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Enantioselective approach to 1-benzyltetrahydroisoquinolines and their five-, seven-, and eight membered homologues

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Erklärung

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1 Introduction

Natural products (NP), historically isolated from plants or microorganisms, have evolved into the most important inspiration for lead structures in drug discovery.[1, 2] This trend still holds true today as 32.6% of small molecule drugs approved by the US Food and Drug administration (FDA) between 1981 and 2010 were inspired by NP or NP derivatives.[3] Moreover, NP are continually investigated and enter clinical evaluation, for example during the COVID-19 pandemic.[4] One of the most significant classes of secondary metabolites is represented by alkaloids. They serve several ecological functions, including competitive interactions, signaling and defense.[5]

1.1 History of alkaloids

Alkaloids, which typically (but not exclusively) derived from plants, are nitrogen-containing organic compounds. In the early 19th century, Friedrich Sertürner isolated morphine from opium (*Papaver somniferum*) and started the groundwork for modern medicinal organic chemistry.[6, 7]

Initially, alkaloids were discovered by their properties. As basic compounds, they are able to form salts with acids, making them extractable *via* simple acid-base chemistry.[8] With technical progress, chromatographic and spectroscopic methods improved the isolation and structural elucidation of these compounds. Important milestones in alkaloid research include the isolation of quinine from *Cinchona pubescens* in 1820 by Pelletier and Caventou as well as caffeine from coffee beans by Runge.[9] These are only two examples of alkaloids in our every day life. As a consequence of these discoveries, further beneficial properties of alkaloids were investigated and their usage was extended into the fields of analgesia, anesthesia, antimicrobial, antiviral and anti-cancer therapies.[10]

The progression of synthetic chemistry methodologies allowed scientists further investigation of structure-activity relationships (SAR) and modification of naturally occurring alkaloids. Additionally, the interdisciplinary interactions of organic chemistry, pharmacology and clinical sciences have transformed these NPs into lead compounds in drug discovery and development.[11]

1.2 Classification of alkaloids

Alkaloids can be divided into several groups, determined by their molecular structure. The already mentioned morphine is part of the benzylisoquinoline alkaloids (BIAs), as it contains a benzylisoquinoline core structure. The isoquinoline alkaloids represent the largest group amongst the alkaloids.[12] Derived from morphine by partial synthesis, another

pharmaceutically active and more frequently used drug, codeine (Figure 1)[13], is also part of the isoquinoline group. Even though both drugs share similarities, they are approved for different indications. Morphine is used as an analgetic, whereas codeine is mainly used as an antitussive.[14]



Morphine (**1**) Codeine (**2**)

Figure 1 Benzylisoquinoline alkaloids morphine (**1**) and codeine (**2**)

BIAs are a subgroup of alkaloids, characterized by the presence of a benzyl moiety linked to a nitrogen-containing heterocycle, namely an isoquinoline. This typical structure motif is also part of morphine (**1**), codeine (**2**) and (*S*)-coclaurine (**4**, Figure 3). BIAs include approximately 2,500 known structures, and many possess potent pharmacological properties for several indication fields.[15] The structural diversity of BIAs is initially achieved by modifying the 1-benzylisoquinoline backbone but multiplies extensively by addition of various functional groups. Oxidative enzymes (e.g. CYPs) ensure further variations of the 1-benzylisoquinoline scaffold.[16] An overview of the major biosynthetic pathways with intermediates and the utilized enzymes to synthesize BIAs in *Papaver somniferum* is illustrated in Figure 2.

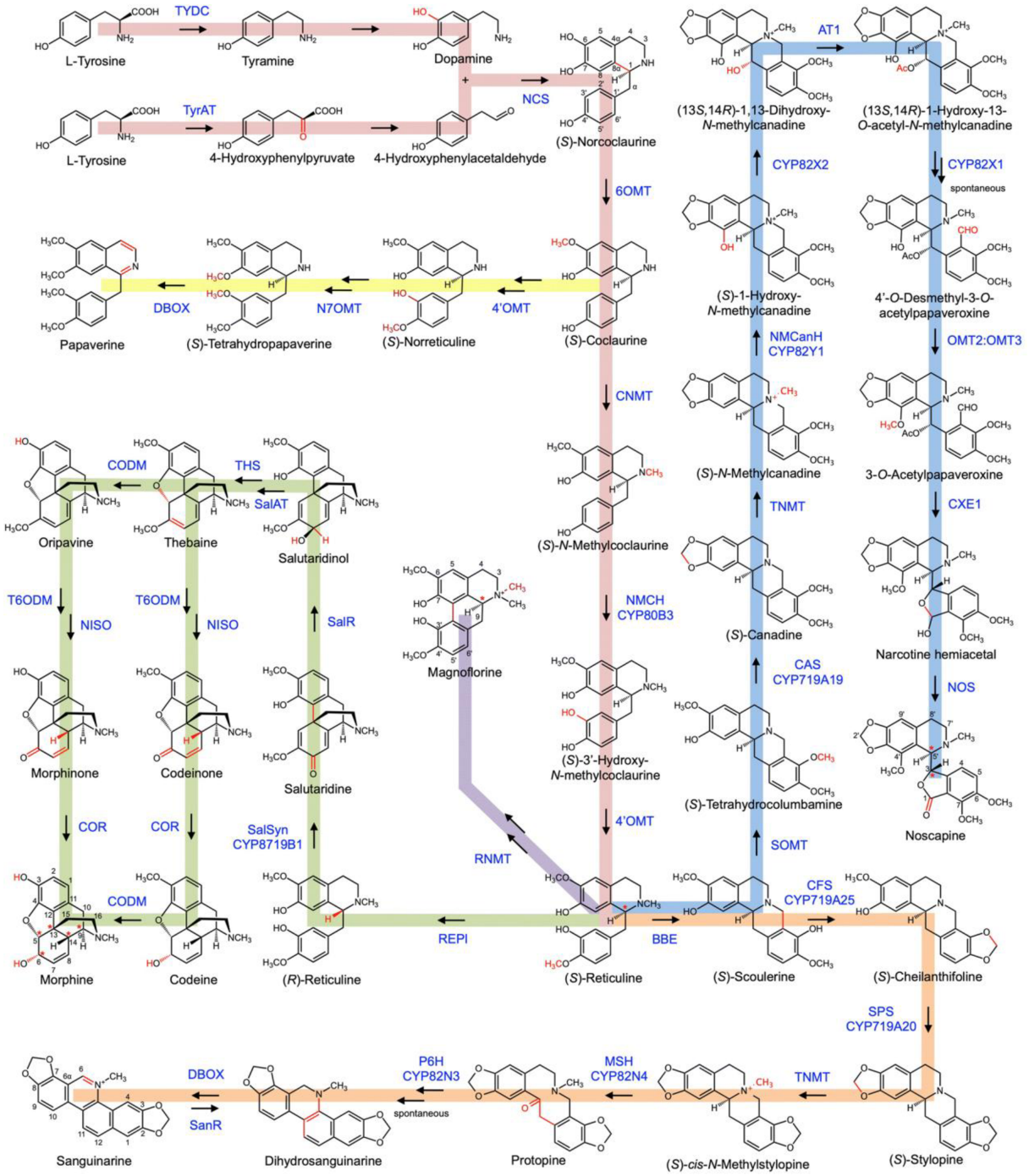
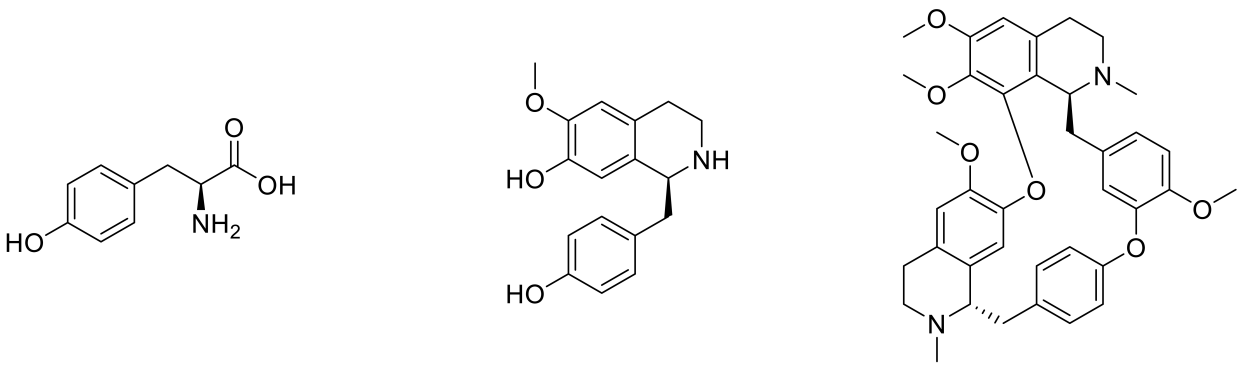


Figure 2 Biosynthesis of BIAs starting from L-tyrosine. Figure adapted from Singh *et al*.[17]

A more complex class of isoquinoline alkaloids are the *bis*benzyltetrahydroisoquinolines (BBTHIQs). These consist of two benzylated tetrahydroisoquinoline precursor units, which are linked by biphenyl bridges, diarylether bridges, phenyl-benzyl ether bridges or a combination of these. Three connection patterns for the monomers are possible and are different in their orientation regarding the isoquinoline (head) and the benzyl (tail) unit: “head to head”, “head to tail” and “tail to tail”.[18] They are less common than their monomeric counterparts and can appear as macrocyclic dimers or in their single chained *seco*-form. Typical substituents of the aromatic moiety in BBTHIQs are hydroxy and methoxy groups. BBTHIQ alkaloids can be found

in higher plants, particularly in the plant families Menispermaceae, Ranunculaceae, Lauraceae and Berberidaceae.[19]

The total synthesis and clean isolation of BBTHIQs is challenging due to their complex molecular structure, which often includes multiple chiral centres and similar physico-chemical properties. The possible biosynthesis of bisbenzylisoquinolines is suspected to start from four molecules of L-tyrosine (**3**) going through (*S*)-coclaurine (**4**) (Figure 3) or its *N*-methyl derivatives as intermediate.[20]



L-Tyrosine (**3**) (*S*)-Coclaurine (**4**) Tetrandrine (**5**)

Figure 3 Possible precursors in bisbenzylisoquinoline biosynthesis and bisbenzylisoquinoline tetrandrine (**5**)

Tetrandrine (**5**), a bisbenzyltetrahydroisoquinoline alkaloid of special interest, has been identified as a potent two poor channel (TPC) 1 and TPC 2 ion channel blocker.[21] Further investigations of the SAR for BBTHIQs within the Bracher group revealed, that truncated versions of **5** result in even more promising blockage of TPC 2, by employing only one benzyltetrahydroisoquinoline moiety with suiting substitution patterns mimicking parts of the second benzyltetrahydroisoquinoline unit of the parent molecule.

1.3 Effects of stereochemistry in drugs

A critical factor in the biological activity of NPs (and also other drugs) is their stereochemistry, the study of three-dimensional arrangement of atoms within molecules. In chiral environment, such as receptor sites or enzyme active sites, one enantiomer may – in most cases will – display different chemical and pharmacological behaviour than the other enantiomer.[22] Enantiomers are mirror-image isomers of chiral compounds. The undesired enantiomer is called “distomer”, which may have undesired bioactivity or is less active or completely ineffective, whereas the enantiomer with the desired pharmacological activity is called “eutomer”. This phenomenon is also known for well-established pharmaceutical drugs, such as ibuprofen[23], citalopram[24], and cetirizine[25], but can also be found in the synthetic morphine analogue methorphan with the dextrorotary enantiomer dextromethorphan as antitussive and its enantiomer levomethorphan as a potent narcotic analgesic[26], the special case of thalidomide[27] and many more[28, 29].

As one of the best-known examples in this context, ibuprofen, undergoes unidirectional metabolic chiral inversion, whereby the – in terms of cyclooxygenase-inhibition – ineffective distomer (*R*)-ibuprofen (**6**) from the racemic drug is converted *in vivo* into the eutomer (*S*)-ibuprofen (**7**) (called “Dexibuprofen”, also an authorized pharmaceutical product) (Figure 4). This unique transformation is catalysed by the enzyme 2-arylpropionyl-coenzyme A epimerase.[30]



6 **7**

Figure 4 Both enantiomers of ibuprofen

As the racemic drug can be administered without inducing adverse effects and the distomer **6** is transformed *in vivo* (at least in very large extent) into the eutomer **7**, it is not really necessary to synthesize the enantiomerically pure ibuprofen. This explains why commercially available ibuprofen is predominantly marketed in its racemic form. Since 2024, the eutomer, dexibuprofen, is also available as an over-the-counter (OTC) product in Germany.

However, metabolic inversion is not always combined with a positive impact. Thalidomide (better known under its brand name Contergan®), initially prescribed as tranquilizer, antiemetic for morning sickness and sedative[31], serves as a dramatic example of the clinical consequences of stereochemistry. While the (*R*)-enantiomer **8** inherits the desired sedative effects, the (*S*)-enantiomer **9** (Figure 5) harbors embryo-toxic and teratogenic side effects. Those teratogenic side effects led to one of the biggest tragedies in the pharmaceutical industry, the Contergan scandal[32] with increased miscarriages and children born with severe deformities.[33]



8 **9**

Figure 5 Both enantiomers of thalidomide

For thalidomide, rapid bidirectional chiral inversion – (*R*)- to (*S*)- and *vice versa* is observed *in vivo*.[34] With this chiral inversion, it remains impossible to avoid the teratogenic effects of the drug, even when applicated in the (*R*) form. Nevertheless, thalidomide remains in therapeutical use for indications without appropriate alternatives, e.g. multiple myeloma under strict control. Furthermore, thalidomide underwent further SAR studies and was the lead structure for a series of immunomodulatory drugs synthesized by modification of the molecular structure[35], such as lenalidomide and pomalidomide. The thalidomide tragedy had far-reaching effects on

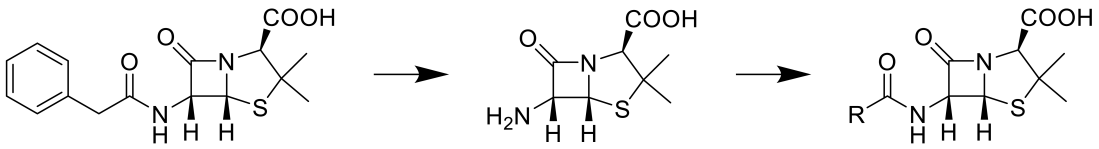
drug regulatory practices and highlighted the necessity of stereochemical knowledge in pharmaceutical agents.

1.4 Contemporary research in the synthesis of enantiomerically pure substances

The isolation of alkaloids from their natural source is often linked to time-consuming and expensive procedures and limited to the availability of the source. To ensure and increase availability, several total synthesis procedures are known in literature[36-39] even though the presence of stereogenic centers complicates the synthesis. Exactly because of these difficulties, the total synthesis of alkaloids and NPs in general remains a benchmark for testing the limits of synthetic organic chemistry. To synthesize enantiomerically pure compounds, three major pathways are possible.[39]

The first pathway is chiral resolution of racemic synthetic compounds. In the case of alkaloids this is feasible, since alkaloids can be converted into separable diastereomeric salts by treatment with homochiral organic acids.

The second pathway is semi-synthetic derivatization of readily available homochiral natural products, which allows modifications of the molecular structure by maintaining the stereochemical integrity. For example the synthesis of codeine from morphine[40] or several semisynthetic penicillin antibiotics[41], derived from benzylpenicillin (**10**) (synthesized by fermentation) with subsequent selective hydrolysis[42, 43] to 6-aminopenicillanic acid (**11**) (Figure 6) are following this principle. Semisynthetic approaches modify biogenic precursors to structural analogues with enhanced pharmacological profile or improved pharmacokinetic properties.

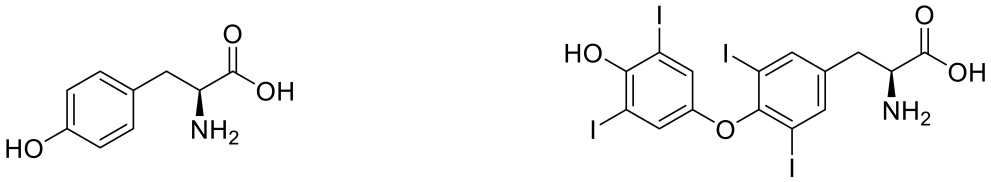


10 **11**

Figure 6 General semisynthetic route with hydrolysis of **10** to **11** and N-acylation to the desired penicillin

The third approach involves the total synthesis of alkaloids. One viable strategy employs chiral pool tools, which enables enantioselective construction of key stereocenters in molecules. Chiral pool synthesis uses commercially available, enantiomerically pure building blocks, which were included into the molecule during synthesis and possess the necessary stereochemical information for the final product. Those building blocks are typically derived from the “chiral pool” of natural products, such as alkaloids, amino acids, carbohydrates and terpenes or from non-natural starting materials.[44] One example of this approach is the method of Chalmers *et al*. for the synthesis of levothyroxine (**12**).[45] The route starts with L-tyrosine (**3**)

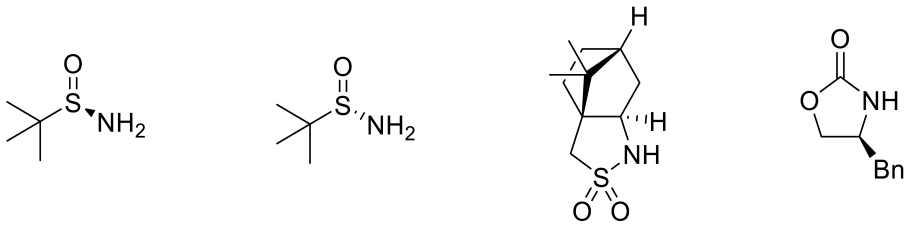
and the stereochemical information of the starting amino acid remains within levothyroxine (**12**) as illustrated in Figure 7.



L-Tyrosine (**3**) Levothyroxine (**12**)

Figure 7 Synthesis of levothyroxine (**12**) from the chiral pool building block L-tyrosine (**3**)

In contrast to the chiral pool synthesis, where the building blocks stay within the final molecule, chiral auxiliaries can provide the stereochemical information, but are removed in later steps of the synthesis. Typical chiral auxiliaries are: Ellman's reagent ((*R*)-(+)-*tert*-butylsulfinamide (**13**) and (*S*)-(-)-*tert*-butylsulfinamide (**14**)), Oppolzer's sultam (**15**, camphor-derived auxiliary) and Evans auxiliary (several oxazolidinones, exemplified by **16**).[46] These auxiliaries are depicted in Figure 8.



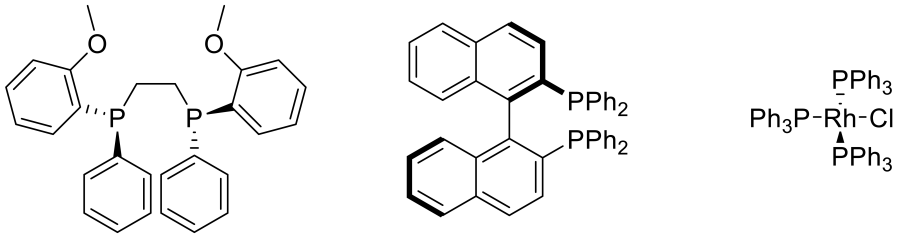
13 **14** **15** **16**

Figure 8 Well established chiral auxiliaries for synthetic organic chemistry

The general procedure consists of covalent attachment of the chiral auxiliaries to the substrate to induce the desired stereoselectivity. Following the stereoselective steps, the auxiliary becomes unnecessary and is typically cleaved under mild conditions, yielding the target compound in enantiomerically pure form. Chiral auxiliaries may be derived from the chiral pool, although this is not a mandatory requirement.

In addition to chiral building blocks and chiral auxiliaries, chiral catalysts are also utilized for asymmetrical synthesis of enantiomerically pure compounds. In 2001, Knowles, Noyori and Sharpless received the Nobel prize in chemistry for their work on chirally catalyzed hydrogenation reactions and chirally catalyzed oxidation reactions.[47] In pharmaceutical context, Knowles applied asymmetric hydrogenation for the industrial production of L-DOPA by employing DiPAMP (**17**), an organophosphorus homochiral ligand, which is complexed with rhodium and used as catalyst.[48] Another well-known homochiral ligand is BINAP (**18**), which was first published by Noyori and his co-workers. BINAP is utilized for asymmetric hydrogenation of β-ketoesters (Ru-BINAP complex catalyst)[49] and the asymmetric synthesis of (-)-menthol (Rh-BINAP complex catalyst).[50] In the context of chiral catalysts, Wilkinson's

catalyst (**19**), a rhodium catalyst, must also be mentioned. Wilkinson's catalyst (**19**), named after Nobel laureate Geoffrey Wilkinson, who first popularized its use, is employed for the hydrogenation of olefins to alkanes.[51] The ligands and the catalyst are illustrated in Figure 9.



17 **18** **19**

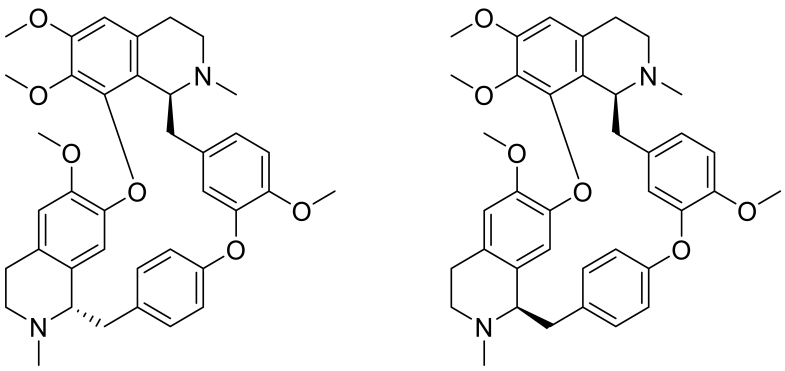
Figure 9 Ligands and catalyst for asymmetric synthesis

2 Objectives

2.1 Racemic synthesis of bisbenzylisoquinolines and truncated analogs

Previous research conducted by Dr. Ramona Schütz in the Bracher group resulted in a new and efficient synthesis of the bisbenzylisoquinoline alkaloids tetrandrine (**5**) and isotetrandrine (**20**). For both molecules (shown in Scheme 1), biological activities such as Ca^{2+} channel blocking[52], anticancer[53-55], multidrug resistance reversing[56, 57], antioxidative[58] and antiviral activity against EBOV[59], MERS-CoV[60] and SARS-CoV-2[61]. Further autoimmune disease modification[62] was reported.

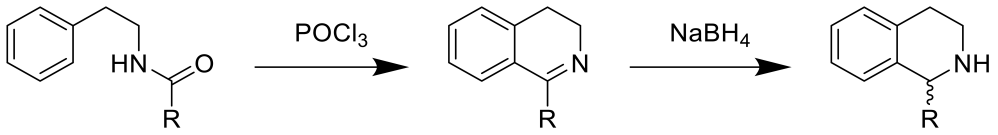
Moreover, tetrandrine (**5**) has been identified as a blocker of two-pore channels (TPCs)[59], which belong to the superfamily of voltage-gated calcium channels.[63] TPCs are situated on the membranes of endolysosomes[63-65], which function as intracellular acidic calcium storage compartiments. These organelles are integral to endocytotic transport mechanisms within cells[63, 64, 66] and are consequently indispensable for maintaining essential physiological functions in cellular processes. Given their key involvement in the pathomechanisms of diseases as mentioned above, TPCs represent a promising pharmacological target and were thoroughly investigated in the Bracher group.



Tetrandrine (**5**) Isotetrandrine (**20**)

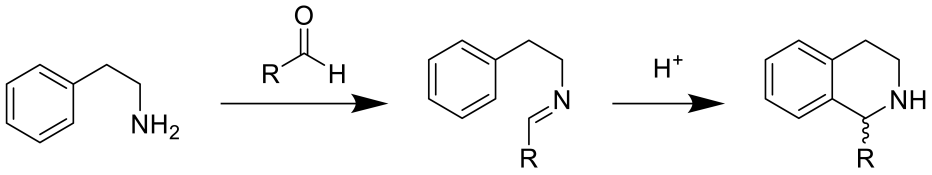
Scheme 1 Structures of tetrandrine and isotetrandrine

Prior to the research of Dr. Ramona Schütz, only two total synthesis approaches were available to obtain **5** [67, 68]. In 1968 Inubushi *et al.* synthesized compound **5** and its stereoisomers in over 20 steps.[67] A Chinese patent[68] describes a synthetic route closely resembling Inubushi's work. This approach employed arylacetic acid and β-phenethylamine building blocks for the Bischler-Napieralski reaction, yielding, after reduction of the imine moiety, racemic 1-benzyltetrahydroisoquinolines. These isoquinolines were subsequently coupled in two consecutive Ullmann couplings as the final steps.



Scheme 2 Typical conditions for the Bischler-Napieralski reaction and subsequent reduction to the racemic tetrahydroisoquinoline

In addition to the Bischler-Napieralski reaction, the Pictet-Spengler reaction[69] represents another widely employed method for the synthesis of tetrahydroisoquinolines (THIQ). This reaction proceeds *via* one-pot process involving β-phenethylamines and aldehydes. As a result of this condensation reaction, an imine is formed, which undergoes intramolecular cyclization the presence of an acid.[70] This method mostly requires elevated temperatures, strong acids and β-phenethylamines with electron donating groups at the ring. In the Pictet-Spengler reaction, the electrophilic component is not limited to aldehydes. Various surrogates such as acetals[71, 72], enamines [73, 74], alkynes[75], and enol ethers [76] can also be utilized.[77] These masked aldehydes are often more stable than arylacetaldehydes (tend to polymerization[78]), which are required for the synthesis of 1-benzyltetrahydroisoquinolines. The broad diversity of starting materials, combined with the ability to construct the tetrahydroisoquinoline core in a single step, makes this approach highly attractive.



Scheme 3 Formation of the racemic 1-benzyltetrahydroisoquinoline *via* Pictet-Spengler reaction

With easily available alkoxystrenes, Dr. Schütz significantly reduced the number of steps required for the total synthesis of tetrandrine. While Inubushi's approach involved more than 20 steps and the Chinese patent described a 19-step synthesis, Dr. Schütz achieved the total synthesis in just 12 steps. This remarkable reduction in synthetic complexity not only improves the efficiency and practicality of producing tetrandrine but also demonstrates the potential of strategic structural modifications to streamline the synthesis of complex natural products.

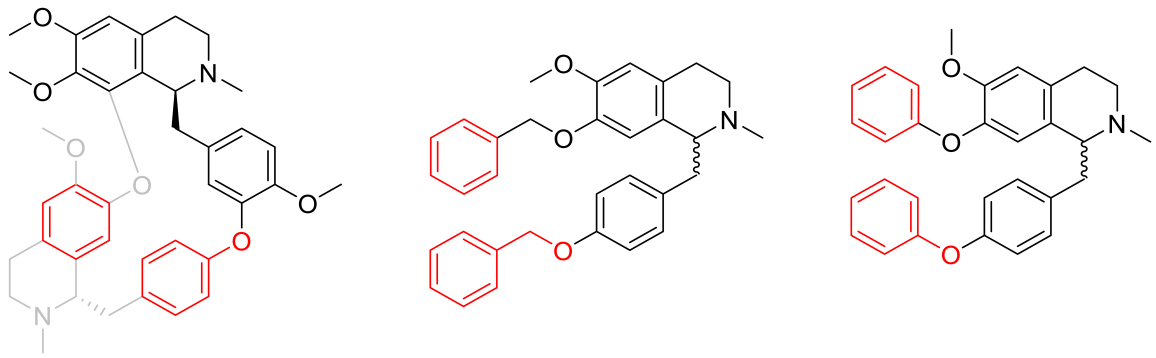
Although tetrandrine (**5**) exhibits a broad range of pharmacological effects, its clinical use as a drug is constrained by its toxicity. Various toxic side effects have been documented for tetrandrine (**5**) and other bisbenzylisoquinolines.[79] In animal models, adverse effects were predominantly observed in the liver and lungs.[80, 81]

Another issue is the poor solubility of alkaloid **5**. Jin *et al.*[80] reported that acidification of the injection solution is required prior to *in vivo* application to ensure sufficient solubility. This necessity highlights the challenges associated with the formulation and administration of compound **5** in biological systems.

Apart from solubility and toxicity issues, another significant drawback is the limited availability of tetrandrine (**5**). It is primarily obtained through the extraction of the roots of *Stephania tetrandra*, a process that is resource-intensive and subject to variability in yield and quality. Alternatively, tetrandrine can be synthesized through complex multi-step chemical processes, which are often time-consuming, costly, and inefficient. These limitations in sourcing and production further complicate the widespread application and study of tetrandrine in both research and therapeutic contexts. The outlined drawbacks were aimed to be overcome through structural simplification, strategic substitutions, and targeted derivatizations. By modifying the core structure of tetrandrine, the goal was to enhance its physicochemical properties, such as solubility and bioavailability, while reducing toxicity and simplifying its synthesis. These modifications were designed to retain or improve the desired biological activity while addressing the limitations associated with the natural product, thereby facilitating its potential application in therapeutic and research settings.

To address these issues, Iturriaga-Vásquez *et al*. developed simplified and more accessible analogs of tetrandrine (**5**) as potential antihypertensive agents, which retained only one benzylisoquinoline unit of the original molecule.[82] These analogs were further enhanced with structural modifications, such as the introduction of *O*-benzyl groups. Despite their reduced structural complexity, these derivatives exhibited comparable efficacy in blocking calcium channels to that of tetrandrine (**5**). This strategy underscores the potential to maintain critical pharmacological properties while simplifying the molecular framework, thereby enhancing synthetic feasibility and enabling a more detailed investigation of structure-activity relationships. The presence of *O*-benzyl substituents effectively mimics the two aromatic rings of the second benzylisoquinoline moiety found in the parent compound. This design results in analogs that are comparable in size to tetrandrine (**5**) but exhibit significantly greater conformational flexibility. This enhanced flexibility is anticipated to facilitate optimal adaptation of these compounds to the binding pockets of their target proteins, potentially improving their binding affinity and functional efficacy.

In her dissertation in the Bracher group, Dr. Susanne Gerndt concentrated her synthetic efforts on these racemic, truncated versions of tetrandrine (**5**), leading to the development of compounds such as SG-005 (**21**) (*O*-benzyl) and SG-094 (**22**) (*O*-phenyl, which is closer in structure to the diaryl ether configuration characteristic of bisbenzylisoquinoline alkaloids than a benzyl ether arrangement) (Scheme 4). These molecules have since become the standard chemical tools globally for the detailed study of two-pore channel (TPC)-type cation channels. Their simplified structures, combined with retained or enhanced biological activity, make them invaluable for probing the function and pharmacology of TPC channels, thereby advancing research in this field.



Tetrandrine (**5**) SG-005 (**21**) SG-094 (**22**)

Scheme 4 Tetrandrine (**5**) and the truncated analogs **21** and **22**, containing one 1-benzyltetraydroisoquinoline unit (in black) of **5** as well as two aromatic residues (in red) resembling the truncated second 1-benzyltetrahydroisoquinoline unit.

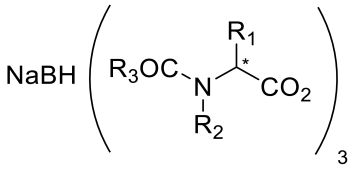
Dr. Gerndt's synthetic route primarily centered on the utilization of the previously described Pictet-Spengler reaction and Chan-Evans-Lam coupling reactions for the construction of key structures such as diaryl ethers exemplified by compound **22**. The Chan-Evans-Lam coupling offers several advantages, including milder reaction conditions, such as room temperature and tolerance to the presence of oxygen, the use of inexpensive copper catalysts, consistently good to excellent yields, and a broad substrate scope[83] compared to classical Ullmann couplings.[84]

Although her synthetic route provided a very efficient pathway to the target compounds, the methods employed yielded only racemic mixtures. Enantiomerically pure compounds could only be obtained through additional steps, such as preparative chiral HPLC separation, highlighting the urgent need for a flexible and efficient synthesis route that directly produces enantiomerically pure compounds.

2.2 Enantioselective synthesis of THIQ's

2.2.1 Asymmetric reduction

As illustrated in Scheme 2, a commonly utilized approach for the synthesis of tetrahydroisoquinolines involves the reduction of dihydroisoquinolines. This transformation can be rendered enantioselective by replacing $NaBH_4$ with a chiral reducing agent. For instance, Yamada *et al*. systematically evaluated various chiral sodium triacyloxyborohydrides (see Scheme 5) (synthesized *via* reaction of $NaBH_4$ and N-acyl derivatives of optically active α-amino acids) in different solvents, achieving moderate to good chemical yields of enantiomerically pure compounds combined with bad to moderate optical yields.[85]



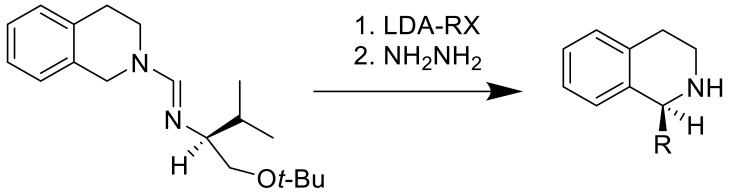
Scheme 5 General structure of chiral sodium triacyloxyborohydride analogs

Another approach is described in the 1985 patent by Rice[86], which is applicable to the synthesis of our target 1-benzyl-1,2,3,4-tetrahydroisoquinolines. The patent outlines various reduction methods, including both chemical and catalytic strategies. However, the catalysts proposed are not readily accessible or expensive, rendering the asymmetric hydrogenation of dihydroisoquinolones challenging and inefficient. From a chemical reduction perspective, in addition to chiral sodium triacyloxyborohydrides, Rice also employs optically active pinene in combination with BH_3. This method necessitates the addition of HCl during the workup, leading to the formation of the hydrochloride salt of the desired tetrahydroisoquinoline.

Numerous additional catalysts have been successfully tested and reviewed by Asif *et al*.[87] In this context, the imine generated from the Bischler-Napieralski reaction was also reduced to enantiomerically pure compounds using numerous chiral hydride reducing agents or enzymatic catalysis. Mechanistically, they investigated a wide array of reactions, including asymmetric hydrogenation, asymmetric transfer hydrogenation, catalytic asymmetric hydrogenation, and the use of achiral metallic hydride reducing agents. Even after evaluating all these methods, no specific, general, or straightforward approach for the synthesis of all types of tetrahydroisoquinoline alkaloids was identified in their research. Additional challenges included moderate to poor yields and stereoselectivity, as well as the inaccessibility or high cost of starting materials and reagents, highlighting the urgent need for alternative synthetic routes.

2.2.2 Use of chrial auxiliaries

Another approach for the synthesis of enantiomerically pure compounds involves the use of chiral auxiliaries. A notable example of this methodology is demonstrated in the work by Meyers *et al*.[88] In their study, chiral formamidines were employed, which were attached to variously substituted tetrahydroisoquinolines (shown in Scheme 6). This strategy facilitated asymmetric carbon-carbon (C-C) bond-forming reactions occurring α- to the amino group (meaning at C-1), thereby enabling the production of enantiomerically enriched products. Similarly high levels of enantiomeric purity were achieved using unsubstituted tetrahydroisoquinolines. This demonstrates that the presence of substituents on the tetrahydroisoquinoline framework is not a prerequisite for attaining excellent stereocontrol in the asymmetric C-C bond-forming reactions. The use of unsubstituted tetrahydroisoquinolines, in conjunction with chiral formamidine auxiliaries, underscores the robustness and versatility of this synthetic approach for generating enantiomerically pure compounds.



X= Cl, Br

Scheme 6 General synthesis procedure according to Meyers *et al*. using chiral formamidines

This method is constrained by the requirement for preformed tetrahydroisoquinolines that are unsubstituted at the α-position, thereby limiting its applicability. Additionally, the approach is not suitable for the total synthesis of the desired compounds, as it relies on the availability of specific starting materials rather than enabling *de novo* construction of the molecular framework. Consequently, while effective for achieving high enantiomeric purity in certain cases, this strategy is not universally applicable for synthetic routes requiring the assembly of complex structures from simpler precursors.

2.2.3 Our concept: Use of Ellman's auxiliary

In contrast to the aforementioned methods described in the literature, our objective was to develop a unified, robust methodology for the synthesis of enantiomerically pure THIQs, starting from inexpensive and readily available chemical precursors. Additionally, the synthetic route should accommodate structural variations with high flexibility.

One of the most commonly employed auxiliaries for the synthesis of amines is the Ellman's auxiliary (*tert*-butylsulfinamide, Scheme 7)[89], a chiral reagent recognized for its versatility and accessibility in asymmetric synthesis. According to the Ellman group, this reagent is utilized more frequently than any other chiral reagent, auxiliary, or catalyst for the synthesis of amines.[90]

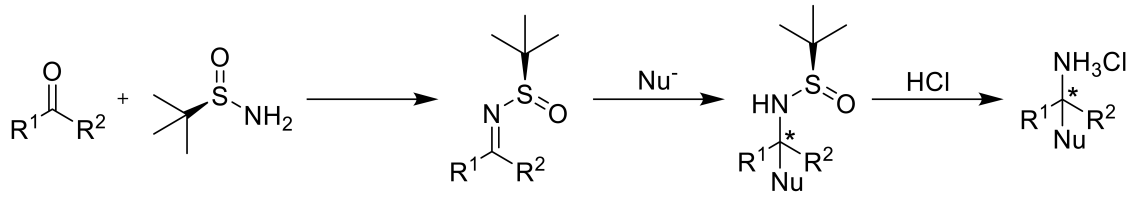


Scheme 7 (*R*)- and (*S*)-*tert*-butylsulfinamides

Ellmans' auxiliary is widely used for the assembly of chiral nitrogen-containing compounds, including heterocycles.[91] A comprehensive overview of the topic, along with a detailed discussion of various other synthetic applications, is provided in a review article by Robak *et al*.[92] This work offers an in-depth analysis of the methodologies, scope, and versatility of the approach, highlighting its significance in modern synthetic chemistry.

The enantioselective synthesis of amines employing *N*-*tert*-butylsulfinamide follows a well-established strategy, as illustrated in Scheme 8. This methodology is extensively utilized in both academic research and industrial applications due to several inherent advantages. Firstly,

both enantiomers of Ellman's auxiliary are readily available at low cost and can be easily sourced. Secondly, this approach offers the significant advantage that, utilizing the same synthesis route, both enantiomers of the target compound can be efficiently and selectively synthesized. This eliminates the need for separate synthetic routes or extensive modifications to produce each enantiomer individually. By enabling access to both enantiomers through a unified process, this method not only streamlines synthetic efforts but also provides a robust platform for the systematic exploration of stereochemical effects on the properties and functions of the target molecule. Thirdly, the approach outlined in Scheme 8 is highly robust, widely applicable, and experimentally straightforward to execute.[92]



R^1 = alkyl, aryl
R^2 =/≠ H

A **B** **C**

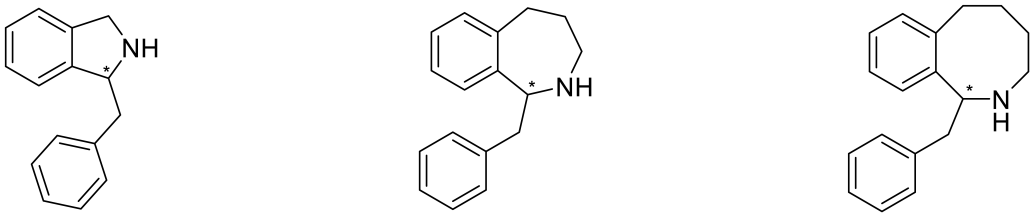
Scheme 8 Enantioselective preparation of amines employing *N-tert*-butylsulfinamide as a key reagent.[92]

Under mild reaction conditions, the direct condensation of a pure enantiomer of Ellman's auxiliary with an aldehyde or ketone results in the formation of stable *N-tert*-butylsulfinyl imines (**A**) with high efficiency. In contrast to conventional *N*-alkyl, *N*-aryl, or *N*-acyl imines, **A** demonstrates superior resistance to hydrolysis and tautomerization while simultaneously exhibiting increased electrophilicity due to the substantial partial positive charge on the sulfur center.[92] This enhanced reactivity facilitates addition reactions with a diverse range of nucleophiles, including organometallic reagents such as organomagnesium, organolithium, and organozinc compounds, as well as enolates to give products of type **B**. Additionally, non-carbon-based nucleophiles, including boron and silicon species or hydride donors, can engage in these transformations.[92]

A further advantage of the chiral *tert*-butylsulfinyl group is its ability to coordinate metal ions, enabling diastereoselective additions to **A**, ultimately leading to the formation of the chiral *N*-sulfinylamine **B**. The diastereomeric products **B** can often be separated chromatographically *via* FCC, thereby enabling the isolation of enantiomerically pure amines. Once separated, each diastereomer can be further processed to yield the corresponding enantiomerically pure amine. The presence of the sulfinyl protecting group attenuates the amine's nucleophilicity, enhancing its synthetic utility. Furthermore, this protecting group exhibits exceptional stability under strongly basic and nucleophilic conditions and remains unaffected by the conditions of palladium-catalyzed cross-coupling reactions.[92] Finally, cleavage can be efficiently achieved by treatment with hydrochloric acid, yielding the free amine **C** (see Scheme 8).

In recent years, this approach has been successfully applied to synthesize the FDA-approved antibiotic eravacycline[93] and the anticancer drug larotrectinib.[94]

Leveraging these advantages, our objective was to develop a versatile synthetic strategy for the preparation of enantiomerically pure THIQs and to expand its applicability toward the synthesis of 1-benzylisoindolines (**D**), 1-benzyl-2,3,4,5-tetrahydro-1*H*-benzo[c]azepines (**E**), and 1-benzyl-1,2,3,4,5,6-hexahydrobenz[c]azocines (**F**).



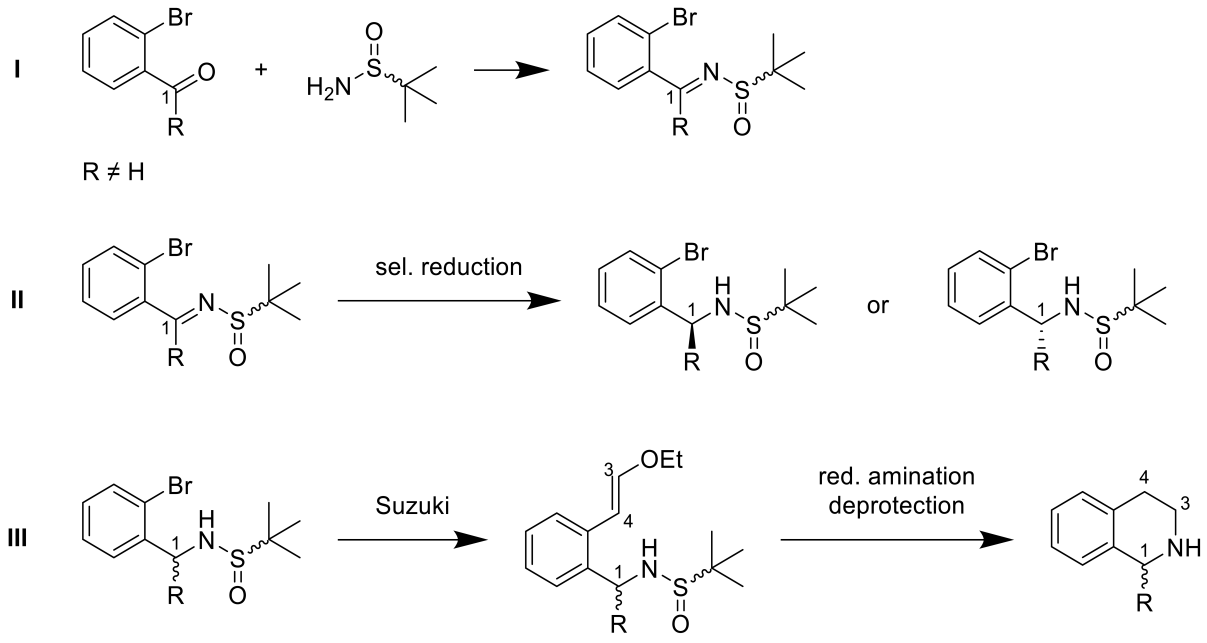
D **E** **F**

Scheme 9 Additional target compounds of this thesis

3 Strategy of synthesis

Our initial conceptual approach involved the design of a model reaction consisting of four steps, aimed at the synthesis of an enantiomerically pure 1-methyl-1,2,3,4-tetrahydroisoquinoline. This strategy was devised to systematically evaluate the viability and effectiveness of our proposed synthetic methodology, with the overarching goal of determining whether the underlying concept could be successfully realized. To ensure precise stereochemical control and achieve high enantiomeric purity, we integrated Ellman's auxiliary into the synthetic route. This approach not only underscores our commitment to achieving enantiomeric purity but also provides a robust framework for assessing the feasibility and scalability of the proposed synthetic pathway.

Our plan commences with a starting material that must consist of an aromatic ketone featuring a bromine substituent at the *ortho* position. This ketone incorporates the essential aromatic ring and the C-1 carbon of the target tetrahydroisoquinoline carrying the desired residue. Upon selection of the appropriate ketone, a condensation reaction with Ellman's auxiliary will be employed to introduce the requisite nitrogen functionality, the required chiral information, and the resulting imine will be reduced by selective hydride reduction, to obtain the desired stereochemistry. Subsequently, an acetaldehyde equivalent will be incorporated into the structure *via* Suzuki cross coupling, replacing the *ortho* bromine and generating the C-3 and C-4 carbons of the target tetrahydroisoquinoline. Finally, a ring closure will be accomplished through an intramolecular reductive amination and sulfinamide deprotection to yield the desired cyclic amine structure. An overview of our proposed synthetic pathway is depicted in Scheme 10.

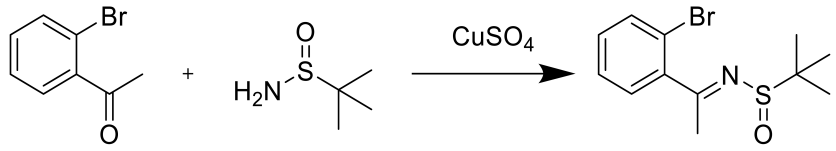


Scheme 10 Short overview of our planned synthetic pathway.
As educt for step **III** both diastereomers from step **II** can be used

For our first model reaction, we selected 2'-bromoacetophenone (**G**) due to its commercial availability and low stereochemical complexity. For the synthesis of the benzyltetrahydroisoquinolines of special interest, a more complex arylbenzyl ketone would be required.

Condensation with Ellman's auxiliary

In the initial phase of the synthetic protocol, racemic 2-methylpropane-2-sulfinamide (Ellman's auxiliary) should be employed as a cost-effective alternative to its enantiomerically pure counterparts. This choice was deemed entirely suitable for the development and optimization of the synthetic methodology. The first step in the proposed synthesis involved the condensation of 2′-bromoacetophenone (**G**) with 2-methylpropane-2-sulfinamide in the presence of copper(II) sulfate as a catalyst, forming ketimine **H** (Scheme 11). Zhang *et al.*[95] employed $CuSO_4$ as a catalyst for the condensation reaction between aldehydes and Ellman's auxiliary and we aimed to adopt the same method for the condensation of our ketones of choice with Ellman's auxiliary.

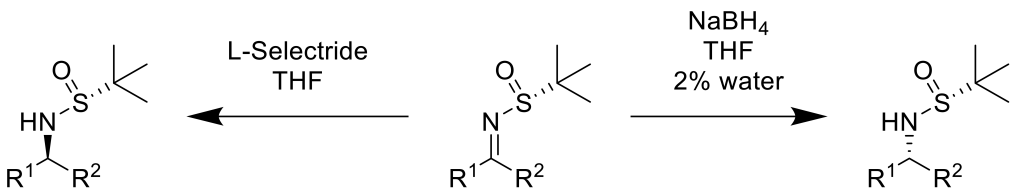


G **H**

Scheme 11 Implementing Ellman's auxiliary

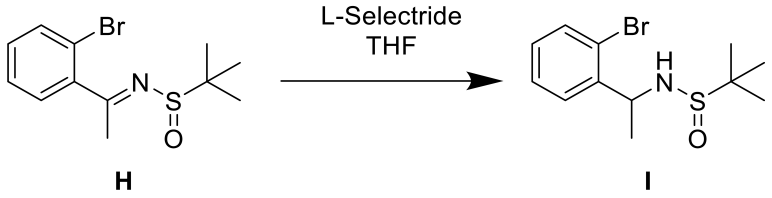
Selective hydride reduction of the *N-tert*-butylsulfinylimines

Following the reduction methods described by Colyer *et al.*[96], we aimed to synthesize the desired stereoisomer of the *tert*-butylsulfinamide **I**. Notably, both diastereomers can be obtained from the same starting material (Scheme 12). The reported synthetic approach consistently achieves high conversion rates and excellent stereoselectivity. Specifically, the reduction using L-Selectride (lithium tri-*sec*-butylborohydride) in THF yields the opposite diastereomer compared with reduction with $NaBH_4$ in THF containing 2% water.



Scheme 12 Reduction possibilities according to Colyer *et al.*[96]

In our case, intermediate **H** was intended to be reduced to compound **I**, following the published method, applying the reduction with L-Selectride in THF to achieve high diastereoselectivity and full conversion (Scheme 13).



Scheme 13 Diastereoselective reduction of **H** to intermediate **I**

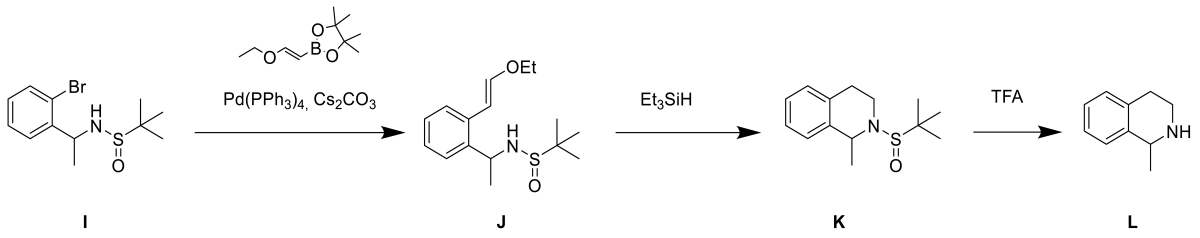
C_2-chain extension, deprotection and cyclization

The final step of the synthetic sequence was designed to be a multi-step synthesis without purification of the intermediates to streamline the workflow and improve overall efficiancy. Established protocols from the Bracher group were employed to ensure the reliability and reproducibility of these reactions.

The first step involved a Suzuki cross-coupling reaction using 2-ethoxyvinyl pinacolboronate, Cs_2CO_3, $Pd(PPh_3)_4$ and **I**, following a protocol developed by Kamlah and Bracher for the construction of Ring A of β-carbolines.[97] The resulting enol ether **J** has to be isolated *via* a standard work-up procedure, a liquid-liquid extraction with water/DCM to remove the catalyst and base, but will be used without further purification for the subsequent step.

In a one-pot procedure, enol ether **J** should undergo cyclization and deprotection. Initially, intramolecular reductive amination should afford the protected compound **K** which incorporates a tetrahydroisoquinoline core**.** This step should be followed by the cleavage of the acid-labile Ellman's auxiliary under acidic conditions, yielding target compound **L**. Following this order the transformation using a combination of triethylsilane (Et_3SiH) and trifluoroacetic acid (TFA) in DCM, as reported by Vögerl *et al*. in the Bracher group[98] for the arylethylation of weakly basic amines, should be achieved. Maintaining this order is crucial, as this method is not applicable to more basic aliphatic amines.[98]

A complete overview of this section is shown in Scheme 14.



Scheme 14 Synthesis of 1-methyl-1,2,3,4-tetrahydroisoquinoline **L** over 2 consecutive steps

The proposed synthetic route, in which the methyl ketone **G** is substituted by a benzyl ketone, offers a promising and efficient approach for the enantioselective synthesis of the desired 1-benzyl-1,2,3,4-tetrahydroisoquinolines. By appropriately decorating the benzyl ketone, we can also access substituted THIQs. This approach allows for the introduction of diverse substituents, thereby expanding the scope and versatility of the synthetic route.

By introducing the benzyl ketone as the starting material, the structural complexity and functionality of the target molecule are systematically constructed. This approach not only ensures high yields but also excellent enantioselectivity, which is crucial for the synthesis of chiral compounds.

This methodology demonstrates the potential to achieve precise stereocontrol in the synthesis of complex heterocyclic structures.

4 Results and discussion

In the subsequent section, a comprehensive analysis and discussion of the findings presented in this thesis will be conducted. The results will be critically examined in relation to the research objectives, existing literature, and theoretical framework.

4.1 Initial synthethic pathway

As outlined in the proposed synthetic pathway, the initial step involves the condensation of 2'-bromoacetophenone (**G**) with Ellman's auxiliary to form the corresponding *N*-sulfinyl ketimine **H** (see Scheme 11). The initial attempt to synthesize ketimine **H** was conducted using $CuSO_4$ as a catalyst. In contrast to the work of *Zhang et al*.[95] we employed $CuSO_4$ for ketones and not for aldehydes. However, after 24 hours of reaction time, no formation of **H** was observed. This issue aligns with findings reported by Liu *et al*. in 1999[99], who demonstrated that *N*-sulfinyl ketimine formation is not obtained in the presence of $CuSO_4$. To address this challenge, Liu *et al*. proposed a modified approach, which involved replacing $CuSO_4$ with $Ti(OEt)_4$ (tetraethylorthotitanate) as the catalyst, switching the solvent from DCM to THF, and conducting the reaction under reflux conditions. In their hands, these adjustments were found to facilitate the efficient formation of *N*-sulfinyl ketimines, providing a viable solution to the observed limitations.

In our case, even after implementing these modifications, no conversion to the desired *N*-sulfinyl ketimine **H** was not achieved at all, as confirmed by analytical methods such as TLC or ASAP analysis.

Due to the inability to form *N*-sulfinyl ketimine **H** despite optimization efforts, we were compelled to revise our synthetic strategy. As the result, an alternative synthetic pathway was developed to achieve enantiomerically pure 1-substituted tetrahydroisoquinolines. This revised approach circumvents the challenges associated with the initial *N*-sulfinyl ketimine formation step and focuses on more robust and reliable methods to introduce chirality and functionalization. The details of this alternative route, including its design, execution, and outcomes, will be discussed in the following sections.

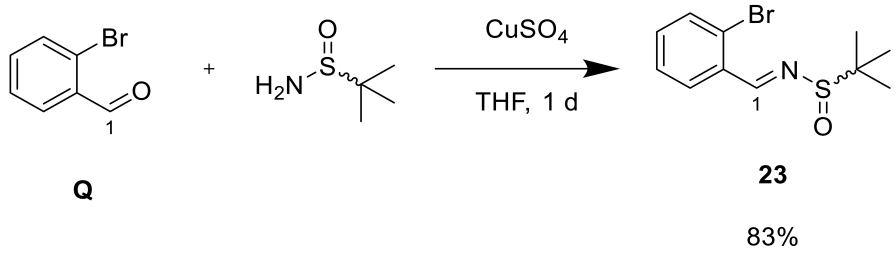
4.2 Alternative synthesis pathway

4.2.1 Condensation of aldehydes with Ellman's auxiliary

To address this issue, we decided to modify the starting material **G**, replacing the ketone with an aldehyde. Aldehydes are known to be more reactive towards nucleophiles than ketones.[100] This increased reactivity was expected to facilitate a condensation with Ellman's auxiliary, thereby improving the likelihood of obtaining the desired imine (**23**). The selection of 2-bromobenzaldehyde (**Q**) as the starting material was guided by its structural compatibility with

the initially proposed synthetic pathway, allowing us to maintain the original strategy without introducing many additional synthetic steps. This approach not only simplifies the overall process but also minimizes potential side reactions and inefficiencies associated with further transformations.

In accordance with the procedure outlined by Liu *et al.*[99], the condensation reaction is carried out with the $CuSO_4$ catalysis under continuous stirring for 12 – 24 hours, yielding the desired imine **23** with high yield of approximately 90%. Based on these findings, we adopted the same methodology for our synthesis to achieve comparable results. The reaction is shown in Scheme 15.



Q **23**

83%

Scheme 15 Synthesis of the desired *N*-sulfinyl aldimine **23**

The condensation of aldehyde **Q** with racemic Ellman's auxiliary proceeded successfully, yielding the desired compound **23** with an isolated yield of 83%. This result confirmed the effectiveness of the modified approach using aldehyde **Q** instead of the previously attempted ketone **G**. Further optimization of the reaction conditions as described by Collados *et al.*[101] led to a significant improvement in efficiency. By replacing $CuSO_4$ with $Ti(OEt)_4$ as the catalyst and employing microwave irradiation (40 W, 70 °C, neat conditions), the reaction time was drastically reduced from 24 hours to just 20 minutes. This optimized protocol not only enhanced the reaction kinetics but also maintained high yields (90 – 99%), demonstrating the potential advantages of microwave-assisted synthesis.

With *N*-sulfinyl imine **23** in hand, selective hydride reduction is not feasible. After reduction, C_1 would bear a hydrogen, rendering it inactive for subsequent synthetic transformation. This absence of functionalization at the C_1 position limits its reactivity and prevents further derivatization or participation in downstream reactions. Therefore, it is necessary to determine a suitable synthetic pathway for the introduction of the desired benzyl group onto the imine.

4.2.2 1,2-Addition of organic residues to *N*-sulfinylimines

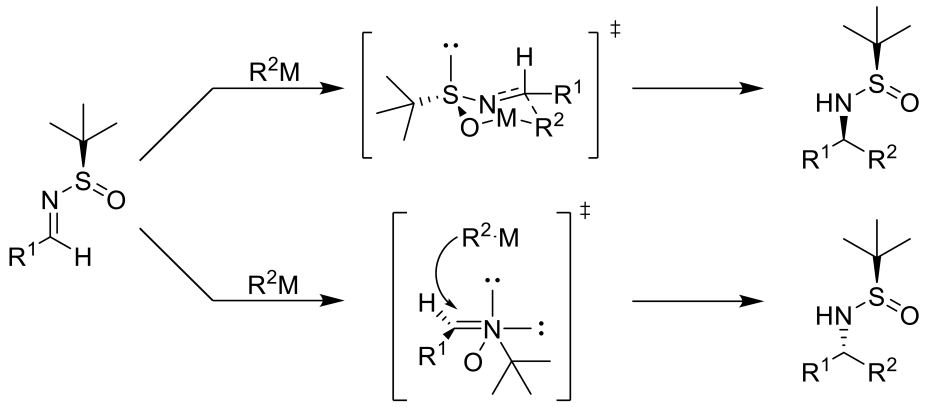
4.2.2.1 Addition of organometallic reagents

A common method for the asymmetric synthesis of chiral amines involves the addition of organometallic reagents to *N-tert*-butylsulfinyl imines. This approach leverages the chiral auxiliary properties of the *N-tert*-butylsulfinyl group to induce high stereoselectivity during nucleophilic addition. Research conducted by Cogan *et al.*[102] in 1999 provided valuable

insights into this reaction step, particularly for Mg- and Li-based organometallic reagents. Their work demonstrated that the choice of metal significantly influences the reactivity, selectivity, and stereochemical outcome of the addition.

These authors also observed that the diastereoselectivity of the addition is profoundly influenced by the choice of reaction solvent and the solvent in which the Grignard reagent is prepared. While coordinating solvents such as THF often failed to achieve high selectivity in certain cases, the use of DCM as a non-coordinating solvent, combined with Grignard reagents prepared in Et_2O, resulted in exceptionally high diastereoselectivity.

In their study, the authors proposed a six-membered ring transition state to explain the stereochemical outcome (see top of Scheme 16). In this transition state, the magnesium ion (denoted as **M** in Scheme 16) coordinates with the oxygen of the sulfinyl group. This arrangement positions the bulky *tert*-butyl group in the equatorial position, thereby directing the nucleophilic addition to occur from the same face consistently.[92, 102] Conversely, the use of coordinating solvents or organolithium reagents favors an open transition state (see bottom of Scheme 16), which disrupts the formation of the six-membered ring. This leads to the formation of the alternative diastereomer or a mixture of products, as these conditions interfere with the stabilization provided by the cyclic transition state. These findings underscore the critical role of solvent and reagent coordination in controlling the stereoselectivity of nucleophilic additions to *N*-*tert*-butylsulfinyl imines.



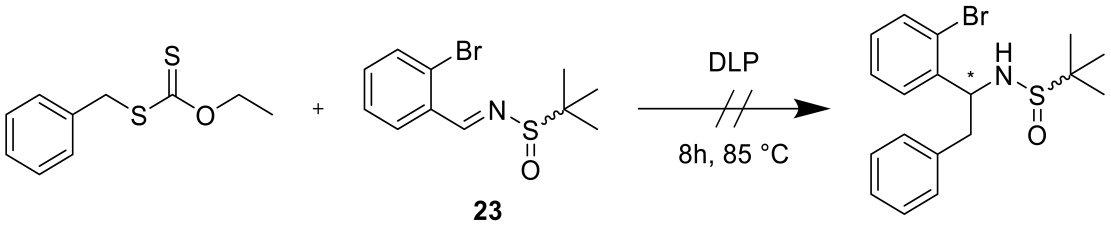
Scheme 16 Schematic representation of transition states governing the formation of different diastereomers in the 1,2-addition of organometallic reagents to *N*-tert-butylsulfinyl imines[92, 102]

4.2.2.2 Radical addition

Another promising method was reported by Quiclet-Sire and Zard[103], involving radical addition-transfer reactions of xanthate-derived radicals onto alkenes, including Michael systems. Given that Michael systems rely on polarized bonds, we considered utilizing *N*-sulfinylimines as an alternative source of polarized bonds instead of a traditional Michael system. To the best of our knowledge, no published method exists that employs xanthate-derived radicals in combination with Ellman's auxiliary. This represents a novel approach, as the integration of xanthate radical chemistry with the Ellman's auxiliary could offer unique

reactivity and selectivity profiles, potentially enabling new synthetic pathways or improving existing methodologies

In our approach, the xanthate served as the benzyl radical donor, while the *N*-suflinylimine was used instead of a polarized alkene as the substrate. Dilauroyl peroxide (DLP) was selected as the radical initiator. However, this strategy led to the decomposition of educt **23** and the formation of numerous products that could not be characterized. This reaction is depicted in Scheme 17. Consequently, this reaction pathway was not pursued further due to the observed decomposition.

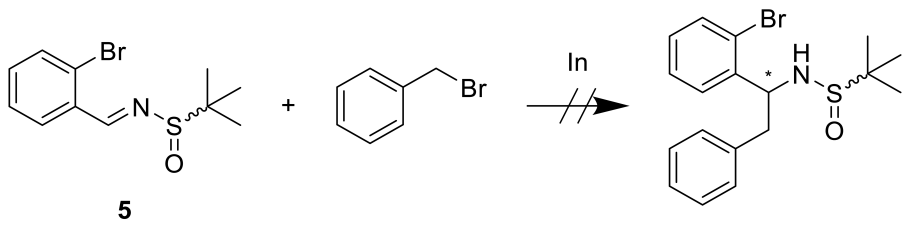


Scheme 17 Attempted radical addition following the method of Quiclet-Sire and Zard

4.2.2.3 Addition of organoindium compounds

Given that organometallic chemistry appears to be more promising than radical additions, another metal was investigated for its suitability in our reactions and evaluated to determine whether it meets our requirements. This will be discussed in detail in the following section.

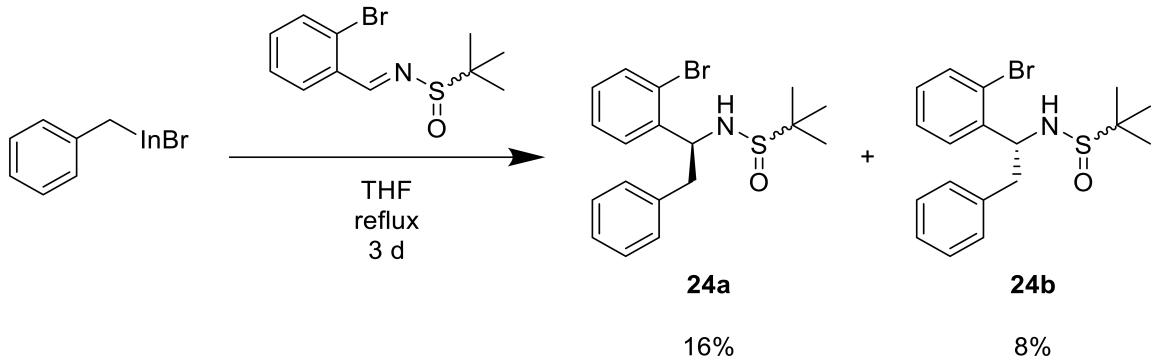
In addition to organometallic nucleophiles derived from Mg and Li, which were extensively studied by Cogan *et al*.[102], organoindium compounds have also emerged as promising candidates for 1,2-additions. A method reported by Sirvent *et al*.[104] demonstrates the use of indium to facilitate the addition of bromo compounds to structures bearing an *N*-sulfinyl group like *N*-sulfinyl aldimine **23**. The use of indium could provide an alternative pathway for the introduction of the desired benzyl group to the *N*-sulfinyl imine, warranting further investigation in the context of our synthetic objectives. The execution of this reaction is illustrated in Scheme 18. However, in all three tested reaction durations (6 h, 12 h, and 72 h), no conversion of starting material **23** to the desired product was observed.



Scheme 18 No reaction could be observed by using a one-pot method of Sirvent *et al*. [104]

Although the one-pot synthesis failed to yield the desired products, a two-step approach successfully generated the target compounds **24a** and **24b**. First, the benzyl-indium reagent was prepared from benzyl bromide and indium according to the method reported by Sahu *et al*.[105] This reagent was then added to *N*-sulfinyl imine **23** in THF, and the reaction mixture was

heated to reflux for 3 days. While this procedure produced racemic **24a** and **24b**, complete conversion of the starting material **23** was not achieved, even after the extended reaction time (Scheme 19). Due to the incomplete conversion, the lengthy reaction duration and bad diastereoselectivity of 2:1, this approach was ultimately abandoned in favour of the more efficient and higher-yielding results obtained using Grignard reagents.

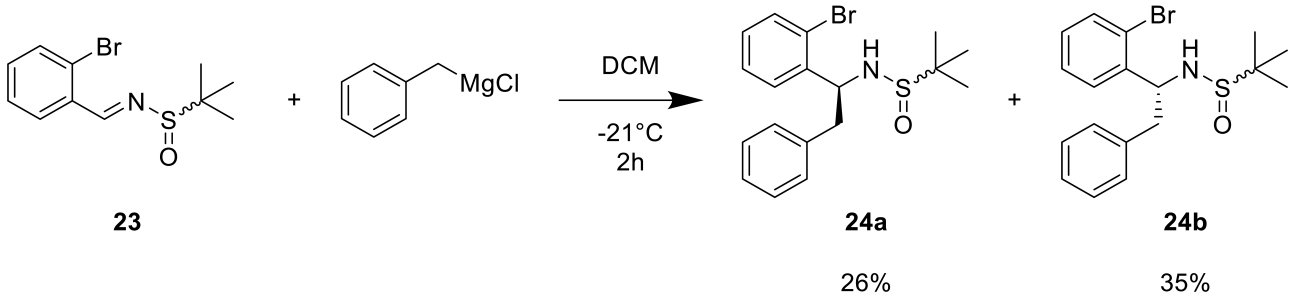


Scheme 19 Conversion of **23** to diastereomers **24a** and **24b**

During purification, it was discovered that compounds **24a** and **24b** could be conveniently separated using flash column chromatography (FCC). This separation allowed for the isolation of the individual diastereomers in pure form, facilitating their further characterization and analysis. The use of FCC proved to be an effective method for resolving the mixture, underscoring its utility in the purification of structurally similar compounds.

4.2.2.4 Addition of Grignard reagents

The next approach involved the use of commercially available benzyl Grignard reagents. By adapting a modified method based on the work of Reddy *et al.*[106], compound **23** was successfully converted to diastereomers **24a** and **24b** in moderate yields within just 2 hours (Scheme 20). This method demonstrated significant advantages in terms of reaction efficiency and simplicity compared to previous attempts. As a result, this approach was established as the preferred pathway for the synthesis of the target compounds.

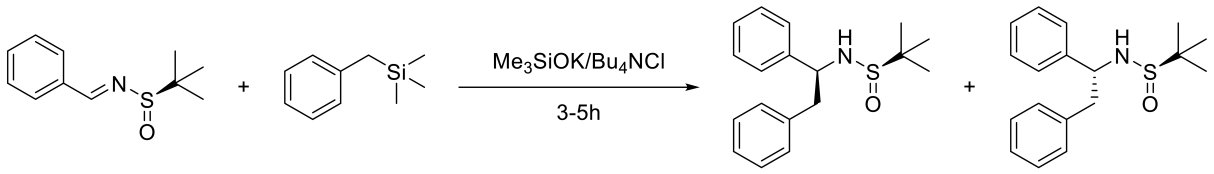


Scheme 20 Grignard addition to *N*-sulfinylimine **23**

Further optimizations of this synthesis step will be discussed in detail in the upcoming sections. These optimizations aim to enhance reaction efficiency, improve yields, and refine the overall process to achieve a better synthetic route.

