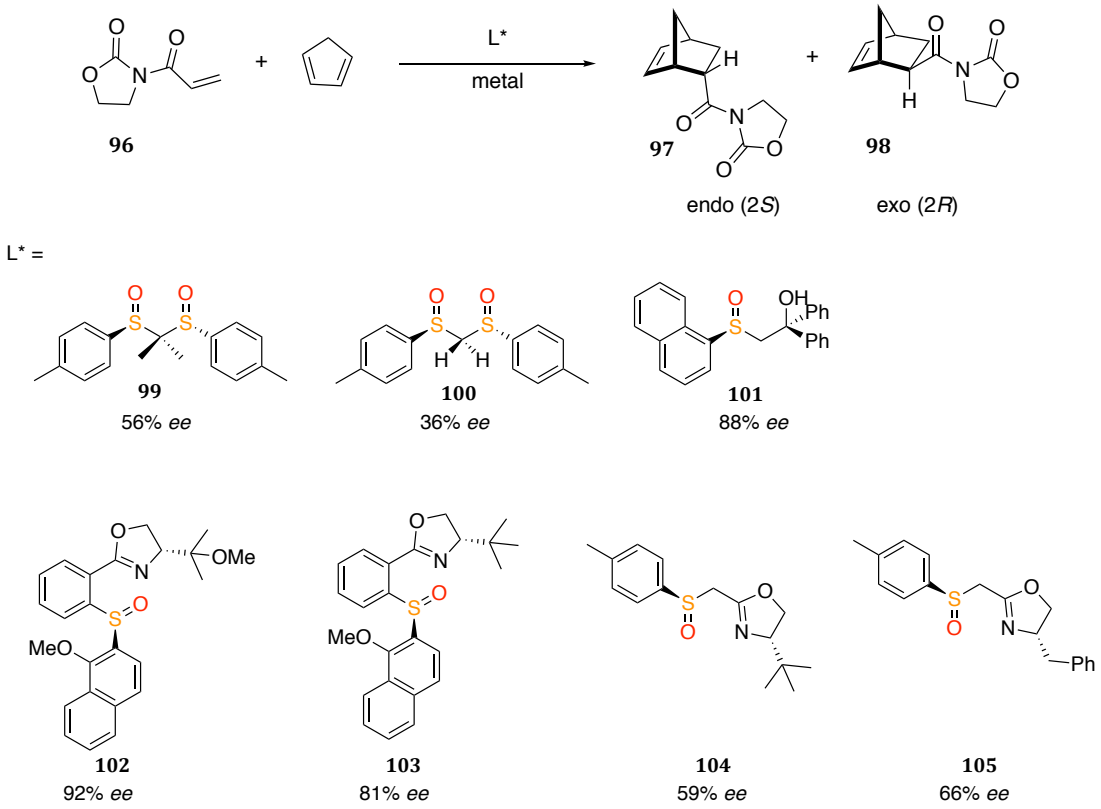
Figure 1. 17 Proposed transition state for DIBAL-H reduction in the presence of $ZnCl_2$

Chiral sulfoxides have been also employed in alkylation reactions. When aromatic β-ketosulfoxides, bearing ether groups in the *ortho* position, were reacted with trichloromethyltitanium, excellent results were reported. This methodology was applied for (-)-sydowic acid **95** synthesis (Scheme 1. 40).[130]



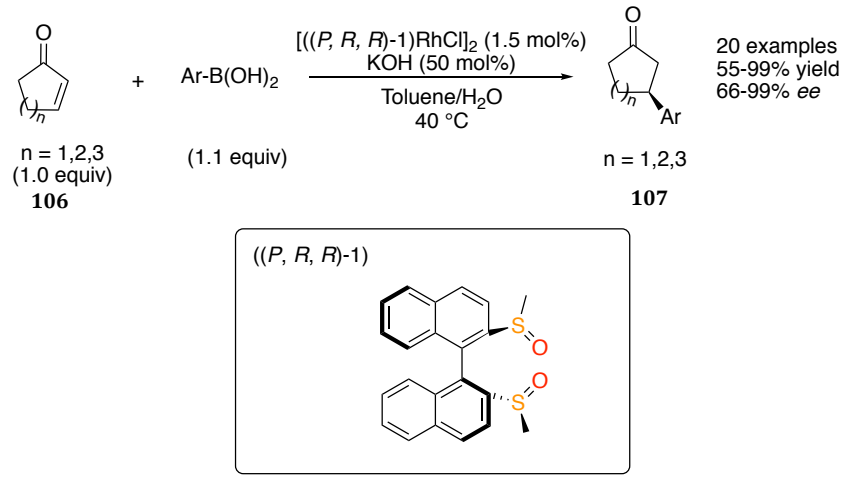
Scheme 1. 40 Synthesis of (-)-sydowic acid

The application of sulfoxides as ligands for transition metals has been less explored than their use as chiral auxiliaries.[129,131] The first example of the application of chiral sulfoxides in a catalytic Diels-Alder reaction with excellent diastereoselectivity, was reported by Kiar and Fernandez in 1993 (Scheme 1. 41).[132] A series of metals were tested in the reaction (i.e. FeI_3, $MgBr_2$, CuI_2) however, MgI_2 proved to be the best for ligand **102**, obtaining the adduct in 92% *ee*.



Scheme 1. 41 Diels-Alder reaction with chiral sulfoxides ligands

Recently Dorta reported the first highly enantioselective reaction using a bis-sulfoxide ligand.[133] The rhodium/bis-sulfoxide catalysed conjugate addition of aryl boronic acids to a α,β-unsaturated ketone **106** to afford ketone **107** in excellent yields and enantioselectivity (Scheme 1. 42).



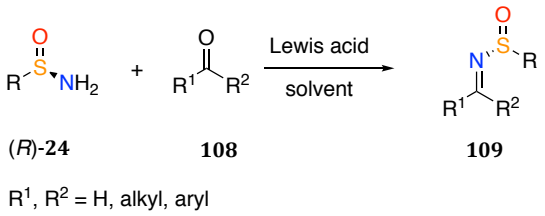
Scheme 1. 42 Enantioselective synthesis *via* bis-sulfoxide ligand

In this section different types of reactions, emplyoing enantiopure sulfoxides, have been examined. Sulfoxides proved capable to control the stereoselectivity delivering the desired products in high *ee*. We must highlight though that, the wide majority of the above described S(IV) reagents employed both in metal catalysis and asymmetric synthesis derive from Anderson's auxiliary.[21,22] This means that the electronic and steric studies of the reactions are rather limited to the aromatic substituent on the sulfur.

1.5.2 Chiral sulfinamides

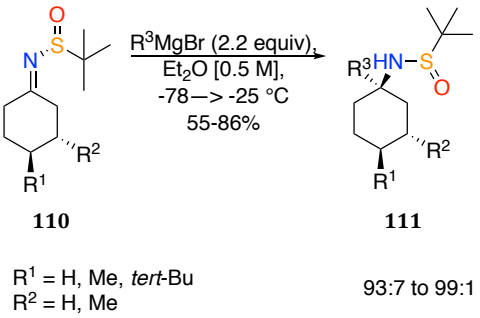
Over recent years sulfinamides have been studied as useful and versatile chiral building blocks for the synthesis of chiral amines, formed by the addition of a nucleophile or by reduction. Chiral amines are of great value not only in the chemistry of natural products and as active pharmaceutical ingredients (Tamiflu, Plavix, Januvia, etc.), but also as chiral auxiliaries and as ligands for homogeneous catalysis.[134–137]

Sulfinamides **24** can be condensed with aldehydes or ketones **108** to form *N*-sulfinimines **109** in good yields (Scheme 1. 43). Nucleophilic addition, followed by cleavage of sulfinyl group, leads to chiral primary amines.



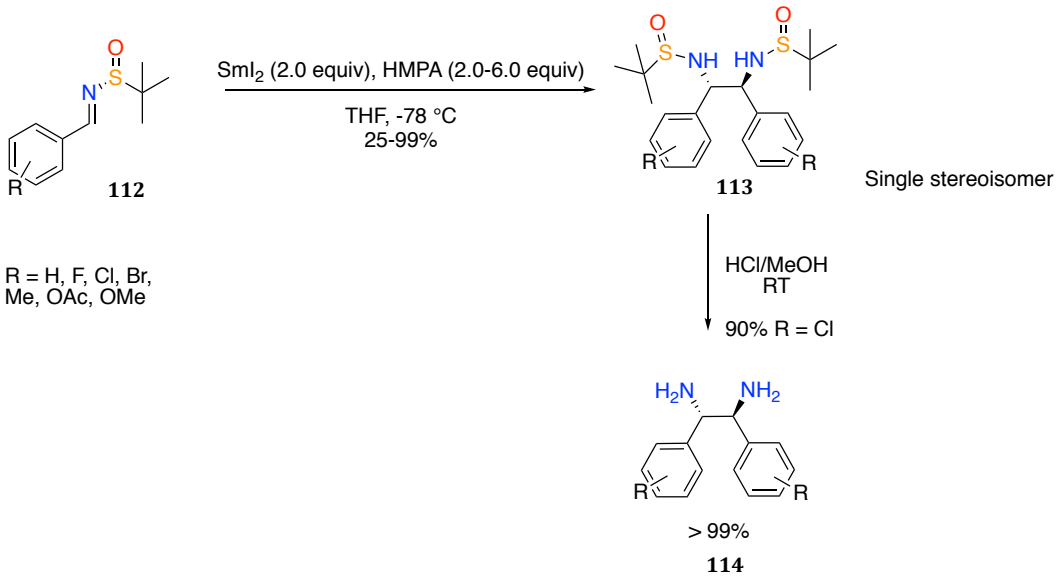
Scheme 1. 43 Synthesis of sulfinimines

In the past, Davis and Ellman employed this methodology extensively to produce a variety of chiral amines starting from *p*-tolyl and t*ert*-butyl sulfinamides (Scheme 1. 44).[138–142] Sulfinamides **111** were obtained in high yields and selectivity, however it is believed that the selectivity of the reaction was directed by the R^1 and R^2 groups on the cyclohexane ring rather than the sulfinamide moiety.[143]



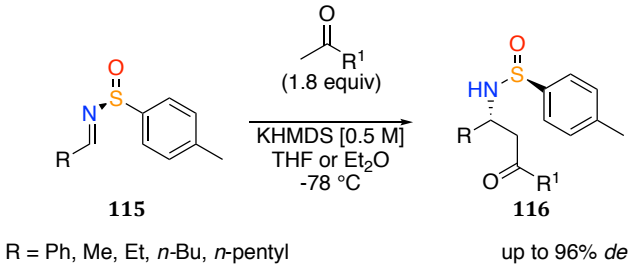
Scheme 1. 44 Asymmetric synthesis of α-substituted cyclohexylamines

Later, a novel and highly efficient synthesis of C_2-symmetrical vicinal diamines was also developed by Xu and co-workers. Acid mediated cleavage of the sulfinyl group led to enantiopure diamine products **114** (Scheme 1. 45).[75]



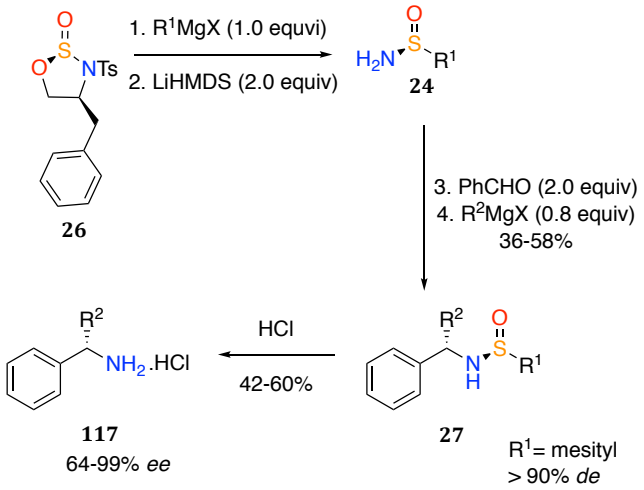
Scheme 1. 45 Asymmetric synthesis of C_2-symmetrical vicinal diamines

Even if the addition of metallo enolates to sulfinyl imines to afford β-amino esters has been previously reported by the groups of both Ellman[144] and Davis,[145] the diastereoselective addition of ketone enolates to sulfinimines has received less attention. In this light, Davis and co-workers reported a practical synthesis towards β-amino ketones from addition of potassium enolates of methyl ketones to sulfinimine **115** with high diastereoselectivity (Scheme 1. 46).[146]



Scheme 1. 46 Asymmetric synthesis of β-amino ketones

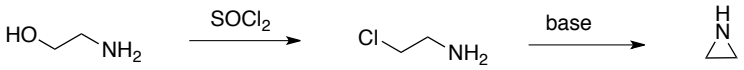
As mentioned earlier, also in our group synthesis of chiral amines has been achieved (see chiral sulfinamides, Scheme 1. 11) employing chiral sulfinimines (Scheme 1. 47).[42,43] Adding an aldehyde to **24** leads to the *in situ* formation of a sulfinimine which then is further reacted with a Grignard reagent to give sulfinamide **27** in good yield and diastereoselectivity (33-58%, >90% de). Unlike other analogous reactions previously reported, this method allows for the production of an amine bonded to a large number of R^2 groups, dependent upon the choice of Grignard reagent and carbonyl compound. There are a number of advantages to this particular one-pot procedure, including; the rapidity of synthesis, the low cost of the chiral auxiliary and the elimination of unnecessary purifications steps, hence the minimisation of large volumes of required solvents.[20, 21]



Scheme 1. 47 One-pot, five steps procedure towards chiral amines

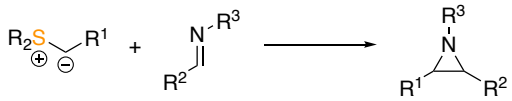
Moreover, chiral sulfinimines, derived from sulfinamides, are important building blocks for synthesis of aziridines. These nitrogen heterocycles are versatile building blocks for the synthesis of many biologically important molecules (amino acids,[147,148] alkaloids[149] and heterocycles[150,151]). In recent years a variety of methods have been optimised and developed for synthesising functionalised aziridines. The nucleophilic

displacement of a leaving group with amino groups at the 2-position represents the oldest strategy for the synthesis of aziridines as reported by Gabriel (Scheme 1. 48).[152,153]



Scheme 1. 48 Gabriel's synthesis of aziridines

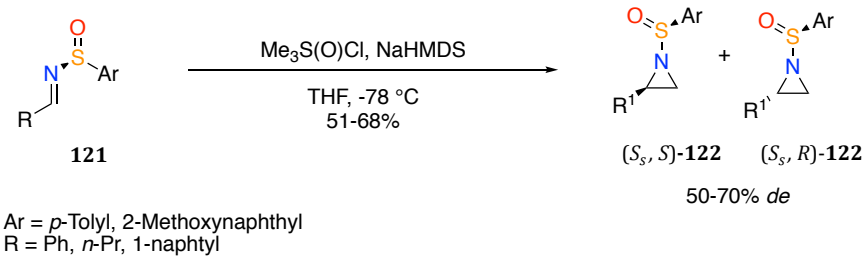
Direct aziridation of alkenes is also another appealing way to produce aziridines given the large variety of alkenes available.[154–157] Analogous to the addition of nitrenes to alkenes, the reaction where an ylide is treated with an imine with formation of "betaine" followed by a consequent heteroatom elimination to form the aziridine product, is a well-known process. Although, this methodology didn't become synthetically valuable until the development of dimethylsulfonium methylide **118** reagent developed by Corey and Chaykovsky (Scheme 1. 49).[12]



118 **119** **120**

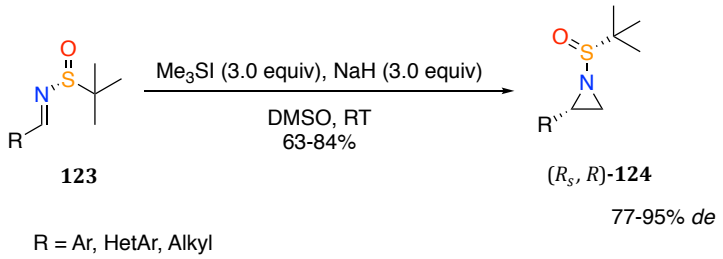
Scheme 1. 49 Ylide-mediated aziridination formation

Twenty years ago, Garcia-Ruano[158,159] and Davis[160] reported the use of chiral sulfinyl imines to direct a Corey-Chaykovsky[12] type ylide aziridination. Garcia-Ruano reported, instead, the aziridines synthesis reacting *para*-toluenesulfinyl and *tert*-butyl sulfinyl imine, derived from benzaldehyde and cinnamaldehyde, with both dimethyloxosulfinium methylide and dimethylsulfonium methylide reactants. The best yield obtained was 72% (70% and 64% *de*) for benzaldehyde and cinnamaldehyde derived substrates respectively.[158,159] Davis, on the other hand, focused his research on the addition of dimethyloxosulfonium methylide with *p*-toluenesulfinyl imines, to give 1-napthaldehyde and butanal **122** in good yields (51-68%) and moderate diastereomeric excess (50-70%) (Scheme 1. 50).[160]



Scheme 1. 50 Davis' aziridine synthesis

Inspired by the previous work done by Garcia-Ruano and Davis, also in the Stockman group synthesis of aziridines, *via* Corey-Chaykovsky[12] reaction, was pursued (Scheme 1. 51). A range of aromatic, heterocyclic and aliphatic *tert*-butylsulfinyl imines were reacted with dimethylsulfonium methylide forming aziridines in 63-84% yields and 77-95% diastereomeric excess (Scheme 1. 51).[161]



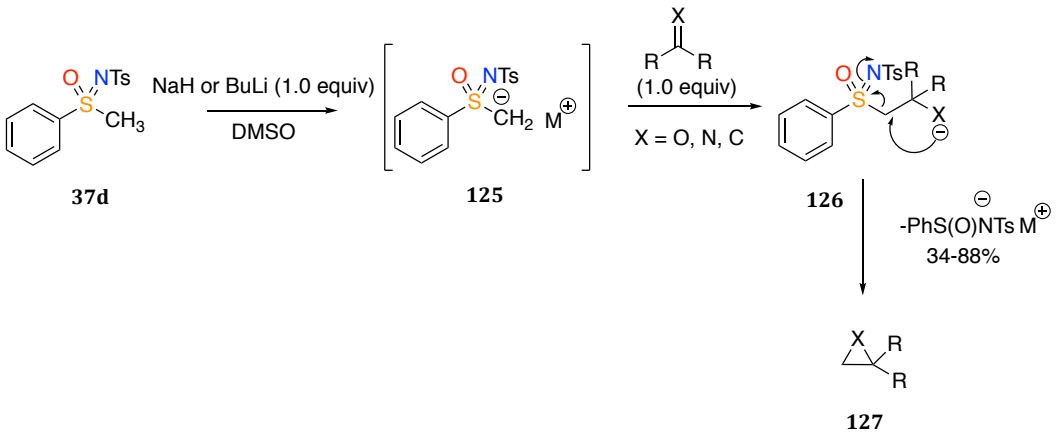
Scheme 1. 51 Stockman's aziridines synthesis

Sulfinamides' role in the formation of aziridines and amines is well established. Currenlty on the market only *p*-tolyl and *tert*-butyl sulfinamides are available, therefore, once a modular synthesis of chiral sulfinamides will be achieved, we predict that use of sulfinamides as reagent will increase significantly.

1.5.3 Chiral sulfoximines

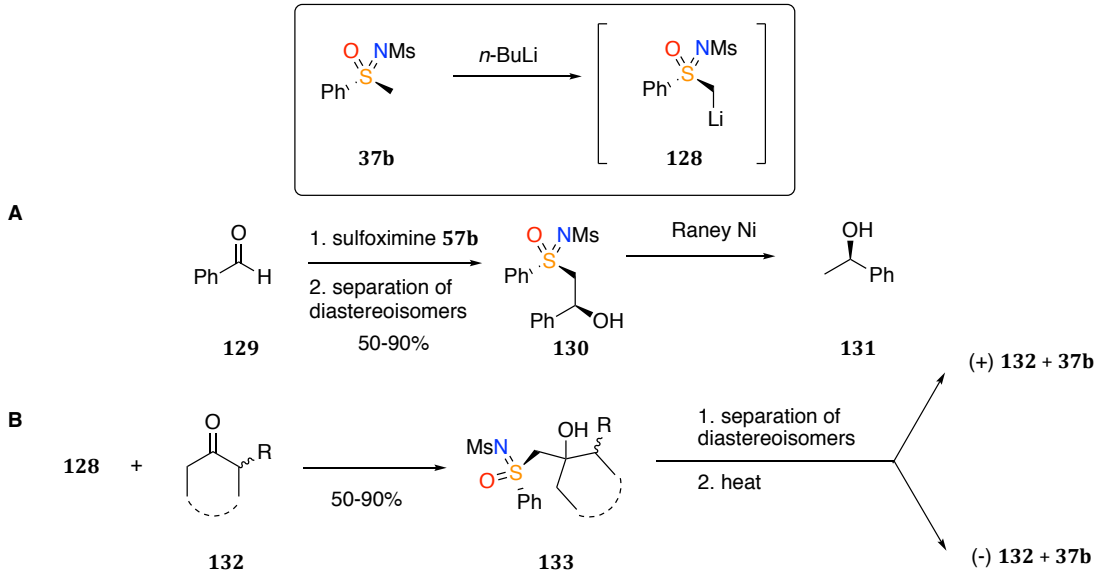
1.5.3.1 Applications in asymmetric synthesis

In 1970 sulfoximines were still fairly novel compounds therefore their properties and uses were little known. Johnson was the first to investigate their uses in asymmetric synthesis, initially examining sulfonimidoyl stabilised carbanion's role as a chiral auxiliary to access epoxides, cyclopropanes and aziridines (Scheme 1. 52).[52,67,162–167]



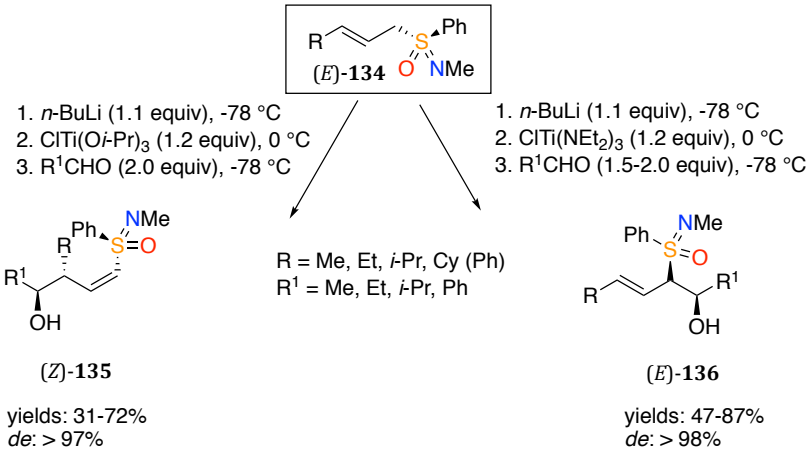
Scheme 1. 52 Sulfoximines as chiral auxiliaries

A few years later, Johnson saw the potential of lithiated *N*-methyl sulfoximine as nucleophiles to react with aldehydes and ketones.[168,169] In the first case, both enantiomers of the secondary alcohol were separated, by column chromatography and after desulfurisation (Raney nickel) were collected.[52,67,162–166,170] On the other hand, when the sulfoximine was mixed with ketone and heated up enantiomeric and diastereomeric products were obtained (Scheme 1. 53).



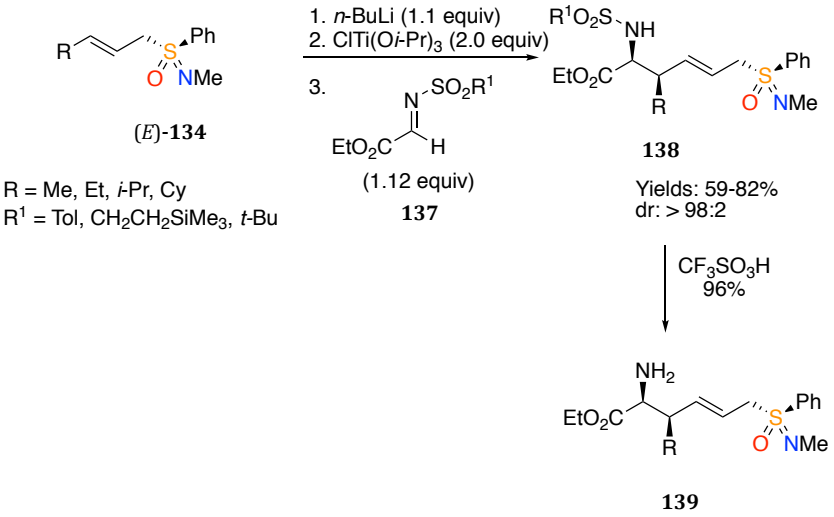
Scheme 1. 53 A) Reaction of **128** with aldehyde **129**; **B)** Reaction of sulfoximine **128** with ketone **132**

In 1995, Gais reported the use of sulfoximine coordinated with titanium as a chiral auxiliary.[171] A few years later subsequent publications were released on the synthesis of β- and δ-sulfonimidolyl substituted homoallylic alcohols starting from enantiopure allylic sulfoximine **134**.[172] In general, the reaction proceeds with good stereocontrol according to the choice of the titanium reagent involved (Scheme 1. 54).



Scheme 1. 54 Gais' use of sulfoximines **134** as auxiliary

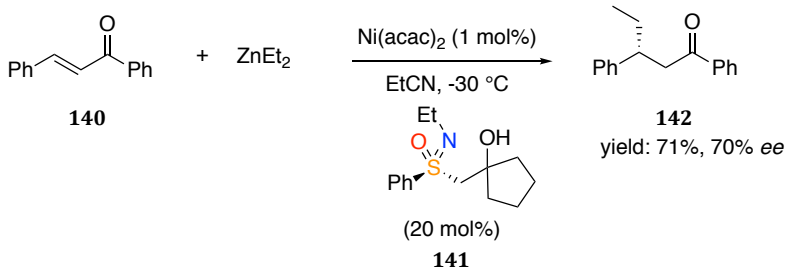
Recently, a synthesis towards the formation of azaspirocycles has been reported.[173] The alkenyl sulfoximine **134** could also be reacted together with *N*-protected imino ester **137** to give the vinyl sulfoximine product **138** in high yield and selectivity.[174] The important advantage of this methodology is the possibility to regenerate the auxiliary (Scheme 1. 55).[82,175,176]



Scheme 1. 55 First steps towards the asymmetric synthesis of aza-spirocycles

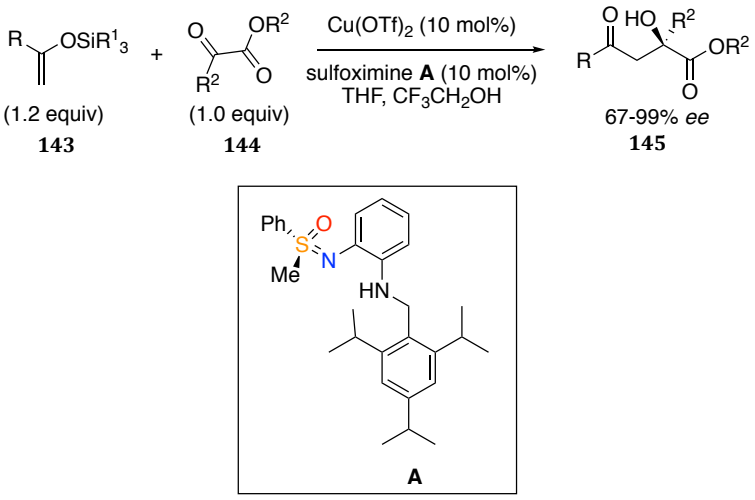
1.5.3.2 As chiral ligands

In the early 1990's several investigations to use sulfoximine derivatives as chiral ligands in metal catalysed processes were performed. The first report describes the use of β-hydroxysulfoximines **140** in a nickel-catalysed synthesis where the product of reaction (**142**) of chalcone with diethyl zinc was in fact formed in 71% yield and 70% *ee* (Scheme 1. 56).[177]



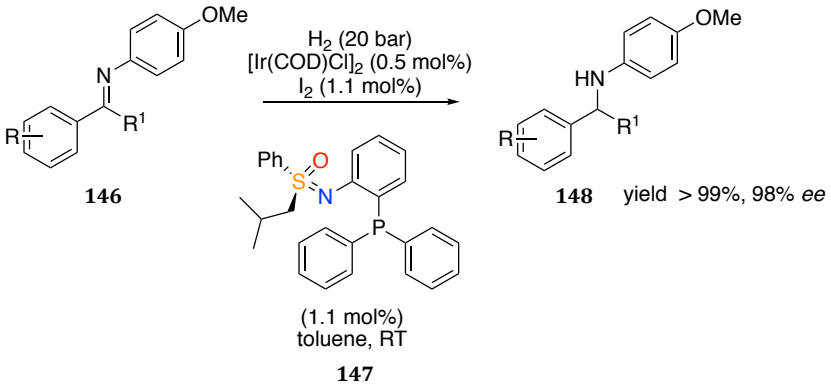
Scheme 1. 56 Use of β-hydroxysulfoximines as ligand, in a nickel catalysed synthesis

After this first application many others followed; β-hydroxysulfoximines were also used for enantioselective borane reduction of ketones and imine derivatives,[178–181] asymmetric 1,2-addition of dialkylzinc reagents on aldehydes,[182–184] and asymmetric cyanohydrin formations.[185,186] In the reactions described so far the zinc reagents had a dual role; they were both involved in the catalyst formation and as alkyl, aryl carrier. The sulfoximines on the other hand had unique properties as ligands.[187–189] Bolm and co-workers reported a valuable mechanistic study revealing how certain types of sulfoximines (**A**) were able to interact with copper-salts in order to direct the C-C bond formation enantioselectively (Scheme 1. 57).[187,188]



Scheme 1. 57 Bolm's asymmetric copper catalysis

Finally a copper-catalysed *N*-arylation[190] gave the first example of P,N-type sulfoximines **147**, [191,192]which were applied for an iridium catalysed hydrogenation of imines. [191,192] The reaction gave excellent enantioselectivity (up to 98% *ee*) and furthermore it was the first example of an asymmetric transition metal-catalysed reaction with a phosphenyl sulfoximine ligand (Scheme 1. 58).



Scheme 1. 58 Imine hydrogenation reaction catalised by iridium

Although sulfoximines have been overlooked over the past 15-20 years, they are now gaining a growing interest from the chemistry community as a key component in the organic chemist's "toolbox". Their role in asymmetric synthesis and as ligands in metal catalysis has been well explored, providing a straightforward approach towards elaborate products with a high degree of selectivity.

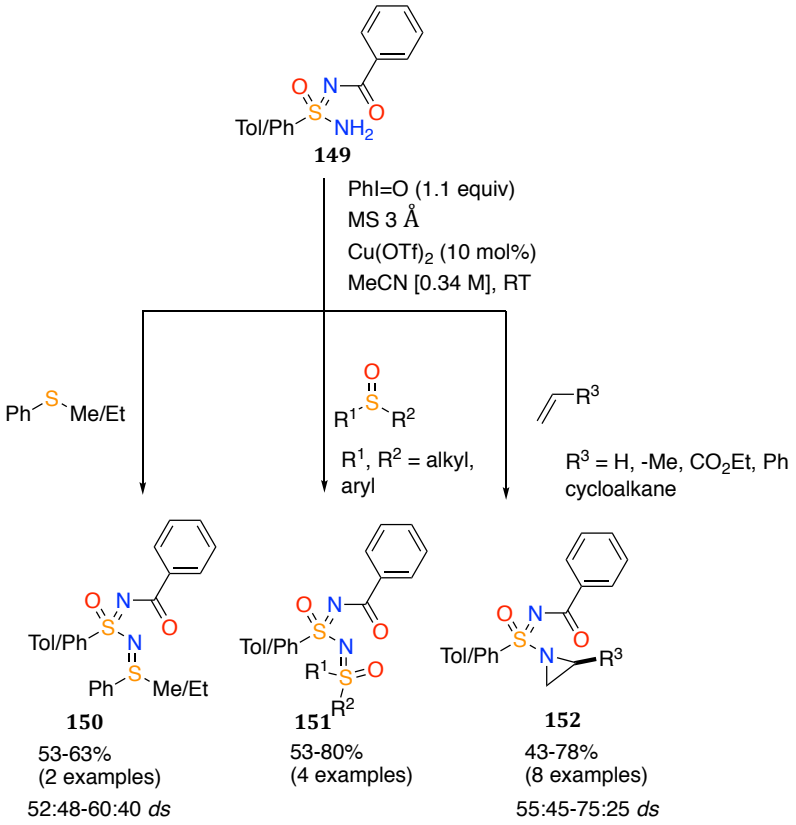
1.5.4 Sulfonimidamides

Nitrogen atoms are abundant in all organisms in Nature, primarily in alkaloids and amino acids. Therefore, interest in new methodologies to insert nitrogen atom into

different molecules keeps growing. Until now, the most popular methodology for C-N bond construction was given by reacting electrophiles with amines (S_N2 type reaction)[193,194] and by functionalisating alkenes and alkanes by nitrene insertion process.[102,195,196] So far chemistry of sulfonimidamides has been focusing mainly on three aspects: chemistry on the sp^2 N atom;[197] chemistry on the sp^3 N atom;[197–201] use of chiral SIAs in asymmetric hydrogenation,[99] metal catalysed CH- amination and aziridation,[202–209] and their use as chiral ligands in aldol[210] and Henry reactions.[211]

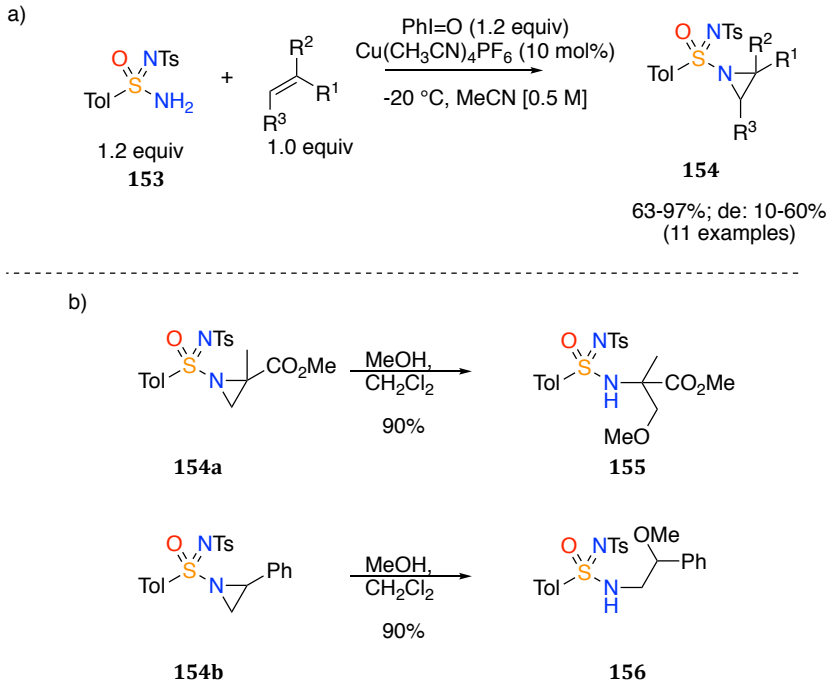
1.5.4.1 Synthesis of aziridines

In 2004 Malacria and co-workers used sulfonimidamide **149** as a nitrene transfer agent on sulfides and sulfoxides, to form the corresponding sulfimides and sulfoximines in good to high yield. [202] When **149** was reacted together with enantiopure sulfoxides, a mixture of diastereomers were obtained. These could be easily separated by flash column chromatography whilst retaining stereochemistry at the sulfur atom of the sulfoxide. Furthermore, when sulfonimidamides **149** were reacted with an olefin under the previously described conditions, the corresponding aziridines **152** were obtained (Scheme 1. 59).



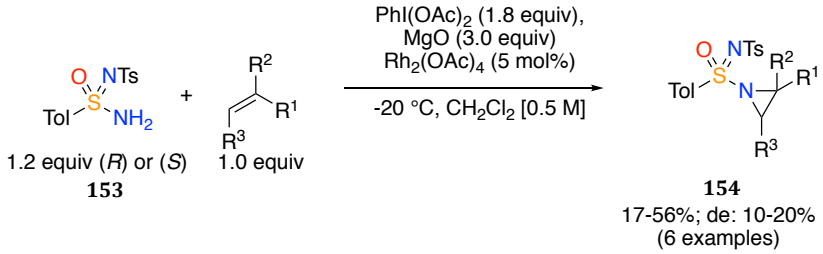
Scheme 1. 59 Malacria's use of SIAs as nitrine transfer agent

Shortly after Malacria's work,[202] Dodd and co-workers started to expand the scope of aziraidation of sulfonimidamides.[203] Treating sulfonimidamides **153** with iodosobenzene, chiral iminoiodinane was generated *in situ*. This species is a very reactive nitrene source, and upon further reaction with an olefin, in the presence of catalytic $Cu(CH_3CN)_4PF_6$, the corresponding aziridines **154** were produced in good to excellent yields (Scheme 1. 60a), but with modest diastereomeric excess. In addition to simple olefins, α,β-unsaturated olefins featuring an ester group were also compatible under the reaction conditions. To further verify the presence of an aziridine, compounds **154a** and **154b** were subjected to nucleophilic ring opening with methanol to provide products **158** and **156** in high yields (Scheme 1. 60b).[203]



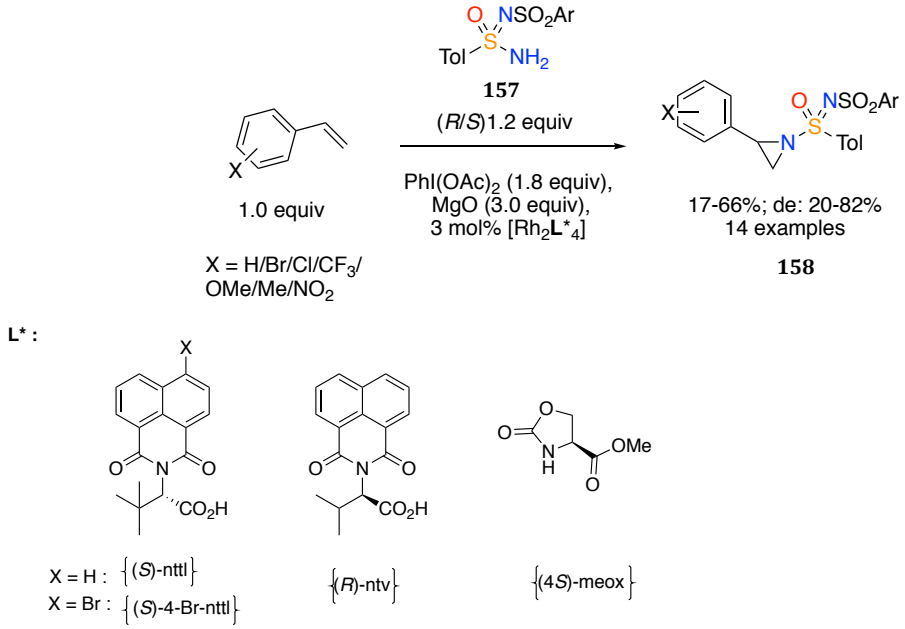
Scheme 1. 60 a) Copper catalysed aziridination with SIA **153**; b) nucleophilic aziridines ring opening

After this first publication for Cu-catalysed aziridines synthesis, Dauben, Dodd and co-workers expanded their study looking into rhodium(II) catalysed aziridation instead. First, enantiopure sulfonimidamide **153** was synthesised (both *R* and S) using Tsushima *et al.* protocol,[125] and then reacted with several olefins in the presence of diacetoxyiodobenzene and rhodium acetate ($Rh_2(OAc)_4$) to give the desired aziridines **154** in modest to good yield, and low diastereoselectivity (Scheme 1. 61).[36]



Scheme 1. 61 Rhodium(II) catalysed synthesis of aziridines

In order to improve yields and diastereoselectivity, the authors investigated the reaction using a chiral Rh(II) carboxylate catalyst and carboxamidate together with mesityl and nosyl sulfonimidamides **157**. With those reaction conditions in hand, aziridines **158** were obtained in low to good yields, and improved diastereoselectivity (20-82%) (Scheme 1. 62).



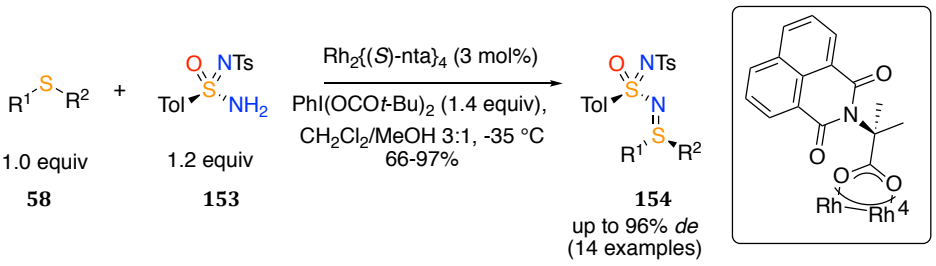
Scheme 1. 62 Diastereoselective synthesis of aziridines

Interestingly, while copper-salts gave the best results when reacted with α, β-unsaturated carbonyl compounds, rhodium(II) catalysis seems more suitable for styrene derivatives.[204]

1.5.4.2 Imination of sulfides

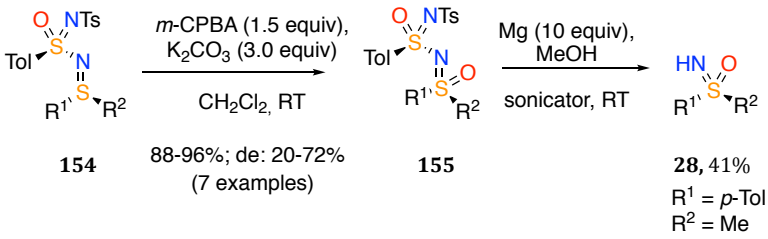
As previously reported by Malacria and co-workers,[202] sulfonimidamides can be seen as a means to transfer a nitrogen atom onto sulfoxides or sulfides, to achieve more complex molecules. In 2008, Dauban, Dodd and Collet explored the synthesis of chiral

sulfilimines and sulfoximines.[206] The reaction was a rhodium(II)-catalysed transfer of nitrogen, generated from the enantioenriched sulfonimidamide **153** in the presence of hypervalent iodine reagent. Products, **154** and **155**, were obtained in excellent yields (up to 97%) and good diastereoselectivity (up to 96%) (Scheme 1. 63).



Scheme 1. 63 Use of SIAs for synthesis of sulfilimines **154**

Chiral sulfilimines were oxidised with *m*-CPBA to form the protected sulfoximines in high yield, after which the sulfonimidoyl group can be removed by treatment of sulfoximine **155** with 10 equivalents of magnesium under sonication in methanol, to afford free NH sulfoximine in 41% yield (Scheme 1. 64).

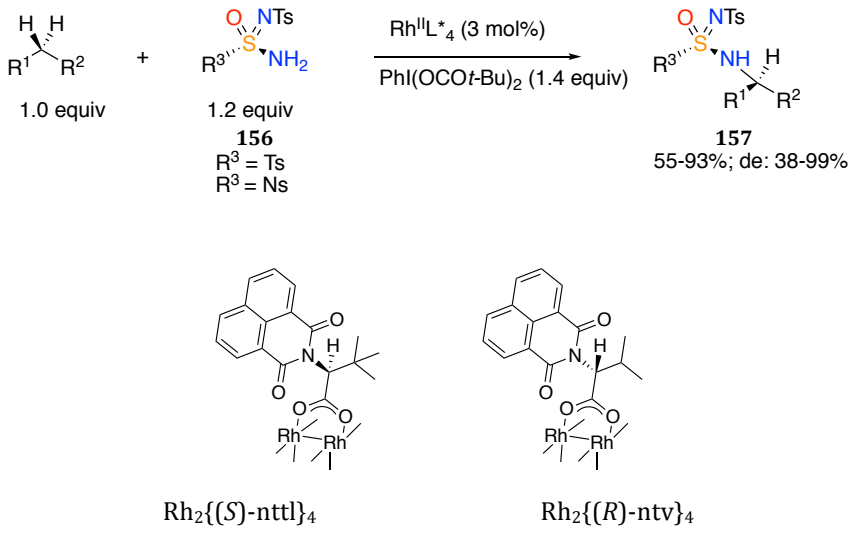


Scheme 1. 64 Transformation of sulfilimine **154** into the corresponding free NH sulfoximine

1.5.4.3 C-H Amination *via* nitrene transfer processes

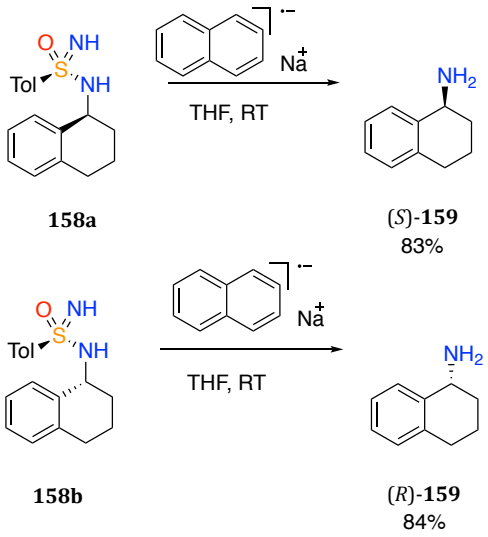
Important results for C-H amination were pioneered by Breslow[212,213] and Mansuy[214], using iminoiodanes as the starting point for transition-metal-catalysed nitrene processes. After these discoveries for the formation of hypervalent iodine(III) reagents *in situ*,[215–217] many others followed. Whilst the intramolecular reactions were well established the same can't be said for intermolecular, which still suffered from low conversion of starting material.[216,218–221]

In order to improve this, Dauban, Dodd and co-workers in 2006 developed an efficient intermolecular rhodium-catalysed C-H amination, using a nitrene precursor to enantiopure SIA **156** (Scheme 1. 65).[205] After an extensive optimisation, they found that when benzylic, allylic and alkane substrates were reacted together with chiral catalyst $Rh_2\{(S)\text{-nttl}\}_4$, enantiopure sulfonimidamide **156** (R^3 = Ts), in the presence of iodine oxidant $PhI(OCOtBu)_2$, the corresponding aminated product **157** was generated in good to excellent yields and high diastereoselectivity (up to 99% de) (Scheme 1. 65).



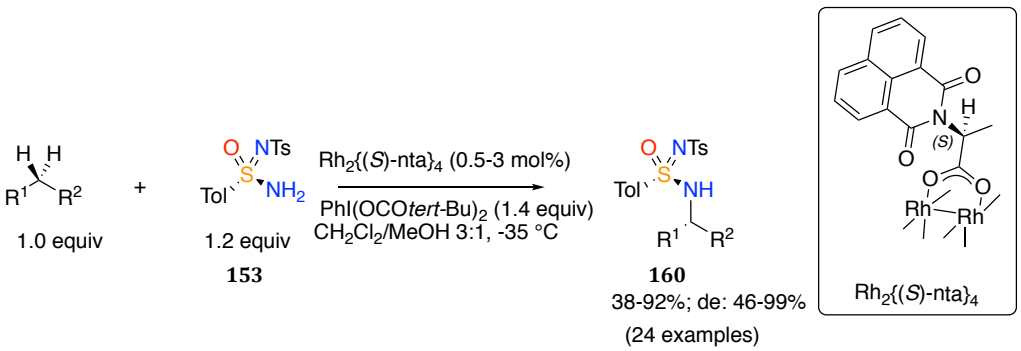
Scheme 1. 65 Rh-catalysed C-H amination of alkanes

A wide range of substrates were well tolerated (adamantane, benzylic, allylic, alkyl etc.), showing the high applicability of these reaction conditions. Rhodium catalyst $Rh_2\{(S)\text{-nttl}\}_4$ was preferred to $Rh_2\{(R)\text{-ntv}\}_4$ as it provided better selectivity and yields. Finally, deprotection of sulfonimidoyl moiety was successfully tested and results indicate that NH transfer onto C-H bond happens with retention of configuration, through a concerted nitrene insertion (Scheme 1. 66).[205]



Scheme 1. 66 Deptrotection of amine functionality under reductive conditions

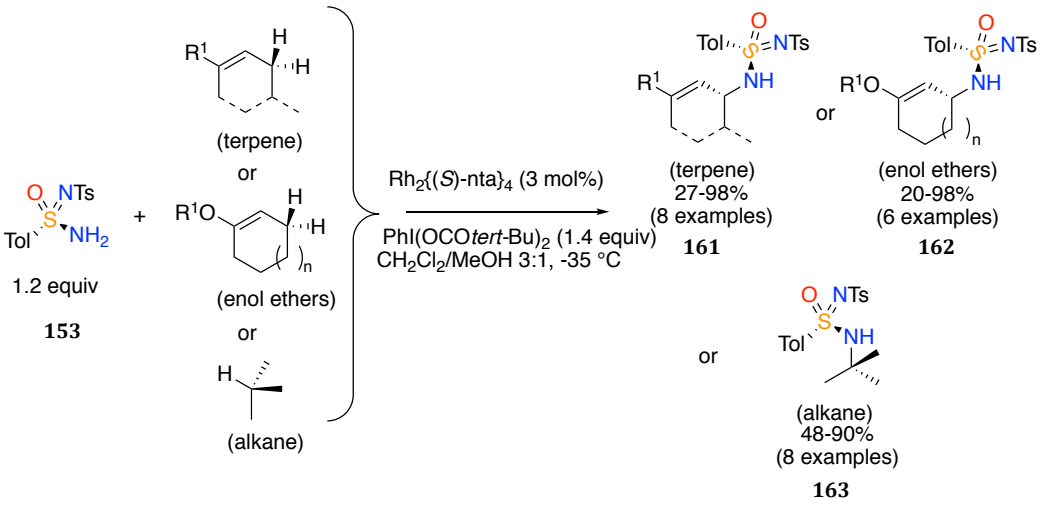
A few years later Dauban, Dodd and co-workers, reported an improved stereoselective intermolecular C-H amination with both cyclic and linear alkanes, which can be efficiently transformed to give the desired molecules in high yields and excellent stereoselectivities (up to 99%), expanding the reaction scope (Scheme 1. 67). Substrates were used as the limiting agent and Rh_2\{(*S*)-nttl\}$_4$ was replaced by Rh_2\{(S)-nta\}$_4$ (nta: *N*-(1,8-naphthoyl)-alanine) because of its higher catalytic activity, giving up to 97% de, whilst a reduced catalyst loading could be used (0.5 mol% instead of 3 mol% in some cases).[207]



Scheme 1. 67 C-H amination of benzylic and allylic positions *via* rhodium catalysis

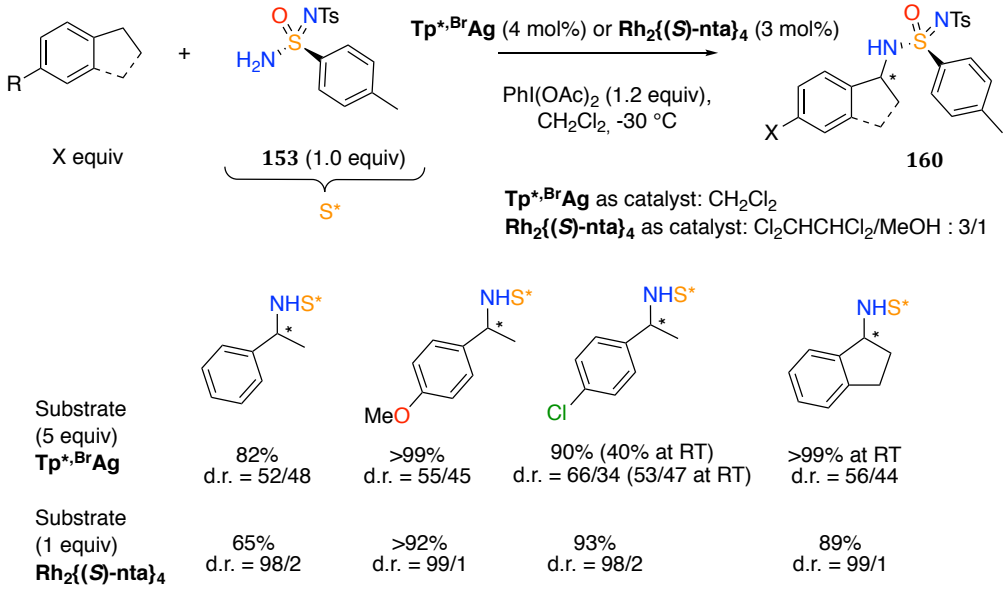
Encouraged by these excellent results, Dauban, Dodd and co-workers applied previous reaction conditions to more complex molecules. Allylic amination of various terpenes and enol ethers provided the aminated products in modest-high yields (27-98%), high chemo-, regio- and diastereoselectivity with only a single isomer isolated (Scheme 1. 68).

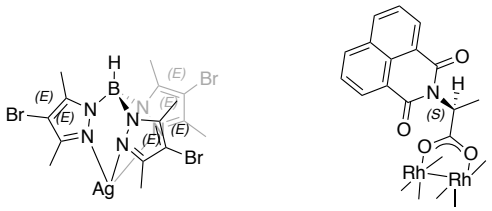
C-H amination of less reactive alkanes was also reported, highlighting a preference for nitrogen insertion on tertiary equatorial position in good to high yields (up to 88%). The products outcome can be explained by steric and hyperconjugative effects (Scheme 1. 68).[222]



Scheme 1. 68 Rhodium catalysis on complex molecules

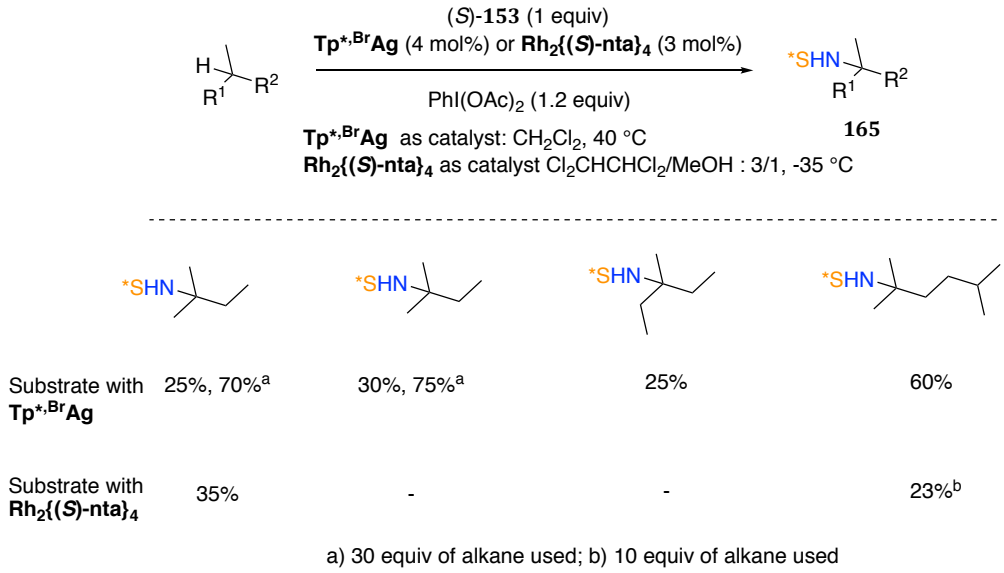
In 2013 Perez and Dauban, expanded the study on sulfonimidamides as nitrene transfer agent.[209] Both silver complex $[Tp^{*,Br}Ag]_2$ ($Tp^{*,Br}$: hydrotris(4-bromo-3,5-dimethyl)pyrazolyl borate) and rhodium catalyst $[Rh_2\{(S)\text{-nta}\}_4]$ (nta: *N*-(1,8-naphthoyl)-alanine) were reacted together with non-activated alkanes which showed comparable conversion when compared to benzylic positions; rhodium, however, provided better diastereoselectivity (Scheme 1. 69).





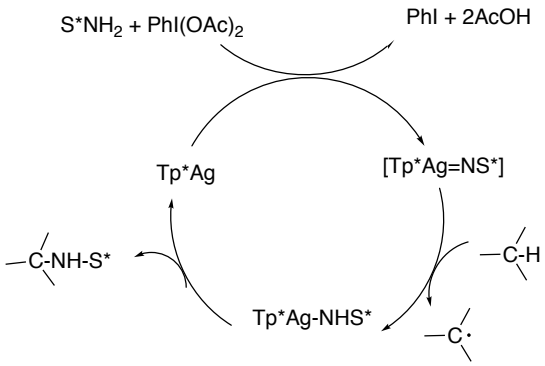
Scheme 1. 69 Silver(I) and Rhodium(II) catalysis on benzylic C-H

Silver complexes, on the other hand, seemed more suitable catalysts for alkanes, like pentane (providing three constitutional isomers) and C_6-C_8 branched non-activated hydrocarbons. The C-H amination on the tertiary position was promoted in good to high yields (up to 70%). However, an excess of the selected alkane was needed, unlike rhodium reaction conditions, and yield could be improved by increasing the amount of the starting material (Scheme 1. 70).



Scheme 1. 70 C-H amination of non-activated C_6-C_8 alkanes with Ag^I and Rh^{II}

Furthermore, the absence of products generated from the nitrene insertion on a secondary or a primary alkane suggests a radical mechanism (Scheme 1. 71).[209]



Scheme 1. 71 Proposed mechanism for silver catalysed C-H amination

1.5.4.4 Aldol reactions

Aldol reaction has been acknowledged as a useful and powerful tool for construction of new carbon-carbon bonds in organic chemistry.[223,224] Hence, an established methodology for asymmetric aldol reaction is high desirable. In the past, proline sulfonamides (SAs) have been used as organocatalysts,[224,225] therefore, given the extensive knowledge of sulfur chemistry as well as metal and organo-catalysis, in 2009 Bolm and co-workers, employed sulfonimidamides, aza analogue of sulfonamides, as novel catalysts for asymmetric aldol reactions (Figure 1. 18).

