Syntheses, Modifications and Biological Applications of Sulfoximines and Aromatic Pentafluorosulfanyl Compounds

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

vorgelegt von

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What the elements are to chemistry,
what the sounds are to music,
are words to language.

Ernest Klein

To my roots, to my wings

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1 Introduction

"*Sulphur exists in two distinct crystalline forms and in an amorphous form. It is manufactured largely from native sulphides of copper and iron; when refined and cast into moulds, it is the roll sulphur or stick sulphur of commerce. It is highly inflammable, and is used in the manufacture of matches, gunpowder, and sulphuric acid, for vulcanizing rubber, in bleaching, and as a disinfectant. In popular belief sulphur has been associated with the fires of hell, with devils, and with thunder and lightning.*"
The Oxford English Dictionary.[1]

Already known since the ancient Egyptians 3000 BCE, sulfur has been a fascinating element due to its variable appearance and diverse properties.[2] It is essential for life.[3] From the healing effects of sulfur-rich springs also present in Aachen[4] to modern drug development,[5] the biological activities of sulfur compounds have always played a valuable role. To date, the incorporation of sulfur-containing functional groups into organic molecules receives growing interest, including sulfoximines, sulfilimines, and pentafluorosulfanyl compounds that are the subject of this work.

1.1 Sulfoximines and Sulfilimines

1.1.1 Physicochemical properties and applications

Varying the oxidation state of the sulfur atom (IV, VI) and changing the number of S–O and S–N bonds generates tetracoordinated and tricoordinated sulfur-containing motifs (Figure 1.1). Well-known tetracoordinated sulfur compounds are sulfones, containing two oxygen atoms connected to the sulfur atom.[6] Replacing an oxygen atom by nitrogen leads to sulfoximines, their mono-aza analogs.[7] Contrary to sulfones, they can bear a stereogenic center depending on the R^1, R^2 substitution pattern. Exchanging both oxygen atoms by nitrogen provides sulfondiimines, their di-aza analogs.[8] Important tricoordinated sulfur compounds are sulfoxides, comprising one oxygen atom binding to the sulfur.[9] Depending on the substituents R^1 and R^2 they can be chiral. Exchanging the oxygen atom by nitrogen leads to sulfilimines (sulfimides), their aza-analogs.[10]

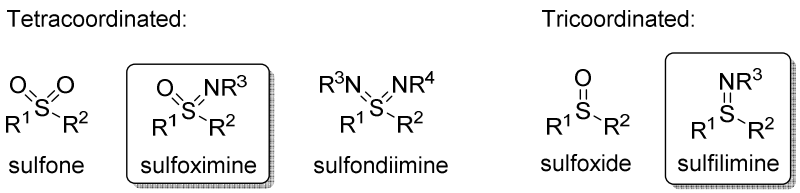


Figure 1.1: Sulfur compounds including sulfoximines and sulfilimines.

Sulfoximines exhibit the coordination sphere of a slightly distorted tetrahedron at the stereogenic sulfur atom and a high double bond character of the S–O and S–N bonds (Figure 1.2).[7b,11] Typically, the nitrogen atom possesses an amphoteric character. It is nucleophilic and basic, while the imine hydrogen atom is acidic ($pK_a \sim 24$ for R^1 = Ph, R^2 = H, R^3 = H).[7b,12] The hydrogen atoms in α-position to the sulfur atom are acidic as

well ($pK_a \sim 32$ for R^1 = Ph, R^2 = H, R^3 = Me; $pK_a \sim 23$ for R^1 = Ph, R^2 = H, R^3 = Ts). Sulfoximidoyl functionalities feature high thermal, chemical, and configurative stability.

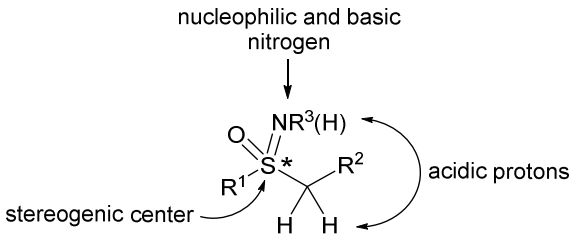


Figure 1.2: Properties of sulfoximidoyl functionalities.

Owing to their unique properties, sulfoximines have widespread applications in organic synthesis and catalysis.[7,13] Their biochemical uses[11b] range from backbones of pseudopeptides[14] to functionalities in drugs[15] and crop protecting agents.[16]

Contrary to sulfoximines, the structure and physicochemical properties of sulfilimines have not yet been sufficiently explained. Crystal structure analyses of several derivatives reveal that the stereogenic sulfur atom, which is surrounded by two substituents R^1 and R^2, a nitrogen atom, and a free electron pair, displays the structure of a trigonal pyramid (Figure 1.3).[17] Though single enantiomers are stable at ambient temperature, racemization is observed at elevated temperatures (100 °C), presumably due to pyramidal inversion.[18] There is no standardized concept explaining the character of the S–N bond in sulfilimines. Generally, the stability of the S–N bond is highly dependent on the nature of the R^3 substituent at the nitrogen atom. Electron-withdrawing substituents can stabilize the negative charge thus leading to stable sulfilimines.[10a,10c,19] Notably, as the oxidation state at the sulfur atom is IV, sulfilimines can be reactive intermediates, allowing further substitution at the sulfur atom.

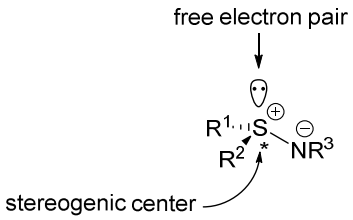


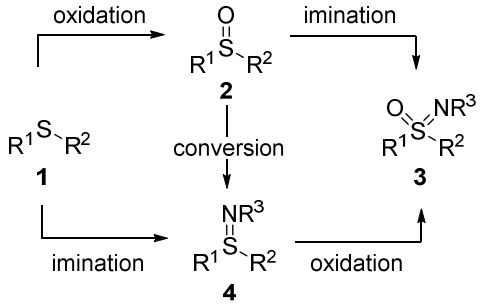
Figure 1.3: Properties of sulfilimidoyl functionalities.

Sulfilimines have been utilized in chemical synthesis[10b] and stereoselective reactions.[10a] However, contrary to sulfoximines, their use in this field is still limited as the number of efficient methods for their enantiopure preparation is short.[20] Sulfilimines are increasingly recognized as useful intermediates in the synthesis of racemic sulfoximines.[7b,21] Only few studies on their biological activities have been reported.[22]

1.1.2 Synthetic routes to sulfoximines and sulfilimines

There are two main synthetic routes from sulfides **1** to sulfoximines **3**. Following a frequently applied pathway, sulfide oxidation to sulfoxides **2** is performed first. Subsequent imination involves sulfoximine formation (Scheme 1.1, top). An alternate

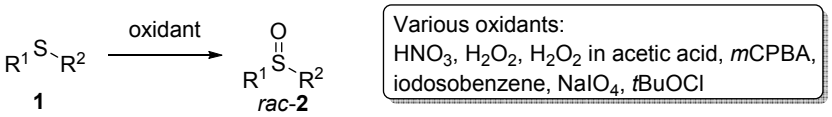
route comprises sulfide imination to sulfilimines **4**, followed by oxidation (Scheme 1.1, bottom). Less common are sulfoxide-to-sulfilimine conversions, giving sulfilimines **4** by using special conditions or reagents (Scheme 1.1, middle).



Scheme 1.1: Routes to sulfoximines **3** and sulfilimines **4**.

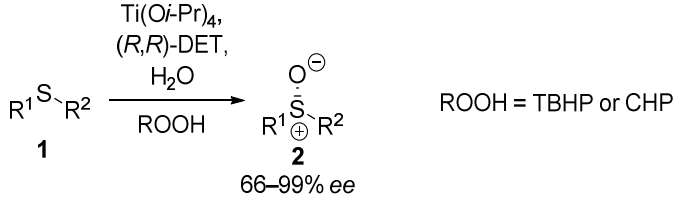
Oxidations of sulfides to sulfoxides

Sulfoxides find numerous applications in organic synthesis and catalysis,[9b,23] and pharmaceutical compounds.[24] Consequently, plenty of methods for their preparation have been developed. Racemic sulfoxides **2** can be synthesized from sulfides **1** by using various oxidants including nitric acid,[25] hydrogen peroxide,[26] hydrogen peroxide in acetic acid,[27] *meta*-chloroperbenzoic acid (*m*CPBA),[28] iodosobenzene,[29] sodium periodate,[30] and *tert*-butyl hypochlorite (Scheme 1.2).[31]



Scheme 1.2: Racemic sulfoxidation.

The preparation of enantioenriched sulfoxides **2** has been widely explored. For example, they can be obtained by chiral resolution of racemic sulfoxides, from diastereochemically pure sulfinates (*Andersen's* method[32]) and sulfinamides with use of organometallic reagents. Alternatively, prochiral sulfides can be oxidized enantioselectively with enzymes or metal catalysts. Among the latter, sulfoxidations utilizing titanium-DET complexes, generated from Ti(O*i*-Pr)$_4$, (*R*,*R*)-DET, water, and *tert*-butyl hydroperoxide (TBHP) or cumene hydroperoxide (CHP), in stoichiometric and later catalytic amounts (*Kagan's* method[33]), have emerged as useful tools, even in large-scale pharmaceutical applications[34] (Scheme 1.3). A variety of other methods includes vanadium-catalyzed[35] and iron-catalyzed[36] asymmetric sulfide oxidations by *Bolm* and others, affording sulfoxides in high yields and high enantioselectivities.

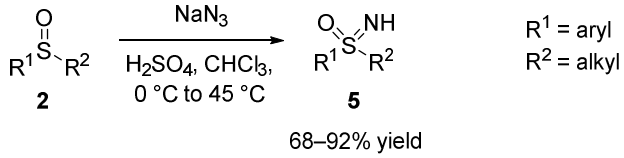


Scheme 1.3: Enantioselective catalytic sulfoxidation with Ti/DET-complexes.

Imination methods for sulfoxides and sulfides

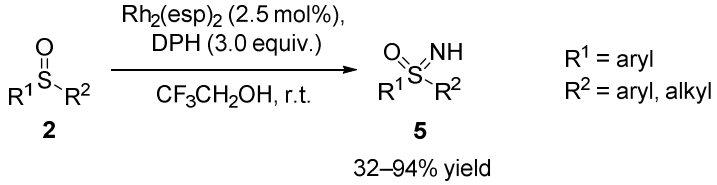
The research interest in sulfoximines and their derivatives gave rise to various methods, developed for the imination of sulfoxides and sulfides, which employ different nitrene sources.[21a] Several allow the direct formation of *N*H-sulfoximines (most *N*H-sulfilimines are unstable), while others introduce *N*-protecting groups.

The oldest but still frequently applied procedure is the imination of sulfoxides with hydrazoic acid, *in situ* generated from sodium azide and sulfuric acid, leading directly to *N*H-sulfoximines **5** (Scheme 1.4).[37,38] Since then, iminations of sulfides and sulfoxides with azides have been developed further by using iron[39] and ruthenium catalysts.[40] It is important to note that safety precautions must be taken due to the toxicity and explosiveness of these reagents.[41]



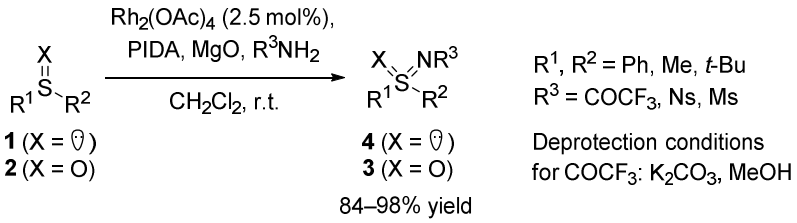
Scheme 1.4: Sulfoxide imination with *in situ* generated hydrazoic acid.

Early reported imination methods utilize hydroxylamine-*O*-sulfonic acid (HOSA)[42] or *O*-mesitylensulfonylhydroxylamine (MSH).[43] Contrary to HOSA, MSH is a well known, but thermally unstable imination agent for sulfides and sulfoxides, requiring special care.[44] A recently developed procedure enables the direct synthesis of *N*H-sulfoximines **5** from sulfoxides avoiding dangerous reagents. $Rh_2(esp)_2$ as the catalyst and *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) as nitrene source provide access to *N*H-sulfoximines **5** that are generally obtained in good yields (Scheme 1.5).[45]



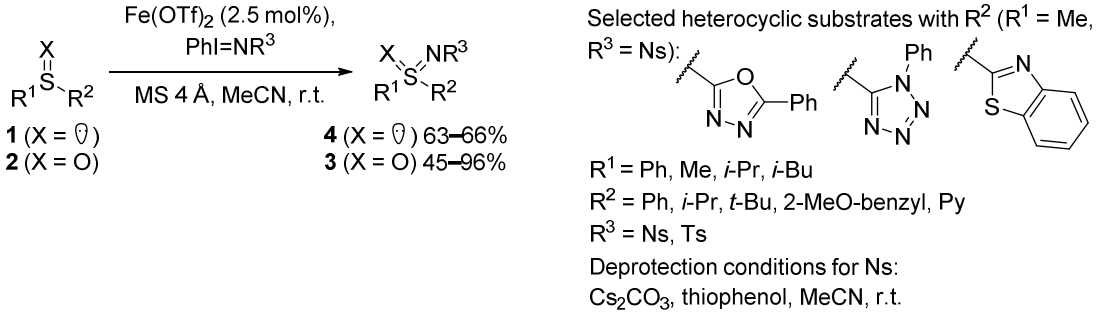
Scheme 1.5: Rhodium-catalyzed sulfoxide imination with DPH.

An important class of iminating agents are iminoiodinanes ($R^1N{=}IR^2$) that can be used with or without metal catalyst[46] under mild and safe conditions. Either added to the reaction mixture as preformed reagents or, advantageously, generated *in situ*, they lead to the formation of *N*-protected sulfilimines **4** or sulfoximines **3**. These reactions can be catalyzed by copper whereas the generally introduced *N*-tosyl group is difficult to remove.[13c,47] A solution to this problem is the application of $Rh_2(OAc)_4$ as the catalyst, reported by the group of *Bolm* (Scheme 1.6).[48] *N*-trifluoroacetyl sulfoximines are prepared under mild conditions at room temperature and can easily be deprotected by using potassium carbonate in methanol.[49] Several industrial processes have been reported taking advantage of this procedure.[50] Under adjusted conditions *N*-carbamoyl-sulfoximines can be synthesized from sulfoxides using $Rh_2(OAc)_4$ as the catalyst.[51]



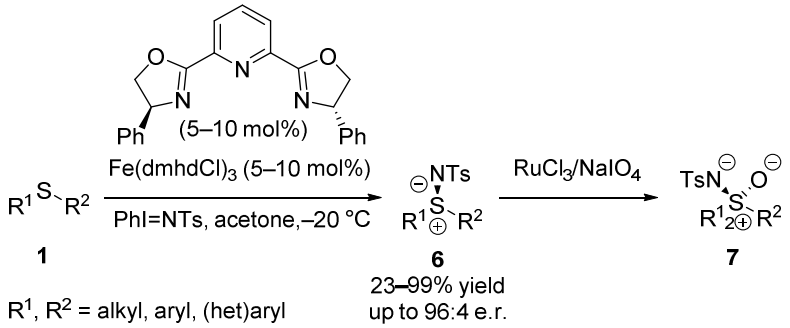
Scheme 1.6: $Rh_2(OAc)_4$-catalyzed iminations with iminoiodinanes.

To replace the expensive rhodium catalysts, silver[52] and iron have been applied as metals. Considering costs and efficiency, iron catalysis has been explored increasingly. $Fe(acac)_3$ promoted the iminations of sulfides **1** with a variety of sulfonimidoiodinanes, leading to sulfilimines, for example bearing tosyl or nosyl groups.[53] Sulfoxides **2** showed lower reactivity under those conditions. Further improvement was achieved by using $Fe(OTf)_2$ as the catalyst (Scheme 1.7).[54] Advantageously, the iminations of sulfides **1** and sulfoxides **2** proceeded well with low catalyst loadings. The optimized conditions proved suitable for a variety of sterically demanding and heterocyclic substrates of biological interest.[55] Deprotections of the introduced nosyl groups can be performed by using cesium carbonate and thiophenol in acetonitrile at room temperature.[52]



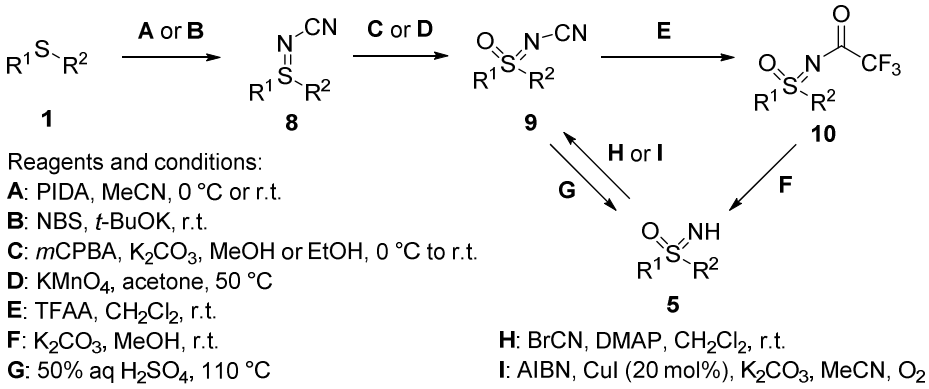
Scheme 1.7: $Fe(OTf)_2$-catalyzed iminations with iminoiodinanes.

The above described imination procedures for sulfoxides proceed stereospecifically, allowing to obtain enantioenriched sulfoximines from previously formed enantio-enriched sulfoxides. Contrarily, enantioselective iminations of sulfides have always been challenging. Realizing that expedient methods were rare, the group of *Bolm* developed a useful protocol for enantioselective iminations of sulfides **1**. Employing $Fe(dmhdCl)_3$ as catalyst in combination with a PyBOX ligand gave *N*-tosyl sulfilimines **6** in high yields with enantiomeric ratios of up to 96:4 for a broad substrate scope (Scheme 1.8).[20a] Subsequent oxidations with *in situ* generated ruthenium tetroxide[56] provided the corresponding sulfoximines **7** in excellent yields with retention of the configuration. Changing the iron catalyst to $Fe(acacCl)_3$ allowed a kinetic resolution of racemic chiral sulfoxides that were transferred into the corresponding sulfoximines in only moderate yields, but high enantiomeric ratios.[57] Lately, a procedure for diastereoselective syntheses of chiral sulfilimines with use of *N*-mesyloxycarbamates has been reported.[20b]



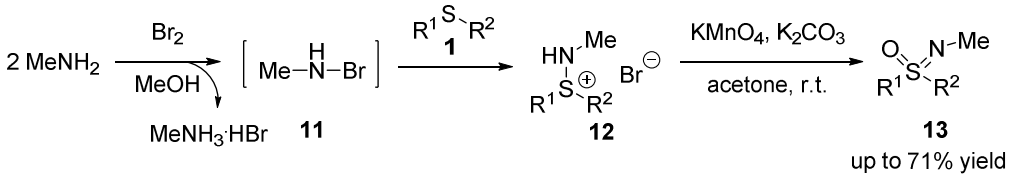
Scheme 1.8: Fe(dmhdCl)$_3$-catalyzed enantioselective iminations of sulfides.

The safety problems associated with azides or MSH and the high cost of most metal catalysts stimulated the interest in straight-forward metal-free approaches towards *N*H-sulfoximines **5**.[58] The group of *Bolm* developed a relatively mild and safe procedure which found its way into industrial large-scale applications.[16c] First, sulfide imination with cyanamide by either forming PhI=NCN with PIDA (**A**)[59] or by employing NBS and a base (**B**)[49] is performed to generate *N*-cyanosulfilimines **8** (Scheme 1.9). Subsequent oxidations with use of *m*CPBA and potassium carbonate (**C**)[49] or potassium permanganate (**D**)[55] give *N*-cyanosulfoximines **9**. They can be transformed into the corresponding *N*-trifluoroacetylsulfoximines **10** by reaction with TFAA (**E**), followed by deprotection (**F**).[49] When the products prove sufficiently stable, deprotections of *N*-cyanosulfoximines **9** using 50% aqueous sulfuric acid at 110 °C (**G**) provide *N*H-sulfoximines **5**.[60] *N*-Cyanations of the latter employing cyanogen bromide (**H**)[59] or AIBN (**I**)[61] afford *N*-cyanosulfoximines **9**.



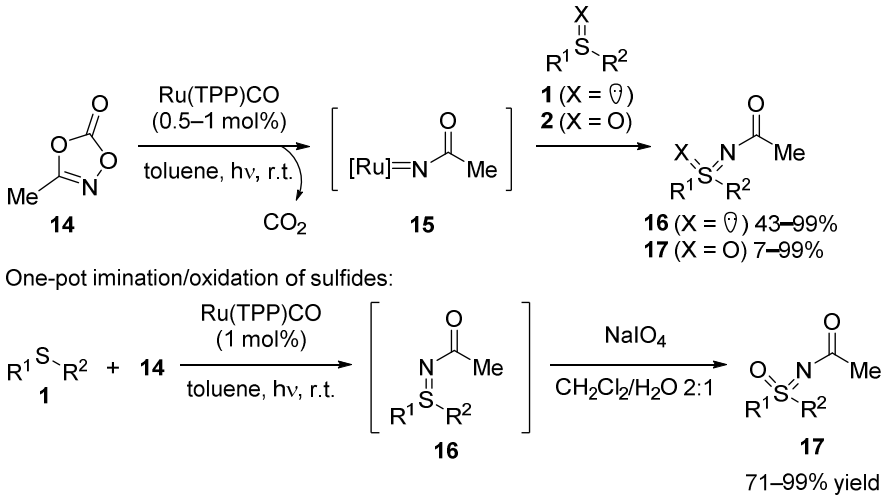
Scheme 1.9: Metal-free synthetic routes to *N*H-sulfoximines **5**.

Recently, methods providing access to *N*-methylsulfoximines starting from sulfides have been reported.[62] Metal-free iminations of sulfides with alkylamines such as methylamine, investigated by the group of *Bolm*, led to the corresponding *N*-methylsulfoximines **13** after subsequent oxidation (Scheme 1.10).[62b] Treating methylamine with bromine involved the formation of methylaminobromide **11**, which was then applied to convert sulfides **1** into methyl sulfiliminium bromides **12**. Finally, oxidation with potassium permanganate and potassium carbonate in acetone afforded *N*-methylsulfoximines **13** in moderate to good yields.



Scheme 1.10: Metal-free syntheses of *N*-methyl sulfoximines **13**.

More unusual nitrene sources, compared to the frequently used iminoiodanes and *N*-haloamides, are nitrogen-containing heterocycles. In early studies employing oxaziridines, the desired sulfilimines had been obtained together with high amounts of unrequested sulfoxides.[63] First attempts by *Sauer* and *Mayer* using 3-substituted-1,4,2-dioxazol-5-ones under thermal conditions involved product formation only in moderate yields.[64] A productive imination procedure, especially useful for the preparation of *N*-acetylsulfilimines **16** and *N*-acetylsulfoximines **17**, has recently been reported by the group of *Bolm* (Scheme 1.11).[65] Applying Ru(TPP)CO as catalyst, under irradiation with visible light, decarboxylation of 1,4,2-dioxazol-5-one **14** leads to formation of rutheno *N*-acyl nitrene intermediates **15**. These highly electrophilic species react with both sulfides **1** and sulfoxides **2**, affording sulfilimines **16** in high yields. Sulfoximines **17** are generally obtained in lower yields. A one-pot imination/oxidation procedure offered a solution to this problem, leading to *N*-acetylsulfoximines **17** by oxidations of unisolated sulfilimines **16** under phase-transfer conditions employing sodium periodate.



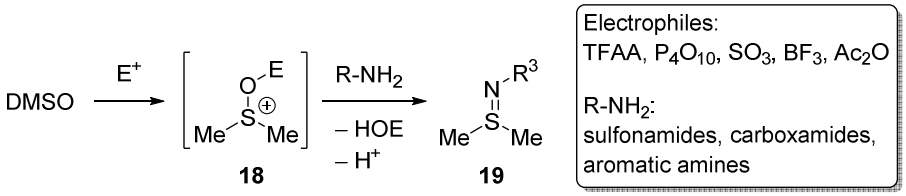
Scheme 1.11: Light-induced, Ru(TPP)CO-catalyzed imination.

Sulfoxide-to-sulfilimine conversions

First extensive investigations into the (stereospecific) transformations of sulfoxides into sulfilimines were carried out in the 1960s and 1970s. More than thirty years later, renewed interest in such reactions became apparent. However, in total, only few methods with serious limitations are available for sulfoxides-to-sulfilimine conversions to date and will be summarized hereinafter.

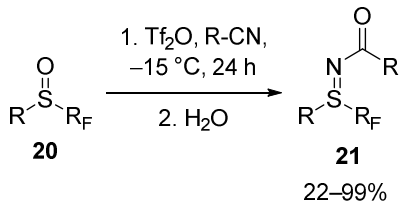
Early approaches to sulfilimines reported by *Swern* describe the activations of sulfoxides, mostly DMSO, with electrophiles such as TFAA, phosphorous pentoxide,

sulfur trioxide, or boron trifluoride to form sulfonium salt **18** (Scheme 1.12).[66] Subsequent condensations with nucleophiles such as sulfonamides, carboxamides, or aromatic amines provided the desired sulfilimines **19**. The reactions in DMSO have to be performed carefully, as there is a risk of explosions.



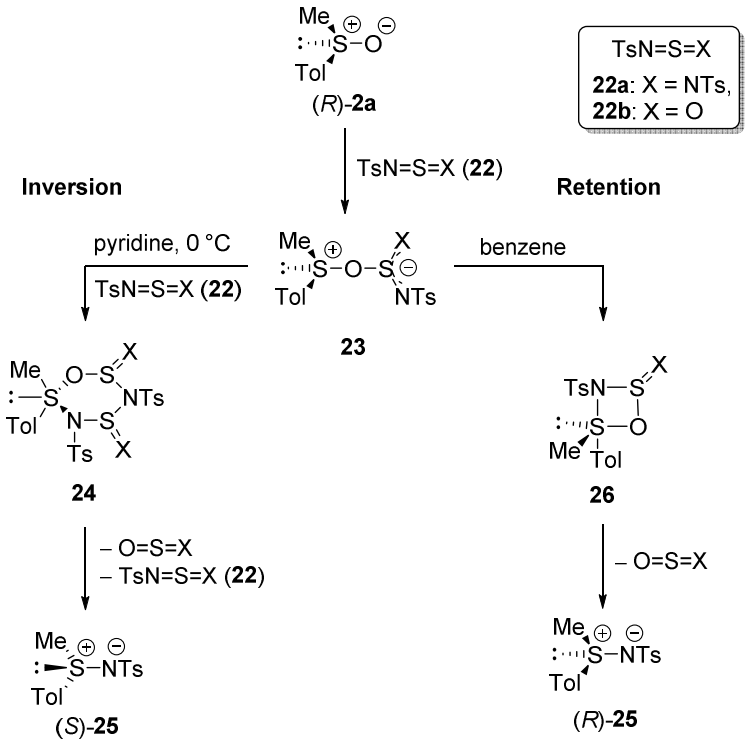
Scheme 1.12: Sulfilimine synthesis by electrophilic activation of DMSO and subsequent nucleophilic attack by an amide or amine.

More than 30 years later, *Magnier* and coworkers reported the activations of perfluoroalkyl sulfoxides **20** with trifluoromethanesulfonic anhydride and their subsequent reactions with nitriles such as acetonitrile, giving perfluoroalkyl sulfilimines **21** in moderate to high yields (Scheme 1.13).[67]



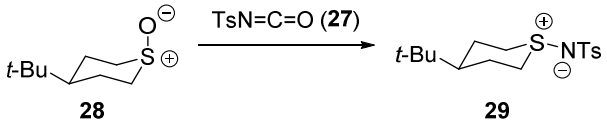
Scheme 1.13: Syntheses of sulfilimines **21** from perfluoroalkyl sulfoxides **20**.

In the 1960s and 1970s, aiming to perform stereospecific conversions of enantio-enriched sulfoxides in the absence of activating electrophiles,[68,69] *Cram* and coworkers utilized *N*,*N*-ditosyl sulfur diimide (**22a**) and *N*-sulfinyl-*p*-toluenesulfonamide (**22b**) (Scheme 1.14). Deduced from experiments with enantiopure methyl *p*-tolyl sulfoxide (*R*)-**2a**, the authors proposed that the electron-deficient sulfur atom attacks the electron-rich sulfoxide-oxygen atom to form zwitterionic sulfonium salt **23** (Scheme 1.14). The subsequent transformation into sulfilimines (*S*)-**25** and (*R*)-**25** appeared highly solvent-depending. Using pyridine at 0 °C, inversion of the configuration was observed, presumably resulting from a six-membered transition state **24** with both the nucleophile and the leaving group in equatorial positions (Scheme 1.14, left).[69a] The same stereochemistry was found for the corresponding transformation of a cyclic sulfoxide. Contrarily, using benzene as the solvent, retention of the configuration occurred. As the described model was not applicable any more, *Cram* and *Christensen* suggested four-membered transition state **27** with the nucleophile and the leaving group being in axial and equatorial positions, respectively, leading to retention (Scheme 1.14, right).[69b,70] To explain these findings it was proposed that unlike benzene, the nucleophilic solvent pyridine stabilizes intermediate **23**, thereby facilitating the incorporation of a second reagent **22**, leading to transition state **24**.



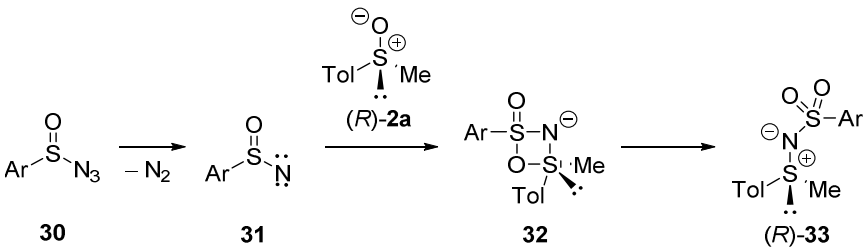
Scheme 1.14: Transition states involving inversion and retention of the configuration.

A third reagent, namely isocyanate **27**,[71] has been applied by *Johnson* and *Rigau* to convert *cis*-sulfoxide **28** to *trans*-sulfilimine **29** (Scheme 1.15). With reagent **22b**, the same transformation occurred.[72] Unfortunately, purification and handling of the presented reagents **22** and **27** proved difficult, and therefore the generality of the described methods is limited.



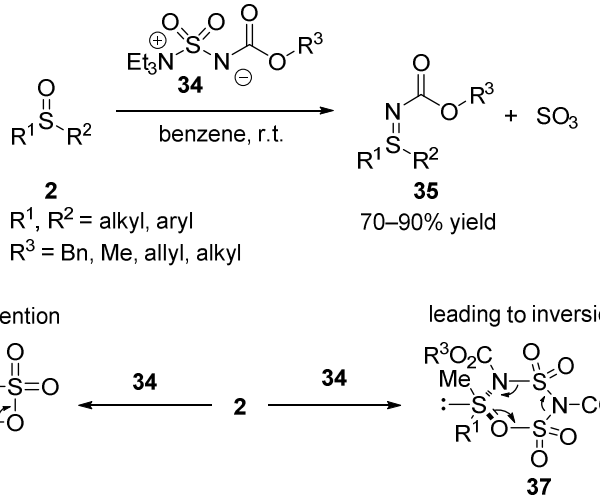
Scheme 1.15: Application of isocyanate **27** in the sulfilimine formation.

Further investigations into the syntheses of sulfilimines from sulfoxides pointed out the utility of arenesulfinyl azides **30** (Scheme 1.16). Contrary to arenesulfonyl azides that form the corresponding sulfoximines,[73] arenesulfinyl azides decompose to arenesulfinyl nitrenes **31** under the release of nitrogen gas.[74] In 1974, *Maricich* and *Hoffmann* hypothesized that these active species react with sulfoxides in a 1,2-dipolar cycloaddition to form four-membered transition states **32**. When using an enantioenriched sulfoxide such as (*R*)-**2a**, to a high degree retention of the configuration was observed, offering *N*-sulfonylsulfilimine (*R*)-**33**. Employing several racemic sulfoxides such as DMSO, diphenyl sulfoxide, and methyl *p*-tolyl sulfoxide, the corresponding sulfilimines were obtained in low to good yields. However, arenesulfinyl azides are no easy-to-use imination agents due to their instability and danger of explosions.



Scheme 1.16: Syntheses of sulfilimines from sulfoxides with arenesulfinyl azides.

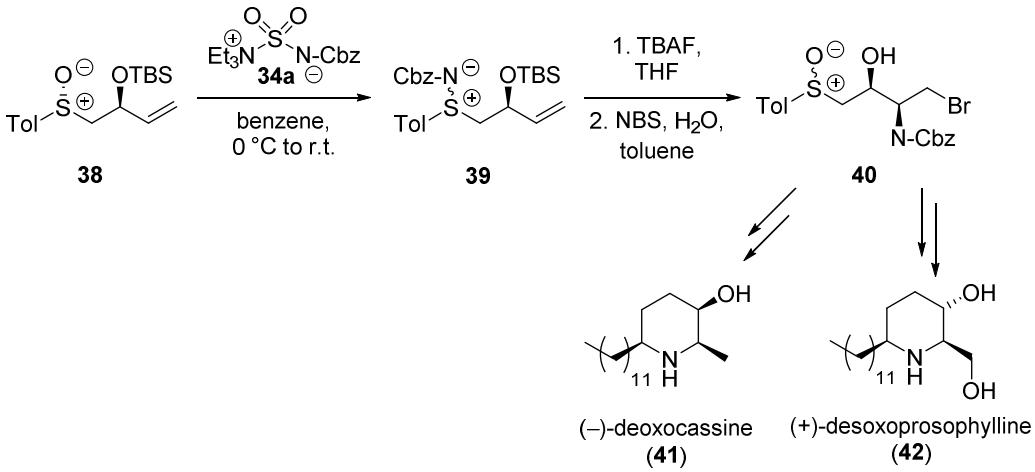
A more convenient approach to sulfoxide-to-sulfilimine conversions under mild conditions was discovered by *Raghavan* and coworkers in 2008.[75] They found that *N*-(triethylammoniumsulfonyl)carbamates **34**, also referred to as Burgess reagents,[76] were useful tools to form *N*-carbamate-like sulfilimines **35** from sulfoxides **2** in good yields (Scheme 1.17, top). The proposed transition states **36** and **37** led to retention or inversion of the configuration (Scheme 1.17, bottom). Unfortunately, using enantiopure methyl *p*-tolyl sulfoxide, under those conditions only racemic sulfilimine **35** was formed. An experiment showing racemization of sulfoxides **2** in presence of reagents **34** confirmed the hypothesis that the epimerization of the enantiomerically pure sulfoxides **2** by **34** was faster than the reactions of sulfoxides **2** with reagent **34** to form sulfilimines **35**.



Scheme 1.17: Syntheses of sulfilimines **35** by using Burgess reagents **34**.

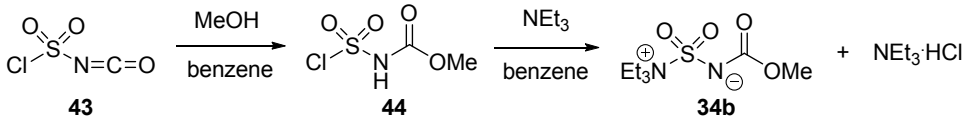
This method has been extended by the authors to the total synthesis of biologically relevant piperidine alkaloids deoxocassine (**41**) and desoxoprosophylline (**42**) (Scheme 1.18).[77] Treating sulfoxide **38** with Burgess reagent **34a** provided *N*-Cbz sulfilimine **39**. Its subsequent deprotection and reaction with NBS furnished carbamate **40**, a precursor for **41** and **42**.

The Burgess reagent is well-known for its rich chemistry; therefore, a short overview will be given. The first Burgess reagent, namely ethyl *N*-(triethylammonium-sulfonyl)carbamate, was discovered by *Burgess* and *Atkins* during their research on *N*-sulfonylamines in 1968. [78]



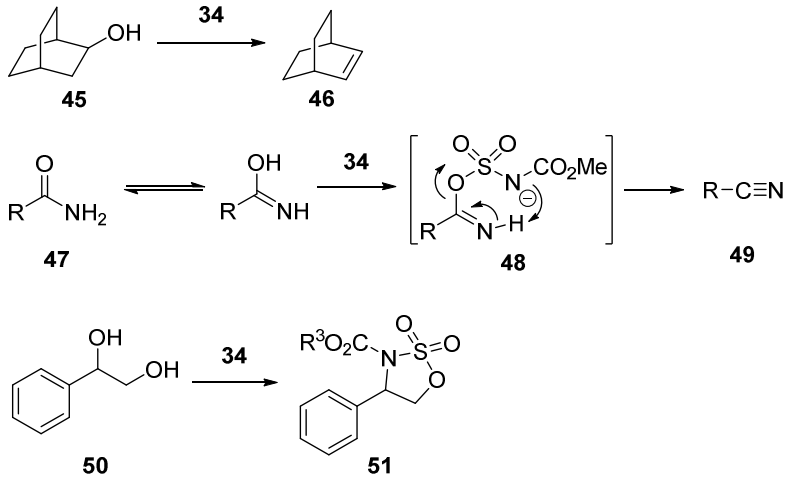
Scheme 1.18: Applications of Burgess reagent **34a** in total synthesis.

Two years later, they reported methyl carbamate **34b**, the compound which was later called "Burgess reagent".[79] It can be synthesized from chlorosulfonyl isocyanate **43** by reaction with methanol to form intermediate **44** and subsequent substitution with triethylamine (Scheme 1.19).



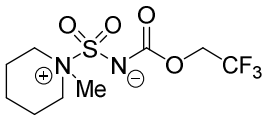
Scheme 1.19: Synthesis of Burgess reagent **34b**.

Reagents **34** have wide-spread applications.[76] For example, they have been extensively used as mild and selective dehydration agents for secondary and tertiary alcohols such as the dehydration of **45** to form alkene **46** (Scheme 1.20, top).[79] Further implementations include reactions of primary amides **47** to nitriles **49** *via* intermediates **48** (Scheme 1.20, middle)[80] and conversions of diols such as **50** to sulfamidates **51** (Scheme 1.20, bottom).[81]



Scheme 1.20: Further applications of Burgess reagents **34**.

Burgess reagents **34** exhibit low thermal stability and lability towards acids, making them difficult to handle. Replacing triethylamine by the more electron-donating *N*-methylpiperidine to better stabilize the positive charge, and changing the methoxy group into an electron-withdrawing 2,2,2-trifluoroethyloxy substituent in order to stabilize the negative charge, the group of *Hudlicky* synthesized the thermally stable Burgess reagent **52** (Figure 1.4).[82]



52

Figure 1.4: Thermally stable Burgess reagent.

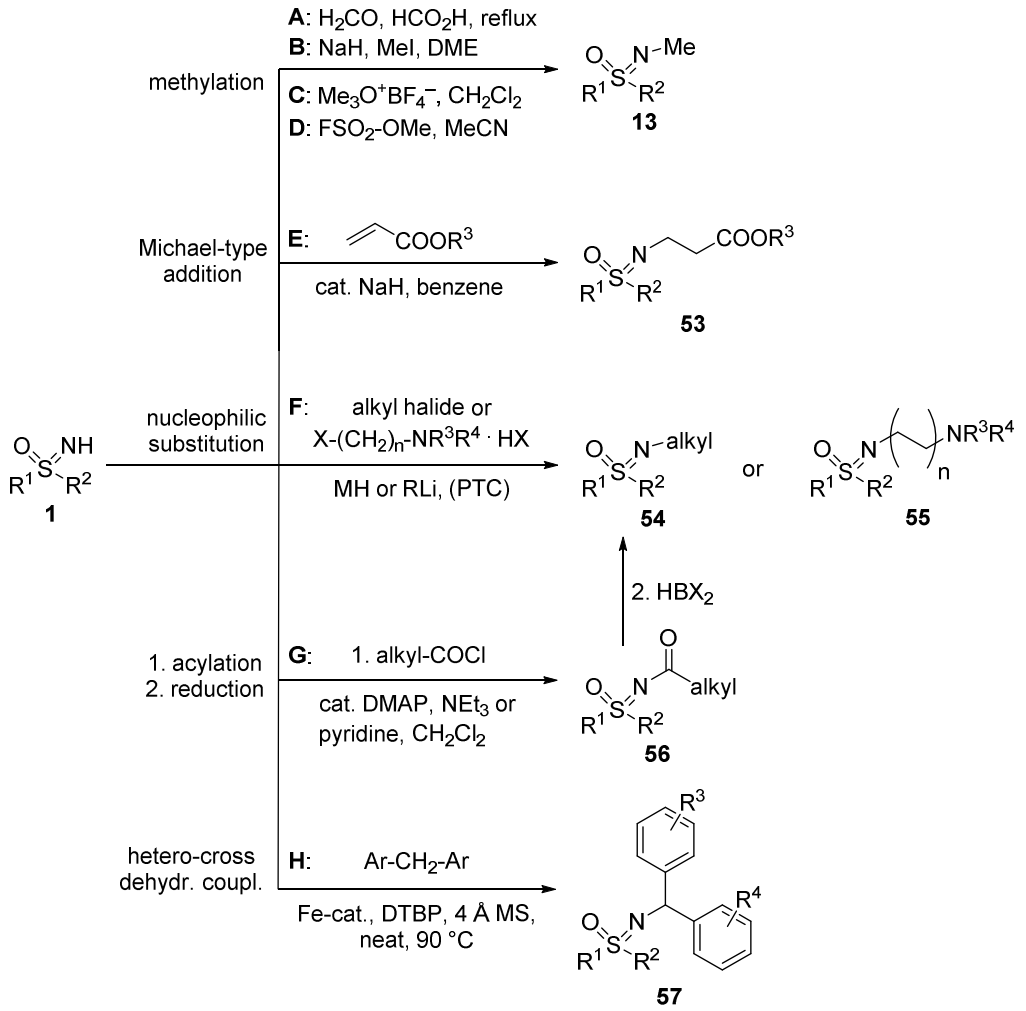
1.1.3 *N*-Functionalizations of *N*H-sulfoximines

Advantageously, in contrast to sulfones, sulfoximines are modifiable at the imine nitrogen atom allowing numerous functionalizations at the *N*H-group. These modifications are of high interest considering the advances of sulfoximines in asymmetric catalysis and their biological applications. Selected methods and examples, relevant in this work, will be discussed in the following.

N-Alkylations of *N*H-sulfoximines

Despite they have been long known, *N*-alkylations of sulfoximines present a significant challenge. This is due to the low nucleophilicity of the nitrogen anion,[83] generated by relatively easy deprotonation. Typical procedures for *N*-methylations of *N*H-sulfoximines **5** include Eschweiler-Clark conditions (Scheme 1.21, **A**), namely a mixture of formaldehyde and formic acid under reflux,[84] or the application of methyl iodide as methyl transfer agent in presence of sodium hydride as base (Scheme 1.21, **B**).[85] Furthermore, strong methyl transfer agents such as trimethyloxonium tetrafluoroborates (Scheme 1.21, **C**)[37b,86] and methyl fluorosulfate, known as "magic methyl" (Scheme 1.21, **D**),[87] have been employed in these transformations. Generally, when attempts were performed to introduce longer chains, these methods remained unsuccessful. Notable exceptions are certain *N*-ethylations[84b,88] and a Michael-type addition with an alkene by using catalytic amounts of NaH, leading to *N*-alkylsulfoximines **53** (Scheme 1.21, **E**).[86]

Consequently, procedures for the *N*-alkylation with long-chain alkyl halides have been developed. Typically, these nucleophilic substitution reactions require strong bases such as alkali metal hydrides (MH) or butyl lithium under anhydrous conditions in presence of a phase-transfer catalyst (PTC) (Scheme 1.21, **F**).[83,85,89] Proceeding under strictly anhydrous conditions for long reaction times, the *N*-alkylated products **54** were obtained in acceptable yields which strongly depend on the electronic and steric properties of each substrate. Similar conditions, using an aminoalkyl halide hydrochloride and NaH, led to *N*-dialkylaminoalkylsulfoximines **55** in low yields (Scheme 1.21, **F**).[90]



Scheme 1.21: *N*-Alkylation methods for *N*H-sulfoximines **5**.

Realizing the limited scope and the unsatisfying reaction conditions of such alkylations, efforts have been made towards alternate procedures. The group of *Bolm* reported a two-step process that provides *N*-alkylated sulfoximines **54.** First, acylations with acid chlorides are performed, followed by reductions of *N*-acylsulfoximines **56** by boron-containing reducing agents (Scheme 1.21, **G**).[91] Indeed, the procedure proved advantageous in several cases; albeit an efficient one-step procedure would be desirable. In this context, *Bolm* and coworkers developed an *N*-alkylation reaction utilizing various diarylmethanes. The corresponding *N*-diarylmethyl sulfoximines **57** were obtained in moderate to good yields through a hetero-cross dehydrogenative coupling process employing $FeBr_3$ as the catalyst and di-*tert*-butyl peroxide (DTBP) as oxidant (Scheme 1.21, **H**).[92]

Of note, *N*-alkylated sulfoximines can serve as intermediates for consecutive transformations. Sulfoximines with alkenyl and alkynyl functionalities have been subjected to cyclization reactions such as ring-closing metathesis (RCM)[93] and ring-closing eyne methathesis (RCEYM)[94], investigated by the group of *Bolm*. *Harmata* and coworkers observed that *N*-alkenyl-*S*-alkenylsulfoximines underwent intramolecular redox reactions.[95] Furthermore, the group of *Bolm* presented *N*-propargylsulfoximines

as starting materials in palladium/copper co-catalyzed domino reactions with functionalized 2-iodoarenes, leading to various benzo[*b*]furanes and indoles.[96] A recent iron-catalyzed dealkylation protocol for sulfoximines covers the formation of acylsulfoximines and their subsequent hydrolysis providing the corresponding *N*H-sulfoximines.[97]

Cross-coupling reactions of *N*H-sulfoximines with aryl halides, and *S*-bromoaryl sulfoximines with amines

N-arylated sulfoximines have been of high importance as selective ligands in asymmetric metal catalysis.[13b,13d,98] Utilizing sulfoximine ligands **58** and **59**, (Figure 1.5) high enantioselectivities were achieved in (hetero)-Diels-Alder and Mukaiyama-aldol reactions.[98a,99]

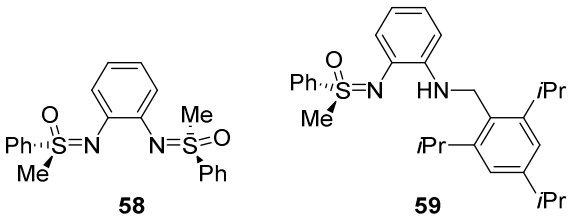
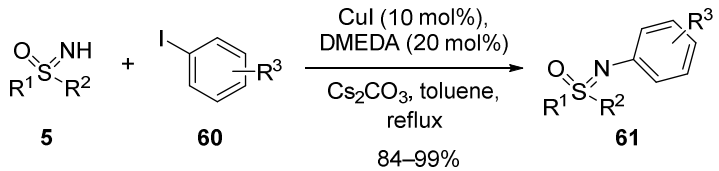


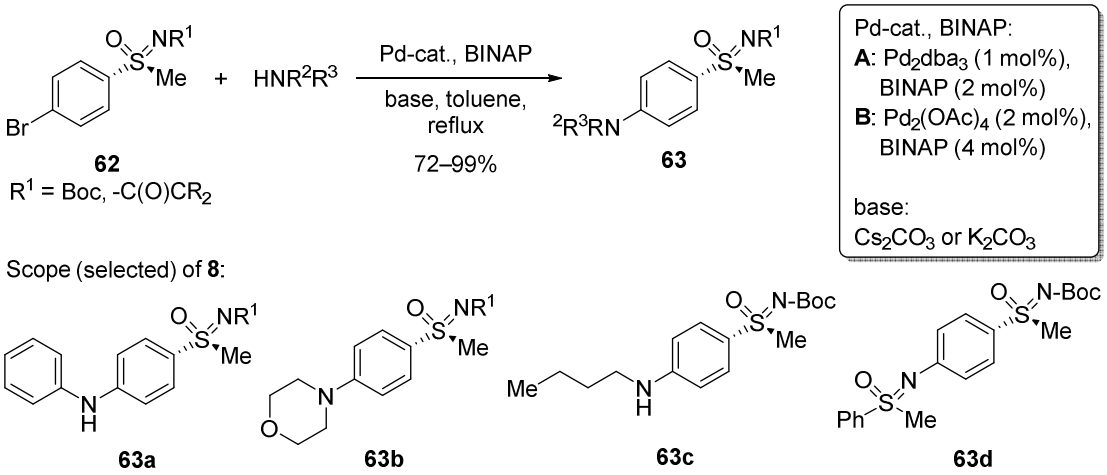
Figure 1.5: Important sulfoximine-based ligands.

The main breakthrough came with the development of Buchwald-Hartwig aminations; more precisely palladium-catalyzed cross-coupling reactions of amines with aryl halides.[100] Since their discovery, these processes have been of high value in the syntheses of natural products and pharmaceuticals. Applying the principle of Buchwald-Hartwig aminations to sulfoximines, *Bolm* and coworkers enabled first *N*-arylations of *N*H-sulfoximines with aryl bromides and iodides using palladium catalysts and bisphosphine ligands.[101] Further developments include palladium-catalyzed *N*-arylations with aryl chlorides under specified conditions, reported by *Harmata* and coworkers.[102] The replacement of palladium by stoichiometric amounts of copper, investigated by the group of *Bolm*, allowed less-expensive *N*-arylations under mild conditions.[103] In this context, the application of catalytic amounts of copper represented a significant improvement.[104] Using an aryl iodide **60** (readily available or generated from bromides in a Finkelstein reaction), 10 mol% of copper(I)iodide, DMEDA as ligand, and caesium carbonate as base, provided various *N*-arylated sulfoximines **61** in high yields (Scheme 1.22).[104a] Later, a less expensive and environmentally friendly iron-catalyzed version has been reported, giving high amounts of various *N*-arylated sulfoximines.[105]



Scheme 1.22: Copper-catalyzed *N*-arylations of aryl iodides.

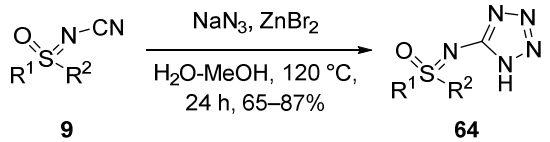
According to the *N*-arylations of *N*H-sulfoximines **5**, *S*-halophenylsulfoximines can undergo cross-coupling reactions with amines. Investigating this pathway, the group of *Bolm* applied enantiopure 4-bromophenyl methyl sulfoximines **62** as aryl halides in Buchwald-Hartwig aminations with primary and secondary amines (Scheme 1.23).[106] The catalytic systems, consisting of Pd_2dba_3 and $Pd_2(OAc)_4$ as metal catalysts in combination with BINAP as ligand and caesium carbonate or potassium carbonate as base, furnished the corresponding cross-coupling products **63** in good to high yields. Arylations using aniline, alkylations applying morpholine and 1-aminobutane, as well as a reaction with an *N*H-sulfoximine were performed, giving the desired products **63a–d**. Interestingly, in a recent study, bioactive sulfoximine derivatives were obtained using similar protocols.[107]



Scheme 1.23: Buchwald-Hartwig aminations of 4-bromophenyl methyl sulfoximines **62**.

N-Cyanosulfoximines in the preparation of *N*-(1*H*)-tetrazoles

Tetrazoles are carboxylic acid isosters with exceptional biological profiles, and therefore attractive functionalities in drug design.[108] Based on a report by *Sharpless* on safe tetrazole syntheses[109] from nitriles, *Bolm* and coworkers investigated the syntheses of *N*-(1*H*)-tetrazole sulfoximines from *N*-cyanosulfoximines **9** (Scheme 1.24).[59] By using sodium azide and zinc(II)bromide several tetrazole-containing sulfoximines **64** could be prepared in good yields.

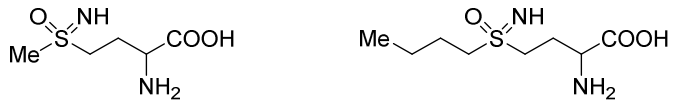


Scheme 1.24: Synthesis of *N*-(1*H*)-tetrazole sulfoximines **64**.

1.1.4 Bioactivities of sulfoximines and sulfilimines

The discovery of sulfoximines in the 1940s is strongly connected to their biological activities.[110] Investigating the toxic factor in wheat causing canine hysteria, *Bentley* and *Whitehead* made an important finding: bleaching wheat with nitrogen trichloride converted the amino acid methionine into methionine sulfoximine **65** (MSO, Figure 1.6).

This transformation involved a major bioactivity change resulting in the detrimental inhibition of glutamine synthetase.

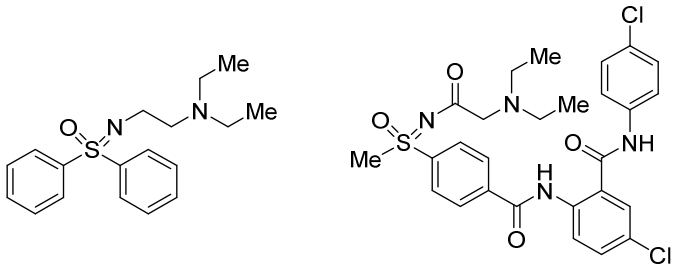


65 (MSO) **66** (BSO)

Figure 1.6: Methionine sulfoximine (MSO) and buthionine sulfoximine (BSO).

A related synthetic amino acid, buthionine sulfoximine **66** (BSO), has been regarded as a promising agent in the treatment of cancer (Scheme 1).[111] BSO is an inhibitor of γ-glutamylcysteine synthetase, an enzyme associated with the formation of glutathione (GSH) and the protection of the intracellular environment. As a reduced GSH-synthesis enhances the cytotoxicity of anti-cancer agents, BSO has proved attractive for the treatment of drug-resistant tumors depending on a high GSH-production. Recently, the group of *Bolm* reported safe and mild synthetic routes to MSO and BSO using the aforementioned light-induced ruthenium catalysis (see Scheme 1.11).[112]

Although long neglected, their interesting biological profiles and the recent developments of straight-forward synthetic methods promoted sulfoximines as attractive functionalities in drug design and crop protection. *N*-alkylaminosulfoximine **67** reported by *Satzinger* and *Stoss* (Gödecke), known as suloxifen, represents an example of pioneering work on sulfoximines as pharmacophores (Figure 1.7). Showing promising spasmolytic and antiasthmatic activity, it was selected for clinical studies, but never reached the market.[90,113] Lately, a new series of *N*-alkylamino sulfoximines, analogs of the Xa inhibitor betrixaban, has been explored by *Pandya* and coworkers (Zydus). Lead optimization identified sulfoximine **68** as most promising anticoagulant (Figure 1.7).[38a]



67 (suloxifen)
Gödecke
antiasthmatic

68
Zydus
anticoagulant

Figure 1.7: Biologically active *N*-alkylaminosulfoximines **67** and **68**.

Despite many reports on their profound activities exist; no sulfoximine-containing drug has been available on the market to date. A promising compound in clinical development is BAY 1000394 **69** (Bayer Pharma), a low-molecular-weight inhibitor of cyclin-dependent kinases (CDK) with high anti-tumor potency (Figure 1.8, left).[114] Sulfoximine AZD6738 **70** (Astra Zeneca), an ATR inhibitor showing anti-cancer activity, has also entered clinical studies (Figure 1.8, left).[50c] Interestingly, according to the observations

of *Goldberg* and coworkers (Astra Zeneca), sulfoximines exhibit higher solubility compared to the corresponding sulfones and "*N-Me sulfoximines are typically isolipophilic to a sulfone, yet also typically improve solubility*".[115] Exemplified by sulfoximine analogs **72** and **73** of sulfone-based ATR inhibitor VX-970 **71** (Vertex) showing a ~30-fold, respectively >200-fold higher solubility in aqueous solutions (Figure 1.8, right), these findings demonstrate the potential benefit of sulfoximines as structural alternatives to sulfones in the design of biologically active compounds.

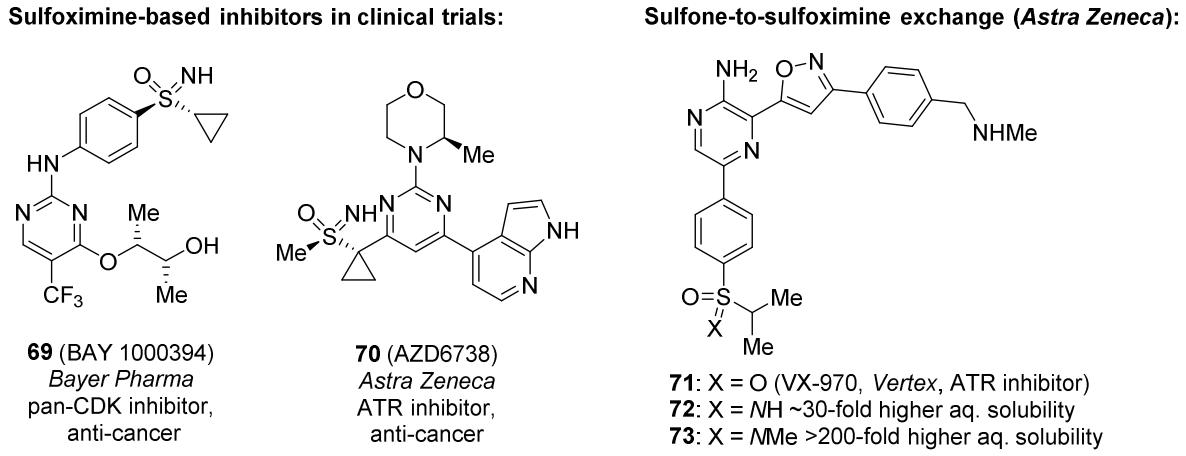


Figure 1.8: Sulfoximine-based inhibitors in clinical trials (left) and sulfone-to-sulfoximine exchanges leading to major solubility changes (right).

In several cases, sulfoximine-analogs showed superior activities compared to the corresponding sulfones, revealing the prominent role of the stereochemistry at the sulfur atom. In this context, *Posner* and coworkers synthesized sulfone **74** and sulfoximine **75** (Figure 1.9, left), analogs of the natural hormone calcitriol.[116] Sulfoximine **75** with (*S*)-configuration proved a 4-fold higher inhibitory activity against CYP24 hydroxylase enzyme compared to sulfone **74**. A study by *Walker* (Pfizer) on PYK2-inhibitors **76** developed for the potential treatment of osteoporosis assigned (*S*)-sulfoximine analog **77** equal potency, good oral exposure in rats and reduced hERG activity, an indication for cardiovascular safety (Figure 1.9, right).[117] Among a variety of *N*-substituents, the highest activity was observed for the *N*-methyl group. Inspired by these results, the group of *Bolm* prepared sulfoximine-analogs of the COX-2 inhibitor vioxx® (**78**), a nonsteroidal anti-inflammatory drug (NSAID) that had been withdrawn from the market because of its cardiovascular risks (Figure 1.9, bottom). The corresponding sulfoximine **79** showed only moderate COX-inhibition, but the desired reduced hERG activity (higher cardiovascular safety).[118]

Further investigations into bioactive sulfoximines by the group of *Bolm* include the syntheses and biological evaluation of COX-2 inhibitors containing *N*-cyanosulfoximidoyl functionalities,[119] sulfoximine-analogs of dapson (drug against leprosy),[120] and sulfoximine-based acyclic triaryl olefins showing blocking potency for estrogen receptors.[121]

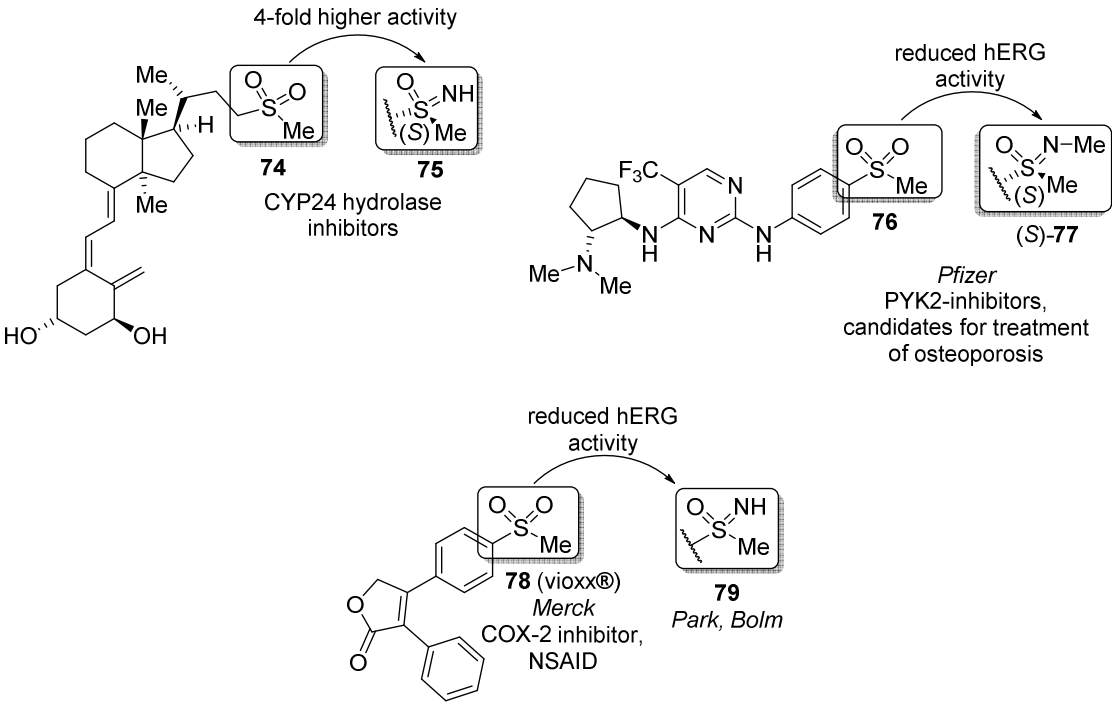


Figure 1.9: Sulfone-to-sulfoximine exchanges in selected drugs.

In addition to their applications in medicinal chemistry, sulfoximines proved useful in crop protection (Figure 1.10) such as sulfoximine **80** (Syngenta) that was active against insects.[122] Of special interest is *N*-cyanosulfoximine **81**, namely sulfoxaflor (Dow Agroscience). It has been used as insecticide in 22 countries and, notably, represents the only sulfoximine-based bioactive compound introduced to the market.[16,123] Compared to sulfoximines, the scarcity of approaches employing the structurally strongly related sulfilimines is remarkable.

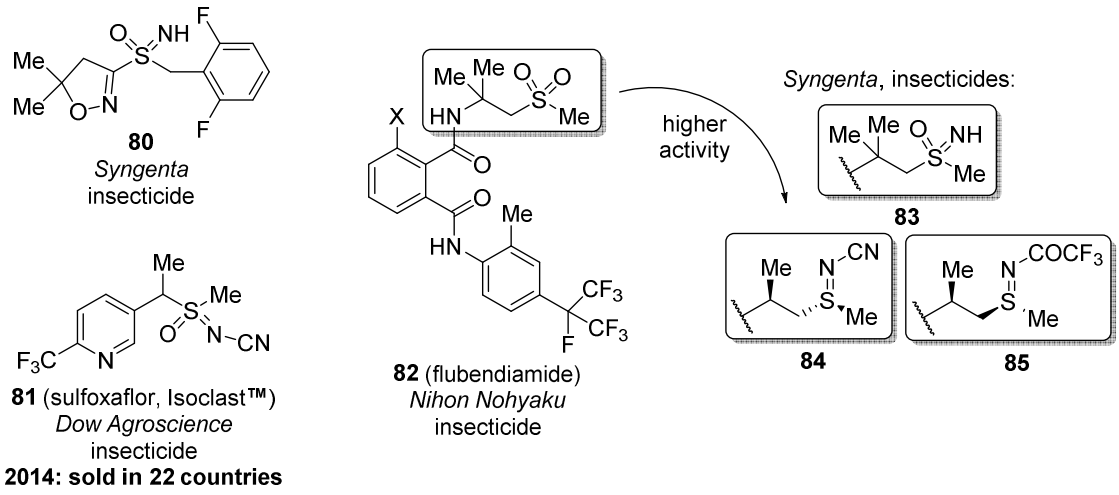


Figure 1.10: Selected sulfoximine- and sulfilimine-based insecticides.

However, in a recent study covering derivatizations of the commercially available insecticide flubendiamide (**82**) (Nihon Nohyaku), sulfoximine **83** and sulfilimines **84** and **85** (Syngenta) were reported (Figure 1.10).[22a,50a,124] Biological tests disclosed the

potential of the sulfilimine-derivatives: *N*-cyanosulfilimine **84** and *N*-trifluoroacetylsulfilimine **85** showed higher activities against insects than the original sulfone **82**, revealing the significance of the stereochemistry at the alkylsulfilimidoyl-group.Although the unique biological properties of sulfoximines have been known for more than 70 years, the introduction of sulfoximines and sulfilimines as bioisosters or in opportunistic approaches is still limited. The initially unsatisfying access has been improved by a variety of new synthetic routes developed in the last years; however, there is still a lack of mild synthetic methods suitable for the incorporation of sulfoximines and sulfilimines into highly functionalized backbones. Likewise, comparative studies are needed to evaluate the present synthetic procedures regarding their benefit in different molecular settings of various target compounds.

1.2 Aromatic Pentafluorosulfanyl Compounds

1.2.1 Introduction to fluorine and organofluorine compounds

Fluorine presents itself as a very special element based on its extreme and often surprising behavior.[125] In nature, fluorine is generally present in form of inorganic fluoride salts, such as fluorspar (CaF_2), cryolite (Na_3AlF_6) or fluoroapatite ($Ca_5(PO_4)_3F$), an important component of tooth enamel.[126] Contrarily, organofluorine compounds are extremely rare in the biosphere, and no identified central metabolic process is dependent on fluorine.[127] Consequently, many organofluorine compounds are xenobiotics. In modern synthetic organic chemistry, fluoro (–F) or fluorine-containing substituents such as $–CF_3$, $–SCF_3$, $–OCF_3$, and $–SF_5$ are of high benefit and indispensible in the area of pharmaceuticals, crop protection agents and materials science.[125a,128] 20% of all drugs and up to 30% of all crop protection compounds contain at least one fluorine atom.[129]

The physicochemical properties of fluorine are unique, resulting in fundamental and often unpredictable changes in fluorine-containing molecules.[125b] Fluorine is the element with the highest electronegativity, and the difference in electronegativity of fluorine and carbon is significant (3.98 versus 2.55).[130] Thus, the polarization of carbon-fluorine bonds is very high.[131] The resulting electronic effects can enhance the acidity of neighboring functional groups[125b] and the binding affinity (hydrogen bridging) of a fluorine-containing compound to a target.[127] Contrary to the strong effect on the electronic properties of a molecule, the comparably small fluorine substituent (vdW radius of 1.47 Å) can replace a hydrogen substituent (vdW radius of 1.20 Å) without significant changes in the molecular geometry.[132] Both the high electronegativity and the moderate size involve very low polarizability of fluorine.[131]

The local dipole moments in perfluorinated substituents mostly compensate each other making them non-polar.[125a] Hence, an increased lipophilicity of such fluorine-containing pharmaceuticals is observed, affecting their resorption and distribution in the living organism.[132] In contrast to the toxic molecular fluorine (F_2 gas) which is highly reactive due to its low dissociation energy, fluorides and most organofluorine compounds are extremely stable. Owing to the chemical inertness of organofluorine bioactives to

metabolic processes, fluorination is a functional tool in the development of drugs and crop protecting agents. Of special benefit is the bioisosteric replacement of metabolically unstable functionalities by stable fluorine groups that mimic the properties of the original substituent.[133] In addition, pharmaceuticals can be equipped with the artificial ^{18}F isotope, fluorine-18, which is helpful in medical imaging to identify cancer and brain diseases.[134]

To date, the number of publications on bioactive organofluorine compounds has increased dramatically, and research in this field continues unabated.[5a,135] Fluorinated pesticides such as the CF_3-containing sulfoximine[136] sulfoxaflor[16c] (see Figure 1.10), and fluorinated pharmaceuticals such as BAY 1000394[114b] (see Figure 1.8) are of high relevance. CF_3-containing pharmaceuticals, particularly important for the presented work, are torcetrapib[137] (**86**), an inhibitor of cholesteryltransfer protein (CETP), and flufenamic acid[138] (FFA, **87a**) possessing anti-inflammatory and anti-cancer properties and potential as ion-channel modulator (Figure 1.11).