4.2.2.5 Addition of organotrimethylsilane reagents

Another method published by Das *et al*.[107] is the addition of organotrimethylsilane reagents to *N*-sulfinylimines with high stereoselectivity by employing Me_3SiOK/Bu_4NCl as activator. According to the authors, the silane reagents exhibit lower reactivity compared to Li-, Mg- or In-reagents. Unfortunately, we took note of this method after the experimental work of this thesis had been completed. Therefore, silane reagents were not tested but represent a promising possibility for the addition of the benzyl group. No reactions were performed for *ortho*-brominated compounds by Das, which leads to uncertainties as to whether the reaction is also feasible for us. The reaction according to the authors is illustrated in Scheme 21.

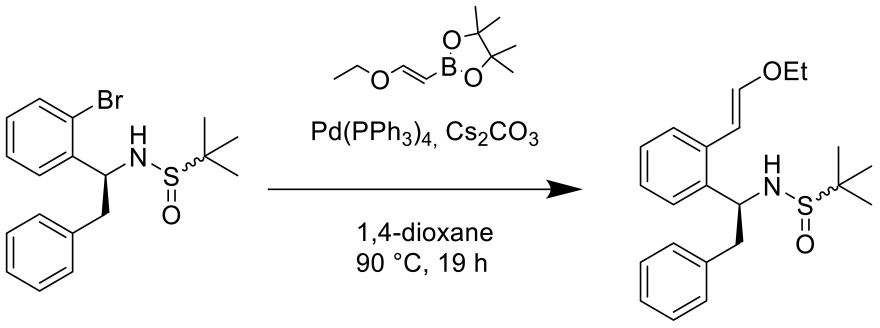


Scheme 21 Addition of benzyltrimethylsilane to *N*-sulfinylimines according to Das *et al*.[107]

A method for the synthesis of benzyl-TMS derivatives is also published by Das *et al*.[108] The authors employ suitably substituted toluene derivatives, LiNK metalation conditions (BuLi/KO^{t}Bu/TMP(H) (2,2,6,6-tetramethylpiperidine)) and chloromethylsilane in a one-pot procedure for the synthesis of substituted benzyltrimethylsilanes. The investigated substituents included alkoxy groups, which are of particular interest for our work.

4.3 Suzuki cross coupling and ring closure

As described in Section 3, the next step involves the introduction of a masked acetaldehyde (C_2 unit), cyclization and deprotection. The first step involves a Suzuki cross-coupling reaction[109] using 2-ethoxyvinyl pinacolboronate, Cs_2CO_3, $Pd(PPh_3)_4$ and **24a**. The resulting enol ether **25**, with its reaction progress monitored by TLC and ASAP, must be separated through a standard work-up procedure, including liquid-liquid extraction with water and DCM to remove the catalyst and base. However, enol ether **25** will be used in the subsequent step without further purification.



24a **25**

80%

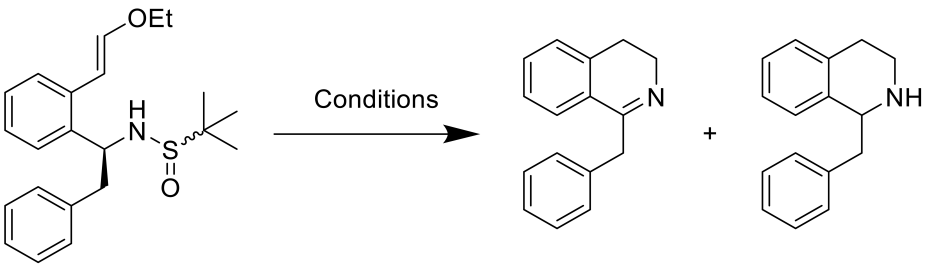
Scheme 22 Suzuki coupling resulting in crude enol ether **25**

While the formation of crude **7** was successfully achieved in 80% yield (as depicted in Scheme 22), the subsequent one-pot cyclization and deprotection step, inspired by the method of Vögerl *et al*.[98] using Et_3SiH and trifluoroacetic acid TFA, did not proceed as expected. As a result, several optimization attempts were undertaken to improve the efficiency and success of this final step. The outcomes of these optimization experiments are summarized in Table 1, which details the varying conditions, reagents, and results explored to achieve the desired cyclization and deprotection. These efforts aimed to identify the optimal parameters for completing the synthesis of the target compound.

Reductive amination is a widely used method for the synthesis of nitrogen-containing heterocycles.[110] To the best of our knowledge, no direct reductive aminations involving sulfinamides have been performed or published. Sulfinamides, while valuable as chiral auxiliaries or protecting groups, have not been extensively explored in the context of direct reductive amination reactions. This gap in the literature presents an opportunity for developing new methodologies that leverage the unique reactivity of sulfinamides, potentially expanding the scope of reductive amination chemistry and enabling the synthesis of structurally diverse amine-containing compounds. The Methods described by Fadeyi *et al*.[111], Senter *et al*.[112], Medjahdi *et al*.[113] or Zhang *et al*.[114], all focus on performing reductive amination after the cleavage of Ellman's auxiliary using acidic conditions such as TFA/water or HCl (4M in dioxane). This sequential approach involves first removing the sulfinamide protecting group to generate the free amine, which is then subjected to reductive amination with carbonyl compounds. According to these publications and the review article of Robak *et al*.[92], the cleavage of Ellman's auxiliary is typically achieved under strongly acidic conditions, specifically using TFA/water or HCl (4M in dioxane) in the presence of a protic solvent. These conditions are necessary to effectively remove the sulfinamide protecting group and generate the free amine.

However, as outlined in Table 1, multiple attempts under varying conditions failed to produce the desired product. These attempts included the use of different reducing agents, solvents,

and reaction temperatures, but none of these modifications led to successful ring closure or the formation of the target structure.



25 **26** **27**

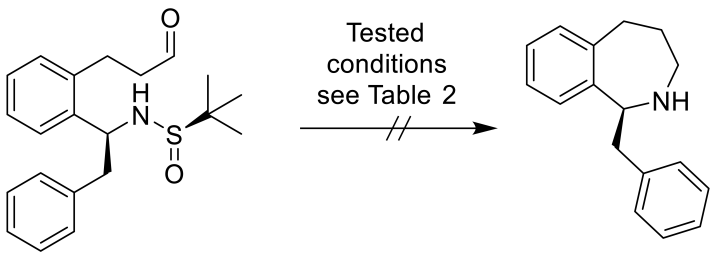
Entry	Solvent	Reducing Agent (eq)	Acid (eq)	Temp. (°C)	Time (h)	Result
1 (one pot synthesis)	DCM	Et_3SiH (2.5)	TFA (13)	RT	3.5	-
2	DCM	Et_3SiH (2.5)	TFA (13)	RT	12	**27** traces
3[115]	TFA / Water (95/5)	Et_3SiH (10)	-	RT	24	**27** traces
4[115]	TFA / Water (50/50)	Et_3SiH (>20)	-	RT	24	**26** traces
5[114]	TFA / Water (50/50)	$Na(CH_3COO)_3BH$ (3)	-	-10 – 0	12	-
6[115, 116]	TFA / Water (95/5), MeOH	$NaBH_4$ (2.7)	-	RT – 0	1.5	**27** traces
7[115, 116]	TFA / Water (95/5), MeOH	$Na(CN)BH_3$ (3)	-	RT – 0	12	**26**
8[117]	MeOH	-	HCl_{aq} (2M, 4eq)	60	1	**26**
9[106, 117]	MeOH	$NaBH_4$ (3)	HCl_{aq} (2M, 4eq)	55	2	**26** + **27** traces
10	MeOH	Et_3SiH (15)	HCl_{aq} (2M, 4eq)	60 - RT	4	**27** traces
11	MeOH, DCM	Et_3SiH (15)	HCl_{aq} (2M, 4eq), TFA (20)	55 - RT	4	**27**, 31%
12[118]	MeOH, EtOAc	Pd/C (0.1)	HCl_{aq} (2M, 4eq)	55 - RT	24	**27**, 3%

Table 1 Results of several attempts for ring closure by means of intramolecular reductive amination

Based on the conducted experiments, it is evident that these approaches are insufficient to establish a reliable standard procedure. Even Experiment 11, which initially showed promise, could not be reproduced, as compound **27** could not be yielded again with this method. The target compound, 1-benzyl-1,2,3,4-tetrahydroisoquinoline (**27**), was typically obtained only in trace amounts.

A major problem in this process is the formation of the achiral side product 1-benzyl-3,4-dihydroquinoline (**26**). The generation of this side product complicates the reaction pathway, as the formation of side product **26** destroys the desired stereochemistry. If **26** is formed first and subsequently reduced to the tetrahydroisoquinoline (THIQ), a new stereocenter is introduced, but its configuration remains uncontrolled and unknown, leading to racemic THIQ's. This lack of stereochemical control poses a major obstacle, particularly in the application of this thesis, where precise stereochemistry is critical. A possible explanation for the formation of **26** is provided by Mukade *et al*.[119], suggesting that the thermal decomposition of the sulfinamide could lead, under 1,2-elimination of a sulfinic acid, to the generation of this undesired imine-type side product **26**.

Further efforts to apply reductive amination under varying conditions and work-up procedures for the synthesis of 1-benzyltetrahydro-2-benzazepines, as detailed in Section 4.17.7, were also undertaken and are summarized in Table 2. Despite these additional experiments, the results remained unsatisfactory, with no significant conversion to the desired product observed. Since the results from Table 1 suggest that the most effective ring closure occurs through the hydrolysis of the enol ether with HCl and that the deprotection proceeds successfully with HCl, HCl was also employed in the case of benzazepines.



52a **55**

Entry	HCl	Condi-tions	Work-up	Reducing Agent	Conditions	Result
1	2M HCl (aq.)	MeOH, 55 °C, 2 h	DCM Extraction	$NaBH_4$ (1.5 eq.)	MeOH, 0 °C to rt, 18 h	No product observed
2	2M HCl (aq.)	MeOH, 55 °C, 2 h	pH > 8 with $NaHCO_3$ (aq.), DCM Extraction	$NaBH(OAc)_3$ (1.2 eq.)	THF, 0 °C to rt, 18 h	No Product observed
3	4M HCl (in diox-ane)	MeOH, rt, 1 h	Evaporation	$NaBH(OAc)_3$ (1.5 eq.)	MeOH, 0 °C to rt, 18 h	Product mass observed (traces), no purification possible
4	4M HCl (in diox-ane)	Dioxane, rt, 1 h	pH > 8 with Na_2CO_3 (aq.), DCM Extraction	$NaBH(OAc)_3$ (1.5 eq.)	THF, 2.0 eq. AcOH, 0 °C to rt, 18 h	Product mass observed (traces), no purification possible

Table 2 Reaction conditions tested for further reductive aminations. All entries were performed with 1.0 eq. of **52a**

The consistent lack of success across these attempts indicated that direct intramolecular reductive amination is not a feasible approach for this specific transformation. Given the persistent challenges and unsatisfactory outcomes, another alternative synthetic route was pursued to achieve the desired target compound.

4.4 Alternative strategy for ring closure

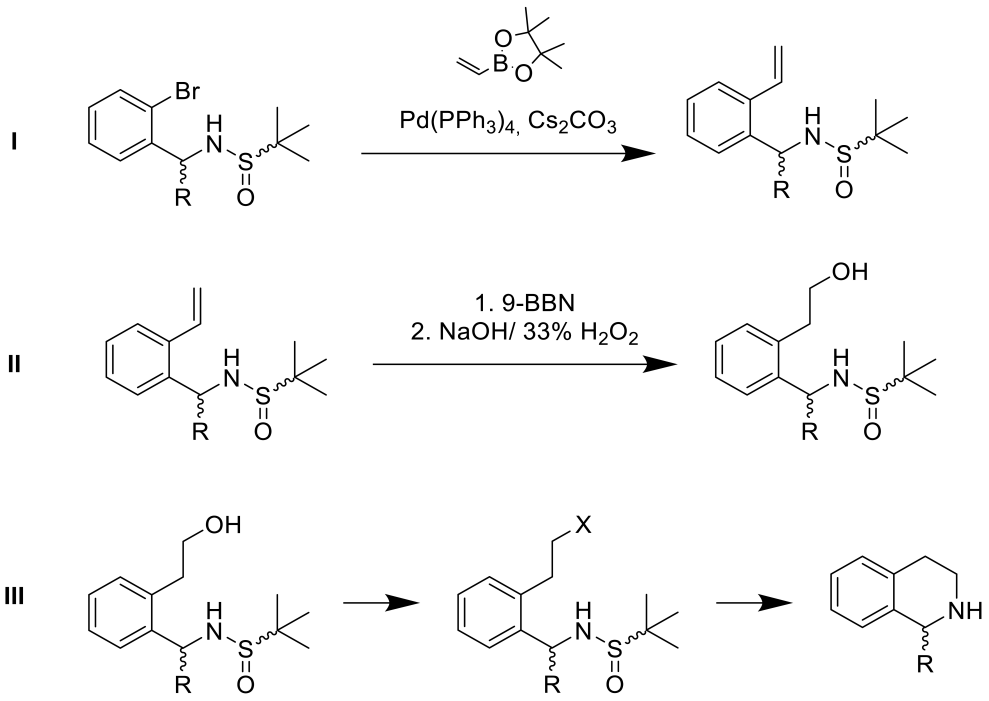
Another approach for the ring closure reaction involved intramolecular *N*-alkylation, which could be performed starting either from the protected or unprotected amine.

For this approach, utilization of the masked arylacetaldhehyde (enolether) intermediate was avoided, and a direct approach towards an arylethyl moiety bearing a leaving group was attempted. For this purpose, it was necessary to substitute the bromine residue on aromatic ring A with a saturated C_2-unit bearing a terminal halogen or another suitable leaving group. Due to the lack of practicable methods for direct 2-haloethylation of bromoarenes, our plan

was to introduce a vinyl group in place of the bromine, followed by hydroboration and oxidation to convert the aromatic vinyl group into a primary alcohol.

Having obtained the desired primary alcohol, two distinct strategies for ring closure can be pursued. The first approach involves the conversion of the hydroxyl group within the sulfinyl-protected intermediate into a suitable leaving group such as a halide or tosylates, to enable the intramolecular N-alkylation step. The second strategy involves the initial removal of the sulfinamide protecting group, resulting in the formation of an aminoalcohol intermediate, which then undergoes ring closure through an intramolecular N-alkylation process. This sequence aimed to construct the desired heterocyclic framework by leveraging the reactivity of the vinyl intermediate and the versatility of the resulting alcohol-derived leaving group. Our alternative synthetic route will prioritize the second strategy, which involves the initial removal of the protecting group to generate the corresponding aminoalcohol intermediate. This intermediate will then undergo intramolecular ring closure to achieve the desired tetrahydroisoquinoline structure.

However, the feasibility and efficiency of this approach would depend on the successful execution of each transformation, particularly the hydroboration-oxidation and the subsequent activation of the primary alcohol. An overview of our proposed synthetic pathway is depicted in Scheme 13.



Scheme 23 Overview of the alternative ring closure pathway. Step **III** involves *N*-sulfinyl deprotection and ring closure

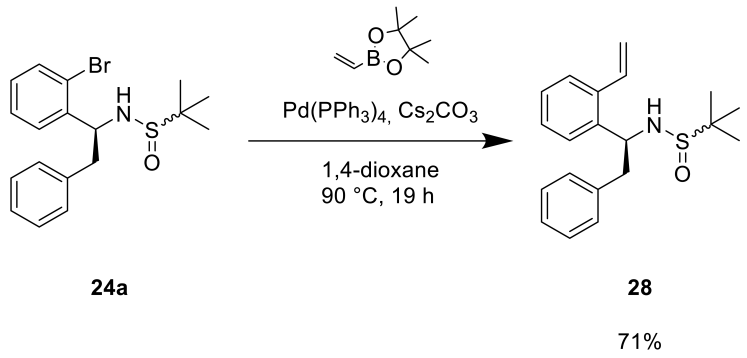
4.4.1 Introduction of the vinyl group

The reaction mechanism of the Suzuki cross coupling involves the oxidative addition of an aryl halide (in this case, the brominated *N*-sulfinylamine) to a palladium(0) catalyst, forming a

palladium(II) complex. This intermediate then undergoes transmetalation with a vinylboronic acid/ester reagent, followed by reductive elimination to yield the coupled product, in this instance, the vinyl-substituted arene. The reaction typically requires basic conditions to facilitate the transmetalation step, with common bases.

The Suzuki cross-coupling is particularly advantageous due to its mild reaction conditions, high functional group tolerance, and the commercial availability of a wide range of boronic acid derivatives and palladium catalysts. These attributes make it an ideal choice for the synthesis of complex organic molecules, including the target styrene compounds in this study.

This alternative approach involves replacing the bromine residue in compound **24a** with a vinyl group. In this route, vinylboronic acid pinacol ester was used as the reagent instead of 2-ethoxyvinyl pinacolboronate (Scheme 24). The vinylic compound **28** was obtained in a yield comparable to that of compound **25** (Yield of **28**: 71%, Yield of **25**: 80%). The reaction was conducted under the same conditions as described in Scheme 22, maintaining consistency in the reaction setup and parameters.



24a **28**

71%

Scheme 24 Suzuki coupling leading to vinyl compound **28**

Another advantage of this method is the greater stability of the synthesized compound **28** compared to enolether **25**. While compound **25** decomposed over time, compound **28** remained stable for several months under identical storage conditions. Additionally, purity analysis indicated that compound **28** was more efficiently purified than compound **25**. Both compounds underwent a single round of purification *via* FCC; however, compound **25** exhibited a higher level of impurities, requiring an additional purification step.

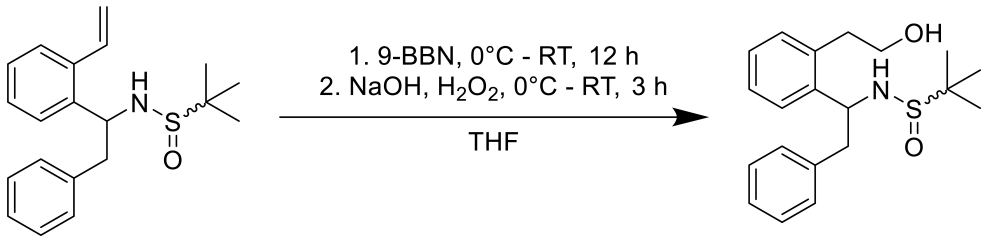
4.5 Hydroboration and deprotection

4.5.1 Hydroboration and oxidation

The reaction was published by Brown in 1956 for the conversion of olefins into organoboranes and corresponding alcohols.[120] The hydroboration step was carried out using 9-borabicyclo[3.3.1]nonane (9-BBN), a sterically hindered borane reagent known for its high regioselectivity and functional group tolerance. The reaction proceeds *via* a concerted, *syn*-

addition mechanism, wherein the boron and hydrogen atoms add across the carbon-carbon double bond in a single step, avoiding the formation of a carbocation intermediate.

To enable ring closure, a modification of the introduced vinyl group was necessary. The process involved hydroboration of the styrene derivative **28** by the use of 9-borabicyclo[3.3.1]nonane (9-BBN), followed by oxidation of the resulting organoborane with H_2O_2 and NaOH. The organoborane intermediate was not purified, as the reaction proceeds rapidly and quantitatively to yield the desired anti-Markovnikov product. The steric hindrance of 9-BBN ensures high regioselectivity, consistently producing the primary alcohol in good yields.[121] This reaction (Scheme 25) yielded arylethanol **29** in a first attempt in moderate yield (35%). Through further optimization, the yield was improved up to 62%. A version of the method reported by Kudale *et al*.[122] was modified by our group and implemented to improve the efficiency of the transformation. The authors employed the hydroboration-oxidation reaction for aliphatic vinyl groups, whereas in our case, the vinyl group in compound **28** is adjacent to an aromatic ring system. While the proposed reaction conditions suggested that 2 hours were sufficient for the hydroboration step, we observed that full conversion of **28** required an extended reaction time of 12 hours. This difference in reactivity can likely be attributed to the electronic and steric effects imposed by the aromatic ring, which may hinder the accessibility of the vinyl group to the hydroboration reagent. The prolonged reaction time underscores the importance of optimizing conditions for substrates with varying electronic environments, particularly when aromatic systems are involved.



28 **29**

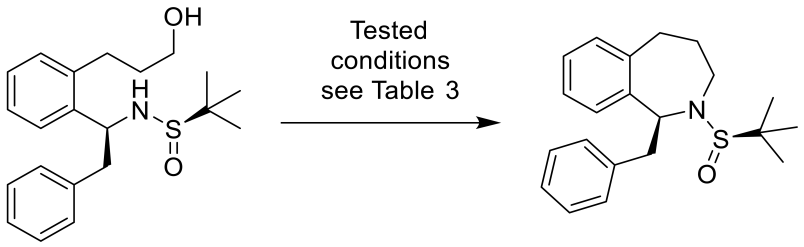
62%

Scheme 25 Hydroboration/oxidation of the vinyl group

With compound **29** in hand, two distinct pathways for ring closure are feasible. The first approach involves the generation of a leaving group from the alcohol moiety of the sulfinyl-protected compound **29**, facilitating cyclization. The second pathway entails the cleavage of the sulfinamide protecting group first, yielding an aminoalcohol **30**, followed by ring closure *via* intramolecular N-alkylation.

4.5.2 Ring closure without deprotection

The ring closure to form the tetrahydroisoquinoline core can be conducted, without prior removal of the sulfinamide protecting group, through N-alkylation. An example of this approach is demonstrated by Reddy *et al.*[106], where chlorine serves as the leaving group instead of the primary alcohol. Another approach was published by Reddy *et al.*[123] for the synthesis of tetrahydro-β-carboline alkaloids. In a similar manner, chlorine was employed as the leaving group, and ring closure occurred without deprotection of the sulfinamide protecting group.
In parallel to the work on THIQs, the homologous benzazepines were also investigated, and systematic studies on cyclization were conducted for these compounds as well. Several leaving groups were synthesized and tested in an effort to obtain 1-benzyltetrahydro-2-benzazepines without cleavage of the sulfinamide group. The following Table 3 summarizes the various attempts made to achieve this transformation including a classical Mitsunobu reaction (entry 2).



Entry	Reagents	Conditions	Result
1	1. Ms-Cl (1.5 eq.), Et_3N (2.4 eq.) 2. NaH (2.2 eq.)	1. DCM, 0°C, 90 min 2. DMF, 0°C to rt, 18 h	No full purification after step 1 Isolated yield: 17%
2	DIAD (1.3 eq.), PPh_3 (1.2 eq.)	THF, rt, 18 h; THF, 60 °C, 3 h	No product observed
3	$SOCl_2$ (1.1 eq.), Et_3N (3.0 eq.)	DCM, 0 °C to rt, 18 h	No product observed
4	*p*-Ts-Cl (1.1 eq.), NaH (2.0 eq.)	THF, reflux, 3 h	Traces of product observed
5	Ts-Cl (1.1 eq.), KOH (3.0 eq.)	THF, reflux, 3 h	Traces of product observed
6	Ts-Cl (1.1 eq.), Et_3N (3.0 eq.)	THF, reflux, 3 h	Traces of product observed
7	Ts-Cl (1.1 eq.), KO^{t}Bu (2.0 eq.)	THF, reflux, 3h	Isolated yield 14%

Table 3 Reaction conditions tested for the ring closure *via* leaving groups

Despite these efforts, the results remained largely unsatisfactory, as none of the tested leaving groups provided a reliable pathway to the desired 1-benzyltetrahydro-2-benzazepines *via*

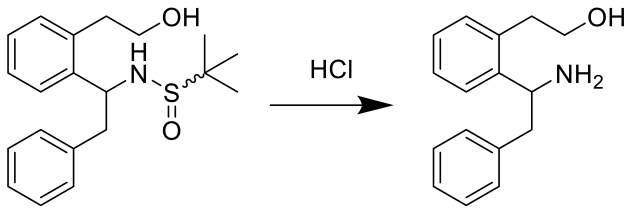
intramolecular *N*-alkylation of the sulfinamide. The major challenges encountered included poor reactivity of the modified substrates, competing side reactions that led to undesired byproducts, and the formation of unstable intermediates that hindered the progress of the reaction. The results from these investigations led to the decision not to employ intramolecular N-alkylation without prior removal of the protecting group for the synthesis of THIQs. Consequently, this approach was not pursued further in the synthetic route.

An alternative approach is reported by Cole *et al*.[124] in the context of their flow chemistry methodology. This method involves the initial tosylation of a sulfinamide alcohol, followed by the removal of the *N*-sulfinyl group under acidic conditions using hydrochloric acid. Subsequent alkalinization of the reaction medium induces cyclization, leading to the formation of the desired THIQs. This approach is comparable to entry 4 of Table 3. In their study, the authors used aqueous Na_2CO_3 instead of NaH. Since the entry failed to synthesize 1-benzyltetrahydro-2-benzazepines, we opted to exclude this methodology.

These findings further emphasized the inherent limitations of this approach and reinforced the necessity of exploring alternative synthetic strategies to achieve efficient and selective ring closure. As a result of these reactions, we conclude that the *N*-sulfinyl deprotection step must be performed prior to the ring closure to ensure successful cyclization. This sequence is critical because the presence of protecting groups can hinder the reactivity or accessibility of key functional groups necessary for the ring closure. By carrying out the deprotection first, the reactive sites are fully exposed, enabling the intramolecular cyclization to proceed efficiently.

4.5.3 *N*-Sulfinyl deprotection

Based on the findings outlined in Section 4.3, the optimal sulfinyl deprotecting conditions were achieved using HCl in dioxane, with deprotection performed as a separate step (Scheme 26) rather than as part of a one-pot synthesis with the ring closure. The method employed, as described by Reddy *et al*.[106], resulted in the formation of aminoalcohol **30** with a yield of 35%.



29 **30**

35%

Scheme 26 Deprotection conditions: 0 °C to RT, 4M HCl in dioxane

The resulting compound **30** features a free primary aliphatic amine and a primary alcohol, both of which are suitable for the subsequent *de novo* construction of the 1-benzyltetrahydroisoquinoline scaffold. Due to the high polarity of the deprotected aminoalcohol **30**, FCC resulted in an extremely time-consuming purification process. Based on this insight,

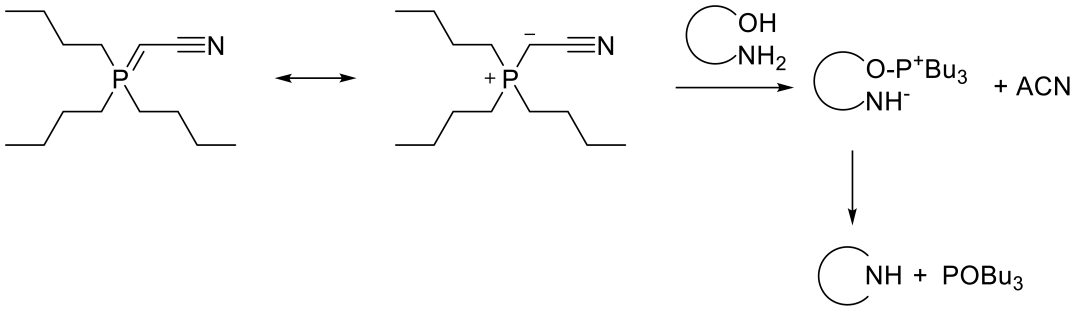
FCC was not performed for every analogue of this step for the compounds of this thesis. The collected data reveal that the yield of this step is highly dependent on the purity of the precursor, underscoring the importance of obtaining high-quality intermediates for successful deprotection and subsequent transformations.

4.6 Ring closure

4.6.1 Mitsunobu type reaction

In the context of an intramolecular ring-closing reaction, the Mitsunobu reaction employing Tsunoda's reagent (cyanomethylene tributylphosphorane, CMBP), serves as an effective strategy for the formation of cyclic amines from aminoalcohol precursors. The mechanism follows a modified Mitsunobu pathway, leveraging the electrophilic activation of the alcohol and the nucleophilicity of the neighboring amine.

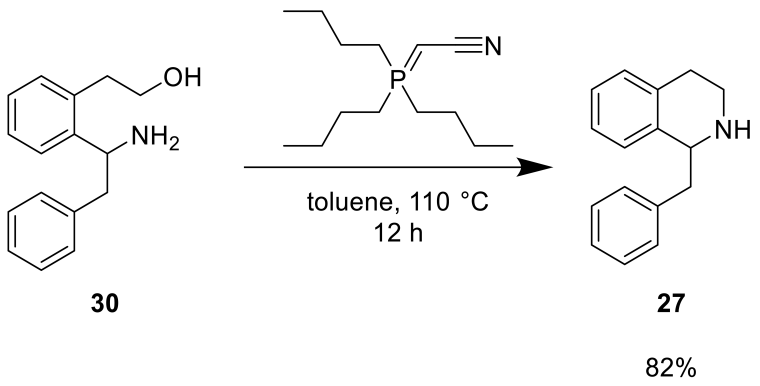
Initially, the hydroxyl group undergoes activation through interaction with CMBP, forming an alkoxyphosphorane intermediate. Unlike classical Mitsunobu conditions[125], which utilize azodicarboxylates, the electrophilic cyanomethylene moiety of CMBP promotes the elimination of acetonitrile, leading to the generation of a highly reactive phosphonium species. This transformation enhances the leaving group ability of the hydroxyl moiety, facilitating a nucleophilic attack by the pendant amine[126] (see Scheme 27).



Scheme 27 Reaction with CMBP according to Tsunoda *et al.*[127, 128] modified for our intramolecular ring clousre

The process culminates in the formation of a stable phosphine oxide byproduct, shifting the reaction equilibrium toward product formation. The use of CMBP in such transformations provides distinct advantages, including enhanced reaction efficiency, and the avoidance of azodicarboxylate-based reagents, making it a powerful tool for the synthesis of nitrogen-containing heterocycles.

Finally, this type of reaction for ring closure was investigated using CMBP, and compound **30**, following a modified procedure adapted from Kudale *et al.*[122] Unlike the original study, where CMBP was utilized for ring closure to 2-substituted monocylclic amines starting from *tert*-butylsulfinamide precursors, this reaction (Scheme 28) successfully generated the desired racemic 1-benzyl-1,2,3,4-tetrahydroisoquinoline **27** in 82% yield after purification *via* flash column chromatography (FCC).



Scheme 28 Final ring closure with CMBP resulting in the desired 1-benzyltetrahydroisoquinoline

Classic Mitsunobu conditions are suitable for intramolecular carbon-nitrogen bond formations, as described in a review article by Hughes[129], but CMBP offers several advantages over classic Mitsunobu reagents, such as the combination of triphenylphosphine (PPh_3) with diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), or tetramethylazodicarboxamide (TMAD), as outlined by Wyatt[130].

Mitsunobu reactions require typically a relatively acidic nucleophile, such as hydroxyl (-OH), thiol (-SH) or amino (-NH) groups, with a pK_a ≤ 15, ideally even below 11. Tolerated functional groups for classic Mitsunobu reactions are amine derivatives such as imides and sulfonamides, thiols and phenols. As suitable substrates, primary or secondary alcohols were employed and chiral secondary alcohols undergo a complete inversion of stereochemistry. Intramolecular Mitsunobu reactions forming lactams, cyclic ethers, amines etc. can also be executed. Common solvents for the reaction are e.g. THF, toluene, DMF, DCM and 1,4-dioxane. The preferred phosphine component is PPh_3, which is cheap and commercially available. The triphenylphosphine oxide byproduct and unreacted PPh_3 are water-insoluble and require chromatographically separation from the product.[131]

Tsunoda *et al*. further demonstrated that CMBP often delivers higher yields compared to conventional Mitsunobu reagents.[126] The use of CMBP in our study not only facilitated the successful ring closure to form compound **27** but also achieved an 82% yield after purification, underscoring its effectiveness and reliability in complex synthetic transformations. These advantages make CMBP a valuable tool for organic synthesis, particularly in challenging reactions where traditional Mitsunobu conditions may fall short e.g. for amines and derivatives therof with low acidity (pK_a > 15).

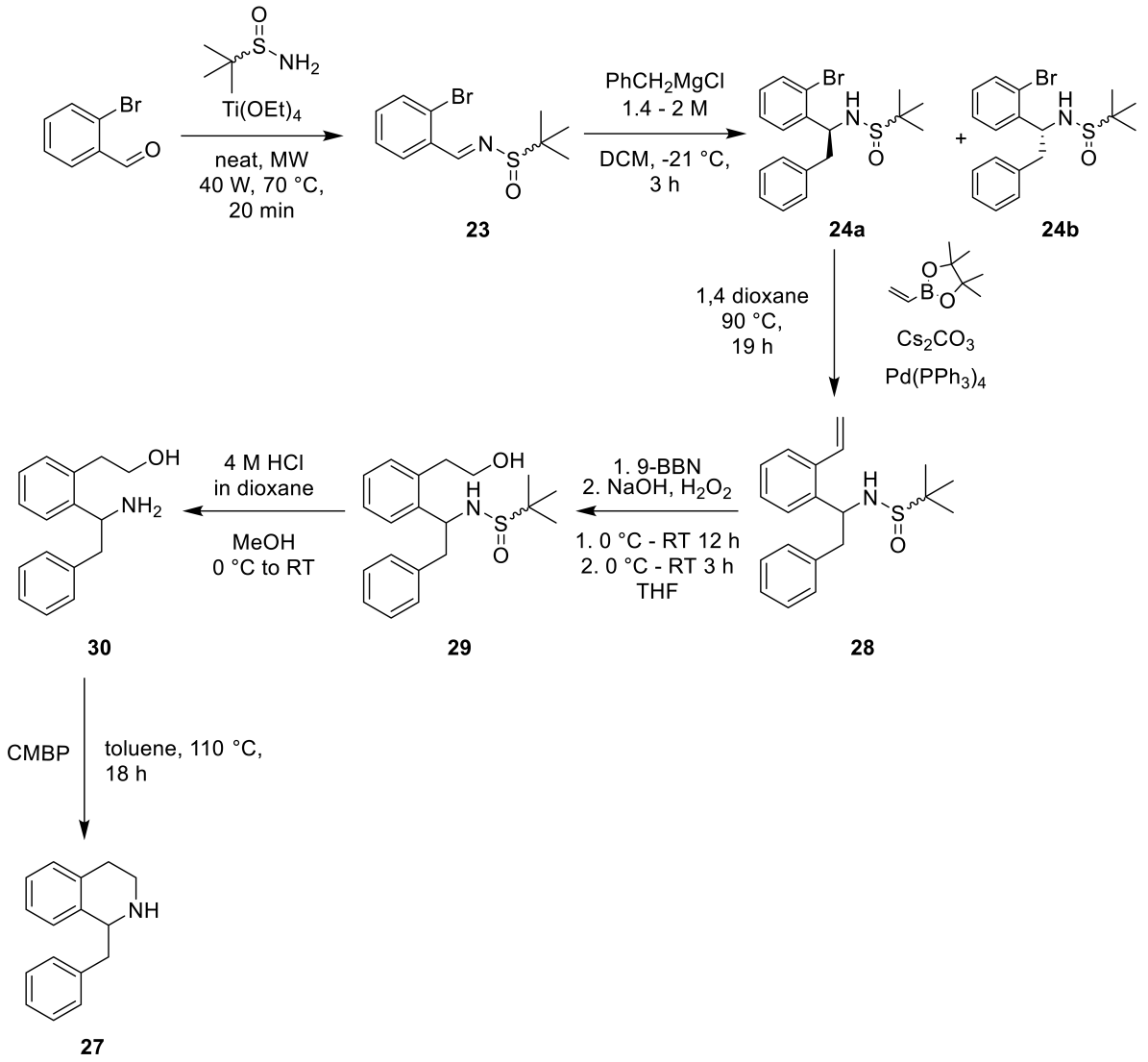
4.6.2 Alternative leaving groups

Forming other leaving groups from the free aminoalcohol **30** would not be possible due to the nucleophilicity of the free amine. The nucleophilicity of the free amine in aminoalcohol **30** precludes the direct formation of conventional leaving groups (e.g., sulfonates, halides) at the alcohol moiety. The unprotected amine would readily react with electrophilic activating agents

(e.g., tosyl chloride, mesyl chloride) under typical derivatization conditions, leading to undesired side reactions such as amine sulfonylation rather than alcohol activation.
Therefore, the most viable and effective approach for the ring closure reaction remains the Mitsunobu-type cyclization. This method offers a robust and reliable pathway for the formation of the desired cyclic structure, taking advantage of the *in situ* generation of a leaving group and which means activation of the alcohol moiety under mild conditions. The Tsunoda reaction is particularly advantageous in this context, as it avoids the challenges associated with the nucleophilicity of the free amine and ensures high yield. Consequently, this strategy represents the optimal choice for achieving the target ring closure.

4.7 Summary of the optimized synthesis route

An overview of the developed synthetic route to racemic 1-benzyl-1,2,3,4-tetrahydroisoquinoline (**27**) is presented in Scheme 29. The optimized strategy affords the 1-benzyltetrahydroisoquinoline **27** in six steps, starting from commercially available and cost-effective 2-bromobenzaldehyde and utilizing racemic Ellman's reagent.



Scheme 29 Overview of the developed synthesis route

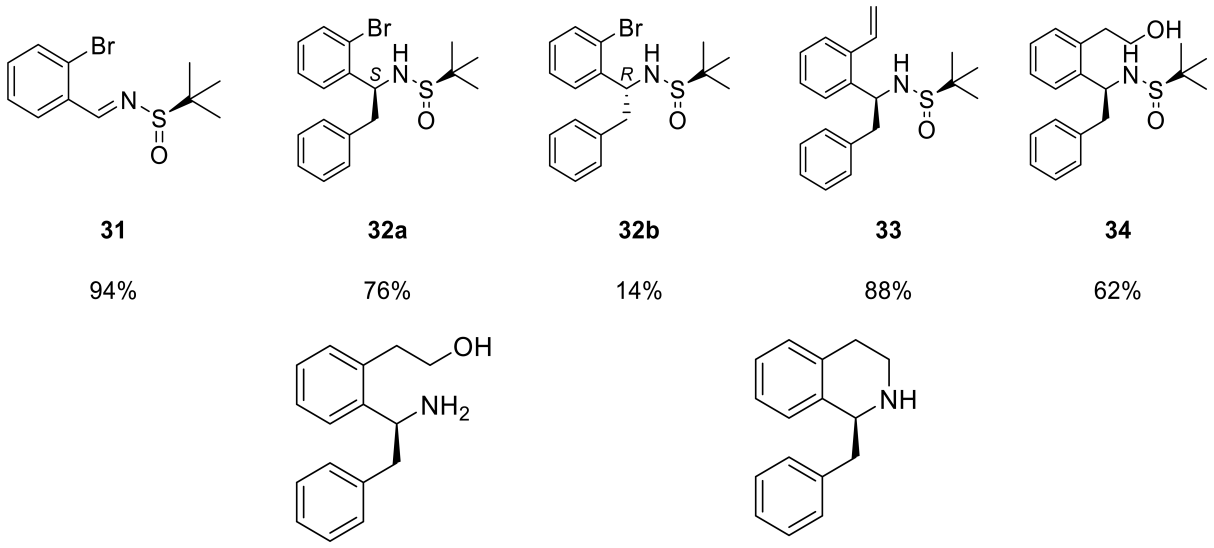
After establishing the general synthetic route, the initial objective was the synthesis of enantiomerically pure 1-benzyltetrahydroisoquinolines using commercially available and cost-effective enantiomerically pure Ellman's reagent. Subsequently, the focus shifted to expand the structural diversity of the target compounds, with a particular focus on incorporating ether substituents into the aromatic moieties. This strategy was motivated by the bioactive properties of 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids and truncated analogues from our group, as discussed in Section 2. The scope and limitations of the developed synthetic approach will be critically evaluated in the following sections.

4.8 Synthesis with enantiomerically pure Ellman's auxiliary

The next step involved the preparation of the target compounds using enantiomerically pure starting materials to ensure high stereochemical integrity. Henceforth, only (*R*)-(+)-*tert*-butylsulfinamide will be utilized in the condensation step to introduce the necessary chiral information carrier for subsequent transformations. This decision was primarily based on cost

considerations, as the (*R*)-enantiomer is generally more economical when purchased in larger quantities compared to its (*S*)-counterpart.

The procedure outlined in Scheme 29 was followed, resulting in the synthesis of compounds **31** (94% yield), separable diastereomers **32a** (76% yield, (*S*)-configuration at C-1) and **32b** (14% yield, (*R*)-configuration at C-1), **33** (88% yield from **32a**), and **34** (62% yield). The deprotection of compound **34** yielded aminoalcohol **35** (45% yield), which subsequently underwent ring closure to form (*S*)-1-benzyl-1,2,3,4-tetrahydroisoquinoline **36** (84% yield) (see Scheme 30).



31 94%

32a 76%

32b 14%

33 88%

34 62%

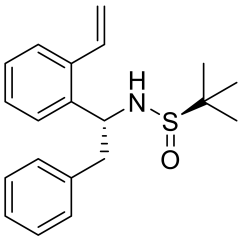
35 45%

36 84%

Scheme 30 Compounds of the synthesis with enantiomerically pure Ellman's auxiliary

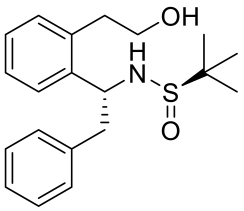
The yield and selectivity of the Grignard addition were significantly enhanced by employing enantiomerically pure Ellman's reagent and by lowering the reaction temperature from -21°C to -78°C. Employing the chiral auxiliary in its enantiomerically pure form increased the overall yield to 90%, compared to 61% achieved with the racemic auxiliary. Furthermore, the enantioselectivity for the desired (*S*)-configuration at C-1 improved markedly from 26% to 76% as a result of these modifications. In conclusion, future Grignard additions will be conducted at -78°C to optimize yield and enantioselectivity, building on the demonstrated improvements in reaction performance.

To investigate the applicability of the synthetic route for the (*R*)-configuration at C-1, the reaction sequence was also carried out using compound **32b** as the starting material. The results indicated that the route was equally effective, yielding the desired products **37** (86% yield), **38** (71% yield), aminoalcohol **39** (98% yield) and (*R*)-1-benzyl-1,2,3,4-tetrahydroisoquinoline (**40**) (68% yield) in high yields (Scheme 31).



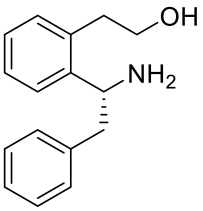
37

86%



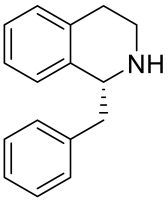
38

71%



39

98%



40

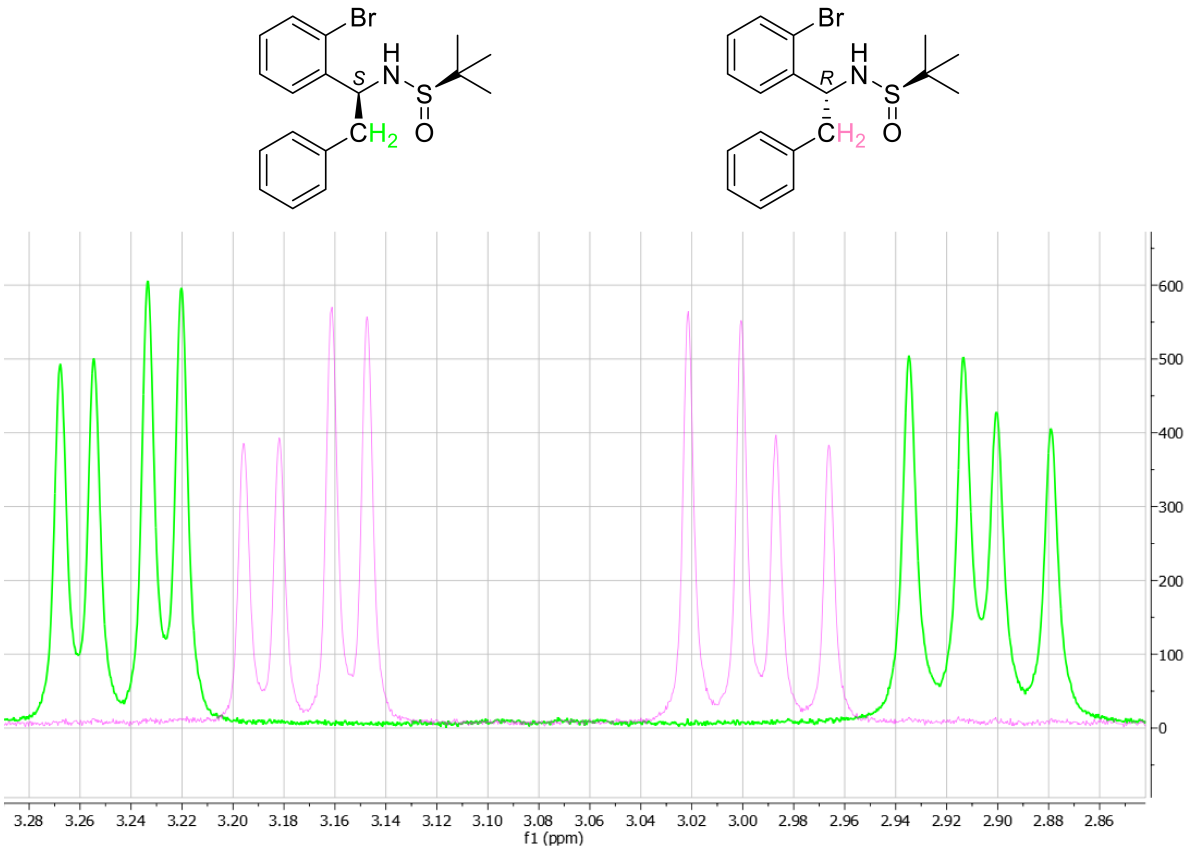
68%

Scheme 31 Intermediates of the synthesis to benzyltetrahydroisoquinoline **40**

This outcome confirms that the synthetic pathway is versatile and suitable for both enantiomeric forms, thereby underscoring its robustness and broad utility in the preparation of stereochemically defined tetrahydroisoquinoline derivatives.

4.8.1 Determination of the absolute configuration

One common method for the determination of the absolute configuration of enantiomers is circular dichroism (CD) spectroscopy, whereby the different absorption of left- and right-circularly polarized light by optically active, chiral molecules is measured. Additionally, X-ray crystallography[132] can confirm the assignment. For our compounds, these analytical experiments were not necessary, as the ^{1}H-NMR spectra already revealed the configuration of the synthesized molecules, indicated by the differences in chemical shifts and in *J*-couplings. As an example, the ^{1}H-NMR spectra (referenced to CD_2Cl_2 as solvent) of **32a** (green) and **32b** (pink) were superimposed and illustrated in Scheme 32. The origins of these signals are the CH_2 groups of the added benzyl Grignard reagent.



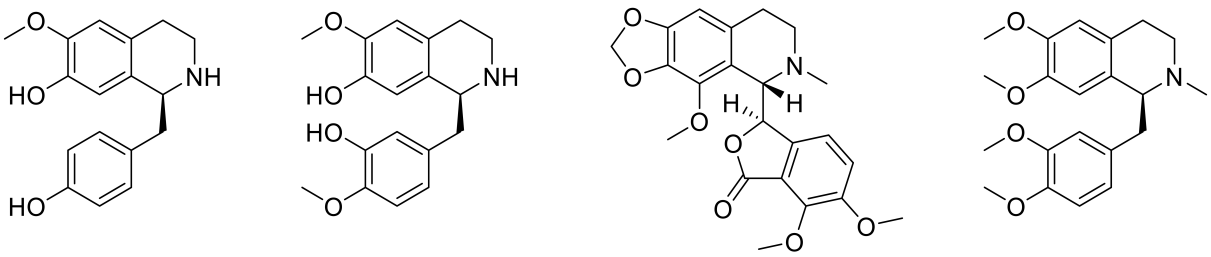
Scheme 32 Superimposed ^{1}H-NMR spectras of **32a** and **32b** in the section of the benzylic CH_2 group

This pattern was detected in ^{1}H-NMR spectra for every synthesized compound after the benzyl Grignard addition. The assignment of absolute configuration performed *via* ^{1}H-NMR spectroscopy was based on an analogy to a previously reported similar *ortho*-chloro substituted compound by Das *et al.*[107] The data from these authors are in alignment with the reports of Buesking *et al.*[133] for the chloro compound.

The assignment can also be confirmed by the optical rotation $\boldsymbol{\alpha_{598}^{20}}$ of the final product. For the previously synthesized (*S*)-1-benzyl-1-2-3-4-tetrahydroisoquinoline (**36**), our result of -55 in $CHCl_3$ is consistent in sign and value with the published literature value of -58 by Xie *et al.*[134]

4.9 Ether derivatives

All lead structures **5**, **21**, and **22** incorporate ether groups on the aromatic A-ring, which play a critical role in modulating the biological activity of these compounds. In addition to the aforementioned compounds, numerous tetrahydroisoquinoline alkaloids (examples shown in Scheme 33) also feature ether groups on the aromatic A-ring, which are known to significantly influence their biological activity and pharmacological properties. These ether functionalities are often critical for the interaction of the alkaloids with their molecular targets, underscoring the importance of their inclusion in synthetic and structural studies.

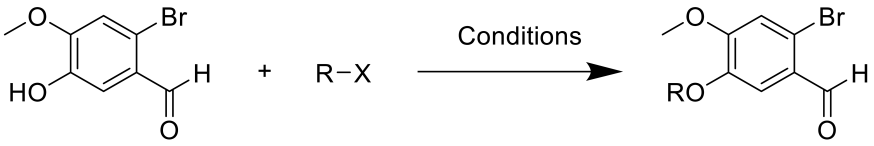


(*S*)-Coclaurine (*S*)-Norreticuline (*S*,*R*)-Noscapin (*S*)-Laudanosine

Scheme 33 Several natural alkaloids with ether groups on ring A

In this section, the synthesis and evaluation of various ether derivatives is discussed. While 2-bromo-4-methoxybenzaldehyde (**41**) is commercially available at low cost, other *ortho*-bromobenzaldehyde precursors required targeted synthesis. 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (**42**) was selected as the starting material for the preparation of subsequent compounds.

To optimize the introduction of ether functionalities, various conditions for the Williamson ether synthesis (Scheme 34) were systematically evaluated, as summarized in Table 4. The results demonstrated that the combination of K_2CO_3, DMF, and an alkyl/benzyl halide (iodomethane for **43** and benzyl bromide for **44**) provided the highest efficiency for the synthesis of the desired ether. A notable advantage of this method is that the product meets the required purity standards without the need for further purification by FCC, enabling its direct use in subsequent reactions.



42 R ≠ Ph
X = Br, I

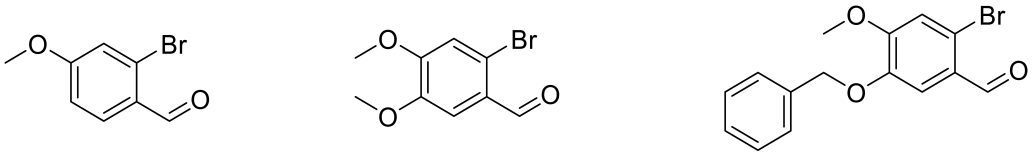
Scheme 34 General procedure of the Williamson ether synthesis

Entry	Solvent	Halide (eq)	Base (eq)	Catalyst (eq)	Temp. (°C)	Time (h)	Result
1[135]	Acetone	1	K_2CO_3 (2)	KI (0.02)	reflux	12	29%
2[135]	Acetone	1	*t*-BuOK (2)	KI (0.02)	RT	12	traces
3[135]	THF	1	NaH (2)	KI (0.02)	RT	12	traces
4*	THF	1.5	K_2CO_3 (2.5)	-	reflux	72	traces
5*	DMF	1.5	K_2CO_3 (2.5)	-	RT	12	quant.

Table 4 Optimization of the Williamson ether synthesis
*__42__ was pre-mixed with the solvent and base. After 1 hour, iodomethane or benzyl bromide were introduced dropwise to the reaction mixture.

Using this optimized method, both 2-bromo-4,5-dimethoxybenzaldehyde (**43**) and 5-(benzyloxy)-2-bromo-4-methoxybenzaldehyde (**44**) were efficiently synthesized from the

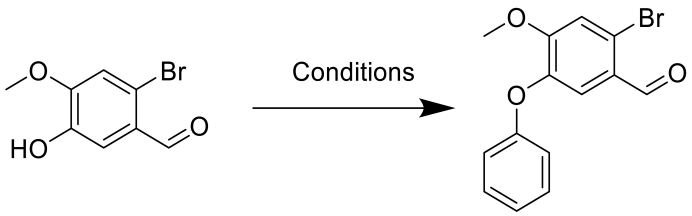
common starting material **42** (see Scheme 35). For the synthesis of **43**, iodomethane was utilized as the alkyl halide, while benzyl bromide was employed for the preparation of benzyl ether **44**. This approach highlights the versatility of the Williamson ether synthesis in introducing diverse ether functionalities under mild and efficient conditions.



41 **43** **44**

Scheme 35 Necessary starting materials for further synthesis

Unfortunately, diaryl ethers cannot be accessed *via* the Williamson ether synthesis, which posed a significant challenge given that the diaryl ether moiety in SG-094 (**22**) is a critical structural feature for its biological activity. Consequently, the development of an alternative synthetic strategy became necessary to incorporate this key functionality into the desired structural motif. Several established methods for the synthesis of diaryl ethers are known and will be discussed in the following section. The desired reaction to form diaryl ether **45** is shown in Scheme 36.



42 **45**

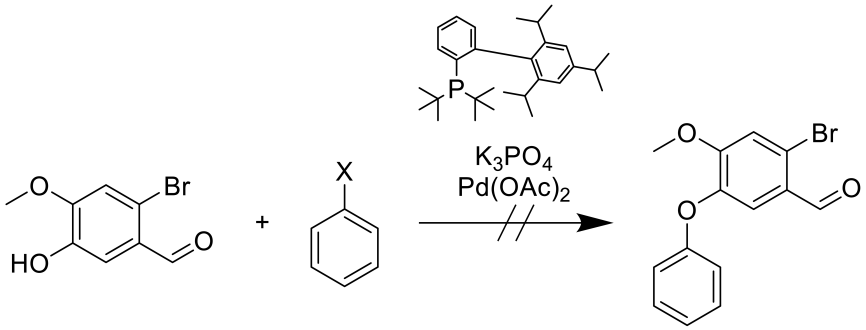
Scheme 36 Synthesis of the desired diaryl ether **45**

As outlined in Section 2.1, Dr. Gerndt selected the Chan-Evans-Lam coupling reaction for the synthesis of diaryl ethers. Following the methodology established by Evans *et al.*[136] each phenolic group was subjected to 1 equivalent of $Cu(OAc)_2$, 3 equivalents of phenylboronic acid, and a mixture of NEt_3/pyridine in a 1:1 ratio (2.5 equivalents) in DCM as solvent.

Building on this approach, compound **24** was utilized as the starting material for the synthesis of **45**. In accordance with the literature[136], only NEt_3 was employed as the base in this reaction. However, this approach, despite an extended reaction time of over 3 days instead of 18 hours as mentioned in literature, yielded only trace amounts of the target compound **45** with the starting material **42** still not fully consumed, as indicated *via* TLC analysis. During the reaction time, further conversion was continuously observed, but the reaction progressed very inefficient, although several examples of Chan-Evans-Lam couplings with aryl halides are documented in the literature[136-138]. An alternative method, reported by Subbareddy[139], involves the use of ultrasonic irradtion to faciliate Chan-Lam coupling reactions within 20 minutes. In this approach, 2,2'-bipyridine serves as ligand. Unfortunately, no conversion was

observed under these conditions. Another approach reported by Chen *et al*.[140] involved microwave-assisted, copper-promoted N-arylation of amines with arylboronic acids. Even though this methodology is not described for phenols, we applied it to the synthesis of compound **45**, employing DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base. Since this approach resulted in no conversion, we subsequently attempted the reaction using NEt_3[141], which is commonly used as base for such reactions. While the formation of diaryl ether **45** was observed under these conditions, the method was not further explored due to the availability of more efficient alternatives. Continuing with microwave-assisted methodologies, Sarkate *et al*.[142] reported a strategy employing nitroarenes for the synthesis of nonsymmetrical diaryl ethers under microwave irradiation. In our study, phenol **42** was combined with DMSO, K_2CO_3 and nitrobenzene. However, no conversion to the desired product **45** was observed under these conditions. After thorough investigation of these reactions, we concluded that the Chan-Evans-Lam coupling and related reactions failed to deliver the desired product with satisfactory yield.

The next two attempts involved Buchwald-Hartwig couplings, following a method reported by Burgos *et al*.[143] for the synthesis of various diaryl ethers. This approach utilizes aryl halides, a phenol group, K_3PO_4, 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl as the ligand, $Pd(OAc)_2$ as the catalyst and toluene as solvent. In our case, the phenol group of **42** was intended react with either iodobenzene or bromobenzene as illustrated in Scheme 37.



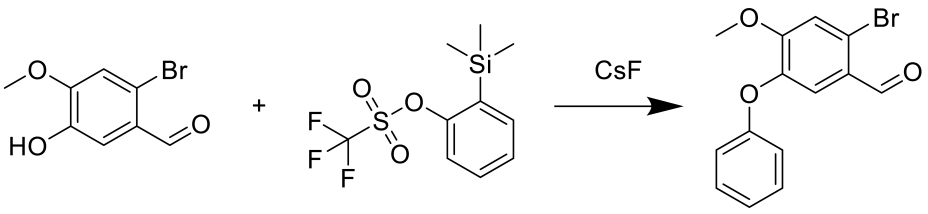
42 **45**

X= Br, I

Scheme 37 Attempted Buchwald-Hartwig cross coupling reaction to form **45**

Nonetheless, both reactions failed to form compound **45**, prompting us to explore alternative synthetic routes for its preparation.

Further research led us to a publication by Liu *et al*.[144], which describes a facile O-arylation of phenols using *ortho*-silylated aryl triflates and CsF (resulting in an *in situ* formed aryne) in acetonitrile (MeCN). To evaluate this method on the highly substituted compound **42**, we employed 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as the aryl triflate as shown in Scheme 38.

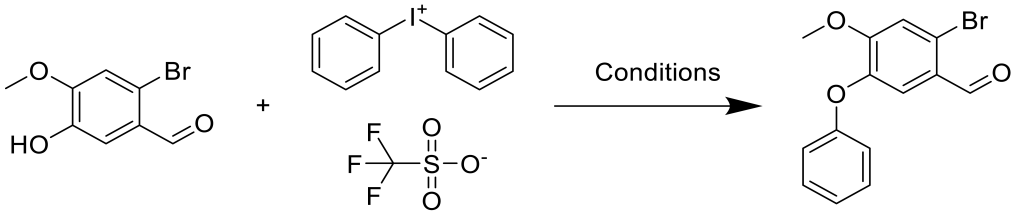


42 **45**

Scheme 38 Alternative reaction to form **45**

Reaction monitoring *via* TLC and ASAP indicated complete consumption of starting material **42** but the formation of multiple undesired byproducts complicated the purification of compound **45**. Given these challenges, this approach is not suitable for the synthesis of diaryl ether **45**, as the purification efficiency is insufficient for proceeding to the subsequent reaction.

Another approach to the synthesis of diaryl ethers was published by Hillmann in 1956 for the preparation of levothyroxine.[145] In this method, the author utilized diaryliodonium salts as key reagents. Inspired by this type of reaction, we identified a publication by Jalalian *et al*.[146], which systematically evaluates various diaryliodonium salts and bases for the arylation of oxygen nucleophiles. Our results are listed below in Table 5:



42 **45**

Entry	Solvent	Base (eq)	Result
1	THF	*t*-BuOK (1.1)	Decomposition
2	DMF	K_2CO_3 (2)	Multiple products
3	THF	K_2CO_3 (2)	Full conversion

Table 5 Results monitored by TLC and ASAP, all reactions were carried out at RT for 12 hours. 1.0 eq. of **42** and 1.2 eq. of the diaryliodonium salt

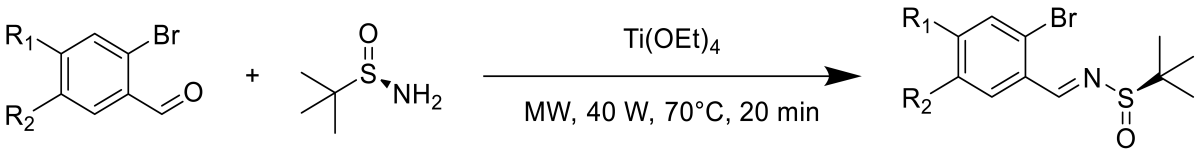
Entry 1 was conducted following the optimized conditions of Jalalian *et al*.[146] This resulted in the decomposition of compound **42** into multiple unidentified products. Based on the previously employed Williamson ether synthesis, we attempted to replicate its conditions (entry 2) to achieve comparable results. Entry 3, which combined elements of both approaches, yielded the best outcome according to TLC analysis, showing complete consumption of compound **42**. After purification of diaryl ether **45** *via* FCC, a yield of 21% was obtained. Although TLC analysis suggested a significantly higher yield, the challenges associated with purifying aldehydes *via* FCC are well-documented. A specialized workup procedure, based on the reactivity of aldehydes with sodium bisulfite, as described by Boucher *et al*.[147], was applied in an attempt to improve the yield. However, this approach resulted in significant product loss

rather than an improved yield. Consequently, we decided to use compound **45** without further purification.

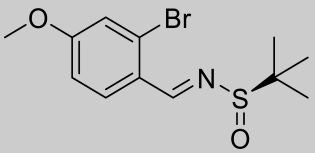
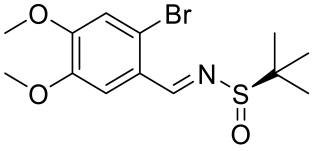
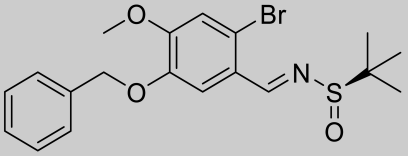
The synthesis of the ether derivatives was a necessary initial step in our synthetic route, as the presence of a free phenol would render the subsequent addition of Grignard reagents unfeasible. Without prior etherification, the highly nucleophilic Grignard reagent would preferentially react with the acidic hydroxyl group of the phenol, leading to unwanted side reactions and reduced efficiency. Alternatively, a protection and deprotection strategy could have been employed to temporarily mask the phenol functionality. This would introduce additional synthetic steps, potentially decreasing the overall yield and efficiency of the process unless the desired final THIQ is a phenol. This phenol could then be synthesized by simple cleavage of the protection group.

4.10 Condensation of ether-substituted 2-bromobenz-aldehydes with enantiomerically pure Ellman's reagent

With 2-bromo-4-methoxybenzaldehyde (**41**) and the successfully synthesized ether compounds **43**, **44** and **45**, the following step is the condensation with enantiomerically pure (*R*)-(+)-*tert*-butylsulfinamide to achieve the corresponding *N*-sulfinylimines **46**, **47**, **48** and **49**. Using the microwave assisted method of Collados *et al.*[101], these compounds were synthesized in excellent yields of: **46** (100%), **47** (96%), **48** (97%) and **49** (51% over 2 steps) (Scheme 39, Table 6).



Scheme 39 General procedure to synthesize *N*-sulfinylimines

Aldehyde	R_1	R_2	Product	Structure	Yield
41	-OCH_3	-H	**46**		100%
43	-OCH_3	-OCH_3	**47**		96%
44	-OCH_3	-OBn	**48**		97%

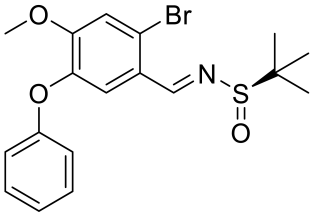
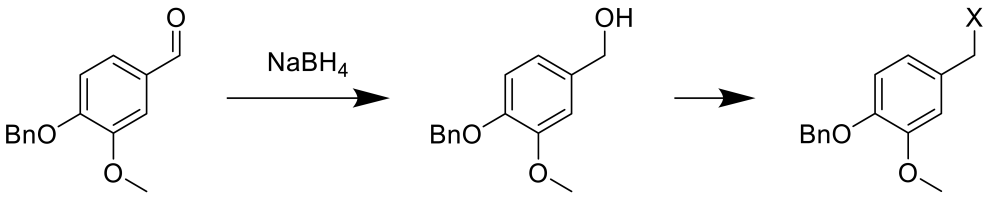
45	-OCH_3	-OPh	**49**		51% (over 2 steps)

Table 6 Resulting *N*-sulfinylimines

4.11 Synthesis of organometallic reagents

4.11.1 Preparation of benzyl halides

After successfully synthesizing the required ether-substituted bromobenzaldehydes and the corresponding *N*-sulfinylimines, the subsequent phase of the experimental procedure involved the modification of the benzyl Grignard reagent to generate further ring-substituted reagents. To synthesize the desired Grignard reagent, an appropriately substituted benzyl halide is required. The benzyl halides were prepared from substituted benzaldehydes through a two-step process (Scheme 40). First, the benzaldehyde was reduced to the corresponding benzyl alcohol. Subsequently, the benzyl alcohol was converted into the benzyl halide *via* a halogenation reaction. This transformation was essential to ensure the successful formation of the Grignard reagent, as the halide serves as the key precursor for the organometalic species. In our study, both benzyl bromides and chlorides were synthesized. These halides were chosen due to their varying reactivity in Grignard reagent formation, with benzyl bromides generally exhibiting higher reactivity compared to their chloride counterparts.



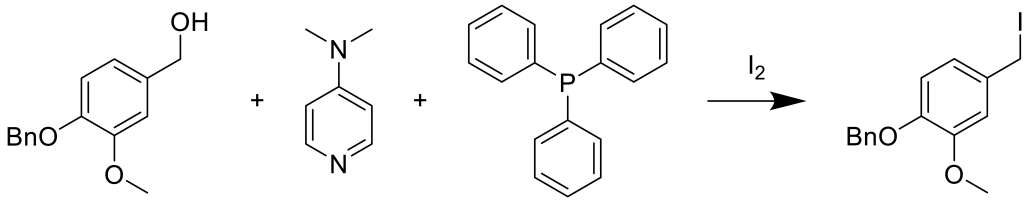
50: X=Cl
51: X=Br

Scheme 40 Two-step synthesis of the benzyl halide. By employing $SOCl_2$ in the second step, the chlorine substitution is achieved while with PBr_3 the bromine compound is synthesized

The reduction of the substituted benzaldehyde was carried out using 1.2 equivalents of $NaBH_4$ in MeOH at 0°C. This mild and selective reducing agent enabled the efficient conversion of the aldehyde to the corresponding benzyl alcohol. Following the completion of the reaction, a standard aqueous work-up with water and DCM was performed to extract the organic product. The organic phase was subsequently evaporated to dryness, and the resulting crude benzyl alcohol was utilized directly in the next step without further purification.

For the halogenation reaction, the crude alcohol was dissolved in DCM, and the appropriate halogenating reagent – either thionyl chloride ($SOCl_2$) for benzyl chloride **50** synthesis or phosphorus tribromide (PBr_3) for benzyl bromide **51** synthesis – was added dropwise at 0°C. These reagents efficiently converted the alcohol into the corresponding benzyl halides under mild conditions. Notably, all reactions proceeded with quantitative yields, eliminating the need for further purification before use in subsequent synthetic steps.

To synthesize the benzyl iodide **52** from the benzyl alcohol, a method reported by Yoshida *et al*.[148] for alkyl alcohols was employed using PPh_3, 4-DMAP and iodine (Scheme 41). This procedure is similar to an appel reaction.



52

15%

Scheme 41 First synthesis of the benzyl iodide **52**

Due to the requirement for FCC and the relatively low yield of only 15%, this method was not pursued further. The need for extensive purification, coupled with the poor efficiency of the reaction, rendered this approach impractical for large-scale synthesis. Consequently, alternative methods for benzyl iodide preparation were considered to improve both yield and practicality. As an alternative to the low-yielding iodination method, a Finkelstein reaction was attempted, following the procedure reported by Ley *et al*.[149] for benzyl bromide. This approach used the previously synthesized benzyl bromide derivative **51** as the starting material and involved a nucleophilic halide exchange with sodium iodide (NaI) in dry acetone. The reaction should proceed efficiently, driven by the precipitation of sodium bromide (NaBr), and yielded the corresponding benzyl iodide. In our study, even with the use of molecular sieves, the reaction conditions were not sufficiently dry to induce the precipitation of NaBr. The presence of residual moisture likely hindered the efficient conversion of the benzyl bromide derivative to benzyl iodide derivative by preventing the precipitation of NaBr. Since the Finkelstein reaction relies on a strictly anhydrous environment to drive the halide exchange *via* salt precipitation, the persistence of moisture in the reaction medium prevented the desired product formation. Considering the results of Section 4.11.2.2, the synthesis of the benzyl iodide **52** was not further pursued.