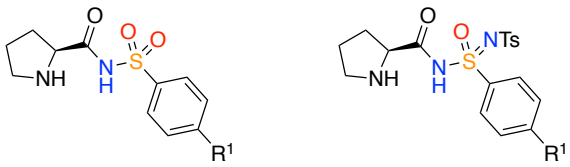
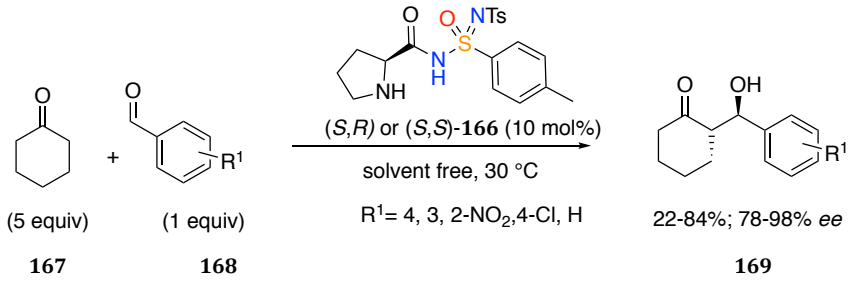


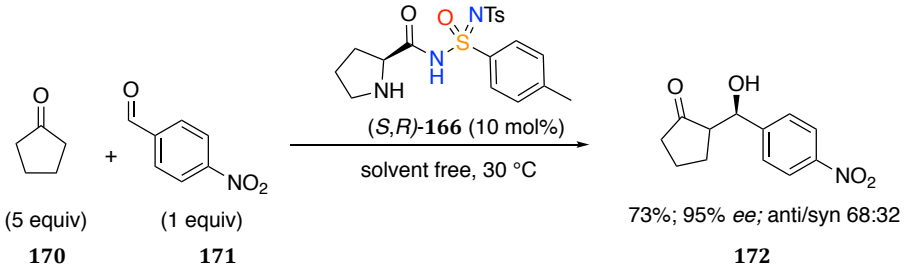
Figure 1. 18 Structures of proline-SAs and proline-SIAs

In order to verify whether the sulfonimidamide had any selective and catalytic potential, cyclohexanone (**167**) and *p*-nitrobenzaldehyde (**168**) were reacted together with 20 mol% of a 1:1 diastereomeric mixture of sulfonimidamide **166**, at room temperature. Initial results were encouraging, giving **169** after 3 days, 86% yield with 95:5 anti/syn ratio and 95% *ee*. Next, reaction conditions were optimised, (*S,R*)-**166** proved to be a better catalyst, and different aromatic aldehydes were tested reporting products in good to excellent stereoselectivity and good to high yields (78-84%) (Scheme 1. 72). Interestingly, studies on the reaction showed that the stereogenic sulfur had very little impact on the products configuration.



Scheme 1. 72 Sulfonimidamide (*S,R*) or (*S,S*)-**166** used as organocatalyst in aldol reaction

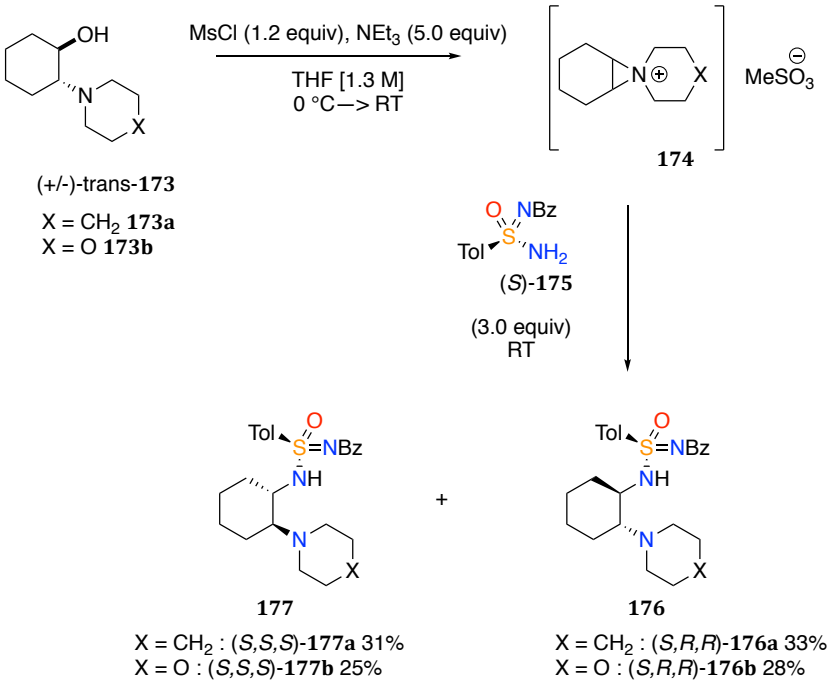
Finally, the cyclohexanone was replaced by cyclopentanone and subjected to standard reactions conditions with **171** obtaining desired product in good yield (73%), high enantioselectivity (95% *ee*) but low diastereomeric excess (36% de) (Scheme 1. 73).



Scheme 1. 73 Catalytic use of SIA (*S,R*)-**166** with cyclopentanone **170** and aldehyde **171**

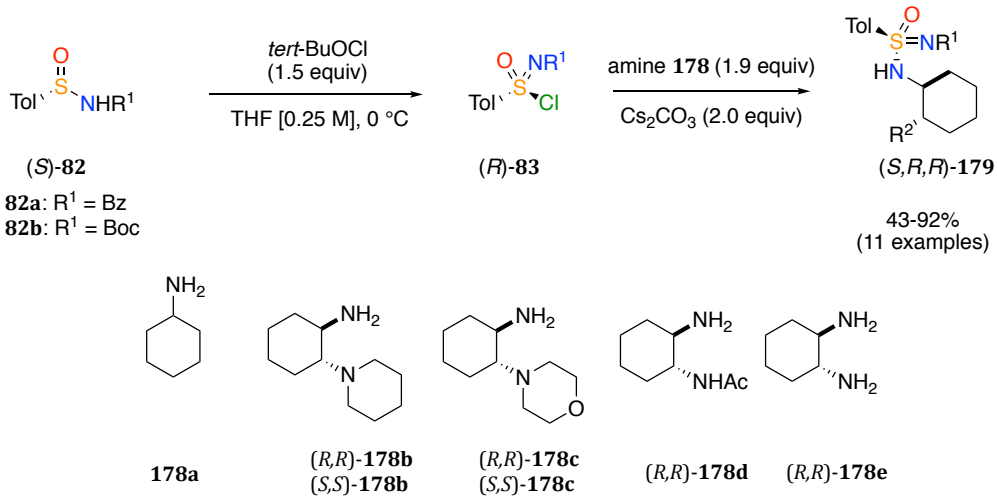
1.5.4.5 Henry reactions

Henry reaction, also known as "nitro-aldol" reaction, represents another useful tool for the formation of new carbon-carbon bonds. It is analogous to the aldol synthesis using a nitroalkane instead of a ketone. On the basis of their previous experience of sulfonimidamides as organocatalyst for aldol reactions, Bolm and co-workers expanded SIAs scope as ligand for asymmetric copper-catalysed Henry reaction. For this purpose, amino-functionalised sulfonimidamides have been synthesised *via* two different routes: aziridinium ring opening and the classic nucleophilic substitution of sulfonimidoyl chloride. The aziridine ring opening sequence involved use of enantiopure benzoyl-protected sulfonimidamide (*S*)-**175** in a one-pot reaction with racemic *trans*-piperidinyl- and *trans* morpholinyl-substituted aminoalcohols (**173a** and **173b**). Formation of the aziridinium ion intermediate **174** drove the reaction to trans products as mixture of 1:1 diastereoisomers, separable by column chromatography in modest yields (Scheme 1. 74).



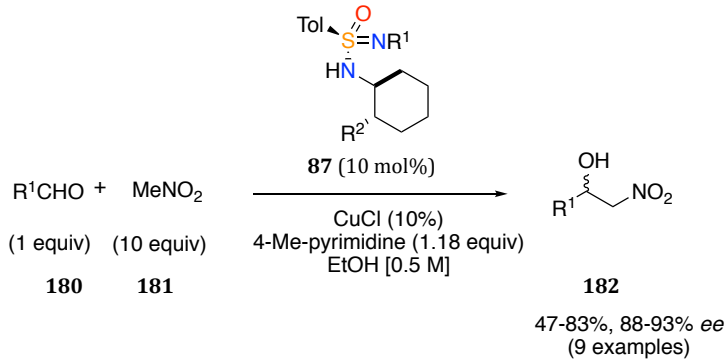
Scheme 1. 74 One-pot formation of enantiopure amino functionalised SIAs *via* aziridine ring opening

The second way Bolm and co-workers developed this reaction was to make amino-substituted sulfonimidamides by treatment of sulfonimidoyl chloride intermediate (*R*)-**83**. The latter was prepared according to previously reported procedures with different amino components **178** in the presence of Cs_2CO_3 at room temperature.[109,126,226] The desired product was obtained as a single stereoisomer in good to high yields even though Boc-protected SIA **179** provided better results (Scheme 1. 75).



Scheme 1. 75 Sulfonimidamides formation *via* nucleophilic addition to sulfonimidoyl chloride **83**

Finally, the previously synthesised amine-derived sulfonimidamides were tested for asymmetric copper catalysed Henry reaction between aromatic aldehydes **180** and nitromethane **181** (Scheme 1. 76).



Scheme 1. 76 Substrate scope for asymmetric Henry reaction

Best results were achieved when **176b** and **177b** were used in a 1:1 ratio with catalytic CuCl, the latter one in particular proved a more effective organocatalyst than **176b** delivering many enantioselective products (Scheme 1. 76). All reactions with aromatic aldehydes provided high *ee* in contrast to aliphatic ones, which resulted in a mixture of enantiomers. Given the data collected so far, Bolm and co-workers envisaged that the enantioselectivity of the product was controlled by the two stereogenic centres on the cyclohexane moiety rather than the chiral sulfur atom. Furthermore, sulfonimidamides (SIAs) ligands proved superior selectivity to sulfonamides-based catalyst (SAs), which afforded good activity but rather low selectivity.[211]

1.6 *N*-Functionalisation

Exploration of chemical space of small molecules is an enduring challenge in life science. To address this challenge, new synthetic methods, which allow modulation and further insight into the physicochemical properties of chemical compounds, need to be developed.[227] In the past years sulfoximines, the aza analogue of sulfones, have been successfully employed in asymmetric synthesis and as active compounds in drug discovery (see Chapter 1). At the present time, synthesis of sulfoximines has been essentially solved,[68] therefore accessing these molecules is no longer an issue. In light of these developments futher derivatisation of NH-sulfoximines has been widely explored. To date there are a large number of methods to functionalise the nitrogen in a sulfoximine: silylation,[228–231] halogenation,[232] alkylation,[175,233–235] arylation,[190,236–243] nitration,[244] vinylation,[245,246] cyanation,[247–254] trifluoromethylation,[255] alkynylation[256] and many others.

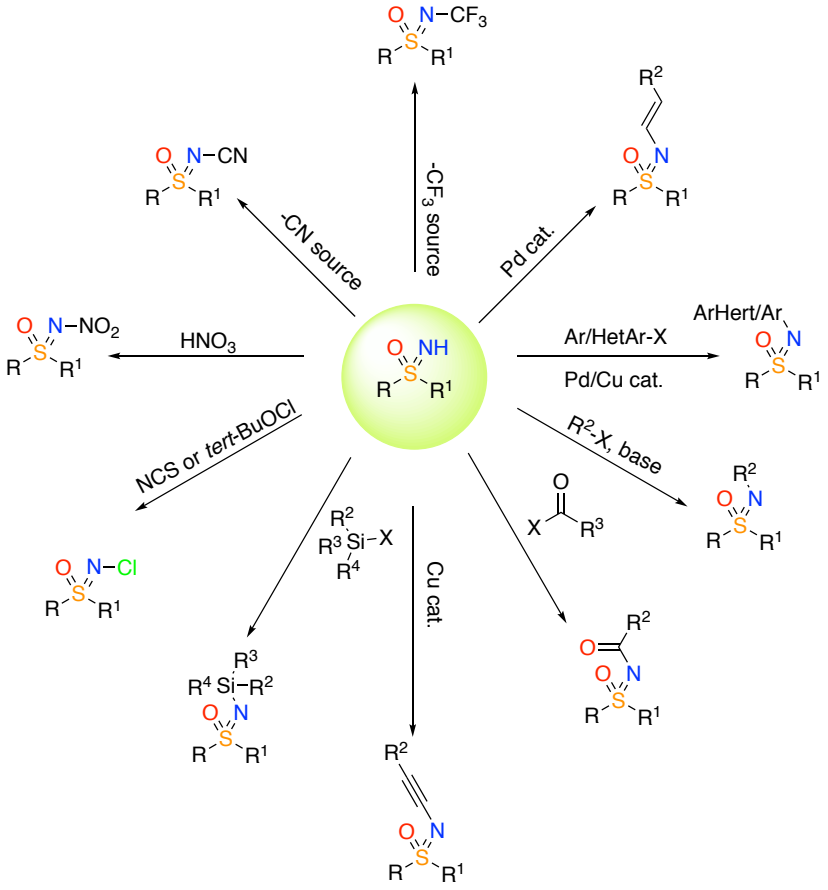


Figure 1. 19 NH-functionalisation of sulfoximines

However, in contrast to the broad variety of functionalisation methods available for NH-sulfoximines, there are only few reports about *N*-fuctionalisation of sulfonimidamides. Recently, new methodologies for accessing of NH-sulfonimidamides,

a bioisostere of sulfonamides, have been established (see Chapter 1), however NH-functionalisation remains still fairly unexplored. To date, the known methodologies for functionalising these class of compounds include arylation,[197,198,201,257,258] alkylation,[259] alkynylation,[260] acetylation[105,199,210,261–263] and vinylation.[264]

In this chapter we are going to differentiate between functionalisation on the amine position and imine position according to which nitrogen of the sulfonimidamides we are going to talk about (Figure 1. 20). As most of our work was focused on the functionalisation of the latter we are going to refer to it during the discussion as NH position as well. Furthermore, the functionalisation on the imino nitrogen will be defined as *N*-functionalisation while the one on the amino position as *N'*-functionalisation.

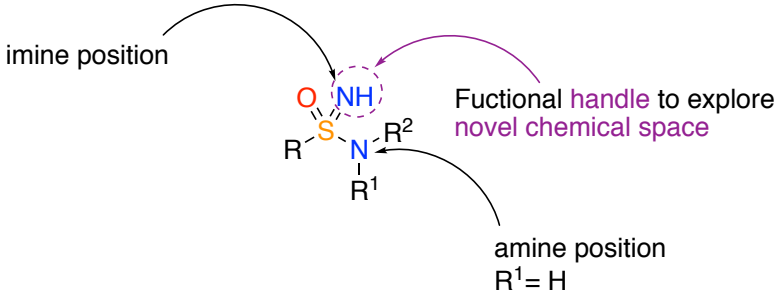
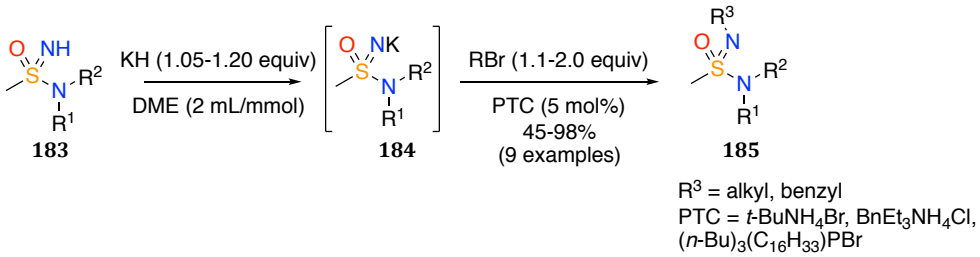


Figure 1. 20 Structure of sulfonimidamides

1.6.1 Alkylation

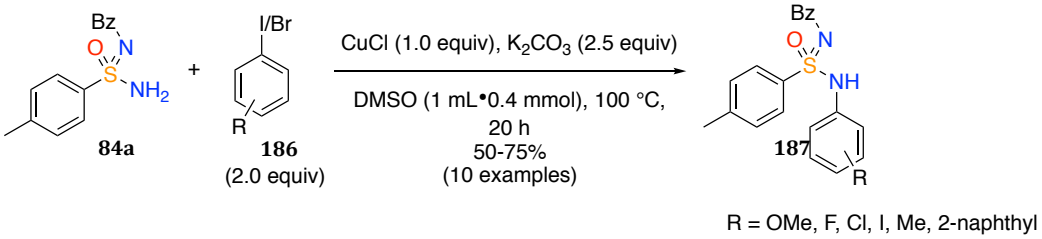
Very little attention was paid to functionalisation of SIAs until 1993, when Johnson and Lavergne developed the first alkylation on **183** with potassium hydride in 1,2-dimethoxyethane generating intermediate **184** which then was further reacted with primary alkyl bromides in the presence of a phase transfer (PTC).[259] Desired *N*-alkylated SIAs **185** were obtained in good to excellent yields (Scheme 1. 77). However, when secondary alkyl bromides were employed no product formation was observed.



Scheme 1. 77 *N*-alkylation of SIAs

1.6.2 Arylation

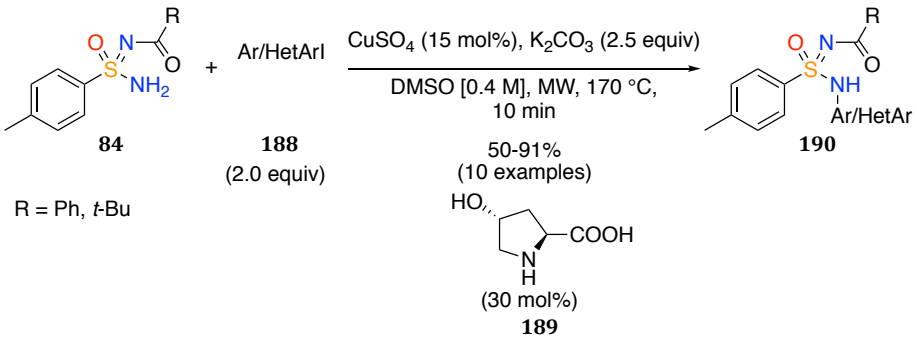
Bolm and co-workers reported the first *N*-arylation of NH-protected sulfonimidamides employing a copper catalysed cross-coupling procedure with aryl bromides and aryl iodides. The *N*-alkylated products were isolated from modest to good yield (50-75%) and no double arylation product was observed even when an excess of **84a** (2 equiv) was used (Scheme 1. 78). However, when the aryl bromide reagent was employed as coupling partner instead of aryl iodides, the reaction proceeded slower and the product was isolated in lower yields (50%).[201]



Scheme 1. 78 Bolm's copper catalysed *N*-arylation

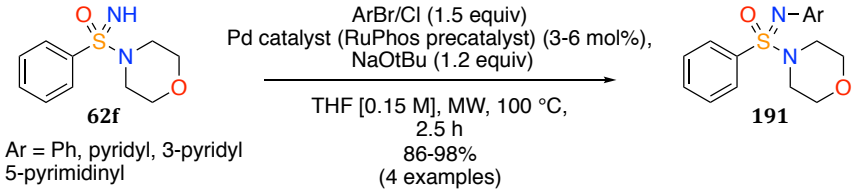
In addition to this, Malacria and co-workers developed an efficient microwave (MW) assisted copper catalysis for arylating sulfonimidamides on the amino moiety with aryl iodides. Microwave irradiation resulted in reduced reaction times and higher yields in comparison to Bolm's procedure.[201] The reaction was performed using $CuSO_4$ in a catalytic amount, K_2CO_3 and 4-hydroxyproline (as ligand) in DMSO. Both aryl and heteroaryl groups were well tolerated, even if best results remained when **7** was coupled with simple phenyl iodide (Scheme 1. 79).

Although a chiral ligand was also tested, no resolution was observed and the product obtained was a racemic mixture. Moreover, the reaction was limited to the arylation of the amino functionality and the imino position remained untouched, even when the NH was unprotected.



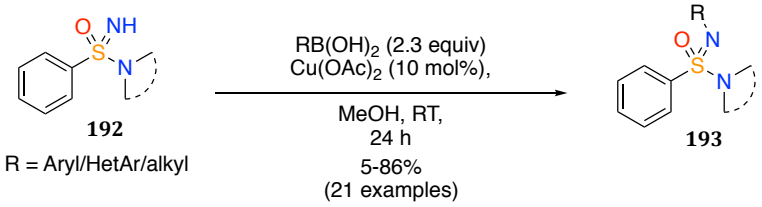
Scheme 1. 79 MW assisted Cu-catalised *N*-arylation of SIAs

In 2012, Arvidsson and co-workers reported the first Pd-catalysed arylation reaction on the free NH-sulfonimidamides and once again microwave-assisted catalysis was employed to reduce the reaction times. The isolated yields of the arylated SIAs ranged from high to excellent (86-98%), however the substrate scope was limited as only four examples were reported (Scheme 1. 80).[197]



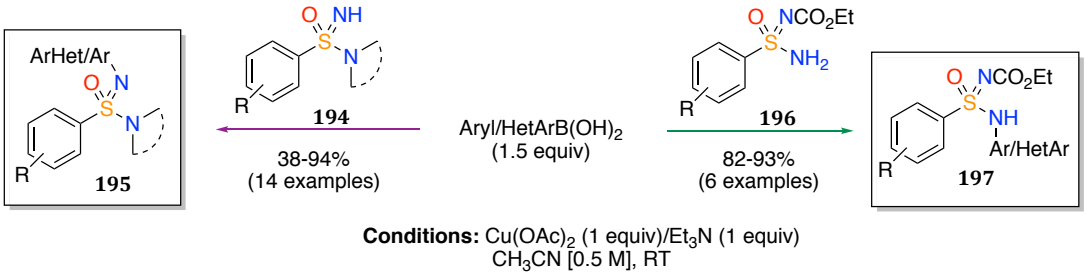
Scheme 1. 80 Palladium catalysed *N*-arylation of SIAs

In 2014, Battula and co-workers and Arvidsson and co-worker reported, almost simultaneously, a robust synthesis employing Chan-Lam-Evans cross-coupling reaction conditions to arylate NH-unsubstituted sulfonimidamides.[257,258] The first research group used catalytic amount of $Cu(OAc)_2$, with different aryl, heteroaryl, and cyclopropyl boronic acids to obtain after 24 hours *N*-functionalised **193** in yields from good to high (5-86%). In general the reaction scope of the boronic acids was wide, but it was limited to the functionalisation onto the imine moiety of SIAs (Scheme 1. 81).



Scheme 1. 81 Chan-Lam-Evans protocol for *N*-arylation

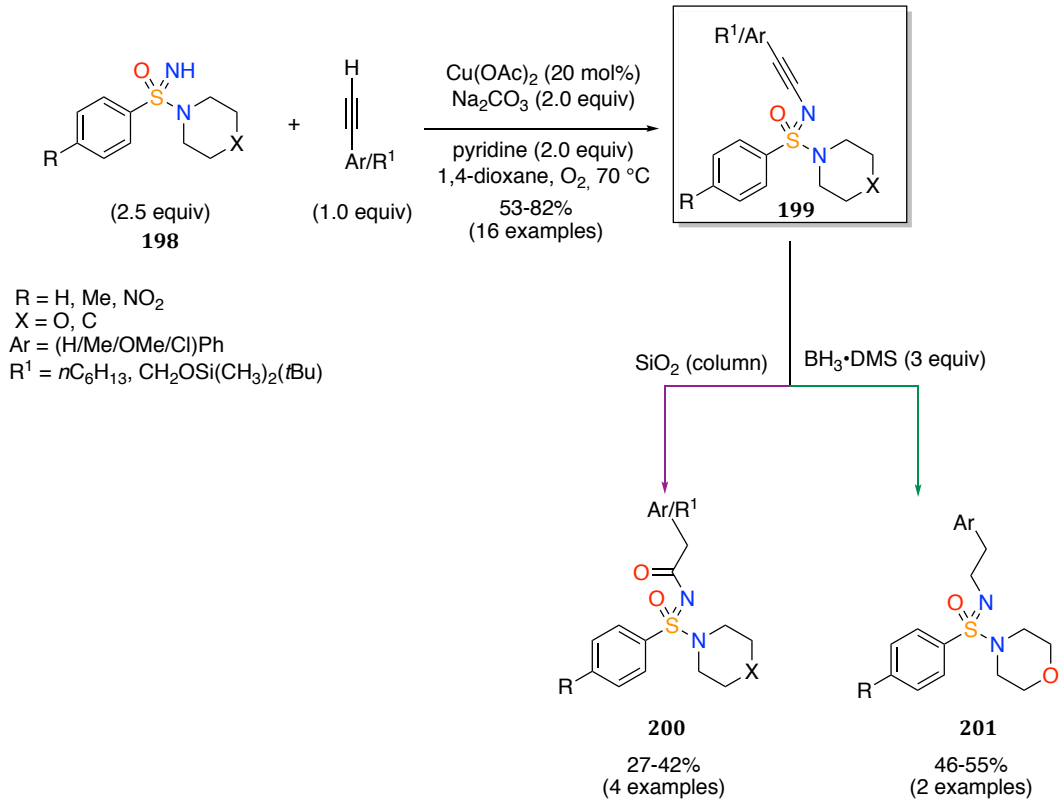
Arvidsson and co-workers on the other hand, employing a stoichiometric amount of the same copper catalyst in combination with triethylamine, developed a protocol which could be used for functionalising both tertiary **194** and primary **196** sulfonimidamides. The authors discovered that the triethylamine addition increased the reactivity of both substrates **194** and **196** towards the boronic acids and reduced the catalyst loading.[258] The reaction proceeds at room temperature and provides a variety of sulfonimidamides in yields from high to excellent, however when a heteroaromatic group (i.e. thienyl boronic acid) was used the yield dropped to 38% (Scheme 1. 82).



Scheme 1. 82 Arvidsson's adaptation of Chan-Lam-Evans cross-coupling for SIAs **194** and **196** functionalisation

1.6.3 Alkynylation

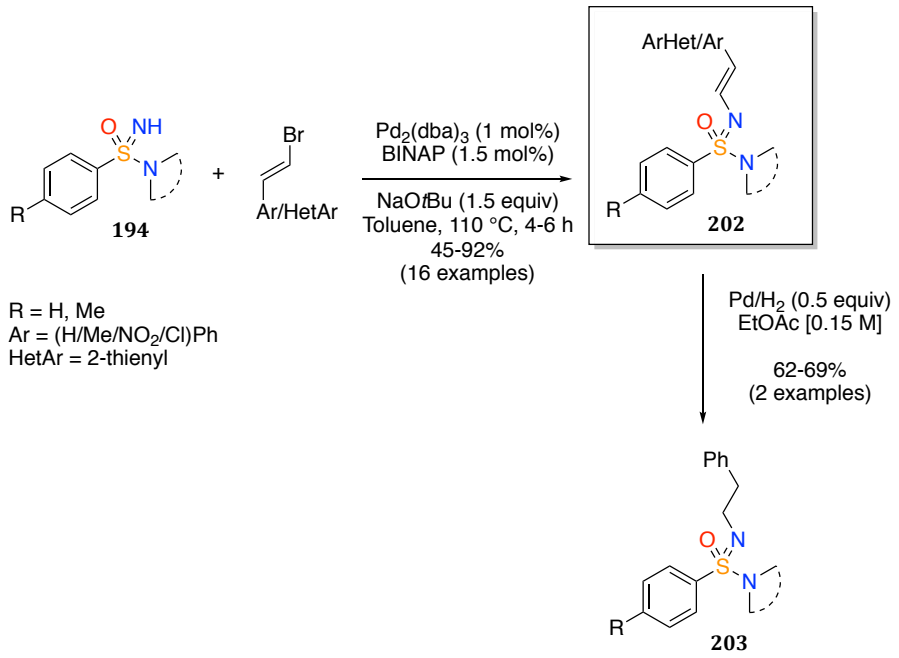
In continuation of their work to explore *N*-sulfonimidamide functionalisation, Arvidsson and co-workers developed an optimal procedure to react different terminal alkynes groups with NH functionality on **198**. The treatment of **198** with catalytic amount of $Cu(OAc)_2$, pyridine, Na_2CO_3 in dioxane using oxygen as oxidant gave the unprecedented C-H/N-H coupling products **199** in good to high yields. Furthermore, functionalised **199** could be further reacted to provide corresponding acyl SIAs **200**, when purified on silica gel column, and alkanes SIAs **201** when treated with borane-dimethyl sulfide reducing agent (Scheme 1. 83). Interestingly, prolonged exposure of **199** to silicon dioxide led to decomposition rather then hydrolysis.[260]



Scheme 1. 83 Copper catalysed alkynylation of SIAs **199** followed by formation of *N*-acyl **200** and *N*-alkyl **201**

1.6.4 Vinylation

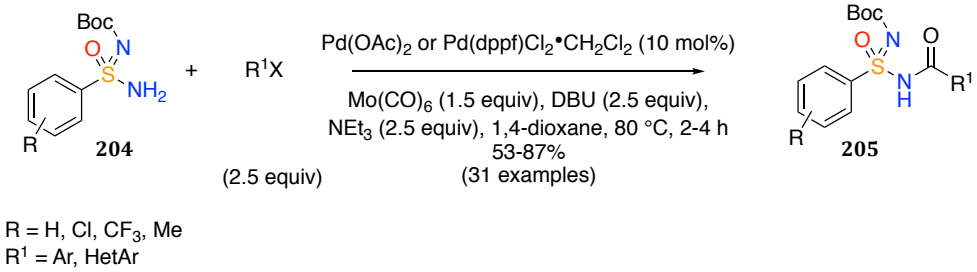
Given the growing interest of sulfonimidamides in life science and in an attempt to better understand their structural and medicinal relevant properties, Arvidsson and co-workers explored another key transformation of S(VI) compounds: vinylation of NH sulfonimidamides.[264] A variety of aromatic, aliphatic cyclic and acyclic vinyl bromides were successfully coupled with **194.** The reaction was performed employing a palladium catalyst, in a type of Buchwald-Hartwig C-N coupling procedure.[265] Interestingly, the stereochemistry around the vinylic double bond of **202** was retained during the coupling, and a further confirmation of this was provided by a single X-ray diffraction. Moreover, the newly formed **202** could deliver the corresponding *N*-alkyl sulfonimidamide **203**, when subjected to hydrogenation with Pd-C/H_2 (Scheme 1. 84). An attempt to use previously applied conditions for reducing the alkyl compound **202** with BH_3•DMS (see Scheme 1. 84) proved unsuccessful.



Scheme 1. 84 *N*-vinylation of SIAs

1.6.5 Acylation

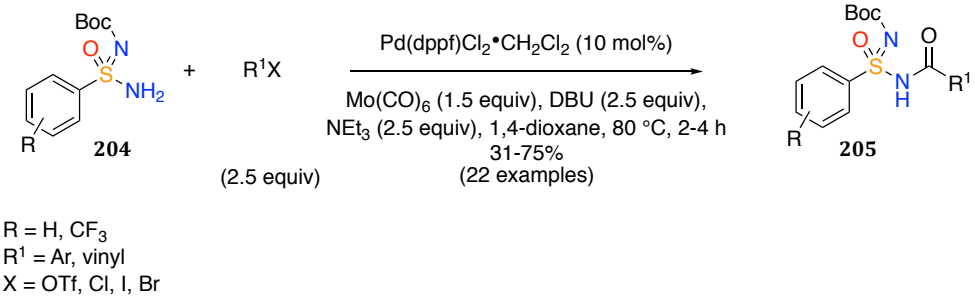
In comparison to previously described *N*-functionalisation of sulfonimidamides (i.e. vinylation, alkynylation and arylation), *N*-acylation has been far more investigated by different research groups due to the possibility to use them as carboxylic acid replacement in target molecules.[199] In 2013, Arvidsson and co-workers reported the first synthesis of aryl and heteroaryl acyl sulfonimidamides **205** employing a Pd-catalysed carbonylation. During the course of the reaction CO gas was produced *ex situ* from solid $Mo(CO)_6$ in a sealed two chamber system. The corresponding *N*-acylated SIAs **205** were obtained in high yields (Scheme 1. 85).[199]



Scheme 1. 85 Pd-catalysed *N*-acylation of SIAs

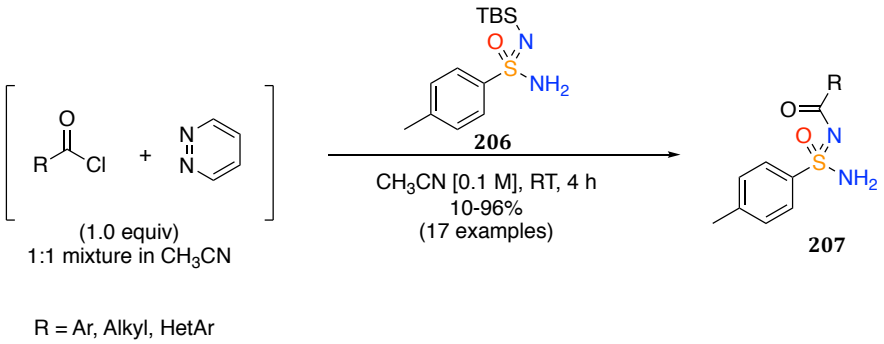
Later, the same authors expanded the procedure to form unprecedented vinyl/acyl **205** by employing **204** as nucleophile to couple with different vinyl halides/triflates and aryl triflates. The reaction shows high tolerance to a variety of functional groups allowing isolation of unsaturated sulfonimidamides **205** in good yields (Scheme 1. 86).

Furthermore, during the course of this investigation, a facile thermolytic Boc deprotection of *N*-(α,β-unsaturated)sulfonimidamides **205** in DMSO at low temperature was achieved.[262]



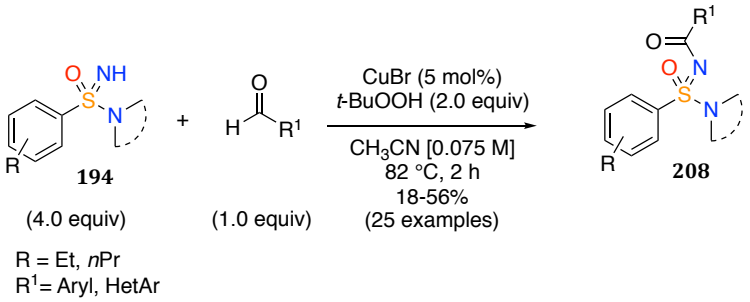
Scheme 1. 86 *N*-acylation of SIAs **204** using vinyl/aryl triflates as electrophiles

Later, Chen and co-workers successfully achieved the first metal free NH mono-acetylation of TBS protected sulfonimidamide **206.**[261] When SIA **206** is added to a pre-mixed solution of acyl chloride and pyridazine (1:1 ratio) in acetonitrile, the TBS group is cleaved *in situ*, providing mono-acetylated products **207** in yields from poor to high (Scheme 1. 87). In general, the reaction scope was wide and examples of aryl, alkyl and heteroaryl acyl sulfonimidamides were reported. Furthermore, when benzoic acid was used as acylating agent together with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) as coupling partner, solely *N,N'*-diacylation product was observed.



Scheme 1. 87 *N*-acylation of SIAs with acyl chlorides as acylating agents

Finally in 2017, Nandi and Raju developed a Cu-catalysed acetylation *via* C-H/N-H activation to functionalise the imino end of tertiary sulfonimidamides **194**.[263]
The reaction was performed using as acylating agent different aldehydes (aryl and heteroaryl), *tert*-butyl hydrogen peroxide as oxidant with a catalytic amount of CuBr in acetonitrile. Although products **208** were obtained in modest yield and an excess of **194** was needed, the coupling reaction provided new information regarding the reactivity of the NH handle together with novel structurally diverse *N*-acyl sulfonimidamides (Scheme 1. 88).



Scheme 1. 88 *N*-acetylation *via* Cu-catalysed reaction

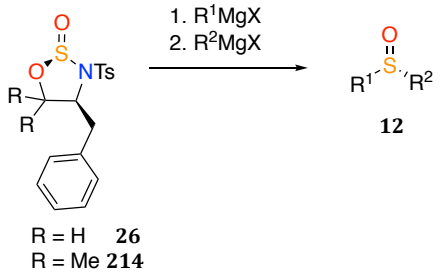
1.7 Aims and Objectives

Over the past 10 years, sulfoximines have been emerging as novel and valuable isosteres in medicinal chemistry and crop protection, with the potential to modulate physicochemical properties. While initial protocols for synthesising sulfoximines relied on harsh conditions, more recent methods, involving commercially available reagents, allow safer access to the desired sulfoximines. Furthermore, the aforementioned methodologies give the possibility to retain the stereochemistry on the sulfur centre, when a chiral starting material is employed (i.e. sulfoxides). To date, two main routes give easy access to optically active sulfoxides: Anderson's auxiliary and Senanayake's norephedrine derived template. However, these methods have their drawbacks:

- Anderson's auxiliary allows modification of just one side of the molecule
- Senanayake's template derives from a controlled and expensive substance

The lack of a general and direct approach for the enantioselective production of sulfoxides raises opportunities to develop novel strategies for their synthesis. Therefore our aim is to:

- Synthesise chiral sulfoxides employing as key intermediate chiral templates **26** and **214,** analogues to Senanayake's template**,** previously used for the generation of chiral sulfinimines. [42,43]



Scheme 1. 89 Synthesis of chiral sulfoxides *via* templates **214** and **26**

- Investigate different oxidative imination reactions onto chiral sulfoxides, which should provide the corresponding sulfoximines in high yield and high enantiomeric excess.

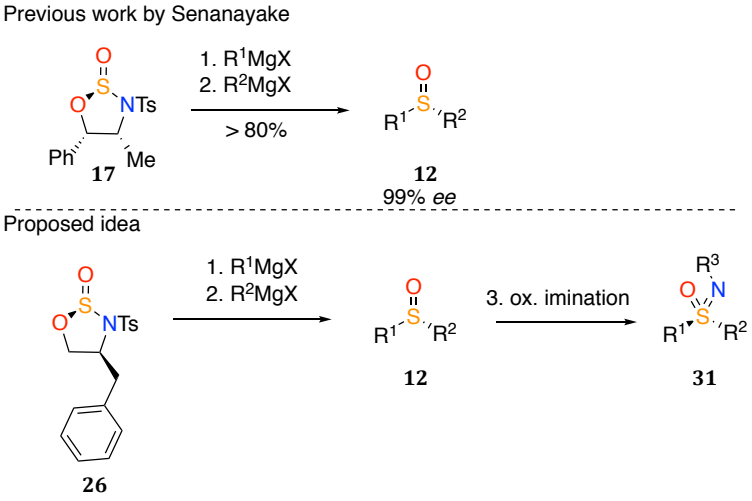
In contrast to the sulfoximine, the sulfonimidamide functionality has been far less explored. The sulfonimidamide functional group was first synthesised in the 1960s,[113] but surprisingly it was left in the shade until recently, despite being the aza analogue of sulfonamide and offering interesting properties.[104] Possible reasons for the neglected use of SIAs are the lack of commercial availability together with limited synthetic approaches and an incomplete understanding of the properties relevant to medicinal chemistry. The synthetic limitation of the sulfonimidamide led to reduced studies of the *N*-fuctionalisation. Therefore our aim for this part of the report is to:

- Develop a shorter and milder route to synthesise sulfonimidamides starting from sulfinamides.
- Make chiral sulfinamides as a starting material for the synthesis of enantioenriched sulfonimidamides, possibly using sulfur templates **26** and **214**.
- Explore the *N*-functionalisation of tertiary unprotected sulfonimidamides using published procedures for functionalising sulfoximines.
- Gain further insight into the medicinally relevant properties of the newly synthesised SIAs

Chapter 2: Results and Discussion

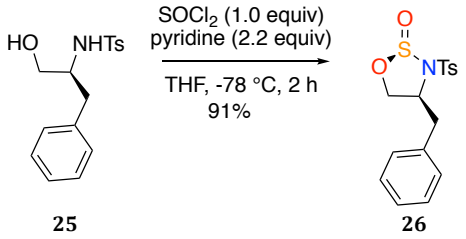
2.1 Sulfoximines

The Stockman research group is interested in accessing novel chiral sulfoximines for medicinal applications.[49,266] With the development and application of sulfoximine synthesis from sulfoxides and sulfides being relatively well understood,[90–92] it is proposed that access to novel stereochemically defined sulfoximines could be achieved by employing enantiopure starting materials. To exploit and exemplify our in house methodology of chiral sulfur templating, a variety of synthetic routes to chiral sulfoximines, involving Grignard addition and imination, was investigated. The use of transition metal catalysis and nitrene precursors was employed to promote the oxidation of a chiral sulfur(IV) to the desired sulfoximine product **31** in good yields and with retention of configuration (Scheme 2. 1).



Scheme 2. 1 Proposed synthesis of sulfoximines

Inspired by Senanayake's work the Stockman research group has achieved the synthesis of an analogue chiral template **26**. The advantages of replacing the precursor norephedrine with L-phenylalanine are obvious. Norephedrine not only is an expensive reagent but is also a controlled substance, therefore the ability to scale up is limited. The in house synthesis of **26** can be readily performed yielding gram quantities available for use. Template **26** derived from the reaction of **25** together with $SOCl_2$ (1.0 equiv) in the presence of pyridine (2.2 equiv). The product can be isolated in a 91% yield after 2 hours following a quick purification by filtration. It was in fact noticed that prolonged exposure of **26** to silica resulted in epimerisation of the S=O stereocenter.

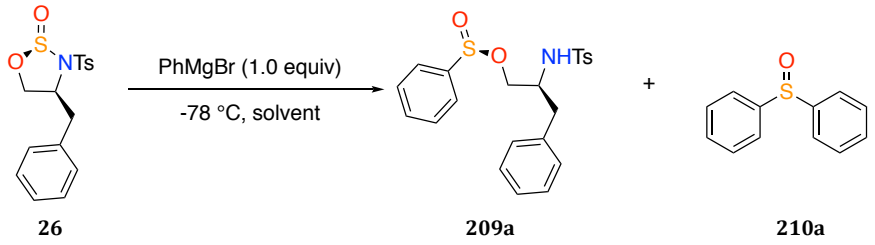


25 26

Scheme 2. 2 Synthesis of chiral template **26**

In order to develop a more flexible synthetic strategy to produce sulfoximines with high structural diversity, we focused our attention on the search for a single key intermediate, which can be easily synthesised and produced on a large scale. For this purpose initial investigations explored the addition of phenyl magnesium bromide to chiral template (**26**) under a range of conditions (temperature, solvent and concentration) (Table 2. 1). However, initial addition of the Grignard reagent to **26** resulted in a mixture of products: intermediate **209a** and double addition product **210a** (Table 2. 1, entry 1). Switching solvent from THF to dichloromethane and quenching the reaction with HCl after 1 hour resulted in only 8% chemical yield for product **209a** (Table 2. 1, entry 10). Quencing the reaction after one hour with water at -78 °C and diluting by ten fold the solution gave the best results collected so far (Table 2. 1, entry 12 and 16).

Table 2. 1 Reaction conditions for R^1MgBr addition on **26**



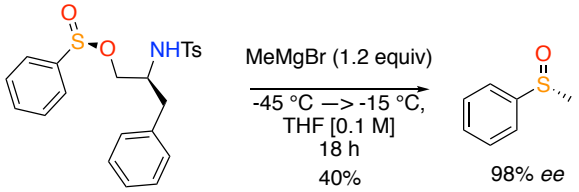
26 209a 210a

Entry	Conc react [M]	Solvent	T (°C)	Quench	t (h)	209a(%)	210a(%)
1[a]	0.285	THF	-78	HCl	0.17	33	16
2[a]	0.285	THF	-78	HCl	0.50	41	23
3[a]	0.285	THF	-78	HCl	0.67	53	23
4[a]	0.285	THF	-78	HCl	1.00	35	26
5[a]	0.285	THF	-78	HCl	1.50	47	27
6[a]	0.285	THF	-78	HCl	1.75	57	20

7[a]	0.285	THF	-78	HCl	2.00	45	28
8[b]	0.285	THF	-78	HCl	0.50	49	17
9[b]	0.285	CH_2Cl_2	-78	HCl	0.17	17	20
10[b]	0.285	CH_2Cl_2	-78	HCl	1.00	8	36
11[a]	0.285	THF	-70	H_2O	1.00	12	32
12[a]	0.285	THF	-78	H_2O	1.00	65	0
13[a]	0.014	THF	-78	H_2O	1.00	22	0
14[c]	0.285	THF	-78	H_2O	1.00	38	0
15[a]	0.057	THF	-78	H_2O	1.00	40	0
16[a]	0.030	THF	-78	H_2O	1.00	70	0

a) Extraction with ethylacetate; **b)** Extraction with chloroform; **c)** reaction quenched at room temperature.

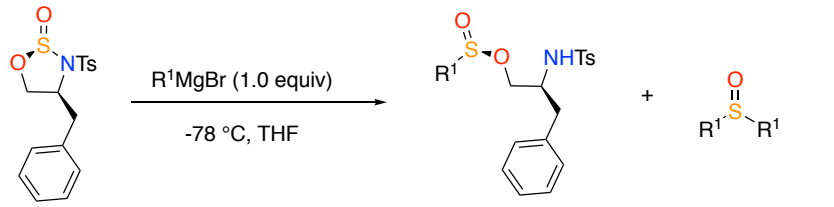
With substrate **209a** in our hands methyl phenyl sulfoxide was being produced (40% yield) in excellent *ee* (98%), according to the multistep route (Scheme 2. 3).



209a **36a**

Scheme 2. 3 Addition of MeMgBr on intermediate **209a**

Next, to explore the reaction scope, template **26** was reacted with MesMgBr and *p*-TolMgBr using the optimised reaction conditions (Scheme 2. 4).



26

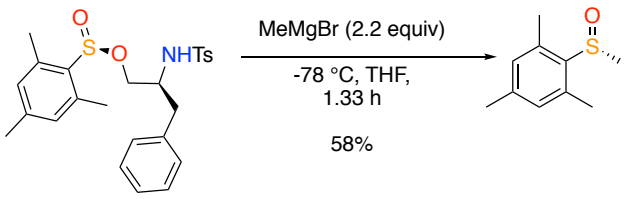
209b R^1 = *p*-Tol 59% yield
209c R^1 = Mes 62% yield

210b R^1 = *p*-Tol
210c R^1 = Mes

Scheme 2. 4 Addition of R^1MgBr to template **26**

After one hour the reaction was quenched, products isolated and purified by flash column chromatography. Even if formation of double addition product were observed, in both cases the desired compounds were obtained in good yields. Intermediate **209c**

was subsequently used to form chiral sulfoxide **36b**, to verify how the steric hindrance of the R^1 group would affect sulfoxide formation (Scheme 2. 5).[i]

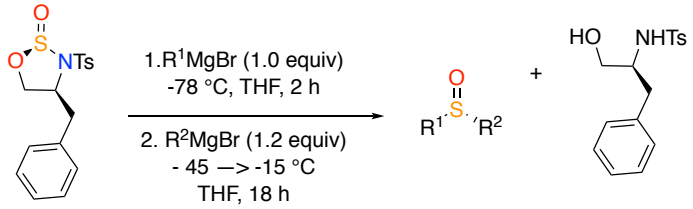


209c **36b**

Scheme 2. 5 Addition of MeMgBr to intermediate **209c**

Good results were achieved performing this multi-step route, but in attempt to improve the overall yield of chiral sulfoxides a one-pot approach was carried out. Substrate **26** was reacted according to Senanayake's protocol:[29] R^1MgBr (1.0 equiv) added dropwise in THF at -78 °C for 2 h, then R^2MgBr (1.2 equiv) is added slowly and reaction temperature is gradually raised. The mixture is warmed up from -45 °C to -15 °C and left stirring for 18 h (Table 2. 2).

Table 2. 2 Reagent and conditions for one-pot Grignard addition[i]



26 **25**

Entry	Name	R^1	R^2	Yield (%)
1	**36b**	Mes	Me	43
2	**36c**	Mes	Et	19
3	**36a**	Ph	Me	20

For the result displayed in entry 1 (Table 2. 2) the first attempt of purification by column chromatography yielded sulfoxide **36b** as a mixture of two compounds (one still unidentified), so it was purified again, increasing solvent polarity to achieve a better separation and to yield **36b** in 43%. However, the efficiency is inferior in comparison to the results reported in the multistep route (Scheme 2. 5). Sulfoxides with a low molecular weight are extremely soluble in aqueous media and very polar to purify on column chromatography. Therefore, a repeat of the one-pot reaction was

[i] *ee* for the sulfoxides wasn't measured

performed changing the second Grignard reagent to ethyl magnesium bromide to increase the lipophilicity and aid purification (Table 2. 2, entry 2). After column chromatography on silica gel, only 19% of pure sulfoxide **36c** was obtained. The remaining released auxiliary **25** could not be separated from **36c**. Finally, phenyl Grignard was used as R^1MgBr and under the same reaction conditions the one-pot procedure was carried out. Much to our surprise the sulfoxide was formed only in 20% yield (Table 2. 2, entry 3), with the diphenyl sulfoxide as the major product. We believe that this result was due to the reduced steric hinderance of the R^1 group which made the sulfur center more accessible towards the nucleophilic attack. Continuing efforts are ongoing to optimise the one-pot procedure employing the knowledge gained in these studies. Unfortunately we could not replicate Senanayake's yields with the analogous template. Even if the enantiomeric excess of sulfoxide **36a** derived from chiral template **26** was excellent the same can't be said for the yields.

When the first Grignard reagent is added to **26**, a portion of material forms a double addition product. Senanayake's and co-workers in their methodology didn't encounter this problem, therefore we believe this is due to sterics. Having a less substituted ring makes it more accessible for nucleophilic addition and allows less stereocontrol over double addition side products. Moreover, chiral template **26** is not bench stable. After a month of storage at room temperature epimerisation and decomposition is observed.
Therefore, inspired by Davies's "SuperQuat" reagent **215**[267] and with the goal to overcome the current preparative limitations of template **26**, an improved route towards synthesis of templated sulfur(IV) **214**, for sulfoxide formation, was designed (Figure 2. 1).[43] The geminal dimethyl group should make the molecule more stable and less accessible for double addition products (Figure 2. 1).

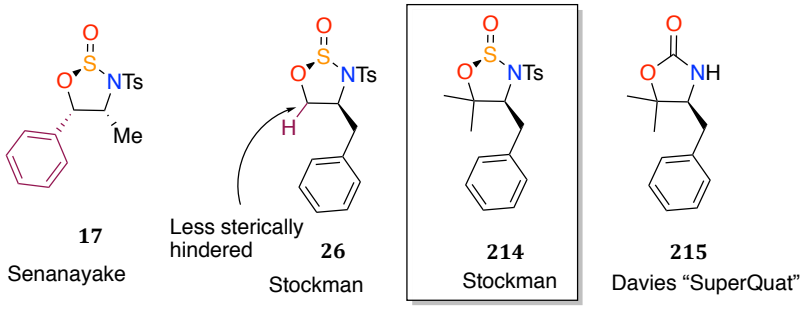
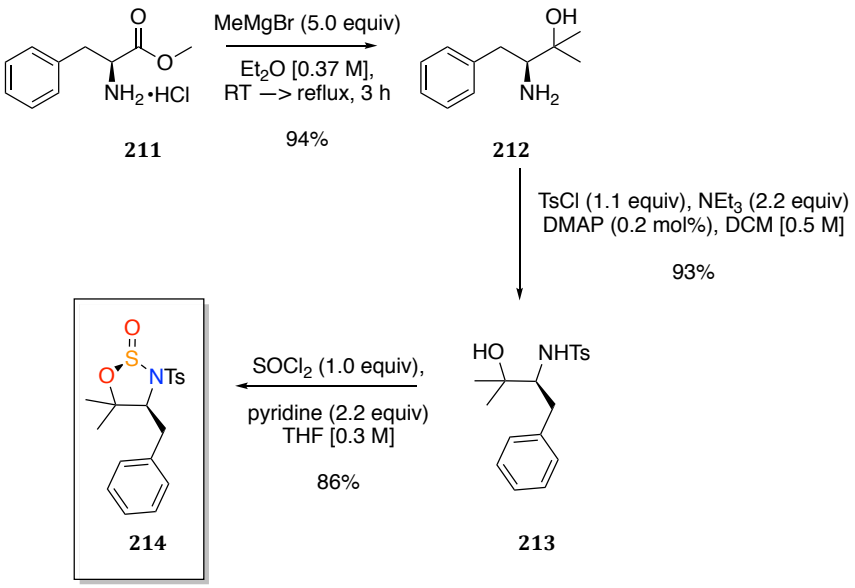


Figure 2. 1 Senanayake's chiral auxiliary **17**, Stockman's group chiral auxiliaries **26** and **114**, and Davies' "SuperQuat" reagent **215**

First, commercially available **211** was added portion-wise to a MeMgBr/diethyl ether solution under argon atmosphere, to give after 3 h product **212** in excellent yield

(94%). Then, L-phenylalanine derivative **212** was tosylated using standard reaction conditions to give product **213**, after a simple aqueous work-up and recrystallisation (dichloromethane/petrol), in excellent yield (93%). In the Stockman group the route towards oxathiazolidine-2-oxide (**26**) template has previously been reported (see Scheme 2. 2). The in house synthesis of **26** can be readily performed yielding gram quantities available for use.[42,43] For this reason, the ring closing of **213** was performed following this known protocol. After purification of the reaction mixture by flash column chromatography, the new chiral template **214** was obtained in high yield (86%) (Scheme 2. 6).[ii]

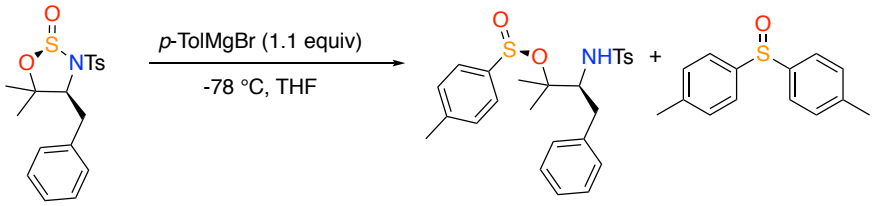


Scheme 2. 6 Synthesis of chiral template **214**

Once the new chiral template **214** was synthesised, an intense screen to identify optimal reaction conditions, to obtain chiral sulfoxides began. As previously seen for **26**, we first focused our attention on R^1MgBr nucleophilic addition step.

[ii] *ee* for template **214** wasn't measured as the compound was already known in the Stockman group

Table 2. 3 Reaction conditions for R^1MgBr addition on **214**[iii]



214 **216a** **210b**

Entry	Grignard add. time (min)	216a (%)[b]	210b (%)[b]
1	1	73	9
2	2	60	4
3	5	66	5
4	10	60	4
5	15	42	3
6	1[a]	70	13

a) Grignard added without cooling it to -78 °C; **b)** NMR yields using 1,3,5-trimethoxybenzene as internal standard

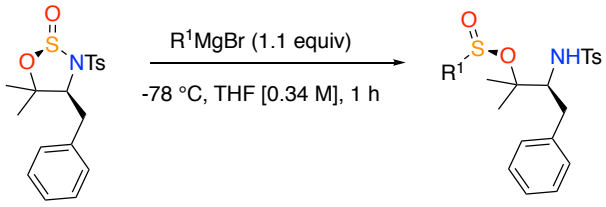
p-TolMgBr was used as a nucleophile to find optimal reaction conditions for the first nuclephilic addition. The main feature we were looking at was Grignard addition time. Given our previous experience with template **26**, we knew that it was key to improve the chemical yield of product **216a** despite **210b** formation. To avoid tedious purifications, product formation was calculated using 1,3,5-trimethoxybenzene as internal standard. Increasing the addition time to 15 minutes seemed detrimental for **216a** formation, Table 2.3, entry 5), while optimal conditions were achieved when the nuclephile was added over one minute, along the flask walls (Table 2. 3, entry 1). No substantial difference in yield was observed when *p*-TolMgBr was instead added at room temperature over 1 minute (Table 2. 3, entry 6).

With optimal reaction conditions in hand the reaction scope was tested. Much to our delight, the substrate would tolerate not only electron-withdrawing (EWG) (Table 2. 4, entry 3-4) and electron-donating groups (EDG) (Table 2. 4, entry 5) on the aryl ring but also heteroatoms (Table 2. 4, entry 7) reporting high yields for intermediate **216h**. Moreover, when alkyl Grignards were tested desired compounds were achieved in yields from good to high (Table 2. 4, entries 8 and 10-11). For the alkyl Grignards higher yields were obtained for compound **216j** (83%) indicating that nucleophilic addition onto **214** doesn't appear to be affected by the steric bulk of the R^1MgX reagent

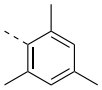
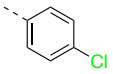
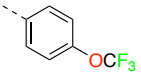
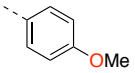
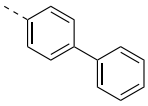
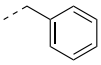
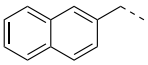
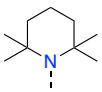
[iii] **216a** was obtained in every case as single diastereoisomer (verified by NMR)

(Table 2. 4, entry 9). To expand our table of results, 2,2,6,6-tetramethylpiperidinylmagnesium chloride was employed as R^1MgX, surprisingly **214m** was obtained in excellent yield (Table 2. 4, entry 12).

Table 2. 4 Addition of R^1MgBr to **214**[iv]



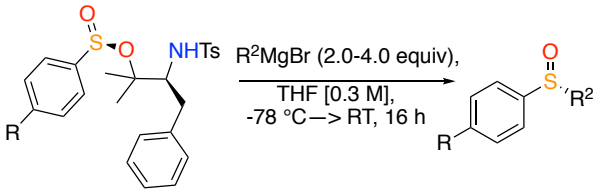
214 **216b-n**

Entry	Compound	R^1	Yield(%)
1	**216b**		92
2	**216c**		63
3	**216d**		79
4	**216e**		58
5	**216f**		72
6	**216g**		66
7	**216h**		93
8	**216i**		96
9	**216j**		83
10	**216k**		53
11	**216l**		58
12	**216m**		83

[iv] Compounds were obtained as single diastereoisomers (verified by NMR)

Encouraged by these first results for the initial addition step, we moved to the second step of our envisaged strategy. We used as key intermediate compounds **216c** and **216a.** Two main features were changed in this case: number of equivalents and lipophilicity of R^2.