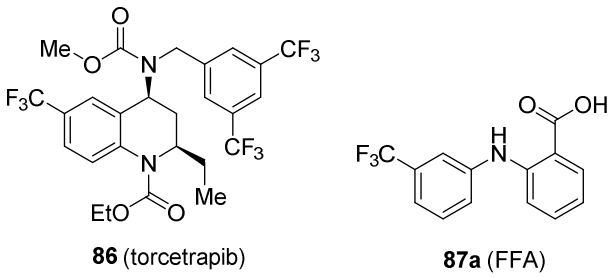
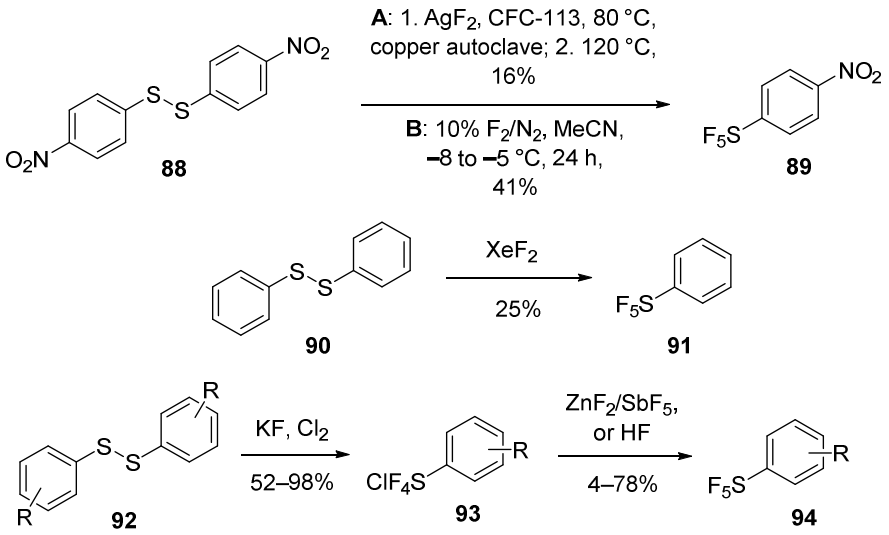


Figure 1.11: CF_3-containing bioactive compounds relevant for this work.

1.2.2 Syntheses and derivatizations of pentafluorosulfanyl arenes

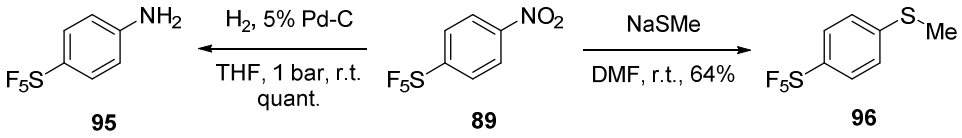
Among fluorine-containing substituents, pentafluorosulfanyl groups (SF_5) are taking on a special role.[139] Their chemistry is still underdeveloped, and the initially inconvenient synthetic access and prejudices against their hydrolytic stability long prevented considerable advances.[140] The breakthrough came in the 1960s with the first practicable synthetic routes to aromatic SF_5-containing compounds from diphenyl disulfides such as **88**, reported by *Sheppard*, by using expensive silver difluoride as fluorination agent (**A**, Scheme 1.25).[141] It was only thirty years later, that a significantly improved direct fluorination of *p*-bis(nitrophenyl)disulfide (**88**) with 10% F_2/N_2 in acetonitrile by *Bowden* and coworkers provided *p*-SF_5-nitrobenzene **89** in commercial quantities (**B**, Scheme 1.25).[142]

Later, *Ou* and *Janzen* presented an alternate approach, replacing silver difluoride by XeF_2 to convert diphenyl disulfide **90** to phenyl sulfurpentafluoride **91**, albeit in significantly lower yield (25%, Scheme 1.25, middle).[143] A safer and cheaper access avoiding fluorine gas was explored by *Umemoto*. Following the Halex process, diaryl disulfides **92** were stepwisely oxidized to SF_4Cl-containing compounds **93** in presence of potassium fluoride and chlorine gas. Subsequent displacement of the chloride by using zinc fluoride, antimony pentafluoride, or hydrogenfluoride led to formation of products **94** (Scheme 1.25, bottom).[144]



Scheme 1.25: Synthetic routes to aromatic SF_5-compounds.

Starting from *p*-SF_5-nitrobenzene (**89**), a variety of SF_5 aryls are available. *p*-SF_5-aniline (**95**) and methyl *p*-SF_5-phenyl sulfide (**96**), substrates relevant for this thesis, can be synthesized by palladium-catalyzed hydrogenation[141b] or nucleophilic aromatic substitution with methanethiolate,[145] respectively (Scheme 1.26).



Scheme 1.26: Routes to *p*-SF_5-aniline and methyl *p*-SF_5-phenyl sulfide.

1.2.3 Properties, applications, and biological activities: pentafluorosulfanyl versus trifluoromethyl

The sulfur atom in SF_5-substituents diplays a unique octahedral geometry and the fluorine atoms take a square pyramidal order around the sulfur. This accounts for a reduced rotation barrier, relevant in the optimization of drug-receptor interactions. The SF_5 group is often considered as 'super-trifluoromethyl' group to point out its superiority to CF_3 groups (with respect to several properties) and its special role among the highly flourinated groups with similar behavior (–CF_3, –OCF_3, –SCF_3).[139a]

Aromatic SF_5 groups exhibit a high thermal stability and their chemical inertness towards hydrolysis exceeds that of CF_3 groups, tolerating strong Brønsted acids and bases.[141b,142a] Their polarity and electronegativity is higher (EN 3.62) compared to CF_3 (EN 3.45), and their electron withdrawing effect is stronger.[146] Consequently, the introduction of an SF_5-substituent generates a strong dipole moment in the corresponding molecule, important in the development of functional organic materials. Interestingly, the lipophilicity of SF_5 groups is very high, a phenomenon not often observed in functionalities showing high electronegativity.[139a] Hence, the *Hansch* lipophilicity parameter of SF_5 groups is higher than that of CF_3 (π = +1.23 versus +0.88), leading to a particular solubility behavior of SF_5-containing compounds.[147] The steric

demand of an SF_5 group is slightly decreased compared to a *tert*-butyl group, but higher than the steric demand of a CF_3 group.[148] Together with the prominent hydrophobicity, the steric effects of an SF_5-substituent can influence the conformation of molecules in aqueous solutions.[139a] Studies on the photodegradation of pentafluorosulfanylbenzene revealed the formation of benzenesulfonate under mild environmentally relevant conditions.[149]

In the past decade, the amount of patents and scientific publications including SF_5 as a structural motif has increased, demonstrating growing interest in this field.[150]

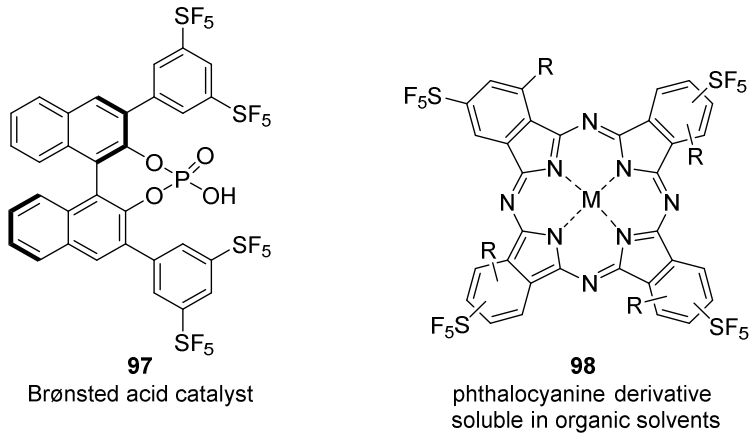


Figure 1.12: Aromatic SF_5-substituents present in a Brønsted acid catalyst and phthalocyanine.

For example, SF_5 groups have been incorporated in chiral Brønsted acid catalyst **97** leading to high enantioselectivities,[151] and in phthalocyanine derivative **98** showing excellent solubility in organic solvents (Figure 1.12).[152]

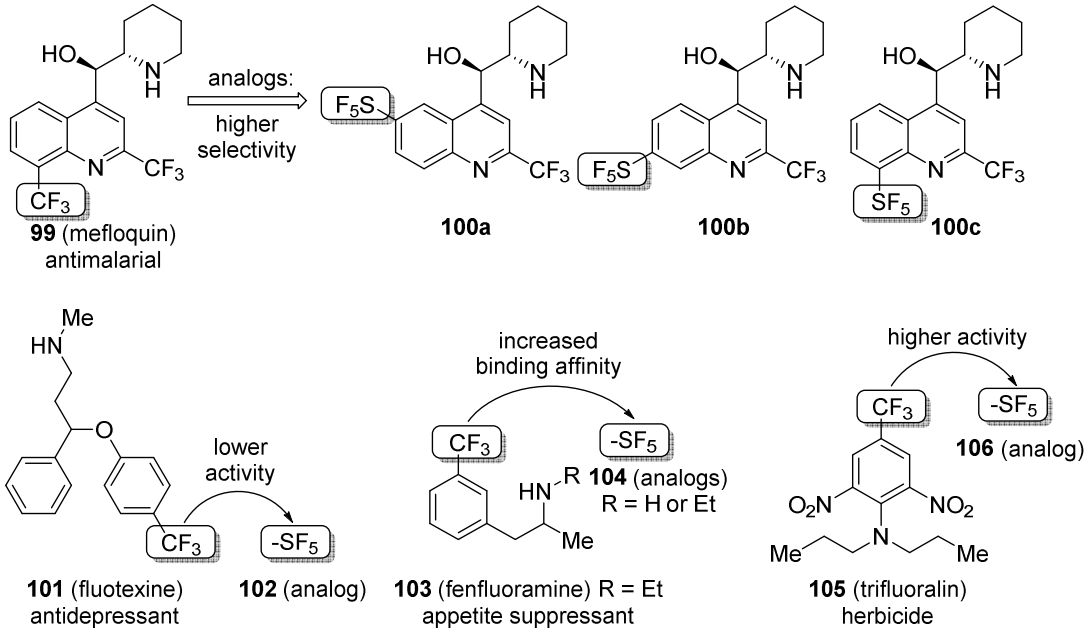


Figure 1.13: Exchange of CF_3 by SF_5 involving bioactivity changes.

Particularly intriguing is the exchange of CF_3 to SF_5 in pharmaceuticals and crop protection agents.[133] *Wipf* and coworkers synthesized the first SF_5-containing quinolines **100**, analogs of the CF_3-based antimalarial drug mefloquine (**99**) (Figure 1.13).[153] Compounds **100a** and **100b** showed equal or higher activities against resistant malaria parasite strains. Fluotexine (**101**), an antidepressant, and fenfluoramine (**103**), an appetite suppressant, are serotonin receptor binders (Figure 1.13). Syntheses and biological efficacy tests by *Welch* and *Lim* revealed a reduced activity for fluotexine analog **102**, however an enhanced potency for the flenfluoramine analogs **104** (Figure 3).[154] Furthermore, *Thrasher* and coworkers reported the synthesis of SF_5 analog **106** of the herbicide trifluoralin (**105**)[155] showing improved weed control (Figure 1.13)**.**[155-156]

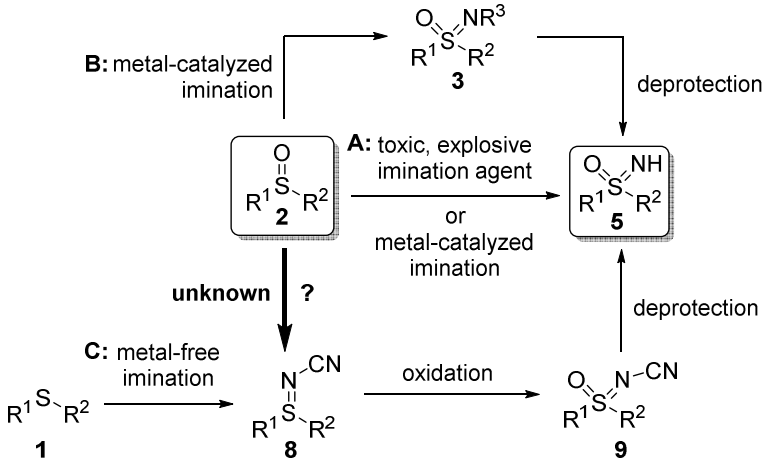
To date, as a result of their unique properties and improved synthetic access, SF_5 groups are emerging as attractive structural motifs; however, their incorporation into bioactive compounds is not widespread. Further studies on CF_3-to-SF_5 exchanges are needed to overcome synthetic challenges and evaluate the benefits of SF_5 groups in comparison to the already widely applied fluoro- and CF_3-substituents.

2 Sulfoxide-to-Sulfilimine Conversions with Modified Burgess-type Reagents

2.1 Background and Aim of the Project

To date, many methods exist for the synthesis of *N*H-sulfoximines **5** (see Chapter 1.1.2).[21a] Most procedures focus on the imination of sulfoxides **2**, employing toxic and explosive reagents or expensive transition-metal catalysts (Scheme 2.1, **A** and **B**). By using the latter (conditions **B**), *N*-protected sulfoximines **3** are obtained, mostly needing cumbersome deprotection. A widely applied metal-free route to *N*H-sulfoximines **5**, albeit starting from sulfides **1**, involves the synthesis of *N*-cyanosulfilimines **8**, their oxidation to *N*-cyanosulfoximines **9** and subsequent deprotection (Scheme 2.1, **C**).[49,59]

Apparently, no straight-forward route based on metal-free imination has been reported for the syntheses of *N*H-sulfoximines **5** from sulfoxides **2**. Such a route would be of special benefit in cases, where only sulfoxides are available as starting materials, for example in bioactive compounds.



Scheme 2.1: Synthetic routes towards *N*H-sulfoximines.

Considering previous investigations into this field, our attention was caught by sulfoxide-to-sulfilimine conversions; largely unexploited processes enabling the syntheses of sulfilimines from sulfoxides (see Chapter 1.1.2). Most procedures were rather old, often using explosive or instable reagents, or having a limited scope. More recently, the group of *Raghavan* employed Burgess reagents **34** in such transformations, giving access to *N*-C(O)OR sulfilimines (Figure 2.1).[75]

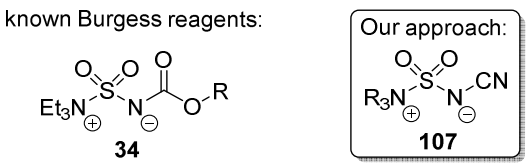


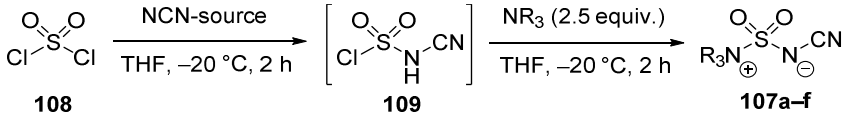
Figure 2.1: Known Burgess reagents **34** and *N*-cyano Burgess-type reagents **107**.

To find a non-hazardous metal-free route to *N*H-sulfoximines starting from sulfoxides, we aimed to synthesize new *N*-cyano-substituted Burgess-type reagents **107** (Figure 2.1), and explore their application in the unprecedented transformations of sulfoxides **2** into *N*-cyanosulfilimines **8** (Scheme 2.1).[157]

2.2 Results and Discussion

Attempting to prepare Burgess-type reagents **107**, a two-step sequence was performed. Sulfuryl chloride **108** was first treated with an NCN-source such as sodium hydrogencyanamide or potassium hydrogencyanamide at low temperature. The resulting intermediate **109** was not isolated due to its low stability and subsequently added to an amine NR_3 in order to obtain reagents **107** (Table 2.1).

Table 2.1: Synthesis of Burgess-type reagents **107a–f**.



108 **109** **107a–f**

Entry	NCN-source (equiv.)	NR_3	107a–f	Yield of 107 [%]
1	NaNHCN (1.0)	NEt_3	**a**	45[a]
2	NaNHCN (1.0)	*N*-Me piperidine	**b**	42[a]
3	NaNHCN (1.5)	*N*-Me piperidine	**b**	46[b]
4	NaNHCN (2.0)	*N*-Me piperidine	**b**	61[b]
5[c]	NaNHCN (2.0)	*N*-Me piperidine	**b**	32[b]
6	KNHCN (2.0)	*N*-Me piperidine	**b**	37[b]
7[d]	KNHCN (2.0)	*N*-Me piperidine	**b**	35[b]
8[e]	NaNHCN (2.0)	*N*-Me piperidine	**b**	77[b]
9[e]	NaNHCN (2.0)	NEt_3	**a**	62[a]
10	NaNHCN (2.0)	*N*-Me morpholine	**c**	–
11	NaNHCN (2.0)	quinuclidine[f]	**d**	48[b]
12	NaNHCN (2.0)	DABCO	**e**	–
13	NaNHCN (2.0)	urotropine	**f**	–

[a] Yield after extraction.
[b] Yield after column chromatography.
[c] Addition of 15-crown-5 (1.5 equiv.).
[d] Addition of 18-crown-6 (1.5 equiv.).
[e] THF, sulfuryl chloride, and NR_3 were freshly distilled under argon prior to use, evaporation of the solvent at 30 °C under argon during work up.
[f] 1.5 equiv. of quinuclidine.

Typically, Burgess reagents are sensitive to air and moisture. Thus, reactions were performed by using dry reagents under an argon atmosphere. To our delight, employing sodium hydrogencyanamide (1.0 equiv.) as NCN-source and triethylamine, reagent **107a** was formed. Surprisingly, it showed acceptable stability in the presence of water and could be isolated in sufficient purity by aqueous extraction in 45% yield (Table 2.1, entry 1). However, reagent **107a** decomposed when stored for a longer time even at low temperature.

Searching for alternatives, we came across a study on thermally stable Burgess-type reagents by *Hudlicky*, where *N*-methylpiperidine had proved to be advantageous.[82] As expected, by using *N*-methylpiperidine the corresponding Burgess-type reagent **107b** could be obtained in 42% yield after extraction (Table 2.1, entry 2). X-ray crystal structure analysis (performed by *Atodiresei*) revealed the molecular structure of **107b** (Figure 2.2).[158] Its improved stability allowed purification by column chromatography. Using higher amounts of NCN-source (1.5 to 2.0 equiv.) facilitated the product formation, providing an increased yield of 46% or 61% (Table 2.1, entries 3 and 4), respectively. In an effort to improve the reactivity of the NCN-source by catching the Na^+ ions, 15-crown-5 was added, however, giving **107b** in only 32% yield (Table 2.1, entry 5). Similarly, employing potassium hydrogen cyanamide resulted in low product formation, irrespective of additions of 18-crown-6 (37% and 35% yield, respectively, Table 2.1, entries 6 and 7). Finally, applying freshly distilled, anhydrous sulfuryl chloride, THF and *N*-methylpiperidine, keeping the reaction temperature strictly at –20 °C, and removing the solvents during work up at maximum 30 °C under argon atmosphere was beneficial, furnishing reagent **107b** in 77% yield (Table 2.1, entry 8). The optimal conditions in hand, the reaction with triethylamine was repeated, resulting in an improved yield of 62%, notably after extraction, as the reagent was not stable on silica (Table 2.1, entry 9 compared to entry 1).

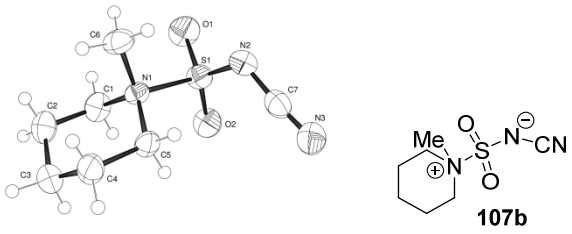
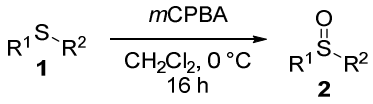


Figure 2.2: X-ray crystal structure of reagent **107b**.

To expand the variety of NCN-substituted reagents, other tertiary amines were applied (Table 2.1, entries 10–13). While the reaction with *N*-methylmorpholine failed (Table 1, entry 10), 1-azabicyclo[2.2.2]octane (quinuclidine) was reactive and generated reagent **2c** in 48% yield (Table 2.1, entry 11). Contrarily, using 1,4-diazabicyclo[2.2.2]octane (DABCO) (Table 2.1, entry 12) or hexamethylenetetramine (urotropine) (Table 2.1, entry 13) no product formation could be observed. Attempts to form reagents **107** by employing aromatic amines such as *N*-methyl indole and *N*-methyl pyrrole remained unsuccessful.

Next, various sulfoxides **2** were prepared as starting materials for the envisaged sulfoxide-to-sulfilimine conversions. Following a protocol by *Shreeve*, sulfides **1** were treated with *m*CPBA in CH_2Cl_2 at 0 °C, forming sulfoxides **2** (Table 2.2).[28]

Table 2.2: Synthesis of sulfoxides **2** as the starting materials.



Entry	R^1, R^2	2	Yield 2 [%][a]
1	4-Me-Ph, Me	**a**	94
2	Ph, Me	**b**	90
3	4-Br-Ph, Me	**c**	98
4	4-Cl-Ph, Me	**d**	92
5	4-NO_2-Ph, Me	**e**	74
6	2-Me-Ph, Me	**f**	75
7	3-Me-Ph, Me	**g**	70
8	4-*t*-butyl-Ph, Me	**h**	56
9	2-Br-Ph, Me	**i**	56
10	4-OMe-Ph, Me	**j**	86
11	3-OMe-Ph, Me	**k**	66
12	Ph, Et	**l**	91
13	Ph, cyclopropyl	**m**	95
14	2-pyridyl, Me	**n**	91
15	naphthyl, Me	**o**	87
16	cyclohexyl, Me	**p**	99
17	Bn, Et	**q**	67
18	Ph, *i*-Pr	**r**	97
19	Bn, Ph	**s**	87
20	Ph, CF_3	**t**	92

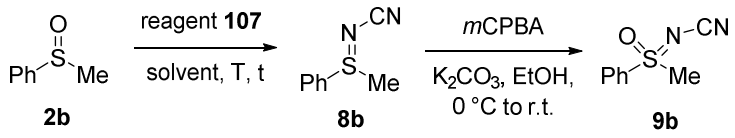
[a] Yield after column chromatography.

Aryl-methyl sulfoxides with different substitution patterns on the aromatic rings were prepared in good to high yields. Generally, electron-withdrawing and electron-donating groups in *para*-position such as bromide, chloride, nitro, methyl, or methoxy

substituents were well tolerated (74 to 98%, Table 2.2, entries 1, 3–5 and 10). In contrast, substituents in *ortho*- and *meta*-position decreased the product formation (56 to 75% yield, Table 2.2, entries 6, 7, 9, and 11). Aryl-Alkyl sulfoxides with alkyl substituents such as ethyl, cyclopropyl, isopropyl, and trifluoromethyl were obtained in good to high yields (67 to 97%, Table 2.2, entries 12, 13, 17, 18, and 20). Similarly, syntheses of sulfoxides bearing benzyl, 2-pyridyl, and naphthyl substituents proceeded well (67 to 91% yield, Table 2.2, entries 14, 15, 17, 19). As representative for alkyl-alkyl sulfoxides, cyclohexyl methyl sulfoxide (**2p**) was synthesized (99% yield, Table 2.2, entry 16).

To investigate the utility of our approach, we tested reagents **107a–c** in sulfoxide-to-sulfilimine conversions. Methyl phenyl sulfoxide (**2b**), used as a model substrate, should be transformed into the corresponding *N*-cyanosulfilimine **8b** (Table 2.3).

Table 2.3: Attempts to form sulfilimines **8b** using Burgess-type reagents **107a–c**.



Entry	Reagent (equiv.)	solvent	T, t	Yield 8b [%][a]	Yield 9b [%][a]
1	**107a** (2.0)	THF	r.t., 16 h	25	
2	**107b** (2.0)	THF	r.t., 16 h	not isolated	26[b]
3	**107c** (1.2)	THF	r.t., 16 h	– [c]	
4	**107b** (2.0)	MeOH	r.t., 16 h	–	
5	**107b** (2.0)	benzene	r.t., 16 h	not isolated[d]	
6	**107b** (2.0)	MeCN	r.t., 16 h	–	
7	**107b** (2.0)	THF/CH_2Cl_2 (1:1)	MW 40 °C, 40 min	not isolated	40[b]

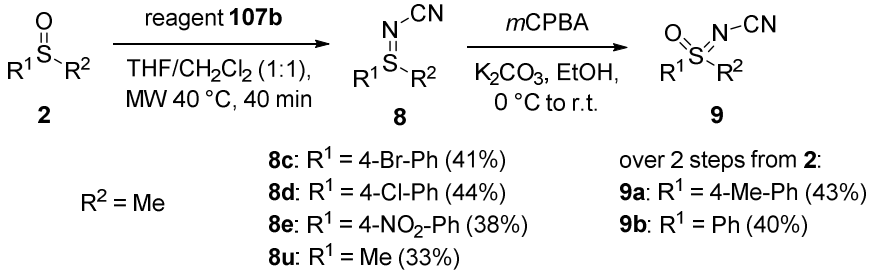
[a] Yield after column chromatography.
[b] Yield over 2 steps from **2b**. Due to the cumbersome purification of **8b**, oxidation to **9b** was performed.
[c] No reaction.
[d] Very low product formation observed on TLC, product not isolated.

Initially, triethylamino-substituted reagent **107a** was utilized in the conversion of sulfoxide **2b** in THF at room temperature. The desired *N*-cyanosulfilimine **8b** was formed, albeit in low yield of 25% (Table 2.3, entry 1). As reagent **107a** appeared to be instable under those conditions, *N*-methylpiperidinyl-substituted reagent **107b** was used, offering higher thermal stability (Table 2.3, entry 2). The desired product was observed, but the separation of *N*-cyanosulfilimine **8b** from the concomitantly produced *N*-methylpiperidine remained unsatisfactory. In this case, oxidation of **8b** with *m*CPBA[49] gave access to the corresponding *N*-cyanosulfoximine **9b** in 26% yield. Contrarily, the

reaction of sulfoxide **2b** with quinuclidine-based reagent **107c** did not proceed (Table 2.3, entry 3).

Concluding that reagent **107b** was most suitable in terms of stability and reactivity, a screening of solvents such as methanol, benzene, and acetonitrile was performed (Table 2.3, entries 4-6). Unfortunately, only little or no product formation occurred. Finally, conditions which previously proved useful in reactions with the original Burgess reagent were applied.[159] Performing the reaction in a 1:1 mixture of THF/CH_2Cl_2 at 40 °C under the influence of microwave irradiation increased the yield of sulfoximine **9b** to 40% (Table 2.3, entry 7). Further extensive investigations did not lead to improvement, showing that higher temperatures and/or longer reaction times resulted in decomposition of reagent **107b**.

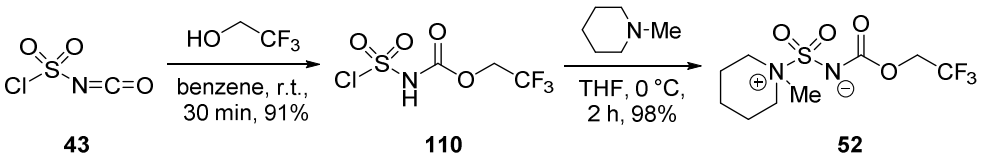
Given that this approach to *N*-cyanosulfilimines was entirely new, we aimed to investigate the scope of these conversions. Several representative aryl methyl sulfoxides **2a–e** were treated with reagent **107b**, (conditions: Table 2.3, entry 7) giving the corresponding *N*-cyanosulfilimines **8c–e** and *N*-cyanosulfoximines **9a** and **9b** in moderate yields (up to 44%, Scheme 2.2). Using DMSO as alkyl-alkyl substrate provided *N*-cyanosulfilimine **8u** in 33% yield. Although having opened a new pathway in the syntheses of *N*-cyanosulfilimines **8** and *N*-cyanosulfoximines **9** from sulfoxides **2**, the insufficient yields suggested searching for alternate routes to *N*H-sulfoximines **5** starting from sulfoxides **2**.



Scheme 2.2: Syntheses of *N*-cyanosulfilimines **8** and *N*-cyanosulfoximines **9**.

Considering again the conversion of sulfoxides into carbamate-based sulfilimines using reagents **34**, reported by *Raghavan*,[75] we decided to utilize Burgess-type reagent **52** (Scheme 2.3), reported by *Hudlicky* and coworkers, as it had shown improved thermal stability and reactivity compared to the original Burgess reagent.[82] Hence, it appeared as a suitable alternative to reagents **34** and **107** in sulfoxide-to-sulfilimine conversions.

Modifying the published synthetic route to reagent **52**[82] slightly, proved beneficial. The reaction of chlorosulfonylcarbamate **43** with trifluoroethanol proceeded well, affording 2,2,2-trifluoroethyl chlorosulfonylcarbamate **110** in 91% yield. The latter compound was subsequently converted with freshly destilled dry *N*-methylpiperidine and THF as solvent to furnish reagent **52** in 98% yield (Scheme 2.3).

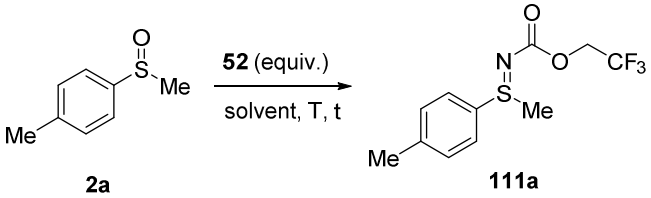


43 **110** **52**

Scheme 2.3: Synthesis of Burgess-type reagent **52**.

In order to study its reactivity in sulfoxide-to-sulfilimine conversions, reactions of **52** with methyl *p*-tolyl sulfoxide (**2a**) were attempted. Varying the amount of reagent **52**, solvent, temperature, and reaction time, the optimal conditions for the formation sulfilimine **111a** were determined (Table 2.4).

Table 2.4: Optimization of the sulfoxide-to-sulfilimine conversions with reagent **52**.



2a **111a**

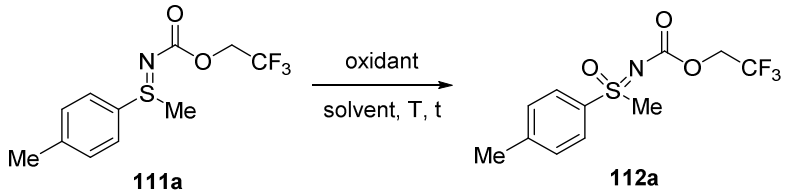
Entry	52 (equiv.)	Solvent	T	Time [h]	Yield 111a [%][a]
1	1.5	THF	r.t.	2	–[b]
2	1.5	THF	r.t.	4	72
3	1.5	THF	r.t.	24	73
4	1.5	THF	MW, 40 °C	0.6	70
5	1.5	benzene	reflux	2	63
6	2.0	Me-THF	reflux	2	–
7	2.0	THF	reflux	2	78

[a] Yield after column chromatography.
[b] Conversion not complete, starting material remained.

Sulfoxide **2a** was first treated with reagent **52** (1.5 equiv.) in THF at room temperature, and the conversion was monitored. After 2 h, the conversion was still incomplete (Table 2.4, entry 1), while a reaction time of 4 h provided sulfilimine **111a** in 72% yield (Table 2.4, entry 2). Allowing the reaction to proceed for 24 h did not lead to further improvement (Table 2.4, entry 3). Thus, the conditions were changed, and the reaction was performed at 40 °C under microwave irradiation for 40 min, albeit involving a decrease in yield (70%, Table 2.4, entry 4). When applying conditions reported by *Raghavan*,[75] performing the reaction under reflux for 2 h in benzene, the yield dropped even more (63%, Table 2.4, entry 5). Enhancing the amount of reagent **52** (2.0 equiv.) using Me-THF as solvent did not lead to any product. Fortunately, employing reagent **52** (2.0 equiv.) and THF as solvent under reflux for 2 h afforded **111a** in good yield of 78%.

Continuing our investigations into the new route to *N*H-sulfoximines, oxidations of sulfilimine **111a** to sulfoximine **112a** were now performed. Various oxidants and solvent combinations were applied to optimize the reaction yield (Table 2.5).

Table 2.5: Oxidations of sulfilimine **111a** to sulfoximine **112a**.



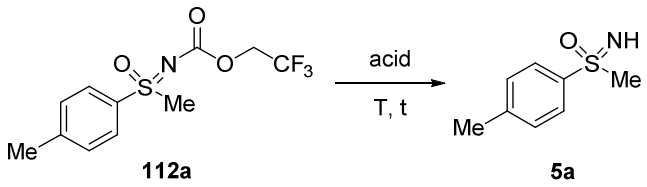
111a **112a**

Entry	Oxidant	Solvent	T [°C]	Time [h]	Yield of 112a [%][a]
1	*m*CPBA, K_2CO_3	EtOH	r.t.	16	–
2	$KMnO_4$, NaOH	H_2O	110	2.0	–
3	MMPP	CH_2Cl_2 /MeOH	r.t.	2.5	–[b]
4	$NaIO_4$, $RuCl_3{\cdot}4H_2O$ (cat.)[c]	MeCN/H_2O 1:1.5	r.t.	2.5	78
5	$NaIO_4$, $RuCl_3{\cdot}4H_2O$ (cat.)[c]	MeCN/H_2O 1:1.3	r.t.	2.5	84
6	$NaIO_4$, $RuCl_3{\cdot}4H_2O$ (cat.)[c]	MeCN/H_2O 1:2	r.t.	2.5	88
7	$NaIO_4$, $RuCl_3{\cdot}4H_2O$ (cat.)[c]	MeCN/H_2O 1:2	r.t.	1.0	99

[a] Yield of pure compound after extraction.
[b] Conversion not complete.
[c] 5 equiv. of $NaIO_4$ were used.

First attempts with *m*CPBA and potassium carbonate in ethanol at room temperature[49] (Table 2.5, entry 1), or potassium permanganate and sodium hydroxide in water at 110 °C (Table 2.5, entry 2) that had proved beneficial in oxidations of *S*-perfluoroalkyl sulfilimines,[67] did not afford any product. Applying magnesium bis(mono-peroxyphthalate) hexahydrate (MMPP) in CH_2Cl_2/methanol at room temperature, a useful method for sulfide oxidation,[160] the conversion was not sufficient (Table 2.5, entry 3). However, employing catalytic amounts of $RuCl_3{\cdot}4H_2O$ and sodium periodate in acetonitrile/water (1:1.5), the *in situ* generated ruthenium tetroxide[56] oxidized sulfilimine **111a** to sulfoximine **112a** in 78% yield (Table 2.5, entry 4). By varying the acetonitrile/water ratio the yield could be improved (84 and 88%, Table 2.5, entries 5 and 6). Performing the oxidation for 1 h instead of 2.5 h provided sulfoximine **112a** in 99% yield and excellent purity after extraction (Table 2.5, entry 7) avoiding cumbersome chromatographic isolation. Considering these major advantages, it was decided to accept metal-catalyzed oxidation in this process. Motivated by the positive results, attempts were performed to deprotect sulfoximine **112a** under acidic conditions to *N*H-sulfoximine **5a** (Table 2.6).

Table 2.6: Deprotection of sulfoximine **112a**.



112a **5a**

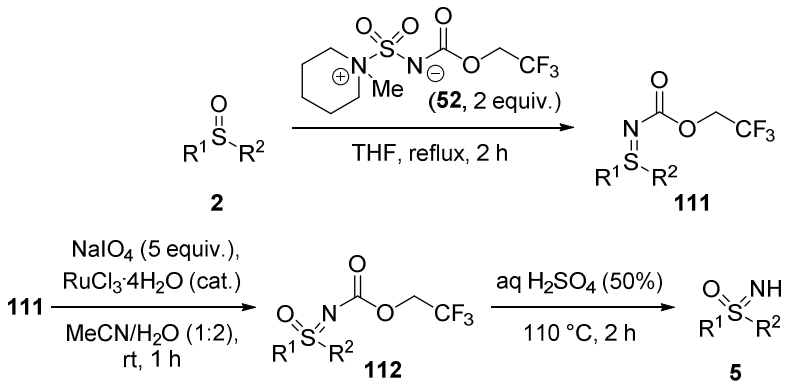
Entry	Acid	T [°C]	Time [h]	Yield of 5a [%][a]
1	HCl (1 N)	110	2	–
2	TFA	60	2	–[b]
3	50% aq H_2SO_4	110	1	92
4	50% aq H_2SO_4	110	2	96

[a] Yield of pure compound after extraction.
[b] Conversion not complete, observed on TLC.

In a first reaction, sulfoximine **112a** was exposed to HCl (1 N) at 110 °C for 2 h, but no product was obtained (Table 2.6, entry 1). By using trifluoroacetic acid (TFA) at 60 °C, *N*H-sulfoximine **5a** could be observed in low amounts (Table 2.6, entry 2). Applying 50% aqueous sulfuric acid[60] for 1 h at 110 °C, the reaction performed well and provided sulfoximine **5a** in 92% (Table 2.6, entry 3). A reaction time of 2 h under the same conditions proved optimal, giving **5a** in 96% yield and high purity after extraction (Table 2.6, entry 4).

The optimized conditions in hand, we aimed to demonstrate the generality of the new synthetic route and investigated the scope of sulfoxides **2**. The formation of sulfilimines **111** by using reagent **52**, subsequent oxidations to sulfoximines **112**, and final deprotections to obtain *N*H-sulfoximines **5** were studied (Table 2.7). Conversions of aryl-alkyl sulfoxides generally proceeded smoothly, affording the corresponding sulfilimines **111** in high yields (up to 81%, Table 2.7, entries 1–14). Sulfilimines **111c–d** with halo-substituents in *para*-position were obtained in 72% and 71% yield, respectively (Table 2.7, entries 3 and 4). Accordingly, substituents in *ortho*- and *meta*-position such as present in sulfoxides **2f–g** and **2k** were generally well tolerated (Table 2.7, entries 5, 6, and 10). However, 2-bromophenyl methyl sulfoxide **2i** was obtained in moderate yield (37%, Table 2.7, entry 8). Reactions of sulfoxides **2l–m** and **2q** with reagent **52** provided the corresponding ethyl- and cyclopropyl-substituted sulfilimines **111l–m** and **111q** in yields between 68% and 78% (Table 2.7, entries 11, 12, 16). Dialkyl sulfoxide **2p** underwent the process smoothly, generating sulfilimine **111p** in 80% yield (Table 2.7, entry 15).

Table 2.7: Synthetic route to *N*H-sulfoximines **5**.



Entry	R^1, R^2	2	Yield of 111 [%][a]	Yield of 112 [%][b]	Yield of 5 [%][b]
1	4-Me-Ph, Me	**a**	78	99	96
2	Ph, Me	**b**	79	98	99
3	4-Br-Ph, Me	**c**	72	99	96
4	4-Cl-Ph, Me	**d**	71	99	97
5	2-Me-Ph, Me	**f**	72	98	99
6	3-Me-Ph, Me	**g**	63	99	97
7	4-*t*-Bu-Ph, Me	**h**	70	98	99
8	2-Br-Ph, Me	**i**	37	99	76
9	4-MeO-Ph, Me	**j**	75	97	90
10	3-MeO-Ph, Me	**k**	81	99	99
11	Ph, Et	**l**	78	99	99
12	Ph, cyclopropyl	**m**	72	95	98
13	2-pyridyl, Me	**n**	–[c]	54[d]	84
14	2-naphthyl, Me	**o**	70	70[e]	83
15	cyclohexyl, Me	**p**	80	82	–
16	Bn, Et	**q**	68	92	–
17	Ph, *i*-Pr	**r**	–	–	–
18	Bn, Ph	**s**	–	–	–
19	Ph, CF_3	**t**	–	–	–

[a] Yield after column chromatography.
[b] Yield of pure compound after extraction.
[c] Not isolated.
[d] Yield over 2 steps from **2n**.
[e] $KMnO_4$ (16 equiv.), acetone, 60 °C, 24 h.

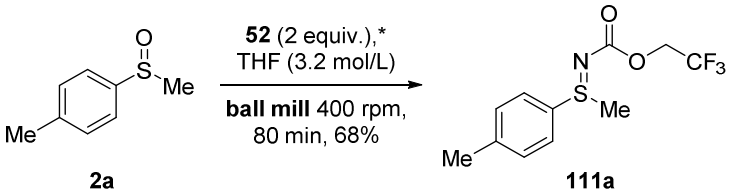
Typically, sulfilimines **111** exhibited high stability. However methyl 2-pyridyl sulfilimine **111n** proved very sensitive (Table 2.7, entry 13) and was oxidized without previous purification. Presumably by reason of steric hindrance as for sulfoxides **6r** and **6s**, or high electron deficiency resulting from a trifluoromethyl substituent (sulfoxide **6t**) at the sulfur atom, the corresponding sulfilimines were not formed (Table 2.7, entries 17–19).

Next, oxidations of sulfilimines **111** with *in situ* generated ruthenium tetroxide were performed. Applying the optimal conditions (Table 2.5, entry 7), the corresponding sulfoximines **112** were generally obtained in excellent yields after only 1 h reaction time and subsequent extraction. Of note, as sulfilimine **111n** could not be isolated, oxidation furnished methyl 2-pyridyl sulfoximine **5n** in 54% yield over two steps (Table 2.7, entry 13). Methyl 2-naphthyl sulfoximine **5o** was instable under the standard oxidation conditions (Table 2.7, entry 14). Fortunately, oxidation of sulfilimine **111o** with potassium permanganate proceeded well, giving **112o** in 70% yield.

The last step of the three-step-sequence comprised deprotections of sulfoximines **112** leading to *N*H-sulfoximines **5**, accomplished under previously optimized acidic conditions (Table 2.6, entry 4). Subsequent extractions provided most *N*H-sulfoximines **5** in excellent yields, and no further purification was necessary. Only deprotection attempts for cyclohexyl methyl and benzyl ethyl sulfoximines **5p** and **5q** were not successful (Table 2.7, entries 15 and 16), most likely due to decomposition of the corresponding *N*H-sulfoximines under the acidic reaction conditions.

After successfully establishing a safe straight-forward route to *N*H-sulfoximines, we intended to further explore the sulfoxide-to-sulfilimine conversions. Searching for alternate reaction conditions, our interest was caught by mechanochemical reactions, performed under solvent-free or solvent-reduced conditions. Ball milling, industrially applied for grinding of minerals and ores, has already shown its benefits in many chemical reactions, and has emerged as valuable method in organic synthesis.[161] However, to the best of our knowledge, applications of Burgess-type reagents in a ball mill have not been performed up to now.

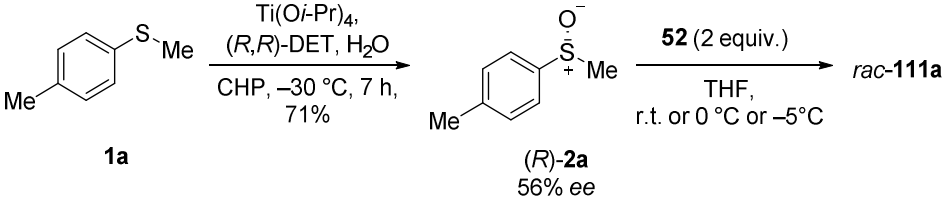
Following our continuing interest in mechanochemically influenced reactions,[162] we were curious whether the sulfoxide-to-sulfilimine conversions would proceed in a ball-mill. When treating sulfoxide **2a** with reagent **52** or **107b** for 80 min milling time, decomposition of **107b** was observed, presumably due to its low stability. Under the same conditions reagent **52** provided the corresponding sulfilimine **111a** in 68% yield (Scheme 2.4).



Scheme 2.4: Application of Burgess-type reagent **52** in a ball mill; ***107b** decomposed.

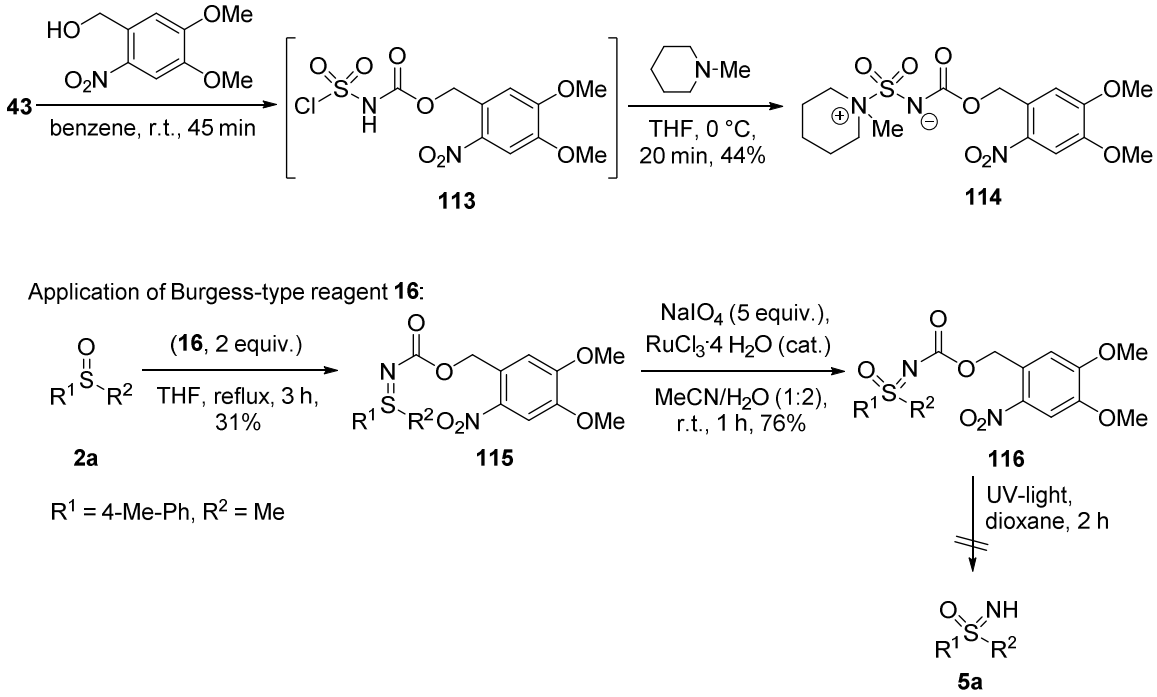
Completely solvent-free reactions were not successful. Nevertheless, these findings might be inspiring for future applications of Burgess reagents under solvent-reduced conditions.

As stereospecific sulfoxide-to-sulfilimine conversions are underdeveloped,[70–72,163] we envisaged such a reaction. To this end, enantioenriched sulfoxide (*R*)-**2a** was prepared following a procedure by *Kagan*,[33b] employing titanium isopropoxide, (*R*,*R*)-diethyl tartrate and cumene hydroperoxide (71% yield, 56% *ee*, Scheme 2.5). Unfortunately however, the conversion of (*R*)-**2a** with reagent **52** resulted in complete racemization, irrespective of temperature (–5 °C, 0 °C, r.t.), or the substrate concentration in the reaction mixture (0.2 mol/L and 3.2 mol/L). These observations are in accordance with the findings of *Raghavan*.[75] Computational calculations to investigate the transition states have been performed by the group of *Bolm* (*Engel*).[164]



Scheme 2.5: Synthesis of enantioenriched (*R*)-**2a** and its reaction with reagent **52**.

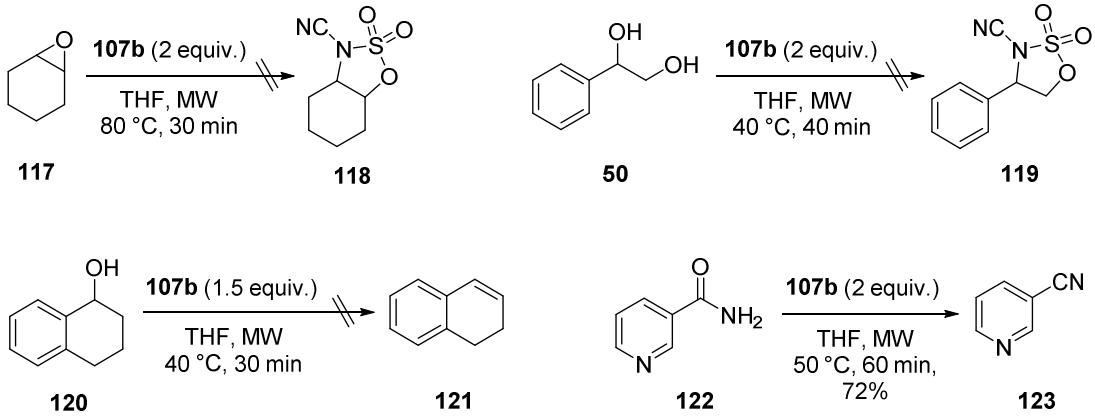
Especially regarding the syntheses of acid- and base-sensitive sulfoximines, it is favorable to introduce easily cleavable *N*-protecting groups that can be removed under neutral conditions. Along those lines, we had the idea to synthesize a Burgess-type reagent able to transfer a photolabile protecting group, and apply it in sulfoxide-to-sulfilimine conversions.[81]



Scheme 2.6: Preparation of Burgess-type reagent **114**, containing a photolabile protecting group, and its application.

Treating chlorosulfonyl isocyanate **43** with 6-nitroveratryl, a protecting group generally removed at λ>350 nm,[165] afforded intermediate **113**. Subsequent substitution with *N*-methylpiperidine at 0 °C provided Burgess-type reagent **114**, bearing a 6-nitroveratryl protecting group, in 44% yield (Scheme 2.6, top). To our delight, using reagent **114**, sulfoxide **2a** was converted into sulfilimine **115**, albeit in moderate yield (37%, Scheme 2.6, middle). Following oxidation under standard conditions proceeded smoothly; leading to the corresponding sulfoximine **116** in 76% yield (Scheme 2.6, middle). Unfortunately, when attempting to deprotect **116** under UV-light (λ>350 nm and <350 nm), decomposition occurred, and the desired *N*H-sulfoximine **5a** was not obtained (Scheme 2.6, bottom).

Since their discovery, the "traditional" Burgess reagents have been applied in numerous reactions including sulfamidate formations leading to carbamate-like structures,[81] dehydration reactions of alcohols,[79] and cyanation reactions (see Scheme 1.20).[80] In this context, we investigated the behavior of *N*-cyano Burgess-type reagent **107b** in corresponding transformations (Scheme 2.7). Unfortunately, the syntheses of *N*-cyanosulfamidates starting from epoxide **117** or diol **50**, respectively, did not involve product formation (Scheme 2.7, top). Similarly, the dehydration of alcohol **120** to alkene **121** did not occur when reagent **107b** was applied (Scheme 2.7, bottom). However, a cyanation reaction of nicotinamide (**122**) using **107b** was successful, providing the desired product **123** in 72% yield (Scheme 2.7, bottom).



Scheme 2.7: Miscellaneous reactions of *N*-cyano Burgess-type reagent **107b**.

2.3 Summary

In this study a straight-forward route to *N*H-sulfoximines starting from sulfoxides was investigated. This task was successfully accomplished relying on the chemistry of Burgess-type reagents. In the course of our studies, the rather unexplored field of sulfoxide-to-sulfilimine conversions emerged as a playground, stimulating our interest in unusual transformations and reaction conditions.

In an initial approach, a new *N*-cyano Burgess-type reagent has been developed. It was applied in unprecedented conversions of sulfoxides into *N*-cyanosulfilimines, giving the products in moderate yields. Thus, it might be especially useful in reactions, where only

sulfoxides are available as starting materials. In addition, it proved capable to transform a primary amide into a corresponding nitrile.

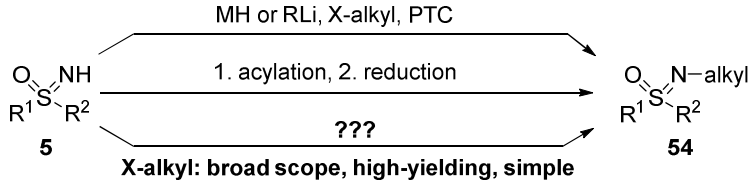
Sulfoxide-to-sulfilimine conversions were performed employing a thermally stable Burgess-reagent, giving access to *N*H-sulfoximines from sulfoxides in a straight-forward 3-step route: mild, metal-free conversion of sulfoxides into sulfilimines, followed by fast and quantitative metal-catalyzed oxidation, and subsequent metal-free deprotection. A reaction of this reagent in a ball mill under solvent-reduced conditions was successful and therefore represents the first application of a Burgess-type reagent under such non-conventional conditions. However, an attempted stereospecific conversion of a sulfoxide into the corresponding sulfilimine led to racemization.

Moreover, a new Burgess-type reagent bearing a 6-nitroveratryl group was prepared in moderate yield. The transformation of a sulfoxide into a photolabile-protected sulfilimine occurred, albeit the deprotection of the corresponding sulfoximine has not yet been achieved.

3 *N*-Alkylations of *N*H-Sulfoximines by Using KOH in DMSO

3.1 Background and Aim of the Project

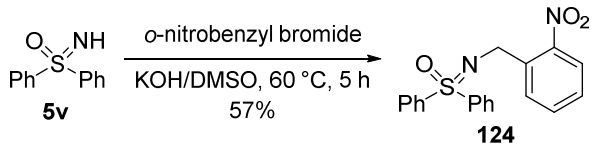
N-Alkylsulfoximines **54** and especially their *N*-aminoalkyl and *N*-methyl derivatives are important entities in bioactive compounds (see Chapter 1.1.3), and several protocols for their preparation from *N*H-sulfoximines **5** exist (see Chapter 1.1.2). Disadvantageously, these methods proved not successful for *N*-alkylations with longer alkyl chains. The latter can be introduced under strongly basic conditions by using alkali metal hydrides (MH) or butyllithium in combination with a phase transfer catalyst (PTC) (Scheme 3.1).[83,89] To obtain the products in reasonable yields, strictly anhydrous conditions, long reaction times, and substrates with suitable steric and electronic properties are indespensable. In a few cases, a two-step acylation/reduction-protocol turned out to be helpful,[91] but generally, the product scope has been limited (Scheme 3.1). Thus, we were interested in developing a simple and high-yielding method for the introduction of alkyl-substituents to *N*H-sulfoximines **5** (Scheme 3.1).



Scheme 3.1: Synthetic strategies towards *N*-alkylsulfoximines.

Searching for suitable reaction conditions, we came across our previous studies employing KOH in DMSO as a superbasic reaction medium[166] in various processes.[167] Of note, in 1973 *Heaney* and *Ley* had used KOH in DMSO for *N*-alkylations of indoles and pyrroles with alkyl halides, suggesting that the strongly ionizing solvents had been necessary to enhance the reactivity of the hypothetically formed *N*-metalated intermediates for the following nucleophilic substitutions with alkyl halides.[168]

Considering the low nucleophilicity of the sulfoximine nitrogen atom and our previous successful introduction of a light-cleavable *N*-(*o*-nitrobenzyl) group to an *N*H-sulfoximine **5v** in KOH/DMSO (Scheme 3.2) leading to **124**,[169] we decided to apply our established method and perform *N*-alkylations under those conditions.[170]



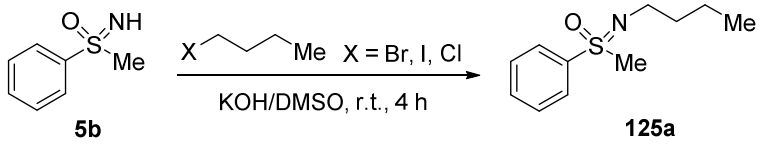
Scheme 3.2: *N*-Benzylation of sulfoximine **5v** with a light-cleavable protecting group.

3.2 Results and Discussion

In an initial attempt, hoping for a similar reactivity in the *N*-alkylation of *N*H-sulfoximines with long alkyl chains, we performed a reaction of sulfoximine **5b** with *n*-butyl bromide (2 equiv.) using KOH (2 equiv.) in DMSO. To our delight, the reaction at

room temperature for 4 h proceeded well, furnishing *N*-butylated sulfoximine **125a** in 83% yield (Table 3.1, entry 1). Advantageously, employing a lower amount of *n*-butyl bromide (1.5 equiv.), the product could be isolated in the same yield (Table 3.1, entry 2). Applying butyl iodide enhanced the yield even more, while the corresponding chloride involved a decrease in yield (95% versus 62%, Table 3.1, entries 3 and 4). Longer reaction times (15 h) led to lower amounts of the *N*-alkylated product, presumably due to its decomposition when being exposed to the superbasic medium for a longer period (Table 3.1, entry 5). As reactions at elevated temperatures (60 or 90 °C) did not show further improvement, performing the reactions at room temperature proved optimal (Table 3.1, entries 6 and 7).

Table 3.1: Optimization of reaction conditions for the *N*-alkylation.

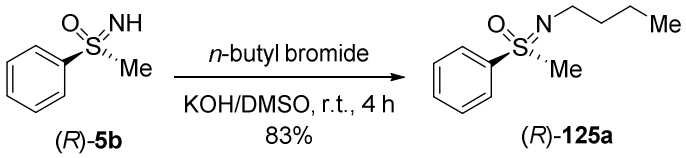


5b **125a**

Entry	X	Butyl-X (equiv.)	T [°C]	Time [h]	Yield of 125a [%][a]
1	Br	2.0	r.t.	4	83
2	Br	1.5	r.t.	4	83
3	I	1.5	r.t.	4	95
4	Cl	1.5	r.t.	4	62
5	Br	1.5	r.t.	15	78
6	Br	1.5	60	4	83
7	Br	1.5	90	4	80

[a] Yield after column chromatography.

Generally, racemic sulfoximines were applied. An additional reaction of enantiopure (*R*)-**5b**[171] with *n*-butyl bromide confirmed the expected stereospecificity, as only formation of (*R*)-**125a** was observed (Scheme 3.3).

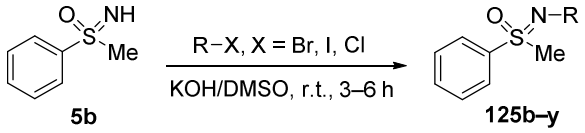


(*R*)-**5b** (*R*)-**125a**

Scheme 3.3: Stereospecific *N*-alkylation of (*R*)-**5b**.

Continuing our investigations, the scope of alkyl halides was explored under the optimized reaction conditions with use of sulfoximine **5b** as representative starting material. With respect to yield, cost, accessibility, and environmental impact, in most cases alkyl bromides were chosen as substrates (Table 3.2).

Table 3.2: Scope of alkyl halides for the *N*-alkylation of sulfoximine **5b**.



5b **125b–y**

Entry	R	X	125	Yield [%][a]
1	ethyl	Br	**b**	87
2	pentyl	Cl	**c**	61
3	heptyl	Br	**d**	89
4	nonyl	Cl	**e**	59
5	dodecyl	Br	**f**	80
6	tetradecyl	Br	**g**	82
7	octadecyl	I	**h**	92
8	cyclohexyl	Br	**i**	–
9	*i*-propyl	Br	**j**	14
10	*i*-butyl	Br	**k**	34
11	*i*-amyl	Br	**l**	95
12	(*S*)-citronellyl	Br	**m**	97[b]
13	2-cyclohexylethyl	Br	**n**	83
14	allyl	Br	**o**	79
15	4-pentenyl	Br	**p**	81
16	10-undecenyl	Br	**q**	83
17	prenyl	Br	**r**	50
18	geranyl	Br	**s**	41
19	cinnamyl	Br	**t**	60
20	propargyl	Br	**u**	83
21	2-pentynyl	Br	**v**	93
22	benzyl	Br	**w**	75
23	2-phenylethyl	Br	**x**	traces
24	3-phenylpropyl	Br	**y**	88

[a] Yield after column chromatography.
[b] The product was isolated as a mixture of diastereomers.

Initially, *N*-alkylations with linear alkyl halides were performed (Table 3.2, entries 1–7). All reactions with alkyl bromides led to the corresponding *N*-alkylsulfoximines in high yields (80–89%) irrespective of the chain lengths. As observed during the optimization (Table 3.1, entry 4), the use of alkyl chlorides (Table 3.2, entries 2 and 4) involved a

decrease in yield (59–61%). Accordingly, applying an alkyl iodide, (here: octadecyl iodide), increased the product formation (92% yield, Table 3.2, entry 7).

N-alkylations with cyclic and branched alkyl bromides were attempted next (Table 3.2, entries 8–13). The results show a strong dependence of the product formation on the position of the branch, indicated by the yields of sulfoximines **125i–n**. While *N*-alkylations with cyclohexylbromide and *i*-propylbromide did not afford any (Table 3.2, entry 8) or very few product (14%, Table 3.2, entry 9), the yield of *N*-*i*-butylsulfoximine **125k** was increased (34%, Table 3.2, entry 10) and reached a very high level for *N*-*i*-amylsulfoximine **125l** (95%, Table 2, entry 11). Similarly, the natural product derived (*S*)-citronellyl-bromide, bearing a methyl substituent in the same position, afforded sulfoximine **125m** in 97% yield in a 1:1 mixture of diastereomers (Table 3.2, entry 12). *N*-Alkylation with 2-cyclohexylethyl bromide proceeded equally well, giving sulfoximine **125n** in 87% yield (Table 3.2, entry 13).

Moreover, various unsaturated substituents could be introduced. In all cases, the unsaturated moieties were preserved (Table 3.2, entries 14–21). Sulfoximines **125o–q**, containing linear alkenyl chains, were obtained in good yields (79–83%, Table 3.2, entries 14–16) while branched alkenyl bromides such as prenyl bromide, geranyl bromide, and cinnamyl bromide decreased the product formation, providing sulfoximines **125r–t** in lower yields (41–60%, Table 3.2, entry 17–19). *N*-Alkynylated sulfoximines **125u** and **125v** were formed in high amounts (83% and 93% yield, Table 3.2, entries 20 and 21).

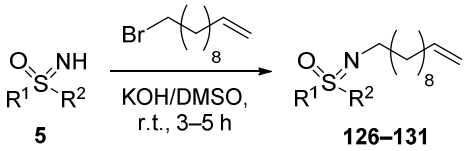
To further demonstrate the generality of the newly derived method, aryl-substituted alkyl bromides with different alkyl chain lengths were applied. As expected, *N*-benzylsulfoximine **125w** could be obtained in good yield (75%, Table 3.2, entry 22). Surprisingly, *N*-2-phenylethylsulfoximine **125x** was only formed in traces (Table 3.2, entry 23), and the *N*-alkylation reaction provided *N*-3-phenylpropyl sulfoximine **125y** in high yield (88%, Table 3.2, entry 24).

Supplementary attempts such as *N*-alkylations with perfluoroalkyl bromides and iodides, alkyl dibromides, hydroxyalkyl bromides, *N*-alkynylation with ethynyl bromide as well as *N*-arylations with phenyl bromide and naphthyl bromide remained unsuccessful. A reaction with ethynyl benzene in order to form a *cis*-enamine type compound did not lead to product formation.

Next, we focused our attention on the *N*-alkylation of diversely substituted *N*H-sulfoximines **5**. To this end, reactions with 10-undecenyl bromide were performed (Table 3.3). Various substituent combinations at the sulfur atom such as diaryl, aryl/alkyl, and alkyl/alkyl were tolerated well, affording the corresponding *N*-alkylated products in high yields (83–91%, Table 3.3, entries 1-5). Reactions with sulfoximines **5j** and **5c**, containing an electron-donating *S*-methoxyphenyl or an electron-withdrawing *S*-bromophenyl substituent proceeded well (Table 3.3, entries 4-5). Both substituents were kept intact, which might be beneficial regarding further transformations. However, a strongly electron-withdrawing *S*-nitrophenyl group prevented product formation, and

only traces of *N*-alkylated sulfoximine **131** were observed (Table 3.3, entry 6). Of note, the rather unexploited electron-withdrawing *S*-(4-SF_5-phenyl) substituent allowed product formation in 76% yield (see Scheme 8.3).

Table 3.3: Scope of Sulfoximines.

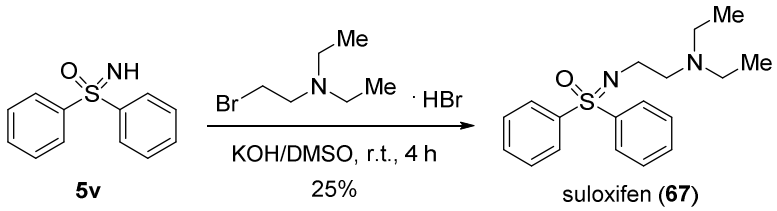


5 **126–131**

Entry	Starting Material	R^1	R^2	Product	Yield [%][a]
1	**5v**	Ph	Ph	**126**	88
2	**5m**	Ph	cyclopropyl	**127**	91
3	**5u**	Me	Me	**128**	88
4	**5j**	4-MeO-C_6H_4	Me	**129**	87
5	**5c**	4-Br-C_6H_4	Me	**130**	83
6	**5e**	4-NO_2-C_6H_4	Me	**131**	traces

[a] Yield after column chromatography.

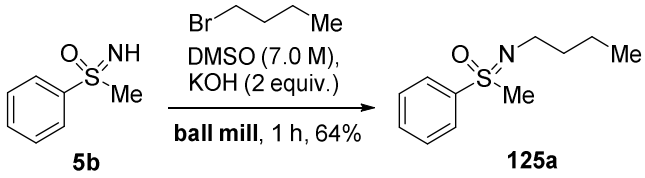
As an application, we envisaged the synthesis of *N*-aminoalkylated diphenyl sulfoximine **67**, namely suloxifen, which has been known as a both orally and parentally effective spasmolytic and antiasthmatic agent (Scheme 3.4).[90,113] To our delight, using KOH in DMSO, the one-step *N*-alkylation of sulfoximine **5v** with 1-bromo-2-(diethylamine)-ethane hydrobromide gave access to suloxifen (**67**), albeit in low yield (25%).



5v suloxifen (**67**)

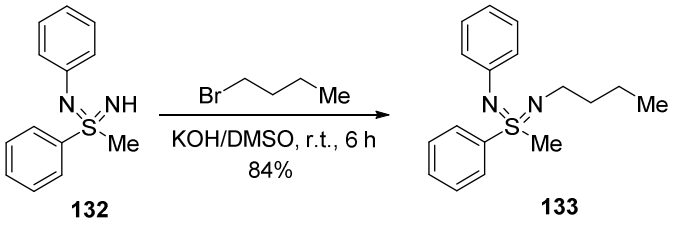
Scheme 3.4: Synthesis of suloxifen.

By reason of practicability, environmental impact, and industrial applicability, it was of interest to reduce the amount of DMSO used in the performed *N*-alkylations. Along those lines, a reaction of sulfoximine **5b** with *n*-butyl bromide was attempted in a planetary ball mill (for another herein described application, see Scheme 2.4), using KOH and a 10-fold reduced amount of DMSO (7.0 M instead of 0.7 M, Scheme 3.5). Proving our concept, *N*-butylsulfoximine **125a** was obtained in 64% yield after 1 h reaction time. However, completely solvent-free conditions in a ball mill did not afford any product, presumably because the required superbase could not be formed under those conditions.



Scheme 3.5: Reaction in a planetary ball mill; 3 cycles@400 rpm (15 min milling, 5 min pause).

In constrast to sulfoximines, the access to their diaza analogues, namely sulfondiimines, is challenging,[8] and only few synthetic applications are reported.[172] As *N*-alkylated sulfondiimines are rare,[173] reactions of *N*H-sulfondiimines with alkyl halides in KOH/DMSO were attempted by the group of *Bolm* (*Bohmann*). A reaction of *N*H-sulfondiimine **132** with butyl bromide in KOH/DMSO yielded the corresponding *N*-butylated sulfondiimine **133** in 84% (Scheme 3.6). To our delight, various *N*-alkylated sulfondiimines were obtained in high yields employing this protocol.[170]



Scheme 3.6: *N*-Alkylation of sulfondiimine **132**.

3.3 Summary

A straight-forward and cost-effective *N*-alkylation method for sulfoximines mediated by KOH in DMSO has been developed. Various alkyl bromides, as well as chlorides and iodides can be employed to prepare the corresponding *N*-alkylated sulfoximines in good to excellent yields. The method has been applied to synthesize the biologically active suloxifen. In order to reduce the amount of DMSO, an *N*-alkylation reaction was performed in a ball mill, and the desired product was obtained in good yield under solvent-reduced conditions. Of special interest, it was proven that this *N*-alkylation protocol is applicable to the rather underdeveloped substrate class of sulfondiimines.

4 Syntheses and Biological Activities of Sulfoximine-based ATR Inhibitors

4.1 Background and Aim of the Project

Ataxia telangiectasia and Rad3-related (ATR) kinase and ataxia telangiectasia mutated (ATM) kinase regulate the response of cells to DNA damage (DNA damage response DDR). They activate CHK1 and CHK2 (cell cycle checkpoint kinases), which leads to repair of DNA single-strand and double-strand breaks. When DDR is inhibited, cells are more sensitive to DNA damage and die more quickly.[174]

ATR has been considered an important factor of the DDR in response to disrupted DNA replication. As growing tumor cells suffer from replicative stress, ATR is more important for cancer cells to survive than for normal healthy cells. The inhibition of ATR can deactivate the DDR signaling pathways, thereby sensitizing tumor cells to DNA damaging agents. For that reason, ATR inhibitors are promising in the treatment of cancer, either applied alone or combined with other anti-cancer agents provoking DNA damage.[175]

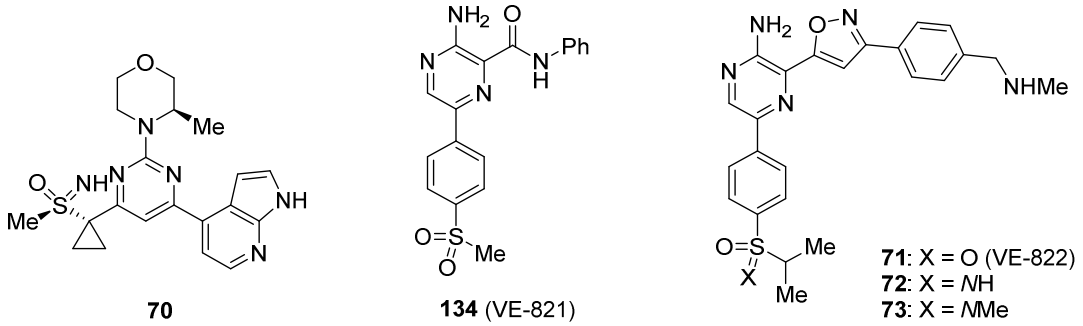


Figure 4.1: ATR inhibitors: **70** (in clinical studies, AstraZeneca), **134** (Vertex), **71** (in clinical studies, Vertex), **72** and **73** (AstraZeneca, mentioned in the literature).