4.11.2 Grignard reagents

As a versatile chemical tool, Grignard reagents are highly valuable in organic synthesis due to the reversed polarity (Umpolung) of the carbon atom compared to the corresponding benzyl

halide. In the benzyl halide, the carbon bonded to the halogen is electrophilic, as the halogen withdraws electron density. Upon formation of the Grignard reagent, the carbon-magnesium bond introduces a nucleophilic character to the benzyl carbon. This polarity switch transforms the carbon into a strong nucleophile, capable of attacking electrophilic centers such as carbonyl groups (aldehydes, ketones, esters, etc.), epoxides or imines, including *N*-sulfinylimines.

This reactivity makes Grignard reagents indispensable for forming carbon-carbon bonds, enabling the construction of more complex molecular architectures (Figure 10). For example, they can be used to synthesize alcohols, carboxylic acids, or extended carbon chains through addition reactions. The ability to generate these reagents from readily available benzyl halides further enhances their utility in synthetic chemistry. Despite the challenges in handling (e.g., sensitivity to moisture and air), their versatility and reactivity make Grignard reagents a cornerstone of organic synthesis.

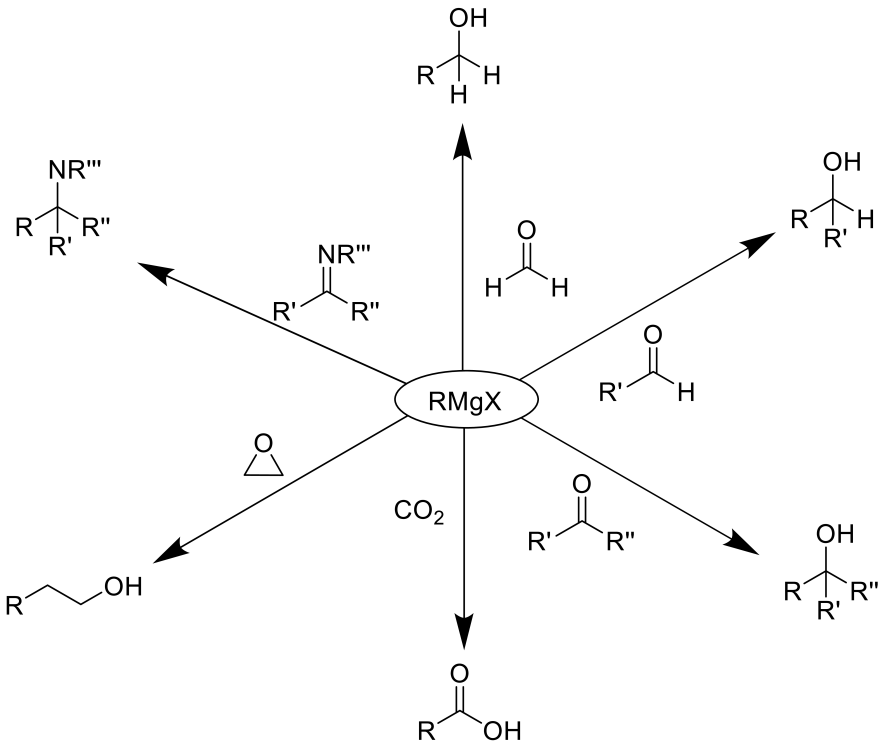
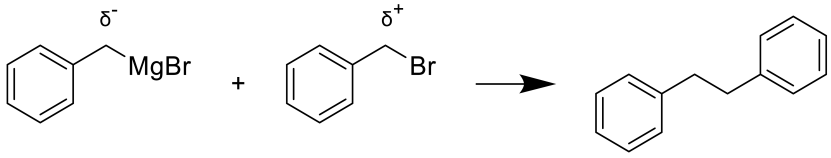


Figure 10 Overview of several Grignard reactions. X=Cl, Br, I

4.11.2.1 Wurtz product

The formation of Wurtz-type coupling products (Scheme 42) represents a significant challenge in the synthesis of benzyl Grignard reagents. This side reaction occurs when the benzyl halide reacts with the nascent Grignard reagent, resulting in the formation of unwanted dimerized byproducts. This coupling reaction is particularly problematic in the synthesis of benzyl Grignard reagents due to the inherent reactivity of the benzyl halide and the intermediate organomagnesium species, which can readily participate in such side reactions.



Scheme 42 Formation of a Wurtz product from a benzyl Grignard compound

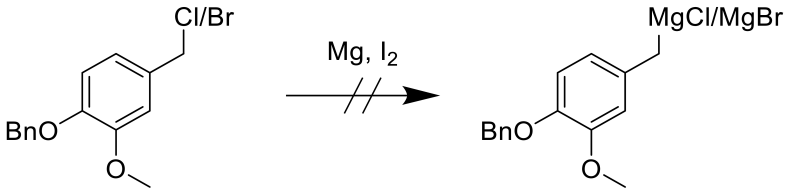
The formation of Wurtz products is influenced by several factors, including the concentration of the benzyl halide, the reaction temperature, and the presence of impurities or moisture. High concentrations of the benzyl halide increase the probability of coupling, as the likelihood of collisions between the benzyl halide and the Grignard reagent is heightened. Elevated temperatures further exacerbate this issue by accelerating the reaction kinetics, thereby promoting the formation of the undesired bibenzyl product. Additionally, trace amounts of water or oxygen can deactivate the Grignard reagent, leading to incomplete conversion of the benzyl halide and further favouring side reactions such as Wurtz coupling.

To mitigate the formation of Wurtz products, careful optimization of the reaction conditions is essential. This typically involves using dilute solutions of the benzyl halide to reduce the probability of coupling reactions. Maintaining low reaction temperatures is also critical to slow down the kinetics of the side reaction and favour the formation of the desired Grignard reagent. Furthermore, ensuring rigorously anhydrous and oxygen-free conditions is paramount, as even trace amounts of moisture or oxygen can lead to the decomposition of the Grignard reagent and promote the formation of side products. The use of high-purity solvents and reagents, along with the implementation of inert atmosphere techniques, is therefore necessary to achieve successful synthesis. Despite these precautions, the formation of Wurtz products remains a persistent issue in the synthesis of benzyl Grignard reagents.

4.11.2.2 Synthesis of Grignard reagents

To circumvent the formation of the Wurtz product, we adopted a method published by Kadam *et al*.[150], which involves the use of benzyl bromide or benzyl chloride, Mg turnings and iodine in Et_2O. The authors systematically investigated the influence of the solvent on the synthesis of Grignard reagents from benzyl bromide and benzyl chloride, demonstrating that the choice of solvent significantly impacts the reaction efficiency and selectivity. Their findings revealed that Et_2O or 2-Metyhltetrahydrofuran (2-MeTHF) yielded the best results, providing optimal conditions for the formation of the benzyl Grignard reagent while minimizing side reactions such as Wurtz coupling. The reaction outcomes were analyzed using GC-MS, allowing for precise determination of the Grignard reagent yield and purity. While benzyl chloride and benzyl bromide are liquids and readily form a solution as described in the published method, compounds **50** and **51** are solids and must be dissolved prior to their addition to the reaction mixture containing iodine, Mg turnings and Et_2O (Scheme 43). However, both benzyl halides **50** and **51** exhibited poor solubility in Et_2O, complicating their direct use under the reported

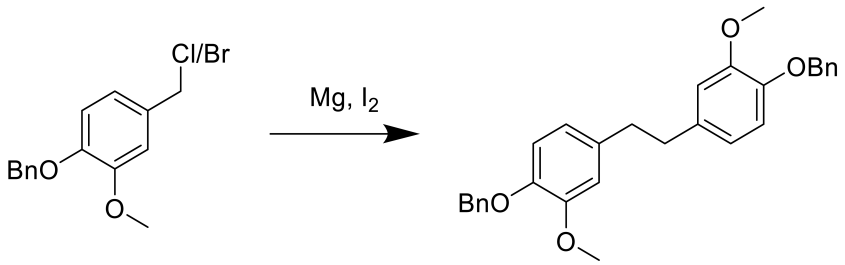
conditions. To address this issue, an increased volume of solvent was required to achieve complete dissolution of our halide compounds, ensuring uniform mixing and efficient reaction initiation. This modification was necessary to maintain a homogeneous reaction environment, facilitate optimal contact between the reactants, and prevent localized precipitation, which could otherwise hinder the formation of the desired Grignard reagent.



50/51

Scheme 43 Attempted formation of the desired benzyl Grignard reagent using **50** or **51**

Following the method described by Kadam *et al.*[150], no exothermic reaction was observed, indicating that the initiation of benzyl Grignard reagent formation did not occur under the reported conditions. In an attempt to activate the reaction, the mixture was heated to 35°C, corresponding to the boiling point of Et_2O. However, this thermal activation led predominantly to the formation of the undesired Wurtz coupling product **53** (Scheme 44), suggesting that the elevated temperature promoted side reactions rather than facilitating the intended Grignard reagent synthesis.



50/51 **53**

Scheme 44 Formation of the dimerized Wurtz product **53**

The formation of the Wurtz product **53** under these conditions highlights the challenges associated with the synthesis of benzyl Grignard reagents from less reactive or sterically hindered substrates. Elevated temperatures, while intended to initiate the reaction, likely promoted the coupling of the benzyl halide with the nascent Grignard intermediate, favouring the formation of the bibenzyl derivative.

An alternative approach for the synthesis of benzyl Grignard reagents was described by Metzger *et al.*[151] within the Knochel research group. The authors employed dry THF as the solvent and utilized lithium chloride as an additive. Although the benzyl halides **50** and **51** demonstrated good solubility in THF, titration of the supernatant from the mixture of halide, Mg and LiCl in dry THF into a solution of iodine and lithium chloride in dry THF produced no observable change of colour in the iodine solution.[152] Analysis *via* ASAP revealed the

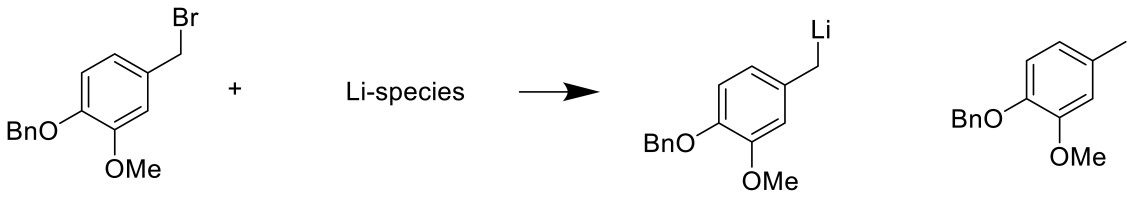
formation of bibenzyl **53**, indicating that while the desired Grignard reagents were initially generated, they rapidly underwent Wurtz coupling, resulting in the dimerization product. Attempts to control this side reaction by cooling the reaction mixture to 0 °C were ineffective, as Wurtz coupling persisted. Further lowering the temperature to -21°C and -78°C impeded the activation of the Grignard reagent synthesis entirely.

The presence of an ether substituent in the *para* position of benzyl halides can complicate the synthesis of benzyl Grignard reagents. Ether groups are strong electron-donating substituents through resonance, increasing the electron density on the aromatic ring and at the benzylic position. This heightened electron density, caused by the +M effect, increases the reactivity (nucleophilicity) of the Grignard reagent, potentially leading to side reactions such as Wurtz-type coupling, where dimerization occurs. Additionally, the increased electron density may hinder effective coordination between the magnesium and the benzyl halide, disrupting the formation of the Grignard reagent. Therefore, the synthesis of benzyl Grignard reagents with *para*-ether substituents often requires precise control of reaction conditions, such as temperature and the use of additives, to suppress side reactions and achieve the desired product.

Despite systematic modifications to reaction parameters, including variations in solvent, temperature, and reagent composition, a viable method to halt the reaction mixture at the benzyl Grignard reagent stage could not be established. The reaction consistently proceeded directly to the undesired bibenzyl **53**, indicating rapid and uncontrollable homo-coupling. Due to these persistent challenges, the decision was made to replace Mg with Li as the metal of choice, aiming to circumvent the issues associated with Grignard reagent formation and stability.

4.11.3 Organolithium reagents

According to a publication by Truong *et al*.[153], the diastereoselective 1,2-addition of aryllithium reagents to *N*-sulfinylimines represents a viable reaction pathway. In contrast, our approach aimed to synthesize benzyllithium reagents through a lithium-halogen exchange reaction. Such exchange reactions can be performed using various organolithium reagents, including *n*-BuLi, *sec*-BuLi, *tert*-BuLi, and (for corresponding organomagnesium product) turbo-Grignard. These reagents differ in their reactivity and selectivity, influencing the efficiency and outcome of the lithium-halogen exchange process. An insertion reaction with Li powder is also a possibility to synthesize the desired benzyllithium compound **54**. Commonly, those exchange reactions were executed with the benzyl bromide **51** or iodide **52** compound. The results are presented in Table 7.



51 **54** **55**

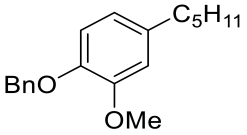
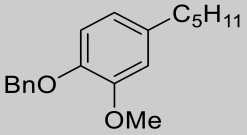
Entry	Li	Conditions	Result
1	powder	0 °C, 1.0 eq. **51**, 2.2 eq. Li	**54** (33% conversion) and **51** (66% starting material)
2	*n*-BuLi	-78 °C,1.0 eq. **51**, 1.2 eq. *n*-BuLi (2.5 M in hexanes)	
3	*sec*-BuLi	-78 °C, 1.0 eq. **51**, 1.2 eq. *sec*-BuLi (1.4 M in cyclohexane)	
4	*tert*-BuLi	-78 °C, 1.0 eq. **51**, 2.5 eq. *tert*-BuLi (1.7 M in pentane)	**54** (25% conversion) and **51** (75% starting material)
5	iPrMgCl*LiCl (Turbo Grignard)	-78 °C to reflux, 1.0 eq. **51**, 1.2 eq. Turbo grignard (1.3 M in THF)	No conversion

Table 7 Attempted conversion to the desired benzyllithium reagent **54**. Conversion determined by GC-MS areas of the resulting quenched (with water) toluene derivative **55**

The magnesium-halogen exchange reaction using turbo Grignard[154] yielded no conversion to the desired benzyl Grignard reagent, even under reflux conditions. Instead, the starting material **51** decomposed into multiple side products. When *n*-BuLi and *sec*-BuLi were employed, C-butylation of the benzyl halide **51** to give pentylbenzenes was observed, a common side reaction in such exchange processes.[155] To circumvent butylation, the sterically hindered *tert*-BuLi was successfully utilized, enabling the formation of the benzyllithium reagent **54** (25% conversion). However, increasing the equivalents of *tert*-BuLi did not improve the conversion. The most promising results, with a conversion of 33%, were achieved using lithium powder for the insertion reaction. Unfortunately, optimization and scaling-up attempts with both *tert*-BuLi and lithium powder proved inconsistent and difficult to control, leading to unreliable outcomes.

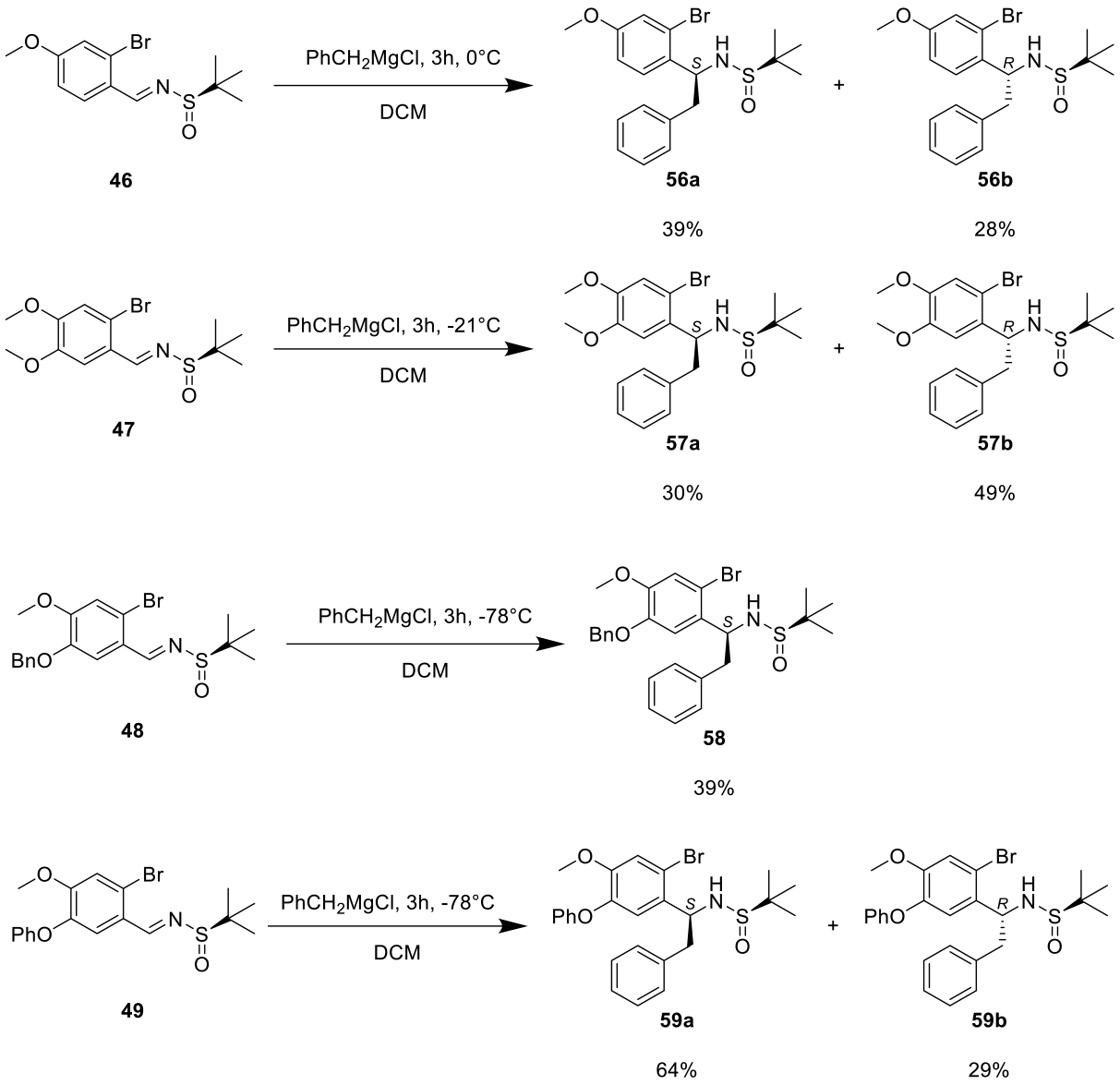
4.11.4 Summary of the investigations on benzylic organometallic reagents

Although the benzylic organometallic reagents could be synthesized, we decided not to pursue further investigation into the variation of the organometallic reagents. Consequently, we opted to synthesize the target 1-benzyltetrahydroisoquinolines using commercially available benzyl Grignard reagents. This decision was driven by the impracticality of developing and optimizing individual protocols for each substrate requiring organometallic transformation, which would have significantly impeded the progress of this work.

Furthermore, we aimed to extend our structure-activity relationship (SAR) analysis of this chemotype to include five-, seven-, and eight-membered ring analogues of ring A of the tetrahydroisoquinoline moiety. In the case of the seven-membered analogues, we sought to mimic the benzodiazepine structure, a well-known pharmacologically active class of compounds. A detailed discussion of this topic is presented in Section 4.17.

4.12 Addition of the benzyl Grignard reagent

With the *N*-suflinylimines **46**, **47**, **48** and **49**, synthesized as described in Section 4.10 in hands, the subsequent step involved the diastereoselective 1,2-addition reaction of a benzyl Grignard reagent. Following a modified literature procedure reported by Reddy *et al*.[106], where we substituted benzylmagnesium bromide solution with a solution of benzylmagnesium chloride in THF, which was added dropwise to a solution of the *N*-sulfinylimines in DCM at -78°C, yielding the corresponding *N*-sulfinylamines **56a** (yield: 39%), **56b** (yield: 28%), **57a** (yield: 30%), **57b** (yield: 49%), **58** (yield: 39%), **59a** (yield: 64%), **59b** (yield: 29%). In all cases, both diastereomers were obtained but could be separated *via* FCC to yield the two enantiomerically pure compounds. The sole exception was the benzyl ether derivative, for which only the (*S*)-configured product **58** was isolated in pure form, while the other fraction was obtained as a mixture of (*R*) and (*S*) enantiomers. All reactions are shown in Scheme 45. The absolute configuration was determined according to Section 4.8.1 *via* ^{1}H-NMR spectroscopy.



Scheme 45 Addition of benzylmagnesium chloride solution to *N*-sulfinylimines

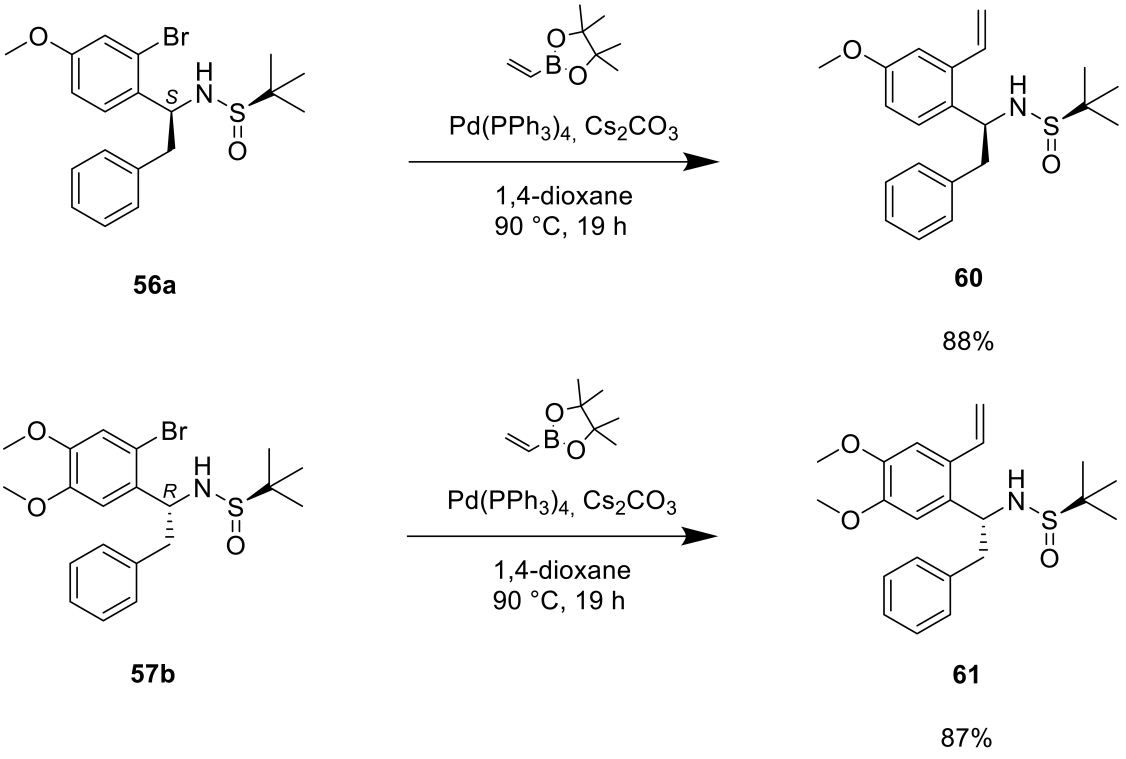
Due to technical issues, the synthesis of compounds **56a**/**56b** and **57a**/**57b** had to be carried out at 0°C or -21°C instead of the optimal reaction temperature of -78°C. This deviation from the optimal reaction conditions had a detrimental impact on both the overall yield and the diastereoselectivity of the reaction. The higher temperatures resulted in reduced control over the reaction kinetics and stereochemical outcomes, leading to diminished efficiency. Furthermore, the relatively low yield of *N*-sulfinylamine **58** can be attributed to the incomplete separation of enantiomers during FCC, resulting in mixed fractions of the (*S*)- and (*R*)-configured products and consequently lowering the overall efficiency of the purification process. An interesting aspect of the FCC separation was that the steric bulk and size of the ether substituent at the *para* position relative to the bromine significantly influenced the separation process. Specifically, as the steric hindrance and size of the *para*-substituted ether group increased, the separation became more difficult. This trend highlights the critical role of

steric factors in the chromatographic behaviour of these molecules, making the isolation of individual compounds increasingly challenging.

4.13 Suzuki cross coupling

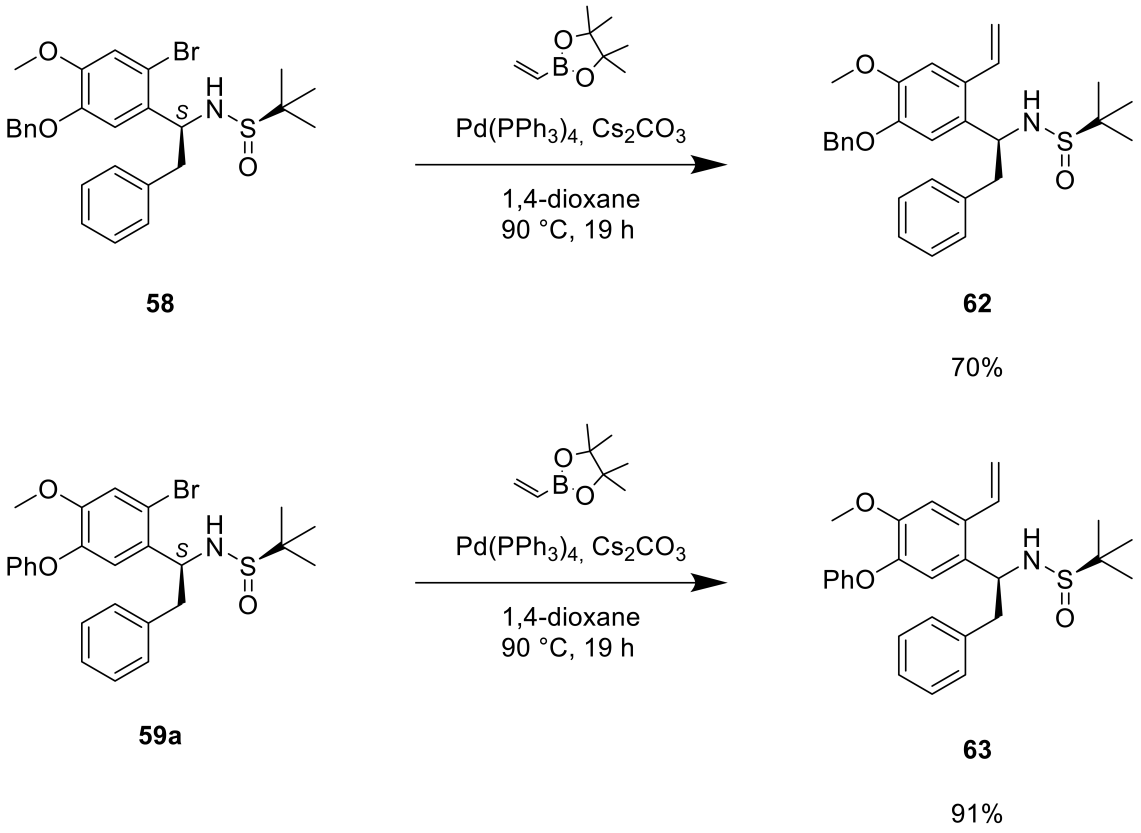
In the next step, the bromine substituent on the *N*-sulfinylamines is to be replaced with a vinyl group to enable the synthesis of the desired styrene derivatives. This transformation was effectively achieved *via* a Suzuki cross-coupling reaction (as discussed in Section 4.4.1), a widely utilized method in organic synthesis. The Suzuki cross-coupling reaction, first reported by Miyaura and Suzuki in 1979[156], represents a robust and versatile strategy for forming carbon-carbon bonds between aryl halides and organoboron compounds.

In our study, tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) was employed as the catalyst, vinylboronic acid pinacol ester as boronic acid derivative, caesium carbonate (Cs_2CO_3) as base and anhydrous 1,4-dioxane as solvent. The conducted reactions are depicted in Scheme 46.



56a → **60** 88%

57b → **61** 87%



Scheme 46 Performed Suzuki-cross coupling reactions resulting in styrene derivatives

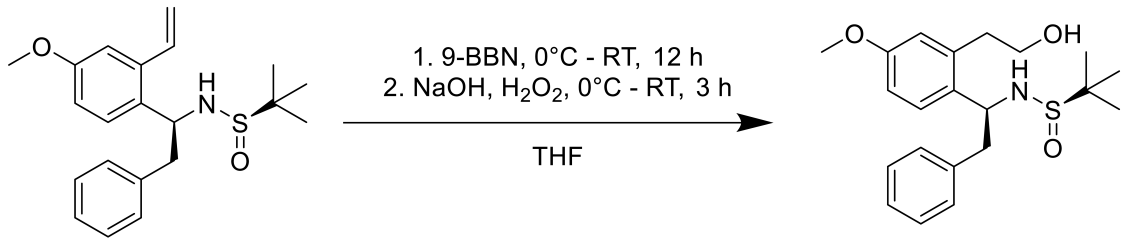
The reactions resulted in the styrene derivatives **60** (yield: 88%), **61** (yield: 87%), **62** (yield: 70%) and **63** (yield: 91%) with high to excellent yields. As outlined in the preceding section, dimethoxy compound **57b** was synthesized in higher yields compared to **57a**. Consequently, **57b** was selected as the substrate for the Suzuki cross-coupling reaction. By utilizing the (*R*)-configurated compound **57b**, we were also able to pursue possible different outcomes of the following reactions. This parallel approach of employing (*S*)- and (*R*)-configurated starting materials enabled us to evaluate the applicability of our synthetic route to ether-substituted THIQs in both configurations. Such a comparative analysis provides valuable insights into the versatility and generality of the synthetic methodology, particularly in the context of stereochemical and functional group variations.

4.14 Hydroboration and oxidation of styrene derivatives

In this section, the hydroboration of styrene derivatives and subsequent oxidation of the resulting organoborane intermediates are described, as discussed earlier in Section 4.5.1.
Due to the pronounced steric hindrance imposed by the 9-BBN framework, the boron atom selectively attaches to the less substituted (terminal) carbon of the styrene derivative, ensuring exclusive formation of the anti-Markovnikov product. This regioselectivity is further reinforced by electronic effects, as the π-electron density of the aromatic ring disfavours boron addition at the benzylic position. The resulting organoborane intermediates were not isolated, as the

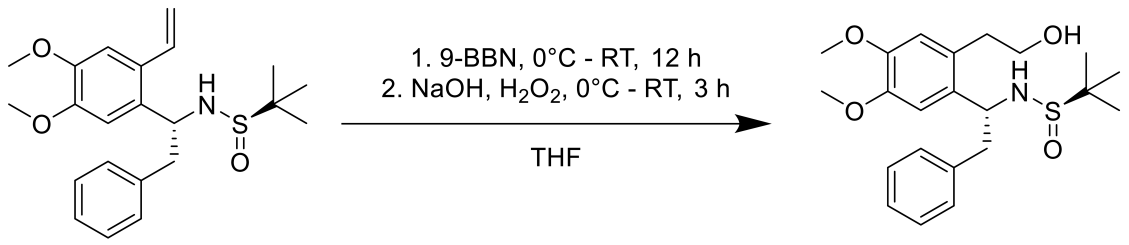
reaction proceeds quantitatively under mild conditions, and the crude products were directly subjected to oxidation without purification.

The oxidation step was performed using an alkaline hydrogen peroxide solution (H_2O_2/NaOH), which smoothly converts the organoborane species into the corresponding primary alcohol *via* a sequential borate ester formation and 1,2-alkyl migration. This transformation occurs under retention of configuration at the migrating carbon, consistent with the well-established mechanism of peroxide-mediated boron oxidation. The overall two-step sequence – hydroboration followed by oxidation – provides an efficient and reliable synthetic route to anti-Markovnikov alcohols in high yields, with minimal byproduct formation.[121] The robustness of this methodology is further underscored by its compatibility with a variety of substituted styrenes, demonstrating broad functional group tolerance and scalability. The results of these reactions are presented in Scheme 47.



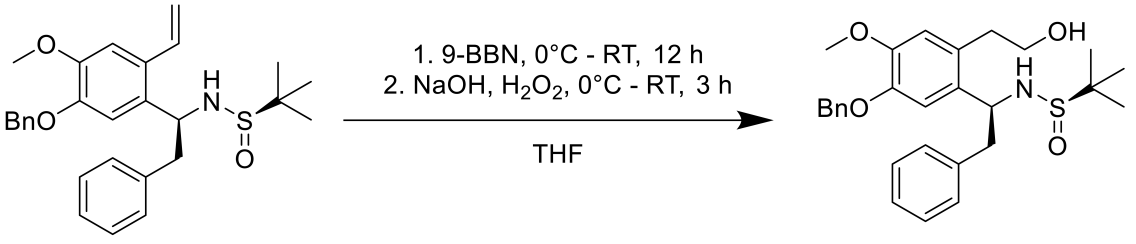
60 **64**

92%



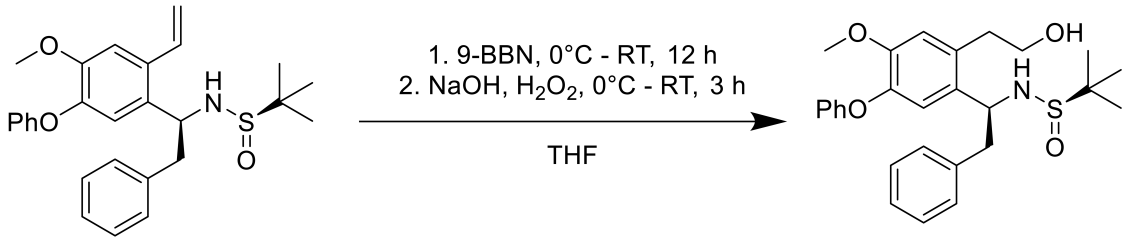
61 **65**

70%



62 **66**

71%



63 **67**

77%

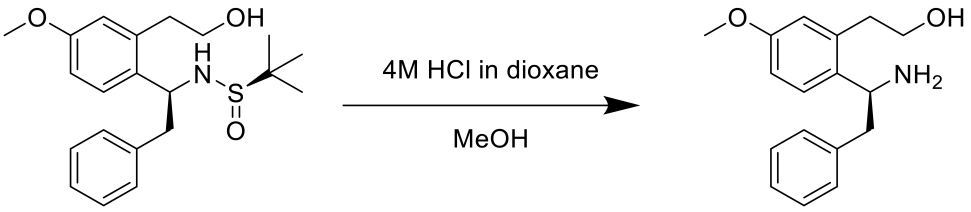
Scheme 47 Performed hydroboration – oxidation reactions to synthesize primary alcohols

All executed reactions formed the desired primary alcohols **64** (yield: 92%), **65** (yield: 70%), **66** (yield: 71%) and **67** (yield: 77%) in good yields. The styrene derivatives **60**, **61**, **62** and **63** were fully converted into the organoborane intermediates within 12 hours, as monitored by TLC and ASAP analysis. The crude intermediates were then oxidized by treatment with alkaline hydrogen peroxide solution. After 3 hours, the crude products were purified by FCC, isolating the desired anti-Markovnikov alcohols in high yields and purities.

4.15 Deprotection of Ellman's auxiliary

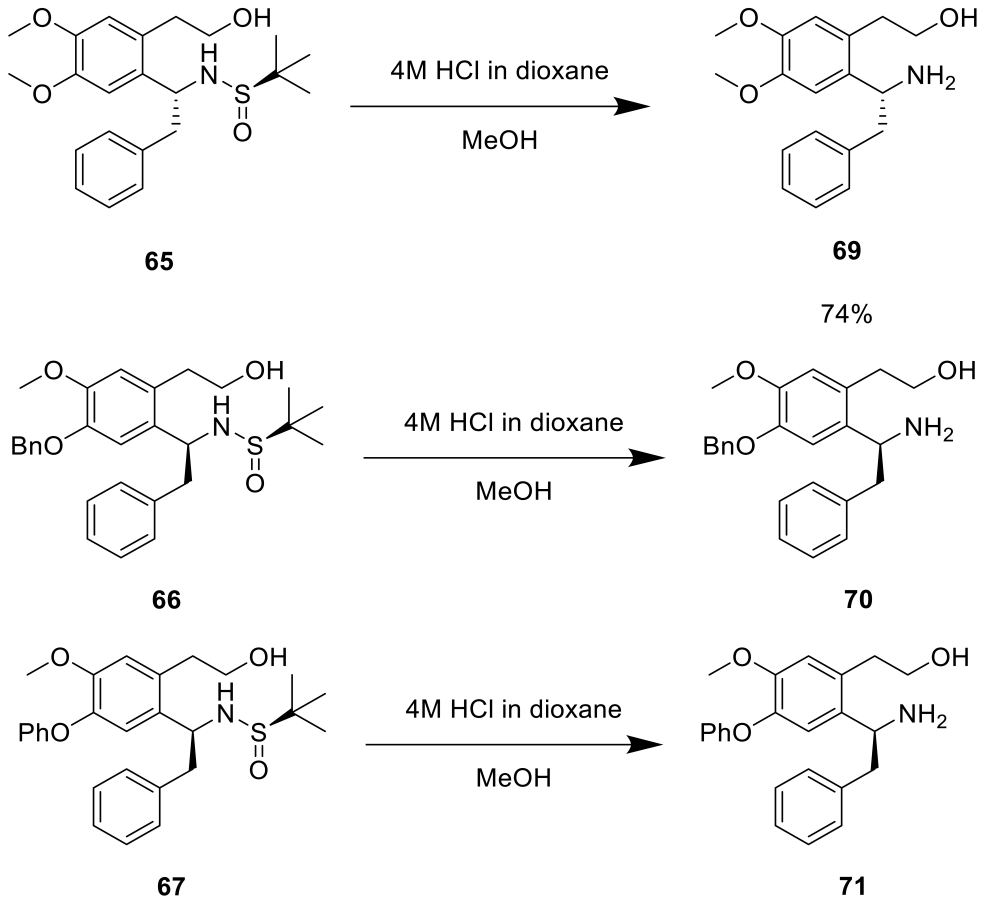
As discussed in Section 4.5.2, cyclization to form the target THIQ framework cannot proceed without prior removal of Ellman's sulfinamide auxiliary. Deprotection of this chiral group is conventionally achieved under acidic conditions.

In alignment with the experimental observations detailed in Section 4.3 and consistent with the comprehensive review article of Robak *et al.*[92] the optimized protocol employs 4M HCl in dioxane as the acidic cleavage reagent, with methanol as the solvent. This system has been demonstrated to efficiently cleave the sulfinyl group while maintaining the integrity of sensitive functionalities.



64 **68**

42%



Scheme 48 Cleavage of Ellman's auxiliary

As illustrated in Scheme 48, the primary alcohols **64**, **65**, **66** and **67** were successfully converted into the corresponding aminoalcohols **68** (yield: 42%), **69** (yield: 74%), **70** and **71**. Due to the high polarity of the deprotected aminoalcohol products, FCC was not performed after each synthesis. Products **70** and **71** were emoployed in the subsequent reactions without further purification by FCC.

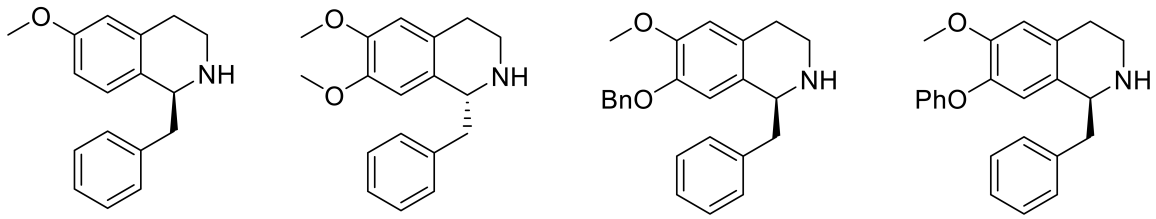
Instead, a workup procedure was implemented, which involved basifying the reaction mixture to a pH > 10 with 2M $NaOH_{(aq.)}$, followed by liquid-liquid extraction using water and DCM. After phase separation, the organic layer was evaporated to dryness, and the resulting crude aminoalcohols were directly utilized in subsequent steps.

The deprotection of Ellman's chiral auxiliary proceeds *via* an acid-catalyzed hydrolytic cleavage mechanism. Under the influence of 4M HCl in dioxane, protonation of the sulfinyl group occurs, increasing its electrophilicity and facilitating nucleophilic attack by methanol, depending on the reaction medium. This nucleophilic substitution leads to the cleavage of the C-S bond, generating the volatile *tert*-butanesulfinyl methyl ester.[92] Concurrently, the liberated amine undergoes protonation under the acidic conditions, yielding the corresponding ammonium salt. Upon basification with aqueous NaOH, the free amine is regenerated, allowing for its isolation and further synthetic application.

4.16 Ring closure *via* Mitsunobu type reaction

The last step of the synthesis is the ring closure to the desired enantiomerically pure THIQ by employing Tsunoda's reagent (CMBP). The general reaction is depicted in Section 4.6.1 in Scheme 17.

In accordance to this procedure, the enantiomerically pure THIQs **72** (yield: 83%), **73** (yield: 66%), **74** (yield: 60%) and **75** (yield: 61%) were successfully synthesized from the corresponding aminoalcohols in good yields, high purities and are illustrated in Scheme 49.



72 83%

73 66%

74 60%

75 61%

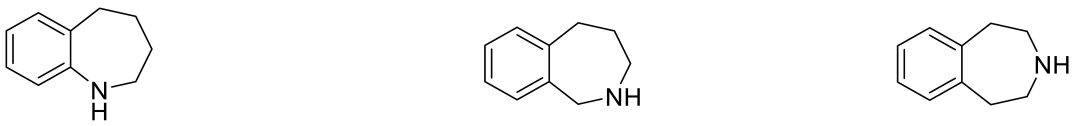
Scheme 49 Synthesized enantiomerically pure THIQs with several ether groups at Ring A

Following the successful synthesis of these THIQ derivatives, the subsequent objective was to expand the synthetic methodology to access enantiomerically pure five-, seven-, and eight-membered homologues of 1-benzyltetrahydroisoquinolines.

4.17 Tetrahydrobenzazepines

4.17.1 Overview of tetrahydrobenzazepines

Depending on the position of the nitrogen atom within the saturated seven-membered heterocycle fused to the benzenoid moiety, the resulting tetrahydrobenzazepine is classified as either a tetrahydro-1-benzazepine, tetrahydro-2-benzazepine, or tetrahydro-3-benzazepine (Scheme 50).



tetrahydro-1-benzazepine tetrahydro-2-benzazepine tetrahydro-3-benzazepine

Scheme 50 Benzazepine structures

Over the past decades, representatives of all these compounds have been demonstrated to exhibit noteworthy biological and pharmacological activities across a broad range of substitution patterns, often necessitating specifically tailored synthetic approaches[157-159]. Given that the central focus of this thesis lies on substituted 1-benzyltetrahydro-2-

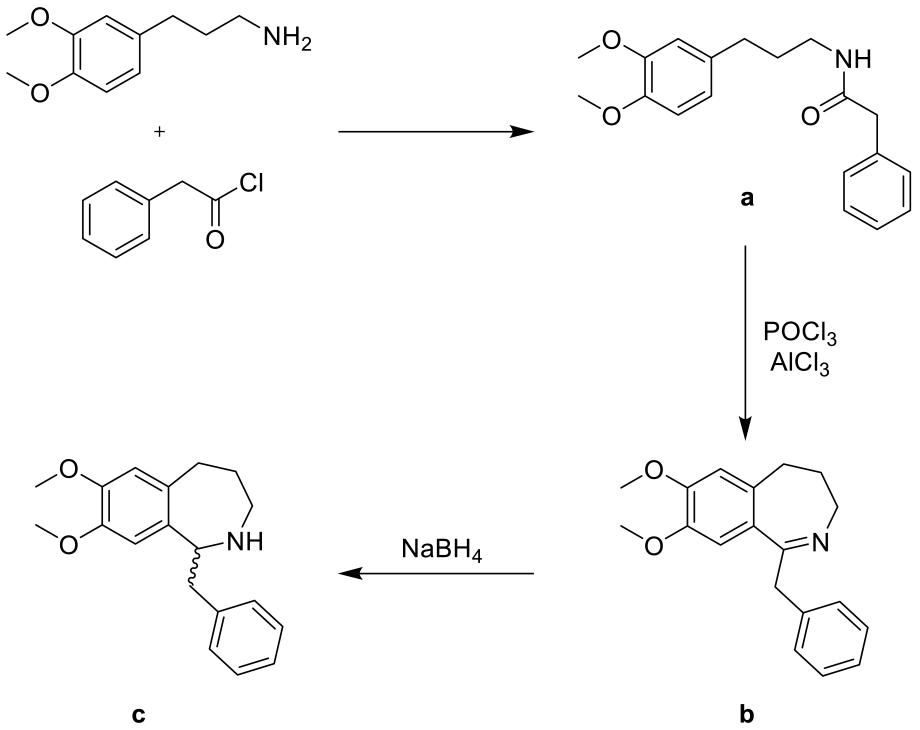
benzazepines, key synthetic strategies for their preparation will be discussed in the subsequent sections.

4.17.2 Synthesis of 1-benzyltetrahydro-2-benzazepines

The tetrahydro-2-benzazepine scaffold is structurally closely related to 1,2,3,4-tetrahydroisoquinoline, differing by only a single additional methylene group in the saturated heterocyclic ring. Consequently, classical synthetic approaches for tetrahydroisoquinolines have been adapted to achieve the synthesis of tetrahydro-2-benzazepines.

In 1976, Berney and Jauner[160] reported the synthesis of 1-benzyltetrahydro-2-benzazepines bearing methoxy substituents on the aromatic ring *via* Bischler-Napieralski cyclization. Their strategy involved the N-acylation of 3-phenylpropylamines with phenylacetyl chlorides to afford the corresponding amides (e.g., compound **a** in Scheme 51), which were subsequently cyclized to yield 4,5-dihydro-3*H*-2-benzazepines (**b**). Reduction of this imine intermediate furnished the target compound **c** (Scheme 51), while the secondary amine was further derivatized using the Eschweiler-Clarke methylation[160].

Although this method provides access to 1-benzyltetrahydro-2-benzazepines, a major limitation is that the final product is obtained as a racemic mixture.



Scheme 51 Synthesis of 1-benzyltetrahydro-2-benzazepines according to Berney and Jauner[160]

A related strategy utilizing the Bischler-Napieralski reaction for ring closure, but employing different reagents and incorporating alternative substituents on the aromatic moieties, was later reported by Clark *et al*.[161] However, in general, the application of the Bischler-Napieralski reaction has proven to be ineffective for aromatic systems lacking electron-donating groups.[162]

An alternative photochemical approach for the synthesis of unsubstituted 1-benzyltetrahydro-2-benzazepines *via* a radical mechanism was subsequently described by Lewis and Reddy.[163] However, their study primarily focused on investigating the general feasibility of this method rather than developing an enantioselective synthesis.

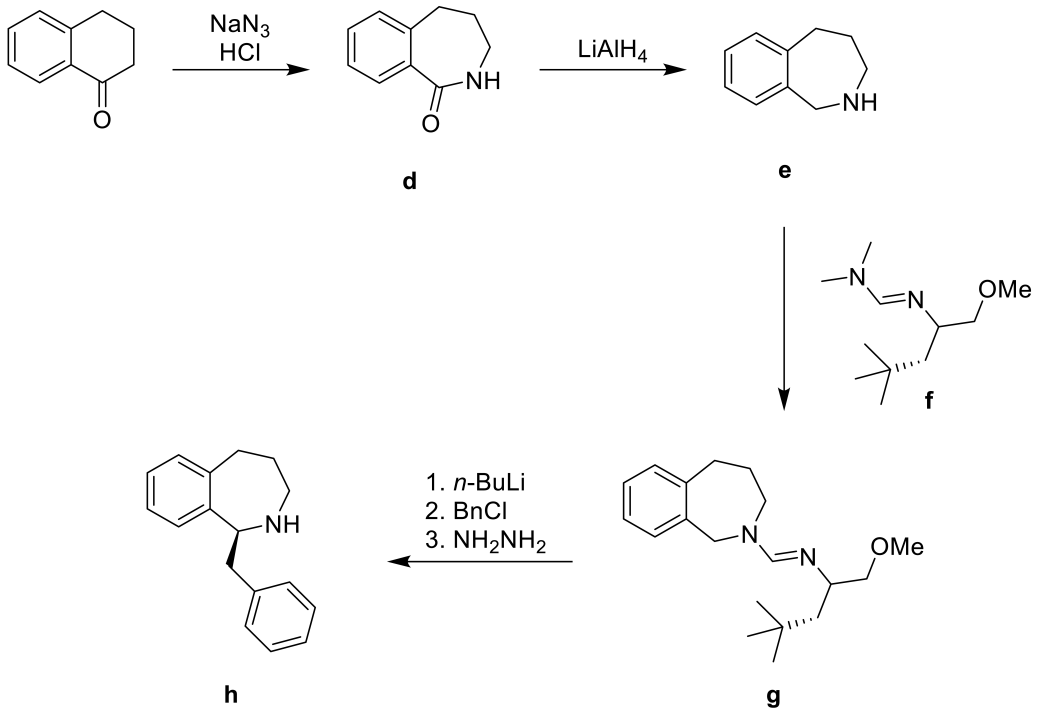
4.17.3 Asymmetric synthesis of 1-benzyltetrahydro-2-benzazepines

The inaugural enantioselective synthesis of 1-alkyltetrahydro-2-benzazepines was achieved in 1993 by the Meyers group.[162] Their methodology built upon their established expertise in chiral formamidine chemistry and previous accomplishments in the asymmetric synthesis of tetrahydroisoquinoline alkaloids.[164]

The synthetic route commenced with 1-tetralones, which underwent ring-expanding Schmidt reaction to produce a mixture of benzazepinone regioisomers. This transformation yielded two constitutional isomers: 2-benzazepin-1-one (**d**) and 1-benzazepin-2-one, which were successfully separated *via* FCC. Subsequent $LiAlH_4$ reduction afforded the unsubstituted tetrahydro-2-benzazepine (**e**) scaffold (Scheme 52).[162]

For the critical asymmetric functionalization, Meyers and coworkers adapted their proven tetrahydroisoquinoline methodology. The secondary amine was first converted to a chiral formamidine **g** using an amino acid-derived auxiliary **f**, which served dual purposes: first, enabling α-deprotonation and second, stabilizing the resulting carbanion through chelation control.[164] The generated nucleophile underwent alkylation with various electrophiles (e.g., benzyl chloride (BnCl)), followed by hydrazinolysis of the formamidine protecting group to deliver the target 1-substituted tetrahydro-2-benzazepines (**h**) (Scheme 52).

This seminal work demonstrated the successful translation of their asymmetric strategy from six-membered to the more conformationally constrained seven-membered ring systems, thereby expanding the scope of accessible chiral benzazepine architectures.[162]



Scheme 52 Asymmetric synthesis of 1-benzyltetrahydro-2-benzazepines according to Meyers and Hutchings[162]

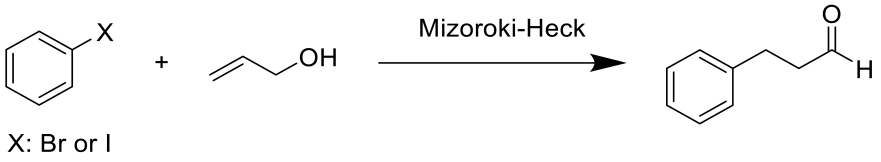
4.17.4 Ellman's auxiliary for the synthesis of enantiomerically pure 1-benzyltetrahydro-2-benzazepines

Although Ellman's auxiliary has been extensively employed in the synthesis of nitrogen-containing heterocycles[91] and chiral amines in general[90, 92], it has not yet been utilized for the preparation of 1-substituted tetrahydro-2-benzazepines.

Therefore, the Master's thesis of Mika Kintzel, conducted under my supervision, focused on developing an innovative *N-tert*-butylsulfinamide-mediated synthetic strategy. The experimental results obtained in this thesis work are presented and discussed in the following section.

Rather than introducing a C_2 unit *via* Suzuki cross-coupling (as discussed in Section 4.3 for 1-benzyltetrahydroisoquinolines), it was necessary to incorporate a C_3 building block to generate the required intermediate for cyclization. To achieve this, a Mizoroki-Heck reaction – a palladium-catalyzed transformation involving organic halides and olefins – was selected as a suitable approach, given its broad applicability in carbon-carbon bond formation.

Allyl alcohol, an important C_3 building block, has been demonstrated to participate as the alkene component in the Mizoroki-Heck reaction, leading to the formation of 3-arylpropanals (see Scheme 53), as isomerization can occur following the cross-coupling step leading to an allyl alcohol first.[165] Furthermore, studies have shown that, under certain catalytic conditions, it is possible to exert a degree of control over the selectivity between β-arylated carbonyl compounds and arylated allyl alcohol products.[166]

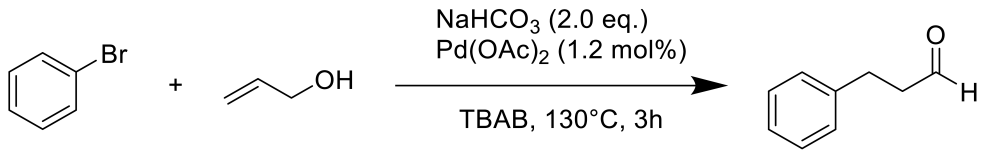


Scheme 53 Reaction scheme to access 3-arylpropanals

While conventional Mizoroki-Heck conditions employing palladium/phosphine ligand systems are well-established for this transformation and demonstrate tolerance toward various functional groups including fluorides, nitriles, and carboxylic acid esters on the aryl halide[167], alternative catalytic systems utilizing palladium nanoparticles derived from palladium(II) acetate in combination with ionic nitrogen species, such as ionic liquids or tetraalkylammonium salts[166] appear particularly promising. These systems have demonstrated comparable functional group tolerance while offering potential advantages in catalyst stability and reactivity. A comprehensive discussion of palladium nanoparticle/ionic nitrogen compound systems in cross-coupling reactions has been published by Chernyshev *et al.*[168] in a review article for detailed coverage of this topic.

4.17.5 Mizoroki-Heck reaction with aryl bromides

A procedure described by Calò *et al.*[166] was initially conducted using bromobenzene as a model substrate to assess whether the reported results could be reproduced and to determine the formation of 3-phenylpropanal (see Scheme 54). The reaction was carried out at 130°C, a temperature at which the ionic liquid tetrabutylammonium bromide (TBAB) remains in the liquid state. $Pd(OAc)_2$ was employed as catalyst and $NaHCO_3$ as base. Subsequent to the reaction work-up, analysis of the crude product by ^{1}H-NMR spectroscopy and TLC staining with 2,4-dinitrophenylhydrazine (DNPH) confirmed the formation of the target aldehyde. The yield of this reaction was not determined, as it only served as a model reaction.

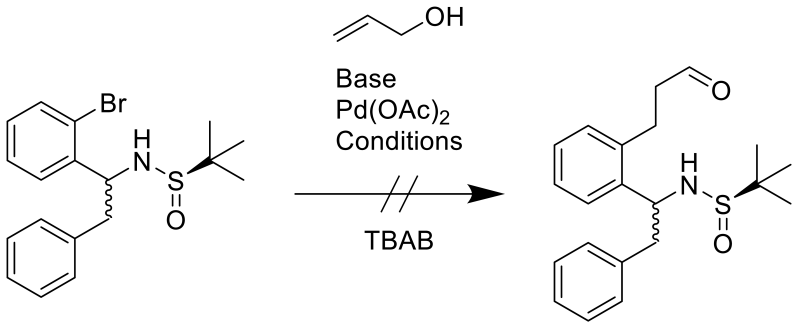


Scheme 54 Reaction scheme and conditions for the synthesis of 3-phenylpropanal according to Calò *et al.*[166]

Since the model reaction conducted under the conditions reported by Calò *et al.*[166] successfully yielded the desired product, the same approach was explored using **14a** and **14b** as the aryl bromides (see Table 8). However, when Calò's reaction conditions were applied to **14a**, no product formation was observed in the reaction monitoring (see Table 8, entry 1). Given that allyl alcohol evaporates below the reaction temperature, the reaction was subsequently performed in a sealed pressure tube to prevent substrate loss. Despite this modification, along with an increased catalyst loading and prolonged reaction time, no formation of aldehyde **52a** was detected (see Table 8, entry 2).

In subsequent attempts, the reaction time was further extended, and additional equivalents of allyl alcohol were introduced. However, variations in substrate equivalents, the use of K_2CO_3 as the base, a different batch of TBAB, or the addition of *N,N*-dimethylformamide (DMF) as a co-solvent did not result in the formation of the target product (see Table 8, entries 3-7). Notably, when K_2CO_3 was employed as the base (see Table 8, entries 4 and 5), the reaction mixture darkened over time but did not turn completely black, as observed in all other cases. In all entries presented in Table 8, the starting material was no longer detectable after the reaction, which could potentially be attributed to decomposition at the elevated temperature of 130°C.

A plausible explanation for the lack of product formation is that **32a** and **32b**, as aryl bromides, may not be sufficiently reactive to undergo the Mizoroki-Heck reaction under these conditions. Furthermore, Calò *et al*.[166] did not investigate bulkier substituents at the *ortho* position relative to the bromide, suggesting that the 1-benzyl-*tert*-butylsulfinylamide moiety may impose excessive steric hindrance, thereby inhibiting the reaction.

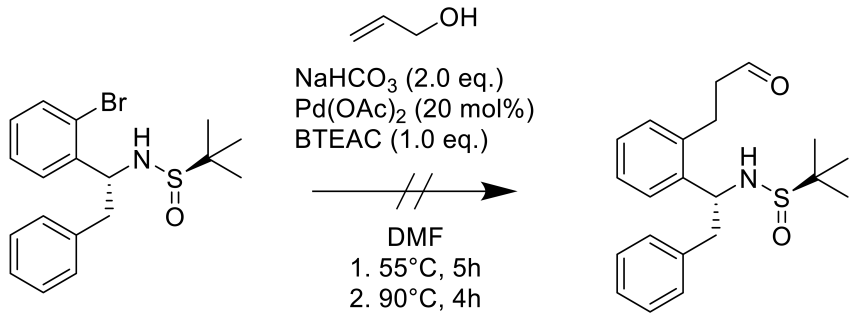


32a/b **76a/b**

Entry	Aryl bromide	Allyl Alcohol	$Pd(OAc)_2$	Base	TBAB (eq.)	Time	Result[e]
1[a]	**32a** (1.2 eq.)	1.0 eq.	5 mol%	$NaHCO_3$ (2.0 eq.)	5.0	3 h	No product observed
2[b]	**32a** (1.2 eq.)	1.0 eq.	10 mol%	$NaHCO_3$ (2.0 eq.)	3.5	4 h	No Product observed
3[b]	**32b** (1.0 eq.)	10 eq.	10 mol%	$NaHCO_3$ (2.0 eq.)	3.5	18 h	No Product observed
4[b]	**32b** (1.0 eq.)	10 eq.	10 mol%	K_2CO_3 (2.0 eq.)	3.5	18 h	No product observed
5[b]	**32b** (1.0 eq.)	5.0 eq.	10 mol%	K_2CO_3 (2.0 eq.)	3.5	18 h	No product observed
6[b,c]	**32b** (1.0 eq.)	5.0 eq.	10 mol%	$NaHCO_3$ (2.0 eq.)	3.5	18 h	No product observed
7[b,d]	**32b** (1.0 eq.)	5.0 eq.	10 mol%	$NaHCO_3$ (2.0 eq.)	3.5	18 h	No product observed

Table 8 Tested reaction conditions. All reactions were carried out at 130°C. [a]: Reaction Vessel: Schlenk flask with reflux condenser. [b]: Reaction vessel: sealed pressure tube. [c]: Other batch TBAB used. [d]: DMF added (0.5 mL for 0.2 mmol of **32b**). [e]: Reaction control *via* ASAP and TLC using 2,4-dinitrophenylhydrazine DNPH as stain for aldehydes.

Subsequently, an alternative approach was undertaken to synthesize **76b** from **32b** by employing modified Heck reaction conditions previously reported by Shang *et al*.[169] In contrast to the previously applied conditions, this reaction was conducted in DMF as the solvent, utilizing benzyltriethylammonium chloride (BTEAC) as the ionic nitrogen species (see Scheme 55). However, no substrate conversion was observed. This outcome may once again be attributed to the lower reactivity of aryl bromides compared to their aryl iodide counterparts[170], as Shang *et al*.[169] exclusively employed the corresponding iodo derivatives.



32b **76b**

Scheme 55 Conditions adapted from Shang *et al*.[169]
Both reactions for the synthesis of aldehyde **76b** were carried out with 3.0 eq. of allyl alcohol

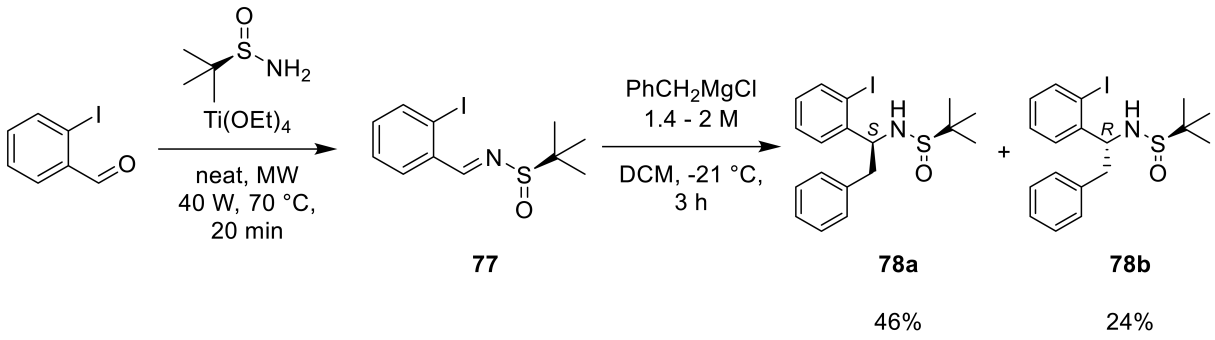
In light of the unsuccessful attempts with the bromo substrates **32a/b**, attention was subsequently directed toward investigating their respective aryl iodide counterparts.

4.17.6 Mizoroki-Heck reaction with aryl iodides

4.17.6.1 Synthesis of iodine precursors

Following an analogous procedure to the *N*-sulfinyl imine synthesis described in Section 4.10, the corresponding iodo derivative was prepared from commercially available 2-iodobenzaldehyde and (*R*)-(+)-*tert*-butylsulfinamide. The condensation of these precursors afforded *N*-sulfinyl imine **77** in quantitative yield with sufficient purity for subsequent use without further purification.

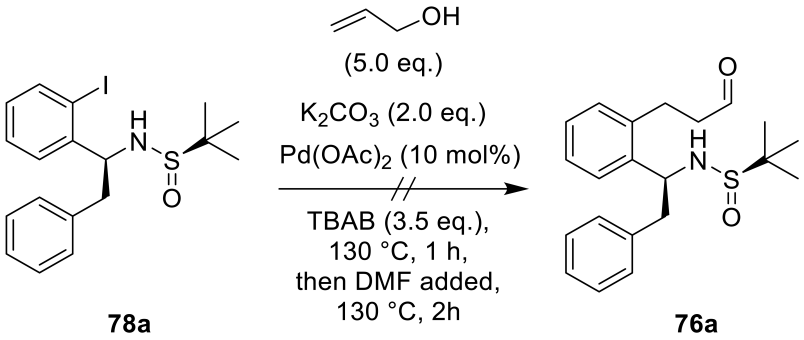
As previously discussed in Section 4.12, the next step involved the addition of the benzyl Grignard reagent to *N*-sulfinylimine **77**. This nucleophilic addition afforded the diastereomers **78a** (yield: 46%) and **78b** (yield 24%), which were successfully separated by FCC. The absolute configurations were determined according to Section 4.8.1 *via* ^{1}H-NMR spectroscopy. The total yield of the reaction was 70%. The reaction was conducted at -21°C. An overview of these synthetic steps is depicted in Scheme 56.



Scheme 56 Synthesis of aryl iodides **78a** and **78b**

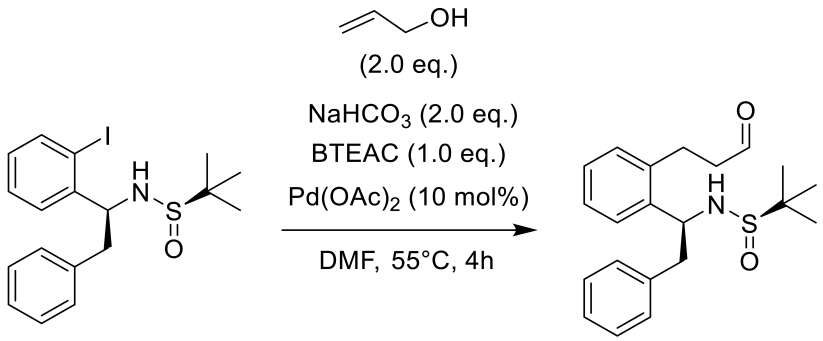
4.17.6.2 Mizoroki-Heck reaction with aryl iodide 78a

With iodoarene **78a** successfully obtained, we subsequently explored its application in the Mizoroki-Heck coupling with allyl alcohol. Initial attempts employed reaction conditions analogous to those reported in Table 8, entry 5 (Scheme 57). Upon reaching the target reaction temperature, at which point TBAB achieved complete liquefaction, visual inspection revealed only a heterogeneous suspension of **78a** in the reaction medium. To facilitate substrate dissolution, a small amount of DMF (1.0 mL) was added to the reaction mixture after 1 hour. However, no noticeable change occurred. Reaction monitoring confirmed the absence of product formation.



Scheme 57 Attempted Mizoroki-Heck reaction to form **76a**

Alternatively, we investigated the modified protocol reported by Shang *et al.*[169] (Scheme 58). Under these optimized conditions, complete substrate conversion was achieved within 4 hours, with clear evidence of product formation observed by analytical monitoring *via* TLC staining, TLC-MS and ASAP analysis. Following chromatographic purification, the desired compound **76a** was isolated in 82% yield.



78a **76a**

82%

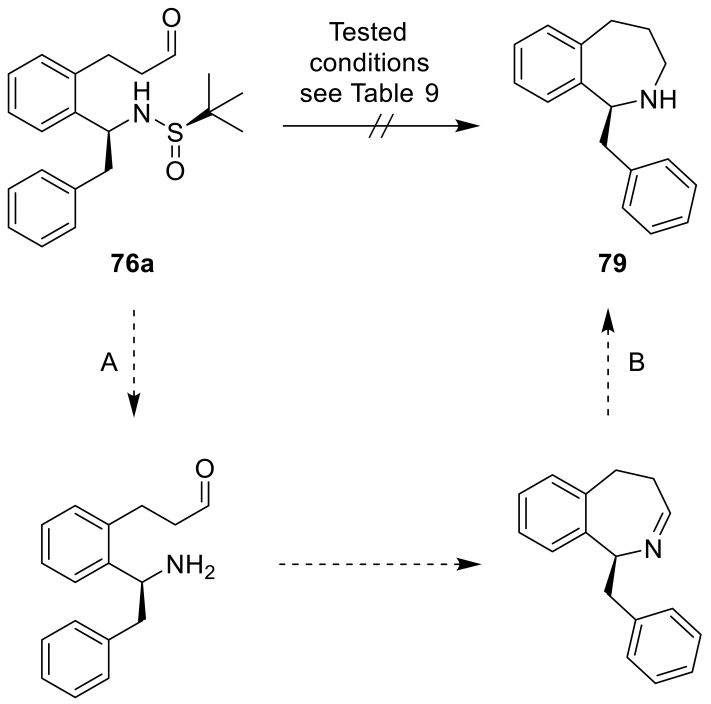
Scheme 58 Successful synthesis of 3-phenylpropanal derivative **76a**

This successful outcome demonstrates the superior reactivity of the aryl iodide derivative **78a** in the Mizoroki-Heck transformation, establishing it as the preferred substrate for installation of the C_3 building block. This finding represents a critical advancement in our synthetic route towards 1-benzyltetrahydro-2-benzazepines.

4.17.7 Ring closure

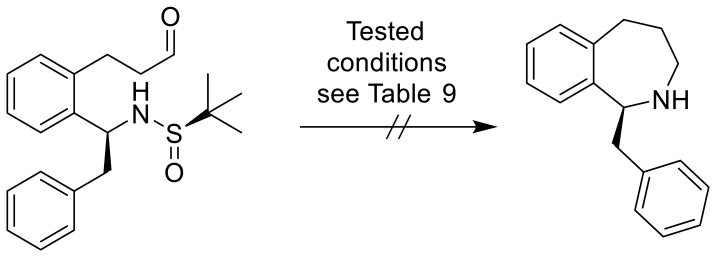
4.17.7.1 Ring closure via reductive amination and deprotection

The next planned step in the synthetic route toward 1-benzyltetrahydro-2-benzazepines involved a sulfinamide deprotection and intramolecular reductive amination sequence (see Scheme 59). The *tert*-butylsulfinyl protecting group on the amine is acid-labile and can be cleaved using a mixture of methanol and $HCl_{(aq.)}$. The rationale behind this reaction design was to remove the protecting group under acidic conditions (see Scheme 59, step A), leading to the formation of the protonated amine in close proximity to the aldehyde, thereby facilitating an intramolecular condensation to generate an imine intermediate. Subsequent application of a reducing agent, following a work-up to remove excess HCl, was expected to yield the final compound **79** (see Scheme 59, step B).