Table 2. 5 Addition of R^2MgBr to **91c** and **91a**



91c R = H
91a R = CH_3

Entry	Compound	R	R^2	X (equiv)	Yield (%)[v]
1	**36a**	H	Me	4.0	20
2	**36d**	H	Et	4.0	41
3	**36e**	H	*p*-(OMe)C_6H_4	2.0	quantitative
4	**36f**	H	C_4H_4S	4.0	91
5	**36g**	H	2-biphenyl	4.0[a]	quantitative
6	**36h**	Me	Me	3.0	21
7	**36i**	Me	Et	4.0	50
8	**36l**	Me	cyclopropyl	4.0	47
9	**36j**	Me	*tert*-Bu	4.0	56
10	**36k**	Me	*n*-Bu	4.0	51

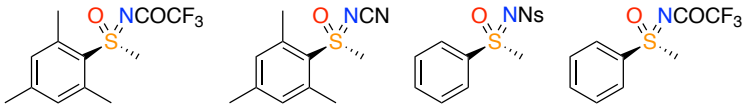
a) reaction performed initially with 3.0 equiv, after 5 h another equiv added

The number of equivalents of the nuclephile added in solution varies according to how the reaction proceeds (monitored by TLC). In most cases 4.0 equivalents were employed to get higher chemical yields. Even if no major side product had been observed, and two main spots were visible on the TLC belong to the S(IV) product and the released auxiliary **213**, yields for sulfoxides were modest (Table 2. 5, entries 2-3 and 7-10). In this series, very poor yields were obtained for sulfoxides **36a** and **34h** (Table 2. 5, entries 1 and 6). We believe the loss in yields happens during the aqueous work-up of the reaction mixture, due to the high solubility of the molecules in water. To prove our hypothesis, thiophene and biphenyl were chosen as R^2 groups for their hydrophobic character. Much to our delight, products **36e**, **36f** and **36g** were isolated

[v] *ee* for the sulfoxides wasn't measured

in excellent yields (Table 2. 5, entries 3-5). The aforementioned studies, have clarified and improved several points of our initial sulfoxides synthesis. Addition time, concentration, equivalents quantity of nucleophile and choice of the R^2 have been extensively investigated. Even though we couldn't match Senanayake's yields with the analogous templates **26** and **214** fully, the work done so far is just a first step to disclose the synthesis of enantiomerically pure sulfoxides.

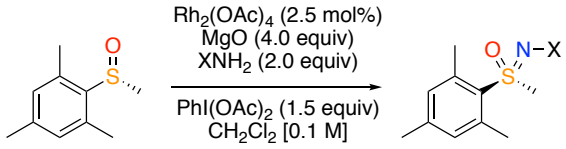
Since different examples of chiral sulfoxides were made in good yield, we had enough starting material to focus on the synthesis of chiral sulfoximines. We planned to synthesise sulfoximines **217a-d**.



217a **217b** **217c** **217d**

Scheme 2. 7 Target sulfoximines

The formation of **217a** and **217b** was investigated through rhodium(II) catalysis, following standard procedure and using Schlenk techniques. Taking into account the bulky substituent on these two compounds, alternative sources of nitrogen were explored under optimised conditions. Simple and easy to deprotect amides, such as trifluoroacetamide and the synthetically useful cyanamide, were reacted together with mesityl methyl sulfoxide[vi] (Scheme 2. 8).[90]



36b

217a X = $COCF_3$ 11%
217b X = CN 8%

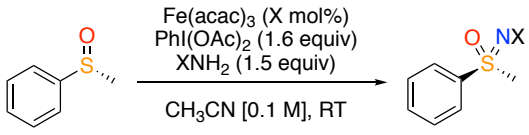
Scheme 2. 8 Oxidative imination, catalysed by rhodium(II), on **36b**

The reaction proceeded at room temperature for 15 and 48 h respectively. The formation of the product was followed by TLC. Unfortunately the sulfoximine was not the only compound formed in the reaction. After flash column chromatography the sulfoximines were obtained in 8% (**217b**) and 11% (**217a**), respectively. Although most of the starting material remained unreacted, no epimerisation on both **217a** and **217b** sulfoximines, was observed (Scheme 2. 8). Suspecting that the sterically hindered aryl group was the main cause of the poor yield reported, methyl phenyl sulfoxide was

[vi] *ee* for the sulfoximines **217a-b** wasn't measured

then employed as the starting material. The high cost of rhodium salts limits the large-scale application of this protocol, therefore the equally efficient iron catalyst is deemed preferable. Using sulfonyl amides or trifluoroacetamide (1.5 equiv.), $PhI(OAc)_2$ (1.6 equiv.) in dry acetonitrile (0.1 M) with iron(III) employing Schlenk technique delivers the product in the improved yield of 44% (Table 2. 6).

Table 2. 6 Iron catalysed imination on methyl phenyl sulfoxide **36a**[vii]



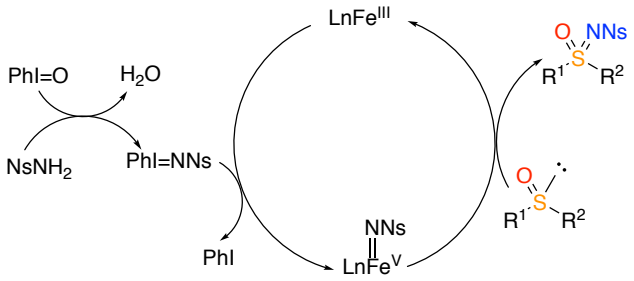
36a **217c-d**

Entry	Product	X (mol %)	X =	t (h)	Yield (%)
1	**217c**	(5 %)	-Ns	17	44
2	**217d**	(10 %)	$-COCF_3$	48	11

After 6 h, formation of the product was visible (TLC), and the colour of the mixture changed from bright red to bright orange. In the iron catalysed imination, the full conversion of starting material was not observed, but a better selectivity, made it preferable to rhodium methodology. The formation the sulfoximines was confirmed both by the ^1H NMR, and ESI-MS. On the ^1H NMR spectrum of sulfoximine **217c** shifts of the main peaks were visible, and furthermore around 8.33 ppm and 7.98 ppm signals belonging to nosyl group were present. Nevertheless, isolating **217c** was challenging and it was collected as a mixture of product and impurity.

Reaction mechanism for the iron catalysis wasn't investigated in our group as Bolm and co-workers had already described it.[92] It was assumed that the mechanism involved the *in situ* formation of nitrene species PhI=NNs which then would react with Fe^{III}, generating a nitrene-iron complex. This iron intermediate would then be attacked by the lone pair on the sulfoxide to produce the corresponding sulfoximine molecule (Scheme 2. 9).

[vii] *ee* for the sulfoximines **217c-d** wasn't measured

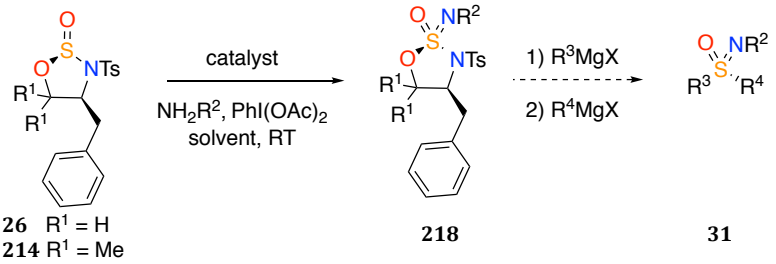


Scheme 2. 9 Proposed Fe^{III} catalysed imination mechanism of sulfoximines

We were positively encouraged by the results achieved so far with the nosyl sulfoximine **217c** but we would like to improve the yield for sulfoximine **217d**. Trifluoroacetamide is a very good protecting group and nevertheless is generally easy to cleave. Therefore achieving better yield for this protected sulfoximine would be ideal.

Nowadays, many mild and robust methodologies have been developed for iminating sulfoxides without need of protecting groups on the nitrogen. This is obviously advantageous as it reduces the steps necessary for the free NH sulfoximines synthesis. Therefore, we are confident that once the route to produce optically active sulfoxides **36a-k** is optimised, the synthesis of enantioenriched sulfoximines will be straightforward.

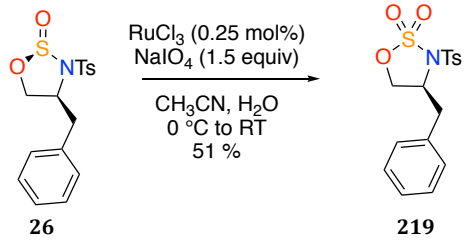
Encouraged by the results gained with the chiral sulfoxides, direct imination of chiral templates **26** and **214** was explored. We thought that if $=NR^2$ transfer was feasible, subsequent addition of two Grignard reagents to **218** would provide the desired enantiopure sulfoximines **31.** In this light both substrates were tested according to Bolm's and Bull's oxidative imination conditions for sulfoxides (Scheme 2. 10).[79,90–92]



Scheme 2. 10 Oxidative imination of templates **26** and **214**

Unfortunately treatment of templates **26** and **214** under Bolm's and Bull's oxidative imination conditions, resulted in no conversion to **218**, while under prolonged reactions times and forcing condition led to decomposition or cleavage of the S-N bond.

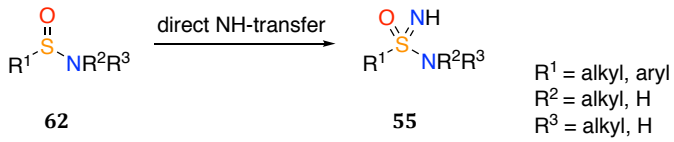
Therefore it was evident that the direct imination of the sulfur contained in the chiral templates was not straightforward. This was quite surprising considering previous work by the Gallagher group where template **26** was subjected to further oxidation providing cyclic sulfamidate **219** (Scheme 2. 11).[268] As a result, subsequent work would explore the direct imination of sulfinamides.



Scheme 2. 11 Gallagher's ruthenium oxidation of **26**

2.2 Sulfonimidamides

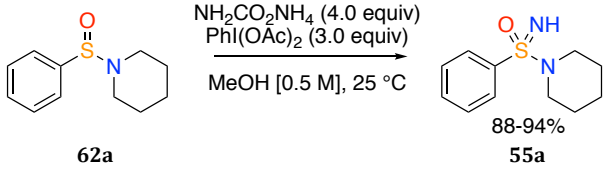
Before Willis'[121] and Sharpless' work,[122] a facile synthesis of free NH-sulfonimidamides had never been reported; during the course of our research on sulfoximines we have observed a significant improvement towards a versatile and safe synthetic method for sulfoximines preparation. In 2016 Bull and Luisi reported the first metal free example of direct NH transfer to a sulfoxide to make free NH sulfoximines, with wide substrate scope using commercially available reagents.[79] Therefore, inspired by this research, we wondered if applying the same reaction conditions on tertiary sulfinamides would give us the desired sulfonimidamides (Scheme 2. 12).



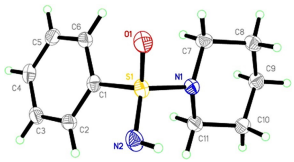
Scheme 2. 12 Proposed synthesis of SIAs **55**

In order to test this hypothesis commercially available 1-(phenylsulfinyl)piperidine **62a** was reacted together diacetoxyiodobenzene (3.0 equiv), ammonium carbamate (4.0 equiv) in methanol at room temperature, according to Bull and Luisi's conditions for sulfoxides.[79] Surprisingly, after 1 hour, the reaction was complete (solution monitored by UPLC-MS) and the unprotected tertiary sulfonimidamide was isolated in 94% yield (Scheme 2. 13). Scaling up sulfinamide **62a** (4.0 g) resulted in a clean

reaction mixture and very good yields (88%). Product **55a** was confirmed by X-ray analysis.



62a **55a**

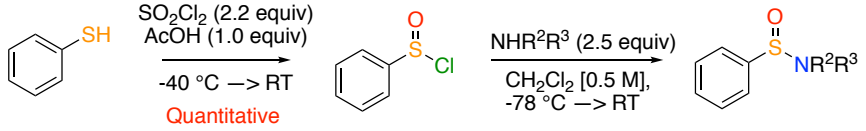


Scheme 2. 13 Direct imination of tertiary sulfinamide **62a**

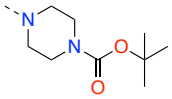
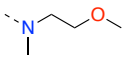
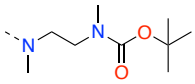
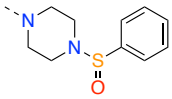
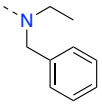
Unlike Bull's reaction procedure, where MeOH was simply removed under reduced pressure and the crude reaction mixture purified by flash column chromatography,[79] aqueous sodium carbonate was added and mixture extracted with ethyl acetate. It was preferred to remove the excess reagents prior to purification to avoid formation of the sulfonamide side product and to better facilitate separation on flash column chromatography. In contrast to previously reported procedures,[102,108] this robust synthesis didn't require air sensitive set up (Schlenk line) or prior drying of solvents. On the contrary, the reaction vessel was left open to air to allow CO_2 exhaustion produced by the nitrene species formation.[79]

With optimal reaction conditions in hand, substrate scope was explored next. Initially, the amine fragment of **62**, was varied keeping the phenyl group fixed. Using a previously reported route by Perrio and co-workers,[269] sulfinyl chloride **47a** was easily synthesised from thiophenol in the presence of acetic acid and sulfuryl chloride. Intermediate **47a** was obtained in quantitative yield and reacted immediately, without further purification, with an excess of both symmetric and asymmetric amines. Generally, the reaction was performed on 1.6 mmol of **47a** obtaining the desired tertiary sulfinamides in modest to excellent yields (Table 2. 7). Dimethyl and diethyl sulfinamides **62b** and **62c** were synthesised in excellent yields (Table 2. 7), while cyclic sulfinamides also common in medicinal chemistry were isolated in good yields (**62e-92h**). Given our interest in medicinal chemistry, more complex secondary amines, commonly included in drug candidates, were chosen. However, we were disappointed to obtain only modest yields for compounds **62i** and **62j** (Table 2. 7). Interestingly, when benzenesulfinyl chloride **47a** was reacted together with 2.5 equivalents of piperazine, double addition was observed resulting in **62k** as the isolated product (37% yield).

Table 2. 7 Synthesis of tertiary sulfinamides



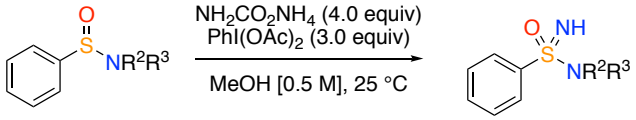
220 **47a** **62b-k**

Compounds	NR^2R^3	Yield [%]
62b	NMe_2	99
62c	NEt_2	99
62d	N*i*Pr_2	76
62e	1-azetidinyl	67
62f	1-pyrrolidinyl	75
62g	4-morpholinyl	77
62h		76
62i		43[a]
62j		23[a]
62k		37
62l		72

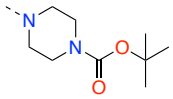
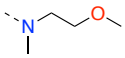
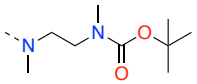
a) reaction performed on 2.49 mmol of **47a**

Next, previously synthesised tertiary sulfinamides **62b-k** were further subjected to the optimised reaction conditions for oxidative imination. Once again, the reaction mixture didn't present any undesired side product and different amines groups were well tolerated under the conditions resulting in the desired free NH-sulfonimidamides **55b-k** in good yields (up to 77%) (Table 2. 8). Only SIA **55d** was isolated in a poor yield (17%), presumably due to steric hindrance of the *N,N*-diisopropylamino group. On the contrary 1,4-bis(phenylsulfinyl)piperazine **62k** was successfully double iminated providing desired product **55k** in modest yield (50%) (Table 2. 8).

Table 2. 8 Synthesis of free NH sulfonimidamides



62b-k **55b-j**

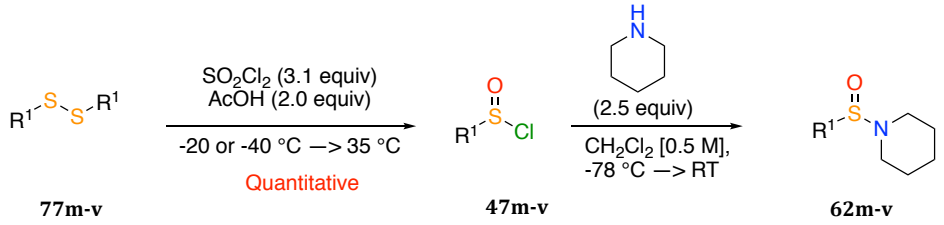
Compounds	NR^2R^3	Yield [%]
55b	NMe_2	72
55c	NEt_2	77
55d	$NiPr_2$	17
55e	1-azetidinyl	71
55f	1-pyrrolidinyl	77
55g	4-morpholinyl	77
55h		65
55i		67[a]
55j		78[a]
55k		50

a) Reaction on 0.48 mmol of sulfinamides **b)** Reaction performed on 0.52 mmol of sulfinamides

Once the reaction scope for NR^2R^3 was well established, R^1 group was changed. Different alkyl and aryl substituents were tested. This time, synthesis of sulfinyl chlorides **47m-u** was more challenging, as it required longer reaction times (5-6 hours), according to the R^1 groups, in comparison to **47a**. Furthermore, exploration of substrate scope was limited to previously reported procedures for sulfinyl chlorides, as this class of compounds can be rather sensitive to temperature and unstable for prolonged handling.[270,271] For 1-(tert-butylsulfinyl)piperidine **62v** the corresponding sulfinyl chloride **47v** was commercially available, therefore it was reacted straightaway with piperidine to yield 86% of the desired sulfinamide (Table 2. 9)

The reaction employing aryl disulfides bearing electron withdrawing groups proceeded in yields from modest to good (**62m-o** and **62r-s**) while **62p** was obtained in a very poor yield (16%). Significant increase in product formation was achieved when alkyl disulfides were used (Table 2. 9, compounds **62t** and **62v**).

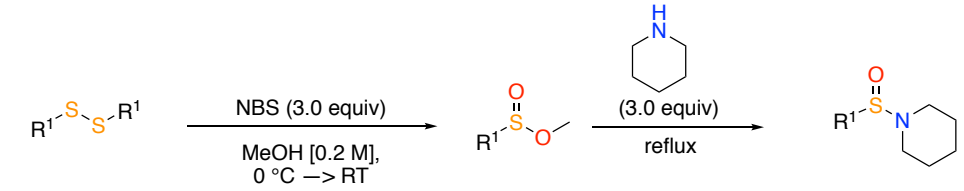
Table 2. 9 Synthesis of piperidine sulfinamides



77m-v **47m-v** **62m-v**

Compounds	R¹	Yield [%]
62m	4-$MeOC_6H_4$	54
62n	4-FC_6H_4	24
62o	4-$O_2NC_6H_4$	56
62p	3-$F_3CC_6H_4$	16
62q	4-MeC_6H_4	83
62r	3-ClC_6H_4	67
62s	2-ClC_6H_4	56
62t	cyclohexyl	83
62u	*i*Pr	50
62v	*tert*-Bu	86

To synthesise sulfinamides bearing hetero aromatics on R¹, sulfinyl chloride methodology (Table 2. 9) were employed, however no product was formed. For this reason 2-pyridyl **62w** and 3-pyridyl **62y** were made from the sulfinate ester **221** instead.[272] After aqueous work up with sodium bicarbonate, **221w** and **221y** were immediately refluxed in piperidine to provide the desired compounds **62w** and **62y** (Scheme 2. 14).[104,273]



R¹ = 2-pyridyl **77w**
R¹ = 3-pyridyl **77y**

R¹ = 2-pyridyl **221w**
R¹ = 3-pyridyl **221y**

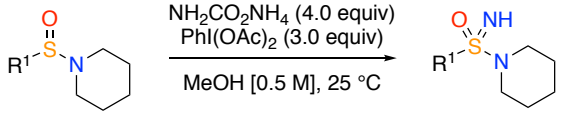
R¹ = 2-pyridyl **62w** 39%
R¹ = 3-pyridyl **62y** 36%

Scheme 2. 14 Synthesis of piperidine sulfinamides **92v-w** from sulfinate esters **96v-w**

Next, tertiary sulfinamides **62m-y** were further subjected to oxidative imination according to standard reaction conditions (Table 2. 10).[104] Once again starting materials **62m-y** were fully converted to iminated products **55m-y** in good to excellent yields. A broad variety of substituents common in medicinal chemistry were tested,

both electron withdrawing and electron donating groups on the aryl ring were well tolerated, as well as heteroatoms **55w-y**. Gratifyingly, also alkyl sulfinamides **62t-v** were successfully iminated in very good yields showing broad reaction scope of this new mild route towards sulfonimidamides. Only 2-(chlorophenyl)sulfonimidoyl piperidine **55s** was obtained in 29% yield. This was probably due to steric hindrance of chlorine group in *ortho* position. Although when the reaction was repeated adding another fold of reagents, an improvement in yields was observed, and product **55s** was isolated in 48% yield, together with unreacted starting material **62s**.

Table 2. 10 Synthesis of free NH piperidine sulfonimidamides **55m-y**



62m-y **55m-y**

Compounds	R¹	Yield [%]
55m	4-$MeOC_6H_4$	87
55n	4-FC_6H_4	89
55o	4-$O_2NC_6H_4$	62
55p	3-$F_3CC_6H_4$	81
55q	4-MeC_6H_4	95
55r	3-ClC_6H_4	85
55s	2-ClC_6H_4	29(48)[a]
55t	cyclohexyl	88
55u	*i*Pr	70
55v	*t*Bu	83
55w	2-pyridyl	85
55y	3-pyridyl	53

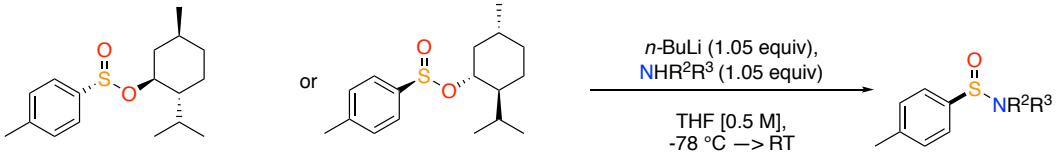
a) reaction repeated adding $NH_2CO_2NH_4$ (8.0 equiv) and $PhI(OAc)_2$ (6.0 equiv)

Confident of the results obtained so far on racemic S(IV) compounds, we wanted to apply this methodology using enantioenriched sulfonimidamides to verify the stereospecificity of this process. Chiral sulfinamides were initially prepared from commercially available Anderson's auxiliaries (Table 2. 11) in which the reaction proceeds with inversion of configuration.

Sulfinamides **221a-b** and **62q** were made from (1*S*, 2*R*, 5*S*)-(+)-menthyl **2** analogue while morpholinyl-**221c** and **221d** were prepared using both diastereoisomers (Table

2. 11). Desired compounds were isolated in good yields, however when sulfinamide **62q** was subjected to chiral HPLC, it showed modest enantiomeric excess (51% *ee*).[viii] Even if we didn't verify it, we believe that this result is probably due to low purity of commercially available starting material (*R*)-**2**.

Table 2. 11 Synthesis of enantioenriched sulfinamides

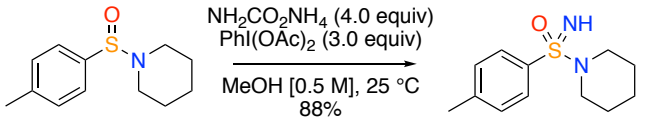


(*1S*, *2R*, *5S*)-(+)-Menthyl-(*R*) **2** (*1R*, *2S*, *5R*)-(-)-Menthyl-(*S*) **2** (*R*) or (*S*)-**221a-s** (*R*)-**62q**

Compounds	NR^2R^3	Yield [%]
221a	NMe_2[a]	58
221b	pyrrolidinyl[a]	57
221c	morpholinyl[a]	51
221d	morpholinyl[b]	32
62q	piperidinyl[a]	83(51% *ee*)

a) reaction performed on (+)- (*R*)-**2**; **b)** reaction performed on (-)- (*S*)-**2**

Nevertheless, **62q** was further reacted under optimised imination conditions. Even if a low degree of erosion was observed we were pleased to confirm that the NH transfer proceeded stereospecifically in 48% *ee* (Scheme 2. 15). Given the loss of only 3% in enantiopurity for **55q**, we believe the main cause to be an error in the measurement/HPLC instrument.

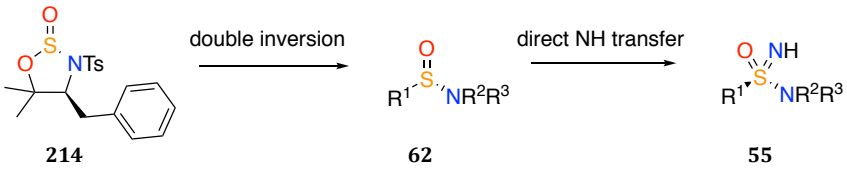


(*R*) or (*S*)-**62q** (51% *ee*) (*R*) or (*S*)-**55q** (48% *ee*)

Scheme 2. 15 Synthesis of enantioenrieched **55q**

As previously mentioned in section 2.1, we have developed a useful building block derived from L-phenylalanine for synthesis of enantiopure sulfoxides in high yields and selectivity, therefore we were curious to verify whether it could also be used to produce chiral sulfinamides in high *ee* (Scheme 2. 16).

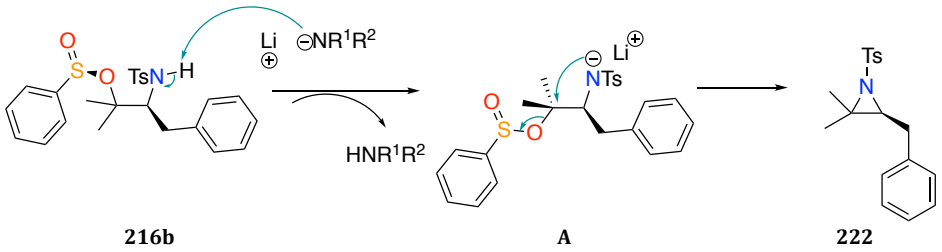
[viii] *ee* was measured by chiral HPLC only for compound **62q**



Scheme 2. 16 Envisaged synthesis of chiral sulfonimidamides

First, intermediate **214** was prepared according to the previously reported method for sulfoxides (see section 2.1). Nucleophilic addition of metal amide to intermediate **214** resulted in S-O bond cleavage with inversion of configuration to furnish desired sulfinamide **62**. It is important to highlight that **214** could be synthesised on large scale (8-10 grams) and stored in the fridge for months without observing decomposition, a feature which made our investigation less tedious and more feasible.

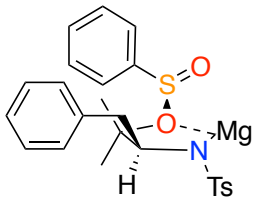
Intermediate **216b** was reacted with a pre-mixed solution of piperidine and *n*-BuLi in 1:1 ratio at -78 °C. After 2 hours all starting material remained unreacted, for this reason, the mixture was warmed to room temperature and stirred overnight. Using an internal standard (1,3,5-trimethoxybenzene) product conversion was calculated. Unfortunately, only aziridine was obtained but no peaks corresponding to product were seen on the ^{1}H-NMR (Table 2. 12, entry 1). Formation of **222** over tertiary sulfinamide product was rationalised by the initial deprotonation of the nitrogen on intermediate **216b** from the lithiated secondary amine, which then eliminates to give aziridine **222** (Scheme 2. 17).



Scheme 2. 17 Proposed mechanism for the aziridine formation

A repeat of the one-pot reaction was performed investigating temperature change (Table 2. 12, entry 2). After 2 hours at 0 °C two spots on the TLC, associated both aziridine (side product) and desired sulfinamide **62a,** were visible. Conversion of **216b** to **62a** in 64% yield was confirmed by ^{1}H-NMR. A repeat of the previous reaction was carried out to verify the former results. Once again sulfinamide **62a** was synthesised in 63% yield (Table 2. 12, entry 3). Next, freshly titrated phenylmagnesium bromide was selected as base to deprotonate piperidine. We believed that using a Grignard reagent

would limit the aziridine formation whilst enhancing sulfinamide **62a** formation instead. Changing the organometallic reagent from lithium to magnesium allowes the metal to coordinate both the oxygen lone pair and the nitrogen negative charge, creating a stable intermediate **B** and increasing the control of the reaction (Scheme 2. 18).

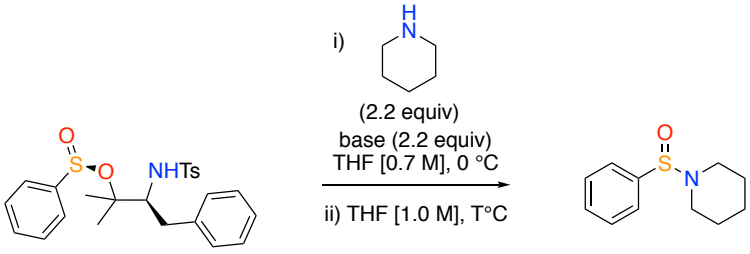


B

Scheme 2. 18 Proposed intermediate **B**

Much to our delight, this assumption was correct and product was formed in 74% yield (Table 2. 12, entry 4). These initial studies showed the importance of the selected base, which is key to improve chemical yields for sulfinamide formation.[ix]

Table 2. 12 Synthesis of enantioenrieched sulfinamides using intermediate **216b**



216b **62a**

Entry	base	T (°C)	Yield [%][a]
1	*n*-BuLi	-78	-
2	*n*-BuLi	0	64
3	*n*-BuLi	0	63
4	PhMgBr	0	74

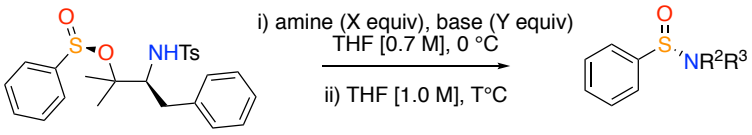
a) yield calculated by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard

Since an optimal route for enantioenriched sulfinamides was developed, different amines were tested to study the reaction scope. When dimethylamine and diethylamine were employed, no product was formed and most of the starting material remained unreacted **216b** (Table 2. 13, entry 1-2). A possible reason for it is given by the unequal

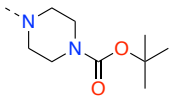
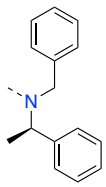
[ix] *ee* for **216b** wasn't measured

ratio of the amine/Grignard reagent in the pre-mixed solution (it should be 1:1). This is because both amines are sold in solution, given their very low molecular weight, therefore it is possible that the quantity injected in the Grignard solution is less than expected. In general, the best results were obtained when pyrrolidine and piperidine were used (Table 2. 13, entry 4 and 6), while employing dipentylamine, and morpholine (Table 2. 13, entry 3 and 5) gave product **223a** (as a mixture of the auxiliary with the sulfinamide) and **62g**, respectively, in modest yields. Much to our delight, when **62a** was subjected to chiral HPLC, enantiomeric excess was found to be 89%. Comparing the enantioselectivity gained for tertiary sulfinamide **62a** using the Stockman group chiral template instead of Andersen's auxiliary for **62q**, we can see an evident superiority in selectivity from our methodology. Even if we still need to optimise this procedure, initial results are very encouraging and optically active sulfinamides having diverse R^1 and the NR^2R^3 groups could be obtained. Further studies are on the way.

Table 2. 13 Synthesis of enantioenrieched phenyl sulfinamides from **216b**[x]



216b

Entry	Compound	amine	X	Y	Yield [%]
1	**62b**	NMe_2	2.2	2.2	-
2	**62c**	NEt_2	2.2	2.2	-
3	**223a**	$N[(CH_2)CH_3]_2$	4.0	4.0	48[a]
4	**62f**	1-pyrrolidinyl	3.0	3.0	80(95)[b]
5	**62g**	1-mopholinyl	4.0	4.0	43
6	**62a**	1-piperidinyl	3.0	3.0	95(89% *ee*)
7	**62h**		6.0	6.0	-
8	**223b**		4.0	4.0	traces

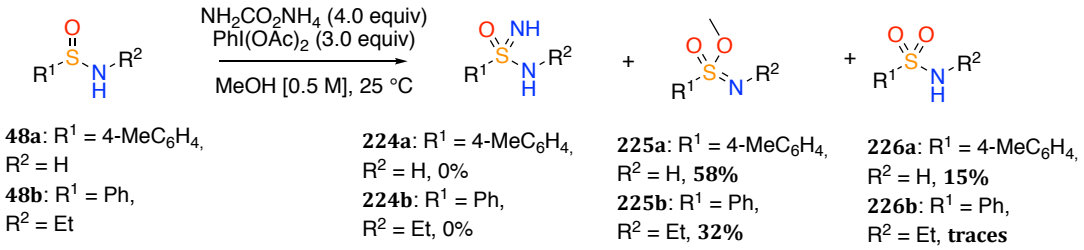
a) mixture of products; **b)** reaction performed on 0.5 g of **216b**

[x] *ee* measured by chiral HPLC only for compound **62a** at Bayer AG

Moving on, we wanted to apply previously discussed oxidative imination to both secondary and primary sulfinamides **48a** and **48b**. We found, however that this method was limited to the use of tertiary sulfinamides **62a-y**. When commercial sulfinamide **48a** was reacted together with ammonium carbamates and diacetoxyiodobenzene in methanol, **224a** didn't form, instead sulfonimidate **225a** (58% yield) and sulfonamide **226a** (15% yield) were isolated (Scheme 2. 19).

Reaction of **48b** under standard oxidative imination conditions gave a complex mixture from which sulfonimidate **225b** was isolated as main product (Scheme 2. 19).

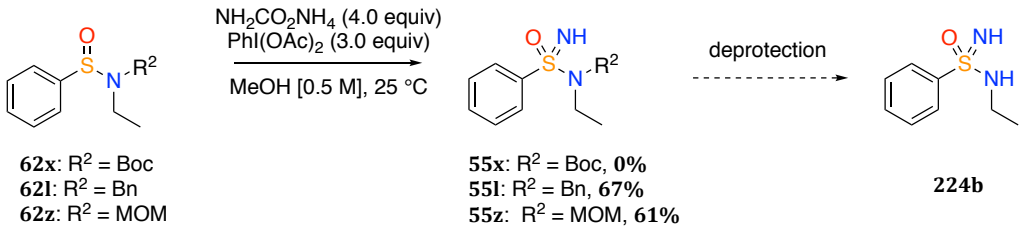
These results are in line with previously published articles on synthesis of sulfonimidates by Malacria and co-workers, where hypervalent iodine(III) reagents and suitable alcohols were employed.[274–276]



Scheme 2. 19 NH transfer on primary and secondary sulfinamides

Given the previous success with tertiary sulfinamides, we aimed to synthesise compounds **62x-z** and **62l** bearing common protecting groups easy to cleave once the corresponding sulfonimidamide **55** would form (Scheme 2. 20).

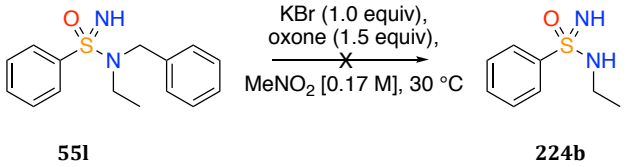
Boc (*tert*-butyloxycarbonyl) was initially preferred, but unfortunately when NH transfer conditions were applied no product was formed (reaction monitored by TLC) and **62x** remained unreacted. We believe that the electron-withdrawing character of the Boc group inhibited the NH transfer. Similar results were reported by Bull and Luisi, when a sulfoxide was bearing the trifluoromethyl group.[79]



Scheme 2. 20 Proposed synthesis for secondary sulfonimidamides

Since many secondary benzylamines are commercially available, we reacted sulfinamide **62l**, which had benzyl (Bn) group as R^2, under known reaction conditions. Sulfonimidamide **55l** was obtained in 67% yield. We didn't expect an easy deprotection

of benzyl group, as we knew they could be tricky to remove. We first tried to cleave *N*-Bn bond by $H_2/Pd(OH)_2$ both under atmospheric pressure and high pressure (20 bar), unfortunately starting material remained unreacted (monitored by ESI-MS, and TLC). Then, given the close similarity of the functional groups, we applied a method which employed potassium bromide and oxone for oxidative debenzylation of sulfonamides (Scheme 2. 21).[277] Even if new spots were formed on the TLC none of these belonged to **224b** (verified by ESI-MS analysis).



55l **224b**

Scheme 2. 21 Oxidative debenzylation of sulfonimidamide **55l**

Finally, R^2 was replaced by MOM (methoxymethyl ether) group (Scheme 2. 20). Imination step proceeded smoothly providing desired sulfonimidamide **55z** in good yield (61%). Unfortunately, the last deprotection step couldn't be performed as the S(VI) compound decomposed under the condition. Continuing efforts to find a suitable R^2 protecting group for secondary sulfinamides will be carried out.

2.2.1 In vitro assay

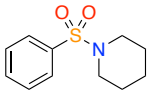
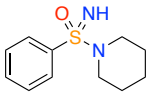
For a compound to be considered as a possible candidate in Drug Discovery certain elements, commonly referred to as ADME (absorption, distribution, metabolism and excretion), must be examined.[278]

- **Absorption** describes the process by which the molecule moves though the system from the site of administration. However, most of the small molecules are designed for oral administration and for this reason we can talk of **dissolution** through the gastrointestinal part
- **Distribution** defined as the movement of the drug from the vascular system to the extravascular sites (i.e. blood-brain barrier)
- **Metabolism** is the enzymatic breakdown of a drug
- **Excretion** is the active or passive transport of drugs into the urine or bile

The first screening of the molecule will be performed *in vitro*, and if all the above parameters are within acceptable range then the biological study of the molecule will continue *in vivo*. In order for a drug-like molecule to fulfil the previous requirements it also needs to possess certain properties such as: solubility (logP/D), potency (IC_{50}), lipophilic efficiency and molecular weight.

To improve our general understanding of the SIAs functional group, scientists from Bayer AG (Berlin) tested sulfonimidamide **55a** physiochemical properties and compared them to its matched pair sulfonamide **227** in a selected in vitro assay. Hydrolytic stability of these two compounds was tested at five different pHs. Sulfonimidamide **55a** showed after 24 hours of stirring in aqueous media, with a pH ranging from 2.0-8.0, 100% recovery, while sulfonamide **227** showed moderate stability at basic pH (67% recovery, pH 8.0). Then metabolic stability was examined, highlighting for sulfonamide **227** a moderate metabolic stability in human liver microsomes, resulting in a moderate predicted blood clearance 0.41 $Lh^{-1}kg^{-1}$, while a low metabolic stability and high predicted blood clearance was reported both for liver microsomes in rat and mouse (3.8 $Lh^{-1}kg^{-1}$ and 4.0 $Lh^{-1}kg^{-1}$ respectively). High blood clearance in rat hepatocytes was also measured (4.0 $Lh^{-1}kg^{-1}$).

Table 2. 14 Comparison of the in vitro properties of sulfonamide **227** and NH sulfonimidamide **55a**

Compound	Recovery [%][a] (pH)	CL_b[b] h/r/m]-LMs [$Lh^{-1}kg^{-1}$]	CL_b[b] rHep [$Lh^{-1}kg^{-1}$]	P_{app} A-B[c] [nms^{-1}]	Efflux ratio[c]	log*D* pH 7.5[d]
 **227**	91 (2.0) 85 (4.5) 100 (6.5) 100 (7.4) 67 (8.0)	0.41 (h) 3.8 (r) 4.0 (m)	4.0	393	0.64	2.6
 **55a**	100 (2.0) 100 (4.5) 100 (6.5) 100 (7.4) 100 (8.0)	0.04 (h) 3.0 (r) 1.1 (m)	3.6	378	0.59	1.9

[a] Hydrolytic stability measured as recovery of test compound after 24 hours with stirring at pH 2.0 (citrate buffer), pH 4.5 (citrate buffer), pH 6.5 (phosphate-buffered saline), pH 7.4 (phosphate-buffered saline), and pH 8.0 (sodium borate buffer).[279] **[b]** Predicted hepatic metabolic clear- ance based on a high-throughput metabolic stability assay using i) pooled human liver microsomes (hLMs), ii) pooled rat liver microsomes (rLMs), iii) pooled mouse liver microsomes (mLMs), and iv) freshly harvest- ed rat hepatocytes (rHep).[280] **[c]** P_{app} A–B (apical to basolateral) and efflux ratio (ER) data were generated in a bidirectionally performed Caco2 per- meability assay in a 24-well format; ER was calculated as P_{app} B–A/P_{app} A– B.[280] **[d]** Determined by reversed-phase HPLC.[281]

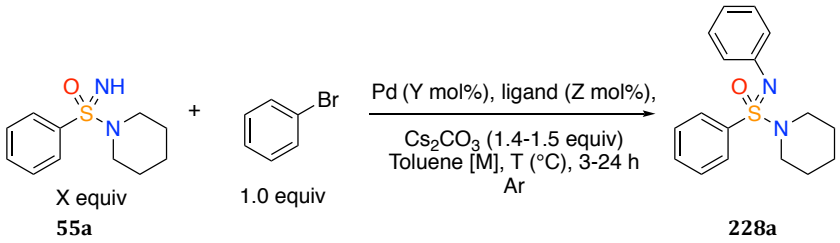
The analogue sulfonimidamide **55a** exhibited on the other hand, a trend in rats for a higher metabolic stability (high CL_b in rat liver microsomes 3.0 $Lh^{-1}kg^{-1}$ and rat hepatocites 3.6 $Lh^{-1}kg^{-}1$) in comparison to sulfonamide **227.** Values for liver microsomes in humans and mouse were, on the contrary, low (CL_b 0.04 $Lh^{-1}kg^{-1}$ and 1.1 $Lh^{-1}kg^{-1}$ respectively). Finally, using a Caco2 screening assay both sulfonimidamide **55a** and sulfonamide **227** had high permeability values, measured through the gut walls, (P_{app} A-B: 378 and 393 nms^{-1} respectively) without signs of efflux. The most remarkable result obtained in this study for sulfonimidamide **55a**, however, was the lipophilicity, measured as logD, which results in a significant decrease (1.9) in comparison to analogue sulfonamide **227** (2.6).

2.3 Sulfonimidamides *N*-functionalisation

Once the synthesis of NH-sulfonimidamides was well established (section 2.2), we focused our attention on their functionalisation. To explore the desired transformations we selected 1-(*S*-phenylsulfonimidoyl)piperidine **55a** as model compound to use, which was synthesised on gram scale from sulfinamide **62a**, according to previously reported methodology from our group (see Chapter 2). With respect to reactivity of the NH-position, we envisaged the similarity between sulfonimidamides and sulfoximines. Therefore, functionalisation reactions already in use at Bayer AG or previously published for sulfoximines,[57,58,252,255,282–285] were applied on our substrate **55a**. First, we looked into the Pd-catalysed arylation of **55a**. Unlike the broad variety of *N*-arylation methods available for sulfoximines, as far as we know, only a palladium catalysed reaction for the analogue sulfonimidamides have been reported so far.[197,286] Hence, NH-sulfonimidamide **55a**, was initially reacted with $Pd(OAc)_2$, phenyl bromide, Cs_2CO_3, and racemic BINAP (30%) in toluene. Product was isolated in 69% yield after 24 hours. In order to optimise the reaction conditions and obtain comparable yield to Arvidsson's and co-workers for *N*-arylation of SIAs,[197] some parameters were changed (Table 2. 15). Two palladium catalysts, commonly employed for arylation of sulfoximines, were tested and temperature, reaction time, equivalents and concentration were modified.

We found that using a lower amount of catalyst/ligand for 24 hours improved the product formation (Table 2. 15, entries 3-5). Moreover, the combination of $Pd_2(dba)_3$ with Xantphos gave the best results collected so far and after purification *via* flash column chromatography the desired product was obtained in 83% yield (Table 2. 15, entry 5). However, due to difficulties with purification in the $Pd_2(dba)_3$ case the scope of the reaction was explored using the $Pd(OAc)_2$/Xantphos system (Table 2. 15, entry 6).

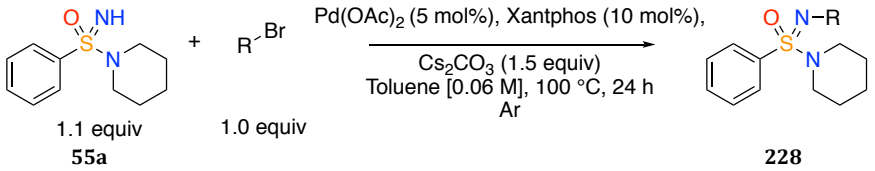
Table 2. 15 Optimisation of Pd catalysed arylation on SIA **55a**



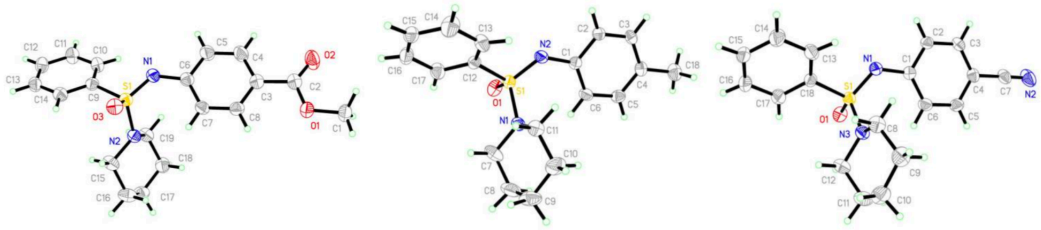
Entry	X	Pd	Y	ligand	Z	[M]	T (°C)	t (h)	Yield (%)
1	1.25	$Pd(OAc)_2$	10	BINAP	30	0.1	110	24	69
2	1.25	$Pd(OAc)_2$	10	BINAP	15	0.1	110	24	72
3	1.10	$Pd_2(dba)_3$	20	Xantphos	40	0.06	100	3	55
4	1.10	$Pd_2(dba)_3$	20	Xantphos	40	0.06	100	3	53
5	1.10	$Pd_2(dba)_3$	5	Xantphos	10	0.06	100	24	83
6	1.10	$Pd(OAc)_2$	5	Xantphos	10	0.06	100	24	72

A variety of aryl bromides were reacted under optimised reaction conditions providing a broad substrate scope. Both electron withdrawing and electron donating substituents on the aryl ring were well tolerated, and the desired coupling products were obtained in all cases, most of them in good to excellent yield (Table 2. 16). Sulfonimidamide **228l** in particular was formed in quantitative yield. The only exception was given by **228h**, which was isolated in 3% yield (Table 2. 16, entry 8). This is probably due to the steric hinderance of the two methyl groups in *ortho* position on the aryl bromide. Furthermore, when various heteroaryl bromides were reacted under selected reaction conditions, the corresponding heteroaromatic products were isolated in good yields (Table 2. 16, entries 13-17).

Table 2. 16 Exploration of the substrate scope of the palladium-catalysed *N*-arylation of sulfonimidamide **55a**



Entry	name	RBr	Yields (%)
1	**228a**	bromobenzene	86
2	**228b**	1-bromo-2-fluorobenzene	46
3	**228c**	1-bromo-3-fluorobenzene	97
4	**228d**	1-bromo-4-fluorobenzene	72
5	**228e**	2-bromotoluene	97
6	**228f**	3-bromotoluene	84
7	**228g**	4-bromotoluene	99
8	**228h**	2-bromo-1,3,5-trimethylbenzene	3
9	**228i**	3-bromoanisole	65
10	**228j**	4-bromobenzonitrile	88
11	**228k**	methyl 4-bromobenzoate	99
12	**228l**	4-bromobenzotrifluoride	quant.
13	**228m**	2-bromopyridine	71
14	**228n**	3-bromopyridine	77
15	**228o**	4-bromopyridine	72
16	**228p**	2-bromopyrimidine	77
17	**228q**	2-bromo-1,3-thiazole	45



228i **228g** **228j**

Figure 2. 2 X-ray structures of compounds **228i, 228g** and **228j**

Another important transformation for sulfonimidamides, which has been little explored in the past, is the *N*-alkylation. It is worth mentioning that the sulfoximines that are currently under clinical evaluation as kinase inhibitors, such as **BAY1000394**,[287,288] **AZD 6738**[59] and **BAY1251152**, contain a free NH sulfoximine as

a warhead (Figure 2. 3). However, such unprotected sulfoximines can have permeability issues and high values for efflux;[289] *N*-alkylation can be instead a way of improving the permeability properties.[290]

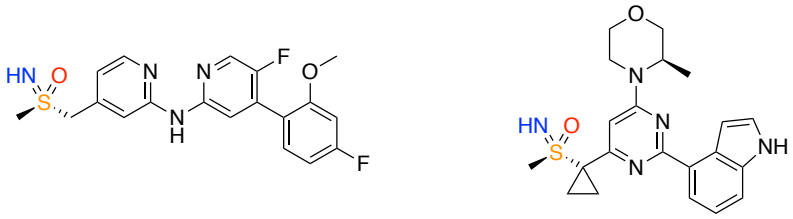
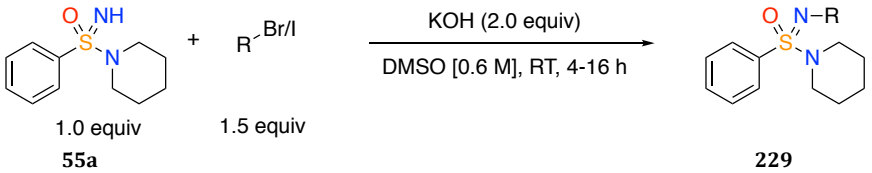


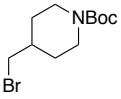
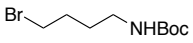
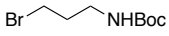
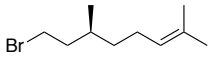
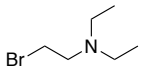
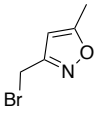
Figure 2. 3 Examples of sulfoximines under clinical trial

Unfortunately, alkylating sulfoximines is not an easy task, as the nucleophilicity of the nitrogen is highly reduced due to sterics and electronic effects of the vicinal tetrahedral sulfur.[259] A significant contribution to solve this matter came from Bolm and co-workers, who developed a mild methodology for alkylating sulfoximines and sulfondiimides.[284] Therefore, inspired by their work we decided to apply their reaction conditions on our model compound. Sulfonimidamide **55a** was treated with KOH (2.0 equiv) as a base and ethyl bromide (1.5 equiv) in DMSO under inert atmosphere. Desired alkylated sulfonimidamide **229a** was achieved in almost quantitative yield after 4 h (Table 2. 17, entry 1). After this first success, reaction scope was explored and more complex alkyl bromides were tested. Products were isolated in yields from modest to good (Table 2. 17).

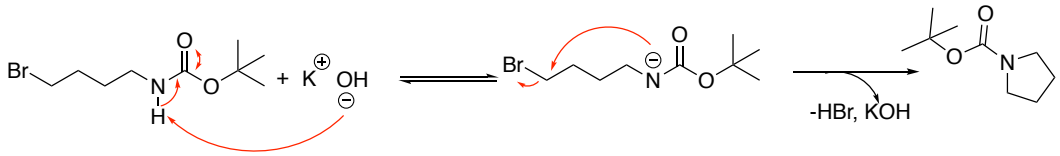
Unlike Johnson and Lavergnes's method, these reaction conditions also allowed the reaction with secondary alkyl bromides, albeit in low yield of 38% (Table 2. 17, entry 2).[259] Since methyl bromide is a gas we used methyl iodide as alkylating reagent obtaining SIA **229n** in good yield (Table 2. 17, entry 14). Similar result was achieved when benzyl bromide was reacted with **55a** (Table 2. 17, entry 15).

Table 2. 17 Exploration of substrate scope of the *N*-alkylation on SIA **55a**



Entry	name	RBr/I	Yields (%)
1	**229a**	bromoethane	99
2	**229b**	2-bromopropane	38
3	**229c**	(bromomethyl)cyclobutane	61
4	**229d**	(bromomethyl)cyclopentane	29
5	**229e**	(bromomethyl)cyclohexane	71
6	**229f**	4-(bromomethyl)tetrahydro-2H-pyran	60
7	**229g**		35
8	**229h**		13
9	**229i**		50
10	**229j**		46
11	**229k**	1-bromo-2-methoxyethane	80
12	**229l**	ethyl bromoacetate	40
13	**229m**		13
14	**229n**	methyl iodide	59
15	**229o**	benzyl bromide	57
16	**229p**		62
17	**229q**	allyl bromide	72
18	**229r**	propargyl bromide	63
19	**229s**	1-bromobut-2-yne	71

However, low yields were obtained in the case of compounds **229h** and **229m**. For the former, we envisaged this was due to a cyclisation of the alkyl bromide initiated by the deprotonation of the NH on the amide to form a pyrrolidine ring (Scheme 2. 22).



Scheme 2. 22 Proposed side reaction of 4-(Boc-amino)butyl bromide

To test this hypothesis we reacted 3-(Boc-amino)propyl bromide, which contains one less CH_2 carbon, with our substrate **55a** and as expected product **229i** was formed in higher yield (Table 2. 17, entry 9). In the case of compound **229m** we obtained lower yields to the one reported by Bolm and co-workers for the potent spasmolytic and antiasthmatic agent suloxifen (Figure 2. 4).[284]

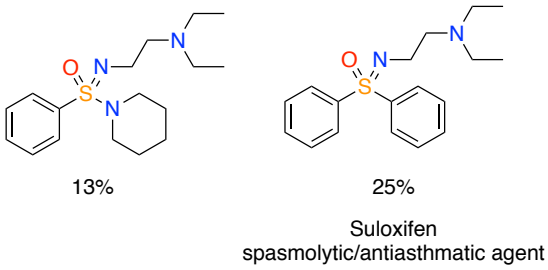


Figure 2. 4 Molecular structure of **229m** and suloxifen

Finally, allyl and propargylic bromides provided the corresponding products in good yields (Table 2. 17, entries 17 and 18).

The introduction of a trifluoromethyl group into an organic compound is a well established strategy in drug discovery to alter the physical and biological properties of a drug candidate, such as lipophilicity, metabolic stability and conformational behaviour.[291] Therefore, we were intrigued to verify whether this structural modification would have been possible for our **55a** sulfonimidamide. To do so, we applied a silver catalysed reaction published recently by Bolm and co-workers for trifluoromethylating NH-sulfoximines.[255] This radical process relies on the use of trimethyl(trifluoromethyl)silane ($TMSCF_3$), as trifluoromethylating agent, silver carbonate and 1,10-phenanthroline in 1,4-dioxane under oxygen atmosphere (Figure 2. 5).

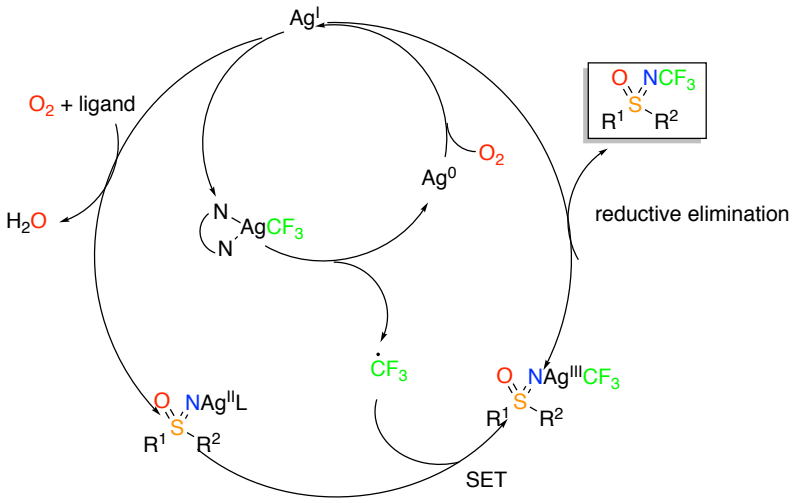
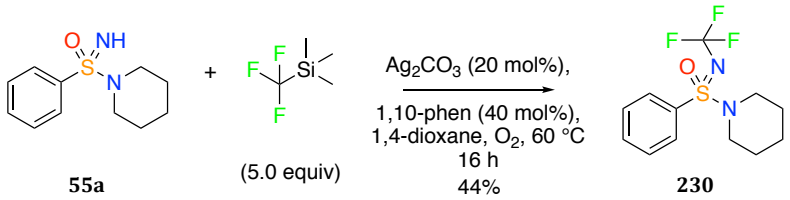


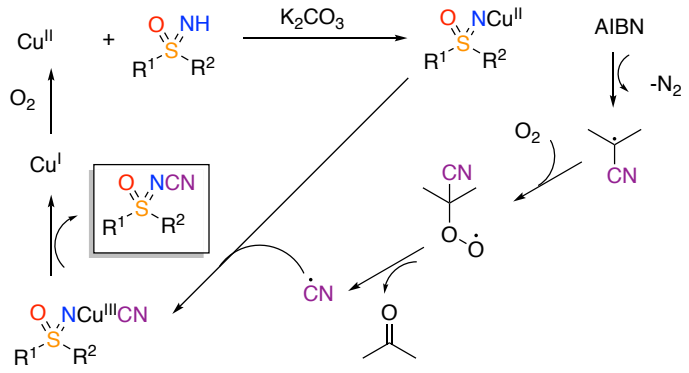
Figure 2. 5 Proposed mechanism for trifluoromethylation of sulfoximines

Gratifyingly, desired trifluoromethylated sulfonimidamide **230** was obtained in 44% yield after 16 h (Scheme 2. 23). However, we noticed that storing the isolated product at room temperature for a prolonged amount of time results in decomposition.



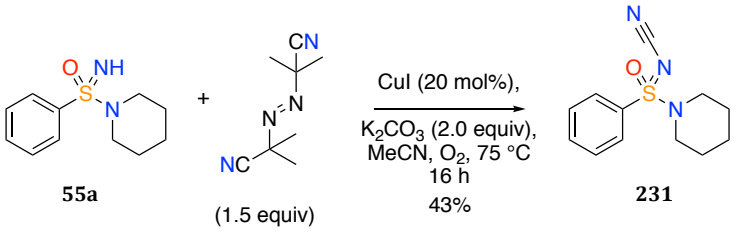
Scheme 2. 23 Synthesis of CF_3-sulfonimidamide **230**

N-Cyanation is another interesting structural modification widely applied in medicinal chemistry. The commercially available insecticide sulfoxaflor, for instance, contains the =N-CN functionality.[247,248] Furthermore, Gnamm and co-workers reported the first cyanation of a sulfonimidamide in 2012. However, the -CN transfer was achieved employing the highly toxic cyanogen bromide.[253] For this reason our attention was caught by a publication from Teng *et al*. where AIBN was used in a radical fashion, to transfer the CN group on the free NH sulfoximine (Scheme 2. 24).[254]



Scheme 2. 24 Cheng's proposed mechanism for cyano sulfoximines formation

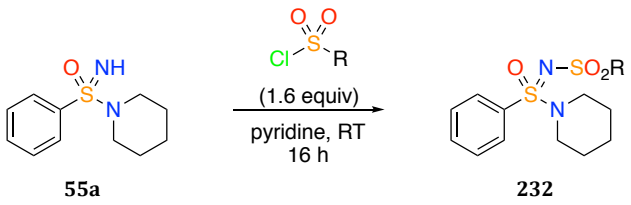
To our delight, reacting sulfonimidamide **55a** in the presence of AIBN, metal catalyst CuI, K_2CO_3 in acetonitrile under oxygen atmosphere provided the desired functionalised product **231** in 43% yield (Scheme 2. 25).