To date, specific ATR inhibitors are still underdeveloped as concerns about the functional inhibition of ATR hindered investigations into this field.[176] In the last years, *N*H-sulfoximine **70** (AstraZeneca),[50c,177] sulfone **134** (VE-821, Vertex),[178] and sulfone **71** (VE-822, Vertex)[179] have been reported to be potent ATR-inhibitors (Figure 4.1). Among them, compounds **70** and **71** are in clinical studies (see Chapter 1.1.4). *N*H-sulfoximine **72** and *N*-methylsulfoximine **73** are analogs of **71**.[115]

As specific ATR inhibitors are rare, following our interest in sulfilimine and sulfoximine analogs of bioactive sulfones, we aimed the derivatization of VE-821 (**134**). Sulfilimine **135** and sulfoximines **136** were synthesized (Figure 4.2), and their inhibitory activity on ATR was evaluated.[180a]

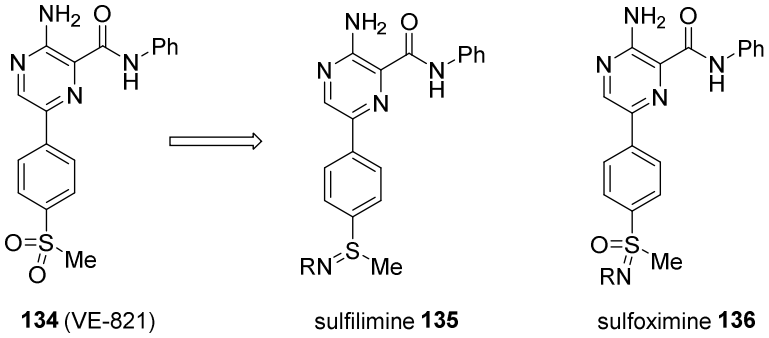


Figure 4.2: VE-821 (**134**) and its sulfilimine and sulfoximine analogs.

4.2 Results and Discussion

4.2.1 Syntheses of the target compounds

Regarding the synthesis of sulfilimines **135** and sulfoximines **136**, three important bond formations became evident: the synthesis of carboxamide **A**, the Suzuki coupling to form carbon–carbon bond **B**, and the functionalized sulfur **C** modified by imination and oxidation reactions (Figure 8.3). Considering patent literature, commercial availability of starting materials and accessibility of unknown intermediates, three synthetic routes were regarded constructive:

Route I: use of easily prepared sulfoximine **C** bearing an *S*-(4-bromophenyl) substituent for coupling with a pyrazine-based boronic acid to form **B** and subsequent introduction of carboxamide **A**.

Route II: formation of C–C bond **B** by coupling of an easily prepared pyrazine-based bromide with commercially available methyl(thiophenyl)boronic acid, followed by sulfur functionalization **C** and subsequent formation of carboxamide **A**.

Route III: formation of a carboxamide-**A**-containing pyrazine-based bromide and coupling with commercially available methyl(thiophenyl)boronic acid to form C–C bond **B** and subsequent sulfur functionalization **C**.

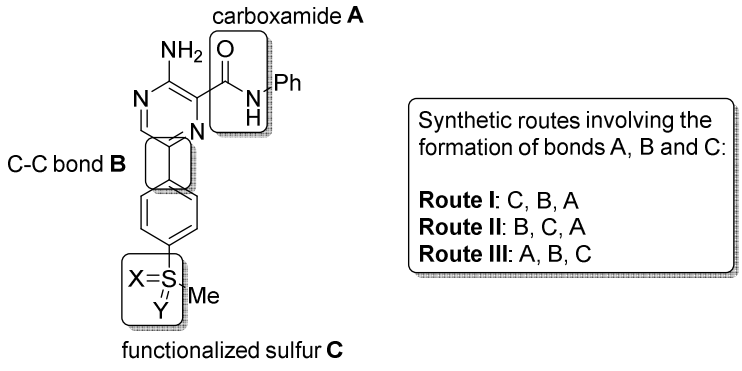
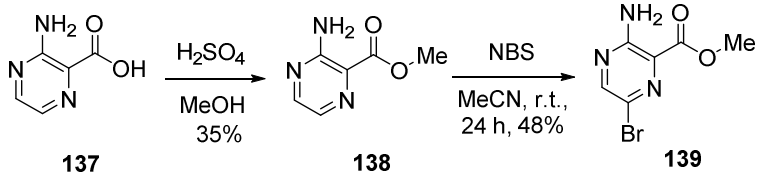


Figure 4.3: Three important bond formations: carboxamide **A**, carbon–carbon bond **B**, and functionalized sulfur **C**.

Following route I

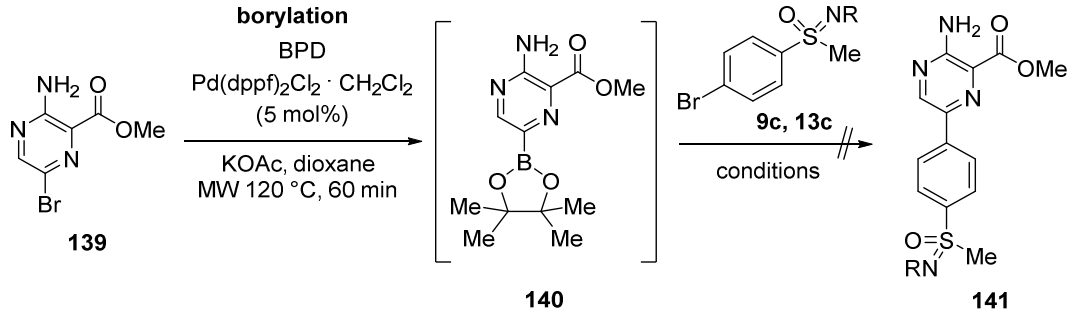
In order to synthesize methyl carboxylate **139**, 3-aminopyrazine-2-carboxylic acid (**137**) was esterified with methanol to form **138** in 35% yield.[180b] Subsequent bromination with NBS provided building block **139** in 48% yield (Scheme 4.1).[179]



Scheme 4.1: Synthesis of building block **139**.

The starting material in hand, we attempted to convert bromide **139** into pinacol boronic ester **140** (Table 4.1, borylation). Initially, reactions were performed by using bis(pinacolato)diboron (BPD), $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ as the catalyst, potassium acetate as base, and degassed dioxane at 120 °C under microwave irradiation.[181] However, despite a new product was observed by NMR spectroscopy, the isolation of **140** failed, presumably for instability reasons (product **138** was obtained instead). Hence, the unpurified boronic ester **140** was directly subjected to Suzuki couplings with sulfoximines **9c** and **13c** (Table 4.1).

Table 4.1: Route I, attempts to synthesize sulfoximine **141** *via* boronic acid **140**.



Entry	Conditions	Sulfoximine 9c, 13c	Yield of 141 [%][a]
1	$Pd(PPh_3)_4$ (3 mol%), K_2CO_3, MeCN-H_2O 3:1, reflux, 16 h	**9c** (R = CN)	–
2	$Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ (13 mol%), DME, 2 M Na_2CO_3, MW, 120 °C, 60 min	**9c** (R = CN)	–
3	$Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ (13 mol%), DME, 2 M Na_2CO_3, 110 °C, 16 h	**13c** (R = Me)	–

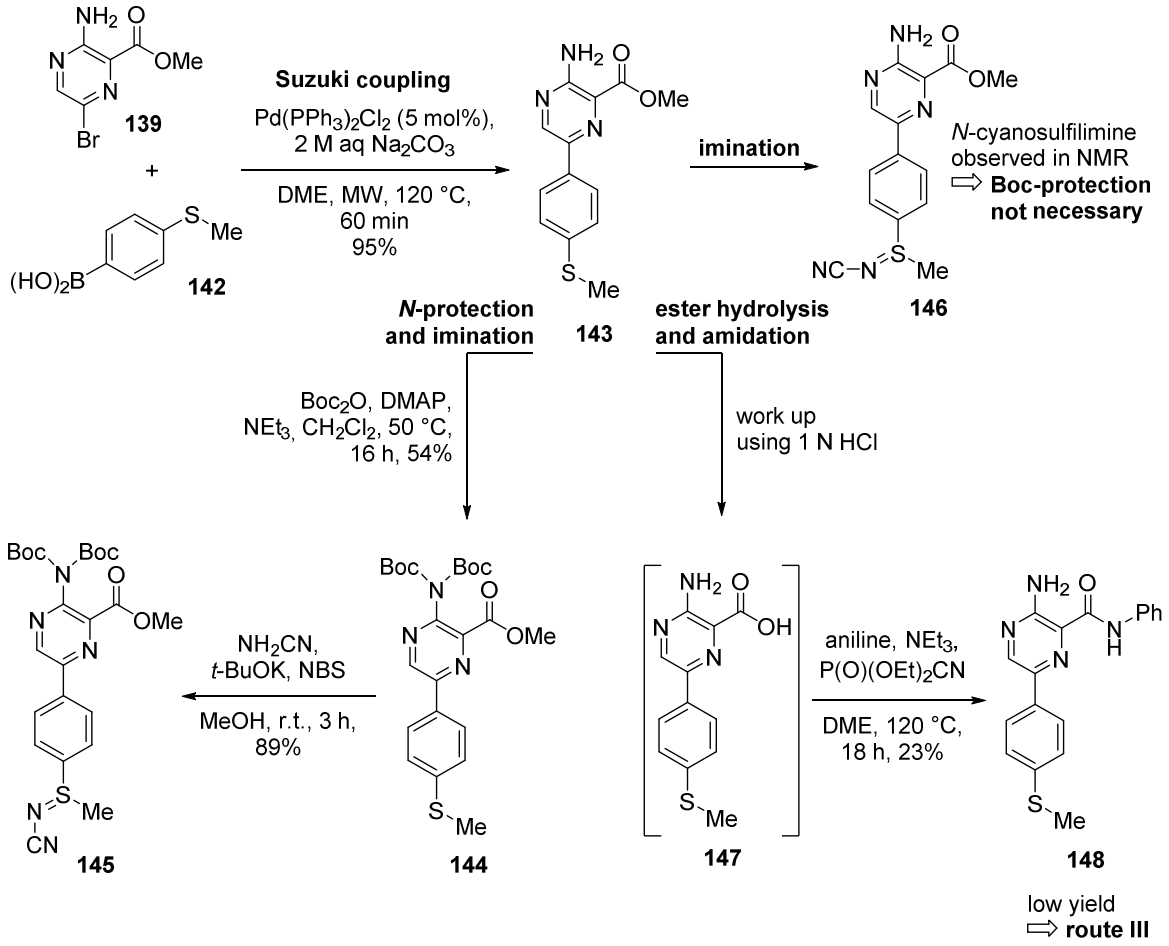
[a] Yield after column chromatography.

First, a protocol by *Cho* and *Bolm*[106] was used that had proved beneficial in Suzuki couplings of 4-bromophenyl sulfoximines with various aromatic boronic acids. By employing $Pd(PPh_3)_4$ as catalyst and potassium carbonate as base in an acetonitrile-water mixture under reflux, a coupling of **140** with *N*-cyanosulfoximine **9c** was

attempted. However, no product could be observed (Table 4.1, entry 1). Next, conditions that had been successful in the coupling of *N*-containing heterocycles were tested.[181] Unfortunately, using $Pd(dppf)_2Cl_2{\cdot}CH_2Cl_2$, DME and 2 M Na_2CO_3 solution under microwave or oil bath heating, did not lead to product formation, neither with **9c** nor *N*-methyl sulfoximine **13c** (Table 4.1, entries 2 and 3). Presumably, these attempts failed due to an early decomposition of boronic ester **140** under those conditions, and it was therefore decided to change the synthetic strategy and follow route II.

Following Route II

To our delight, the envisaged coupling of bromide **139** with commercially available boronic acid **142** using $Pd(PPh_3)_2Cl_2$ as catalyst and sodium carbonate as base[179] was successful, providing the desired sulfide **143** in 95% yield (Scheme 4.2, Suzuki coupling). To protect the amino group during subsequent sulfur functionalizations, sulfide **143** was treated with Boc_2O, DMAP and NEt_3 in CH_2Cl_2 (Scheme 4.2, *N*-protection and imination), affording Boc-protected amine **144** in 54% yield.[182]



Scheme 4.2: Attempts following Route II.

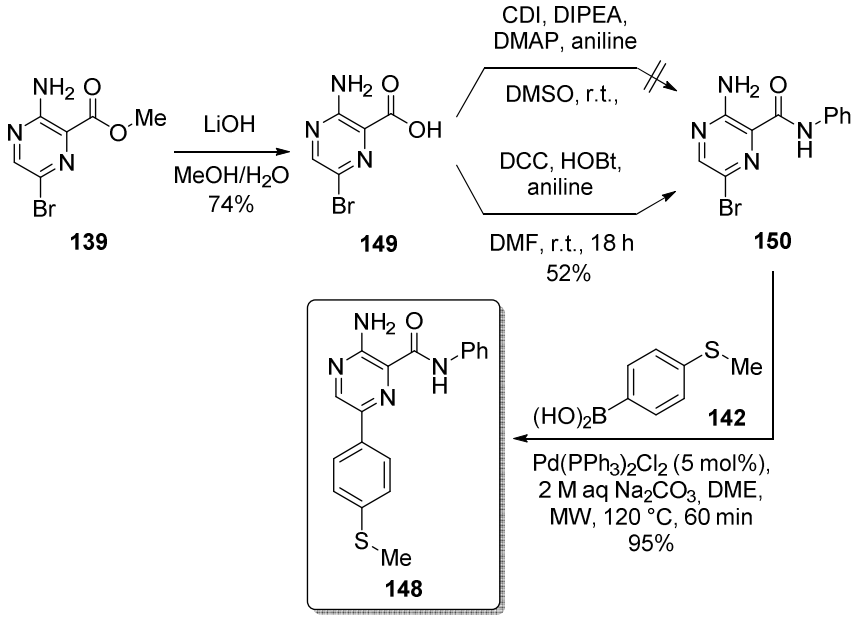
Subsequent imination with cyanamide, potassium *tert*-butoxide, and NBS was successful, giving the desired sulfilimine **145** in 89% yield.[49] Unexpectedly, in an additional attempt to iminate unprotected sulfide **143** under the same conditions, we

observed the corresponding *N*-cyanosulfilimine **146** (Scheme 4.2, imination), proving that a protection of the amino group was not necessary during imination.

Provided that the Suzuki coupling of bromide **139** and subsequent sulfur functionalization proceeded well, the final carboxamide formation had to be investigated. Employing **143** as the model compound, acidic work up with 1 N HCl after the coupling reaction led to ester hydrolysis generating carboxylic acid **147** (Scheme 4.2, hydrolysis and amidation). Subsequent amidation using aniline, diethoxyphosphoryl formonitrile, and triethylamine afforded carboxamide **148**; however, in low yield of 23%.[179] Realizing that the carboxamide formation in the final stage proved unsatisfying, we focused on route III.

Following route III

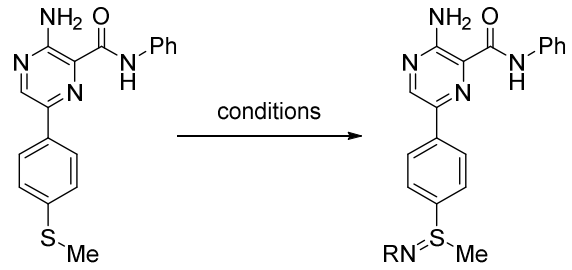
Initially, hydrolysis of the ester moiety in compound **139** was performed by using lithium hydroxide, to form carboxylic acid **149** in 74% yield (Scheme 4.3).[179] In the literature, amidations of **149** with aniline using CDI, DIPEA and DMAP had been reported.[179] Surprisingly, these conditions did not lead to success. Carboxamide **150** was finally prepared by DCC-coupling with aniline in satisfying yield of 52% (Scheme 4.3). Additional attempts in order to obtain carboxamide **150** directly by aminolysis of carboxylic acid **139** failed. The important Suzuki coupling of **150** with boronic acid **142** gave a better access to sulfide **148** (compare to Scheme 4.2), providing the key compound in excellent yield (95%).[179]



Scheme 4.3: Route III; improved synthesis of key compound **148**.

Considering route III an easier access to the carboxamide-based target products **135** and **136** regarding yields and step economy, imination reactions of **148** were performed without previous protection of the amino group (Table 4.2).

Table 4.2: Route III; imination of sulfide **148** to sulfilimines **135**.



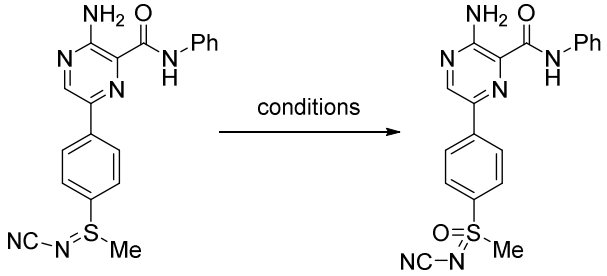
148 **135**

Entry	Conditions	R	Product	Yield [%][a]
1	Ru(TPP)CO (1 mol%), 3-methyl-1,4,2-dioxazol-5-one, toluene, *hν*, r.t., 1 h	COMe	–	–
2	NH_2CN, *t*-BuOK, NBS, MeOH, r.t., 3 h	CN	**135a**	64
3	NH_2CN, PIDA, MeCN, r.t., 2 h	CN	**135a**	93

[a] Yield after column chromatography.

Light-promoted ruthenium-catalyzed imination conditions,[65a] developed by the group of *Bolm*, were applied to sulfide **148**. Unfortunately, despite the very mild conditions, no imination occurred on the sulfur atom (Table 4.2, entry 1). Contrarily, imination using cyanamide, potassium-*tert*-butoxide and NBS[49] offered the first target product **135a** in 64% yield (Table 4.2, entry 2). Employing PIDA in acetonitrile,[59] the imination could be improved, affording *N*-cyanosulfilimine **135a** in high yield (93%, Table 4.2, entry 3).

Table 4.3: Route III; oxidation of sulfilimine **135a** to sulfoximine **136a**.



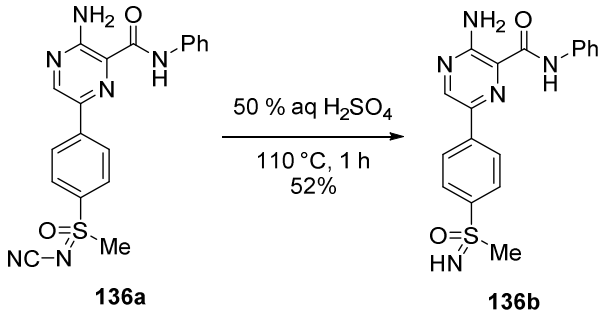
135a **136a**

Entry	Conditions	Yield of 136a [%][a]
1	*m*CPBA, K_2CO_3, MeOH, r.t., 16 h	41
2	$KMnO_4$, acetone, 50 °C, 2 h	77
3	Bu_4NBr, aq 13% NaOCl, AcOEt, r.t., 4 h	–
4	$RuCl_3 \cdot 4\ H_2O$ (cat.), $NaIO_4$, MeCN–H_2O 1:2, r.t., 1 h	3

[a] Yield after column chromatography.

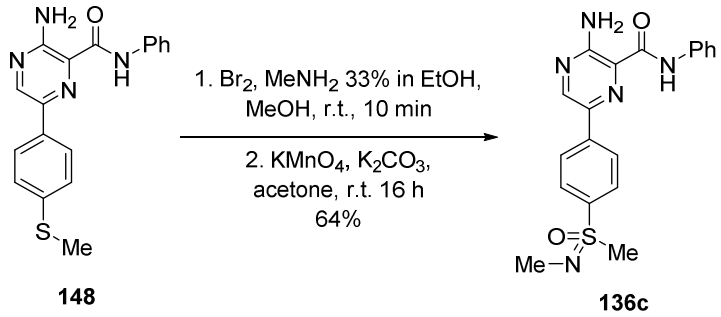
Next, various oxidation methods were tested in order to synthesize *N*-cyanosulfoximine **136a** starting from **135a** (Table 4.3). To this end, sulfilimine **135a** was treated with *m*CPBA and potassium carbonate as base,[49] furnishing target product **136a** in 41% yield (Table 4.3, entry 1), though after a long reaction time of 16 h. Faster oxidation in only 2 h occurred using potassium permanganate in acetone at 50 °C[55], affording **136a** in good yield (77%, Table 4.3, entry 2). Additional attempts to improve the oxidation by applying sodium hypochlorite as mild oxidant (Table 4.3, entry 3)[183] or *in situ* generated ruthenium tetroxide (Table 4.3, entry 4)[56] were not successful.

At the final stage, *N*-cyanosulfoximine **136a** was deprotected by using 50% aqueous sulfuric acid at 110 °C,[60] providing the synthetically and biologically interesting *N*H-sulfoximine **136b** in 52% (Scheme 4.4).



Scheme 4.4: Deprotection of **136a** to afford *N*H-sulfoximine **136b**.

N-Methylsulfoximines are of interest as they can enhance the aqueous solubility compared to the corresponding sulfones.[115] Therefore interested in its biological profile, we prepared *N*-methylsulfoximine **136c** from sulfide **148** following a protocol recently developed by the group of *Bolm*, involving the formation of a methyliminium salt and subsequent oxidation (see Scheme 1.10).[62b] Employing first methylamine and bromine in methanol, subsequent treatment with a mixture of potassium permanganate and potassium carbonate afforded **136c** in 64% yield (Scheme 4.5).



Scheme 4.5: Synthesis of *N*-methylsulfoximine **136c**.

4.2.2 Biological tests

ATR inhibition

ATR and ATM show strong similarities with respect to sequence homology and function, and their signaling pathways are interconnected. However, they feature functional

differences, relevant in the development of new anti-cancer treatments.[176,184] Activation of ATR and ATM involves selective phosphorylation of CHK1 and CHK2, respectively, inducing various specified downstream responses.[185] Wheras ATR is mostly activated by single-stranded DNA, ATM activation is triggered by double strand DNA breaks. ATM is not essential for cells to survive. Contrarily, knockout of ATR is lethal as every replicating cell is dependent on ATR. In cancer cells that suffer from oncogene-induced replicative stress, ATR is especially important. Consequently, in contrast to ATM, the inhibition of ATR is more toxic to cancer cells than to normal cells.[186]

ATR inhibition can support the efficacy of chemotherapeutic drugs such as cisplatin by blocking the DDR signaling pathway to CHK1. VE-821 (**134**) revealed potential to sensitize tumor cells to DNA damaging agents.[187] Hence, it was of interest to study the ATR-inhibition potential of derivatives **135a** and **136a–c**. The corresponding biological tests and evaluations were performed by *Hartkamp* and *Lüscher* (Institute for Biochemistry and Molecular Biology, RWTH Aachen University).

U2OS (human osteosarcoma) cells were treated with etoposide, a blocking agent for topoisomerase II inducing double strand (and single strand) DNA breaks. After the addition of DMSO (reference), VE-821, VX-970, **135a** or **136a–c**, respectively, 10 µM 1 h prior to stimulation, phosphorylation of CHK1 and CHK2 was examined by using phospho-specific antibodies. Applying etoposide for 20 min, phosphorylation of CHK1 was inhibited by VE-821, VX-970, and all novel derivatives **135a** and **136a–c**, proving inhibitiory activity of ATR. Contrarily, phosphorylation of CHK2 was observed in all cases, demonstrating inhibitory selectivity of all compounds for ATR in cells, not affecting ATM. These results reveal high inhibitory potency and selectivity for ATR by sulfilimine and sulfoximine analogs **135a** and **136a–c**, comparable to VE-821 and VX-970. Hence, they can be regarded as potential drug candidates for the treatment of cancer by inhibition of the ATR signaling pathway.

NCI 60 Cell One-Dose Screen

N-Cyanosulfilimine **135a**, *N*-cyanosulfoximine **136a**, and *N*-methylsulfoximine **136c** were selected for the NCI 60 Cell One-Dose Screen within the Developmental Therapeutics Program of the NCI/NIH. The anti-cancer test was performed at a single high dose (10^{-5} M) (Table 4.4).

Table 4.4: NCI 60 Cell One-Dose Screen.

Entry	Compound	Growth percent at 10 µM		
		Mean	Delta	Range
1	**135a**	83.45	34.30	71.17
2	**136a**	83.05	39.02	119.0
3	**136c**	101.28	32.82	51.77

Mean: Average Growth Percent
Delta: Mean – minimum value of Growth Percent
Range: Maximum – minimum value of Growth Percent

N-Cyanosulfilimine **135a** and *N*-cyanosulfoximine **136a** showed low growth inhibition, namely mean values of 83% (Table 4.4, entries 1 and 2). *N*-Methylsulfoximine **136c** did not lead to any growth inhibition.

4.3 Summary

Four analogs of ATR-inhibitor VE-821 have been synthesized. The best synthetic route in order to synthesize the backbone involved formation of a carboxamide-containing pyrazine-based bromide, followed by Suzuki coupling with commercially available methyl(thiophenyl)boronic acid. Subsequent sulfur functionalization reactions led to an *N*-cyanosulfilimine and *N*-cyano-, *N*H-, and *N*-methylsulfoximines in good to high yields. The compounds were not effective in NCI 60 Cell One-Dose Screens; however, biological tests revealed that all analogs block the signaling pathway between CHK1 and ATR in cells. They show high inhibitory potency and selectivity for ATR and do not affect ATM, making them of interest as potential drug candidates.

5 Synthesis and Biological Activity of a Sulfoximine-Analog of BTB06584, a Mitochondrial F_1Fo-ATPase Inhibitor

5.1 Background and Aim of the Project

When the blood supply to tissues is restricted (ischaemia), caused by e.g. tromboses, the mitochondrial respiration is disturbed. In order to maintain the mitochondrial membrane potential, F_1Fo-ATPsynthase reverses and acts as an ATPase, thereby depleting ATP. The resulting accelerated cell death leads to injuries in the affected tissues.[188]

In 2014, *Campanella* and coworkers reported BTB06584, a sulfone-based small molecule inhibitor, containing an aryl ring with an electron-withdrawing nitro-substituent and a 4-chlorobenzoyl ester group (Figure 5.1). It selectively inhibits mitochondrial F_1Fo-ATPase activity without interfering with ATP synthesis. Hence, it appears to be a promising candidate against ischaemia-induced injuries.[189]

Attracted by the biological activity of BTB06584 and the synthetic challenge arising from the functionalized backbone, we were interested in the syntheses of sulfoximine-analogs **151** and later evaluation of their biological activity (Figure 5.1).

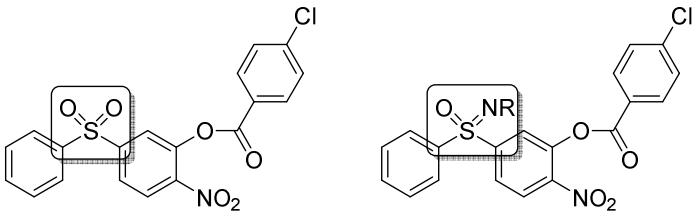


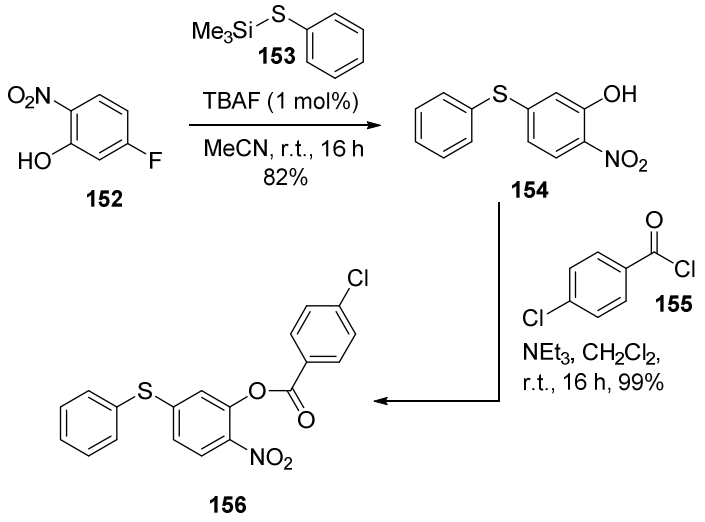
Figure 5.1: Inhibitor BTB06584 and sulfoximine-analog.

5.2 Results and Discussion

5.2.1 Synthesis of the target compound

Initially, in order to prepare the aryl-containing backbone, a TBAF-catalyzed S_NAr-reaction of 2-fluoro-5-nitrophenol **152** with phenylthiotrimethylsilane **153** was performed, providing thioether **154** in 82% yield (Scheme 5.1).[190] Subsequent esterification[191] with 4-chlorobenzoyl chloride **155** gave the desired sulfide **156** in quantitative amount.

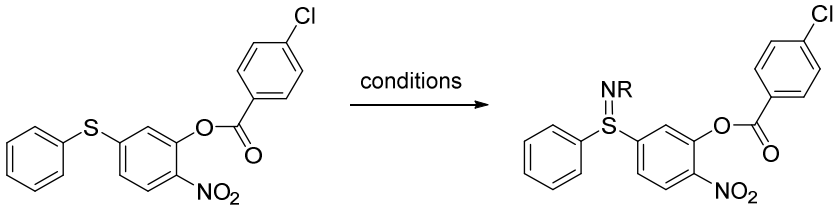
Focusing our attention on the sulfur imination (Table 5.1), metal-free iminations with cyanamide were performed, but either decomposition occurred (Table 5.1, entry 1)[49] or the desired product was only observed in trace amounts (Table 5.1, entry 2).[59]



Scheme 5.1: Synthesis of sulfide **156**.

Unfortunately, using our ruthenium-catalyzed light-promoted imination protocol[65a] led to decomposition of the starting material (Table 5.1, entry 3). Contrarily, imination with trifluoroacetamide[48] in presence of a rhodium-catalyst proceeded well, affording the desired sulfilimine **157a** in 82% yield (Table 5.1, entry 4).

Table 5.1: Imination of sulfide **156**.

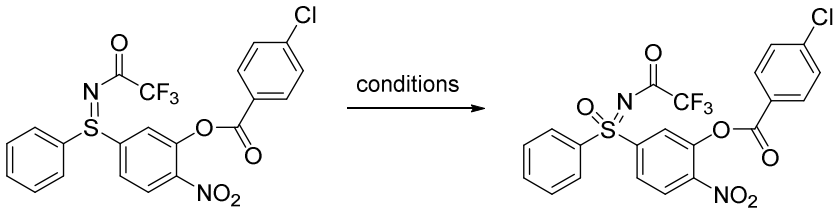


Entry	Conditions	R	Yield of 157 [%][a]
1	NH_2CN, *t*-BuOK, NBS, MeOH, r.t., 16 h	CN	–[b]
2	NH_2CN, PIDA, MeCN, r.t., 16 h	CN	traces
3	Ru(TPP)CO (1 mol%), 3-methyl-1,4,2-dioxazol-5-one, toluene, *hν* , r.t., 4 h	COMe	–[c]
4	$Rh_2(OAc)_4$ (2.5 mol%), trifluoroacetamide, MgO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 20 h	$COCF_3$	82 (**157a**)

[a]Yield after column chromatography.
[b]Decomposition.
[c]No conversion.

In order to synthesize sulfoximine **151a**, oxidation reactions of **157a** were attempted by using *m*CPBA with potassium carbonate in methanol (Table 5.2, entry 1)[49] or potassium permanganate in acetone (Table 5.2, entry 2).[55] However, no product could be observed in both cases.

Table 5.2: Attempts to oxidize sulfilimine **157a**.



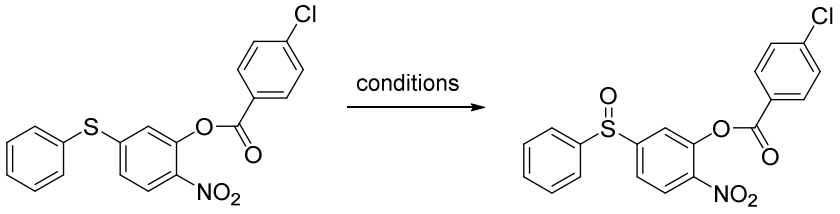
157a **151a**

Entry	Conditions	Yield of 151a [%]
1	*m*CPBA, K_2CO_3, MeOH, r.t., 18 h	–[a]
2	$KMnO_4$, acetone, 50 °C	–[a]

[a] No product formation was observed on TLC.

Changing our strategy, we decided to perform sulfur oxidation and subsequent imination. Using *m*CPBA in CH_2Cl_2,[28] sulfide **156** underwent the process providing sulfoxide **158** in 33% yield (Table 5.3, entry 1), though accompanied by significant amounts of remaining sulfone (BTB06584). Oxidation employing *in situ* generated peracetic acid[27] proved more effective, affording product **158** in 75% yield (Table 5.3, entry 2).

Table 5.3: Oxidation of sulfide **156**.



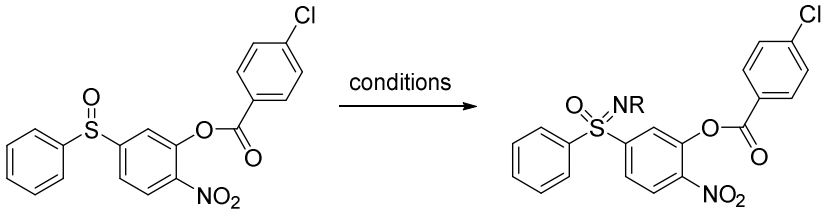
156 **158**

Entry	Conditions	Yield of 158 [%][a]
1	*m*CPBA, CH_2Cl_2, 0 °C, 18 h	33[b]
2	aq. H_2O_2 (30%), CH_3COOH, CH_2Cl_2, 0 °C to r.t., 18 h	75

[a] Yield after column chromatography.
[b] Significant amounts of sulfone observed on TLC.

Next, we investigated the imination of sulfoxide **158**. As compared to the successful imination of sulfide **156** to sulfilimine **157a** (Table 5.1, entry 4), rhodium-catalyzed imination of sulfoxide **158** with trifluoroacetamide[48] gave sulfoximine **151a** in 69% yield (Table 5.4, entry 1). Iron-catalyzed imination using PhI=NNS as nitrogen source[54] proceeded smoothly, leading to *N*-nosylsulfoximine **151b** in 74% yield (Table 5.4, entry 2). Contrarily, light-promoted imination[65a] in order to obtain *N*-acetylsulfoximine **151c** did not involve product formation.

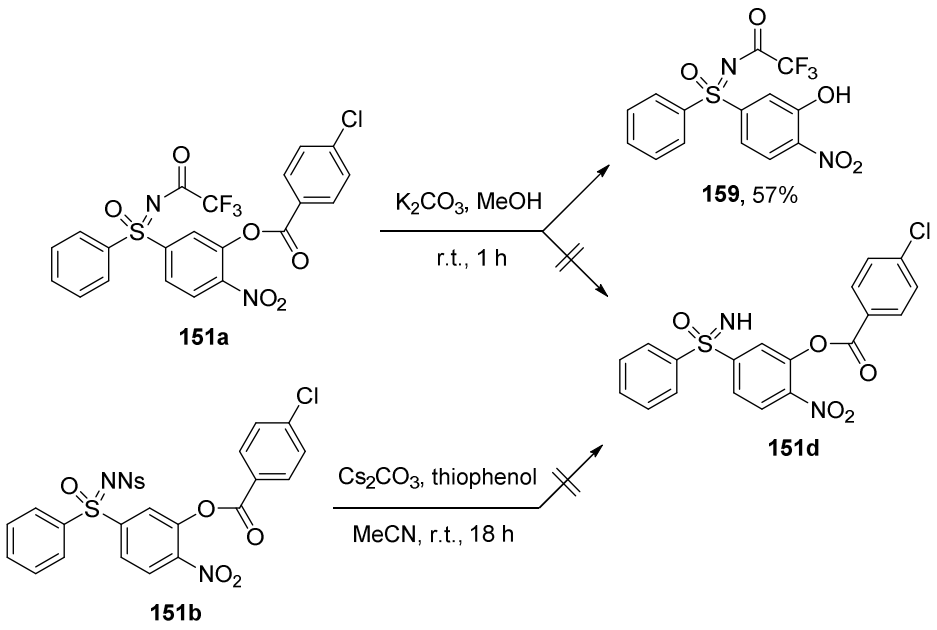
Table 5.4: Imination of sulfoxide **158**.



Entry	Conditions	R	Product	Yield [%][a]
1	$Rh_2(OAc)_4$ (2.5 mol%), trifluoroacetamide, MgO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 20 h	$COCF_3$	**151a**	69
2	$Fe(OTf)_2$ (15 mol%), PhI=NNS, 4 Å molecular sieves, MeCN, 50 °C, 16 h	nosyl	**151b**	74
3	Ru(TPP)CO (1 mol%), 3-methyl-1,4,2-dioxazol-5-one, toluene, *hν*, r.t., 5 h	COMe	**151c**	–

[a]Yield after column chromatography.

Encouraged by these results, we aimed to perform deprotections of sulfoximines **151a** and **151b** in order to obtain *N*H-sulfoximine **151d**, our most interesting target (Scheme 5.2). Unexpectedly, the reaction of **151a** with potassium carbonate in methanol[49] did not lead to deprotection of the sulfoximine nitrogen. Instead, the ester bond was cleaved, and sulfoximine **159**, having an intact *N*-trifluoroacetyl group, was obtained in 57% yield (Scheme 5.2). An attempt to deprotect **151b** employing cesium carbonate and thiophenol involved decomposition of the starting material (Scheme 5.2).[52]

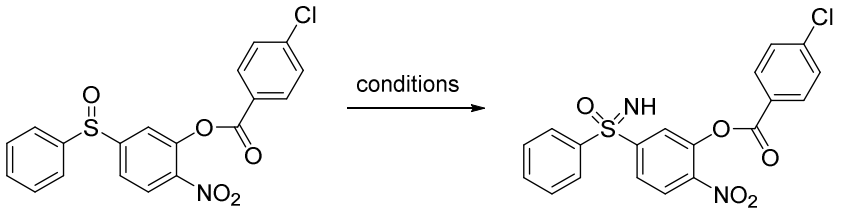


Scheme 5.2: Attempts to deprotect sulfoximines **151a** and **151b**.

Considering the previously failed imination, oxidation and deprotection attempts, we concluded that the backbone of our target molecule, especially the ester bond, was very sensitive towards bases such as potassium carbonate, cesium carbonate, and potassium *tert*-butoxide. Consequently, in all reaction steps the use of bases was avoided.

Along those lines, we decided to apply imination protocols that lead directly to *N*H-sulfoximine **151d** (Table 5.5). First, sulfoxide **158** was treated with hydrazoic acid, *in situ* generated from sodium azide and sulfuric acid.[37a] However, under those conditions, no conversion was observed (Table 5.5, entry 1). In a recent publication, an imination protocol using *O*-(2,4-dinitrophenyl)hydroxylamine as nitrogen source and a rhodium catalyst had been reported.[45] To our delight, these conditions led to success and provided the desired *N*H-sulfoximine **151d** in 75% yield (Table 5.5, entry 2).

Table 5.5: Imination of sulfoxide **158** to afford *N*H-sulfoximine **151d**.



158 **151d**

Entry	Conditions	Yield of 151d [%][a]
1	NaN_3, H_2SO_4, CH_2Cl_2, 0 °C to r.t., 17 h	–[b]
2	$Rh_2(esp)_2$, *O*-(2,4-dinitrophenyl)hydroxylamine, 2,2,2-trifluoroethanol, 0 °C, 17 h	75

[a] Yield after column chromatography.
[b] No conversion.

5.2.2 Biological test

NCI 60 Cell One-Dose Screen

*N*H-sulfoximine **151d** was selected for the NCI 60 Cell One-Dose Screen within the Developmental Therapeutics Program of the NCI/NIH. The anti-cancer test was performed at a single high dose (10^{-5} M). Compound **151d** showed only low growth inhibition (average growth percent of 76.9) (Table 5.6).

Table 5.6: NCI 60 Cell One-Dose Screen

Compound	Growth percent at 10 µM		
	Mean	Delta	Range
151d	76.90	34.99	70.71

Mean: Average Growth Percent
Delta: Mean – minimum value of Growth Percent
Range: Maximum – minimum value of Growth Percent

5.3 Summary

Three sulfoximine analogs of BTB06584 have been synthesized, containing *N*-trifluoroacetyl, *N*-nosyl, and *N*H-sulfoximidoyl moieties. The preparation of the latter proved challenging as the ester bond was sensitive to basic reaction conditions; however, a recently reported imination method allowed obtaining the *N*H-sulfoximine in good yield. The *N*H-sulfoximine showed only low growth inhibition in the NCI 60 Cell One-Dose Screen. Its inhibitory activity on mitochondrial F_1Fo-ATPase is currently under investigation.

6 Syntheses and Biological Activities of 4-(*N*-Indolyl)phenyl Methyl Sulfoximines

6.1 Background and Aim of the Project

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are frequently applied medications against inflammation, fever, and pain (Figure 6.1).[192] NSAIDs inhibit cyclooxygenase (COX), an enzyme responsible for the synthesis of prostaglandins (PGs), lipid compounds concerned with the regulation of inflammation and pain. Two isozymes of COX exist, namely COX-1 and COX-2. While COX-1 is involved in the formation of gastroprotective PGs, COX-2 is responsible for the synthesis of inflammatory PGs such as PGH_2. Thus, non-selective COX-inhibitors show side-effects such as gastrointestinal toxicity, and consequently the development of selective COX-2 inhibitors (COXIBs) is of special interest.

Studies of COXIBs introduced to the market revealed their potential as anti-tumor agents, making COX-2 a promising target for the prevention and treatment of cancer.[193] However, due to severe cardiovascular side effects, long-term use of COXIBs such as rofecoxib and celecoxib (Figure 6.1) is limited, and led to withdrawals, for example rofecoxib (known as vioxx®).[194] A sulfoximine-based analog (see Figure 1.9) reported by the group of *Bolm* showed reduced hERG activity, an indication of cardiovascular safety.[118]

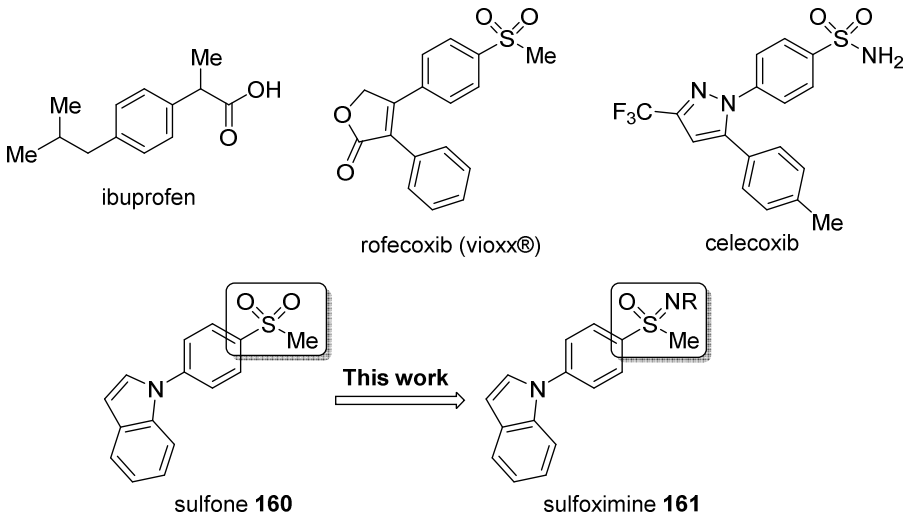


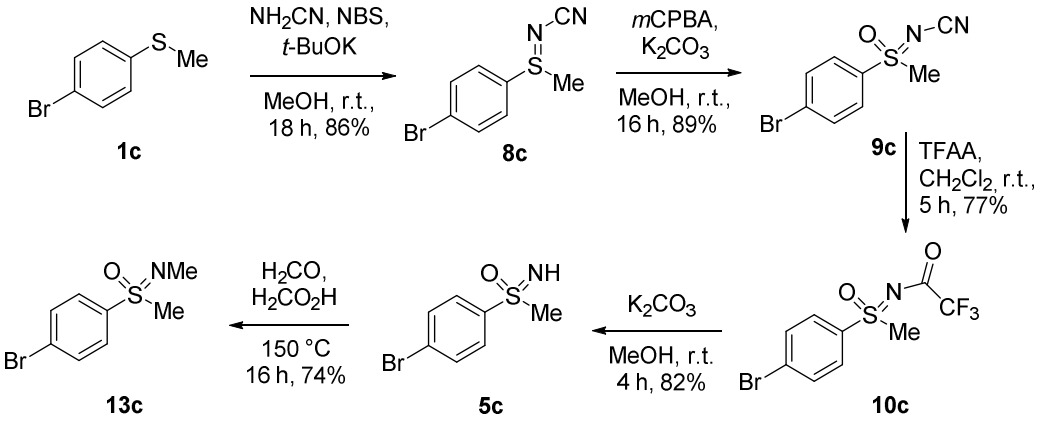
Figure 6.1: COX-inhibitors, and envisaged sulfone-to-sulfoximine exchange on sulfone **160**.

Recently, our interest was caught by a study of *Pouplana*, *Pujol*, and coworkers, covering computational design, syntheses and biological tests of 4-(aryloyl)phenyl methyl sulfones.[193b] In particular, *N*-arylindole **160** (Figure 6.1) showed the highest COX-2 inhibitory activity and COX-2 selectivity among the tested compounds. Attracted by the biological potential of **160**, as part of our continuing research on sulfone-to-sulfoximine exchanges, we envisaged the synthesis of unprecedented 4-*N*-indolylphenyl methyl sulfoximines **161** and their biological evaluation.

6.2 Results and Discussion

6.2.1 Syntheses of the target compounds

Considering the reported synthesis of sulfone **160**,[195] we aimed to prepare sulfoximines **161** by Buchwald–Hartwig couplings of indole with sulfoximine-based aryl bromides. To this end, differently *N*-substituted 4-bromophenyl methyl sulfoximines were synthesized as the starting materials (Scheme 6.1). Following a frequently applied protocol by the group of *Bolm*,[49] imination of sulfide **1c** with cyanamide afforded *N*-cyanosulfilimine **8c** in 86% yield. Subsequent oxidation with *m*CPBA provided sulfoximine **9c** in 89% yield. The *N*-cyano protecting group was changed to a trifluoroacetyl group by treatment with trifluoroacetic anhydride, giving sulfoximine **10c** in 77% yield. Its mild deprotection furnished *N*H-sulfoximine **5c** in 82% yield. Final methylation under Eschweiler-Clark conditions proceeded smoothly and allowed to obtain *N*-methylsulfoximine **13c** in 74% yield.[84a]

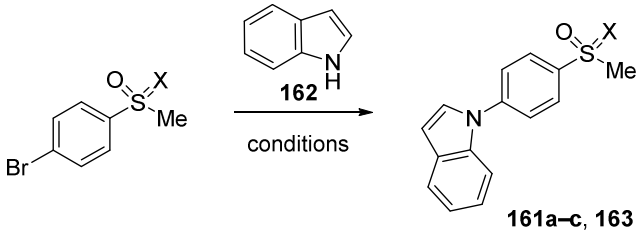


Scheme 6.1: Syntheses of 4-bromophenyl methyl sulfoximines.

With a range of starting materials now present, we attempted couplings of indole (**162**) with sulfoximines **9c**, **10c**, **5c**, **13c**, and sulfoxide **2c** (Table 6.1). Initially, coupling conditions by *Pujol* and coworkers, generally proceeding with very low catalyst loadings, were applied (Table 6.1, entry 1).[195] However, employing $Pd[P(o\text{-tolyl})_3]_2Cl_2$ as catalyst, BINAP as ligand and cesium carbonate as base, no formation of coupling products **161a–d** and **163** could be observed.

In a previous study by the group of *Bolm*, focused on Buchwald–Hartwig aminations of 4-bromophenyl methyl sulfoximines with primary and non-aromatic amines, $Pd(OAc)_2$ and $Pd_2(dba)_3$ proved beneficial (see Scheme 1.23).[106] Under those conditions, utilizing $Pd(OAc)_2$ provided the corresponding coupling products **161a** and **161c** in low to moderate yields (57% and 32%, Table 6.1, entry 2). However, a coupling reaction in order to obtain *N*H-sulfoximine **161c** did not proceed, thus revealing that a protecting group (such as cyano or methyl) on the sulfoximine nitrogen atom was crucial for product formation. An attempt to synthesize sulfoxide **163** also failed under those conditions.

Table 6.1: Couplings of sulfoximines **161a–d** and sulfoxide **163** with indole.



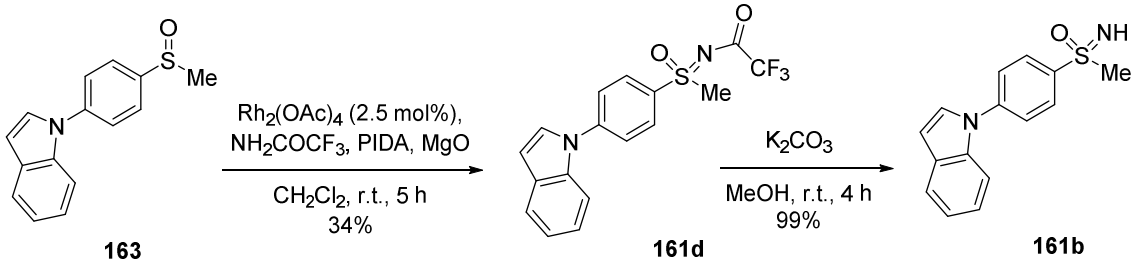
161a–c, **163**

Entry	Conditions	Yield (substituent X) [%][a]				
		161a (*N*CN)	**161b** (*N*H)	**161c** (*N*Me)	**161d** ($COCF_3$)	**163** (none)
1	$Pd[P(o\text{-tolyl})_3]_2Cl_2$ (0.12 mol%), BINAP (0.75 mol%), Cs_2CO_3, toluene, 120 °C, 2 h	–[b]	–[b]	–[b]	n.d.	–[b]
2	$Pd(OAc)_2$ (2 mol%), BINAP (4 mol%), Cs_2CO_3, toluene, 110 °C, 18 h	57	–[b]	32	n.d.	–[b]
3	$Pd_2(dba)_3$ (2 mol%), BINAP (4 mol%), Cs_2CO_3, toluene, 110 °C, 18 h	84	–[b]	55	–[c]	75

[a] Yield after column chromatography.
[b] No reaction.
[c] Decomposition.

Continuing our investigations, $Pd_2(dba)_3$ showed a general superiority as catalyst compared to $Pd(OAc)_2$ (Table 6.1, entry 3), providing *N*-cyanosulfoximine **161a** and *N*-methylsulfoximine **161c** in higher yields (84% and 55%, respectively). While *N*H-sulfoximine **161b** was again not formed, the valuable sulfoxide **163** could be isolated in 75% yield. Considering that couplings towards *N*H-sulfoximine **161b** had failed, the synthesis of *N*-trifluoroacetylsulfoximine **161d** was attempted, presumably giving *N*H-sulfoximine **161b** by *in situ* deprotection. However, only decomposition was observed.

Following a new strategy to access sulfoximine **161b**, rhodium-catalyzed imination of sulfoxide **163** with trifluoroacetamide gave sulfoximine **161d** in low yield (Scheme 6.2).[48] As anticipated, subsequent quantitative deprotection by using potassium carbonate afforded *N*H-sulfoximine **161b** (Scheme 6.2).[49]



163 **161d** **161b**

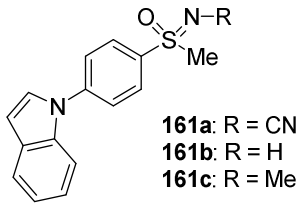
Scheme 6.2: Synthesis of *N*H-sulfoximine **161b**.

Considering previous studies on the bioactivity of *N*-cyanosulfoximines and *N*H-sulfoximines as well as investigations revealing improved solubility of *N*-methylsulfoximines compared to corresponding sulfones, sulfoximines **161a**, **161b** and **161c** were chosen for a COX-2 inhibition assay. As it was of interest to study the activity of each enantiomer, the corresponding compounds were separated by preparative HPLC or SFC.

6.2.2 Biological tests

In order to determine the inhibitory activity of compounds **161a–c** on the conversion of arachidonic acid into PGH_2, their COX-1 and COX-2 inhibitory potency and COX-2 selectivity were studied by *Pujol* (Laboratori de Química Farmacèutica, University of Barcelona) (Table 6.2). The tests were performed by using a COX (ovine) inhibitor screening assay kit (cat. N. 60101; Cayman Chemical, Ann Arbor, MI). The corresponding IC_{50} values for sulfoximines **161a–c**, sulfone **160**, ibuprofen, rofecoxib, and celecoxib were determined (Table 6.2).

Table 6.2: Comparative study of COX-1 and COX-2 inhibition by **161a–c**.



161a: R = CN
161b: R = H
161c: R = Me

Entry	Compound	COX-1 IC_{50} (µM)[a]	COX-2 IC_{50} (µM)[a]	Selectivity index (SI) COX-2 (COX-1/COX-2)
1	**160** (sulfone)	78.7±3.60	0.30±0.04	262
2	(+)-**161a** (R = CN)	1.52±0.62	1.69±0.57	0.9
3	(−)-**161a** (R = CN)	1.87±0.30	1.46±0.25	1.3
4	(+)-**161b** (R = H)	3.24±0.56	0.30±0.04	10.8
5	(−)-**161b** (R = H)	1.40±0.52	0.81±0.06	1.7
6	(+)-**161c** (R = Me)	5.43±0.09	124.80±2.43	0.04
7	(−)-**161c** (R = Me)	0.45±0.06	4.10±0.08	0.1
8	ibuprofen	3.35	1.40	2.4
9	rofecoxib	23.3	0.79	29
10	celecoxib	7.10	0.11	65

[a] Values are expressed as the mean (n = 3) of the % inhibition of PGH2 production by test compounds with respect to control samples.

As observed in previous studies, sulfone **160** is a potent and selective COX-2 inhibitor (Table 6.2, entry 1).[193b] All novel sulfoximines **161a–c** were active against COX; however, mostly nonselective for COX-2 such as *N*-cyanosulfoximines (+)-**161a** and (−)-**161a** (SI = 0.9, 1.3, Table 6.2, entries 2 and 3). Thus, only *N*H-sulfoximine (+)-**161b** showed moderate COX-2 selectivity (SI = 10.8, Table 6.2, entry 4), higher than ibuprofen (SI = 2.4, Table 6.2, entry 8) and higher potency against COX-2 than rofecoxib (Table 6.2, entry 9). Its enantiomer (−)-**161b** was potent, but much less selective against COX-2 (SI = 1.7, Table 6.2, entry 5).

Interestingly, *N*-methylsulfoximines (+)-**161c** and (−)-**161c** targeted COX-1 with high selectivity (SI = 0.04, 0.1, Table 6.2, entries 6 and 7). Of note, enantiomer (+)-**161c** exhibited very low potency against COX-2 (125 μM) compared to its 23-fold higher potency against COX-1 (5.4 μM). Generally, all enantiomers **161a-c** proved more potent against COX-1 than ibuprofen, rofecoxib and celecoxib.

6.3 Summary

Previously unknown 4-indolylphenyl methyl sulfoximines have been prepared by Buchwald–Hartwig couplings of 4-bromosulfoximines and indole. They are analogs of 4-indolylphenyl methyl sulfone, a known potent COX-2 inhibitor. The enantiomers of all obtained *N*-cyano, *N*H-, and *N*-methyl derivatives were potent COX-inhibitors. While the *N*-cyanosulfoximines were nonselective, (+)-*N*H-sulfoximine showed moderate COX-2 selectivity. Of interest in further studies, (+)-*N*-methylsulfoximine was 23-fold more selective against COX-1.

7 Syntheses of Sulfoximine-Containing Zolimidine Analogs

7.1 Background and Aim of the Project

Zolimidine **1** is a sulfone-based drug used for the treatment of peptic ulcer due to its gastroprotective effect.[196] Although not applied in patients anymore today, it is a well-known representative of the expanding group of imidazo[1,2-α]pyridine-containing pharmaceuticals.[197] Noteworthy are the antibiotic rifaximin,[198] the anxioloytic agents alpidem, zolpidem, necopidem, and saripidem,[199] a drug for treatment of heart failure (olprinone),[200] and a candidate for the treatment of HIV (GSK81239)[201] (Figure 7.1). This variety of applications results from the broad spectrum of biological activities covered by imidazo[1,2-α]pyridines such as antiulcer,[196,202] antifungal,[203] anti-viral,[204] antibacterial,[205] and anticancer.[206]

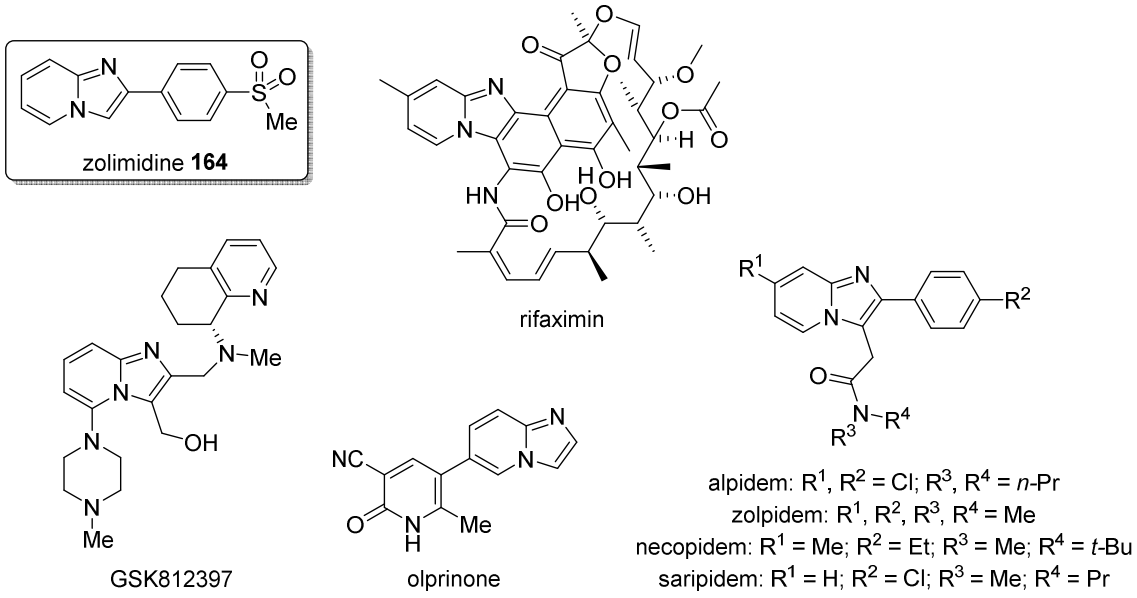
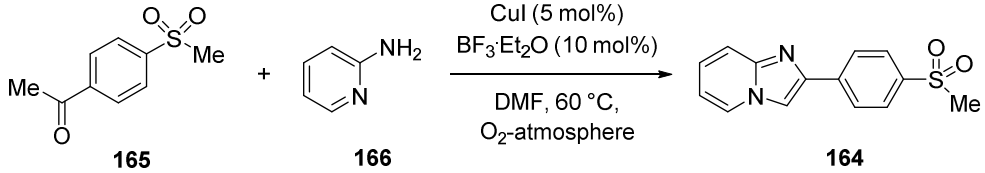


Figure 7.1: Imidazo[1,2-α]pyridine-based drugs.

Stimulated by their extraordinary biological activities, especially in the last years many synthetic routes to imidazo[1,2-α]pyridines have been developed.[197a] For example, zolimidine has been prepared in gram-scale by the reaction of 4-methylsulfonylacetone **165** and 2-aminopyridine **166**.[207] In a recently reported protocol by *Adimurthy*,[207a] the reaction was performed under oxygen atmosphere using copper(I)iodide as catalyst and boron trifluoride diethyl etherate as an additive (Scheme 7.1).



Scheme 7.1: Synthesis of zolimidine by *Adimurthy*.[207a]

Considering the high impact of imidazo[1,2-α]pyridines and the fact that sulfilimines and sulfoximines containing such heterocycles were unprecedented, we aimed to perform a formal sulfone-to-sulfoximine exchange on zolimidine **164**. In addition to the formation of biologically interesting products, the preparation of the corresponding sulfilimines **167** and sulfoximines **168** should enable the evaluation of the present synthetic procedures regarding the syntheses of heterocycle-containing targets (Figure 7.2).[208]

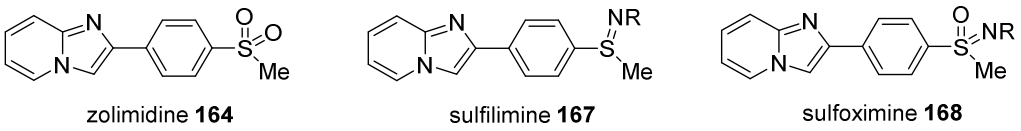


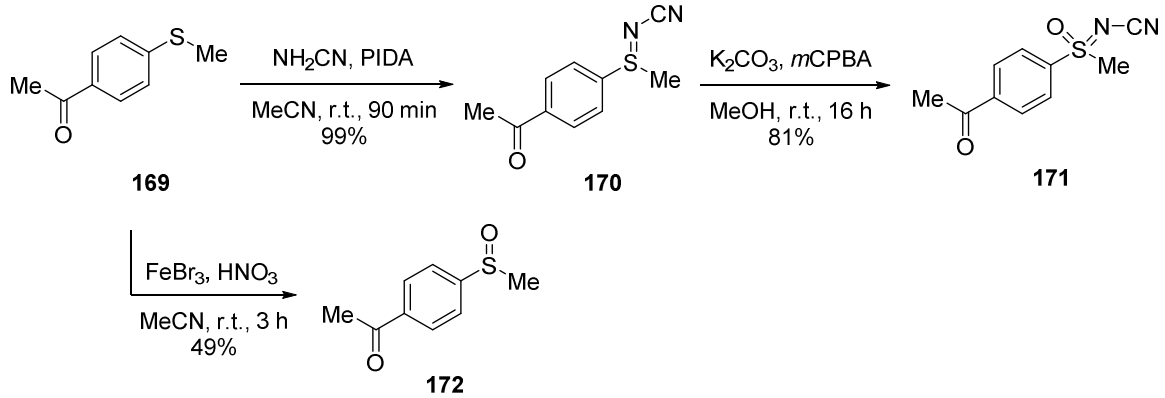
Figure 7.2: Zolimidine **164**, sulfilimine **167** and sulfoximine **168**.

7.2 Results and Discussion

At the beginning of our investigations, different strategies for the introduction of the sulfilimidoyl and sulfoximidoyl entities, and the formation of the imidazo[1,2-α]pyridine moiety, were evaluated. The order of sulfoximine and heterocycle synthesis seemed crucial for the success of the synthetic route. First attempts included the formation of the imidazo[1,2-α]pyridine-unit using previously prepared sulfoximine-containing building blocks.

7.2.1 Attempts with sulfilimine and sulfoximine building blocks

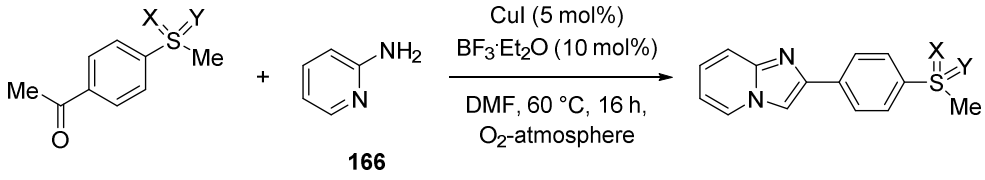
Initially, imination and oxidation of 1-(4-methylthio)acetophenone (**169**) were performed to obtain sulfilimine- and sulfoximine-containing starting materials. In consideration of the previously reported bioactivities of *N*-cyanosulfilimines and -sulfoximines, it was decided to introduce a cyano group for the protection of the sulfilimine and sulfoximine nitrogen atom. Metal-free imination using cyanamide and PIDA[59] afforded the corresponding *N*-cyanosulfilimine **170** in excellent yield (99%, Scheme 7.2). Following oxidation with *m*CPBA and potassium carbonate[49] provided *N*-cyanosulfoximine **171** in 81% yield. Sulfoxide **172** could be prepared by iron(III)catalyzed oxidation with nitric acid.[209]

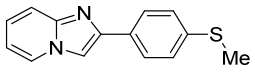
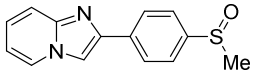
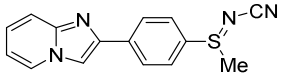
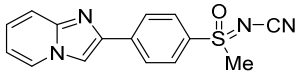


Scheme 7.2: Syntheses of sulfilimine, sulfoximine, and sulfoxide building blocks.

In order to synthesize the imidazo[1,2-*a*]pyridine moiety, the prepared building blocks were treated with 2-aminopyridine (**166**), by using the method described by *Adimurthy* (Table 7.1).[207a] As expected, the desired sulfide **173** and sulfoxide **174** were obtained in good yields (Table 7.1, entries 1 and 2). However, *N*-cyanosulfilimine **170** and *N*-cyanosulfoximine **171** did not involve formation of products **167a** and **168a** (Table 7.1, entries 3 and 4). Instead, decomposition of the starting material was observed.

Table 7.1: Synthesis of zolimidine derivatives.



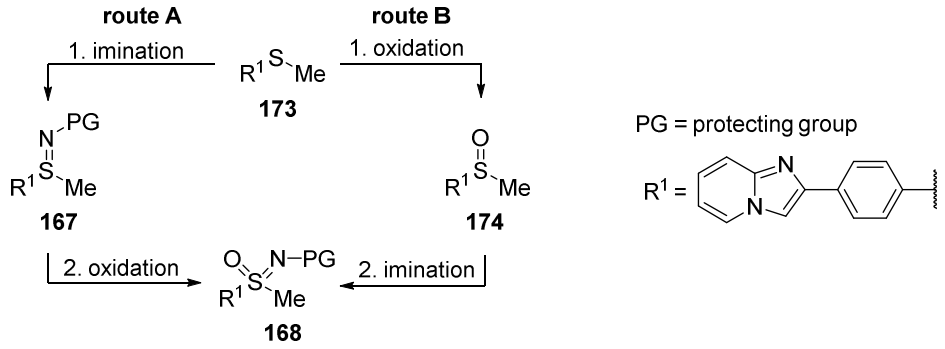
Entry	Starting Material	Product	Yield [%][a]
1	**169**	 **173**	61
2	**172**	 **174**	58
3	**170**	 **167a**	–
4	**171**	 **168a**	–

[a] Yield after column chromatography.

Realizing that the synthesis of the imidazo[1,2-α]pyridine moiety using preformed sulfilimine and sulfoximine building blocks was troublesome, it was decided to attempt sulfilimine and sulfoximine syntheses on the bases of the obtained sulfide and sulfoxide backbones **173** and **174**.

7.2.2 Iminations and oxidations on the imidazo[1,2-α]pyridine-containing backbone

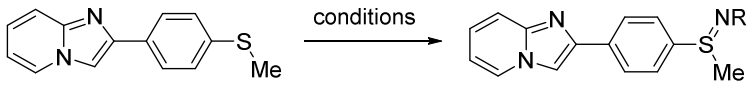
Two different synthetic pathways were taken into account: starting from sulfide **173** an imination/oxidation sequence (Scheme 7.3, route A) would lead to sulfoximine **168** *via* the desired sulfilimine **167**. As an alternative, an oxidation/imination sequence was considered (Scheme 7.3, route B).



Scheme 7.3: Synthetic routes towards sulfilimine **167** and sulfoximine **168**.

Following route A, metal-free imination of sulfide **173** with cyanamide was first attempted. However, by using NBS and potassium-*tert*-butoxide,[49] bromination of the heterocycle was solely observed (Table 7.2, entry 1).[210] Replacement of NBS and the base by PIDA[59] led to traces of sulfoxide **174** instead of the desired sulfilimine (Table 7.2, entry 2). Hence, we switched to metal-catalyzed imination procedures that would come along with different protecting groups on the sulfilimine nitrogen atom. Along those lines, a frequently applied rhodium-catalyzed protocol was employed, involving imination with trifluoroacetamide.[48] Unexpectedly, decomposition occurred (Table 7.2, entry 3). An iron-catalyzed method which had previously proven to be mild and suitable for heterocyclic starting materials[46,54] did not lead to any conversion (Table 7.2, entry 4).

Table 7.2: Imination of sulfide **173**.