Scheme 59 Reaction scheme and possible intermediates for the synthesis of **79** from **76a** *via* conditions listed in Table 9

Various reaction conditions were explored for this sequence, as summarized in Table 9 and earlier discussed in Section 4.3.



Entry	HCl	Condi-tions	Work-up	Reducing Agent	Conditions	Result
1	2M HCl (aq.)	MeOH, 55 °C, 2 h	DCM Extraction	$NaBH_4$ (1.5 eq.)	MeOH, 0 °C to rt, 18 h	No product observed
2	2M HCl (aq.)	MeOH, 55 °C, 2 h	pH > 8 with $NaHCO_3$ (aq.), DCM Extraction	$NaBH(OAc)_3$ (1.2 eq.)	THF, 0 °C to rt, 18 h	No Product observed
3	4M HCl (in diox-ane)	MeOH, rt, 1 h	Evaporation	$NaBH(OAc)_3$ (1.5 eq.)	MeOH, 0 °C to rt, 18 h	Product mass observed (traces), no purification possible

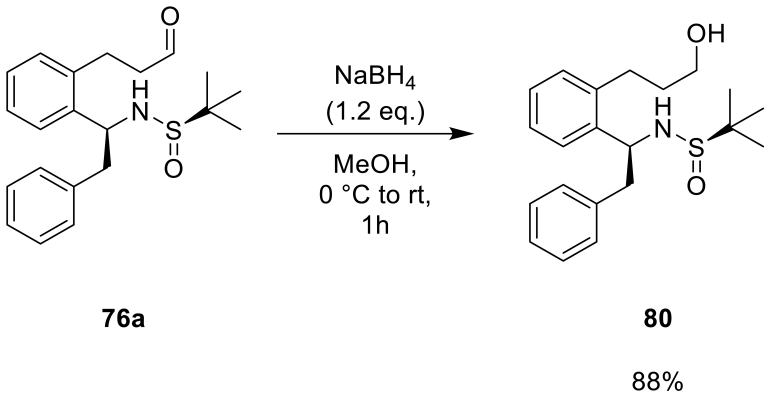
4	4M HCl (in diox-ane)	Dioxane, rt, 1 h	pH > 8 with Na_2CO_3 (aq.), DCM Extraction	$NaBH(OAc)_3$ (1.5 eq.)	THF, 2.0 eq. AcOH, 0 °C to rt, 18 h	Product mass observed (traces), no purification possible

Table 9 Reaction conditions tested for further reductive aminations. All entries were performed with 1.0 eq. of **76a**

Deprotection of the amine was carried out using either aqueous HCl in methanol (Table 9, entries 1 and 2) or HCl in dioxane with methanol as the reaction solvent (Table 9, entries 3 and 4). In all cases, **76a** was completely consumed and was not detectable in the reaction monitoring after the specified reaction time. Furthermore, TLC with DNPH staining did not reveal the presence of an aldehyde functional group in any of the entries listed in Table 9.
Despite testing various work-up and reduction conditions, no product formation was observed in entries 1 and 2. In entry 3, after deprotection, all volatiles were removed by evaporation, and sodium triacetoxyborohydride ($NaBH(OAc)_3$) in methanol was employed as the reducing agent, leading to the detection of trace amounts of the desired (*S*)-1-benzyl-2,3,4,5-tetrahydrobenzazepine (**79**) in the reaction monitoring. However, isolation and purification were not feasible. A modification of the work-up and reduction conditions while maintaining the same deprotection conditions (Table 9, entry 4) yielded the same outcome.
Given the unsuccessful outcome of the deprotection-reductive amination sequence, alternative strategies for ring closure were systematically evaluated. The chosen approach involved replacing the aldehyde functionality with a primary alcohol.

4.17.7.2 Leaving groups

To investigate alternative cyclization strategies employing a terminal alcohol group in place of the aldehyde functionality, we first performed a functional group transformation. The aldehyde moiety in **76a** was efficiently reduced to the corresponding primary alcohol **80** using sodium borohydride ($NaBH_4$) in MeOH at 0°C, cleanly affording compound **80** in 88% yield. This reaction is depicted in Scheme 60.

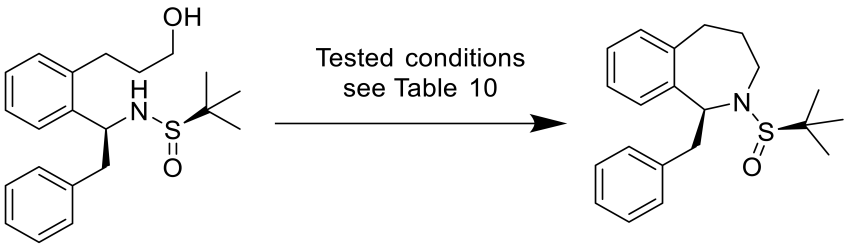


76a **80**

88%

Scheme 60 Reduction of the aldehyde functionality of **76a** to a primary alcohol

With alcohol **80** available, various ring-closing reactions could be explored. Although the *N*-*tert*-butylsulfinyl protecting group reduces the nucleophilicity of the amine, it can still participate as a nucleophile in a nucleophilic substitution-based ring-closing reaction, as previously demonstrated in the synthesis of three- to six-membered saturated nitrogen heterocycles.[91, 106, 123] Since the hydroxyl group itself is a poor leaving group, it is generally necessary to first convert the alcohol into a more suitable leaving group under appropriate reaction conditions, as depicted in Table 10.



80 **81**

Entry	Reagents	Conditions	Result
1	1. Ms-Cl (1.5 eq.), Et_3N (2.4 eq.) 2. NaH (2.2 eq.)	1. DCM, 0°C, 90 min 2. DMF, 0°C to rt, 18 h	No full purification after step 1 Isolated yield: 17%
2	DIAD (1.3 eq.), PPh_3 (1.2 eq.)	THF, rt, 18 h, THF, 60 °C, 3 h	No product observed
3	$SOCl_2$ (1.1 eq.), Et_3N (3.0 eq.)	DCM, 0 °C to rt, 18 h	No product observed
4	*p*-Ts-Cl (1.1 eq.), NaH (2.0 eq.)	THF, reflux, 3 h	Traces of product observed
5	Ts-Cl (1.1 eq.), KOH (3.0 eq.)	THF, reflux, 3 h	Traces of product observed
6	Ts-Cl (1.1 eq.), Et_3N (3.0 eq.)	THF, reflux, 3 h	Traces of product observed
7	Ts-Cl (1.1 eq.), KO^{t}Bu (2.0 eq.)	THF, reflux, 3h	Isolated yield 14%

Table 10 Reaction conditions tested for the ring closure *via* leaving groups

The initial strategy explored in this context involved converting the alcohol into a more effective mesyloxy leaving group by employing methanesulfonyl chloride (Ms-Cl). Following an aqueous work-up of the reaction mixture, the crude mesylated intermediate was treated with sodium hydride (NaH) as a strong base in DMF to facilitate nucleophilic substitution (Table 10, entry 1). This procedure yielded compound **81**, albeit in a modest yield of 17%. The experiment demonstrated that the general approach of enhancing the leaving group ability of the alcohol,

followed by nucleophilic substitution, was applicable for the formation of the seven-membered ring. However, due to the low yield, alternative conditions were investigated.

Next, classical Mitsunobu cyclization conditions employing DIAD and PPh_3 were evaluated (Table 10, entry 2). This approach was previously reported by Anton-Torrecillas and Gonzalez-Gomez[171] for the synthesis of a five-membered ring from an *N*-sulfinylamine alcohol precursor. However, no formation of heterocycle **81** was observed under either room temperature or elevated temperature conditions.

Moreover, treatment of alcohol **80** with thionyl chloride ($SOCl_2$) in the presence of triethylamine did not yield the desired product (Table 10, entry 3). Given that HCl is a byproduct of the hydroxyl-to-chlorine conversion using $SOCl_2$, cleavage of the sulfinyl protecting group was a potential outcome; however, no corresponding mass was detected during reaction monitoring. Additionally, since only triethylamine was employed as a weak base, the formation of a product in which the hydroxyl group was replaced by chlorine while retaining the protecting group and without cyclization to the seven-membered ring was conceivable. Nevertheless, no evidence for the formation of such a product was observed in the reaction analysis.

Since mesylation followed by nucleophilic substitution, albeit with low efficiency, was successful in principle, a similar strategy employing the more sterically demanding tosyl group was investigated. Thus, alcohol **80** was treated with *p*-toluenesulfonyl chloride (*p*-Ts-Cl) in the presence of various bases (Table 10, entries 4-7). Although traces of the desired product were detected in all reactions, significant substrate conversion was only observed when using the sterically hindered base potassium *tert*-butoxide (KO^tBu), yielding 14% of compound **81** (Table 10, entry 7). However, the overall yield remained low and did not improve compared to Entry 1.

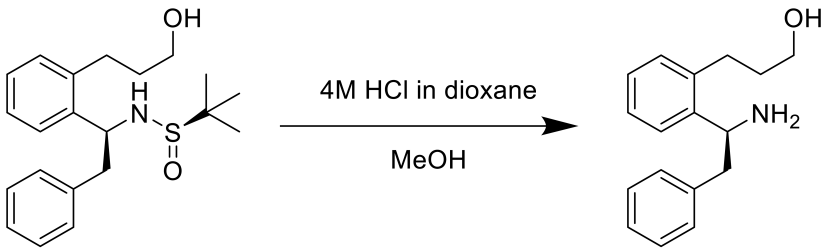
Nonetheless, using **81**, the final (*S*)-1-benzytetrahydro-2-benzazepine (**79**) could be generated in 92% yield by simple cleavage of the sulfinyl protecting group with 4M HCl in dioxane and MeOH, as described in Section 4.15.

4.17.7.3 Ring closure after deprotection

Consequently, the objective of asymmetrically synthesizing 1-benzyltetrahydro-2-benzazepine was successfully attained. However, due to the limitations of the current synthetic route, particularly in the heterocycle formation step, further investigation was necessary. One potential avenue for exploration involved altering the sequence of the final two steps. First removing the *N*-sulfinyl protecting group, followed by executing the ring-closing Mitsunobu reaction with Tsunoda's reagent (CMBP), as discussed for THIQs in Section 4.6.1, in the last step using a free aminoalcohol intermediate.

Therefore, aminoalcohol **82** was synthesized from the alcohol-sulfinyl intermediate **80** under standard acidic conditions with 4M HCl in dioxane and MeOH (Scheme 61). The relatively low yield of 60% for a protecting group cleavage was attributed to challenges in purifying

aminoalcohol **82** *via* FCC. To enhance the overall yield, the feasibility of employing crude **82** in the subsequent step could be investigated.

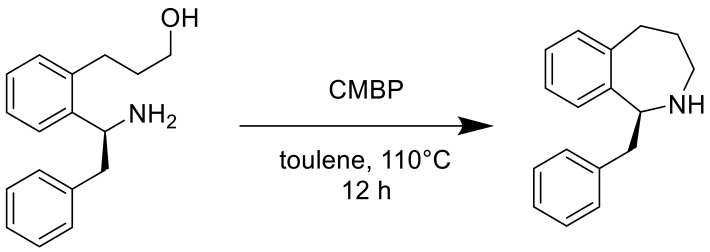


80 **82**

60%

Scheme 61 Cleavage of the *N*-sulfinyl protecting group

With aminoalcohol **82** in hand, a Mitsunobu-type ring-closing reaction was explored utilizing CMBP and **82**, following a modified procedure adapted from Kudale *et al.*[122] (Scheme 62). The same modified procedure was also employed for the synthesis of THIQs (see Section 4.6.1). In contrast to the original study, in which CMBP was employed for the ring-closing reactions of four- to six-membered saturated nitrogen-containing heterocycles derived from *N*-sulfinylamine precursors[122], this investigation aimed to extend the methodology to the synthesis of (*S*)-1-benzyltetrahydro-2-benzazepine **79**. The reaction proceeded efficiently, leading to the formation of the desired product with a yield of 73% after purification. This outcome demonstrated the applicability of the Mitsunobu approach with Tsunoda's reagent in the construction of the benzazepine scaffold, highlighting its potential for broader synthetic utility.



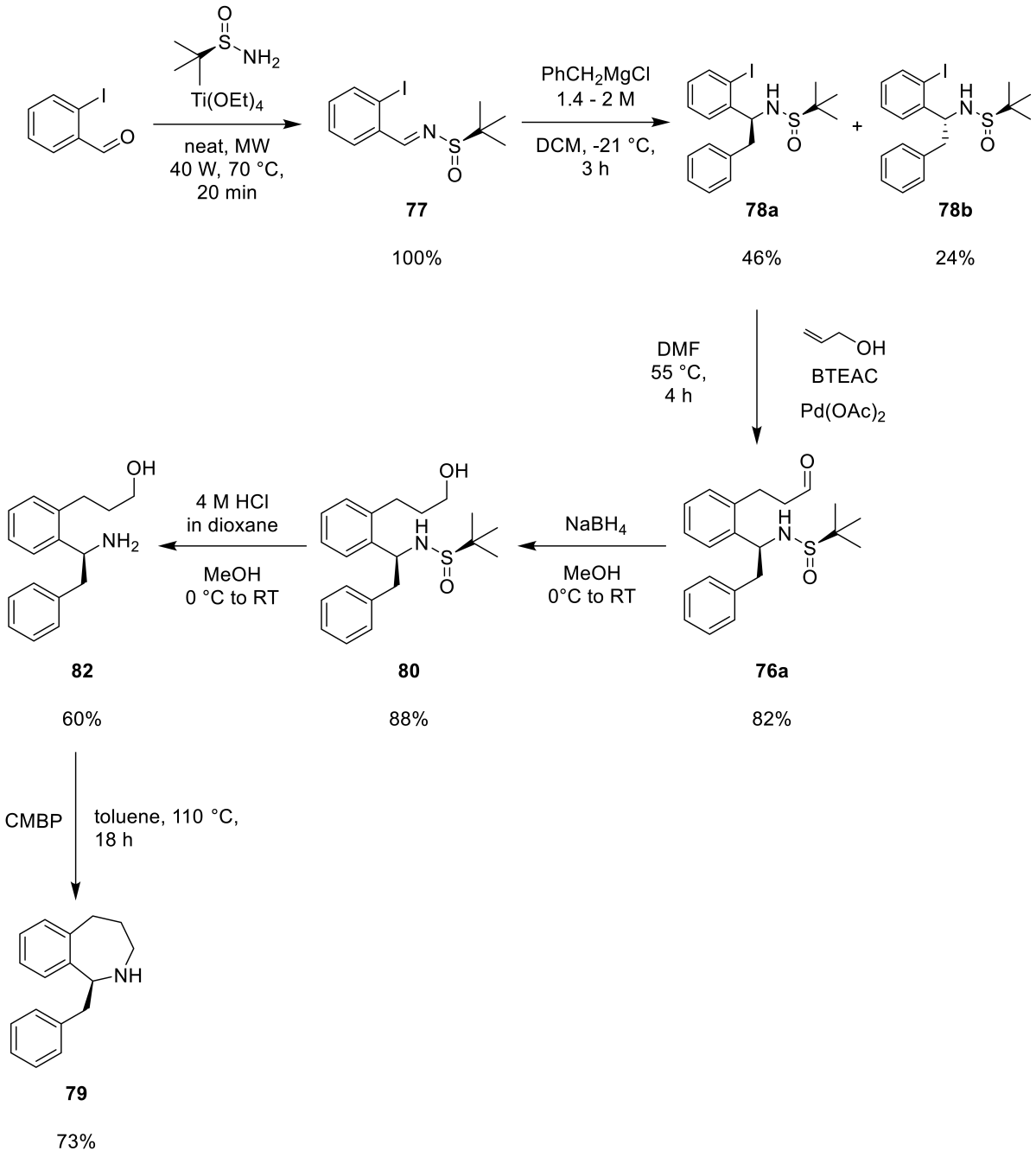
82 **79**

73%

Scheme 62 Successful formation of (*S*)-1-benzyltetrahydro-2-benzazepine (**79**)

4.17.8 Overview of the established route

A schematic overview of the optimized synthetic route to (*S*)-1-benzyltetrahydro-2-benzazepine **79** is presented in Scheme 63. The developed methodology enables the synthesis of enantiomerically pure benzazepine **79** in six steps, commencing from the commercially available and cost-effective 2-iodobenzaldehyde.



Scheme 63 Overview of the developed synthesis route

Following the successful establishment of the general synthetic route, subsequent efforts were directed towards the preparation of additional derivatives, with particular emphasis on introducing ether substituents to ring A. This structural modification strategy was motivated by the known bioactivity of 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids, as discussed in the Objectives in Section 2.

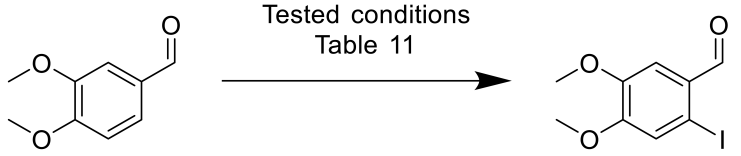
4.17.9 Iodination of 3,4-disubstituted benzaldehydes

Since our starting aryl bromides from the THIQ synthesis are unsuitable for the Mizoroki-Heck reaction in this synthesis, aryl iodides were required as alternative substrates. 2-

Iodobenzaldehydes bearing ether substituents at the C-4 and C-5 positions, potential starting materials for the synthesis, are either commercially expensive or not readily accessible. Therefore, as part of this work, their preparation from more readily available non-halogenated benzaldehyde derivatives was investigated.

Several synthetic approaches for the preparation of 2-iodo-4,5-dimethoxybenzaldehyde (**83**) from 3,4-dimethoxybenzaldehyde (Table 11) have been reported in the literature. These include the use of *N*-iodosuccinimide (NIS) with a strong hydrogen-bond donor, such as hexafluoro-2-propanol (HFIP)[172] or TFA[173], as well as silver nitrate or periodic acid in combination with iodine[174]. The procedure developed by Tang *et al.*[172] appeared particularly promising and was therefore selected for initial evaluation (Table 11, entry 1). However, despite the authors' report of complete substrate conversion and a 94% yield after 30 minutes, the reaction under identical conditions in this study afforded only trace amounts of the desired product, with minimal substrate conversion observed even after an extended reaction time of 16 hours.

Next, an iodination protocol reported by Morita *et al.*[154] for the iodination of isoxazoles was evaluated (see Table 9, entry 2). This method utilizes short reaction times under microwave irradiation with TFA as the solvent. Under these conditions, the target iodinated benzaldehyde **83** was obtained with an isolated yield of 53%. Notably, the yield was significantly enhanced up to 90% by the addition of a small amount of trifluoroacetic anhydride (TFAA) (see Table 11, entry 3). A plausible explanation for this improvement is that the reaction is sensitive to the presence of water, and TFAA functions as a water scavenger, thereby facilitating a more efficient iodination process.



83

Entry	Conditions	Result
1	NIS (1.0 eq.), HFIP, rt, 16 h	Traces of product observed, no full substrate conversion
2	NIS (1.1 eq.), TFA, MW, 120 °C, 300 W, 15 min	Isolated yield: 53%
3	NIS (1.1 eq.), TFAA (0.05 eq.), TFA, MW, 120 °C, 300 W, 15 min	Isolated yield: 90%

Table 11 Conditions for the synthesis of iodobenzaldehyde **83**.

All entries were performed with 1.0 eq. of 3,4-dimethoxybenzaldehyde

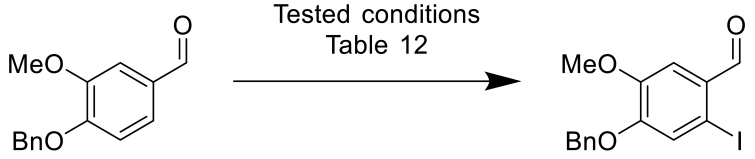
An additional promising starting material for this investigation was 2-iodo-4-benzyloxy-5-methoxybenzaldehyde (**84**). This compound offered dual advantages: enabling examination of

the synthetic route with a sterically demanding benzyloxy substituent on the A-ring while simultaneously providing two orthogonally protected phenol groups in the final product.

The synthesis commenced with commercially available 3-methoxy-4-benzyloxybenzaldehyde, applying reaction conditions similar to those used for the preparation of compound **83** (Table 10, entry 1). No formation of aldehyde **84** was observed, and the starting material was completely consumed, suggesting possible debenzylation under these harsh reaction conditions.

To mitigate this issue, milder conditions were explored, replacing TFA as the solvent with MeCN while employing TFA catalytically at a lower temperature and without microwave irradiation (Table 12, entries 2 and 3). Iodination in MeCN using NIS with catalytic amounts of TFA has been previously reported in the literature.[173, 175] Under these conditions, product formation was observed, but the substrate was only partially consumed. A subsequent attempt utilizing TFA as the reaction solvent at room temperature did not yield any detectable product (Table 12, entry 4).

Further optimization involved the use of a MeCN/TFA solvent mixture (4:1) at mild temperatures under microwave irradiation (Table 12, entry 5). This approach resulted in significant product formation, yielding **84** in an isolated yield of 50%. Given the similarity to the results obtained in Table 10, entry 2, the effect of adding a small amount of TFAA was investigated. Contrary to previous observations, the yield decreased to 28% (Table 12, entry 6). However, it is important to note that entry 6 was conducted using a different batch of NIS from an alternative supplier.



84

Entry	Conditions	Result
1	NIS (1.1 eq.), TFAA (0.05 eq.), TFA, MW, 120 °C, 300 W, 15 min	No product observed
2	NIS (1.1 eq.), TFA (0.3 eq.), MeCN, 65 °C, 36 h	Product observed, no full substrate conversion
3	NIS (1.1 eq.), TFA (0.3 eq.), MeCN, rt, 36 h	Product observed, no full substrate conversion
4	NIS (1.1 eq.), TFA, rt, 24 h	No product observed
5	NIS (1.2 eq.), MeCN/TFA (4:1), MW, 65 °C, 200 W, 70 min	Isolated yield 50%
6[a]	NIS (1.2 eq.), TFAA (0.05 eq.) MeCN/TFA (4:1), MW, 65 °C, 200 W, 70 min	Isolated yield 28%

Table 12 Tested conditions for the synthesis of **84**. [a]: different batch of NIS employed

4.17.10 Synthesis of ether derivatives of 1-benzyltetrahydrobenzazepines

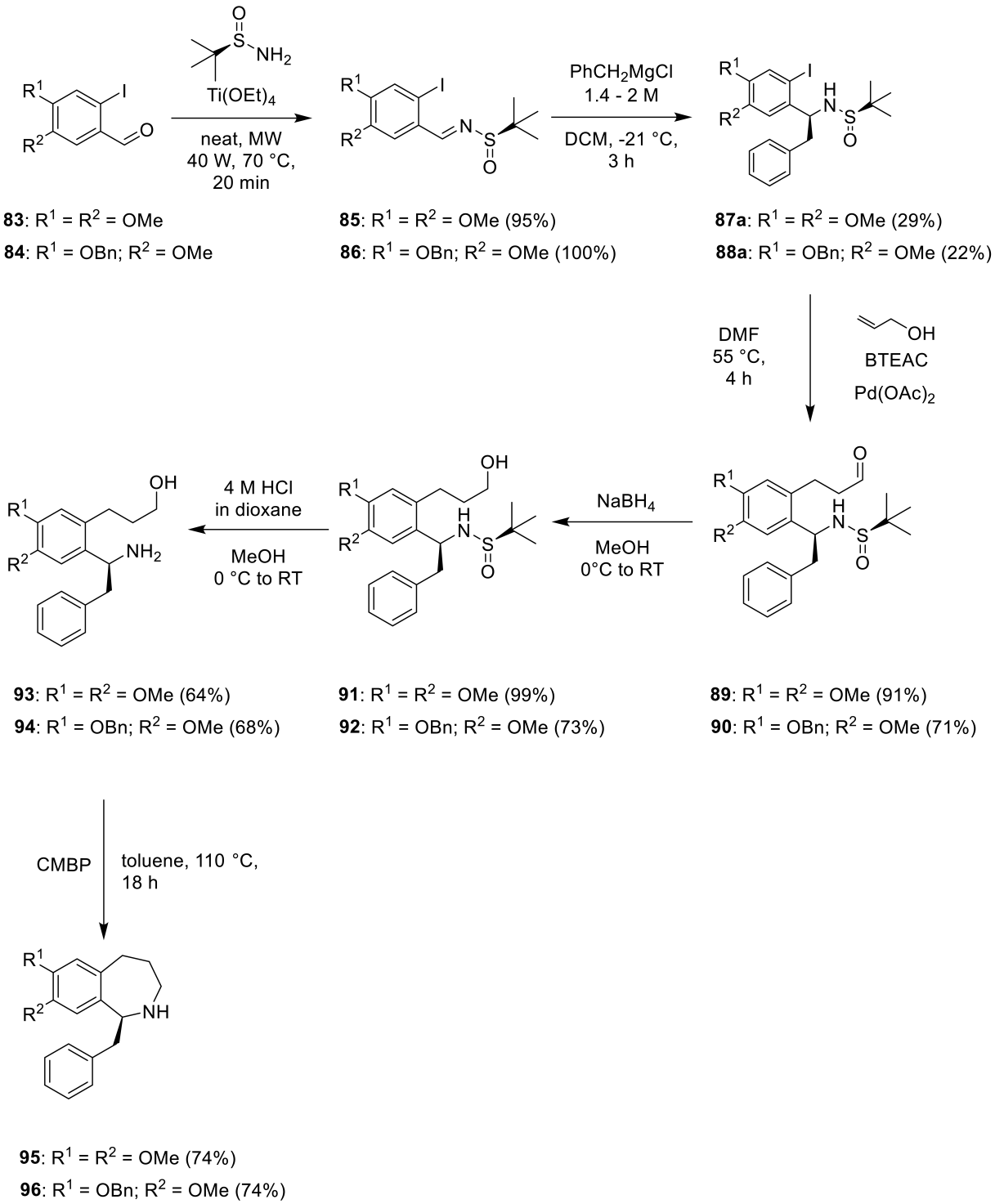
Having successfully obtained 2-iodobenzaldehydes **83** and **84**, we proceeded to investigate the synthetic route's tolerance for *meta*- and *para*-ether substituents on the final A-ring of tetrahydrobenzazepines. The complete synthetic procedure was executed using both **83** and **84** as starting materials, which enabled the successful preparation of (*S*)-1-benzyl-7,8-dimethoxytetrahydro-2-benzazepine (**95**) and (*S*)-1-benzyl-7-benzyloxy-8-methoxytetrahydro-2-benzazepine (**96**) in six steps, respectively. This systematic approach allowed for direct comparison of the synthetic outcomes with different ether substitution patterns.

For both compounds, the Grignard addition to the *N*-sulfinylimines **85** and **86** resulted in the formation of diastereomeric mixtures of the *N*-sulfinylamines **87a/b** and **88a/b**, respectively. The absolute configurations were determined according to Section 4.8.1 *via* ^{1}H-NMR spectroscopy. These diastereomers were subsequently separated by silica gel flash column chromatography. The diastereomers **87a** and **88a** possess an absolute *S* configuration at the α-position relative to the amine. Compound **87b** was obtained in a yield of 30%, nearly equimolar to **87a**, while **88b** was isolated with an even higher yield of 48%. The potential reasons for the lack of diastereoselectivity, as well as avenues for further investigation, have already been discussed in Section 4.12. Nevertheless, the separation of diastereomers *via* FCC allows for the synthesis of enantiomerically pure final compounds **95** and **96**. Moreover, while the overall yield of the Grignard addition was comparable across all imines **77**, **85** and **86**, the diastereomeric ratios varied.

The presence of the sterically demanding benzyloxy substituent resulted in notably diminished yields for both the Mizoroki-Heck reaction (aldehydes **89** with 91% yield and **90** with 71% yield) and subsequent aldehyde reduction steps (**89** to **91** and **90** to **92**, Scheme 64) compared to their methoxy-substituted counterparts. In the Mizoroki-Heck reaction, this reduced efficiency may be attributed to steric hindrance from the *meta*-positioned bulky substituent, potentially impeding catalyst-substrate interactions. Nevertheless, the reaction yield remained satisfactory for synthetic purposes. While the significant yield reduction observed in the reduction step currently lacks definitive mechanistic explanation, the reaction demonstrated sufficient reproducibility for further systematic investigation.

The cleavage of the *tert*-butyl sulfinyl protecting group to synthesize the aminoalcohols **93** (yield: 64%) and **94** (yield: 68%), followed by ring closure using the CMBP reagent, proceeded equally well for both tested compounds and yielded the enantiomerically pure (*S*)-1-benzyl-7,8-dimethoxytetrahydro-2-benzazepine (**95**) and (*S*)-1-benzyl-7-benzyloxy-8-methoxytetrahydro-2-benzazepine (**96**) (Scheme 64). Those results are comparable to reactions performed in the absence of ether substituents. These findings demonstrate that the

synthetic route is compatible with both methoxy and benzyloxy substituents at the investigated positions.



83: $R^1 = R^2 = OMe$
84: $R^1 = OBn$; $R^2 = OMe$

85: $R^1 = R^2 = OMe$ (95%)
86: $R^1 = OBn$; $R^2 = OMe$ (100%)

87a: $R^1 = R^2 = OMe$ (29%)
88a: $R^1 = OBn$; $R^2 = OMe$ (22%)

89: $R^1 = R^2 = OMe$ (91%)
90: $R^1 = OBn$; $R^2 = OMe$ (71%)

91: $R^1 = R^2 = OMe$ (99%)
92: $R^1 = OBn$; $R^2 = OMe$ (73%)

93: $R^1 = R^2 = OMe$ (64%)
94: $R^1 = OBn$; $R^2 = OMe$ (68%)

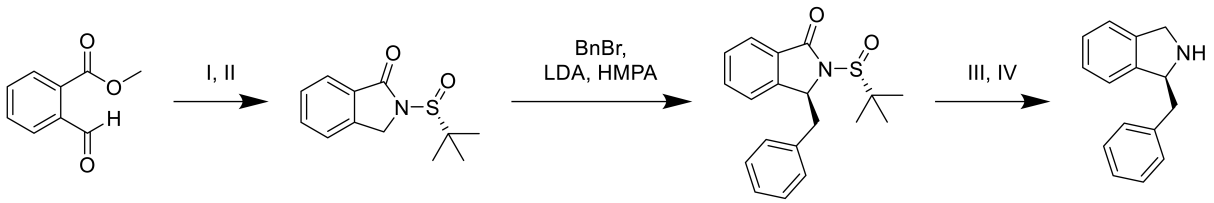
95: $R^1 = R^2 = OMe$ (74%)
96: $R^1 = OBn$; $R^2 = OMe$ (74%)

Scheme 64 Synthesis route and conditions for the synthesis of **95** and **96** from **83** and **84**

With establishing a new synthesis route to enantiomerically pure 1-benzyltetrahydro-2-benzazepines, the main objective of the Master's thesis was achieved.

4.18 1-Benzylisoindoline synthesis

Following the successful synthesis of benzazepines, the next objective was to develop a synthetic route toward enantiomerically pure 1-benzylisoindolines as the lower homologues of the THIQs. One established approach is the method reported by Ogata *et al*.[176], *via* a chiral bisoxazoline-lithium amide-catalyzed asymmetric hydroamination. More recently, Yin *et al*.[177] published an alternative strategy involving asymmetric C-benzylation and subsequent reduction with borane dimethyl sulfide of an *N*-sulfinylindolinone and cleavage of the *tert*-butyl sulfinyl group, as illustrated in Scheme 65.



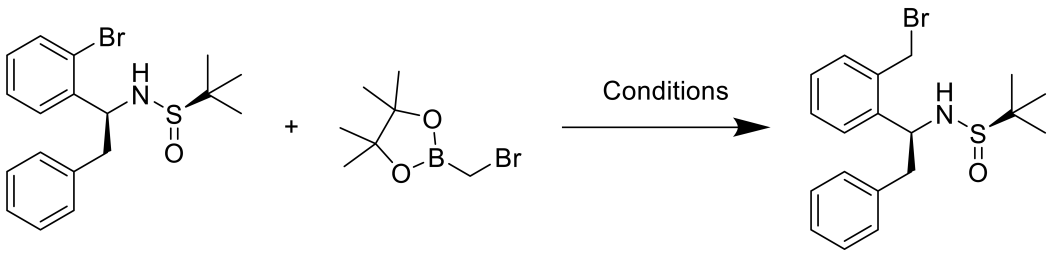
Scheme 65 Synthesis of 1-benzylisoindoline according to Yin *et al*.[177]
Reagents: (I) (*S*)-*tert*-butylsulfinamide, $Ti(OEt)_4$, (II) $NaBH_4$, (III) BH_3-Me_2S, (IV) aq. HCl

In contrast to these established methodologies, our synthetic strategy aimed to access enantiomerically pure benzylisoindolines from common precursors shared with the previously discussed THIQs and benzazepines. This approach offers potential advantages in terms of synthetic convergence and precursor economy.

4.18.1 C1 extension of intermediate **14a**

4.18.1.1 Suzuki cross coupling for C_1 unit extension

Our initial approach involved the substitution of the bromine atom in **32a** with a C_1 unit containing a suitable leaving group *via* Suzuki cross-coupling, enabling the subsequent ring-closing reaction. As suitable boron derivative, bromomethylboronic acid pinacol ester was chosen. The resulting alkyl halide would incorporate all the necessary functional groups required for the subsequent ring-closing reaction. Commonly, bromomethylboronic acid pinacol ester is used for borylation of aryl halides.[178, 179] Several conditions were tested and are listed in Table 13 below.



32a

Entry	Catalyst	Solvent	Result
1	$Pd(dppf)Cl_2$	Dioxane	Dehalogenated
2	$Pd(dppf)Cl_2$	Toluene	Starting material
3	$Pd(PPh_3)_4$ + CuI	Dioxane	Starting material
4	$Pd(PPh_3)_4$	DMF	Starting material
5	$Pd(PPh_3)_4$ + CuI	Dioxane/DMF	Starting material
6	$Pd(PPh_3)_2Cl_2$	Dioxane/Toluene	Dehalogenated

Table 13 All reactions were carried out at 90°C for 12 h. Cs_2CO_3 was used as base (5.0 eq.).

All examined reaction conditions either yielded no conversion of the starting material or led to the dehalogenation of **32a**, as confirmed by ASAP-MS analysis. The characteristic bromine isotope doublet peaks were absent in the mass spectra, with only the mass signal corresponding to dehalogenated **32a** being observed. This side reaction is also known in the literature.[180, 181]

Since the attempted Suzuki-Miyaura cross-coupling reactions did not yield the desired product, instead resulting in either no conversion or dehalogenation of **32a**, alternative synthetic approaches were investigated.

4.18.1.2 Extension *via* halogen-metal exchange

Given the unsuccessful Suzuki cross-coupling attempts with substrate **32a**, we investigated alternative functionalization strategies, including a halogen-metal exchange approach. Morita *et al.*[154] successfully demonstrated this method for C_1-extension of iodo-substituted isoxazoles. It is important to note that their protocol was specifically developed for heteroaryl iodides, a typically more reactive class of halides in such exchange reactions. This method adopted to our compounds involves treating the brominated substrate **32a** with turbo-Grignard at -78°C to generate the corresponding arylmagnesium intermediate, which could subsequently be trapped with DMF to directly introduce a formyl group. This transition-metal-free approach offers several advantages, including the direct conversion of the aryl bromide to an aldehyde in a single step while circumventing the dehalogenation issues encountered in our palladium-mediated coupling attempts.

For *N*-sulfinylimines, Fjelbye *et al.*[182], Panossian *et al.*[183] and Sealy *et al.*[184] executed the halogen-metal exchange prior to the addition of the resulting metal species to the *N*-sulfinylimine. To the best of our knowledge, no halogen-metal exchange besides Ellman's auxiliary is reported.

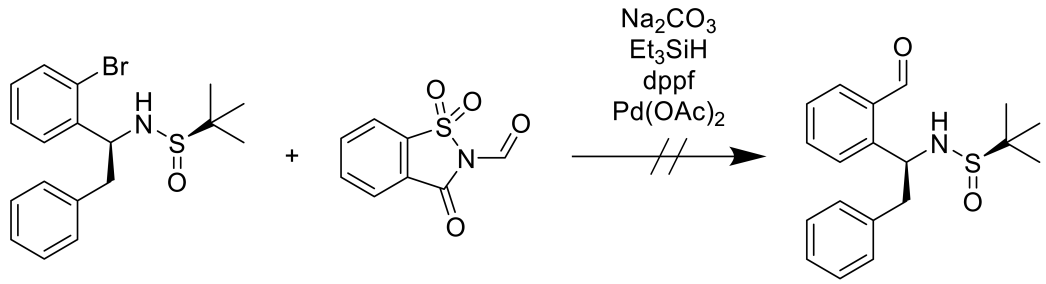
Two experimental attempts were systematically investigated to evaluate the halogen-magnesium exchange on substrate **32a**. In the initial experiment, treatment with 1.0 equivalent of turbo-Grignard reagent in THF at -78°C for 30 minutes showed no conversion by TLC and ASAP analysis. Prolonging the reaction time to 3 hours under these conditions similarly failed to produce the desired organomagnesium intermediate, with only starting material being recovered.

However, given the strongly basic nature of the reagent, competitive deprotonation of the *N*-sulfinylamine moiety is a plausible side reaction, which would effectively inhibit the desired Br/Mg exchange. In the second attempt, the turbo-Grignard loading was therefore increased to 2.0 equivalents to enhance reactivity. Monitoring after 30 minutes at -78°C again revealed no conversion. To further probe reactivity, the temperature was incrementally raised to room temperature and finally to reflux (THF, 66°C) while maintaining the reaction for an additional 6 hours. Despite these intensified conditions, no evidence of halogen-magnesium exchange or subsequent formylation was observed, as confirmed by analytical methods.

These results suggest that the brominated substrate **32a** exhibits significantly lower reactivity towards halogen-metal exchange compared to the sulfinamide-free iodinated systems reported by Morita *et al*.[154], likely due to both the inherent stability of the C–Br bond and the competing Brønsted basicity of the turbo-Grignard reagent toward acidic N–H sites.

4.18.1.3 Formylation employing N-formylsaccharin

Alternatively, we investigated the reductive carbonylation approach reported by Ueda *et al*.[185] The authors employed 4-bromoanisole as substrate with *N*-formylsaccharin as CO source, Et_3SiH as reductant, Na_2CO_3 as base, $Pd(OAc)_2$ as catalyst, several ligands and DMF as solvent at 85°C for 16 hours. In our system, this methodology was tested using bromoarene **32a** and dppf (1,1′-bis(diphenylphosphino)ferrocene) as ligand (see Scheme 66)



32a **97**

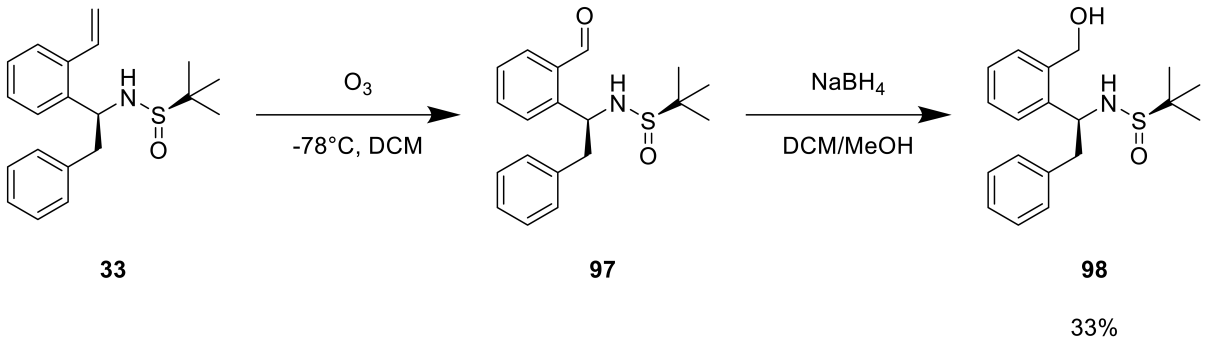
Scheme 66 Attempted formylation of **32a**

However, no conversion to aldehyde **97** was observed, suggesting **32a** may be less reactive than the reported aryl bromide system. The lack of reactivity could stem from either the decreased electrophilicity of the aromatic ring or potential catalyst inhibition by the bulky *N*-sulfinylamine moiety.

4.18.2 Shortening of the vinyl unit *via* ozonolysis

In the ozonolysis of a vinyl group, the reaction begins with the 1,3-dipolar cycloaddition of ozone (O_3) to the carbon-carbon double bond, forming a molozonide (1,2,3-trioxolane) intermediate. This unstable species rapidly rearranges into a more stable ozonide. Upon aquatic workup, the ozonide undergoes cleavage, yielding an aldehyde as the primary product. The formed aldehyde can then be further reduced to a primary alcohol using mild reducing agents such as sodium borohydride ($NaBH_4$) or catalytic hydrogenation. This two-step transformation is particularly useful in synthetic organic chemistry for converting alkenes into alcohols while avoiding over-oxidation. The selective reduction of the aldehyde ensures controlled functionalization of the molecular framework.

Rather than extending bromoarene **32a** with a C_1 unit to the desired chain length, an alternative approach is to shorten the vinyl group of **33** (previously synthesized for the synthesis of THIQs, see Section 4.8) from a C_2 unit to the desired C_1 unit through ozonolysis. The resulting aldehyde **97** could then be reduced with $NaBH_4$ to the primary alcohol **98** with a yield of 33% over two steps (Scheme 67).

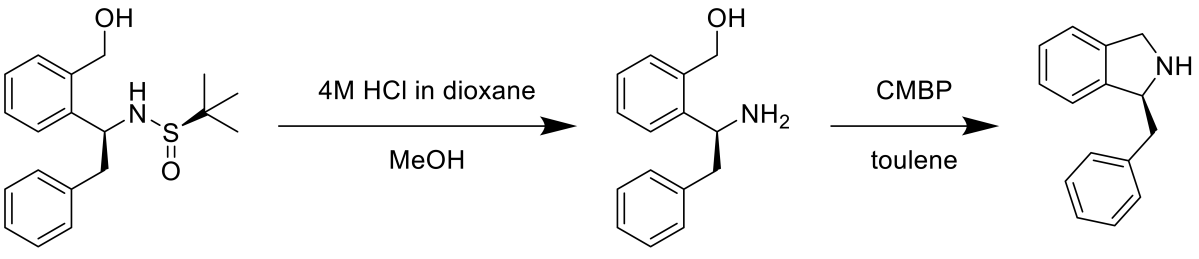


33 **97** **98**

33%

Scheme 67 Ozonolysis of styrene derivative **33** with reductive workup to primary alcohol **98**

Following the cleavage of Ellman's group under standard acidic conditions, the free aminoalcohol **99** underwent ring closure, without prior purification, *via* a Mitsunobu-type reaction using Tsunoda's reagent to yield the desired enantiomerically pure (*S*)-1-benzylisoindoline (**100**) with a yield of 22% over two steps (Scheme 68). The final two steps, deprotection and ring closure, represent the same synthetic sequence as employed in the synthesis of THIQs and tetrahydrobenzazepines before, demonstrating the general applicability of our ring closing strategy.



98 **99** **100**

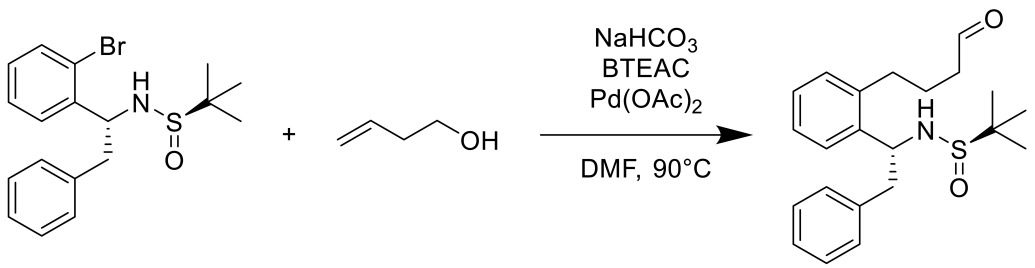
22%

Scheme 68 Deprotection and ring closure for the synthesis of (*S*)-1-benzylisoindoline (**100**)

This synthetic approach enabled the successful preparation of 1-benzylisoindoline **100** from the same precursor used for THIQ **36** synthesis, demonstrating the strategic advantage of late-stage diversification through ozonolysis. This methodology maximizes synthetic efficiency through shared intermediate utilization, improving atom economy and reducing redundant synthetic steps.

4.19 Hexahydrobenzazocine synthesis

After synthesizing the 5-, 6-, and 7-membered homologues, the next step was the expansion to 8-membered homologues, also referred to as hexahydrobenzazocines. The objective was once again the synthesis of this homologue from a precursor derived from the previously mentioned synthetic pathways. Instead of a C_3-extension of iodoarenes **78a**/**78b**, as discussed in Section 4.17.6 for tetrahydrobenzazepines, the focus in this case is on a C_4-extension. Furthermore, it should be investigated whether the presence of aryl bromide or aryl iodide is necessary for the successful execution of this coupling reaction, given that the synthesis of benzazepines was only feasible with aryl iodines. Following the procedure developed by Ma *et al.*[186] for the synthesis of ω-arylalkanals derived from aryl iodides, we initially attempted the synthesis using brominated compound **32b** in a Mizoroki-Heck-type reaction with 3-buten-1-ol (Scheme 69).



32b **101**

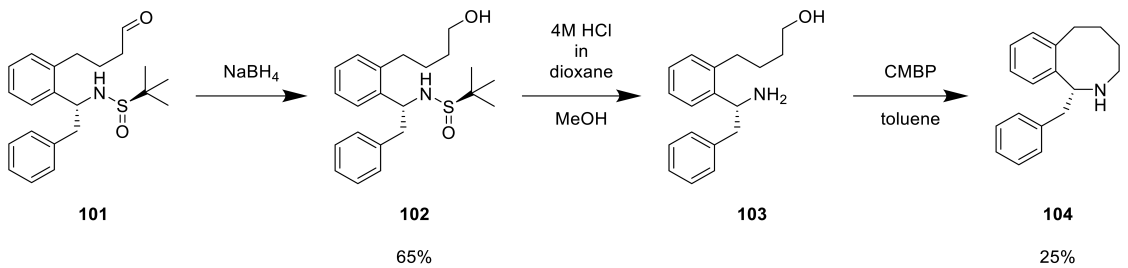
10%

Scheme 69 Synthesis of arylbutyraldehyde **101**

In contrast to the observations made in the synthesis of tetrahydrobenzazepines, the aryl bromide **32b** exhibited sufficient reactivity in this case, allowing for the successful formation of the desired arylbutyraldehyde **101**. However, the purification process proved challenging, significantly limiting the isolated yield. FCC furnished the product in only 10% yield, despite TLC analysis indicating a substantially higher crude yield. This discrepancy suggests potential decomposition or adsorption losses during chromatographic separation, possibly due to the inherent instability of the aldehyde under silica gel conditions. As an alternative, the liquid-liquid extraction protocol reported by Boucher *et al.*[147] was attempted but yielded even poorer results. This extraction protocol consists of two steps. In the first part, the aldehyde is mixed with saturated $NaHSO_{3(aq)}$ solution and shaken for approximately 30 seconds, forming a salt ("bisulfite adduct") which is soluble in water. Nonionic components are removed by extraction with EtOAc/hexanes for three times. Then, the aqueous layer is basified with 50% NaOH solution for decomposition of the adduct and extracted with EtOAc/hexanes for three times. Herein, the aldehyde is recovered into the organic phase from the previously formed water-soluble salt.

Given these challenges, it is reasonable to consider bypassing further purification and proceeding directly with the crude aldehyde **101** in the subsequent reduction step to the primary alcohol **102**. This strategy would minimize unnecessary handling and reduce exposure to conditions that could promote decomposition. Since the reduction step employs $NaBH_4$, which is often tolerant of impurities, the crude material should be suitable for conversion without prior purification. An alternative approach to enhancing the yield could involve replacing the brominated substrate **32b** with the aryl iodide derivatives **78a/b**, which are expected to exhibit higher reactivity compared to their brominated counterparts in cross-coupling reactions. Although this strategy was not explored due to shortage of time in the present study, it would represent a straightforward modification for future investigations.

After reduction of the previously purified arylbutyraldehyde **101** to the primary alcohol **102** with 65% yield, deprotection under standard acidic conditions yielded aminoalcohol **103**, which was employed without further purification for subsequent ring closure using Tsunoda's reagent to form the desired (*R*)-1-benzyl-1,2,3,4,5,6-hexahydrobenz[c]azocine (**104**) with 25% yield over both steps (Scheme 70).



Scheme 70 Transformation of aldehyde **101** to the desired enantiomerically pure product **104**

Once again, the successful synthesis of an additional homologue from a pre-existing precursor was achieved, further demonstrating the versatility and robustness of our synthetic strategy for accessing enantiomerically pure compounds. Notably, this approach maintains remarkable consistency in reagent utilization across different homologues, underscoring its operational efficiency. The minimal variation in required reagents not only simplifies the synthetic workflow but also represents a significant cost-effective advantage, as it reduces the need for extensive re-optimization and minimizes procurement of diverse chemical entities. This methodological consistency enhances the scalability and practicality of the synthetic route, making it particularly valuable for systematic structural diversification while maintaining high enantiopurity.

4.20 Scope and limitations of the developed synthesis route

After extensive optimization of the ether substituents on ring A to establish optimal reaction conditions for electron-rich starting aromatic aldehydes, the scope and limitations of the synthetic methodology should be rigorously evaluated. This includes systematic investigation of electron-deficient aromatic aldehydes, to assess electronic effects on reactivity and yield. Furthermore, the compatibility of heterocyclic aldehydes should be examined to determine the generality of the synthetic route and its potential applicability. Such studies would provide critical insights into functional group tolerance, possible side reactions, and the versatility of the method for broader substrate diversity.

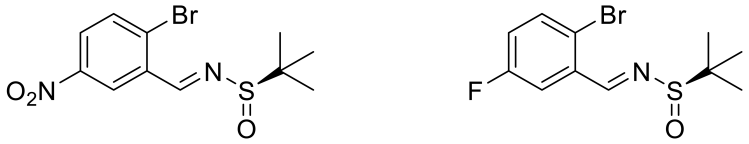
4.20.1 Electron-deficient aldehydes

To systematically evaluate the method's tolerance toward electron-deficient aldehydes, two representative substrates were selected: 2-bromo-5-nitrobenzaldehyde, serving as a strongly electron-deficient model due to the nitro group's combined −M (resonance withdrawal) and −I (inductive) effects, and 2-bromo-5-fluorobenzaldehyde, representing moderate electronic deactivation where fluorine's −I effect dominates with minimal +M compensation. By comparing these electronically diverse but structurally analogous aromatic aldehydes, we simultaneously probed the reaction's fundamental feasibility under electron-poor conditions and its efficiency through direct yield and stereoselectivity comparisons. This approach identifies critical limitations imposed by substrate electronics while maintaining experimental uniformity.

Furthermore, a fluorine substituent is introduced at this position to prevent metabolic oxidation. The incorporation of fluorine is a well-established strategy in medicinal chemistry, as it can significantly improve the metabolic stability of drug candidates by blocking sites of oxidative metabolism, particularly those catalyzed by cytochrome P450 enzymes. Due to its high electronegativity and small size, fluorine can effectively mimic hydrogen while resisting

enzymatic attack, thereby enhancing the compound's pharmacokinetic profile. This approach was previously applied in the structure-activity relationship (SAR) studies of the cholesterol absorption inhibitor ezetimibe, where fluorination proved beneficial in optimizing metabolic stability.[187]

In the first step, the condensation reaction with Ellman's auxiliary resulted in the corresponding *N*-sulfinylimines **104** (yield: 84%) and **105** (quantitative yield) (Scheme 71).



104 **105**

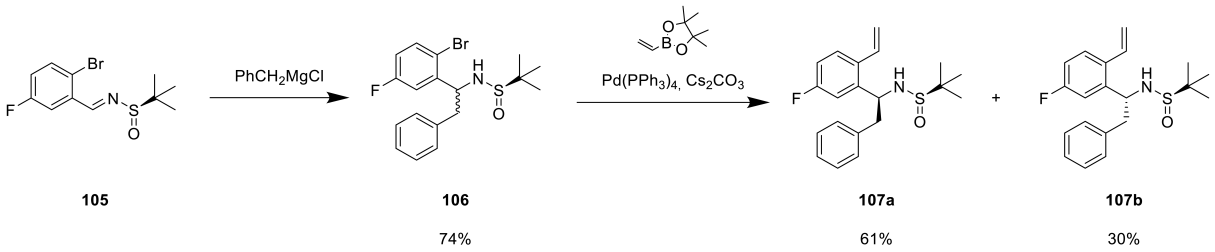
84% 100%

Scheme 71 Condensation products of the starting aldehydes with (*R*)-(+)-*tert*-butylsulfinamide

The benzyl Grignard reaction with nitro-substituted substrate **104** yielded atypical results for our synthesis route, with exhibiting complete decomposition of the starting material. This observation aligns with established literature documenting the incompatibility of Grignard reagents with nitroalkenes, as reported by Knochel[188]. In our study, the aromatic compound **104** was likewise affected by this issue.

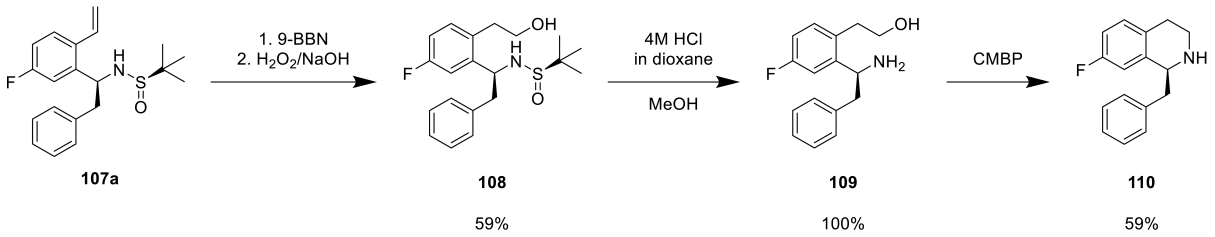
However, nitro groups participate in redox reactions with Grignard reagents, where the nitro functionality can be reduced to hydroxylamine or amine derivatives while the organomagnesium compound is oxidized.[189] Based on these findings, further investigation of the synthetic route for nitro-group-substituted compounds was discontinued. The observed incompatibility of nitro functionalities with the applied Grignard conditions, consistent with established literature precedents, rendered this substrate class unsuitable for the current methodology.

In contrast to the observations with *N*-sulfinylimine **104**, the synthesis of compound **106** from the fluorinated sulfinylimine **105** proceeded without complications, achieving a total yield of 74%. However, in this case, the separation of diastereomers *via* FCC was not feasible at this stage, despite systematic evaluation of multiple eluent systems. ^{1}H NMR analysis consistently indicated the presence of a diastereomeric mixture. Therefore, the diastereomeric mixture **106** was directly utilized in the subsequent Suzuki cross-coupling reaction, which successfully yielded the separable styrene diastereomers **107a** (yield: 61%) and **107b** (yield: 30%) (Scheme 72).



Scheme 72 Synthesis of the separable fluorinated styrenes **107a** and **107b**

In accordance with our established synthetic route, hydroboration of styrene **107a** followed by oxidation afforded the primary alcohol **108** in a yield of 59%. Subsequent deprotection of **108** with 4M HCl in dioxane quantitatively furnished the corresponding aminoalcohol **109**. Application of Tsunoda's reagent enabled the synthesis of the enantiomerically pure fluorinated 1-benzyltetrahydroisoquinoline derivative **110** in 59% yield, as illustrated in Scheme 73.



Scheme 73 Synthesis route to (*S*)-1-benzyl-7-fluoro-1,2,3,4-tetrahydroisoquinoline (**110**)

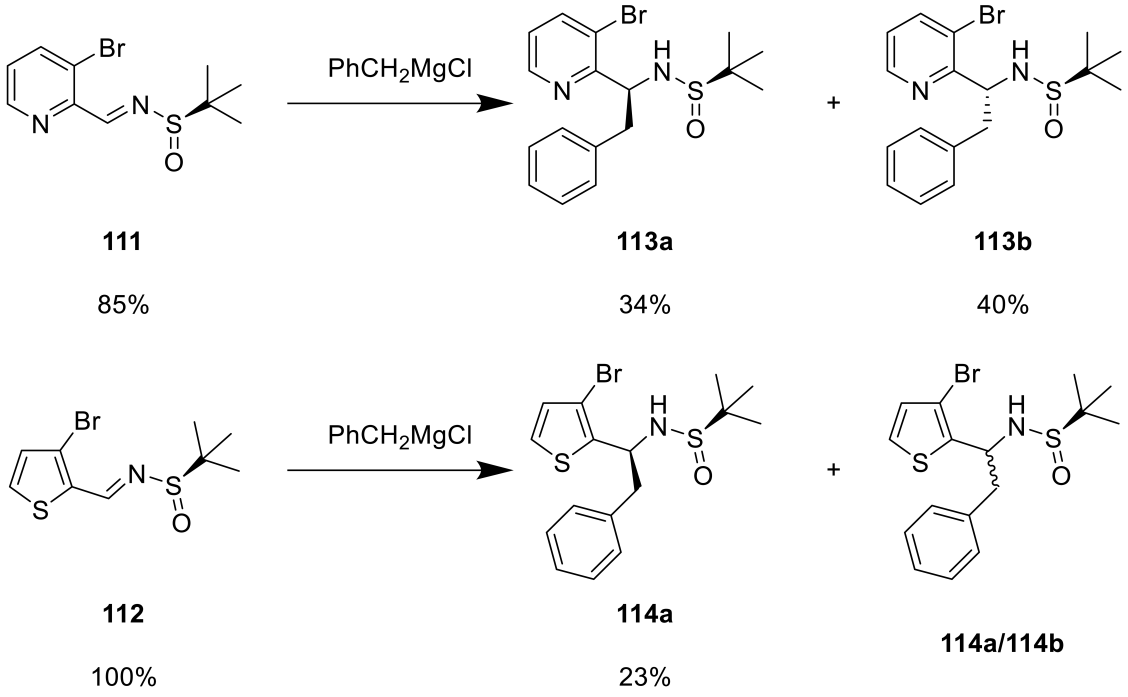
4.20.2 Heterocycles as ring A

Following the investigation of electron-rich and electron-deficient aromatic aldehydes, the subsequent phase of the study focused on the synthesis utilizing heterocyclic starting aldehyde derivatives. Specifically, 2-bromo-3-formylpyridine and 3-bromo-2-thiophenecarbaldehyde were selected as representative substrates to probe electronic and structural influences on the reaction pathway. The pyridine-based aldehyde is inherently electron-deficient due to the nitrogen atom's strong electron-withdrawing effect, which lowers the π-electron density of the aromatic system. In contrast, the thiophene derivative exhibits electron-rich characteristics, as the sulfur atom enhances charge delocalization through its lone pair electrons. By comparing these two heterocycles, the study aimed to elucidate how variations in electronic properties and ring heteroatoms affect the reactivity and outcome of the synthetic transformation. This systematic evaluation not only highlights the adaptability of the methodology but also provides valuable insights into the interplay between heterocyclic structure and reaction efficiency.

To incorporate the required chiral information into the target molecules, the initial step again involved the condensation of the selected heterocyclic aldehydes with Ellman's chiral sulfinamide auxiliary. This reaction afforded the corresponding *N*-sulfinylimines – **111** in 85% isolated yield and **112** in a quantitative yield. Notably, both condensation reactions proceeded

efficiently under mild conditions, and in the case of compound **112**, the product was obtained in high purity without the need for further purification by FCC.

The subsequent nucleophilic addition of the benzyl Grignard reagent to the previously formed *N*-sulfinylimines led to the formation of the corresponding diastereomeric *N*-sulfinylamines. Specifically, pyridine compounds **113a** and **113b** were obtained in yields of 34% and 40%, respectively, while the reaction involving the second *N*-sulfinylimine yielded thiophene derivative **114a** (23%) along with a diastereomeric mixture of **114a** and **114b**. The latter mixture could not be fully resolved using FCC under the initially applied conditions (Scheme 74). The absolute configuration was determined according to Section 4.8.1 *via* ^{1}H-NMR spectroscopy.

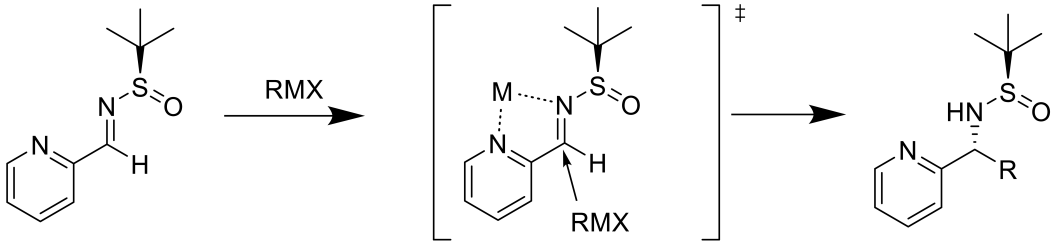


Scheme 74 Formation of the diastereomeric heterocycles

Although complete separation of the diastereomers **114a** and **114b** could be achieved through further optimization of the chromatographic parameters, such as modification of the eluent system or stationary phase, this aspect was not pursued in the present study, as it fell outside the primary scope of the investigation.

Interestingly, the relative distribution and overall yields of the diastereomers of the pyridine derivatives **113a** (34% yield, (*S*)-configuration at C-1) and **113b** (40% yield, (*R*)-configuration at C-1) differed from the trends observed with the non-heterocyclic substrates. This deviation may be attributed to a coordination interaction between the Grignard reagent and the lone pair electrons on the nitrogen atom of the pyridine ring. Such coordination could alter the direction of nucleophilic attack on the imine carbon, thereby influencing the diastereoselectivity and potentially leading to a reversal in the preferential formation of one diastereomer over the other. This reversal of the diastereoselectivity in the 1,2-addition of Grignard reagents to *N*-sulfinylimines with a 2-pyridyl moiety was already reported by Kuduk *et al*.[190] In the case of 2-

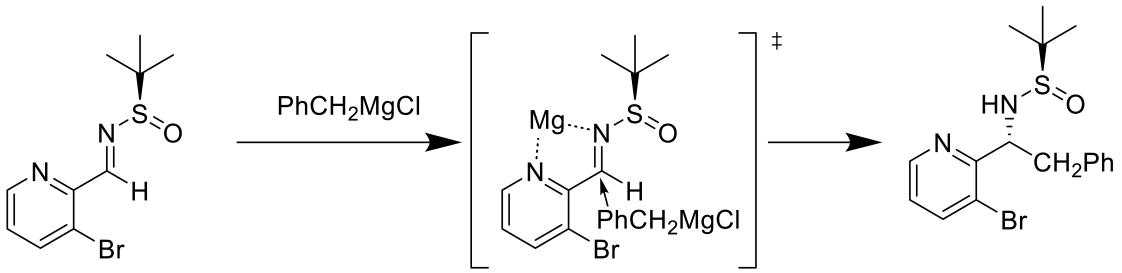
pyridyl-*N*-suflinylimines, the metal is coordinated between the pyridine and the imine nitrogens and not with the sulfoxide oxygen. During the subsequent addition step of the nucleophile, instead of a chair-like transition state, an open transition state occurs. This addition is depicted in Scheme 75.



R= alkyl-, vinyl-, allyl-, alkinyl-, aryl-
M= Mg, Li
X= Cl, Br

Scheme 75 Addition of organometallic reagents to pyridine-containing *N*-sulfinylimines without *ortho*-bromination according to Kuduk *et al*.[190]

Applied to our reaction, this insight confirms the obtained results for compounds **113a** and **113b**. The outcome of the reaction remains unchanged even when the employed organometallic reagent is a benzyl Grignard reagent and the pyridine heterocycle is *ortho*-brominated to the *N*-sulfinylimine. The process is illustrated in Scheme 76.



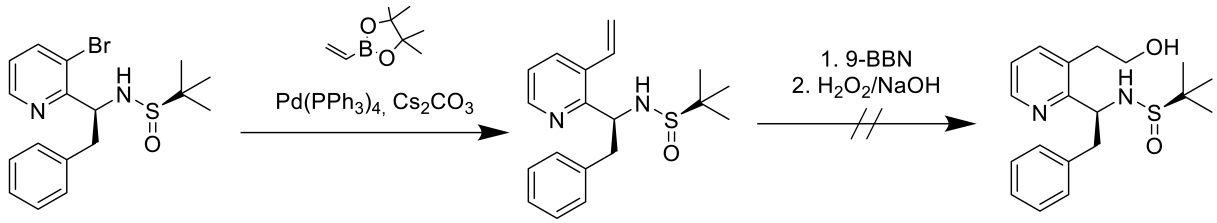
111 **113b**

Scheme 76 Addition of the benzyl Grignard reagent to pyridine-containing, *ortho*-brominated *N*-sulfinylimine **111**

In the subsequent Suzuki cross-coupling step, the well-documented catalyst deactivating effect of pyridine derivatives[191] posed a significant challenge for compound **113a**. Under the applied conditions, the starting material underwent decomposition, resulting in the formation of multiple side products. Although traces of the desired styrene derivative **115** were detected by ASAP mass spectrometry, isolation and purification *via* standard chromatographic methods proved unsuccessful.

Due to the inability to isolate compound **115**, the crude reaction mixture was directly subjected to the subsequent hydroboration-oxidation sequence. However, no conversion to the target primary alcohol was observed (Scheme 77). This lack of reactivity may be attributed to the strong tendency of 9-BBN to form stable Lewis adducts with pyridine-containing compounds,

as previously reported by Wrackmeyer *et al.*[192] Such coordination could effectively inhibit the hydroboration step by blocking the reactive site on the borane reagent.

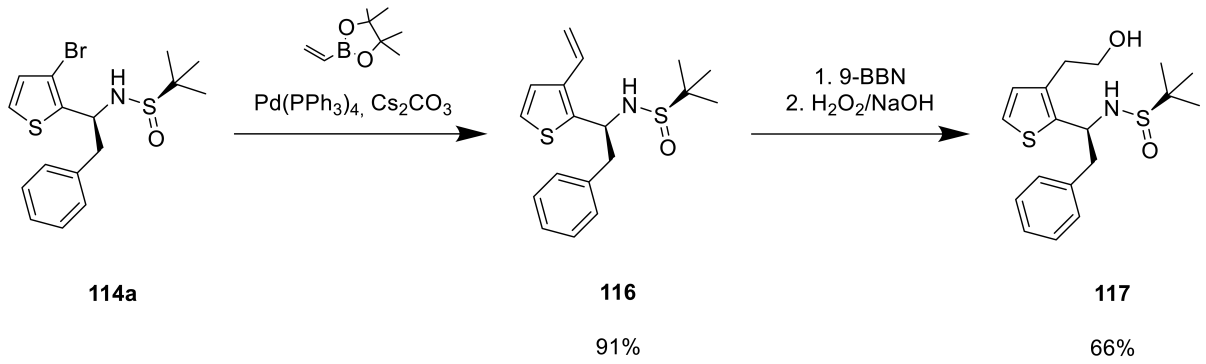


113a **115**

Scheme 77 Attempted transformation of vinylpyridine derivative **113a** to a primary alcohol

Given the operational challenges encountered in those two synthetic steps of our methodology, further optimization studies were deemed beyond the scope of this investigation. The observed limitations – particularly the competing decomposition pathways and unsuccessful functionalization – suggested fundamental incompatibilities with the current approach that would require substantial methodological redesign to overcome. While these unresolved challenges represent limitations of the current study, they provide valuable insights for future work in this area, particularly regarding the handling of heterocyclic systems in transition metal-catalyzed and borane-mediated transformations. Consequently, we focused our remaining efforts on characterizing successful intermediate transformations rather than pursuing incremental improvements to these problematic stages.

With this target in focus, the Suzuki cross-coupling of the thiophene halide **114a** to afford the desired vinylthiophene derivative **116** was successfully carried out, delivering an excellent isolated yield of 93%. To ensure efficient catalytic turnover, an increased catalyst loading (0.3 equivalents instead of the standard 0.1 equivalents) was applied. This adjustment was made in consideration of the thiophene ring's electron-rich nature, particularly its free electron pair, which may interfere with the catalytic cycle by coordinating to the palladium center or altering its reactivity. The high yield and clean conversion observed under these modified conditions stand in marked contrast to the challenges encountered with analogous pyridine substrate, underscoring the critical influence of heterocycle electronics on cross-coupling efficiency. The successful outcome with **114a** not only demonstrates the compatibility of electron-rich thiophene derivatives within our developed methodology but also provides valuable empirical evidence that increased catalyst loading can effectively mitigate coordination-induced deactivation in sulfur-containing systems.