Scheme 2. 25 Synthesis of CN-sulfonimidamide **231**

Previously, sulfonimidamides were synthesised bearing a protecting group on the =N, then deprotected to access the free NH functionality. We wanted to try the opposite; with free NH sulfonimidamide **55a** in hand, we wanted to test whether we could protect the nitrogen *via* a direct reaction with sulfonyl chlorides. When **55a** was reacted together with methanesulfonyl chloride and *p*-toluenesulfonyl chloride in pyridine at room temperature, desired coupling products were obtained in 62 and 58% yield respectively (Table 2. 18).

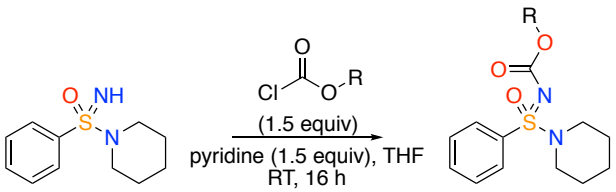
Table 2. 18 *N*-Sulfonylation of **55a**



Entry	name	R	Yields (%)
1	**232a**	methyl	62
2	**232b**	*p*-toluene	58

The carbamate functionality is also commonly investigated in medicinal chemistry as well as being present in many common protecting groups, in fact it is a key structural motif in many approved drugs.[292] Moreover, the alkoxy and aryloxy groups react readily with nucleophiles allowing further functionalisation of the carbonyl sulfonimidamide. To the best of our knowledge, there is only one publication where direct carbonylation on a sulfonimidamide was achieved.[57,293,294] Therefore, to get a further insight on the reactivity on the NH position, sulfonimidamide **55a** was reacted with phenyl and ethyl chloroformates, in the presence of pyridine. The coupling products were isolated in good yields (Table 2. 19).

Table 2. 19 *N*-Alkoxycarbonylation of **55a**



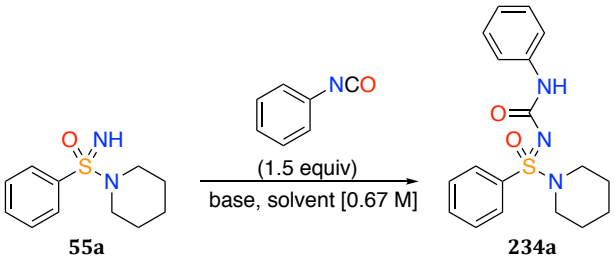
55a **233**

Entry	name	R	Yields (%)
1	**233a**	phenyl	60
2	**233b**	ethyl	69

Finally, we investigated the reaction between isocyanates and sulfonimidamide **55a**. Like the carbamate group also the urea moiety is of great interest in life science.[295,296] There are very few examples of sulfonimidamide-based ureas in the literature,[297–300] and as far as we know, none of them were made *via* direct reaction between NH-sulfonimidamides and isocyanates. We believed, in order to make the reaction happen, a base was necessary to deprotonate the =NH sulfonimidamide which then would have reacted with the isocyanate to form the urea-product. Therefore, we attempted to apply the previous successful reaction conditions for alkylating **55a** (see Table 2. 17) for our purpose. Unfortunately a complex mixture was obtained and none of the desired product was found (Table 2. 20, entry 1). Therefore, we modified the selected reaction conditions. Good results were achieved in DMSO when NaH was employed, providing SIA **234a** in 43% yield (Table 2. 20, entry 3). Changing solvent to CH_2Cl_2 in combination with KOH gave the best results collected so far (Table 2. 20, entry 4). However, isolating product **234a** was challenging as side products were also formed, and purification on column chromatography was repeated twice to purify the urea-sulfonimidamide **234a**.

A paper from the Bolm group caught our attention, where NH-sulfoximine was reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate in CH_2Cl_2 to give the corresponding thiourea-product.[285] Gratifyingly, applying the same reaction conditions without need of a base, sulfonimidamide **234a** was obtained in 79% yield (Table 2. 20, entry 5).

Table 2. 20 Optimisation of urea-sulfonimidamide **234a**

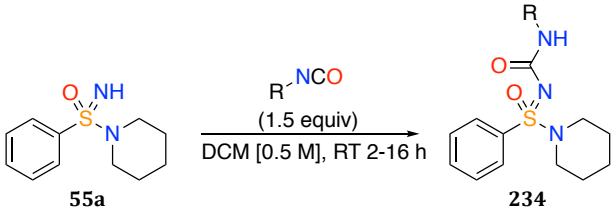


Entry	Base	Solvent	Yields (%)
1	KOH	DMSO	traces
2	K_2CO_3	DMSO	12
3	NaH	DMSO	43
4	KOH	CH_2Cl_2	82
5	/	[a]CH_2Cl_2	79

a) Reaction performed using [0.5 M] of CH_2Cl_2

Reaction scope was broad and a variety of urea-sulfonimidamides were synthesised in good to high yields. Both alkyl and aryl groups were tolerated, as well as bulky substituents (Table 2. 21). Interestingly, in most cases the end of the reaction was observed when a precipitate formed. For urea-sulfonimidamide **234c**, for example, this happened almost immediately, and the reaction went to completion after only 2 h from the isocyanate addition (Table 2. 21, entry 3). For purification of compounds **234a-f**, the precipitate was filtered under reduced pressure and washed by diethyl ether. In most cases no further purification was needed.

Table 2. 21 *N*-Aminocarbonylation of **55a** with isocyanates



55a **234**

Entry	name	R	Yields (%)
1	**234a**	*n*-propyl	65
2	**234b**	phenyl	79
3	**234c**	4-nitrophenyl	82
4	**234d**	2,5-dimethoxyphenyl	75
5	**234e**	4-methoxyphenyl	82
6	**234f**	4-methylbenzenesulfonyl	49

2.3.1 In vitro evaluation

Previously, we studied the medicinally relevant properties of sulfonimidamide **55a** in comparison to its match pair sulfonamide **227**. The previously reported results confirmed the possibility to it use as a novel pharmacophore in medicinal chemistry.

In order to better understand the properties of the *N*-functionalised sulfonimidamide in comparison to **55a**, we selected several examples to be examined in the same in vitro panel at Bayer AG (Berlin). However, we should specify that because these molecules are just fragments it's not possible to draw quantitative conclusions. Instead, we will deliver a comparison between NH-sulfoninimidamides **55a** and sulfonamide **227** and show how the substitution is going to affect the medicinally relevant properties.

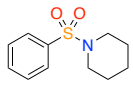
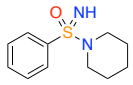
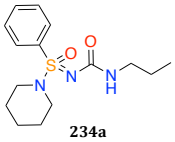
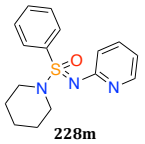
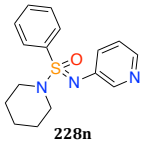
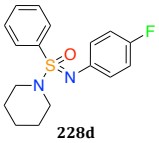
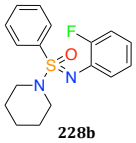
First, pH values for the afore synthesised SIAs were tested, showing in almost all cases very high hydrolytic stabilities after 24 h of stirring in aqueous solutions at pH 1,7 and 10. The only exception was trifluoromethylated sulfonimidamide **230,** which displayed signs of hydrolysis at pH 1 and 10 (Table 2. 22). For this reason is plausible to assume that implementing **230** in a drug molecule could be a cause of instability.

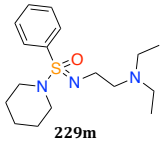
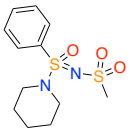
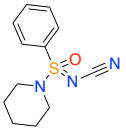
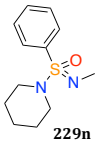
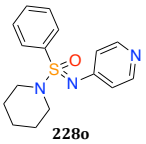
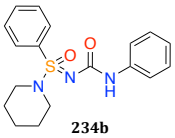
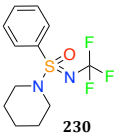
Switching from sulfonamide **227** to sulfonimidamide **55a**, lowers the logD significantly and as expected functionalising NH-sulfonimidamide **55a** affects the lipophilicity. Overall, the values collected are in the range between 1.9 and 4.1. For instance, when

the sulfonimidamide is alkylated with a methyl group (**229n**) the value for lipophilicity is 2.4, whereas increases to 3.7 with the introduction of the trifluoromethylated substituent (**230**).

When the selected compounds were tested in a Caco2 screening assay (P_{app} A-B) they revealed high permeability and no evidence of drug efflux. To complete these studies metabolic stability, given as the maximum oral bioavailability F_{max}, was investigated in liver microsomes of human, rat, mouse and also in rat hepatocytes. The values registered revealed a clear dependence from the species, showing low metabolic stability in rat hepatocytes (F_{max}< 30%) and mild instability in rat liver microsomes. However, in human liver microsomes, the metabolic stabilities cover the whole range of values, from high (F_{max}>70%) to low (F_{max}<30%) (Table 2. 22). One strategy in medicinal chemistry for improving the metabolic stability is to decrease the lipophilicity of a molecule. This is because the binding site of a metabolising enzyme is lipophilic in nature and therefore it willingly accepts lipophilic molecules.[301] Consequently, these F_{max} values correlate nicely with the corresponding logDs as displayed in Figure 2. 6, showing an increase in lipophilicity when the metabolic stability in human is low (Table 2. 22, compound **230**).

Table 2. 22 Comparison of the in vitro properties of sulfonamide **227** and the analogue =NH sulfonimidamide **55a** with a structural variety of the *N*-functionalised sulfonimidamides

Compound	Recovery [%][a] (pH)	F_{max}[b] (h/r/m)-LMs [%]	F_{max}[b] rHep [%]	P_{app} A–B[c] [nm/s]	Efflux ratio[c]	log*D* pH 7.5[d]
 **227**	100 (1) 100 (7) 100 (10)	69 (h) 10 (r) 26 (m)	4.3	393	0.64	2.6
 **55a**	100 (1) 100 (7) 100 (10)	97 (h) 30 (r) 79 (m)	14	378	0.59	1.9
 **234a**	100 (1) 100 (7) 100 (10)	79 (h) 20 (r) 42 (m)	7.7	376	0.59	2.4
 **228m**	100 (1) 100 (7) 100 (10)	65 (h) 6.2 (r) 36 (m)	6.2	447	0.53	2.7
 **228n**	100 (1) 100 (7) 100 (10)	73 (h) 21 (r) 61 (m)	13	365	0.69	2.9
 **229a**	100 (1) 100 (7) 100 (10)	65 (h) 26 (r) 28 (m)	11	297	0.65	3.0
 **229b**	100 (1) 100 (7) 100 (10)	62 (h) 13 (r) 39 (m)	4.9	381	0.51	3.5
 **228d**	100 (1) 100 (7) 100 (10)	14 (h) 5.4 (r) 16 (m)	3.6	386	0.42	4.1
 **228b**	100 (1) 100 (7) 100 (10)	12 (h) 2.5 (r) 13 (m)	0.3	264	0.54	4.1

 **229m**	100 (1) 100 (7) 100 (10)	100 (h) 3.4 (r) 8.2 (m)	3.3	164	1.5	1.9
 **232a**	100 (1) 100 (7) 100 (10)	100 (h) 33 (r) 83 (m)	20	363	0.67	2.0
 **231**	100 (1) 100 (7) 100 (10)	87 (h) 11 (r) 47 (m)	7.8	256	0.73	2.2
 **229n**	100 (1) 100 (7) 100 (10)	84 (h) 18 (r) 47 (m)	19	404	0.57	2.4
 **228o**	100 (1) 100 (7) 100 (10)	82 (h) 18 (r) 67 (m)	26	400	0.61	2.6
 **234b**	100 (1) 100 (7) 100 (10)	65 (h) 26 (r) 28 (m)	11	404	0.57	3.0
 **230**	56 (1) 100 (7) 91 (10)	19 (h) 10 (r) 9.3 (m)	6.8	192	0.70	3.7

[a] Hydrolytic stability measured as recovery of test compound after 24 hours with stirring at pH 1 (HCl buffer), pH 7 (phosphate-buffered saline) and pH 10 (sodium borate buffer).[279] **[b]** Predicted hepatic metabolic first pass given as F_{max} based on a metabolic stability assay using (i) pooled human liver microsomes (hLMs), (ii) pooled rat liver microsomes (rLMs), (iii) pooled mouse liver microsomes (mLMs) and (iv) freshly harvested rat hepatocytes (rHep).[280] **[c]** P_{app} A–B (apical to basolateral) and efflux ratio (ER) data were generated in a bidirectionally performed Caco2 permeability assay in a 24-well format; ER was calculated as P_{app} B–A/P_{app} A–B.[280] **[d]** Determined by reversed-phase HPLC.[281]

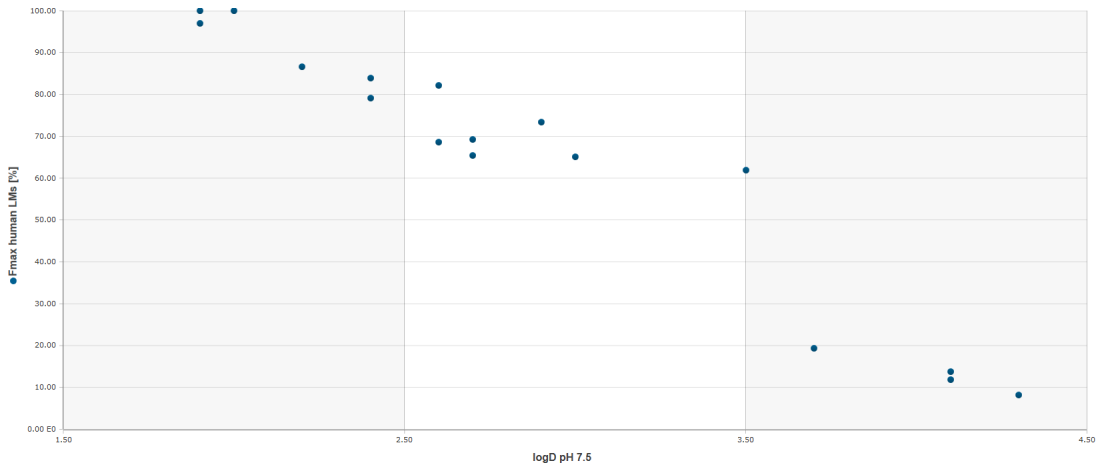
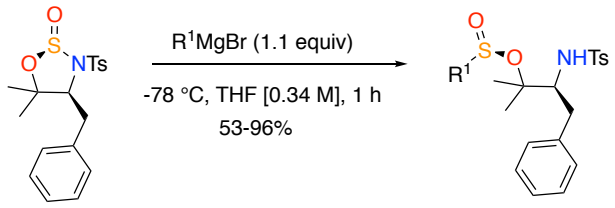


Figure 2. 6 Correlation of predicted metabolic stabilities in human liver microsomes, given as F_{max}, with the corresponding logD values (all tested compounds)

Chapter 3: Conclusions and future work

3.1 Sulfoximines

To conclude, the optimised routes for the synthesis of two chiral templated sulfur(IV) compounds, **26** and **214,** have been developed starting from L-phenylalanine. Template **214** was obtained in 75% overall yield over three steps, showing enhanced stability towards R^1MgX nucleophilic attack providing many examples of enantiopure intermediates (**216a-n**) in good to excellent yields (Scheme 3. 1).

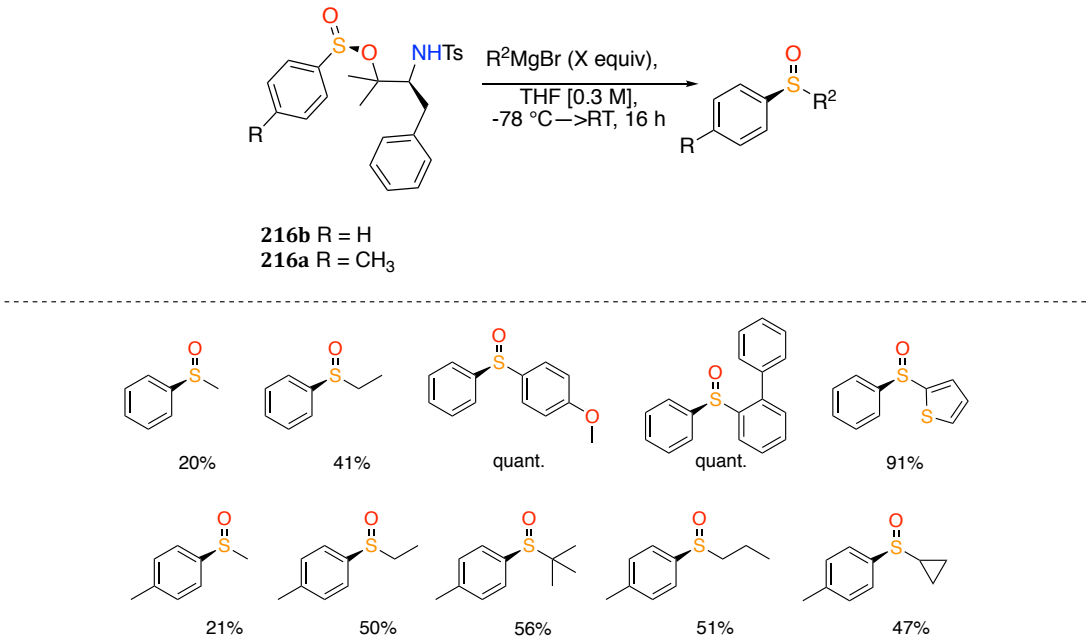


214 **216a-n**

Scheme 3. 1 Nucleophilic addition of R^1MgBr to chiral template **214**

The formation of chiral sulfoxides from **26** and **214** was investigated employing both a multi-step and one pot approach. However, the latter provided the desired compounds only in poor yields but excellent *ee* (98%). For the multi-step route, the addition of R^2MgX reagent proceeded smoothly, although it was discovered that the desired sulfoxides could be isolated only in modest yields even if no side product was isolated and all the starting material was consumed. This interesting trend was assigned to the lipophilicity of the sulfoxide products. Employing 4-methoxyphenyl, 2-thienyl and 2-

biphenyl Grignard as R^2MgX delivered the optically active sulfoxides in excellent yields (Scheme 3. 2).



Scheme 3. 2 Synthesis of chiral sulfoxides

These initial results for the formation of chiral sulfoxides are promising, and prove the validity of our approach. Therefore it would be desirable to optimise the current methodology and find an optimal way to isolate hydrophilic sulfoxides.

Studies toward the synthesis of enantiopure sulfoximines have been investigated using both a rhodium and iron catalised approach previously reported in the Bolm group.[90,92] Oxidative imination on these chiral sulfoxides was found possible and gave a number of sulfoximines with an easy to cleave protecting groups on the nitrogen (Figure 3. 1). Although synthesis towards chiral sulfoximines still needs to be optimised, we are very pleased with the data collected so far, which confirms the validity of this stereocontrolled approach. Furthermore, thanks to Bull and Luisi recent publication[79] synthesis of sulfoximines has been fully disclosed. Therefore, with chiral sulfoxides in hand optically active NH-sulfoximines could be obtained in high yields and enantiomeric excess in one step.

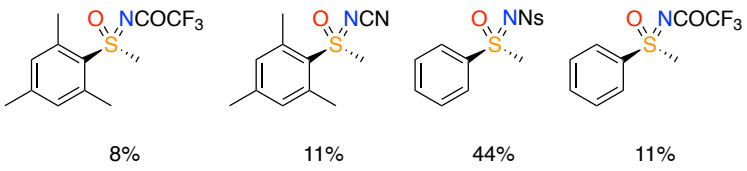
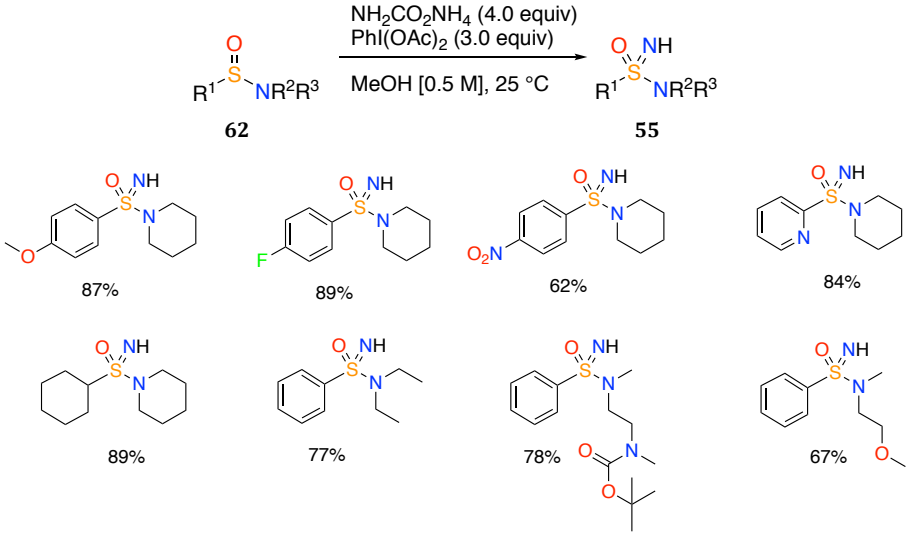


Figure 3. 1 Chiral protected sulfoximines made in the Stockman group

3.2 Synthesis and functionalisation of sulfonimidamides

We have reported a direct synthesis of NH sulfonimidamides starting from tertiary sulfinamides. The protocol relies on cheap and commercially available reagents as well as mild reaction conditions, and it has broad reaction scope providing desired products in yields from good to excellent (Scheme 3. 3). Albeit, we are unable to apply our methodology to secondary and primary sulfonimidamides, which are of great interest in Drug Discovery, with on going work we aim to solve this problem.



Scheme 3. 3 Examples of tertiary SIAs

Enantioenriched sulfinamides were made using Anderson's auxiliaries and initial studies showed that the reaction is stereoselective. Although, the enantiomeric excess measured for sulfinamide and sulfonimidamide was only modest. After an intensive investigation, methodology was developed using Stockman group chiral template **214** to produce chiral sulfinamides. It was found that once the nucleophilic addition takes place with inversion of configuration, desired sulfinamides were obtained in higher *ee* (89% *ee*). Even though these are just preliminary results and the procedure still needs optimisation, we believe there is going to be the possibility to expand the substrate scope.

Preliminary *in vitro* studies on medicinal chemistry relevant properties of sulfonimidamide **55a**, made by scientists at Bayer AG in collaboration with the Stockman group, have not revealed any intrinsic flaw which would prevent use of sulfonimidamide functionality as a new versatile pharmacophore in drug discovery. In contrast, the logD values collected showed enhanced solubility of the SIA in comparison

to its sulfonamide analogue.

Even if they have been neglected so far, sulfonimidamides are starting to raise interest from the scientific community for their potential use as a novel pharmacophores. However till date, very few methodologies for *N*-functionalisation have been reported and the reactivity of the NH position remains fairly unexplored.

In this light, we have successfully applied previously reported reaction conditions for functionalisation of NH-sulfoximines to our model compound **55a**. An unprecedented set of structurally diverse sulfonimidamides has been obtained (48 new molecules).
The methods applied and optimised include arylation, alkylation, cyanation, trifluoromethylation, sulfonylation, alkoxycarbonylation, and aminocarbonylation (urea) (Figure 3. 2). These optimised routes are in some cases complementary to the already existing methods. However, it would be interesting to keep exploring further the reactivity of the *N*-sulfonimidamides, and investigate unprecedented reactions on the NH position such as silylation, halogenation, and nitration. Even though we covered most of the sulfonimidamides *N*-functionalisation, our methodologies were tested just on a single NH-sulfonimidamide **55a**. Therefore it would be intriguing to verify whether these optimised methods could be applied instead to more complex SIAs.

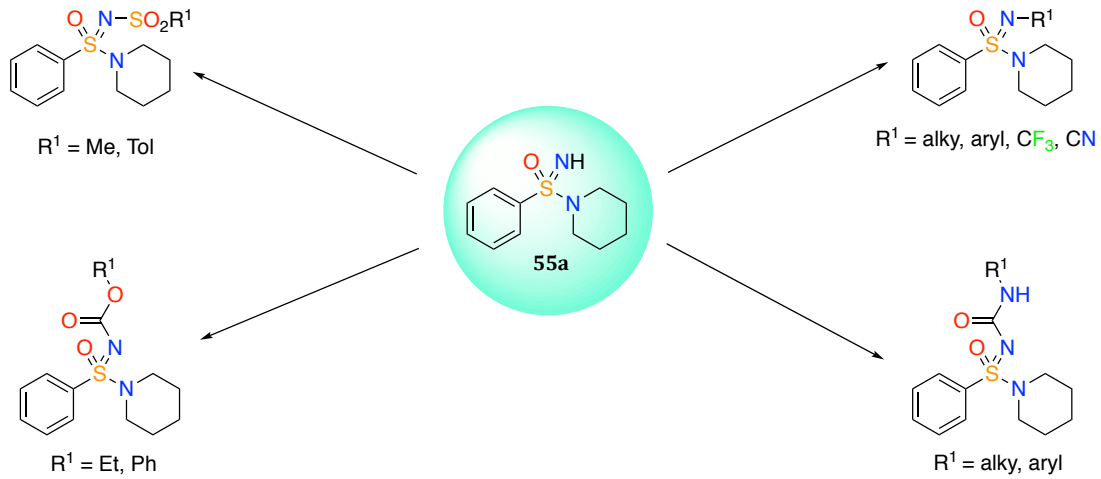


Figure 3. 2 *N*-funcionalisation of SIAs

For the *in vitro* characterisation of *N*-functionalised SIAs, relevant medicinal chemistry properties were analysed: hydrolytic stability, metabolic stability (in liver microsomes of human, rat, mouse and rat hepatocytes), efflux ratio, and finally lipophilicity (logD). The NH position is indeed a powerful handle which allows to adjust, according to the *N*-substituent, the values of the life science relevant properties of these S(VI) compounds.

Although the sulfonimidamides tested so far are just fragment-like molecules the preliminary results for the *in vitro* characterisation show promising properties and didn't reveal any intrinsic flaw to use these fuctionalised compounds as novel pharmacophores in drug discovery. On the contrary, the different values obtained according to the substituent on the nitrogen rapresent a valuable opportunity to regulate the life science relevant properties when the molecule is implemented in a drug target. Finally, the combination of the one-pot synthesis of the NH sulfonimidamides (discussed in Chapter 2) followed by *N*-functionalisation offers a rapid access to highly complex and diverse molecules.

While the exploration of sulfonimidamides has been relatively slow in the past years, this S(VI) compound is now receiving growing attention from the scientific community. A major contribution in this sense was given by Bolm's[105] and Willis'[121] who saw in it an appealing alternative to sulfonamide moiety in molecules such as Tasisulam and Celecoxib. Even if, to date a clinical candidate containing the sulfonimidamide functionality is yet to evaluate, our hope for the future is to see this research carried on and the sulfonimidamide moiety implemented into a drug candidate. The work done so far in our group can be seen as a contribution towards the full disclosure and understanding of these interesting molecules.

Chapter 4: Experimental

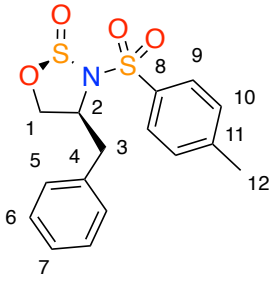
4.1 General methods and physical measurements

Commercially available reagents were purchased from Alfa Aesar, abcr, Acros Organics, Merck or Sigma-Aldrich, and were used without further purification. Tetrahydrofuran was freshly distilled under argon from the sodium anion of benzophenone. Dichloromethane was dried by refluxing over $CaCl_2$ and distilled. All other anhydrous solvents were purchased or obtained from in house solvent purification towers. All reactions were conducted in flame-dried glassware under Ar or O_2 atmosphere. Brine is a saturated aqueous solution of sodium chloride. Solvents evaporation was performed using a rotary evaporator under reduced pressure. Reactions were monitored by TLCs (thin layer chromatography). Analytical TLC was carried out on aluminum-backed plates coated with Merck Kieselgel 60 F254, with visualization under UV light at 254 nm and, where not possible, using $KMnO_4$ stain. Manual column chromatography was performed both on silica gel Fluka 60 or Merck aluminium oxide 90. Flash chromatography was carried out using a Biotage® Isolera™ One system with 200–400 nm variable detector, using Biotage® SNAP KP-Sil and KP-NH cartridges. Preparative HPLC was carried out with a Waters AutoPurification MS Single Quad system; column: Waters XBridge C18 5 mm, 100 × 30 mm; eluent A: H_2O + 0.2 vol% aq NH_3 (32%), eluent B: MeCN; gradient: 0–0.50 min 5% B, flow: 25 mL/min; 0.51–5.50 min 10–100% B, flow: 70 mL/min; 5.51–6.50 min 100% B, flow: 70 mL/min; temperature: 25 °C; DAD scan: 210–400 nm. NMR spectra were recorded on Bruker Avance III HD, Bruker AV400, Bruker AV(III)400, Bruker DPX300, Bruker DPX400, and Bruker600 spectrometers. ^{1}H NMR spectra were obtained at 400, 500 and 600 MHz and referenced to the residual solvent signal (7.26 ppm for $CDCl_3$, 2.50 ppm for [D_6]DMSO). ^{13}C NMR spectra were obtained at 101, 126 and 151 MHz and also referenced to the residual solvent signal (77.16 ppm for $CDCl_3$, 39.52 ppm for [D_6]DMSO). All spectra were obtained at ambient temperature (23 °C). Data are reported as follows: chemical shift (δ) in ppm, multiplicity (standard abbreviations), coupling constant(s) (Hz), integration and identity. The abbreviation app, used in reporting the NMR data, stands for apparent. High-resolution mass spectra were recorded on Bruker microTOF spectrometer. Infrared spectra were recorded using a Bruker Tensor 27 FTIR spectrometer. Melting points were determined with a Büchi B-540 or Stuart Scientific SMP20 melting point apparatus. Compounds were dried over water-repellent filter paper (MACHEREY-NAGEL 617 WA, 125 mm diam) or $MgSO_4$ or Na_2SO_4. Petroleum

ether (PE) refers to the fraction with a boiling range of 40–60 °C. The specific rotations data were collected using a ADF140 machine. Schlenk technique is used on air and moisture sensitive reactions, where a pre-dried schlenk tube is evacuated and back filled with argon three times and all reagents were inserted in through a septum.[302]

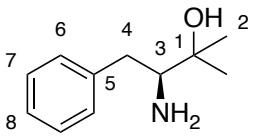
4.2 Synthesis of chiral templates

(2*R*, 4*S*)- 4-Benzyl-3-tosyl-1,2,3-oxathiazolidine 2-oxide (26)



N-[(1*S*)-2-hydroxy-1-(phenylmethyl)ethyl]-4-methylbenzenesulfonamide (5.50 g, 18.0 mmol, 1.00 equiv) **25** was dissolved in dry THF (187 mL), degassed for 15 min under nitrogen and then cooled to -78 °C. Thionyl chloride (1.30 mL, 18.0 mmol, 1.00 equiv) was added *via* dropping funnel and afterwards pyridine (3.20 mL, 39.6 mmol, 2.20 equiv) in dry THF (23 mL) was added dropwise over 15- 20 min. The mixture was stirred at – 78 °C for 2 h. After warming to -20 °C, the solution was filtered through a 2 cm silica pad and washed with DCM to give the title compound **26** (3.27 g, 52%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.3 Hz, 2H, 9-H), 7.38 (d, *J* = 8.3 Hz, 2H, 10-H), 7.31-7.22 (m, 3H, 6-H and 7-H), 7.11 (d, *J* = 6.5 Hz, 2H, 5-H), 4.82 (appt, *J* = 9.4, 1H, 1-H_a), 4.41 (dd, *J* = 9.4, 6.5 Hz, 1H, 1-H_b), 3.91 (dddd, *J* = 10.7, 8.9, 6.5, 4.2 Hz, 1H, 2-H), 3.38 (dd, *J* = 13.6, 4.2 Hz, 1H, 3-H_a), 2.75 (dd, *J* = 13.6, 10.7 Hz, 1H, 3-H_b), 2.46 (s, 3H, 12-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.2 (11-C) 137 (4-C), 130.2 (10-C), 129.0 (5-C), 128.8 (6-C), 127.5 (9-C), 127.4 (7-C), 77.7 (1-C) , 60.4 (2-C), 39.2 (3-C), 21.6 (12-C); IR (KBr): ν = 3022, 2913, 1597, 1493, 1452, 1348, 1188, 1158, 1084 cm^{-1}; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{16}H_{17}NNaO_4S_2$: 374.0491, found: 374.0486. Data consistent with literature.[43]

(*S*)-3-amino-2-methyl-4-phenylbutan-2-ol (212)

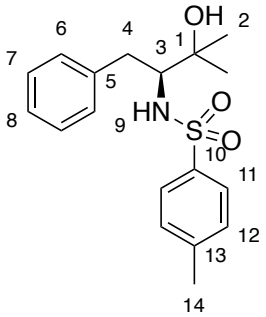


L-Phenylalanine methyl ester hydrochloride **211** (8.00 g, 37.1 mmol, 1.00 equiv), was added in portions over 1 h to a pre-stirred solution of methyl magnesium bromide

(61.7 mL, 185 mmol, of a 3 M solution in diethyl ether, 5.00 equiv) in diethyl ether (100 mL). Solution was stirred under reflux for 3-4 h. After this time, saturated aqueous solution of NH_4Cl was added slowly at 0 °C to quench the reaction. The solution was then warmed to room temperature and made alkaline by addition of NaOH (1 M). The aqueous phase was extracted by EtOAc (3 ×), washed by brine (3 ×) and filtered through water-repellent filter paper. The organic solvent was evaporated to dryness give the desired product **212** as a white solid (6.24 g, 94%) without need of further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.30 (m, 2H, 7-H), 7.25-7.18 (m, 3H, 6-H and 8-H), 3.03 (dd, *J* = 13.5, 2.7 Hz, 1H, 4-H_a), 2.81 (dd, *J* = 11.2, 2.7 Hz, 1H, 3-H), 2.27 (dd, *J* = 13.5, 11.2 Hz, 1H, 4-H_a), 1.30 (s, 3H, 2-H), 1.21 ppm (s, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.9 (5-C), 129.2 (6-C), 128.7 (7-C), 126.5 (8-C), 71.5 (1-C), 61.6 (3-C), 39.2 (4-C), 27.3 (2-C), 23.9 (2-C) ppm; HRMS (ESI-TOF) *m*/*z* [*M* + H]$^+$ calcd for $C_{11}H_{18}NO$ 180.1383, found: 180.1386.

Data consistent with literature.[303]

(*S*)-*N*-(3-hydroxy-3-methyl-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide (213)

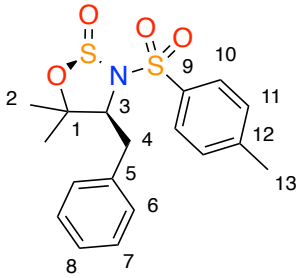


A solution of *p*-tolylsulfonyl chloride (7.01 g, 36.8 mmol, 1.10 equiv) in dry CH_2Cl_2 (73.6 mL) was added dropwise (over 2 h) to a cold (0 °C) solution of **212**, NEt_3 (7.46 g, 73.7 mmol, 2.20 equiv) and DMAP (0.8 g, 6.7 mmol, 0.2 equiv) in CH_2Cl_2 (67 mL). The reaction mixture was allowed to warm up to room temperature and stirred overnight. Once the reaction went to completion (monitored by TLC) it was diluted with CH_2Cl_2 and acidified by HCl (1 M). The collected organics were washed by aqueous, saturated $NaHCO_3$ (3 ×), NaCl (3 ×), and filtered through water-repellent filter paper. The organic solvent was concentrated under reduced pressure, and recrystallised from EtOAc/PE to afford the desired product **213** as white solids (10.3 g, 93%) without need of further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.3 Hz, 2H, 11-H), 7.13-7.03 (m, 5H, 8-H, 12-H and 7-H), 4.68 (d, *J* = 7.9 Hz, 1H, 9-H), 3.44 (ddd, *J* = 9.6, 7.9, 4.2 Hz, 1H, 3-H), 2.98 (dd, *J* = 14.3, 4.2 Hz, 4-H_a), 2.58 (*br*s, 1H, 9-H), 2.42 (dd, *J* = 14.3, 9.6 Hz, 1H, 4-

H_b), 2.37 (s, 3H, 14-H), 1.28 (s, 3H, 2-H), 1.27 ppm (s, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 129.6 (12-C), 129.2 (6-C), 128.7 (7-C), 127.0 (11-C), 126.6 (8-C), 72.9 (1-C), 64.6 (3-C), 37.8 (4-C), 27.9 (2-C), 25.7 (2-C), 21.6 (14-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{18}H_{23}NNaO_3S$ 356.1291, found: 356.1287.

Data consistent with the literature.[304]

(4*S*)-4-benzyl-5,5-dimethyl-3-tosyl-1,2,3-oxathiazolidine 2-oxide (214)

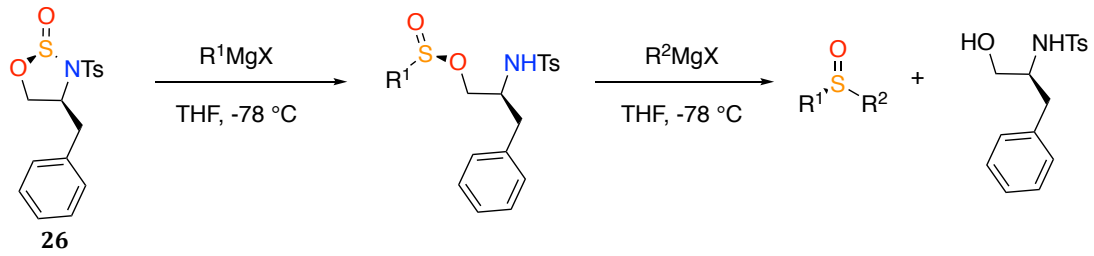


(*S*)-*N*-(3-hydroxy-3-methyl-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide (3.0 g, 9.0 mmol, 1.0 equiv) **213** was dissolved in dry THF (30 mL), degassed for 15 min under argon and then cooled down to -78 °C. Thionyl chloride (0.65 mL, 9.00 mmol, 1.00 equiv) was added *via* syringe pump over 5 min and afterwards pyridine (3.20 mL, 39.6 mmol, 2.20 equiv) in dry THF (6 mL) was added dropwise over 30 min, *via* syringe pump. The mixture was stirred at -78 °C for 3.5 h. After warming up to -6 °C, the solution was filtered through a 2 cm silica pad and washed with DCM. The organic solvent was concentrated under reduced pressure, and the crude purified by flash column chromatography (SiO_2, 100% CH_2Cl_2) to give the title compound **214** (2.96 g, 86%) as white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 7.9 Hz, 2H, 10-H), 7.31 (d, *J* = 7.9 Hz, 2H, 11-H), 7.30-7.21 (m, 3H, 8-H and 7-H), 7.09 (d, *J* = 7.1 Hz, 2H, 6-H), 3.98 (ddd, *J* = 9.3, 5.9, 2.4 Hz, 1H, 3-H), 3.32 (dd, *J* = 15.2, 4.2 Hz, 1H, 4-H_a), 2.77-2.71 (m, 1H, 4-H_b), 2.44 (s, 3H, 13-H), 1.65 (s, 3H, 2-H), 1.02 ppm(s, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.8 (5-C or 12-C or 9-C), 136.6 (5-C or 12-C or 9-C), 136.2 (5-C or 12-C or 9-C), 130.2 (11-C), 129.3 (7-C or 6-C), 128.8 (7-C or 6-C), 127.5 (10-C), 127.1 (8-C), 98.8 (1-C), 68.3 (3-C), 36.2 (4-C), 28.5 (2-C), 24.7 (2-C), 21.8 (13-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{18}H_{21}NNaO_4S_2$ 402.0804, found: 402.0819.

Data consistent with the literature.[43]

General Procedure A: Synthesis of chiral sulfoxides[29]

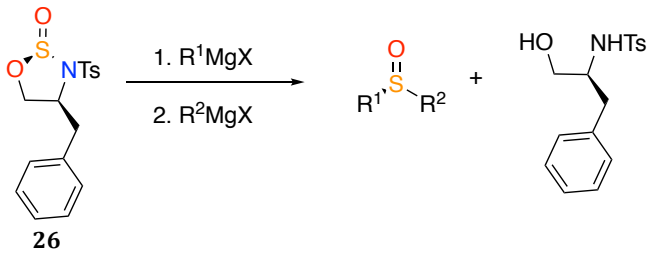


26

Part A: To a solution of **26** (0.50 g, 1.43 mmol, 1.00 equiv) in dry THF (3.50 mL) at -78 °C under argon, a solution of R^1MgBr (1.98 mL, 1.43 mmol, 1.00 equiv) was added dropwise. The reaction was stirred for 1.25 h, then quenched with aqueous, saturated $NaHCO_3$ (3.5 mL) or water (3.5 mL) and diluted with EtOAc (17 mL). The solution was warmed to room temperature, the aqueous phase extracted and the combined organic phase collected, washed with 20% NaCl and dried over Na_2SO_4. The crude collected was evaporated to dryness and purified by flash column chromatography.

Part B: The resulting product was dissolved in dry THF (3.70 mL) and cooled to – 78°C under argon and the second Grignard reagent (R^2MgBr) added dropwise (2.20 equiv). After 1.33 h the reaction mixture was quenced by addition of aqueous, saturated $NaHCO_3$ (3.70 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 ×) and the combined organic layer collected, washed with 20% NaCl and dried over Na_2SO_4. The organic solvent was evaporated and purified by flash column chromatography to give the desired chiral sulfoxide.

General Procedure B: One-pot synthesis of chiral sulfoxides[29]

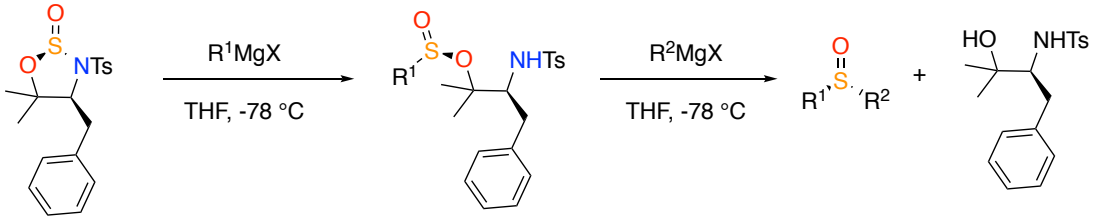


26

To a solution of **26** (0.50 g, 1.43 mmol, 1.00 equiv) in dry THF (3.50 mL) at – 78 °C under argon, a solution of R^1MgBr was added dropwise (1.43 mmol, 1.00 equiv). The reaction mixture was stirred for 1.33 h, then R^2MgBr was added slowly (1.72 mmol, 1.20 equiv). The solution was warmed to -45 °C for 30 min, then the temperature was raised to -15 °C, and stirred overnight. Once the product was formed the mixture was

quenched by aqueous, saturated $NaHCO_3$ (3.50 mL) and diluted with EtOAc (10 mL). The aqueous phase was extracted, the organic layer collected, washed with 20% of NaCl and dried over Na_2SO_4. The crude was evaporated and purified by flash column chromatography to afford the chiral sulfoxide.

General Procedure C: Synthesis of chiral sulfoxides[29]

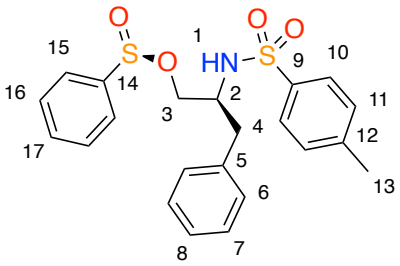


214

Part A: To a solution of **214** (0.10 g, 0.26 mmol, 1.00 equiv) in dry THF (0.77 mL) at -78 °C under argon, a solution of R^1MgBr was added dropwise (0.29 mmol, 1.10 equiv).
The reaction was stirred for 1 h at -78 °C, then temperature was raised to -6 °C for 15 minutes. Finally reaction mixture was quenched with aqueous, saturated $NaHCO_3$ (2 mL) and diluted with EtOAc (4 mL). The solution was warmed up to room temperature, the aqueous phase extracted and the combined organic phase collected, washed with 20% NaCl and filtered through water-repellent filter paper. The crude collected was evaporated to dryness and purified by flash column chromatography.
Part B: The resulting product (0.05 g, 0.13 mmol, 1.00 equiv) was dissolved in dry THF (0.38 mL) and cooled to –78°C under argon and the second Grignard reagent (R^2MgBr) added dropwise (3.0-5.0 equiv). After 10 min the reaction mixture was warmed up to room temperature and stirred overnight. Solution was quenched by addition of aqueous, saturated $NaHCO_3$ (2 mL) and diluted with EtOAc (4 mL). The aqueous phase was extracted, the combined organic layer collected, washed with 20% NaCl and dried over Na_2SO_4 or filtered through water-repellent filter paper. The organic solvent was evaporated and crude purified by flash column chromatography to give the desired chiral sulfoxide.

4.3 Synthesis of intermediate 209a-c and 216a-m

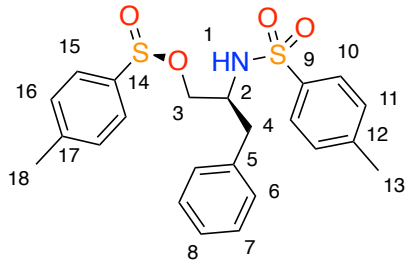
(*S*)-2-((4-methylphenyl)sulfonamido)-3-phenylpropyl (*S*)-benzenesulfinate (209a)



For synthesis of **209a**, **general procedure A part A** was followed using PhMgBr.

To a solution of **26** (0.90 g, 2.56 mmol, 1.00 equiv) in dry THF (85.3 mL) at -78 °C under argon phenyl magnesium bromide (2.72 mL, 2.56 mmol of a 0.94 M solution in diethyl ether, 1.00 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by column chromatography (SiO_2, 30-50% EtOAc in PE) to give the name compound **209a** (0.78 g, 70%) as a white solid. m.p. 92-97 ° C; $[\alpha]_D$ = -102.7 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.65 (2H, m, 15-H), 7.61 (d, *J* = 8.4 Hz, 2H, 10-H), 7.59-7.52 (m, 3H, 16-H and 17-H) 7.20 (d, *J* = 8.4 Hz, 2H, 11-H), 7.19-7.16 (m, 3H, 8-H and 7-H), 7.00-6.98 (m, 2H, 6-H), 4.96 (*br*d, *J* = 8.0 Hz, 1H, 1-H), 3.91 (dd, *J* = 10.7, 4.1 Hz, 1H, 3-H_a), 3.58-3.50 (m, 1H, 2-H), 3.47 (dd, *J* = 10.7, 4.1 Hz, 1H, 3-H_b), 2.77 (d, *J* = 6.9 Hz, 2H, 4-H), 2.41 ppm (s, 3H, 13-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1 (9-C or 14-C), 143.4 (9-C or 14-C), 137.4 (5-C or 12-C), 136.5 (5-C or 12-C), 132.7 (17-C), 129.8 (16-C), 129.4 (7-C and 6-C), 128.8 (11-C), 127.2 (10-C), 126.9 (8-C), 125.7 (15-C), 65.5 (3-C), 54.5 (2-C), 38.4 (4-C), 21.7 (13-C) ppm; IR (KBr): ν = 3420, 2360, 1598, 1456, 1332, 1159, 1120, 1093 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_4S_2$ 430.1142, found 430.1141.

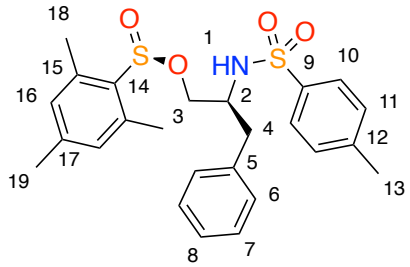
(*S*)-2-((4-methylphenyl)sulfonamido)-3-phenylpropyl (S)-4-methylbenzenesulfinate (209b)



For synthesis of **209b**, **general procedure A part A** was followed using *p*-TolMgBr.

To a solution of **26** (0.030 g, 0.076 mmol, 1.00 equiv) in dry THF (2.6 mL) at -78 °C under argon *p*-tolyl magnesium bromide (0.25 mL, 0.076 mmol of a 0.31 M solution in diethyl ether, 1.00 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (SiO_2, 30-50% EtOAc in PE) to give **209b** as a white semisolid (20 mg, 59%). $[\alpha]_D$ = - 24.1 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.3 Hz, 2H, 10-H), 7.53 (d, *J* = 8.2 Hz, 2H, 15-H), 7.35–7.32 (m, 2H, 16-H), 7.22-7.17 (m, 5H, 11-H, 8-H and 7-H), 7.01-6.98 (m, 2H, 6-H), 5.01 (d, *J* = 7.8 Hz, 1H, 1-H), 3.89 (dd, *J* = 10.7, 4.2 Hz, 1H, 3-H_a), 3.57-3.49 (m, 1H, 2-H), 3.46 (dd, *J* = 10.7, 4.2 Hz, 1H, 3-H_b), 2.77 (d, *J* = 7.1 Hz, 2H, 4-H), 2.99 (s, 3H, 18-H), 2.41 ppm (s, 3H, 13-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.4 (C-9 or C-14), 141.1 (C-9 or C-14), 137.4 (C-5 or C-12), 136.6 (C-5 or C-12), 130.0 (C-16), 129.7 (11-C or 7-C), 129.4 (C-6), 129.8 (11-C or 7-C), 127.2 (10-C), 126.9 (8-C), 125.3 (15-C), 65.3 (3-C), 54.3 (2-C), 38.4 (4-C), 21.7 (18-C or 13-C), 21.7 (18-C or 13-C) ppm; IR (KBr): ν = 3454, 3157, 1159, 1037, 816 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{23}H_{26}NO_4S_2$ 444.1298, found: 444.1299.

(*S*)-2-((4-methylphenyl)sulfonamido)-3-phenylpropyl (*S*)-2,4,6-trimethylbenzenesulfinate (209c)



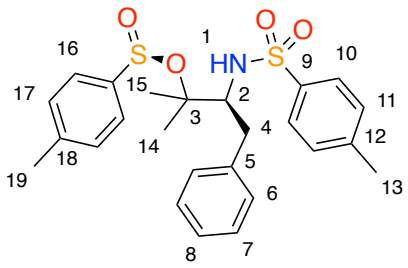
For synthesis of **209c**, **general procedure A part A** was followed using MesMgBr.

To a solution of **26** (0.50 g, 1.43 mmol, 1.00 equiv) in dry THF (3.5 mL) at -78 °C under argon mesityl magnesium bromide (2.00 mL, 1.43 mmol of a 0.72 M solution in diethyl

ether, 1.00 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by column chromatography (SiO_2, 15-25% EtOAc in PE) to give **209c** as a colourless oil (0.42 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.4 Hz, 2H, 10-H), 7.20 (m, 5H, 11-H, 7-H, 8-H), 7.02 (m, 2H, 6-H), 6.88 (s, 2H, 16-H), 5.33 (d, *J* = 8.6 Hz, 1H, 1-H), 3.99 (dd, *J* = 11.0, 3.3 Hz, 1H, 3-H_a), 3.85 (dd, *J* = 11.0, 3.3, Hz, 1H, 3-H_b), 3.61 (m, 1H, 2-H), 2.83 (dd, *J* = 13.6, 8.2, Hz, 2H, 4-H), 2.58 (s, 6H, 18-H), 2.41 (s, 3H, 13-H), 2.31 (s, 3H, 19-H); HRMS (ESI-TOF) *m/z* [*M* + H]$^+$ calcd for $C_{25}H_{29}NNaO_4S_2$ 494.1430, found: 494.1434.

Data consistent with literature.[43]

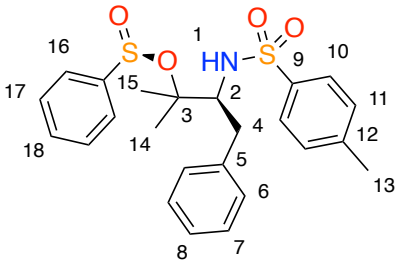
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (S)-4-methylbenzenesulfinate (216a)



For synthesis of **216a**, **general procedure C part A** was followed using *p*-TolMgBr.

To a solution of **214** (1.50 g, 3.95 mmol, 1.00 equiv) in dry THF (11.60 mL) at -78 °C under argon *p*-tolyl magnesium bromide (11.4 mL, 4.34 mmol of a 0.38 M solution in diethyl ether, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (SiO_2, 0-60% EtOAc in PE) to give **216a** as a white solid (1.27 g, 68%). m.p. 111-112 °C; $[\alpha]_D$ = - 155.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.2 Hz, 2H, 16-H), 7.36-7.34 (m, 2H, 17-H), 7.29 (d, *J* = 8.3 Hz, 1H, 10-H), 7.09-6.98 (m, 5H, 8-H, 11-H and 7-H), 6.95-6.93 (m, 2H, 6-H), 5.59 (d, *J* = 9.8 Hz, 1H, 1-H), 3.73 (td, *J* = 9.4, 4.0 Hz, 1H, 2-H), 3.05 (dd, *J* = 14.4, 4.0 Hz, 1H, 4-H_a), 2.60 (dd, *J* = 14.4, 9.4 Hz, 1H, 4-H_b), 2.44 (s, 3H, 19-H), 2.34 (s, 3H, 13-H), 1.77 (s, 3H, 14-H), 1.55 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 142.8, 142.3, 139.1, 138.5, 129.9 (17-C), 129.5 (6-C, 7-C or 11-C), 129.4 (6-C, 7-C or 11-C), 128.5 (6-C, 7-C or 11-C), 126.5 (10-C), 126.2 (8-C), 125.1 (16-C), 87.3 (3-C), 63.9 (2-C), 37.3 (4-C), 28.0 (14-C), 26.0 (14-C), 21.7 (19-C or 13-C), 21.6 (19-C or 13-C) ppm; IR (neat): ν = 3254, 2968, 1241, 1082, 733 cm^{-1}; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{25}H_{29}NNaO_4S_2$ 494.1430, found: 494.1432.

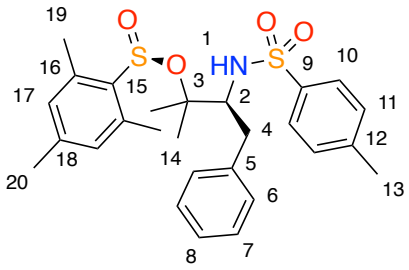
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-benzenesulfinate (216b)



For synthesis of **216b**, **general procedure C part A** was followed using PhMgBr.

To a solution of **214** (1.00 g, 2.63 mmol, 1.00 equiv) in dry THF (7.7 mL) at -78 °C under argon phenyl magnesium bromide (3.15 mL, 2.90 mmol of a 0.92 M solution in diethyl ether, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (SiO_2, 0-50% EtOAc in PE) to give the name compound **216b** as a white solid (1.10 g, 92%). m.p. 90-94 °C; $[\alpha]_D$ -170.8 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.69 (m, 2H, 16-H), 7.58-7.52 (m, 3H, 17-H and 18-H), 7.29 (d, *J* = 8.3 Hz, 2H, 10-H), 7.09-6.98 (m, 3H, 8-H, 7-H and 11-H), 6.95-6.92 (m, 2H, 6-H), 5.54 (d, *J* = 9.8 Hz, 1H, 1-H), 3.74 (td, *J* = 9.5, 4.0 Hz, 1H, 2-H), 3.06 (dd, *J* = 14.4, 4.0 Hz, 1H, 4-H_a), 2.60 (dd, *J* = 14.4, 9.4 Hz, 1H, 4-H_b), 2.34 (s, 3H, 13-H), 1.78 (s, 3H, 14-H), 1.57 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.7 (15-C), 142.4 (12-C), 139.0 (5-C or 9-C), 138.4 (5-C or 9-C), 132.2 (18-C), 129.5 (16-C or 17-C or 6-C or 11-C), 129.4 (16-C or 17-C or 6-C or 11-C), 129.3 (17-C or 16-C), 128.5 (6-C or 7-C), 126.5 (10-C), 126.2 (8-C), 125.1 (16-C or 17-C), 87.5 (3-C), 63.88 (2-C), 37.2 (4-C), 27.9 (14-C), 26.0 (14-C), 21.6 (13-C) ppm; IR (neat): ν = 3250, 1372, 1084, 729 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{27}NNaO_4S_2$ 480.1271, found: 480.1289.

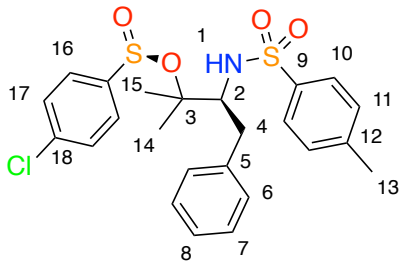
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-2,4,6-trimethylbenzenesulfinate (216c)



For synthesis of **216c**, **general procedure C part A** was followed using MesMgBr.