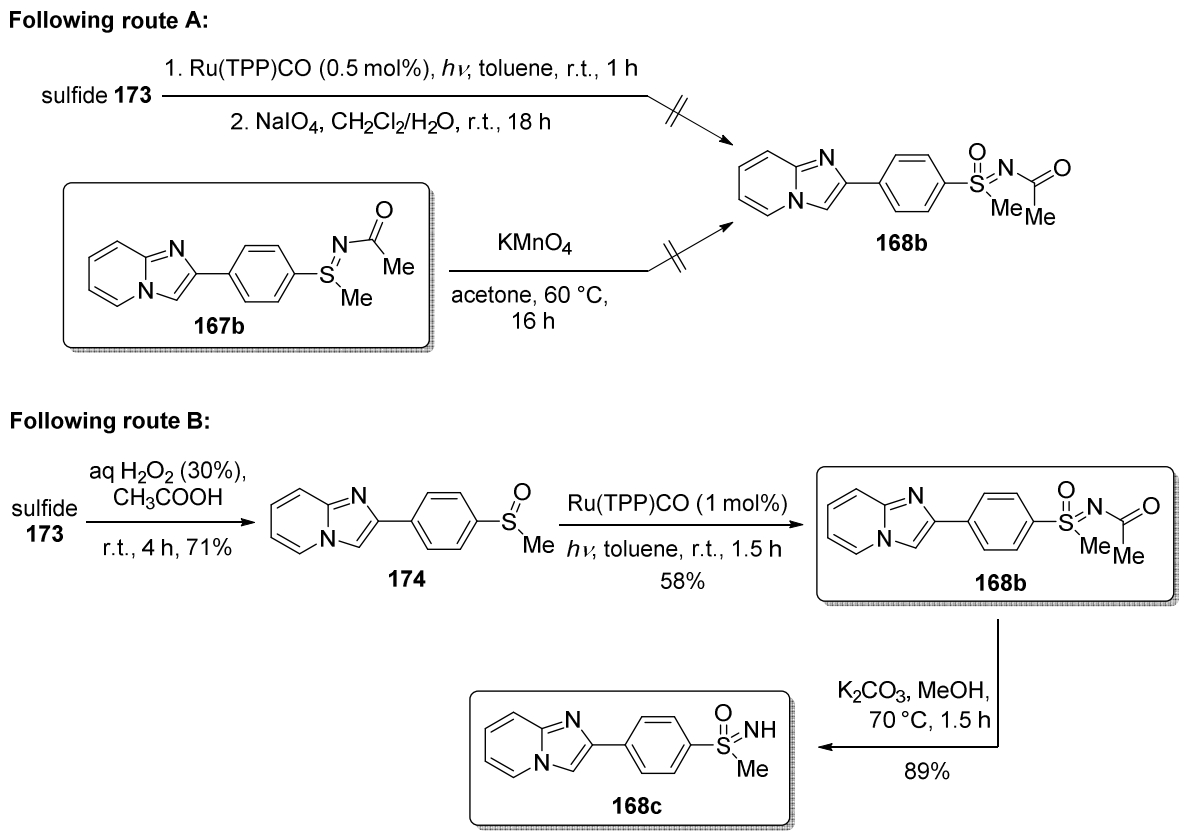
173 **167** **167b** (R = acetyl)

Entry	Conditions	R	Yield of 167 [%][a]
1	NH_2CN, *t*-BuOK, NBS, MeOH, r.t., 30 min	CN	–[b]
2	NH_2CN, $PhI(OAc)_2$, MeOH, r.t., 4 h	CN	–[c]
3	$Rh_2(OAc)_4$ (2.5 mol%), trifluoroacetamide, MgO, $PhI(OAc)_2$, CH_2Cl_2, r.t., 24 h	$COCF_3$	–[d]
4	$Fe(OTf)_2$ (15 mol%), PhI=NNS, 4 Å molecular sieves, MeCN, 50 °C, 20 h	nosyl	–[e]
5	Ru(TPP)CO (0.5 mol%), 3-methyl-1,4,2-dioxazol-5-on, toluene, *hν*, r.t., 1 h	COMe	83 (**167b**)

[a] Yield after column chromatography.
[b] Formation of 3-bromo-2-[4-(methylthio)phenyl]-imidazo[1,2-α]pyridine observed.
[c] Traces of sulfoxide **174** observed on TLC.
[d] Decomposition observed.
[e] No conversion.

Finally, sulfide **173** was subjected to photochemical imination employing 3-methyl-1,4,2-dioxazol-5-one as nitrene source and a ruthenium catalyst (Table 7.2, entry 5).[65a] To our delight, sulfide **173** was successfully iminated providing *N*-acetylsulfilimine **167b** in 83% yield.

Continuing our investigations, oxidation reactions of the newly synthesized compound **167b** were performed (Scheme 7.4). Initially, we applied a one-pot protocol involving photochemical imination and subsequent oxidation with sodium periodate.[65a] Unfortunately, sulfoximine **168b** was not formed. Similarly, an oxidation method employing potassium permanganate which had already been applied to heterocyclic starting materials[55] did not lead to the desired product.



Scheme 7.4: Routes to sulfoximines **168b** and **168c**.

Consequently, we focused our attention on synthetic route B (Scheme 7.4). Oxidation of sulfide **173** using aqeous hydrogen peroxide solution in acetic acid[27] afforded sulfoxide **174** in 71%. Subsequent photochemical imination[65a] gave the desired *N*-acetylsulfoximine **168b** in 58% yield. The final deprotection of the acetyl group, using potassium carbonate in methanol[49] at 70 °C, proceeded smoothly, giving the corresponding *N*H-sulfoximine **168c** in 89% yield.

7.3 Summary

In order to synthesize sulfilimine and sulfoximine analogs of zolimidine, two different synthetic approaches were studied. The copper-catalyzed formation of the imidazo[1,2-

a]pyridine under air using previously formed sulfilimine and sulfoximine building blocks did not lead to success, probably due to decomposition of the starting materials.

Contrarily, imination of the imidazo[1,2-α]pyridine-based backbone using our new light-promoted ruthenium-catalyzed protocol afforded the desired *N*-acetylsulfilimidoyl derivative of zolimidine. However, it proved unstable towards further oxidation. Finally, the *N*-acetylsulfoximidoyl analog was obtained by corresponding imination of the previously formed sulfoxide which smoothly underwent the envisaged deprotection to the corresponding *N*H-sulfoximine. Of note, this study reveals the benefit of light-promoted ruthenium-catalyzed imination using 3-methyl-1,4,2-dioxazol-5-one as iminating agent, giving access to the desired heterocycle-containing sulfoximines by introducing easily cleavable *N*-acetyl groups.

8 Syntheses of Methyl 4-Pentafluorosulfanylphenyl Sulfoximines

8.1 Background and Aim of the Project

Fluorine-containing sulfoximines such as sulfoxaflor, the first sulfoximine on the market,[16b] and pan-CDK inhibitor BAY1000394,[114b] are emerging as beneficial compounds in crop protection and drug design[15] (see also Chapters 1.1.4). Combining the unique steric and electronic properties of fluoro- and trifluoromethyl substituents with the qualities of sulfoximidoyl functionalities can lead to compounds with special features. Hence, there is an active research interest promoting investigations into the syntheses of new fluorine-containing sulfoximines. Known compounds **175** and **176** possess fluorine, fluorinated, perfluorinated, fluoroaryl, or CF_3-aryl substituents on the sulfur atom (Figure 8.1, left).[136,211] Recently, *N*-CF_3 and *N*-SCF_3 derivatives **177** joined the number of available fluorinated sulfoximines.[212] However, to the best of our knowledge, molecules such as **178** featuring SF_5-substituted aryl rings are unprecedented (Figure 8.1, right).[213] Considering the remarkable properties of SF_5 groups and their rare availability in bioactive compounds (see Chapters 1.2.2 and 1.2.3), we were interested in synthesizing sulfoximine **178** as a building block, suitable for the incorporation into larger backbones. Further derivatization of this key compound should give access to new *N*-functionalized SF_5-containing sulfoximines.[214]

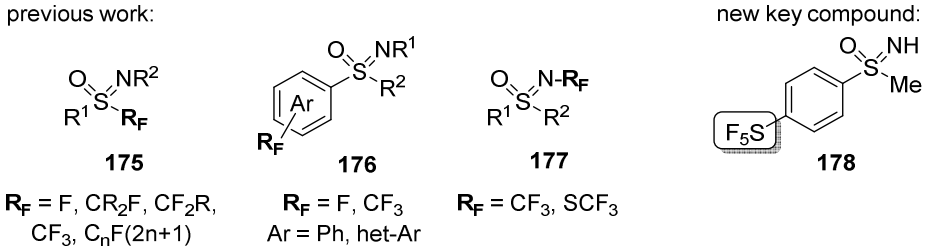
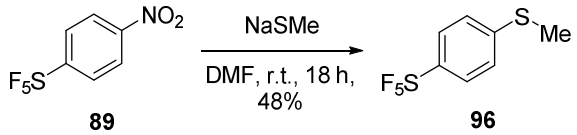


Figure 8.1: Precedented fluorinated sulfoximines and methyl 4-SF_5-phenyl sulfoximine.

8.2 Results and Discussion

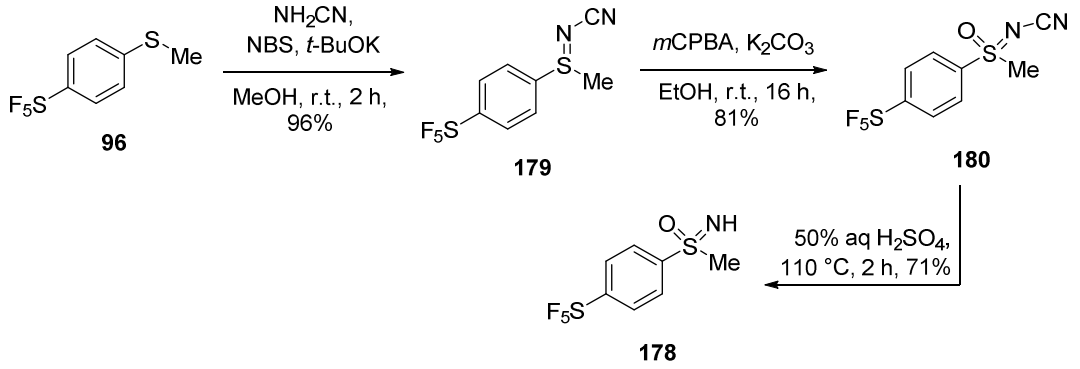
The starting material was prepared following a reported procedure.[145] Nucleophilic aromatic substitution on 4-nitrophenylsulfurpentafluoride **89** using sodium methanethiolate furnished sulfide **96** (Scheme 8.1).



Scheme 8.1: Synthesis of methyl 4-(pentafluorosulfanyl)phenyl sulfide.

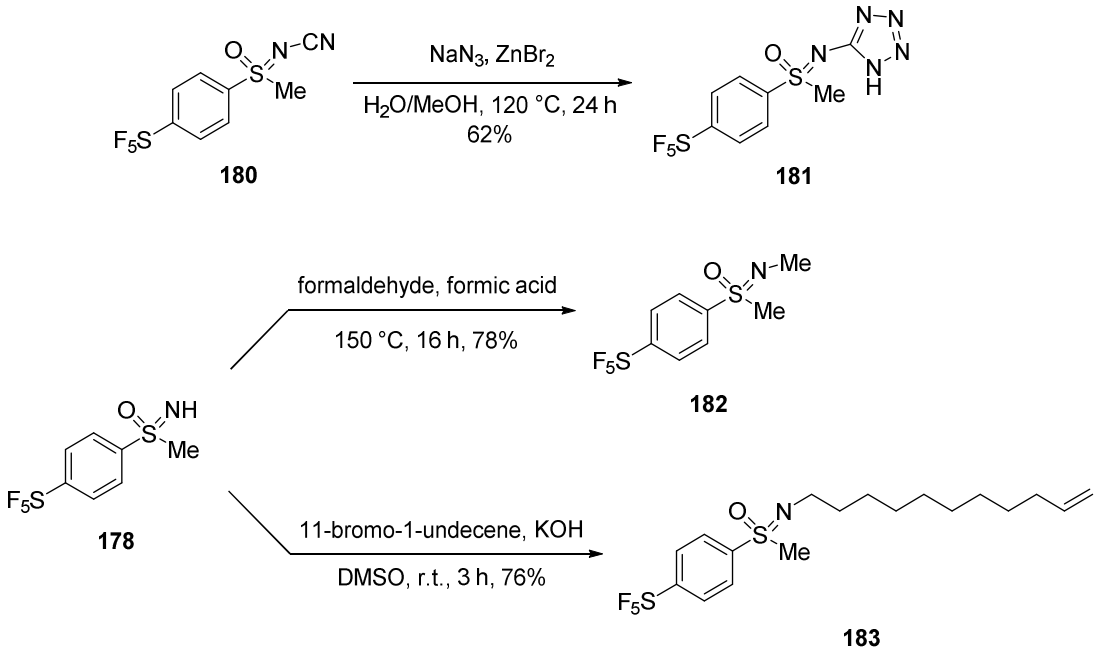
To begin our investigations, imination of sulfide **96** using cyanamide, NBS and potassium-*tert*-butoxide[49] provided *N*-cyanosulfilimine **179**, the first target compound on the way to sulfoximine **178**, in excellent yield (96%, Scheme 8.2). Subsequent oxidation with *m*CPBA[49] proceeded smoothly affording sulfoximine **180** in good yield (81%, Scheme 8.2). To our delight, after deprotection of sulfoximine **180** using 50%

aqueous sulfuric acid at 110 °C[60] the desired *N*H-sulfoximine **178** was obtained in 71% yield. Considering future applications in biologically active compounds, separation conditions for the enantiomers of racemic **178** were determined by analytical CSP HPLC, allowing preparative HPLC separation.



Scheme 8.2: Synthesis of methyl 4-(pentafluorosulfanyl)phenyl sulfoximine **178**.

The fact that tetrazoles are known as carboxylic acid isosters with a special biological behavior[108] aroused our interest in the preparation of a tetrazole derivative starting from *N*-cyanosulfoximine **180**. In the presence of sodium azide and zinc(II)bromide in a water-methanol mixture at 120 °C,[59] *N*-(1*H*)-tetrazole sulfoximine **181** was formed in 62% yield (Scheme 8.3).

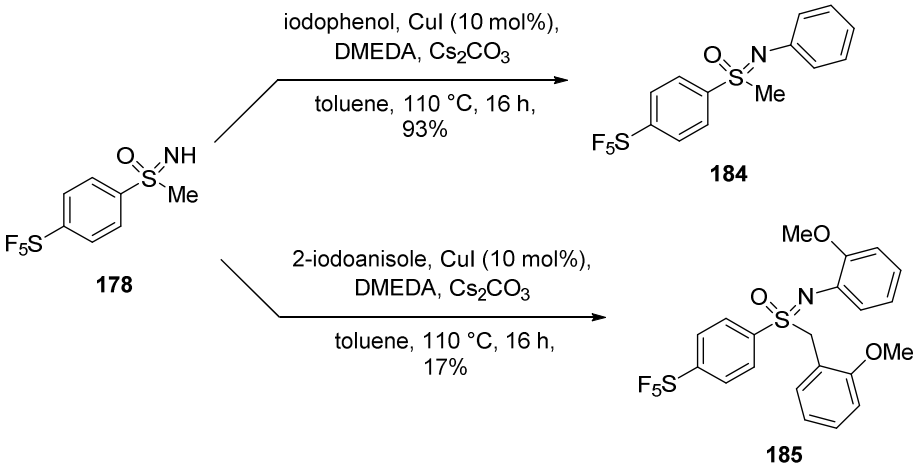


Scheme 8.3: Transformation of *N*-cyanosulfoximine **180** into the corresponding *N*-(1*H*)-tetrazole **181** and *N*-alkylation of *N*H-sulfoximine **178**.

In a recent publication, several *N*-methylsulfoximines have shown to exhibit a higher solubility than the corresponding sulfones.[115] Considering the resulting beneficial effects in previous biological evaluations, we performed an *N*-methylation reaction of *N*H-sulfoximine **178** under Eschweiler-Clark conditions,[84b] leading to *N*-methyl sulfoximine

182 in 78% yield. These findings confirm high stability of the presented pentafluorosulfanyl-containing sulfoximines under acidic conditions (Scheme 8.3). Thus, we were curious to find out whether the superbasic reaction conditions, previously applied for the introduction of long alkyl chains to *N*H-sulfoximines (see Chapter 3), could be applied to our new building block **178**. To this end, sulfoximine **178** was treated with 11-bromo-1-undecene in KOH/DMSO (Scheme 8.3).[170] As envisaged, the *N*-alkylated product **183** could be obtained in 76% yield, thereby demonstrating the stability of our target compound in the presence of very strong bases.

To date, *N*-arylated sulfoximines are established as selective ligands in asymmetric metal catalysis (see Figure 1.5).[98a] Consequently, we were interested in exploring the *N*-arylation of sulfoximine **178**. Using a representative *N*-phenylation protocol,[104a] involving a copper-catalyzed reaction with iodophenol provided the desired *N*-phenylated sulfoximine **184** in excellent yield (Scheme 8.4). Surprisingly, when employing 2-iodoanisole as substrate, significant amounts of starting material were recovered. An unexpected product **185**, containing a 2-methoxyphenyl substituent at the sulfoximine-nitrogen atom and a 2-methoxybenzyl group connected to the sulfur atom, was isolated in 17% yield.



Scheme 8.4: *N*-Arylation of *N*H-sulfoximine **178**.

8.3 Summary

We have demonstrated that methyl 4-(pentafluorosulfanyl)phenyl sulfoximines are readily available compounds, easily prepared following established synthetic methods. Most of their representative modifications were performed successfully in high yields by using standard protocols. Of note, the stability of the synthesized pentafluorosulfanyl-containing compounds was high in acidic as well as superbasic media. These findings promote them as easily manageable building blocks in future transformations leading to synthetically and biologically interesting targets.

9 Syntheses and Biological Activities of Pentafluorosulfanyl-Containing Flufenamic Acid Analogs

9.1 Background and Aim of the Project

Flufenamic acid (**87a**, 2-[(3-CF_3-phenyl)amino]-benzoic acid or FFA), is an aromatic amino acid, containing an *ortho*-carboxylic acid group and a *meta*-trifluoromethyl substituent (Figure 9.1). Since its discovery in the 1960s, FFA has found various biological and medical applications. Early investigations revealed anti-inflammatory and analgesic properties of FFA, belonging to the fenamate class of non-steroidal anti-inflammatory drugs (NSAIDs).[215] However, the use of FFA as drug was limited due to the occurrence of unwanted side effects (Figure 9.1).[138c,216] Later studies in basic research recognized its ability to regulate ionic currents in native tissues, thus to modulate ion channels.[138a] Hence, FFA emerged as a benefical tool to study ion channels such as Cl^-, Ca^{2+}, Na^+, K^+, and GABA channels, and non-selective cation channels. In this context, *Gründer*, *Wiemuth*, and coworkers explored the influence of FFA on rat bile acid-sensitive ion channel (rBASIC).[217]

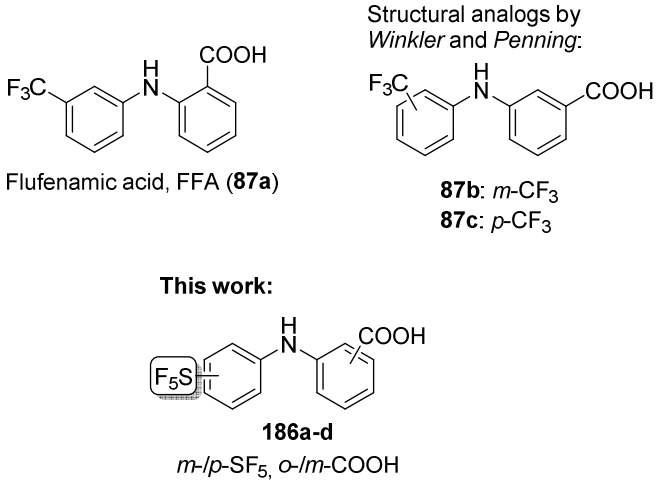


Figure 9.1: Flufenamic acid (**87a**, FFA) and reported derivatives **87b** and **87c**.

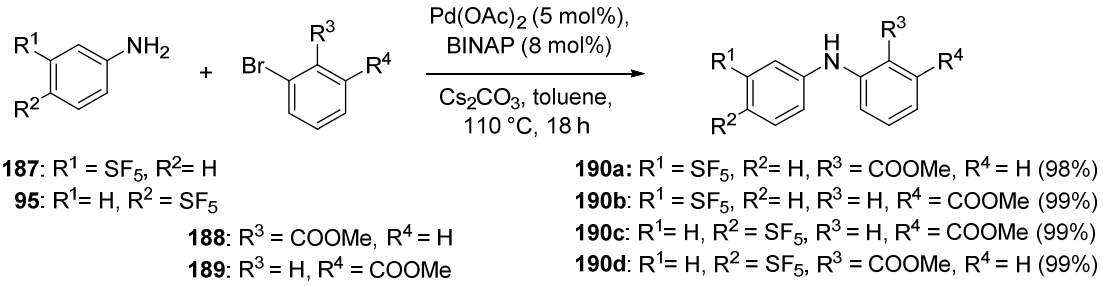
Recently, *Winkler* and *Penning* reported the syntheses and structure-activity relationships of structural FFA analogues regarding their potential in the treatment of castration resistant prostate cancer (CRPC) (Figure 9.1).[138b,218] They found that compounds **87b** and **87c** proved potent and selective inhibitors of aldo-keto reductase 1C3 (AKR1C3), an enzyme overexpressed in (CRPC) required for intratumoral androgen biosynthesis.[219]

Following our interest in pentafluorosulfanyl-containing compounds, we envisaged to prepare structural SF_5-containing FFA derivatives **186a–d** (Figure 9.1). Their structure-activity relationship regarding ion channel modulation and AKR1C3 inhibition was investigated.[220]

9.2 Results and Discussion

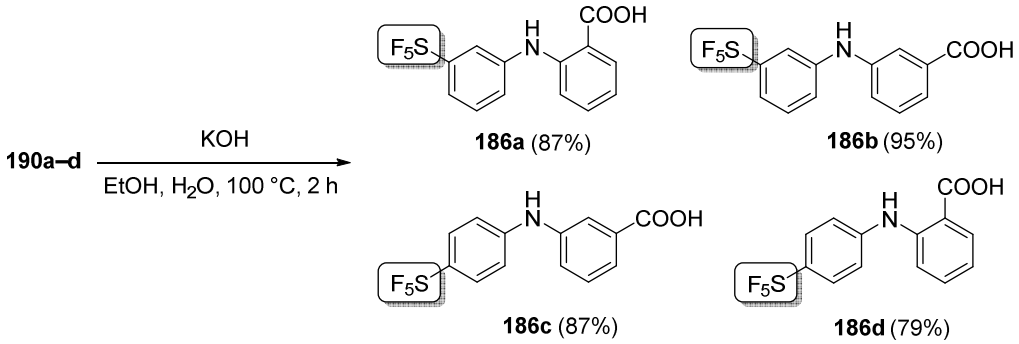
9.2.1 Syntheses of the target compounds

SF_5-containing FFA derivatives **186a–d** were synthesized in a two-step sequence.[138b,220] Buchwald–Hartwig couplings of pentafluorosulfanyl-anilines **187** and **97** with methyl bromobenzoates **188** and **189** were performed, using palladium acetate as catalyst, BINAP as ligand, and cesium carbonate as base. The resulting methyl esters **190a–d** were obtained in excellent yields of 98–99% (Scheme 9.1).



Scheme 9.1: Syntheses of methyl esters **190a–d** by Buchwald–Hartwig couplings.

In the final step, methyl esters **190a–d** were cleaved by saponification by using potassium hydroxide in ethanol–water at 100 °C. To our delight, the desired FFA derivatives **186a–d** were formed and isolated in high yields of 79–95% (Scheme 9.2).



Scheme 9.2: Saponifications of methyl esters **190a–d** to form FFA derivatives **186a–d**.

9.2.2 Computational calculations of structures and properties

Conformational analyses of FFA analogs **186a–d** were performed by *Sanhueza* and *Schoenebeck*.[220] The minimum energy conformations of all analogs proved very similar showing slightly twisted aryl rings. Compounds **186a** and **186d** are stabilized by O···H–N interactions resulting from the carboxygroups in *o*-position neighbouring the NH group. ADMET parameters were calculated including pK_a, LogP and LogD. In summary, the conformational and physical properties are not likely to have an impact on the activity differences.

9.2.3 Biological tests

Activation of bile acid-sensitive ion channel (BASIC)

FFA is known to activate rat bile acid-sensitive ion channel (rBASIC), a cation channel sensitive to changes of its membrane environment.[217,221] Similarly to natural bile acids, FFA is supposed to interact with the cell membrane. Hence, in order to study the activity of SF_5-containing FFA analogs **186a–d** on ion channels, rBASIC was chosen as a model. Alterations of the current amplitude induced by **186a–d** applied at 1 mM to *Xenopus* oocytes heterologously expressing rBASIC, were studied by *Wiemuth* and *Gründer* (Institute of Physiology, RWTH Aachen University).[220]

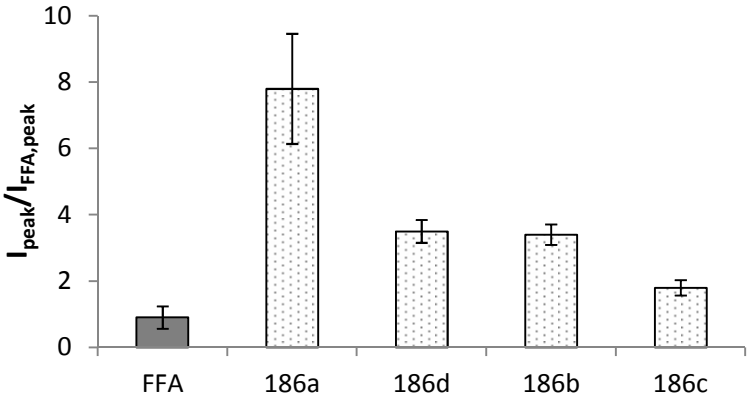


Figure 9.2: Quantitative comparison of peak current amplitudes induced by the application of 1 mM FFA (**87a**) and compounds **186a–d**. Error bars represent S.E.M. (n = 6; **186c** $p < 0.005$; **186a,b,d** $p < 0.001$).

Of note, all SF_5-containing compounds **186a–d** showed a stronger activation of rBASIC than FFA (**87a**), inducing rapid and reversible increases in the current amplitude (Figure 9.2). Compounds **186a–d** caused a 1.5- to 3-fold increase of the current amplitude. Interestingly, the SF_5-analog **186a**, structurally most similar to FFA, even induced an 8-fold larger amplitude than FFA.

Table 9.1: EC_{50} values of flufenamic acid (**87a**) and its SF_5-containing analogs **186a–d**.

Entry	Compound	EC_{50} (mM)[a]
1	FFA (**87a**)	2.6±0.3
2	**186a**	1.4±0.1
3	**186b**	2.9±0.1
4	**186c**	2.8±0.4
5	**186d**	2.6±0.2

[a] EC_{50} values were calculated using the Hill equation: $I = I_{max}/(1+([EC_{50}/c]^n)$, I_{max}: maximal current induced, c: concentration, n: Hill coefficient (n = 9).

In order to investigate the affinities of analogs **186a–d**, their EC_{50} (half maximal effective concentration) values were determined (Table 9.1). As the solubility of flufenamic acid and its derivatives in the aqueous bath solution was limited, the obtained data were not entirely precise, though the EC_{50} of flufenamic acid of 2.6±0.3 mM for rBASIC equaled earlier reported values.[217b] While the affinities of **186b–d** (EC_{50} = 2.6 to 2.9 mM) were in the same range compared to FFA, the affinity of **186a** was significantly higher (EC_{50} = 1.4±0.1 mM). It can be concluded that the CF_3-to-SF_5-exchange in flufenamic acid increases the efficacy of rBASIC modulation, especially considering the results of analog **186a**. The new compounds **186a–d** may interact specifically with rBASIC as their similar chemical properties suggest an activation not solely depending on a membrane-based mechanism.

Inhibitory activities on AKR1C3

Biological tests on the inhibition of AKR1C3 were peformed by *Zang* and *Penning* (Center of Excellence in Environmental Toxicology, Perelman School of Medicine, University of Pennsylvania).[220] As AKR1C2, having a sequence >86% identical to AKR1C3, should not be inhibited, the selectivity for AKR1C3 compared to AKR1C2 was determined (Table 9.2).

Table 9.2: Inhibition of AKR1C3 and AKR1C2.

Entry	Compound	AKR1C3 IC_{50} (µM)	AKR1C2 IC_{50} (µM)	IC_{50} ratio 1C2/1C3[b]	Position COOH	Position SF_5
1[a]	FFA (**87a**)	0.05	0.37	7	*o*	*m*-CF_3
2	**186a**	0.057	0.270	4.7	*o*	*m*
3	**186b**	0.086	14	163	*m*	*m*
4	**186c**	0.035	20	571	*m*	*o*
5	**186d**	0.036	0.15	4.2	*o*	*p*

[a] IC_{50} values previously determined by *Penning*.[138b]
[b] High value = high selectivity for AK1C3.

Compared to FFA (**87a**, Table 9.2, entry 1), SF_5 analog **186a** showed similar inhibitory potency for AKR1C3 (57 nM), but lower selectivity (Table 9.2, entry 2). A shift of the carboxygroup from *o*- to *m*-position (analog **186b**) involved a slight decrease in potency for AKR1C3 (86 nM), but a loss of potency for AKR1C2 (14 µM), resulting in higher selectivity for AKR1C3 (Table 9.2, entry 3).

Moving the SF_5 group into *p*-position (analog **186c**) led to an increased inhibitory activity of AKR1C3 (35 nM) and a strong decrease in potency for AKR1C2 (20 µM), coming along with a remarkably high selectivity for AKR1C3 (Table 9.2, entry 4). Differently, analog **186d**, possessing a carboxygroup in *o*-position and an SF_5 group in *p*-position, showed a higher potency for AKR1C2 (15 nM) than for AKR1C3 (36 nM) and therefore a low selectivity (Table 9.2, entry 5). The loss of inhibitory activity against

AKR1C2 in case the carboxygroup is moved into *m*-position, is in accordance with the previous observations for compounds **87b** and **87c**.[138b]

Due to their high inhibitory potency (< 100 nM) and high selectivity for AKR1C3 (ratio > 150), SF_5 analogs **186b** and **186c** could be considered as new drug candidates for the treatment of CRPC related to an overexpression of AKR1C3.

Inhibitory activities on COX-1 and COX-1

As flufenamic acid is kown as a COX inhibitor, the effect of analogs **186a–d** on the catalysis of the conversion of arachidonic acid to prostaglandin H_2 was investigated by *Zang* and *Penning*.[220] The inhibitory activities towards both COX-1 and COX-2 were determined (Table 9.3).

Table 9.3: Inhibition of COX-1 and COX-2.

Entry	Compound	COX-1 IC_{50} (µM)	COX-2 IC_{50} (µM)
1	**186a**	1.8	12
2	**186b**	>100[a]	>100[b]
3	**186c**	>100[b]	>100[b]
4	**186d**	22	>100[a]

[a] <10% inhibition at 100 µM.
[b] 10-40% inhibition at 100 µM.

Compound **186a** was active against COX-1 and COX-2, while analog **186d** displayed only inhibitory potency to COX-1 (Table 9.3, entries 1 and 4). Interestingly, derivatives **186b** and **186c** showed no considerable inhibitory potencies against COX-1 and COX-2 (Table 9.3, entries 2 and 3), proving again their high inhibitory selectivity towards AKR1C3.

NCI 60 Cell One-Dose Screen

Flufenamic acid analog **186a** was selected for the NCI 60 Cell One-Dose Screen within the Developmental Therapeutics Program of the NCI/NIH. The anti-cancer test was performed at a single high dose (10^{-5} M). Compound **186a** showed almost no growth inhibition (average growth percent of 97.27) (Table 9.4).

Table 9.4: NCI 60 Cell One-Dose Screen

Compound	Growth percent at 10 µM		
	Mean	Delta	Range
186a	97.27	35.37	54.57

Mean: Average Growth Percent
Delta: Mean – minimum value of Growth Percent
Range: Maximum – minimum value of Growth Percent

9.3 Summary

Four unprecedented SF_5-containing flufenamic acid analogs have been synthesized, and computationally and biologically studied. Their structure and ADMET parameters were calculated computationally. All compounds exceeded flufenamic acid with respect to the activation of ion channel rBASIC. Especially analog **186a** was highly potent, inducing 8-fold larger currents than flufenamic acid at 1 nM. Hence, further investigations into such analogs as ion channel modulators should be performed. Contrary to the ineffectiveness of analog **186a** in the NCI 60 Cell One-Dose Screen, compounds **186b** and **186c** showed high potency and inhibitory selectivity for AKR1C3 and should be further studied regarding their potential as new drug candidates for CRPC.

10 Syntheses of Pentafluorosulfanyl-Containing 1,2,3,4-Tetrahydroquinolines

10.1 Background and Aim of the Project

1,2,3,4-Tetrahydroquinolines are important structural motifs with a broad variety of applications in medicine, biology, and synthetic chemistry.[222] They can be found in many natural products and alkaloids such as virantmycin[223] and martinellic acid (Figure 10.1).[224] Their numerous biological activities such as antiviral, antibacterial, antifungal, antitumor, and antimalarial, as well as their abilities to inhibit enzymes and affect membrane and hormone receptors, make them to interesting scaffolds in drug development.[222]

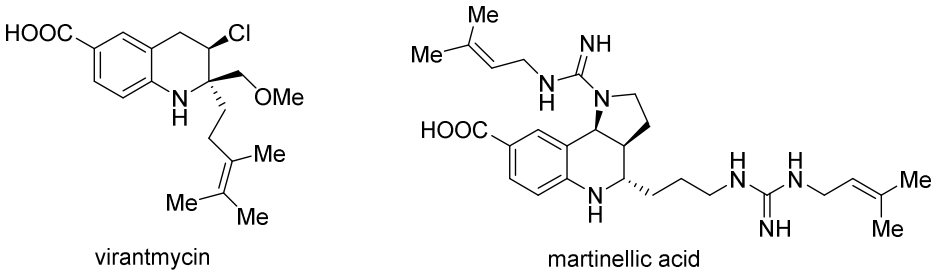
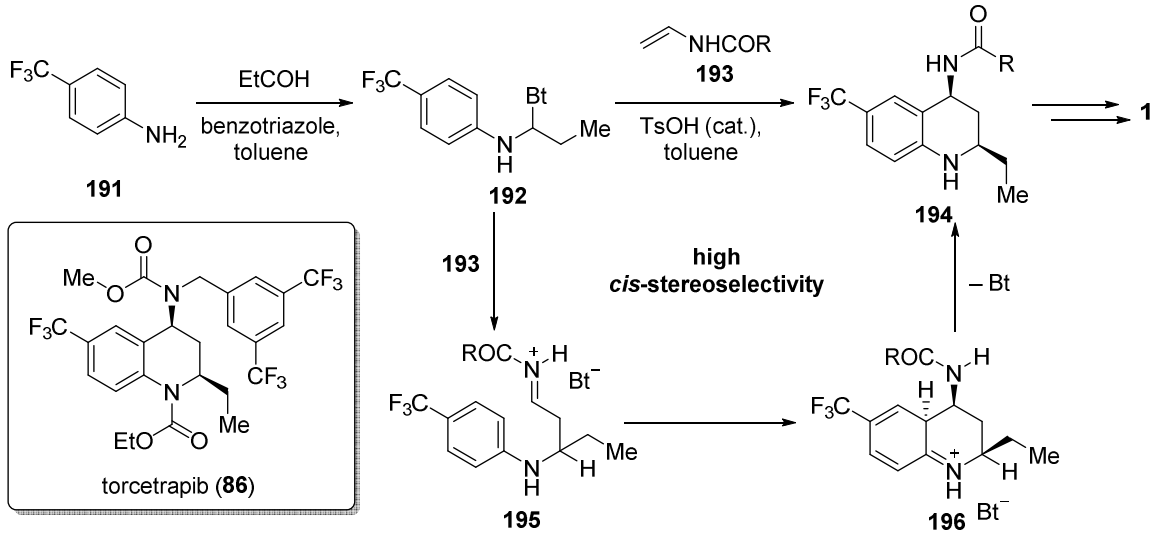


Figure 10.1: 1,2,3,4-Tetrahydrochinoline-containing alkaloids.

In the course of our reseach on fluorine-containing compounds[214,220] we came across torcetrapib (**86**), a 1,2,3,4-tetrahydroquinoline-based inhibitor of cholesteryltransfer protein (CETP)[225] containing a CF_3 group in 6-position, developed for the treatment of artherosclerosis and coronary heart disease (Scheme 10.1).[226]



Scheme 10.1: Synthesis of the tetrahydroquinoline-core of torcetrapib (**86**).

The 1,2,3,4-tetrahydrochinoline core **194** can be prepared from 4-trifluoromethylaniline **191** in multikilogram scale by a Povarov-type reaction mediated by benzotriazole (Bt), involving a rapid intramolecular iminium ion cyclization as the key step.[137,227] First, aniline (**191**) and propionaldehyde form an imine trapped by benzotriazole, giving

adduct **192**. Addition of *N*-vinyl-derivative **193** leads to activated iminium-ion **195** followed by acid-catalyzed cyclization onto the aromatic ring generating cyclic intermediate **196**. The final product **194** is obtained after regeneration of the aromaticity by the release of benzotriazole (Scheme 10.1). The authors observed that the cyclization reaction proceeded highly *cis*-selective, which can be either explained by sterical reasons[227] or by the lower activation energy of the *cis*-cyclization, determined by computational calculations.[137]

Recognizing the success in the preparation of SF_5-containing quinolines, namely mefloquine,[153] we noted that SF_5-substituted 1,2,3,4-tetrahydroquinolines were unprecedented. Hence, we were attracted by the idea to prepare the 6-SF_5-substituted tetrahydroquinoline core **197** (Figure 10.2) and investigate further synthetic steps towards torcetrapib (**86**) (project in cooperation with *Reball*, group of *Bolm*).

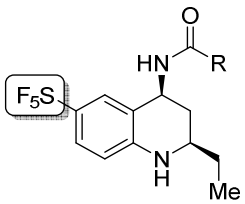
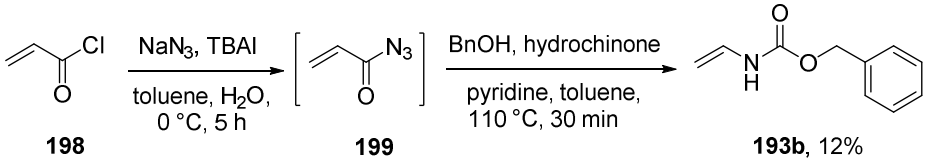


Figure 10.2: Envisaged 6-SF_5 tetrahydroquinoline core.

10.2 Results and Discussion

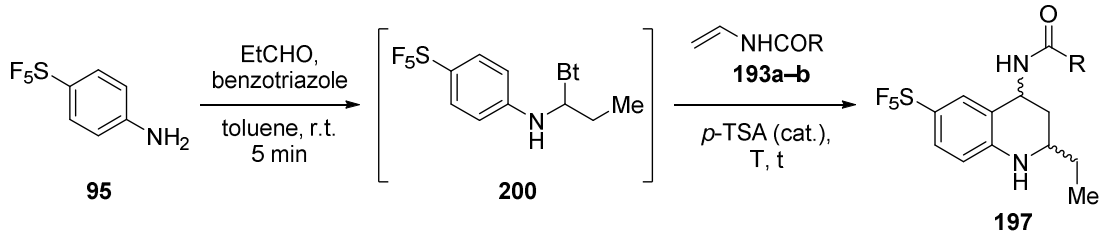
The commercially available *N*-vinylacetamide (**193a**) and benzyl *N*-vinylcarbamate (**193b**) were chosen as starting materials for the cyclization reactions. Compound **193b** was prepared in 12% yield by treatment of acryloylchloride (**198**) with sodium azide to form intermediate **199**, and subsequent conversion with benzyl alcohol (Scheme 10.2).[228]



Scheme 10.2: Synthesis of benzyl *N*-vinylcarbamate **193b**.

Next, by using 4-pentafluorosulfanyl aniline **95** and freshly distilled propionaldehyde under argon, adduct **200** was formed (Table 1.10). As it appeard to be instable upon isolation it was directly subjected to cyclization with **193a** or **193b**, catalyzed by *p*-TSA. Reactions employing *N*-vinylacetamide (**193a**) were performed at room temperature (Table 10.1, entries 1 and 2), and after 2 h full conversion was observed. To our delight, the desired 6-SF_5 tetrahydroquinoline **197a** was formed, albeit with concomitant formation of many side products, in low yield (29%, Table 10.1, entry 1). Enhancing the temperature to 80 °C and allowing the reaction to proceed for 30 min in the microwave, proved beneficial, providing product **197a** in 33% yield (Table 10.1, entry 2).

Table 10.1: Synthesis of tetrahydroquinolines **197**.



Entry	NHCOR 193a–b	R	T [°C]	t [min]	Product	Yield of 197 [%][a]
1	**193a**	Me	r.t.	120	**197a**	29
2	**193a**	Me	MW, 80 °C	30	**197a**	33
3	**193b**	*O*-benzyl	MW, 80 °C	10	**197b**	13
4	**193b**	*O*-benzyl	MW, 100 °C	10	**197b**	48

[a] Yield after column chromatography.

When benzyl *N*-vinylcarbamate (**193b**) was used under the same conditions, after a reaction time of 10 min, 6-SF_5 *N*-Cbz tetrahydroquinoline **197b** was obtained in low yield of only 13% (Table 10.1, entry 3). However, increasing the temperature to 100 °C, gave **197b** in 48% yield (Table 10.1, entry 4).

To determine the relative configuration of 6-SF_5 tetrahydroquinoline **197b**, an X-ray crystal structure analysis was performed (*Raabe*) (Figure 10.3). The crystal structure indicates that the *cis*-diastereomer of **197b** (as compared to torcetrapib) has been isolated.

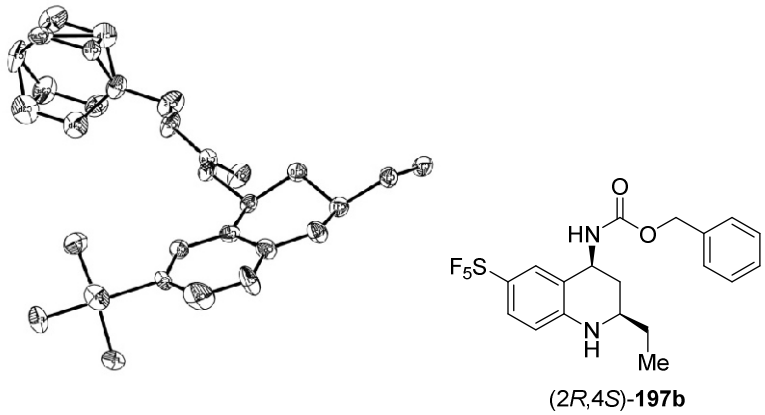


Figure 10.3: X-Ray crystal structure of 6-SF_5 tetrahydroquinoline **197b**, revealing *cis*-configuration.

This is in accordance with previous observations.[137,227] As expected, the geometry around the sulfur atom is pseudooctahedral. The SF_5-substituent has a square pyramid structure and is highly sterically demanding. The benzyl side chain is disordered and both components are present with the same occupation numbers.

Subsequent reactions in order to protect the amine in 1-position with an ethylcarbamoyl group by using different bases such as pyridine and DBU remained unsuccessful. These findings can be explained by the high electron deficiency resulting from the 6-SF_5 substituent and the sterical hindrance by the ethyl group, which already had been troublesome in the previous synthesis of torcetrapib.[137]

10.3 Summary

Unprecedented 6-SF_5 tetrahydroquinolines have been synthesized in moderate yields by a Povarov-type reaction. Further optimization of the reaction yield is required to improve the process. Crystal structure analysis revealed *cis*-configuration of the isolated diastereomer as compared to the parent compound torcetrapib.

11 Conclusion and Outlook

The aim of this thesis was to illuminate the chemistry and biology of sulfur-containing motifs that have been rather neglected in pharmaceuticals despite their unique attractive properties: sulfoximines, sulfilimines, and SF_5-substituted arenes.

In a first project, the development of a new *N*-cyano-based Burgess-type reagent opened up the unprecedented pathway from sulfoxides to *N*-cyanosulfilimines. Demonstrating the potential of the widely unexplored sulfoxide-to-sulfilimine conversions, a straightforward 3-step route from various sulfoxides to the synthetically valuable *N*H-sulfoximines has been developed employing a thermally stable Burgess-type reagent under mild conditions. Further mechanistic investigations into sulfoxide-to-sulfilimine conversions, explaining the observed non-stereospecificity, would be of high value for future research projects in this field. Along those lines, the stereospecific transformation of sulfoxides should be particularly explored, as it would give access to enantiomerically pure sulfilimines.

The *N*H-sulfoximines in hand, a metal-free method for their *N*-alkylation was developed overcoming the drawbacks of the known procedures regarding cost and efficiency. Mediated by KOH in DMSO, *N*-alkylations with long chain, unsaturated, and branched alkyl halides were performed in good to excellent yields. As an application the biologically active suloxifen was prepared. Of note, the new protocol was easily applicable to the rather unkown class of sulfondiimines.

The syntheses of sulfilimidoyl- and sulfoximidoyl-containing analogs of biologically active sulfones have been performed in various examples, uncovering synthetic challenges or leading to interesting bioactivity changes. In this context, the applicability of frequently used and rather novel protocols in different functional and structural environments was evaluated.

Analogs of ATR inhibitor VE-821 have been prepared by using a well-known metal-free protocol for the imination of a heterocycle-containing sulfide. The new sulfilimines and sulfoximines showed high inhibitory potency and selectivity for ATR in the corresponding biological tests by our collaborators, demonstrating the value of such derivatives as potential anti-cancer drugs. Their abilities to sensitize tumor cells to DNA damaging agents should be further explored.

The syntheses of sulfilimine and sulfoximine derivatives of ATPase inhibitor BTB06584, containing a base-labile ester bond, and the anti-ulcer drug zolimidine, bearing an imidazo[1,2-α]pyridine moiety, showed that imination-oxidation sequences can be troublesome in the presence of sensitive backbones. While iminations of the sulfides to sulfilimines performed well, employing established protocols in case of ATPase inhibitor analogs or light-promoted imination in case of zolimidine derivatives, decomposition was observed upon oxidation. Sulfoximines were prepared by iminations of the corresponding sulfoxides by using either a new rhodium-catalyzed protocol to obtain the *N*H-sulfoximine directly in case of the ATPase inhibitor analog or light-promoted

imination in case of zolimidine derivatives. Hence, milder oxidation methods for sulfilimines and a broader choice of mild and neutral imination protocols for both sulfides and sulfoxides appear desirable. Future biological studies on the new analogs are of high interest.

Analogs of 4-(*N*-indolyl)phenyl methyl sulfone, a potent COX-2 inhibitor were synthesized by Buchwald–Hartwig couplings of *S*-4-bromophenyl sulfoximines and indole, revealing the necessity of *N*-protecting groups under those conditions. All enantiomers of the prepared *N*-cyano-, *N*H-, and *N*-methylsulfoximines proved potent, but were mostly non-selective in COX-2-inhibition tests by our collaborators. Unexpectedly, (+)-*N*-methylsulfoximine inhibited highly selectively COX-1, arousing interest in studying the structure-activity relationship.

The straight-forward synthesis and derivatization of *N*H 4-SF_5-phenyl methyl sulfoximine illustrates the connection between the two fields of research explored in this thesis and led to a useful building block showing high stability in acidic and superbasic media. Moreover, two projects covered the CF_3-to-SF_5 exchange in flufenamic acid and in the 1,2,3,4-tetrahydroquinoline core of torcetrapib.

The synthesis of SF_5-containing flufenamic acid analogs provided insights into conformational and biological property changes resulting from the exchange of CF_3 by SF_5. Remarkably, one of the new compounds was an 8-fold more potent activator of the ion channel rBASIC than flufenamic acid. To benefit from this strong effect, further investigations into the modulation of various ion channels should be performed. Of note, two of the prepared SF_5 analogs showed high potency and selectivity for AKR1C3, a target in the treatment of castration resistant prostate cancer. Hence, their potential as anti-cancer drugs should be studied in detail, evaluating the benefit of the SF_5 group.

Unprecedented 6-SF_5 1,2,3,4-tetrahydroquinolines were synthesized, and crystal structure analysis of one analog revealed its *cis*-configuration. Of note, the electron withdrawing SF_5 group involved deactivation of the tetrahydroquinoline system, preventing further modifications at the 1-*N*H group. Thus, a general study on the syntheses and substitutions of SF_5-containing tetrahydroquinolines is required.

Straight-forward routes from sulfoxides to sulfoximines and for the *N*-alkylation of *N*H-sulfoximines have been developed as tools for future syntheses and functionalizations. The incorporations of sulfoximidoyl, sulfilimidoyl and SF_5 groups into various biologically active molecules showed that there is more need for mild and neutral imination and oxidation methods, tolerating functional groups. The synthesized sulfoximines, sulfilimines, and SF_5-containing bioactives demonstrated potency and selectivity in many examples. Hence, these functionalities should always be considered as alternatives to the well-established sulfones and trifluoromethyl groups in future investigations.

12 Experimental Part

12.1 General Information

12.1.1 Techniques

Air-free technique

All reactions sensitive to air or humidity were performed in flame-dried Schlenk flasks flushed with argon. Septums were used and fluids were added by using syringes with one-way needles or V2A steel cannulas.

Microwave

Reactions under microwave irradiation were conducted with a discover® microwave LabMate from CEM featuring an IntelliVent™ Pressure Control System and Synergy™ software. The reaction mixtures were prepared in appropriate glass vessels with a stirring bar.

Ball mill

For the ball milling reactions, a planetary micromill model from Fritsch, Pulverisette 7 was used. The instrument consists of a main disk rotating with a speed of 100-800 rpm, and accomodating two bead containers. The containers (12 mL) as well as the ball mill beads (5 mm diameter) are made of chemically inert and nonabrasive zirconium dioxide. The milling cycles were programmed including a milling and a pause time. The cycles were repeated several times. In each container 20 beads were used.

12.1.2 Solvents and chromatography

Solvents

Drying and purification of solvents was performed by standard techniques.[229] THF and toluene were dried by refluxing over sodium/benzophenone and distillation, CH_2Cl_2 by refluxing over $CaCl_2$ and distillation. Futher dry solvents were purchased from Acros.

Reagents

Sulfuryl chloride was distilled under argon; *N*-methylpiperidine and triethylamine were stored over KOH and subsequently distilled under argon. The other reagents were purchased from commercial suppliers and used without further purification.

Thin layer chromatography

All product mixtures were analyzed by using aluminium foil TLC plates with a fluorescent indicator from Merck. UV active compounds were detected with a UV lamp (λ = 254 nm). Potassium permanganate and ninhydrin solutions were used as staining reagents.

Column chromatography

Glass columns with different sizes were applied, depending on the separation and amount of product mixture. Silica gel (grain size 0.035 – 0.070 mm) from Acros was used as stationary phase. In each case the best eluent was determined by TLC chromatography.

Analytical HPLC

The enantiomeric excess was determined by high performance liquid chromatography (HPLC) with an Agilent 1100 or 1200 series with chiral stationary phases from Chiral Technologies Inc. To identify the enantiomers, the HPLC retentiontimes of the racemates were used.

Preparative HPLC

Preparative HPLC separations were performed with a Varian SD-1 (ProStar 320) with different chiral stationary phases.

Preparative SFC

Preparative supercritical fluid chromatography (SFC) separations were performed with a Thar-SFC Prep 80 (UV) from Waters equipped with a Regispack AD-H column (250 x 20 mm). Analytical chromatograms were recorded with a Method Station II from Thar/Waters equipped with a Regispack AD-H column (250 x 4.6 mm).

12.1.3 Analytics

NMR spectroscopy

^{1}H NMR, ^{13} C NMR and ^{19}F NMR spectra were recorded with a Varian V-NMRS 600, a Varian V-NMRS 400, or a Varian Mercury 300 spectrometer, in different deuterated solvents at 25 °C. Chemical shifts (δ) are reported in ppm relative to the solvent residual peaks ($CDCl_3$, δ = 7.26 ppm, DMSO-d_6, δ = 2.50 ppm, acetone-d_6, δ = 2.05 ppm, MeOH-d_4, δ = 3.31 ppm) and spin-spin coupling constants (*J*) are given in Hz, multiplicities are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), and m (multiplet).

IR spectroscopy

The IR-Spectra were recorded with a Bruker TENSOR 27 FT-IR spectrophotometer (KBr) or a PerkinElmer 100 FT-IR Spectrum spectrometer (neat). The wave numbers of the caracteristic absorption peaks are reported in cm^{-1}.

MS spectroscopy

Mass spectra (MS) were recorded with a Finnigan SSQ 7000 spectrometer (EI, 70 eV; CI, 100 eV). The atomic mass of the molecular ion and the fragments per elementary charge are reported as dimensionless quantities. The intensities are given in percent relative to the base peak. For high resolution mass (HRMS) spectra a Thermo Fisher Scientific LTQ Orbitrap XL spectrometer (electrospray ionisation (ESI)) was used. The resulting signals

are given according to their *m/z* values and their relative intensity is reported in parenthesis.

Elementary analysis

The elementary analysis measurements were performed with a Vario EL machine from Elementar. The values are reported in weight percent. The compounds were considered to be pure when Δ (C, H, N) ≤ 0.4.

Melting points

To determine the melting points with open capillaries, a machine Melting Point B-540 from Büchi was used.

Optical rotation

Optical rotation was measured with a PerkinElmer model 241 polarimeter (20 °C, λ = 589 nm).

12.2 General Procedures

12.2.1 Syntheses of *N*-cyano Burgess-type reagents (GP1)

To a solution of cyanamide (3.0 g, 71.4 mmol) in dry MeOH (30 mL) a solution of sodium methoxide (0.5 M MeOH solution, 143 mL, 71.4 mmol) was added dropwise over 20 min. After stirring for 2 h at r.t. the solvent was removed under reduced pressure and sodium hydrogen-cyanamide[230] (4.3 g, 94%) was obtained as a white solid. ^{1}H-NMR (400 MHz, MeOH-d_4): δ = 5.95 (s, 1H); ^{13}C-NMR (100 MHz, MeOH-d_4): δ = 118.6. Freshly destilled sulfuryl chloride (0.19 mL, 2.34 mmol) was added dropwise to a solution of sodium hydrogencyanamide (300 mg, 4.7 mmol) in THF (2.3 ml) at –20 °C.[231] After stirring for 2 h at –20 °C the suspension was added dropwise to a solution of the corresponding tertiary amine (5.8 mmol) in THF (1.3 mL) cooled to –20 °C. After stirring for 2 h at –20 °C the solvent was removed under reduced pressure at 30 °C and the product was purified by aqueous extraction or column chromatography, respectively.

12.2.2 Syntheses of sulfoxides (GP2)

Syntheses of sulfides from thiols:[232] to a solution of sodium hydroxide (1.5 equiv.) in dry EtOH (1.2 mL/mmol) thiol (1 equiv.) was added and the reaction mixture was stirred for 30 min. Methyl iodide (1.5 equiv.) was added dropwise and the solution was stirred for 3 h at r.t.. The reaction was quenched by the addition of ice-cold water. After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed with brine (2 x 20 mL) and dried with anhydrous magnesium sulfate. The solvent was removed under reduced pressure to yield the product that was directly used in the next step.

Syntheses of sulfoxides from sulfides:[28] a solution of sulfide (1.0 equiv.) in CH_2Cl_2 (12 mL/mmol) was cooled to 0 °C. After addition of *m*CPBA (ca. 70%; 1.3 equiv.) the solution was stirred for 16 h. The reaction mixture was washed with aq saturated Na_2CO_3 solution (50 mL), dried with anhydrous magnesium sulfate and the solvent was

removed under reduced pressure. The product was purified by flash chromatography on silica gel using a mixture of *n*-pentane and acetone to afford the product.

12.2.3 Syntheses of *N*-cyanosulfilimines from sulfoxides (GP3)

To a solution of sulfoxides (1 equiv.) in THF (4.7 mL/mmol) and CH_2Cl_2 (4.7 mL/mmol) reagent **107b** (2 equiv.) was added. The reaction mixture was subjected to microwave irradiation for 40 min at 40 °C. After evaporation of the solvent the product was purified by flash chromatography on silica gel using a mixture of EtOH and *n*-pentane. For further purification the product was dissolved in CH_2Cl_2 (10 mL) and washed with brine (3 x 3 mL). Drying with anhydrous magnesium sulfate and evaporation of the solvent under reduced pressure afforded the product.

12.2.4 Oxidations of *N*-cyanosulfilimines with *m*CPBA (GP4)

A solution of *N*-cyanosulfilimine (1 equiv.) in EtOH or MeOH (10 mL/mmol) and cooled to 0 °C. *m*CPBA (ca. 70%; 2.5 equiv. or 1.5 equiv.) and K_2CO_3 (5 or 3 equiv.) were added and the reaction mixture was stirred at r.t. until the conversion was complete (monitored by TLC). [49] The solvent was removed under reduced pressure, H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. Purification by flash chromatography afforded the pure product.

12.2.5 Syntheses of *N*-(2,2,2-trifluoroethyloxycarbonyl) sulfilimines (GP5)

To a solution of sulfoxide (1 equiv.) in dry THF (5 mL/mmol) was added reagent **52** (2 equiv.). The reaction mixture was stirred under reflux for 2 h. The solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (EtOH/*n*-pentane 1:10).

12.2.6 Syntheses of *N*-(2,2,2-trifluoroethyloxycarbonyl) sulfoximines (GP6)

To a solution of sulfilimines **111** (1 equiv.) in acetonitrile/water (1:2, 32 mL/mmol) was added sodium periodate (5 equiv.). After complete dissolution $RuCl_3 \cdot 4\ H_2O$[56] (7 mg, catalytic amount) was added and the solution was stirred at r. t. for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were stirred with anhydrous magnesium sulfate and active charcoal for 10 min. The mixture was filtered through a pad of silica to remove the solids. After evaporation of the solvent under reduced pressure the product was obtained in high purity.

12.2.7 Syntheses of *N*H-sulfoximines by acidic deprotections (GP7)

A solution of sulfoximines **112** (1 equiv.) in aq 50% H_2SO_4 (10 mL/mmol) was stirred at 110 °C for 1-2 h.[60,118] The solution was cooled to 0 °C and a pH of 8-9 was adjusted by addition of aq saturated $NaHCO_3$ solution and aq conc NaOH solution. The solution was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to afford the product generally in high purity. Otherwise the purification by column chromatography provided the pure product.

12.2.8 *N*-Alkylations of *N*H-sulfoximines with KOH in DMSO (GP8)

To an argon-flushed Schlenk tube was added *N*H-sulfoximine (1 equiv.) and potassium hydroxide (2 equiv.). The mixture was dissolved in DMSO (1.5 mL/mmol) and stirred for 5 min. Alkyl bromide (1.5 equiv.) was added, and the reaction mixture was stirred for 3-6 h at r. t.. Water (6 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were dried with anhydrous magnesium sulfate, and the solvents were removed under reduced pressure. Finally, the product was purified by flash column chromatography.

12.2.9 Suzuki-couplings with $Pd(PPh_3)_2Cl_2$ (GP9)

To a mixture of 3-amino-6-bromopyrazine (1 equiv.), 4-(methylthio)phenylboronic acid (1.2 equiv.) and bis(triphenylphosphine)palladium(II) dichloride (5 mol%) was added degassed aqueous 2 M Na_2CO_3 solution (3 equiv. Na_2CO_3) and degassed dimethoxyethane (3 mL/mmol).[179] After stirring the reaction mixture under microwave irradiation for 60 min at 120 °C, the mixture was filtered through a paper filter and washed with AcOEt. The solvents were removed under reduced pressure and subsequent purification by flash column chromatography yielded the product.

12.2.10 Syntheses of *N*-cyanosulfilimines from sulfides with cyanamide, *t*-BuOK and NBS (GP10)

A mixture of sulfide (1 equiv.), cyanamide (1.3 equiv.), *t*-BuOK (1.2 equiv.) and MeOH (6 mL/ mmol) was cooled to 0 °C. NBS (1.5 equiv.) was added and the reaction mixture was stirred at r. t. until the conversion was complete (monitored by TLC).[49] Water was added and the aqueous phase was extracted with CH_2Cl_2. After purification by column chromatography the product was obtained.

12.2.11 Syntheses of *N*-cyanosulfilimines from sulfides with cyanamide and PIDA (GP11)

A mixture of sulfide (1 equiv.) and cyanamide (1.5 equiv.) was dissolved in dry acetonitrile (3.3 mL/mmol). PIDA (1.1 equiv.) was added, and the reaction mixture was stirred at r. t. for 1-2 h.[59] The solvent was removed under reduced pressure and the product was purified by flash column chromatography.

12.2.12 Iminations with 2,2,2-trifluoroacetamide (GP12)

A mixture of sulfide or sulfoxide (1 equiv.), 2,2,2-trifluoroacetamide (2 equiv.), magnesium oxide (4 equiv.) and $Rh_2(OAc)_4$ (2.5 mol%) in CH_2Cl_2 (10 mL/ mmol) was added PIDA (1.5 equiv.).[48] The reaction mixture was stirred at r. t. for 2 h. After removing the solvent under reduced pressure and by subsequent purification by column chromatography (AcOEt/*n*-pentane 5:1 to 1:1) the product was obtained.

12.2.13 Sulfoxidations with hydrogen peroxide and acetic acid (GP13)

To a mixture of sulfide (1 equiv.) and acetic acid (5 mL/mmol) at 0 °C was added aq 30% hydrogen peroxide solution (0.5 mL/mmol).[27] When the solubility of the sulfide was insufficient, CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at r. t. for 18 h. Water was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. After purification by column chromatography the product was obtained.

12.2.14 Deprotections with potassium carbonate in MeOH (GP14)

A mixture of *N*-(2,2,2-trifluoroacetyl) sulfilimine or sulfoximine (1 equiv.), K_2CO_3 (5 equiv.) and MeOH (3 mL/mmol) was stirred at r.t. until the conversion was complete.[49] After removing the solvent under reduced pressure, purification by column chromatography afforded the product.

12.2.15 *N*-Methylations of *N*H-sulfoximines (Eschweiler-Clark) (GP15)

A solution of *N*H-sulfoximine (1 equiv.), formaldehyde (5 equiv.) and formic acid (8.8 mL/mmol) was stirred in a closed vial at 150 °C for 16 h.[84b] After cooling down to r.t. water was added and the reaction mixture was extracted with CH_2Cl_2. The combined organic phases were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure and the product was purified by column chromatography.

12.2.16 Buchwald–Hartwig couplings of indole (GP16)

A mixture of sulfoximine or sulfoxide (1 equiv.), indole (1.2 equiv.), Cs_2CO_3 (1.4 equiv.), $Pd_2(dba)_3$ (2 mol%), BINAP (4 mol%) and dry toluene (5 mL/mmol) was stirred at 110 °C for 15 h.[106] After cooling to r.t. 1N HCl was added and the aqueous phase was extracted with AcOEt. The combined organic phases were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by column chromatography provided the product.

12.2.17 Syntheses of imidazo[1,2-α]-pyridines (GP17)

To a solution of 2-aminopyridine (1 equiv.), the corresponding acetophenone (2 equiv.) and copper(I)iodide (5 mol%) in DMF (0.4 mL/mmol) was added boron $BF_3{\cdot}Et_2O$ (10 mol%).[207a] The reaction mixture was stirred under an oxygen atmosphere (atmospheric pressure) at 60 °C for 16 h. Subsequently, the reaction mixture was added to aq saturated Na_2CO_3 solution and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by column chromatography afforded the product.

12.2.18 Light-promoted iminations of sulfides and sulfoxides (GP18)

To a solution of sulfide or sulfoxide (1 equiv.) and 3-methyl-1,4,2-dioxazol-5-one (1 equiv.) in dry toluene under argon was added Ru(TPP)CO.[65a] After stirring at r.t.

under irradiation with a 125 W high-pressure mercury lamp the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the corresponding sulfilimine or sulfoximine, respectively.

12.2.19 *N*-Arylations of *N*H-sulfoximines (GP19)

A flame-dried and argon-flushed Schlenk tube was charged with sulfoximine (1 equiv.), aryl iodide (2 equiv.), CuI (10 mol%), DMEDA (20 mol%) and Cs_2CO_3 (2.5 equiv.).[104a] Anhydrous toluene (1 mL/mmol) was added and the reaction mixture was stirred at 110 °C. Water was added and the reaction mixture was neutralized by addition of 1 N HCl. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure.

12.2.20 Buchwald–Hartwig couplings of pentafluorosulfanyl aniline (GP20)

A flame-dried and argon-flushed Schlenk tube was charged with methyl bromobenzoate (1 equiv.), pentafluorosulfanyl aniline (1.2 equiv.), Cs_2CO_3 (1.4 equiv.), BINAP (8 mol%), $Pd(OAc)_2$ (5 mol%) and dry toluene (10 mL/mmol). The reaction mixture was stirred at 110 °C for 18 h.[138b] AcOEt (5 mL) was added, and the mixture was washed with 1 N HCl solution (2 x 10 mL) and brine (10 mL). The combinded organic phases were dried with anhydrous magnesium sulfate and the product was purified by column chromatography (acetone/*n*-pentane 1:20).

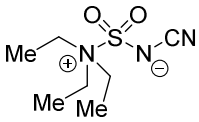
12.2.21 Saponifications of the methyl esters (GP21)

A mixture of methyl ester (1 equiv.), potassium hydroxide (2 equiv.), water (10 mL/mmol) and EtOH (5.2 mL/mmol) was stirred at 100 °C for 2 h.[138b] The reaction mixture was cooled to r.t. and the solvent was removed under reduced pressure. The pH was adjusted to 2 by addition of 1 N HCl solution. The precipitate was filtered off, washed with water (5 mL) and dried under reduced pressure.

12.3 Synthetic Procedures

12.3.1 Syntheses of Burgess-type reagents, sulfoxides, sulfilimines, and sulfoximines

N,*N*-Diethyl-*N*-(cyanamino)sulfonyl-ethanaminium, inner salt (107a)



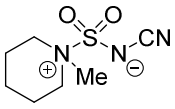
Following GP1 using freshly destilled triethylamine (0.81 mL, 5.8 mmol) provided the product as a white solid (299 mg, 62% yield) after addition of water (4 mL) and extraction with AcOEt (3 x 8 mL).

^{1}H NMR (400 MHz, MeOH-d_4): δ = 3.20 (q, J = 7.3 Hz, 6H), 1.25 (t, J = 7.3 Hz, 9H).

^{13}C NMR (100 MHz, MeOH-d_4): δ = 117.4 (CN), 46.6 (2 CH_2), 7.8 (3 CH_3).

The corresponding spectroscopic data matched that reported in the literature.[169]

N-Methyl-*N*-(cyanamino)sulfonyl-piperidinaminium, inner salt (107b)



Following GP1 using freshly destilled *N*-methylpiperidine (0.7 mL, 5.8 mmol), provided the product (370 g, 77% yield) as colorless crystals after purification by flash chromatography (AcOEt/*n*-pentane 1:4 to 3:1). Mp.: 109 – 110 °C

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.63 – 3.56 (m, 4H), 3.29 (s, 3H), 2.12 – 2.00 (m, 4H), 1.90 – 1.86 (m, 1H), 1.65 – 1.58 (m, 1H).

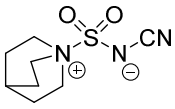
^{13}C NMR (151 MHz, acetone-d_6): δ = 114.2, 57.0, 41.9, 22.6, 21.8.

MS (EI): *m/z* (%) = 203 ([M]$^+$, 2), 99 (63), 98 (100).

IR (KBr): ν = 2962, 2199, 1459, 1348, 1221, 822.

Elemental analysis: calcd. for $C_7H_{13}N_3O_2S$: C 41.36, H 6.45, N 20.67, found: C 41.45, H 6.21, N 21.02.

N-(Cyanamino)sulfonyl-quinuclidinaminium, inner salt (107c)



Following GP1 using sulfuryl chloride (97 μL, 1.2 mmol), sodium hydrogencyanamide (154 mg, 2.4 mmol) and quinuclidine (200 mg, 1.80 mmol), provided the product (124 mg, 48% yield) as colorless crystals after purification by flash chromatography (AcOEt/*n*-pentane 3:2 to 3:1). Mp.: 182 – 184°C

^{1}H NMR (400 MHz, acetone-d_6): δ = 3.65 – 3.62 (m, 5H), 3.28 – 3.24 (m, 1H), 2.20 – 2.15 (m, 5H), 2.12 – 1.98 (m, 2H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 112.6, 50.2, 23.9, 19.5.

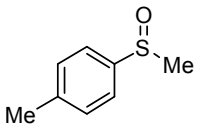
MS (EI): *m/z* (%) = 111 (100), 96 (19), 82 (52).

MS (CI): *m/z* (%) = 216 ([M+H]$^+$, 48), 192 (100), 112 (52).

IR (KBr): ν = 2199, 1464, 1352, 1213, 1150, 832.

Elemental analysis: calcd. for $C_8H_{13}N_3O_2S$: C 44.63, H 6.09, N 19.52, found: C 44.28, H 5.67, N 16.92.

Methyl *p*-tolyl sulfoxide (2a)



Following GP2 using methyl *p*-tolyl sulfide (**1a**) (1.0 g, 7.2 mmol) and *m*CPBA (2.3 g, 9.4 mmol) provided the product (1.0 g, 94% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.59 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 2.77 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, MeOH-d_4): δ = 143.3, 142.5, 131.1, 124.8, 43.3, 21.2.

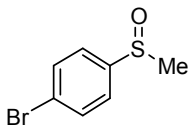
The corresponding spectroscopic data matched that reported in the literature.[233]

Synthesis of enantioenriched (*R*)-**2a**:[33b]

To a mixture of (*R*,*R*)-DET (619 mg, 3.0 mmol) in dry CH_2Cl_2 (12.5 mL) under argon at r. t. was added titanium isopropoxide (0.45 mL, 1.5 mmol), followed by the dropwise addition of distilled water (0.03 mL, 0.15 mmol). After vigorous stirring for 25 min, methyl *p*-tolyl sulfide (0.4 mL, 3.0 mmol), dissolved in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was cooled to –30 °C and stirred for 40 min. Subsequently, cumene hydroperoxide (80%, 0.55 mL, 3.0 mmol) was added and it was stirred for 2 h at −30 °C. After the addition of water (0.5 mL) and stirring at r. t. for 1 h, the reaction mixture was filtered through a pad of celite including washings with CH_2Cl_2. The filtrate was stirred with 2N NaOH solution (8 mL) for 30 min. The two phases were separated and the organic phase was dried with anhydrous magnesium sulfate and the product was purified by column chromatography (AcOEt: *n*-pentane 1:7 to AcOEt). Evaporation of the solvents afforded the product as a white solid (328 mg, 71%).