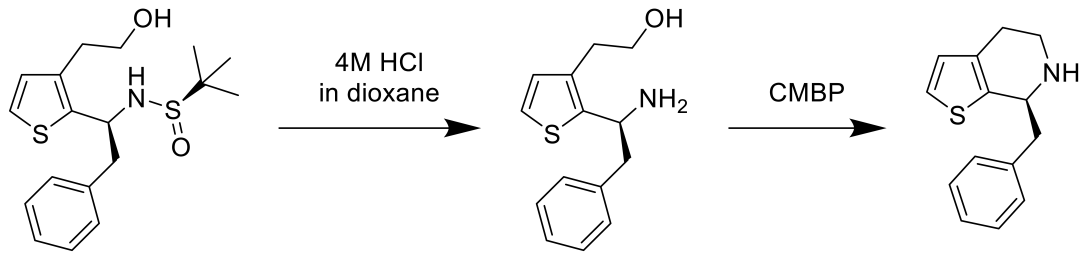
114a **116** **117**

91% 66%

Scheme 78 Transformation of thiophen halide **114a** to the primary alcohol **91**

The subsequent hydroboration-oxidation sequence efficiently converted vinylthiophene derivative **116** to the corresponding primary alcohol **117** in 66% yield (Scheme 78). This transformation proceeded smoothly under standard reaction conditions, requiring no optimization or modification of the established protocol. The observed yield reflects the inherent efficiency of hydroboration chemistry for converting vinyl groups to their corresponding alcohols, while simultaneously demonstrating the compatibility of the thiophene moiety with these reaction conditions.

Following the established protocol, acid-mediated deprotection of compound **117** furnished the corresponding aminoalcohol **118** in 59% yield. In the final step, cyclization with CMBP proceeded smoothly, affording the enantiomerically pure heterocyclic product **119** in a yield of 73% (Scheme 79).



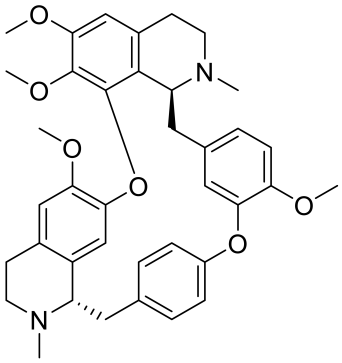
117 **118** **119**

59% 73%

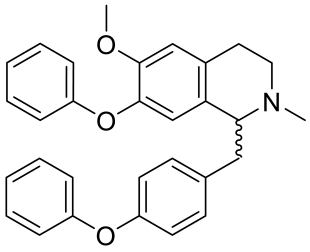
Scheme 79 Successful synthesis of (*S*)-7-benzyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (**119**)

5 Summary

The aim of this thesis was the development of an enantioselective synthesis route for benzyltetrahydroisoquinolines and ring size homologues. This was achieved by employing Ellman's reagent ((*R*)-*tert*-butanesulfinamide) as cost-effective chiral auxiliary. As lead structures, truncated versions of tetrandrine (**5**), e.g. SG-094 (**22**) (Figure 11) were selected.



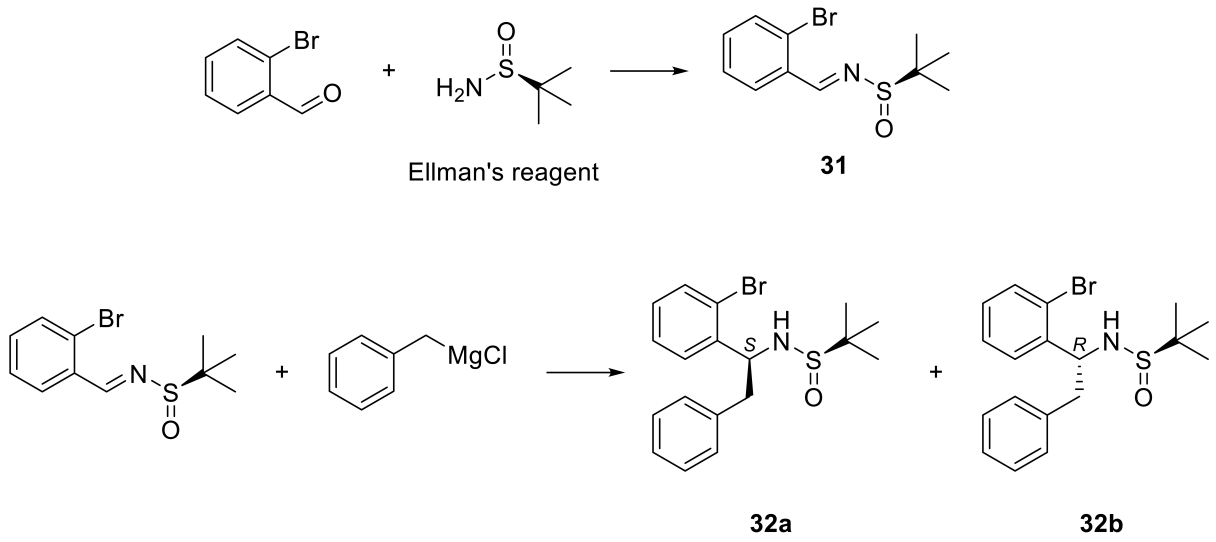
Tetrandrine (**5**)



SG-094 (**22**)

Figure 11 Tetrandrine (**5**) and the previously in the Bracher group synthesized lead structure SG-094 (**22**)

The developed route consists of six steps, starting with a microwave irradiation assisted condensation reaction of Ellman's auxiliary with an *ortho*-halogenated aromatic aldehyde, forming the desired *N*-sulfinylimine. In addition to the good commercial availability and variability of starting *ortho*-brominated aromatic aldehydes for this synthesis step, the efficiency of this reaction step was of interest, as the reaction always proceeds in yields between 85-100% and the purification *via* FCC is often not necessary. In the following step, benzyl Grignard solution is added to the *N*-sulfinylimine, yielding two diastereomers of *N*-sulfinylamines, which are readily separable *via* FCC, yielding an early access to enantiomerically pure intermediates, which do not loose stereochemical integrity in the upcoming synthesis steps. In case this addition reaction occurs with high diastereoselectivity, both enantiomers of the final product are accessible by using the one or other enantiomer of Ellman's reagent. In case the addition reaction takes place with poor diastereoselectivity, both enantiomers of the target compounds are available from separated diastereomers obtained with one enantiomer of the chiral auxiliary. Those two synthesis steps are illustrated in Scheme 80.



Scheme 80 Synthesis steps towards the new stereocenters employing Ellman's reagent

The upcoming Suzuki cross-coupling reaction between the brominated *N*-sulfinylamines and the vinylboronic acid pinacol ester generates styrene intermediates, which includes the necessary C_2-unit into the molecule. The styrene then undergoes hydroboration with 9-BBN, forming the anti-Markownikow borane intermediate, which undergoes (without prior purification) an oxidation step by applying H_2O_2/NaOH to the (2-hydroxyethyl)arene intermediates as precursors for the central ring closing reaction. Cyclization attempts in presence of the N-sulfinyl residue gave disappointing results. Consequently, the sulfinyl residue was cleaved under standard acidic conditions using 4M HCl in dioxane, resulting in the free aminoalcohol. The final step, the ring closure to the THIQ core, was achieved by employing Tsunoda's reagent (CMBP). Following this general procedure, seven benzyltetrahydroisoquinolines with different configurations and one thiophene analogue (illustrated in Figure 12) were successfully synthesized. Furthermore, it was found that sterically demanding ether groups (phenyl and benzyl ethers) and fluorine as substitute on the final ring A are tolerated in this route, whereas a pyridine heterocycle as ring A and a nitro group as substituent on ring A block the synthesis route.

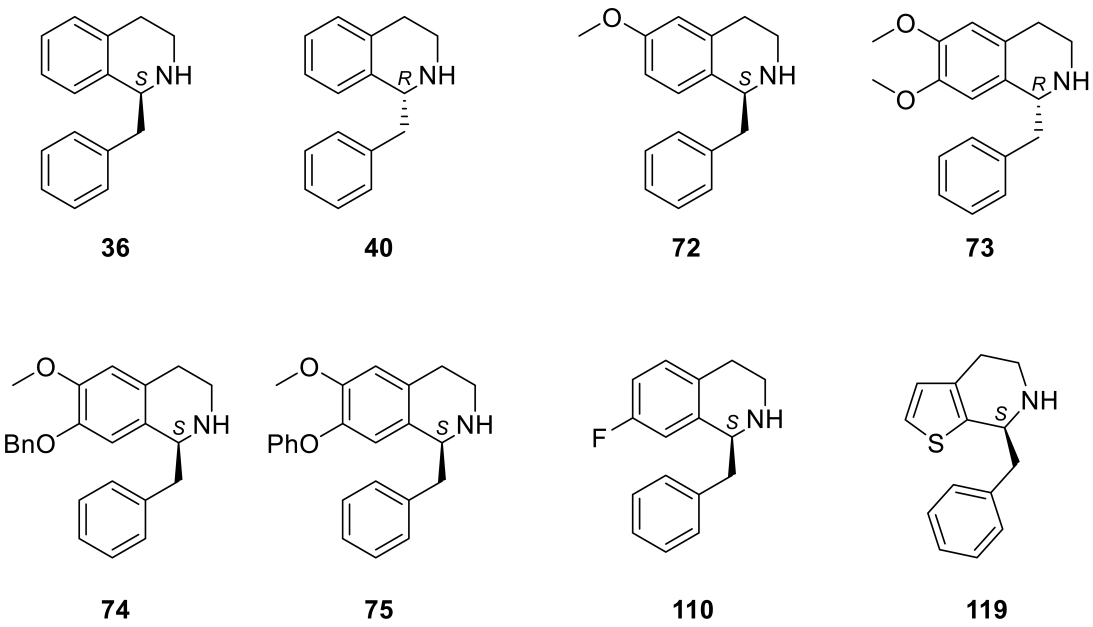


Figure 12 Synthesized enantiomerically pure final products

For the homologous tetrahydrobenzazepines, the same synthesis route was investigated but led to failure during the synthesis of the 3-arylpropanal intermediates from the ortho-brominated *N*-sulfinylamines. Our target was to include a C_3-extension *via* a Mizoroki-Heck cross coupling-reaction, employing allyl alcohol instead of the Suzuki cross-coupling, which was employed for the synthesis of THIQs. Under any of the tested Mizoroki-Heck conditions, it was found out that aryl bromides do not react to the desired 3-arylpropanal derivatives. This problem was solved by employing the more reactive *ortho*-iodinated benzaldehydes as starting material. The first two reaction steps, the condensation with Ellman's auxiliary to form the *N*-sulfinylimines and the addition of the benzyl Grignard reagent to those *N*-sulfinylimines, showed no difference in efficiency and were comparable with the results achieved with the intermediates derived from brominated benzaldehydes.

As the required 2-iodobenzaldehyde starting materials are not easily commercially available, an iodination method for aromatic aldehydes involving TFA, TFAA, NIS and microwave irradiation was explored.

By simply reducing the aldehyde groups of the 3-phenylpropanal derivatives derived from the Mizoroki-Heck cross-coupling reaction into the primary alcohol, we obtained the required 3-(aryloxy)propanol intermediates. From this step on, the synthesis route is the same as for THIQs. In the first step, Ellman's auxiliary is cleaved under acidic conditions, yielding the corresponding aminoalcohol and in the second step, the ring is closed employing CMBP. Following this procedure, three enantiomerically pure (*S*)-configurated tetrahydrobenzazepines were synthesized and are illustrated in Figure 13.

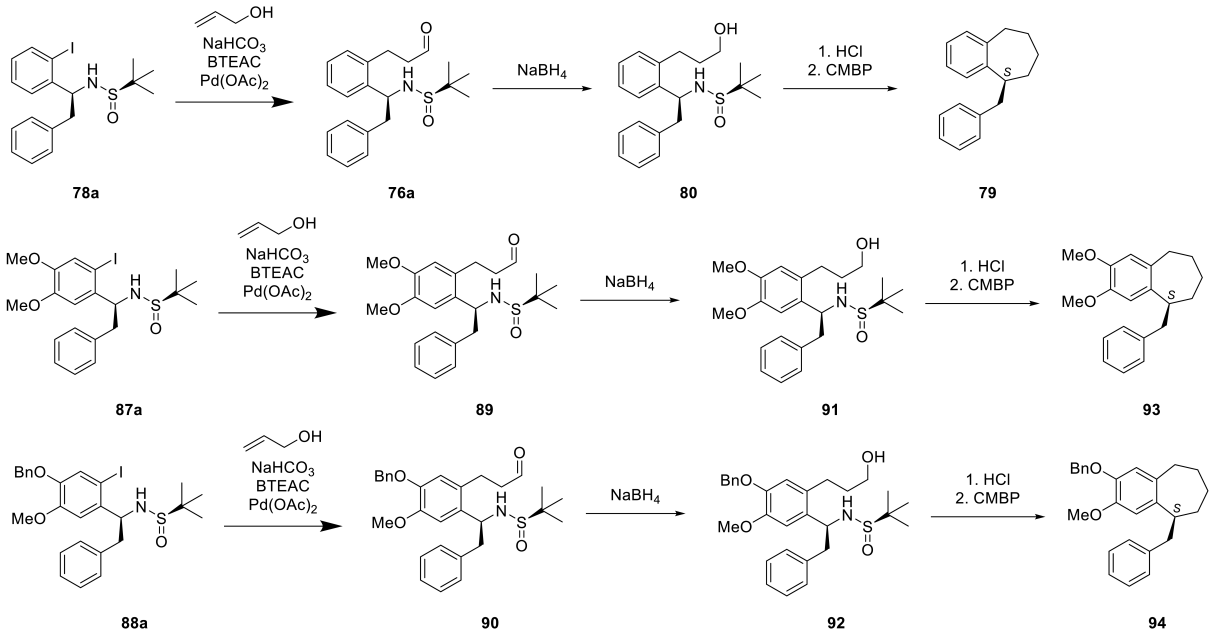
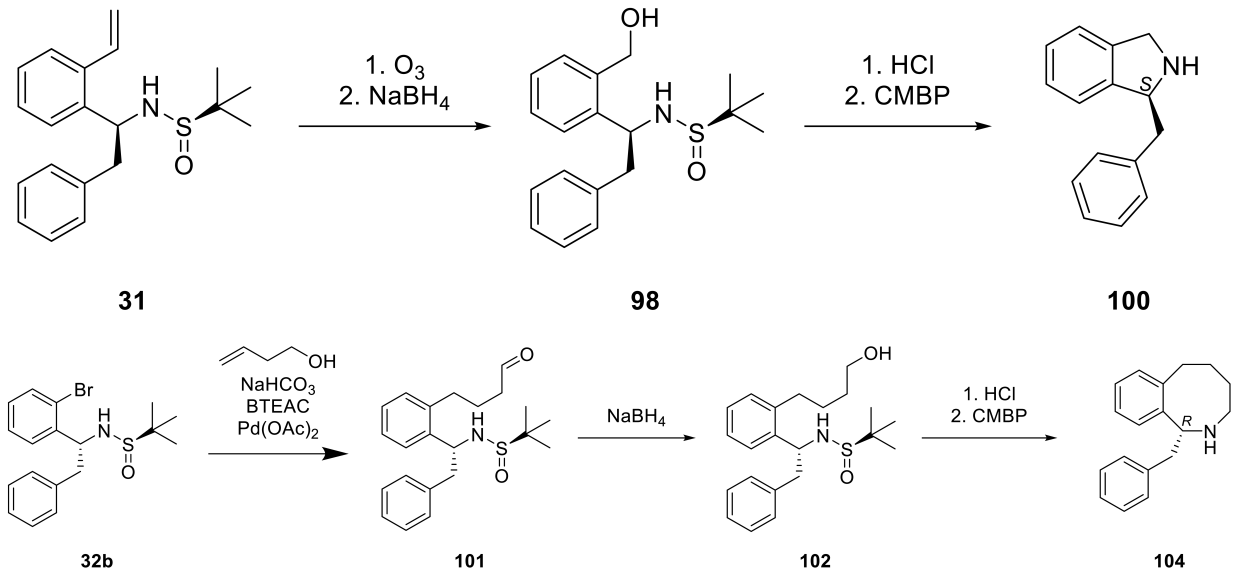


Figure 13 Enantiomerically pure synthesized tetrahydrobenzazepines and central intermediates

In addition to the THIQ and the tetrahydrobenzazepine synthesis, an enantioselective synthesis route towards the lower homologues, 1-benzylisoindolines, was also developed. Starting from a late stage shared precursor for the THIQ synthesis, the styrene derivative **33**, the desired (*S*)-1-benzylisoindoline **100** was synthesized in three steps, consisting of the ozonolysis of the vinyl group followed by reduction $NaBH_4$ to a benzyl alcohol intermediate without purification of the intermediate aldehyde. In the subsequent steps the cleavage of Ellman's auxiliary under standard acidic conditions and the final ring closure employing CMBP to form the cyclized product were executed.

In contrast to reducing the ring size, the further extension of the ring size to an 8-membered homologue, also referred to as hexahydrobenzazocine, employs the *ortho*-brominated *N*-sulfinylamine **32b** as precursor, which was already synthesized during the synthesis of THIQs (see Scheme 80). Although the synthesis of tetrahydrobenzazepines indicated that the lower reactivity of the bromo derivatives prevents the Heck-reaction, it was not necessary to switch the starting material to iodinated *N*-sulfinylamines, as the arylbutryaldehyde **101** was synthesized successfully *via* Heck-coupling reaction employing 3-buten-1-ol. Following the same procedure as executed for benzylisoindolines and tetrahydrobenzazepines, consisting of reducing the aldehyde to a 4-arylbutanol intermediate **102**, cleavage of Ellman's auxiliary under standard acidic conditions and the following ring closure with CMBP, hexahydrobenzazocine **104** was finally yielded. The relevant precursors for the synthesis of benzylisoindolines, hexahydrobenzazocines and the final products thereof are illustrated in Scheme 81.

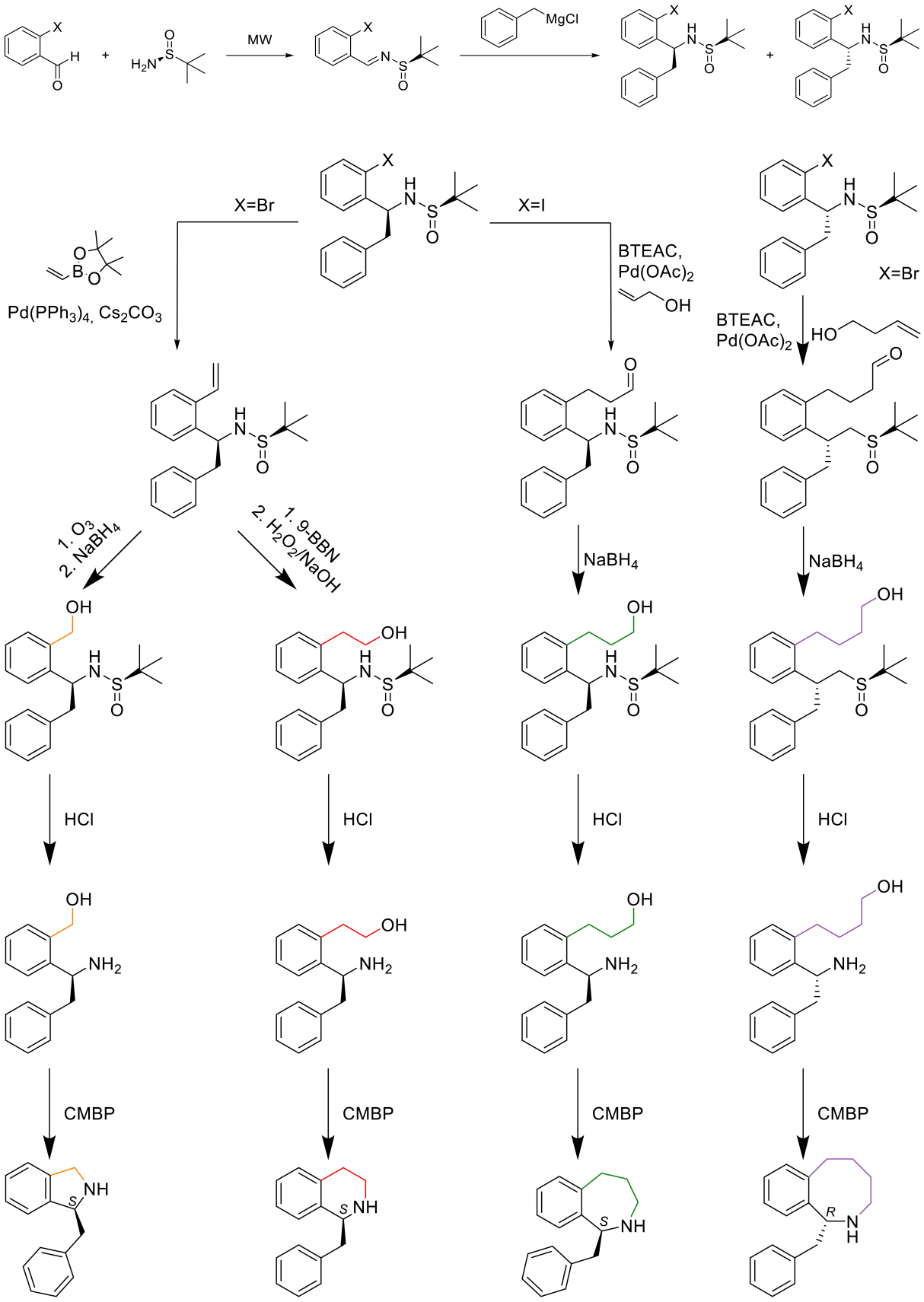


Scheme 81 Synthesis of (*S*)-1-benzylisoindoline (**100**) and (*R*)-1-benzylhexahydrobenzazocine (**104**)

Future research in this area could be directed at using the established routes to synthesize more analogues and further investigate their scope and limitations. Here, especially compounds synthesized with the addition of other benzyl Grignard reagents would be of interest. Moreover, no derivatization (for example alkylation) of the secondary cyclic amines was conducted as part of this work and would certainly be an interesting topic regarding the effect on the biological activity of the compounds.

The synthesized compounds within this project do not correspond to any known natural products and were not tested for their biological activity. This evaluation requires specialized equipment and techniques and was beyond the scope of this thesis. Nonetheless, the biological data is of high interest and immensely important for further SAR studies and novel target molecules.

All in all, synthesis routes towards enantiomerically pure benzylisoindolines, benzyl-THIQs, benzyltetrahydrobenzazepines and benzylhexahydrobenzazocines were developed. All routes share the same basis with Ellman's auxiliary as chiral information and contain similar precursors, which enables the advantage of late-stage diversification. The majority of the reactions require the same reagents, what simplifies the purchasing process and results in cost-effective synthesis. An overview of the established synthesis routes (due to clarity without residues) is illustrated in Scheme 82.



Scheme 82 Complete overview of the novel developed synthesis routes

6 Experimental part

Preparative Methods:

Air or moisture sensitive reactions were performed under inert gas atmosphere using standard Schlenk techniques. Therefore, either a round bottom, microwave or Schlenk flask was provided with a rubber septum, evacuated, and subsequently flushed with nitrogen (three cycles). For flame drying, the flask was additionally heated under active vacuum using a heat gun. Reaction mixtures were stirred using a magnetic stirrer. For reactions performed under elevated temperature either an oil bath with a temperature sensor or a heater block with contact thermometer was used. Cooling of reaction mixtures was achieved using an ice bath or a cryostat.

Microwave-accelerated reactions were carried out using a Discover (S-Class Plus) SP microwave reactor from CEM GmbH (Kamp-Lintfort, Germany).

All commercial reagents, starting materials and dry or HPLC grade solvents for synthesis were used without further purification if not stated otherwise and were purchased from Sigma Aldrich, VWR, abcr, Alfa Aesar, BLDpharm or TCI. All solvents for work-up and purification were purified by distillation.

Reaction Control and Purification:

Reaction control was achieved by either thin layer chromatography (TLC) or by atmospheric pressure solids analysis probe (ASAP) *via* atmospheric-pressure chemical ionization (APCI) on an expression CMS device by Advion (Ithaca, USA). For TLC, polyester sheets coated with silica gel manufactured by Machery-Nagel (Polygram® SIL G/UV_{254}) were used. Visualisation was achieved in the form of exposure to UV light (254 nm) for UV-active substances, unspecific reagents like vanillin + H_2SO_4 and ceric ammonium molybdate (CAM) solution or with the appropriate dye 2,4-dinitrophenylhydrazine (DNPH) for aldehydes and ninhydrin for cyclic secondary amines. Flash column chromatography was performed using a silica gel 60 M (0.040 – 0.063) from Machery-Nagel. Elution was performed with the solvent system indicated in the specific synthesis protocol.

Analytical Methods:

All nuclear magnetic resonance (NMR) spectra (^1H, ^{13}C, DEPT, H-H COSY, HMQC, HSQC, HMBC) were recorded at 23 °C using either an Avance III 400 MHz Bruker BioSpin or Avance III 500 MHz Bruker Biospin instrument (Billerica, USA). For ^1H and ^{13}C NMR chemical shifts (δ) are indicated in parts per million (ppm) and were referenced to the residual solvent peak: DMSO-d_6 = 2.50 ppm, CD_2Cl_2 = 5.32 ppm, and $CDCl_3$ = 7.26 ppm for ^1H; DMSO-d_6 = 39.52 ppm, CD_2Cl_2 = 53.80 ppm, and $CDCl_3$ = 77.16 ppm for ^{13}C.[193] For signal assignment to their multiplicities, the following abbreviations were used. s - singlet, d - duplet, t – triplet, q – quartet, m – multiplet.

High resolution mass spectrometry (HRMS) was performed by the LMU Mass Spectrometry Service. For electron ionisation (EI) a Thermo Finnigan MAT 95 (Thermo Fisher Scientific, Waltham, USA) or Joel MStation Sektorfeld (Akishima, Japan) instrument operating at a core temperature of 250 °C and 70 eV was used. Electron spray ionisation (ESI) spectra were measured using a Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron Resonance machine at 250 °C.

Infrared (IR) spectra were measured on a Perkin Elmer FT-IR BXII/1000 spectrometer (Waltham, USA) combined with DuraSamp IR II Diamond ATR sensor (Smiths Detection, London, England) Characteristic absorption bands were assigned at the wavenumbers (cm^{-1}).

Melting points were determined using a Büchi melting point B-540 instrument (Flawil, Swiss) by applying the open tube capillary method, are uncorrected and reported in °C.

Optical rotations were measured on a Perkin Elmer 241 Polarimeter using a sodium lamp (589 nm).

Purities were determined by HPLC on a HP Agilent 1100 system (Agilent Technologies, Santa Clara, USA) using G1311A QuatPump system, 1100/1200 diode array detector and a G1316A ColComp column oven, detecting at 210 nm and 254 nm. HPLC purity (%) was determined *via* Chromeleon 7.2.9 software (Thermo Fisher Scientific Dionex, Waltham, USA) for processing and analysis of HPLC spectra.

Following methods were performed:

Column: Zorbax Eclipse Plus® C18 5µm (4.6 x 150 mm), flow rate 1.0 – 1.5 mL/min, temp. 30 – 50°C.

Method 1 (pH = 5):

Eluent:

a) Methanol / phosphate buffer pH = 5 (80/20)

b) Methanol / phosphate buffer pH = 5 (70/30)

c) Methanol / phosphate buffer pH = 5 (60/40)

d) Methanol / phosphate buffer pH = 5 (50/50)

Method 2 (pH = 9)

Eluent:

a) Methanol / phosphate buffer pH = 9 (80/20)

b) Methanol / phosphate buffer pH = 9 (70/30)

Software

All visualisations of structures and schematic depictions were made using ChemDraw Professional 20.1 by PerkinElmer. All NMR spectra were processed using MestreNova 14.2 by MestreLab Research S.L.S.

6.1 General procedures

General Procedure (GP) A: Synthesis of *N*-tert-butyl sulfinylimines of aromatic aldehydes

A procedure previously reported by Collados *et al*.[101] was modified and used. The respective benzaldehyde derivative (1.00 eq.) and the required stereoisomer of *N-tert*-butylsulfinamide (1.10 – 1.20 eq.) were suspended in tetraethyl orthotitanate (3.00 eq.) in a 30 mL microwave vessel. Open vessel reactions were carried out in a 100 mL round bottom flask. The mixture was stirred under microwave irradiation (70 °C, 40 W) for 15-30 min. After cooling to room temperature, the mixture was diluted with EtOAc (20 mL) and slowly poured into brine (1 mL/2.50 mmol aldehyde) while being vigorously stirred. The resulting suspension was filtered over a pad of celite and silica. The pad was washed with EtOAc (80 mL) and the combined organic phases were dried over anhydr. Na_2SO_4. The solvent was removed *in vacuo* to yield the desired product. The product was used without further purification.

GP B: Grignard addition to *N-tert*-butyl sulfinylimines

A procedure previously reported by Reddy *et al*.[106] was modified and used. The respective *N-tert*-butyl sulfinylimine derivative (1.00 eq.) was dissolved in anhydr. DCM (final c = 300 mM) using a 100 – 250 mL round bottom flask and the solution cooled to -21 °C or -78 °C. A commercially acquired benzylmagnesium chloride solution (1.40 – 2.00 mol/L in THF, 2.00 - 3.00 eq.) was added dropwise and the reaction solution was stirred for 2 h at the same temperature. The solution was warmed up to 0 °C and the reaction quenched with sat. aq. NH_4Cl. The mixture was extracted with DCM (3 x 40 – 200 mL, 10 mL/mmol imine). The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo.* In all cases, two diastereomers were obtained.

GP C: Suzuki reaction for the synthesis of styrene structures

A procedure previously reported by Sun *et al*.[194] was modified and used.

A 250 mL round bottom flask was charged with the respective bromobenzene derivative (1.00 eq.), Cs_2CO_3 (5.00 eq.), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$ – 0.100 eq), and the components dissolved in 50-150 mL dry dioxane. After 30 minutes, vinylboronic acid pinacol ester (1.10 eq.) was added dropwise and the reaction mixture was stirred at 90 °C for 16 h. The reaction was quenched by addition of water. The catalyst was removed by filtration through a pad of celite and the eluate was extracted with EtOAc (3x 50 – 100 mL).

The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo*.

GP D: Hydroboration and oxidation to primary aliphatic alcohols

A procedure previously reported by Kudale *et al*.[122] was modified and used.

A 250 mL round bottom flask was charged with the respective styrene (1.00 eq.) and dry THF (final c = 0.5 M) was added. The solution was cooled to 0 °C and 9-borabicyclo[3.3.1]nonane solution (0.5 mol/L in THF, 9-BBN, 3.00 eq.) was added dropwise. The resulting mixture was stirred at room temperature for 12 h. After full conversion of the starting material (TLC control), the mixture was cooled to 0 °C and H_2O_2 (33% aqueous solution, 10 eq.) was added dropwise followed by NaOH (2M aqueous solution, 10 eq.). The resulting mixture was warmed to room temperature and stirred for 3 h. Afterwards, water was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo.*

GP E: Amine deprotection

A procedure previously reported by Reddy *et al*.[106] was modified and used.

A 50 mL round bottom flask was charged with the respective *N-tert*-butyl sulfinylamine and HPLC grade MeOH (final c = 100 mM) was added. The solution was cooled to 0 °C and 4 M HCl in dioxane (6.00 eq.) was added slowly. The resulting mixture was stirred for 30 min at 0 °C. Then, the solution was basified to pH 12 with NaOH (2M aqueous solution) and extracted with DCM (3 x 25 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product or used for the subsequent synthesis step without further purification. The product was dried *in vacuo.*

GP F: Mitsunobu reaction for ring closure

A procedure previously reported by Kudale *et al*. was modified and used.[122]

To a 50 mL round bottom flask charged with the respective aminoalcohol (1.00 eq.), anhydr. toluene (final c = 50.0 - 100 mM) and cyanomethylenetributylphosphorane (CMBP – 1.50 eq.) were added. The solution was stirred at 110 °C for 18 h. All volatiles were removed under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo.*

GP G: Suzuki reaction for the synthesis of ethoxyvinylethers

A procedure previously reported by Sun *et al*.[194] was modified and used.

A 250 mL round bottom flask was charged with the respective bromobenzene derivative (1.00 eq.), Cs_2CO_3 (5.00 eq.) and tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$ – 0.10 eq). and the components dissolved in 50-150 mL dry THF. After 30 minutes, (*E*)-2-ethoxyvinyl-boronic acid pinacol ester (2.00 eq.) was added dropwise and the reaction mixture was stirred at 90 °C for 16 h. The reaction was quenched by addition of water. The catalyst was removed by filtration through a pad of celite and the eluate was extracted with EtOAc (3x 50 – 100 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo*.

GP H: Heck reaction for the synthesis of 3-aryl propionaldehydes

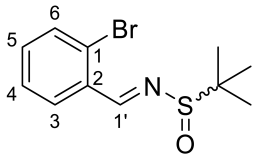
A procedure previously reported by Shang *et al*.[169] was modified and used. A 50 - 100 mL round bottom flask was charged with the respective iodobenzene derivative (1.00 eq.), benzyltriethylammonium chloride (BTEAC) (1.00 eq.), anhydr. $NaHCO_3$ (2.00 eq.) and palladium(II) acetate (10 – 20 mol%). Then, anhydr. DMF (final c = 70 – 160 mM) and allyl alcohol (2.00 eq.) were added and the reaction mixture was stirred at 55 - 60 °C for 2 - 4 h. After cooling to room temperature, the solution was diluted with EtOAc (50 mL). The solution was washed with water (30 mL) and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL). The combined aqueous phases were re-extracted with EtOAc (100 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product. The product was dried *in vacuo*.

GP I: Aldehyde to alcohol reduction:

A 50 mL round bottom flask was charged with the respective aldehyde (1.00 eq.) and HPLC grade MeOH (final c = 100 mM) was added. The solution was cooled to 0 °C and $NaBH_4$ (1.20 - 1.50 eq.) was added. The reaction mixture was stirred for 5 min at 0 °C. Then, the solution was allowed to attain room temperature and stirred for 1 - 2 h. Water was added (30 mL) and the mixture was extracted with DCM (2 x 30 mL) and EtOAc (2 x 50 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified *via* flash column chromatography on silica using the appropriate eluent to yield the desired product or used for synthesis without further purification. The product was dried *in vacuo.*

6.2 Characterization of compounds

(*E*)-*N*-(2-Bromobenzylidene)-2-methylpropane-2-sulfinamide – (23)



$C_{11}H_{14}BrNO_4S$

M = 288.20 g/mol

Synthesized according to **GP A**, using 2-bromobenzaldehyde (944 mg, 5.00 mmol, 1.00 eq.), (+/-) *N*-*tert*-butylsulfinamide (742 mg, 6.00 mmol, 1.20 eq.) and tetraethyl orthotitanate (3.42 g, 3.17 mL, 15.0 mmol, 3.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 95:5

Yield: 1.37 g (4.75 mmol, 95%)

Appearance: yellow oil

R_f: 0.24 (hexanes/EtOAc 95:5)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.98 (s, 1H, 1'-H), 8.04 (dd, *J* = 7.6, 2.0 Hz, 1H, 3-H), 7.65 (dd, *J* = 7.7, 1.5 Hz, 1H, 6-H), 7.42 – 7.37 (m, 1H, 4-H), 7.35 (td, *J* = 7.6, 2.0 Hz, 1H, 5-H), 1.28 (s, 9H, *tert*-butyl).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 162.34 (C-1'), 133.80 (C-5), 133.44 (C-6), 133.04 (C-2), 129.78 (C-3), 127.83 (C-4), 126.56 (C-1), 58.15 (C-$(CH_3)_3$), 22.84 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 2970, 2956, 1583, 1272, 1075, 1025, 755, 741 cm^{-1}

HRMS (ESI): *m/z* **=** 288.0056 $[M+H]^+$ (calculated for $C_{11}H_{15}BrNOS^+$ $[M+H]^+$ 288.0052)

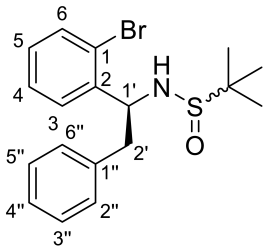
Purity (HPLC) λ_{254}: > 99% (Method 1b)

NMR data according to literature.[195]

***N*-((*S*)-1-(2-Bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (24a)**
and
***N*-((*R*)-1-(2-Bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (24b)**

Synthesized according to **GP B**, using (*E*)-*N*-(2-bromobenzylidene)-2-methylpropane-2-sulfinamide (**23**, 750 mg, 2.60 mmol, 1.00 eq.), and benzylmagnesium chloride solution (1.40 M in THF) (3.71 mL, 5.20 mmol, 2.00 eq.). The reaction was carried out at -21°C.
Eluent for flash column chromatography: hexanes/EtOAc 60:40, order of elution:

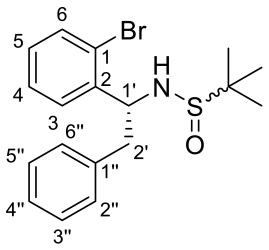
1. 24a
2. 24b



24a

$C_{18}H_{22}BrNOS$
M = 380.34 g/mol

Yield: 251 mg (0.660 mmol, 25%)
Appearance: white solid
Melting point: 130 – 131 °C
R_f: 0.35 (hexanes/EtOAc 60:40)
α_{598}^{20}: -5 (β = 3.10 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57 (dd, J = 8.0, 1.2 Hz, 1H, 6-H), 7.40 (dd, J = 7.8, 1.7 Hz, 1H, 3-H), 7.35 – 7.28 (m, 3H, 3''-H, 4-H, 5''-H), 7.28 – 7.21 (m, 1H, 4''-H), 7.20 – 7.13 (m, 3H, 2''-H, 5-H, 6''-H), 5.10 (ddd, J = 8.4, 5.4, 3.0 Hz, 1H, 1'-H), 3.54 (s, 1H, NH), 3.24 (dd, J = 13.7, 5.3 Hz, 1H, 2'-H), 2.91 (dd, J = 13.7, 8.6 Hz, 1H, 2'-H), 1.11 (s, 9H, *tert*-butyl)
^{13}C NMR (101 MHz, CD_2Cl_2) δ 141.00 (C-2), 137.10 (C-1''), 133.32 (C-6), 129.91 (C-2'', C-6''), 129.57 (C-5), 129.38 (C-3), 129.06 (C-3'', C-5''), 127.91 (C-4), 127.44 (C-4''), 124.00 (C-1), 58.25 (C-1'), 55.92 (C-$(CH_3)_3$), 43.78 (C-2'), 22.61 (3 CH_3)
IR (ATR): $\tilde{\nu}$ = 3304, 2987, 2956, 2916, 1466, 1454, 1439, 1058, 1021, 898, 756, 702 cm^{-1}
HRMS (ESI): *m/z* **=**380.0685 $[M+H]^+$ (calculated for $C_{18}H_{22}BrNOS^+$ $[M+H]^+$ 380.0605)
Purity (HPLC) λ_{254}: > 99% (Method 2a)



24b

Yield: 346 mg (0.910 mmol, 35%)

Appearance: white solid

Melting point: 138 – 139 °C

R_f: 0.18 (hexanes/EtOAc 60:40)

α_{598}^{20}: +3 (β = 2.00 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.56 (dd, J = 8.1, 1.3 Hz, 1H, 6-H), 7.40 (dd, J = 7.8, 1.8 Hz, 1H, 3-H), 7.34 (dddd, J = 7.8, 7.2, 1.3, 0.4 Hz, 1H, 4-H), 7.29 – 7.18 (m, 3H, 3''-H, 4''-H, 5''-H), 7.17 – 7.13 (m, 3H, 2''-H, 5-H, 6''-H), 5.04 – 4.94 (m, 1H, 1'-H), 3.76 (d, J = 7.0 Hz, 1H, NH), 3.17 (dd, J = 13.8, 5.6 Hz, 1H, 2''-H), 2.99 (dd, J = 13.8, 8.3 Hz, 1H, 2''-H), 1.02 (s, 9H, *tert*-butyl)

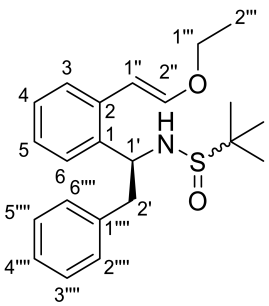
^{13}C NMR (101 MHz, CD_2Cl_2) δ 141.67 (C-2), 137.88 (C-1''), 133.42 (C-6), 130.03 (C-2'', C-6''), 129.48 (C-5), 129.22 (C-3), 128.71 (C-3'', C-5''), 128.03 (C-4), 127.05 (C-4''), 123.55 (C-1), 60.88 (C-1'), 56.52 (C-$(CH_3)_3$), 43.29 (C-2'), 22.45 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3301, 2989, 2956, 2912, 1467, 1454, 1439, 1055, 1024, 898, 757, 701 cm^{-1}

HRMS (ESI): *m/z* **=** 380.0686 $[M+H]^+$ (calculated for $C_{18}H_{22}BrNOS^+$ $[M+H]^+$ 380.0605)

Purity (HPLC) λ_{254}: > 99% (Method 2a)

***N*-((*S*)-1-(2-((*E*)-2-Ethoxyvinyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (25)**



$C_{22}H_{29}NO_2S$

M = 371.54 g/mol

Synthesized according to **GP G**, using *N*-((*S*)-1-(2-bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**24a**, 285 mg, 0.75 mmol, 1.00 eq.), Cs_2CO_3 (1.22 g, 3.75 mmol,

5.00 eq.), Pd(P(Ph$_3$)$_4$) (86.7 mg, 0.080 mmol, 0.100 eq.) and (*E*)-2-ethoxyvinylboronic acid pinacol ester (312 mg, 0.334 mL, 1.50 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 50:50

Yield: 224 mg (0.600 mmol, 81%)

Appearance: orange-brown oil

R$_f$: 0.40 (hexanes/EtOAc 50:50)

α_{598}^{20}: -17 (β = 2.21 · 10^{-3} g/mL, CHCl$_3$)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.34 (m, 1H, 6-H), 7.25 – 7.08 (m, 6H, 3-H, 3''''-H, 4-H, 4''''-H, 5-H, 5''''-H), 7.02 (dd, J = 7.7, 1.8 Hz, 2H, 2''''-H, 6''''-H), 6.58 (d, J = 12.7 Hz, 1H, 2''-H), 5.84 (d, J = 12.6 Hz, 1H, 1''-H), 4.85 (td, J = 7.0, 3.4 Hz, 1H, 1'-H), 3.89 – 3.73 (m, 2H, 1''') -H, 3.57 (d, J = 3.4 Hz, 1H, NH), 3.30 (dd, J = 13.3, 6.7 Hz, 1H, 2'-H), 3.04 (dd, J = 13.3, 7.4 Hz, 1H, 2'-H), 1.32 (t, J = 7.0 Hz, 3H, 2'''-H), 1.15 (s, 9H, *tert*-butyl)

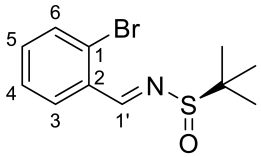
^{13}C NMR (101 MHz, CDCl$_3$) δ 149.34 (C-2''), 138.21 (C-1), 137.76 (C-1''''), 135.49 (C-2), 129.92 (C-2'''', C-6''''), 128.33 (C-3'''', C- 5''''), 127.93 (C-4), 127.07 (C-6), 126.63 (C-3), 126.60 (C-4''''), 126.52 (C-5), 103.01 (C-1''), 65.50 (C-1'''), 56.84 (C-1'), 56.02 (C-(CH$_3$)$_3$), 42.94 (C-2'), 22.72 (3 CH$_3$), 14.93 (C-2''')

IR (ATR): $\tilde{\nu}$ = 3254, 2976, 1633, 1453, 1365, 1155, 1028, 756, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 372.1997 [M+H]$^+$ (calculated for C$_{22}$H$_{30}$NO$_2$S$^+$ [M+H]$^+$ 372.1919)

Purity (HPLC) λ_{254}: > 85% (Method 1b)

(*R,E*)-*N*-(2-Bromobenzylidene)-2-methylpropane-2-sulfinamide – (31)



C$_{11}$H$_{14}$BrNOS

M = 288.20 g/mol

Synthesized according to **GP A**, using 2-bromobenzaldehyde (2.05 g, 10.9 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (1.61 g, 13.0 mmol, 1.20 eq.) and tetraethyl orthotitanate (7.46 g, 6.91 mL, 32.7 mmol, 3.00 eq.). The total batch was divided into four 30 mL microwave vessels for the microwave accelerated reaction and the procedure carried out four times. All batches were combined for work-up.

Yield: 3.08 g (10.7 mmol, 98%)

Appearance: yellow oil

R$_f$: 0.33 (hexanes/EtOAc 90:10)

α_{598}^{20}: -213 (β = 1.5 · 10^{-3} g/mL, CHCl$_3$)

Lit. α_{598}^{20}: -208 (β = 1.1 · 10^{-3} g/mL, CH$_2$Cl$_2$)[104]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.92 (d, *J* = 0.7 Hz, 1H, 1‘-H), 8.06 (dd, *J* = 7.6, 2.0 Hz, 1H, 6-H), 7.70 – 7.64 (m, 1H, 3-H), 7.42 (tdd, *J* = 7.7, 1.5, 0.7 Hz, 1H, 5-H), 7.38 (td, *J* = 7.6, 2.1 Hz, 1H, 4-H), 1.25 (s, 9H, *tert*-butyl).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 162.31 (C-1‘), 133.97 (C-3), 133.77 (C-2), 133.29 (C-1), 130.02 (C-6), 128.22 (C-5), 126.64 (C-2), 58.18 (C-$(CH_3)_3$), 22.77 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 2927, 2867, 1584, 1441, 1427, 1069, 1024, 978, 757, 745, 664 cm^{-1}

HRMS (ESI): *m/z* **=** 288.0051 $[M+H]^+$ (calculated for $C_{11}H_{15}BrNOS^+$ $[M+H]^+$ 288.0052)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

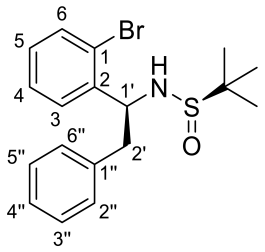
NMR data according to literature.[104]

(*R*)-*N*-((*S*)-1-(2-Bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (32a) and
(*R*)-*N*-((*R*)-1-(2-Bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (32b)

Synthesized according to **GP B**, using (*R*,*E*)-*N*-(2-bromobenzylidene)-2-methylpropane-2-sulfinamide (**31**, 1.40 g, 4.86 mmol, 1.00 eq.) and benzylmagnesium chloride solution (1.40 M in THF, 6.94 mL, 9.72 mmol, 3.00 eq.). Reaction was carried out at -78 °C.

Eluent for flash column chromatography: hexanes/EtOAc 60:40 to 40:60, order of elution:

1. 32a
2. 32b



32a

$C_{18}H_{22}BrNOS$

M = 380.34 g/mol

Yield: 1.06 g (5.54 mmol, 57%)

Appearance: colourless powder

Melting point: 109 – 110 °C.

R_f: 0.50 (hexanes/EtOAc 60:40)

α_{598}^{20}: -109 (β = 3.6 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H, 6-H), 7.41 (dd, *J* = 7.9, 1.8 Hz, 1H, 3-H), 7.35 – 7.28 (m, 3H, 5, 3“, 5“-H), 7.28 – 7.22 (m, 1H, 4-H), 7.20 – 7.17 (m, 2H, 2“, 6“-H), 7.16 – 7.13 (m, 1H, 4“-H), 5.10 (ddd, *J* = 8.3, 5.2, 2.8 Hz, 1H, 1‘-H), 3.54 (s, 1H, NH),

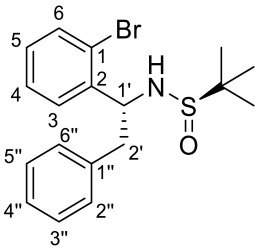
3.24 (dd, *J* = 13.7, 5.3 Hz, 1H, 2‘-H), 2.91 (dd, *J* = 13.7, 8.5 Hz, 1H, 2‘-H), 1.11 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2): δ 141.00 (C-1), 137.11 (C-2), 133.33 (C-6), 129.91 (C-2‘‘,C-6‘‘), 129.57 (C-5), 129.38 (C-3), 129.06 (C-3‘‘,C-5‘‘), 127.91 (C-4‘‘), 127.44 (C-4), 124.00 (C-1‘‘), 58.25 (C-1‘), 55.92 (C-$(CH_3)_3$), 43.78 (C-2‘), 22.61 (3 CH_3)

IR (ATR) $\tilde{\nu}$ = 3304, 2911, 1507, 1251, 1155, 1061, 1033, 756, 701 cm^{-1}

HRMS (ESI) *m/z* **=** 380.0679 $[M+H]^+$ (calculated for $C_{18}H_{23}BrNOS^+$ $[M+H]^+$ 380.0678)

Purity (HPLC) λ_{254}: > 99% (Method 2b)



32b

Yield: 650 mg (3.40 mmol, 35%)

Appearance: colourless powder

Melting point: 116 – 117 °C

R_f: 0.30 (hexanes/EtOAc 60:40)

α_{598}^{20}: +15 (β = 2.8 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.56 (dd, J = 8.0, 1.3 Hz, 1H, 6-H), 7.40 (dd, J = 7.8, 1.8 Hz, 1H, 3-H), 7.34 (td, J = 7.5, 1.3 Hz, 1H, 5-H), 7.28 – 7.26 (m, 1H, 4-H), 7.23 – 7.18 (m, 2H, 3'', 5''-H), 7.17 – 7.13 (m, 3H, 2'', 4'', 6''-H), 4.99 (td, J = 7.5, 5.6 Hz, 1H, 1'-H), 3.76 (d, J = 7.0 Hz, 1H, NH), 3.17 (dd, J = 13.8, 5.6 Hz, 1H, 2'-H), 2.99 (dd, J = 13.8, 8.3 Hz, 1H, 2'-H), 1.02 (s, 9H, *tert*-butyl)

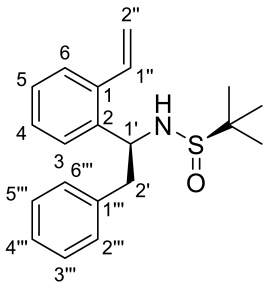
^{13}C NMR (101 MHz, CD_2Cl_2) δ 141.67 (C-1), 137.88 (C-2), 133.42 (C-6), 130.03 (C-2'', C-6''), 129.48 (C-4), 129.22 (C-3), 128.71 (C-3'', C-5''), 128.03 (C-5), 127.05 (C-4''), 123.55 (C-1''), 60.88 (C-1'), 56.52 (C-$(CH_3)_3$), 43.29 (C-2'), 22.45 (3 CH_3)

IR (ATR) $\tilde{\nu}$ = 3190, 2952, 1455, 1041, 1024, 938, 759, 745, 704 cm^{-1}

HRMS (ESI) *m/z* **=** 380.0679 $[M+H]^+$ (calculated for $C_{18}H_{23}BrNOS^+$ $[M+H]^+$ 380.0680)

Purity (HPLC) λ_{254}: > 95% (Method 2a)

(*R*)-2-Methyl-*N*-((*S*)-2-phenyl-1-(2-vinylphenyl)ethyl)propane-2-sulfinamide – (33)



$C_{20}H_{25}NOS$

M = 327.17 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*S*)-1-(2-bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**32a**, 2.00 g, 5.26 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (608 mg, 0.526 mmol, 0.100 eq.), Cs_2CO_3 (8.57 g, 26.3 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (1.67 g, 1.84 mL, 10.5 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 60:40.

Yield: 1.52 g (4.63 mmol, 88%)

Appearance: yellow gum

R_f: 0.18 (hexanes/EtOAc 70:30)

α_{598}^{20}: -83 (β = 2.23 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.41 (ddd, *J* = 15.2, 7.2, 1.9 Hz, 2H, 3, 6-H), 7.28 (pd, *J* = 7.3, 1.7 Hz, 2H, 4, 5-H), 7.24 – 7.15 (m, 3H, 3''', 4''', 5'''-H), 7.09 – 7.03 (m, 2H, 2''', 6'''-H), 6.98 (dd, *J* = 17.3, 11.0 Hz, 1H, 1''-H), 5.54 (dd, *J* = 17.3, 1.5 Hz, 1H, 2''-H), 5.29 (dd, *J* = 10.9, 1.5 Hz, 1H, 2''-H), 4.88 (td, *J* = 7.1, 4.6 Hz, 1H, 1'-H), 3.21 (dd, *J* = 13.5, 7.3 Hz, 1H, 2'-H), 3.07 (dd, *J* = 13.6, 6.9 Hz, 1H, 2'-H), 1.09 (s, 9H, *tert*-butyl)

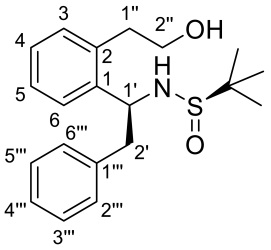
^{13}C NMR (126 MHz, CD_2Cl_2) δ 139.30 (C-1), 138.19 (C-1'''), 137.35 (C-2), 134.70 (C-1''), 130.08 (C-2''', C-6'''), 128.59 (C-3''', C-5'''), 128.27 (C-5), 128.14 (C-4), 127.27 (C-4'''), 126.99 (C-3), 126.83 (C-6), 117.31 (C-2''), 57.30 (C-1'), 56.14 (C-$(CH_3)_3$), 43.53 (C-2'), 22.61 (3 CH_3)

IR (ATR) $\tilde{\nu}$ = 3196, 1454, 1065, 1043, 913, 754, 702 cm^{-1}

HRMS (ESI) *m/z* **=** 328.1731 $[M+H]^+$ (calculated for $C_{20}H_{26}NOS^+$ $[M+H]^+$ 328.1657)

Purity (HPLC) λ_{254}: > 99% (Method 2a)

(*R*)-*N*-((*S*)-1-(2-(2-Hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (34)



$C_{20}H_{27}NO_2S$

M = 345.50 g/mol

Synthesized according to **GP D**, using (*R*)-2-methyl-*N*-((*S*)-2-phenyl-1-(2-vinylphenyl)ethyl)propane-2-sulfinamide (**33**, 1.00 g, 3.05 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 21.4 mL, 10.7 mmol, 3.50 eq.), H_2O_2 33% (3.46 g, 3.43 mL, 30.5 mmol, 10.0 eq.) and 2.00 M NaOH solution (22.9 g, 15.3 mL, 30.5 mmol, 10.0 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 5:95

Yield: 653 mg (1.89 mmol, 62%)

Appearance: yellow oil

R_f: 0.20 (hexanes/EtOAc 5:95)

α_{598}^{20}: -69 (β = 2.47· 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H, 6-H), 7.33 – 7.26 (m, 3H, 3'''-, 5, 5'''-H), 7.26 – 7.21 (m, 2H, 4, 4'''-H), 7.15 (td, *J* = 7.4, 1.4 Hz, 3H, 2''', 3, 6'''-H), 4.93 (ddd, *J* = 8.3, 6.0, 2.3 Hz, 1H, 1'-H), 3.74 (d, *J* = 7.7 Hz, 2H, 2''-H), 3.11 (dd, *J* = 13.4, 6.1 Hz, 1H, 2'-H), 3.00 (dd, *J* = 13.4, 8.3 Hz, 1H, 2'-H), 2.86 (dt, *J* = 13.6, 6.7 Hz, 1H, 1''-H), 2.80 – 2.69 (m, 1H, 1''-H), 2.53 (t, *J* = 6.0 Hz, 1H, OH), 1.10 (s, 9H, *tert*-butyl)

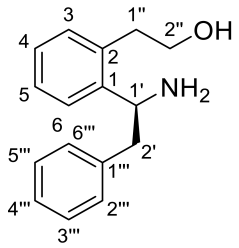
^{13}C NMR (101 MHz, CD_2Cl_2) δ 139.56 (C-2), 138.38 (C-1'''), 137.79 (C-1), 130.67 (C-3), 129.80 (C-2''', C-6'''), 129.03 (C-3''', C-5'''), 128.28 (C-5), 127.96 (C-6), 127.32 (C-4'''), 127.08 (C-4), 63.65 (C-2''), 55.60 (C-$(CH_3)_3$), 54.71 (C-1'), 45.40 (C-2'), 36.32 (C-1''), 22.68 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3331, 2914, 1454, 1071, 1040, 978, 765, 704 cm^{-1}

HRMS (ESI): *m/z* **=** 346.1841 $[M+H]^+$ (calculated for $C_{20}H_{28}NO_2S^+$ $[M+H]^+$ 346.1763)

Purity (HPLC) λ_{254}: > 99% (Method 2a)

(*S*)-2-(2-(1-Amino-2-phenylethyl)phenyl)ethan-1-ol – (35)



$C_{16}H_{19}NO$

M = 241.33 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(2-(2-hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**34**, 653 mg, 1.89 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (0.567 mL, 11.5 mmol, 6.09 eq.).

Eluent for flash column chromatography: DCM/EtOAc 50:50 + 1% NEt_3

Yield: 157 mg (0.651 mmol, 34%)

Appearance: yellow oil

R_f: 0.25 (DCM/EtOAc 50:50 + 1% NEt_3)

α_{598}^{20}: +23 (β = 1.55 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.55 – 7.47 (m, 1H, 6-H), 7.33 – 7.23 (m, 4H, 3''', 4, 5, 5'''-H), 7.22 (dt, J = 6.9, 1.5 Hz, 4H, 2''', 3, 4''', 6'''-H), 4.38 (dd, J = 9.1, 5.1 Hz, 1H, 1'-H), 3.83 (dt, J = 10.3, 5.1 Hz, 1H, 2''-H), 3.64 (ddd, J = 10.5, 9.2, 4.4 Hz, 1H, 2''-H), 3.17 (dd, J = 13.4, 5.0 Hz, 1H, 2'-H), 3.02 (dd, J = 8.8, 5.3 Hz, 1H, 2'-H), 3.00 – 2.96 (m, 1H, 1''-H), 2.79 (dt, J = 14.1, 4.7 Hz, 1H, 1''-H)

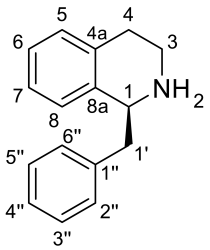
^{13}C NMR (101 MHz, CD_2Cl_2) δ 142.62 (C-1'''), 139.55 (C-1), 139.10 (C-2), 130.77 (C-3), 129.72 (C-2''', C-6'''), 128.92 (C-3''', C-5'''), 127.88 (C-4), 127.03 (C-5), 126.87 (C-4'''), 125.93 (C-6), 64.02 (C-2''), 52.90 (C-1'), 44.56 (C-2'), 35.94 (C-1'')

IR (ATR): $\tilde{\nu}$ = 3027, 2924, 1555, 1494, 1401, 1046, 1014, 750, 734, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 242.1548 $[M+H]^+$ (calculated for $C_{16}H_{20}NO^+$ $[M+H]^+$ 242.1467)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*S*)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline – (36)



$C_{16}H_{17}N$

M = 223.32 g/mol

Synthesized according to **GP F**, using (*S*)-2-(2-(1-amino-2-phenylethyl)phenyl)ethan-1-ol (**35**, 150 mg, 0.622 mmol, 1.00 eq.) and CMBP (230 mg, 0.249 mL, 0.932 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 40:60 + 1% NEt_3

Yield: 116 mg (0.519 mmol, 84%)

Appearance: yellow oil

R_f: 0.24 (hexanes/EtOAc 40:60 + 1% NEt_3)

α_{598}^{20}: -55 (β = 1.2 · 10^{-3} g/mL, $CHCl_3$)

Lit. α_{598}^{20}: -58 (β = 1.0 · 10^{-3} g/mL, $CHCl_3$)[134]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.36 – 7.30 (m, 2H, 3'', 5''-H), 7.30 – 7.21 (m, 4H, 2'', 6, 6'', 8-H), 7.20 – 7.13 (m, 2H, 4'', 7-H), 7.13 – 7.08 (m, 1H, 5-H), 4.18 (dd, *J* = 10.4, 3.7 Hz, 1H, 1-H), 3.28 – 3.15 (m, 2H, 1', 3''-H), 2.93 – 2.84 (m, 2H, 1', 3'-H), 2.84 – 2.75 (m, 2H, 4-H), 1.68 (s, 2H, NH_2)

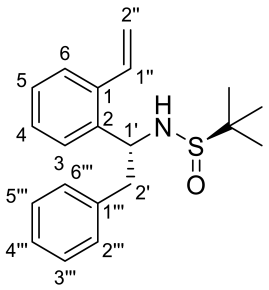
^{13}C NMR (101 MHz, CD_2Cl_2) δ 139.99 (C-1''), 139.46 (C-8a), 135.94 (C-4a), 129.78 (C-2'', C-6''), 129.65 (C-5), 128.84 (C-3'', C-5''), 126.67 (C-6), 126.61 (C-8), 126.39 (C-4''), 125.97 (C-7), 57.63 (C-1), 42.92 (C-3), 40.79 (C-1'), 30.37 (C-4)

IR (ATR): $\tilde{\nu}$ = 3060, 3024, 2921, 2800, 1493, 1452, 1315, 1123, 749, 735, 697 cm^{-1}

HRMS (ESI): *m/z* **=** 224.1428 $[M+H]^+$ (calculated for $C_{16}H_{18}N^+$ $[M+H]^+$ 224.1361)

Purity (HPLC) λ_{210}: > 99% (Method 1c)

(*R*)-2-Methyl-*N*-((*R*)-2-phenyl-1-(2-vinylphenyl)ethyl)propane-2-sulfinamide – (37)



$C_{20}H_{25}NOS$

M = 327.17 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*R*)-1-(2-bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**32b**, 2.86 g, 7.52 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (869 mg, 0.752 mmol, 0.100 eq.), Cs_2CO_3 (12.3 g, 37.6 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (2.39 g, 2.63 mL, 15.0 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 50:50.

Yield: 2.12 g (4.63 mmol, 86%)

Appearance: yellow gum

R_f: 0.36 (hexanes/EtOAc 50:50)

α_{598}^{20}: -53 (β = 1.43 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.45 – 7.36 (m, 2H, 3-H, 4'''-H), 7.32 – 7.17 (m, 5H, 3'''-H, 4-H, 5-H, 5'''-H, 6-H), 7.08 – 7.04 (m, 2H, 2'''-H, 6'''-H), 6.98 (dd, *J* = 17.3, 11.0 Hz, 1H, 1''-H), 5.53 (dd, *J* = 17.3, 1.5 Hz, 1H, 2''-H), 5.28 (dd, *J* = 11.0, 1.5 Hz, 1H, 2''-H), 4.88 (td, *J* = 7.1, 4.6 Hz, 1H, 1'-H), 3.60 (d, *J* = 4.6 Hz, 1H, NH), 3.21 (dd, *J* = 13.5, 7.3 Hz, 1H, 2'-H), 3.06 (dd, *J* = 13.5, 6.9 Hz, 1H, 2'-H), 1.19 (s, 9H, *tert*-butyl)

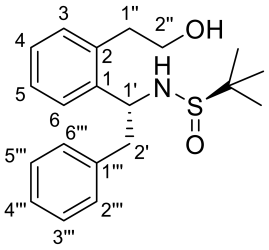
^{13}C NMR (101 MHz, CD_2Cl_2) δ 139.29 (C-1'''), 138.19 (C-1), 137.36 (C-2), 134.70 (C-1''), 130.08 (C-2''', C-6'''), 128.59 (C-3''', C-5'''), 128.27 (C-4), 128.15 (C-5), 127.27 (C-6), 126.99 (C-3), 126.84 (C-4'''), 117.31 (C-2''), 57.30 (C-1'), 56.16 (C-$(CH_3)_3$), 43.53 (C-2'), 25.03 (3 CH_3)

IR (ATR) $\tilde{\nu}$ = 3198, 1455, 1061, 1044, 910, 755, 702 cm^{-1}

HRMS (ESI) *m/z* **=** 328.1712 $[M+H]^+$ (calculated for $C_{20}H_{26}NOS^+$ $[M+H]^+$ 328.1657)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*R*)-*N*-((*R*)-1-(2-(2-Hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (38)



$C_{20}H_{27}NO_2S$

M = 345.50 g/mol

Synthesized according to **GP D**, using (*R*)-2-methyl-*N*-((*R*)-2-phenyl-1-(2-vinylphenyl)ethyl)propane-2-sulfinamide (**37**, 820 mg, 2.50 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 17.5 mL, 8.76 mmol, 3.50 eq.), H_2O_2 33% (2.58 g, 2.55 mL, 25.0 mmol, 10.0 eq.) and 2.00 M NaOH solution (18.8 g, 12.5 mL, 25.0 mmol, 10.0 eq.).

Eluent for flash column chromatography: EtOAc/DCM 80:20

Yield: 223 mg (0.645 mmol, 71%)

Appearance: yellow oil

R_f: 0.13 (hexanes/EtOAc 5:95)

α_{598}^{20}: -94 (β = 1.76· 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.49 (dd, *J* = 7.3, 2.0 Hz, 1H, 6-H), 7.30 – 7.24 (m, 2H, 4-H, 5-H), 7.23 – 7.12 (m, 4H, 3-H, 3'''-H, 4'''-H, 5'''-H), 7.11 – 7.07 (m, 2H, 2'''-H, 6'''-H), 4.96 (ddd, *J* = 8.5, 6.4, 3.6 Hz, 1H, 1'-H), 3.84 (dq, *J* = 10.7, 5.2 Hz, 1H, 2''-H), 3.76 (d, *J* = 3.5 Hz, 1H, NH), 3.57 (dtd, *J* = 11.1, 8.4, 5.3 Hz, 1H, 2''-H), 3.29 (dd, *J* = 13.7, 6.4 Hz, 1H, 2'-H), 3.13 (dd, *J* = 13.7, 8.4 Hz, 1H, 2'-H), 2.93 (ddd, *J* = 14.4, 8.7, 5.9 Hz, 1H, 1''-H), 2.71 – 2.59 (m, 2H, 1''-H, OH), 1.13 (s, 9H, *tert*-butyl)

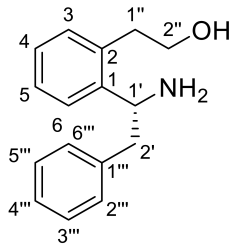
^{13}C NMR (101 MHz, CD_2Cl_2) δ 140.45 (C-1), 138.45 (C-1'''), 138.44 (C-2), 130.67 (C-3), 129.89 (C-2''', C-6'''), 128.60 (C-3''', C-5'''), 128.29 (C-4), 127.19 (C-5), 127.11 (C-6), 126.75 (C-4'''), 64.03 (C-2''), 56.30 (C-1'), 56.00 (C-$(CH_3)_3$), 43.20 (C-2'), 35.74 (C-1''), 22.66 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3317, 2925, 2864, 1453, 1364, 1040, 1006, 755, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 346.1833 $[M+H]^+$ (calculated for $C_{20}H_{28}NO_2S^+$ $[M+H]^+$ 346.1763)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*)-2-(2-(1-Amino-2-phenylethyl)phenyl)ethan-1-ol – (39)



$C_{16}H_{19}NO$

M = 241.33 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*R*)-1-(2-(2-hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**38**, 200 mg, 0.579 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (0.881 mL, 3.52 mmol, 6.09 eq.).

Eluent for flash column chromatography: DCM/MeOH 100:10 + 1% NEt_3

Yield: 137 mg (0.568 mmol, 98%)

Appearance: yellow oil

R_f: 0.36 (DCM/MeOH 100:10 + 1% NEt_3)

$\boldsymbol{\alpha_{598}^{20}}$: -92 (β = 0.96 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.55 – 7.46 (m, 1H, 6-H), 7.34 – 7.28 (m, 2H, 3'''-H, 5'''-H), 7.27 – 7.25 (m, 1H, 5-H), 7.25 – 7.20 (m, 5H, 2'''-H, 3-H, 4-H, 4'''-H, 6'''-H), 4.35 (dd, *J* = 9.3, 4.8 Hz, 1H, 1'-H), 3.83 (dt, *J* = 10.4, 5.2 Hz, 1H, 2''-H), 3.65 (ddd, *J* = 10.4, 9.0, 4.5 Hz, 1H, 2''-H), 3.16 (dd, *J* = 13.3, 4.7 Hz, 1H, 2'-H), 3.06 – 3.00 (m, 1H, 1''-H), 2.96 (dd, *J* = 13.2, 9.2 Hz, 1H, 2'-H), 2.81 (dt, *J* = 14.0, 4.8 Hz, 1H, 1''-H), 2.30 (s, 3H, NH_2, OH)

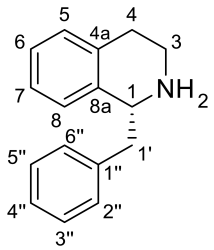
^{13}C NMR (101 MHz, CD_2Cl_2) δ 143.14 (C-2), 139.79 (C-1), 139.06 (C-1'''), 130.75 (C-3), 129.72 (C-2''', C-6'''), 128.92 (C-3''', C-5'''), 127.76 (C-5), 126.99 (C-4'''), 126.83 (C-4), 125.88 (C-6), 64.06 (C-2''), 52.98 (C-1'), 44.96 (C-2'), 35.99 (C-1'')

IR (ATR): $\tilde{\nu}$ = 3277, 3025, 2917, 1493, 1451, 1045, 757, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 242.1498 $[M+H]^+$ (calculated for $C_{16}H_{20}NO^+$ $[M+H]^+$ 242.1467)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$: > 99% (Method 1d)

(*R*)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline – (40)



$C_{16}H_{17}N$

M = 223.32 g/mol

Synthesized according to **GP F**, using (*R*)-2-(2-(1-amino-2-phenylethyl)phenyl)ethan-1-ol (**39**, 156 mg, 0.646 mmol, 1.00 eq.) and CMBP (239 mg, 0.259 mL, 0.970 mmol, 1.50 eq.).