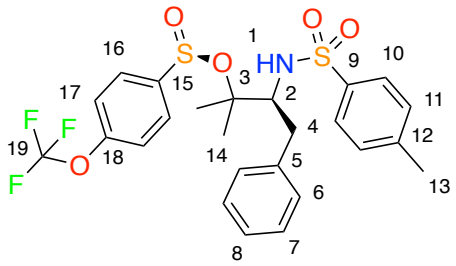
To a solution of **214** (0.10 g, 0.27 mmol, 1.00 equiv) in dry THF (0.77 mL) at -78 °C under argon 2-mesityl magnesium bromide (0.65 mL, 0.29 mmol of a 0.44 M solution in THF, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-30% EtOAc in PE) to give **216c** as a colourless oil (73 mg, 56%). $[\alpha]_D$ = - 159.7 (c = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, J = 9.4 Hz, 2H, 10-H), 7.09-6.98 (m, 5H, 8-H, 7-H and 11-H), 6.93 (d, J = 7.3 Hz, 6-H), 6.88 (s, 2H, 17-H), 5.68 (d, J = 9.7 Hz, 1H, 1-H), 3.75-3.69 (m, 1H, 2-H), 3.14-3.09 (m, 1H, 4-H_a), 2.69 (dd, J = 14.1, 9.9 Hz, 1H, 4-H_b), 2.61 (s, 6H, 19-H), 2.34 (s, 3H, 13-H), 2.30 (s, 3H, 20-H), 1.73 (s, 3H, 14-H), 1.48 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3 (9-C), 142.2 (15-C or 18-C or 16-C or 5-C), 139.0 (12-C), 138.5 (16-C or 18-C), 138.4 (15-C or 18-C or 16-C or 5-C), 137.5 (15-C or 18-C or 16-C or 5-C), 130.9 (17-C), 129.5 (11-C or 7-C or 6-C), 129.4 (11-C or 7-C or 6-C), 128.5 (6-C or 7-C), 126.5 (10-C), 126.2 (8-C), 87.2 (3-C), 64.1 (2-C), 37.5 (4-C), 28.1 (14-C), 25.5 (14-C), 19.3 (13-C or 20-C), 21.2 (14-C), 14.3 (19-C) ppm; IR (KBr): ν = 3259, 2928, 1154, 1084, 666 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{27}H_{33}NNaO_4S_2$ 522.1743, found: 522.1742.

(S)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (S)-4-chlorobenzenesulfinate (216d)



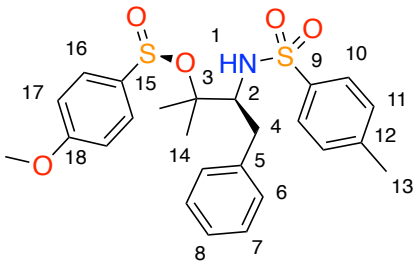
For synthesis of **216d**, **general procedure C part A** was followed using *p*-ClPhMgBr. To a solution of **214** (0.10 g, 0.27 mmol, 1.00 equiv) in dry THF (0.77 mL) at -78 °C under argon *p*-chloro phenyl magnesium bromide (0.20 mL, 0.29 mmol of a 1.41 M solution in diethyl ether, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-30% EtOAc in PE) to give the name compound **216d** as white solid (100 mg, 79%). m.p. 110-112 °C; $[\alpha]_D$ = - 183.1 (*c* = 1.0 in CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.7 Hz, 2H, 16-H), 7.52 (d, *J* = 8.7 Hz, 2H, 17-H), 7.29 (d, *J* = 8.3 Hz, 2H, 10-H), 7.09-6.99 (m, 5H, 8-H, 7-H and 11-H), 6.93-6.91 (m, 2H, 6-H), 5.46 (d, *J* = 9.5 Hz, 1H, 1-H), 3.73 (td, *J* = 9.5, 4.0 Hz, 1H, 2-H), 3.04 (dd, *J* = 14.4, 4.0 Hz, 1H, 4-H_a), 2.57 (dd, *J* = 14.4, 9.5 Hz, 1H, 4-H_b), 2.34 (s, 3H, 13-H), 1.77 (s, 3H, 14-H), 1.56 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.2, 142.5, 138.9, 138.6, 138.2, 129.6 (6-C or 17-C), 129.5 (6-C or 17-C), 129.5 (7-H or 11-H), 128.5 (7-H or 11-H), 126.6 (10-C or 16-C), 126.5 (10-C or 16-C), 126.3 (8-C), 87.9 (3-C), 63.8 (2-C), 37.2 (4-C), 27.9 (14-C), 26.0 (14-C), 21.6 (13-C) ppm; IR (neat): ν = 3343, 3038, 1303, 1137, 1116, 747 cm^{-1}; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{26}ClNNaO_4S_2$ 514.0884, found: 514.0882.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-4-(trifluoromethoxy)benzenesulfinate (216e)



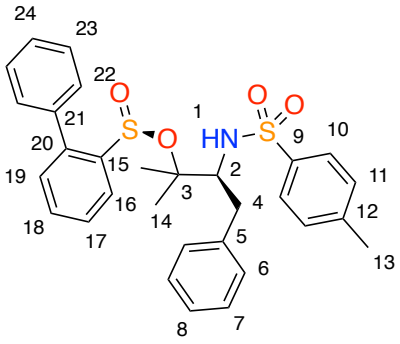
For synthesis of **216e**, **general procedure C part A** was followed using *p*-(CF_3O)PhMgBr. To a solution of **214** (0.20 g, 0.53 mmol, 1.00 equiv) in dry THF (1.55 mL) at -78 °C under argon *p*-(Trifluoromethoxy)phenyl magnesium bromide (1.16 mL, 0.58 mmol of a 0.5 M solution in THF, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-60% EtOAc in PE) to give **216e** (166 mg, 58%) as a white solid: m.p. 79-84 °C; $[\alpha]_D$ = - 127.4 (*c* = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.9 Hz, 2H, 16-H or 17-H), 7.38 (m, 2H, 17-H or 16-H), 7.30 (d, *J* = 8.3 Hz, 2H, 10-H), 7.09-6.99 (m, 5H, 8-H, 7-H, and 11-H), 6.94-6.91 (m, 2H, 6-H), 5.42 (d, *J* = 9.7 Hz, 1H, 1-H), 3.74 (td, *J* = 9.7, 4.1 Hz, 2-H), 3.05 (dd, *J* = 14.4, 4.1 Hz, 1H, 4-H_a), 2.58 (dd, *J* = 14.4, 9.3 Hz, 1H, 4-H_b), 2.35 (s, 3H, 13-H), 1.78 (s, 3H, 14-H), 1.58 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.9, 133.3, 129.5 (7-C or 11-C or 6-C), 129.5 (7-C or 11-C or 6-C), 128.5 (7-C or 11-C), 127.2 (16-C or 17-C), 126.5 (10-C), 126.3 (8-C), 121.4 (16-C or 17-C), 88.1 (3-C), 63.8 (2-C), 37.2 (4-C), 27.9 (14-C), 26.0 (14-C), 21.6 (13-C) ppm; IR (KBr): ν = 3240, 1257, 1151, 1082, 669 cm^{-1} HRMS (ESI-TOF) *m*/*z* [*M* + Na]$^+$ calcd for $C_{25}H_{26}F_3NNaO_5S_2$ 564.1097, found: 564.1114.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-4-methoxybenzenesulfinate (216f)



For synthesis of **216f**, **general procedure C part A** was followed using *p*-(MeO)PhMgBr. To a solution of **214** (0.20 g, 0.53 mmol, 1.00 equiv) in dry THF (1.55 mL) at -78 °C under argon *p*-methoxyphenyl magnesium bromide (1.23 mL, 0.58 mmol of a 0.47 M solution in THF, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-40% EtOAc in PE) to give **216f** as a white solid (184 mg, 72%). m.p. 85-90 °C; $[\alpha]_D$ = - 132.8 (*c* = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.8 Hz, 2H, 16-H or 17-H), 7.29 (d, *J* = 8.3 Hz, 2H, 10-H), 7.09-6.99 (m, 7H, 8-H, 7-H, 11-H and 17-H or 16-H), 6.96-6.93 (m, 2H, 5-H), 5.60 (d, *J* = 9.8 Hz, 1H, 1-H), 3.87 (s, 3H, 19-H), 3.73 (td, *J* = 9.8, 4.1 Hz, 1H, 2-H), 3.05 (dd, *J* = 14.4, 4.1 Hz, 1H, 4-H_a), 2.61 (dd, *J* = 14.4, 9.8 Hz, 1H, 4-H_b), 2.34 (s, 3H, 13-H), 1.76 (s, 3H, 14-H), 1.54 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.8, 142.3, 139.1, 138.5, 129.5 (7-C or 11-C or 17-C or 16-C, or 6-C), 129.4 (7-C or 11-C or 17-C or 16-C, or 6-C), 128.5 (7-C or 11-C or 17-C or 16-C), 126.9 (16-C or 17-C), 126.5 (10-C), 126.2 (8-C), 114.6 (7-C or 11-C or 17-C or 16-C), 87.1 (3-C), 63.9 (2-C), 55.7 (19-C), 37.3 (4-C), 28.0 (14-C), 26.4 (14-C), 21.6 (13-C) ppm; IR (KBr): ν = 3239, 1256, 1082, 666 cm^{-1}; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{25}H_{29}NNaO_5S_2$ 510.1379, found: 510.1387.

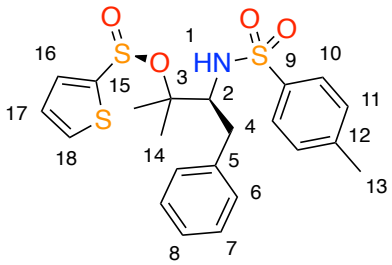
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-[1,1'-biphenyl]-4-sulfinate (216g)



For synthesis of **216g**, **general procedure C part A** was followed using 2-biphMgBr.

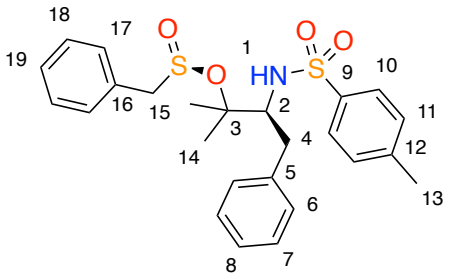
To a solution of **214** (0.10 g, 0.27 mmol, 1.00 equiv) in dry THF (0.80 mL) at -78 °C under argon 2-biphenyl magnesium bromide (0.79 mL, 0.30 mmol of a 0.38 M solution in diethyl ether, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (SiO_2, 0-50% EtOAc in PE) to give **216g** as a yellow solid (96 mg, 66%). $[\alpha]_D$ = -280.0 (*c* = 1.0 in CH_3Cl); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18-813 (m, 1H, 24-H), 7.64-7.58 (m, 2H, 23-H), 7.48-7.42 (m, 3H, 17-H, 18-H, and 16-H or 19-H), 7.41-7.35 (m, 3H, 22-H and 16-H or 19-H), 7.23 (d, *J* = 8.3 Hz, 2H, 10-H), 7.07-6.96 (m, 5H, 8-H, 7-H and 11-H), 6.90-6.88 (m, 2H, 6-H), 5.69 (d, *J* = 9.6 Hz, 1H, 1-H), 3.52 (td, *J* = 9.6, 3.9 Hz, 1H, 2-H), 2.85 (dd, *J* = 14.4, 3.9 Hz, 1H, 4-H_a), 2.49 (dd, *J* = 14.4, 9.6 Hz, 1H, 4-H_b), 2.33 (s, 3H, 13-H), 1.24 (s, 3H, 14-H), 1.02 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.3, 142.2, 141.4, 139.1, 138.6, 138.1, 132.1 (23-C), 130.8 (16-C or 19-C or 18-C or 17-C), 129.7 (6-C), 129.5 (16-C or 19-C or 18-C or 17-C), 129.4 (11-C or 7-C), 128.6 (22-C), 128.4 (16-C or 19-C or 18-C or 17-C), 128.3 (16-C or 19-C or 18-C or 17-C), 126.4 (10-C), 126.1 (8-C), 124.0 (24-C), 87.6 (3-C), 63.8 (2-C), 37.1 (4-C), 27.2 (14-C), 24.9 (14-C), 21.6 (13-C) ppm; IR (KBr): ν = 3265, 2982, 1329, 1153, 1086, 698 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{31}NNaO_4S_2$ 556.1587, found: 556.1601.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-thiophene-2-sulfinate (216h)



For synthesis of **216h**, **general procedure C part A** was followed using 2-thienylMgBr. To a solution of **214** (0.20 g, 0.53 mmol, 1.00 equiv) in dry THF (1.55 mL) at -78 °C under argon 2-thienyl magnesium bromide (0.67 mL, 0.58 mmol of a 0.86 M solution in THF, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-30% EtOAc in PE) to give **216h** as a yellow semisolid (230 mg, 93%). $[\alpha]_D$ = -107.1 (*c* = 1.0 in CH_3Cl); ^1H NMR (500 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 5.0, 1.4 Hz, 1H, 18-H or 16-H), 7.50 (dd, *J* = 3.8, 1.4 Hz, 1H, 18-H or 16-H), 7.28 (d, *J* = 8.3 Hz, 2H, 10-H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H, 17-H), 7.10-7.03 (m, 3H, 8-H and 7-H), 7.00 (d, *J* = 8.3 Hz, 2H, 11-H), 6.97-6.96 (m, 2H, 6-H), 3.75 (td, *J* = 9.6, 4.1 Hz, 1H, 2-H), 3.13 (dd, *J* = 14.4, 4.1 Hz, 1H, 4-H_a), 2.64 (dd, J = 14.4, 9.6 Hz, 1H, 4-H_b), 2.34 (s, 3H, 13-H), 1.75 (s, 3H, 14-H), 1.58 ppm (s, 3H, 14-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.3 (5-C or 9-C or 12-C or 15-C), 142.5 (5-C or 9-C or 12-C or 15-C), 138.9 (5-C or 9-C or 12-C or 15-C), 138.3 (5-C or 9-C or 12-C or 15-C), 131.6 (16-C or 18-C), 129.9 (16-C or 18-C), 129.5 (11-C or 6-C or 7-C or 8-C), 129.5 (11-C or 6-C or 7-C or 8-C), 128.5 (11-C or 6-C or 7-C or 8-C), 127.8 (17-C), 126.5 (10-C), 126.3 (11-C or 6-C or 7-C or 8-C), 88.0 (3-C), 64.0 (2-C), 37.3 (4-C), 27.7 (14-C), 25.9 (14-C), 21.6 (13-C) ppm; IR (KBr): ν = 3238, 1327, 1153, 1084, 665 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{26}NO_4S_3$ 464.1024, found: 464.1027.

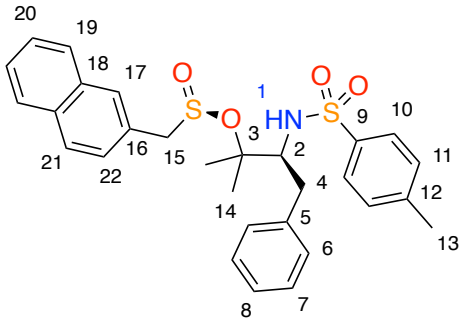
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl(*S*)-phenylmethanesulfinate (216i)



For synthesis of **216i**, **general procedure C part A** was followed using BnMgBr.

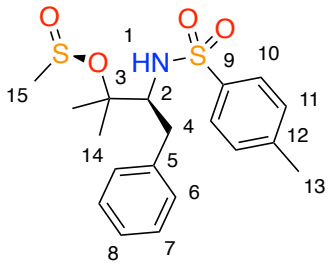
To a solution of **214** (200 mg, 0.53 mmol, 1.00 equiv) in dry THF (1.55 mL) at -78 °C under argon benzyl magnesium bromide (0.40 mL, 0.58 mmol of a 1.45 M solution in diethyl ether, 1.10 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (SiO_2, 0-50% EtOAc in PE) to give **216i** as a colourless semisolid (0.24 g, 96%). $[\alpha]_D$ = - 147.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.33 (m, 3H, 17-H or 18-H and 19-H), 7.30-7.28 (m, 2H, 17-H or 18-H), 7.27-7.24 (m, 2H, 10-H), 7.09-7.03 (m, 3H, 8-H and 6-H or 7-H), 7.00-6.98 (m, 2H, 11-C), 6.92-6.90 (m, 2H, 7-H or 6-H), 5.31 (d, *J* = 9.7 Hz, 1H, 1-H), 4.00 (q, *J* = 13.0 Hz, 2H, 15-H), 3.62 (td, *J* = 9.7, 4.1 Hz, 1H, 2-H), 2.95 (dd, *J* = 14.4, 4.1 Hz, 1H, 4-H_a), 2.44 (dd, *J* = 14.4, 9.7 Hz, 1H, 4-H_b), 2.33 (s, 3H, 13-H), 1.47 (s, 3H, 14-H), 1.32 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.4 (16-C or 5-C or 9-C or 12-C), 139.0 (16-C or 5-C or 9-C or 12-C), 138.4 (16-C or 5-C or 9-C or 12-C), 130.7 (17-C or 18-C), 129.5 (11-C), 129.4 (6-C or 7-C), 129.0 (16-C or 5-C or 9-C or 12-C), 128.9 (17-C or 18-C), 128.6 (19-C), 128.5 (6-C or 7-C), 126.5 (10-C), 126.3 (8-C), 87.1 (3-C), 54.5 (15-C), 53.7 (2-C), 37.1 (4-C), 27.2 (14-C), 25.9 (14-C), 21.5 (13-C) ppm; IR (neat): ν = 3222, 2924, 1289, 1097, 698 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{29}NNaO_4S_2$ 494.1430, found: 494.1435.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-naphthalen-2-ylmethanesulfinate (216j)



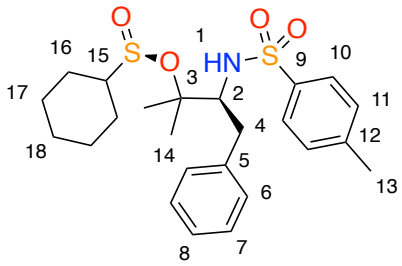
For synthesis of **216j**, **general procedure C part A** was followed using 2-naphthalenylmethylMgBr. To a solution of **214** (0.20 g, 0.53 mmol, 1.00 equiv) in dry THF (1.55 mL) at -78 °C under 2-naphthalenylmethyl magnesium bromide (2.76 mL, 0.58 mmol of a 0.21 M solution in diethyl ether, 1.00 equiv) was added dropwise. The crude collected was evaporated to dryness and purified by flash column chromatography (KP-Sil, 0-40% EtOAc in PE) to give **216j** (0.23 g, 83%) as a colourless oil. $[\alpha]_D$ = - 159.9 (*c* = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86-7.83 (m, 2H, 19-H), 7.79 (s, 1H, 17-H), 7.53-7.49 (m, 2H, 20-H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 22-H), 7.22 (d, *J* = 8.3 Hz, 2H, 10-H), 7.10-6.95 (m, 6H, 8-H, 7-H, 11-H and 21-H), 5.27 (d, *J* = 9.7 Hz, 1H, 1-H), 4.17 (q, *J* =12.9 Hz, 2H, 15-H), 3.60 (td, *J* = 9.7, 4.2 Hz, 1H, 2-H), 2.93 (dd, *J* = 14.4, 4.2 Hz, 1H, 4-H_a), 2.41-2.32 (m, 4H, 4-H_b and 13-H), 1.47 (s, 3H, 14-H), 1.31 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3, 138.9, 138.3, 133.4, 133.1, 130.0 (17-C), 129.4 (6-C), 128.6 (21-C), 128.4 (19-C), 128.1 (22-C), 128.0 (8-C), 127.9 (11-C or 7-C), 126.7 (7-C or 11-C), 126.6 (20-C), 126.4 (10-C), 87.1 (3-C), 64.7 (15-C), 63.7 (2-C), 37.1 (4-C), 27.0 (14-C), 26.1 (14-C), 21.5 (13-C) ppm; IR (neat): ν = 3225, 3025, 1322, 1152, 1092 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [*M* + Na]$^+$ calcd for $C_{29}H_{31}NNaO_4S_2$ 544.1587, found: 544.1605.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-methanesulfinate (216k)



For synthesis of **216k**, **general procedure C part A** was followed using methylMgBr (0.12 mL, 0.29 mmol of a 2.40 M solution in diethyl ether, 1.10 equiv) as R^1MgBr. Crude purified by flash column chromatography (KP-Sil, 0-50% EtOAc in PE) to give **216k** as a white solid (60 mg, 53%). m.p. 115-117 °C; $[\alpha]_D$ = - 109.2 (*c* = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.3 Hz, 2H, 10-H), 7.12-6.97 (m, 7H, 11-H, 6-H, 7-H and 8-H), 5.49 (d, *J* = 9.8 Hz, 1H, 1-H), 3.68 (ddd, *J* = 9.8, 9.1, 4.1 Hz, 1H, 2-H), 3.07 (dd, *J* = 14.4, 4.1 Hz, 1H, 4-H_a), 2.65-2.59 (m, 4H, 4-H_b and 15-H), 2.34 (s, 3H, 13-H), 1.60 (s, 3H, 14-H), 1.49 ppm (s, 3H, 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.4 (9-C), 139.0 (5-C or 12-C), 138.4 (5-C or 12-C), 129.6 (6-C or 7-C or 11-C), 129.5 (6-C or 7-C or 11-C), 128.5 (6-C or 7-C), 126.5 (10-C), 126.3 (8-C), 86.8 (3-C), 63.6 (2-C), 44.7 (15-C), 37.2 (4-C), 27.5 (14-C), 25.8 (14-C), 21.6 (13-C) ppm; IR (neat): ν = 3164, 2924, 1154, 1083, 697 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_4S_2$ 418.1119, found: 418.1117.

(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-cyclohexanesulfinate (216l)

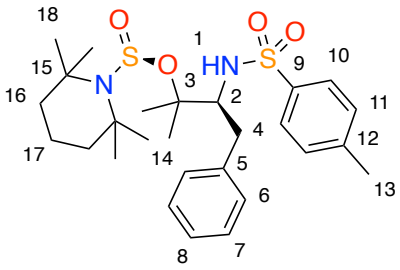


For synthesis of **216l**, **general procedure C part A** was followed using cyclohexylMgBr (0.30 mL, 0.29 mmol of a 0.94 M solution in diethyl ether, 1.10 equiv) as R^1MgBr.

Crude purified by flash column chromatography (KP-Sil, 0-40% EtOAc in PE) to give **216l** as a white solid (70 mg, 58%). m.p. 130-132 °C; $[\alpha]_D$ = - 106.5 (*c* = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28-7.26 (m, 2H, 10-H), 7.10-7.02 (m, 3H, 8-H and 7-H or 6-H), 7.00-6.95 (m, 4H, 11-H and 6-H or 7-H), 5.73 (d, *J* = 9.8 Hz, 1H, 1-H), 3.70 (td, *J* =

9.8, 3.9 Hz, 1H, 2-H), 3.07 (dd, J = 14.4, 3.9 Hz, 1H, 4-H_a), 2.64-2.51 (m, 2H, 4-H_b and 15-H), 2.34 (s, 3H, 13-H), 2.04-1.95 (m, 2H, 16-H or 17-H or 18-H), 1.92-1.86 (m, 2H, 16-H or 17-H or 18-H), 1.71 (d, J = 11.9 Hz, 1H, 16-H or 17-H or 18-H), 1.62 (s, 3H, 14-H), 1.42 (s, 3H, 14-H), 1.44-1.19 ppm (m, 5H, 16-H or 17-H or 18-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.2 (5-C or 9-C or 12-C), 139.2 (5-C or 9-C or 12-C), 138.6 (5-C or 9-C or 12-C), 129.6 (11-C or 6-C or 7-C), 129.4 (11-C or 6-C or 7-C), 128.5 (6-C or 7-C), 126.4 (10-C), 126.2 (8-C), 86.6 (3-C), 63.8 (2-C), 37.2 (4-C), 27.8 (14-C), 25.8 (14-C), 25.3 (16-C or 17-C or 15-C or 18-C), 25.2 (16-C or 17-C or 15-C or 18-C), 24.9(16-C or 17-C or 15-C or 18-C), 24.6 (16-C or 17-C or 15-C or 18-C), 21.6 (13-C) ppm; IR (neat): ν = 3231, 2995, 2861, 1324, 1085, 669 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{33}NNaO_4S_2$ 486.1743, found: 486.1754.

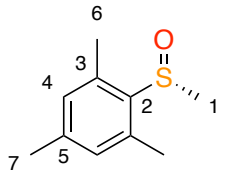
(*S*)-2-methyl-3-((4-methylphenyl)sulfonamido)-4-phenylbutan-2-yl (*S*)-2,2,6,6-tetramethylpiperidine-1-sulfinate (216m)



For synthesis of **216m**, **general procedure C part A** was followed using 2,2,6,6-TetramethylpiperidinylMgCl lithium chloride complex (0.62 mL, 0.29 mmol of a 0.46 M solution in THF) as R^{1}MgCl. Crude purified by flash column chromatography (KP-Sil 0-50% EtOAc in PE) to give **216m** as a colourless semisolid (123 mg, 91%). $[\alpha]_D$ = - 62.6 (c = 1.0 in CH_3Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.25 (m, 2H, 10-H), 7.10-7.03 (m, 3H, 8-H and 6-H or 7-H), 7.00-6.97 (m, 4H, 11-H and 6-H or 7-H), 6.02 (d, J = 9.6 Hz, 1H, 1-H), 3.66-3.60 (m, 1H, 2-H), 3.10 (dd, J = 14.4, 4.0 Hz, 1H, 4-H_a), 2.71 (dd, J = 14.4, 9.6 Hz, 1H, 4-H_b), 2.33 (s, 3H, 13-H), 1.68-1.46 ppm (m, 24H, 16-H, 17-H, 18-H and 14-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.9 (9-C), 139.4 (12-C or 5-C), 139.1 (12-C or 5-C), 129.4 (11-C or 6-C or 7-C), 129.2 (11-C or 6-C or 7-C), 128.3 (6-C or 7-C), 126.3 (10-C), 125.9 (8-C), 84.2 (3-C), 65.6 (2-C), 58.4 (15-C), 42.3 (17-C or 16-C), 37.8 (4-C), 31.3 (17-C or 16-C or 18-C), 28.8 (17-C or 16-C or 18-C), 25.5 (17-C or 16-C or 18-C), 21.5 (13-C), 17.0 (17-C or 16-C or 18-C) ppm; IR (neat): ν = 3187, 2979, 1325, 1192, 666 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{27}H_{40}N_2NaO_4S_2$ 543.2322, found: 543.2320.

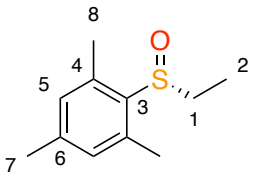
4.4 Synthesis of sulfoxides:

(*R*)-1,3,5-trimethyl-2-(methylsulfinyl)benzene (36b)



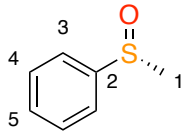
For synthesis of **36b**, **general procedure A part B** was followed using MeMgBr.
To a solution of compound **209c** (0.42 g, 0.89 mmol, 1.00 equiv) in THF (3.70 mL) at -78 °C, MethylMgBr (0.89 mL, 1.96 mmol of 2.00 M solution in diethyl ether, 2.20 equiv) was added. The crude was purified by column chromatography (SiO_2, 40-60% EtOAc in PE) to give **36b** as colourless oil (82 mg, 51%). $[\alpha]_D$ = +35.5 (*c* = 2.0, $CHCl_3$); lit:[305] $[\alpha]_D$ = +94.0 (*c* = 0.28, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (s, 2H, 4-H), 2.83 (s, 3H, 1-H), 2.53 (s, 6H, 6-H), 2.23 (s, 3H, 7-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.1 (2-C), 137.9 (5-C), 135.9 (3-C), 131.0 (4-C), 38.4 (1-C), 21.0 (7-C), 19.0 (6-C); IR (KBr): ν = 1064, 1041, 1022 cm^{-1}. HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{10}H_{14}NaOS$ 205.0675, found: 205.0658. Data consistent with literature.[305]

(*R*)-2-(ethylsulfinyl)-1,3,5-trimethylbenzene (36c)



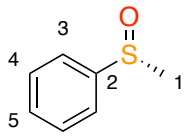
For synthesis of **36c**, **general procedure A part B** was followed using EtMgBr.
To a solution of compound **209c** (0.50 g, 1.43 mmol, 1.00 equiv) in THF (5 mL) at -78 °C, ethyl magnesium bromide (3.06 mL, 1.71 mmol, of a 0.56 M in diethyl ether, 1.20 equiv) was added. The crude was purified by column chromatography (SiO_2, 10-40% EtOAc in PE) to give **36c** as a yellow oil (50 mg, 19 %). $[\alpha]_D$ = +148.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 2H, 5-H), 3.22 (dq, *J* = 13.0, 7.5 Hz, 1H, 1-H_a), 2.94 (dq, *J* = 13.0, 7.5 Hz, 1H, 1-H_b), 2.53 (s, 6H, 8-H), 2.27 (s, 3H, 7-H), 1.27 (dd, *J* = 7.5 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.2 (3-C), 138.6 (6-C), 134.5 (4-C), 131.0 (5-C), 46.2 (1-C), 21.1 (7-C), 19.3 (8-C), 8.5 (2-C); IR (KBr): ν = 1065, 1044, 1013 cm^{-1}; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_{11}H_{16}NaOS$ 219.0814, found: 219.0829. Data consistent with literature.[306]

(*R*)-(methylsulfinyl)benzene (36a)



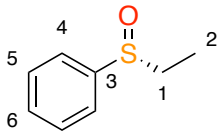
For the synthesis of **36a general procedure B** was followed. Template **26** (1.80 g, 5.10 mmol, 1.00 equiv) was reacted with phenylMgBr (2.0 mL, 5.1 mmol, of a 2.5 M solution in diethyl ether, 1.0 equiv) and methylMgBr (3.42 mL, 6.12 mmol of a 2.00 M solution in diethyl ether, 1.20 equiv). The crude was purified by column chromatography (SiO_2, 30-100% EtOAc in PE) to give **36a** as a colourless oil (0.14 g, 20%). $[\alpha]_D$ = + 62.3 (*c* =1.0, $CHCl_3$); lit:[307] $[\alpha]_D$ = +138.8 (*c* = 2.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 -7.56 (m, 2H, 3-H), 7.48-7.42 (m, 3H, 4-H and 5-H), 2.66 (s, 3H, 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.5 (2-C), 130.9 (5-C), 129.3 (4-C), 123.4 (3-C), 43.9 (1-C); IR (KBr): ν = 1641, 1478, 1445, 1416, 1302, 1090, 1019 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for C_7H_8NaOS 163.0188, found: 163.0191. Data consistent with literature.[308]

(*R*)-(methylsulfinyl)benzene (36a)



For the synthesis of **36a general procedure C part B** was followed using MeMgBr. To a solution of compound **216b** (0.20 g, 0.44 mmol, 1.00 equiv) in THF (1.54 mL) at -78 °C, methyl magnesium bromide (0.92 mL, 1.76 mmol of a 1.92 M solution in diethyl ether, 4.00 equiv) was added. The crude was purified by flash column chromatography (KP-Sil, 0-100% EtOAc in PE) to give **36a** as a colourless oil (25 mg, 40%).

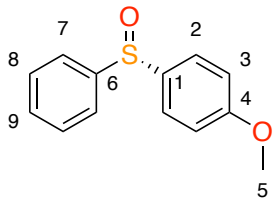
(*R*)-(ethylsulfinyl)benzene (36d)



For the synthesis of **36d general procedure C part B** was followed using EtMgBr. To a solution of compound **216b** (0.20 g, 0.44 mmol, 1.00 equiv) in THF (1.54 mL) at -78 °C, ethyl magnesium bromide (4.63 mL, 1.76 mmol of a 0.38 M solution in diethyl ether, 4.00 equiv) was added. The crude purified by flash column chromatography (KP-Sil, 0-100 % EtOAc in PE) to give **36d** as a white solid (28 mg, 41%). $[\alpha]_D$ = + 72.3 (*c* =1.0, $CHCl_3$); lit:[309] $[\alpha]_D$ = + 151.5 (*c* = 0.3, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62-7.60 (m, 2H, 4-H), 7.54-7.47 (m, 3H, 6-H and 5-H), 2.95-2.86 (m, 1H, 1-H_a), 2.81-2.72 (m, 1H,

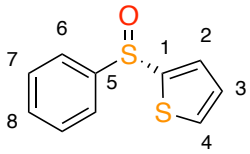
1-H_b), 1.20 ppm (t, *J* = 7.4 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.1 (3-C), 130.9 (6-C), 129.0 (5-C), 124.1 (4-C), 50.2 (1-C), 5.8 (2-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + Na]$^+$ calcd for $C_8H_{10}NaOS$ 177.0345, found: 177.0349. Data consistent with literature.[310]

Synthesis of (*S*)-1-methoxy-4-(phenylsulfinyl)benzene (36e)



For the synthesis of the title compound **36e general procedure C part B** was followed using *p*-(MeO)PhMgBr. To a solution of compound **216b** (0.20 g, 0.44 mmol, 1.00 equiv) in THF (1.54 mL) at -78 °C, *p*-methoxyphenyl magnesium bromide (4.63 mL, 1.76 mmol of a 0.47 M solution in THF, 4.00 equiv) was added. The crude purified by flash column chromatography (KP-Sil, 0-60 % EtOAc in PE) to give 0.218 g of a 1:1 mixture of released auxiliary **213** and product **36e**. Recrystallisation from EtOAc/PE gave **36e** as a colourless oil (102 mg, 100%). $[\alpha]_D$ = - 59.0 (*c* =1.0, $CHCl_3$); lit:[311] $[\alpha]_D$ = - 52.0 (*c* =0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62-7.60 (m, 2H, 7-H or 8-H), 7.57 (d, *J* = 8.9 Hz, 2H, 2-H or 3-H), 7.48-7.42 (m, 3H, 9-H and 8-H or 7-H), 6.95 (d, *J* = 8.9 Hz, 2H, 3-H or 2-H), 3.81 ppm (s, 3H, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.2 (4-C), 142.9 (6-C), 136.9 (1-C), 130.9 (9-C), 129.3 (8-C or 7-C), 127.4 (2-C or 3-C), 124.7 (8-C or 7-C), 115.0 (3-C or 2-C), 55.6 (5-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + H]$^+$ calcd for $C_{13}H_{13}O_2S$ 233.0631, found: 233.0635. Data consistent with literature.[311]

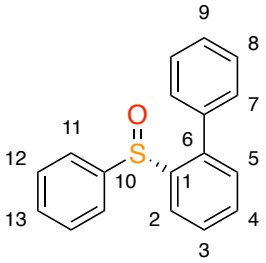
(*S*)-2-(phenylsulfinyl)thiophene (36f)



For the synthesis of the title compound **36f general procedure C part B** was followed using 2-thienylMgBr. To a solution of compound **216b** (0.20 g, 0.44 mmol, 1.00 equiv) in THF (1.54 mL) at -78 °C, 2-thienyl magnesium bromide (2.04 mL, 1.76 mmol of a 0.82 M solution in THF, 4.00 equiv) was added. The crude was purified by flash column chromatography (KP-Sil, 0-60 % EtOAc in PE) to give **36f** as a white solid (84 mg, 91%). m.p. 56-60 °C; $[\alpha]_D$ = + 20.6 (*c* =1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.69 (m, 2H, 6-H), 7.59-7.56 (m, 2H, 2-H and 4-H), 7.53-7.48 (m, 3H, 8-H and 7-H), 7.06

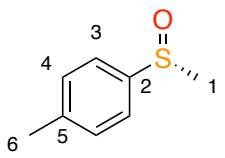
ppm (dd, J = 5.0, 3.7 Hz, 1H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.2 (5-C or 1-C), 145.3 (1-C or 5-C), 132.5 (2-C or 4-C), 131.5 (8-C), 131.3 (2-C or 4-C), 129.3 (7-C), 127.4 (3-C), 124.5 (6-C) ppm; IR (KBr): ν = 3075, 1403, 1034, 735 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{10}H_8NaOS_2$ 230.9909, found: 230.9916.

(*S*)-2-(phenylsulfinyl)-1,1'-biphenyl (36g)



For the synthesis of the title compound **36g general procedure C part B** was followed using 2-biphenylMgBr. To a solution of compound **216b** (0.20 g, 0.44 mmol, 1.00 equiv) in THF (1.54 mL) at -78 °C, 2-biphenyl magnesium bromide (3.47 mL, 1.32 mmol of a 0.38 M solution in diethyl ether, 3.00 equiv) was added. After 5h the reaction didn't go to completion (reaction monitored by TLC), another equivalent of the Grignard reagent was added in solution (1.16 mL, 0.44 mmol, 1.00 equiv). The crude was purified by flash column chromatography (KP-Sil, 0-60% EtOAc in PE) to give **36g** as a brown oil (123 mg, 100%). $[\alpha]_D$ = – 238.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, J =7.9, 1.4 Hz, 1H, 2-H or 5-H), 7.59 (td, J = 7.9, 1.4 Hz, 1H, 4-H or 3-H), 7.50 (td, J = 7.9, 1.4 Hz, 1H, 4-H or 3-H), 7.41-7.36 (m, 3H, 7-H or 8-H or 9-H), 7.30-7.27 (m, 1H, 13-H), 7.24-7.19 (m, 5H, 11-H or 12-H, 7-H or 8-H or 9-H), 7.09-7.06 ppm (m, 2H, 11-H or 12-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.0, 143.7, 140.9, 138.2, 130.9 (13-C), 130.9, 130.5, 129.8 (7-C or 8-C or 11-C or 12-C), 129.5 (9-C), 128.9 (8-C or 7-C), 128.7 (3-C or 4-C), 128.6, 128.3, 125.7 (11-C or 12-C), 124.9 (4-C or 3-C), 124.3 (2-C or 5-C) ppm; IR (KBr): ν = 3053, 1443, 1044, 747 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{15}OS$ 279.0838, found: 279.0853.

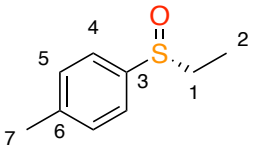
(*R*)-1-methyl-4-(methylsulfinyl)benzene (36h)



For the synthesis of the title compound **36h general procedure C part B** was followed using MeMgBr. To a solution of compound **216a** (0.10 g, 0.21 mmol, 1.00 equiv) in THF (0.62 mL) at -78 °C, methyl magnesium bromide (0.27 mL, 0.85 mmol of a 3.0 M

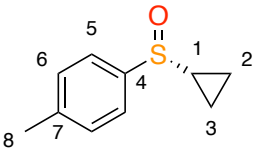
solution in diethyl ether, 4.00 equiv) was added. The crude was purified by flash column chromatography (KP-Sil, 0-60% EtOAc in PE) to give **36h** as a white semisolid (15 mg, 21%). $[\alpha]_D$ = + 172.0 (*c* = 1.0 in CH_3Cl); lit:[307] $[\alpha]_D$ = + 116.0 (*c* =1.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.2 Hz, 2H, 3-H), 7.33 (d, *J* = 8.1 Hz, 2H, 4-H), 2.70 (s, 3H, 6-H), 2.42 ppm (s, 3H, 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6, 141.7, 130.2 (4-C), 123.7 (3-C), 44.2 (1-C), 21.6 (6-C) ppm; IR (KBr): ν = 3052, 2906, 1087, 814 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_8H_{10}NaOS$ 177.0345, found: 177.0342. Data consistent with literature.[307]

(*R*)-1-(ethylsulfinyl)-4-methylbenzene (36i)



For the synthesis of the title compound **36i general procedure C part B** was followed using ethyl magnesium bromide (0.62 mL, 0.52 mmol of a 3.0 M solution in diethyl ether, 4.00 equiv) as R^2MgBr. The crude was purified by flash column chromatography (SiO_2, 0-60% EtOAc in PE), to give **36i** as a colourless oil (10 mg, 50%). $[\alpha]_D$ = + 150.0 (*c* = 1.0 in CH_3Cl); lit:[307] $[\alpha]_D$ = + 168.0 (*c* =1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59-7.38 (m, 2H, 4-H), 7.37-7.25 (m, 2H, 5-H), 2.85 (dq, *J* = 13.0, 7.4 Hz, 1H, 1-H_a), 2.73 (dt, *J* = 13.0, 7.4 Hz, 1H, 1-H_a), 2.39 (s, 3H, 7-H), 1.16 ppm (t, *J* = 7.4 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.2 (3-C or 6-C), 140.0 (3-C or 6-C), 129.8 (5-C), 124.2 (4-C), 50.2 (1-C), 21.4 (7-C), 6.0 (2-C) ppm; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_9H_{12}NaOS$ 191.0501, found: 191.0501. Data consistent with literature.[312]

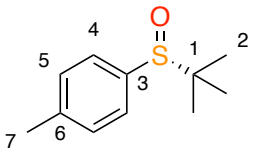
(*R*)-1-(cyclopropylsulfinyl)-4-methylbenzene (36l)



For the synthesis of the title compound **36l general procedure C part B** was followed using cyclopropyl magnesium bromide (2.08 mL, 0.52 mmol of a 0.25 M solution in THF, 4.00 equiv) as R^2MgBr. The crude was purified by flash column chromatography (KP-Sil, 10-50% EtOAc in PE), to give **36l** as a colourless oil (11 mg, 47%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.2 Hz, 2H, 5-H), 7.32 (d, *J* = 8.2 Hz, 2H, 6-H), 2.41 (s, 3H, 8-H), 2.24 (tt, *J* = 7.9, 5.0 Hz, 1H, 1-H), 1.23 (dt, *J* = 9.0, 5.0 Hz, 1H, 2-H_a), 1.02-0.97 (m, 1H, 3-H_a), 0.95-0.91 ppm (m, 2H, 3-H_b and 2-H_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.8 (4-C or 7-C), 141.5 (7-C or 4-C), 130.0 (6-C), 124.2 (5-C), 34.0 (1-C), 21.6 (8-C), 3.45 (3-C),

3.0 (2-C) ppm; IR (neat): ν = 3474, 3005, 2922, 1041, 1014, 806 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{13}OS$ 181.0687, found: 181.0688.

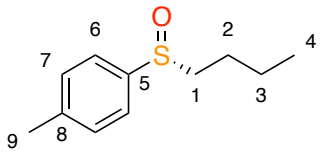
(*R*)-1-(tert-butylsulfinyl)-4-methylbenzene (36j)



For the synthesis of the title compound **36j general procedure C part B** was followed using *tert*-butyl magnesium bromide (0.62 mL, 0.52 mmol of a 0.68 M solution in THF, 4.00 equiv) as R^2MgBr. The crude was purified by column chromatography (SiO_2, 10-50% EtOAc in PE), to give **36j** as a colourless oil (12 mg, 56%). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.2 Hz, 2H, 4-H), 7.28 (d, J = 8.2 Hz, 2H, 5-H), 2.41 (s, 3H, 7-H), 1.16 ppm (s, 9H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.7 (3-C or 6-C), 136.8 (6-C or 3-C), 129.2 (5-C), 126.4 (4-C), 55.7 (1-C), 22.9 (2-C), 21.6 (7-C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{16}NaOS$ 219.0814, found: 219.0811.

Data consistent with literature.[313]

(*R*)-1-(butylsulfinyl)-4-methylbenzene (36k)

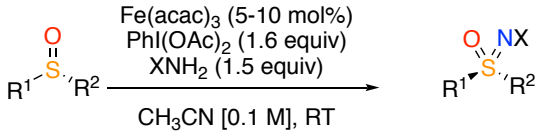


For the synthesis of the title compound **36k general procedure C part B** was followed using *n*-butyl magnesium bromide (0.63 mL, 0.52 mmol of a 0.68 M solution in THF, 4.00 equiv) as R^2MgBr. The crude was purified by column chromatography (SiO_2, 10-60% EtOAc in PE), to give **36k** as a colourless oil (13 mg, 51%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.2 Hz, 2H, 6-H), 7.32 (d, J = 8.2 Hz, 2H, 7-H), 2.83-2.71 (m, 2H, 1-H), 1.76-1.53 (m, 2H, 2-H), 1.49-1.37 (m, 2H, 3-H), 0.91 ppm (t, J = 7.3 Hz, 3H, 4-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.5 (5-C or 8-C), 140.9 (8-C or 5-C), 130.0 (7-C), 124.2 (6-C), 57.3 (1-C), 24.3 (2-C), 22.1 (3-C), 21.6 (9-C), 13.8 (4-C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{16}NaOS$ 219.0814, found: 219.0816.

Data consistent with literature.[306]

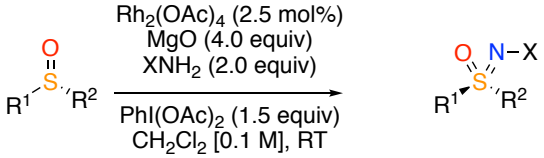
4.5 Synthesis of protected sulfoximines :

General Procedure D : Oxidative imination *via* iron catalysis



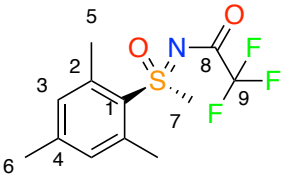
In this procedure Schlenk technique was performed.[302] To a mixture of sulfoxide (0.28 mmol, 1.00 equiv), sulfonyl amide or trifluoroacetoamide (0.42 mmol, 1.50 equiv), iodobenzene diacetate or iodosylbenzene (0.45 mmol, 1.60 equiv) in dry CH_3CN (3 mL), $Fe(acac)_3$ 5-10% (0.005-0.010 g, 0.014-0.028 mmol) was added and the reaction stirred at room temperature. Once the starting material was consumed (reaction monitored by TLC), it was concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding sulfoximines.

General Procedure E : Oxidative imination *via* rhodium catalysis



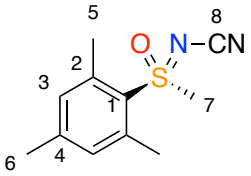
For this reaction Schlenk technique was performed.[302] To a suspension of sulfoxide (1.00 mmol, 1.00 equiv), sulfonylamide or trifluoroacetoamide (2.00 mmol, 2.00 equiv), MgO (0.16 g, 4.00 mmol, 4.00 equiv), and $Rh_2(OAc)_4$ (11 mg, 2.5% mol) in dry CH_2Cl_2 (10 mL), $PhI(OAc)_2$ (483 mg, 1.50 mmol, 1.5 equiv) was added at room temperature. When the reaction was completed (monitored by TLC) the crude was purified by flash column chromatography to afford the corresponding sulfoximines.

***N*-(Trifluoroacetyl)-(*R*)-mesithyl methylsulfoximine (217a)**



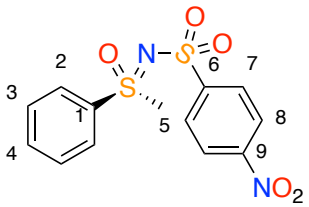
For the synthesis of the chiral sulfoximine **217a general procedure D** was followed, stirring sulfoxide **36b** (140 mg, 0.77 mmol, 1.00 equiv) together with NH_2COCF_3 (174 mg, 1.54 mmol, 2.00 equiv) for 15 h. The crude was purified by column chromatography (SiO_2, 10–40% EtOAc in PE) to give **217a** as a colourless oil (17 mg, 8%). $[\alpha]_D$ = -21.9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 2H, 3-H), 3.46 (s, 3H, 7-H), 2.67 (s, 6H, 5-H), 2.32 ppm (s, 3H, 6-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.8 (q, *J* = 37.7 Hz, 8-C), 144.5 (2-C), 143.4 (4-C or 1-C), 133.2 (3-C), 130.6 (1-C or 4-C), 116.2 (q, *J* = 288.2 Hz, 9-C), 45.07(7-C), 22.7 (5-C), 21.1 (6-C); IR (KBr): ν = 1670, 1178 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [*M* + H]$^+$ calcd for $C_{12}H_{15}F_3NO_2S$ 294.0770, found: 294.0767.

***N*-(Cyano)-(*R*)-mesithyl methylsulfoximine (217b)**



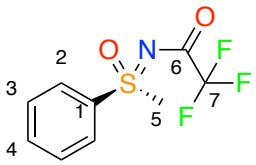
For the synthesis of the chiral sulfoximine **217b general procedure D** was followed stirring sulfoxide **36b** (58.0 mg, 0.27 mmol, 1.00 equiv) with NH_2CN (23 mg, 0.55 mmol, 2.00 equiv) for 48 h. The crude was purified by column chromatography (SiO_2, 40-80% EtOAc in PE) to afford **217b** as a colourless oil (8 mg, 13%). $[\alpha]_D$ = -48.7 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (s, 2H, 3-H), 3.35 (s, 3H, 7-H), 2.70 (s, 6H, 5-H), 2.34 ppm (s, 3H, 6-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.5 (1-C or 4-C), 140.5 (2-C), 133.5 (3-C), 130.2(4-C or 1-C), 112.4 (8-C), 44.7 (7-C), 22.9 (5-C), 21.2 (6-C) ppm; IR (KBr): ν = 1600, 1459, 1119 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [*M* + H]$^+$ calcd for $C_{11}H_{15}N_2OS$ 223.0909, found: 223.0900.

***N*-(4-Nitro-benzenesulfonyl)-(*R*)-methyl phenylsulfoximine (217c)**



For the synthesis of the chiral sulfoximine **217c general procedure E** was followed, mixing the chiral sulfoxide **36a** (36.0 mg, 0.26 mmol, 1.00 equiv) together with $NsNH_2$ (78.0 mg, 0.38 mmol, 1.50 equiv), iodobenzene diacetate (132 mg, 0.41 mmol, 1.60 equiv) and $Fe(acac)_3$ (0.004 g, 0.013 mmol, 5 mol%) for 17 h. The crude was purified by column chromatography (SiO_2 50-60% EtOAc in PE) to give **217c** as a white solid (28 mg, 33%). m.p. 129-135 °C; $[\alpha_D]$ = -69.2 (*c* = 1.0, H_3CCN); ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 8.33 (d, *J* = 9.0 Hz, 2H, 8-H), 7.99 (d, *J* = 10.0, 9.0 Hz, 2H, 7-H), 7.98-7.95 (m, 2H, 2-H), 7.79 (t, *J* = 7.4 Hz, 1H, 4-H), 7.68 (t, *J* = 7.4 Hz, 2H, 3-H), 3.70 (s, 3H, 5-H). ^{13}C NMR (101 MHz, $[D_6]$DMSO): δ = 149.7 (9-C), 149 (6-C or 1-C), 138 (1-C or 6-C), 134.5 (4-C), 129.6 (3-C) 127.7 (2-C), 127.3 (7-C) 124.34 (8-C), 44.7 (5-C). IR (KBr): ν = 1644, 1091; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{12}NaO_5S_2$ 363.0080, found: 363.0086.

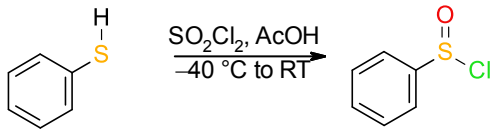
***N*-(Trifluoroacetyl)-(*R*)-methyl phenylsulfoximine (217d)**



For the synthesis of the the chiral sulfoximine **217d general procedure E** was followed, mixing chiral sulfoxide **36a** (69.0 mg, 0.49 mmol, 1.00 equiv) together with NH_2COCF_3 (83.0 mg, 0.74 mmol, 1.50 equiv), $PhI(OAc)_2$ (252 mg, 0.78 mmol, 1.60 equiv) and $Fe(acac)_3$ (17.00 mg, 0.049 mmol, 10 mol%) for 48 h. The crude was purified by flash column chromatography (SiO_2, 50-60% EtOAc in PE) to give of **217d** as an orange oil (8 mg, 11%). $[\alpha]_D$ = - 4.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01-7.99 (m, 2H, 2-H), 7.76 (t, *J* = 7.4 Hz, 1H, 4-H), 7.66 (m, 2H, 3-H), 3.46 (s, 3H, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4 (q, *J* = 39.0 Hz, 6-C), 136.9 (1-C), 134.9 (4-C), 130.2 (3-C), 125.3 (2-C), 116.9 (q, *J* = 288.0 Hz, 7-C), 44.04 (5-C); IR (KBr): ν = 1657, 1449, 1313, 1215, 1174, 1148, 1091 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_9H_9F_3NO_2S$: 252.0300, found 252.0301.

4.6 Preparation of sulfinamides:

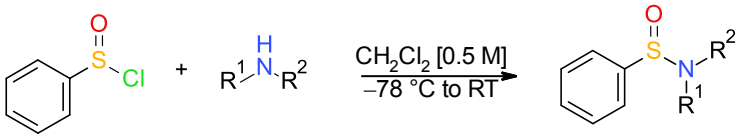
Procedure F: synthesis of benzenesulfinyl chloride 47a



Prepared according to a published procedure.[269]

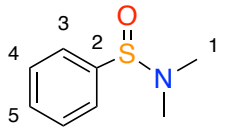
A solution of thiophenol (0.47 mL, 4.5 mmol, 1.0 equiv) and acetic acid (0.26 mL, 4.5 mmol, 1.0 equiv) was cooled to –40 °C, then sulfuryl chloride (0.81 mL, 10 mmol, 2.2 equiv) was added dropwise to the frozen mixture over 30 min, during which time gas evolution began. When the addition was completed, the reaction mixture was stirred for a further 30 min at –40 °C and then slowly warmed to RT and stirred for a further 3 h. Then, the volatiles were removed under reduced pressure (without warming, because of explosion risk) to give benzenesulfinyl chloride as a yellow oil. This compound was used directly in the next reaction without purification.

General procedure G: synthesis of sulfinamides 62b-k



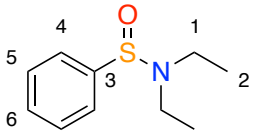
A solution of the appropriate secondary amine (3.9 mmol, 2.5 equiv) in CH_2Cl_2 (7.8 mL) was cooled to –78 °C. Freshly prepared benzenesulfinyl chloride (0.25 g, 1.6 mmol, 1.0 equiv) was diluted in CH_2Cl_2 (1.6 mL), and added dropwise to the frozen mixture over 15 min. After 10 min, the temperature was raised and the mixture was stirred at RT overnight. The reaction mixture was quenched by addition of an aqueous, saturated $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine (3 ×), collected and dried over water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

***N,N*-Dimethylbenzenesulfinamide (62b)**



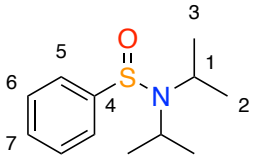
Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **62b** as a yellow oil (261 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 2H, 3-H), 7.55–7.46 (m, 3H, 4-H and 5-H), 2.68 ppm (s, 6H, 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.6 (2-C), 130.8 (5-C), 128.8 (3-C or 4-C), 126.0 (3-C or 4-C), 37.2 (1-C) ppm; IR (KBr): ν = 1442, 1088, 924, 754, 690, 653 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{12}NOS$: 170.0640, found: 170.0639.

***N,N*-Diethylbenzenesulfinamide (62c)**



Prepared according to **general procedure G,** but on different scale (benzenesulfinyl chloride: 1.00 g, 6.23 mmol); crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62c** as a colourless oil (1.22 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.65 (m, 2H, 4-H), 7.53–7.45 (m, 3H, 6-H and 5-H), 3.14 (app qd, J = 7.20, 1.27 Hz, 4H, 1-H), 1.13 ppm (t, J = 7.20 Hz, 6H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.3 (3-C), 130.5 (6-C), 128.7 (5-C), 126.3 (4-C), 42.0 (1-C), 14.4 (2-C) ppm; IR (KBr): ν = 2974, 1445, 1090, 1059, 754 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{16}NOS$: 198.0953, found: 198.0954.

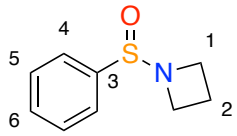
***N,N*-Diisopropylbenzenesulfinamide (62d)**



Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **62d** as a white solid (266 mg, 76%): m.p. 80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 2H, 5-H), 7.52–7.42 (m, 3H, 7-H and 6-H), 3.56 (sept, J = 6.76 Hz, 2H, 1-H), 1.42 (d, J = 6.76 Hz, 6H, 2-H or 3-H), 1.12 ppm (d, J = 6.76 Hz, 6H, 3-H or 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.6 (4-C), 130.1 (7-C), 128.6 (6-C), 126.6 (5-C), 46.6 (1-C), 23.8 (3-C and 2-C) ppm; IR (KBr): ν

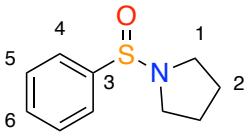
= 1365, 1178, 1084, 1055, 947, 752, 700 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{20}NOS$: 226.1266, found: 226.1267.

1-(Phenylsulfinyl)azetidine (62e)



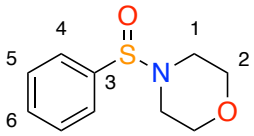
Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62e** as a colourless oil (188 mg, 67%): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.42 (m, 2H, 4-H), 7.31–7.24 (m, 3H, 5-H and 6-H), 3.69 (app q, J = 7.6 Hz, 2H, 1-H_a), 3.30 (app q, J = 7.60 Hz, 2H, 1-H_b), 2.00 ppm (app quin, J = 7.6 Hz, 2H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9 (3-C), 130.7 (6-C), 128.7 (5-C), 125.5 (4-C), 45.1 (1-C), 16.7 (2-C) ppm; IR (KBr): ν = 2964, 1445, 1089, 1059, 924, 752, 690, 573 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{12}NOS$: 182.0640, found: 182.0638.

1-(Phenylsulfinyl)pyrrolidine (62f)



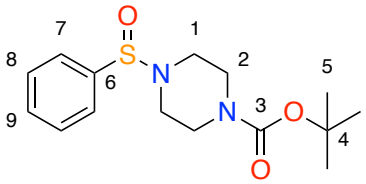
Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62f** as a colourless oil (228 mg, 75%): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 2H, 4-H), 7.54–7.43 (m, 3H, 6-H and 5-H), 3.42–3.30 (m, 2H, 1-H_a), 3.07–2.96 (m, 2H, 1-H_b), 1.92–1.80 ppm (m, 4H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.5 (3-C), 130.5 (6-C), 128.8 (5-C), 125.8 (4-C), 46.0 (1-C), 26.0 (2-C) ppm; IR (KBr): ν = 2964, 1445, 1057, 966, 754, 698, 567 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{14}NOS$: 196.0796, found: 196.0798.

4-(Phenylsulfinyl)morpholine (62g)



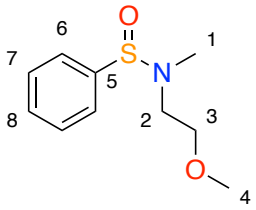
Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **62g** as a white solid (253 mg, 77%): m.p. 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 2H, 4-H), 7.56–7.48 (m, 3H, 6-H and 5-H), 3.78–3.68 (m, 4H, 1-H or 2-H), 3.18 (m, 2H, 2-H or 1-H), 3.01–2.94 ppm (m, 2H, 2-H or 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.2 (3-C), 131.1 (6-C), 128.9 (5-C), 126.2 (4-C), 66.9 (1-C or 2-C), 45.8 (1-C or 2-C) ppm; IR (KBr): ν = 1439, 1257, 1051, 906, 756, 694 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{14}NO_2S$: 212.0745, found: 212.0744.