HPLC: t_r = 12.5 min [minor], t_r = 19.6 min [major] (Chiralcel OB-H column, flow rate 0.4 mL/min, heptane/*i*-PrOH = 50:50, λ = 210 nm, 20 °C); *ee* = 56%.

4-Bromophenyl methyl sulfoxide (2c)



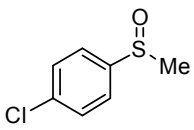
Following GP2 using 4-bromophenyl methyl sulfide (**1c**) (1.0 g, 4.9 mmol) and *m*CPBA (1.6 g, 6.4 mmol) provided the product (1.1 g, 98% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 – 7.64 (m, 2H), 7.52 – 7.50 (m, 2H), 2.71 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 107.3, 95.0, 87.8, 87.5, 6.4.

The corresponding spectroscopic data matched that reported in the literature.[233]

4-Chlorophenyl methyl sulfoxide (2d)



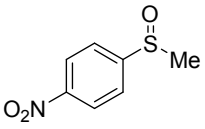
Following GP2 using 4-chlorophenyl methyl sulfide (**1d**) (1.0 g, 6.3 mmol) and *m*CPBA (2.0 g, 8.2 mmol) provided the product (1.0 g, 92% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.70 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, MeOH-d_4): δ = 145.0, 138.6, 130.9, 126.7, 43.6.

The corresponding spectroscopic data matched that reported in the literature.[233]

Methyl 4-nitrophenyl sulfoxide (2e)



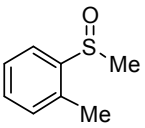
Following GP2 methyl 4-nitrophenyl sulfide (**1e**) (1.0 g, 5.9 mmol) and *m*CPBA (1.9 g, 7.7 mmol) provided the product (0.81 g, 74% yield) as a pale-yellow solid after purification by flash chromatography (acetone/*n*-pentane 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 2H), 2.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 149.5, 124.6, 124.4, 43.8.

The corresponding spectroscopic data matched that reported in the literature.[234]

Methyl *o*-tolyl sulfoxide (2f)



Following GP2, methyl *o*-tolyl sulfide (**1f**) was prepared from 2-methylbenzenethiol (1.0 g, 8.1 mmol) and methyl iodide (1.7 g, 12.1 mmol. Subsequent oxidation with *m*CPBA (2.6 g, 10.5 mmol) afforded the product (0.94 g, 75% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

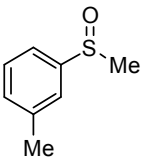
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89 (dd, J = 7.8, 1.4 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.32 (td, J = 7.5, 1.5 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 2.62 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.8, 133.7, 130.5, 130.4, 127.2, 122.7, 41.9, 17.9.

The corresponding spectroscopic data matched that reported in the literature.[235]

Methyl *m*-tolyl sulfoxide (2g)

Following GP2, methyl *m*-tolyl sulfide (**1g**) was prepared from 3-methylbenzenethiol



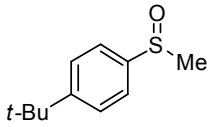
(1.0 g, 8.1 mmol) and methyl iodide (1.7 g, 12.1 mmol). Subsequent oxidation with *m*CPBA (2.6 g, 10.5 mmol) afforded the product (0.88 g, 70% yield) as a colorless liquid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 – 7.44 (m, 1H), 7.38 – 7.36 (m, 2H), 7.27 – 7.26 (m, 1H), 2.68 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 145.5, 139.6, 131.8, 129.1, 123.7, 120.6, 43.9, 21.4.

The corresponding spectroscopic data matched that reported in the literature.[236]

Methyl 4-*tert*-butylphenyl sulfoxide (2h)



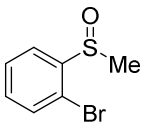
Following GP2, methyl 4-*t*-butylphenyl sulfide (**1h**) was prepared from 3-methylbenzenethiol (1.0 g, 6.0 mmol) and methyl iodide (1.3 g, 9.0 mmol). Subsequent oxidation with *m*CPBA (1.9 g, 7.8 mmol) afforded the product (0.66 g, 56% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57 – 7.51 (m, 4H), 2.70 (s, 3H), 1.32 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.6, 142.4, 126.3, 123.4, 43.9, 35.0, 31.2.

The corresponding spectroscopic data matched that reported in the literature.[237]

2-Bromophenyl methyl sulfoxide (2i)



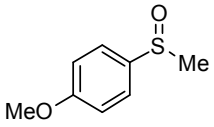
Following GP2, methyl 2-bromophenyl methyl sulfide (**1i**) was prepared from 2-bromobenzene thiol (1.0 g, 5.3 mmol) and methyl iodide (1.1 g, 7.9 mmol). Subsequent oxidation with *m*CPBA (1.7 g, 6.9 mmol) afforded the product (0.66 g, 56% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.36 – 7.33 (m, 1H), 2.79 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 145.3, 132.9, 132.2, 128.7, 125.6, 118.4, 1.9.

The corresponding spectroscopic data matched that reported in the literature.[233]

4-Methoxyphenyl methyl sulfoxide (2j)



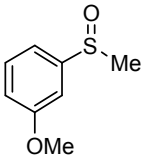
Following GP2 using 4-methoxyphenyl methyl sulfide (**1j**) (1.0 g, 6.5 mmol) and *m*CPBA (2.1 g, 8.4 mmol) provided the product (0.95 g, 86% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 2.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =151.9, 136.6, 125.4, 114.8, 55.4, 44.0.

The corresponding spectroscopic data matched that reported in the literature.[233]

3-Methoxyphenyl methyl sulfoxide (2k)



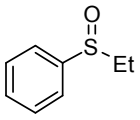
Following GP2, 3-methoxyphenyl methyl sulfide (**1k**) was prepared from 3-methoxybenzene thiol (1.0 g, 7.1 mmol) and methyl iodide (1.5 g, 10.7 mmol). Subsequent oxidation with *m*CPBA (2.3 g, 9.2 mmol) according to the general procedure afforded the product (0.79 g, 66% yield) as a colorless liquid after purification by flash chromatography (acetone/*n*-pentane 1:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.08 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H), 7.00 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 3.81 (s, 3H), 2.67 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.3, 147.0, 130.2, 117.2, 115.3, 107.7, 55.4, 43.9. The corresponding spectroscopic data matched that reported in the literature.[234]

Ethyl phenyl sulfoxide (2l)

Following GP2 using ethylphenyl sulfide (**1l**) (1.0 g, 7.2 mmol) and *m*CPBA (2.3 g, 9.4 mmol) provided the product (1.0 g, 91% yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 1:4).

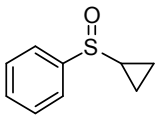


^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 – 7.53 (m, 2H), 7.49 – 7.41 (m, 3H), 2.85 (dq, *J* = 13.3, 7.5 Hz, 1H), 2.71 (dq, *J* = 13.3, 7.5 Hz, 1H), 1.14 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 130.8, 129.0, 124.0, 50.1, 5.8.

The corresponding spectroscopic data matched that reported in the literature.[233]

Cyclopropyl phenyl sulfoxide (2m)



Following GP2 using cyclopropyl phenyl sulfide (**1m**) (1.0 g, 6.7 mmol) and *m*CPBA (2.1 g, 8.7 mmol) provided the product (1.0 g, 95% yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 1:4).

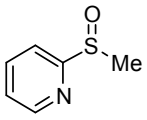
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.65 – 7.63 (m, 2H), 7.51 – 7.45 (m, 3H), 2.26 – 2.21 (m, 1H), 1.23 – 1.19 (m, 1H), 1.03 – 0.99 (m, 1H), 0.96 – 0.88 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 144.9, 130.9, 129.1, 124.0, 33.8, 3.4, 2.7.

The corresponding spectroscopic data matched that reported in the literature.[233]

Methyl 2-pyridyl sulfoxide (2n)

Following GP2 using methyl 2-pyridyl sulfide (**1n**) (1.0 g, 8.0 mmol) and *m*CPBA (2.6 g, 10.4 mmol) provided the product (1.0 g, 91% yield) as a colorless liquid after purification by flash chromatography (acetone/*n*-pentane 1:2).

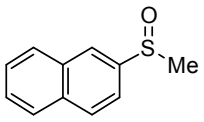


^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.61 – 8.60 (m, 1H), 8.02 – 8.01 (m, 1H), 7.95 – 7.92 (m, 1H), 7.38 – 7.35 (m, 1H), 2.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 149.5, 138.1, 124.5, 119.2, 41.3.

The corresponding spectroscopic data matched that reported in the literature.[238]

Methyl 2-naphthyl sulfoxide (2o)

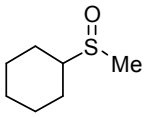


Following GP2 using methyl naphthyl sulfide (**1o**) (1.0 g, 5.7 mmol) and *m*CPBA (1.8 g, 7.5 mmol) provided the product (0.95 g, 87% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22 – 8.21 (m, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.61 – 7.58 (m, 3H), 2.79 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.7, 134.4, 132.9, 129.6, 128.5, 128.0, 127.8, 127.3, 124.0, 119.4, 43.8.
The corresponding spectroscopic data matched that reported in the literature.[239]

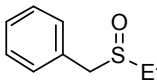
Cyclohexyl methyl sulfoxide (2p)



Following GP2 using cyclohexyl methyl sulfide (**1p**) (1.0 g, 7.7 mmol) and *m*CPBA (2.5 g, 10.0 mmol) provided the product (1.1 g, 99% yield) as a colorless oil.

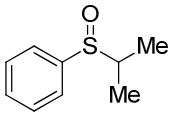
^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.40 – 2.35 (m, 4H), 2.01 – 2.98 (m, 1H), 1.82 – 1.70 (m, 3H), 1.60 – 1.57 (m, 1H), 1.43 – 1.10 (m, 5H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 60.4, 34.8, 25.7, 25.2, 25.0, 24.8, 24.4.
The corresponding spectroscopic data matched that reported in the literature.[238]

Benzyl ethyl sulfoxide (2q)



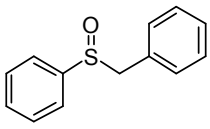
Following GP2 using benzyl ethyl sulfide (**1q**) (1.0 g, 6.6 mmol) and *m*CPBA (2.1 g, 8.5 mmol) provided the product (0.74 g, 67% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:5).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.26 (m, 5H), 4.01 (d, *J* = 12.9 Hz, 1H), 3.92 (d, *J* = 12.9 Hz, 1H), 2.66 – 2.49 (m, 2H), 1.31 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.9, 129.9, 128.9, 128.2, 57.6, 44.0, 6.6.
The corresponding spectroscopic ^{1}H-NMR data matched that reported in the literature.[240]

Isopropyl phenyl sulfoxide (2r)



Following GP2 using isopropyl phenyl sulfide (**1r**) (1.0 g, 6.6 mmol) and *m*CPBA (2.1 g, 8.5 mmol) provided the product (1.08 g, 97% yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 1:4).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.79 (m, 2H), 7.47 – 7.40 (m, 3H), 2.76 (sept, *J* = 6.9 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 130.8, 128.7, 124.8, 54.3, 15.7, 13.7.
The corresponding spectroscopic data matched that reported in the literature.[241]

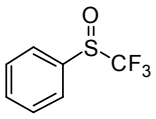
Benzyl phenyl sulfoxide (2s)



Following GP2 using benzyl phenyl sulfide (**1s**) (1.0 g, 5.0 mmol) and *m*CPBA (1.6 g, 6.5 mmol) provided the product (0.94 g, 87% yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 1:6).

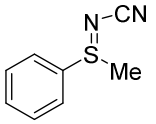
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.32 (m, 5H), 7.28 – 7.20 (m, 3H), 6.96 – 6.94 (m, 2H), 4.06 (AB-system, J = 12.6 Hz, 1H), 3.96 (AB-system, J = 12.6 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 131.1, 130.3, 129.1, 128.8, 128.4, 128.2, 124.4, 63.6.
The corresponding spectroscopic data matched that reported in the literature.[233]

Phenyl trifluoromethyl sulfoxide (2t)



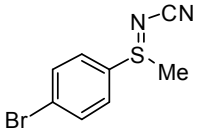
Following GP2 using phenyl trifluoromethyl sulfide (**1t**) (1.0 g, 5.6 mmol) and *m*CPBA (1.8 g, 7.3 mmol) provided the product (1.0 g, 92% yield) as a colorless liquid after purification by flash chromatography (acetone/*n*-pentane 1:30).
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 – 7.80 (d, J = 8.2 Hz, 2H), 7.67 (t, J = 7.7 Hz, 1H), 7.62 (t, J = 7.7 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 135.6, 133.5, 129.5, 125.9, 124.6 (q, $^1J_{C\text{-}F}$ = 334.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.5.
The corresponding spectroscopic data matched that reported in the literature.[242]

***N*-Cyano methyl phenyl sulfilimine (8b)**



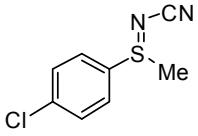
Following GP3 using sulfoxide **2b** (86 mg, 0.7 mmol) and reagent **107a** (285 mg, 1.4 mmol) provided the product (29 mg, 25% yield) as a white solid after flash chromatography (EtOH/*n*-pentane 1:3).
^{1}H NMR (400 MHz, MeOH-d_4): δ = 7.82 – 7.84 (m, 2H), 7.65 – 7.60 (m, 3H), 3.02 (s, 3H).
^{13}C NMR (100 MHz, MeOH-d_4): δ = 136.0, 132.9, 130.0, 126.0, 121.1, 35.2.
The corresponding spectroscopic data matched that reported in the literature.[59]

***N*-Cyano 4-bromophenyl methyl sulfilimine (2c)**



Following GP3 using sulfoxide **2c** (153 mg, 0.7 mmol) and reagent **107b** (285 mg, 1.4 mmol) provided the product (70 mg, 41% yield) as a white solid after flash chromatography (EtOH/*n*-pentane 1:3). Mp.: 104 – 106 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 – 7.72 (m, 2H), 7.67 – 7.65 (m, 2H), 3.01 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 133.6, 128.1, 127.4, 119.9, 36.6.
MS (EI): *m/z* (%) = 244 ($[M+H]^+$, 8), 243 ($[M]^+$, 3), 242 (7), 204 (70), 203 (100), 201 (91), 187 (56).
IR (KBr): ν = 2920, 2129, 1384, 1148, 965, 738.
HRMS (ESI): 264.9406, calcd. for $C_8H_7N_2BrNaS$: 264.9406.

N-Cyano 4-chlorophenyl methyl sulfilimine (8d)



Following GP3 using sulfoxide **2d** (122 mg, 0.7 mmol) and reagent **107b** (285 mg, 1.4 mmol) provided the product (61 mg, 44% yield) as a white solid after flash chromatography (EtOH/*n*-pentane 1:3). Mp.: 106 – 108 °C

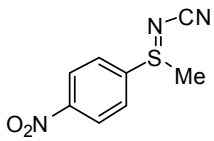
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.9 Hz, 2H), 3.01 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 134.6, 130.6, 127.3, 120.0, 36.7.

MS (EI): *m/z* (%) = 199 ([M+H]$^+$, 4), 198 ([M]$^+$, 6), 158 (56), 157 (100), 143 (49).[243]

The corresponding NMR spectroscopic data matched that reported in the literature.

N-Cyano methyl 4-nitrophenyl sulfilimine (8e)



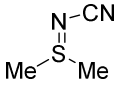
Following GP3 using sulfoxide **2e** (130 mg, 0.7 mmol) and reagent **107b** (285 mg, 1.4 mmol) provided the product (56 mg, 38% yield) as a yellow solid after flash chromatography (EtOH/*n*-pentane 3:1 and subsequently CH_2Cl_2/acetone 3:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.54 – 8.52 (m, 2H), 8.24 – 8.22 (m, 2H), 3.27 (s, 3H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 150.3, 144.2, 127.6, 124.9, 119.1, 35.8.

The corresponding spectroscopic data matched that reported in the literature.[59]

N-Cyano dimethyl sulfilimine (8u)



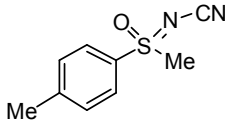
Following GP3 using dimethyl sulfoxide **2u** (80 mg, 1.02 mmol) and reagent **107b** (411 mg, 2.02 mmol) provided the product (34 mg, 33% yield) as a white solid after flash chromatography (AcOEt/*n*-pentane 3:1 to AcOEt).

^{1}H NMR (400 MHz, MeOH-d_4): δ = 2.82 (s, 6H).

^{13}C NMR (100 MHz, MeOH-d_4): δ = 120.7, 33.4.

The corresponding spectroscopic data matched that reported in the literature.[243]

N-Cyano methyl *p*-tolyl sulfoximine (9a)



Following GP3 using sulfoxide **2a** (108 mg, 0.7 mmol) and reagent **107b** (285 mg, 1.4 mmol) provided the corresponding *N*-cyanosulfilimine **8a** that was subsequently oxidized following GP4 using *m*CPBA (444 mg, 1.8 mmol) and K_2CO_3 (484 mg, 3.5 mmol) to provide the product (58 mg, 43% yield) as a white solid after flash chromatography (EtOH/*n*-pentane 1:5). Mp.: 88 – 89 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 – 7.84 (m, 2H), 7.46 – 7.44 (m, 2H), 3.30 (s, 3H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.0, 132.9, 130.9, 128.0, 112.0, 44.9, 21.7.

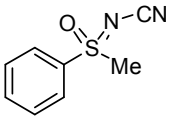
MS (EI): *m/z* (%) = 195 ([M+H]$^+$, 70), 194 ([M]$^+$, 78), 154 (60), 139 (100).

IR (KBr): ν = 3000, 2182, 1593, 1403, 1237, 1181, 813.

Elemental analysis: calcd. for $C_9H_{10}N_2OS$: C 55.65, H 5.19, N 14.42, found: C 55.35, H 5.26, N 14.37.

N-Cyano methyl phenyl sulfoximine (9b)

Following GP3 using sulfoxide **2b** (126 mg, 0.9 mmol) and reagent **107b** (365 mg, 1.8 mmol) provided the corresponding *N*-cyanosulfilimine **8b** that was subsequently oxidized following GP4 using *m*CPBA (554 mg, 2.3 mmol) and K_2CO_3 (622 mg, 4.5 mmol) to afford the product (65 mg, 40% yield) as a white solid after flash chromatography (EtOH/*n*-pentane 1:4).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 8.1 Hz, 2H), 3.34 (s, 3H).

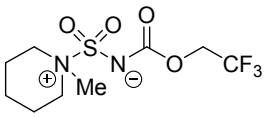
^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 135.4, 130.1, 127.7, 111.8, 44.6.

The corresponding spectroscopic data matched that reported in the literature.[59]

N-Methyl-*N*-[(2,2,2-trifluoroethyloxycarbonyl)-amino]-sulfonyl-piperidinaminium, inner salt (52)

To a solution of chlorosulfonylisocyanate (**43**) (4.0 mL, 46 mmol) in dry benzene (15 mL) was added dropwise a solution of 2,2,2-trifluoroethanol (3.4 mL, 46 mmol) in dry benzene (10 mL) at r.t. After stirring for 30 min the product was precipitated with cold hexane (40 mL), filtered and washed with cold hexane (2 x 10 mL) to afford 2,2,2-trifluoroethyl chlorosulfonylcarbamate (**110**) (10.1 g, 91% yield) as colorless crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.75 (s, 1H), 4.66 (q, *J* = 8.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 147.3, 121.5 (q, $J_{C\text{-}F}$ = 277.4 Hz), 62.9 (q, *J* = 37.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −73.9 (t, *J* = 8.0 Hz).

To a solution of freshly destilled dry *N*-methylpiperidine (5 mL) in THF (43 mL) at 0 °C under an argon atmosphere was added dropwise a solution of 2,2,2-trifluoroethyl chlorosulfonylcarbamate (8.9 g, 37 mmol) in freshly destilled dry THF (65 mL). The reaction mixture was stirred at 0 °C for 2 h. *N*-methylpiperidinium chloride was removed by filtration under an argon atmosphere. The filtrate was dried by evaporation of the solvent under reduced pressure at 30 °C under an argon atmosphere to afford the product (11.0 g, 98% yield) as a white solid.



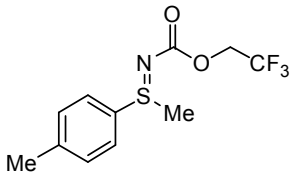
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (q, *J* = 8.5 Hz, 2H), 3.63 – 3.56 (m, 2H), 3.45 – 3.41 (m, 2H), 3.13 (s, 3H), 1.98 – 1.76 (m. 5H), 1.54 – 1.43 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 121.3 (q, $J_{C\text{-}F}$ = 277.8 Hz), 61.9 (q, *J* = 36.1 Hz), 54.8, 40.1, 21.4, 20.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = −73.9 (t, *J* = 8.5 Hz).

The corresponding spectroscopic data matched that reported in the literature.[82]

N-(2,2,2-trifluoroethyloxycarbonyl) methyl *p*-tolyl sulfilimine (111a)



Following GP5 using sulfoxide **2a** (154 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (218 mg, 78% yield) as a white solid. Mp.: 105 – 106 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.46 – 4.38 (m), 2.83 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.6, 143.6, 132.2, 130.7, 126.3, 123.0 (q, $^1J_{C\text{-}F}$ = 277.7 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.9 Hz), 36.0, 21.4.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.05 (t, J = 8.7 Hz)

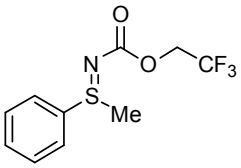
MS (EI): *m/z* (%) = 280 ([M+H]$^+$, 21), 279 ([M]$^+$, 61), 233 (100), 180 (31), 138 (71).

IR (KBr): ν = 3034, 1621, 1415, 1306, 1246, 1158, 1111, 816.

Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_2S$: C 47.31, H 4.33, N 5.02, found: C 46.94, H 4.32, N 4.98.

HPLC: t_r = 9.7 and 10.5 min (Chiralcel IA column, flow rate 0.6 mL/min, heptane/*i*-PrOH = 70:30, λ = 210 nm, 20 °C); *racemic*.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl phenyl sulfilimine (111b)



Following GP5 using sulfoxide **2b** (140 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (210 mg, 79% yield) as a white solid. Mp.: 42 – 43 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 – 7.77 (m, 2H), 7.60 – 7.54 (m, 3H), 4.48 – 4.38 (m, 2H), 2.85 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.6, 135.6, 132.7, 130.1, 124.3, 123.2 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.9 ($^2J_{C\text{-}F}$ = 36.0 Hz), 36.1.

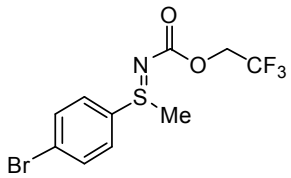
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.06 (t, J = 8.6 Hz)

MS (EI): *m/z* (%) = 266 ([M+H]$^+$, 18), 165 ([M]$^+$, 39), 219 (94), 166 (48), 124 (100).

IR (KBr): ν = 3064, 1626, 1442, 1412, 1300, 1244, 1155, 1113, 747.

Elemental analysis: calcd. for $C_{10}H_{10}F_3NO_2S$: C 45.28, H 3.80, N 5.28, found: C 45.29, H 3.60, N 5.28.

N-(2,2,2-trifluoroethyloxycarbonyl) 4-bromophenyl methyl sulfilimine (111c)



Following GP5 sulfoxide **2c** (219 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (248 mg, 72% yield) as a white solid. Mp.: 78 – 79 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 – 7.69 (m, 2H), 7.66 – 7.64 (m, 2H), 4.47 – 4.39 (m, 2H), 2.85 (s, 3H).

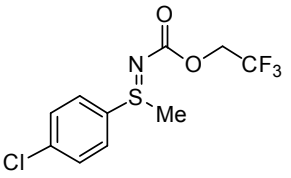
^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.5, 134.7, 133.4, 127.6, 123.0 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.9 ($^2J_{C\text{-}F}$ = 36.0 Hz), 36.0.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.08 (t, J = 8.6 Hz).

MS (EI): *m/z* (%) = 345 ([M+H]$^+$, 45), 344 ([M]$^+$, 14), 343 (42), 299 (100), 297 (96), 246 (29), 204 (64), 202 (64).

IR (KBr): ν = 3086, 1620, 1306, 1248, 1179, 1110, 820.
Elemental analysis: calcd. for $C_{10}H_9BrF_3NO_2S$: C 34.90, H 2.64, N 4.07, found: C 34.69, H 2.07, N 3.89.

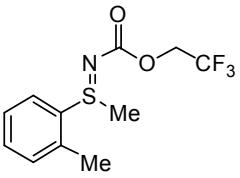
N-(2,2,2-trifluoroethyloxycarbonyl) 4-chlorophenyl methyl sulfilimine (111d)



Following GP5 using sulfoxide **2d** (175 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (213 mg, 71% yield) as a grey solid. Mp.: 82 – 84 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 4.48 – 4.37 (m, 2H), 2.85 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.5, 139.3, 134.1, 130.4, 127.7, 123.1 (q, $^1J_{C\text{-}F}$ = 277.7 Hz), 61.9 ($^2J_{C\text{-}F}$ = 35.9 Hz), 36.0.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.08 (t, J = 8.6 Hz)
MS (EI): *m/z* (%) = 300 ([M+H]$^+$, 21), 299 ([M]$^+$, 50), 253 (100), 200 (39), 158 (92).
IR (KBr): ν = 3033, 2961, 1617, 1572, 1415, 1307, 1247, 1107, 823.
Elemental analysis: calcd. for $C_{10}H_9ClF_3NO_2S$: C 40.08, H 3.03, N 4.67, found: C 40.21, H 3.00, N 4.59.

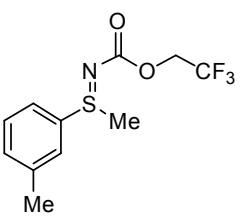
N-(2,2,2-trifluoroethyloxycarbonyl) methyl *o*-tolyl sulfilimine (111f)

Following GP5 using sulfoxide **2f** (154 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (201 mg, 72% yield) as a white solid. Mp.: 44 – 46 °C.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97 – 7.96 (m, 1H), 7.45 – 7.43 (m, 2H), 7.28 – 7.27 (m, 1H), 4.47 – 4.38 (m, 2H), 2.79 (s, 3H), 2.58 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.4, 137.0, 134.4, 132.3, 131.3, 128.2, 125.2, 122.8 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.9 Hz), 34.8, 18.8.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.08 (t, J = 8.7 Hz)
MS (EI): *m/z* (%) = 280 ([M+H]$^+$, 34), 279 ([M]$^+$, 37), 180 (19), 138 (38), 137 (100).
IR (KBr): ν = 2965, 1648, 1412, 1302, 1246, 1165, 1116, 976.
Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_2S$: C 47.31, H 4.33, N 5.02, found: C 46.96, H 4.25, N 4.97.

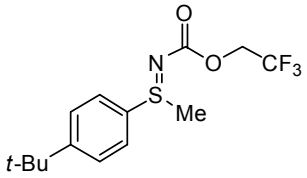
N-(2,2,2-trifluoroethyloxycarbonyl) methyl *m*-tolyl sulfilimine (111g)



Following GP5 using sulfoxide **2g** (154 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (176 mg, 63% yield) as a white solid. Mp.: 36 – 38 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.59 (br s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 4.47 – 4.39 (m, 2H), 2.84 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.6, 140.6, 135.3, 133.5, 129.8, 126.4, 123.6 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 123.4, 61.7 ($^2J_{C\text{-}F}$ = 35.9 Hz), 36.0, 21.3.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.06 (t, J = 8.7 Hz)
MS (EI): *m/z* (%) = 280 ([M+H]$^+$, 100), 279 ([M]$^+$, 71), 233 (55), 180 (46), 138 (83).
IR (KBr): ν = 2962, 1628, 1412, 1293, 1239, 1155, 1115, 964.
HRMS (ESI): 302.0432, calcd. for $C_{11}H_{12}O_2NF_3NaS$: 302.0433.

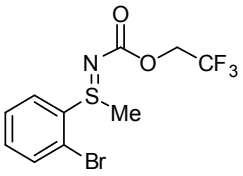
N-(2,2,2-trifluoroethyloxycarbonyl) *p*-*t*-butylphenyl methyl sulfilimine (111h)



Following GP5 using sulfoxide **2h** (196 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (225 mg, 70% yield) as a white solid. Mp.: 134 – 136 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 – 7.69 (m, 2H), 7.58 – 7.55 (m, 2H), 4.45 – 4.40 (m, 2H), 2.85 (s, 3H), 1.33 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 156.6, 132.1, 127.2, 126.2, 123.2 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.9 Hz), 35.9, 35.1, 31.0.
^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.07 (t, J = 8.7 Hz).
MS (EI): *m/z* (%) = 322 ([M+H]$^+$, 84), 321 ([M]$^+$, 60), 306 (100), 222 (14), 165 (21).
IR (KBr): ν = 2962, 1633, 1407, 1299, 1244, 1156, 1113, 834.
Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_2S$: C 52.32, H 5.65, N 4.36, found: C 52.14, H 5.53, N 4.34.

N-(2,2,2-trifluoroethyloxycarbonyl) 2-bromophenyl methyl sulfilimine (111i)

Following GP5 using sulfoxide **2i** (219 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (127 mg, 37% yield) as a white solid. Mp.: 134 – 136 °C.

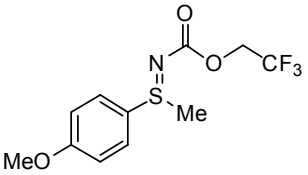


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 (dd, J = 8.0, 1.1 Hz, 1H), 7.58 (td, J = 7.5, 1.2 Hz, 1H), 7.44 (td, J = 7.5, 1.2 Hz, 1H), 4.49 – 4.43 (m, 2H), 2.90 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.4, 136.0, 133.7, 133.6, 129.2, 127.0, 123.3 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 121.2, 61.9 ($^2J_{C\text{-}F}$ = 36.0 Hz), 35.0.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.08 (t, J = 8.7 Hz).
MS (EI): *m/z* (%) = 345 ([M+H]$^+$, 9), 344 ([M]$^+$, 5), 343 (8), 264 (100), 249 (22), 218 (20), 202 (21).
IR (KBr): ν = 2967, 1653, 1413, 1303, 1246, 1166, 1117, 978.
HRMS (ESI): 343.9558, calcd. for $C_{10}H_{10}O_2NBrF_3S$: 343.9562.

N-(2,2,2-trifluoroethyloxycarbonyl) 4-methoxyphenyl methyl sulfilimine (111j)

Following GP5 using sulfoxide **2j** (170 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (222 mg, 75% yield) as a white solid. Mp.: 84 – 85 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 4.46 – 4.87 (m, 2H), 3.85 (s, 3H), 2.83 (s, 3H).



^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.2, 128.5, 126.0, 124.3 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.9 Hz), 55.7, 36.0.

^{19}F NMR (564 MHz, $CDCl_3$): δ = −74.05 (t, J = 8.7 Hz).

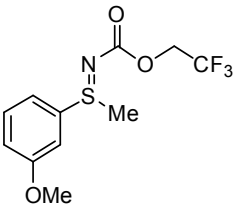
MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 15), 295 ([M]$^+$, 60), 248 (69), 196 (25), 181 (38), 154 (100), 139 (87), 123 (43).

IR (KBr): ν = 2969, 1625, 1589, 1500, 1410, 1299, 1247, 1154, 1110, 825.

Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_3S$: C 44.74, H 4.10, N 4.74, found: C 44.70, H 3.91, N 4.68.

N-(2,2,2-trifluoroethyloxycarbonyl) 3-methoxyphenyl methyl sulfilimine (111k)

Following GP5 using sulfoxide **2k** (170 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (239 mg, 81% yield) as a white solid. Mp.: 59 – 61 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (t, J = 8.3 Hz, 1H), 7.31 – 7.29 (m, 2H), 7.10 – 7.07 (m, 1H), 4.44 (q, J = 8.7 Hz, 2H), 3.85 (s, 3H), 2.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 160.8, 136.9, 131.0, 123.3 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 119.0, 118.3, 110.5, 62.0 ($^2J_{C\text{-}F}$ = 35.8 Hz), 55.7, 36.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = −75.00 (t, J = 8.7 Hz).

MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 28), 295 ([M]$^+$, 100), 249 (86), 196 (25), 154 (51).

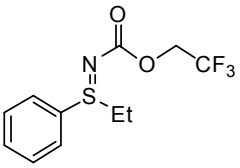
IR (KBr): ν = 2952, 1625, 1422, 1299, 1241, 1148, 1115, 955.

Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_3S$: C 44.74, H 4.10, N 4.74, found: C 44.50, H 4.02, N 4.74.

N-(2,2,2-trifluoroethyloxycarbonyl) ethyl phenyl sulfilimine (111l)

Following GP5 using sulfoxide **2l** (154 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (218 mg, 78% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.75 – 7.74 (m, 2H), 7.59 – 7.53 (m, 3H), 4.49 – 4.40 (m, 2H), 3.15 (dq, J = 13.0, 7.4 Hz, 1H), 3.06 (dq, J = 13.0, 7.4 Hz, 1H), 1.26 (t, J = 7.4 Hz, 3H).



^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.9, 133.6, 132.6, 129.9, 126.9, 123.2 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.8 Hz), 45.4, 7.8.

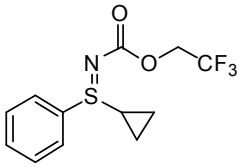
^{19}F NMR (564 MHz, $CDCl_3$): δ = −74.04 (t, J = 8.7 Hz)

MS (EI): *m/z* (%) = 280 ([M+H]$^+$, 58), 279 ([M]$^+$, 98), 251 (68), 219 (100), 180 (50), 151 (61), 109 (72).

IR (KBr): ν = 2973, 1653, 1409, 1303, 1245, 1166, 1117, 753.

HRMS (ESI): 302.0432, calcd. for $C_{11}H_{12}O_2NF_3NaS$: 302.0433.

N-(2,2,2-trifluoroethyloxycarbonyl) cyclopropyl phenyl sulfilimine (111m)



Following GP5 using sulfoxide **2m** (166 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (210 mg, 72% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78 – 7.77 (m, 2H), 7.57 – 7.51 (m, 3H), 4.46 – 4.39 (m, 2H), 2.56 – 2.51 (m, 1H), 1.38 – 1.34 (m, 1H), 1.10 – 1.07 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.0, 135.4, 132.4, 129.8, 126.6, 123.9 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.8 Hz), 29.2, 5.3, 4.9.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, J = 8.7 Hz).

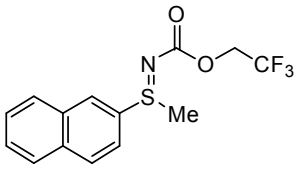
MS (EI): *m/z* (%) = 292 ([M+H]$^+$, 87), 291 ([M]$^+$, 100), 250 (36), 192 (37), 150 (67), 109 (52).

IR (KBr): ν = 2963, 1652, 1445, 1410, 1301, 1243, 1165, 1115, 841.

HRMS (ESI): 292.0614, calcd. for $C_{12}H_{13}O_2NF_3S$: 292.0614.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl 2-naphthyl sulfilimine (111o)

Following GP5 using sulfoxide **2o** (190 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (220 mg, 70% yield) as a white solid. Mp.: 48 – 50 °C



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.32 (m, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.91 (dd, J = 20.8, 7.9 Hz, 2H), 7.76 (dd, J = 8.7, 1.9 Hz, 1H), 7.65 – 7.59 (m, 2H), 4.49 – 4.41 (m, 2H), 2.92 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.7, 135.0, 132.8, 132.2, 130.7, 128.8, 128.7, 128.1, 127.9, 127.8, 123.3 (q, $^1J_{C\text{-}F}$ = 277.9 Hz), 120.8, 61.9 ($^2J_{C\text{-}F}$ = 35.9 Hz), 36.0.

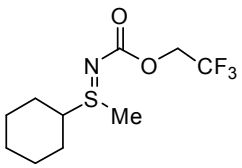
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.01 (t, J = 8.7 Hz).

MS (EI): *m/z* (%) = 316 ([M+H]$^+$, 45), 315 ([M]$^+$, 100), 269 (45), 174 (53), 115 (35).

IR (KBr): ν = 2925, 1649, 1414, 1301, 1245, 1165, 1116, 975.

Elemental analysis: calcd. for $C_{14}H_{12}F_3NO_3S$: C 53.33, H 3.84, N 4.44, found: C 53.01, H 3.97, N 4.49.

N-(2,2,2-trifluoroethyloxycarbonyl) cyclohexyl methyl sulfilimine (111p)



Following GP5 using sulfoxide **2p** (146 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (217 mg, 80% yield) as a white solid. Mp.: 64 – 65 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.43 (dq, J = 8.7, 1.5 Hz, 2H), 2.94 (tt, J = 11.4, 3.6 Hz, 1H), 2.59 (s, 3H), 2.14 – 2.11 (m, 1H), 2.01 – 1.99 (m, 1H), 1.92 – 1.88 (m, 2H), 1.71 – 1.69 (m, 1H), 1.49 – 1.42 (m, 2H), 1.40 – 1.32 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.3, 123.3 (q, $^1J_{C\text{-}F}$ = 277.8 Hz), 61.7 ($^2J_{C\text{-}F}$ = 35.8 Hz), 57.7, 28.0, 26.5, 26.3, 25.1, 25.0.

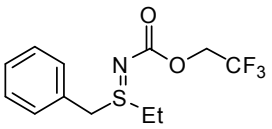
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.06 (t, J = 8.7 Hz).

MS (EI): *m/z* (%) = 272 ([M+H]$^+$, 3), 271 ([M]$^+$, 1), 189 (46), 144 (27), 83 (33).

IR (KBr): ν = 2935, 1642, 1412, 1295, 1236, 1157, 1107, 959, 828.

Elemental analysis: calcd. for $C_{10}H_{16}F_3NO_2S$: C 44.27, H 5.94, N 5.16, found: C 44.04, H 5.96, N 5.11.

N-(2,2,2-trifluoroethyloxycarbonyl) benzyl ethyl sulfilimine (111q)



Following GP5 using sulfoxide **2q** (168 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded the product (199 mg, 68% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40 – 7.39 (m, 3H), 7.33 – 7.31 (m, 2H), 4.52 – 4.39 (m, 2H), 4.43 (d, *J* = 13.0 Hz, 1H), 4.07 (d, *J* = 13.0 Hz, 1H), 2.86 – 2.78 (m, 2H), 1.34 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.2, 130.2, 129.3, 129.3, 128.1, 122.8 (q, $^1J_{C\text{-}F}$ = 277.9 Hz), 61.8 ($^2J_{C\text{-}F}$ = 35.8 Hz), 51.3, 38.3, 7.7.

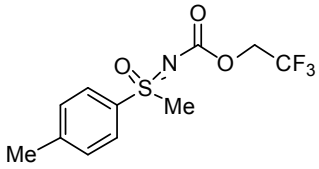
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.08 (t, *J* = 8.7 Hz).

MS (EI): *m/z* (%) = 293 ([M]$^+$, 1), 232 (4), 194 (2), 91 (100), 65 (13).

IR (KBr): ν = 2973, 1649, 1409, 1303, 1246, 1165, 1116, 983.

HRMS (ESI): 316.0588, calcd. for $C_{12}H_{14}O_2NF_3NaS$: 316.0589.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl *p*-tolyl sulfoximine (112a)



Following GP6 using sulfilimine **111a** (139 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (146 mg, 99% yield) as a white solid.

Mp.: 75 – 76 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 4.41 (dq, *J* = 8.5, 3.0 Hz, 2H), 3.31 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.2, 145.6, 134.4, 130.5, 127.3, 122.9 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.7 ($^2J_{C\text{-}F}$ = 36.3 Hz), 44.6, 21.6.

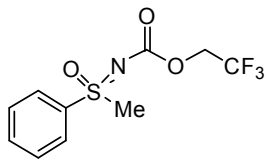
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.99 (t, *J* = 8.4 Hz).

MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 12), 295 ([M]$^+$, 5), 280 (39), 196 (54), 107 (100).

IR (KBr): ν = 2938, 1679, 1407, 1302, 1221, 1150, 1088, 956.

Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_3S$: C 44.74, H 4.10, N 4.74, found: C 45.14, H 4.11, N 4.41.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl phenyl sulfoximine (112b)



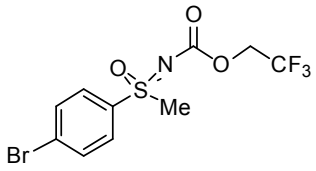
Following GP6 using sulfilimine **111b** (132 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (138 mg, 98% yield) as a white solid. Mp.: 44 – 46 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00 – 7.98 (m, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 2H), 4.44 – 4.39 (m, 2H), 3.34 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.0, 137.6, 134.3, 129.8, 127.3, 122.5 (q, $^1J_{C\text{-}F}$ = 277.5 Hz), 61.7 ($^2J_{C\text{-}F}$ = 35.3 Hz), 44.5.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, J = 8.4 Hz).
MS (EI): *m/z* (%) = 282 ([M+H]$^+$, 27), 281 ([M]$^+$, 5), 266 (100), 188 (19), 182 (98).
IR (KBr): ν = 2932, 1660, 1413, 307, 1230, 1147, 969, 743.
Elemental analysis: calcd. for $C_{10}H_{10}F_3NO_3S$: C 42.70, H 3.58, N 4.98, found: C 42.90, H 3.64, N 4.68.

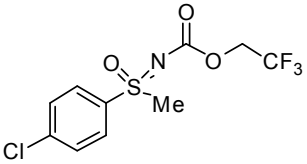
N-(2,2,2-trifluoroethyloxycarbonyl) 4-bromophenyl methyl sulfoximine (112c)



Following GP6 using sulfilimine **112c** (172 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (176 mg, 99% yield) as a white solid. Mp.: 72 – 74 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 4.45 – 4.38 (m, 2H), 3.34 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9, 136.6, 133.2, 129.9, 128.9, 122.1, (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 61.8 ($^2J_{C\text{-}F}$ = 36.4 Hz), 44.5.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.99 (t, J = 8.5 Hz).
MS (EI): *m/z* (%) = 362 ([M+2]$^+$, 42), 356 ([M]$^+$, 42), 346 (100), 344 (98), 262 (83), 188 (59).
IR (KBr): ν = 2939, 1660, 1414, 1295, 1224, 1159, 1017, 960.
HRMS (ESI): 359.9511, calcd. for $C_{10}H_{10}O_3NBrF_3S$: 359.9511.

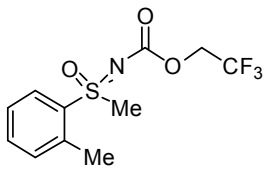
N-(2,2,2-trifluoroethyloxycarbonyl) 4-chlorophenyl methyl sulfoximine (112d)

Following GP6 using sulfilimine **111d** (150 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (156 mg, 99% yield) as a white solid. Mp.: 75 – 77 °C.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 4.46 – 4.36 (m, 2H), 3.33 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9, 141.3, 136.0, 130.2, 128.8, 122.8 (q, $^1J_{C\text{-}F}$ = 277.5 Hz), 61.8 ($^2J_{C\text{-}F}$ = 36.3 Hz), 44.5.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, J = 8.5 Hz).
MS (EI): *m/z* (%) = 316 ([M]$^+$, 25), 302 (37), 300 (100), 218 (37), 216 (93), 188 (56), 159 (27), 127 (45).
IR (KBr): ν = 2938, 1662, 1414, 1294, 1233, 1161, 1084, 960.
HRMS (ESI): 337.9836, calcd. for $C_{10}H_{19}O_3NClF_3NaS$: 337.9836.

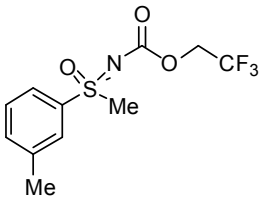
N-(2,2,2-trifluoroethyloxycarbonyl) methyl *o*-tolyl sulfoximine (112f)



Following GP6 using sulfilimine **111f** (139 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (144 mg, 98% yield) as a white solid. Mp.: 49 – 50 °C
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (m, 2H), 7.50 (m, 2H), 4.44 – 4.40 (m, 2H), 3.32 (s, 3H), 2.47 (s, 3H).

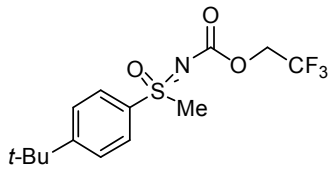
^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.1, 140.3, 137.3, 135.1, 129.7, 127.5, 125.6, 122.9 (q, $^{1}J_{C\text{-}F}$ = 277.7 Hz), 61.7 ($^{2}J_{C\text{-}F}$ = 36.3 Hz), 44.6, 21.4.
MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 12), 295 ([M]$^+$, 5), 280 (39), 196 (54), 107 (100).
IR (KBr): ν = 2938, 1679, 1407, 1302, 1221, 1150, 1088, 956.
HRMS (ESI): 318.0383, calcd. for $C_{11}H_{12}O_3NF_3NaS$: 318.0382.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl *m*-tolyl sulfoximine (112g)



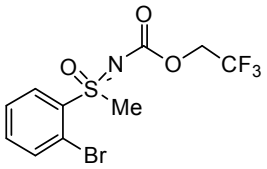
Following GP6 using sulfilimine **111g** (139 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (146 mg, 99% yield) as a white solid. Mp.: 64 – 65 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 4.39 (dq, *J* = 8.5, 1.4 Hz, 2H), 3.34 (s, 3H), 2.68 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9, 137.5, 135.5, 134.2, 133.3, 129.5, 127.2, 122.1 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz), 61.8 (q, $^{2}J_{C\text{-}F}$ = 36.4 Hz), 43.3, 20.3.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, *J* = 8.5 Hz).
MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 46), 295 ([M]$^+$, 33), 280 (100), 196 (31).
IR (KBr): ν = 2941, 1679, 1402, 1297, 1237, 1160, 1127, 963.
HRMS (ESI): 318.0382, calcd. for $C_{11}H_{12}O_3NF_3NaS$: 318.0382.

N-(2,2,2-trifluoroethyloxycarbonyl) 4-*t*-butylphenyl methyl sulfoximine (112h)



Following GP6 using sulfilimine **111h** (161 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (165 mg, 98% yield) as a white solid. Mp.: 151 – 153 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 4.43 – 4.49 (m, 2H), 3.31 (s, 3H), 1.35 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.4, 157.1, 134.3, 127.2, 126.9, 122.8 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz), 61.7 ($^{2}J_{C\text{-}F}$ = 36.3 Hz), 44.7, 35.4, 31.0.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.99 (t, *J* = 8.5 Hz).
MS (EI): *m/z* (%) = 338 ([M+H]$^+$, 21), 337 ([M]$^+$, 41), 322 (64), 238 (42), 149 (100).
IR (KBr): ν = 2969, 1680, 1404, 1301, 1225, 1130, 1083, 969.
Elemental analysis: calcd. for $C_{14}H_{12}F_3NO_3S$: C 49.84, H 5.38, N 4.15, found: C 49.54, H 5.44, N 4.03.

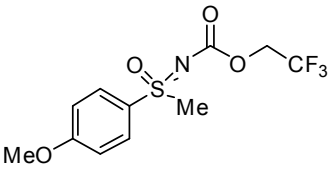
N-(2,2,2-trifluoroethyloxycarbonyl) 2-bromophenyl methyl sulfoximine (112i)



Following GP6 using sulfilimine **111i** (172 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (178 mg, 99% yield) as a white solid. Mp.: 98 – 100 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.28 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.60 (dt, *J* = 7.5, 1.1 Hz, 1H), 7.53 (dt, *J* = 7.6,

1.6 Hz, 1H), 4.42 – 4.35 (m, 2H), 3.50 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.3, 136.6, 135.8, 135.2, 132.2, 128.6, 122.8 (q, $^{1}J_{C\text{-}F}$ = 277.5 Hz), 119.5, 61.8 ($^{2}J_{C\text{-}F}$ = 36.5 Hz), 41.9.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, J = 8.4 Hz).
MS (EI): *m/z* (%) = 362 ([M+2]$^+$, 54), 360 ([M]$^+$, 53), 346 (56), 344 (54), 280 (100), 262 (65), 260 (70).
IR (KBr): ν = 2926, 1681, 1411, 1293, 1241, 1155, 961.
Elemental analysis: calcd. for $C_{10}H_9BrF_3NO_3S$: C 33.35, H 2.52, N 3.89, found: C 33.58, H 2.28, N 3.84.

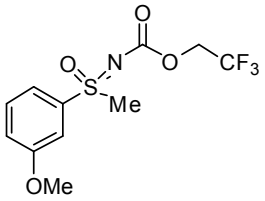
N-(2,2,2-trifluoroethyloxycarbonyl) 4-methoxyphenyl methyl sulfoximine (112j)



Following GP6 using sulfilimine **111j** (148 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (154 mg, 99% yield) as a colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.45 – 4.39 (m, 2H), 3.90 (s, 3H), 3.32 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.3, 157.2, 129.6, 128.3, 122.8 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz), 115.1, 61.8 ($^{2}J_{C\text{-}F}$ = 36.3 Hz), 55.8, 44.9.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.97 (t, J = 8.4 Hz).
MS (EI): *m/z* (%) = 312 ([M+H]$^+$, 3), 311 ([M]$^+$, 1), 248 (4), 212 (23), 155 (16), 123 (100).
IR (KBr): ν = 3022, 1689, 1454, 1302, 1216, 757.
HRMS (ESI): 334.0331, calcd. for $C_{11}H_{12}O_4NF_3NaS$: 334.0331.

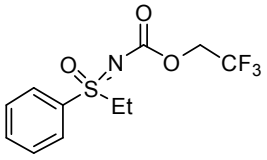
N-(2,2,2-trifluoroethyloxycarbonyl) 3-methoxyphenyl methyl sulfoximine (112k)

Following GP6 using sulfilimine **111k** (148 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (154 mg, 99% yield) as a white solid. Mp.: 37 – 39 °C
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 – 7.51 (m, 2H), 7.46 (m, 1H), 7.21 (ddd, J = 7.7, 2.5, 1.5 Hz, 1H), 4.41 (dq, J = 8.5, 1.0 Hz, 2H), 3.88 (s, 3H), 3.32 (s, 3H).



^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.4, 157.0, 138.7, 130.9, 122.9 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz), 120.8, 119.3, 111.9, 61.7 ($^{2}J_{C\text{-}F}$ = 36.4 Hz), 55.8, 44.6.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, J = 8.5 Hz).
MS (EI): *m/z* (%) = 312 ([M+H]$^+$, 14), 311 ([M]$^+$, 85), 296 (83), 264 (33), 212 (100), 124 (83).
IR (KBr): ν = 2967, 1677, 1441, 1299, 1220, 1158, 977.
Elemental analysis: calcd. for $C_{11}H_{12}F_3NO_4S$: C 42.44, H 3.89, N 4.50, found: C 42.77, H 3.94, N 4.46.

N-(2,2,2-trifluoroethyloxycarbonyl) ethyl phenyl sulfoximine (112l)



Following GP6 using sulfilimine **111l** (140 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (146 mg, 99% yield) as a white solid. Mp.: 41 – 42 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 – 7.92 (m, 2H), 7.71 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.62 (t, *J* = 8.3 Hz, 2H), 4.44 – 4.36 (m, 2H), 3.48 (dq, *J* = 14.3, 7.3 Hz, 1H), 3.39 (dq, *J* = 14.3, 7.3 Hz, 1H), 1.28 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.2, 135.3, 134.2, 129.7, 128.1, 122.9 (q, $^1J_{C\text{-}F}$ = 277.5 Hz), 61.7 ($^2J_{C\text{-}F}$ = 36.2 Hz), 50.8, 6.8.

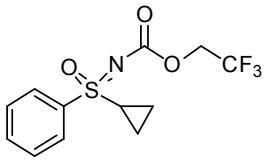
^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.02 (t, *J* = 8.5 Hz).

MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 5), 295 ([M]$^+$, 3), 266 (100), 196 (26), 125 (31).

IR (KBr): ν = 2942, 1688, 1410, 1303, 1245, 1168, 1190, 969.

HRMS (ESI): 318.0383, calcd. for $C_{11}H_{12}O_3NF_3NaS$: 318.0382.

N-(2,2,2-trifluoroethyloxycarbonyl) cyclopropyl phenyl sulfoximine (112m)



Following GP6 using sulfilimine **111m** (146 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (146 mg, 95% yield) as a white solid. Mp.: 51 – 53 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 – 7.91 (m, 2H), 7.68 (tt, *J* = 7.5, 1.8 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 2H), 4.39 – 4.34 (m, 2H), 2.68 (sept, *J* = 4.9 Hz, 1H), 1.68 – 1.62 (m, 1H), 1.28 – 1.21 (m, 2H), 1.23 – 0.81 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.8, 138.0, 133.9, 129.7, 127.3, 122.9 (q, $^1J_{C\text{-}F}$ = 277.7 Hz), 61.6 ($^2J_{C\text{-}F}$ = 36.3 Hz), 33.5, 6.8, 5.3.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, *J* = 8.5 Hz).

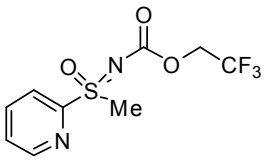
MS (EI): *m/z* (%) = 309 ([M+H]$^+$, 24), 308 ([M]$^+$, 86), 266 (49), 214 (24), 208 (100), 125 (24).

IR (KBr): ν = 2925, 1692, 1413, 1300, 1244, 1169, 887.

HRMS (ESI): 308.0564, calcd. for $C_{12}H_{12}O_3NF_3S$: 308.0563.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl 2-pyridyl sulfoximine (112n)

Following GP5 using methyl 2-pyridyl sulfoxide **2n** (141 mg, 1 mmol) and reagent **52** (609 mg, 2 mmol) afforded sulfilimine **111n** that was subjected to oxidation without further purification. Following GP6 using sodium periodate (1.1 g, 5 mmol) afforded the product (152 mg, 54% yield) as a pale yellow oil.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.74 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H), 8.27 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.02 (td, *J* = 7.8, 1.7 Hz, 1H). 7.60 (ddd, J = 7.7, 4.7 1.1 Hz, 1H), 4.42 – 4.28 (m, 2H), 3.46 (s, 3H).

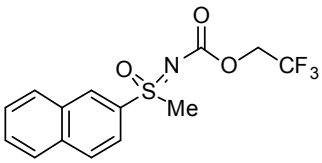
^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9, 155.7, 150.2, 138.3, 127.8, 123.5, 122.8 (q, $^1J_{C\text{-}F}$ = 277.4 Hz), 61.8 ($^2J_{C\text{-}F}$ = 36.5 Hz), 39.9.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.93 (t, *J* = 8.5 Hz).

MS (EI): *m/z* (%) = 283 ([M + H]$^+$, 35), 267 (100), 183 (97), 78 (41).
IR (KBr): ν = 2933, 1628, 1414, 1297, 1234, 1157, 970, 766.
HRMS (ESI): 283.0359, calcd. for $C_9H_{10}O_3N_2F_3S$: 283.0259.

N-(2,2,2-trifluoroethyloxycarbonyl) methyl 2-naphthyl sulfoximine (112o)

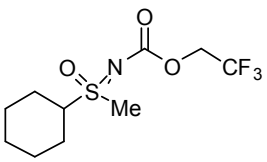
Sulfilimine **111o** (126 mg, 0.4 mmol) was dissolved in acetone (4 mL). While stirring under reflux for 8 h, small portions of $KMnO_4$ (2.0 g, 12.5 mmol) were added.[20] After refluxing for additional 8 h the manganese dioxide was filtered off and the solvent was evaporated. Purification by flash chromatography (acetone/*n*-pentane 1:10 to 1:5) provided the product (93 mg, 70% yield) as a white solid. Mp.: 107 – 108 °C



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.60 (m, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.71 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.67 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 4.45 – 4.39 (m, 2H), 3.41 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.2, 135.5, 134.1, 132.3, 130.3, 129.8, 129.7, 129.4, 128.1, 128.1, 122.8 (q, $^1J_{C\text{-}F}$ = 277.6 Hz), 121.3, 61.8 ($^2J_{C\text{-}F}$ = 36.4 Hz), 44.6.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.96 (t, *J* = 8.5 Hz).
MS (EI): *m/z* (%) = 332 ([M+H]$^+$, 30), 331 ([M]$^+$, 54), 316 (19), 284 (27), 232 (46), 143 (100), 127 (52), 115 (70).
IR (KBr): ν = 2926, 1664, 1416, 1301, 1237, 1151, 1002, 746.
Elemental analysis: calcd. for $C_{14}H_{12}F_3NO_3S$: C 50.75, H 3.65, N 4.23, found: C 50.60, H 3.89, N 4.18.

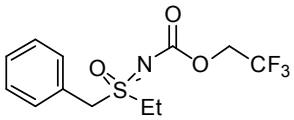
N-(2,2,2-trifluoroethyloxycarbonyl) cyclohexyl methyl sulfoximine (112p)

Following GP6 using sulfilimine **111p** (136 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (118 mg, 82% yield) as white solid. Mp.: 64 – 66 °C



^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.50 – 4.41 (m, 2H), 2.94 (tt, *J* = 12.3, 3.4 Hz, 1H), 3.18 (s, 3H), 2.31 (d, *J* = 12.6 Hz, 1H), 2.24 (d, *J* = 12.5 Hz, 1H), 1.98 (m, 2H), 1.76 (d, *J* = 13.2 Hz, 1H), 1.58 – 1.51 (m, 2H), 1.38 – 1.31 (m, 2H), 1.26 – 1.21 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.8, 123.1 (q, $^1J_{C\text{-}F}$ = 277.5 Hz), 62.7, 61.7 ($^2J_{C\text{-}F}$ = 36.3 Hz), 35.2, 25.6, 25.1, 25.1, 25.0, 24.8.
^{19}F NMR (564 MHz, $CDCl_3$): δ = –73.88 (t, *J* = 8.6 Hz).
MS (EI): *m/z* (%) = 288 ([M+H]$^+$, 1), 287 ([M]$^+$, 10), 206 (38), 188 (19), 106 (15), 83 (44).
IR (KBr): ν = 2941, 1674, 1407, 1302, 1238, 1164, 1125, 967.
Elemental analysis: calcd. for $C_{10}H_{16}F_3NO_3S$: C 41.81, H 5.61, N 4.88, found: C 41.89, H 5.59, N 4.83.

N-(2,2,2-trifluoroethyloxycarbonyl) benzyl ethyl sulfoximine (112q)



Following GP6 using sulfilimine **111q** (147 mg, 0.5 mmol) and sodium periodate (535 mg, 2.5 mmol) afforded the product (143 mg, 92% yield) as colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 – 7.36 (m, 5H), 4.73 (m, 2H), 4.54 (dq, *J* = 12.7, 8.5 Hz, 1H), 4.43 (dq, *J* = 12.5, 8.5 Hz, 1H), 3.15 – 3.08 (m, 2H), 1.36 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.7, 130.8, 129.7, 129.3, 126.7, 123.0 (q, $^1J_{C\text{-}F}$ = 277.7 Hz), 61.7 ($^2J_{C\text{-}F}$ = 36.2 Hz), 56.9, 44.6, 6.1.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –74.00 (t, *J* = 8.6 Hz).

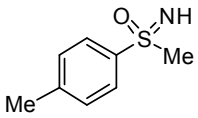
MS (EI): *m/z* (%) = 310 ([M+H]$^+$, 1), 309 ([M]$^+$, 2), 232 (29), 91 (100).

IR (KBr): ν = 2939, 1679, 1454, 1410, 1243, 1163, 969.

HRMS (ESI): 332.0535, calcd. for $C_{12}H_{14}O_3NF_3NaS$: 332.0538.

*N*H Methyl *p*-tolyl sulfoximine (5a)

Following GP7 using sulfoximine **112a** (118 mg, 0.4 mmol) afforded the product (65 mg, 96% yield) as a white solid.



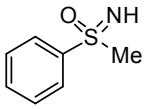
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.06 (s, 3H), 2.56 (br s, 1H), 2.41 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.9, 140.5, 129.8, 127.7, 46.3, 21.5.

The corresponding spectroscopic data matched that reported in the literature.[244]

*N*H Methyl phenyl sulfoximine (5b)

Following GP7 using sulfoximine **112d** (113 mg, 0.4 mmol) afforded the product (61 mg, 99% yield) as a white solid.

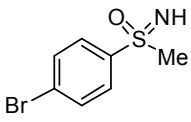


^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04 – 7.97 (m, 2H), 7.64 – 7.58 (m, 1H), 7.58 – 7.50 (m, 2H), 3.10 (s, 3H), 2.57 (br s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.5, 133.0, 129.2, 127.7, 46.2.

The corresponding spectroscopic data matched that reported in the literature.[49]

*N*H 4-Bromophenyl methyl sulfoximine (5c)



Following GP7 using sulfoximine **112c** (144 mg, 0.4 mmol) afforded the product (90 mg, 96% yield) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.85 (m, 2H), 7.71 – 7.66 (m, 2H), 3.09 (s, 3H), 2.71 (br s, 1H).

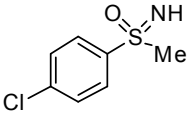
^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.6, 132.5, 129.3, 128.3, 46.2.

The corresponding spectroscopic data matched that reported in the literature.[106]

*N*H 4-Chlorophenyl methyl sulfoximine (5d)

Following GP7 using sulfoximine **112d** (126 mg, 0.4 mmol) afforded the product (74 mg, 97% yield) as a white solid. Mp.: 50 – 52 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 – 7.91 (m, 2H), 7.50 – 7.48 (m, 2H), 3.07 (s, 3H), 2.73 (br s, 1H).



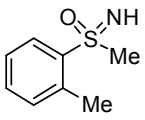
^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 139.6, 129.4, 129.2, 46.1.

MS (EI): *m/z* (%) = 192 ([M+2]$^+$, 18), 190 ([M]$^+$, 56), 174 (33), 128 (38), 126 (100).

IR (KBr): ν = 3272, 1577, 1465, 1223, 1086, 1002, 761.

The corresponding spectroscopic data matched that reported in the literature.[45]

*N*H Methyl *o*-tolyl sulfoximine (12f)



Following GP7 using sulfoximine **11f** (118 mg, 0.4 mmol) afforded the product (67 mg, 99% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 – 7.78 (m, 2H), 7.42 – 7.39 (m, 2H), 3.08 (s, 3H), 2.58 (br s, 1H), 2.48 (s, 3H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 146.4, 140.9, 134.9, 130.7, 129.7, 126.5, 47.6, 22.3.

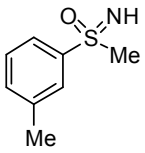
MS (EI): *m/z* (%) = 170 ([M+H]$^+$, 38), 169 ([M]$^+$, 100), 154 (55).

IR (KBr): ν = 3271, 1465, 1221, 1015, 746.

HRMS (ESI): 170.0632, calcd. for $C_8H_{12}ONS$: 170.0634.

The corresponding spectroscopic data matched that reported in the literature.[45]

*N*H Methyl *m*-tolyl sulfoximine (5g)



Following GP7 using sulfoximine **112g** (118 mg, 0.4 mmol) afforded the product (66 mg, 97% yield) as a colorless oil.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.07 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.39 (t, *J* = 7.3 Hz, 2H), 3.16 (br s, 1H), 3.07 (s, 3H), 2.74 (s, 3H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 144.5, 139.2, 134.4, 134.3, 130.9, 128.1, 21.7.

MS (EI): *m/z* (%) = 170 ([M+H]$^+$, 77), 169 ([M]$^+$, 100).

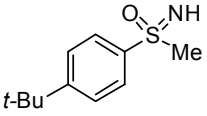
IR (KBr): ν = 3272, 1461, 1221, 1001, 748.

HRMS (ESI): 170.0632, calcd. For $C_8H_{12}ONS$: 170.0634.

The corresponding ^{1}H NMR spectroscopic data matched that reported in the literature.[45]

*N*H 4-*t*-Butylphenyl methyl sulfoximine (5h)

Following GP7 using sulfoximine **112h** (135 mg, 0.4 mmol) afforded the product (84 mg, 99% yield) as a white solid.



Mp.: 98 – 100 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 3.09 (s, 3H), 2.64 (br s, 1H), 1.34 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9, 140.4, 127.5, 126.2, 46.2, 35.1, 31.1.

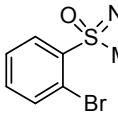
MS (EI): *m/z* (%) = 212 ([M+H]$^+$, 17), 211 ([M]$^+$, 26), 196 (32), 148 (100), 133 (41).

IR (KBr): ν = 3186, 2952, 1395, 1212, 1092, 999, 839.

HRMS (ESI): 234.0919, calcd. For $C_{11}H_{17}ONNaS$: 234.0923.

*N*H 2-Bromophenyl methyl sulfoximine (5i)

Following GP7 using sulfoximine **112i** (144 mg, 0.4 mmol) afforded the product (71 mg, 76% yield) as a white solid.

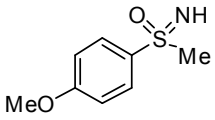


^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.76 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 1.2 Hz, 1H), 7.42 (td, *J* = 7.6, 1.7 Hz, 1H), 3.32 (s, 3H), 2.87 (br s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.6, 135.6, 133.9, 130.9, 128.0, 120.7, 43.1.

The corresponding spectroscopic data matched that reported in the literature.[245]

*N*H 4-Methoxyphenyl methyl sulfoximine (5j)



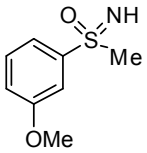
Following GP7 using sulfoximine **112j** (124 mg, 0.4 mmol) afforded the product (67 mg, 90% yield) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 – 7.88 (m, 2H), 6.98 – 6.96 (m, 2H), 3.84 (s, 3H), 3.05 (s, 3H), 2.63 (br s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.2, 135.0, 129.7, 114.3, 55.6, 46.5.

The corresponding spectroscopic data matched that reported in the literature.[49]

*N*H 3-Methoxyphenyl methyl sulfoximine (5k)



Following GP7 using sulfoximine **112k** (124 mg, 0.4 mmol) afforded the product (73 mg, 99% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56 – 7.54 (m, 1H), 7.48 – 7.47 (m, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.10 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 3.84 (s, 3H), 3.07 (s, 3H), 2.68 (br s, 1H).

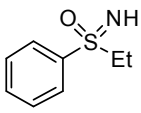
^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.0, 144.7, 130.2, 119.7, 119.4, 112.1, 55.6, 46.0.

MS (EI): *m/z* (%) = 186 ([M+H]$^+$, 52), 185 ([M]$^+$, 61), 170 (47), 122 (100), 107 (50), 95 (32), 92 (34).

IR (KBr): ν = 3273, 1592, 1474, 1425, 1224, 1004, 745.

HRMS (ESI): 186.0581, calcd. For $C_8H_{12}O_2NS$: 186.0583.

*N*H Ethyl phenyl sulfoximine (5l)



Following GP7 using sulfoximine **112l** (118 mg, 0.4 mmol) afforded the product (67 mg, 99% yield) as a colorless oil.

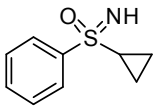
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.93 – 7.92 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 2H), 3.31 (q, *J* = 7.5 Hz, 2H), 2.55 (br s, 1H), 1.41 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.2, 132.9, 129.0, 128.4, 51.7, 7.8.

The corresponding spectroscopic data matched that reported in the literature.[244]

*N*H Cyclopropyl phenyl sulfoximine (5m)

Following GP7 using sulfoximine **112m** (123 mg, 0.4 mmol) afforded the product (71 mg, 98% yield) as a colorless oil.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.00 – 7.94 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 2H), 2.68 (br s, 1H), 1.52 (tt, *J* = 7.9, 4.8 Hz, 1H), 1.40 – 1.35 (m, 1H), 1.20 – 1.16 (m, 1H), 1.06 – 1.01 (m, 1H), 1.09 – 0.70 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.1, 132.7, 129.0, 127.8, 34.2, 5.9, 5.6.

MS (EI): *m/z* (%) = 183 ([M+H]$^+$, 4), 182 ([M]$^+$,32), 147 (22), 140 (33), 125 (26), 92 (72).

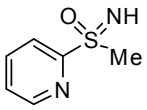
IR (KBr): ν = 3270, 3060, 1445, 1224, 1092, 980, 559.

Elemental analysis: calcd. for $C_9H_{11}NOS$: C 59.64, H 6.12, N 7.73, found: C 59.27, H 6.38, N 7.69.

The corresponding spectroscopic data matched that reported in the literature.[84c]

*N*H Methyl 2-pyridyl sulfoximine (5n)

Following GP7 using sulfoximine **112n** (113 mg, 0.4 mmol) afforded the product (52 mg, 84% yield) as a white solid.



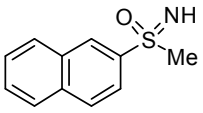
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.3 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.94 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 3.26 (s, 3H), 2.73 (br s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.5, 150.0, 138.2, 126.7, 121.0, 42.3.

The corresponding spectroscopic data matched that reported in the literature.[49]

*N*H Methyl 2-naphthyl sulfoximine (5o)

Following GP7 using sulfoximine **112o** (132 mg, 0.4 mmol) afforded the product (68 mg, 83% yield) as a white solid.



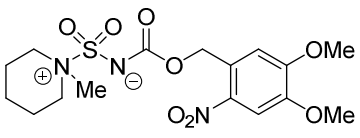
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.57 (m, 1H), 8.05 – 8.00 (m, 3H), 7.94 – 7.92 (m, 1H), 7.68 – 7.60 (m, 2H), 3.17 (s, 3H), 2.57 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 135.0, 132.3, 129.5, 129.3, 129.0, 128.9, 127.9, 127.6, 122.8, 46.2.