Eluent for flash column chromatography: DCM/EtOAc 50:50 + 1% NEt_3

Yield: 97.6 mg (0.437 mmol, 68%)

Appearance: yellow oil

R_f: 0.31 (DCM/EtOAc 50:50 + 1% NEt_3)

α_{598}^{20}: +57 (β = 1.6 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.36 – 7.30 (m, 2H, 3''-H, 5''-H), 7.30 – 7.21 (m, 4H, 4''-H, 5-H, 6-H, 7-H), 7.20 – 7.06 (m, 3H, 2''-H, 6''-H, 8-H), 4.18 (dd, *J* = 10.4, 3.7 Hz, 1H, 1-H), 3.28 – 3.15 (m, 2H, 1'-H, 4-H), 2.93 – 2.84 (m, 2H, 1'-H, 4-H), 2.82 – 2.70 (m, 2H, 3-H), 1.61 (s, 2H, NH_2)

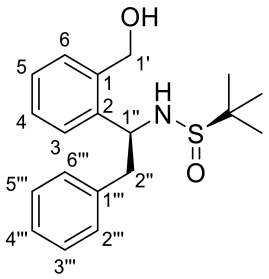
^{13}C NMR (101 MHz, CD_2Cl_2) δ 140.03 (C-4a), 139.52 (C-8a), 135.98 (C-1''), 129.78 (C-2'', C-6''), 129.65 (C-5), 128.83 (C-3'', C-5''), 126.66 (C-4''), 126.61 (C-6), 126.37 (C-7), 125.96 (C-8), 57.65 (C-1), 42.94 (C-4), 40.81 (C-1'), 30.41 (C-3)

IR (ATR): $\tilde{\nu}$ = 3059, 3023, 2921, 2800, 1491, 1457, 1311, 1120, 745, 735, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 224.1312 $[M+H]^+$ (calculated for $C_{16}H_{18}N^+$ $[M+H]^+$ 224.1361)

Purity (HPLC) λ_{210}: > 97% (Method 2b)

(*R*)-*N*-((*S*)-1-(2-(Hydroxymethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (98)



$C_{19}H_{25}NO_2S$

M = 331.47 g/mol

Synthesized by ozonolysis (60 L/h, 60 W) of (*R*)-2-methyl-*N*-((*S*)-2-phenyl-1-(2-vinylphenyl)ethyl)propane-2-sulfinamide (**33**, 1.00 g, 3.05 mmol, 1.00 eq.) at -78 °C in 15 mL DCM, followed by addition of methanol (5 mL) and reduction with $NaBH_4$ (1.16g, 30.5 mmol, 10 eq.). After 30 minutes, the mixture was extracted with DCM (3 x 50 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified *via* flash column chromatography on silica using EtOAc/hexanes 90:10.

Yield: 330 mg (0.996 mmol, 33%)

Appearance: brown gum

R_f: 0.37 (hexanes/EtOAc 10:90)

α_{598}^{20}: -79 (β = 1.1 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.56 (dt, *J* = 7.5, 1.1 Hz, 1H, 4'''-H), 7.38 – 7.23 (m, 6H, 3, 3''', 4, 5, 5''', 6-H), 7.18 – 7.14 (m, 2H, 2''', 6'''-H), 4.92 (ddd, *J* = 8.6, 6.2, 2.6 Hz, 1H, 1''-H), 4.69 (dd, *J* = 12.3, 2.8 Hz, 1H, 1'-H), 4.38 (dd, *J* = 12.3, 8.0 Hz, 1H, 1'-H), 3.72 (s, 1H, NH), 3.15 (dd, *J* = 13.3, 6.1 Hz, 2H, 2''-H), 3.06 (dd, *J* = 13.3, 8.3 Hz, 1H, 2''-H), 1.10 (s, 9H, *tert*-butyl)

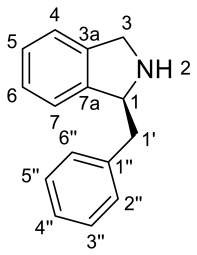
^{13}C NMR (101 MHz, CD_2Cl_2) δ 140.29 (C-1), 138.99 (C-2), 137.84 (C-1'''), 130.12 (C-6), 129.75 (C-3''', C-5'''), 129.05 (C-2''', C-6'''), 128.72 (C-5), 128.54 (C-4), 128.41 (C-3), 127.35 (C-4'''), 75.19 (C-$(CH_3)_3$), 63.13 (C-1'), 44.99 (C-2''), 22.68 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3376, 3062, 3029, 2978, 1453, 1365, 1029, 948, 759, 736, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 332.1684 $[M+H]^+$ (calculated for $C_{19}H_{26}NO_2S^+$ $[M+H]^+$ 332.1606)

Purity (HPLC) λ_{254}: 59% (Method 1b)

(*S*)-1-Benzylisoindoline – (100)



$C_{15}H_{15}N$

M = 209.29 g/mol

Synthesized according to **GP F**, using (*R*)-*N*-((*S*)-1-(2-(Hydroxymethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**98**, 485 mg, 2.13 mmol, 1.00 eq.) and CMBP (788 mg, 0.856 mL, 3.20 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 70:30 + 1% NEt_3

Yield: 100 mg (0.478 mmol, 22% over 2 steps)

Appearance: brown-red oil

R_f: 0.27 (hexanes/EtOAc 70:30 + 1% NEt_3)

α_{598}^{20}: -31 (β = 0.65 · 10^{-3} g/mL, $CHCl_3$)

Lit. α_{598}^{20}: -23 (β = 1.00 · 10^{-3} g/mL, $CHCl_3$)[176]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.33 – 7.27 (m, 2H, 3''-H, 5''-H), 7.27 – 7.18 (m, 6H, 2''-H, 4-H, 4''-H, 5-H, 6-H, 6''-H), 7.15 – 7.10 (m, 1H, 7-H), 4.64 (m, 1H, 1-H), 4.21 – 4.07 (m, 2H, 3-H), 3.13 (dd, *J* = 13.5, 4.8 Hz, 1H, 1'-H), 2.81 (dd, *J* = 13.5, 8.5 Hz, 1H, 1'-H)

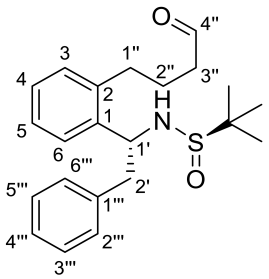
^{13}C NMR (101 MHz, CD_2Cl_2) δ 144.68 (C-7a), 142.26 (C-3a), 139.79 (C-1''), 129.79 (C-2'', C-6''), 128.66 (C-3'', C-5''), 127.28 (C-5), 126.84 (C-4''), 126.54 (C-6), 122.79 (C-7), 122.70 (C-4), 65.08 (C-1), 51.63 (C-3), 43.22 (C-1')

IR (ATR): $\tilde{\nu}$ = 3026, 2922, 2852, 1696, 1453, 754, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 210.1276 $[M+H]^+$ (calculated for $C_{15}H_{15}N$ $[M+H]^+$ 210.1204)

Purity (HPLC) λ_{210}: > 99% (Method 1c)

(*R*)-2-Methyl-*N*-((*R*)-1-(2-(4-oxobutyl)phenyl)-2-phenylethyl)propane-2-sulfinamide – (101)



$C_{22}H_{29}NO_2S$

M = 371.54 g/mol

Synthesized from (*R*)-*N*-((*R*)-1-(2-bromophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**32b**, 3.47 g, 9.12 mmol, 1.00 eq.), $Pd(OAc)_2$ (410 mg, 1.82 mmol, 0.200 eq.), $NaHCO_3$ (1.92 g, 22.8 mmol, 2.50 eq.) and benzyltriethylammonium chloride (2.08 g, 9.12 mmol, 1.00 eq.), which were dissolved in 50 mL dry DMF. 3-Buten-1-ol (987 mg, 1.18 mL, 13.7 mmol, 1.50 eq.) was added *via* a syringe and the reaction mixture was stirred for 12 h at 90 °C. The reaction was quenched with water (20 mL). The mixture was diluted with EtOAc (20 mL), brine (50 mL) was added to the mixture and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL). The organic phase was dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Eluent for flash column chromatography: DCM 100 + 1% MeOH

Yield: 350 mg (0.942 mmol, 10%)

Appearance: yellow oil

R_f: 0.22 (hexanes/EtOAc 60:40)

α_{598}^{20}: -69 (β = 0.84 · 10^{-3} g/mL, $CHCl_3$)

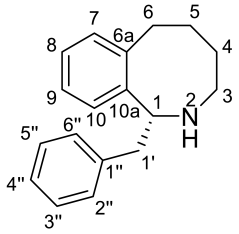
^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.66 (t, *J* = 1.5 Hz, 1H, CHO), 7.49 (dd, *J* = 7.7, 1.4 Hz, 1H, 6-H), 7.30 – 7.14 (m, 6H, 3'''-H, 4-H, 4'''-H, 5-H, 5'''-H), 7.07 – 7.03 (m, 2H, 2'''-H, 6'''-H), 4.83 (td, *J* = 7.3, 4.2 Hz, 1H, 1'-H), 3.52 (d, *J* = 4.2 Hz, 1H, NH), 3.25 (dd, *J* = 13.4, 6.6 Hz, 1H, 2'-H), 3.04 (dd, *J* = 13.4, 7.8 Hz, 1H, 2'-H), 2.49 (ddd, *J* = 8.8, 7.0, 1.3 Hz, 2H, 1''-H), 2.36 (tt, *J* = 7.0, 1.5 Hz, 2H, 3''-H), 1.78 – 1.60 (m, 2H, 2''-H), 1.11 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 202.47 (CHO), 140.35 (C-1), 139.76 (C-2), 138.30 (C-1'''), 130.08 (C-2''', C-6'''), 130.00 (C-3), 128.61 (C-3''', C-5'''), 128.02 (C-4), 127.31 (C-6), 127.08 (C-5), 126.85 (C-4'''), 56.02 (C-$(CH_3)_3$), 44.29 (C-2'), 43.68 (C-3''), 31.97 (C-1''), 23.70 (C-2''), 22.63 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3226, 3207, 2925, 1495, 1453, 1363, 1042, 954, 755, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 394.1815 $[M+Na+H]^+$ (calculated for $C_{22}H_{30}NO_2S^+$ $[M+Na+H]^+$ 394.1919)
Purity (HPLC) λ_{254}**:** > 96% (Method 1a)

(*R*)-1-Benzyl-1,2,3,4,5,6-hexahydrobenzo[*c*]azocine – (104)

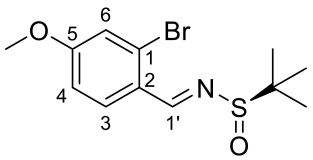


$C_{18}H_{21}N$

M = 251.37 g/mol

Synthesized according to **GP F**, using (*R*)-4-(2-(1-amino-2-phenylethyl)phenyl)butan-1-ol (250 mg, 0.928 mmol, 1.00 eq.) and CMBP (343 mg, 0.372 mL, 1.39 mmol, 1.50 eq.).
Eluent for flash column chromatography: hexanes/EtOAc 90:10 + 1.5% NEt_3 to hexanes/EtOAc 70:30 + 1.5% NEt_3
Yield: 59.0 mg (0.235 mmol, 25% over 2 steps)
Appearance: yellow oil
$\mathbf{R_f}$: 0.16 (hexanes/EtOAc 55:45 + 1.5% NEt_3)
$\boldsymbol{\alpha_{598}^{20}}$**:** +27 (β = 1.30 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37 (dd, *J* = 7.7, 1.5 Hz, 1H, 10-H), 7.27 (d, *J* = 5.1 Hz, 2H, 3''-H, 5''-H), 7.24 – 7.12 (m, 5H, 2''-H, 4''-H, 6''-H, 8-H, 9-H), 7.08 (dd, *J* = 7.5, 1.6 Hz, 1H, 7-H), 4.35 (t, *J* = 7.1 Hz, 1H, 1-H), 3.14 – 3.10 (m, 2H, 1'-H), 2.96 – 2.89 (m, 2H, 6-H), 2.79 (ddd, *J* = 13.4, 7.9, 1.2 Hz, 1H, 4-H), 2.13 (ddd, *J* = 13.7, 8.3, 1.8 Hz, 1H, 4-H), 1.92 (dq, *J* = 10.2, 5.2 Hz, 1H, 3-H), 1.68 (dddd, *J* = 11.7, 8.4, 5.4, 1.8 Hz, 1H, 3-H), 1.45 – 1.33 (m, 2H, 5-H)
^{13}C NMR (101 MHz, CD_2Cl_2) δ 142.50 (C-6a), 140.93 (C-10a), 140.43 (C-1''), 129.81 (C-7), 129.57 (C-2'', C-6''), 128.72 (C-3'', C-5''), 127.50 (C-8), 126.88 (C-9), 126.48 (C-4''), 126.30 (C-10), 56.93 (C-1), 46.41 (C-4), 42.49 (C-1'), 33.64 (C-6), 31.31 (C-5), 29.48 (C-3)
IR (ATR): $\tilde{\nu}$ = 3060, 3025, 2920, 2846, 1493, 1453, 1121, 752, 721, 696 cm^{-1}
HRMS (ESI): *m/z* **=** 252.1747 $[M+H]^+$ (calculated for $C_{18}H_{22}N^+$ $[M+H]^+$ 252.1674)
Purity (HPLC) λ_{210}**:** > 94% (Method 1c)

(*R,E*)-*N*-(2-Bromo-5-methoxybenzylidene)-2-methylpropane-2-sulfinamide – (46)



$C_{12}H_{16}BrNO_2S$

M = 318.23 g/mol

Synthesized according to **GP A**, using 2-bromo-4-methoxybenzaldehyde (1.00 g, 4.60 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (683 mg, 5.52 mmol, 1.20 eq.) and tetraethyl orthotitanate (3.15 g, 2.92 mL, 13.8 mmol, 3.00 eq.). The crude product was used without further purification.

Yield: 1.46 g (4.60 mmol, 100%)

Appearance: yellow oil

R_f: 0.09 (hexanes/EtOAc 30:70)

α_{598}^{20}: -44 (β = 1.42 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, *J* = 0.7 Hz, 1H, 1'-H), 8.00 (d, *J* = 8.8 Hz, 1H, 3-H), 7.15 (d, *J* = 2.5 Hz, 1H, 6-H), 6.92 (ddd, *J* = 8.8, 2.5, 0.7 Hz, 1H, 4-H), 3.86 (s, 3H, 5-OCH_3), 1.26 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.15 (C-5), 161.46 (C-1'), 130.89 (C-3), 127.89 (C-2), 126.03 (C-1), 118.16 (C-6), 114.69 (C-4), 57.91 (C-$(CH_3)_3$), 55.95 (5-OCH_3), 22.79 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3344, 2926, 1608, 1453, 1238, 1041, 1006, 699 cm^{-1}

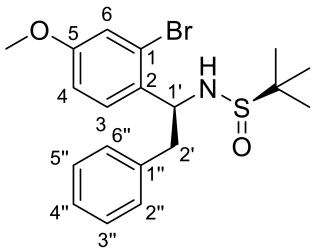
HRMS (ESI): *m/z* **=** 318.0164 $[M+H]^+$ (calculated for $C_{12}H_{17}BrNO_2S^+$ $[M+H]^+$ 318.0085)

Purity (HPLC) λ_{254}: > 94% (Method 1b)

(*R*)-*N*-((*S*)-1-(2-Bromo-5-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (56a)
and
(*R*)-*N*-((*R*)-1-(2-Bromo-5-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (56b)

Synthesized according to **GP B**, using (*R,E*)-*N*-(2-bromo-5-methoxybenzylidene)-2-methylpropane-2-sulfinamide (**46**, 1.60 g, 5.03 mmol, 1.00 eq.), and benzylmagnesium chloride solution (2.00 M in THF, 5.03 mL, 10.1 mmol, 2.00 eq.). The reaction was carried out at 0 °C.
Eluent for flash column chromatography: hexanes/EtOAc 60:40 to EtOAc 100 + 5% MeOH, order of elution:

1. 56a
2. 56b



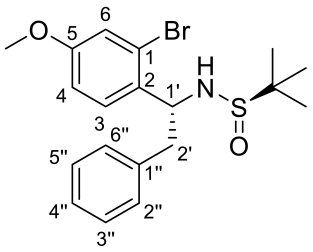
56a

$C_{19}H_{24}BrNO_2S$
M = 410.37 g/mol

Yield: 800 mg (1.95 mmol, 39%)
Appearance: white powder
Melting point: 107 – 108 °C
R_f: 0.35 (hexanes/EtOAc 60:40)
α_{598}^{20}: -95 (β = 3.89 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.33 – 7.27 (m, 3H, 3"-H, 5"-H, 6-H), 7.27 – 7.22 (m, 1H, 4"-H), 7.20 – 7.15 (m, 2H, 2"-H, 6"-H), 7.10 (d, *J* = 2.6 Hz, 1H, 3-H), 6.88 (dd, *J* = 8.7, 2.6 Hz, 1H, 4-H), 5.03 (ddd, *J* = 8.4, 5.6, 2.8 Hz, 1H, 1'-H), 3.79 (s, 3H, 5-OCH_3), 3.51 (d, *J* = 2.7 Hz, 1H, NH), 3.19 (dd, *J* = 13.7, 5.6 Hz, 1H, 2'-H), 2.91 (dd, *J* = 13.7, 8.4 Hz, 1H, 2'-H), 1.10 (s, 9H, *tert*-butyl)
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.76 (C-5), 137.29 (C-2), 132.68 (C-1), 130.05 (C-4), 129.89 (C-2", C-6"), 129.02 (C-3", C-5"), 127.35 (C-4"), 124.29 (C-1"), 117.99 (C-3), 114.34 (C-6), 57.75 (C-1'), 55.95 (5-OCH_3), 55.82 (C-$(CH_3)_3$), 44.04 (C-2'), 22.63 (3 CH_3)
IR (ATR): $\tilde{\nu}$ = 3228, 2953, 1601, 1488, 1230, 1065, 1040, 805, 700 cm^{-1}

HRMS (ESI): *m/z* **=** 410.0786 $[M+H]^+$ (calculated for $C_{19}H_{24}BrNO_2S^+$ $[M+H]^+$ 410.0711)

Purity (HPLC) λ_{254}**:** > 97% (Method 1a)



56b

Yield: 561 mg (1.37 mmol, 27%)

Appearance: white powder

Melting point: 109 – 110 °C

R_f: 0.15 (hexanes/EtOAc 60:40)

α_{598}^{20}**:** +8 (β = 3.33 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.30 (d, *J* = 8.7 Hz, 1H, 6-H), 7.28 – 7.17 (m, 3H, 3''-H, 4''-H, 5''-H), 7.16 – 7.12 (m, 2H, 2''-H, 6''-H), 7.10 (d, *J* = 2.6 Hz, 1H, 3-H), 6.89 (ddd, *J* = 8.7, 2.7, 0.5 Hz, 1H, 4-H), 4.92 (dt, *J* = 8.0, 6.2 Hz, 1H, 1'-H), 3.79 (s, 3H, 5-OCH_3), 3.69 (d, *J* = 6.6 Hz, 1H, NH), 3.12 (dd, *J* = 13.7, 5.9 Hz, 1H, 2'-H), 3.02 (dd, *J* = 13.7, 8.1 Hz, 1H, 2'-H), 1.03 (s, 9H, *tert*-butyl)

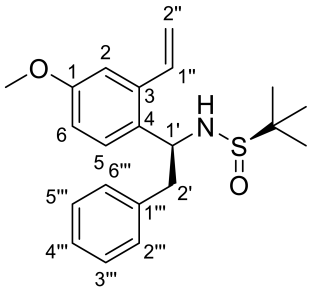
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.81 (C-5), 138.00 (C-2), 133.41 (C-1), 130.04 (C-2'', C-6''), 129.71 (C-6), 128.68 (C-3'', C-5''), 126.97 (C-4''), 123.88 (C-1''), 118.43 (C-3), 114.01 (C-4), 60.24 (C-1'), 56.40 (C-$(CH_3)_3$), 55.96 (5-OCH_3), 43.40 (C-2'), 22.47 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3231, 2953, 1601, 1482, 1231, 1059, 1038, 811, 702 cm^{-1}

HRMS (ESI): *m/z* **=** 410.0769 $[M+H]^+$ (calculated for $C_{19}H_{24}BrNO_2S^+$ $[M+H]^+$ 410.0711)

Purity (HPLC) λ_{254}**:** > 99% (Method 1a)

(*R*)-*N*-((*S*)-1-(5-Methoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (60)



$C_{21}H_{27}NO_2S$

M = 357.51 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*S*)-1-(2-bromo-5-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**56a**, 763 mg, 1.86 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (215 mg, 0.186 mmol, 0.100 eq.), Cs_2CO_3 (3.03 g, 3.72 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (590 mg, 0.650 mL, 3.72 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 60:40

Yield: 585 mg (1.64 mmol, 88%)

Appearance: yellow oil

R_f: 0.35 (hexanes/EtOAc 60:40)

α_{598}^{20}: -61 (β = 1.76 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.31 – 7.25 (m, 3H, 3'''-H, 2-H, 5'''-H), 7.24 – 7.19 (m, 1H, 4'''-H), 7.11 (dt, *J* = 6.2, 1.5 Hz, 2H, 2'''-H, 6'''-H), 7.10 – 7.04 (m, 1H, 1''-H), 6.94 (d, *J* = 2.7 Hz, 1H, 5-H), 6.84 (dd, *J* = 8.6, 2.7 Hz, 1H, 6-H), 5.57 (dd, *J* = 17.3, 1.5 Hz, 1H, 2''-H), 5.33 (d, *J* = 1.5 Hz, 0.5H, 2''-H), 5.30 (d, *J* = 1.4 Hz, 0.5H, 2''-H), 4.85 (ddd, *J* = 8.5, 6.2, 2.4 Hz, 1H, 1'-H), 3.81 (s, 3H, 1-OCH_3), 3.50 (s, 1H, NH), 3.09 (dd, *J* = 13.5, 6.2 Hz, 1H, 2'-H), 2.97 (dd, *J* = 13.5, 8.1 Hz, 1H, 2'-H), 1.20 (s, 9H, *tert*-butyl)

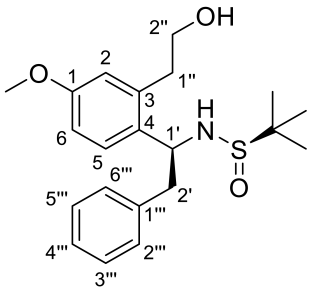
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.38 (C-1), 139.12 (C-3), 137.72 (C-4), 134.78 (C-1''), 130.78 (C-1'''), 129.81 (C-2''', C-6'''), 129.49 (C-2), 128.96 (C-3''', C-5'''), 127.21 (C-4'''), 117.22 (C-2''), 114.17 (C-6), 111.54 (C-5), 75.19 ($C(CH_3)_3$), 55.59 (1-OCH_3), 55.18 (C-1'), 44.77 (C-2'), 25.03 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3417, 2977, 1604, 1570, 1493, 1236, 1029, 883, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 358.1848 $[M+H]^+$ (calculated for $C_{21}H_{28}NO_2S^+$ $[M+H]^+$ 358.1763)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*)-*N*-((*S*)-1-(2-(2-Hydroxyethyl)-5-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (64)



$C_{21}H_{29}NO_3S$

M = 375.53 g/mol

Synthesized according to **GP D**, using (*R*)-*N*-((*S*)-1-(5-methoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**60**, 650 mg, 1.82 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 12.7 mL, 6.36 mmol, 3.50 eq.), H_2O_2 (33% in water, 2.04 mL, 18.2 mmol, 10.0 eq.) and NaOH (2.00 M in water, 9.09 mL, 18.2 mmol, 10.0 eq.).

Eluent for flash column chromatography: DCM 100 + 1.5% MeOH

Yield: 629 mg (1.67 mmol, 92%)

Appearance: yellow oil

R_f: 0.16 (DCM 100 + 1.5% MeOH)

α_{598}^{20}: -54 (β = 3.45 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.40 (d, *J* = 8.7 Hz, 1H, 2-H), 7.31 – 7.26 (m, 2H, 3'''-H, 5'''-H), 7.25 – 7.20 (m, 1H, 4'''-H), 7.17 – 7.09 (m, 2H, 2'''-H, 6'''-H), 6.84 (dd, *J* = 8.7, 2.8 Hz, 1H, 6-H), 6.68 (d, *J* = 2.8 Hz, 1H, 5-H), 4.84 (ddd, *J* = 8.4, 6.2, 2.2 Hz, 1H, 1'-H), 3.79 (s, 3H, 1-OCH_3), 3.75 – 3.70 (m, 2H, 1''-H), 3.65 (d, *J* = 2.2 Hz, 1H, NH), 3.07 (dd, *J* = 13.3, 6.3 Hz, 1H, 2'-H), 2.98 (dd, *J* = 13.3, 8.1 Hz, 1H, 2'-H), 2.82 (dt, *J* = 13.6, 6.7 Hz, 1H, 2''-H), 2.75 – 2.64 (m, 1H, 2''-H), 1.10 (s, 9H, *tert*-butyl)

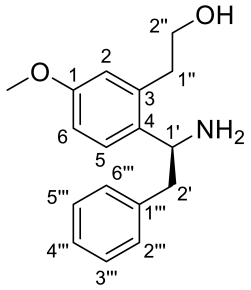
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.25 (C-1), 139.94 (C-1'''), 137.96 (C-4), 131.32 (C-3), 129.80 (C-2''', C-6'''), 129.58 (C-2), 129.00 (C-3''', C-5'''), 127.25 (C-4'''), 115.22 (C-5), 113.07 (C-6), 63.56 (C-1''), 55.50 (1-OCH_3, $C(CH_3)_3$), 54.24 (C-1'), 45.50 (C-2'), 36.52 (C-2''), 22.72 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3327, 2950, 1608, 1454, 1238, 1158, 1041, 734, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 376.1937 $[M+H]^+$ (calculated for $C_{21}H_{30}NO_3S^+$ $[M+H]^+$ 376.1868)

Purity (HPLC) λ_{254}: > 99% (Method 2b)

(*S*)-2-(2-(1-Amino-2-phenylethyl)-4-methoxyphenyl)ethan-1-ol – (68)



$C_{17}H_{21}NO_2$

M = 271.36 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(2-(2-hydroxyethyl)-5-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**64**, 620 mg, 1.65 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (2.51 mL, 10.0 mmol, 6.09 eq.).

Eluent for flash column chromatography: EtOAc 100 + 1.5% NEt_3

Yield: 183 mg (0.674 mmol, 42%)

Appearance: yellow oil

R_f: 0.29 (EtOAc 100 + 1.5% NEt_3)

α_{598}^{20}: +56 (β = 1.18 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.41 (d, *J* = 8.5 Hz, 1H, 2-H), 7.34 – 7.28 (m, 2H, 3'''-H, 5'''-H), 7.22 (td, *J* = 6.4, 1.6 Hz, 3H, 2'''-H, 4'''-H, 6'''-H), 6.80 (dd, *J* = 8.6, 2.8 Hz, 1H, 6-H), 6.75 (d, *J* = 2.7 Hz, 1H, 5-H), 4.28 (dd, *J* = 9.2, 5.0 Hz, 1H, 1'-H), 3.83 (dt, *J* = 10.2, 5.0 Hz, 1H, 2''-H), 3.79 (s, 3H, 1-OCH_3), 3.64 (ddd, *J* = 10.4, 9.3, 4.2 Hz, 1H, 2''-H), 3.16 (dd, *J* = 13.3, 5.0 Hz, 1H, 2'-H), 3.03 – 2.98 (m, 1H, 1''-H), 2.98 – 2.93 (m, 1H, 2'-H), 2.76 (dt, *J* = 14.0, 4.6 Hz, 1H, 1''-H), 2.38 (s, 3H, OH,NH_2)

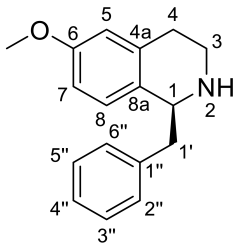
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.20 (C-1), 140.84 (C-3), 139.80 (C-1'''), 135.00 (C-4), 129.72 (C-2''', C-6'''), 128.92 (C-3''', C-5'''), 127.06 (C-2), 126.82 (C-4'''), 115.95 (C-5), 112.21 (C-6), 63.98 (C-2''), 55.53 (1-OCH_3), 52.50 (C-1'), 44.85 (C-2'), 36.16 (C-1'')

IR (ATR): $\tilde{\nu}$ = 3026, 2936, 1607, 1576, 1495, 1453, 1252, 1044, 812, 736, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 272.1639 $[M+H]^+$ (calculated for $C_{17}H_{22}NO_2^+$ $[M+H]^+$ 272.1572)

Purity (HPLC) λ_{254}: > 99% (Method 1d)

(*S*)-1-Benzyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline – (72)



$C_{17}H_{19}NO$

M = 253.35 g/mol

Synthesized according to **GP F**, using (*S*)-2-(2-(1-amino-2-phenylethyl)-4-methoxyphenyl)ethan-1-ol (**68**, 168 mg, 0.619 mmol, 1.00 eq.) and CMBP (229 mg, 0.248 mL, 0.929 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 70:30 + 1.5% NEt_3

Yield: 130 mg (0.513 mmol, 83%)

Appearance: brown oil

R_f: 0.25 (hexanes/EtOAc 70:30 + 1.5% NEt_3)

α_{598}^{20}: -45 (β = 1.15 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.35 – 7.30 (m, 2H, 3''-H, 5''-H), 7.29 – 7.22 (m, 3H, 2''-H, 4''-H, 6''-H), 7.18 – 7.14 (m, 1H, 5-H), 6.73 (ddt, *J* = 8.6, 2.8, 0.7 Hz, 1H, 7-H), 6.65 – 6.62 (m, 1H, 8-H), 4.12 (dd, *J* = 10.2, 3.7 Hz, 1H, 1-H), 3.77 (s, 3H, 6-OCH_3), 3.25 – 3.12 (m, 2H, 1'-H, 4'-H), 2.91 – 2.80 (m, 2H, 1'-H, 4''-H), 2.79 – 2.70 (m, 2H, 3-H), 1.68 (s, 2H, NH_2)

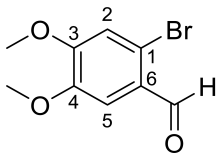
^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.17 (C-6), 140.04 (C-1''), 137.22 (C-8a), 131.72 (C-4a), 129.79 (C-2'', C-6''), 128.81 (C-3'', C-5''), 127.57 (C-5), 126.62 (C-4''), 113.98 (C-8), 112.28 (C-7), 57.21 (C-1), 55.52 (6-OCH_3), 43.04 (C-4), 40.89 (C-1'), 30.73 C- (3)

IR (ATR): $\tilde{\nu}$ = 3025, 2922, 2832, 1607, 1500, 1451, 1253, 1243, 1127, 1039, 741, 697 cm^{-1}

HRMS (ESI): *m/z* **=** 254.1533 $[M+H]^+$ (calculated for $C_{17}H_{20}NO^+$ $[M+H]^+$ 254.1467)

Purity (HPLC) λ_{210}: > 98% (Method 1c)

2-Bromo-4,5-dimethoxybenzaldehyde – (43)



$C_9H_9BrO_3$

M = 245.07 g/mol

Synthesized from 2-bromo-5-hydroxy-4-methoxybenzaldehyde (10.0 g, 42.9 mmol, 1.00 eq.) and K_2CO_3 (14.8 g, 107 mmol, 2.50 eq.), which were dissolved in 125 mL DMF and stirred for 1 h at room temperature. Afterwards, iodomethane (4.01 mL, 64.3 mmol, 1.50 eq.) was added and the reaction mixture was stirred for 16 h. The mixture was treated with water (25 mL) and diluted with EtOAc (150 mL). The mixture was washed with brine (100 mL) and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL). The organic phase was dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was used without further purification.

Yield: 10.0 g (40.9 mmol, 95%)

Appearance: off-white powder

Melting point: 150-151 °C

^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.16 (s, 1H, CHO), 7.39 (s, 1H, 5-H), 7.08 (s, 1H, 2-H), 3.92 (s, 3H, 3-OCH_3), 3.88 (s, 3H, 4- OCH_3)

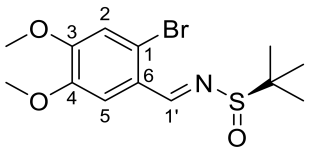
^{13}C NMR (101 MHz, CD_2Cl_2) δ 190.86 (CHO), 155.13 (C-4), 149.51 (C-3), 126.89 (C-1), 120.49 (C-6), 115.97 (C-2), 110.82 (C-5), 56.84 (3- OCH_3), 56.44 (4- OCH_3)

IR (ATR): $\tilde{\nu}$ = 3077, 3008, 2865, 1666, 1584, 1503, 1384, 1269, 1153, 1013, 864, 736 cm^{-1}

HRMS (EI): *m/z* **=** 243.9728 [M] (calculated for $C_9H_9BrNO_3$ [M] 243.9735)

Data according to literature.[196]

(*R*,*E*)-*N*-(2-Bromo-4,5-dimethoxybenzylidene)-2-methylpropane-2-sulfinamide – (47)



$C_{13}H_{18}BrNO_3S$

M = 348.26 g/mol

Synthesized according to **GP A**, using 2-bromo-4,5-dimethoxybenzaldehyde (**43**, 1.00 g, 4.08 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (0.757 g, 6.12 mmol, 1.50 eq.) and tetraethyl orthotitanate (2.79 g, 2.59 mL, 12.2 mmol, 3.00 eq.). The product was used without further purification.

Yield: 1.37 g (3.93 mmol, 96%)

Appearance: yellow solid

Melting point: 104 – 105 °C

$\boldsymbol{\alpha_{598}^{20}}$**:** -122 (β = 2.10 · 10^{-3} g/mL, $CHCl_3$)

Lit. $\boldsymbol{\alpha_{598}^{20}}$**:** -65 (β = 3.50 · 10^{-3} g/mL, $CHCl_3$)[197]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.79 (s, 1H, 1'-H), 7.55 (s, 1H, 5-H), 7.09 (s, 1H, 2-H), 3.90 (s, 3H, 3- OCH_3), 3.87 (s, 3H, 4- OCH_3), 1.24 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.66 (C-1'), 153.71 (C-3), 149.39 (C-4), 125.72 (C-1), 119.13 (C-6), 115.85 (C-2), 111.11 (C-5), 57.95 (C-$(CH_3)_3$), 56.71 (3- OCH_3), 56.35 (4- OCH_3), 22.75 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 2958, 1576, 1505, 1439, 1389, 1254, 1213, 1165, 1078, 1024, 866, 758 cm^{-1}

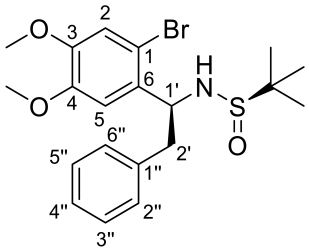
HRMS (ESI): *m/z* **=** 348.0264 $[M+H]^+$ (calculated for $C_{13}H_{18}BrNO_3S^+$ $[M+H]^+$ 348.0191)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$**:** > 99% (Method 1b)

(*R*)-*N*-((*S*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (57a)
and
(*R*)-*N*-((*R*)-1-(2-Bromo-4,5-dimethoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (57b)

Synthesized according to **GP B**, using (*R*,*E*)-*N*-(2-bromo-4,5-dimethoxybenzylidene)-2-methylpropane-2-sulfinamide (**47**, 1.64 g, 4.71 mmol, 1.00 eq.), and benzylmagnesium chloride solution (1.40 M in THF) (10.1 mL, 14.1 mmol, 3.00 eq.). The reaction was carried out at -21°C.
Eluent for flash column chromatography: hexanes/EtOAc 30:70, order of elution:

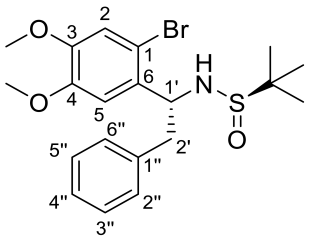
1. 57a
2. 57b



57a

$C_{20}H_{26}BrNO_3S$
M = 440.40 g/mol

Yield: 618mg (1.40 mmol, 30%)
Appearance: white powder
Melting point: 154 - 155°C
R_f: 0,36 (hexanes/EtOAc 30:70)
α_{598}^{20}: -97 (β = 1.51 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.29 (m, 2H, 3'', 5''-H), 7.28 – 7.23 (m, 1H, 4''-H), 7.21 – 7.17 (m, 2H, 2'', 6''-H), 7.01 (s, 1H, 2-H), 6.89 (s, 1H, 5-H), 5.01 (ddd, J = 7.8, 5.2, 2.1 Hz, 1H, 1'-H), 3.82 (s, 3H, 3-OCH_3), 3.76 (s, 3H, 4-OCH_3), 3.18 (dd, J = 13.7, 5.3 Hz, 1H, 2'-H), 2.88 (dd, J = 13.7, 8.6 Hz, 1H, 2'-H), 1.12 (s, 9H, *tert*-butyl)
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.52 (C-3), 149.14 (C-4), 137.21 (C-6), 132.53 (C-1''), 129.88 (C-2'', C-6''), 129.05 (C-3'', C-5''), 127.42 (C-4''), 115.77 (C-2), 113.87 (C-1), 112.07 (C-5), 57.90 (C-1'), 56.44 (3-OCH_3), 56.20 (4-OCH_3), 55.78 (C-$(CH_3)_3$), 43.93 (C-2'), 22.65 (3 CH_3)
IR (ATR): $\tilde{\nu}$ = 3245, 2957, 1602, 1502, 1252, 1161, 1049, 1029, 798, 699 cm^{-1}
HRMS (ESI): *m/z* **=** 440.0888 $[M+H]^+$ (calculated for $C_{20}H_{26}BrNO_3S^+$ $[M+H]^+$ 440.0817)
Purity (HPLC) λ_{254}: > 99% (Method 1a)



57b

Yield: 1.01 g (2.29 mmol, 49%)

Appearance: colourless powder

Melting point: 128 - 129 °C

R_f: 0.16 (hexanes/EtOAc 30:70)

α_{598}^{20}: +36 (β = 2.27 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.26 (td, J = 7.5, 1.3 Hz, 2H, 3'', 5''-H), 7.23 – 7.18 (m, 1H, 4''-H), 7.17 – 7.13 (m, 2H, 2'', 6''-H), 7.01 (s, 1H, 2-H), 6.88 (s, 1H, 5-H), 4.89 (dt, J = 8.1, 5.9 Hz, 1H, 1'-H), 3.82 (s, 3H, 3-OCH_3), 3.78 (s, 3H, 4-OCH_3), 3.15 (dd, J = 13.7, 5.8 Hz, 1H, 2'-H), 2.99 (dd, J = 13.7, 8.0 Hz, 1H, 2'-H), 1.03 (s, 9H, *tert*-butyl)

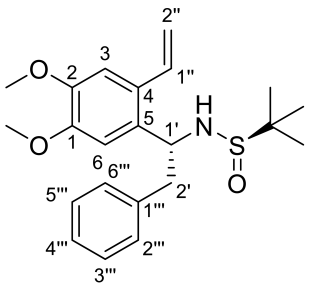
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.52 (C-3), 149.09 (C-4), 137.85 (C-6), 133.23 (C-1''), 130.04 (C-3'', C-5''), 128.71 (C-2'', C-6''), 127.06 (C-4''), 116.01 (C-2), 113.32 (C-1), 112.30 (C-5), 56.51 (3-OCH_3), 56.47 (4-OCH_3), 56.42 (C-$(CH_3)_3$), 43.10 (C-2'), 22.44 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3247, 2952, 1603, 1502, 1255, 1163, 1051, 1030, 799, 698 cm^{-1}

HRMS (ESI): 440.0888 $[M+H]^+$ (calculated for $C_{20}H_{26}BrNO_3S^+$ $[M+H]^+$ 440.0817)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*R*)-*N*-((*R*)-1-(4,5-Dimethoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (61)



$C_{22}H_{29}NO_3S$

M = 387.54 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*R*)-1-(2-bromo-4,5-dimethoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**57b**, 3.50 g, 7.95 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (918 mg, 0.795 mmol, 0.100 eq.), Cs_2CO_3 (12.9 g, 39.7 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (2.52 g, 2.78 mL, 15.9 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 30:70

Yield: 2.66 g (6.87 mmol, 87%)

Appearance: yellow gum

R_f: 0.25 (hexanes/EtOAc 30:70)

α_{598}^{20}: -23 (β = 1.22 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.27 – 7.12 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 7.09 – 7.02 (m, 2H, 2'''-H, 6'''-H), 6.93 (s, 1H, 3-H), 6.91 (dd, *J* = 17.3, 10.9 Hz, 1H, 1''-H), 6.84 (s, 1H, 6-H), 5.47 (dd, *J* = 17.2, 1.4 Hz, 1H, 2''-H), 5.19 (dd, *J* = 11.0, 1.4 Hz, 1H, 2''-H), 4.85 (td, *J* = 7.0, 4.0 Hz, 1H, 1'-H), 3.84 (s, 3H, 2-OCH_3), 3.79 (s, 3H, 1-OCH_3), 3.53 (d, *J* = 4.0 Hz, 1H, NH), 3.19 (dd, *J* = 13.5, 6.9 Hz, 1H, 2'-H), 3.05 (dd, *J* = 13.5, 7.1 Hz, 1H, 2'-H), 1.10 (s, 9H, *tert*-butyl)

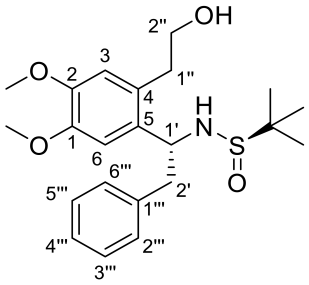
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.39 (C-1), 148.96 (C-2), 138.12 (C-5), 134.05 (C-1''), 131.65 (C-1'''), 130.08 (C-2''', C-6'''), 129.71 (C-4), 128.59 (C-3''', C-5'''), 126.84 (C-4'''), 115.23 (C-2''), 110.84 (C-6), 109.53 (C-3), 60.64 (C-$(CH_3)_3$), 56.28 (1-OCH_3), 56.13 (2-OCH_3), 43.39 (C-2'), 22.63 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3245, 2955, 2864, 1511, 1464, 1453, 1262, 1210, 1098, 1046, 864, 734, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 388.1942 $[M+H]^+$ (calculated for $C_{22}H_{30}NO_3S^+$ $[M+H]^+$ 388.1868)

Purity (HPLC) λ_{254}: > 99% (Method 2a)

(*R*)-*N*-((*R*)-1-(2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (65)



$C_{22}H_{31}NO_4S$

M = 405.55 g/mol

Synthesized according to **GP D**, using (*R*)-*N*-((*R*)-1-(4,5-dimethoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**61**, 1.43 g, 3.69 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 25.8 mL, 12.9 mmol, 3.50 eq.), H_2O_2 (33% in water, 4.14 mL, 36.9 mmol, 10.0 eq.) and NaOH (2.00 M in water, 18.5 mL, 36.9 mmol, 10.0 eq.).

Eluent for flash column chromatography: DCM 100 + 3% MeOH

Yield: 1.04 g (2.57 mmol, 70%)

Appearance: yellow gum

R_f: 0.22 (DCM 100 + 3% MeOH)

α_{598}^{20}: -103 (β = 2.13 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23 – 7.17 (m, 2H, 3'''-H, 5'''-H), 7.17 – 7.12 (m, 1H, 4'''-H), 7.11 – 7.08 (m, 2H, 2'''-H, 6'''-H), 6.94 (s, 1H, 6-H), 6.63 (s, 1H, 3-H), 4.89 (ddd, *J* = 8.9, 6.1, 2.9 Hz, 1H, 1'-H), 3.84 (s, 3H, 1-OCH_3), 3.80 (s, 3H, 2-OCH_3), 3.82 – 3.76 (m, 1H, 2''-H), 3.72 (d, *J* = 2.9 Hz, 1H, NH), 3.57 – 3.48 (m, 1H, 2''-H), 3.29 (dd, *J* = 13.7, 6.0 Hz, 1H, 2'-H), 3.11 (dd, *J* = 13.7, 8.7 Hz, 1H, 2'-H), 2.86 (ddd, *J* = 14.5, 8.9, 5.8 Hz, 1H, 1''-H), 2.69 (dd, *J* = 8.3, 4.9 Hz, 1H, OH), 2.57 (dt, *J* = 14.3, 5.0 Hz, 1H, 1''-H), 1.14 (s, 9H, *tert*-butyl)

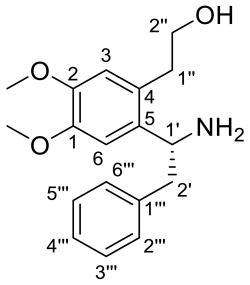
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.17 (C-2), 148.20 (C-1), 138.46 (C-1'''), 132.08 (C-5), 130.97 (C-4), 129.88 (C-2''', C-6'''), 128.61 (C-3''', C-5'''), 126.74 (C-4'''), 113.38 (C-3), 110.83 (C-6), 64.03 (C-2''), 56.44 (1-OCH_3), 56.05 (C-1'), 55.96 (C-$(CH_3)_3$, 2-OCH_3), 42.95 (C-2'), 35.44 (C-1''), 22.68 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3259, 2934, 1515, 1453, 1254, 1216, 1100, 1038, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 404.1902 $[M-H]^-$ (calculated for $C_{22}H_{30}NO_4S^-$ $[M-H]^-$ 404.1974)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*)-2-(2-(1-Amino-2-phenylethyl)-4,5-dimethoxyphenyl)ethan-1-ol – (69)



$C_{18}H_{23}NO_3$

M = 301.39 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*R*)-1-(2-(2-hydroxyethyl)-4,5-dimethoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**65**, 1.00 g, 2.47 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (3.76 mL, 15.0 mmol, 6.09 eq.).

Eluent for flash column chromatography: EtOAc 100 + 1% NEt_3 + 0.5% MeOH

Yield: 551 mg (1.83 mmol, 74%)

Appearance: yellow oil

R_f: 0.09 (EtOAc 100 + 1% NEt_3 + 0.5% MeOH

α_{598}^{20}: -50 (β = 1.21 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.33 – 7.27 (m, 2H, 3'''-H, 5'''-H), 7.26 – 7.18 (m, 3H, 2'''-H, 4'''-H, 6'''-H), 7.02 (s, 1H, 6-H), 6.69 (s, 1H, 3-H), 4.32 (dd, *J* = 8.9, 5.1 Hz, 1H, 1'-H), 3.85 (s, 3H, 1-OCH_3), 3.81 (s, 3H, 2-OCH_3), 3.84 – 3.75 (m, 1H, 2''-H), 3.62 (ddd, *J* = 10.4, 8.9, 4.5 Hz, 1H,

2''-H), 3.12 (dd, *J* = 13.3, 5.1 Hz, 1H, 2'-H), 2.94 (ddd, *J* = 14.3, 9.0, 5.0 Hz, 2H, 1''-H, 2'-H), 2.72 (dt, *J* = 14.2, 4.8 Hz, 1H, 1''-H)

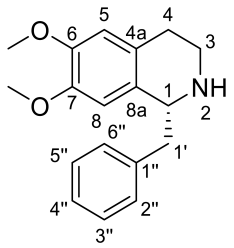
^{13}C NMR (101 MHz, CD_2Cl_2) δ 148.66 (C-2), 148.14 (C-1), 139.71 (C-1'''), 135.08 (C-5), 130.99 (C-4), 129.70 (C-2''', C-6'''), 128.89 (C-3''', C-5'''), 126.81 (C-4'''), 113.86 (C-3), 109.94 (C-6), 64.03 (C-2''), 56.42 (1-OCH_3), 56.16 (2-OCH_3), 52.81 (C-1'), 45.11 (C-2'), 35.69 (C-1'')

IR (ATR): $\tilde{\nu}$ = 2934, 1607, 1513, 1452, 1262, 1214, 1041, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 302.1751 $[M+H]^+$ (calculated for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1678)

Purity (HPLC) λ_{254}: > 98% (Method 1d)

(*R*)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline – (73)



$C_{18}H_{21}NO_2$

M = 283.37 g/mol

Synthesized according to **GP F**, using (*R*)-2-(2-(1-amino-2-phenylethyl)-4,5-dimethoxyphenyl)ethan-1-ol (**69**, 550 mg, 1.82 mmol, 1.00 eq.) and CMBP (674 mg, 0.732 mL, 2.74 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 50:50 + 1.5% NEt_3

Yield: 340 mg (1.20 mmol, 66%)

Appearance: brown-yellow oil

R_f: 0.11 (hexanes/EtOAc 50:50 + 1.5% NEt_3)

α_{598}^{20}: +14 (β = 2.28 · 10^{-3} g/mL, $CHCl_3$)

Lit. α_{598}^{20}: +15 (β = 0.5 – 1.0 · 10^{-3} g/mL, Acetone)[198]

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.35 – 7.30 (m, 2H, 3''-H, 5''-H), 7.29 – 7.25 (m, 2H, 2''-H, 6''-H), 7.25 – 7.21 (m, 1H, 4''-H), 6.64 (s, 1H, 8-H), 6.59 (s, 1H, 5-H), 4.11 (dd, *J* = 9.8, 4.3 Hz, 1H, 1-H), 3.80 (s, 3H, 6-OCH_3), 3.76 (s, 3H, 7-OCH_3), 3.23 – 3.12 (m, 2H, 1'-H, 3-H), 2.93 – 2.80 (m, 2H, 1'-H, 3-H), 2.68 (td, *J* = 6.3, 5.3 Hz, 2H, 4-H), 1.66 (s, 1H, NH).

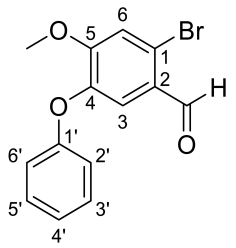
^{13}C NMR (101 MHz, CD_2Cl_2) δ 147.98 (C-6), 147.53 (C-7), 140.08 (C-8a), 131.30 (C-1''), 129.82 (C-2'', C-6''), 128.81 (C-3'', C-5''), 127.93 (C-4a), 126.62 (C-4''), 112.49 (C-5), 110.24 (C-8), 57.30 (C-1), 56.24 (6-OCH_3), 56.11 (7-OCH_3), 43.13 (C-1'), 40.84 (C-3), 29.90 (C-4)

IR (ATR): $\tilde{\nu}$ = 2998, 2931, 2832, 1609, 1511, 1463, 1451, 1285, 1221, 1110, 748, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 284.1645 $[M+H]^+$ (calculated for $C_{18}H_{22}NO_2^+$ $[M+H]^+$ 284.1572)

Purity (HPLC) λ_{210}: > 97% (Method 2b)

2-Bromo-4-methoxy-5-phenoxybenzaldehyde – (45)



$C_{14}H_{11}BrO_3$

M = 307.14 g/mol

Synthesized from 2-bromo-5-hydroxy-4-methoxybenzaldehyde (200 mg, 0.848 mmol, 1.00 eq.) and K_2CO_3 (234 mg, 1.70 mmol, 2.00 eq.), which were dissolved in 10.0 mL dry THF and stirred for 15 minutes at 0 °C. Afterwards, diphenyliodonium trifluoromethanesulfonate (447 mg, 1.02 mmol, 1.20 eq.) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction was quenched with water at 0 °C. The mixture was extracted with Et_2O (3 x 25 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography on silica. The product was dried *in vacuo*.

Eluent for flash column chromatography: hexanes/EtOAc 85:15

Yield: 54.0 mg (0.176 mmol, 21%)

Appearance: off-white solid

Melting point: 144 – 145 °C

R_f: 0.24 (hexanes/EtOAc 85:15)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.14 (s, 1H, CHO), 7.45 (s, 1H, 6-H), 7.37 – 7.31 (m, 2H, 3'-H, 5'-H), 7.24 (s, 1H, 3-H), 7.12 (ddt, J = 7.8, 7.1, 1.1 Hz, 1H, 4'-H), 6.98 – 6.89 (m, 2H, 2'-H, 6'-H), 3.92 (s, 3H, 5-OCH_3)

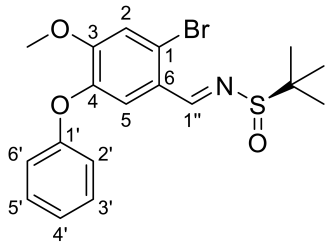
^{13}C NMR (101 MHz, CD_2Cl_2) δ 190.36 (CHO), 157.14 (C-4), 156.94 (C-5), 145.89 (C-1'), 130.26 (C-3', C-5'), 127.35 (C-1), 123.92 (C-4'), 123.32 (C-2), 120.54 (C-6), 118.01 (C-2', C-6'), 117.49 (C-3), 57.03 (3-OCH_3)

IR (ATR): $\tilde{\nu}$ = 1675, 1498, 1265, 1208, 1139, 1019, 776, 701 cm^{-1}

HRMS (EI): *m/z* **=** 305.9890 $[M+H]^+$ (calculated for $C_{14}H_{12}BrO_3^+$ $[M+H]^+$ 306.9892)

Purity (HPLC) λ_{254}: > 96% (Method 1a)

(*R*,*E*)-*N*-(2-Bromo-4-methoxy-5-phenoxybenzylidene)-2-methylpropane-2-sulfinamide – (49)



$C_{18}H_{20}BrNO_3S$

M = 410.33 g/mol

Synthesized according to **GP A**, using 2-bromo-4-methoxy-5-phenoxybenzaldehyde (**45**, 293 mg, 0.954 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (142 mg, 1.14 mmol, 1.20 eq.) and tetraethyl orthotitanate (653 mg, 0.605 mL, 2.86 mmol, 3.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 85:15

Yield: 200 mg (0.487 mmol, 51% over 2 steps)

Appearance: pale yellow gum

R_f: 0.18 (hexanes/EtOAc 85:15)

α_{598}^{20}: -41 ($\beta = 0.74 \cdot 10^{-3}$ g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.77 (s, 1H, 1''-H), 7.70 (s, 1H, 5-H), 7.36 – 7.27 (m, 2H, 3'-H, 5'-H), 7.26 (s, 1H, 2-H), 7.12 – 7.04 (m, 1H, 4'-H), 6.96 – 6.87 (m, 2H, 2'-H, 6'-H), 3.87 (s, 3H, 3-OCH_3), 1.17 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.11 (C-1''), 157.68 (C-1'), 155.73 (C-3), 144.99 (C-4), 130.10 (C-3', C-5'), 126.45 (C-1), 123.38 (C-4'), 122.64 (C-6), 121.68 (C-5), 117.41 (C-2), 117.17 (C-2', C-6'), 58.05 (C-$(CH_3)_3$), 56.89 (3-OCH_3), 22.69 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 2960, 1582, 1489, 1392, 1269, 1210, 1147, 1081, 1021, 749, 730, 689 cm^{-1}

HRMS (ESI): *m/z* **=** 410.0420 $[M+H]^+$ (calculated for $C_{18}H_{21}BrNO_3S^+$ $[M+H]^+$ 410.0347)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*R*)-*N*-((*S*)-1-(2-Bromo-4-methoxy-5-phenoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (59a)

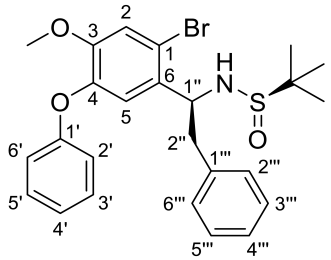
and

(*R*)-*N*-((*R*)-1-(2-Bromo-4-methoxy-5-phenoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (59b)

Synthesized according to **GP B**, using (*R*,*E*)-*N*-(2-bromo-4-methoxy-5-phenoxybenzylidene)-2-methylpropane-2-sulfinamide (**49**, 2.50 g, 6.09 mmol, 1.00 eq.), and benzylmagnesium chloride solution (2.00 M in THF, 7.52 mL, 15.2 mmol, 2.50 eq.). The reaction was carried out at -78 °C.

Eluent for flash column chromatography: hexanes/EtOAc 70:30, order of elution:

1. 59a
2. 59b



59a

$C_{25}H_{28}BrNO_3S$

M = 502.47 g/mol

Yield: 1.946 g (3.87 mmol, 64%)

Appearance: white gum

R_f: 0.29 (hexanes/EtOAc 70:30)

α_{598}^{20}: -74 (β = 3.38 · 10^{-3} g/mL, $CHCl_3$)

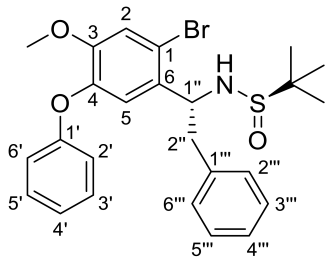
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 – 7.27 (m, 2H, 3'-H, 5'-H), 7.26 – 7.18 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 7.17 (s, 1H, 2-H), 7.11 – 7.07 (m, 2H, 2'''-H, 6'''-H), 7.07 – 7.03 (m, 1H, 4'-H), 6.97 (s, 1H, 5-H), 6.87 – 6.79 (m, 2H, 2'-H, 6'-H), 4.92 (q, *J* = 6.8 Hz, 1H, 1''-H), 3.79 (s, 3H, 3-OCH_3), 3.63 (d, *J* = 6.6 Hz, 1H, NH), 3.06 (dd, *J* = 6.9, 4.7 Hz, 2H, 2''-H), 1.04 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.03 (C-1'), 151.80 (C-3), 144.23 (C-4), 137.56 (C-6), 134.05 (C-1), 130.07 (C-2''', C-6'''), 130.00 (C-3', C-5'), 128.68 (C-3''', C-5'''), 127.00 (C-4'''), 122.94 (C-4'), 122.02 (C-5), 118.05 (C-1'''), 117.51 (C-2), 116.94 (C-2', C-6'), 59.84 (C-1''), 56.63 (C-$(CH_3)_3$), 56.44 (3-OCH_3), 42.87 (C-2''), 22.51 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3284, 3028, 2958, 1593, 1489, 1258, 1211, 1141, 1058, 1026, 750, 734, 697 cm^{-1}

HRMS (ESI): *m/z* **=** 502.1041 $[M+H]^+$ (calculated for $C_{25}H_{29}BrNO_3S^+$ $[M+H]^+$ 502.0973)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$**:** > 99% (Method 1a)



59b

Yield: 868 mg (1.73 mmol, 28%)

Appearance: white gum

R_f: 0.22 (hexanes/EtOAc 70:30)

$\boldsymbol{\alpha_{598}^{20}}$**:** +15 (β = 1.48 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.22 (m, 5H, 3'-H, 3'''-H, 4'''-H, 5'-H, 5'''-H), 7.18 (s, 1H, 2-H), 7.16 – 7.12 (m, 2H, 2'''-H, 6'''-H), 7.10 – 7.01 (m, 1H, 4'-H), 6.96 (s, 1H, 5-H), 6.87 – 6.82 (m, 2H, 2'-H, 6'-H), 4.99 (ddd, *J* = 8.2, 5.6, 2.6 Hz, 1H, 1''-H), 3.81 (s, 3H, 3-OCH_3), 3.44 (s, 1H, NH), 3.15 (dd, *J* = 13.6, 5.6 Hz, 1H, 2''-H), 2.87 (dd, *J* = 13.6, 8.2 Hz, 1H, 2''-H), 1.00 (s, 9H, *tert*-butyl)

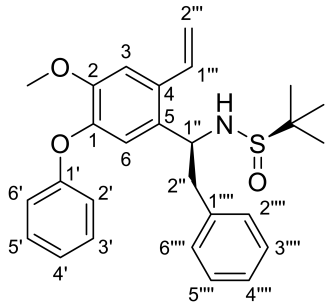
^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.93 (C-1'), 151.63 (C-3), 144.92 (C-4), 136.97 (C-6), 133.23 (C-1), 130.04 (C-2''', C-6'''), 129.91 (C-3', C-5'), 129.04 (C-3''', C-5'''), 127.40 (C-4'''), 123.19 (C-4'), 121.65 (C-5), 118.18 (C-1'''), 117.49 (C-2', C-6'), 117.30 (C-2), 57.72 (C-1''), 56.65 (3-OCH_3), 55.83 (C-$(CH_3)_3$), 43.78 (C-2''), 22.55 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3284, 3031, 2961, 1589, 1488, 1258, 1212, 1140, 1057, 1022, 750, 731, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 502.1039 $[M+H]^+$ (calculated for $C_{25}H_{29}BrNO_3S^+$ $[M+H]^+$ 502.0973)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$**:** > 97% (Method 1a)

(*R*)-*N*-((*S*)-1-(4-methoxy-5-phenoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (63)



$C_{27}H_{31}NO_3S$

M = 449.61 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*S*)-1-(2-bromo-4-methoxy-5-phenoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**59a**, 1.95 g, 3.87 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (447 mg, 0.387 mmol, 0.100 eq.), Cs_2CO_3 (6.31 g, 19.4 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (676 mg, 0.745 mL, 4.26 mmol, 1.10 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 70:30

Yield: 1.22 g (2.71 mmol, 70%)

Appearance: yellow-brown solid

Melting point: 120 – 121 °C

R_f: 0.26 (hexanes/EtOAc 70:30)

α_{598}^{20}: -83 (β = 1.90 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.33 – 7.24 (m, 2H, 3', 5'), 7.23 – 7.14 (m, 3H, 3''''-H, 4''''-H, 5''''-H), 7.06 – 6.99 (m, 4H, 2''''-H, 3-H, 4'-H, 6''''-H), 6.99 – 6.90 (m, 2H, 1'''-H, 6-H), 6.87 – 6.79 (m, 2H, 2'-H, 6'-H), 5.54 (dd, *J* = 17.2, 1.3 Hz, 1H, 2'''-H), 5.29 (dd, *J* = 10.9, 1.3 Hz, 1H, 2'''-H), 4.83 (td, *J* = 7.0, 4.2 Hz, 1H, 1''-H), 3.81 (s, 3H, 2-OCH_3), 3.48 (d, *J* = 4.2 Hz, 1H, NH), 3.20 (dd, *J* = 13.5, 6.5 Hz, 1H, 2''-H), 2.97 (dd, *J* = 13.4, 7.7 Hz, 1H, 2''-H), 1.09 (s, 9H, *tert*-butyl)

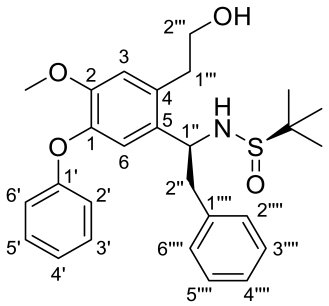
^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.43 (C-1'), 151.30 (C-2), 144.40 (C-1), 137.89 (C-5), 134.25 (C-4), 134.13 (C-1'''), 132.16 (C-1''''), 130.09 (C-2'''', C-6''''), 129.93 (C-3', C-5'), 128.58 (C-3'''', C-5''''), 126.80 (C-4''''), 122.67 (C-4'), 120.82 (C-6), 116.85 (C-2', C-2''', C-6'), 111.06 (C-3), 56.30 (C-1'', 2-OCH_3), 56.11 (C-$(CH_3)_3$), 43.16 (C-2''), 22.63 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3279, 2979, 2958, 1590, 1503, 1302, 1269, 1219, 1065, 1056, 863, 747, 699, 687 cm^{-1}

HRMS (ESI): *m/z* **=** 450.2103 $[M+H]^+$ (calculated for $C_{27}H_{32}NO_3S^+$ $[M+H]^+$ 450.2025)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*R*)-*N*-((*S*)-1-(2-(2-Hydroxyethyl)-4-methoxy-5-phenoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (67)



$C_{27}H_{33}NO_4S$

M = 467.62 g/mol

Synthesized according to **GP D**, using (*R*)-*N*-((*S*)-1-(4-methoxy-5-phenoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**63**, 1.20 g, 2.67 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 18.7 mL, 9.34 mmol, 3.50 eq.), H_2O_2 (33% in water, 3.00 mL, 26.7 mmol, 10.0 eq.) and NaOH (2.00 M in water, 13.3 mL, 26.7 mmol, 10.0 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 5:95

Yield: 957 mg (2.05 mmol, 77%)

Appearance: pale yellow oil

R_f: 0.22 (hexanes/EtOAc 5:95)

α_{598}^{20}: -70 (β = 2.70 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 – 7.26 (m, 2H, 3'-H, 5'-H), 7.23 – 7.14 (m, 3H, 3''''-H, 4''''-H, 5''''-H), 7.13 (s, 1H, 6-H), 7.08 – 6.99 (m, 3H, 2''''-H, 4'-H, 6''''-H), 6.88 – 6.80 (m, 2H, 2'-H, 6'-H), 6.77 (s, 1H, 3-H), 4.89 (ddd, J = 9.1, 5.9, 3.1 Hz, 1H, 1''-H), 3.86 (s, 1H, 2'''-H), 3.76 (s, 3H, 2-OCH_3), 3.58 (s, 1H, 2'''-H), 3.27 (dd, J = 13.7, 5.8 Hz, 1H, 2''-H), 2.99 (dd, J = 13.7, 9.3 Hz, 1H, 2''-H), 2.95 – 2.88 (m, 1H, 1'''-H), 2.62 (dt, J = 14.1, 4.9 Hz, 1H, 1'''-H), 1.13 (s, 9H, *tert*-butyl)

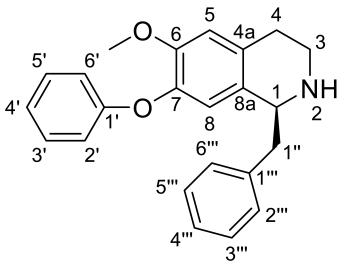
^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.78 (C-1'), 151.51 (C-2), 143.02 (C-1), 138.22 (C-5), 135.92 (C-4), 132.80 (C-1''''), 129.91 (C-2'''', C-6''''), 129.88 (C-3', C-5'), 128.60 (C-3'''', C-5''''), 126.72 (C-4''''), 122.48 (C-4'), 120.94 (C-6), 116.59 (C-2', C-6'), 114.71 (C-3), 63.96 (C-2'''), 56.22 (2-OCH_3), 55.98 (C-$(CH_3)_3$), 42.71 (C-2''), 35.73 (C-1'''), 22.65 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3332, 2925, 2857, 1511, 1489, 1215, 1041, 1005, 734, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 468.2220 $[M+H]^+$ (calculated for $C_{27}H_{34}NO_4S^+$ $[M+H]^+$ 468.2130)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*S*)-1-Benzyl-6-methoxy-7-phenoxy-1,2,3,4-tetrahydroisoquinoline – (75)



$C_{23}H_{23}NO_2$

M = 345.44 g/mol

Synthesized according to **GP F**, using (*S*)-2-(2-(1-amino-2-phenylethyl)-5-methoxy-4-phenoxyphenyl)ethan-1-ol (960 mg, 2.64 mmol, 1.00 eq.) and CMBP (976 mg, 0.921 mL, 3.96 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 40:60 + 1.5% NEt_3

Yield: 560 mg (1.62 mmol, 61%)

Appearance: orange-yellow solid

Melting point: 102 – 103 °C

R_f: 0.29 (hexanes/EtOAc 40:60 + 1.5% NEt_3)

α_{598}^{20}: +32 (β = 2.76 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.23 – 7.17 (m, 4H, 3'-H, 3'''-H, 5'-H, 5'''-H), 7.15 – 7.12 (m, 3H, 2'''-H, 4'''-H, 6'''-H), 6.95 – 6.90 (m, 1H, 4'-H), 6.84 (s, 1H, 8-H), 6.81 – 6.76 (m, 2H, 2'-H, 6'-H), 6.67 (s, 1H, 5-H), 4.05 – 3.95 (m, 1H, 1-H), 3.68 (s, 3H, 6-OCH_3), 3.11 (ddd, *J* = 11.4, 6.0, 5.0 Hz, 1H, 3-H), 3.03 (dd, *J* = 13.6, 3.8 Hz, 1H, 1''-H), 2.81 (ddd, *J* = 11.9, 6.9, 5.2 Hz, 1H, 3-H), 2.77 – 2.65 (m, 3H, 1''-H, 4-H)

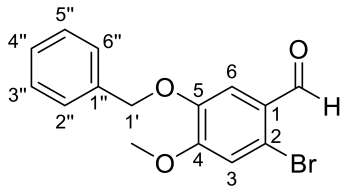
^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.08 (C-1'), 150.41 (C-6), 142.26 (C-7), 139.75 (C-1'''), 133.09 (C-4a), 132.20 (C-8a), 129.85 (C-3''', C-5'''), 129.78 (C-2''', C-6'''), 128.80 (C-3', C-5'), 126.65 (C-4'''), 122.23 (C-4'), 120.24 (C-8), 116.39 (C-2', C-6'), 113.74 (C-5), 57.10 (C-1), 56.26 (6-OCH_3), 42.83 (C-1''), 40.99 (C-3), 30.30 (C-4)

IR (ATR): $\tilde{\nu}$ = 2930, 1590, 1506, 1489, 1268, 1220, 1117, 1024, 892, 751, 691 cm^{-1}

HRMS (ESI): *m/z* **=** 346.1809 $[M+H]^+$ (calculated for $C_{23}H_{24}NO_2^+$ $[M+H]^+$ 346.1729)

Purity (HPLC) λ_{210}: > 95% (Method 1c)

5-(Benzyloxy)-2-bromo-4-methoxybenzaldehyde – (44)



$C_{15}H_{15}BrO_3$

M = 321.17 g/mol

Synthesized from 2-bromo-5-hydroxy-4-methoxybenzaldehyde (3.03 g, 13.0 mmol, 1.00 eq.) and K_2CO_3 (8.86 g, 32.5 mmol, 2.50 eq.), which were dissolved in 50.0 mL DMF and stirred for 1 h at room temperature. Afterwards, benzyl bromide (3.40 g, 2.37 mL, 19.5 mmol, 1.50 eq.) was added and the reaction mixture was stirred for 16 h. The reaction mixture was treated with water (20 mL) and EtOAc (150 mL). Brine (100 mL) was added to the mixture and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL). The organic phase was dried over anhydr. Na_2SO_4 and concentrated under reduced pressure. The product was purified *via* flash column chromatography.