***tert*-Butyl 4-(phenylsulfinyl)piperazine-1-carboxylate (62h)**



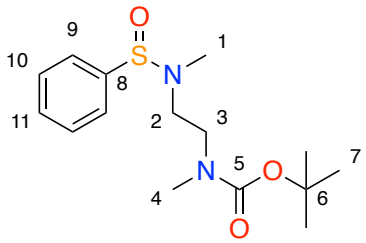
Prepared according to **general procedure G**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62h** as a colourless oil (369 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 2H, 7-H), 7.57–7.49 (m, 3H, 9-H and 8-H), 3.55–3.38 (m, 4H, 1-H or 2-H), 3.18–3.06 (m, 2H, 1-H or 2-H), 2.95 (*br*s, 2H, 1-H or 2-H), 1.45 ppm (s, 9H, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.5 (3-C), 142.5 (6-C), 131.1 (9-C), 128.9 (8-C), 126.1 (7-C), 80.2 (4-C), 45.7 (1-C), 48.9 (2-C), 28.3 (5-C) ppm; IR (KBr): ν = 2974, 1691, 1415, 1246, 1165, 1092, 905, 754, 690 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{23}N_2O_3S$: 311.1429, found: 311.1430.

***N*-(2-Methoxyethyl)-*N*-methylbenzenesulfinamide (62i)**



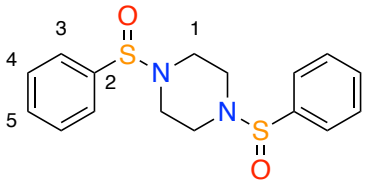
Prepared according to **general procedure G**, but on different scale (benzenesulfinyl chloride: 400 mg, 2.49 mmol); crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **62i** as an orange oil (228 mg, 43%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J = 7.5, 1.9 Hz, 2H, 6-H), 7.53–7.46 (m, 3H, 8-H and 7-H), 3.54 (t, J = 5.3 Hz, 2H, 3-H), 3.43–3.36 (m, 1H, 2-H_a), 3.35 (s, 3H, 4-H), 3.31–3.21 (m, 1H, 2-H_b), 2.63 ppm (s, 3H, 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.9 (5-C), 130.8 (8-C), 128.8 (7-C), 126.2 (6-C), 70.9 (3-C), 58.7 (4-C), 51.7 (2-C), 33.5 (1-C) ppm; IR (KBr): ν = 3485, 2880, 1445, 1090, 1059, 756, 692 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{16}NO_2S$: 214.0902, found: 214.0881.

***tert*-Butyl methyl{2-[methyl(phenylsulfinyl)amino]ethyl}carbamate (62j)**



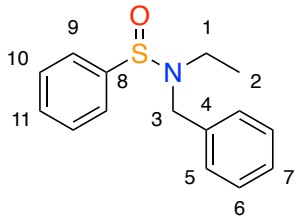
Prepared according to **general procedure G**, but on different scale (benzenesulfinyl chloride: 400 mg, 2.49 mmol); crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **62j** as a colourless oil (180 mg, 23%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 6.1 Hz, 2H, 9-H), 7.52–7.44 (m, 3H, 11-H and 10-H), 3.55–3.38 (m, 1H, 2-H_a), 3.30 (*br*t, J = 6.7 Hz, 2H, 3-H), 3.20–3.10 (m, 1H, 2-H_b), 2.73 (*br*d, J = 11.9 Hz, 3H, 4-H), 2.62 (s, 3H, 1-H), 1.44 ppm (app d, J = 17.7 Hz, 9H, 7-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4 (5-C), 143.5 (8-C), 130.9 (11-C), 128.9 (10-C), 126.1 (9-C), 79.6 (6-C), 49.9 (3-C or 2-C), 46.7 (2-C or 3-C), 34.1 (4-C or 1-C), 33.1 (1-C or 4-C), 28.4 (7-C) ppm; IR (KBr): ν = 3553, 2972, 1688, 1153, 1088, 1057, 870, 752, 690 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{25}N_2O_3S$: 313.1586, found: 313.1585.

1,4-Bis(phenylsulfinyl)piperazine (62k)



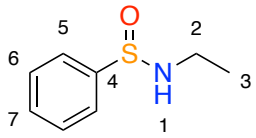
Prepared according to **general procedure G**; crude purified by flash column chromatography (NH cartridges, 0–60% EtOAc in hexane) to give **62k** as a white solid (192 mg, 37%): m.p. 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.57 (m, 4H, 3-H), 7.55–7.41 (m, 6H, 4-H and 5-H), 3.26–3.15 (m, 4H, 1-H_a), 3.09–2.98 ppm (m, 4H, 1-H_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.3 (2-C), 131.2 (5-C), 129.0 (4-C), 126.2 (3-C), 45.9 (1-C) ppm; IR (KBr): ν = 2853, 1445, 1256, 1090, 1055, 905, 744, 685, 575 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_2O_2S_2$: 335.0888, found: 335.0887.

***N*-Benzyl-*N*-ethylbenzenesulfinamide (62l)**



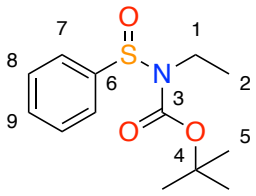
A solution of *N*-ethylbenzylamine (0.84 mL, 5.60 mmol, 1.50 equiv) and Hunig base (1.30 mL, 7.46 mmol, 2.00 equiv) in CH_2Cl_2 (11.2 mL) was cooled to –78 °C. Freshly prepared benzenesulfinyl chloride **47a** (600 mg, 3.73 mmol, 1.00 equiv) was diluted in CH_2Cl_2 (3.73 mL) and added dropwise to the frozen mixture over 15 min. After 10 min, the temperature was raised and the mixture stirred at RT overnight. The reaction mixture was quenched by addition of an aqueous, saturated $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (3 × 5 mL), collected and filtered through water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography (KP-Sil, 0-50% EtOAc in PE) to give **62l** as a yellow oil (696 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.73 (m, 2H, 9-H), 7.54 – 7.47 (m, 3H, 10-H and 11-H), 7.32 – 7.21 (m, 5H, 5-H and 6-H and 7-H), 4.20 – 4.12 (m, 2H, 3-H), 3.09 (app q, J = 7.2 Hz, 2H, 1-H), 1.11 ppm (app t, J = 7.2 Hz, 3H, 2-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 144.3 (4-C), 137.0 (8-C), 131.0 (11-C), 129.0 (10-C), 128.7 (6-C or 5-C), 128.6 (5-C or 6-C), 127.6 (7-C), 126.4 (9-C), 50.8 (3-C), 43.0 (1-C), 14.2 (2-C) ppm; IR (neat): ν = 3060, 2972, 1474, 1204, 1088, 1058, 996, 872 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{18}NOS$: 260.1104, found: 260.1105.

_N_-Ethylbenzenesulfinamide (48b)



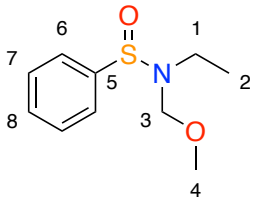
Prepared according to **general procedure G**, but on different scale (benzenesulfinyl chloride **47a**: 500 mg, 3.15 mmol); crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **48b** as a colorless oil (509 mg, 95%): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73–7.69 (m, 2H, 5-H), 7.52–7.47 (m, 3H, 7-H and 6-H), 4.01 (*br*s, 1H, 1-H), 3.21–3.15 (m, 1H, 2-H$_a$), 2.91–2.83 (m, 1H, 2-H$_b$), 1.16 ppm (app t, J = 7.3 Hz, 3H, 3-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 144.3 (4-C), 130.8 (7-C), 128.8 (6-C), 125.9 (5-C), 36.2 (2-C), 16.0 (3-C) ppm; IR (KBr): ν = 3431, 1443, 1018, 953, 750, 694, 573 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_{12}NOS$: 170.0640, found: 170.0640.

***tert*-butyl ethyl(phenylsulfinyl)carbamate (62x)**



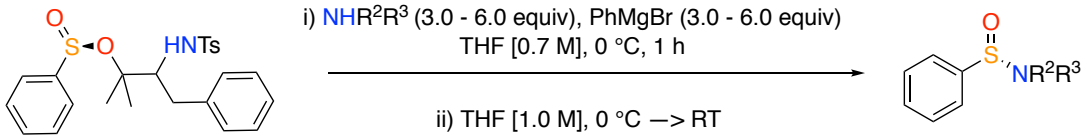
A solution of sulfinamide **48b** (300 mg, 1.77 mmol, 1.00 equiv) in dry THF (7.08 mL) under Ar was cooled to -78 °C. Immediately after addition of *n*-BuLi (0.90 mL, 2.12 mmol, 1.20 equiv, 2.36 M in Hexane), di-*tert*-butyl dicarbonate (2.12 mL, 2.12 mmol, 1.20 equiv, 1.00 M in THF) was added to the reaction mixture and stirred for 2 h at -78 °C. After this time the reaction mixture was allowed to warm to RT and stirred for further 3 h. Once the starting material had been consumed (monitored by TLC), aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (1 x 5 mL), then filtered through water-repellent filter paper. Solvent was removed in vacuo and the crude product purified by flash column chromatography (KP-Sil, 0-50% EtOAc in PE) to give **62x** as a colourless oil (314 mg, 66%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.68–7.62 (m, 5H, 7-H and 8-H and 9-H), 3.19 (dq, J = 14.2, 7.1 Hz, 1H, 1-H$_a$), 3.04 (dq, J = 14.2, 7.1 Hz, 1-H$_b$), 1.49 (s, 9H, 5-H), 0.75 ppm (app t, J = 7.1 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 152.7 (3-C), 143.0 (6-C), 132.0 (9-C), 129.5 (8-C), 124.8 (7-C), 82.6 (4-C), 35.6 (1-C), 27.7 (5-C), 14.7 (2-C) ppm; IR (KBr): ν = 3059, 2977, 1710, 1288, 1154, 752 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{20}NO_3S$: 270.1158, found: 270.1165.

***N*-Ethyl-*N*-(methoxymethyl)benzenesulfinamide (62z)**



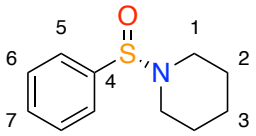
A solution of sulfinamide **48b** (200 mg, 1.18 mmol, 1.00 equiv) in dry THF (11.8 mL) under Ar was cooled to -78 °C. *n*-BuLi (0.50 mL, 1.18 mmol, 1.00 equiv, 2.36 M in Hexane) was added and the mixture stirred for 10 min. Finally MOM-Br was added to the reaction mixture and the solution was stirred for 1 h at -78 °C. Once the starting material had been consumed (monitored by TLC), aqueous, saturated $NaHCO_3$ was added and the mixture extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 × 5 mL), then filtered through water-repellent filter paper. Solvent was removed in vacuo and the crude product purified by flash column chromatography (KP-Sil, 0-60% EtOAc in PE) to give **62z** as a colourless oil (109 mg, 44%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.67 (m, 2H, 6-H), 7.54-7.48 (m, 3H, 8-H and 7-H), 4.78 (d, J = 10.8 Hz, 1H, 3-H_a), 4.67 (d, J = 10.8 Hz, 1H, 3-H_b), 3.38 (s, 3H, 4-H), 3.04 (app q, J = 7.4 Hz, 2H, 1-H), 0.99 ppm (app t, J = 7.4 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.1 (5-C), 131.1 (8-C), 129.0 (7-C), 126.2 (6-C), 82.8 (3-C), 55.9 (4-C), 38.4 (1-C), 14.1 (2-C) ppm ; IR (neat): ν = 3205, 2921, 1462, 1214, 1090, 890 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{15}NNaO_2S$: 236.0716, found: 236.0723.

General procedure H: synthesis of enantiopure sulfinamides



PhMgBr (3.00 equiv, 0.92 M in THF) was added dropwise to a solution of the selected amine (0.66 mmol, 3.00 equiv) in THF [0.7 M] at 0 °C. The mixture was stirred at this temperature for 1 hour, then it was added to a solution of intermediate **216b** (100 mg, 0.22 mmol, 1.00 equiv) in THF [1.0 M] at 0 °C. Reaction was stirred at 0 °C for 2 h then temperature was raised to RT. When all starting material had been consumed (monitored by TLC), aqueous, saturated $NaHCO_3$ was added and mixture extracted by EtOAc (3 × 5 mL). The combined organic phases were washed with brine (3 × 5 mL) and filtered through water repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

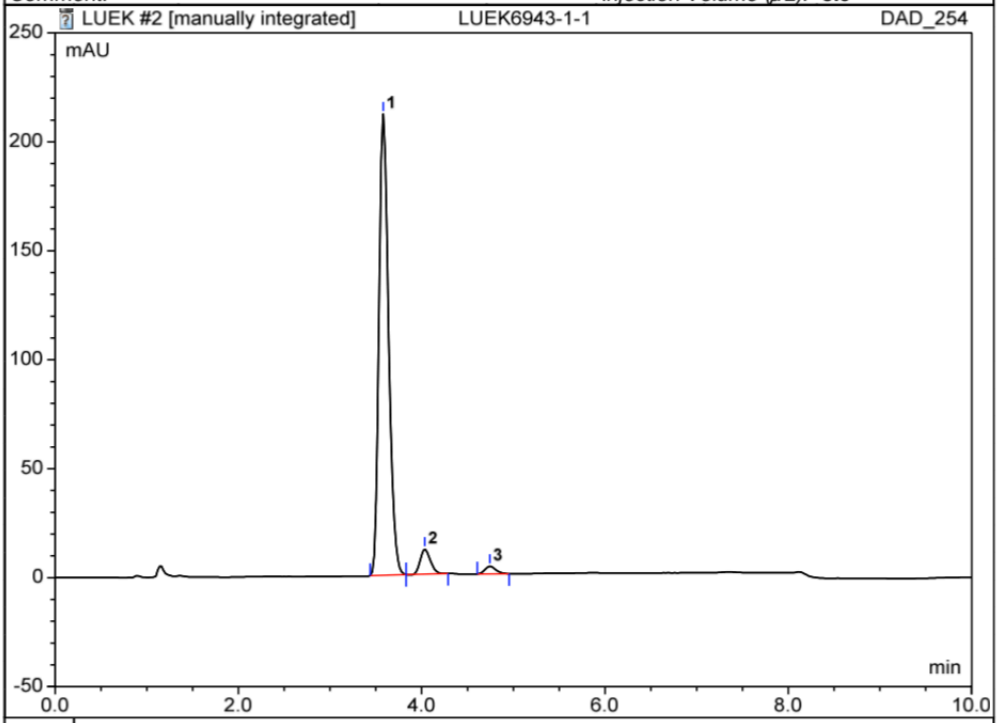
(*S*)-4-(phenylsulfinyl)piperidine (62a*)



Prepared according to **general procedure H**, by reacting intermediate **216b** (300 mg, 0.65 mmol, 1.00 equiv) with piperidine (167 mg, 1.96 mmol, 3.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **62a*** as a colourless oil (130 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67-7.64 (m, 2H, 5-H), 7.52-7.44 (m, 3H, 7-H and 6-H), 3.11 (ddd, J = 11.2, 5.1, 2.5 Hz, 2H, 1-H_a), 2.98-2.92 (m, 2H, 1-H_b), 1.67-1.48 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5 (4-C), 130.8 (7-C), 128.9 (6-C), 126.3 (5-C), 47.1 (1-C), 26.3 (2-C), 24.0 (3-C) ppm; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{15}NNaOS$: 232.0767, found: 232.0767. Chiral HPLC: instrument: Agilent HPLC 1260; column: Chiralpak IG 3 mm, 100 × 4.6 mm; eluent A: hexane, eluent B: 2-Propanol; gradient: 0–7 min 20–50% B; flow: 1.4 mL/min; temperature: 25 °C; DAD: 254 nm. 89% ee.

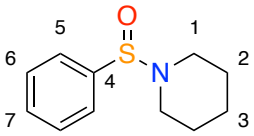
BPH-GDD-GCGE-MCB-MC5-HPLC

Sample Name:	**LUEK6943-1-1**	*Recording Date:*	**29.11.17 13:51**
Sample ID:	**4883809**		
Method:	**Enantiomerenbest**		
Column:	**Chiralpak IC 3µ 100x4.6**		
Solvent:	**20-50% IPA/Hexan in 7min**	*Wavelength (nm):*	**DAD_254**
Puffer:		*Flow (ml/min):*	**1.40**
Gradient:	**S3_20_50_IPA_HEXAN**	*Run Time (min):*	**10.00**
Solution:		*Vial Number:*	**P1:A2**
Comment:		*Injection Volume (µL):*	**5.0**



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	3.58		211.591	25.750	93.07	n.a.	2.3
2	4.03		11.358	1.438	5.20	n.a.	3.4
3	4.74		3.505	0.478	1.73	n.a.	n.a.
Total:			226.454	27.667	100.00	0.000	

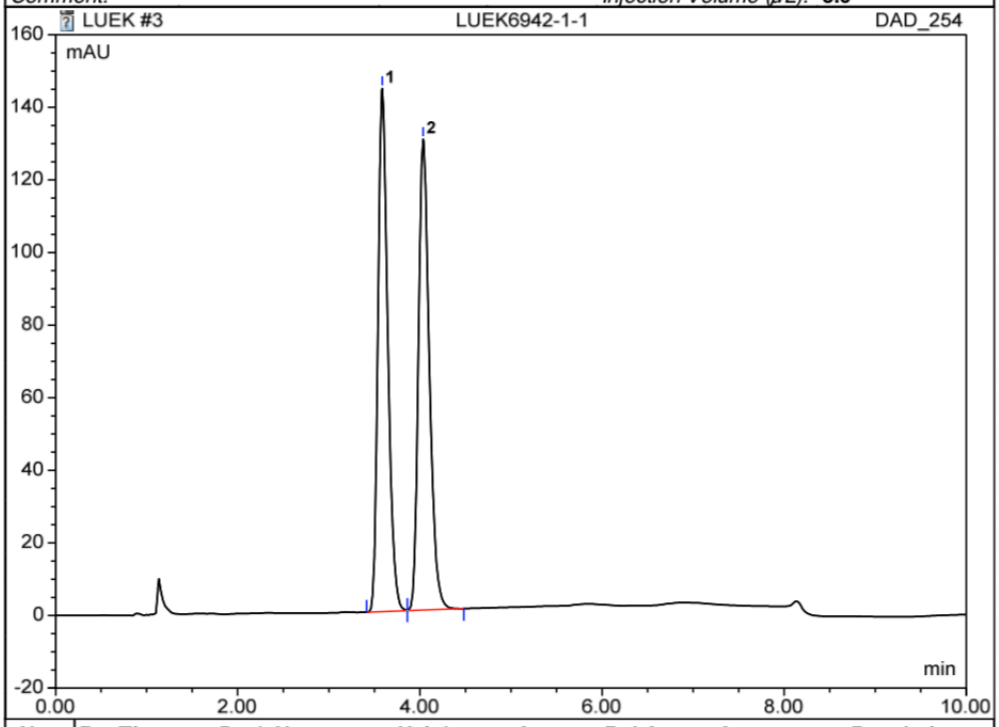
(*rac*)-4-(phenylsulfinyl)piperidine (62a)



Compound was purchased from Sigma-Aldrich.

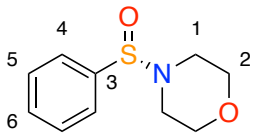
BPH-GDD-GCGE-MCB-MC5-HPLC

Sample Name:	**LUEK6942-1-1**	*Recording Date:*	**28.11.17 14:35**
Sample ID:	**4883796**		
Method:	**Enantiomerenbest**		
Column:	**Chiralpak IC 3µ 100x4.6**		
Solvent:	**20-50% IPA/Hexan in 7min**	*Wavelength (nm):*	**DAD_254**
Puffer:		*Flow (ml/min):*	**1.40**
Gradient:	**S3_20_50_IPA_HEXAN**	*Run Time (min):*	**10.00**
Solution:		*Vial Number:*	**P1:A3**
Comment:		*Injection Volume (µL):*	**5.0**



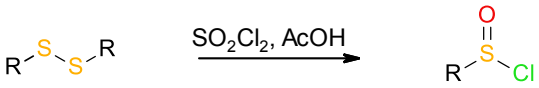
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	3.59		144.116	17.997	49.98	n.a.	2.2
2	4.04		129.741	18.008	50.02	n.a.	n.a.
Total:			273.857	36.004	100.00	0.000	

(*S*)-4-(phenylsulfinyl)morpholine (62g*)



Prepared according to **general procedure H**, by reacting intermediate **216b** (100 mg, 0.22 mmol, 1.00 equiv) with morpholine (77 mg, 0.88 mmol, 4.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **62g*** as a colourless oil (20.5 mg, 43%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 2H, 4-H), 7.56–7.48 (m, 3H, 6-H and 5-H), 3.78–3.68 (m, 4H, 1-H or 2-H), 3.18 (m, 2H, 2-H or 1-H), 3.01–2.94 ppm (m, 2H, 2-H or 1-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.2 (3-C), 131.1 (6-C), 128.9 (5-C), 126.2 (4-C), 66.9 (1-C or 2-C), 45.8 (1-C or 2-C) ppm; IR (KBr): ν = 1439, 1257, 1051, 906, 756, 694 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{14}NO_2S$: 212.0745, found: 212.0744.

General procedure I: synthesis of sulfinyl chlorides

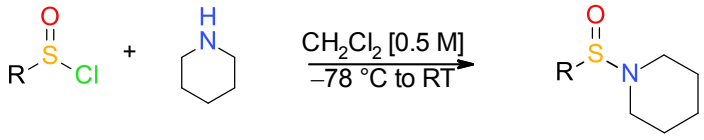


Prepared according to a published procedure, with slight modifications.[270]

The disulfide (1.96 mmol, 1.00 equiv) and acetic acid (0.22 mL, 3.93 mmol, 2.00 equiv) were cooled to the temperature indicated in the table below. Sulfuryl chloride (0.49 mL, 6.09 mmol, 3.10 equiv) was added dropwise over 30 min. The reaction mixture was stirred at –20 °C for the time indicated in the table and then slowly allowed to warm to RT over 2 h (gas evolution observed). Finally, the mixture was warmed to 35 °C for 1 h and concentrated under reduced pressure (without further warming). The crude product was used without further purification.

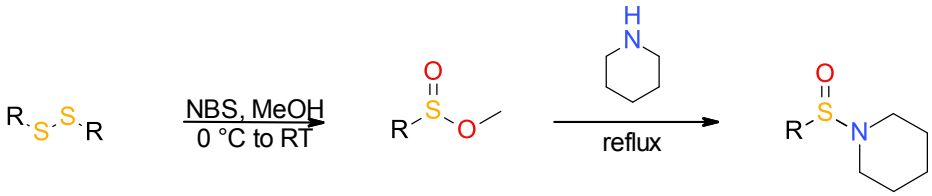
R	Temp (°C)	Time (h)
4-$MeOC_6H_4$	–40	3
4-$O_2NC_6H_4$	–40	3
4-FC_6H_4	–40	3
3-ClC_6H_4	–40	2
3-$F_3CC_6H_4$	–20	3
*i*Pr	–40	1
2-ClC_6H_4	–40	3

General procedure L: synthesis of sulfinamides 62m-v



A solution of piperidine (2.5 equiv) in CH_2Cl_2 [0.5 M] was cooled to –78 °C. The freshly prepared sulfinyl chloride (1.0 equiv) was diluted in CH_2Cl_2 [1.0 M], and added dropwise to the frozen mixture over 15 min. After 10 min, the temperature was raised and the mixture was stirred at RT overnight. The reaction mixture was quenched by addition of an aqueous, saturated $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 ×). The combined organic layers were washed with brine (3 ×), collected and dried over water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

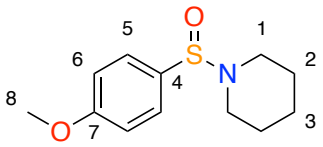
General procedure J: synthesis of (piperidinylsulfinyl)pyridines 62w, 62y



Compounds prepared according to published procedures[272,273]

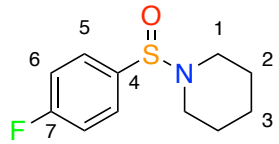
NBS (969 mg, 5.40 mmol, 3.00 equiv) was added to a solution of the disulfide (400 mg, 1.80 mmol, 1.00 equiv) in methanol (9 mL) at 0 °C and the reaction mixture was stirred at this temperature for 10 min. The ice bath was removed and the reaction mixture was stirred at RT for 2–3 h until the colour of the solution changed from bright orange to colourless. Aqueous, saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with water (2 ×), filtered over water-repellent filter paper and concentrated to give the crude product, which was purified by flash column chromatography. The collected product (310 mg, 2.0 mmol, 1.00 equiv) was immediately reacted with piperidine (504 mg, 5.90 mmol, 3.00 equiv) in a sealed microwave tube flushed with argon, and the mixture was heated to reflux for 3 h. Then, aqueous, saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (3 ×). The combined extracts were washed with brine (3 ×) and dried over water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

1-[(4-Methoxyphenyl)sulfinyl]piperidine (62m)



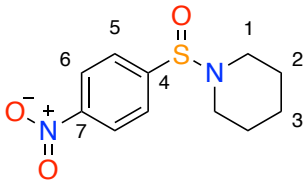
Prepared according to **general procedure L**, by reacting 4-methoxybenzenesulfinyl chloride (250 mg, 1.31 mmol, 1.00 equiv) with piperidine (279 mg, 3.28 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **62m** as a colourless oil (170 mg, 54%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.9 Hz, 2H, 6-H), 7.00 (d, J = 8.9 Hz, 2H, 5-H), 3.86 (s, 3H, 8-H), 3.12–3.07 (m, 2H, 1-H_a), 2.98–2.92 (m, 2H, 1-H_a), 1.66–1.48 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.5 (7-C), 134.5 (4-C), 127.8 (6-C), 114.1 (5-C), 55.4 (1-C), 46.7 (2-C), 26.1 (8-C), 23.9 (3-C) ppm; IR (KBr): ν = 2935, 1593, 1493, 1248, 1088, 1061, 1026, 908, 831, 565 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{18}NO_2S$: 240.1058, found: 240.1058.

1-[(4-Fluorophenyl)sulfinyl]piperidine (62n)



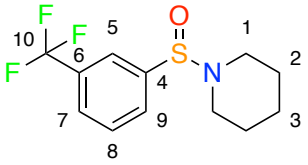
Prepared according to **general procedure L**, by reacting 4-fluorobenzenesulfinyl chloride (493 mg, 2.76 mmol, 1.00 equiv) with piperidine (578 mg, 6.90 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **92m** as a white solid (152 mg, 24%): m.p. 99–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 2H, 6-H), 7.23–7.16 (m, 2H, 5-H), 3.14–3.09 (m, 2H, 1-H_a), 2.97–2.92 (m, 2H, 1-H_b), 1.68–1.51 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2 (d, J = 250.9 Hz, 7-C), 139.0 (d, J = 3.0 Hz, 4-C), 128.5 (d, J = 8.9 Hz, 5-C), 115.9 (d, J = 22.5 Hz, 6-C), 46.9 (1-C), 26.1 (2-C), 23.9 (3-C) ppm; IR (KBr): ν = 2943, 1583, 1489, 1221, 1059, 902, 845, 569 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{15}NOSF$: 228.0858, found: 228.0862.

1-[(4-Nitrophenyl)sulfinyl]piperidine (62o)



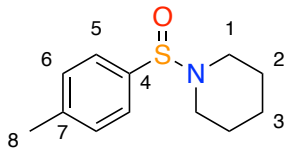
Prepared according to **general procedure L**, by reacting 4-nitrobenzenesulfinyl chloride (320 mg, 1.56 mmol, 1.00 equiv) with piperidine (331 mg, 3.89 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62o** as a yellow solid (221 mg, 56%): m.p. 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, J = 8.9 Hz, 2H, 6-H or 5-H), 7.87 (d, J = 8.9 Hz, 2H, 5-H or 6-H), 3.20–3.15 (m, 2H, 1-H_a), 2.99–2.94 (m, 2H, 1-H_b), 1.70–1.53 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.6 (7-C), 137.1 (4-C), 127.6 (6-C or 5-C), 123.9 (5-C or 6-C), 47.5 (1-C), 26.1 (2-C), 23.6 (3-C) ppm; IR (KBr): ν = 2949, 1518, 1340, 1082, 1063, 916, 851, 687, 567 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_3S$: 255.0803, found: 255.0806.

1-{[3-(Trifluoromethyl)phenyl]sulfinyl}piperidine (62p)



Prepared according to **general procedure L**, by reacting 4-(trifluoromethyl)benzenesulfinyl chloride (430 mg, 1.88 mmol, 1.00 equiv) with piperidine (400 mg, 4.70 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62p** as a colourless oil (84 mg, 16%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1H, 5-H), 7.86 (d, J = 7.9 Hz, 1H, 9-H or 7-H), 7.75–7.73 (m, 1H, 7-H or 9-H), 7.64 (t, J = 7.9 Hz, 1H, 8-H), 3.18–3.11 (m, 2H, 1-H_a), 2.98-2.93 (m, 2H, 1-H_b), 1.70–1.51 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.1 (4-C), 131.5 (q, J = 33.1 Hz, 6-C), 129.7 (d, J = 1.3 Hz, 8-C), 129.4 (9-C), 127.5 (q, J = 3.4 Hz, 7-C or 5-C), 123.6 (q, J = 273.0 Hz, 10-C), 123.5 (q, J = 3.8 Hz, 7-C or 5-C), 47.2 (1-C), 26.1 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 2939, 1321, 1124, 1065, 910, 802, 698 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{15}NOSF_3$: 278.0826, found: 278.0830.

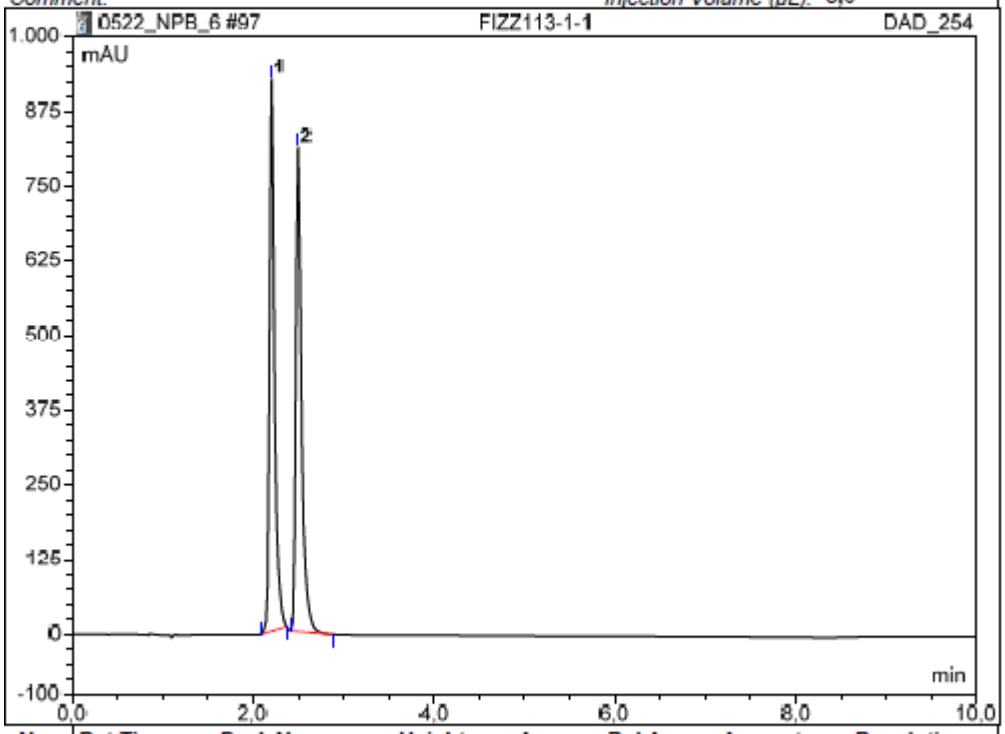
(*rac*)-1-[(4-Methylphenyl)sulfinyl]piperidine (62q)



4-Methylbenzenesulfinyl chloride was prepared according to a published procedure.[271]

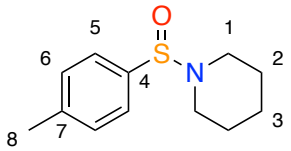
Compound **62q** was prepared according to **general procedure L**, by reacting 4-methylbenzenesulfinyl chloride (500 mg, 2.86 mmol) with piperidine (609 mg, 7.16 mmol). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62q** as a white solid (533 mg, 83%): m.p. 64–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.4 Hz, 2H, 5-H), 7.32–7.28 (m, 2H, 6-H), 3.14–3.07 (m, 2H, 1-H_a), 2.99–2.92 (m, 2H, 1-H_b), 2.42 (s, 3H, 8-H), 1.68–1.47 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.9 (7-C), 140.2 (4-C), 129.5 (6-C), 126.2 (5-C), 46.8 (1-C), 26.1 (8-C), 23.9 (2-C), 21.3 (3-C) ppm; IR (KBr): ν = 2939, 2833, 1448, 1207, 1084, 1061, 893, 818, 565 cm^{-1} ; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{18}NOS$: 224.1109, found: 224.1110. Analytical data are in agreement with literature data.[314] Chiral HPLC: instrument: Agilent HPLC 1260; column: Chiralpak IG 3 mm, 100 × 4.6 mm; eluent A: hexane + 0.1 vol% diethylamine (99%), eluent B: EtOH; gradient: 0–7 min 20–50% B; flow: 1.4 mL/min; temperature: 25 °C; DAD: 254 nm.

Column:	Chiralpak IG 3µ 100x4.6		
Solvent:	20-50% EtOH/Hexan in 7min	*Wavelength (nm):*	DAD_254
Puffer:	+ 0.1% DEA	*Flow (ml/min):*	1,40
Gradient:	S6_20_50_ETOH_HEXAN_DEA	*Run Time (min):*	10,00
Solution:		*Vial Number:*	P1:F3
Comment:		*Injection Volume (µL):*	5,0



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	2,21		924,418	59,812	50,20	n.a.	2,9
2	2,50		810,533	59,347	49,80	n.a.	n.a.
Total:			1734,951	119,159	100,00	0,000	

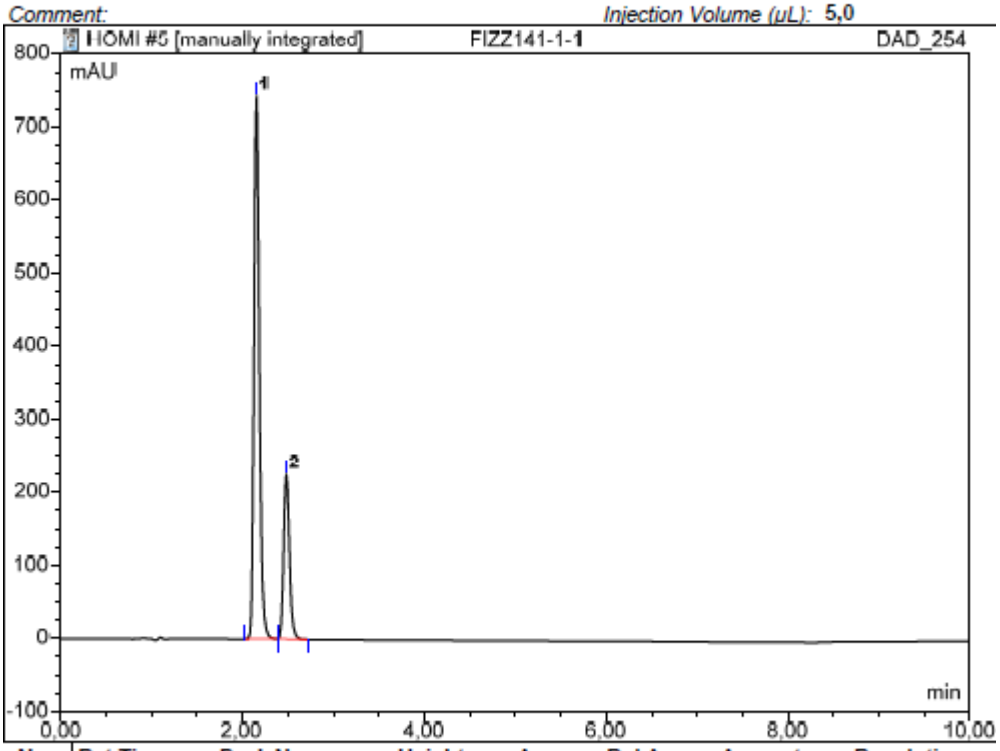
(+)-1-[(4-Methylphenyl)sulfinyl]piperidine (62q*)



Prepared according to a published procedure.[127]

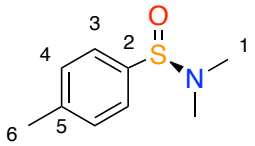
$[\alpha]_D$ = +59.8 (c = 1.0 in DMSO); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, J = 8.4 Hz, 2H), 7.32–7.28 (m, 2H), 3.14–3.07 (m, 2H), 2.99–2.92 (m, 2H), 2.42 (s, 3H), 1.68–1.47 ppm (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 140.9, 140.2, 129.5, 126.2, 46.8, 26.1, 23.9, 21.3 ppm; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{18}NOS$: 224.1109, found: 224.1110; chiral HPLC: instrument: Agilent HPLC 1260; column: Chiralpak IG 3 mm, 100 × 4.6 mm; eluent A: hexane + 0.1 vol% diethylamine (99%), eluent B: EtOH; gradient: 0–7 min 20–50% B; flow: 1.4 mL/min; temperature: 25 °C; DAD: 254 nm; 51% ee.

Column:	Chiralpak IG 3µ 100x4.6		
Solvent:	20-50% EtOH/Hexan in 7min	*Wavelength (nm):*	DAD_254
Puffer:	+0.1% DEA	*Flow (ml/min):*	n.a.
Gradient:	S6_20_50_ETOH_HEXAN_DEA	*Run Time (min):*	10,00
Solution:		*Vial Number:*	P2:A2
Comment:		*Injection Volume (µL):*	5,0



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	2,16		743,741	51,003	75,36	n.a.	3,0
2	2,48		226,081	16,674	24,64	n.a.	n.a.
Total:			969,822	67,677	100,00	0,000	

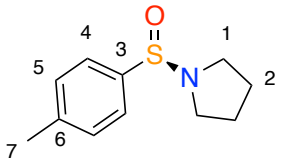
(*R*)-*N, N*-4-Trimethylbenzenesulfinamide(221a)



Prepared according to a published procedure.[127]

Compound **221a** was prepared by reacting 4-methylbenzenesulfinyl chloride (300 mg, 1.02 mmol, 1.00 equiv) with dimethylamine (46 mg, 1.02 mmol, 1.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **221a** as a white oil (108 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.2 Hz, 2H, 3-H), 7.29 (d, J = 8.2 Hz, 2H, 4-H), 2.65 (s, 6H, 1-H), 2.40 ppm (s, 3H, 6-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.3 (5-C), 140.6 (2-C), 129.7 (4-C), 126.1 (3-C), 37.3 (1-C), 21.5 (6-C) ppm; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{14}NOS$: 184.0796, found: 184.0797. Analytical data are in agreement with literature data.[127]

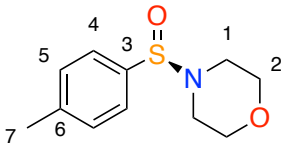
(*R*)-1-(*p*-Tolylsulfinyl)pyrrolidine(221b)



Prepared according to a published procedure.[127]

Compound **221b** was prepared by reacting 4-methylbenzenesulfinyl chloride (300 mg, 1.02 mmol, 1.00 equiv) with pyrrolidine (145 mg, 2.04 mmol, 2.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **221b** as a white oil (122 mg, 57%); $[\alpha]_D$ = +3.7 (*c* = 1.0 in DMSO); lit:[315] $[\alpha]_D$ = - 175.0 (*c* =1.2, EtOH);^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.3 Hz, 2H, 4-H), 7.28 (d, *J* = 8.3 Hz, 2H, 5-H), 3.33 (qd, *J* = 7.0, 2.8 Hz, 2H, 1-H_a), 3.00 (qd, *J* = 7.0, 2.8 Hz, 2H, 1-H_b), 2.40 (s, 3H, 7-H), 1.89 – 1.79 ppm (m, 4H, 2-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.6 (6-C), 140.9 (3-C), 129.6 (5-C), 125.9 (4-C), 46.1 (1-C), 26.1 (2-C), 21.5 (7-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + H]$^+$ calcd for $C_{11}H_{16}NOS$: 210.0953, found: 210.0952. Analytical data are in agreement with literature data.[127]

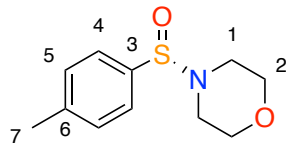
(*R*)-4-(*p*-Tolylsulfinyl)morpholine (221c)



Prepared according to a published procedure.[127]

Compound **221c** was prepared by reacting 4-methylbenzenesulfinyl chloride (300 mg, 1.02 mmol, 1.00 equiv) with morpholine (177 mg, 2.04 mmol, 2.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **221c** as a white oil (116 mg, 51%); $[\alpha]_D$ = +17.3 (*c* = 1.0 in DMSO); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.3 Hz, 2H, 4-H), 7.32 (d, *J* = 8.3 Hz, 2H, 5-H), 3.76 – 3.67 (m, 4H, 2-H), 3.15 (app dddd, *J* = 12.1, 6.3, 3.5, 1.0 Hz, 2H, 1-H_a), 2.96 (app dddd, *J* = 12.2, 6.3, 3.5, 1.0 Hz, 2H, 1-H_b), 2.42 ppm (s, 3H, 7-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.6 (6-C), 139.2 (3-C), 129.8 (5-C), 126.3 (4-C), 67.1 (2-C), 45.8 (1-C), 21.5 (7-C) ppm; HRMS (ESI-TOF) *m/z* [*M* + H]$^+$ calcd for $C_{11}H_{16}NO_2S$: 226.0902, found: 226.0896. Analytical data are in agreement with literature data.[127]

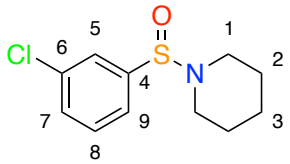
(*S*)-4-(*p*-Tolylsulfinyl)morpholine (221d)



Prepared according to a published procedure.[127]

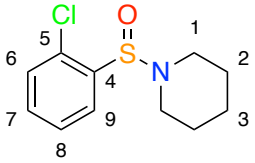
Compound **221d** was prepared by reacting 4-methylbenzenesulfinyl chloride (100 mg, 0.34 mmol, 1.00 equiv) with morpholine (62 mg, 0.72 mmol, 2.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **221d** as a white oil (24 mg, 32%); $[\alpha]_D$ = -2.5 (*c* = 1.0 in $CHCl_3$); lit:[127] $[\alpha]_D$ = - 2.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.3 Hz, 2H, 4-H), 7.32 (d, *J* = 8.3 Hz, 2H, 5-H), 3.76 – 3.67 (m, 4H, 2-H), 3.15 (app dddd, *J* = 12.1, 6.3, 3.5, 1.0 Hz, 2H, 1-H_a), 2.96 (app dddd, *J* = 12.2, 6.3, 3.5, 1.0 Hz, 2H, 1-H_b), 2.42 ppm (s, 3H, 7-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.6 (6-C), 139.2 (3-C), 129.8 (5-C), 126.3 (4-C), 67.1 (2-C), 45.8 (1-C), 21.5 (7-C) ppm; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{16}NO_2S$: 226.0902, found: 226.0896. Analytical data are in agreement with literature data.[127]

1-[(3-Chlorophenyl)sulfinyl]piperidine (62r)



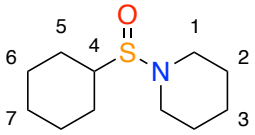
Prepared according to **general procedure L**, by reacting 3-chlorobenzenesulfinyl chloride (502 mg, 2.57 mmol, 1.00 equiv) with piperidine (547 mg, 6.43 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **62r** as a yellow solid (422 mg, 67%): m.p. 62–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 1H, 5-H), 7.56–7.52 (m, 1H, 8-H), 7.46–7.42 (m, 2H, 7-H and 9-H), 3.16–3.10 (m, 2H, 1-H_a), 2.99–2.94 (m, 2H, 1-H_b), 1.67–1.49 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.6 (6-C), 135.1 (4-C), 130.8 (5-C or 7-C or 8-C or 9-C), 130.0 (5-C or 7-C or 8-C or 9-C), 126.4 (5-C or 7-C or 8-C or 9-C), 124.4 (5-C or 7-C or 8-C or 9-C), 47.1 (1-C), 26.1 (2-C), 23.8 (3-C) ppm; IR (KBr): ν = 2939, 1448, 1213, 1061, 897, 793, 677 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{11}H_{15}NOSCl$: 244.0563, found: 244.0564.

1-[(2-Chlorophenyl)sulfinyl]piperidine (62s)



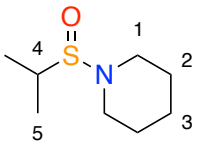
Prepared according to **general procedure L**, by reacting 2-chlorobenzenesulfinyl chloride (500 mg, 2.56 mmol, 1.00 equiv) with piperidine (546 mg, 6.41 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–80% EtOAc in hexane) to give **62s** as a colourless oil (348 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.4 Hz, 1H, 6-H), 7.48–7.38 (m, 3H, 7-H and 8-H and 9-H), 3.19–3.11 (m, 2H, 1-H_a), 2.98 (ddd, J = 12.2, 7.1, 2.8 Hz, 2H, 1-H_b), 1.64–1.49 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.5 (5-C), 132.4 (4-C), 131.9 (6-C or 7-C or 8-C or 9-C), 130.4 (6-C or 7-C or 8-C or 9-C), 127.7 (6-C or 7-C or 8-C or 9-C), 126.7 (6-C or 7-C or 8-C or 9-C), 46.5 (1-C), 26.1 (2-C), 24.0 (3-C) ppm; IR (KBr): ν = 3547, 2935, 1445, 1082, 1028, 908, 758 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{15}NOSCl$: 244.0563, found: 244.0566.

1-(Cyclohexylsulfinyl)piperidine (62t)



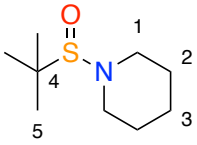
Prepared according to **general procedure L**, by reacting cyclohexanesulfinyl chloride (620 mg, 3.72 mmol, 1.00 equiv) with piperidine (633 mg, 7.44 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–80% EtOAc in hexane) to give **62t** as a colorless oil (665 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.20–3.10 (m, 2H, 1-H_a), 3.10–2.98 (m, 2H, 1-H_b), 2.75–2.62 (m, 1H, 4-H), 2.13–2.08 (m, 1H, 5-H_a), 1.92–1.84 (m, 1H, 5-H_a), 1.79–1.76 (m, 2H, 6-H_a), 1.69–1.61 (m, 5H, 2-H and 5-H_b), 1.57–1.51 (m, 2H, 7-H), 1.42–1.17 ppm (m, 5H, 3-H, 6-H_b and 5-H_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 58.9 (4-C), 47.1 (1-C), 27.3, 26.8, 26.2, 25.5, 25.3, 24.2 ppm; IR (KBr): ν = 2924, 2851, 1447, 1061, 908 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{22}NOS$: 216.1422, found: 216.1422.

1-(Isopropylsulfinyl)piperidine (62u)



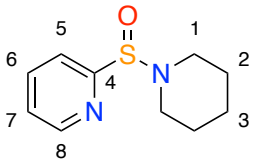
Prepared according to **general procedure L**, by reacting propane-2-sulfinyl chloride (600 mg, 4.74 mmol, 1.00 equiv) with piperidine (1.00 g, 11.8 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **62u** as a colourless oil (418 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.17–3.12 (m, 2H, 1-H_a), 3.07–3.01 (m, 2H, 1-H_a), 2.90 (sept, J = 6.8 Hz, 1H, 4-H), 1.70–1.50 (m, 6H, 2-H and 3-H), 1.30 (d, J = 6.8 Hz, 3H, 5-H_a), 1.11 ppm (d, J = 6.8 Hz, 3H, 5-H_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 51.0 (4-C), 47.1 (1-C), 26.1 (2-C), 24.2 (3-C), 17.1 (5-C), 16.8 (5-C) ppm; IR (KBr): ν = 2962, 1456, 1149, 1024, 947, 713 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{18}NOS$: 176.1109, found: 176.1109.

1-(*tert*-Butylsulfinyl)piperidine (62v)



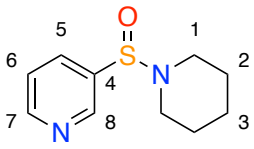
Prepared according to **general procedure L**, by reacting commercial 2-methylpropane-2-sulfinyl chloride (250 mg, 1.78 mmol, 1.00 equiv; Sigma-Aldrich) with piperidine (378 mg, 4.44 mmol, 2.50 equiv). Crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **62v** as a yellow oil (288 mg, 86%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.16–3.07 (m, 2H, 1-H_a), 3.02–2.94 (m, 2H, 1-H_b), 1.62–1.53 (m, 6H, 2-H and 3-H), 1.16 ppm (s, 9H, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 58.2 (4-C), 47.9 (1-C), 26.2 (2-C), 24.5 (3-C), 23.2 (5-C) ppm; IR (KBr): ν = 2934, 1454, 1360, 1078, 908, 675 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{20}NOS$: 190.1266, found: 190.1265.

2-(Piperidin-1-ylsulfinyl)pyridine (62w)



Prepared according to **general procedure J**, by reacting methyl pyridine-2-sulfinate (310 mg, 1.97 mmol, 1.00 equiv) with piperidine (504 mg, 5.92 mmol, 3.00 equiv). Crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **62w** as a white solid (160 mg, 39%): m.p. 40–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H, 8-H), 8.03–7.99 (m, 1H, 5-H), 7.92 (app td, J = 7.6, 1.8 Hz, 1H, 7-H or 6-H), 7.40 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H, 6-H or 7-H), 3.23–3.14 (m, 2H, 1-H_a), 2.97–2.89 (m, 2H, 1-H_b), 1.72–1.47 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.7 (4-C), 149.9 (8-C or 5-C), 137.4 (8-C or 5-C), 124.9 (6-C or 7-C), 121.5 (6-C or 7-C), 47.1 (1-C), 26.0 (2-C), 23.9 (3-C) ppm; IR (KBr): ν = 3043, 2939, 1574, 1419, 1024, 773, 563 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{15}N_2OS$: 211.0905, found: 211.0905.

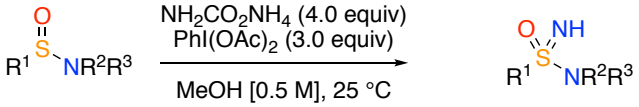
3-(Piperidin-1-ylsulfinyl)pyridine (62y)



Prepared according to **general procedure J**, by reacting methyl pyridine-3-sulfinate (511 mg, 3.25 mmol, 1.00 equiv) with piperidine (830 mg, 9.75 mmol, 3.00 equiv). Crude purified by flash column chromatography (NH-Sil, 0–100% EtOAc in hexane) to give **62y** as a yellow-orange oil (248 mg, 36%): ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 8.61 (d, J = 2.3 Hz, 1H, 8-H), 8.48 (dd, J = 4.8, 2.0 Hz, 1H, 7-H), 8.03 (app dt, J = 7.7, 2.0 Hz, 1H, 6-H), 7.36 (dd, J = 7.7, 4.8 Hz, 1H, 5-H), 2.93-2.91 (m, 4H, 1-H_a), 1.61 (app quint, J = 5.8 Hz, 2-H), 1.53 – 1.49 ppm (m, 2H, 3-H); ^{13}C NMR (126 MHz, [D_6]DMSO): δ = 153.7 (1-C), 149.1 (7-C), 146.6 (8-C), 132.1 (5-C), 123.4 (6-C), 47.3 (1-C), 26.1 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 2937, 2853, 1571, 1412, 1070, 912, 706 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{15}N_2OS$: 211.0905, found: 211.0906.

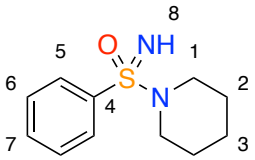
4.7 Preparation of sulfonimidamides

General procedure K: synthesis of sulfonimidamides 62a-z and 48a-b



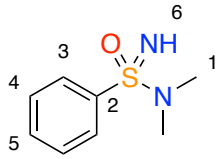
To the sulfinamide (0.48 mmol, 1.00 equiv) were added $PhI(OAc)_2$ (1.43 mmol, 3.00 equiv), ammonium carbamate (1.91 mmol, 4.00 equiv) and finally MeOH (0.96 mL). The mixture was stirred in an open flask at RT for 0.5–2 h. When all the starting material had been consumed (as monitored by TLC and UPLC-MS), saturated aqueous $NaHCO_3$ solution and EtOAc were added, and the mixture was stirred for 5 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 ×). The organic phases were combined, washed with brine (3 ×) and dried over water-repellent filter paper. The volatiles were removed under reduced pressure and the crude product was purified by flash column chromatography.

1-(*S*-Phenylsulfonimidoyl)piperidine (55a)



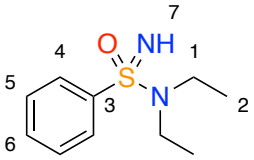
Prepared according to **general procedure K**, from commercial 1-(phenylsulfinyl)piperidine (Sigma-Aldrich); crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **55a** as a yellow-orange solid (105 mg, 94%): m.p. 99–100 °C; ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.79–7.74 (m, 2H, 5-H), 7.66–7.61 (m, 1H, 7-H), 7.60–7.55 (m, 2H, 6-H), 4.29 (s, 1H, 8-H), 2.91–2.74 (m, 4H, 1-H), 1.56–1.44 (m, 4H, 2-H), 1.30 ppm (q, J = 5.8 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.6 (4-C), 132.0 (7-C), 128.7 (6-C), 127.7 (5-C), 47.4 (1-C), 25.2 (2-C), 23.2 (3-C) ppm; IR (KBr): ν = 3234, 2989, 2933, 2837, 1445, 1256, 907, 721, 687, 575 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{17}N_2OS$: 225.1062, found: 225.1066.

***N,N*-Dimethylbenzenesulfonimidamide (55b)**



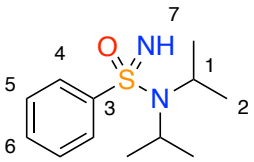
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **55b** as a white solid (64 mg, 72%): m.p. 74–75 °C; ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.75 (d, J = 7.6 Hz, 2H, 3-H), 7.63–7.59 (m, 1H, 5-H), 7.58–7.54 (m, 2H, 4-H), 4.33 (s, 1H, 6-H), 2.50 ppm (s, 6H, 1-H); ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 135.8 (2-C), 132.1 (5-C), 128.8 (4-C), 127.8 (3-C), 38.6 (1-C) ppm; IR (KBr): ν = 3283, 2953, 1443, 1252, 1130, 937, 717, 663 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_{13}N_2OS$: 185.0749, found: 185.0750.

***N,N,N*-Diethylbenzenesulfonimidoamide (55c)**



Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **55c** as a colourless oil (78 mg, 77%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.85–7.80 (m, 2H, 4-H), 7.61–7.50 (m, 3H, 5-H and 6-H), 4.23 (s, 1H, 7-H), 3.31–3.04 (m, 4H, 1-H), 0.98 ppm (app t, J = 7.1 Hz, 6H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 141.9 (3-C), 132.2 (6-C), 129.5 (5-C), 127.4 (4-C), 42.9 (1-C), 15.0 (2-C) ppm; IR (KBr): ν = 3275, 2974, 1445, 1244, 993, 687 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{17}N_2OS$: 213.1062, found: 213.1060.

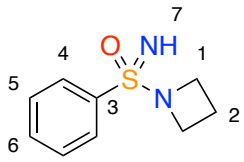
***N,N*-Diisopropylbenzenesulfonimidoamide (55d)**



Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **55d** as a white solid (20 mg, 17%): m.p. 80–81 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.88 (d, J = 6.5 Hz, 2H, 4-H), 7.56–7.46 (m, 3H, 5-H and 6-H), 4.20 (s, 1H, 7-H), 3.76 (sept, J = 6.8 Hz, 2H, 1-H), 1.22 (d, J = 6.8 Hz, 6H, 2-H), 0.98 ppm (d, J = 6.8 Hz, 6H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 144.2 (3-C), 131.2 (6-C), 128.6 (4-C), 126.8 (5-C), 48.1 (1-C), 23.0 (2-C),

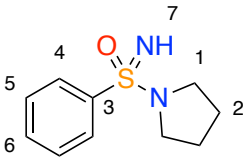
20.8 (2-C) ppm; IR (KBr): ν = 3261, 2972, 1445, 1244, 1157, 1119, 991, 957, 752, 689, 636, 565 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{21}N_2OS$: 241.1375, found: 241.1374.

1-(*S*-Phenylsulfonimidoyl)azetidine (55e)



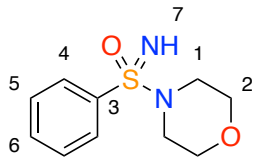
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–70% EtOAc in hexane) to give **55e** as a white solid (67 mg, 71%): m.p. 81–82 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.88–7.79 (m, 2H, 4-H), 7.72–7.61 (m, 3H, 5-H and 6-H), 4.25 (*brs*, 1H, 7-H), 3.57–3.44 (m, 4H, 1-H), 1.87-1.80 ppm (m, 2H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.2 (3-C), 132.5 (6-C), 128.9 (5-C), 128.5 (4-C), 50.9 (1-C), 13.7 (2-C) ppm; IR (KBr): ν = 3250, 2966, 2876, 1443, 1252, 756, 687, 600 cm^{-1}; ESI-MS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{13}N_2OS$: 197.0753, found: 197.0749.