The corresponding spectroscopic data matched that reported in the literature.[49]

N-Methyl-*N*-[(4,5-dimethoxy-2-nitrobenzyloxycarbonyl)-amino]-sulfonyl-piperidinaminium, inner salt (114)

To a solution of chlorosulfonylisocyanate (**43**) (0.44 mL, 5.0 mmol) in dry benzene (3 mL) at r.t. was added 4,5-dimethoxy-2-nitrobenzyl alcohol (1.07 g, 5 mmol) in small portions. After stirring for 45 min, the reaction mixture was filtered and the solids were dried under vacuum. Subsequently, the solids were added in small portions to a solution of *N*-methylpiperidine (1.34 mL, 11.0 mmol) in dry THF (17 mL) at 0 °C. After stirring at 0 °C for 20 min, the precipitate was filtered off.



Purification by flash column chromatography (AcOEt) afforded the product as a light-yellow solid (918 mg, 44%). Mp.: 132 – 134 °C.

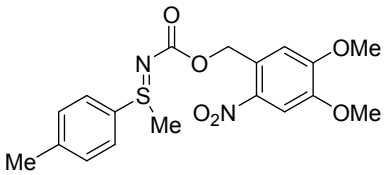
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (s, 1H), 7.16 (s, 1H), 5.51 (s, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 3.61 (dt, *J* = 13.2, 3.2 Hz, 2H), 3.44 (d, *J* = 12.2 Hz, 2H), 3.13 (s, 3H), 1.96– 1.78 (m, 5H), 1.52 – 1.44 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.8, 153.8, 147.9, 139.4, 128.2, 110.0, 108.0, 64.9, 56.6, 56.4, 54.8, 40.2, 21.5, 20.6.

IR (KBr): ν = 1687, 1521, 1329, 1260, 1202, 1088, 734.

HRMS (ESI): 440.1092, calcd. for $C_{16}H_{23}O_8N_3NaS$: 440.1098.

N-(4,5-Dimethoxy-2-nitrobenzyloxycarbonyl) methyl *p*-tolyl sulfilimine (115)



Following GP5 using sulfoxide **2a** (39 mg, 0.25 mmol), reagent **114** (185 mg, 1.8 mmol) and THF (2.5 mL), followed by purification by flash column chromato-graphy (AcOEt) afforded the product (30 mg, 31% yield) as a yellow solid. Mp.: 46 – 48 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 – 7.66 (m, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (s, 1H), 7.52 (d, *J* =3.9 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 2.84 (s, 3H), 2.40 (s, 3H).

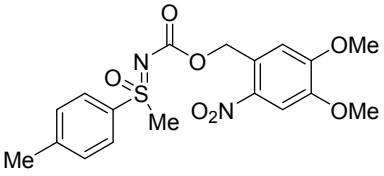
^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.0, 153.6, 147.6, 143.5, 139.4, 132.8, 130.7, 130.0, 126.4, 109.6, 107.9, 64.4, 56.4, 56.3, 35.7, 21.5.

IR (KBr): ν = 1632, 1579, 1516, 1263, 1217, 1084, 789.

HRMS (ESI): 415.0915, calcd. for $C_{18}H_{20}O_6N_2NaS$: 415.0940.

N-(4,5-Dimethoxy-2-nitrobenzyloxycarbonyl) methyl *p*-tolyl sulfoximine (116)

Following GP6 using sulfilimine **115** (42 mg, 0.1 mmol) and sodium periodate (114 mg, 0.5 mmol) afforded the product (31 mg, 76% yield) as yellow solid. Mp.: 174 – 176 °C.



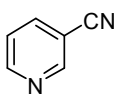
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.3 Hz, 2H), 7.69 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 5.57 (AB-system, *J* = 15.5 Hz, 1H), 5.43 (AB-system, *J* = 15.5 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.32 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 153.8, 147.9, 145.4, 139.3, 135.0, 130.4, 128.4, 127.3, 109.8, 108.0, 64.6, 56.6, 56.4, 44.8, 21.6.

IR (KBr): ν = 1696, 1519, 1251, 1211.

HRMS (ESI): 431.0869, calcd. for $C_{18}H_{20}O_7N_2NaS$: 431.0889.

Nicotinonitrile (123)



To a solution of nicotinamide (122 mg, 1.0 mmol) in THF (5 mL) was added reagent **107b** (203 mg, 1.0 mmol) and the reaction mixture was heated under microwave irradiation to 50 °C. After 30 min another portion of reagent **107b**

(203 mg, 1.0 mmol) was added and again the reaction mixture was stirred under microwave irradiation at 50 °C for 30 min. The solvent was removed under reduced pressure. Purification by column chromatography (AcOEt/*n*-pentane = 1:3) afforded the product (75 mg, 72%) as colorless needles.

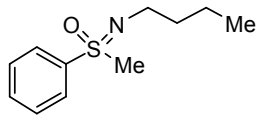
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.89 – 8.88 (m, 1H), 8.81 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.98–7.95 (m, 1H), 7.43 (ddd, *J* = 8.0, 5.0, 0.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 152.4, 139.2, 123.6, 116.5, 110.1.

The corresponding spectroscopic data matched that reported in the literature.[246]

12.3.2 Syntheses of *N*-alkylated sulfoximines

N-Butyl methyl phenyl sulfoximine (125a)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromobutane (206 mg, 1.5 mmol) provided the product (170 mg, 83% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 1:4).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 – 7.90 (m, 2H), 7.61 – 7.55 (m, 3H), 3.08 (s, 3H), 2.98 – 2.94 (m, 1H), 2.80 – 2.76 (m, 1H), 1.57 – 1.52 (m, 2H), 1.37 – 1.33 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

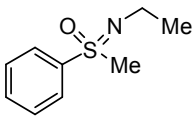
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.7, 132.7, 129.2, 128.6, 45.2, 43.6, 35.0, 20.3, 13.8.

The corresponding spectroscopic data matched that reported in the literature.[83]

The preparation of (*R*)-*N*-butyl methyl phenyl sulfoximine (**125a**) was performed following GP8, using (*R*)-methyl phenyl sulfoximine **5b**. $[\alpha]_D$ = –118 (*c* = 1.0 in $CHCl_3$).

HPLC: t_r = 16.0 [minor], t_r = 17.9 min [major] (Chiralcel OJ column, flow rate 0.5 mL/min, heptane/*i*-PrOH = 95:5, λ = 210 nm, 20 °C); *ee* = 100%.

N-Ethyl methyl phenyl sulfoximine (125b)



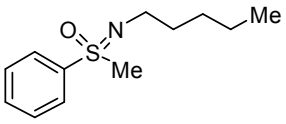
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and bromoethane (163 mg, 1.5 mmol) provided the product (154 mg, 87% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 1:3).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 – 7.91 (m, 2H), 7.62 – 7.56 (m, 3H), 3.09 (s, 3H), 3.05 – 2.99 (m, 1H), 2.88 – 2.83 (m, 1H), 1.18 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.4, 132.7, 129.2, 128.5, 45.1, 38.4, 18.1.

The corresponding spectroscopic data matched that reported in the literature.[91]

N-Pentyl methyl phenyl sulfoximine (125c)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-chloropentane (159 mg, 1.5 mmol) provided the product (180 mg, 82% yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.82 – 7.80 (m, 2H), 7.52 – 7.45 (m, 3H), 2.98 (s, 3H), 2.88 – 2.81 (m, 1H), 2.70 – 2.63 (m, 1H), 1.48 – 1.44 (m, 2H), 1.21 – 1.17 (m, 4H), 0.78 – 0.74 (m, 3H).

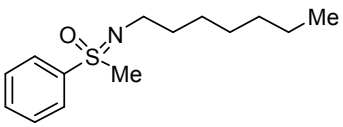
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.4, 132.5, 129.1, 128.4, 44.9, 43.6, 32.2, 29.1, 22.1, 13.8.

MS (EI): *m/z* (%) = 225 ([M]$^+$, 3), 210 (6), 169 (9), 168 (100), 141 (47), 140 (11), 125 (15), 77 (7).

IR (KBr): ν = 2930, 1446, 1238, 1136, 754.

HRMS (ESI): 248.10808, calcd. for $C_{12}H_{19}NONaS$.: 248.10796.

N-Heptyl methyl phenyl sulfoximine (125d)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromoheptane (269 mg, 1.5 mmol) provided the product (222 mg, 89% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 3:1).

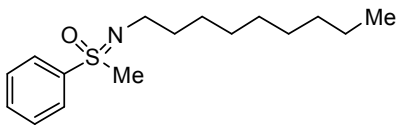
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.83 – 7.82 (m, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 3.00 (s, 3H), 2.86 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.68 (dt, *J* = 12.1, 7.2 Hz, 1H), 1.47 (quint, *J* = 7.2 Hz, 2H), 1.23 – 1.15 (m, 8H), 0.77 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.5, 132.5, 129.2, 128.5, 45.0, 43.7, 32.6, 31.6, 28.9, 27.0, 22.4, 13.9.

The corresponding spectroscopic data matched that reported in the literature.[83]

N-Nonyl methyl phenyl sulfoximine (125e)

Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-clorononane (251 mg, 1.5 mmol) provided the product (164 mg, 59 % yield) as a white solid after purification by flash chromatography (acetone/*n*-pentane 5:1).

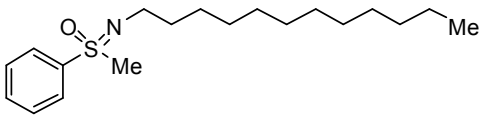


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.2 Hz, 2H), 7.62 – 7.60 (m, 1H), 7.57 – 7.55 (t, *J* = 7.3 Hz, 2H), 3.09 (s, 3H), 2.95 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.77 (dt, *J* = 12.1, 7.2 Hz, 1H), 1.55 (quint, *J* = 7.3 Hz, 2H), 1.31 – 1.24 (m, 12 H), 0.88 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.7, 132.8, 129.4, 128.7, 45.2, 43.9, 32.8, 31.9, 29.6, 29.4, 29.3, 27.2, 22.7, 14.1.

MS (EI): *m/z* (%) = 282 ([M+H]$^+$, 62), 169 (9), 168 (100), 156 (4), 141 (43), 125 (11), 77 (5).
IR (KBr): ν = 2922, 2853, 1450, 1235, 1134, 741.
HRMS (ESI): 282.18909, calcd. for $C_{16}H_{28}NOS$: 282.18861.

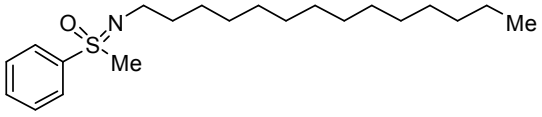
N-Dodecyl methyl phenyl sulfoximine (125f)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromododecane (374 mg, 1.5 mmol) provided the product (251 mg, 72% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 3:1). Mp.: 48 – 49 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89 – 7.87 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 2H), 3.05 (s, 3H), 2.93 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.73 (dt, *J* = 12.1, 7.2 Hz, 1H), 1.53 (quint, *J* = 7.5 Hz, 2H), 1.27 – 1.21 (m, 18 H), 0.85 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.7, 132.7, 129.3, 128.6, 45.2, 43.9, 32.8, 31.9, 29.6, 29.6 (3C), 29.3, 29.3, 27.2, 22.6, 14.1.
MS (EI): *m/z* (%) = 324 ([M+H]$^+$, 54), 323 ([M]$^+$, 3), 322 (9), 224 (6), 184 (7), 168 (100), 141 (49), 125 (12).
IR (neat): ν = 2848, 1469, 1246, 1132, 743.
Elemental analysis: calcd. for $C_{19}H_{33}NOS$: C 70.54, H 10.28, N 4.33, found: C 70.33, H 10.41, N 4.27.

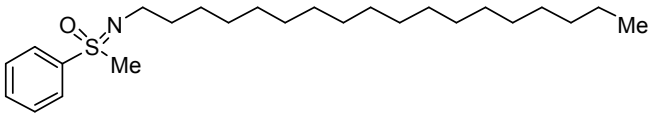
N-Tetradecyl methyl phenyl sulfoximine (125g)

Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromotetradecane (416 mg, 1.5 mmol) provided the product (285 mg, 82% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 5:1). Mp.: 55 – 57 °C.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.88 (m, 2H), 7.60 – 7.58 (m, 1H), 7.55 – 7.53 (m, 2H), 3.06 (s, 3H), 2.93 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.74 (dt, *J* = 12.1, 7.3 Hz, 1H), 1.54 (quint, *J* = 7.5 Hz, 2H), 1.29 – 1.22 (m, 22 H), 0.86 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.7, 132.7, 129.3, 128.6, 45.1, 43.9, 32.8, 31.9, 29.6, 29.6 (2C), 29.6, 29.6 (2C), 29.4, 29.3, 27.2, 22.6, 14.1.
MS (EI): *m/z* (%) = 352 ([M+H]$^+$, 68), 351 ([M]$^+$, 4), 224 (6), 212 (8), 169 (10), 168 (100), 156 (7), 141 (43), 140 (20).
IR (neat): ν = 2913, 2847, 1469, 1247, 1133, 743.
Elemental analysis: calcd. for $C_{21}H_{37}NOS$: C 70.74, H 10.61, N 3.98, found: C 70.45, H 10.24, N 3.93.

N-Octadecyl methyl phenyl sulfoximine (125h)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-iodooctadecane (571 mg, 1.5 mmol) provided the product (368 mg, 92% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 10:1 to 3:1). Mp.: 67 – 69 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 – 7.90 (m, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.57 – 7.54 (m, 2H), 3.08 (s, 3H), 2.95 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.76 (dt, *J* = 12.1, 7.3 Hz, 1H), 1.55 (quint, *J* = 7.4 Hz, 2H), 1.30 – 1.23 (m, 30 H), 0.88 (t, *J* = 7.0 Hz, 3H).

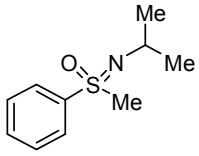
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.8, 132.7, 129.3, 128.7, 45.2, 44.0, 32.9, 31.9, 29.7 (8C), 29.6, 29.6, 29.4, 29.4, 27.3, 22.7, 14.1.

(EI): *m/z* (%) = 406 ([M–H]$^+$, 2), 268 (13), 224 (6), 169 (8), 168 (100), 156 (8), 141 (33), 140 (23), 125 (8).

IR (neat): ν = 2913, 2849, 1469, 1251, 1133, 972, 744.

Elemental analysis: calcd. for $C_{25}H_{45}NOS$: C 73.65, H 11.13, N 3.44, found: C 73.37, H 11.26, N 3.43.

N-Isopropyl methyl phenyl sulfoximine (125j)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 2-bromopropane (184 mg, 1.5 mmol) provided the product (26 mg, 14% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 5:1). Mp.: 63 – 66 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 – 7.90 (m, 2H), 7.63 – 7.52 (m, 3H), 3.24 (sept, *J* = 6.3 Hz, 1H), 3.06 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.3 Hz, 3H).

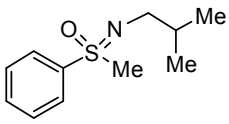
^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 132.7, 129.3, 128.7, 46.4, 45.6, 27.0, 26.1.

(EI): *m/z* (%) = 198 ([M+H]$^+$, 4), 197 ([M]$^+$, 2), 183 (10), 182 (100), 141 (35), 125 (12), 124 (6), 77 (9).

IR (neat): ν = 2963, 2924, 1445, 1224, 1127, 1103, 744.

HRMS (ESI): 198.0953, calcd. for $C_{10}H_{16}NOS$ [M+H]$^+$: 198.0947.

N-(2-Methylpropyl) methyl phenyl sulfoximine (125k)

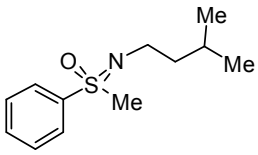


Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromo-2-methylpropane (387 mg, 1.5 mmol) provided the product (70 mg, 34% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 – 7.87 (m, 2H), 7.59 – 7.56 (m, 1H), 7.54 – 7.52 (m, 2H), 3.05 (s, 3H), 2.73 (dd, *J* = 11.9, 6.6 Hz, 1H), 2.53 (dd, *J* = 11.9, 7.3 Hz, 1H), 1.73 (nonet, *J* = 6.7 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.8, 132.6, 129.3, 128.6, 51.6, 45.1, 30.8, 20.5, 20.4.
The corresponding spectroscopic data matched that reported in the literature.[247]

N-(3-Methylbutyl) methyl phenyl sulfoximine (125l)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromo-3-methylbutane (227 mg, 1.5 mmol) provided the product (207 mg, 95% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.88 (m, 2H), 7.62 – 7.53 (m, 3H), 3.06 (s, 3H), 3.00 – 2.93 (m, 1H), 2.81 – 2.74 (m, 1H), 1.65 (nonet, *J* = 6.7 Hz, 1H), 1.49 – 1.42 (m, 2H), 0.83 (t, *J* = 6.0 Hz, 6H).

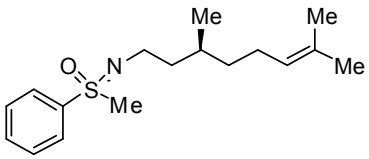
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.8, 132.7, 129.3, 128.6, 45.2, 42.0, 41.9, 25.7, 22.5, 22.5.

MS (EI): *m/z* (%) = 226 ([M+H]$^+$, 15), 210 (18), 169 (9), 168 (100), 156 (3), 141 (47), 125 (17), 77 (8).

IR (neat): ν = 2952, 2924, 1639, 1583, 1467, 1446, 1239, 1133, 743.

Elemental analysis: calcd. for $C_{12}H_{19}NOS$: C 63.96, H 8.50, N 6.22, found: C 63.57, H 8.22, N 6.54.

N-(*S*)-Citronellyl methyl phenyl sulfoximine (125m)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and (*S*)-citronellylbromide (329 mg, 1.5 mmol) provided the product (273 mg, 97% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1). The product was isolated as a mixture of diastereomers.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.91 – 7.90 (m, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.57 – 7.54 (m, 2H), 5.07 – 5.04 (m, 1H), 3.08 (s, 3H), 3.92 – 2.92 (m, 1H), 2.83 – 2.73 (m, 1H), 1.95 – 1.90 (m, 2H), 1.65 (s, 3H), 1.63 – 1.58 (m, 1H), 1.56 (s, 3H), 1.53 – 1.46 (m, 1H), 1.43 – 1.35 (m, 1H), 1.30 – 1.24 (m, 1H), 1.12 – 1.06 (m, 1H), 0.81 (t, *J* = 6.6 Hz, 3H).

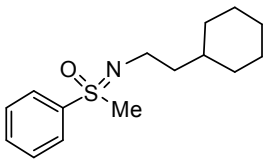
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.6, 139.6, 132.8, 130.9, 129.4, 128.6, 124.9, 124.9, 45.2, 41.9, 41.8, 40.0, 39.9, 37.1, 30.4, 30.4, 25.7, 25.4, 25.4, 19.4, 19.4, 17.6.

MS (EI): *m/z* (%) = 294 ([M+H]$^+$, 51), 293 ([M]$^+$, 25), 278 (7), 208 (90), 168 (100), 156 (30), 141 (68), 140 (25), 125 (22).

IR (neat): ν = 2918, 2857, 1449, 1233, 1134, 741.

HRMS (ESI) 294.1884, calcd. for $C_{17}H_{28}NOS$ [M+H]$^+$: 294.1886.

N-(2-Cyclohexylethyl) methyl phenyl sulfoximine (125n)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromo-2-cyclohexylethane (287 mg, 1.5 mmol) provided the product (217 mg, 83% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.88 (m, 2H), 7.61 – 7.59 (m, 1H), 7.56 – 7.54 (t, *J* = 7.2 Hz, 2H), 3.08 (s, 3H), 2.97 (dt, *J* = 12.3, 7.5 Hz, 1H), 2.78 (dt, *J* = 12.3, 7.4 Hz, 1H), 1.65 – 1.58 (m, 5H), 1.46 (q, *J* = 7.2 Hz, 2H), 1.34 – 1.30 (m, 1H), 1.22 – 1.06 (m, 3H), 0.86 – 0.79 (m, 2H).

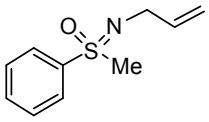
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.6, 132.8, 129.3, 128.6, 45.2, 41.5, 40.3, 35.3, 33.2, 33.2, 26.6, 26.3 (2C).

MS (EI): *m/z* (%) = 266 ($[M+H]^+$, 10), 250 (5), 168 (29), 156 (4), 141 (10), 85 (63), 83 (100).

IR (neat): ν = 2919, 2847, 1445, 1230, 1132, 743.

HRMS (ESI): 266.1573, calcd. for $C_{15}H_{24}NOS$ $[M+H]^+$: 266.1573.

N-Allyl methyl phenyl sulfoximine (125o)



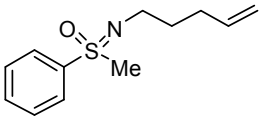
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and allylbromide (181 mg, 1.5 mmol) provided the product (149 mg, 79% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1 to 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87 – 7.85 (m, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.50 (m, 2H), 5.90 – 5.84 (m, 1H), 5.20 – 5.17 (m, 1H), 5.00 – 4.98 (m, 1H), 3.57 – 3.54 (m, 1H), 3.40 – 3.37 (m, 1H), 3.06 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.2, 137.6, 132.8, 129.3, 128.5, 114.5, 46.1, 45.1.

The corresponding spectroscopic data matched that reported in the literature.[93]

N-(5-Pentenyl) methyl phenyl sulfoximine (125p)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 5-bromo-1-pentene (224 mg, 1.5 mmol) provided the product (178 mg, 81% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1).

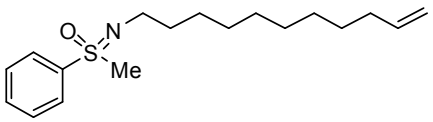
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.89 (m, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.57 – 7.54 (m, 2H), 5.81 – 5.74 (m, 1H), 4.99 – 4.96 (m, 1H), 4.91 – 4.89 (m, 1H), 3.08 (s, 3H), 2.96 (dt, *J* = 12.2, 7.1 Hz, 1H), 2.79 (dt, *J* = 12.2, 7.2 Hz, 1H), 2.09 (q, *J* = 6.8 Hz, 2H), 1.65 (quint, *J* = 7.4 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.6, 138.5, 132.8, 129.4, 128.6, 114.4, 45.2, 43.3, 31.9, 31.3.

MS (EI): *m/z* (%) = 224 ([M+H]$^+$, 10), 222 ([M–H]$^+$, 5), 208 (10), 168 (62), 141 (79), 140 (15), 132 (100), 125 (39), 124 (11), 77 (15).
IR (neat): ν = 2926, 2844, 1444, 1237, 1134, 982, 743.
HRMS (ESI): 224.1100, calcd. for $C_{12}H_{18}NOS$ [M+H]$^+$: 224.1104.
The compound was mentioned in the literature without analytical data.[93]

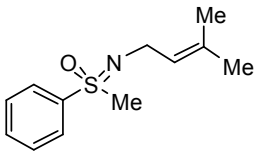
N-(10-Undecenyl) methyl phenyl sulfoximine (125q)

Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product (248 mg, 83% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1).



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 – 7.89 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.53 (m, 3H), 5.85 – 5.75 (m, 1H), 5.00 – 4.90 (m, 2H), 3.07 (s, 3H), 2.94 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.76 (dt, *J* = 12.1, 7.3 Hz, 1H), 2.02 (q, *J* = 7.1 Hz, 2H), 1.55 (quint, *J* = 7.2 Hz, 2H), 1.37 – 1.25 (m, 12H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 139.2, 132.7, 129.3, 128.7, 114.0, 45.2, 43.9, 33.8, 32.9, 29.5, 29.4, 29.4, 29.1, 28.9, 27.2.
MS (EI): *m/z* (%) = 308 ([M+H]$^+$, 10), 307 ([M]$^+$, 17), 266 (5), 224 (6), 169 (9), 169 (100), 156 (6), 141 (36), 125 (11).
IR (neat): ν = 2924, 2850, 1446, 1236, 1135, 741.
Elemental analysis: calcd. for $C_{18}H_{29}NOS$: C 70.31, H 9.51, N 4.56, found: C 69.91, H 9.50, N 4.77.

N-(3-Methylbut-2-enyl) methyl phenyl sulfoximine (125r)



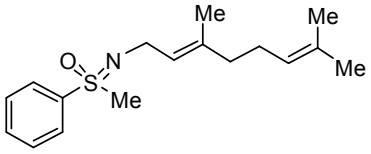
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 3,3-dimethylallyl bromide (224 mg, 1.5 mmol) provided the product (107 mg, 50 % yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 – 7.91 (m, 2H), 7.61 – 7.59 (m, 1H), 7.56 – 7.54 (m, 2H), 5.30 – 5.28 (m, 1H), 3.56 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.40 (dd, *J* = 13.9, 7.1 Hz, 1H), 3.09 (s, 3H), 1.65 (s, 3H), 1.51 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.5, 133.3, 132.3, 129.3, 128.7, 124.0, 45.3, 41.3, 25.1, 17.6.
The corresponding spectroscopic data matched that reported in the literature.[95]

N-Geranyl methyl phenyl sulfoximine (125s)

Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and geranyl bromide (326 mg, 1.5 mmol) provided the

product (117 mg, 41% yield) as a colorless oil after purification by flash chromatography (acetone/*n*-pentane 5:1).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.92 – 7.91 (m, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.56 – 7.54 (m, 2H), 5.31 – 5.29 (m, 1H), 5.08 – 5.05 (m, 1H), 3.59 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.44 (dd, *J* = 14.1, 7.1 Hz, 1H), 3.09 (s, 3H), 2.05 – 2.01 (m, 2H), 1.95 – 1.93 (m, 2H), 1.66 (s, 3H), 1.57 (s, 3H), 1.49 (s, 3H).

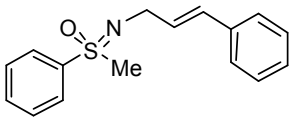
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.7, 136.5, 132.8, 131.3, 129.3, 128.7, 124.2, 123.8, 45.4, 41.3, 39.6, 26.4, 25.7, 17.6, 16.1.

MS (EI): *m/z* (%) = 291 ([M]$^+$, 4), 222 (30), 208 (16), 168 (32), 156 (93), 141 (100), 140 (28), 124 (33).

IR (KBr): ν = 2968, 2921, 1446, 1219, 1126, 743.

HRMS (ESI): 292.17267, calcd. for $C_{17}H_{26}ONS$: 292.17296.

N-Cinnamyl methyl phenyl sulfoximine (125t)



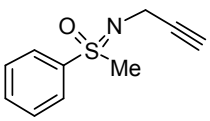
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and cinnamyl bromide (296 mg, 1.5 mmol) provided the product (160 mg, 60 % yield) as a yellow oil after purification by flash chromatography (acetone/*n*-pentane 10:1 to 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 – 7.93 (m, 2H), 7.63 – 7.53 (m, 3H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.28 – 7.25 (m, 2H), 7.20 – 7.16 (m, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.31 – 6.24 (m, 1H), 3.79 (ddd, *J* = 15.3, 5.6, 1.5 Hz, 1H), 3.61 (ddd, *J* = 15.3, 6.2, 1.3 Hz, 1H), 3.13 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.5, 137.3, 132.9, 130.0, 129.4, 128.7, 128.3, 127.0, 126.3, 45.7, 45.3.

The corresponding spectroscopic data matched that reported in the literature.[95]

N-Propargyl methyl phenyl sulfoximine (125u)



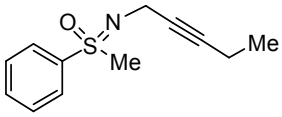
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and propargylbromide (178 mg, 1.5 mmol) provided the product (155 mg, 83% yield) as a yellow oil after purification by flash column chromatography (acetone/*n*-pentane 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 – 7.93 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 3.77 (dd, *J* = 17.3, 2.5 Hz, 1H), 3.64 (dd, *J* = 17.3, 2.5 Hz, 1H), 3.11 (s, 3H), 2.16 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 138.8, 133.2, 129.4, 128.6, 82.8, 70.4, 45.4, 32.6.

The corresponding spectroscopic data matched that reported in the literature.[96]

N-(3-Pentynyl) methyl phenyl sulfoximine (125v)



Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromo-2-pentyne (221 mg, 1.5 mmol) provided the product (203 mg, 93% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1 to 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 – 7.95 (m, 2H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.57 – 7.55 (m, 2H), 3.79 (dt, *J* = 16.9, 2.2 Hz, 1H), 3.64 (dt, *J* = 16.9, 2.2 Hz, 1H), 3.12 (s, 3H), 2.12 (qt, *J* = 7.5, 2.2 Hz, 2H), 1.05 (t, *J* = 7.5 Hz, 3H).

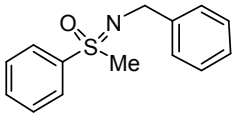
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.2, 133.0, 129.4, 128.7, 84.4, 77.8, 45.5, 33.0, 13.8, 12.5.

MS (EI): *m/z* (%) = 222 ([M+H]$^+$, 11), 221 ([M]$^+$, 22), 192 (32), 158 (39), 143 (52), 141 (37), 140 (15), 125 (100), 124 (79), 77 (40).

IR (neat): ν = 2977, 2927, 1719, 1639, 1446, 1265, 1218, 1124, 745.

HRMS (ESI) 222.0947, calcd. for $C_{12}H_{16}NOS$ [M+H]$^+$: 222.0947.

N-Benzyl methyl phenyl sulfoximine (125w)



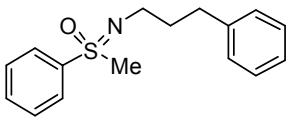
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and benzylbromide (257 mg, 1.5 mmol) provided the product (182 mg, 75% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1 to 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 – 7.93 (m, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 4.20 (d, *J* = 14.3 Hz, 1H), 3.98 (d, *J* = 14.3 Hz, 1H), 3.13 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.1, 139.4, 132.8, 129.4, 128.6, 128.2, 127.5, 126.5, 47.3, 45.2.

The corresponding spectroscopic data matched that reported in the literature.[248]

N-(3-Phenylpropyl) methyl phenyl sulfoximine (125y)



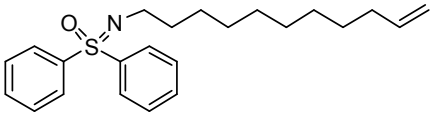
Following GP8 using methyl phenyl sulfoximine **5b** (155 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 1-bromo-3-phenylpropane (299 mg, 1.5 mmol) provided the product (237 mg, 88% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 5:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.90 – 7.89 (m, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.55 – 7.54 (m, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.18 – 7.13 (m, 3H), 3.09 (s, 3H), 3.01 (dt, *J* = 12.1, 7.0 Hz, 1H), 2.84 (dt, *J* = 12.2, 7.1 Hz, 1H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.92 – 1.86 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 142.3, 139.6, 132.7, 129.4, 128.6, 128.4, 128.1, 125.5, 45.2, 43.4, 34.2, 33.4.

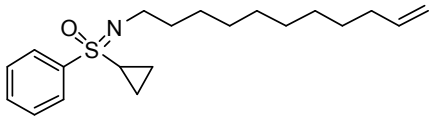
MS(EI): *m/z* (%) = 274 ([M+H]$^+$, 21), 273 (6), 258 (5), 181 (31), 169 (8), 168 (100), 156 (4), 141 (68), 125 (30), 77 (19).
IR (neat): ν = 2928, 2848, 1446, 1235, 1132, 973, 742.
HRMS (ESI): 274.1266, calcd. for $C_{16}H_{20}NOS$ [M+H]$^+$: 274.1260.

N-(10-Undecenyl) diphenyl sulfoximine (126)



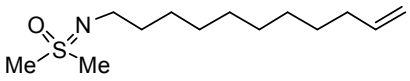
Following GP8 using diphenyl sulfoximine **5v** (217 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product (163 mg, 88% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 30:1).
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.98 – 7.96 (m, 4H), 7.50 – 7.44 (m, 6H), 5.84 – 5.77 (m, H), 5.00 – 4.97 (m, 1H), 4.93 – 4.91 (m, 1H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.65 (quint, *J* = 7.5 Hz, 2H), 1.39 – 1.35 (m, 4H), 1.27 (m, 8H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.0, 139.2, 132.2, 129.0, 128.5, 114.0, 43.9, 33.8, 33.0, 29.5, 29.4, 29.4, 29.1, 28.9, 27.3.
MS (EI): *m/z* (%) = 370 ([M+H]$^+$, 10), 369 ([M]$^+$, 28), 328 (7), 286 (11), 230 (100), 203 (60), 186 (13), 154 (13), 125 (13).
IR (neat): ν = 2923, 2852, 1637, 1447, 1234, 1138, 907, 726.
Elemental analysis: calcd. for $C_{23}H_{21}NOS$: C 74.75, H 8.46, N 3.79, found: C 74.75, H 8.35, N 4.04.

N-(10-Undecenyl)-*S*-cyclopropyl-*S*-phenyl sulfoximine (127)



Following GP8 using cyclopropyl phenyl sulfoximine **5m** (181 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product (210 mg, 91% yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 15:1 to 10:1).
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.86 – 7.83 (m, 2H), 7.59 – 7.50 (m, 3H), 5.84 – 5.74 (m, 1H), 4.97 (ddd, *J* = 17.1, 3.7, 1.6 Hz, 1H), 4.92 – 4.88 (m, 1H), 2.98 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.82 (dt, *J* = 12.1, 7.3 Hz, 1H), 2.55 (tt, *J* = 7.9, 4.7 Hz, 1H), 2.01 (dd, *J* = 14.5, 6.8 Hz, 2H), 1.58 – 1.44 (m, 3H), 1.36 – 1.23 (m, 12H), 1.10 – 0.98 (m, 2H), 0.81 – 0.74 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.0, 139.2, 132.4, 129.1, 128.7, 114.0, 44.0, 33.8, 32.9, 32.8, 29.5, 29.4, 29.3, 29.1, 28.9, 27.2, 5.9, 4.8.
MS (EI): *m/z* (%) = 334 ([M+H]$^+$, 13), 333 ([M]$^+$, 24), 292 (7), 194 (100), 167 (21), 124 (30).
IR (neat): ν = 2924, 2852, 1444, 1239, 1134, 721.
Elemental analysis: calcd. for $C_{20}H_{31}NOS$: C 72.02, H 9.37, N 4.20, found: C 71.90, H 9.24, N 4.59.

N-(10-Undecenyl)-*S*,*S*-dimethyl sulfoximine (128)



Following GP8 using dimethyl sulfoximine **5u** (93 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product (210 mg, 88% yield) as a white solid after purification by flash column chromatography (acetone/*n*-pentane 3:1). Mp.: 49 – 50 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.79 – 5.72 (m, 1H), 4.95 – 4.92 (d, *J* = 17.1 Hz, 1H), 4.88 – 4.86 (d, *J* = 10.1 Hz, 1H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.96 (s, 6H), 1.99 (q, *J* = 7.2 Hz, 2H), 1.51 (quint, *J* = 7.3 Hz, 2H), 1.33 – 1.27 (m, 5H), 1.23 (m, 7H).

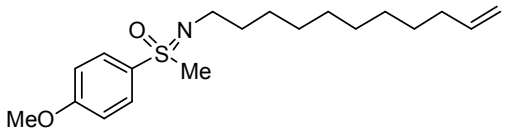
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.1, 114.0, 43.4, 41.8, 33.7, 32.8, 29.4, 29.3, 29.3, 29.3, 29.0, 28.8, 27.1.

MS (EI): *m/z* (%) = 246 ([M+H]$^+$, 4), 245 ([M]$^+$, 12), 204 (4), 106 (100), 94 (7), 79 (27).

IR (KBr): ν = 2916, 2847, 1468, 1199, 1124, 972.

Elemental analysis: calcd. for $C_{13}H_{27}NOS$: C 63.62, H 11.09, N 5.71, found: C 63.76, H 11.07, N 5.48.

N-(10-Undecenyl)-*S*-(4-methoxyphenyl)-*S*-methyl sulfoximine (129)



Following GP8 using 4-methoxyphenyl methyl sulfoximine **5j** (234 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product (239 mg, 86% yield) as a colorless oil purification by flash column chromatography (acetone/*n*-pentane 6:1 to 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.83 – 5.76 (m, 1H), 4.99 – 4.90 (m, 2H), 3.88 (s, 3H), 3.05 (s, 3H), 2.93 (dt, *J* = 12.1, 7.1 Hz, 1H), 2.75 (dt, *J* = 12.1, 7.3 Hz, 1H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.55 (quint, *J* = 7.3 Hz, 2H), 1.36 – 1.24 (m, 12 H).

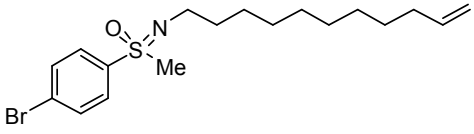
^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.06, 139.2, 131.0, 130.8, 114.4, 114.0, 55.6, 45.6, 43.9, 33.8, 32.9, 29.5, 29.4, 29.4, 29.1, 28.9, 27.3.

MS (EI): *m/z* (%) = 338 ([M+H]$^+$, 7), 337 ([M]$^+$, 23), 296 (7), 254 (8), 198 (100), 171 (35), 155 (42), 122 (10).

IR (neat): ν = 2923, 2850, 1741, 1589, 1491, 1457, 1241, 1130, 977.

Elemental analysis: calcd. for $C_{19}H_{31}NO_2S$: C 67.61, H 9.26, N 4.15, found: C 67.22, H 9.07, N 4.40.

N-(10-Undecenyl)-*S*-(4-bromophenyl)-*S*-methyl sulfoximine (130)

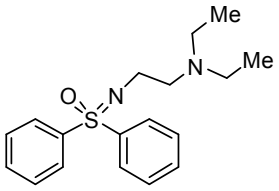


Following GP8 using 4-bromophenyl methyl sulfoximine **5c** (234 mg, 1.0 mmol), potassium hydroxide (112 mg, 2.0 mmol) and 11-bromo-1-undecene (350 mg, 1.5 mmol) provided the product

(128 mg, 79 % yield) as a colorless oil after purification by flash column chromatography (acetone/*n*-pentane 6:1).
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 5.84 – 5.77 (m, 1H), 5.00 – 4.91 (m, 2H), 3.06 (s, 3H), 2.93 (dt, *J* = 12.1, 7.1 Hz, 1H), 2.74 (dt, *J* = 12.1, 7.2 Hz, 1H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.53 (quint, *J* = 7.3 Hz, 2H), 1.37 – 1.25 (m, 12 H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.2, 139.0, 132.7, 130.0, 127.9, 114.1, 45.2, 43.9, 33.8, 32.8, 29.5, 29.4, 29.4, 29.1, 28.9, 27.2.
MS (EI): *m/z* (%) = 388 ([M+2]$^+$, 5), 387 ([M+1]$^+$, 15), 336 ([M]$^+$, 6), 248 (100), 247 (7), 246 (94), 221 (38), 219 (38), 205 (12), 204 (13), 92 (10).
IR (neat): ν = 2923, 2852, 1721, 1572, 1464, 1238, 1134, 977, 768.
Elemental analysis: calcd. for $C_{18}H_{28}BrNOS$: C 55.95, H 7.30, N 3.63, found: C 55.92, H 7.12, N 3.79.

N-(*N'*,*N'*-Diethylamino)-*S*,*S*-diphenyl sulfoximine (Suloxifen) (67)

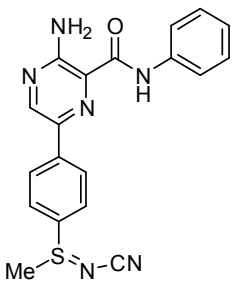
Following GP8 using diphenyl sulfoximine **5v** (217 mg, 1.0 mmol), potassium hydroxide (168 mg, 3.0 mmol) and 2-bromo-*N*,*N*-diethylethanamine hydrobromide (391 mg, 1.5 mmol) provided the product (79 mg, 25% yield) as light brown oil after purification by flash column chromatography (EtOH to EtOH/MeOH 4:1).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.97 – 7.96 (m, 4H), 7.50 – 7.44 (m, 6H), 3.14 (t, *J* = 7.8 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 2.52 (q, *J* = 7.2 Hz, 4H), 0.98 (t, *J* = 7.2 Hz, 6H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 140.7, 132.3, 129.1, 128.6, 55.6, 47.6, 42.3, 11.9.
MS (EI): *m/z* (%) = 317 ([M+H]$^+$, 41), 315 ([M–H]$^+$, 8), 239 (15), 230 (21), 203 (11), 86 (100).
IR (KBr): ν = 2966, 2929, 1446, 1256, 1138, 1070, 726.
HRMS (ESI): 339.1498, calcd. for $C_{18}H_{24}N_2ONaS$ [M+Na]$^+$: 229.1502.

12.3.3 Syntheses of ATR inhibitors

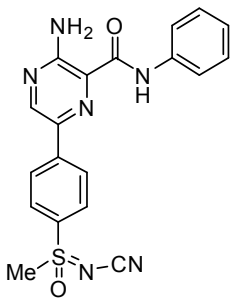
3-Amino-6-[4-(*N*-cyano-*S*-methylsulfilimidoyl)phenyl]-*N*-phenylpyrazine-2-carboxamide (135a)



Following GP11 using 3-amino-6-[4-(methylthio)phenyl]-*N*-phenylpyrazine-2-carboxamide (**148**) (100 mg, 0.3 mmol), cyanamide (19 mg, 0.45 mmol), acetonitrile (1 mL) and PIDA (105 mg, 0.33 mmol) provided the product as a yellow solid (105 mg, 93%) after purification by flash column chromatography (AcOEt/*n*-pentane 3:1 to AcOEt).
Mp: 165 – 167 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.42 (s, 1H), 9.00 (s, 1H), 8.49 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 8.6 Hz, 2H), 7.83 – 7.77 (m, 4H), 7.37 (t, J = 8.2 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 3.18 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 155.2, 145.7, 140.3, 138.3, 137.0, 136.1, 129.1, 127.4, 127.3, 124.8, 124.7, 121.7, 120.7, 35.2.
MS (EI): m/z (%) = 336 (sulfide, 17), 242 (5), 214 (45), 200 (10), 168 (63), 161 (19), 146 (31), 118 (47), 93 (100).
IR (KBr): ν = 3418, 3328, 2143 (CN), 1665, 1592, 1521 cm^{-1}.
HRMS (ESI): 399.1002, calcd. for $C_{19}H_{16}ON_6NaS$ [M+Na]$^+$: 399.0999.

3-Amino-6-[4-(*N*-cyano-*S*-methylsulfoximidoyl)phenyl]-*N*-phenylpyrazine-2-carboxamide (136a)

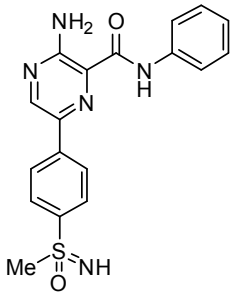


A mixture of 3-amino-6-[4-(*N*-cyano-*S*-methylsulfilimidoyl)-phenyl]-*N*-phenylpyrazine-2-carboxamide (**135a**) (60 mg, 0.16 mmol), potassium permanganate (50 mg, 3.2 mmol) in acetone (1.6 mL) was stirred at 50 °C for 2 h. The reaction mixture was filtered through a paper filter and the solvent was removed under reduced pressure. Purification by flash column chromatography (AcOEt/*n*-pentane 2:1 to AcOEt) provided the product as a yellow solid (48 mg, 77%). Mp: 229 – 231 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.45 (s, 1H), 9.05 (s, 1H), 8.59 (d, J = 8.7 Hz, 2H), 8.09 (d, J = 8.7 Hz, 2H), 7.91 (s, 2H), 7.79 (d, J = 8.6 Hz, 2H), 7.38 (t, J = 8.3 Hz, 2H), 7.14 (t, J = 7.4 Hz, 1H), 3.75 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.7, 155.3, 146.1, 142.6, 138.2, 136.3, 135.3, 129.1, 128.6, 127.2, 125.1, 124.8, 121.7, 112.8, 43.2.
IR (KBr): ν = 3422, 3141, 2189 (CN), 1663, 1594, 1530, 1097.
HRMS (ESI): 415.0951, calcd. for $C_{19}H_{16}O_2N_6NaS$ [M+Na]$^+$: 415.0953.

3-Amino-6-[4-(*N*H-*S*-methylsulfoximidoyl)phenyl]-*N*-phenylpyrazine-2-carboxamide (136b)

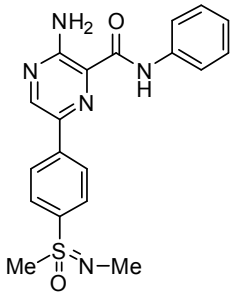
Following GP7 using 3-amino-6-[4-(*N*-cyano-*S*-methylsulfoximidoyl)phenyl]-*N*-phenylpyrazine-2-carboxamide (**135a**) (51 mg, 0.13 mmol) and 50% aq sulfuric acid (6 mL) the product was obtained as a yellow solid (25 mg, 52%) after purification by flash column chromatography (AcOEt/*n*-pentane 5:1 to AcOEt). Mp: 180 – 182 °C.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.43 (s, 1H), 9.01 (s, 1H), 8.44 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H), 7.90 – 7.81 (m, 4H), 7.40 (t, J = 8.3 Hz, 2H), 7.17 (t, J = 7.4 Hz, 1H), 4.27 (s, 1H), 3.11 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 155.1, 145.7, 143.7, 140.0, 138.3, 137.3, 129.1, 128.1, 126.5, 124.8, 124.7, 121.7, 46.3.

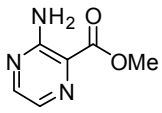
MS (EI): *m/z* (%) = 368 ([M+H]$^+$, 23), 367 ([M]$^+$, 96), 337 (5), 304 (100), 247 (9), 196 (15).
IR (KBr): ν = 3267, 2924, 1667, 1592, 1524, 1209, 1097 cm^{-1}.
HRMS (ESI): 368.1176, calcd. for $C_{18}H_{18}O_2N_5S$ [M+H]$^+$: 368.1176.
Analytical HPLC: t_r = 45.1 [50%], t_r = 64.2 min [50%] (Chiralpak AD-H column, flow rate 0.5 mL/min, heptane/*i*-PrOH = 50:50, λ = 210 nm, 20 °C).
Preparative HPLC: t_{r1} = 74.2 min [50%], t_{r2} = 80.6 min [50%] (Chiralpak AD-H 250 x 50 mm, flow rate 35 mL/min, *n*-hexane/EtOH = 50:45, λ = 275 nm, 28 °C).
Optical rotation: $[\alpha]_D^{20}$ (t_{r1}) = −10.0 (c = 0.2, acetone), $[\alpha]_D^{20}$ (t_{r2}) = +12.0 (c = 0.16, acetone).

3-Amino-6-[4-(*N*-methyl-*S*-methylsulfoximidoyl)phenyl]-*N*-phenylpyrazine-2-carboxamide (136c)



To a solution of methylamine in MeOH (33%, 0.45 mmol, 54 µL) diluted in MeOH (1 mL), bromine (15 µL, 0.23 mmol) was added and the mixture was stirred at r.t. for 5 min.[62b] 3-Amino-6-(4-(methylthio)phenyl)-*N*-phenylpyrazine-2-carboxamide (**148**) (50 mg, 0.15 mmol) and additional MeOH (1 mL) were added and the reaction mixture was stirred for 10 min. The solvents were removed under reduced pressure and acetone (5 mL) was added. The resulting precipitate was filtered of and the filtrate was concentrated under reduced pressure. Acetone (1 mL), K_2CO_3 (42 mg, 0.3 mmol) and potassium permanganate (71 mg, 0.45 mmol) were added subsequently and the reaction mixture was stirred for 16 h at r.t.. The solvent was removed under reduced pressure. Purification by flash column chromatography (acetone/AcOEt 1:2 to acetone) provided the product as a yellow solid (37 mg, 64%). Mp: 209 – 211 °C.
^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.44 (s, 1H), 9.01 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 2H), 7.91 – 7.81 (m, 6H), 7.40 (t, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 3.34 (s, 3H), 3.17 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 155.1, 145.7, 140.3, 138.6, 138.3, 137.2, 129.1, 129.1, 126.9, 124.8, 124.7, 121.6, 44.1, 29.6.
MS (EI): *m/z* (%) = 382 ([M+H]$^+$, 12), 381 ([M]$^+$, 29), 337 (10), 318 (100), 197 (24), 169 (19).
IR (KBr): ν = 3401, 1670, 1592, 1529, 1237, 1144, 1102 cm^{-1}.
HRMS (ESI): 382.1318, calcd. for $C_{19}H_{20}O_2N_5S$ [M+H]$^+$: 382.1332.

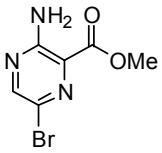
Methyl 3-Aminopyrazine-2-carboxylate (138)



3-Amino-2-pyrazinecarboxylic acid (**137**) (6.0 g, 43.2 mmol) was dissolved in absolute MeOH (60 mL). Conc sulfuric acid (6 mL) was added and the reaction mixture was stirred at r. t. for 24 h. After the addition of ice water (60 mL) the pH was adjusted to 10 using ammonium hydroxide solution (30 – 35 %). The reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined

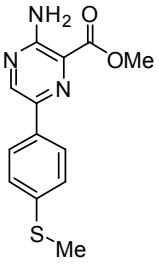
organic layers were washed with brine, dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. The product was obtained as a yellow solid (2.3 g, 35%).
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.18 (d, J = 2.2 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 3.97 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.8, 155.9, 147.5, 133.6, 124.3, 52.8.
The corresponding spectroscopic data matched that reported in the literature.[180b]

Methyl 3-amino-6-bromopyrazine-2-carboxylate (139)



Methyl 3-aminopyrazine-2-carboxylate (**138**) (2.3 g, 15.0 mmol) was suspended in acetonitrile (27 mL). NBS (2.7 g, 15 mmol) was added and the reaction mixture was stirred at r. t. for 24 h. The solvent was removed under reduced pressure. Purification by flash column chromatography (acetone/*n*-pentane 1:10) provided the product as a yellow solid (1.67 g, 48%).
^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.40 (s, 1H), 7.53 (s, 2H, NH_2), 3.83 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 156.8, 155.4, 150.6, 123.1, 122.9, 52.8.
The corresponding spectroscopic data matched that reported in the literature.[179]

Methyl 3-amino-6-[4-(methylthio)phenyl]-pyrazine-2-carboxylate (143)

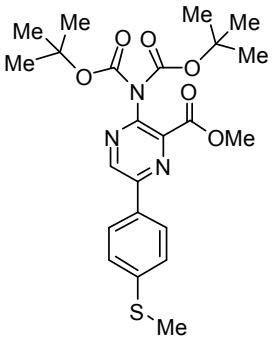


Following GP9 using methyl 3-amino-6-bromopyrazine-2-carboxylate (**139**) (300 mg, 1.29 mmol), 4-(methylthio)phenylboronic acid (261 mg, 1.55 mmol), bis(triphenylphosphine)palladium(II) dichloride (45 mg, 5 mol%), aqueous 2 M Na_2CO_3 solution (1.9 mL), and dimethoxyethane (3.6 mL), provided the product as a yellow solid (339 mg, 95%) after flash column chromatography (AcOEt).
Mp: 226 – 228 °C.
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.64 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.47 (s, 2H), 4.00 (s, 3H), 2.51 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.1, 154.4, 144.6, 141.8, 139.4, 133.0, 126.7, 126.2, 123.1, 52.8, 15.6.
MS (EI): m/z (%) = 276 ([M+H]$^+$, 11), 275 ([M]$^+$, 60), 273 (100), 215 (83), 199 (38), 168 (58), 146 (62), 114 (46), 107 (39) ppm.
IR (KBr): ν = 3423, 3131, 1690, 1617, 1448, 1192, 1105, 821.
HRMS (ESI): 298.0629, calcd. for $C_{13}H_{13}O_2N_3NaS$ [M+Na]$^+$: 298.0621.

Methyl 3-(*N*,*N*-di-Boc-amino)-6-[4-(methylthiophenyl)-phenyl]-*N*-pyrazine-2-carboxylate (144)

To a solution of methyl 3-amino-6-[4-(methylthio)phenyl]-*N*-pyrazine-2-carboxy-late (**143**) (150 mg, 0.55 mol) in CH_2Cl_2 (2.5 mL) was added DMAP (6.7 mg, 0.06 mg), Boc_2O (359 mg, 1.65 mmol), and triethylamine (0.12 mL, 0.83 mmol). The reaction mixture was

stirred at 50 °C for 16 h. Water (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by flash column chromatography (acetone/*n*-pentane 1:20 to 1:10) provided the product as a light-yellow oil (141 mg, 54%).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.00 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 3.97 (s, 3H), 2.50 (s, 3H), 1.39 (s, 18 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.8, 150.6, 150.1, 145.9, 142.5, 141.9, 140.8, 131.0, 127.4, 126.7, 83.6, 53.1, 27.8, 15.1.

MS (EI): *m/z* (%) = 475 ([M]$^+$, 2), 318 (10), 300 (100), 275 (46), 273 (86), 242 (8), 213 (17).

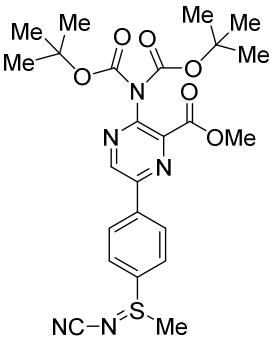
MS (CI): *m/z* (%) = 476 ([M+H]$^+$, 26), 377 (68), 320 (29), 301 (27), 113 (100).

IR (KBr): ν = 2981, 1734, 1596, 1441, 1364, 1245, 1101, 832 cm^{-1}.

HRMS (ESI): 498.1676, calcd. for $C_{23}H_{29}O_6N_3NaS$ [M+Na]$^+$: 498.1669.

Methyl 3-(*N*,*N*-di-Boc-amino)-6-[4-(*N*-cyano-*S*-methylsulfilimidoyl)-phenyl]-*N*-pyrazine-2-carboxylate (145)

Following GP10 using methyl 3-(*N*,*N*-di-Boc-amino)-6-[4-(*N*-cyano-*S*-methyl-sulfilimidoyl)-phenyl]-*N*-pyrazine-2-carboxylate (**144**) (133 mg, 0.28 mmol), cyanamide (15 mg, 0.36 mmol), *t*-BuOK (38 mg, 0.34 mmol), NBS (75 mg, 0.42 mmol) and MeOH (1.8 mL) provided the product as a colorless oil (129 mg, 89%) after purification by flash column chromatography (acetone/*n*-pentane 1:4 to 1:1).



^{1}H NMR (400 MHz, acetone-d_6): δ = 9.10 (s, 1H), 8.33 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 4.00 (s, 3H), 3.07 (s, 3H), 1.42 (s, 18 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 158.2, 144.8, 143.4, 142.2, 137.3, 136.2, 134.1, 133.0, 123.8, 121.5, 114.8, 78.9, 48.1, 31.4, 22.6.

MS (EI): *m/z* (%) = 273 (18), 214 (9), 91 (25), 59 (100).

MS (CI): *m/z* (%) = 476 (1), 377 (5), 155 (14), 132 (30), 113 (100).

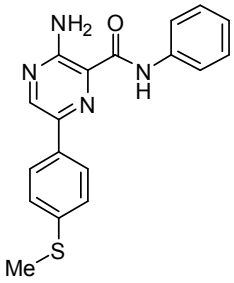
IR (KBr): ν = 2979, 2149, 1799, 1732, 1445, 1366, 1244, 1102, 844, 765 cm^{-1}.

HRMS (ESI): 538.1737, calcd. for $C_{24}H_{29}O_6N_5NaS$ [M+Na]$^+$: 538.1736.

3-Amino-6-[4-(methylthio)phenyl]-*N*-phenylpyrazine-2-carboxamide (148)

Following GP9 using 3-amino-6-bromo-*N*-phenylpyrazine-2-carboxamide (**150**) (100 mg, 0.34 mmol), 4-(methylthio)phenylboronic acid (69 mg, 0.41 mmol), bis(triphenyl-phosphine)palladium(II) dichloride (12 mg, 5 mol%), aqueous 2 M Na_2CO_3 solution (0.5 mL), and degassed dimethoxyethane (0.95 mL) provided the product as a yellow solid (113 mg, 99%) after purification by flash column chromatography (aceto-ne/*n*-pentane 1:10 to1:6). Mp: 187 – 189 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.87 (s, 1H), 8.63 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 2.53 (s, 3H).



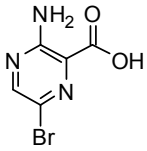
^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.0, 153.9, 144.3, 139.8, 139.6, 137.4, 132.6, 129.1, 126.6, 125.9, 124.6, 124.5, 119.9, 15.6.

MS (EI): *m/z* (%) = 336 ([M]$^+$, 12), 242 (4), 214 (29), 198 (9), 169 (30), 162 (21), 146 (27), 93 (100).

IR (KBr): ν = 3391, 3016, 1740, 1367, 1214 cm^{-1}.

HRMS (ESI): 337.1117, calcd. for $C_{18}H_{17}ON_4S$ [M+H]$^+$: 337.1118.

3-Amino-6-bromopyrazine-2-carboxylic acid (149)



A mixture of methyl 3-amino-6-bromopyrazine-2-carboxylate (**139**) (1.0 g, 4.3 mmol), lithium hydroxide (516 mg, 21.6 mmol) in water (4.0 mL) and MeOH (4 mL) was stirred at 90 °C for 3 h. The pH was adjusted to 5-4 by addition of 6 M HCl. The yellow precipitate was filtered off and washed with cold water. After removing the solvents under reduced pressure the product was obtained as a yellow solid (692 mg, 74%).

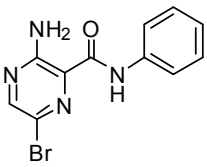
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17 (s, 1H), 7.72 (s, 2H, NH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.4, 155.6, 150.0, 124.0, 122.9.

The corresponding spectroscopic data matched that reported in the literature.[179]

3-Amino-6-bromo-*N*-phenylpyrazine-2-carboxamide (150)

To 3-amino-6-bromopyrazine-2-carboxylic acid (**149**) (400 mg, 1.8 mmol) and HOBt (140 mg, 0.92 mmol) was added a solution of DCC (1 M in CH_2Cl_2, 2.2 mL, 2.2 mmol). Dry DMF (18 mL) was added and the resulting solution was stirred at r.t. for 45 min. Subsequently, aniline (171 mg, 1.8 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. Brine (60 mL) was added and the aqueous phase was extracted with AcOEt (3 x 80 mL). The combined organic layers were washed with brine (4 x 60 mL) and dried with anhydrous magnesium sulfate. The solvents were removed under reduced pressure. Purification by flash column chromatography (AcOEt/*n*-pentane 1:10 to 1:6) provided the product as a yellow solid (280 mg, 52%).



^{1}H NMR (600 MHz, MeOH-d_4): δ = 8.30 (s, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 8.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 1H).

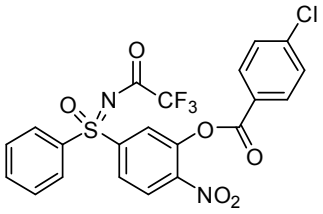
^{13}C NMR (151 MHz, MeOH-d_4): δ = 163.6, 154.6, 149.2, 137.6, 128.5, 125.3, 124.2, 121.8, 120.3.

The corresponding spectroscopic data matched that reported in the literature.[179]

12.3.4 Syntheses of ATPase inhibitors

2-Nitro-5-[*N*-(2,2,2-trifluoroacetyl)phenylsulfonimidoyl]phenyl 4-chlorobenzoate (151a)

Following GP12 using 2-nitro-5-(phenylsulfinyl)phenyl 4-chlorobenzoate (**158**) (61 mg, 0.15 mmol), trifluoroacetamide (34 mg, 0.30 mmol), magnesium oxide (25 mg, 0.61 mmol), $Rh_2(OAc)_4$ (1.7 mg, 2.5 mol%), PIDA (73 mg, 0.23 mmol) and CH_2Cl_2 (1.5 mL) the product was obtained as a white solid (54 mg, 69%). Mp.: 52 – 50 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.7 Hz, 1H), 8.10 – 8.03 (m, 5H), 7.96 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.67 – 7.63 (m, 1H), 7.53 – 7.50 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.8 (q, *J* = 38.6 Hz), 162.7, 144.9, 144.6, 143.9, 141.6, 135.8, 135.4, 132.0, 130.4, 129.4, 128.0, 127.2, 125.8, 125.5, 125.0.

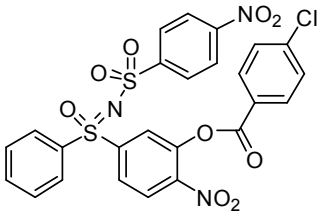
^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.92.

IR (KBr): ν = 1750, 1689, 1536, 1357, 1155, 1047, 830 cm^{-1}.

HRMS (ESI): 534.9940 calcd. for $C_{21}H_{12}O_6N_2ClF_3NaS$ $[M+Na]^+$: 534.9949.

2-Nitro-5-(*N*-(nosyl)phenylsulfonimidoyl)phenyl 4-chlorobenzoate (151b)

To a mixture of 2-nitro-5-(phenylsulfinyl)phenyl 4-chlorobenzoate (**158**) (53 mg, 0.13 mmol), PhI=NNs (69 mg, 0.17 mmol), $Fe(OTf)_2$ (7 mg, 15 mol%) and MeCN (1.3 mL) was added MS 4 Å (2 beads)[54] and the reaction mixture was stirred at r.t. for 16 h. After removing the solvent under reduced pressure and subsequent purification by column chromatography (AcOEt/*n*-pentane 1:5) the product was obtained as a white solid (55 mg, 69%). Mp.: 69 – 71 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.7 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 8.10 – 8.07 (m, 3H), 8.05 – 8.02 (m, 3H), 7.73 – 7.69 (m, 1H), 7.62 (t, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H).

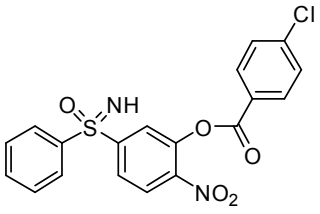
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 149.9, 148.4, 145.5, 144.9, 144.5, 141.6, 137.3, 135.3, 132.0, 130.3, 129.4, 128.1, 128.0, 127.1, 125.8, 125.7, 125.0, 124.1.

IR (KBr): ν = 1745, 1596, 1530, 1351, 1086, 741 cm^{-1}.

HRMS (ESI): 623.9883 calcd. for $C_{25}H_{16}O_9N_3ClNaS_2$ $[M+Na]^+$: 623.9809.

2-Nitro-5-(phenylsulfonimidoyl)phenyl 4-chlorobenzoate (151d)

A flame-dried and argon-flushed Schlenk tube was charged with $Rh_2(esp)_2$ (6.6 mg, 3.5 mol%), *O*-(2,4-dinitrophenyl)hydroxylamine (149 mg, 0.75 mmol) and 2,2,2-trifluoroethanol (2.5 mL).[45] After cooling to 0 °C, 2-nitro-5-(phenylsulfinyl)phenyl 4-chlorobenzoate (**158**) (100 mg,



0.25 mmol) was added and the reaction mixture was stirred at 0 °C for 17 h. Water (5 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. After purification by column chromatography (AcOEt/*n*-pentane 5:1 to 2:1) the product was obtained as a white solid (78 mg, 75%). Mp.: 57 – 59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.6 Hz, 1H), 8.09 – 8.03 (m, 6H), 7.61 – 7.57 (m, 1H), 7.55 – 7.48 (m, 4H), 2.67 (s, 1H).

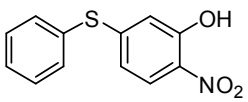
^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.0, 149.7, 144.2, 144.0, 141.5, 141.3, 133.6, 131.9, 129.6, 129.3, 128.3, 126.6, 126.2, 126.0, 125.1.

MS (EI): *m/z* (%) = 416 ([M]$^+$, 2), 141 (32), 139 (100), 125 (45), 111 (27), 92 (65).

IR (KBr): ν = 1747, 1594, 1530, 1346, 1210, 1049, 834 cm^{-1}.

HRMS (ESI): 417.0305 calcd. for $C_{19}H_{14}O_5N_2ClS$ [M+H]$^+$: 417.0307.

(3-Hydroxy-4-nitro)phenylthioether (154)



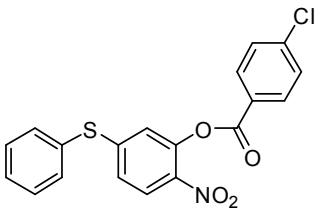
A mixture of 5-fluoro-2-nitrophenol (**152**) (300 mg, 1.9 mmol), phenylthiotrimethylsilane (**153**) (0.44 mL, 2.3 mmol), TBAF (5 mg, 0.02 mmol) and acetonitrile (3.8 mL) was stirred at r.t. for 16 h. The solvent was removed under reduced pressure. After purification by column chromatography (AcOEt/*n*-pentane 100:1 to 50:1) the product was obtained as a yellow solid (413 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.73 (s, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.56 – 7.45 (m, 5 H), 6.67 – 6.64 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 152.8, 135.3, 130.09, 130.1, 129.3, 125.2, 117.9, 115.2.

The corresponding spectroscopic data matched that reported in the literature.[190]

2-Nitro-5-(phenylthio)phenyl 4-chlorobenzoate (156)



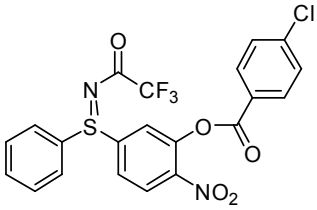
To a solution of (3-hydroxy-4-nitro)phenylthioether (**154**) (1.4 g, 5.3 mmol) in dry CH_2Cl_2 (28 mL) under argon was added triethylamine (1.1 mL, 8.0 mmol). 4-Chlorobenzoyl chloride (**155**) (0.75 mL, 5.9 mmol) was added and the reaction mixture was stirred at r.t. for 16 h. Water (20 mL) was added and the two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried with anhydrous magnesium sulfate. After removing the solvents under reduced pressure and purification by column chromatography (Et_2O/*n*-pentane 20:1) the product was obtained as a light yellow solid (2.0 g, 97%) Mp.: 95 – 96 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.6 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.58 – 7.57 (m, 2H), 7.49 – 7.47 (m, 5H), 7.07 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 149.4, 144.7, 140.7, 138.4, 135.0, 131.8, 130.2, 130.0, 129.6, 129.1, 126.4, 123.9, 122.0.
MS (EI): *m/z* (%) = 385 ([M]$^+$, 4), 339 (2), 171 (10), 141 (57), 139 (100), 113 (15), 111 (50).
IR (KBr): ν = 3054, 1740, 1580, 1500, 1329, 1063, 741 cm^{-1}.
HRMS (ESI): 408.0066, calcd. for $C_{19}H_{12}O_4NClNaS$ [M+Na]$^+$: 408.0068.

2-Nitro-5-[*N*-(2,2,2-trifluoroacetyl)phenylsulfilimidoyl]phenyl 4-chloro-benz-oate (157a)

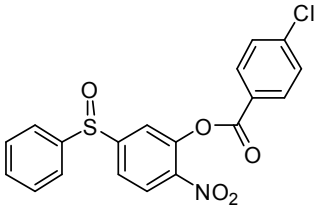
Following GP12 using 2-nitro-5-(phenylthio)phenyl 4-chlorobenzoate (**156**) (50 mg, 0.13 mmol), trifluoroacetamide (29 mg, 0.26 mmol), magnesium oxide (21 mg, 0.52 mmol), $Rh_2(OAc)_4$ (1.4 mg, 2.5 mol%), PIDA (63 mg, 0.2 mmol) and CH_2Cl_2 (1.3 mL) the product was obtained as a white solid (53 mg, 82%). Mp.: 48 – 50 °C.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 1.9 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.78 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.64 – 7.56 (m, 3H), 7.50 (d, *J* = 8.7 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0 (q, *J* = 35.7 Hz), 162.8, 144.9, 144.0, 141.5, 140.7, 133.9, 132.5, 132.0, 130.8, 129.3, 128.3, 127.3, 125.9, 125.5, 124.6, 121.1, 116.8 (q, *J* = 287.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.41.
MS (EI): *m/z* (%) = 496 ([M]$^+$, 2), 358 (9), 289 (12), 247 (14), 141 (31), 139 (100), 111 (32).
IR (KBr): ν = 1750, 1638, 1593, 1533, 1255, 1205, 1046 cm^{-1}.
HRMS (ESI): 518.9984 calcd. for $C_{21}H_{12}O_5N_2ClF_3NaS$ [M+Na]$^+$: 518.9999.

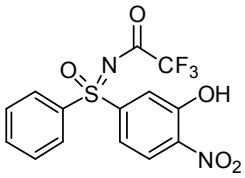
2-Nitro-5-(phenylsulfinyl)phenyl 4-chlorobenzoate (158)

Following GP13 using 2-nitro-5-(phenylthio)phenyl 4-chlorobenzoate (**156**) (200 mg, 0.52 mmol), aq 30% hydrogen peroxide solution (0.24 mL) and CH_2Cl_2 (1 mL) provided the product as a light yellow solid (157 mg, 75%) after purification by column chromatography (AcOEt/*n*-pentane 3:1 to1:1).
Mp.: 106 – 107 °C.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.70 – 7.68 (m, 2H), 7.63 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.51 – 7.49 (m, 5H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.1, 153.3, 144.7, 144.0, 142.8, 141.1, 132.3, 131.9, 129.9, 129.2, 126.7, 126.3, 125.0, 122.2, 121.8.
MS (EI): *m/z* (%) = 401 ([M]$^+$, 3), 141 (32), 139 (100), 111 (8).
IR (KBr): ν = 3084, 1737, 1586, 1516, 1256, 1051, 834 cm^{-1}.
HRMS (ESI): 424.0017 calcd. for $C_{19}H_{12}O_5NClNaS$ [M+Na]$^+$: 424.0017.