Eluent for flash column chromatography: hexanes/EtOAc 90:10

Yield: 4.00 g (12.5 mmol, 96%)

Appearance: yellow powder

Melting point: 142 – 143 °C

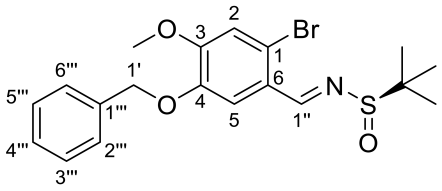
R_f: 0.29 (hexanes/EtOAc 90:10)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 10.16 (s, 1H, CHO), 7.47 (s, 1H, 6-H), 7.46 – 7.32 (m, 5H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 7.11 (s, 1H, 3-H), 5.11 (s, 2H, 1'-H), 3.93 (s, 3H, 5-OCH_3)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 190.80 (CHO), 155.55 (C-4), 148.53 (C-5), 136.55 (C-1"), 129.01 (C-3", C-5"), 128.71 (4"), 128.29 (2", 6"), 126.83 (2), 120.81 (1), 116.25 (3), 112.59 (6), 71.37 (1'), 56.90 (5-OCH_3)

Data according to literature.[199]

(*R*,*E*)-*N*-(5-(Benzyloxy)-2-bromo-4-methoxybenzylidene)-2-methylpropane-2-sulfinamide – (48)



$C_{19}H_{22}BrNO_3S$

M = 424.35 g/mol

Synthesized according to **GP A** for 30 minutes, using 5-(benzyloxy)-2-bromo-4-methoxybenzaldehyde (**44**, 1.00 g, 3.02 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (448 mg, 3.62 mmol, 1.20 eq.) and tetraethyl orthotitanate (2.07 g, 1.91 mL, 9.06 mmol, 3.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 80:20

Yield: 1.24 g (2.92 mmol, 97%)

Appearance: yellow solid

Melting point: 107 – 108 °C

R_f: 0.27 (hexanes/EtOAc 80:20)

α_{598}^{20}: -97 (β = 1.38 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.75 (s, 1H, 1''-H), 7.61 (s, 1H, 2-H), 7.46 – 7.41 (m, 2H, 2'''-H, 6'''-H), 7.41 – 7.30 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 7.11 (s, 1H, 5-H), 5.18 – 5.09 (m, 2H, 1'-H), 3.91 (s, 3H, 3-OCH_3), 1.21 (s, 9H, *tert*-butyl)

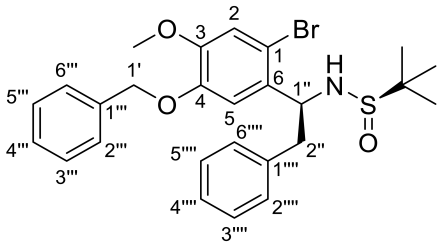
^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.50 (C-1''), 154.14 (C-6), 148.26 (C-4), 136.75 (C-1'''), 129.03 (C-3''', C-5'''), 128.64 (C-4'''), 128.21 (C-2''', C-6'''), 125.64 (C-3), 119.44 (C-1), 116.10 (C-5), 113.30 (C-2), 71.40 (C-1'), 57.98 (C-$(CH_3)_3$), 56.78 (3-OCH_3), 22.75 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 2967, 1583, 1499, 1436, 1256, 1208, 1165, 1081, 1026, 865, 747, 725, 694 cm^{-1}

HRMS (ESI): *m/z* **=** 424.0577 $[M+H]^+$ (calculated for $C_{19}H_{23}BrNO_3S^+$ $[M+H]^+$ 424.0504)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*R*)-*N*-((*S*)-1-(5-(Benzyloxy)-2-bromo-4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (58)



$C_{26}H_{30}BrNO_3S$

M = 516.49 g/mol

Synthesized according to **GP B**, using (*R*,*E*)-*N*-(5-(benzyloxy)-2-bromo-4-methoxybenzylidene)-2-methylpropane-2-sulfinamide (**48**, 6.50 g, 15.3 mmol, 1.00 eq.) and benzylmagnesium chloride solution (2.00 M in THF) (15.3 mL, 30.6 mmol, 2.00 eq.). The reaction was carried out at -78 °C.

Eluent for flash column chromatography: hexanes/EtOAc 50:50

Yield: 3.04 g (5,89 mmol, 39%)

Appearance: white powder

Melting point: 116 – 117 °C

R_f: 0.40 (hexanes/EtOAc 50:50)

α_{598}^{20}: +12 (β = 2.28 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.44 – 7.38 (m, 4H, 2'''-H, 3'''-H, 5'''-H, 6'''-H), 7.37 – 7.33 (m, 1H, 4'''-H), 7.27 – 7.18 (m, 3H, 3''''-H, 4''''-H, 5''''-H), 7.08 – 7.04 (m, 2H, 2''''-H, 6''''-H), 7.02 (s, 1H, 2-H), 6.91 (s, 1H, 5-H), 5.01 (s, 2H, 1'-H), 4.90 (dt, *J* = 7.6, 6.0 Hz, 1H, 1''-H), 3.83 (s, 3H, 3-OCH_3), 3.58 (d, *J* = 5.6 Hz, 1H, NH), 3.03 (qd, *J* = 13.7, 6.8 Hz, 2H, 2''-H), 1.04 (s, 9H, *tert*-butyl)

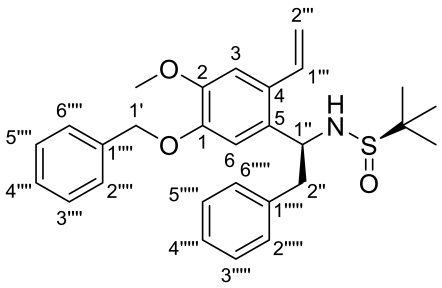
^{13}C NMR (101 MHz, CD_2Cl_2) δ 150.08 (C-3), 148.09 (C-4), 137.68 (C-1'''), 137.23 (C-6), 133.09 (C-1''''), 130.10 (C-2'''', C-6''''), 128.97 (C-3'''', C-5''''), 128.64 (C-2''', C-6'''), 128.50 (C-4''''), 128.18 (C-3''', C-5'''), 127.00 (C-4'''), 116.25 (C-2), 114.59 (C-5), 114.11 (C-1), 71.64 (C-1'), 59.86 (C-1''), 56.53 (3-OCH_3), 56.40 (C-$(CH_3)_3$), 42.99 (C-2''), 22.51 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3221, 2948, 1601, 1504, 1248, 1158, 1046, 1030, 835, 734, 696 cm^{-1}

HRMS (ESI): *m/z* **=** 516.1218 $[M+H]^+$ (calculated for $C_{26}H_{31}BrNO_3S^+$ $[M+H]^+$ 516.1130)

Purity (HPLC) λ_{254}: > 99% (Method 2a)

(*R*)-*N*-((*S*)-1-(5-(Benzyloxy)-4-methoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (62)



$C_{28}H_{33}NO_3S$

M = 463.64 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*S*)-1-(5-(benzyloxy)-2-bromo-4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**58**, 3.28 g, 6.35 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (734 mg, 0.635 mmol, 0.100 eq.), Cs_2CO_3 (10.4 g, 31.8 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (1.11 g, 1.22 mL, 6.99 mmol, 1.10 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 60:40

Yield: 2.67 g (5.76 mmol, 91%)

Appearance: brown oil

R_f: 0.22 (hexanes/EtOAc 60:40)

α_{598}^{20}: -45 (β = 3.03 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.45 – 7.30 (m, 5H, 3''''-H, 3'''''-H, 4''''-H, 5''''-H, 5'''''-H), 7.21 – 7.12 (m, 3H, 2''''-H, 4'''''-H, 6''''-H), 6.99 – 6.94 (m, 2H, 2'''''-H, 6'''''-H), 6.93 (s, 1H, 3-H), 6.89 – 6.80 (m, 2H, 1'''-H, 6-H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1H, 2'''-H), 5.17 (dd, *J* = 10.9, 1.4 Hz, 1H, 2'''-H), 5.05 (s, 2H, 1'-H), 4.82 (td, *J* = 6.9, 3.7 Hz, 1H, 1''-H), 3.86 (s, 3H, 2-OCH_3), 3.42 (d, *J* = 3.7 Hz, 1H, NH), 3.17 (dd, *J* = 13.4, 6.5 Hz, 1H, 2''-H), 2.94 (dd, *J* = 13.4, 7.5 Hz, 1H, 2''-H), 1.09 (s, 9H, *tert*-butyl)

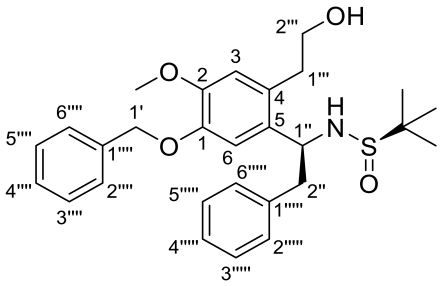
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.49 (C-2), 148.35 (C-1), 137.98 (C-1''''), 137.56 (C-1''''), 133.99 (C-1'''), 131.50 (C-5), 130.35 (C-4), 130.11 (C-2'''', C-6''''), 128.95 (C-3'''', C-5''''), 128.52 (C-3'''', C-5''''), 128.40 (C-4''''), 128.07 (C-2'''', C-6''''), 126.78 (C-4''''), 115.45 (C-2'''), 113.15 (C-6), 109.79 (C-3), 71.40 (C-1'), 56.22 (2-OCH_3), 56.14 (C-1''), 56.05 (C-$(CH_3)_3$), 43.30 (C-2''), 22.66 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3246, 2957, 1603, 1510, 1454, 1265, 1050, 732, 697 cm^{-1}

HRMS (ESI): *m/z* **=** 464.2261 $[M+H]^+$ (calculated for $C_{28}H_{34}NO_3S^+$ $[M+H]^+$ 464.2181)

Purity (HPLC) λ_{254}: > 97% (Method 1a)

(*R*)-*N*-((*S*)-1-(5-(Benzyloxy)-2-(2-hydroxyethyl)-4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (66)



$C_{28}H_{35}BrNO_4S$

M = 481.65 g/mol

Synthesized according to **GP D**, using (*R*)-*N*-((*S*)-1-(5-(benzyloxy)-4-methoxy-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**62**, 1.81 g, 3.91 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 27.4 mL, 13.7 mmol, 3.50 eq.), H_2O_2 (33% in water, 4.39 mL, 39.1 mmol, 10.0 eq.) and NaOH (2.00 M in water, 19.5 mL, 39.1 mmol, 10.0 eq.).

Eluent for flash column chromatography: EtOAc 100 + 1% NEt_3

Yield: 1.34 g (2.79 mmol, 71%)

Appearance: yellow/brown oil

R_f: 0.24 (EtOAc 100 + 1% NEt_3)

α_{598}^{20}: -83 (β = 2.47 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.46 (dtd, *J* = 6.7, 1.4, 0.6 Hz, 2H, 2'''', 6''''), 7.40 (tt, *J* = 6.5, 1.0 Hz, 2H, 3'''', 5''''), 7.36 – 7.30 (m, 1H, 4''''), 7.21 – 7.08 (m, 3H, 3''''''-H, 4''''''-H, 5''''''-H), 6.98 – 6.93 (m, 3H, 2''''''-H, 6-H, 6''''''-H), 6.64 (s, 1H, 3-H), 5.10 (d, *J* = 2.3 Hz, 2H, 1'-H), 4.83 (ddd, *J* = 8.8, 5.7, 2.7 Hz, 1H, 1''-H), 3.82 (s, 3H, 2-OCH_3), 3.76 (d, *J* = 10.0 Hz, 2H, 2'''-H), 3.62 (d, *J* = 2.6 Hz, 1H, NH), 3.49 (s, 1H, 2'''-H), 3.24 (dd, *J* = 13.6, 5.7 Hz, 1H, 2''-H), 2.97 (dd, *J* = 13.6, 9.0 Hz, 1H, 2''-H), 2.81 (ddd, *J* = 14.6, 8.9, 6.0 Hz, 1H, 1'''-H), 2.69 (s, 1H, OH), 2.52 (dt, *J* = 14.2, 5.0 Hz, 1H, 1'''-H), 1.13 (s, 9H, *tert*-butyl)

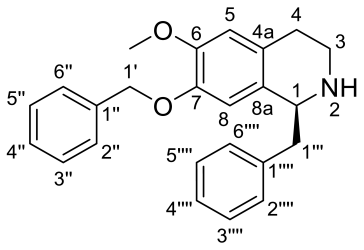
^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.74 (C-2), 147.04 (C-1), 138.30 (C-1''''), 137.80 (C-1''''''), 131.97 (C-5), 131.62 (C-4), 129.87 (C-2''''''', C-6''''''), 128.97 (C-3'''', C-5''''), 128.55 (C-3''''''', C-5'''''), 128.37 (C-4''''), 128.04 (C-2'''', C-6''''), 126.67 (C-4''''''), 113.66 (C-3), 113.44 (C-6), 71.57 (C-1'), 63.94 (C-2'''), 56.13 (2-OCH_3), 55.89 (C-$(CH_3)_3$), 55.62 (C-1''), 42.84 (C-2''), 35.49 (C-1'''), 22.68 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3339, 2926, 1514, 1453, 1255, 1098, 1039, 1007, 732, 697 cm^{-1}

HRMS (ESI): *m/z* **=** 482.2344 $[M+H]^+$ (calculated for $C_{28}H_{36}BrNO_4S^+$ $[M+H]^+$ 482.2287)

Purity (HPLC) λ_{254}: > 99% (Method 1a)

(*S*)-1-Benzyl-7-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline – (74)



$C_{24}H_{25}NO_2$

M = 359.47 g/mol

Synthesized according to **GP F**, using (*R*)-*N*-((*S*)-1-(5-(benzyloxy)-2-(2-hydroxyethyl)-4-methoxyphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**66**, 850 mg, 2.25 mmol, 1.00 eq.) and CMBP (832 mg, 0.903 mL, 3.38 mmol, 1.50 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 50:50 + 1.5% NEt_3 to EtOAc 100 + 1.5% NEt_3

Yield: 486 mg (1.35 mmol, 60% over 2 steps)

Appearance: yellow oil

R_f: 0.31 (hexanes/EtOAc 10:90 + 1.5% NEt_3)

α_{598}^{20}: +18 (β = 1.90 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.47 – 7.41 (m, 2H, 2''-H, 6''-H), 7.39 (ddd, *J* = 7.7, 6.7, 0.9 Hz, 2H, 3''-H, 5''-H), 7.35 – 7.29 (m, 3H, 3''''-H, 4''-H, 5''''-H), 7.26 – 7.20 (m, 3H, 2''''-H, 4''''-H, 6''''-H), 6.72 (s, 1H, 8-H), 6.63 (s, 1H, 5-H), 5.00 (s, 2H, 1'-H), 4.08 (dd, *J* = 9.6, 4.2 Hz, 1H, 1-H), 3.82 (s, 3H, 6-OCH_3), 3.17 (ddd, *J* = 11.9, 6.4, 5.2 Hz, 1H, 3-H), 3.10 (dd, *J* = 13.6, 4.2 Hz, 1H, 1'''-H), 2.91 – 2.85 (m, 1H, 3''-H), 2.85 – 2.78 (m, 1H, 1'''-H), 2.69 (q, *J* = 6.0 Hz, 2H, 4-H)

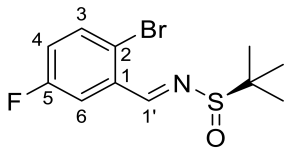
^{13}C NMR (101 MHz, CD_2Cl_2) δ 148.60 (C-6), 146.51 (C-7), 140.01 (C-1''''), 137.86 (C-1''), 131.25 (C-8a), 129.83 (C-2'''', C-6''''), 128.86 (C-3'', C-5''), 128.81 (C-3'''', C-5''''), 128.73 (C-4a), 128.30 (C-4''), 128.19 (C-2'', C-6''), 126.63 (C-4''''), 112.89 (C-8), 112.86 (C-5), 71.59 (C-1'), 57.22 (C-1), 56.22 (6-OCH_3), 43.05 (C-1'''), 40.87 (C-3), 29.93 (C-4)

IR (ATR): $\tilde{\nu}$ = 3027, 2930, 2835, 1605, 1509, 1452, 1257, 1218, 1109, 1018, 733, 695 cm^{-1}

HRMS (ESI): *m/z* **=** 360.1972 $[M+H]^+$ (calculated for $C_{24}H_{26}NO_2^+$ $[M+H]^+$ 360.1885)

Purity (HPLC) λ_{210}: > 97% (Method 1c)

(*R*,*E*)-*N*-(2-Bromo-5-fluorobenzylidene)-2-methylpropane-2-sulfinamide – (105)



$C_{11}H_{13}BrFNOS$

M = 306.19 g/mol

Synthesized according to **GP A**, using 2-bromo-5-fluorobenzaldehyde (1.00 g, 4.78 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (1.61 g, 7.17 mmol, 1.50 eq.) and tetraethyl orthotitanate (3.27 g, 3.03 mL, 14.3 mmol, 3.00 eq.). The crude product was used without further purification.

Yield: 1.46 g (4.78 mmol, 100%)

Appearance: yellow oil

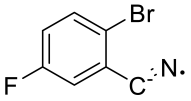
$\boldsymbol{\alpha_{598}^{20}}$**:** -176 (β = 2.99 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.92 (d, *J* = 2.2 Hz, 1H, 1'-H), 7.74 (dd, *J* = 9.1, 3.1 Hz, 1H, 3-H), 7.61 (dd, *J* = 8.8, 5.0 Hz, 1H, 6-H), 7.10 (ddd, *J* = 8.8, 7.5, 3.1 Hz, 1H, 4-H), 1.28 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 163.28/160.81 (d, C-5), 161.48 (d, C-1'), 135.17 (d, C-6), 134.49 (C-1), 120.85 (d, C-4), 120.69 (C-2), 116.20 (d, C-3), 58.41 (C-$(CH_3)_3$), 22.86 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3068, 2959, 1590, 1461, 1363, 1256, 1083, 1029, 975, 878, 823, 723 cm^{-1}

HRMS (EI): *m/z* **=** 198.9427 $[Fr\text{-}H]^{\bullet-}$ (calculated for $C_7H_3BrFN^{\bullet-}$ $[Fr\text{-}H]^{\bullet-}$ 198.9438)



$[Fr\text{-}H]^{\bullet-}$

Purity (HPLC) $\boldsymbol{\lambda_{254}}$: > 96% (Method 1b)

NMR data according to literature.[104]

(*R*)-*N*-((*S*)-1-(5-Fluoro-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (107a)

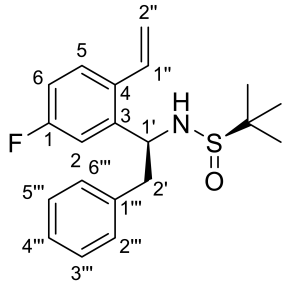
and

(*R*)-*N*-((*R*)-1-(5-Fluoro-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (107b)

Synthesized according to **GP C**, using (*R*)-*N*-(1-(2-bromo-5-fluorophenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (200 mg, 0.502 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (58.0 mg, 0.050 mmol, 0.100 eq.), Cs_2CO_3 (818 mg, 2.51 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (159 mg, 0.176 mL, 1.00 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 75:25, order of elution:

1. 107a
2. 107b



107a

$C_{20}H_{24}FNOS$

M = 345.48 g/mol

Yield: 106 mg (0.308 mmol, 61%)

Appearance: off-white solid

Melting point: 144 – 145 °C

R_f: 0.20 (hexanes/EtOAc 75:25)

α_{598}^{20}: -73 (β = 2.48 · 10^{-3} g/mL, $CHCl_3$)

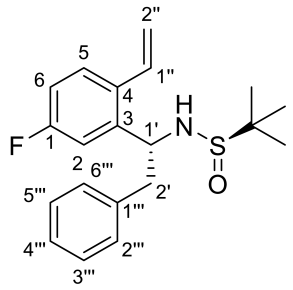
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.40 (dd, *J* = 8.6, 5.9 Hz, 1H, 5-H), 7.24 – 7.18 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 7.10 (dd, *J* = 10.2, 2.7 Hz, 1H, 2-H), 7.07 – 7.01 (m, 2H, 2'''-H, 6'''-H), 6.97 (td, *J* = 8.4, 2.7 Hz, 1H, 6-H), 6.86 (dd, *J* = 17.3, 11.0 Hz, 1H, 1''-H), 5.47 (dd, *J* = 17.2, 1.3 Hz, 1H, 2''-H), 5.26 (dd, *J* = 11.0, 1.3 Hz, 1H, 2''-H), 4.87 (tdd, *J* = 6.8, 4.7, 1.4 Hz, 1H, 1'-H), 3.19 (dd, *J* = 13.6, 7.1 Hz, 1H, 2'-H), 3.03 (dd, *J* = 13.6, 6.9 Hz, 1H, 2'-H), 1.10 (s, 9H, *tert*-butyl)

^{13}C NMR (126 MHz, CD_2Cl_2) δ 162.86 (d, C-1), 141.80 (d, C-3), 137.62 (C-1'''), 133.63 (C-1''), 133.52 (d, C-4), 130.07 (C-2''', C-6'''), 128.87 (d, C-5), 128.67 (C-3''', C-5'''), 117.37 (d, C-2''), 115.06 (d, C-6), 114.03 (d, C-2), 56.78 (C-1'), 56.29 (C-$(CH_3)_3$), 43.37 (C-2'), 22.59 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3194, 3056, 2920, 1491, 1240, 1041, 914, 826, 748, 703 cm^{-1}

HRMS (ESI): *m/z* **=** 346.1636 $[M+H]^+$ (calculated for $C_{20}H_{25}FNOS^+$ $[M+H]^+$ 346.1563)

Purity (HPLC) λ_{254}**:** > 99% (Method 1a)



107b

Yield: 51.0 mg (0.147 mmol, 29%)

Appearance: off-white solid

Melting point: 122 – 123 °C

R_f: 0.15 (hexanes/EtOAc 75:25)

α_{598}^{20}**:** +79 (β = 3.60 · 10^{-3} g/mL, $CHCl_3$)

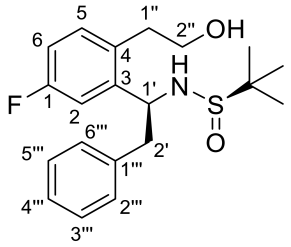
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.42 (dd, *J* = 8.6, 5.9 Hz, 1H, 6-H), 7.32 – 7.21 (m, 3H, 3'''-H, 5-H, 5'''-H), 7.14 – 7.08 (m, 3H, 2'''-H, 4'''-H, 6'''-H), 7.04 – 6.95 (m, 2H, 1''-H, 2-H), 5.52 (dd, *J* = 17.2, 1.3 Hz, 1H, 2''-H), 5.35 – 5.29 (m, 1H, 2''-H), 4.93 (td, *J* = 7.1, 2.1 Hz, 1H, 1'-H), 3.11 (dd, *J* = 13.6, 5.8 Hz, 1H, 2'-H), 2.94 (dd, *J* = 13.6, 8.3 Hz, 1H, 2'-H), 1.12 (s, 9H, *tert*-butyl)

^{13}C NMR (126 MHz, CD_2Cl_2) δ 162.94 (d, C-1), 141.43 (d, C-3), 137.02 (C-1'''), 133.98 (d, C-4), 133.63 (C-1''), 129.83 (C-2''', C-6'''), 129.07 (C-3''', C-5'''), 128.87 (d, C-6), 127.46 (C-5), 117.38 (C-2''), 114.97 (d, C-2), 114.42 (d, C-4'''), 55.84 (C-$(CH_3)_3$), 54.97 (C-1'), 44.48 (C-2'), 22.61 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3188, 3050, 2920, 1489, 1241, 1037, 917, 822, 748, 701 cm^{-1}

HRMS (ESI): *m/z* **=** 346.1611 $[M+H]^+$ (calculated for $C_{20}H_{25}FNOS^+$ $[M+H]^+$ 346.1563)

(*R*)-*N*-((*S*)-1-(5-Fluoro-2-(2-hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (108)



$C_{20}H_{26}FNO_2S$

M = 363.49 g/mol

Synthesized according to **GP D**, using (*R*)-*N*-((*S*)-1-(5-fluoro-2-vinylphenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**107a**, 1.30 g, 3.76 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 26.3 mL, 13.2 mmol, 3.50 eq.), H_2O_2 (33% in water, 4.22 mL, 37.6 mmol, 10.0 eq.) and NaOH (2.00 M in water, 18.8 mL, 37.6 mmol, 10.0 eq.).

Eluent for flash column chromatography: DCM 100 + 1% MeOH

Yield: 806 mg (2.22 mmol, 59%)

Appearance: yellow solid

Melting point: 67 – 68 °C

R_f: 0.13 (DCM 100 + 1% MeOH)

α_{598}^{20}: -119 (β = 1.47 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.15 – 7.03 (m, 5H, 2-H, 3'''-H, 4'''-H, 5-H, 5'''-H), 7.03 – 6.98 (m, 2H, 2'''-H, 6'''-H), 6.87 (td, *J* = 8.4, 2.8 Hz, 1H, 6-H), 4.84 (dddd, *J* = 8.3, 5.8, 3.5, 1.7 Hz, 1H, 1'-H), 3.72 (dq, *J* = 10.6, 5.2 Hz, 1H, 2''-H), 3.67 (d, *J* = 3.5 Hz, 1H, NH), 3.45 (dtd, *J* = 11.2, 8.3, 5.2 Hz, 1H, 2''-H), 3.20 (dd, *J* = 13.7, 6.3 Hz, 1H, 2'-H), 2.99 (dd, *J* = 13.7, 8.5 Hz, 1H, 2'-H), 2.77 (ddd, *J* = 14.4, 8.7, 5.8 Hz, 1H, 1''-H), 2.57 – 2.47 (m, 1H, 1''-H), 1.05 (s, 9H, *tert*-butyl)

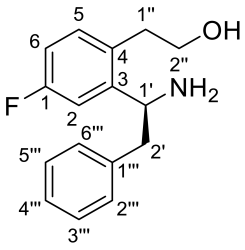
^{13}C NMR (101 MHz, CD_2Cl_2) δ 161.99 (d, C-1), 142.70 (d, C-3), 137.94 (C-1'''), 134.16 (d, C-4), 132.27 (d, C-5), 129.86 (C-2''', C-6'''), 128.68 (C-3''', C-5'''), 126.90 (C-4'''), 115.19 (d, C-6), 113.90 (d, C-2), 63.85 (C-2''), 56.13 (C-$(CH_3)_3$), 56.12 (C-1'), 43.08 (C-2'), 35.12 (C-1''), 22.64 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3198, 2959, 1497, 1240, 1047, 1026, 1014, 735, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 364.1745 $[M+H]^+$ (calculated for $C_{20}H_{27}FNO_2S^+$ $[M+H]^+$ 364.1688)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*S*)-2-(2-(1-Amino-2-phenylethyl)-4-fluorophenyl)ethan-1-ol – (109)



$C_{16}H_{18}FNO$

M = 259.32 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(5-fluoro-2-(2-hydroxyethyl)phenyl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**108**, 633 mg, 1.74 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (2.65 mL, 10.6 mmol, 6.09 eq.). The crude product was used without further purification.

Yield: 452 mg (1.74 mmol, 100%)

Appearance: yellow oil

$\boldsymbol{\alpha_{598}^{20}}$**:** -26 (β = 2.58 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.28 (m, 2H, 3'''-H, 5'''-H), 7.27 – 7.25 (m, 1H, 2-H), 7.24 – 7.20 (m, 3H, 2'''-H, 4'''-H, 6'''-H), 7.19 – 7.16 (m, 1H, 5-H), 6.94 (td, *J* = 8.3, 2.8 Hz, 1H, 6-H), 4.37 – 4.32 (m, 1H, 1'-H), 3.80 (dt, *J* = 10.7, 5.4 Hz, 1H, 2''-H), 3.64 (ddd, *J* = 10.5, 8.6, 4.9 Hz, 1H, 2''-H), 3.10 (dd, *J* = 13.3, 4.7 Hz, 1H, 2'-H), 2.96 (ddd, *J* = 14.2, 8.7, 5.5 Hz, 1H, 1''-H), 2.88 (dd, *J* = 13.4, 9.2 Hz, 1H, 2'-H), 2.78 (dt, *J* = 14.2, 5.1 Hz, 1H, 1''-H), 2.05 (s, 3H, NH_2, OH)

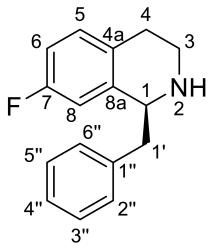
^{13}C NMR (101 MHz, CD_2Cl_2) δ (101 MHz, CD_2Cl_2) δ 162.10 (d, C-1), 145.80 (d, C-3), 139.32 (C-1'''), 134.21 (d, C-4), 132.16 (d, C-5), 129.70 (C-2''', C-6'''), 128.95 (C-3''', C-5'''), 126.95 (C-4'''), 114.20 (C-6), 112.87 (d, C-2), 63.93 (C-2''), 52.92 (C-1'), 45.11 (C-2')

IR (ATR): $\tilde{\nu}$ = 3278, 2921, 1588, 1493, 1046, 1029, 736, 699 cm^{-1}

HRMS (ESI): *m/z* **=** 260.1445 $[M+H]^+$ (calculated for $C_{16}H_{19}FNO^+$ $[M+H]^+$ 260.1372)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$: > 93% (Method 1b)

(*S*)-1-Benzyl-7-fluoro-1,2,3,4-tetrahydroisoquinoline – (110)



$C_{16}H_{16}FN$

M = 241.31 g/mol

Synthesized according to **GP F**, using (*S*)-2-(2-(1-amino-2-phenylethyl)-4-fluorophenyl)ethan-1-ol (**109**, 220 mg, 0.848 mmol, 1.00 eq.) and CMBP (313 mg, 0.340 mL, 1.27 mmol, 1.50 eq.). Eluent for flash column chromatography: DCM/EtOAc 50:50

Yield: 120 mg (0.497 mmol, 59%)

Appearance: brown-yellow oil

R_f: 0.27 (DCM/EtOAc 50:50)

α_{598}^{20}: +57 (β = 3.30 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.38 – 7.30 (m, 2H, 3''-H, 5''-H), 7.29 – 7.22 (m, 3H, 2''-H, 4''-H, 6''-H), 7.08 (dd, *J* = 8.4, 6.0 Hz, 1H, 5-H), 6.96 (dd, *J* = 10.2, 2.7 Hz, 1H, 8-H), 6.87 (td, *J* = 8.5, 2.7 Hz, 1H, 6-H), 4.15 (dd, *J* = 10.1, 3.8 Hz, 1H, 1-H), 3.23 – 3.14 (m, 2H, 1'-H, 3-H), 2.91 – 2.84 (m, 2H, 1'-H, 3-H), 2.73 (qt, *J* = 15.8, 5.7 Hz, 2H, 4-H), 1.59 (s, 2H, NH)

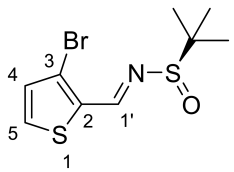
^{13}C NMR (126 MHz, CD_2Cl_2) δ 161.29 (d, C-7), 141.46 (d, C-8a), 139.61 (C-1''), 131.66 (d, C-4a), 131.04 (s, C-5), 129.76 (C-2'', C-6''), 128.87 (C-3'', C-5''), 126.78 (C-4''), 113.37 (d, C-6), 112.93 (d, C-8), 57.67 (d, C-1), 42.76 (C-1'), 40.92 (C-3), 29.74 (C-4)

IR (ATR): $\tilde{\nu}$ = 3337, 2918, 1495, 1236, 782, 743, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 241.1334 $[M+H]^+$ (calculated for $C_{16}H_{17}FN^+$ $[M+H]^+$ 242.1267)

Purity (HPLC) λ_{210}: > 95% (Method 2b)

(*R*,*E*)-*N*-((3-Bromothiophen-2-yl)methylene)-2-methylpropane-2-sulfinamide – (112)



$C_9H_{12}BrNOS_2$

M = 294.23 g/mol

Synthesized according to **GP A**, using 3-brom-2-thiophenecarbaldehyde (1.00 g, 4.97 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (923 mg, 7.46 mmol, 1.50 eq.) and tetraethyl

orthotitanate (3.40 g, 3.15 mL, 14.9 mmol, 3.00 eq.). The crude product was used without further purification.

Eluent for flash column chromatography: hexanes/EtOAc 60:40

Yield: 1.46 g (4.97 mmol, 100 %)

Appearance: yellow soild

Melting point: 97 – 98 °C

$\boldsymbol{\alpha_{598}^{20}}$**:** -115 (β = 3.39 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.1 Hz, 1H, 1'-H), 7.54 (dd, *J* = 5.3, 1.0 Hz, 1H, 5-H), 7.10 (d, *J* = 5.3 Hz, 1H, 4-H), 1.26 (s, 9H, *tert*-butyl)

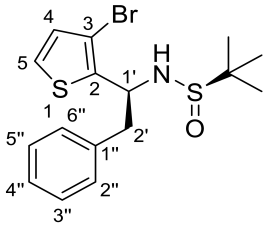
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.88 (C-1'), 135.07 (C-3), 132.18 (C-4), 131.89 (C-5), 118.18 (C-2), 58.34 (C-$(CH_3)_3$), 22.78 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3221, 3104, 2956, 1572, 1418, 1079, 1065, 887, 745, 725 cm^{-1}

HRMS (ESI): *m/z* **=** 293.9621 $[M+H]^+$ (calculated for $C_9H_{13}BrNOS_2^+$ $[M+H]^+$ 293.9544)

Purity (HPLC) $\boldsymbol{\lambda_{254}}$: > 87% (Method 1b)

(*R*)-*N*-((*S*)-1-(3-Bromothiophen-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (114a)



$C_{16}H_{20}BrNOS_2$

M = 386.37 g/mol

Synthesized according to **GP B**, using (*R*,*E*)-*N*-((3-bromothiophen-2-yl)methylene)-2-methylpropane-2-sulfinamide (9.00 g, 30.6 mmol, 1.00 eq.), and benzylmagnesium chloride solution (2.00 M in THF) (38.2 mL, 76.5 mmol, 2.50 eq.). The reaction was carried out at -78 °C.

Eluent for flash column chromatography: hexanes/EtOAc 70:30

Yield: 2.66 g (6.88 mmol, 23%)

Appearance: white solid

Melting point: 108 – 109 °C

$\boldsymbol{R_f}$: 0.18 (hexanes/EtOAc 70:30)

$\boldsymbol{\alpha_{598}^{20}}$**:** -95 (β = 1.92 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.29 (m, 3H, 3"-H, 4-H, 5"-H), 7.28 – 7.23 (m, 1H, 4"-H), 7.22 – 7.15 (m, 2H, 2"-H, 6"-H), 6.93 (d, *J* = 5.3 Hz, 1H, 5-H), 5.04 (dddd, *J* = 8.4, 6.0, 2.5, 0.6

Hz, 1H, 1'-H), 3.62 (s, 1H, NH), 3.23 (dd, *J* = 13.6, 5.9 Hz, 1H, 2'-H), 3.05 (dd, *J* = 13.6, 8.1 Hz, 1H, 2'-H), 1.13 (s, 9H, *tert*-butyl)

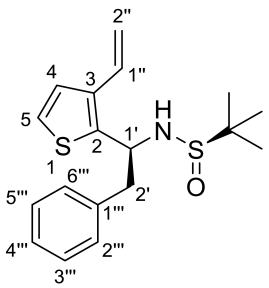
^{13}C NMR (126 MHz, CD_2Cl_2) δ 140.76 (C-2), 136.55 (C-1''), 130.21 (C-5), 129.81 (C-2'', C-6''), 129.08 (C-3'', C-5''), 127.56 (C-4), 125.82 (C-4''), 109.52 (C-3), 56.13 (C-$(CH_3)_3$), 54.96 (C-1'), 44.66 (C-2'), 22.59 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3298, 2954, 1456, 1350, 1063, 877, 754, 700 cm^{-1}

HRMS (ESI): *m/z* **=** 386.0225 $[M+H]^+$ (calculated for $C_{16}H_{21}BrNOS_2^+$ $[M+H]^+$ 386.0170)

Purity (HPLC) λ_{254}: > 98% (Method 1b)

(*R*)-2-Methyl-*N*-((*S*)-2-phenyl-1-(3-vinylthiophen-2-yl)ethyl)propane-2-sulfinamide – (116)



$C_{18}H_{23}NOS_2$

M = 333.51 g/mol

Synthesized according to **GP C**, using (*R*)-*N*-((*S*)-1-(3-bromothiophen-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**114a**, 2.75 g, 7.12 mmol, 1.00 eq.), $Pd(PPh_3)_4$ (2.47 g, 2.14 mmol, 0.300 eq.), Cs_2CO_3 (11.6 g, 35.6 mmol, 5.00 eq.) and vinylboronic acid pinacol ester (2.26 g, 2.49 mL, 14.2 mmol, 2.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 70:30

Yield: 2.21 g (6.63 mmol, 93%)

Appearance: yellow solid

Melting point: 102 – 103 °C

R_f: 0.33 (hexanes/EtOAc 70:30)

α_{598}^{20}: -67 (β = 2.14 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 – 7.27 (m, 2H, 3'''-H, 5'''-H), 7.26 – 7.21 (m, 2H, 4'''-H, 5-H), 7.20 – 7.12 (m, 3H, 2'''-H, 4-H, 6'''-H), 6.78 – 6.66 (m, 1H, 1''-H), 5.53 (dd, *J* = 17.4, 1.3 Hz, 1H, 2''-H), 5.20 (dd, *J* = 11.0, 1.3 Hz, 1H, 2''-H), 5.05 (ddd, *J* = 8.1, 6.3, 2.0 Hz, 1H, 1'-H), 3.61 (s, 1H, NH), 3.15 (dd, *J* = 13.5, 6.3 Hz, 1H, 2'-H), 3.07 (dd, *J* = 13.5, 8.0 Hz, 1H, 2'-H), 1.12 (s, 9H, *tert*-butyl)

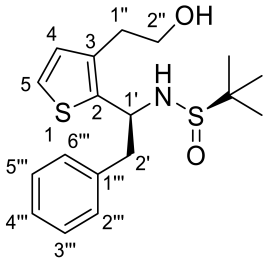
^{13}C NMR (101 MHz, CD_2Cl_2) δ 141.50 (C-2), 137.80 (C-3), 137.03 (C-1'''), 129.76 (C-2''', C-6'''), 129.12 (C-1''), 129.08 (C-3''', C-5'''), 127.50 (C-4'''), 125.33 (C-4), 124.99 (C-5), 114.87 (C-2''), 55.93 (C-$(CH_3)_3$), 53.30 (C-1'), 46.06 (C-2'), 22.67 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3297, 3099, 2953, 1807, 1627, 1380, 1061, 1021, 971, 900, 748, 706, 688 cm^{-1}

HRMS (EI): *m/z* **=** 334.1299 $[M+H]^+$ (calculated for $C_{18}H_{24}NOS_2^+$ $[M+H]^+$ 334.1221)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*)-*N*-((*S*)-1-(3-(2-Hydroxyethyl)thiophen-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (117)



$C_{18}H_{25}NO_2S_2$

M = 351.52 g/mol

Synthesized according to **GP D**, using (*R*)-2-methyl-*N*-((*S*)-2-phenyl-1-(3-vinylthiophen-2-yl)ethyl)propane-2-sulfinamide (**116**, 2.20 g, 6.60 mmol, 1.00 eq.), 9-BBN (0.500 M in THF, 46.2 mL, 23.1 mmol, 3.50 eq.), H_2O_2 (33% in water, 7.40 mL, 66.0 mmol, 10.0 eq.) and NaOH (2.00 M in water, 33.0 mL, 66.0 mmol, 10.0 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 20:80 + 1% NEt_3 to EtOAC 100 + 10% MeOH + 1% NEt_3

Yield: 1.54 g (4.37 mmol, 66%)

Appearance: yellow oil

R_f: 0.24 (hexanes/EtOAc 20:80 + 1% NEt_3)

α_{598}^{20}: -64 (β = 2.25 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 – 7.26 (m, 3H, 3'''-H, 5-H, 5'''-H), 7.26 – 7.21 (m, 1H, 4'''-H), 7.19 – 7.12 (m, 2H, 2'''-H, 6'''-H), 6.83 (d, *J* = 5.1 Hz, 1H, 4-H), 4.95 (tdd, *J* = 6.8, 2.3, 0.8 Hz, 1H, 1'-H), 3.76 (d, *J* = 8.0 Hz, 2H, NH, OH), 3.71 – 3.59 (m, 2H, 2''-H), 3.19 – 3.04 (m, 2H, 2'-H), 2.77 – 2.57 (m, 2H, 1''-H), 1.12 (s, 9H, *tert*-butyl)

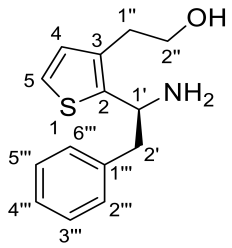
^{13}C NMR (101 MHz, CD_2Cl_2) δ 139.78 (C-3), 138.53 (C-2), 137.54 (C-1'''), 129.71 (C-2''', C-6'''), 129.01 (C-3''', C-5'''), 128.94 (C-4), 127.40 (C-4'''), 125.23 (C-5), 62.86 (C-2''), 55.69 (C-$(CH_3)_3$), 53.50 (C-1'), 46.30 (C-2'), 32.27 (C-1''), 22.76 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3355, 2924, 2860, 1454, 1365, 1035, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 352.1408 $[M+H]^+$ (calculated for $C_{18}H_{26}NO_2S_2^+$ $[M+H]^+$ 352.1327)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*S*)-2-(2-(1-Amino-2-phenylethyl)thiophen-3-yl)ethan-1-ol – (118)



$C_{14}H_{17}NOS$

M = 247.36 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(3-(2-hydroxyethyl)thiophen-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (**117**, 1.55 g, 4.41 mmol, 1.00 eq.) and 4.00 M HCl in dioxane (6.71 mL, 26.8 mmol, 6.09 eq.).

Eluent for flash column chromatography: EtOAc 100 + 1.5% NEt_3 to EtOAc 100 + 10% MeOH + 1.5% NEt_3

Yield: 642 mg (2.60 mmol, 59%)

Appearance: brown oil

R_f: 0.24 (EtOAc 100 + 1.5% NEt_3)

α_{598}^{20}: +21 (β = 2.10 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 – 7.26 (m, 2H, 3'''-H, 5'''-H), 7.25 – 7.20 (m, 3H, 2'''-H, 4-H, 6'''-H), 7.19 (d, *J* = 5.1 Hz, 1H, 4'''-H), 6.86 (d, *J* = 5.1 Hz, 1H, 5-H), 4.45 (ddd, *J* = 8.9, 5.4, 0.5 Hz, 1H, 1'-H), 3.70 (dt, *J* = 10.5, 5.3 Hz, 1H, 2''-H), 3.59 (ddd, *J* = 10.5, 8.4, 4.8 Hz, 1H, 2''-H), 3.17 (dd, *J* = 13.3, 5.4 Hz, 1H, 2'-H), 2.94 (dd, *J* = 13.3, 8.8 Hz, 1H, 2'-H), 2.82 – 2.73 (m, 2H, 1''-H)

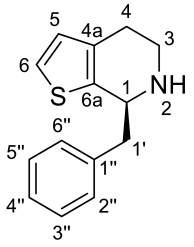
^{13}C NMR (101 MHz, CD_2Cl_2) δ 144.24 (C-2), 139.10 (C-1'''), 136.58 (C-3), 129.69 (C-2''', C-6'''), 129.65 (C-5), 128.90 (C-3''', C-5'''), 126.97 (C-4), 123.17 (C-4'''), 63.03 (C-2''), 51.40 (C-1'), 46.61 (C-2'), 32.42 (C-1'')

IR (ATR): $\tilde{\nu}$ = 3284, 2919, 2863, 2168, 1601, 1494, 1453, 1047, 1029, 730, 699, 661 cm^{-1}

HRMS (ESI): *m/z* **=** 248.1106 $[M+H]^+$ (calculated for $C_{14}H_{17}NOS^+$ $[M+H]^+$ 248.1031)

Purity (HPLC) λ_{254}: 93% (Method 1d)

(*S*)-7-Benzyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine – (119)



$C_{14}H_{15}NS$

M = 229.34 g/mol

Synthesized according to **GP F**, using (*S*)-2-(2-(1-amino-2-phenylethyl)thiophen-3-yl)ethan-1-ol (**118**, 199 mg, 0.804 mmol, 1.00 eq.) and CMBP (297 mg, 0.323 mL, 1.21 mmol, 1.50 eq.). Eluent for flash column chromatography: hexanes/EtOAc 60:40 + 1.5% NEt_3

Yield: 135 mg (0.589 mmol, 73%)

Appearance: brown oil

R_f: 0.25 (hexanes/EtOAc 60:40 + 1.5% NEt_3)

α_{598}^{20}: -101 (β = 3.22 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.35 – 7.22 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.12 (dd, *J* = 5.1, 0.9 Hz, 1H, 6-H), 6.80 (d, *J* = 5.1 Hz, 1H, 5-H), 4.26 (ddd, *J* = 9.1, 4.4, 2.2 Hz, 1H, 1-H), 3.25 – 3.13 (m, 2H, 1'-H, 3-H), 2.93 – 2.81 (m, 2H, 1'-H, 3-H), 2.74 – 2.53 (m, 2H, 4-H), 1.59 (s, 2H, NH_2^+)

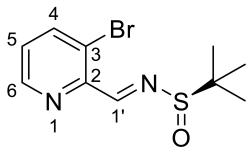
^{13}C NMR (101 MHz, CD_2Cl_2) δ 139.12 (C-1''), 139.04 (C-4a), 135.35 (C-6a), 129.84 (C-2'', C-6''), 128.76 (C-3'', C-5''), 127.88 (C-5), 126.85 (C-4''), 122.36 (C-6), 56.59 (C-1), 44.33 (C-1‘ or C-3), 42.75 (C-1‘ or C-3), 27.33 (C-4)

IR (ATR): $\tilde{\nu}$ = 3060, 3026, 2917, 2833, 1737, 1602, 1494, 1452, 1429, 1118, 744, 696 cm^{-1}

HRMS (ESI): *m/z* **=** 230.0993 $[M+H]^+$ (calculated for $C_{14}H_{16}NS^+$ $[M+H]^+$ 230.0925)

Purity (HPLC) λ_{210}: > 93% (Method 2b)

(*R*,*E*)-*N*-((3-Bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide – (111)



$C_{10}H_{13}BrN_2OS$

M = 287.99 g/mol

Synthesized according to **GP A**, using 2-bromo-3-formylpyridine (150 mg, 0.790 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (147 mg, 1.19 mmol, 1.50 eq.) and tetraethyl orthotitanate (541 mg, 0.501 mL, 2.37 mmol, 3.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 80:20

Yield: 201 mg (0.695 mmol, 88%)

Appearance: yellow solid

Melting point: 47 – 48 °C

R_f: 0.31 (hexanes/EtOAc 80:20)

α_{598}^{20}: -228 (β = 1.58 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H, 1'-H), 8.49 (dd, *J* = 4.7, 2.1 Hz, 1H, 6-H), 8.30 (dd, *J* = 7.7, 2.0 Hz, 1H, 4-H), 7.39 (ddd, *J* = 7.7, 4.6, 0.7 Hz, 1H, 5-H), 1.28 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.19 (C-1'), 152.92 (C-6), 144.95 (C-2), 137.78 (C-4), 130.57 (C-3), 123.34 (C-5), 58.52 (C-$(CH_3)_3$), 22.86 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3077, 2955, 1571, 1386, 1334, 1080, 1047, 811, 671 cm^{-1}

HRMS (ESI): *m/z* **=** 289.0004 $[M+H]^+$ (calculated for $C_{10}H_{14}BrN_2OS^+$ $[M+H]^+$ 288.0052)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*)-*N*-((*S*)-1-(3-Bromopyridin-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (113a)

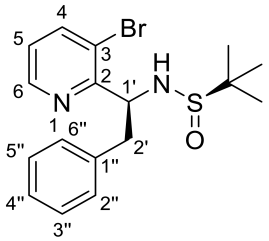
and

(*R*)-*N*-((*R*)-1-(3-Bromopyridin-2-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide – (113b)

Synthesized according to **GP B**, using (*R*,*E*)-*N*-((3-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**111**, 1.00 g, 3.46 mmol, 1.00 eq.), and benzylmagnesium chloride solution (2.00 M in THF) (4.33 mL, 8.65 mmol, 2.50 eq.). The reaction was carried out at -78 °C.

Eluent for flash column chromatography: hexanes/EtOAc 50:50, order of elution:

1. 113a
2. 113b



113a

$C_{17}H_{21}BrN_2OS$

M = 381.33 g/mol

Yield: 320 mg (0.840 mmol, 34%)

Appearance: white solid

Melting point: 153 – 154 °C

R_f: 0.51 (hexanes/EtOAc 50:50)

α_{598}^{20}: -114 (β = 1.19 · 10^{-3} g/mL, $CHCl_3$)

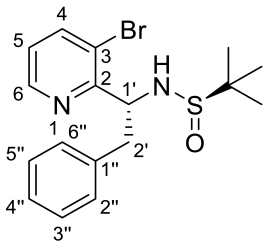
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.27 (dd, *J* = 4.6, 2.0 Hz, 1H, 6-H), 7.66 (dd, *J* = 7.6, 2.0 Hz, 1H, 4-H), 7.32 (ddt, *J* = 8.0, 6.5, 1.3 Hz, 2H, 3''-H, 5''-H), 7.30 – 7.24 (m, 2H, 4''-H, 5-H), 7.21 – 7.14 (m, 2H, 2''-H, 6''-H), 5.05 (ddd, *J* = 8.2, 5.2, 2.9 Hz, 1H, 1'-H), 3.58 (s, 1H, NH), 3.28 (dd, *J* = 13.8, 5.2 Hz, 1H, 2'-H), 2.92 (dd, *J* = 13.8, 8.4 Hz, 1H, 2'-H), 1.11 (s, 9H, *tert*-butyl)

^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.46 (C-6), 143.56 (C-3), 138.47 (C-1''), 137.96 (C-4), 136.45 (C-2), 129.93 (C-2'', C-6''), 129.18 (C-3'', C-5''), 127.66 (C-5), 123.35 (C-4''), 57.62 (C-1'), 56.08 (C-$(CH_3)_3$), 43.26 (C-2'), 22.58 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3306, 2952, 2922, 1560, 1401, 1064, 1046, 797, 739, 706, 695 cm^{-1}

HRMS (ESI): *m/z* **=** 379.0484 $[M-H]^-$ (calculated for $C_{17}H_{20}BrN_2OS^-$ $[M-H]^-$ 379.0558)

Purity (HPLC) λ_{254}: > 99% (Method 1b)



113b

Yield: 378 mg (0.990 mmol, 40%)

Appearance: off-white solid

Melting point: 65 – 66 °C

R_f: 0.15 (hexanes/EtOAc 50:50)

α_{598}^{20}: +42 (β = 1.16 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.27 (dd, *J* = 4.6, 1.9 Hz, 1H, 6-H), 7.69 (ddd, *J* = 7.7, 2.0, 0.5 Hz, 1H, 4-H), 7.32 – 7.26 (m, 3H, 3''-H, 4''-H, 5''-H), 7.26 – 7.20 (m, 1H, 5-H), 7.19 – 7.10 (m, 2H, 2''-H, 6''-H), 4.93 (td, *J* = 7.9, 5.3 Hz, 1H, 1'-H), 3.80 (d, *J* = 7.3 Hz, 1H, NH), 3.23 (dd, *J* = 13.8, 5.3 Hz, 1H, 2'-H), 2.97 (dd, *J* = 13.8, 8.4 Hz, 1H, 2'-H), 1.02 (s, 9H, *tert*-butyl)

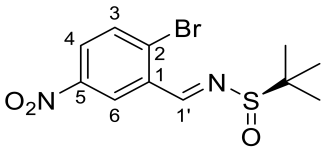
^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.44 (C-6), 143.15 (C-3), 138.91 (C-1''), 137.82 (C-4), 137.21 (C-2), 130.00 (C-2'', C-6''), 128.90 (C-3'', C-5''), 127.35 (C-5), 123.35 (C-4''), 60.28 (C-1'), 56.76 (C-$(CH_3)_3$), 42.78 (C-2'), 22.38 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3301, 2955, 2919, 1560, 1400, 1067, 1046, 797, 735, 706, 699 cm^{-1}

HRMS (ESI): 379.0482 $[M-H]^-$ (calculated for $C_{17}H_{20}BrN_2OS^-$ $[M-H]^-$ 379.0558)

Purity (HPLC) λ_{254}: > 99% (Method 1b)

(*R*,*E*)-*N*-(2-Bromo-5-nitrobenzylidene)-2-methylpropane-2-sulfinamide – (104)



$C_{11}H_{13}BrN_2O_3S$

M = 333.20 g/mol

Synthesized according to **GP A**, using 2-bromo-5-nitrobenzaldehyde (300 mg, 1.30 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (241 mg, 1.95 mmol, 1.50 eq.) and tetraethyl orthotitanate (893 mg, 0.824 mL, 3.90 mmol, 3.00 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 90:10

Yield: 362 mg (1.09 mmol, 84%)

Appearance: yellow-white solid

Melting point: 83 – 84 °C

R_f: 0.18 (hexanes/EtOAc 90:10)

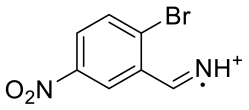
α_{598}^{20}**:** -87 (β = 3.13 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.95 (s, 1H, 1'-H), 8.82 (d, *J* = 2.8 Hz, 1H, 6-H), 8.18 (dd, *J* = 8.8, 2.8 Hz, 1H, 4-H), 7.88 (d, *J* = 8.7 Hz, 1H, 3-H), 1.28 (s, 9H, *tert*-butyl)

^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.72 (C-1'), 147.99 (C-5), 135.33 (C-3), 134.54 (C-1), 132.86 (C-2), 127.23 (C-4), 124.63 (C-6), 58.76 (C-$(CH_3)_3$), 22.85 (3 CH_3)

IR (ATR): $\tilde{\nu}$ = 3092, 3072, 2977, 1595, 1520, 1340, 1078, 1030, 826, 738 cm^{-1}

HRMS (ESI): *m/z* **=** 227.9352 $[Fr1+H]^{\bullet+}$ (calculated for $C_7H_5BrN_2O_2S^{\bullet+}$ $[Fr1+H]^{\bullet+}$ 227.9529)



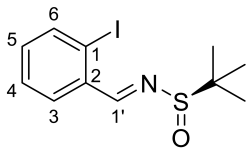
$[Fr1+H]^{\bullet+}$

Purity (HPLC) λ_{254}: > 97% (Method 1b)

Data according to literature.[200]

<u>The following molecules were Synthesized by Mika Kintzel during his master thesis under my supervision:</u>

(*R*)-(*E*)-*N*-(2-Iodobenzylidene)-*tert*-butylsulfinamide – (77)



$C_{11}H_{14}INOS$

M = 355.20 g/mol

Synthesized according to **GP A**, using 2-iodobenzaldehyde (6.03 g, 25.2 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (3.43 g, 27.7 mmol, 1.10 eq.) and tetraethyl orthotitanate (17.2 g, 16.0 mL, 75.6 mmol, 3.00 eq.). The total batch was divided into four 30 mL microwave vessels for the microwave accelerated reaction and the procedure carried out four times. All batches were combined for work-up.

Yield: 8.45 g (25.2 mmol, 100%)

Appearance: yellowish oil

R_f: 0.30 (hexanes/EtOAc 95:5)

α_{598}^{20}**:** -201 (β = 11 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.73 (s, 1H, 1'-H), 8.01 (dd, *J* = 7.9, 1.8 Hz, 1H, 6-H), 7.96 (dd, *J* = 8.1, 1.2 Hz, 1H, 3-H), 7.45 (dddd, *J* = 7.9, 7.3, 1.2, 0.7 Hz, 1H, 4-H), 7.21 (td, *J* = 7.9, 1.7 Hz, 1H, 5-H), 1.25 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 166.7 (C-1'), 140.7 (C-3), 135.8 (C-2), 133.8 (C-5), 130.1 (C-6), 129.0 (C-4), 101.5 (C-1), 58.2 (C-$(CH_3)_3$), 22.8 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3404, 2959, 2866, 1580, 1067, 1012, 756, 737, 648 cm^{-1}

HRMS (ESI): *m/z* **=** 278.9198 [M-^{t}Bu+H]$^{+\cdot}$ (calculated for $C_7H_6INOS^{+\cdot}$ [M-^{t}Bu+H]$^{+\cdot}$ 278.9209)

NMR data is in alignment with literature NMR data recorded in $CDCl_3$.[201]

(*S*)-*N*-1-(2-Iodoophenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (78a)

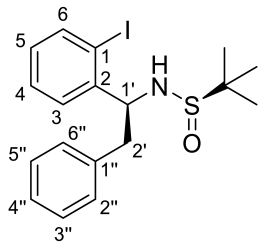
and

(*R*)-*N*-1-(2-Iodoophenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (78b)

Synthesized according to **GP B**, using (*R*)-*N*-1-(2-iodophenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**77**, 6.40 g, 19.1 mmol, 1.00 eq.) and benzylmagnesium chloride solution (1.40 M in THF, 27.3 mL, 38.2 mmol, 2.00 eq.). Reaction was carried out at -21 °C.

Eluent for flash column chromatography: hexanes/EtOAc 50:50 to 40:60, order of elution:

1. 78a
2. 78b



78a

$C_{18}H_{22}INOS$

M = 427.34 g/mol

Yield: 3.75 g (8.77 mmol, 46%)

Appearance: colourless powder

Melting point: 113 – 114 °C

$\boldsymbol{\alpha_{598}^{20}}$**:** -107 (β = 2.0 · 10^{-3} g/mL, $CHCl_3$)

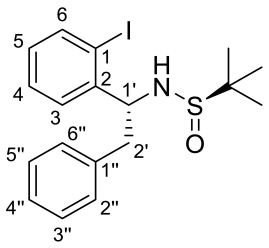
$\mathbf{R_f}$: 0.50 (hexanes/EtOAc 40:60)

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.86 (dd, *J* = 7.9, 1.2 Hz, 1H, 6-H), 7.41 – 7.31 (m, 4H, 3-H, 4-H, 3''-H, 5''-H), 7.31 – 7.22 (m, 3H, 2''-H, 4''-H, 6''-H), 7.00 (dt, *J* = 6.2, 1.5 Hz, 1H, 5-H), 4.94 (ddd, *J* = 8.8, 5.1, 2.4 Hz, 1H, 1'-H), 3.54 (s, 1H, NH), 3.22 (dd, *J* = 13.8, 5.1 Hz, 1H, 2'-H), 2.84 (dd, *J* = 13.8, 8.9 Hz, 1H, 2'-H), 1.10 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 143.8 (C-2), 140.0 (C-6), 136.6 (C-1''), 129.9 (C-3'', C-5''), 129.7 (C-4), 129.2 (C-5), 129.1 (C-2'', C-6''), 128.8 (C-3), 127.5 (C-4''), 100.0 (C-1), 62.9 (C-1'), 55.9 (C-$(CH_3)_3$), 44.1 (C-2'), 22.6 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3304, 2917, 1454, 1065, 1012, 899, 754, 703 cm^{-1}

HRMS (ESI): *m/z* **=** 428.0557 $[M+H]^+$ (calculated for $C_{18}H_{23}INOS^+$ $[M+H]^+$ 428.0540)



78b

Yield: 1.97 g (4.62 mmol, 24%)

Appearance: colourless powder

Melting point: 119 - 120 °C

$\boldsymbol{\alpha_{598}^{20}}$**:** +8.0 (β = 4.9 · 10^{-3} g/mL, $CHCl_3$)

R_f: 0.20 (hexanes/EtOAc 50:50)

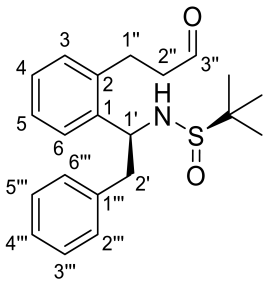
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.85 (dd, *J* = 7.9, 0.9 Hz, 1H, 6-H), 7.40 – 7.18 (m, 7H, 3-H, 4-H, 2-‘’H, 3’’-H, 4’’-H, 5’’-H, 6’’-H), 7.03 – 6.98 (m, 1H, 5-H), 4.84 (ddd, *J* = 8.6, 6.4, 5.4 Hz, 1H, 1’-H), 3.74 (d, *J* = 6.4 Hz, 1H, NH), 3.15 (dd, *J* = 13.8, 5.4 Hz, 1H, 2’-H), 2.94 (dd, *J* = 13.8, 8.5 Hz, 1H, 2’-H), 1.02 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 144.5 (C-2), 140.2 (C-6), 137.8 (C-1’’), 130.1 (C-3’’, C-5’’), 129.8 (C-4), 128.9 (C-3), 128.8 (C-2’’, C-6’’), 127.1 (C-4’’), 99.8 (C-1), 65.2 (C-1’), 56.5 (C-$(CH_3)_3$), 43.6 (C-2’), 22.5 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3196, 2948, 1561, 1040, 1011, 749, 704 cm^{-1}

HRMS (ESI): *m/z* **=** 428.0557 $[M+H]^+$ (calculated for $C_{18}H_{23}INOS^+$ $[M+H]^+$ 428.0558)

(*R*)-*N*-((*S*)-1-(2-(3-Oxopropyl)phenyl)-2-phenylethyl)*tert*-butylsulfinamide – (76a)



$C_{21}H_{27}NO2S$

M = 357.51 g/mol

Synthesized according to **GP H**, using (*R*)-*N*-(*S*)-1-(2-iodophenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**78a**, 1.00 g, 2.35 mmol, 1.00 eq.), benzyltriethylammonium chloride (535 mg, 2.35 mmol, 1.00 eq.), $NaHCO_3$ (395 mg, 4.70 mmol, 2.00 eq.), $Pd(OAc)_2$ (52.8 mg, 0.235 mmol, 0.100 eq.), anhydr. DMF (15.0 mL) and allyl alcohol (276 mg, 0.323 mL, 4.70 mmol,

2.00 eq.). The reaction mixture was stirred at 55 °C for 4 h.Eluent for flash column chromatography: hexanes/EtOAc 30:70.

Yield: 688 mg (1.92 mmol, 82%)

Appearance: reddish oil

R_f: 0.40 (hexanes/EtOAc 30:70)

α_{598}^{20}: +17 (β = 2.3 · 10^{-3} g/mL, $CHCl_3$)

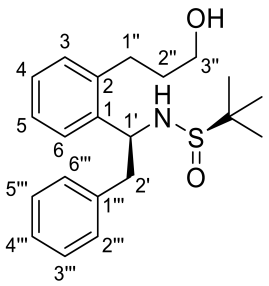
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.71 (t, *J* = 1.1 Hz, 1H, CHO), 7.50 (dd, *J* = 7.7, 1.6 Hz, 1H, 6-H), 7.32 – 7.19 (m, 5H, 4-H, 5-H, 3'''-H, 4'''-H, 5'''-H), 7.12 – 7.10 (m, 3H, 3-H, 2'''-H, 6'''-H), 4.79 (dt, *J* = 6.5, 2.2 Hz, 1H, 1'-H), 3.56 (s, 1H, NH), 3.15 – 2.97 (m, 2H, 2'-H), 2.91 – 2.69 (m, 3H, 1''-H, 2''-H), 2.56 – 2.45 (m, 1H, 2''-H), 1.11 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 201.6 (CHO), 139.6 (C-2), 139.2 (C-1), 137.6 (C-1'''), 129.8 (C-3, C-2''', C-6'''), 129.1 (C-3''', C-5'''), 128.4 (C-6), 128.0 (C-4'''), 127.4 (C-5), 127.2 (C-4), 55.6 (C-$(CH_3)_3$), 54.6 (C-1'), 45.6 (C-2''), 45.3 (C-2'), 25.1 (C-1''), 22.6 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2957, 1720, 1677, 1454, 1048, 891, 759, 722 cm^{-1}

HRMS (ESI): *m/z* **=** 358.1836 $[M+H]^+$ (calculated for $C_{21}H_{28}NO_2S^+$ $[M+H]^+$ 358.1835)

(*R*)-*N*-((*S*)-1-(2-(3-Hydroxypropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (80)



$C_{21}H_{29}NO_2S$

M = 359.53 g/mol

Synthesized according to **GP I**, using (*R*)-*N*-((*S*)-1-(2-(3-oxopropyl)phenyl)-2-phenylethyl)*tert*-butylsulfinamide (**76a**, 319 mg, 881 µmol, 1.00 eq.) and $NaBH_4$ (40.0 mg, 1.06 mmol, 1.20 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 20:80 to EtOAc.

Yield: 280 mg (779 µmol, 88%)

Appearance: colourless oil

R_f: 0.10 (hexanes/EtOAc 30:70)

α_{598}^{20}: -86 (β = 4.6 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.50 – 7.48 (m, 1H, 6-H), 7.33 – 7.15 (m, 8H, 3-H, 4-H, 5-H, 2'''-H, 3'''-H, 4'''-H, 5'''-H, 6'''-H), 5.10 – 5.06 (m, 1H, 1'-H), 3.58 (s, 1H, NH), 3.53 – 3.46 (m,

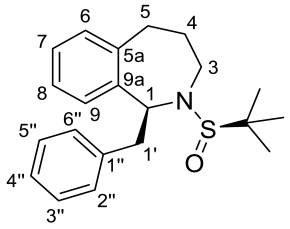
2H, 3''-H), 3.10 – 3.06 (m, 2H, 2'-H, OH), 2.95 – 2.86 (m, 2H, 2'-H, 1''-H), 2.52 – 2.45 (m, 1H, 1''-H), 1.93 – 1.83 (m, 1H, 2''-H), 1.74 – 1.67 (m, 1H, 2''-H), 1.12 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 141.1 (C-1), 139.5 (C-2), 137.7 (C-1'''), 130.0 (C-3), 129.7 (C-2''', C-6'''), 129.1 (C-3''', C-5'''), 127.9 (C-4'''), 127.8 (C-5), 127.4 (C-6), 126.6 (C-4), 60.4 (C-3''), 55.8 (C-$(CH_3)_3$), 53.9 (C-1'), 45.8 (C-2'), 34.6 (C-2''), 27.6 (C-1''), 22.7 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3284, 2926, 1735, 1454, 1364, 1031, 953, 891, 762, 700 cm^{-1}

HRMS (ESI): *m/z* **=** 382.1809 $[M+Na]^+$ (calculated for $C_{21}H_{29}NO_2SNa^+$ $[M+Na]^+$ 382.1811)

(*S*)-1-Benzyl-2-((*R*)-*tert*-butylsulfinyl)-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine – (81)



$C_{21}H_{27}NOS$

M = 341.51 g/mol

Method A:

A 50 mL two necked round bottom flask was charged with (*R*)-*N*-(*S*)-1-(2-(3-hydroxypropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**80**, 300 mg, 834 µmol, 1.00 eq.) and equipped with a reflux condenser. Potassium *tert*-butoxide (187 mg, 1.67 mmol, 2.00 eq.), *p*-toluenesulfonyl chloride (175 mg, 918 µmol, 1.10 eq.) and anhydr. tetrahydrofuran (8.0 mL) were added and the reaction mixture stirred for 3 h under reflux. After cooling to room temperature, water (30 mL) was added and the solution extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydr. Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified *via* flash column chromatography on silica with an eluent: hexanes/EtOAc 60:40. The product was dried *in vacuo*.

Yield: 40.0 mg (117 µmol, 14%)

Method B:

To a 50 mL round bottom flask was charged with (*R*)-*N*-((*S*)-1-(2-(3-hydroxypropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**80**, 320 mg, 890 µmol, 1.00 eq.), anhydr. DCM (5.0 mL) and Et_3N (0.30 mL, 2.15 mmol, 2.42 eq.) were added. The solution was cooled to 0 °C. Methanesulfonyl chloride (0.10 mL, 1.29 mmol, 1.45 eq.) was added and the solution stirred for 90 min at the same temperature. The reaction mixture was quenched using sat. aq. NH_4Cl. The mixture was extracted with DCM (3 x 30 mL) and the combined organic phases washed with brine (20 mL). The combined organic phases were dried over anhydr. Na_2SO_4 and the solvent removed under reduced pressure. The intermediate compound was re-dissolved in

anhydr. DMF (6.0 mL). In another flask, NaH (78.4 mg, 1.96 mmol, 2.20 eq.) was suspended in anhydr. DMF (4.0 mL) and cooled to 0 °C. The solution containing the intermediate compound was added dropwise to the NaH suspension. The reaction mixture was allowed to attain room temperature and stirred for 18 h. Water (20 mL) was added and the solution extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydr. Na_2SO_4. The solvent was removed under reduced pressure and the crude product purified *via* flash column chromatography on silica with an eluent: hexanes/EtOAc 50:50. The product was dried *in vacuo*.