1-(*S*-Phenylsulfonimidoyl)pyrrolidine (55f)



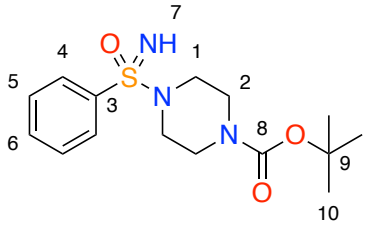
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **55f** as a yellow-orange solid (77 mg, 77%): m.p. 93–94 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.86 (d, J = 7.4 Hz, 2H, 4-H), 7.69–7.50 (m, 3H, 5-H and 6-H), 4.40 (*brs*, 1H, 7-H), 3.05 (app s, 4H, 1-H), 1.57 ppm (app s, 4H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 137.5 (3-C), 132.0 (6-C), 128.8 (5-C), 127.6 (6-C), 48.3 (1-C), 24.8 (2-C) ppm; IR (KBr): ν = 3252, 2964, 1470, 1246, 982, 768, 692, 573 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{15}N_2OS$: 211.0905, found: 211.0904.

4-(*S*-Phenylsulfonimidoyl)morpholine (55g)



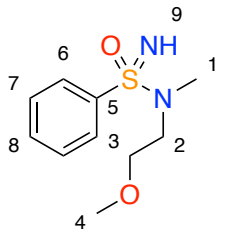
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–70% EtOAc in hexane) to give **55g** as a white solid (83 mg, 77%): m.p. 97–98 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.77 (d, J = 7.7 Hz, 2H, 4-H), 7.70–7.65 (m, 1H, 6-H), 7.64–7.58 (m, 2H, 5-H), 4.52 (s, 1H, 7-H), 3.58 (app t, J = 4.7 Hz, 4H, 2-H), 2.83–2.73 ppm (m, 4H, 1-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.6 (3-C), 132.4 (6-C), 128.9 (5-C), 127.9 (4-C), 65.7 (2-C), 46.8 (1-C) ppm; IR (KBr): ν = 3259, 1254, 924, 723, 688, 602 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{15}N_2O_2S$: 227.0854, found: 227.0856.

***tert*-Butyl 4-(*S*-phenylsulfonimidoyl)piperazine-1-carboxylate (55h)**



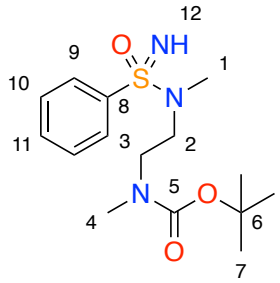
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **55h** as a white solid (101 mg, 65%): m.p. 145–147 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.76 (d, J = 7.1 Hz, 2H, 4-H), 7.68–7.63 (m, 1H, 6-H), 7.62–7.56 (m, 2H, 5-H), 4.57 (s, 1H, 7-H), 3.33 (app s, 4H, 2-H), 2.77 (m, 4H, 1-H), 1.32 ppm (s, 9H, 10-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 153.4 (C-8), 135.9 (3-C), 132.4 (6-C), 128.9 (5-H), 127.8 (4-C), 79.2 (9-C), 46.5 (1-C), 42.9 (2-C), 27.9 (10-C) ppm; IR (KBr): ν = 3234, 2924, 1690, 1416, 1265, 1124, 908, 725, 688, 580 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{24}N_3O_3S$: 326.1538, found: 326.1542.

***N*-(2-Methoxyethyl)-*N*-methylbenzenesulfonimidoamide (55i)**



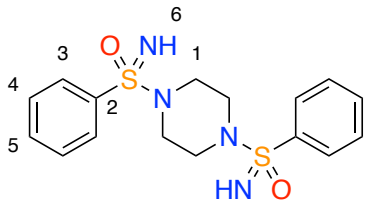
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55i** as a colourless oil (73 mg, 67%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.81 (d, J = 7.7 Hz, 2H, 6-H), 7.63–7.54 (m, 3H, 7-H and 8-H), 4.30 (s, 1H, 9-H), 3.42 (app t, J = 5.8 Hz, 2H, 3-H), 3.21 (s, 3H, 4-H), 3.12–2.99 (m, 2H, 2-H), 2.66 ppm (s, 3H, 1-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.3 (5-C), 131.9 (8-C), 128.9 (7-C), 127.3 (6-C), 70.5 (3-C), 58.0 (4-C), 49.7 (2-C), 36.6 (1-C) ppm; IR (KBr): ν = 3265, 2883, 1447, 1254, 1115, 719, 690 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{17}N_2O_2S$: 229.1011, found: 229.1010.

***tert*-Butyl methyl{2-[methyl(*S*-phenylsulfonimidoyl)amino]ethyl}carbamate (55j)**



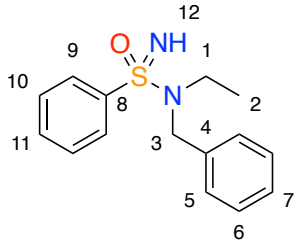
Prepared according to **general procedure K**, but on a different scale (**62j** : 120 mg, 0.38 mmol); crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55j** as a colourless oil (98 mg, 78%): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.81 (d, J = 7.5 Hz, 2H, 9-H), 7.64–7.61 (m, 1H, 11-H), 7.59–7.56 (m, 2H, 10-H), 4.25 (*br*s, 1H, 12-H), 3.29–3.24 (m, 2H, 3-H), 3.01–2.95 (m, 2H, 2-H), 2.80–2.77 (m, 3H, 1-H or 4-H), 2.64 (s, 3H, 4-H or 1-H), 1.38 ppm (s, 9H, 7-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 154.6 (5-C), 138.3 (8-C), 132.0 (11-C), 128.9 (10-C), 127.2 (9-C), 78.6 (6-C), 48.2 (2-C), 46.6 (3-C), 35.9 (4-C or 1-C), 34.4 (1-C or 4-C), 28.1 (7-C) ppm; IR (KBr): ν = 3261, 2974, 1686, 1254, 1155, 717, 690 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{26}N_3O_3S$: 328.1695, found: 328.1695.

1,4-Bis(*S*-phenylsulfonimidoyl)piperazine (55k)



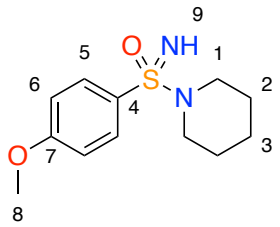
Prepared according to **general procedure K**, but on a different scale (**62k**: 69 mg, 0.2 mmol) and using $PhI(OAc)_2$ (6.0 equiv) and ammonium carbamate (8.0 equiv). No workup was performed. Once the reaction was complete, a white precipitate formed which was collected under vacuum filtration and washed with MeOH to give **55k** as a white solid (38 mg, 50%): m.p. 185–187 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.75–7.69 (m, 4H, 3-H), 7.67–7.61 (m, 2H, 5-H), 7.60–7.53 (m, 4H, 4-H), 4.47 (app d, J = 3.3 Hz, 2H, 6-H), 2.85 ppm (s, 8H, 1-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.0 (2-C), 132.4 (5-C), 128.9 (4-C), 127.6 (3-C), 46.2 (1-C) ppm; IR (KBr): ν = 3277, 2854, 1242, 1090, 935, 721, 688, 590 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{21}N_4O_2S_2$: 365.1106, found: 365.1104.

***N*-Benzyl-*N*-ethylbenzenesulfonimidamide (55l)**



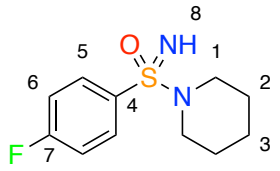
Prepared according to **general procedure K**, but on a different scale (**62l**: 135 mg, 0.52 mmol); crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **55l** as a yellow solid (95.4 mg, 67%): m.p. 66-67 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.91-7.89 (m, 2H, 9-H), 7.64–7.55 (m, 3H, 10-H and 11-H), 7.37–7.29 (m, 4H, 5-H and 6-H), 7.28–7.23 (m, 1H, 7-H) 4.48 (*br*s, 1H, 12-H), 4.33 (d, J = 14.9 Hz, 3-H$_a$), 4.24 (d, J = 14.9 Hz, 3-H$_b$), 3.08 (app ddt, J = 18.0, 14.3, 7.1 Hz, 2H, 1-H), 0.74 ppm (app t, J = 7.1 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 141.3 (4-C), 138.1 (8-C), 131.7 (11-C), 128.9 (10-C), 128.2 (5-C or 6-C), 128.0 (6-C or 5-C), 127.2 (7-C), 126.8 (9-C), 51.4 (3-C), 42.8 (1-C), 13.4 (2-C) ppm; IR (KBr): ν = 3285, 3260, 2853, 1447, 1249, 970, 884 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}N_2OS$: 275.1213, found: 275.1235.

1-[*S*-(4-Methoxyphenyl)sulfonimidoyl]piperidine (55m)



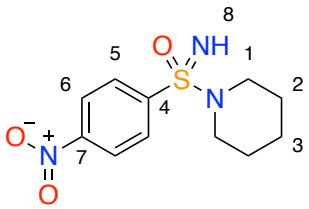
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **55m** as a yellow oil (106 mg, 87%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.77–7.66 (m, 2H, 5-H or 6-H), 7.14–7.06 (m, 2H, 6-H or 5-H), 4.13 (s, 1H, 9-H), 3.83 (s, 3H, 8-H), 2.85–2.73 (m, 4H, 1-H), 1.56–1.43 (m, 4H, 2-H), 1.35–1.22 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 161.9 (7-C), 129.8 (5-C or 6-C), 128.2 (4-C), 113.8 (6-C or 5-C), 55.6 (8-C), 47.4 (1-C), 25.7 (2-C), 23.2 (3-C) ppm; IR (KBr): ν = 3281, 2934, 2837, 1593, 1495, 1246, 1128, 910, 833, 700, 573 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{19}N_2O_2S$: 255.1167, found: 255.1169.

1-[*S*-(4-Fluorophenyl)sulfonimidoyl]piperidine (55n)



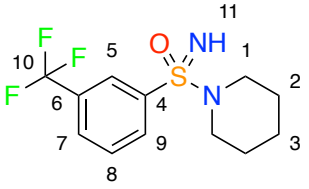
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **55n** as a yellow oil (100 mg, 89%): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.81 (dd, J = 9.0, 5.7 Hz, 2H, 5-H), 7.41 (app t, J = 9.0 Hz, 2H, 6-H), 4.38 (s, 1H, 8-H), 2.88–2.74 (m, 4H, 1-H), 1.58–1.43 (m, 4H, 2-H), 1.35–1.24 ppm (m, 2H, 3-H); ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 164.2 (d, J = 249.9 Hz, 1C, 7-C), 133.2 (d, J = 2.5 Hz, 1C, 4-C), 130.7 (d, J = 9.5 Hz, 2C, 5-C), 115.9 (d, J = 22.9 Hz, 2C, 6-C), 47.5 (1-C), 25.3 (2-C), 23.2 (3-C) ppm; IR (KBr): ν = 3279, 2937, 2853, 1587, 1489, 1252, 1132, 912, 837, 700, 569 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}N_2OSF$: 243.0967, found: 243.0965.

1-[*S*-(4-Nitrophenyl)sulfonimidoyl]piperidine (55o)



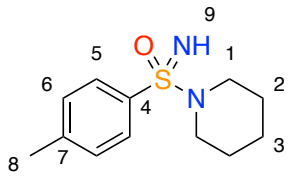
Prepared according to general procedure **K**; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **55o** as a yellow solid (80 mg, 62%): m.p. 134–135 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.40 (d, J = 8.6 Hz, 2H, 5-H), 8.00 (d, J = 8.6 Hz, 2H, 6-H), 4.76 (s, 1H, 8-H), 2.94–2.79 (m, 4H, 1-H), 1.57–1.45 (m, 4H, 2-H), 1.37–1.18 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 149.4 (7-C), 142.9 (4-C), 129.1 (6-C), 123.9 (5-C), 47.0 (1-C), 24.9 (2-C), 22.8 (3-C) ppm; IR (KBr): ν = 3281, 2928, 2856, 1522, 1346, 1240, 995, 932, 852, 731, 561 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}N_3O_3S$: 270.0912, found: 270.0912.

1-{*S*-[3-(Trifluoromethyl)phenyl]sulfonimidoyl}piperidine (55p)



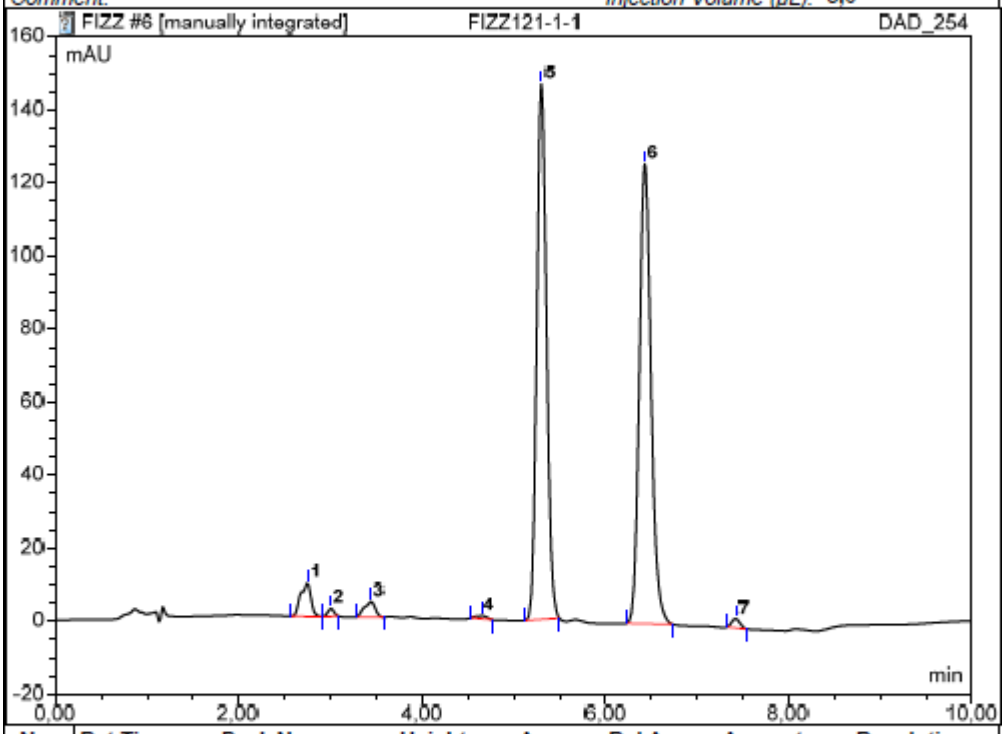
Prepared according to **general procedure K**, but on a different scale (**62p**: 60 mg, 0.2 mmol); crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **55p** as a white solid (51 mg, 81%): m.p. 103–105 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.07–8.02 (m, 2H, 7-H and 9-H), 7.99 (s, 5-H), 7.85 (app t, J = 7.8 Hz, 1H, 8-H), 4.69 (s, 1H, 11-H), 2.91–2.82 (m, 4H, 1-H), 1.51 (app quin, J = 5.6 Hz, 4H, 2-H), 1.31 ppm (quin, J = 5.6 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.4 (4-C), 131.6 (8-C or 9-C), 130.5 (9-C or 8-C), 129.5 (q, J = 32.6 Hz, 6-C), 128.7 (q, J = 3.7 Hz, 5-C or 7-C), 123.9 (q, J = 3.8 Hz, 7-C or 5-C), 123.6 (q, J = 274.2 Hz, 10-C), 47.3 (1-C), 25.1 (2-C), 23.0 (3-C) ppm; IR (KBr): ν = 3252, 2949, 1323, 1263, 1117, 910, 810, 692 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{16}N_2OSF_3$: 293.0935, found: 293.0945.

(*rac*)-1-[*S*-(4-Methylphenyl)sulfonimidoyl]piperidine (55q)



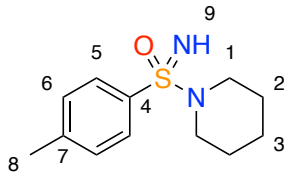
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55q** as a white solid (109 mg, 95%): m.p. 79–80 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.64 (d, J = 8.4 Hz, 2H, 5-H), 7.37 (d, J = 8.4 Hz, 2H, 6-H), 4.19 (s, 1H, 9-H), 2.87–2.73 (m, 4H, 1-H), 2.38 (s, 3H, 8-H), 1.50 (app quin, J = 5.6 Hz, 4H, 2-H), 1.35–1.22 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.1 (7-C), 133.7 (4-C), 129.2 (6-C), 127.7 (5-C), 47.4 (1-C), 25.2 (2-C), 23.2 (3-C), 20.9 (8-C) ppm; IR (KBr): ν = 3279, 2935, 1252, 1132, 914, 700, 571 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{12}H_{19}N_2OS$: 239.1218, found: 239.1220; chiral HPLC: instrument: Agilent HPLC 1260; column: Chiralpak IC 3 mm, 100 × 4.6 mm; eluent A: hexane + 0.1 vol% diethylamine (99%), eluent B: EtOH; gradient: 0–7 min 20–50% B; flow: 1.4 mL/min; temperature: 25 °C; DAD: 254 nm.

Column:	Chiralpak IC 3µ 100x4.6		
Solvent:	20-50% EtOH/Hexan in 7min	*Wavelength (nm):*	DAD_254
Puffer:	+0.1% DEA	*Flow (ml/min):*	n.a.
Gradient:	S3_20_50_ETOH_HEXAN_DEA	*Run Time (min):*	10,00
Solution:		*Vial Number:*	P1:F2
Comment:		*Injection Volume (µL):*	5,0



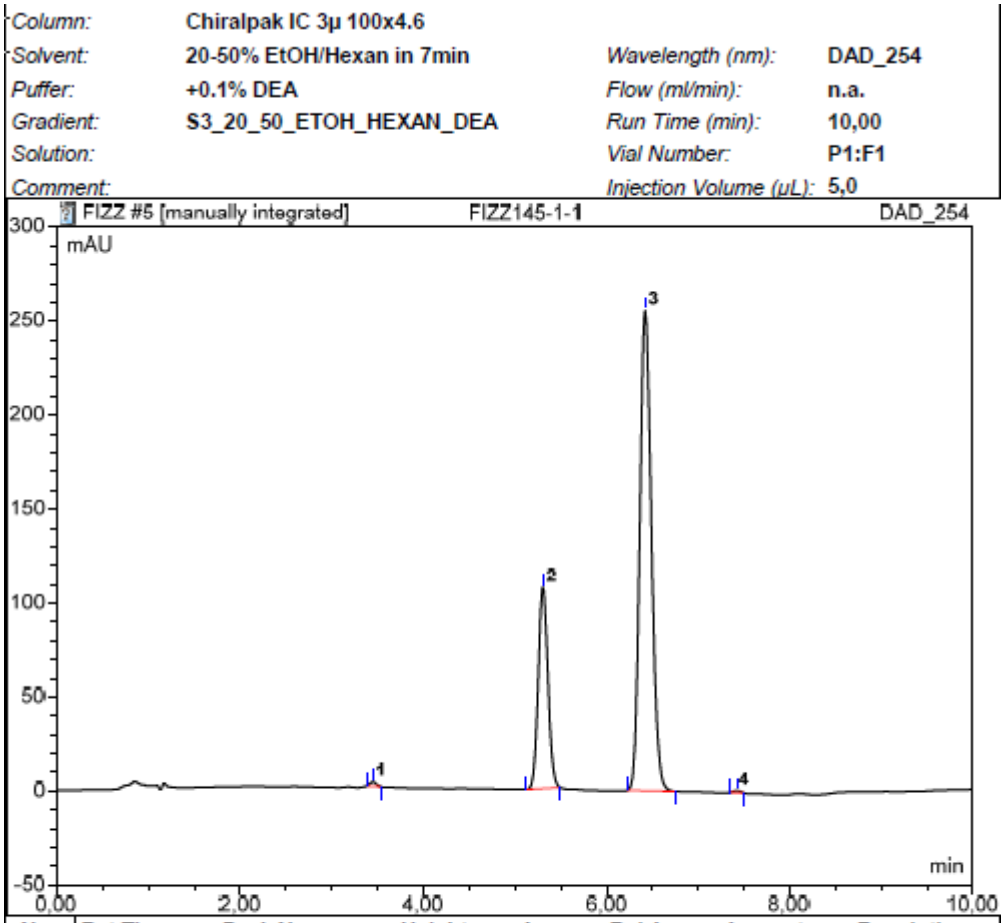
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	2,75		9,171	1,173	3,01	n.a.	1,4
2	3,00		2,205	0,169	0,43	n.a.	2,4
3	3,44		4,298	0,582	1,49	n.a.	4,9
4	4,65		0,852	0,119	0,31	n.a.	2,9
5	5,30		146,630	18,043	46,27	n.a.	5,3
6	6,43		125,937	18,650	47,83	n.a.	5,0
7	7,42		2,532	0,259	0,66	n.a.	n.a.
Total:			291,624	38,994	100,00	0,000	

(–)-1-[*S*-(4-Methylphenyl)sulfonimidoyl]piperidine (55q*)



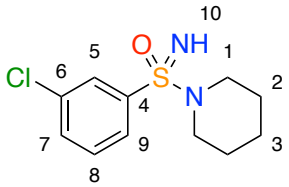
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **55q*** as a colourless oil (100 mg, 88%): $[\alpha]_D$ = –7.2 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.64 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 4.19 (s, 1H), 2.86–2.73 (m, 4H), 2.38 (s, 3H), 1.50 (app quin, J = 5.6 Hz, 4H), 1.28 ppm (app quin, J = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.1, 133.7, 129.2, 127.7, 47.4, 25.2, 23.2, 20.9 ppm; IR (KBr): ν = 3277, 2934, 2831, 1250, 1132, 910, 813, 698 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd

for $C_{12}H_{19}N_2OS$: 239.1218, found: 239.1217; chiral HPLC: instrument: Agilent HPLC 1260; column: Chiralpak IC 3 mm, 100 × 4.6 mm; eluent A: hexane + 0.1 vol% diethylamine (99%), eluent B: EtOH; gradient: 0–7 min 20–50% B; flow: 1.4 mL/min; temperature: 25 °C; DAD: 254 nm; 48% ee.



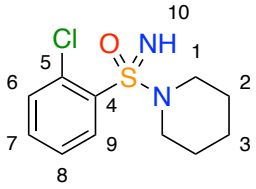
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount n.a.	Resolution
1	3,45		2,515	0,199	0,39	n.a.	11,5
2	5,31		107,095	13,108	25,75	n.a.	5,2
3	6,42		255,537	37,491	73,65	n.a.	5,2
4	7,42		1,205	0,107	0,21	n.a.	n.a.
Total:			366,351	50,905	100,00	0,000	

1-[*S*-(3-Chlorophenyl)sulfonimidoyl]piperidine (55r)



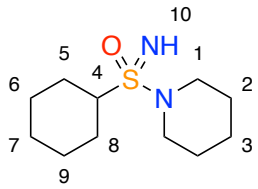
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **55r** as a white solid (105 mg, 85%): m.p. 89–90 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.75–7.67 (m, 3H, 5-H, 7-H and 9-H), 7.66–7.57 (m, 1H, 8-H), 4.57 (s, 1H, 10-H), 2.92–2.77 (m, 4H, 1-H), 1.51 (app q, J = 5.6 Hz, 4H, 2-H), 1.38–1.24 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 139.0 (6-C), 133.5 (4-C), 132.0 (5-C or 7-C or 8-C or 9-C), 130.9 (5-C or 7-C or 8-C or 9-C), 127.1 (5-C or 7-C or 8-C or 9-C), 126.3 (5-C or 7-C or 8-C or 9-C), 47.3 (1-C), 25.2 (2-C), 23.1 (3-C) ppm; IR (KBr): ν = 3254, 2922, 2849, 1572, 1456, 1256, 1136, 907, 787, 677, 588 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}N_2OSCl$: 259.0672, found: 259.0673.

1-[*S*-(2-Chlorophenyl)sulfonimidoyl]piperidine (55s)



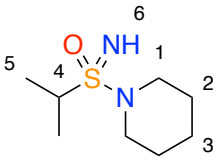
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **55s** as a yellow semisolid (60 mg, 48%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.03 (dd, J = 7.7, 1.7 Hz, 1H, 9-H), 7.64–7.53 (m, 2H, 6-H and 8-H), 7.52–7.45 (m, 1H, 7-H), 4.66 (s, 1H, 10-H), 3.16–3.04 (m, 4H, 1-H), 1.54–1.33 ppm (m, 6H, 2-H and 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 138.3 (5-C), 133.2 (6-C or 7-C), 132.2 (7-C or 6-C), 131.4 (9-C), 130.9 (4-C), 127.3 (8-C), 46.4 (1-C), 25.5 (2-C), 23.4 (3-C) ppm; IR (KBr): ν = 3277, 2935, 1450, 1248, 1047, 924, 746, 689 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{16}N_2OSCl$: 259.0672, found: 259.0673.

1-(*S*-Cyclohexylsulfonimidoyl)piperidine (55t)



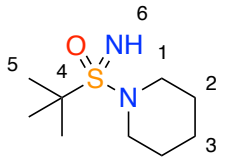
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55t** as a colourless oil (97 mg, 88%): ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 3.27-3.12 (m, 4H, 1-H), 2.85 (m, 1H, 4-H), 2.05-1.90 (m, 2H, 5-H), 1.82-1.70 (m, 2H, 6-H), 1.65-1.55 (m, 1H, 7-H), 1.48 (*br*s, 6H, 2-H and 3-H), 1.40-1.30 (m, 2H, 5-H), 1.28-1.17 (m, 2H, 6-H), 1.15-1.03 ppm (m, 1H, 7-H); ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 60.4 (4-C), 47.0 (1-C), 27.0 (5-C or 6-C or 7-C) , 26.6 (5-C or 6-C or 7-C), 26.2 (2-C), 25.0 (5-C or 6-C or 7-C), 23.8 (3-C) ppm; IR (KBr): ν = 3275, 2930, 1448, 1236, 1043, 928, 685 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{11}H_{23}N_2OS$: 231.1531, found: 231.1532.

1-(*S*-Isopropylsulfonimidoyl)piperidine (55u)



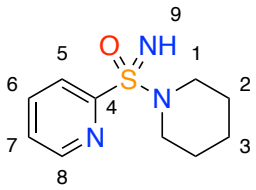
Prepared according to general procedure **K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55u** as a colourless oil (64 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.39–3.31 (m, 4H, 1-H), 3.24 (app dt, J = 13.7, 6.8 Hz, 1H, 4-H), 1.65–1.54 (m, 6H, 2-H and 3-H), 1.38 (d, J = 6.8 Hz, 3H, 5-H), 1.34 ppm (d, J = 6.8 Hz, 3H, 5-H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 53.5 (4-C), 47.8 (1-C), 26.6 (2-C), 24.2 (3-C), 17.6 (5-C), 17.0 (5-C) ppm; IR (KBr): ν = 3277, 2934, 2851, 1230, 1041, 930, 704 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_{19}N_2OS$: 191.1218, found: 191.1215.

1-(*S*-*tert*-Butylsulfonimidoyl)piperidine (55v)



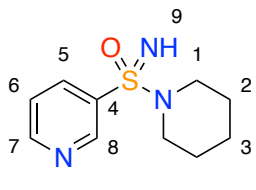
Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55v** as a yellow solid (82 mg, 83%): m.p. 53–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (app *br*s, 4H, 1-H), 1.95 (*br*s, 1H, 6-H), 1.57 (app s, 6H, 2-H and 3-H), 1.37 ppm (s, 9H, 5-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 61.9 (4-C), 48.9 (1-C), 26.9 (2-C), 25.1 (5-C), 24.2 (3-C) ppm; IR (KBr): ν = 3254, 2930, 2851, 1230, 1041, 930, 694 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_9H_{21}N_2OS$: 205.1375, found: 205.1374.

2-[*S*-(Piperidin-1-yl)sulfonimidoyl]pyridine (55w)



Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55w** as a colourless oil (92 mg, 85%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.73–8.66 (m, 1H, 8-H), 8.09–8.00 (m, 1H, 6-H), 7.99–7.91 (m, 1H, 5-H), 7.64–7.56 (m, 1H, 7-H), 4.42 (*br*s, 1H, 9-H), 3.20–2.98 (m, 4H, 1-H), 1.57–1.44 (m, 4H, 2-H), 1.44–1.28 ppm (m, 2H, 3-H); ^{13}C NMR (151 MHz, [D$_6$]DMSO): δ = 157. 2 (4-C), 149.4 (8-C), 138.2 (6-C), 126.3 (7-C), 122.7 (5-C), 47.6 (1-C), 25.4 (2-C), 23.4 (3-C) ppm; IR (KBr): ν = 3263, 2935, 1576, 1423, 1257, 920, 735 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{16}N_3OS$: 226.1014, found: 226.1015.

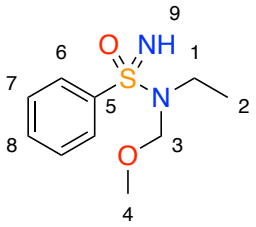
3-[*S*-(Piperidin-1-yl)sulfonimidoyl]pyridine (55y)



Prepared according to **general procedure K**; crude purified by flash column chromatography (KP-NH, 0–50% EtOAc in hexane) to give **55y** as a white solid (57 mg, 53%): m.p. 107–108 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.90 (d, J = 1.8 Hz, 1H, 8-H), 8.80 (dd, J = 4.8, 1.5 Hz, 1H, 7-H), 8.12 (app dt, J = 8.1, 1.9 Hz, 1H, 5-H), 7.63 (dd, J = 8.1, 4.8 Hz, 1H, 6-H), 4.65 (s, 1H, 9-H), 2.93–2.82 (m, 4H, 1-H), 1.54–1.48 (m, 4H, 2-H), 1.32

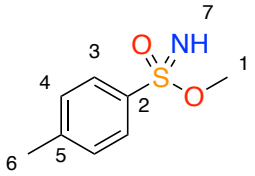
ppm (quin, J = 5.8 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 152.6 (7-C), 148.1 (8-C), 135.7 (5-C), 133.3 (4-C), 123.9 (6-C), 47.3 (1-C), 25.1 (2-C), 23.0 (3-C) ppm; IR (KBr): ν = 3290, 3047, 1257, 1144, 922, 741, 694, 580 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{16}N_3OS$: 226.1014, found: 226.1015.

_N_-Ethyl-_N_-(methoxymethyl)benzenesulfonimidamide (55z)



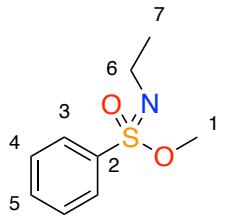
Prepared according to **general procedure K**, but on a different scale (**62z**: 0.05 mg, 0.23 mmol); crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in hexane) to give **55z** as a colourless oil (33 mg, 61%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.86-7.84 (m, 2H, 6-H), 7.60-7.50 (m, 3H, 8-H and 7-H), 4.69–4.63(m, 2H, 3-H), 4.52 (*br*s, 1H, 9-H), 3.19-3.10 (m, 2H, 1-H), 2.08 (s, 3H, 4-H), 1.02 ppm (t, J = 7.1 Hz, 3H, 2-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 142.3 (5-C), 131.7 (8-C), 128.7 (7-C), 126.7(6-C), 79.6 (3-C), 54.8 (1-C), 41.8 (4-C), 14.3 (2-C) ppm; IR (KBr): ν = 3271, 2976, 1463, 1254, 975, 893 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{16}N_2O_2S$: 229.1005, found: 229.0995.

Methyl 4-methylbenzenesulfonimidate (225a)



Prepared according to **general procedure K**, from commercially available (*S*)-4-methylbenzenesulfinamide; crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **225a** as a white solid (52 mg, 58%): m.p. 36–38 °C; ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 7.78 (d, J = 8.2 Hz, 2H, 3-H), 7.41 (d, J = 8.2 Hz, 2H, 4-H), 5.54 (s, 1H, 7-H), 3.34 (s, 3H, 1-H), 2.39 ppm (s, 3H, 6-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 143.3 (5-C), 135.0 (2-C), 129.6 (4-C), 127.2 (3-C), 54.9 (1-C), 21.0 (6-C) ppm; IR (KBr): ν = 3298, 1595, 1265, 1148, 951, 814, 712 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_8H_{12}NO_2S$: 186.0589, found: 186.0589.

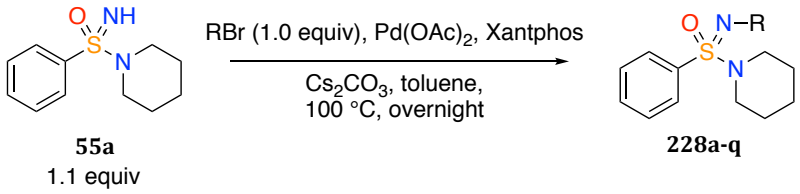
Methyl *N*-ethylbenzenesulfonimidate (225b)



Prepared according to **general procedure K**, from *N*-ethylbenzenesulfinamide (**48b**); crude purified by flash column chromatography (KP-Sil, 0–60% EtOAc in hexane) to give **225b** as a colourless oil (31 mg, 32%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.90 (d, J = 7.3 Hz, 2H, 3-H), 7.73–7.68 (m, 1H, 5-H), 7.65–7.59 (m, 2H, 4-H), 3.51 (s, 3H, 1H), 3.27–3.11 (m, 2H, 6-H), 1.17 ppm (t, J = 7.2 Hz, 3H, 7-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 136.4 (2-C), 133.2 (5-C), 129.3 (4-C), 127.3 (3-C), 55.5 (1-C), 36.7 (6-C), 17.9 (7-C) ppm; IR (KBr): ν = 2970, 2868, 1446, 1296, 1269, 1169, 978, 739, 687, 675, 600 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_9H_{14}NO_2S$: 200.0745, found: 200.0744.

4.8 *N*-Arylation of sulfonimidamide 55a

General procedure M:

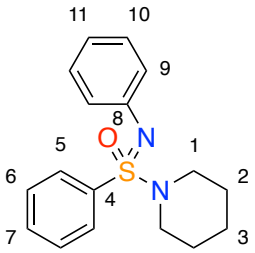


55a
1.1 equiv

228a-q

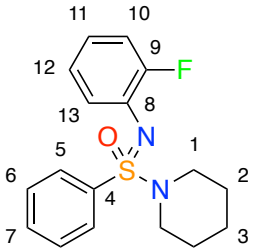
In a dry MW vial flushed with Ar, sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.10 equiv) and an aryl bromide (0.40 mmol, 1.00 equiv) were dissolved in toluene (6.8 mL). The mixture was then degassed for 10 min and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%), Xantphos (23 mg, 0.04 mmol, 10 mol%) and Cs_2CO_3 (200 mg, 0.60 mmol, 1.50 equiv) were added at RT. The reaction mixture was heated to 100 °C and stirred overnight. Once the starting material had been consumed (monitored by TLC), the mixture was cooled, diluted with methyl *tert*-butyl ether, filtered through a pad of Celite under reduced pressure and washed with methyl *tert*-butyl ether. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography.

1-(*N*,*S*-Diphenylsulfonimidoyl)piperidine (228a)



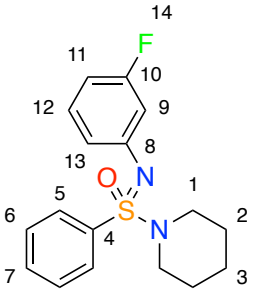
Prepared according to **general procedure M**, from bromobenzene; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in PE) to give **228a** as a white solid (104 mg, 86%): m.p. 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.96 (m, 2H, 5-H), 7.62–7.52 (m, 3H, 6-H and 7-H), 7.27 (d, J = 6.1 Hz, 2H, 9-H or 10-H), 7.25 (d, J = 2.4 Hz, 2H, 9-H or 10-H), 6.98 (app tt, J = 6.1, 2.4 Hz, 1H, 11-H), 3.10–2.99 (m, 4H, 1-H), 1.58–1.49 (m, 4H, 2-H), 1.37 ppm (quin, J = 6.1 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.9 (8-C), 136.6 (4-C), 132.3 (7-C), 129.9 (9-C or 10-C or 6-C), 128.9 (9-C or 10-C or 6-C), 127.9 (5-H), 123.9 (10-C or 9-C), 121.8 (11-C), 47.6 (1-C), 25.4 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 3074, 2939, 2849, 1585, 1485, 1306, 1219, 931, 781, 694 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{21}N_2OS$: 301.1375, found: 301.1378.

1-[*N*-(2-Fluorophenyl)-*S*-phenylsulfonimidoyl]piperidine (228b)



Prepared according to **general procedure M**, from 1-bromo-2-fluorobenzene; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228b** as a white solid (59 mg, 46%): m.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.97 (m, 2H, 5-H), 7.62–7.50 (m, 3H, 6-H and 7-H), 7.43 (app td, J = 8.2, 1.8 Hz, 1H, 13-H), 7.05 (ddd, J = 10.9, 7.9, 1.8 Hz, 1H, 10-H), 6.98 (app td, J = 7.9, 1.8 Hz, 1H, 12-H), 6.95–6.88 (m, 1H, 11-H), 3.04 (app t, J = 5.5 Hz, 4H, 1-H), 1.59-1.43 (m, 4H, 2-H), 1.39–1.30 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.9 (d, J = 244.2 Hz, 9-C), 136.5 (4-C), 132.5 (7-C), 131.7 (d, J = 11.4 Hz, 8-C), 129.0 (6-C), 128.1 (5-C), 125.6 (d, J = 1.9 Hz, 13-C), 124.1 (d, J = 3.8 Hz, 12-C), 122.7 (d, J = 7.3 Hz, 11-C), 115.9 (d, J = 20.4 Hz, 10-C), 47.6 (1-C), 25.5 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 3076, 2935, 2849, 1603, 1495, 1315, 1227, 928, 750 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{17}H_{20}N_2OFS$: 319.1280, found: 319.1281.

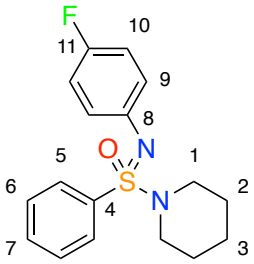
1-[*N*-(3-Fluorophenyl)-*S*-phenylsulfonimidoyl]piperidine (228c)



Prepared according to **general procedure M**, from 1-bromo-3-fluorobenzene; crude purified by flash column chromatography (KP-Sil, 0–20% EtOAc in hexane) to give **228c** as a white solid (124 mg, 97%): m.p. 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.93 (m, 2H, 5-H), 7.63–7.49 (m, 3H, 6-H and 7-H), 7.16 (app td, J = 8.1, 6.8 Hz, 1H, 12-H), 7.01 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H, 13-H), 6.97 (app dt, J = 11.1, 2.3 Hz, 1H, 9-H), 6.66 (app tdd, J = 8.1, 2.6, 1.0 Hz, 1H, 11-H), 3.11–2.94 (m, 4H, 1-H), 1.54 (m, 4H, 2-H), 1.37 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.2 (d, J = 244 Hz,10-C), 145.6 (d, J = 10.5 Hz, 8-C), 136.1 (4-C), 132.4 (7-C), 129.6 (d, J = 9.8 Hz, 12-C), 128.8 (6-C), 127.7 (5-C), 119.4 (d, J = 2.6 Hz, 13-C), 110.6 (d, J = 22.8 Hz, 9-C), 108.4 (d, J = 21.3 Hz, 11-C), 47.4 (1-C), 25.3 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 3076, 2937, 2849,

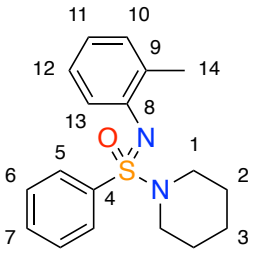
1604, 1225, 1148, 1094 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{20}N_2OFS$: 319.1280, found: 319.1281.

1-[*N*-(4-Fluorophenyl)-*S*-phenylsulfonimidoyl]piperidine (228d)



Prepared according to **general procedure M**, from 1-bromo-4-fluorobenzene; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228d** as a white solid (91 mg, 72%): m.p. 83–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.94 (m, 2H, 5-H), 7.58–7.51 (m, 3H, 6-H and 7-H), 7.21 (m, 2H, 9-H), 6.95 (m, 2H, 10-H), 3.01 (m, 4H, 1-H), 1.59–1.44 (m, 4H, 2-H), 1.37 ppm (quin, J = 5.8 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.5(d, J = 239.6 Hz, 11-C), 139.8 (d, J = 2.6 Hz, 8-C), 136.4 (4-C), 132.4 (7-C), 128.9 (6-C), 127.9 (5-C), 124.8 (d, J = 7.7 Hz, 9-C), 115.5 (d, J = 22.1 Hz, 10-C), 47.6 (1-C), 25.4 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 3053, 2939, 2847, 1499, 1207, 1016, 919 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{20}N_2OFS$: 319.1280, found: 319.1281.

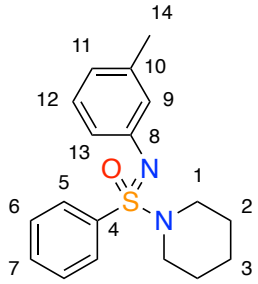
1-[*S*-Phenyl-*N*-(2-tolyl)sulfonimidoyl]piperidine (228e)



Prepared according to **general procedure M**, from 2-bromotoluene; crude purified by flash column chromatography (KP-Sil, 0–20% EtOAc in hexane) to give **228e** as a yellow oil (122 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00–7.97 (m, 2H, 5-H), 7.60–7.51 (m, 3H, 6-H and 7-H), 7.38 (dd, J = 8.0, 1.2 Hz, 1H, 13-H), 7.15 (dd, J = 7.4, 1.7 Hz, 1H, 10-H), 7.06 (app td, J = 7.4, 1.7 Hz, 1H, 12-H), 6.88 (app td, J = 7.4, 1.7 Hz, 1H, 11-H), 3.06 (ddd, J = 11.4, 7.0, 3.9 Hz, 2H, 1-H), 2.96 (ddd, J = 11.4, 7.0, 3.9 Hz, 2H, 1-H), 2.39 (s, 3H, 14-H), 1.60–1.45 (m, 4H, 2-H), 1.36 ppm (quin, J = 6.1 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.1 (8-C), 137.1 (4-C), 132.2 (9-C), 132.0 (7-C), 130.2 (10-C), 128.7 (6-C), 127.8 (5-C), 126.2 (12-C), 122.1 (13-C), 121.5 (11-C), 47.3 (1-C), 25.3 (2-C), 23.6

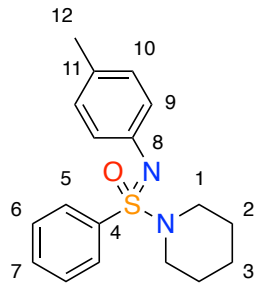
(3-C), 18.8 (14-C) ppm; IR (KBr): ν = 3063, 3015, 2935, 2849, 1596, 1487, 1313, 1290, 1269, 1227, 1121, 914 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2OS$: 315.1531, found: 315.1534.

1-[*S*-Phenyl-*N*-(3-tolyl)sulfonimidoyl]piperidine (228f)



Prepared according to **general procedure M**, from 3-bromotoluene; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228f** as a white solid (106 mg, 84%): m.p. 67–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.95 (m, 2H, 5-H), 7.59–7.50 (m, 3H, 6-H and 7-H), 7.12 (app t, J = 7.5 Hz, 1H, 12-H), 7.08–7.06 (m, 2H, 13-H and 9-H), 6.81–6.76 (m, 1H, 11-H), 3.09–2.98 (m, 4H, 1-H), 2.31 (s, 3H, 14-H), 1.61–1.45 (m, 4H, 2-H), 1.37 ppm (quin, J = 5.7 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.5 (8-C), 138.5 (10-C), 136.5 (4-C), 132.1 (7-C), 128.7 (6-C), 128.6 (12-C), 127.8 (5-C), 124.5 (13-C or 9-C), 122.6 (11-C), 120.6 (13-C or 9-C), 47.4 (1-C), 25.3 (2-C), 23.6 (3-C), 21.5 (14-C) ppm; IR (KBr): ν = 3070, 2932, 2853, 1597, 1485, 1300, 1223, 1059, 926 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2OS$: 315.1531, found: 315.1535.

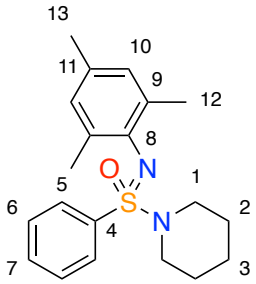
1-[*S*-Phenyl-*N*-(4-tolyl)sulfonimidoyl]piperidine (228g)



Prepared according to **general procedure M**, from 4-bromotoluene; crude purified by flash column chromatography (KP-Sil, 0–20% EtOAc in hexane) to give **228g** as a white solid (125 mg, 99%): m.p. 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.95 (m, 2H, 5-H), 7.59–7.50 (m, 3H, 6-H and 7-H), 7.15–7.12 (m, 2H, 9-H), 7.05–7.03 (m, 2H, 10-H), 3.02 (app qt, J = 11.2, 4.8 Hz, 4H, 1-H), 2.28 (s, 3H, 12-H), 1.60–1.45 (m, 4H, 2-H), 1.36 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.8 (8-C), 136.5 (4-H),

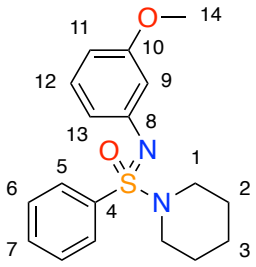
132.1 (7-C), 131.0 (11-C), 129.5 (11-C), 128.7 (6-C), 127.8 (5-C), 123.5 (9-C), 47.4 (1-C), 25.3 (2-C), 23.6 (3-C), 20.8 (12-C) ppm; IR (KBr): ν = 3026, 2935, 2847, 1506, 1310, 1221, 1055, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2OS$: 315.1531, found: 315.1530.

1-(*N*-Mesityl-*S*-phenylsulfonimidoyl)piperidine (228h)



Prepared according to **general procedure M**, from 2-bromo-1,3,5-trimethylbenzene; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228h** as a white solid (4 mg, 3%): m.p. 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2H, 5-H), 7.55–7.48 (m, 3H, 6-H and 7-H), 6.81 (s, 2H, 10-H), 3.02 (app t, J = 5.4 Hz, 4H, 1-H), 2.32 (s, 6H, 12-H), 2.22 (s, 3H, 13-H), 1.58 (m, 4H, 2-H), 1.41–1.35 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.6 (8-C), 137.8 (4-C), 133.2 (9-C), 131.6 (7-C), 128.9 (5-C or 6-C or 10-C), 128.5 (5-C or 6-C or 10-C), 127.6 (5-C or 6-C or 10-C), 47.5 (1-C), 25.5 (2-C), 23.7 (3-C), 20.7 (12-C), 20.6 (13-C) ppm; IR (KBr): ν = 3056, 2936, 1479, 1272, 1222, 1059, 903 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{27}N_2OS$: 343.1839, found: 343.1849.

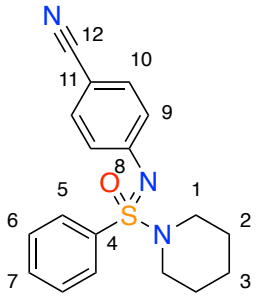
1-[*N*-(3-Methoxyphenyl)-*S*-phenylsulfonimidoyl]piperidine (228i)



Prepared according to **general procedure M**, from 3-bromoanisole; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228i** as a yellow solid (86 mg, 65%): m.p. 69–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2H, 5-H), 7.60–7.51 (m, 3H, 6-H and 7-H), 7.13 (app t, J = 8.1 Hz, 1H, 12-H), 6.86 (ddd, J = 8.1, 2.0, 1.0 Hz, 1H, 11-H or 13-H), 6.81 (app t, J = 2.2 Hz, 9-H), 6.54 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H, 11-H or 13-H), 3.79 (s, 3H, 14-H), 3.03 (app qdd, J = 11.6, 6.5, 4.1 Hz, 4H, 1-H), 1.60–1.50 (m, 4H, 2-H), 1.36 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ =

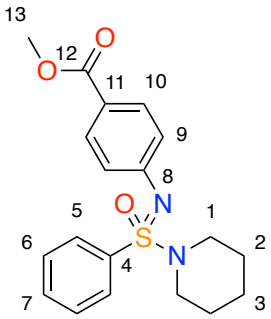
160.1 (8-C or 10-C), 145.0 (10-C or 8-C), 136.5 (4-C), 132.2 (7-C), 129.4 (12-C), 128.8 (6-C), 127.8 (5-C), 116.2 (13-C or 11-C), 109.2 8 (9-C), 107.8 (13-C or 11-C), 55.2 (14-C), 47.4 (1-C), 25.3 (2-C), 23.6 (3-C) ppm; IR (KBr): ν = 3063, 2995, 2937, 2833, 1593, 1236, 1200, 1159, 916 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_2S$: 331.1480, found: 331.1480.

4-{[Oxo(phenyl)(piperidin-1-yl)-λ^6-sulfanylidene]amino}benzonitrile (228j)



Prepared according to **general procedure M**, from 4-bromobenzonitrile; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228j** as a white solid (115 mg, 88%): m.p. 136–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 2H, 5-H), 7.64–7.60 (m, 1H, 7-H), 7.59–7.54 (m, 2H, 6-H), 7.52–7.49 (m, 2H, 10-H), 7.29–7.27 (m, 2H, 9-H), 3.06 (app ddd, J = 11.4, 7.1, 3.8 Hz, 2H, 1-H), 2.97 (app ddd, J = 11.4, 7.1, 3.8 Hz, 2H, 1-H), 1.62–1.47 (m, 4H, 2-H), 1.38 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.0 (11-C), 135.6 (4-C), 133.1 (10-C), 132.8 (7-C), 129.0 (6-C), 127.7 (5-C), 123.8(9-C), 119.8 (12-C), 104.1 (8-C), 47.3 (1-C), 25.2 (2-C), 23.4 (3-C) ppm; IR (KBr): ν = 3057, 2941, 2849, 2226, 1599, 1497, 1227, 845, 741 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{20}N_3OS$: 326.1327, found: 326.1325;

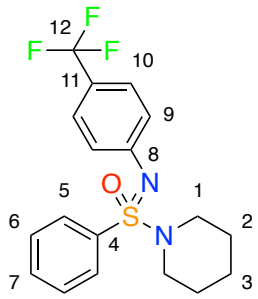
Methyl 4-{[oxo(phenyl)(piperidin-1-yl)-λ^6-sulfanylidene]amino}benzoate (228k)



Prepared according to **general procedure M**, from methyl 4-bromobenzoate; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **228k** as a white solid (142 mg, 99%): m.p. 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2H, 5-H), 7.94–7.90 (m, 2H, 10-H), 7.62–7.52 (m, 3H, 6-H and 7-H), 7.28–

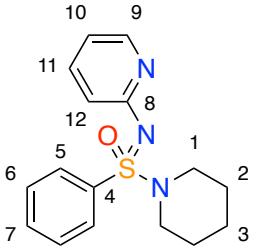
7.25 (m, 2H, 9-H), 3.88 (s, 3H, 13-H), 3.06 (app ddd, J = 11.5, 7.1, 3.8 Hz, 2H, 1-H_a), 2.98 (app ddd, J = 11.5, 7.1, 3.8 Hz, 2H, 1-H_b), 1.60–1.45 (m, 4H, 2-H), 1.36 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.3 (12-C), 149.2 (11-C), 136.0 (4-C), 132.5 (7-C), 130.7 (10-C), 128.9 (6-C), 127.8 (5-C), 123.1 (9-C), 123.0 (8-C), 51.8 (13-C), 47.3 (1-C), 25.2 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 2941, 2837, 1713, 1269, 1101, 916 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{23}N_2O_3S$: 359.1429, found: 359.1427.

1-{*S*-Phenyl-*N*-[4-(trifluoromethyl)phenyl]sulfonimidoyl}piperidine (228l)



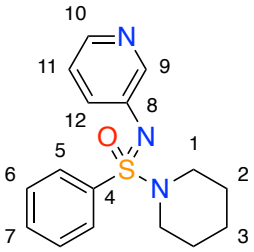
Prepared according to **general procedure M**, from 4-bromobenzotrifluoride; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **228l** as a white solid (149 mg, quantitative): m.p. 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2H, 5-H), 7.63–7.53 (m, 3H, 6-H and 7-H), 7.47 (d, J = 8.8 Hz, 2H, 10-H), 7.30 (d, J = 8.8 Hz, 2H, 9-H), 3.06 (app ddd, J = 11.4, 7.1, 3.9 Hz, 2H, 1-H_a), 2.98 (app ddd, J = 11.4, 7.1, 3.9 Hz, 2H, 1-H_b), 1.62–1.47 (m, 4H, 2-H), 1.37 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.5 (8-C), 135.9 (4-C), 132.5 (7-C), 128.9 (6-C), 127.8 (5-C), 126.1 (q, J = 3.7 Hz, 10-C), 123. 3 (q, J = 32.3 Hz, 11-C) 123.3 (9-C), 47.4 (1-C), 25.2 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 3065, 2939, 2851, 1610, 1512, 1308, 1229, 1101 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{20}N_2OF_3S$: 369.1248, found: 369.1243.

2-{[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}pyridine (228m)



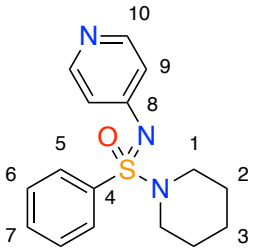
Prepared according to **general procedure M**, from 2-bromopyridine; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **228m** as a white solid (85 mg, 71%): m.p. 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (ddd, J = 5.0, 2.1, 1.1 Hz, 1H, 11-H or 10-H), 8.01–7.99 (m, 2H, 5-H), 7.59–7.49 (m, 4H, 6-H and 7-H and 9-H or 12-H), 7.10 (app dt, J = 8.2, 1.1 Hz, 1H, 12-H or 9-H), 6.83 (ddd, J = 7.3, 5.0, 1.1 Hz, 1H, 11-H or 10-H), 3.10 (app t, J = 5.5 Hz, 4H, 1-H), 1.54 (m, 4H, 2-H), 1.38 ppm (quin, J = 5.7 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.3 (8-C), 148.6 (11-C or 10-C), 137.5 (12-C or 9-C), 136.6 (4-C), 132.3 (7-C), 128.8 (6-C), 127.9 (5-C), 117.3 (12-C or 9-C), 116.8 (10-C or 11-C), 47.2 (1-C), 25.3 (2-C), 23.6 (3-C) ppm; IR (KBr): ν = 2935, 2922, 2854, 2843, 1585, 1554, 1462, 1423, 1228, 1095, 980 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}N_3OS$: 302.1327, found: 302.1330.

3-{[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}pyridine (228n)



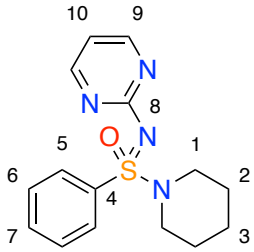
Prepared according to **general procedure M**, from 3-bromopyridine; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **228n** as a colorless oil (93 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dd, J = 2.7, 0.8 Hz, 1H, 9-H), 8.20 (dd, J = 4.8, 1.5 Hz, 1H, 10-H), 7.99–7.96 (m, 2H, 5-H), 7.63–7.54 (m, 4H, 6-H and 7-H and 12-H), 7.15 (ddd, J = 8.2, 4.8, 0.8 Hz, 1H, 11-H), 3.06 (ddd, J = 11.2, 7.1, 3.9 Hz, 2H, 1-H$_a$), 2.98 (ddd, J = 11.2, 7.1, 3.9 Hz, 2H, 1-H$_b$), 1.61–1.46 (m, 4H, 2-H), 1.36 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.5 (9-C), 142.6 (10-C), 140.8 (8-C), 135.8 (4-C), 132.5 (7-C), 130.0 (12-C), 128.9 (6-C), 127.8 (5-C), 123.5 (11-C), 47.4 (1-C), 25.2 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 3059, 3028, 2939, 2851, 1578, 1560, 1475, 1294, 1230, 1107, 1063, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}N_3OS$: 302.1327, found: 302.1326.

4-{[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}pyridine (228o)



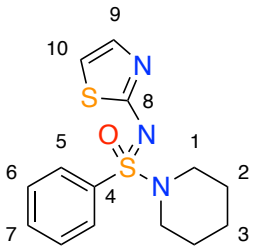
Prepared according to **general procedure M**, from 4-bromopyridine; crude purified by flash column chromatography (KP-Sil, 0–80% EtOAc in hexane) to give **228o** as a colorless oil (87 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37–8.35 (m, 2H, 10-H or 9-H), 7.96–7.93 (m, 2H, 5-H), 7.64–7.54 (m, 3H, 6-H and 7-H), 7.12–7.10 (m, 2H, 9-H or 10-H), 3.07 (ddd, J = 11.6, 7.2, 4.0 Hz, 2H, 1-H_a), 2.97 (ddd, J = 11.6, 7.2, 4.0 Hz, 2H, 1-H_b), 1.64–1.49 (m, 4H, 2-H), 1.39 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.8 (8-C), 150.3 (10-C or 9-C), 135.6 (4-C), 132.7 (7-C), 129.0 (6-C), 127.7 (5-C), 118.5 (9-C or 10-C), 47.3 (1-C), 25.2 (2-C), 23.4 (3-C) ppm; IR (KBr): ν = 3059, 3016, 2937, 2849, 1587, 1315, 1298, 1230, 1209, 1103, 1016 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}N_3OS$: 302.1327, found: 302.1327.

2-{[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}pyrimidine (228p)



Prepared according to **general procedure M**, from 2-bromopyrimidine; crude purified by flash column chromatography (KP-NH, 0–50% EtOAc in hexane) to give **228p** as a yellow solid (93 mg, 77%): m.p. 122–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 4.8 Hz, 2H, 9-H), 7.99–7.96 (m, 2H, 5-H), 7.59–7.55 (m, 1H, 7-H), 7.53–7.49 (m, 2H, 6-H), 6.76 (t, J = 4.8 Hz, 1H, 10-H), 3.22–3.13 (m, 4H, 1-H), 1.61 (m, 4H, 2-H), 1.43 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.2 (8-C), 158.3 (9-C), 136.7 (4-C), 132.4 (7-C), 128.8 (6-C), 127.9 (5-C), 113.8 (10-C), 46.8 (1-C), 25.3 (2-C), 23.6 (3-C) ppm; IR (KBr): ν = 3026, 2947, 2849, 1545, 1408, 1238, 926 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{19}N_4OS$: 303.1280, found: 303.1280.