N-(2,2,2-trifluoroacetyl)-*S*-(3-hydroxy-4-nitro)phenyl-*S*-phenyl sulfoximine (159)



Following GP14 using 2-nitro-5-[*N*-(2,2,2-trifluoroacetyl)phenyl-sulfonimidoyl]-phenyl 4-chlorobenzoate (**151a**) (54 mg, 0.13 mmol), K_2CO_3 (89 mg, 0.65 mmol) and MeOH (4 mL) the product was obtained as a yellow solid (28 mg, 57%) after purification by column chromatography (AcOEt to AcOEt/MeOH 15:1). Mp.: 116 – 118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 – 7.89 (m, 3H), 7.62 – 7.58 (m, 2H), 7.57 – 7.53 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 5.17 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 143.0, 139.9, 133.3, 129.8, 128.2, 126.6, 119.8, 117.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –73.65.

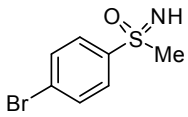
MS (EI): *m/z* (%) = 278 (*N*H-sulfoximine, 2), 125 (46), 92 (68), 77 (97), 51 (100).

IR (KBr): ν = 3278, 1684, 1528, 1426, 1198, 1132, 997, 717 cm^{-1}.

HRMS (ESI): 397.0077 calcd. for $C_{14}H_9O_5N_2F_3NaS$ $[M+Na]^+$: 397.0077.

12.3.5 Syntheses of 4-(*N*-indolyl)phenyl methyl sulfoximines

*N*H 4-Bromophenyl methyl sulfoximine (5c)



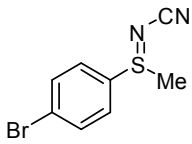
Following GP14 using *N*-(2,2,2-trifluoroacetyl) 4-bromophenyl methyl sulfoximine (**10c**) (856 mg, 2.6 mmol), K_2CO_3 (1.84 g, 13.3 mmol) and MeOH (18.6 mL) the product was obtained as a white solid (509 mg, 82%) after purification by column chromatography (acetone/*n*-pentane 1:3 to 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 3.09 (s, 3H), 2.57 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 133.4, 130.5, 128.6, 44.2.

The corresponding spectroscopic data matched that reported in the literature.[106]

N-Cyano 4-bromophenyl methyl sulfilimine (8c) (big scale synthesis)



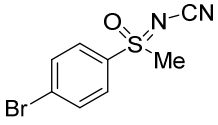
Following GP10 using 4-bromophenyl methyl sulfide (**1c**) (6.0 g, 29.5 mmol), cyanamide (1.6 g, 38.4 mmol), *t*-BuOK (4.0 g, 35 mmol), NBS (7.9 g, 44.3 mmol) and MeOH (177 mL) provided the product a white solid (6.17 g, 86%) after purification by flash column chromatography (AcOEt/*n*-pentane 1:3 to 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 3.01 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 135.2, 133.6, 128.2, 127.4, 119.9, 36.6.

For further spectral data, see small scale synthesis using Burgess-type reagent.

N-Cyano 4-bromophenyl methyl sulfoximine (9c)



Following GP4 using *N*-cyano 4-bromophenyl methyl sulfilimine (**8c**) (7.1 g, 29.5 mmol), *m*CPBA (10.8 g, 44.3 mmol), potassium carbonate (12.2 g, 88.5 mmol) and MeOH (308 mL) provided the product as a white solid (6.8 g, 89%) after purification by flash column chromatography (acetone/*n*-pentane 1:2 to 1:1). Mp.: 116 – 118 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 9.0 Hz, 2H), 7.85 (d, *J* = 8.9 Hz, 2H), 3.37 (s, 3H).

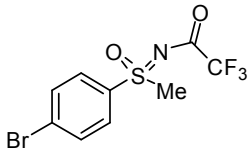
^{13}C NMR (151 MHz, $CDCl_3$): δ = 135.0, 133.7, 131.3, 129.4, 111.5, 44.8.

MS (EI): *m/z* (%) = 260 ([M+H]$^+$, 32), 258 ([M–H]$^+$, 37), 205 (100), 203 (94), 157 (21), 155 (22).

IR (KBr): ν = 3000, 2188, 1710, 1566, 1384, 1237, 1168, 977, 774 cm^{-1}.

Elemental analysis: calcd. for $C_8H_7BrN_2OS$: C 37.08, H 2.72, N 10.81, found: C 37.12, H 2.83, N 10.79.

N-(2,2,2-Trifluoroacetyl) 4-bromophenyl methyl sulfoximine (10c)



To a solution of *N*-cyano 4-bromophenyl methyl sulfoximine (**9c**) (1.0 g, 3.9 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added trifluoroacetic anhydride (1.62 mL, 11.6 mmol). The reaction mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure and subsequent purification by column chromatography (AcOEt/*n*-pentane 1:3) provided the product as a white solid (990 mg, 77%).

Mp.: 99 – 101 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.9 Hz, 2H), 7.80 (d, *J* = 8.9 Hz, 2H), 3.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 135.7, 133.4, 130.5, 128.6, 44.2.

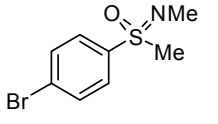
^{19}F NMR (376 MHz, $CDCl_3$): δ = –76.04.

MS (EI): *m/z* (%) = 330 ([M$^+$], 2), 262 (97), 260 (100), 205 (18), 203 (18), 173 (38), 171 (42), 157 (22), 155 (21), 145 (16), 143 (16).

IR (KBr): ν = 1676, 1569, 1382, 1141, 978, 829 cm^{-1}.

Elemental analysis: calcd. for $C_9H_7BrF_3NO_2S$: C 32.75, H 2.14, N 4.24, found: C 32.80, H 2.25, N 4.28.

N-Methyl 4-bromophenyl methyl sulfoximine (13c)

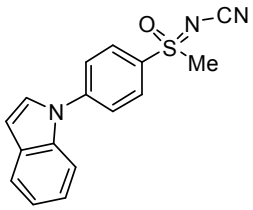


Following GP15 using *N*H 4-bromophenyl methyl sulfoximine (**5c**) (300 mg, 1.3 mmol), formaldehyde (195.2 mg, 6.5 mmol), formic acid (5 mL) provided the product as a white solid (234 mg, 74%) after purification by flash column chromatography (acetone/*n*-pentane 1:5 to 1:2). Mp.: 68 – 69 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 3.05 (s, 3H), 2.62 (3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 132.7, 130.3, 128.0, 44.8, 29.4.
MS (EI): *m/z* (%) = 249 ([M+H]$^+$,13), 248 ([M$^+$], 24), 246 (39), 232 (22), 230 (18), 186 (32), 185 (38), 184 (100), 155 (27), 105 (25), 105 (51), 76 (47).
IR (KBr): ν = 2910, 1568, 1464, 1384, 1227, 1146, 971, 768 cm^{-1}.
Elemental analysis: calcd. for $C_8H_{10}BrNOS$: C 38.72, H 4.06, N 5.64, found: C 38.76, H 4.26, N 5.53.

N-Cyano 4-(*N*-indolyl)phenyl methyl sulfoximine (161a)

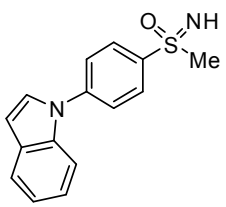


Following GP16 using *N*-cyano 4-bromophenyl methyl sulfoximine (**9c**) (77.7 mg, 0.3 mmol), indole (42.1 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (7.5 mg, 4 mol%), $Pd_2(dba)_3$ (5.5 mg, 2 mol%) and toluene (1.5 mL) provided the product as a light-yellow solid (74.4 mg, 84%) after purification by column chromatography (acetone/*n*-pentane 1:3). Mp.: 144 – 147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.70 (dd, *J* = 18.4, 7.9 Hz, 2H), 7.36 (d, *J* = 3.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 6.78 (d, *J* = 3.4 Hz, 1H) 3.39 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.0, 135.1, 132.0, 130.2, 130.0, 127.0, 124.2, 123.6, 121.8, 121.7, 111.8, 110.4, 106.6, 45.0.
MS (EI): *m/z* (%) = 295 ([M$^+$], 13), 260 (63), 258 (65), 220 (82), 218 (88), 205 (100), 203 (92), 157 (22), 155 (24), 96 (40), 75 (76).
IR (KBr): ν = 3012, 2921, 2194, 1585, 1338, 1241, 1192, 745 cm^{-1}.
HRMS (ESI): 318.0679 calcd. for $C_{16}H_{13}ON_3NaS$ [M+Na]$^+$: 318.0972.
Analytical HPLC: t_r = 25.8 min [50%], t_r = 27.9 min [50%] (Chiralpak IB column, flow rate 0.6 mL/min, heptane/EtOH = 70:30, λ = 210 nm, 20 °C).
Preparative HPLC: t_{r1} = 22.0 [50%], t_{r2} = 26.0 min [50%] (Chiralpak AD-H column, flow rate 40 mL/min, *n*-hexane/*i*-PrOH = 87.5:12.5, λ = 254 nm, 28 °C).
Optical rotation: $[\alpha]_D^{20}$ (t_{r1}) = −189.5 (c = 0.24, acetone), $[\alpha]_D^{20}$ (t_{r2}) = +177.6 (c = 0.29, acetone).

*N*H 4-(*N*-indolyl)phenyl methyl sulfoximine (161b)

Following GP14 using *N*-(2,2,2-trifluoroacetyl) 4-(*N*-indolyl)phenyl methyl sulfoximine (**161d**) (33 mg, 0.09 mmol), K_2CO_3 (62 mg, 0.45 mmol) and MeOH (0.6 mL) the product was obtained as a white solid (24 mg, 99%) after purification by column chromatography (acetone/*n*-pentane 1:1). Mp.: 150 – 152 °C (decomposition).

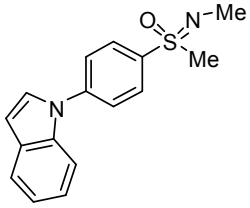


^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 3H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 3.3 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.24 – 7.21 (m, 1H), 6.76 (d, *J* = 3.3 Hz, 1H), 3.19 (s, 3H), 2.68 (br s, 1H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 144.0, 140.5, 135.5, 129.9, 129.6, 127.3, 123.9, 123.2, 121.6, 121.3, 110.4, 105.5, 46.4.

MS (EI): *m/z* (%) = 271 ([M$^+$], 19), 270 ([M+H]$^+$, 100), 240 (10), 207 (95), 192 (29), 191 (58).
IR (KBr): ν = 3255, 1586, 1490, 1448, 1333, 1203, 1091, 1001, 733 cm^{-1}.
HRMS (ESI): 271.0906 calcd. for $C_{15}H_{15}ON_2S$ [M+H]$^+$: 271.0900.
Analytical HPLC: t_r = 23.5 [50%], t_r = 25.9 min [50%] (Chiralpak IB column, flow rate 0.7 mL/min, heptane/EtOH = 80:20, λ = 210 nm, 20 °C).
Preparative HPLC: t_{r1} = 39.5 [50%], t_{r2} = 46.3 min [50%] (Chiralcel OD-H column, flow rate 40 mL/min, *n*-hexane/EtOH = 9:1, λ = 254 nm, 28 °C).
Optical rotation: $[\alpha]_D^{20}$ (t_{r1}) = +18.8 (c = 0.24, acetone), $[\alpha]_D^{20}$ (t_{r2}) = −22.9 (c = 0.24, acetone).

N-Methyl 4-(*N*-indolyl)phenyl methyl sulfoximine (161c)

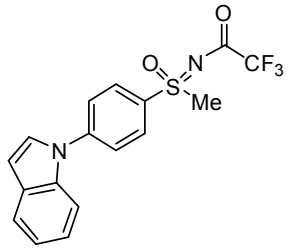
Following GP16 using *N*-methyl 4-bromophenyl methyl sulfoximine (**13c**) (74.4 mg, 0.3 mmol), indole (42.1 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (7.5 mg, 4 mol%), $Pd_2(dba)_3$ (5.5 mg, 2 mol%) and toluene (1.5 mL) provided the product as a yellow oil (74.4 mg, 84%) after purification by column chromatography (acetone/*n*-pentane 1:3).



^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.5 Hz, 2H), 7.77 – 7.74 (m, 3H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 3.3 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 3.2 Hz, 1H), 3.19 (s, 3H), 2.76 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.9, 135.9, 135.4, 130.7, 129.9, 127.3, 124.2, 123.2, 121.6, 121.3, 110.5, 105.5, 45.2, 29.7.
MS (EI): *m/z* (%) = 285 ([M+H]$^+$, 284 ([M$^+$], 100), 240 (28), 221 (62), 191 (32).
IR (KBr): ν = 2920, 1589, 1498, 1454, 1335, 1232, 1139, 744 cm^{-1}.
HRMS (ESI): 285.1061 calcd. for $C_{16}H_{17}ON_2S$ [M+H]$^+$: 285.1056.
Analytical HPLC: t_r = 22.8 [50%], t_r = 25.2 min [50%] (Chiralpak AD-H column, flow rate 0.8 mL/min, heptane/*i*-PrOH/MeOH = 84:8:8, λ = 210 nm, 20 °C).
Preparative SFC: t_{r1} = 24.8 min [50%], t_{r2} = 27.5 min [50%] (65 mL CO_2/min 22% cosolvent MeOH, λ = 240 nm, 35 °C)
Optical rotation: $[\alpha]_D^{20}$ (t_{r1}) = +79.2 (c = 0.12, acetone), $[\alpha]_D^{20}$ (t_{r2}) = −82.2 (c = 0.14, acetone).

N-(2,2,2-Trifluoroacetyl) 4-(*N*-indolyl)phenyl methyl sulfoximine (161d)

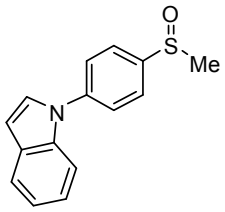
Following GP12 using 4-(*N*-indolyl)phenyl methyl sulfoxide (**163**) (100 mg, 0.39 mmol), trifluoroacetamide (88 mg, 0.78 mmol), magnesium oxide (63 mg, 1.57 mmol), $Rh_2(OAc)_4$ (4.4 mg, 2.5 mol%), PIDA (188 mg, 0.59 mmol) and CH_2Cl_2 (3 mL) provided the product as a white solid (48.5 mg, 34%) after purification by column chromatography (acetone/*n*-pentane 1:6 to 1:1).



Mp.: 158 – 160 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 3.2 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.21 – 7.25 (m, 1H), 6.77 (d, *J* = 3.3 Hz, 1H), 3.51 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.2 (q, *J* = 38.2 Hz), 145.5, 135.1, 132.8, 130.1, 129.1, 127.0, 124.2, 123.5, 121.7, 121.7, 115.5 (q, *J* = 288.1 Hz), 110.4, 106.4, 44.4.
^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.93.
MS (EI): *m/z* (%) = 367 ([M+H]$^+$, 9), 366 ([M$^+$], 41), 297 (11), 240 (47), 208 (100), 191 (58), 149 (20).
IR (KBr): ν = 3108, 1674, 1588, 1335, 1232, 1141, 1090, 746 cm^{-1}.
HRMS (ESI): 367.0729 calcd. for $C_{17}H_{14}O_2N_2F_3S$ [M+H]$^+$: 367.0723.

4-(*N*-Indolyl)phenyl methyl sulfoxide (163)

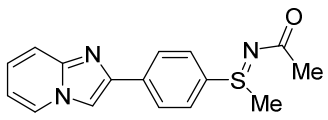


Following GP16 4-bromophenyl methyl sulfoxide (**2c**) (65.7 mg, 0.3 mmol), indole (42.1 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (7.5 mg, 4 mol%), $Pd_2(dba)_3$ (5.5 mg, 2 mol%) and toluene (1.5 mL) provided the product as a white solid (57.5 mg, 75%) after purification by column chromatography (acetone/*n*-pentane 1:3). Mp.: 70 – 73 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.7 Hz, 2H), 7.69 – 7.67 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 3.3 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.21 – 7.17 (m, 1H), 6.72 (d, *J* = 3.3 Hz, 1H), 2.79 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$): δ = 143.1, 142.3, 135.5, 129.6, 127.5, 125.2, 124.7, 122.9, 121.4, 121.0, 110.3, 104.8, 44.1.
MS (EI): *m/z* (%) = 256 ([M+H]$^+$, 255 ([M$^+$], 83), 220 (13), 218 (12), 205 (16), 203 (16), 85 (64), 83 (100).
IR (KBr): ν = 2903, 1587, 1494, 1451, 1332, 1210, 1040, 732 cm^{-1}.
HRMS (ESI): 278.0616 calcd. for $C_{15}H_{13}ONNaS$ [M+Na]$^+$: 278.0610.

12.3.6 Syntheses of zolimidine derivatives

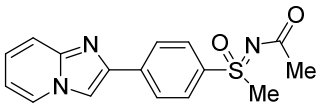
2-[4-(*N*-Acetyl-*S*-methylsulfilimidoyl)phenyl]-imidazo[1,2-α]pyridine (167b)



Following GP18 using 2-(4-methylsulfanylphenyl)-imidazo[1,2-α]pyridine (**173**) (120 mg, 0.5 mmol), 3-methyl-1,4,2-dioxazol-5-one (51 mg, 0.5 mmol), Ru(TPP)CO (1.9 mg, 0.5 mol%) and dry toluene (5 mL), reaction time 1 h, the product was obtained as a light brown solid (123 mg, 83%) after column chromatography (AcOEt). Mp.: 176 – 179 °C.
^{1}H NMR (600 MHz, C*D*Cl_3): δ = 8.11 (d, *J* = 6.7 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.91 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.20 – 7.17 (m, 1H), 6.79 (t, *J* = 6.7, 1H), 2.82 (s, 3H), 2.13 (s, 3H).
^{13}C NMR (151 MHz, C*D*Cl_3): δ = 182.0, 145.8, 143.7, 137.9, 134.1, 127.2, 127.1, 125.7, 125.3, 117.7, 112.9, 109.2, 34.5, 24.3.

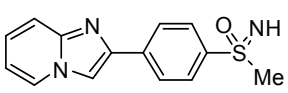
MS (EI): *m/z* (%) = 297 ([M]$^+$, 2), 207 (28), 190 (74), 179 (27), 166 (33), 155 (35), 146 (26), 120 (25), 103 (43), 78 (100).
IR (KBr): ν = 3004, 1739, 1568, 1359, 1293 cm^{-1}.
HRMS (ESI): 298.1010, calcd. for $C_{16}H_{16}ON_3S$ [M+H]$^+$: 298.1009.

2-[4-(*N*-Acetyl-*S*-methylsulfoximidoyl)phenyl]-imidazo[1,2-α]pyridine (168b)



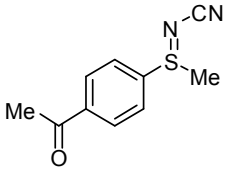
Following GP18 using 2-(4-methanesulfinylphenyl)-imidazo[1,2-α]pyridine (**174**) (64 mg, 0.25 mmol), 3-methyl-1,4,2-dioxazol-5-one (25 mg, 0.25 mmol), Ru(TPP)CO (1.9 mg, 1 mol%) and dry toluene (3 mL), reaction time 1.5 h, the product was obtained as a light brown solid (45 mg, 58%) after column chromatography (acetone/AcOEt 1:5). Mp.: 198 – 200 °C (decomposition).
^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.60 (s, 1H), 8.57 (d, *J* = 5.9 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.31 – 7.28 (m, 1H), 6.95 – 6.93 (m, 1H), 3.47 (s, 3H), 2.00 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 178.8, 145.5, 142.8, 139.3, 137.6, 128.1, 127.6, 126.6, 126.1, 117.4, 113.2, 111.5, 43.6, 26.9.
MS (EI): *m/z* (%) = 313 ([M]$^+$, 2), 296 (5), 240 (19), 238 (19), 208 (98), 206 (100), 192 (19), 190 (17), 180 (16), 178 (17).
IR (KBr): ν = 3022, 1627, 1360, 1268, 1201, 1032 cm^{-1}.
HRMS (ESI): 314.0956, calcd. for $C_{16}H_{16}O_2N_3S$ [M+H]$^+$: 314.0958.

2-[4-(*N*H-*S*-methylsulfoximidoyl)phenyl]-imidazo[1,2-α]pyridine (168c)



Following GP14 using 2-[4-(*N*-acetyl-S-methylsulfoximidoyl)-phenyl]-imidazo[1,2-α]pyridine (**168b**) (69 mg, 0.22 mmol), potassium carbonate (152 mg, 1.10 mmol) and MeOH (3.65 mL), 70 °C reaction temperature, provided the product as a white solid (53 mg, 89%) after purification by column chromatography (AcOEt/MeOH 9:1).
Mp: 200 – 202 °C.
^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.56 – 8.55 (m, 2H), 8.17 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 6.94 – 6.92 (m, 1H), 4.24 (s, 1H), 3.10 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 145.0, 142.7 (2C), 137.7, 127.8, 127.1, 125.7, 125.5, 116.8, 112.6, 110.6, 45.8.
MS (EI): *m/z* (%) = 271 ([M]$^+$, 4), 207 (61), 178 (99), 164 (100), 138 (78), 127 (65), 113 (44), 101 (36).
IR (KBr): ν = 3207, 1596, 1406, 1213, 1096 cm^{-1}.
HRMS (ESI): 272.0851, calcd. for $C_{14}H_{14}ON_3S$ [M+H]$^+$: 272.0852.

1-[4-(*N*-Cyanomethylsulfilimidoyl)phenyl]ethanone (170)



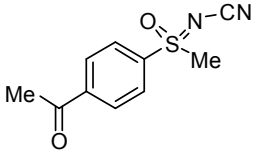
Following GP11 using 1-(4-methylthio)-acetophenone (**169**) (100 mg, 0.6 mmol), cyanamide (38 mg, 0.9 mmol), PIDA (213 mg, 0.66 mmol) and acetonitrile (2 mL) provided the product as a white solid (122 mg, 99%) after purification by column chromatography (AcOEt to acetone/AcOEt 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 3.05 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.3, 140.7, 140.4, 129.9, 126.1, 119.8, 36.6, 26.8.

The corresponding spectroscopic data matched that reported in the literature.[118]

1-[4-(*N*-Cyanomethylsulfonimidoyl)phenyl]ethanone (171)



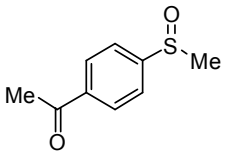
Following GP4 using 1-[4-(*N*-cyanomethylsulfilimidoyl)-phenyl]ethanone (**170**) (100 mg, 0.49 mmol), K_2CO_3 (201 mg, 1.45 mmol), *m*CPBA (70%, 179 mg, 0.73 mmol) and MeOH (5 mL) provided the product as a white solid (88 mg, 81%) after purification by column chromatography (AcOEt/*n*-pentane 1:5 to 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.6 Hz, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 3.38 (s, 3H), 2.69 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.1, 142.2, 139.8, 129.8, 128.4, 111.3, 44.6, 27.0.

The corresponding spectroscopic data matched that reported in the literature.[118]

1-[4-Methylsulfinyl)phenyl]ethanone (172)



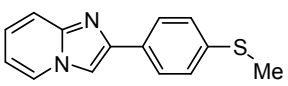
A mixture of 1-(4-methylthio)-acetophenone (**169**) (500 mg, 3.0 mmol), iron(III)bromide (44.5 mg, 20 mol%), HNO_3 (16 µL, 0.39 mmol) and acetonitrile (7.8 mL) was stirred at r.t. for 4 h.[209] After removing the solvents under reduced pressure, CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with water (3 x 5 mL). The organic phase was dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. Purification by column chromatography (AcOEt/*n*-pentane 1:1 to acetone/AcOEt 1:2) provided the product as a white solid (269 mg, 49%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 2.76 (s, 3H), 2.65 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 197.0, 151.0, 139.1, 129.1, 123.7, 43.8, 26.8.

The corresponding spectroscopic data matched that reported in the literature.[209]

2-(4-Methylsulfanylphenyl)-imidazo[1,2-α]pyridine (173)



Following GP17 2-aminopyridine (300 mg, 3.19 mmol), 1-(4-methylthio)-acetophenone (**169**) (1.06 g, 6.38 mmol), copper(I)-iodide (30 mg, 5 mol%), $BF_3{\cdot}Et_2O$ (45.2 mg, 10 mol%) and DMF (1.3 mL) provided the

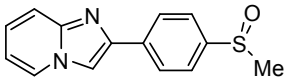
product as a white solid (469 mg, 61%) after purification by column chromatography (AcOEt/*n*-pentane 1:2 to1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 6.7 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.80 (s, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.75 (t, *J* = 6.7 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 145.6, 145.3, 138.1, 130.6, 126.6, 126.3, 125.5, 124.6, 117.4, 112.4, 107.8, 15.7.

The corresponding spectroscopic data matched that reported in the literature.[207a]

2-[4-(Methylsulfinyl)phenyl]-imidazo[1,2-α]pyridine (174)



Route I: Following GP17 using 2-aminopyridine (68.4 mg, 0.73 mmol), 1-(4-methansulfinylphenyl)-ethanone (**172**) (265 mg, 1.45 mmol), copper(I)iodide (6.9 mg, 5 mol%), $BF_3{\cdot}Et_2O$ (10.3 mg, 10 mol%) and DMF (0.29 mL) provided the product as a light brown solid (108 mg, 58%) after purification by column chromatography (acetone/AcOEt 1:1).

Route II: Following GP13 using 2-(4-methylsulfanylphenyl)-imidazo[1,2-α]pyridine (70 mg, 0.29 mmol), acetic acid (1.39 mL) and aq hydrogen peroxide solution (0.13 mL, 0.29 mmol, 30%) provided the product as a light brown solid (53 mg, 71%) after purification by column chromatography (acetone/AcOEt 1:1 to acetone/MeOH 20:1). Mp.: 160 – 163 °C.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.50 (d, *J* = 6.8 Hz, 1H), 8.40 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 9.1 Hz, 1H), 7.28 – 7.25 (m, 1H), 6.90 (dt, *J* = 6.7, 1.0 Hz, 1H), 2.74 (s, 3H).

^{13}C NMR (151 MHz, acetone-d_6): δ = 146.2, 145.6, 144.1, 136.9, 126.7, 126.4, 125.0, 123.8, 117.1, 112.4, 109.6, 43.4.

MS (EI): *m/z* (%) = 256 ([M]$^+$, 41), 238 (100), 224 (9), 206 (12), 192 (31), 190 (17), 180 (8).

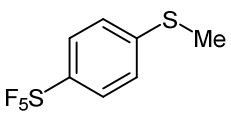
IR (KBr): ν = 3134, 1633, 1499, 1404, 1088, 1038 cm^{-1}.

Elementary analysis: calcd. for $C_{14}H_{12}N_2OS$: C 65.60, H 4.72, N 10.93; found: C 65.41, H 4.68, N 10.64.

12.3.7 Syntheses of methyl 4-SF_5-phenyl sulfoximines

Methyl 4-pentafluorosulfanyl sulfide (96)

To a solution of 4-nitrophenyl sulfur pentafluoride (**89**) (150 mg, 0.6 mmol) in dry DMF (0.75 mL) was added sodium methanethiolate (126 mg, 1.8 mmol) in 2 portions every 5 min.[145] After stirring the reaction mixture r.t. for 18 h aq saturated NH_4Cl solution (2 mL) was added and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic phases were washed with brine (5 x 5 mL), dried with anhydrous magnesium sulfate and the solvent was



removed under reduced pressure. Purification by column chromatography (*n*-pentane) afforded the product as a colorless liquid (73 mg, 48%).

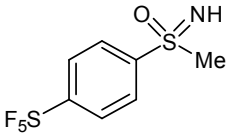
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.9 Hz, 2H), 7.25 (d, J = 8.9 Hz, 2H), 2.50 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.4 (quin, $^2J_{CF}$ = 18.0 Hz, *C*-SF_5), 144.0, 126.2 (quin, $^3J_{CF}$ = 4.7 Hz, $C_{AR}H$), 125.1, 14.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 85.1 (quin, J = 149.6 Hz, 1F), 63.5 (d, J = 150.7 Hz, 4F).

The corresponding spectroscopic data matched that reported in the literature.[145]

*N*H Methyl 4-pentafluorosulfanylphenyl sulfoximine (178)



Following GP7 using *N*-cyano methyl 4-pentafluorosulfanylphenyl sulfoximine (**180**) (72 mg, 0.23 mmol) and 50% aq H_2SO_4 (2.3 mL), 2 h reaction time, provided the product was obtained as a white solid (46 mg, 71%) after purification by column chromatography (acetone/*n*-pentane 1:1). Mp: 88 – 90 °C

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 3.11 (s, 3H), 2.84 (s, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9 (t, $^2J_{CF}$ = 18.4 Hz, *C*-SF_5), 146.8, 128.4, 127.2 – 127.1 (m, $C_{Ar}H$), 45.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 81.8 (quin, J = 150.1 Hz, 1F), 62.5 (d, J = 150.5 Hz, 4F).

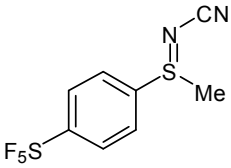
MS (EI): *m/z* (%) = 282 ([M+H]$^+$, 63), 281 ([M]$^+$, 12), 267 (14), 266 (100), 251 (6), 139 (12), 127 (9).

IR (KBr): ν = 1396, 1222, 1101, 1006, 815, 752 cm^{-1}.

HRMS (ESI): 282.0039, calcd. for $C_7H_9ON_2F_5S_2$ [M+H]$^+$: 282.0040.

Analytical HPLC: t_r = 26.9, 47.4 min (Chiralcel OJ column, flow rate 0.7 mL/min, *n*-heptane/*i*-PrOH = 85:15, λ = 210 nm, 20 °C).

N-Cyano methyl 4-pentafluorosulfanylphenyl sulfilimine (179)



Following GP10 using methyl 4-pentafluorosulfanylphenyl sulfide (**96**) (250 mg, 1.0 mmol), NH_2CN (76 mg, 1.8 mmol), *t*-BuOK (191 mg, 1.7 mmol), NBS (356 mg, 2.0 mmol) and MeOH (6 mL), 2 h reaction time, provided the product as a colorless oil (279 mg, 96%) after purification by column chromatography (acetone/*n*-pentane 1:3 to 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 – 7.97 (m, 2H), 7.92 (d, J = 8.8 Hz, 2H), 3.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7 (t, $^2J_{CF}$ = 18.9 Hz, *C*-SF_5), 140.1, 128.1 (quin, $^3J_{C\text{-}F}$ = 4.7 Hz, $C_{Ar}H$), 126.4, 119.8, 37.0.

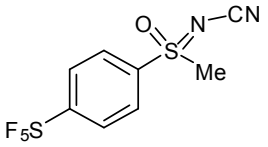
^{19}F NMR (376 MHz, $CDCl_3$): δ = 81.4 (quin, J = 149.6 Hz, 1F), 62.4 (d, J = 150.7 Hz, 4F).

MS (EI): *m/z* (%) = 291 ([M+H]$^+$, 59), 290 ([M]$^+$, 16), 250 (100), 142 (15), 127 (11).

IR (neat): ν = 2150, 1725, 1399, 1162, 824 cm^{-1}.

HRMS (ESI): 312.9861, calcd. for $C_8H_7N_2F_5NaS_2$ [M+Na]$^+$: 312.9863.

N-Cyano methyl 4-pentafluorosulfanylphenyl sulfoximine (180)



Following GP4 using *N*-cyano methyl 4-pentafluorosulfanyl-phenyl sulfilimine (**179**) (87 mg, 0.3 mmol), *m*CPBA (ca. 70%, 101 mg, 0.45 mmol) and EtOH (2.7 mL), reaction time 16 h, provided the product as a white solid (75 mg, 81%) after purification by column chromatography (acetone/*n*-pentane 1:1). Mp: 99 – 102 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13 (d, J = 9.0 Hz, 2H), 8.09 – 8.06 (m, 2H), 3.38 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 158.6, 139.4, 128.9, 128.3 – 128.2 (m, C_{ArH}), 110.9, 44.6.

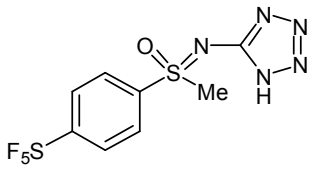
^{19}F NMR (376 MHz, $CDCl_3$): δ = 81.1 – 79.6 (m, 1F), 62.4 (d, J = 150.7 Hz, 4F).

MS (EI): *m/z* (%) = 307 ([M+H]$^+$, 41), 306 ([M]$^+$, 96), 266 (100), 251 (62), 143 (36).

IR (KBr): ν = 2201, 1395, 1239, 1186, 818, 749 cm^{-1}.

HRMS (ESI): 328.9812, calcd. for $C_8H_7ON_2F_5NaS_2$ [M+Na]$^+$: 328.9812.

N-(1*H*)-Tetrazole methyl 4-pentafluorosulfanylphenyl sulfoximine (181)



A mixture of *N*-cyano methyl 4-pentafluorosulfanylphenyl sulfoximine (**180**) (120 mg, 0.39 mmol), NaN_3 (30 mg, 0.47 mmol) and $ZnBr_2$ (105 mg, 0.47 mmol) in H_2O/MeOH 4:1 (1 mL) was vigorously stirred in a sealed tube at 120 °C for 24 h. After cooling to r.t., 1 N HCl (3 mL) was added and the aqueous phase was extracted with AcOEt (3 x 6 mL). The organic layers were combined and the solvent was removed under reduced pressure. To the residue was added 1 N NaOH (10 mL) and the mixture was stirred for 20 min. After filtration the filtrate was acidified to pH 1-2 by addition of 1 N HCl and extracted with AcOEt (4 x 10 mL). The combined organic layers were dried with anhydrous magnesium sulfate and the solvents were removed under reduced pressure. After triturating with Et_2O/*n*-pentane 1:1 and subsequent recrystallization from AcOEt/hexane the product was obtained as colorless crystals (85 mg, 62%). Mp: 173 – 175 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.26 (d, J = 9.0 Hz, 2H), 8.22 (d, J = 8.8, 2.1 Hz, 2H), 3.72 (s, 3H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 155.9 (t, $^2J_{CF}$ = 17.1 Hz, C-SF_5), 155.0, 141.9, 129.3, 127.3, 43.4.

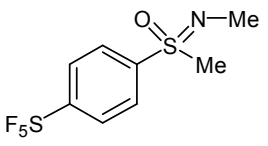
^{19}F NMR (376 MHz, DMSO-d_6): δ = 84.7 (quin, J = 151.6 Hz, 1F), 63.6 (d, J = 151.3 Hz, 4F).

MS (EI): *m/z* (%) = 350 ([M+H]$^+$, 10), 349 ([M]$^+$, 23), 334 (100), 292 (41), 291 (51), 266 (85), 251 (89), 179 (22), 143 (49).

IR (KBr): ν = 1559, 1394, 1232, 1102, 834 cm^{-1}.

HRMS (ESI): 350.0163, calcd. for $C_8H_9ON_5F_5S_2$ [M+H]$^+$: 350.0163.

N-Methyl methyl 4-pentafluorosulfanylphenyl sulfoximine (182)



Following GP15 using methyl 4-pentafluorosulfanylphenyl sulfoximine **178** (50 mg, 0.18 mmol), formaldehyde (27 mg, 0.89 mmol) and formic acid (1.6 mL), 16 h reaction time, provided

the product as a white solid (41 mg, 78%) after purification by column chromatography (AcOEt/*n*-pentane 1:1) Mp: 73 – 75 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 3.10 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.9 (t, $^{2}J_{CF}$ = 18.8 Hz, *C*-SF_5), 142.6, 129.5, 127.4 – 127.3 (m, C_{ArH}), 44.8, 29.5.

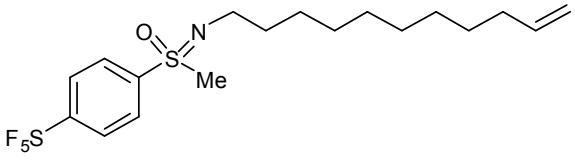
^{19}F NMR (376 MHz, $CDCl_3$): δ = 82.0 (quin, *J* = 150.7 Hz, 1F), 62.6 (d, *J* = 150.5 Hz, 4F).

MS (EI): *m/z* (%) = 296 ([M+H]$^+$, 47), 295 ([M]$^+$, 100), 294 (62), 279 (82), 266 (12), 250 (7), 231 (18).

IR (KBr): ν = 1396, 1243, 1151, 1098, 819, 768 cm^{-1}.

HRMS (ESI): 296.0195, calcd. for $C_8H_{11}ONF_5S_2$ [M+H]$^+$: 296.0197.

N-(10-undecenyl) methyl 4-pentafluorosulfanylphenyl sulfoximine (183)



Following GP8 using methyl 4-pentafluorosulfanylphenyl sulfoximine **178** (48 mg, 0.17 mmol), 11-bromo-1-undecene (60 mg, 0.26 mmol), potassium hydroxide (19 mg, 0.34 mmol) and DMSO (0.26 mL) provided the product as a colorless oil (56 mg, 76%) after purification by column chromatography (acetone/*n*-pentane 1:10 to 1:5).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 5.84 – 5.74 (m, 1H), 5.00 – 4.89 (m, 2H), 3.09 (s, 3H), 2.95 (dt, *J* = 12.1, 7.1 Hz, 1H), 2.74 (dt, *J* = 12.1, 7.1 Hz, 1H), 2.02 (q, *J* = 7.5 Hz, 2H), 1.54 (d, *J* = 7.5 Hz, 2H), 1.36 – 1.25 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 156.8 (t, $^{2}J_{CF}$ = 19.0 Hz, *C*-SF_5), 143.5, 139.2, 129.3, 127.3 – 127.2 (m, C_{ArH}), 114.04, 45.0, 43.9, 33.8, 32.7, 29.5, 29.4, 29.3, 29.0, 28.9, 27.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 82.1 (quin, *J* = 150.4 Hz, 1F), 62.6 (d, *J* = 150.4 Hz, 4F).

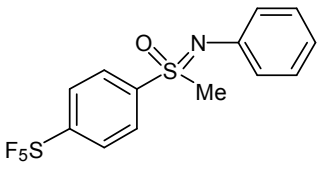
MS (EI): *m/z* (%) = 435 ([M+2H]$^+$, 17), 434 ([M+H]$^+$, 100), 432 (22), 294 (28), 267 (11).

IR (neat): ν = 2924, 2856, 1240, 1136, 838, 771 cm^{-1}.

HRMS (ESI): 434.1593, calcd. for $C_{18}H_{29}ONF_5S_2$ [M+H]$^+$: 434.1605.

N-Phenyl methyl 4-pentafluorosulfanylphenyl sulfoximine (184)

Following GP19 methyl 4-pentafluorosulfanylphenyl sulfoximine **178** (37 mg, 0.13 mmol), iodobenzene (53 mg, 0.26 mmol), CuI (2.5 mg, 10 mol%), DMEDA (2.3 mg, 20 mol%), Cs_2CO_3 (108 mg, 0.33 mmol) and toluene (0.13 mL) provided the product as a white solid (43 mg, 93%) after purification by column chromatography (AcOEt/*n*-pentane 1:3 to 1:2).



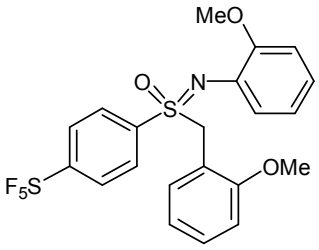
Mp: 69 – 71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.7 Hz, 2H), 7.92 (dt, *J* = 8.8, 2.1 Hz, 2H), 7.18 – 7.13 (m, 2H), 7.02 – 6.99 (m, 2H), 6.94 – 6.90 (m, 1H), 3.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0 (t, $^{2}J_{CF}$ = 18.1 Hz, *C*-SF_5), 144.1, 143.0, 129.3, 129.2, 127.4 – 127.3 (m, C_{ArH}), 123.2, 122.3, 45.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 81.8 (quin, *J* = 150.1 Hz, 1F), 62.5 (d, *J* = 150.5 Hz, 4F).
MS (EI): *m/z* (%) = 358 ([M+H]$^+$, 16), 357 ([M]$^+$, 100), 342 (5), 250 (16), 230 (9), 167 (100), 91 (42).
IR (KBr): ν = 1591, 1486, 1396, 1285, 1203, 1101, 1041, 836 cm^{-1}.
HRMS (ESI): 358.0353, calcd. for $C_{13}H_{13}ONF_5S_2$ [M+H]$^+$: 358.0353.

N-(2-Methoxyphenyl) 2-methoxybenzyl phenyl 4-pentafluorosulfanylphenyl sulfoximine (185)

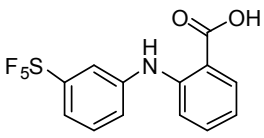


Following GP19 methyl 4-pentafluorosulfanylphenyl sulfoximine **178** (38 mg, 0.14 mmol), 2-iodoanisole (35 µL, 0.27 mmol), CuI (2.6 mg, 10 mol%), DMEDA (29 µL, 20 mol%), Cs_2CO_3 (110 mg, 0.34 mmol) and toluene (0.14 mL) provided the product as a white solid (11 mg, 17%) after purification by column chromatography (AcOEt/*n*-pentane 1:10 to 1:1). Mp: 123 – 125 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.37 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.15 (dd, *J* = 6.3, 1.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.92 (dt, *J* = 8.0, 1.5 Hz, 1H), 6.84 (d, *J* = 7.1 Hz, 1H), 6.76 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 4.85 (d, *J* = 13.7 Hz, 1H), 4.60 (d, *J* = 13.7 Hz, 1H), 3.83 (s, 3H), 3.20 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.3, 156.6 (t, $^2J_{CF}$ = 17.9 Hz, *C*-SF_5), 152.8, 141.9, 133.6, 133.4, 130.7, 130.4, 125.8, 124.4, 122.9, 121.0, 120.6, 116.3, 111.7, 109.7, 57.5, 55.7, 54.4.
^{19}F NMR (376 MHz, $CDCl_3$): δ = 82.4 (quin, *J* = 150.5 Hz, 1F), 62.6 (d, *J* = 150.3 Hz, 4F).
MS (EI): *m/z* (%) = 358 ([M+H]$^+$, 16), 357 ([M]$^+$, 100), 342 (5), 250 (16), 230 (9), 167 (100), 91 (42).
IR (KBr): ν = 2919, 1739, 1592, 1494, 1228, 1107, 1023, 823, 748 cm^{-1}.
HRMS (ESI): 516.0695, calcd. for $C_{21}H_{20}O_3NF_5NaS_2$ [M+Na]$^+$: 516.0697.

12.3.8 Syntheses of flufenamic acid derivatives

N-(3-Pentafluorosulfanylphenyl)anthranilic acid (186a)

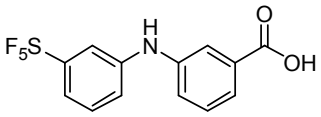


Following GP21, using methyl ester **190a** (88 mg, 0.25 mmol), KOH (28 mg, 0.5 mmol), water (2.5 mL) and EtOH (1.3 mL), the product was obtained as a white solid (74 mg, 87%).
Mp.: 188 – 190 °C.

^{1}H NMR (400 MHz, acetone-d_6) : δ = 9.84 (s, 1H), 8.07 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.75 (m, 1H), 7.69 – 7.58 (m, 2H), 7.54 – 7.52 (m, 1H), 7.49 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.92 (t, *J* = 8.0 Hz, 1H).

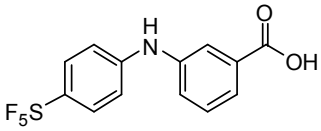
^{13}C NMR (100 MHz, acetone-d_6): δ = 169.4, 154.4 (quin, $^2J_{CF}$ = 16.4 Hz, *C*-SF_5), 146.4, 142.1, 134.4, 132.2, 130.0, 124.2, 119.8 (t, *J* = 4.5 Hz), 118.8, 118.1 (t, *J* = 4.3 Hz), 114.4, 113.5.
^{19}F NMR (376 MHz, acetone-d_6): δ = 84.4 (quin, *J* = 148.3 Hz, 1F), 62.0 (d, *J* = 148.2 Hz, 4F).
MS (EI): *m/z* (%) = 340 ([M+H]$^+$, 8), 339 ([M]$^+$, 52), 213 (17), 194 (100), 166 (77), 139 (28).
IR (KBr): ν = 1657, 1584, 1427, 1244, 819.
HRMS (ESI): 340.0430, calcd. for $C_{13}H_{11}O_2NF_5S$ [M+H]$^+$: 340.0425.

3-[(3-Pentafluorosulfanylphenyl)amino]benzoic acid (186b)



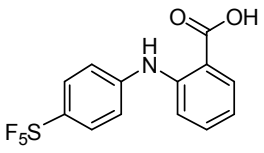
Following GP21, using methyl ester **190b** (88 mg, 0.25 mmol), KOH (28 mg, 0.5 mmol), water (2.5 mL) and EtOH (1.3 mL), the product was obtained as a light-brown solid (81 mg, 95%). Mp.: 159 – 161 °C.
^{1}H NMR (400 MHz, acetone-d_6): δ = 11.29 (s, 1H), 8.04 (s, 1H), 7.86 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.56 (m, 1H), 7.51 – 7.40 (m, 4H), 7.35 (dd, *J* = 8.1, 1.6 Hz, 1H).
^{13}C NMR (100 MHz, acetone-d_6): δ = 166.6, 154.6 (quin, $^2J_{CF}$ = 16.2 Hz, *C*-SF_5), 144.3, 142.7, 131.8, 129.9, 129.6, 122.7, 122.4, 119.6, 118.8, 117.2 (t, *J* = 4.6 Hz), 113.9 (t, *J* = 4.6 Hz).
^{19}F NMR (376 MHz, acetone-d_6): δ = 84.9 (quin, *J* = 148.2 Hz, 1F), 61.8 (d, *J* = 148.0 Hz, 4F).
MS (EI): *m/z* (%) = 340 ([M+H]$^+$, 17), 339 ([M]$^+$, 100), 212 (6), 167 (25).
IR (KBr): ν = 1688, 1593, 1420, 1295, 814.
HRMS (ESI): 340.0423, calcd. for $C_{13}H_{11}O_2NF_5S$ [M+H]$^+$: 340.0425.

3-[(4-Pentafluorosulfanylphenyl)amino]benzoic acid (186c)



Following GP21 using methyl ester **190c** (88 mg, 0.25 mmol), KOH (28 mg, 0.5 mmol), water (2.5 mL) and EtOH (1.3 mL), the product was obtained as a light-brown solid (74 mg, 87%). Mp.: 177 – 178 °C.
^{1}H NMR (400 MHz, acetone-d_6): δ = 11.30 (s, 1H), 8.21 (s, 1H), 7.90 (s, 1H), 7.73 – 7.69 (m, 3H), 7.51 – 7.46 (m, 2H), 7.22 (d, *J* = 8.8 Hz, 2H).
^{13}C NMR (100 MHz, acetone-d_6): δ = 166.5, 146.9, 144.8 (quin, $^2J_{CF}$ = 16.7 Hz, *C*-SF_5), 141.8, 131.8, 129.6, 127.4 (t, *J* = 4.5 Hz), 123.7, 123.4, 120.2, 114.6.
^{19}F NMR (376 MHz, acetone-d_6): δ = 87.4 (quin, *J* = 148.5 Hz, 1F), 63.8 (d, *J* = 148.4 Hz, 4F).
MS (EI): *m/z* (%) = 340 ([M+H]$^+$, 17), 339 ([M]$^+$, 100), 231 (8), 167 (15).
IR (KBr): ν = 3438, 1686, 1584, 1308, 802.
HRMS (EI): 339.0346, calcd. for $C_{13}H_{10}O_2NF_5S$ [M]$^+$: 339.0347.

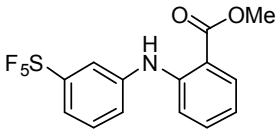
N-(4-Pentafluorosulfanylphenyl)anthranilic acid (186d)



Following GP21, using methyl ester **190d** (88 mg, 0.25 mmol), KOH (28 mg, 0.5 mmol), water (2.5 mL) and EtOH (1.3 mL), the product was obtained as a white solid (67 mg, 79%).
Mp.: 191 – 193 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 11.60 (s, 1H), 9.93 (s, 1H), 8.08 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 7.80 (d, J = 9.1 Hz, 2H), 7.56 – 7.51 (m, 2H), 7.42 (d, J = 8.9 Hz, 2H), 6.98 (dd, J = 14.8 Hz, 1.3 Hz, 1H).
^{13}C NMR (100 MHz, acetone-d_6): δ = 169.4, 146.7 (quin, $^2J_{CF}$ = 16.9 Hz, *C*-SF$_5$), 145.2, 144.8, 134.3, 132.2, 127.4 (t, J = 4.5 Hz), 119.6, 118.3, 115.8, 114.5.
^{19}F NMR (376 MHz, acetone-d_6): δ = 86.4 (quin, J = 148.6 Hz, 1F), 63.4 (d, J = 148.4 Hz, 4F).
MS (EI): *m/z* (%) = 340 ([M+H]$^+$, 7), 339 ([M]$^+$, 46), 194 (100), 166 (77), 140 (20).
IR (KBr): ν = 3027, 1661, 1590, 1522, 1244, 825.
HRMS (ESI): 362.0255, calcd. for $C_{13}H_{10}O_2NF_5NaS$ [M+Na]$^+$: 362.0245.

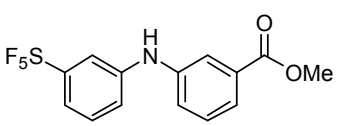
N-(3-Pentafluorosulfanylphenyl)anthranilic acid methyl ester (190a)



Following GP20, using methyl 2-bromobenzoate (**188**) (65 mg, 0.3 mmol), 3-(pentafluorosulfanyl)aniline (**187**) (79 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (15 mg, 8 mol%), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and toluene (3 mL), the product was obtained as a white solid (104 mg, 98%). Mp.: 69 – 71 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1H), 8.00 – 7.98 (m, 1H), 7.62 – 7.61 (m, 1H), 7.42 – 7.34 (m, 4H), 7.26 – 7.24 (m, 1H), 6.82 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 3.90 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 154.7 (t, $^2J_{CF}$ = 17.6 Hz, *C*-SF$_5$), 146.4, 141.6, 134.3, 131.8, 129.4, 124.2, 120.2 (t, J = 4.6 Hz), 118.9 (t, J = 4.6 Hz), 118.6, 114.1, 113.1, 52.0.
^{19}F NMR (376 MHz, $CDCl_3$): δ = 84.4 (quin, J = 150.0 Hz, 1F), 62.7 (d, J = 149.9 Hz, 4F).
MS (EI): *m/z* (%) = 354 ([M+H]$^+$, 18), 353 ([M]$^+$, 100), 321 (17), 213 (18), 194 (84), 166 (67).
IR (KBr): ν = 3312, 1688, 1588, 1517, 1450, 1260, 835.
HRMS (ESI): 376.0406, calcd. for $C_{14}H_{12}O_2NF_5NaS$ [M+Na]$^+$: 376.0401.

3-[(3-Pentafluorosulfanylphenyl)amino]benzoic acid methyl ester (190b)

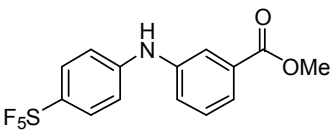


Following GP20, using methyl 3-bromobenzoate (**189**) (65 mg, 0.3 mmol), 3-(pentafluorosulfanyl)aniline (**187**) (79 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (15 mg, 8 mol%), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and toluene (3 mL), the product was obtained as a white solid (105 mg, 99%). Mp.: 122 – 124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (m, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.42 (m, 1H), 7.39 – 7.27 (m, 4H), 7.19 (d, J = 7.8 Hz, 1H), 6.04 (s, 1H), 3.91 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 154.9 (t, $^2J_{CF}$ = 16.9 Hz, *C*-SF$_5$), 143.2, 142.0, 131.6, 129.6, 129.5, 123.3, 122.6, 119.9, 119.3, 118.4 (t, J = 4.6 Hz), 115.0 (t, J = 4.6 Hz), 52.3.

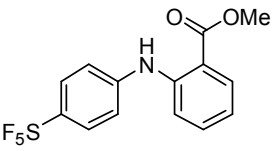
^{19}F NMR (376 MHz, $CDCl_3$): δ = 84.6 (quin, J = 150.0 Hz, 1F), 62.4 (d, J = 149.9 Hz, 4F).
MS (EI): m/z (%) = 354 ([M+H]$^+$, 21), 353 ([M]$^+$, 100), 322 (14), 167 (18).
IR (KBr): ν = 3350, 1706, 1597, 1484, 1327, 1289, 811.
HRMS (ESI): 392.0142, calcd. for $C_{14}H_{12}O_2NF_5KS$ [M+K]$^+$: 392.0141.

3-[(4-Pentafluorosulfanylphenyl)amino]benzoic acid methyl ester (190c)



Following GP20, using methyl 3-bromobenzoate (**189**) (65 mg, 0.3 mmol), 3-(pentafluorosulfanyl)aniline (**95**) (79 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (15 mg, 8 mol%), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and toluene (3 mL), the product was obtained as a white solid (105 mg, 99%). Mp.: 177 – 178 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 – 7.81 (m, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 9.1 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.34 – 7.33 (m, 1H), 6.99 (d, J = 8.9 Hz, 2H), 6.12 (s, 1H), 3.92 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 145.9 (t, $^2J_{CF}$ = 17.4 Hz, C-SF_5), 145.7, 141.1, 131.6, 129.6, 127.5 (t, J = 4.7 Hz), 124.2, 124.1, 120.8, 114.8, 52.3.
^{19}F NMR (376 MHz, $CDCl_3$): δ = 86.7 (quin, J = 150.4 Hz, 1F), 64.1 (d, J = 150.2 Hz, 4F).
MS (EI): m/z (%) = 354 ([M+H]$^+$, 18), 353 ([M]$^+$, 100), 322 (12), 167 (22).
IR (neat): ν = 3366, 1707, 1581, 1325, 1098, 815.
HRMS (ESI): 392.0140, calcd. for $C_{14}H_{12}O_2NF_5KS$ [M+K]$^+$: 392.0141.

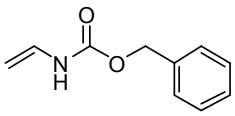
N-(4-Pentafluorosulfanylphenyl)anthranilic acid methyl ester (190d)



Following GP20, using methyl 2-bromobenzoate (**188**) (65 mg, 0.3 mmol), 4-(pentafluorosulfanyl)aniline (**95**) (79 mg, 0.36 mmol), Cs_2CO_3 (137 mg, 0.42 mmol), BINAP (15 mg, 8 mol%), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and toluene (3 mL), the product was obtained as a white solid (105 mg, 99%). Mp.: 49 – 50 °C.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1H), 8.02 – 8.00 (m, 1H), 7.67 (d, J = 9.1 Hz, 2H), 7.42 – 7.41 (m, 2H), 7.24 (d, J = 9.0 Hz, 2H), 6.89 (ddd, J = 8.1, 5.8, 2.5 Hz, 1H), 3.92 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 147.5 (t, $^2J_{CF}$ = 17.7 Hz, C-SF_5), 145.3, 144.1, 134.1, 131.8, 127.3 (t, J = 4.5 Hz), 119.3, 118.8, 115.4, 114.1, 52.0.
^{19}F NMR (376 MHz, $CDCl_3$): δ = 86.0 (quin, J = 149.9 Hz, 1F), 63.8 (d, J = 150.1 Hz, 4F).
MS (EI): m/z (%) = 354 ([M+H]$^+$, 16), 353 ([M]$^+$, 100), 194 (58), 166 (33).
IR (KBr): ν = 3305, 1680, 1590, 1520, 1448, 1270, 821.
HRMS (ESI): 354.0585, calcd. for $C_{14}H_{13}O_2NF_5S_2$ [M+H]$^+$: 354.0582.

12.3.9 Syntheses of SF_5-containing 1,2,3,4-tetrahydroquinolines

N-Benzylvinylcarbamate (193b)



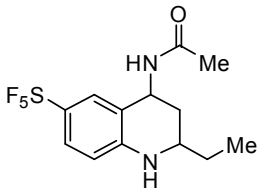
To a solution of sodium azide (7.8 g, 120 mmol) in water (100 mL) at 0 °C was added a solution of acryloyl chloride (8.1 mL, 100 mmol) and TBAI (1.85 g, 5.0 mmol) in toluene (50 mL). After stirring the reaction mixture for 5 h at 0 °C the two phases were separated. The organic phase was dried with anhydrous magnesium sulfate and added to a solution of hydrochinone (549 mg, 4.9 mmol), pyridine (0.45 mL, 6.0 mmol) and benzylalcohol (12.5 mL, 120 mmol) at 100 °C. The reaction mixture was stirred at 100 °C for 30 min.[228] Subsequently, the solvents were removed under reduced pressure. Purification by column chromatography (AcOEt/*n*-pentane 1:10) afforded the product as a white solid (2.14 g, 12%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 – 7.44 (m, 5H), 6.66 – 6.79 (m, 1H), 6.50 (s, 1H), 5.16 (s, 2H), 4.49 (d, *J* = 15.9 Hz, 1H), 4.31 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.4, 135.8, 129.7, 128.6, 128.4, 128.3, 93.4, 67.2.

The corresponding spectroscopic data matched that reported in the literature.[249]

4-*N*-Acetyl-2-ethyl-7-pentafluorosulfanyl-1,2,3,4-tetrahydroquinoline (197a)



A microwave-vial was charged with intermediate **200**, *N*-vinylacetamide (**193a**) (78 mg, 0.92 mmol), *p*-TSA (cat.)[137] and toluene (1.2 mL). The reaction mixture was stirred under microwave irradiation at 80 °C for 30 min. After removing the solvent under reduced pressure, purification by column chromatography (acetone/*n*-pentane 1:10) provided the product as a white solid (15 mg, 33%).

Mp.: 163 – 165 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (s, 1H), 7.36 (dd, J = 8.7, 2.2 Hz, 1H), 6.41 (d, *J* = 8.9 Hz, 1H), 5.84 (d, J = 8.9 Hz, 1H), 5.29 – 5.23 (m, 1H), 4.22 (s, 1H), 3.43 – 3.37 (m, 1H), 2.32 – 2.26 (m, 1H), 2.09 (s, 3H), 1.58 – 1.52 (m, 2H), 1.47 (q, *J* = 11.6 Hz, 1H), 0.99 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 147.1, 143.3 (t, $^2J_{CF}$ = 16.5 Hz, *C*-SF_5), 126.2, 124.5, 120.3, 112.6, 52.1, 45.9, 34.6, 28.9, 23.4, 9.6.

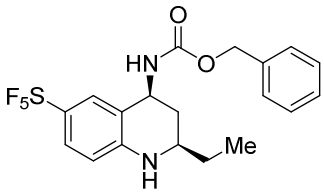
^{19}F NMR (376 MHz, $CDCl_3$): δ = 88.0 (quin, *J* = 151.0 Hz, 1F), 64.6 (d, *J* = 151.0 Hz, 4F).

MS (EI): *m/z* (%) = 345 ($[M+H]^+$, 8), 344 ($[M]^+$, 21), 285 (20), 284 (29), 256 (100), 148 (18), 129 (13).

IR (KBr): ν = 3325, 1628, 1511, 1298, 1095, 891, 819 cm^{-1}.

HRMS (ESI): 367.0875, calcd. for $C_{13}H_{17}ON_2F_5NaS$ $[M+Na]^+$: 367.0874.

4-(*S*)-*N*-Benzylvinylcarbamate-2-(*R*)-ethyl-7-pentafluorosulfanyl-1,2,3,4-tetrahydroquinoline (197b)



A microwave-vial was charged with intermediate **200**, *N*-benzylvinylcarbamate (**193b**) (162 mg, 0.92 mmol), *p*-TSA (cat.)[137] and toluene (0.6 mL). The reaction mixture was stirred under microwave irradiation at 100 °C for 10 min. After removing the solvent under reduced pressure, purification by column chromatography (acetone/*n*-pentane 1:10) provided the product as a white solid (147 mg, 48%). Mp.: 144 – 146 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (s, 1H), 7.43 – 7.34 (m, 6H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.21 (s, 2H), 5.03 (dt, *J* = 10.7, 5.4 Hz, 1H), 4.90 (d, *J* = 9.4 Hz, 1H), 4.15 (s, 1H), 3.48 – 3.40 (m, 1H), 2.37 – 2.31 (m, 1H), 1.61 – 1.53 (m, 2H), 1.47 (q, *J* = 11.9 Hz, 1H), 1.00 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.4, 146.9, 143.4 (t, $^2J_{CF}$ = 16.4 Hz, *C*-SF_5), 136.2, 128.6, 128.3, 128.2, 126.3, 124.5, 120.4, 112.5, 67.1, 52.2, 47.9, 35.0, 29.0, 9.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 87.9 (quin, *J* = 150.4 Hz, 1F), 64.7 (d, *J* = 150.8 Hz, 4F).

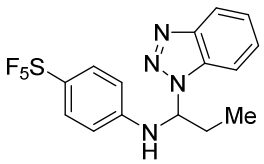
MS (EI): *m/z* (%) = 437 ([M+H]$^+$, 15), 436 ([M]$^+$, 32), 345 (65), 301 (100), 286 (27), 284 (45), 256 (49), 91 (40).

IR (KBr): ν = 3320, 2952, 1687, 1608, 1516, 1346, 1240, 810 cm^{-1}.

HRMS (ESI): 459.1129, calcd. for $C_{19}H_{21}O_2N_2F_5NaS$ [M+Na]$^+$: 459.1136.

N-(1-(1*H*-benzo[d][1,2,3]triazolyl)propyl)-4-pentafluorosulfanylaniline (200)

An argon-flushed Schlenk-tube was charged with 4-amino(pentafluorosulfanyl)-benzene



(**95**) (202 mg, 0.92 mmol), 1,2,3-benzotriazole (110 mg, 0.92 mmol)[137] and toluene (0.5 mL). Dry freshly distilled propionaldehyde (74 µL, 1.0 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 5 min until it solidified. The solid was washed with toluene (3 x 1.0 mL) and the solvent was removed under reduced pressure. The product was directly used in the next step without further purification.

^{1}H NMR (600 MHz, acetone-d_6): δ = 8.07 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 2H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.28 (br d, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.57 – 6.53 (m, 1H), 2-49 – 2.36 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 148.5, 148.4, 146.5, 143.9 (t, $^2J_{CF}$ = 16.8 Hz, *C*-SF_5), 131.3, 127.2 – 127.1 (m, 3 CH_{Ar}), 123.9, 119.7, 112.1 (2C), 110.7, 71.0, 27.9, 9.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = 87.6 (quin, *J* = 148.4 Hz, 1F), 64.0 (d, *J* = 148.3 Hz, 4F).

MS (EI): *m/z* (%) = 378 ([M]$^+$, 2), 260 (27), 259 (77), 258 (34), 230 (100), 203 (36), 119 (54).

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14 Appendix

14.1 Abbreviation List

Ac	acetate
ADMET	absorption, distribution, metabolism, excretion, toxicity
AIBN	azobis(isobutyronitril)
AKR	aldoketoreductase
Ar	aryl
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
ATR	ataxia telangiectasia and Rad3 related
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BPD	bispinacolatodiboron
BSO	buthionine sulfoximine
Bu	butyl
Bt	benzotriazole
cat.	catalyst
Cbz	carboxybenzyl
CDI	carbonyl diimidazole
CDK	cyclin dependent kinase
CETP	cholesterylester transfer protein
CFC-113	1,1,2-trichloro-1,2,2-trifluoroethane
CHK	checkpoint kinase
CHP	cumene hydroperoxide
CI	chemical ionization
COX	cyclooxygenase
COXIB	cyclooxygenase-2 inhibitor
CRPC	castration-resistant prostate cancer

Cyp24	25-hydroxyvitamin D3-24-hydroxylase
d	doublet
d	deuterated
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DET	diethyltartrate
DDR	DNA damage response
DIPEA	*N*,*N*-di*iso*propylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	dimethylformamide
dmhd	dimethyl-2,4-hexadiene
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DPH	*O*-(2,4-dinitrophenyl)hydroxylamine
dppf	1,1'-bis(diphenylphosphino)ferrocene
DTBP	di-*tert*-butylhypochlorite
E^+	electrophile
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EI	electron ionization
EN	electronegativity
ESI	electrospray ionization
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
equiv.	equivalent
FFA	flufenamic acid
F_1F_o	F_1 portion of ATP synthase
GABA	gamma-amino butyric acid

GP	general procedure
GSH	glutamyl cysteine synthetase
hERG	human *ether-à-go-go*-related gene
het	heterocycle
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole
HOSA	hydroxylamine-*O*-sulfonic acid
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
i	*iso*
I	electric current
IC_{50}	half maximal inhibitory concentration
IR	infrared spectrometry
LogP	partition coefficient
LogD	distribution coeffient
m	multiplet
m	*meta*
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MH	alkali metal hydride
MMPP	magnesium bis(monoperoxyphthalate)
Mp.	melting point
Ms	mesyl
MS	molecular sieves
MS	mass spectrometry
MSH	*O*-mesitylenhydroxylamine
MSO	methionine sulfoximine
MW	microwave
NBS	*N*-bromosuccinimide
NCI	National Cancer Institute
n.d.	not determined

NIH	National Institute of Health
NMR	nuclear magnetic resonance
Ns	nosyl
NSAID	nonsteroidal anti-inflammatory drug
o	*ortho*
π	Hansch lipophilicity parameter
p	*para*
PG	protecting group
PG	protaglandin
Ph	phenyl
PIDA	phenyliododiacetate
Pr	propyl
PTC	phase transfer catalyst
Py	pyridyl
PyBOX	pyridyl bisoxazoline
PyK2	protein tyrosine kinase 2
q	quartet
quant.	quantitative
quin	quintet
R	*R*-configuration
R	residue
rac	racemic
rBASIC	rat bile-sensitive ion channel
reflux	refluxing
R_F	perfluorinated residue
RCM	ring-closing metathesis
RCEYM	ring-closing eyne metathesis
rpm	revolutions per minute
r.t.	room temperature
s	singlet
S	*S*-configuration

S.E.M.	standard error of the mean
SFC	supercritical fluid chromatography
SI	selectivity index
S_NAr	nucleophilic aromatic substitution
t	tertiary
t	triplet
t	time
t_r	retention time
T	temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	triflyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TLC	thin layer chromatography
Tol	tolyl
TPP	tetraphenyl porphyrin dianion
Ts	tosyl
UV	ultraviolett
vdW	van-der-Waals
X	halide
Xa	blood coagulation factor

14.2 Crystal Structural Data

Compound (2*R*,4*S*)-197b

Experimental details

Crystal data	
Chemical formula	C19H17F5N2O2S
*M*r	432.44
Crystal system, space group	Monoclinic, *P*21/*c*
Temperature (K)	120
a, *b*, *c* (Å)	5.0367 (3), 22.8646 (12), 16.5731 (9)
β (°)	94.712 (3)
V (Å3)	1902.14 (18)
Z	4
Radiation type	Cu *Kα*
μ (mm−1)	2.13
Crystal size (mm)	0.76 × 0.24 × 0.15
Data collection	
Diffractometer	Bruker *APEX*-II CCD diffractometer
Absorption correction	Multi-scan *SADABS*
*T*min, *T*max	0.567, 0.753
No. of measured, independent and observed [*I* > 2.00 sig(*I*)] reflections	45012, 3344, 2723
*R*int	0.11
(sin *θ*/*λ*)max (Å−1)	0.599
Refinement	
R[*F*2 > 2*σ*(*F*2)], *wR*(*F*2), *S*	0.077, 0.054, 0.92
No. of reflections	2723
No. of parameters	299
H-atom treatment	H-atom parameters not refined
Δ*ρ*max, Δ*ρ*min (e Å−3)	0.73, −0.66

Computer programs: Xtal ADDREF SORTRF, Xtal CRYLSQ, Xtal BONDLA CIFIO.

Computing details

Data reduction: *Xtal ADDREF SORTRF*; program(s) used to solve structure: *Xtal*; program(s) used to refine structure: *Xtal CRYLSQ*; molecular graphics: *Xtal*; software used to prepare material for publication: *Xtal BONDLA CIFIO*.