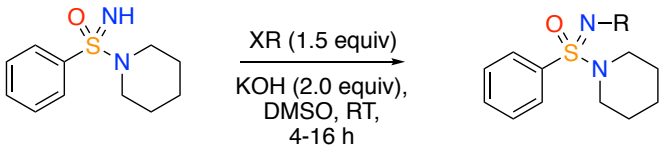
1-[*S*-Phenyl-*N*-(1,3-thiazol-2-yl)sulfonimidoyl]piperidine (228q)



Prepared according to **general procedure M**, from 2-bromo-1,3-thiazole; crude purified by flash column chromatography (KP-NH, 0–40% EtOAc in hexane) to give **228q** as a colorless oil (55 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.98 (m, 2H, 5-H), 7.63–7.59 (m, 1H, 7-H), 7.57–7.53 (m, 2H, 6-H), 7.34 (d, J = 3.8 Hz, 1H, 9-H), 6.79 (d, J = 3.8 Hz, 1H, 10-H), 3.12 (app t, J = 5.5 Hz, 4H, 1-H), 1.64–1.56 (m, 4H, 2-H), 1.42 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4 (8-C), 139.1 (9-C), 135.5 (4-C), 132.9 (7-C), 129.0 (5-C), 127.8 (6-C), 112.8 (10-C), 47.2 (1-C), 25.1 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 3067, 2937, 2849, 1439, 1223, 1140, 916 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{18}N_3OS_2$: 308.0891, found: 308.0893.

4.9 *N*-Alkylation of sulfonimidamide 55a

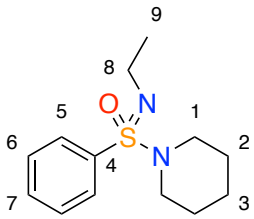
General procedure N:[2]



55a **229a-s**

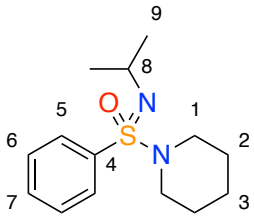
In a dry MW vial flushed with Ar, sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.00 equiv) and KOH (50 mg, 0.89 mmol, 2.00 equiv) were stirred in DMSO (0.7 mL) at RT for 15 min. Then, an alkyl bromide/iodide (0.67 mmol, 1.50 equiv) was added and the mixture was stirred at RT for 4–16 h. Once the starting material had been consumed (monitored by TLC), H_2O was added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were filtered through water-repellent filter paper. Solvent was removed under reduced pressure and the crude product was purified by flash column chromatography or preparative HPLC.

1-(*N*-Ethyl-*S*-phenylsulfonimidoyl)piperidine (229a)



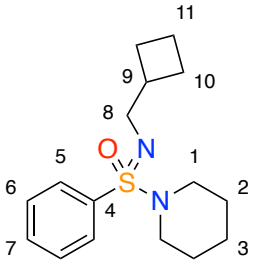
Prepared according to **general procedure N**, from bromoethane; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229a** as a colorless oil (111 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.63 (m, 2H, 5-H), 7.33–7.24 (m, 3H, 7-H and 6-H), 3.10 (dq, J = 12.3, 7.2 Hz, 1H, 8-H_a), 2.93 (dq, J = 12.3, 7.2 Hz, 1H, 8-H_b), 2.71 (app qt, J = 11.7, 5.6 Hz, 4H, 1-H), 1.39 (app quin, J = 5.6 Hz, 4H, 2-H), 1.17 (app tt, J = 8.3, 5.6 Hz, 2H, 3-H), 1.06 ppm (app t, J = 7.2 Hz, 3H, 9-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1 (4-C), 131.8 (7-C), 128.5 (5-C), 127.7 (6-C), 47.7 (1-C), 36.8 (8-C), 25.5 (2-C), 23.7 (3-C), 18.3 (9-C) ppm; IR (KBr): ν = 3063, 2934, 2853, 1254, 1153, 914 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{21}N_2OS$: 253.1375, found: 253.1379.

1-(*N*-Isopropyl-*S*-phenylsulfonimidoyl)piperidine (229b)



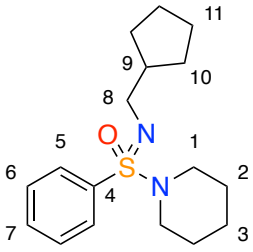
Prepared according to **general procedure N**, from 2-bromopropane; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **229b** as a colorless oil (46 mg, 38%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 2H, 5-H), 7.53–7.44 (m, 3H, 7-H and 6-H), 3.77 (hept, J = 6.4 Hz, 1H, 8-H), 2.96–2.87 (m, 4H, 1-H), 1.60 (app quin, J = 5.6 Hz, 4H, 2-H), 1.40–1.34 (m, 2H, 3-H), 1.25 ppm (app dd, J = 13.1, 6.4 Hz, 6H, 9-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.3 (4-C), 131.6 (7-C), 128.5 (5-C), 127.8 (6-C), 47.9 (1-C), 44.5 (8-C), 26.9 (9-C), 26.0 (9-C), 25.5 (2-C), 23.7 (3-H) ppm; IR (KBr): ν = 3064, 2933, 2854, 1444, 1263, 1145, 916 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{23}N_2OS$: 267.1531, found: 267.1533.

1-[*N*-(Cyclobutylmethyl)-*S*-phenylsulfonimidoyl]piperidine (229c)



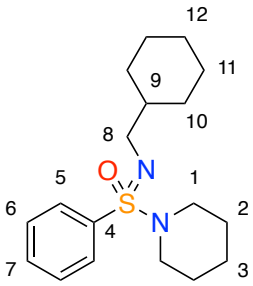
Prepared according to **general procedure N**, from (bromomethyl)cyclobutane; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in PE) to give **229c** as a white solid (80 mg, 61%): m.p. 57–58 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.78–7.75 (m, 2H, 5-H), 7.65–7.56 (m, 3H, 7-H and 6-H), 3.09 (dd, J = 12.3, 7.0 Hz, 1H, 8-H$_a$), 2.97 (dd, J = 12.3, 7.0 Hz, 1H, 8-H$_b$), 2.80 (app t, J = 5.4 Hz, 4H, 1-H), 2.46–2.44 (m, 1H, 9-H), 2.03–1.94 (m, 2H, 11-H), 1.87–1.67 (m, 4H, 10-H), 1.50 (m, 4H, 2-H), 1.31 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.8 (4-C), 132.0 (7-C), 128.8 (6-C), 127.4 (5-C), 47.2 (1-C), 46.6 (8-C), 37.0 (9-C), 25.3 (2-C), 25.1 (10-C), 23.2 (3-C), 17.7 (11-C) ppm; IR (KBr): ν = 3060, 2924, 2828, 1442, 1263, 1146, 913 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{25}N_2OS$: 293.1682, found: 293.1692.

1-[*N*-(Cyclopentylmethyl)-*S*-phenylsulfonimidoyl]piperidine (229d)



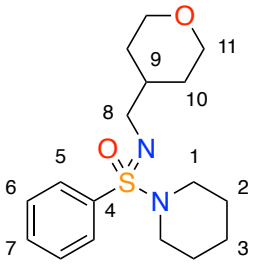
Prepared according to **general procedure N**, from (bromomethyl)cyclopentane; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **229d** as a colourless oil (40 mg, 29%): ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.78–7.76 (m, 2H, 5-H), 7.65–7.56 (m, 3H, 7-H and 6-H), 3.00 (dd, J = 12.0, 6.9 Hz, 1H, 8-H$_a$), 2.87 (dd, J = 12.0, 6.9 Hz, 1H, 8-H$_b$), 2.80 (app t, J = 5.4 Hz, 4H, 1-H), 2.05 (app hept, J = 7.3 Hz, 1H, 9-H), 1.76–1.64 (m, 2H, 10-H$_a$), 1.59–1.46 (m, 8H, 11-H and 2-H), 1.35–1.27 ppm (m, 4H, 10-H$_b$ and 3-H); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.9 (4-C), 132.0 (7-C), 128.8 (6-C), 127.4 (5-C), 47.2 (1-C), 46.0 (8-C), 41.6 (9-C), 30.1 (10-C), 30.0 (10-C), 25.1 (2-C), 25.0 (11-C), 24.9 (11-C), 23.2 (3-C)ppm; IR (KBr): ν = 3065, 2937, 2853, 1265, 1146, 916 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{27}N_2OS$: 307.1844, found: 307.1844.

1-[*N*-(Cyclohexylmethyl)-*S*-phenylsulfonimidoyl]piperidine (229e)



Prepared according to **general procedure N**, from (bromomethyl)cyclohexane; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in PE) to give **229e** as a white solid (102 mg, 71%): m.p. 57–58 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.79–7.76 (m, 2H, 5-H), 7.65–7.56 (m, 3H, 7-H and 6-H), 2.92 (dd, J = 11.9, 6.5 Hz, 1H, 8-H$_a$), 2.81–2.76 (m, 5H, 8-H$_b$ and 1-H), 1.86–1.75 (m, 2H, 10-H$_a$), 1.71–1.61 (m, 3H, 11-H and 12-H), 1.53–1.47 (m, 4H, 2-H), 1.45–1.37 (m, 1H, 9-H), 1.34–1.28 (m, 2H, 3-H), 1.24–1.11 (m, 3H, 11-H and 12-H), 0.94 ppm (qd, J = 12.3, 3.4 Hz, 2H, 10-H$_b$); ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 135.9 (4-C), 132.0 (7-C), 128.8 (6-C), 127.4 (5-C), 47.5 (8-C), 47.1 (1-C), 30.8 (10-C), 26.3 (12-C), 25.6 (11-C), 25.1 (2-C), 23.2 (3-C) ppm; IR (KBr): ν = 3060, 2923, 2832, 1442, 1265, 1156, 917 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{29}N_2OS$: 321.1995, found: 321.2010.

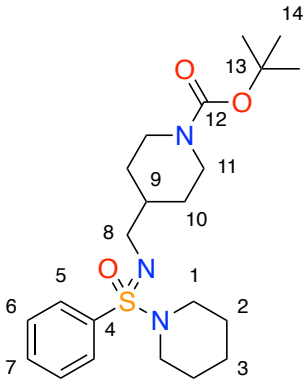
1-[*S*-Phenyl-*N*-(tetrahydro-2*H*-pyran-4-ylmethyl)sulfonimidoyl]piperidine (229f)



Prepared according to **general procedure N**, from 4-(bromomethyl)tetrahydro-2*H*-pyran; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229f** as a colourless oil (86 mg, 60%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 2H, 5-H), 7.55–7.45 (m, 3H, 7-H and 6-H), 3.99 (app ddt, J = 11.7, 4.7, 2.0 Hz, 2H, 11-H$_a$), 3.41 (app tdd, J = 11.7, 4.7, 2.0 Hz, 2H, 11-H$_b$), 3.17 (dd, J = 12.2, 6.1 Hz, 1H, 8-H$_a$), 3.00–2.85 (m, 5H, 1-H and 8-H$_b$), 1.85–1.73 (m, 3H, 9-H and 10-H$_a$), 1.60 (app quin, J = 5.6 Hz, 4H, 2-H), 1.43–1.32 ppm (m, 4H, 10-H$_a$ and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.2 (4-C), 131.8 (7-C), 128.5 (6-C), 127.8 (5-C), 68.0 (11-C), 47.8 (8-C), 47.6 (1-C), 37.6 (9-C), 31.3 (10-C), 31.2 (10-C), 25.5 (2-C), 23.7 (3-C) ppm; IR (KBr): ν =

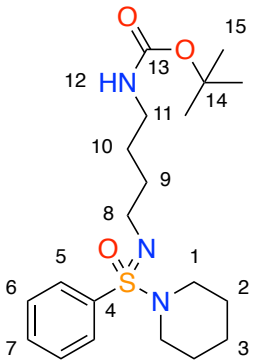
3063, 2918, 2833, 1257, 1153, 918 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{27}N_2O_2S$: 323.1793, found: 323.1793;

tert-Butyl 4-({[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}methyl)piperidine-1-carboxylate (229g)



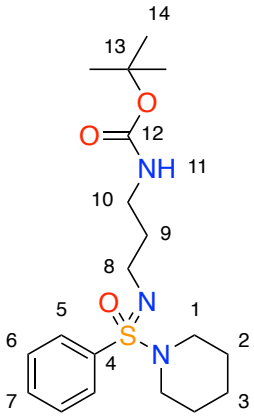
Prepared according to **general procedure N**, from *tert*-butyl 4-(bromomethyl)piperidine-1-carboxylate; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229g** as a colourless oil (65 mg, 35%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.83 (m, 2H, 5-H), 7.55–7.45 (m, 3H, 7-H and 6-H), 4.12 (*br*s, 2H, 11-H_a), 3.17 (dd, J = 12.1, 6.5 Hz, 1H, 8-H_a), 2.96–2.84 (m, 5H, 1-H and 8-H_b), 2.74–2.67 (m, 2H, 11-H_b), 1.90–1.77 (m, 2H, 10-H_a), 1.74–1.64 (m, 1H, 9-H), 1.62–1.57 (m, 4H, 2-H), 1.45 (s, 9H, 14-H), 1.41–1.35 (m, 2H, 3-H), 1.22–1.12 ppm (m, 2H, 10-H_b); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (12-C), 136.2 (4-C), 131.8 (7-C), 128.6 (6-C), 127.8 (5-C), 79.1 (13-C), 47.6 (1-C), 47.5 (8-C), 44.2 (11-C), 38.7 (9-C), 30.3 (10-C), 28.5 (14-C), 25.5 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 3061, 2934, 2918, 2847, 2839, 1690, 1246, 1134, 922 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{36}N_3O_3S$: 422.2477, found: 422.2474.

***tert*-Butyl 4-{[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}butylcarbamate (229h)**



Prepared according to **general procedure N**, from *tert*-butyl 4-bromobutylcarbamate; crude purified by flash column chromatography (KP-NH, 0–100% EtOAc in hexane) to give a mixture of starting material and **229h.** Mixture was purified once more by preparative HPLC (basic gradient E) to give pure product **229h** as an orange oil (22 mg, 13%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.83 (m, 2H, 5-H), 7.55-7.45 (m, 3H, 6-H and 7-H), 7.43 (*brs*, 1H, 12-H), 3.31-3.25 (m, 1H, 8-H_a), 3.19-3.14 (m, 2H, 11-H), 3.09-3.03 (m, 1H, 8-H_b), 2.96-2.84 (m, 4H, 1-H), 1.67-1.57 (m, 8H, 2-H, 9-H and 10-H), 1.45-1.34 ppm (m, 11H, 15-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1 (13-C), 136.3 (4-C), 132.0 (7-C), 128.7 (6-C), 127.9 (5-C), 79.0 (14-C), 47.8 (1-C), 41.8 (8-C), 40.6 (11-C), 30.0 (10-C), 28.6 (15-C), 27.8 (9-C), 25.7 (2-C), 23.9 (3-C) ppm IR (KBr): ν = 3360, 2932, 1693, 1250, 1151 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{36}N_3O_3S$: 396.2321, found: 396.2320.

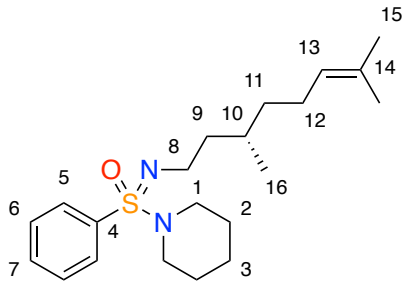
***tert*-Butyl 3-{[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}propylcarbamate (229i)**



Prepared according to **general procedure N**, from *tert*-butyl 3-bromopropylcarbamate; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229i** as a colourless oil (86 mg, 50%): ^{1}H NMR (400 MHz,

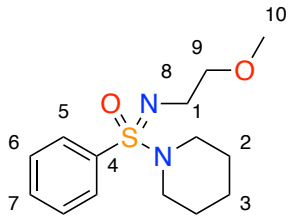
$CDCl_3$): δ = 7.84–7.82 (m, 2H, 5-H), 7.55–7.45 (m, 3H, 7-H and 6-H), 5.33 (*br*s, 1H, 11-H), 3.38–3.24 (m, 3H, 8-H_a and 10-H), 3.12 (dt, J = 12.4, 6.1 Hz, 1H, 8-H_b), 2.99–2.85 (m, 4H, 1-H), 1.76 (m, 2H, 9-H), 1.59 (app quin, J = 5.6 Hz, 4H, 2-H), 1.42–1.34 ppm (m, 11H, 14-H and 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0 (12-C), 136.0 (4-C), 131.9 (7-C), 128.6 (6-C), 127.6 (5-C), 78.6 (13-C), 47.6 (1-C), 39.9 (8-C), 39.4 (10-C), 31.5 (9-C), 28.4 (14-C), 25.5 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 3360, 3063, 2934, 2853, 1707, 1250, 1153, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{32}N_3O_3S$: 382.2164, found: 382.2164.

1-{*N*-[(*S*)-3,7-Dimethyloct-6-en-1-yl]-*S*-phenylsulfonimidoyl}piperidine (229j)



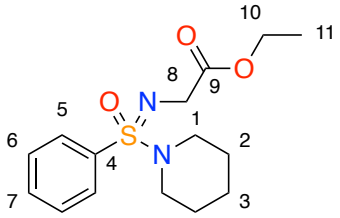
Prepared according to **general procedure N**, from (*S*)-8-bromo-2,6-dimethyloct-2-ene; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229j**, a mixture of diastereoisomers, as a colourless oil (75 mg, 46%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.84 (m, 2H, 5-H), 7.54–7.45 (m, 3H, 7-H and 6-H), 5.11 (tdt, J = 5.7, 2.8, 1.4 Hz, 1H, 13-H), 3.26 (dddd, J = 23.4, 12.3, 8.9, 6.0 Hz, 1H, 8-H_a), 3.10 (dddd, J = 23.4, 12.3, 8.9, 6.0 Hz, 1H, 8-H_b), 2.91 (app qt, J = 11.6, 5.4 Hz, 4H, 1-H), 2.04–1.98 (m, 2H, 12-H), 1.71–1.56 (m, 12H, 10-H, 9-H_a, 2-H and 15-H), 1.52–1.33 (m, 4H, 11-H_a, 9-H_b and 3-H), 1.23–1.13 (m, 1H, 11-H_b), 0.92 ppm (app dd, J = 6.6, 2.0 Hz, 3H, 16-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.3 (4-C), 131.7 (7-C), 131.0 (14-C), 128.5 (6-C), 127.8 (5-C), 125.0 (13-C), 47.7 (1-C), 40.0 (d, J = 10.9 Hz, 8-C or 9-C), 39.9 (8-C or 9-C), 37.2 (11-C), 30.50 (d, J = 17.4 Hz, 10-C), 25.7 (12-C or 15-C), 25.6 (2-C), 25.5 (12-C or 15-C), 23.8 (3-C), 19.6 (16-C), 17.7 (15-C) ppm; IR (KBr): ν = 3065, 2918, 2851, 1445, 1263, 1151, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{35}N_2OS$: 363.2470, found: 363.2469.

1-[*N*-(2-Methoxyethyl)-*S*-phenylsulfonimidoyl]piperidine (229k)



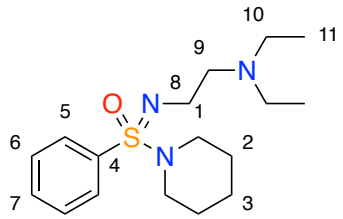
Prepared according to **general procedure N**, from 1-bromo-2-methoxyethane; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in PE) to give **229k** as a yellow oil (100 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.85 (m, 2H, 5-H), 7.55–7.45 (m, 3H, 7-H and 6-H), 3.61–3.57 (m, 2H, 9-H), 3.47–3.41 (m, 1H, 8-H_a), 3.40 (s, 3H, 10-H), 3.27 (dt, J = 12.6, 6.6 Hz, 1H, 8-H_b), 2.95–2.91 (m, 4H, 1-H), 1.60 (app quin, J = 5.7 Hz, 4H, 2-H), 1.40–1.34 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1 (4-C), 132.0 (7-C), 128.7 (6-C), 128.0 (5-C), 74.4 (9-C), 59.0 (10-C), 47.8 (1-C), 41.7 (8-C), 25.7 (2-C), 23.9 (3-C) ppm; IR (KBr): ν = 3063, 2933, 2852, 1445, 1291, 1156, 1118, 917 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{23}N_2O_2S$: 283.1475, found: 283.1489.

Ethyl 2-{[oxo(phenyl)(piperidin-1-yl)-λ^6-sulfanylidene]amino}acetate (229l)



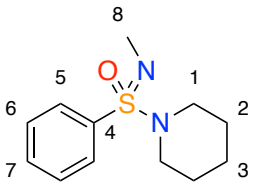
Prepared according to **general procedure N**, from ethyl bromoacetate; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in PE) to give **229l** as a yellow oil (56 mg, 40%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.91 (m, 2H, 5-H), 7.57–7.47 (m, 3H, 6-H and 7-H), 4.22 (tdd, J = 8.2, 6.7, 1.1 Hz, 2H, 10-H), 4.00 (d, J = 17.6 Hz, 1H, 8-H_a), 3.95 (d, J = 17.6Hz, 1H, 8-H_b), 3.01 (dt, J = 11.6, 5.5 Hz, 2H, 1-H_a), 2.93 (dt, J = 11.6, 5.5 Hz, 2H, 1-H_b), 1.62–1.56 (m, 4H, 2-H), 1.39 (quin, J = 6.2 Hz, 2H, 3-H), 1.29 ppm (t, J = 6.7 Hz, 3H, 11-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3 (9-C), 135.7 (4-C), 132.3 (7-C), 128.8 (6-C), 128.1 (5-C), 60.9 (10-C), 47.7 (1-C), 43.8 (8-C), 25.6 (2-C), 23.8 (3-C), 14.4 (11-C) ppm; IR (neat): ν = 3061, 2935, 1747, 1295, 1156, 920 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_3S$: 311.1424, found: 311.1421.

_N_,_N_-Diethyl-2-{[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}ethanamine (229m)



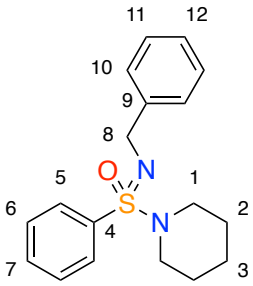
Prepared according to **general procedure N**, from *N*-(2-bromoethyl)-*N*,*N*-diethylamine; crude purified by preparative HPLC (basic gradient F) to give **229m** as a colourless oil (20 mg, 13%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.84 (m, 2H, 5-H), 7.54–7.45 (m, 3H, 7-H and 6-H), 3.40–3.33 (m, 1H, 8-H_a), 3.20–3.13 (m, 1H, 8-H_b), 2.97–2.87 (m, 4H, 1-H), 2.74 (app t, J = 8.0 Hz, 2H, 9-H), 2.61 (q, J = 7.1 Hz, 4H, 10-H), 1.60 (app quin, J = 5.6 Hz, 4H, 2-H), 1.38 (m, 2H, 3-H), 1.06 ppm (t, J = 7.1 Hz, 6H, 11-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1 (4-C), 131.9 (7-C), 128.6 (6-C), 127.8 (5-C), 77.2 (8-C or 9-C or 10-C), 55.3 (8-C or 9-C or 10-C), 47.7 (1-C), 40.3 (9-C or 8-C or 10-C), 25.6 (2-C), 23.7 (3-C), 11.9 (11-C) ppm; IR (KBr): ν = 3063, 2934, 2853, 1265, 1151, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{30}N_3OS$: 324.2110, found: 324.2108.

1-(*N*-Methyl-*S*-phenylsulfonimidoyl)piperidine (229n)



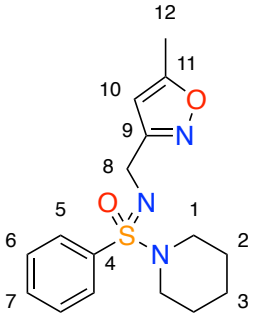
Prepared according to **general procedure N**, from methyl iodide (95 mg, 0.67 mmol, 1.5 equiv); crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229n** as a white solid (63 mg, 59%): m.p. 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 2H, 5-H), 7.55–7.45 (m, 3H, 7-H and 6-H), 2.98–2.85 (m, 4H, 1-H), 2.85 (s, 3H, 8-H), 1.61 (dt, J = 11.5, 5.6 Hz, 4H, 2-H), 1.44–1.35 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.0 (4-C), 131.9 (7-C), 128.6 (6-C), 127.7 (5-C), 47.5 (1-C), 27.9 (8-C), 25.5 (2-C), 23.7 (3-C) ppm; IR (KBr): ν = 2970, 2935, 2812, 1265, 1149, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{19}N_2OS$: 239.1218, found: 239.1218.

1-(*N*-Benzyl-*S*-phenylsulfonimidoyl)piperidine (229o)



Prepared according to **general procedure N**, from benzyl bromide; crude purified by flash column chromatography (KP-Sil, 0–40% EtOAc in hexane) to give **229o** as a colorless oil (80 mg, 57%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.69 (m, 2H, 5-H), 7.34–7.26 (m, 5H, 6-H and 7-H and 10-H), 7.13–7.09 (m, 2H, 11-H), 7.03–6.98 (m, 1H, 12-H), 4.28 (d, J = 14.8 Hz, 1H, 8-H$_a$), 4.11 (d, J = 14.8 Hz, 1H, 8-H$_b$), 2.77–2.64 (m, 4H, 1-H), 1.38–1.30 (m, 4H, 2-H), 1.17–1.12 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.8 (9-C), 136.2 (4-C), 132.0 (7-C), 128.7 (11-C), 128.3 (10-C), 128.0 (6-C), 127.6 (5-C), 126.5 (12-C), 47.8 (1-C), 45.5 (8-C), 25.6 (2-C), 23.8 (3-C) ppm; IR (KBr): ν = 3063, 2937, 1445, 1269, 1151, 924 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{23}N_2OS$: 315.1531, found: 315.1534.

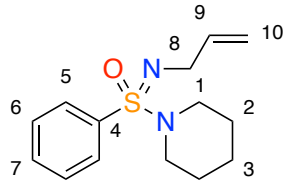
5-Methyl-3-({[oxo(phenyl)(piperidin-1-yl)-λ^6 sulfanylidene]amino}methyl) isoxazole (229p)



Prepared according to **general procedure N**, from 3-(bromomethyl)-5-methylisoxazole; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229p** as a colourless oil (88 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2H, 5-H), 7.57–7.53 (m, 1H, 7-H), 7.51–7.47 (m, 2H, 6-H), 6.16 (s, 1H, 10-H), 4.41 (d, J = 14.8 Hz, 1H, 8-H$_a$), 4.33 (d, J = 14.8 Hz, 1H, 8-H$_b$), 2.99–2.88 (m, 4H, 1-H), 2.39 (s, 3H, 12-H), 1.60 (app quin, J = 5.5 Hz, 4H, 2-H), 1.41–1.35 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.1 (11-C or 9-C), 164.7 (11-C or 9-C), 135.8 (4-C), 132.3 (7-C), 128.8 (6-C), 128.0 (5-C), 101.8 (10-C), 47.8 (1-C), 37.6 (8-C), 25.6 (2-C), 23.8 (3-

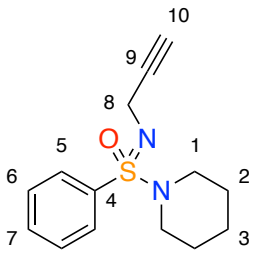
C), 12.4 (12-C) ppm; IR (KBr): ν = 3063, 2935, 2849, 1607, 1445, 1283, 1263, 1148, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{22}N_3O_2S$: 320.1433, found: 320.1434.

1-(*N*-Allyl-*S*-phenylsulfonimidoyl)piperidine (229q)



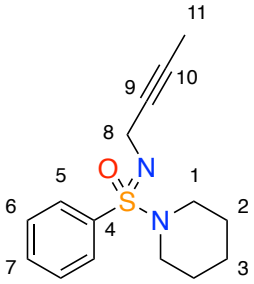
Prepared according to **general procedure N**, from allyl bromide; crude purified by flash column chromatography (KP-Sil, 0–30% EtOAc in hexane) to give **229q** as a yellow oil (85 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2H, 5-H), 7.56–7.46 (m, 3H, 7-H and 6-H), 6.04 (app ddt, J = 17.0, 10.4, 5.3 Hz, 1H, 9-H), 5.36 (app dq, J = 17.0, 1.8 Hz, 1H, 8-H$_a$), 5.09 (app dq, J = 10.4, 1.8 Hz, 1H, 8-H$_b$), 3.89 (app ddt, J = 15.6, 5.3, 1.8 Hz, 1H, 10-H$_a$), 3.77 (app ddt, J = 15.6, 5.3, 1.8 Hz, 1H, 10-H$_b$), 2.98–2.88 (m, 4H, 1-H), 1.60 (dt, J = 11.5, 5.6 Hz, 4H, 2-H), 1.41–1.35 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.1 (9-C), 136.3 (4-C), 132.0 (7-C), 128.7 (6-C), 128.0 (5-C), 114.3 (8-C), 47.8 (1-C), 44.5 (10-C), 25.6 (2-C), 23.8 (3-C) ppm; IR (KBr): ν = 3067, 2935, 2833, 1445, 1269, 1153, 914 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{21}N_2OS$: 265.1375, found: 265.1374.

1-[*S*-Phenyl-*N*-(prop-2-yn-1-yl)sulfonimidoyl]piperidine (229r)



Prepared according to **general procedure N**, from propargyl bromide; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229r** as a yellow oil (74 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2H, 5-H), 7.57–7.47 (m, 3H, 6-H and 7-H), 4.07–3.94 (m, 2H, 8-H), 2.97 (app ddt, J = 12.0, 10.1, 6.3 Hz, 4H, 1-H), 2.22 (app t, J = 2.5 Hz, 1H, 10-H), 1.69–1.56 (m, 4H, 2-H), 1.39 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.4 (4-C), 132.1 (7-C), 128.6 (6-C), 127.7 (5-C), 83.2 (9-C), 69.7 (10-C), 47.7 (1-C), 30.8 (8-C), 25.4 (2-C), 23.6 (3-C) ppm; IR (KBr): ν = 3267, 2937, 2841, 1445, 1269, 1230, 1144, 916 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{19}N_2OS$: 263.1218, found: 263.1219.

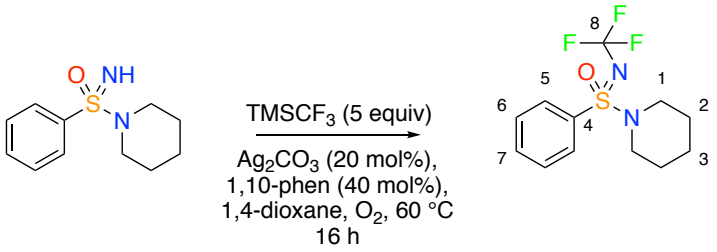
1-[*N*-(But-2-yn-1-yl)-*S*-phenylsulfonimidoyl]piperidine (229s)



Prepared according to **general procedure N**, from 1-bromobut-2-yne; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in hexane) to give **229s** as a yellow oil (87 mg, 71%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2H, 5-H), 7.56–7.46 (m, 3H, 7-H and 6-H), 3.96 (app quin, J = 2.4 Hz, 2H, 8-H), 2.97 (m, 4H, 1-H), 1.83 (app t, J = 2.5 Hz, 3H, 11-H), 1.65–1.59 (m, 4H, 2-H), 1.42–1.36 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.6 (4-C), 132.0 (7-C), 128.6 (6-C), 127.8 (5-C), 78.2 (9-C), 47.8 (1-C), 31.2 (8-C), 25.5 (2-C), 23.7 (3-C), 3.8 (11-C) ppm; IR (KBr): ν = 3063, 2937, 2851, 1672, 1445, 1230, 1149, 916 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}N_2OS$: 277.1375, found: 277.1376.

4.10 *N*-Trifluoromethylation of sulfonimidamide 55a[255]

1-[*S*-Phenyl-*N*-(trifluoromethyl)sulfonimidoyl]piperidine (230)



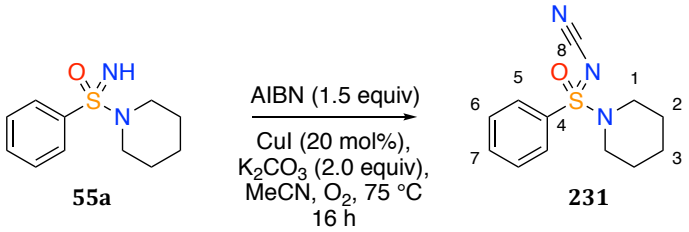
55a **230**

In a MW vial charged with sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.00 equiv), $TMSCF_3$ (4.44 mL, 2.22 mmol, 5.00 equiv; 0.5 M solution in THF), Ag_2CO_3 (24 mg, 0.09 mmol, 0.2 equiv), 1,10-phenanthroline (32 mg, 0.18 mmol, 0.4 equiv) and 1,4-dioxane (8.9 mL) were added. Then, a balloon charged with O_2 was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 60 °C for 16 h. Then, the solution was cooled, solvent removed in vacuo and the crude product purified by flash column chromatography (KP-Sil, 0–50% EtOAc in PE) to give **230** as a yellow oil (57 mg, 44%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.86 (m, 2H, 5-H), 7.65–7.60 (m, 1H, 7-H), 7.57–7.53 (m, 2H, 6-H), 3.11–3.00 (m, 4H, 1-H), 1.68–1.62 (m, 4H, 2-H), 1.48–1.42 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 135.6 (4-C), 133.3 (7-C), 129.2 (6-C), 127.5 (5-C), 121.6 (q, J = 255 Hz, 8-C), 47.5 (1-C), 25.3 (2-

C), 23.7 (3-C) ppm; IR (neat): ν = 3069, 2944, 2856, 1256, 1077, 921 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{16}N_2OF_3S$: 293.0930, found: 293.0935.

4.11 *N*-Cyanation of sulfonimidamide 55a[254]

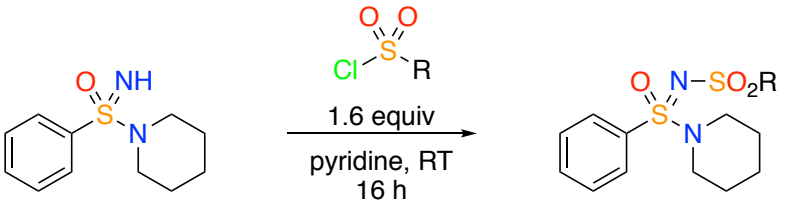
N-[Oxo(phenyl)(piperidin-1-yl)-λ^6-sulfanylidene]cyanamide (231)



In a MW vial charged with sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.0 equiv), AIBN (108 mg, 0.66 mmol, 1.5 equiv), CuI (16 mg, 0.09 mmol, 0.2 equiv), K_2CO_3 (122 mg, 0.88 mmol, 2.0 equiv) and MeCN (6.7 mL) were added. Then, a balloon charged with O_2 was attached to the MW vial and the solution was degassed for 10 min. The mixture was stirred and heated in an oil bath at 75 °C for 16 h. Then, the solution was cooled, filtered and the solids washed with MeCN. The liquid phase was collected, solvent removed in vacuo and the crude product purified by flash column chromatography (KP-Sil, 0–100% EtOAc in PE) to give **231** as a brown oil (47 mg, 43%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2H, 5-H), 7.72–7.67 (m, 1H, 7-H), 7.62–7.57 (m, 2H, 6-H), 3.14 (app td, J = 5.6, 2.2 Hz, 4H, 1-H), 1.77–1.63 (m, 4H, 2-H), 1.54–1.46 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 134.4 (7-C), 133.6 (4-C), 129.7 (6-C), 127.8 (5-C), 111.2 (8-C), 47.4 (1-C), 25.1 (2-C), 23.4 (3-C) ppm; IR (neat): ν = 3063, 2924, 2853, 2151, 1268, 1200, 924 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{16}N_3OS$: 250.1009, found: 250.1011.

4.12 *N*-Sulfonylation of sulfonimidamide 55a

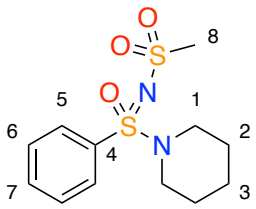
General procedure O:



55a **232a-b**

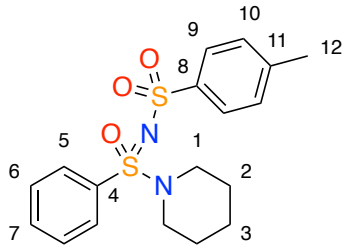
Sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.00 equiv) was dissolved in pyridine (3.0 mL) under Ar atmosphere; then, the appropriate sulfonyl chloride (0.71 mmol, 1.6 equiv) was added. The reaction mixture was stirred at RT overnight; then, the reaction was quenched with aqueous saturated $NaHCO_3$, the organic layer was extracted with EtOAc (3 × 10 mL) and the combined extracts were washed with brine (3 × 10 mL). The organic layers were dried over water-repellent filter paper, solvent removed in vacuo and the crude product purified (when needed).

N-[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]methanesulfonamide (232a)



Prepared according to **general procedure O**, from methanesulfonyl chloride; crude purified by preparative HPLC (basic gradient C) to give **232a** as a white solid (83 mg, 62%): m.p. 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 2H, 5-H), 7.67–7.63 (m, 1H, 7-H), 7.59–7.54 (m, 2H, 6-H), 3.23 (ddd, J = 11.4, 7.1, 4.0 Hz, 2H, 1-H_a), 3.18 (s, 3H, 8-H), 3.10 (ddd, J = 11.4, 7.1, 4.0 Hz, 2H, 1-H_b), 1.74–1.60 (m, 4H, 2-H), 1.49 ppm (quin, J = 5.9 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.1 (4-C), 133.7 (7-C), 129.4 (6-C), 127.6 (5-C), 47.2 (1-C), 45.0 (8-C), 25.1 (2-C), 23.5 (3-C) ppm; IR (KBr): ν = 2939, 2856, 1311, 1246, 1099, 918 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_{19}N_2O_3S_2$: 303.0837, found: 303.0838.

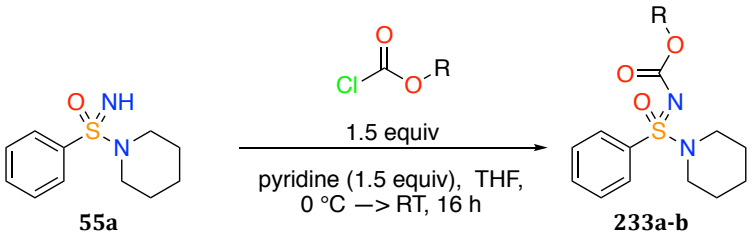
4-Methyl-*N*-[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]benzenesulfonamide (232b)



Prepared according to **general procedure O**, from *p*-toluenesulfonyl chloride; after workup, the ^{1}H NMR spectrum indicated clean formation of **232b** as a yellow solid (97 mg, 58%): m.p. 124–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.84 (m, 4H, 5-H and 9-H), 7.63–7.59 (m, 1H, 7-H), 7.54–7.49 (m, 2H, 6-H), 7.26–7.24 (m, 2H, 10-H), 3.24–3.18 (m, 2H, 1-H_a), 3.11–3.05 (m, 2H, 1-H_b), 2.39 (s, 3H, 12-H), 1.69–1.59 (m, 4H, 2-H), 1.47 ppm (quin, J = 5.7 Hz, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.8 (8-C or 11-C), 141.0, 136.2 (4-C), 133.5 (7-C), 129.3 (6-C or 10-C), 129.2 (10-C or 6-C), 127.7 (9-C or 5-C), 126.9 (5-C or 9-C), 47.2 (1-C), 25.1 (2-C), 23.6 (3-C), 21.7 (12-C) ppm; IR (neat): ν = 3063, 2936, 2857, 1312, 1257, 1155, 1112, 1088, 922 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{18}H_{23}N_2O_3S_2$: 379.1145, found: 379.1151.

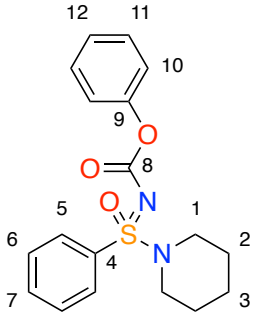
4.13 *N*-Alkoxycarbonylation of sulfonimidamide 55a (carbamate formation)[316]

General procedure P:



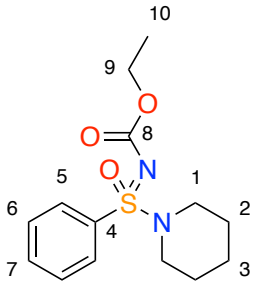
To a solution of sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.0 equiv) and pyridine (54 µL, 0.67 mmol, 1.50 equiv) in THF (0.9 mL) under Ar atmosphere at 0 °C, the corresponding chloroformate (0.67 mmol, 1.50 equiv) was added. As soon as the chloroformate was in solution, a white precipitate formed. The temperature was allowed to rise to RT and the mixture was stirred overnight. The reaction was quenched with aqueous saturated $NaHCO_3$, the organic layer was extracted with Et_2O (3 × 10 mL), and the combined extracts were washed with 1 M HCl (3 × 10 mL) and brine (3 × 10 mL). The extracts were dried over water-repellent filter paper, solvent removed in vacuo and the crude product purified (when needed).

Phenyl [oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]carbamate (233a)



Prepared according to **general procedure P**, from phenyl chloroformate; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in PE) to give **233a** as a white solid (90 mg, 60%): m.p. 114–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2H, 5-H), 7.65–7.60 (m, 1H, 7-H), 7.58–7.53 (m, 2H, 6-H), 7.34–7.29 (m, 2H, 10-H), 7.17–7.11 (m, 3H, 12-H and 11-H), 3.25–3.15 (m, 4H, 1-H), 1.66 (app quin, J = 5.6 Hz, 4H, 2-H), 1.53–1.47 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.1 (8-C), 151.8 (9-C), 136.2 (4-C), 133.4 (7-C), 129.3 (10-C or 6-C), 129.2 (6-C or 10-C), 127.9 (5-C), 125.3 (12-C), 121.8 (11-C), 46.7 (1-C), 25.3 (2-C), 23.7 (3-C) ppm; IR (neat): ν = 3068, 2945, 2856, 1687, 1274, 1248, 1194, 877 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{21}N_2O_3S$: 345.1267, found: 345.1275.

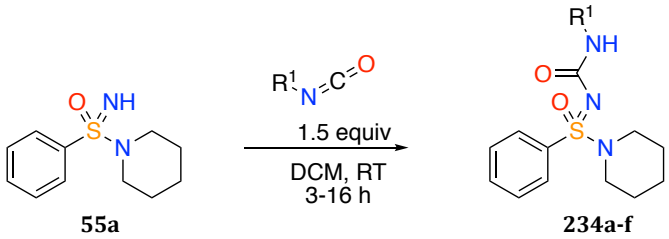
Ethyl [oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]carbamate (233b)



Prepared according to **general procedure P**, from ethyl chloroformate; after workup, the ^{1}H NMR spectrum indicated clean formation of **233b** as a yellow solid (90 mg, 69%): m.p. 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 2H, 5-H), 7.62–7.58 (m, 1H, 7-H), 7.56–7.51 (m, 2H, 6-H), 4.11 (q, J = 7.1 Hz, 2H, 9-H), 3.14 (app td, J = 5.0, 3.0 Hz, 4H, 1-H), 1.64 (app quin, J = 5.7 Hz, 4H, 2-H), 1.50–1.43 (m, 2H, 3-H), 1.23 ppm (app t, J = 7.1 Hz, 3H, 10-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.9 (8-C), 136.4 (4-C), 133.1 (7-H), 129.2 (6-H), 127.8 (5-H), 62.0 (9-C), 46.7 (1-C), 25.3 (2-C), 23.7 (3-C), 14.5 (10-C) ppm; IR (neat): ν = 2946, 1668, 1252, 885 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{21}N_2O_3S$: 297.1267, found: 297.1278.

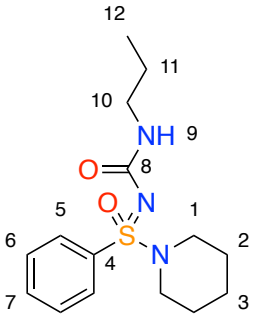
4.14 *N*-Aminocarbonylation of sulfonimidamide 55a (urea formation)[285]

General procedure Q:



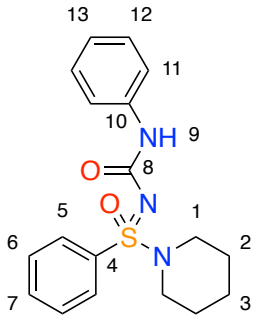
To a solution of sulfonimidamide **55a** (100 mg, 0.45 mmol, 1.0 equiv) in anhydrous DCM (0.9 mL), the corresponding isocyanate (0.66 mmol, 1.5 equiv) was added dropwise at RT under Ar atmosphere. The reaction mixture was stirred until a precipitate formed (3–16 h) and starting material was consumed (TLC analysis). Et_2O was added, and the precipitate was collected by filtration under reduced pressure and washed with Et_2O. The solid was purified by flash column chromatography (when needed).

1-[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]-3-propylurea (234a)



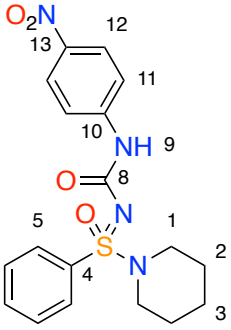
Prepared according to **general procedure Q**, from *n*-propyl isocyanate; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in PE) to give **234a** as a colourless oil (89 mg, 65%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (app dt, J = 8.4, 1.3 Hz, 2H, 5-H), 7.59–7.55 (m, 1H, 7-H), 7.51 (app ddd, J = 8.4, 6.5, 1.3 Hz, 2H, 6-H), 5.16 (*br*s, 1H, 9-H), 3.17–3.06 (m, 6H, 10-H and 1-H), 1.63 (app quin, J = 5.4 Hz, 4H, 2-H), 1.55–1.42 (m, 4H, 3-H and 11-H), 0.92–0.88 ppm (m, 3H, 12-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.4 (8-C), 137.1 (4-C), 132.7 (7-C), 129.0 (6-C), 127.7 (5-C), 46.9 (1-C), 42.4 (10-C), 25.4 (2-C), 23.7 (3-C), 23.3 (11-C), 11.5 (12-C) ppm; IR (neat): ν = 3252, 2931, 2855, 1617, 1520, 1244, 931 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{24}N_3O_2S$: 310.1584, found: 310.1602.

1-[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]-3-phenylurea (234b)



Prepared according to **general procedure Q**, from phenyl isocyanate; crude purified by flash column chromatography (KP-Sil, 0–50% EtOAc in PE) to give **234b** as a white solid (120 mg, 79%): m.p. 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.90 (m, 2H, 5-H), 7.63–7.58 (m, 1H, 7-H), 7.57–7.52 (m, 2H, 6-H), 7.45–7.42 (m, 2H, 11-H), 7.28–7.24 (m, 2H, 12-H), 7.02–6.98 (m, 1H, 13-H), 3.21–3.11 (m, 4H, 1-H), 1.66 (app quin, J = 5.6 Hz, 4H, 2-H), 1.51–1.45 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.3 (10-C), 136.9 (4-C), 133.0 (7-C), 129.2 (6-C or 12-C), 129.0 (12-C or 6-C), 127.8 (5-C), 122.9 (13-C), 118.8 (11-C), 46.3 (1-C), 25.4 (2-C), 23.7 (3-C) ppm; IR (neat): ν = 3296, 2940, 2844, 1632, 1540, 1438, 1235, 939 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{18}H_{22}N_3O_2S$: 344.1438, found: 344.1427.

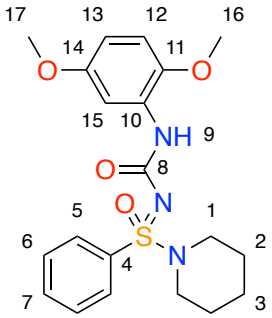
1-(4-Nitrophenyl)-3-[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]urea (234c)



Prepared according to **general procedure Q**, from 4-nitrophenyl isocyanate; after workup, the ^{1}H NMR spectrum indicated clean formation of **234c** as a yellow solid (141 mg, 82%): m.p. >207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16–8.12 (m, 2H, 11-H), 7.92–7.89 (m, 2H, 5-H), 7.66–7.55 (m, 5H, 12-H and 6-H and 7-H), 7.30 (*br*s, 1H, 9-H), 3.19–3.16 (m, 4H, 1-H), 1.67 (app quin, J = 5.9 Hz, 4H, 2-H), 1.53–1.47 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0 (8-C), 145.5 (10-C or 13-C), 142.5 (13-C or 10-C), 136.3 (4-C), 133.4 (7-C), 129.4 (6-C), 127.7 (5-C), 125.2 (11-C), 117.8 (12-C), 46.8 (1-C), 25.3 (2-C), 23.7 (3-C) ppm; IR (neat): ν = 3314, 2923, 1639, 1545, 1491, 1239, 1107,

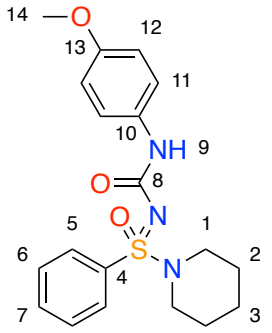
931 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{21}N_4O_4S$: 389.1278, found: 389.1297.

1-(2,5-Dimethoxyphenyl)-3-[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]urea (234d)



Prepared according to **general procedure Q**, from 2,5-dimethoxyphenyl isocyanate; after workup, the ^1H NMR spectrum indicated clean formation of **234d** as a white solid (133 mg, 75%): m.p. 128–130 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (*br*s, 1H, 9-H), 7.93–7.90 (m, 2H, 5-H), 7.62–7.52 (m, 4H, 15-H and 7-H and 6-H), 6.74 (d, J = 8.9 Hz, 1H, 13-H or 12-H), 6.46 (dd, J = 8.9, 3.1 Hz, 1H, 13-H or 12-H), 3.82 (s, 3H, 16-H or 17-H), 3.73 (s, 3H, 16-H or 17-H), 3.20–3.10 (m, 4H, 1-H), 1.68–1.64 (m, 4H, 2-H), 1.50–1.44 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.0 (8-C), 154.1 (10-C or 11-C or 14-C), 141.7 (10-C or 11-C or 14-C), 136.6 (4-C), 132.8 (7-C), 129.8 (15-C), 129.1 (6-C), 127.7 (5-C), 110.8 (13-C or 12-C), 107.3 (13-C or 12-C), 104.6, 56.3 (16-C or 17-C), 55.8 (16-C or 17-C), 46.7 (1-C), 25.3 (2-C), 23.6 (3-C) ppm; IR (neat): ν = 3396, 2982, 2836, 1651, 1527, 1241, 1212, 1041, 934 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{26}N_3O_4S$: 404.1639, found: 404.1656.

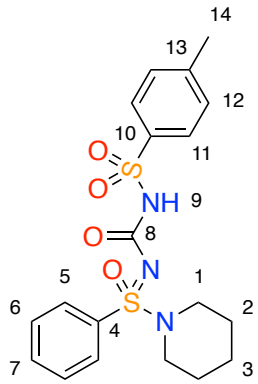
1-(4-Methoxyphenyl)-3-[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]urea (234e)



Prepared according to **general procedure Q**, from 4-methoxyphenyl isocyanate; after workup, the ^1H NMR spectrum indicated clean formation of **234e** as a white solid (134

mg, 82%): m.p. 205–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 7.6 Hz, 2H, 5-H), 7.62–7.58 (m, 1H, 7-H), 7.55–7.51 (m, 2H, 6-H), 7.35 (d, J = 8.6 Hz, 2H, 11-H), 6.87 (*br*s, 1H, 9-H), 6.83–6.79 (m, 2H, 12-H), 3.76 (s, 3H, 14-H), 3.21–3.11 (m, 4H, 1-H), 1.65 (app quin, J = 5.6 Hz, 4H, 2-H), 1.50–1.45 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.0 (4-C), 132.9 (7-C), 129.2 (6-C), 127.8 (5-C), 120.6 (11-C), 114.2 (12-C), 55.7 (14-C), 46.8 (1-C), 25.4 (2-C), 23.7 (3-C) ppm; IR (neat): ν = 3310, 2942, 1629, 1507, 1185, 939 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{19}H_{24}N_3O_3S$: 374.1533, found: 374.1539.

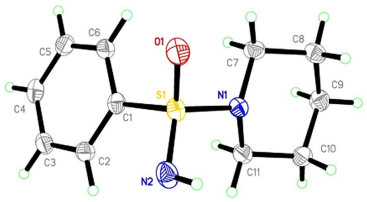
4-Methyl-*N*-{[oxo(phenyl)(piperidin-1-yl)-λ^{6}-sulfanylidene]carbamoyl} benzenesulfonamide (234f)



Prepared according to **general procedure Q**, from 4-methylbenzenesulfonyl isocyanate; crude purified by flash column chromatography (KP-Sil, 0–100% EtOAc in PE) to give **234f** as a colourless oil (92 mg, 49%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.1 Hz, 2H, 11-H), 7.81–7.79 (m, 2H, 5-H), 7.62–7.58 (m, 1H, 7-H), 7.51 (app t, J = 5.9 Hz, 2H, 6-H), 7.24 (d, J = 8.1 Hz, 2H, 12-H), 3.10–2.96 (m, 4H, 1-H), 2.39 (s, 3H, 14-H), 1.58–1.56 (m, 4H, 2-H), 1.44–1.42 ppm (m, 2H, 3-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.4 (8-C), 144.3 (4-C or 13-C or 10-C), 136.7 (4-C or 13-C or 10-C), 135.6 (4-C or 13-C or 10-C), 133.5 (7-C), 129.5 (6-C or 12-C), 129.4 (6-C or 12-C), 128.2 (11-C), 127.8 (5-C), 46.6 (1-C), 25.2 (2-C), 23.6 (3-C), 21.7 (14-C) ppm; IR (neat): ν = 3244, 2940, 2854, 1674, 1329, 1253, 1153, 926 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^{+}$ calcd for $C_{19}H_{24}N_3O_4S_2$: 422.1203, found: 422.1209.

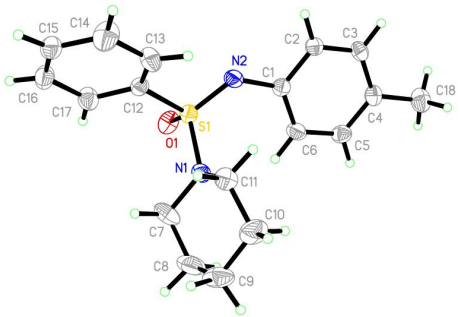
Appendix A: Crystal Structural Data

1-(*S*-Phenylsulfonimidoyl)piperidine (55a)



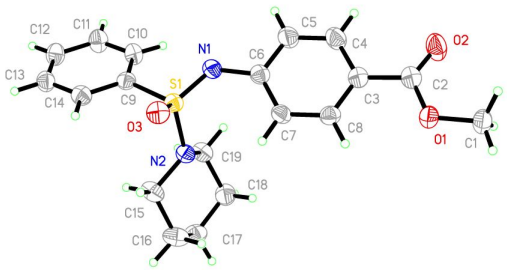
Colorless needles of compound **55a** were obtained by slow evaporation of a DCM solution of the compound at room temperature. A single crystal with dimensions of 0.22 x 0.18 x 0.04 mm^3 was mounted on a CryoLoop using a protective oil. **55a** crystallizes in the orthorhombic space group *Pbca* with cell constants of a = 9.8297(4) Å, b = 12.5188(5) Å and c = 18.3150(7) Å. A total of 45480 reflections of which 1580 are unique (R_{int} = 0.0345) were collected. The final R values were R_1 = 0.0297, I > 2s(I) and wR_2 = 0.0790 for all data. The crystallographic data for **55a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with deposition code CCDC 1569323.

1-[*S*-Phenyl-*N*-(4-tolyl)sulfonimidoyl]piperidine (228g)



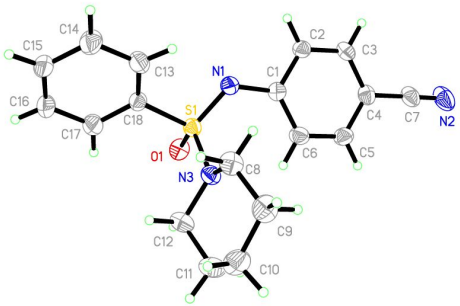
Compound **228g** was crystallized by slow evaporation of a DCM solution of the compound at RT. A single crystal with dimensions of 0.2 × 0.1 × 0.03 mm^3 was mounted on a CryoLoop using a protective oil. **228g** crystallizes in the monoclinic space group *C2/c* with cell constants of a = 27.748(17) Å, b = 7.812(4) Å, c = 19.68(2) Å and b = 130.935(8)°. A total of 36030 reflections of which 2468 are unique (R_{int} = 0.0260) were collected. The final R values were R_1 = 0.0376, I > 2s(I) and wR_2 = 0.1012 for all data. The crystallographic data for **228g** have been deposited with the Cambridge Crystallographic Data Centre with deposition code CCDC 1841270.

Methyl 4-{[oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}benzoate (228i)



Colorless needles of compound **228i** were obtained by slow evaporation of a DCM solution of the compound at RT. A single crystal with dimensions of 0.17 × 0.10 × 0.02 mm³ was mounted on a CryoLoop using a protective oil. **228i** crystallizes in the monoclinic space group *P2(1)/c* with cell constants of *a* = 7.6392(3) Å, *b* = 10.0895(4) Å, *c* = 23.1311(9) Å and b = 91.384(2)°. A total of 35295 reflections of which 2677 are unique (R_{int} = 0.0383) were collected. The final *R* values were R_1 = 0.0335, I > 2s(I) and wR_2 = 0.0929 for all data. The crystallographic data for **228i** have been deposited with the Cambridge Crystallographic Data Centre with deposition code CCDC 1841273.

4-{[Oxo(phenyl)(piperidin-1-yl)-λ⁶-sulfanylidene]amino}benzonitrile (228j)



Compound **228j** was crystallized by slow evaporation of a DCM solution of the compound at RT. A single crystal with dimensions of 0.72 × 0.15 × 0.03 mm³ was mounted on a CryoLoop using a protective oil. **228j** crystallizes in the monoclinic space group *C2/c* with cell constants of *a* = 27.3860(14) Å, *b* = 7.8635(4) Å, *c* = 19.710(1) Å and b = 129.787(1)°. A total of 31481 reflections of which 2289 are unique (R_{int} = 0.0270) were collected. The final *R* values were R_1 = 0.0327, I > 2s(I) and wR_2 = 0.0892

for all data. The crystallographic data for **228j** have been deposited with the Cambridge Crystallographic Data Centre with deposition code CCDC 1841271.

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