(gr0743)

Crystal data

C19H17F5N2O2S*Mr* = 432.44	*F*(000) = 888*D*x = 1.51 Mg m−3
Monoclinic, *P*21/*c*	Cu *Kα* radiation, *λ* = 1.54178 Å
Hall symbol: -p 2ybc	Cell parameters from 3762 reflections
a = 5.0367 (3) Å*b* = 22.8646 (12) Å	*θ* = 3.3–65.7°*μ* = 2.13 mm−1
c = 16.5731 (9) Å	*T* = 120 K
β = 94.712 (3)°	Irregular, colourless

V = 1902.14 (18) Å3	0.76 × 0.24 × 0.15 mm
Z = 4	
Data collection	
Bruker APEX-II CCD	45012 measured reflections
diffractometer	3344 independent reflections
Radiation source: micro source	2723 reflections with I > 2.00 sig(I)
Graphite monochromator	Rint = 0.11
φ and ω scans	θmax = 67.4°, θmin = 3.3°
Absorption correction: multi-scan	h = −6→6
SADABS	k = −27→27
Tmin = 0.567, Tmax = 0.753	l = −19→19
Refinement	
Refinement on F	H-atom parameters not refined
Least-squares matrix: full	w = 1/[4.5σ2(F)]
R[F2 > 2σ(F2)] = 0.077 wR(F2) = 0.054 S = 0.92	$\Delta\rho$max = 0.73 e Å−3 $\Delta\rho$min = −0.66 e Å−3
2723 reflections	Extinction correction: Zachariasen, Eq22 p292 "Cryst.
299 parameters	Comp." Munksgaard 1970
0 restraints	Extinction coefficient: 604 (86)
0 constraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	y	z	Uiso*/Ueq	Occ. (<1)
S	1.0798 (2)	0.25109 (5)	0.20128 (6)	0.0283 (6)	
F3	0.8146 (5)	0.26795 (10)	0.14666 (12)	0.0364 (15)	
F4	1.3552 (5)	0.23131 (10)	0.24604 (13)	0.0375 (15)	
F1	1.1963 (5)	0.22994 (10)	0.11899 (13)	0.0380 (15)	
F5	0.9684 (5)	0.18630 (9)	0.20965 (13)	0.0364 (15)	
F2	1.2008 (5)	0.31372 (10)	0.18381 (14)	0.0400 (16)	
C5	0.6753 (8)	0.34209 (16)	0.3605 (2)	0.024 (2)	
C3	0.9489 (8)	0.27480 (16)	0.2922 (2)	0.023 (2)	
C4	0.7847 (8)	0.32388 (17)	0.2917 (2)	0.025 (2)	
C6	0.7379 (9)	0.31107 (17)	0.4338 (2)	0.029 (3)	
C8	1.0054 (10)	0.24375 (18)	0.3631 (3)	0.041 (3)	
C11	0.4386 (8)	0.37457 (17)	0.5083 (2)	0.027 (2)	
C7	0.9019 (10)	0.26196 (19)	0.4327 (2)	0.044 (3)	
C9	0.4790 (8)	0.39255 (16)	0.3603 (2)	0.024 (2)	
C10	0.4863 (8)	0.42032 (16)	0.4445 (2)	0.027 (2)	
N1	0.5280 (6)	0.43489 (13)	0.29747 (18)	0.025 (2)	
N2	0.6432 (7)	0.32978 (14)	0.50545 (19)	0.030 (2)	
O2	0.4131 (6)	0.50820 (12)	0.21383 (16)	0.0321 (18)	
C14	0.3238 (10)	0.46785 (17)	0.2646 (2)	0.025 (3)	
O1	0.0916 (6)	0.46205 (12)	0.27800 (17)	0.0351 (19)	
C2	0.3031 (9)	0.57383 (18)	0.1031 (3)	0.031 (3)	
C15	0.2128 (10)	0.5505 (2)	0.1815 (3)	0.043 (3)	

C1	0.4502 (10)	0.6166 (2)	−0.0429 (3)	0.043 (3)	
C1a	0.543 (2)	0.6010 (4)	0.1011 (5)	0.028 (6)	0,5
C4a	0.1102 (19)	0.5720 (4)	0.0363 (5)	0.034 (6)	0,5
C3a	0.195 (2)	0.5934 (5)	−0.0382 (6)	0.044 (7)	0,5
C1b	0.396 (2)	0.6296 (4)	0.0979 (6)	0.038 (7)	0,5
C4b	0.3045 (19)	0.5357 (4)	0.0337 (6)	0.037 (6)	0,5
C2a	0.624 (2)	0.6215 (4)	0.0271 (6)	0.037 (6)	0,5
C2b	0.469 (2)	0.6524 (4)	0.0227 (7)	0.045 (7)	0,5
C3b	0.379 (2)	0.5577 (5)	−0.0404 (6)	0.050 (7)	0,5
C12	0.4419 (9)	0.40013 (18)	0.5938 (2)	0.028 (3)	
C13	0.1810 (9)	0.43016 (17)	0.6089 (3)	0.032 (3)	
H11	0.25730	0.35710	0.50000	0,039	
H9	0.28035	0.37685	0.35032	0,037	
H10b	0.36646	0.45207	0.44253	0,041	
H4	0.76420	0.34014	0.23755	0,03	
H10a	0.68130	0.43495	0.46375	0,041	
H_1	0.71986	0.44953	0.29758	0,08	
H7	0.91021	0.23548	0.48264	0,06	
H13b	0.18297	0.44473	0.66414	0,048	
H12a	0.58125	0.42893	0.60958	0,041	
H1	0.50478	0.62612	−0.10277	0,063	
H15a	0.01457	0.52676	0.17135	0,06	
H_2	0.65192	0.29838	0.54738	0,06	
H13c	0.00000	0.39282	0.60851	0,048	
H13a	0.17746	0.46965	0.57687	0,048	
H12b	0.45060	0.36894	0.64182	0,041	
H15b	0.19346	0.58340	0.23179	0,06	
H8	1.12006	0.20900	0.36312	0,063	

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S	0.0268 (7)	0.0288 (6)	0.0290 (6)	0.0012 (5)	−0.0003 (5)	−0.0027 (5)
F3	0.0345 (18)	0.0473 (16)	0.0261 (13)	0.0088 (12)	−0.0055 (11)	−0.0065 (11)
F4	0.0268 (17)	0.0442 (16)	0.0404 (15)	0.0072 (12)	−0.0038 (12)	−0.0072 (12)
F1	0.0415 (19)	0.0454 (16)	0.0279 (13)	0.0098 (13)	0.0088 (11)	−0.0043 (11)
F5	0.0428 (18)	0.0277 (14)	0.0389 (14)	−0.0060 (11)	0.0054 (12)	−0.0078 (11)
F2	0.0436 (19)	0.0306 (15)	0.0472 (16)	−0.0030 (12)	0.0117 (12)	0.0016 (12)
C5	0.022 (3)	0.022 (2)	0.027 (2)	−0.0028 (18)	−0.001 (2)	−0.0001 (18)
C3	0.022 (3)	0.026 (2)	0.020 (2)	0.0036 (18)	0.0022 (19)	−0.0061 (18)
C4	0.024 (3)	0.028 (2)	0.022 (2)	−0.0047 (18)	0.000 (2)	−0.0012 (18)
C6	0.032 (3)	0.029 (2)	0.024 (2)	0.001 (2)	−0.002 (2)	−0.0012 (19)
C8	0.057 (4)	0.035 (3)	0.030 (3)	0.023 (2)	0.000 (2)	−0.002 (2)
C11	0.024 (3)	0.029 (2)	0.027 (2)	−0.0020 (19)	0.002 (2)	0.0000 (19)
C7	0.070 (4)	0.041 (3)	0.021 (2)	0.031 (3)	0.003 (2)	0.002 (2)
C9	0.021 (3)	0.025 (2)	0.026 (2)	0.0008 (18)	0.0052 (18)	0.0022 (18)
C10	0.030 (3)	0.023 (2)	0.029 (2)	0.0052 (19)	0.005 (2)	0.0015 (18)

N1	0.020 (2)	0.027 (2)	0.0269 (19)	0.0005 (15)	0.0035 (15)	0.0047 (15)
N2	0.040 (3)	0.026 (2)	0.025 (2)	0.0094 (17)	0.0048 (18)	0.0015 (16)
O2	0.025 (2)	0.0375 (18)	0.0343 (17)	0.0056 (14)	0.0070 (13)	0.0161 (14)
C14	0.025 (3)	0.028 (2)	0.023 (2)	0.002 (2)	0.003 (2)	−0.0017 (18)
O1	0.020 (2)	0.040 (2)	0.0456 (19)	0.0049 (14)	0.0060 (15)	0.0110 (15)
C2	0.029 (3)	0.034 (3)	0.031 (3)	0.004 (2)	0.004 (2)	0.010 (2)
C15	0.039 (4)	0.046 (3)	0.045 (3)	0.015 (2)	0.008 (2)	0.020 (2)
C1	0.036 (4)	0.063 (4)	0.032 (3)	0.009 (3)	0.012 (2)	0.023 (3)
C1a	0.027 (7)	0.030 (6)	0.028 (5)	−0.002 (5)	0.007 (4)	−0.001 (4)
C4a	0.037 (7)	0.032 (5)	0.033 (5)	0.000 (4)	0.000 (4)	0.008 (4)
C3a	0.036 (8)	0.053 (7)	0.043 (6)	0.001 (5)	0.006 (5)	0.008 (5)
C1b	0.032 (8)	0.040 (7)	0.042 (6)	0.008 (5)	−0.002 (5)	0.004 (5)
C4b	0.023 (6)	0.044 (6)	0.044 (6)	0.005 (5)	0.002 (5)	−0.002 (5)
C2a	0.043 (8)	0.022 (5)	0.047 (6)	−0.004 (5)	0.006 (5)	−0.001 (4)
C2b	0.029 (7)	0.044 (7)	0.062 (8)	0.003 (5)	0.002 (5)	0.012 (6)
C3b	0.044 (8)	0.057 (7)	0.046 (7)	0.008 (6)	−0.004 (5)	0.001 (5)
C12	0.025 (3)	0.034 (3)	0.026 (2)	−0.004 (2)	0.006 (2)	−0.0032 (19)
C13	0.028 (3)	0.029 (3)	0.042 (3)	0.000 (2)	0.014 (2)	0.000 (2)
H11	0.03900	0.03900	0.03900	0	0,0032	0
H9	0.03700	0.03700	0.03700	0	0,00304	0
H10b	0.04100	0.04100	0.04100	0	0,00337	0
H4	0.03000	0.03000	0.03000	0	0,00246	0
H10a	0.04100	0.04100	0.04100	0	0,00337	0
H_1	0.08000	0.08000	0.08000	0	0,00657	0
H7	0.06000	0.06000	0.06000	0	0,00493	0
H13b	0.04800	0.04800	0.04800	0	0,00394	0
H12a	0.04100	0.04100	0.04100	0	0,00337	0
H1	0.06300	0.06300	0.06300	0	0,00518	0
H15a	0.06000	0.06000	0.06000	0	0,00493	0
H_2	0.06000	0.06000	0.06000	0	0,00493	0
H13c	0.04800	0.04800	0.04800	0	0,00394	0
H13a	0.04800	0.04800	0.04800	0	0,00394	0
H12b	0.04100	0.04100	0.04100	0	0,00337	0
H15b	0.06000	0.06000	0.06000	0	0,00493	0
H8	0.06300	0.06300	0.06300	0	0,00518	0

Geometric parameters (Å, º)

S—F4	1.584 (2)	O2—C15	1.466 (5)
S—F2	1.592 (3)	C14—O1	1.215 (6)
S—F5	1.594 (2)	C2—C1a	1.360 (11)
S—F3	1.598 (2)	C2—C1b	1.363 (11)
S—F1	1.603 (3)	C2—C4a	1.412 (9)
S—C3	1.779 (4)	C2—C4b	1.443 (10)
C5—C4	1.371 (6)	C2—C15	1.508 (6)
C5—C6	1.420 (5)	C15—H15b	1.134
C5—C9	1.519 (5)	C15—H15a	1.136

C3—C8	1.382 (5)	C1—H1	1.074
C3—C4	1.394 (5)	C1—C2b	1.359 (12)
C4—H4	0.970	C1—C3b	1.395 (12)
C6—N2	1.383 (5)	C1—C2a	1.400 (10)
C6—C7	1.395 (6)	C1—C3a	1.400 (12)
C8—H8	0.982	C1a—C1b	0.983 (14)
C8—C7	1.368 (6)	C1a—C2a	1.406 (13)
C11—H11	0.996	C4a—C4b	1.286 (13)
C11—N2	1.457 (5)	C4a—C3a	1.426 (13)
C11—C10	1.520 (5)	C3a—C3b	1.239 (15)
C11—C12	1.531 (5)	C1b—C2b	1.427 (15)
C7—H7	1.024	C1b—C2a	1.719 (15)
C9—H9	1.063	C4b—C3b	1.406 (14)
C9—N1	1.458 (5)	C2a—C2b	1.053 (14)
C9—C10	1.531 (5)	C12—H12a	0.982
C10—H10b	0.943	C12—H12b	1.067
C10—H10a	1.061	C12—C13	1.521 (6)
N1—H_1	1.022	C13—H13b	0.973
N1—C14	1.353 (5)	C13—H13a	1.047
N2—H_2	0.998	C13—H13c	1.249
O2—C14	1.351 (5)		
H13b···H13a	1.5526	H9···H4	3.1871
H12a···H12b	1.6303	H12a···H_2	3.1875
H10b···H10a	1.6431	O2···H15a	3.194
H13b···H13c	1.7229	H_1···H15a	3.1950
C1a···C2b	1.769 (14)	C8···H4	3.201
H15a···H15b	1.8287	C1a···C4a	3.204 (14)
C3a···C4b	1.833 (13)	N2···H9	3.215
C3···H4	1.944	C3a···C2a	3.216 (15)
O1···H_1	1.947	C10···C14	3.216 (5)
C4a···C3b	1.959 (14)	F3···F1	3.230 (3)
C6···H_2	1.987	H12a···H13a	3.2320
C13···H12b	1.994	F4···H4	3.241
C12···H11	2.003	C4a···H15b	3.243
C3b···H1	2.007	C10···C13	3.244 (6)
C13···H12a	2.015	C7···C2b	3.246 (11)
C11···H10a	2.023	O1···H13a	3.255
N2···H11	2.037	N2···H10b	3.257
C9···H10b	2.039	O2···H12a	3.259
C7···H8	2.052	F1···C12	3.261 (5)
C3···H8	2.054	C5···H_2	3.265
C10···H9	2.058	H10b···H13a	3.2661
H13c···H13a	2.0583	C5···H11	3.270
N1···H9	2.065	C1b···H8	3.280
C14···H_1	2.068	O1···H4	3.280
C6···H7	2.069	C4b···H1	3.283

C12···H13a	2.078	H11···H7	3.2847
O2···H15b	2.079	N1···H13a	3.285
C8···H7	2.084	C4···H8	3.290
C12···H13b	2.086	F5···H13b	3.293
C11···H10b	2.097	H13a···H13a	3.2964
C3a···H1	2.102)	F3···N2	3.299 (4)
C10···H11	2.107	H9···H4	3.2992
C9···H_1	2.111	C6···H8	3.301
O2···H15a	2.115	C3···H7	3.302
C11···H_2	2.120	F1···C11	3.306 (5)
C5···H4	2.123	C5···H10b	3.307
C3a···C2b	2.127 (14)	C12···H15b	3.317
C5···H9	2.136	F1···C7	3.319 (5)
C4a···C1b	2.147 (13)	F2···C4	3.322 (5)
C9···H10a	2.152	C5···H7	3.323
C2a···C3b	2.163 (14)	C14···H13b	3.329
C11···H12a	2.163	C1b···H15a	3.330
C1a···C4b	2.166 (13)	H9···H_1	3.3302
C2b···H1	2.186	C6···H4	3.334
C2a···H1	2.189	C10···H_2	3.338
F4···F1	2.191 (3)	C13···H10a	3.338
F3···F1	2.192 (3)	F1···N2	3.342 (4)
C2···H15a	2.195	F4···F5	3.357 (3)
F1···F2	2.195 (3)	C8···H9	3.357
F1···F5	2.203 (3)	F5···C13	3.364 (5)
C11···H12b	2.212	F3···C1	3.366 (5)
N1···O2	2.221 (4)	F3···F2	3.369 (3)
F4···F5	2.242 (3)	H10a···H13a	3.3713
H13b···H12b	2.2447	C15···H13b	3.372
F3···F5	2.245 (3)	O2···C1b	3.372 (10)
F3···F2	2.249 (3)	C4a···C4b	3.374 (12)
F4···F2	2.256 (3)	F1···C3	3.382 (4)
C2···H15b	2.256	C13···H15b	3.382
H12a···H13a	2.2618	C11···H13b	3.383
F3···H4	2.263	S···H_2	3.3950
C12···H13c	2.265	C8···C1b	3.397 (11)
H12a···H13c	2.2664	C4a···H1	3.398
H7···H_2	2.2674	C7···C1b	3.399 (11)
O2···O1	2.269 (4)	C10···O1	3.403 (5)
N1···O1	2.282 (4)	C13···H10a	3.403
H13b···H12a	2.2957	H11···H10a	3.4146
O1···H15a	2.313	C3b···H15a	3.415
H9···H10b	2.3180	C1b···H1	3.415
F3···H_2	2.336	C1a···H1	3.417
H13c···H12b	2.3554	H11···H13b	3.4238
C3···C7	2.377 (5)	H10a···H_2	3.4246

C14···C15	2.377 (6)	C3a···H7	3.429
C1···C1b	2.390 (11)	F2···C1	3.429 (6)
C1···C4b	2.392 (11)	C1a···H15a	3.438
C2···C2a	2.394 (11)	O1···C13	3.449 (5)
H7···H8	2.3982	O1···H12a	3.449
O2···C2	2.399 (5)	C1···H4	3.461
O2···H_1	2.400	C1···H7	3.462
C4···C8	2.403 (6)	H11···H_2	3.4799
C2···C3a	2.404 (10)	F4···C5	3.480 (4)
C4···C6	2.404 (5)	O2···C3b	3.482 (11)
H10a···H13a	2.4075	C10···H12b	3.493
C10···N2	2.408 (5)	C6···H9	3.502
C5···C3	2.409 (5)	S···H12b	3.5063
F4···H8	2.409	N1···H1	3.507
C7···N2	2.411 (6)	F1···N2	3.508 (4)
C6···C8	2.412 (6)	C10···H10b	3.513
C1···C1a	2.419 (9)	H13b···H15b	3.5161
C5···C7	2.422 (6)	O2···C4a	3.518 (9)
C1b···C4b	2.422 (13)	C2a···H7	3.518
C3a···C2a	2.426 (14)	H10b···H10a	3.5193
C9···C14	2.427 (5)	C14···H13b	3.521
C2···C2b	2.427 (11)	C4···O1	3.533 (5)
C2b···C3b	2.432 (15)	C4···H1	3.534
C5···N2	2.437 (5)	N1···H12a	3.537
O1···H9	2.439	F3···C2b	3.546 (11)
C1a···C4a	2.439 (13)	C4b···H15b	3.546
H11···H13c	2.4421	H10a···H12a	3.5564
F5···C3	2.449 (4)	N1···C15	3.563 (5)
N2···C12	2.450 (5)	C15···H12a	3.563
F2···C3	2.450 (5)	C2b···H_2	3.569
H11···H10b	2.4517	C10···H12a	3.571
C5···N1	2.453 (5)	C4b···C4b	3.573 (13)
F4···C3	2.454 (5)	H10a···H13b	3.5729
F3···C3	2.456 (4)	H_1···H12a	3.5740
C1···C4a	2.463 (10)	H15b···H8	3.5787
C2···C3b	2.467 (11)	C12···H10b	3.579
C15···C4a	2.469 (9)	F5···C4	3.579 (4)
H11···H_2	2.4725	C7···H9	3.581
F5···H13c	2.480	F2···C8	3.584 (5)
H11···H12b	2.4839	C9···O2	3.587 (5)
C10···N1	2.486 (5)	H10a···H12b	3.5918
C6···C11	2.492 (6)	C14···H1	3.597
F2···H1	2.495	C5···H11	3.597
C14···H15a	2.497	F5···H12a	3.601
C15···C1a	2.497 (11)	C2···C3b	3.601 (12)
C15···C1b	2.501 (11)	C6···H13c	3.604

C5···C10	2.502 (5)	C14···C2	3.605 (6)
C7···H_2	2.507	C8···H11	3.605
C11···C9	2.511 (5)	C1···C4a	3.618 (10)
C13···H11	2.512	F2···C9	3.619 (4)
H10a···H12a	2.5128	O2···H1	3.622
F2···H4	2.513	F4···C1b	3.624 (10)
N2···H10a	2.514	F3···H12b	3.625
H_2···H12b	2.5183	C3a···H15a	3.626
H10b···H13a	2.5246	C13···H10a	3.626
C6···C9	2.529 (5)	C3a···H1	3.628
C4···C9	2.533 (6)	F1···H1	3.638 (
H11···H9	2.5335	S···H13c	3.6402
C3a···C1b	2.535 (13)	F3···C3a	3.642 (10)
C11···C13	2.537 (6)	C4a···C4a	3.648 (12)
H_1···H13b	2.5369	C10···H13c	3.649
C14···H9	2.539	O2···O1	3.650 (4)
C10···C12	2.544 (5)	F5···N2	3.655 (4)
C4b···C2a	2.546 (13)	C3a···H4	3.657
C4a···H15a	2.547	C2b···H7	3.664
C15···C4b	2.551 (10)	F2···N1	3.665 (4)
N2···H7	2.585	F1···C13	3.665 (5)
C4a···C2b	2.602 (14)	S···H7	3.6667
F1···H12b	2.611	C8···N2	3.669 (6)
C1a···C3b	2.615 (13)	C5···C14	3.670 (5)
N1···H10b	2.630	C4···N2	3.672 (5)
H4···H1	2.6311	C13···H10b	3.673
F5···H8	2.646	F3···C7	3.673 (5)
C4b···C3b	2.663 (14)	C2a···H15a	3.674
C11···H9	2.674	F2···C3a	3.675 (10)
C12···H10a	2.676	F4···C8	3.678 (5)
O1···C15	2.679 (5)	F3···C8	3.679 (5)
S···H4	2.6815	F2···C5	3.683 (4)
N2···H12b	2.685	C1···C4b	3.694 (10)
C5···H_1	2.686	F4···C4	3.697 (5)
C4a···C2a	2.688 (14)	N1···C13	3.701 (5)
C2b···H7	2.690	C9···H13a	3.703
C12···H_2	2.694	F2···H7	3.704
F1···H7	2.697	F5···H4	3.704
F5···H15b	2.697	C14···H10a	3.705
N1···H4	2.700	C4a···C2b	3.706 (14)
H4···H_1	2.7078	C2···C2a	3.708 (11)
C5···H10a	2.725	C7···H4	3.710
C1b···H15b	2.730	C15···C1a	3.711 (11)
F3···C4	2.738 (4)	F5···C12	3.714 (5)
F4···C8	2.741 (5)	O2···C13	3.716 (5)
H13b···H15b	2.7424	C14···H4	3.717

S···C8	2.744 (4)	O2···H12b	3.717
C10···H12a	2.745	C6···N1	3.721 (5)
F1···H_2	2.746	C6···H10b	3.736
C4···C7	2.754 (6)	C2a···H7	3.742
O1···H13b	2.755	F5···C15	3.743 (5)
S···C4	2.756 (4)	C15···H12b	3.746
C14···H15b	2.765	F5···C12	3.746 (5)
C2···C1	2.767 (6)	C6···C12	3.748 (6)
C12···H10b	2.772	C8···C2a	3.748 (10)
C9···H11	2.773	C4a···H7	3.751
N2···H13c	2.778	C8···C2b	3.758 (11)
C3···C6	2.781 (5)	C4b···C2a	3.758 (13)
C9···O1	2.785 (5)	C11···C7	3.759 (6)
C1a···C3a	2.787 (13)	C4···C10	3.763 (6)
H12a···H15b	2.7908	C4···H7	3.764
C5···C8	2.794 (6)	C14···H13a	3.764
H10a···H_1	2.7967	C15···C3a	3.765 (10)
H_1···H13a	2.7991	C10···H10a	3.766
N1···H10a	2.800	C12···C13	3.774 (6)
F3···H7	2.800	C4a···H8	3.775
C4b···C2b	2.805 (14)	C5···O1	3.776 (5)
C12···H13c	2.807	C5···H8	3.777
C6···C10	2.813 (5)	N2···C13	3.780 (5)
C4b···H15a	2.815	C1···C3a	3.781 (12)
C1b···C3b	2.815 (14)	F4···H9	3.783
C11···H13a	2.827	F4···H_2	3.787
F1···H11	2.836	C15···C2a	3.789 (11)
S···H8	2.8412	F2···O1	3.792 (4)
C4a···C2a	2.842 (14)	C8···C2b	3.794 (12)
H13a···H12b	2.8478	C1a···C3b	3.795 (14)
C9···H4	2.850	C1a···H15b	3.799
C4···N1	2.853 (5)	F2···C14	3.803 (5)
F5···C8	2.855 (5)	F1···C6	3.803 (4)
C4b···C4b	2.857 (13)	C7···C9	3.804 (6)
H11···H12a	2.8585	S···F4	3.810 (3)
H12b···H15b	2.8587	C4a···C3b	3.810 (14)
C9···N2	2.864 (5)	C15···H13b	3.813
C10···H_1	2.869	C9···H_2	3.816
C4···H9	2.871	C3···C9	3.816 (5)
H10b···H12a	2.8732	C11···N1	3.818 (5)
F2···C4	2.874 (5)	N1···H15a	3.818
H11···H10a	2.8811	C15···C2b	3.820 (12)
N2···H12a	2.882	C9···O1	3.821 (5)
C6···H10a	2.894	C2···H8	3.821
C4···H_1	2.894	C2···H15a	3.823
C11···H13c	2.901	C2···H1	3.831

C5···C11	2.907 (6)	O2···C12	3.835 (5)
H_2···H13c	2.9106	C15···H_1	3.839
H11···H13a	2.9140	C15···C3b	3.841 (11)
H13c···H12b	2.9174	N2···C13	3.845 (5)
C1a···H15b	2.928	O2···H9	3.851
C2a···H8	2.931	C10···H13c	3.857
F4···H12b	2.933	F3···H13c	3.858
C6···H11	2.934	C14···O1	3.858 (6)
O1···H15b	2.935	C6···C2b	3.858 (11)
O2···C1a	2.936 (9)	C4a···C3b	3.860 (14)
H10b···H12a	2.9366	O1···H13c	3.861
H10a···H13c	2.9373	F2···H8	3.864
H13c···H15b	2.9451	C8···H_2	3.866
C6···H11	2.947	C11···C7	3.867 (6)
N1···O1	2.949 (5)	S···H9	3.8703
H10b···H13a	2.9504	C2b···H8	3.871
O2···H13b	2.951	C4a···H1	3.871
H9···H_1	2.9571	F4···H4	3.874
H9···H10a	2.9587	C2···C1a	3.878 (11)
C14···H10b	2.961	C3a···C4b	3.881 (14)
O1···H10b	2.964	C3a···C4b	3.883 (14)
F3···H1	2.965	C4···H10a	3.885
F2···H4	2.966	C6···H_1	3.885
F1···H_2	2.968	C9···C12	3.893 (5)
C7···H11	2.975	C3···C9	3.893 (5)
F1···H13c	2.976	O1···H10a	3.896
C2b···H8	2.982	C14···C13	3.898 (6)
C3···H9	2.982	C13···H10b	3.898
C6···H9	2.994	S···F3	3.901 (3)
C10···H13a	3.010	N1···H15b	3.905
C13···H12a	3.022	O2···H13b	3.906
C13···H10b	3.025	C4b···H15a	3.909
C1a···H8	3.028	C4···C9	3.916 (6)
F5···H12b	3.030	F4···C1a	3.917 (9)
F5···H_2	3.032	O2···H13a	3.920
H10b···H10a	3.0339	C6···C11	3.920 (6)
F5···H12b	3.034	C4a···C3b	3.924 (14)
H12a···H13c	3.0404	C12···H10a	3.926
C4···H9	3.044	S···H1	3.9354
H13b···H15a	3.0487	C4b···C2a	3.940 (14)
O2···C4b	3.056 (10)	C10···C13	3.940 (6)
C1b···H8	3.064	F2···H1	3.942
F3···F4	3.065 (3)	C14···C12	3.944 (6)
C10···H13a	3.069	C15···H13c	3.944
C1a···H15a	3.072	C12···H13b	3.952
F4···C4	3.076 (5)	C13···H15b	3.953

H10a···H13a	3.1015	N1···H15a	3.953
H10b···H_1	3.1056	F3···C6	3.954 (4)
F2···H9	3.111	C1a···C4b	3.956 (13)
H13b···H12a	3.1117	F1···H4	3.956
C1b···H7	3.113	F2···C2a	3.961 (10)
H10b···H10b	3.1338	C3a···H15a	3.966
N1···H13b	3.154	F4···C6	3.968 (4)
C3b···C3b	3.158	C4b···H1	3.968
C14···H12a	3.159	F4···C12	3.971 (5)
C14···H_1	3.162	C1b···C2a	3.972 (15)
N2···H11	3.164	F4···H13c	3.973
C5···H9	3.167	C13···H15a	3.974
O1···H_1	3.167	C6···H8	3.988
C13···H_1	3.176	C12···H_1	3.995
F3···F4	3.177 (3)	C8···C1a	3.996 (10)
F5···F2	3.182 (3)	C15···H_1	3.997
F4···C3	3.185 (5)	C8···C1b	3.999 (11)
C11···H13c	3.187		
F4—S—F2	90.48 (13)	C1b—C2—C4a	101.3 (6)
F4—S—F5	89.70 (13)	C1b—C2—C4b	119.3 (6)
F4—S—F3	173.25 (14)	C1b—C2—C15	121.1 (5)
F4—S—F1	86.82 (13)	C4a—C2—C4b	53.5 (5)
F4—S—C3	93.52 (15)	C4a—C2—C15	115.3 (5)
F2—S—F5	173.90 (14)	C4b—C2—C15	119.6 (5)
F2—S—F3	89.69 (13)	H15b—C15—H15a	107.3
F2—S—F1	86.81 (13)	H15b—C15—O2	105.5
F2—S—C3	93.09 (16)	H15b—C15—C2	116.6
F5—S—F3	89.42 (13)	H15a—C15—O2	108.0
F5—S—F1	87.12 (13)	H15a—C15—C2	111.4
F5—S—C3	92.98 (15)	O2—C15—C2	107.5 (4)
F3—S—F1	86.45 (12)	H1—C1—C2b	127.6
F3—S—C3	93.21 (15)	H1—C1—C3b	108.1
F1—S—C3	179.6 (2)	H1—C1—C2a	124.0
C4—C5—C6	118.9 (4)	H1—C1—C3a	115.7
C4—C5—C9	122.3 (3)	C2b—C1—C3b	124.1 (7)
C6—C5—C9	118.7 (3)	C2b—C1—C2a	44.9 (6)
C8—C3—C4	119.9 (4)	C2b—C1—C3a	100.9 (7)
C8—C3—S	119.9 (3)	C3b—C1—C2a	101.4 (6)
C4—C3—S	120.1 (3)	C3b—C1—C3a	52.6 (6)
H4—C4—C5	129.4 (4)	C2a—C1—C3a	120.1 (7)
H4—C4—C3	109.4 (4)	C1b—C1a—C2	69.0 (9)
C5—C4—C3	121.2 (3)	C1b—C1a—C2a	90.3 (9)
N2—C6—C7	120.5 (3)	C2—C1a—C2a	119.9 (8)
N2—C6—C5	120.8 (4)	C4b—C4a—C2	64.5 (6)
C7—C6—C5	118.7 (4)	C4b—C4a—C3a	84.9 (8)
H8—C8—C7	120.7	C2—C4a—C3a	115.7 (8)

H8—C8—C3	119.7	C3b—C3a—C1	63.5 (7)
C7—C8—C3	119.6 (4)	C3b—C3a—C4a	94.4 (9)
H11—C11—N2	110.9	C1—C3a—C4a	121.2 (8)
H11—C11—C10	112.1	C1a—C1b—C2	68.7 (8)
H11—C11—C12	102.8	C1a—C1b—C2b	92.6 (10)
N2—C11—C10	108.0 (3)	C1a—C1b—C2a	54.9 (8)
N2—C11—C12	110.2 (3)	C2—C1b—C2b	120.9 (8)
C10—C11—C12	113.0 (3)	C2—C1b—C2a	101.3 (7)
H7—C7—C8	120.5	C2b—C1b—C2a	37.7 (6)
H7—C7—C6	116.7	C4a—C4b—C3b	93.3 (8)
C8—C7—C6	121.6 (4)	C4a—C4b—C2	62.0 (6)
H9—C9—N1	109.0	C3b—C4b—C2	120.0 (8)
H9—C9—C5	110.4	C2b—C2a—C1	65.5 (8)
H9—C9—C10	103.5	C2b—C2a—C1a	90.8 (10)
N1—C9—C5	110.9 (3)	C2b—C2a—C1b	56.0 (8)
N1—C9—C10	112.5 (3)	C1—C2a—C1a	119.2 (9)
C5—C9—C10	110.2 (3)	C1—C2a—C1b	99.5 (7)
H10b—C10—H10a	110.0	C1a—C2a—C1b	34.9 (6)
H10b—C10—C11	114.6	C2a—C2b—C1	69.6 (8)
H10b—C10—C9	108.6	C2a—C2b—C1b	86.3 (10)
H10a—C10—C11	101.8	C1—C2b—C1b	118.1 (9)
H10a—C10—C9	110.9	C3a—C3b—C1	63.9 (7)
C11—C10—C9	110.8 (3)	C3a—C3b—C4b	87.5 (9)
H_1—N1—C14	120.4	C1—C3b—C4b	117.3 (8)
H_1—N1—C9	115.6	H12a—C12—H12b	105.3
C14—N1—C9	119.3 (3)	H12a—C12—C13	105.2
H_2—N2—C6	112.1	H12a—C12—C11	117.1
H_2—N2—C11	118.3	H12b—C12—C13	99.3
C6—N2—C11	122.7 (3)	H12b—C12—C11	115.6
C14—O2—C15	115.1 (3)	C13—C12—C11	112.4 (3)
O1—C14—O2	124.3 (4)	H13b—C13—H13a	100.4
O1—C14—N1	125.2 (4)	H13b—C13—H13c	101.0
O2—C14—N1	110.5 (4)	H13b—C13—C12	111.6
C1a—C2—C1b	42.3 (6)	H13a—C13—H13c	127.2
C1a—C2—C4a	123.2 (6)	H13a—C13—C12	106.5
C1a—C2—C4b	101.1 (6)	H13c—C13—C12	109.3
C1a—C2—C15	120.9 (5)		
F3—S—C3—C4	−36.6 (3)	C1b—C2—C4a—C4b	118.2 (7)
F3—S—C3—C8	142.0 (3)	C4b—C2—C4a—C3a	−70.1 (9)
F4—S—C3—C4	144.0 (3)	C4b—C2—C4a—C4b	0.0 (7)
F4—S—C3—C8	−37.5 (4)	C15—C2—C1b—C1a	103.3 (8)
F1—S—C3—C4	−20 (27)	C15—C2—C1b—C2a	148.2 (5)
F1—S—C3—C8	158 (27)	C15—C2—C1b—C2b	−176.9 (7)
F5—S—C3—C4	−126.2 (3)	C1a—C2—C1b—C1a	0.0 (7)
F5—S—C3—C8	52.4 (4)	C1a—C2—C1b—C2a	44.9 (7)
F2—S—C3—C4	53.3 (3)	C1a—C2—C1b—C2b	79.8 (11)

F2—S—C3—C8	−128.2 (3)	C4a—C2—C1b—C1a	−127.7 (8)
C6—C5—C4—C3	1.8 (6)	C4a—C2—C1b—C2a	−82.7 (7)
C6—C5—C4—H4	−179.4	C4a—C2—C1b—C2b	−47.9 (11)
C9—C5—C4—C3	−175.2 (4)	C4b—C2—C1b—C1a	−73.3 (9)
C9—C5—C4—H4	3.6	C4b—C2—C1b—C2a	−28.4 (9)
C4—C5—C6—C7	−2.0 (6)	C4b—C2—C1b—C2b	6.4 (12)
C4—C5—C6—N2	176.6 (4)	C15—C2—C4b—C4a	101.1 (7)
C9—C5—C6—C7	175.1 (4)	C15—C2—C4b—C3b	177.7 (7)
C9—C5—C6—N2	−6.3 (6)	C1a—C2—C4b—C4a	−123.3 (7)
C4—C5—C9—C10	−154.9 (4)	C1a—C2—C4b—C3b	−46.7 (10)
C4—C5—C9—N1	−29.5 (5)	C4a—C2—C4b—C4a	0.0 (6)
C4—C5—C9—H9	91.4	C4a—C2—C4b—C3b	76.6 (9)
C6—C5—C9—C10	28.1 (5)	C1b—C2—C4b—C4a	−82.2 (8)
C6—C5—C9—N1	153.4 (3)	C1b—C2—C4b—C3b	−5.6 (12)
C6—C5—C9—H9	−85.7	C2a—C1—C3a—C4a	−2.8 (13)
S—C3—C4—C5	178.2 (3)	C2a—C1—C3a—C3b	−81.1 (9)
S—C3—C4—H4	−0.9	C2b—C1—C3a—C4a	−46.5 (11)
C8—C3—C4—C5	−0.4 (6)	C2b—C1—C3a—C3b	−124.8 (8)
C8—C3—C4—H4	−179.4	C3b—C1—C3a—C4a	78.3 (10)
S—C3—C8—C7	−179.4 (3)	C3b—C1—C3a—C3b	0.0 (7)
S—C3—C8—H8	1.0	H1—C1—C3a—C4a	172.0
C4—C3—C8—C7	−0.8 (6)	H1—C1—C3a—C3b	93.7
C4—C3—C8—H8	179.5	C3a—C1—C2a—C1a	2.2 (12)
C5—C6—C7—C8	0.9 (7)	C3a—C1—C2a—C1b	−28.6 (9)
C5—C6—C7—H7	−166.9	C3a—C1—C2a—C2b	−74.2 (10)
N2—C6—C7—C8	−177.8 (4)	C2b—C1—C2a—C1a	76.3 (11)
N2—C6—C7—H7	14.5	C2b—C1—C2a—C1b	45.6 (8)
C5—C6—N2—C11	11.6 (6)	C2b—C1—C2a—C2b	0.0 (9)
C5—C6—N2—H_2	162.0	C3b—C1—C2a—C1a	−51.1 (10)
C7—C6—N2—C11	−169.8 (4)	C3b—C1—C2a—C1b	−81.8 (7)
C7—C6—N2—H_2	−19.4	C3b—C1—C2a—C2b	−127.4 (9)
C3—C8—C7—C6	0.6 (7)	H1—C1—C2a—C1a	−172.2
C3—C8—C7—H7	167.9	H1—C1—C2a—C1b	157.0
H8—C8—C7—C6	−179.8	H1—C1—C2a—C2b	111.5
H8—C8—C7—H7	−12.5	C3a—C1—C2b—C1b	48.0 (10)
N2—C11—C10—C9	58.3 (4)	C3a—C1—C2b—C2a	122.0 (9)
N2—C11—C10—H10b	−178.3	C2a—C1—C2b—C1b	−74.0 (10)
N2—C11—C10—H10a	−59.6	C2a—C1—C2b—C2a	0.0 (8)
C12—C11—C10—C9	−179.6 (3)	C3b—C1—C2b—C1b	−4.0 (13)
C12—C11—C10—H10b	−56.2	C3b—C1—C2b—C2a	70.1 (11)
C12—C11—C10—H10a	62.5	H1—C1—C2b—C1b	−177.1
H11—C11—C10—C9	−64.1	H1—C1—C2b—C2a	−103.1
H11—C11—C10—H10b	59.3	C3a—C1—C3b—C3a	0.0 (7)
H11—C11—C10—H10a	178.0	C3a—C1—C3b—C4b	−72.1 (10)
C10—C11—N2—C6	−37.4 (5)	C2a—C1—C3b—C3a	119.3 (8)
C10—C11—N2—H_2	173.9	C2a—C1—C3b—C4b	47.2 (11)

C12—C11—N2—C6	−161.2 (4)	C2b—C1—C3b—C3a	76.7 (9)
C12—C11—N2—H_2	50.2	C2b—C1—C3b—C4b	4.7 (13)
H11—C11—N2—C6	85.7	H1—C1—C3b—C3a	−109.0
H11—C11—N2—H_2	−62.9	H1—C1—C3b—C4b	178.9
C10—C11—C12—C13	79.4 (4)	C2—C1a—C1b—C2	0.0 (3)
C10—C11—C12—H12a	−42.5	C2—C1a—C1b—C2a	−122.1 (7)
C10—C11—C12—H12b	−167.6	C2—C1a—C1b—C2b	−122.2 (7)
N2—C11—C12—C13	−159.8 (3)	C2a—C1a—C1b—C2	122.1 (7)
N2—C11—C12—H12a	78.3	C2a—C1a—C1b—C2a	0.0 (5)
N2—C11—C12—H12b	−46.7	C2a—C1a—C1b—C2b	−0.1 (8)
H11—C11—C12—C13	−41.5	C2—C1a—C2a—C1	3.8 (13)
H11—C11—C12—H12a	−163.5	C2—C1a—C2a—C1b	65.8 (10)
H11—C11—C12—H12b	71.5	C2—C1a—C2a—C2b	66.0 (11)
C5—C9—C10—C11	−54.7 (4)	C1b—C1a—C2a—C1	−62.0 (11)
C5—C9—C10—H10b	178.5	C1b—C1a—C2a—C1b	0.0 (8)
C5—C9—C10—H10a	57.5	C1b—C1a—C2a—C2b	0.2 (11)
N1—C9—C10—C11	−179.1 (3)	C2—C4a—C3a—C1	−2.3 (12)
N1—C9—C10—H10b	54.1	C2—C4a—C3a—C3b	59.2 (10)
N1—C9—C10—H10a	−66.9	C4b—C4a—C3a—C1	−60.7 (10)
H9—C9—C10—C11	63.4	C4b—C4a—C3a—C3b	0.8 (9)
H9—C9—C10—H10b	−63.4	C2—C4a—C4b—C2	0.0 (3)
H9—C9—C10—H10a	175.6	C2—C4a—C4b—C3b	−122.5 (7)
C5—C9—N1—C14	152.4 (3)	C3a—C4a—C4b—C2	121.8 (7)
C5—C9—N1—H_1	−51.9	C3a—C4a—C4b—C3b	−0.7 (8)
C10—C9—N1—C14	−83.5 (4)	C1—C3a—C3b—C1	0.0 (3)
C10—C9—N1—H_1	72.2	C1—C3a—C3b—C4b	122.2 (7)
H9—C9—N1—C14	30.7	C4a—C3a—C3b—C1	−122.9 (7)
H9—C9—N1—H_1	−173.6	C4a—C3a—C3b—C4b	−0.7 (8)
C9—N1—C14—O2	173.9 (3)	C2—C1b—C2a—C1	75.0 (7)
C9—N1—C14—O1	−6.7 (6)	C2—C1b—C2a—C1a	−53.6 (8)
H_1—N1—C14—O2	19.3	C2—C1b—C2a—C2b	126.6 (10)
H_1—N1—C14—O1	−161.2	C1a—C1b—C2a—C1	128.6 (10)
C15—O2—C14—N1	−173.7 (3)	C1a—C1b—C2a—C1a	0.0 (9)
C15—O2—C14—O1	6.8 (5)	C1a—C1b—C2a—C2b	−179.8 (13)
C14—O2—C15—C2	−156.2 (3)	C2b—C1b—C2a—C1	−51.6 (8)
C14—O2—C15—H15a	−35.8	C2b—C1b—C2a—C1a	179.8 (13)
C14—O2—C15—H15b	78.7	C2b—C1b—C2a—C2b	0.0 (10)
C1a—C2—C15—O2	−58.3 (7)	C2—C1b—C2b—C1	−1.8 (14)
C1a—C2—C15—H15a	−176.5	C2—C1b—C2b—C2a	−66.4 (11)
C1a—C2—C15—H15b	59.8	C1a—C1b—C2b—C1	64.7 (12)
C4a—C2—C15—O2	129.4 (5)	C1a—C1b—C2b—C2a	0.2 (11)
C4a—C2—C15—H15a	11.2	C2a—C1b—C2b—C1	64.6 (9)
C4a—C2—C15—H15b	−112.5	C2a—C1b—C2b—C2a	0.0 (7)
C1b—C2—C15—O2	−108.1 (6)	C2—C4b—C3b—C1	0.2 (13)
C1b—C2—C15—H15a	133.7	C2—C4b—C3b—C3a	−58.6 (10)
C1b—C2—C15—H15b	10.1	C4a—C4b—C3b—C1	59.6 (10)

C4b—C2—C15—O2	68.5 (6)	C4a—C4b—C3b—C3a	0.8 (9)
C4b—C2—C15—H15a	−49.7	C1—C2a—C2b—C1	0.0 (3)
C4b—C2—C15—H15b	−173.3	C1—C2a—C2b—C1b	121.8 (8)
C15—C2—C1a—C1b	−103.6 (8)	C1a—C2a—C2b—C1	−121.9 (7)
C15—C2—C1a—C2a	178.8 (7)	C1a—C2a—C2b—C1b	−0.1 (8)
C4a—C2—C1a—C1b	68.1 (10)	C1b—C2a—C2b—C1	−121.8 (8)
C4a—C2—C1a—C2a	−9.5 (12)	C1b—C2a—C2b—C1b	0.0 (6)
C1b—C2—C1a—C1b	0.0 (8)	C11—C12—C13—H13b	177.6
C1b—C2—C1a—C2a	−77.6 (10)	C11—C12—C13—H13c	66.7
C4b—C2—C1a—C1b	121.6 (8)	C11—C12—C13—H13a	−73.8
C4b—C2—C1a—C2a	44.0 (10)	H12a—C12—C13—H13b	−54.0
C15—C2—C4a—C3a	−179.3 (6)	H12a—C12—C13—H13c	−164.8
C15—C2—C4a—C4b	−109.2 (6)	H12a—C12—C13—H13a	54.7
C1a—C2—C4a—C3a	8.6 (11)	H12b—C12—C13—H13b	54.8
C1a—C2—C4a—C4b	78.6 (8)	H12b—C12—C13—H13c	−56.0
C1b—C2—C4a—C3a	48.1 (9)	H12b—C12—C13—H13a	163.5

14.3 NCI One-Dose Screening

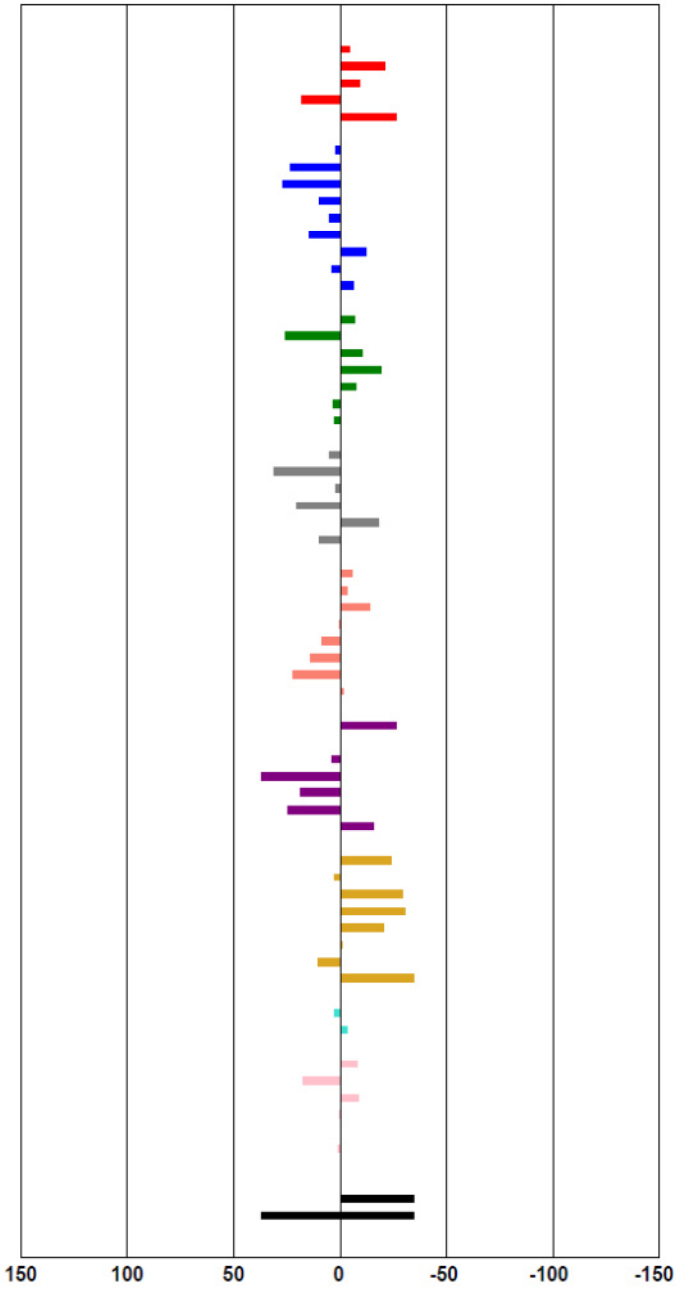
N-Cyanosulfilimine 135a

Developmental Therapeutics Program

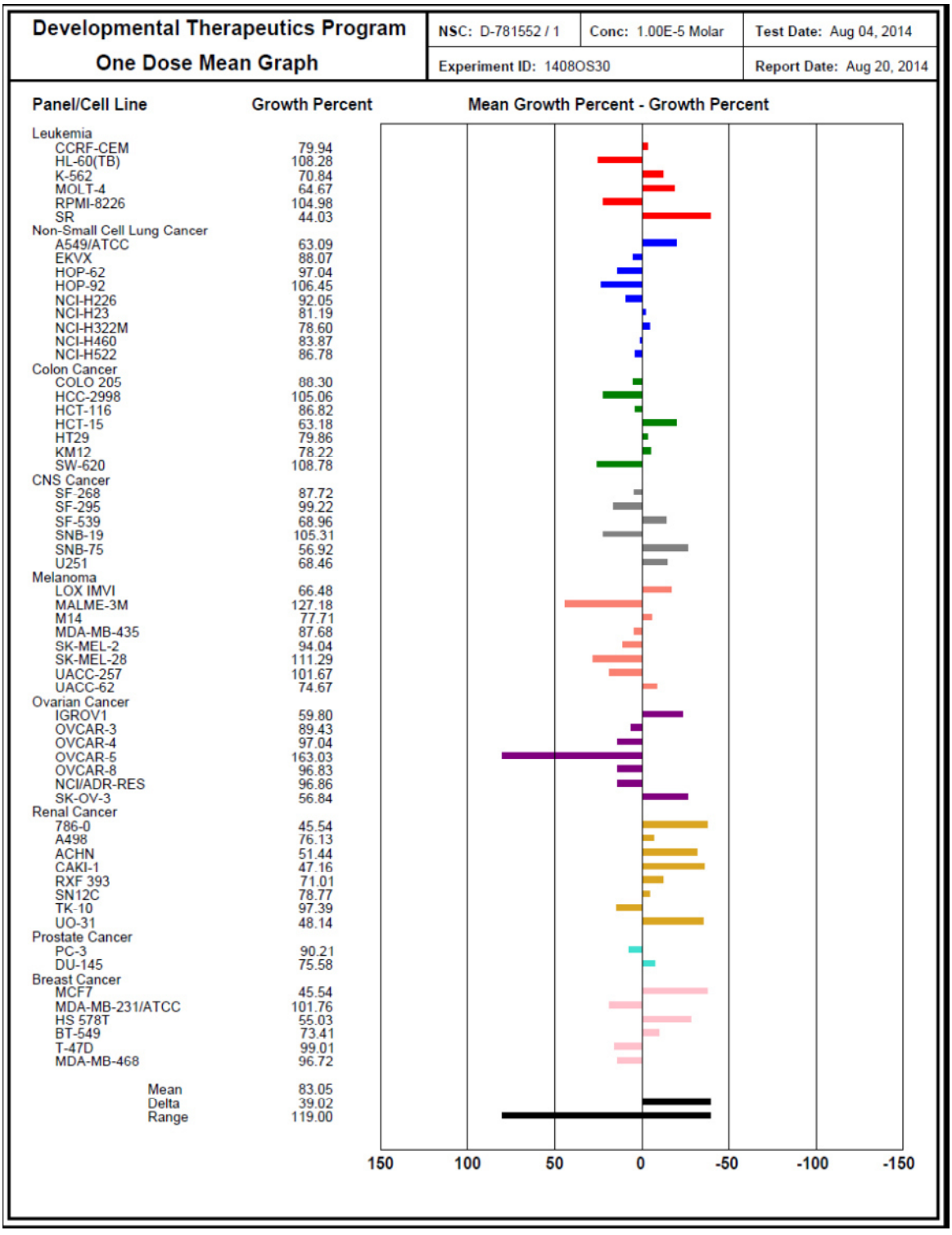
One Dose Mean Graph

NSC: D-781553 / 1	Conc: 1.00E-5 Molar	Test Date: Aug 04, 2014
Experiment ID: 1408OS30		Report Date: Aug 20, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	83.47
HL-60(TB)	79.16
K-562	62.25
MOLT-4	74.50
RPMI-8226	101.35
SR	57.10
Non-Small Cell Lung Cancer	
A549/ATCC	85.44
EKVX	106.81
HOP-62	110.37
HOP-92	93.37
NCI-H226	88.51
NCI-H23	98.25
NCI-H322M	71.32
NCI-H460	87.40
NCI-H522	77.21
Colon Cancer	
COLO 205	76.94
HCC-2998	109.32
HCT-116	73.07
HCT-15	64.23
HT29	76.32
KM12	86.51
SW-620	85.94
CNS Cancer	
SF-268	88.36
SF-295	114.26
SF-539	85.72
SNB-19	104.06
SNB-75	65.25
U251	93.20
Melanoma	
LOX IMVI	77.76
MALME-3M	79.98
M14	69.52
MDA-MB-435	83.97
SK-MEL-2	92.24
SK-MEL-28	97.39
UACC-257	105.56
UACC-62	82.17
Ovarian Cancer	
IGROV1	56.90
OVCAR-3	83.38
OVCAR-4	87.26
OVCAR-5	120.32
OVCAR-8	101.90
NCI/ADR-RES	108.28
SK-OV-3	68.05
Renal Cancer	
786-0	59.47
A498	86.31
ACHN	53.95
CAKI-1	53.24
RXF 393	62.86
SN12C	82.44
TK-10	93.57
UO-31	49.15
Prostate Cancer	
PC-3	86.01
DU-145	80.28
Breast Cancer	
MCF7	75.72
MDA-MB-231/ATCC	100.67
HS 578T	74.64
BT-549	83.49
T-47D	82.90
MDA-MB-468	84.61
Mean	83.45
Delta	34.30
Range	71.17



N-Cyanosulfoximine 136a



Developmental Therapeutics Program
One Dose Mean Graph

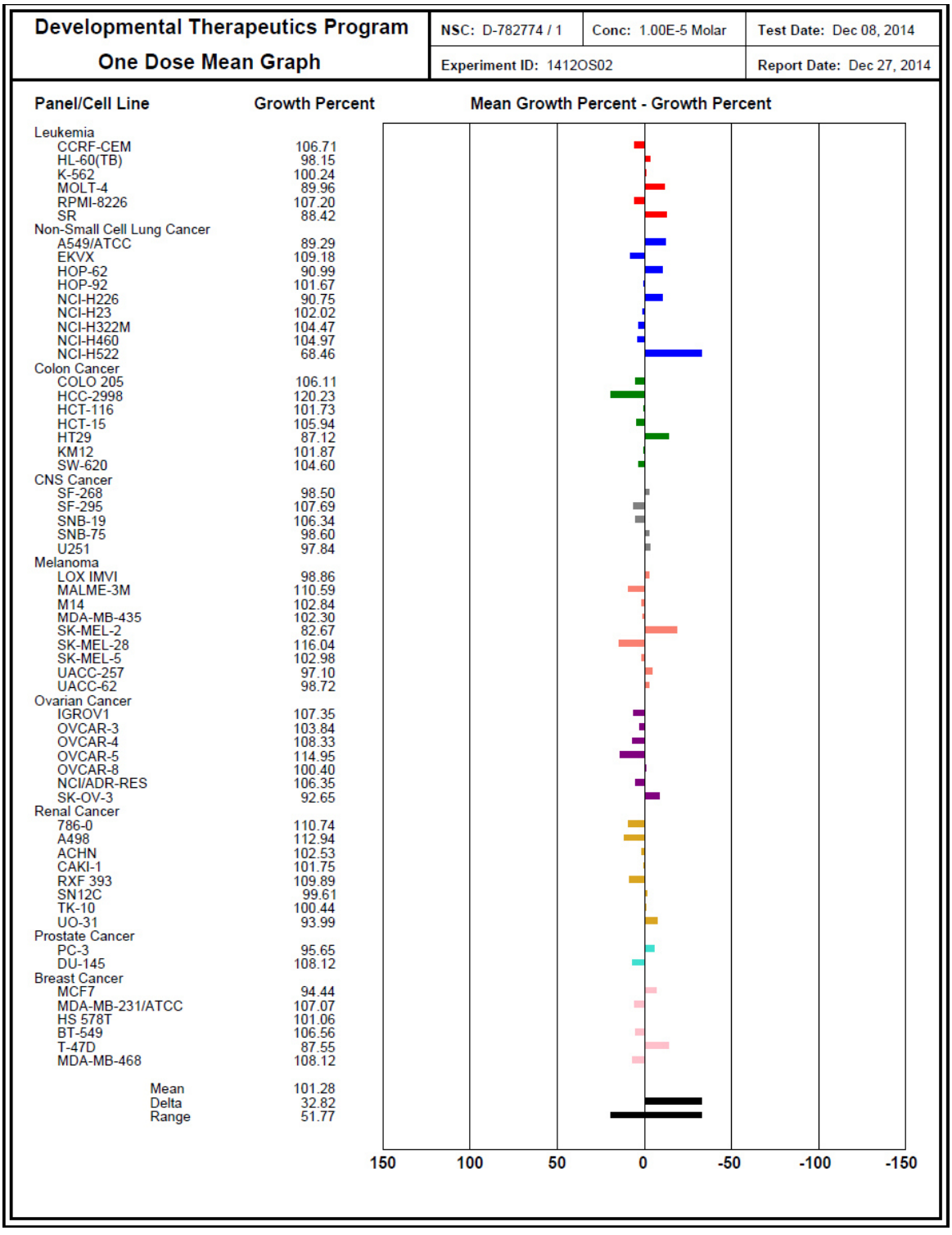
NSC: D-781552 / 1 | Conc: 1.00E-5 Molar | Test Date: Aug 04, 2014
Experiment ID: 1408OS30 | Report Date: Aug 20, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	79.94
HL-60(TB)	108.28
K-562	70.84
MOLT-4	64.67
RPMI-8226	104.98
SR	44.03
Non-Small Cell Lung Cancer	
A549/ATCC	63.09
EKVX	88.07
HOP-62	97.04
HOP-92	106.45
NCI-H226	92.05
NCI-H23	81.19
NCI-H322M	78.60
NCI-H460	83.87
NCI-H522	86.78
Colon Cancer	
COLO 205	88.30
HCC-2998	105.06
HCT-116	86.82
HCT-15	63.18
HT29	79.86
KM12	78.22
SW-620	108.78
CNS Cancer	
SF-268	87.72
SF-295	99.22
SF-539	68.96
SNB-19	105.31
SNB-75	56.92
U251	68.46
Melanoma	
LOX IMVI	66.48
MALME-3M	127.18
M14	77.71
MDA-MB-435	87.68
SK-MEL-2	94.04
SK-MEL-28	111.29
UACC-257	101.67
UACC-62	74.67
Ovarian Cancer	
IGROV1	59.80
OVCAR-3	89.43
OVCAR-4	97.04
OVCAR-5	163.03
OVCAR-8	96.83
NCI/ADR-RES	96.86
SK-OV-3	56.84
Renal Cancer	
786-0	45.54
A498	76.13
ACHN	51.44
CAKI-1	47.16
RXF 393	71.01
SN12C	78.77
TK-10	97.39
UO-31	48.14
Prostate Cancer	
PC-3	90.21
DU-145	75.58
Breast Cancer	
MCF7	45.54
MDA-MB-231/ATCC	101.76
HS 578T	55.03
BT-549	73.41
T-47D	99.01
MDA-MB-468	96.72
Mean	83.05
Delta	39.02
Range	119.00

Mean Growth Percent - Growth Percent

150 100 50 0 -50 -100 -150

N-Methylsulfoximine 136c



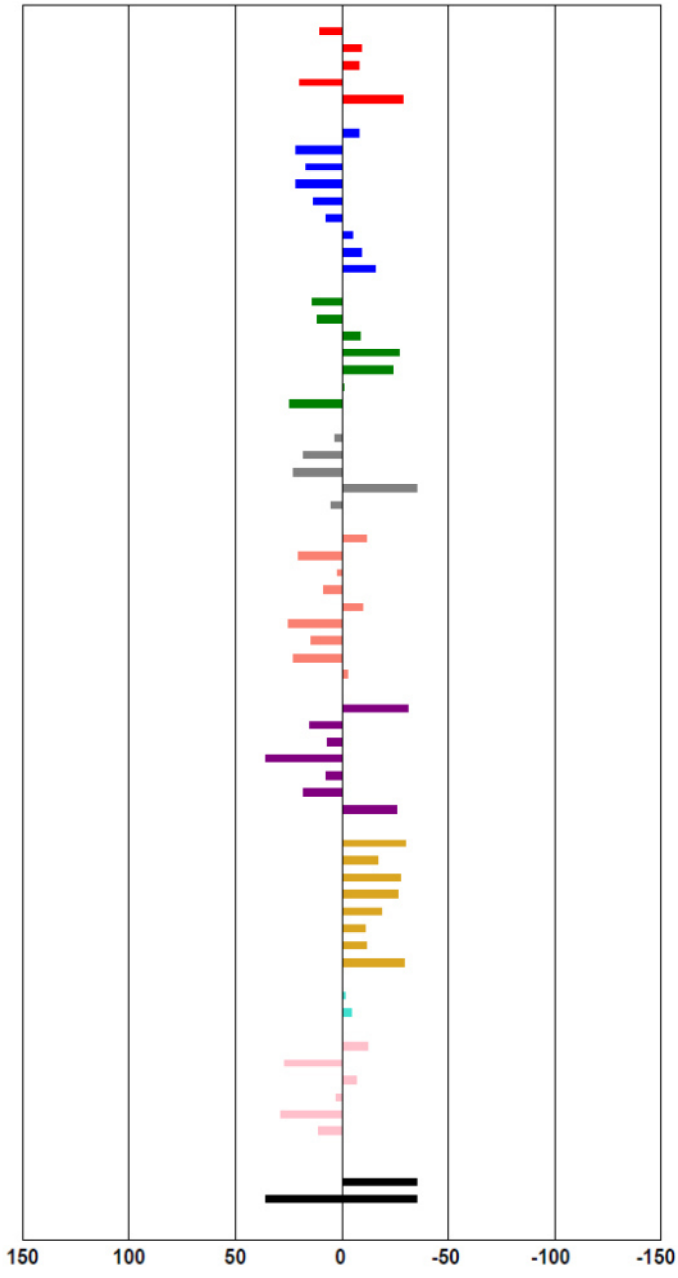
*N*H-sulfoximine 151d

Developmental Therapeutics Program

One Dose Mean Graph

NSC: D-782775 / 1	Conc: 1.00E-5 Molar	Test Date: Dec 08, 2014
Experiment ID: 1412OS02		Report Date: Dec 27, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	87.18
K-562	67.90
MOLT-4	68.76
RPMI-8226	96.66
SR	48.33
Non-Small Cell Lung Cancer	
A549/ATCC	68.98
EKVX	98.62
HOP-62	94.06
HOP-92	98.54
NCI-H226	90.19
NCI-H23	84.10
NCI-H322M	72.19
NCI-H460	67.60
NCI-H522	61.04
Colon Cancer	
COLO 205	90.97
HCC-2998	88.27
HCT-116	68.45
HCT-15	50.24
HT29	52.82
KM12	76.09
SW-620	101.70
CNS Cancer	
SF-268	80.31
SF-295	95.18
SNB-19	99.39
SNB-75	41.91
U251	81.83
Melanoma	
LOX IMVI	65.14
MALME-3M	97.16
M14	79.01
MDA-MB-435	85.24
SK-MEL-2	67.02
SK-MEL-28	101.97
SK-MEL-5	91.60
UACC-257	99.43
UACC-62	74.08
Ovarian Cancer	
IGROV1	45.60
OVCAR-3	91.74
OVCAR-4	83.73
OVCAR-5	112.62
OVCAR-8	84.32
NCI/ADR-RES	95.12
SK-OV-3	51.40
Renal Cancer	
786-0	46.82
A498	60.35
ACHN	49.16
CAKI-1	50.56
RXF 393	58.43
SN12C	65.79
TK-10	65.61
UO-31	47.73
Prostate Cancer	
PC-3	75.74
DU-145	72.22
Breast Cancer	
MCF7	64.72
MDA-MB-231/ATCC	103.81
HS 578T	70.05
BT-549	79.47
T-47D	105.37
MDA-MB-468	88.01
Mean	76.90
Delta	34.99
Range	70.71



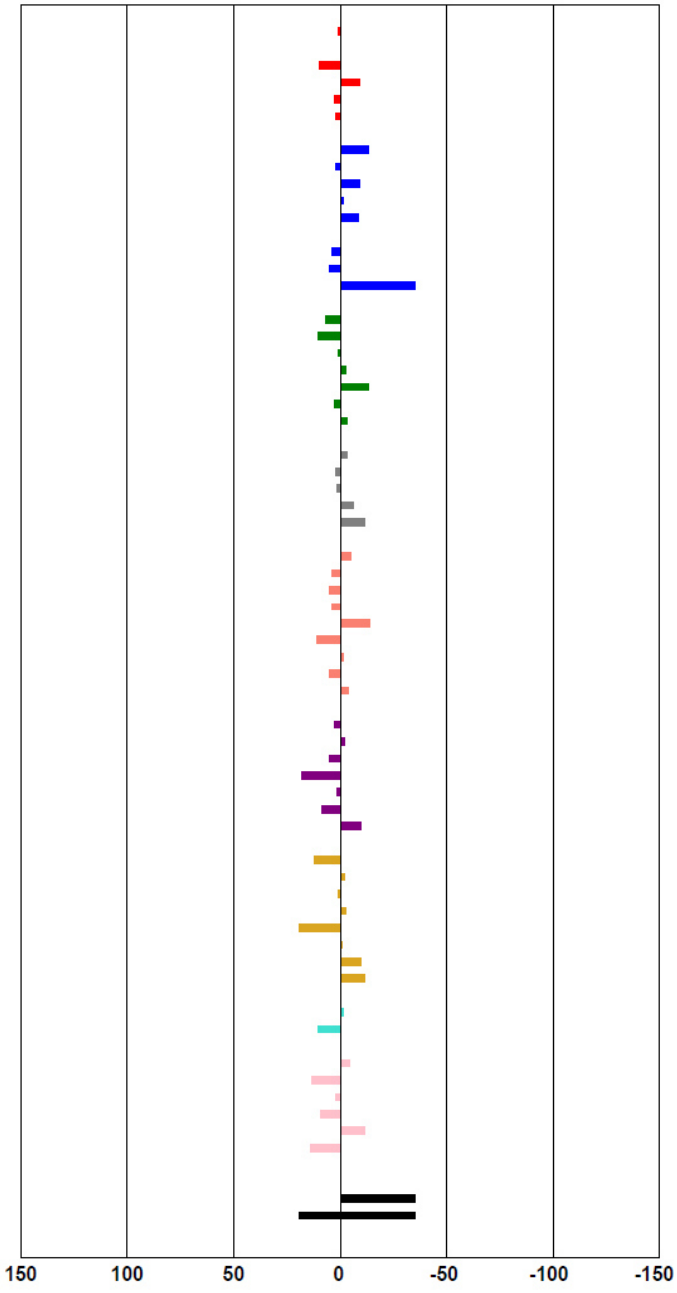
Flufenamic acid analog 186a

Developmental Therapeutics Program
One Dose Mean Graph

NSC: D-782773 / 1 | Conc: 1.00E-5 Molar | Test Date: Dec 08, 2014
Experiment ID: 1412OS02 | Report Date: Dec 27, 2014

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	98.45
HL-60(TB)	96.86
K-562	107.25
MOLT-4	88.09
RPMI-8226	100.08
SR	99.09
Non-Small Cell Lung Cancer	
A549/ATCC	84.19
EKVX	99.32
HOP-62	88.41
HOP-92	96.07
NCI-H226	88.89
NCI-H23	96.83
NCI-H322M	101.20
NCI-H460	102.19
NCI-H522	61.90
Colon Cancer	
COLO 205	103.99
HCC-2998	107.52
HCT-116	98.29
HCT-15	94.68
HT29	84.23
KM12	99.98
SW-620	94.02
CNS Cancer	
SF-268	94.20
SF-295	99.44
SNB-19	98.68
SNB-75	91.34
U251	85.75
Melanoma	
LOX IMVI	92.43
MALME-3M	100.90
M14	102.46
MDA-MB-435	100.92
SK-MEL-2	83.63
SK-MEL-28	107.94
SK-MEL-5	95.57
UACC-257	102.17
UACC-62	93.71
Ovarian Cancer	
IGROV1	99.77
OVCAR-3	95.00
OVCAR-4	102.23
OVCAR-5	115.22
OVCAR-8	98.87
NCI/ADR-RES	106.10
SK-OV-3	87.38
Renal Cancer	
786-0	109.60
A498	95.11
ACHN	98.45
CAKI-1	94.62
RXF 393	116.47
SN12C	96.37
TK-10	87.81
UO-31	85.57
Prostate Cancer	
PC-3	95.92
DU-145	107.48
Breast Cancer	
MCF7	93.11
MDA-MB-231/ATCC	110.36
HS 578T	99.22
BT-549	106.45
T-47D	85.81
MDA-MB-468	111.31
Mean	97.27
Delta	35.37
Range	54.57

Mean Growth Percent - Growth Percent



Curriculum Vitae

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Place of birth: Aachen, Germany

Nationality: German, Dutch

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Master Thesis: *Variations on Sulfur Functionalities*
Group of Prof. Dr. Carsten Bolm, Institute of Organic Chemistry

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08/2011–01/2012

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The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed.

Carl Gustav Jung