Yield: 52.0 mg (152 µmol, 17%)

Appearance: colourless oil

R_f: 0.40 (hexanes/EtOAc 50:50)

α_{598}^{20}: +66 (β = 1.0 · 10^{-3} g/mL, $CHCl_3$)

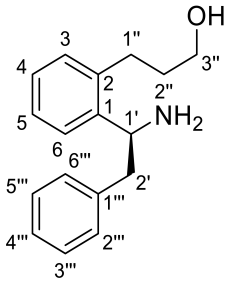
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.24 – 7.06 (m, 7H, 6-H, 7-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.95 (td, *J* = 7.4, 1.6, 1H, 8-H), 6.73 (dd, *J* = 7.5, 1.4 Hz, 1H, 9-H), 4.56 (t, *J* = 7.8 Hz, 1H, 1-H), 3.65 (dt, *J* = 15.0, 4.1 Hz, 1H, 3-H), 3.40 – 3.22 (m, 4H, 3-H, 5-H, 1'-H), 2.96 (dd, *J* = 15.2, 6.5 Hz, 1'-H), 2.13 – 2.05 (m, 1H, 4-H), 1.78 – 1.67 (m, 1H, 4-H), 0.97 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 141.5 (C-9a), 141.0 (C-5a), 138.9 (C-1''), 131.1 (C-6), 129.8 (C-9), 129.7 (C-2'', C-6''), 128.6 (C-3'', C-5''), 127.4 (C-4''), 126.7 (C-7), 126.1 (C-8), 72.2 (C-1), 58.2 (C-$(CH_3)_3$), 41.8 (C-3), 38.3 (C-5), 36.2 (C-1'), 29.8 (C-4), 22.8 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2927, 1603, 1495, 1452, 1359, 1138, 1095, 957, 856, 764, 738, 698 cm^{-1}

HRMS (ESI): *m/z* **=** 364.1703 $[M+Na]^+$ (calculated for $C_{21}H_{27}NOSNa^+$ $[M+Na]^+$ 364.1706)

(*S*)-3-(2-(1-Amino-2-phenylethyl)phenyl)propan-1-ol – (82)



$C_{17}H_{21}NO$

M = 255.36 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(2-(3-hydroxypropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**80**, 150 mg, 417 µmol, 1.00 eq.) and 4 M HCl in dioxane (617 µL, 12.5 mmol, 30.0 eq.).

Eluent for flash column chromatography: EtOAc/DCM 90:10 with 2% Et_3N.

Yield: 90.0 mg (352 µmol, 60%)

Appearance: colourless oil

R_f: 0.15 (EtOAc/DCM 90:10 with 2% Et_3N)

α_{598}^{20}: +30 (β = 0.8 · 10^{-3} g/mL, $CHCl_3$)

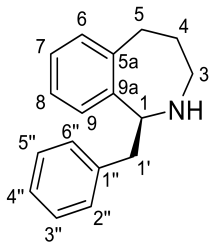
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.52 – 7.49 (m, 1H, 6-H), 7.32 – 7.18 (m, 8H, 3-H, 4-H, 5-H, 2'''-H, 3'''-H, 4'''-H, 5'''-H, 6'''-H), 4.43 (dd, *J* = 9.2, 4.8 Hz, 1H, 1'-H), 3.51 – 3.37 (m, 2H, 3''-H), 3.07 (dd, *J* = 13.2, 4.9 Hz, 1H, 2'-H), 2.92 – 2.85 (m, 2H, 2'-H, 1''-H), 2.72 – 2.66 (m, 1H, 1''-H), 2.15 (s, 3H, NH_2, OH), 1.85 – 1.75 (m, 2H, 2''-H) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 143.1 (C-1), 140.1 (C-2), 139.9 (C-1'''), 129.9 (C-3), 129.7 (C-2''', C-6'''), 128.9 (C-3''', C-5'''), 127.4 (C-4'''), 126.8 (C-5), 126.6 (C-4), 126.2 (C-6), 60.6 (C-3''), 53.3 (C-1'), 45.7 (C-2'), 34.8 (C-2''), 27.8 (C-1'') ppm

IR (ATR): $\tilde{\nu}$ = 2922, 1601, 1583, 1494, 1453, 1374, 1058, 1030, 916, 757 cm^{-1}

HRMS (ESI): *m/z* **=** 256.1696 $[M+H]^+$ (calculated for $C_{17}H_{22}NO^+$ $[M+H]^+$ 256.1696)

(*S*)-1-Benzyl-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine – (79)



$C_{17}H_{19}N$

M = 237.35 g/mol

Method A:

A 50 mL round bottom flask charged with (*S*)-1-benzyl-2-((*R*)-*tert*-butylsulfinyl)-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine (**81**, 50.0 mg, 146 µmol, 1.00 eq.), HPLC grade MeOH (3.5 mL) was added. The solution was cooled to 0 °C and 4 M HCl in dioxane (0.50 mL, 10.2 mmol, 70.0 eq.) was added slowly. The resulting mixture was stirred for 10 min at 0 °C. Then, the solution was allowed to attain room temperature and stirred for 1 h. All volatiles were removed under reduced pressure. The residue was dissolved in water (15 mL) and sat. aq. $NaHCO_3$ was added dropwise until a pH > 10 was attained. The solution was extracted with DCM (3 x 30 mL). The combined organic phases were dried over anhydr. Na_2SO_4, the solvent removed under reduced pressure and the product dried *in vacuo*.

Yield: 32.0 mg (135 µmol, 92%)

Method B:

Synthesized according to **GP F**, using (*S*)-3-(2-(1-amino-2-phenylethyl)phenyl)propan-1-ol (**82**, 80.0 mg, 313 µmol, 1.00 eq.), CMBP (116 mg, 126 µL, 470 µmol, 1.50 eq.) and anhydr. toluene (3.0 mL).

Eluent for flash column chromatography: hexanes/EtOAc = 40:60 with 1.5% Net_3

Yield: 54.0 mg (228 µmol, 73%)

Appearance: yellowish oil

R_f: 0.20 (hexanes/EtOAc 60:40 with 1% NEt_3)

α_{598}^{20}: -15 (β = 4.6 · 10^{-3} g/mL, $CHCl_3$)

Lit. α_{598}^{20}: -11 (β = 2.1 · 10^{-3} g/mL, $CHCl_3$)[162]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 – 7.12 (m, 9H, 6-H, 7-H, 8-H, 9-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 4.19 (dd, *J* = 9.9, 4.9 Hz, 1H, 1-H), 3.33 – 2.85 (m, 6H, 4-H, 5-H, 1'-H), 1.83 – 1.61 (m, 3H, NH, 3-H) ppm

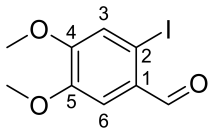
^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.9 (C-9a), 142.1 (C-1''), 139.5 (C-5a), 129.7 (C-6), 129.2 (C-2'', C-6''), 128.6 (C-3'', C-5''), 126.9 (C-7 or C-8 or C-4''), 126.4 (C-7 or C-8 or C-4''), 126.2 (C-7 or C-8 or C-4''), 125.8 (C-9), 62.5 (C-1), 50.4 (C-1'), 39.9 (C-3), 35.3 (C-5), 29.7 (C-4) ppm

IR (ATR): $\tilde{\nu}$ = 2924, 1601, 1495, 1452, 1300, 1133, 1031, 746, 724 cm^{-1}

HRMS (ESI): *m/z* **=** 238.1589 $[M+H]^+$ (calculated for $C_{17}H_{20}N^+$ $[M+H]^+$ 228.1590)

The analytical data is in alignment with the literature.[162]

2-Iodo-4,5-dimethoxybenzaldehyde – (83)



$C_9H_9IO_3$

M = 292.07 g/mol

3,4-Dimethoxybenzaldehyde (3.00 g, 18.1 mmol, 1.00 eq.) was dissolved in trifluoroacetic acid (14.0 mL) and trifluoroacetic anhydride (0.20 mL, 722 µmol, 0.04 eq.) was added. The total batch was divided into two 30 mL microwave vessels. To each vessel, *N*-iodosuccinimide (2.30 g, 9.95 mmol, 1.1 eq.) was added and the reaction mixture stirred under microwave irradiation (120 °C, 300 W) for 15 min. The batches were combined for work-up. The reaction solution was neutralized using sat. aq. $NaHCO_3$ and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with sat. aq. NaS_2O_3. The combined organic phases were dried over anhydr. Na_2SO_4, the solvent removed under reduced pressure and the product dried *in vacuo*.

Yield: 4.72 g (16.2 mmol, 90%)

Appearance: grey solid

Melting point: 104 – 106 °C

R_f: 0.70 (hexanes/EtOAc 70:30)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1H, CHO), 7.37 (s, 1H, 6-H), 7.21 (s, 1H, 3-H), 3.91 (s, 3H, 4-OCH_3), 3.87 (s, 3H, 5-OCH_3) ppm

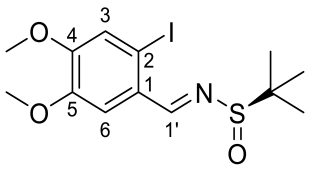
^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.0 (CHO), 154.6 (C-5), 149.9 (C-4), 128.6 (C-1), 122.0 (C-3), 111.3 (C-6), 92.9 (C-2), 56.6 (4-OCH_3), 56.2 (5-OCH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2941, 2856, 1772, 1671, 1580, 1499, 1433, 1378, 1261, 1216, 1152, 1010, 972, 798, 732 cm^{-1}

HRMS (EI): *m/z* **=** 291.9596 $[M]^{+\cdot}$ (calculated for $C_{17}H_{22}NO^{+\cdot}$ $[M]^{+\cdot}$ 291.9596)

NMR spectral data is in alignment with the literature.[202]

(*R*)-(*E*)-*N*-(2-Iodo-4,5-dimethoxybenzylidene)-*tert*-butylsulfinamide – (85)



$C_{13}H_{18}INO_3S$

M = 395.26 g/mol

Synthesized according to **GP A**, using 2-iodo-4,5-dimethoxybenzaldehyde (**83**, 3.00 g, 10.3 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (1.40 g, 11.3 mmol, 1.10 eq.) and tetraethyl orthotitanate (14.0 g, 13.0 mL, 61.6 mmol, 5.98 eq.). The total batch was divided into two 30 mL microwave vessels for the microwave reaction and the procedure carried out twice. Both batches were combined for work-up.

Yield: 3.84 g (9.72 mmol, 95%)

Appearance: yellowish oil

R_f: 0.50 (hexanes/EtOAc 70:30)

α_{598}^{20}: -116 (β = 8.1 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (s, 1H, 1'-H), 7.54 (s, 1H, 6-H), 7.31 (s, 1H, 3-H), 3.93 (s, 3H, 4-OCH_3 or 5-OCH_3), 3.87 (s, 3H, 4-OCH_3 or 5-OCH_3), 1.27 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.1 (C-1'), 153.1 (C-4), 149.7 (C-5), 128.4 (C-1), 121.9 (C-3), 111.2 (C-6), 92.5 (C-2), 58.0 (C-$(CH_3)_3$), 56.5 (4-OCH_3 or 5-OCH_3), 56.1 (4-OCH_3 or 5-OCH_3), 22.8 (3 CH_3) ppm

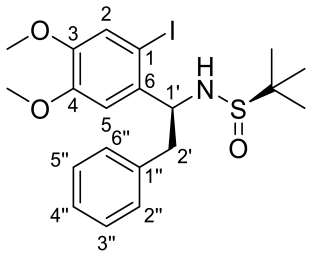
IR (ATR): $\tilde{\nu}$ = 2959, 1716, 1578, 1500, 1436, 1384, 1261, 1211, 1162, 1079, 1020, 866, 810, 759, 724 cm^{-1}

HRMS (ESI): *m/z* = 396.0125 $[M+H]^+$ (calculated for $C_{13}H_{29}NO_3S^+$ $[M+H]^+$ 396.0125)

(*S*)-*N*-1-(2-Iodo-4,5-dimethoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (87a)
and
(*R*)-*N*-1-(2-Iodo-4,5-dimethoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (87b)

Synthesized according to **GP B**, using (*R*,*E*)-*N*-(2-iodo-4,5-dimethoxybenzylidene)-*tert*-butylsulfinamide (**85**, 2.09 g, 5.29 mmol, 1.00 eq.) and benzylmagnesium chloride solution (1.40 M in THF, 11.4 mL, 15.9 mmol, 3.00 eq.). The reaction was carried out at -21 °C.
Eluent for flash column chromatography: hexanes/EtOAc 30:70 to 20:80, order of elution:

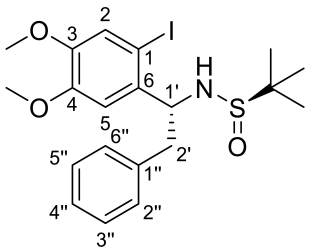
1. 87a
2. 87b



87a

$C_{20}H_{26}INO_3S$
M = 487.40 g/mol

Yield: 741 mg (1.52 mmol, 29%)
Appearance: colourless powder
Melting point: 148 - 150 °C
R_f: 0.30 (hexanes/EtOAc 30:70)
α_{598}^{20}: -94 (β = 3.5 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.34 – 7.21 (m, 6H, 2-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.89 (s, 1H, 5-H), 4.84 (ddd, *J* = 8.9, 5.0, 1.9 Hz, 1H, 1'-H), 3.81 (s, 3H, 4-OCH_3), 3.76 (s, 3H, 3-OCH_3), 3.50 (s, 1H, NH), 3.15 (dd, *J* = 13.7, 5.1 Hz, 1H, 2'-H), 2.81 (dd, *J* = 13.7, 8.9 Hz, 1H, 2'-H), 1.11 (s, 9H, *tert*-butyl) ppm
^{13}C NMR (101 MHz, CD_2Cl_2): δ = 150.1 (C-3), 149.6 (C-4), 137.2 (C-1''), 135.8 (C-6), 129.9 (C-2'', C-6''), 129.1 (C-3'', C-5''), 127.5 (C-4''), 121.9 (C-2), 111.9 (C-5), 87.8 (C-1), 62.7 (C-1'), 56.4 (3-OCH_3 or 4-OCH_3), 56.1 (3-OCH_3 or 4-OCH_3), 55.8 (C-$(CH_3)_3$), 44.2 (C-2'), 22.7 (3 CH_3) ppm
IR (ATR): $\tilde{\nu}$ = 3308, 2956, 1593, 1494, 1250, 1152, 1060, 1025, 897, 791, 758, 703 cm^{-1}
HRMS (ESI): *m/z* = 488.0751 $[M+H]^+$ (calculated for $C_{20}H_{27}NO_3S^+$ $[M+H]^+$ 488.0751)



87b

Yield: 770 mg (1.58 mmol, 30%)

Appearance: colourless foam

Melting point: 137 - 138 °C

R_f: 0.20 (hexanes/EtOAc 30:70)

α_{598}^{20}: +27 (β = 5.6 · 10^{-3} g/mL, $CHCl_3$)

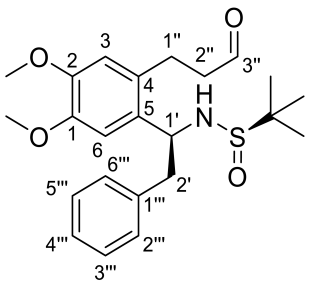
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.29 – 7.17 (m, 6H, 2-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.88 (s, 1H, 5-H), 4.74 (dt, *J* = 8.2, 5.5 Hz, 1H, 1'-H), 3.81 (s, 3H, 4-OCH_3), 3.79 (s, 3H, 3--OCH_3), 3.67 (d, , *J* = 5.5 Hz, 1H, NH), 3.13 (dd, *J* = 13.7, 5.6 Hz, 1H, 2'-H), 2.94 (dd, *J* = 13.7, 8.2 Hz, 1H, 2'-H), 1.03 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 150.1 (C-3), 149.6 (C-4), 137.7 (C-1''), 136.4 (C-6), 130.1 (C-2'', C-6''), 128.8 (C-3'', C-5''), 127.1 (C-4'), 122.2 (C-2), 112.0 (C-5), 87.4 (C-1), 64.7 (C-1'), 56.5 (3-OCH_3 or 4-OCH_3 or C-$(CH_3)_3$), 56.5 (3-OCH_3 or 4-OCH_3 or C-$(CH_3)_3$), 56.3 (3-OCH_3 or 4-OCH_3 or C-$(CH_3)_3$), 43.3 (C-2'), 22.5 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2950, 1596, 1496, 1249, 1209, 1154, 1045, 1028, 792, 698 cm^{-1}

HRMS (ESI): *m/z* = 510.0573 $[M+Na]^+$ (calculated for $C_{20}H_{26}NO_3SNa^+$ $[M+Na]^+$ 510.0570)

(*R*)-*N*-((*S*)-1-(4,5-Dimethoxy-2-(3-oxopropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (89)



$C_{23}H_{31}NO_4S$

M = 417.56 g/mol

Synthesized according to **GP H**, using (*R*)-*N*-(*S*)-1-(2-iodo-4,5-dimethoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**87a**, 615 mg, 1.26 mmol, 1.00 eq.), benzyltriethylammonium chloride (287 mg, 1.26 mmol, 1.00 eq.), $NaHCO_3$ (212 mg, 2.52 mmol, 2.00 eq.), $Pd(OAc)_2$ (56.7 mg, 0.252 mmol, 0.200 eq.), anhydr. DMF (11.5 mL) and

allyl alcohol (148 mg, 173 µL, 2.52 mmol, 2.00 eq.). The reaction mixture was stirred for 3 h at 60 °C.

Eluent for flash column chromatography: hexanes/EtOAc 20:80 to EtOAc.

Yield: 478 mg (1.14 mmol, 91%)

Appearance: brownish oil

R_f: 0.20 (hexanes/EtOAc 30:70)

α_{598}^{20}: -64 (β = 1.5 · 10^{-3} g/mL, $CHCl_3$)

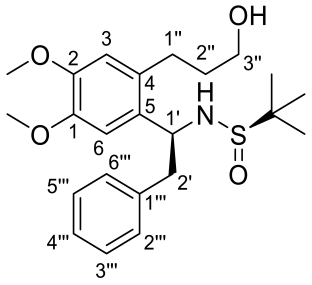
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.69 (t, *J* = 1.2 Hz, 1H, CHO), 7.29 – 7.12 (m, 3H, 3'''-H, 4'''-H, 5'''-H), 7.11 – 7.10 (m, 2H, 2'''-H, 6'''-H), 6.94 (s, 1H, 6-H), 6.59 (s, 1H, 3-H), 4.71 (ddd, *J* = 8.3, 6.8, 1.8 Hz, 1H, 1'-H), 3.81 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.79 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.54 (s, 1H, NH), 3.07 (dd, *J* = 13.3, 6.6 Hz, 1H, 2'-H), 2.98 (dd, *J* = 13.2, 7.5 Hz, 1H, 2'-H), 2.80 – 2.64 (m, 3H, 1''-H, 2''-H), 2.47 – 2.40 (m, 1H, 2''-H), 1.13 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 201.8 (CHO), 148.9 (C-2), 148.4 (C-1), 137.6 (C-5), 132.3 (C-4), 130.5 (C-1'''), 129.9 (C-2''', C-6'''), 129.0 (C-3''', C-5'''), 127.4 (C-4'''), 112.8 (C-3), 111.3 (C-6), 56.1 (1-OCH_3 or 2-OCH_3), 56.0 (1-OCH_3 or 2-OCH_3), 55.5 (C-$(CH_3)_3$), 54.5 (C-1'), 45.7 (C-2''), 45.5 (C-2'), 24.7 (C-1''), 22.7 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2955, 1720, 1670, 1514, 1454, 1254, 1215, 1101, 1053, 869, 726, 700 cm^{-1}

HRMS (ESI): *m/z* = 418.2047 $[M+H]^+$ (calculated for $C_{23}H_{31}NO_4S^+$ $[M+H]^+$ 418.2047)

(*R*)-*N*-((*S*)-1-(2-(3-Hydroxypropyl)-4,5-dimethoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (91)



$C_{23}H_{33}NO_4S$

M = 419.58 g/mol

Synthesized according to **GP I**, using (*R*)-*N*-((*S*)-1-(4,5-dimethoxy-2-(3-oxopropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**89**, 446 mg, 1.07 mmol, 1.00 eq.) and $NaBH_4$ (60.6 mg, 1.60mmol, 1.50 eq.). The product was used for the next step without further purification.

Yield: 445 mg (1.06 mmol, 99%)

Appearance: colourless oil

R_f: 0.20 (hexanes/EtOAc 5:95)

α_{598}^{20}: -67 (β = 4.6 · 10^{-3} g/mL, $CHCl_3$)

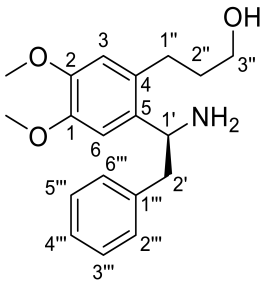
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.32 – 7.24 (m, 3H, 3’’’-H, 5’’’-H), 7.16 – 7.15 (m, 2H, 2’’’-H, 6’’’-H), 6.93 (s, 1H, 6-H), 6.63 (s, 1H, 3-H), 5.02 – 4.98 (m, 1H, 1’-H), 3.81 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.78 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.57 (s, 1H, NH), 3.51 – 3.45 (m, 2H, 3’’-H), 3.23 (t, *J* = 4.8 Hz, 1H, OH), 3.05 (dd, *J* = 13.5, 5.7 Hz, 1H, 2’-H), 2.91 – 2.79 (m, 2H, 2’-H, 1’’-H), 2.40 – 2.33 (m, 1H, 1’’-H), 1.88 – 1.80 (m, 1H, 2’’-H), 1.72 – 1.66 (m, 1H, 2’’-H), 1.14 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 148.9 (C-2), 148.0 (C-1), 137.7 (C-5), 133.5 (C-4), 130.9 (C-1’’’), 129.8 (C-2’’’, C-6’’’), 129.1 (C-3’’’, C-5’’’), 127.3 (C-4’’’), 112.7 (C-3), 110.7 (C-6), 60.2 (C-3’’), 56.0 (1-OCH_3 or 2-OCH_3), 56.0 (1-OCH_3 or 2-OCH_3), 55.7 (C-$(CH_3)_3$), 53.9 (C-1’), 45.7 (C-2’), 34.5 (C-3’’), 27.1 (C-2’’), 22.7 (C-1’’) ppm

IR (ATR): $\tilde{\nu}$ = 2934, 1608, 1513, 1454, 1253, 1215, 1102, 1031, 911, 869, 726 cm^{-1}

HRMS (ESI): *m/z* = 442.2023 $[M+Na]^+$ (calculated for $C_{23}H_{33}NO_4SNa^+$ $[M+Na]^+$ 442.2023)

(*S*)-3-(2-(1-Amino-2-phenylethyl)-4,5-dimethoxyphenyl)propan-1-ol – (93)



$C_{19}H_{25}NO_3$

M = 315.41 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(2-(3-hydroxypropyl)-4,5-dimethoxyphenyl)-2-phenylethyl)-*tert*-butyl-2-sulfinamide (**91**, 271 mg, 646 µmol, 1.00 eq.) and 4 M HCl in dioxane (0.96 mL, 19.4 mmol, 30.0 eq.).

Eluent for flash column chromatography: DCM/MeOH 95:05.

Yield: 130 mg (412 µmol, 64%)

Appearance: colourless oil

R_f: 0.10 (DCM/MeOH 95:5)

α_{598}^{20}: +36 (β = 4.6 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.31 – 7.27 (m, 2H, 3’’’-H, 5’’’-H), 7.23 – 7.19 (m, 3H, 2’’’-H, 4’’’-H, 5’’’-H), 7.01 (s, 1H, 6-H), 6.67 (s, 1H, 3-H), 4.38 (dd, *J* = 9.0, 5.0 Hz, 1H, 1’-H), 3.84 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.80 (s, 3H, 1-OCH_3 or 2-OCH_3), 3.51 – 3.37 (m, 2H, 3’’-H), 3.04 (dd, *J* = 13.3, 4.9 Hz, 1H, 2’-H), 2.90 – 2.77 (m, 2H, 2’-H, 1’’-H), 2.64 - 2.58 (m, 1H,1’’-H), 2.03 (s, 3H, NH_2, OH), 1.83 – 1.71 (m, 2H, 2’’-H) ppm

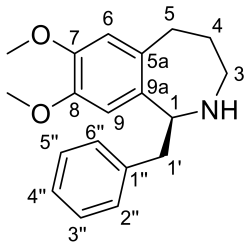
^{13}C NMR (101 MHz, CD_2Cl_2): δ = 148.4 (C-2), 147.8 (C-1), 139.9 (C-5), 135.0 (C-4), 132.3 (C-1’’’), 129.7 (C-2’’’, C-6’’’), 128.8 (C-3’’’, C-5’’’), 126.7 (C-4’’’), 113.1 (C-6), 110.0 (C-3), 60.6 (C-

3''), 56.3 (1-OCH_3 or 2-OCH_3), 56.1 (1-OCH_3 or 2-OCH_3), 53.1 (C-1'), 45.9 (C-2'), 27.4 (C-1''), 22.0 (C-2'') ppm

IR (ATR): $\tilde{\nu}$ = 3290, 2934, 2851, 1607, 1512, 1453, 1261, 1211, 1099, 910, 722, 700 cm^{-1}

HRMS (ESI): *m/z* = 299.1643 $[M\text{-}NH_2]^+$ (calculated for $C_{19}H_{23}O_3^+$ $[M\text{-}NH_2]^+$ 299.1647)

(*S*)-1-Benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine – (95)



$C_{19}H_{23}NO_2$

M = 297.40 g/mol

Synthesized according to **GP F**, using (*S*)-3-(2-(1-amino-2-phenylethyl)-4,5-dimethoxyphenyl)propan-1-ol (**93**, 46.0 mg, 146 µmol, 1.00 eq.), CMBP (53.9 mg, 58.5 µL, 219 µmol, 1.50 eq.) and anhydr. toluene (4.0 mL).

Eluent for flash column chromatography: hexanes/EtOAc = 20:80 with 1.5% Et_3N.

Yield: 32.0 mg (108 µmol, 74%)

Appearance: brownish oil

R_f: 0.20 (hexanes/EtOAc 30:70 with 1.5% Et_3N)

α_{598}^{20}: -3.0 (β = 2.3 · 10^{-3} g/mL, $CHCl_3$)

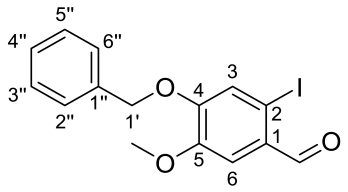
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.31 – 7.19 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 6.68 – 6.66 (m, 2H, 6-H, 9-H), 4.14 (dd, *J* = 9.4, 5.6 Hz, 1H, 1-H), 3.80 (s, 3H, 7-OCH_3 or 8-OCH_3), 3.73 (s, 3H, 7-OCH_3 or 8-OCH_3), 3.22 – 3.17 (m, 2H, 1'-H, 3-H), 3.08 (dd, *J* = 13.6, 9.4 Hz, 1H, 1'-H), 2.93 – 2.90 (m, 2H, 5-H), 2.88 – 2.83 (m, 1H, 3-H), 1.74 – 1.57 (m, 3H, NH, 4-H) ppm

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 147.5 (C-7), 147.0 (C-8), 140.3 (C-9a), 136.8 (C-5a), 134.9 (C-1''), 129.6 (C-2'', C-6''), 128.7 (C-3'', C-5''), 126.5 (C-4''), 114.3 (C-6), 111.5 (C-9), 62.8 (C-1), 56.4 (7-OCH_3 or 8-OCH_3), 56.2 (7-OCH_3 or 8-OCH_3), 50.1 (C-3), 40.6 (C-1'), 35.0 (C-5), 30.5 (C-4) ppm

IR (ATR): $\tilde{\nu}$ = 3262, 2930, 2846, 1736, 1604, 1514, 1456, 1332, 1256, 1227, 1108, 1085, 1011, 860, 783, 692 cm^{-1}

HRMS (ESI): *m/z* = 298.1802 $[M+H]^+$ (calculated for $C_{19}H_{24}NO_2^+$ $[M+H]^+$ 298.1802)

4-(Benzyloxy)-2-iodo-5-methoxybenzaldehyde – (84)



$C_{15}H_{13}IO_3$

M = 368.17 g/mol

4-Benzyloxy-3-methoxybenzaldehyde (1.50 g, 6.19 mmol, 1.00 eq.) and *N*-iodosuccinimide (1.72 g, 7.43 mmol, 1.20 eq.) were divided between three 30 mL microwave vessels and then dissolved in anhydr. acetonitrile (each 8.0 mL). To each vessel, trifluoroacetic acid (2.00 mL, 26.8 mmol, 13.0 eq.) was added and the reaction mixture stirred under microwave irradiation (65 °C, 200 W) for 75 min. The batches were combined for work-up. The reaction solution was neutralized using sat. aq. $NaHCO_3$ and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with sat. aq. NaS_2O_3. The combined organic phases were dried over anhydr. Na_2SO_4, the solvent removed under reduced pressure. The crude product was purified *via* flash column chromatography on silica with an eluent: hexanes/EtOAc 90:10. The product was dried *in vacuo*.

Yield: 1.13 g (3.07 mmol, 50%)

Appearance: orange solid

Melting point: 107 - 108 °C

R_f: 0.60 (hexanes/EtOAc 80:20)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.78 (s, 1H, CHO), 7.63 (s, 1H, 3-H), 7.47 – 7.36 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.34 (s, 1H, 6-H), 5.24 (s, 2H, 1'-H), 3.82 (s, 3H, 5-OCH_3) ppm

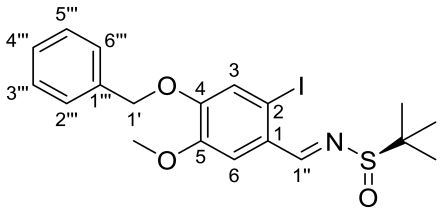
^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.2 (CHO), 153.4 (C-5), 149.5 (C-1), 136.0 (C-4), 128.5 (C-2'', C-6''), 128.2 (C-4''), 128.1 (C-3'', C-5''), 127.9 (C-1''), 123.3 (C-3), 111.3 (C-6), 93.2 (C-2), 70.4 (C-1'), 55.6 (5-OCH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2841, 1678, 1580, 1495, 1379, 1263, 1206, 1100, 987, 863, 745, 696 cm^{-1}

HRMS (EI): *m/z* = 367.9903 $[M]^{+\cdot}$ (calculated for $C_{15}H_{13}IO_3^{+\cdot}$ $[M]^{+\cdot}$ 367.9904)

The compound was previously described in the literature.[203]

(*R*)-*N*-(4-(Benzyloxy)-2-iodo-5-methoxybenzylidene)-*tert*-butylsulfinamide – (86)



$C_{19}H_{22}INO_3S$

M = 471.35 g/mol

Synthesized according to **GP A**, using 4-(benzyloxy)-2-iodo-5-methoxybenzaldehyde (**84**, 1.45 g, 3.94 mmol, 1.00 eq.), (*R*)-*N*-*tert*-butylsulfinamide (560 mg, 4.53 mmol, 1.15 eq.) and tetraethyl orthotitanate (8.99 g, 8.32 mL, 39.4 mmol, 10.0 eq.). The total batch was divided into two 30 mL microwave vessels for the microwave reaction and the procedure carried out twice. Both batches were combined for work-up.

Yield: 1.85 g (3.92 mmol, 100%)

Appearance: yellowish oil

R_f: 0.20 (hexanes/EtOAc 90:10)

α_{598}^{20}: -119 (β = 1.5 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (s, 1H, 1''-H), 7.61 (s, 1H, 3-H), 7.50 (s, 1H, 6-H), 7.47 – 7.36 (m, 5H, 2'''-H, 3'''-H, 4'''-H, 5'''-H, 6'''-H), 5.21 (s, 2H, 1'-H), 3.81 (s, 3H, 5-OCH_3), 1.19 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.1 (C-1''), 152.1 (C-5), 149.5 (C-1), 136.1 (C-4), 128.5 (C-2''', C-6'''), 128.2 (C-4'''), 128.0 (C-3''', C-5'''), 127.2 (C-1'''), 123.1 (C-3), 111.0 (C-6), 93.3 (C-2), 70.3 (C-1'), 57.4 (C-(CH_3)$_3$), 55.6 (5-OCH_3), 22.1 (3 CH_3) ppm

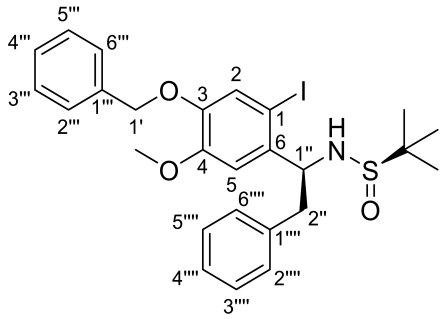
IR (ATR): $\tilde{\nu}$ = 2959, 1735, 1576, 1498, 1454, 1260, 1205, 1166, 1079, 980, 865, 732, 696 cm^{-1}

HRMS (ESI): *m/z* = 472.0444 $[M+H]^+$ (calculated for $C_{19}H_{23}INO_3S^+$ $[M+H]^+$ 472.0438)

(*R*)-*N*-((*S*)1-(4-(Benzyloxy)-2-iodo-5-methoxyphenyl)-2-phenylethyl)-*tert*-butyl-sulfinamide – (88a)
and
(*R*)-*N*-((*R*)1-(4-(Benzyloxy)-2-iodo-5-methoxyphenyl)-2-phenylethyl)-*tert*-butyl-sulfinamide – (88b)

Synthesized according to **GP B**, using (*R*)-*N*-(4-(Benzyloxy)-2-iodo-5-methoxybenzylidene)-*tert*-butylsulfinamide (**86**, 1.75 g, 3.71 mmol, 1.00 eq.) and benzylmagnesium chloride solution (2.00 M in THF, 5.55 mL, 11.1 mmol, 2.99 eq.). The reaction was carried out at -78 °C.
Eluent for flash column chromatography: hexanes/EtOAc 50:50 to 30:70, order of elution:

1. 88a
2. 88b



88a

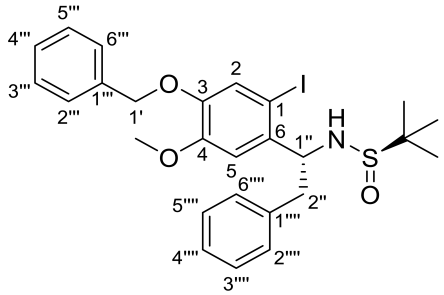
$C_{26}H_{30}INO_3$
M = 563.50 g/mol

Yield: 450 mg (799 µmol, 22%)
Appearance: colourless solid
Melting point: 171 – 173 °C
R_f: 0.50 (hexanes/EtOAc 30:70)
$\boldsymbol{\alpha_{598}^{20}}$**:** -76 (β = 5.2 · 10^{-3} g/mL, $CHCl_3$)
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.45 – 7.22 (m, 11H, 2-H, 2'''-H, 3'''-H, 4'''-H, 5'''H, 6'''-H, 2''''-H, 3''''-H, 4''''-H, 5''''-H, 6''''-H), 6.93 (s, 1H, 5-H), 5.03 (s, 2H, 1'-H), 4.84 (ddd, *J* = 8.9, 5.0, 1.9 Hz, 1H, 1''-H), 3.78 (s, 3H, 4-OCH_3), 3.51 (s, 1H, NH), 3.16 (dd, *J* = 13.6, 5.1 Hz, 1H, 2''-H), 2.82 (dd, *J* = 13.7, 8.9 Hz, 1H, 2''-H), 1.12 (s, 9H, *tert*-butyl) ppm
^{13}C NMR (101 MHz, CD_2Cl_2): δ = 150.6 (C-4), 148.8 (C-3), 137.1 (C-1''' or C-1''''), 136.9 (C-1''' or C-1''''), 136.4 (C-6), 129.9 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 129.1 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 129.0 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 128.6 (C-4''' or C-4''''), 128.3 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 127.5 (C-4''' or C-4''''),

123.8 (C-2), 112.2 (C-5), 87.6 (C-1), 71.6 (C-1'), 62.7 (C-1''), 56.2 (4-OCH_3), 55.8 (C-$(CH_3)_3$), 44.2 (C-2''), 22.7 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3307, 2929, 1506, 1253, 1164, 1043, 730, 694 cm^{-1}

HRMS (ESI): *m/z* = 564.1079 $[M+H]^+$ (calculated for $C_{26}H_{31}INO_3S^+$ $[M+H]^+$ 564.1064)



88b

Yield: 1.00 g (1.78 mmol, 48%)

Appearance: colourless foam

Melting point: 61 °C

R_f: 0.40 (hexanes/EtOAc 30:70)

α_{598}^{20}: +36 (β = 5.2 · 10^{-3} g/mL, $CHCl_3$)

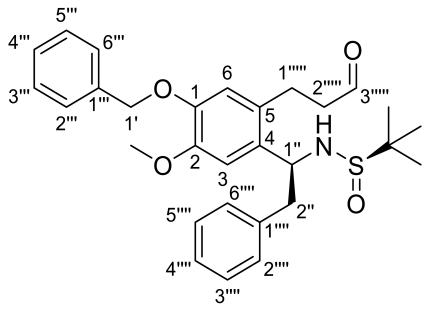
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.45 – 7.18 (s, 11H, 2-H, 2'''-H, 3'''-H, 4'''-H, 5'''H, 6'''-H, 2''''-H, 3''''-H, 4''''-H, 5''''-H, 6''''-H), 6.92 (s, 1H, 5-H), 5.03 (s, 2H, 1'-H), 4.74 (dt, *J* = 8.2, 5.4 Hz, 1H, 1''-H), 3.81 (s, 3H, 4-OCH_3), 3.69 (d, *J* = 5.5 Hz, 1H, NH), 3.14 (dd, *J* = 13.7, 5.5 Hz, 1H, 2''-H), 2.94 (dd, *J* = 13.7, 8.2 Hz, 1H, 2''-H), 1.03 (s, 9H, *tert*-butyl) ppm.

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 150.6 (3-OCH_3), 148.8 (4-OCH_3), 137.7 (C-6 or C-1''' or C-1''''), 137.0 (C-6 or C-1''' or C-1''''), 136.9 (C-6 or C-1''' or C-1''''), 130.1 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 129.0 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 128.8 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 128.6 (C-4''' or C-4''''), 128.3 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 127.1 (C-4''' or C-4''''), 124.2 (C-2), 112.4 (C-5), 87.2 (C-1), 71.6 (C-1'), 64.7 (C-1''), 56.5 (4-OCH_3), 56.4 (C-$(CH_3)_3$), 43.3 (C-2''), 22.5 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2950, 1594, 1494, 1249, 1159, 1047, 731, 693 cm^{-1}

HRMS (ESI): *m/z* = 564.1079 $[M+H]^+$ (calculated for $C_{26}H_{31}INO_3S^+$ $[M+H]^+$ 564.1064)

(*R*)-N-((*S*)-1-(4-(Benzyloxy)-5-methoxy-2-(3-oxopropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (90)



$C_{29}H_{35}NO_4S$

M = 493.66 g/mol

Synthesized according to **GP H**, using (*R*)-*N*-(*S*)-1-(4-(benzyloxy)-2-iodo-5-methoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**88a**, 400 mg, 0.71 mmol, 1.00 eq.), benzyltriethylammonium chloride (162 mg, 0.71 mmol, 1.00 eq.), $NaHCO_3$ (119 mg, 1.42 mmol, 2.00 eq.), $Pd(OAc)_2$ (31.9 mg, 0.142 mmol, 0.200 eq.), anhyr. DMF (10.0 mL) and allyl alcohol (85.4 mg, 100 µL, 1.46 mmol, 2.05 eq.). The reaction mixture was stirred for 3 h at 60 °C

Eluent for flash column chromatography: hexanes/EtOAc 30/70 to 20/80.

Yield: 250 mg (506 µmol, 71%)

Appearance: brownish oil

R_f: 0.30 (hexanes/ EtOAc 30:70)

α_{598}^{20}: -43 (β = 1.2 · 10^{-3} g/mL, $CHCl_3$)

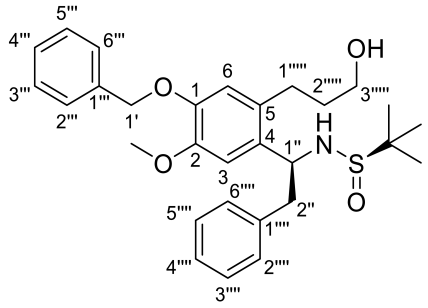
^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.69 (t, *J* = 1.0 Hz, 1H, CHO), 7.46 – 7.35 (m, 5H, 2’’’-H or 3’’’-H or 4’’’-H or 5’’’-H or 6’’’-H or 2’’’’-H or 3’’’’-H or 4’’’’-H or 5’’’’-H or 6’’’’-H), 7.29 – 7.24 (m, 3H, 2’’’-H or 3’’’-H or 4’’’-H or 5’’’-H or 6’’’-H or 2’’’’-H or 3’’’’-H or 4’’’’-H or 5’’’’-H or 6’’’’-H), 6.98 (s, 1H, 3-H), 6.68 (s, 1H, 6-H), 5.04 (s, 2H, 1’-H), 4.71 (ddd, *J* = 8.3, 6.8, 1.8 Hz, 1H, 1’’-H), 3.81 (s, 3H, 2-OCH_3), 3.55 (s, 1H, NH), 3.07 (dd, *J* = 13.3, 6.6 Hz, 1H, 2’’-H), 2.98 (dd, *J* = 13.2, 7.5 Hz, 1H, 2’’-H), 2.78 – 2.61 (m, 3H, 1’’’’-H, 2’’’’-H), 2.45 – 2.38 (m, 1H, 2’’’’-H), 1.13 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 201.8 (CHO), 148.9 (C-1 or C-2), 148.0 (C-1 or C-2), 137.6 (C-1’’’ or C-1’’’’), 137.5 (C-1’’’ or C-1’’’’), 132.2 (C-4 or C-5), 131.2 (C-4 or C-5), 129.9 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 129.0 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 128.9 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 128.5 (C-4’’’ or C-4’’’’), 128.3 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 127.4 (C-4’’’ or C-4’’’’), 114.9 (C-6), 111.7 (C-3), 71.3 (C-1’), 56.2 (2-OCH_3), 55.5 (C-$(CH_3)_3$), 54.5 (C-1’), 45.6 (C-2’’ or C-2’’’’), 45.5 (C-2’’ or C-2’’’’), 24.6 (C-1’’’’), 22.7 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 2953, 1720, 1670, 1511, 1454, 1255, 1101, 1055, 1027, 910, 867, 729, 692 cm^{-1}

HRMS (ESI): *m/z* = 516.2192 $[M+Na]^+$ (calculated for $C_{29}H_{35}INO_4SNa^+$ $[M+Na]^+$ 516.2179)

(*R*)-*N*-((*S*)-1-(4-(Benzyloxy)-2-(3-hydroxypropyl)-5-methoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide – (92)



$C_{29}H_{37}NO_4S$

M = 495.68 g/mol

Synthesized according to **GP I**, using (*R*)-N-((*S*)-1-(4-(benzyloxy)-5-methoxy-2-(3-oxopropyl)phenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**90**, 245 mg, 496 µmol, 1.00 eq.) and $NaBH_4$ (27.0 mg, 1.44 mmol, 1.44 eq.).

Eluent for flash column chromatography: hexanes/EtOAc 5:95 to EtOAc.

Yield: 180 mg (363 µmol, 73%)

Appearance: colourless oil

R_f: 0.10 (hexanes/ EtOAc 05:95)

α_{598}^{20}: -63 (β = 0.8 · 10^{-3} g/mL, $CHCl_3$)

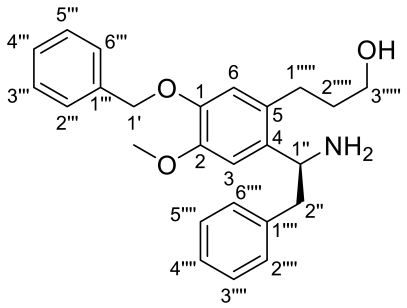
^{1}H NMR (400 MHz, CD_2Cl_2): δ = 7.46 – 7.14 (m, 10H, 2'''-H, 3'''-H, 4'''-H, 5'''H, 6'''-H, 2''''-H, 3''''-H, 4''''-H, 5''''-H, 6''''-H), 6.97 (s, 1H, 3-H), 6.71 (s, 1H, 6-H), 5.05 (s, 2H, 1'-H), 5.02 – 4.98 (m, 1H, 1''-H), 3.80 (s, 3H, 2-OCH_3), 3.57 (s, 1H, NH), 3.48 - 3.42 (m, 2H, 3'''''-H), 3.05 (dd, *J* = 7.7, 5.8 Hz, 1H, 2''-H), 2.91 – 2.72 (m, 2H, 2''-H, 1''''-H), 2.34 (dt, *J* = 13.4, 6.1 Hz, 1H, 1''''-H), 1.84 – 1.79 (m, 1H, 2''''-H), 1.67 – 1.55 (m, 2H, 2''''-H, OH), 1.15 (s, 9H, *tert*-butyl) ppm

^{13}C NMR (101 MHz, CD_2Cl_2): δ = 148.5 (C-1 or C-2), 148.0 (C-1 or C-2), 137.7 (C-1''' or C-1''''), 137.6 (C-1''' or C-1''''), 133.4 (C-4 or C-5), 131.6 (C-4 or C-5), 129.8 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 129.1 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 128.9 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 128.4 (C-4''' or C-4''''), 128.3 (C-2''' or C-3''' or C-5''' or C-6''' or C-2'''' or C-3'''' or C-5'''' or C-6''''), 127.3 (C-4''' or C-4''''), 114.9 (C-6), 111.1 (C-3), 71.2 (C-1'), 60.0 (C-3'''''), 56.2 (2-OCH_3), 55.7 (C-$(CH_3)_3$), 53.9 (C-1''), 45.7 (C-2''), 34.4 (C-2'''''), 26.9 (C-1'''''), 22.7 (3 CH_3) ppm

IR (ATR): $\tilde{\nu}$ = 3381, 2932, 1606, 1511, 1454, 1254, 1210, 1101, 1027, 867, 738, 695 cm^{-1}

HRMS (ESI): *m/z* = 518.2351 $[M+Na]^+$ (calculated for $C_{29}H_{37}INO_4SNa^+$ $[M+Na]^+$ 518.2336)

(*S*)-3-(2-(1-Amino-2-phenylethyl)-5-(benzyloxy)-4-methoxyphenyl)propan-1-ol – (94)



$C_{25}H_{29}NO_3$

M = 391.51 g/mol

Synthesized according to **GP E**, using (*R*)-*N*-((*S*)-1-(4-(benzyloxy)-2-(3-hydroxypropyl)-5-methoxyphenyl)-2-phenylethyl)-*tert*-butylsulfinamide (**92**, 271 mg, 646 µmol, 1.00 eq.) and 4 M HCl in dioxane (531 µL, 10.8 mmol, 30.0 eq.).

Eluent for flash column chromatography: DCM/MeOH 90:10.

Yield: 96.0 mg (245 µmol, 68%)

Appearance: colourless oil

R_f: 0.05 (EtOAc)

α_{598}^{20}: +45 (β = 1.0 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.43 – 7.17 (m, 10H, , 2’’’-H, 3’’’-H, 4’’’-H, 5’’’H, 6’’’-H, 2’’’’-H, 3’’’’-H, 4’’’’-H, 5’’’’-H, 6’’’’-H), 7.09 (s, 1H, 3-H), 6.71 (s, 1H, 6-H), 5.04 (s, 2H, 1’-H), 4.44 (dd, *J* = 8.4, 5.8 Hz, 1H, 1’’-H), 3.87 (s, 3H, 2-OCH_3), 3.44 – 3.40 (m, 1H, 3’’’’-H), 3.34 – 3.29 (m, 1H, 3’’’’-H), 2.82 – 2.71 (m, 3H, NH_2, 1’’’’-H), 2.55 – 2.49 (m, 1H, 1’’’’-H), 1.76 – 1.62 (m, 2H, 2’’’’-H) ppm

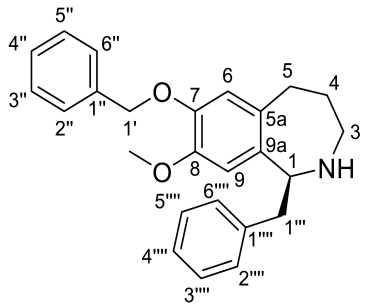
The lower ppm area shows some unknown impurities. One of the unidentified signals could be the OH proton, however, no assignment was possible.

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 148.5 (C-1 or C-2), 147.6 (C-1 or C-2), 139.3 (C-1’’’ or C-1’’’’), 137.7 (C-1’’’ or C-1’’’’), 134.2 (C-4 or C-5), 132.4 (C-4 or C-5), 129.8 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 128.9 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 128.8 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 128.3 (C-4’’’ or C-4’’’’), 128.2 (C-2’’’ or C-3’’’ or C-5’’’ or C-6’’’ or C-2’’’’ or C-3’’’’ or C-5’’’’ or C-6’’’’), 126.8 (C-4’’’ or C-4’’’’), 115.5 (C-6), 110.5 (C-3), 71.3 (C-1’), 60.4 (C-3’’’’), 56.5 (2-OCH_3), 53.1 (C-1’’), 45.0 (C-2’’), 34.5 (C-2’’’’), 27.2 (C-1’’’’) ppm

IR (ATR): $\tilde{\nu}$ = 3290, 2927, 1605, 1511, 1455, 1261, 1209, 1097, 1026, 734, 695 cm^{-1}

HRMS (ESI): *m/z* = 375.1961 $[M\text{-}NH_2]^+$ (calculated for $C_{25}H_{27}O_3^+$ $[M\text{-}NH_2]^+$ 375.1955)

(*S*)-1-Benzyl-7-(benzyloxy)-8-methoxy-2,3,4,5-tetrahydro-1*H*-benzo[c]azepine – (96)



$C_{25}H_{27}NO_2$

M = 373.50 g/mol

Synthesized according to **GP F**, using (*S*)-3-(2-(1-amino-2-phenylethyl)-5-(benzyloxy)-4-methoxyphenyl)propan-1-ol (**94**, 66.6 mg, 170 µmol, 1.00 eq.), CMBP (62.8 mg, 68.2 µL, 255 µmol, 1.50 eq.) and anhydr. toluene (2.0 mL).

Eluent for flash column chromatography: hexanes/EtOAc = 20:80 with 1.5% Et_3N.

Yield: 47.1 mg (126 µmol, 74%)

Appearance: brownish oil

R_f: 0.30 (hexanes/EtOAc = 20:80 with 1.5% Et_3N)

α_{598}^{20}: -12 (β = 0.5 · 10^{-3} g/mL, $CHCl_3$)

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.45 – 7.20 (m, 10H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H, 2''''-H, 3''''-H, 4''''-H, 5''''-H, 6''''-H), 6.75 (s, 1H, 6-H), 6.69 (s, 1H, 9-H), 5.05 (d, *J* = 2.0 Hz, 2H, 1'-H), 4.15 (dd, *J* = 9.3, 5.7 Hz, 1H, 1-H), 3.75 (s, 3H, 8-OCH_3), 3.23 – 3.17 (m, 2H, 3-H, 1'''-H), 3.09 (dd, *J* = 13.6, 9.3 Hz, 1H, 1'''-H), 2.94 – 2.84 (m, 3H, 3-H, 5-H), 2.10 (s, 1H, NH), 1.73 – 1.67 (m, 1H, 4-H), 164 – 1.57 (m, 1H, 4-H) ppm

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 147.6 (C-8), 146.7 (C-7), 140.2 (C-5a or C-9a or C-1'' or C-1''''), 137.9 (C-5a or C-9a or C-1'' or C-1''''), 137.3 (C-5a or C-9a or C-1'' or C-1''''), 134.9 (C-5a or C-9a or C-1'' or C-1''''), 129.6 (C-2'' or C-3'' or C-5'' or C-6'' or C-2'''', C-3'''', C-5'''', C-6''''), 128.6 (C-2'' or C-3'' or C-5'' or C-6'' or C-2'''', C-3'''', C-5'''', C-6''''), 128.7 (C-2'' or C-3'' or C-5'' or C-6'' or C-2'''', C-3'''', C-5'''', C-6''''), 128.3 (C-4'' or C-4''''), 128.1 (C-2'' or C-3'' or C-5'' or C-6'' or C-2'''', C-3'''', C-5'''', C-6''''), 126.6 (C-4'' or C-4''''), 116.6 (C-6), 112.0 (C-9), 71.5 (C-1'), 62.8 (C-1), 56.5 (8-OCH_3), 50.0 (C-3), 40.5 (C-1'''), 35.0 (C-5), 30.4 (C-4) ppm

IR (ATR): $\tilde{\nu}$ = 2927, 1604, 1511, 1452, 1281, 1253, 1103, 1010, 735, 694 cm^{-1}

HRMS (ESI): *m/z* = 374.2125 $[M+H]^+$ (calculated for $C_{25}H_{28}NO_2^+$ $[M+H]^+$ 374.2115)

7 Apendices

7.1 Abbreviations

AcOH	acetic acid
APCI	atmospheric pressure chemical ionization
aq.	aqueous
ATR	attenuated total reflexion
APCI	atmospheric pressure chemical ionization
ASAP	atmospheric pressure solid analysis probe
BBTHIQ	*bis*benzyltetrahydroisoquinoline
BIA	benzylisoquinoline alkaloids
BINAP	([1,1′-binaphthalene]-2,2′-diyl)bis(diphenylphosphane)
Bn	benzyl
BTEAC	benzyltriethylammonium chlrodie
CAM	ceric ammonium molybdate
C-C coupling	carbon-carbon bond coupling
CD	circular dichroism
cf. lit	confere literature (compare)
CMBP	cyanomethylenetributylphosphoran
COSY	correlation spectroscopy
CYP	cytochrome P
d	doublet (NMR)
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIPAMP	(ethane-1,2-diyl)bis[(2-methoxyphenyl)(phenyl)phosphane]
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide

DNPH	1,3-dinitrophenylhydrazine
dppf	ferrocene-1,1′-diyl)bis(diphenylphosphane)
EBOV	ebola virus
e.g.	exempli gratia (for example)
EI	electron impact ionization
eq.	equivalents
ESI	electron spray ionization
et. al.	et alii (and others)
EtOAc	ethylacetate
EtOH	ethanol
FCC	flash column chromatography
FDA	Food and Drug Administration
GC	gas chromatography
GP	general procedure
h	hour
HCl	hydrochloric acid
HMBC	heteronuclear multiple-bond correlation spectroscopy
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
IR	infrared spectroscopy
J	coupling constant
LDA	lithium diisopropylamide
M	molarity
m	multiplet (NMR)
m.p.	melting point
m/z	mass-to-charge ratio
MeCN	acetonitrile
MeOH	methanol

MERS-CoV	middle east respiratory syndrome–related coronavirus
MS	mass spectrometry
M	molecular weight
MW	microwave
NEt_3	triethylamine
NIS	*N*-iososuccinimide
NMR	nuclear magnetic resonance spectroscopy
NP	natural product
OAc	acetate
OTC	over-the-counter
Ph	phenyl
pin	pinacol
PPh_3	triphenylphosphine
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
ppm	parts per million
q	quartet (NMR)
RT	room temperature
R_f	retardation factor
s	singlet (NMR)
SAR	structure-activity relationship
SARS-CoV	severe acute respiratory syndrome coronavirus
t	triplett (NMR)
TBAB	tetrabutylammonium bromide
t-BuOK	potassium *tert*-butoxide
THIQ	tetrahydroisoquinoline
temp.	temperature
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydrid
THF	tetrahydrofuran

TLC	thin layer chromatography
TLC-MS	thin layer chromatography coupled with mass spectrometry
TMAD	tetramethylazodicarboxamide
TPC	two poor channel
UV	ultraviolet
W	Watt
9-BBN	9-borabicyclo[3.3.1]nonane
λ	wavelength
ṽ	wavenumber
δ	chemical shift (commonly expressed in ppm)

7.2 References

[1] Harvey, A.L., *Drug Discov Today*, **2008**, *13(19-20)*, 894-901.
[2] Harvey, A.L., R. Edrada-Ebel, R.J. Quinn, *Nature Reviews Drug Discovery*, **2015**, *14(2)*, 111-129.
[3] Newman, D.J., G.M. Cragg, *J Nat Prod*, **2012**, *75(3)*, 311-35.
[4] Nile, S.H., G. Kai, *Indian J Microbiol*, **2021**, *61(1)*, 10-15.
[5] Kayser, O., N.J.H. Averesch, *Alkaloide*, in *Technische Biochemie: Die Biochemie und industrielle Nutzung von Naturstoffen*, O. Kayser and N.J.H. Averesch, Editors. **2024**, Springer Fachmedien Wiesbaden: Wiesbaden. p. 187-227.
[6] Jurna, I., *Der Schmerz*, **2003**, *17(4)*, 280-283.
[7] Kayser, O., *Morphin – das Geschenk Morpheus*, in *Von den Molukken zu Molekülen: Wie Naturstoffe Geschichte schreiben*, O. Kayser, Editor. **2024**, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1-39.
[8] Friedrich, C., *Friedrich Wilhelm Sertürners Arbeiten zur Entdeckung des Morphins*, in *Friedrich Wilhelm Sertürner*, C. Friedrich, Editor. **2022**, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1-42.
[9] Kayser, O., *Koffein und Viagra*, in *Von den Molukken zu Molekülen: Wie Naturstoffe Geschichte schreiben*, O. Kayser, Editor. **2024**, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 267-292.
[10] Bribi, N., *Asian J. Bot*, **2018**, *1(1)*, 1-6.
[11] Cragg, G.M., D.J. Newman, K.M. Snader, *Journal of Natural Products*, **1997**, *60(1)*, 52-60.
[12] Habermehl, G., P.E. Hammann, H.C. Krebs, W. Ternes, *Biogene Amine und Alkaloide*, in *Naturstoffchemie: Eine Einführung*, G. Habermehl, et al., Editors. **2008**, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 143-249.
[13] Muhtadi, F.J., M.M.A. Hassan, *Codeine Phosphate*, in *Analytical Profiles of Drug Substances*, K. Florey, et al., Editors. **1981**, Academic Press. p. 93-138.
[14] Eddy, N.B., *Annals of Internal Medicine*, **1969**, *71(6)*, 1209-1212.
[15] Hagel, J.M., P.J. Facchini, *Plant and Cell Physiology*, **2013**, *54(5)*, 647-672.
[16] Beaudoin, G.A.W., P.J. Facchini, *Planta*, **2014**, *240(1)*, 19-32.
[17] Singh, A., I.M. Menéndez-Perdomo, P.J. Facchini, *Phytochemistry Reviews*, **2019**, *18(6)*, 1457-1482, *doi.org/10.1007/s11101-019-09644-w, image permitted by Springer Nature and Copyright Clearance Center, License Number: 6030241236687*
[18] Guha, K.P., B. Mukherjee, R. Mukherjee, *Journal of Natural Products*, **1979**, *42(1)*, 1-84.
[19] Weber, C., T. Opatz, *Chapter One - Bisbenzylisoquinoline Alkaloids*, in *The Alkaloids: Chemistry and Biology*, H.-J. Knölker, Editor. **2019**, Academic Press. p. 1-114.
[20] Sugimoto, Y., Y. Sugimura, Y. Yamada, *FEBS Letters*, **1990**, *273(1-2)*, 82-86.
[21] Sperandio, L.P., I.V.F. Lins, A.G. Erustes, A.H.F.F. Leão, F. Antunes, I.B.M. Morais, H.F. Vieira, L.M. de Campos, C. Bincoletto, S.S. Smaili, G.J.S. Pereira, *Toxicology in Vitro*, **2023**, *90*, 105603.
[22] McConathy, J., M.J. Owens, *Primary care companion to the Journal of clinical psychiatry*, **2003**, *5(2)*, 70.
[23] Romero, A.J., C.T. Rhodes, *Journal of Pharmacy and Pharmacology*, **1993**, *45(4)*, 258-262.
[24] Lepola, U., A. Wade, H.F. Andersen, *International Clinical Psychopharmacology*, **2004**, *19(3)*.
[25] Tillement, J.-P., B. Testa, F. Brée, *Biochemical Pharmacology*, **2003**, *66(7)*, 1123-1126.
[26] Bortolotti, F., A. Bertaso, R. Gottardo, G. Musile, F. Tagliaro, *Drug Testing and Analysis*, **2013**, *5(9-10)*, 781-784.
[27] Eriksson, T., S. Björkman, P. Höglund, *European Journal of Clinical Pharmacology*, **2001**, *57(5)*, 365-376.

[28] Lin, G.-Q., J.-G. Zhang, J.-F. Cheng, *Overview of Chirality and Chiral Drugs*, in *Chiral Drugs*. **2011**. p. 3-28.
[29] Calcaterra, A., I. D'Acquarica, *Journal of Pharmaceutical and Biomedical Analysis*, **2018**, *147*, 323-340.
[30] Reichel, C., R. Brugger, H. Bang, G. Geisslinger, K. Brune, *Molecular Pharmacology*, **1997**, *51(4)*, 576-582.
[31] Franks, M.E., G.R. Macpherson, W.D. Figg, *The Lancet*, **2004**, *363(9423)*, 1802-1811.
[32] Kim, J.H., A.R. Scialli, *Toxicological Sciences*, **2011**, *122(1)*, 1-6.
[33] Vargesson, N., *Birth Defects Research Part C: Embryo Today: Reviews*, **2015**, *105(2)*, 140-156.
[34] Teo, S.K., W.A. Colburn, W.G. Tracewell, K.A. Kook, D.I. Stirling, M.S. Jaworsky, M.A. Scheffler, S.D. Thomas, O.L. Laskin, *Clinical Pharmacokinetics*, **2004**, *43(5)*, 311-327.
[35] Bartlett, J.B., K. Dredge, A.G. Dalgleish, *Nature Reviews Cancer*, **2004**, *4(4)*, 314-322.
[36] Ghirga, F., A. Bonamore, L. Calisti, I. D'Acquarica, M. Mori, B. Botta, A. Boffi, A. Macone, *International Journal of Molecular Sciences*, **2017**, *18(11)*.
[37] Schrittwieser, J.H., V. Resch, S. Wallner, W.-D. Lienhart, J.H. Sattler, J. Resch, P. Macheroux, W. Kroutil, *The Journal of Organic Chemistry*, **2011**, *76(16)*, 6703-6714.
[38] Kim, A.N., A. Ngamnithiporn, E. Du, B.M. Stoltz, *Chemical Reviews*, **2023**, *123(15)*, 9447-9496.
[39] Kametani, T., *The Total Syntheses of Isoquinoline Alkaloids*, in *Total Synthesis of Natural Products*. **1977**. p. 1-272.
[40] Garud, M.S., M.J. Oza, A.B. Gaikwad, Y.A. Kulkarni, *Chapter 8 - Natural Remedies for Treatment of Cancer Pain*, in *Nutritional Modulators of Pain in the Aging Population*, R.R. Watson and S. Zibadi, Editors. **2017**, Academic Press. p. 101-106.
[41] Rolinson, G.N., R. Sutherland, *Semisynthetic Penicillins*, in *Advances in Pharmacology*, S. Garaitini, et al., Editors. **1973**, Academic Press. p. 151-220.
[42] Nandi, A., S. Pan, R. Potumarthi, M.K. Danquah, I.P. Sarethy, *Journal of Analytical Methods in Chemistry*, **2014**, *2014(1)*, 413616.
[43] Mai, N.L., Y.-M. Koo, *Enzyme and Microbial Technology*, **2014**, *63*, 34-38.
[44] Blaser, H.U., *Chemical Reviews*, **1992**, *92(5)*, 935-952.
[45] Chalmers, J.R., G.T. Dickson, J. Elks, B.A. Hems, *Journal of the Chemical Society (Resumed)*, **1949***(0)*, 3424-3433.
[46] Gnas, Y., F. Glorius, *Synthesis*, **2006**, *2006(12)*, 1899-1930.
[47] *Nobel Prize in Chemistry 2001*. Outreach [08.05.2025]; Available from: https://www.nobelprize.org/prizes/chemistry/2001/summary/.
[48] Knowles, W.S., *Journal of Chemical Education*, **1986**, *63(3)*, 222.
[49] Kitamura, M., M. Tokunaga, T. Ohkuma, R. Noyori, *Organic Syntheses*, **2003**, *71*, 1-1.
[50] Akutagawa, S., *Topics in Catalysis*, **1997**, *4(3)*, 271-274.
[51] Osborn, J.A., F.H. Jardine, J.F. Young, G. Wilkinson, *Journal of the Chemical Society A: Inorganic, Physical, Theoretical*, **1966***(0)*, 1711-1732.
[52] Manwen, J., F. Dachao, J. Mingxing, *Acta Academiae Medicinae Wuhan*, **1982**, *2(4)*, 223-228.
[53] Mbaveng, A.T., V. Kuete, T. Efferth, *Frontiers in Pharmacology*, **2017**, *8*, 343.
[54] Kuete, V., L.P. Sandjo, A.T. Mbaveng, M. Zeino, T. Efferth, *Phytomedicine*, **2015**, *22(14)*, 1247-1254.
[55] Klausmeyer, P., T.G. McCloud, D.A. Scudiero, M.J. Currens, J.H. Cardellina Ii, R.H. Shoemaker, *Bioorganic & Medicinal Chemistry*, **2012**, *20(15)*, 4646-4652.
[56] Wang, T.-X., X.-H. Yang, *Yao xue xue bao = Acta pharmaceutica Sinica*, **2008**, *43(5)*, 461-466.
[57] Xu, W., S. Chen, X. Wang, H. Wu, H. Yamada, T. Hirano, *Bioorganic & Medicinal Chemistry*, **2020**, *28(12)*, 115553.

[58] Wang, L., X. Ci, H. Lv, X. Wang, F.X. Qin, G. Cheng, *Experimental Biology and Medicine*, **2016**, *241(14)*, 1568-1576.
[59] Sakurai, Y., A.A. Kolokoltsov, C.-C. Chen, M.W. Tidwell, W.E. Bauta, N. Klugbauer, C. Grimm, C. Wahl-Schott, M. Biel, R.A. Davey, *Science*, **2015**, *347(6225)*, 995-998.
[60] Gunaratne, G.S., Y. Yang, F. Li, T.F. Walseth, J.S. Marchant, *Cell Calcium*, **2018**, *75*, 30-41.
[61] Ou, X., Y. Liu, X. Lei, P. Li, D. Mi, L. Ren, L. Guo, R. Guo, T. Chen, J. Hu, Z. Xiang, Z. Mu, X. Chen, J. Chen, K. Hu, Q. Jin, J. Wang, Z. Qian, *Nature Communications*, **2020**, *11(1)*, 1620.
[62] Sun, M., J. Wang, Y. Zhou, Z. Wang, Y. Jiang, M. Li, *Neuroimmunomodulation*, **2016**, *23(2)*, 98-108.
[63] Calcraft, P.J., M. Ruas, Z. Pan, X. Cheng, A. Arredouani, X. Hao, J. Tang, K. Rietdorf, L. Teboul, K.-T. Chuang, P. Lin, R. Xiao, C. Wang, Y. Zhu, Y. Lin, C.N. Wyatt, J. Parrington, J. Ma, A.M. Evans, A. Galione, M.X. Zhu, *Nature*, **2009**, *459(7246)*, 596-600.
[64] Ruas, M., K. Rietdorf, A. Arredouani, L.C. Davis, E. Lloyd-Evans, H. Koegel, T.M. Funnell, A.J. Morgan, J.A. Ward, K. Watanabe, X. Cheng, G.C. Churchill, M.X. Zhu, F.M. Platt, G.M. Wessel, J. Parrington, A. Galione, *Current Biology*, **2010**, *20(8)*, 703-709.
[65] Zong, X., M. Schieder, H. Cuny, S. Fenske, C. Gruner, K. Rötzer, O. Griesbeck, H. Harz, M. Biel, C. Wahl-Schott, *Pflügers Archiv - European Journal of Physiology*, **2009**, *458(5)*, 891-899.
[66] Patel, S., *Science Signaling*, **2015**, *8(384)*, re7-re7.
[67] Inubushi, Y., Y. Masaki, S. Matsumoto, F. Takami, *Tetrahedron Letters*, **1968**, *9(30)*, 3399-3402.
[68] Jin, Q., B. Yu, Z. Ge, Y. Dai, Y. Chen, Y. Jin, M. Zhou, W. Yuan, *CN109942593* **2019**
[69] Pictet, A., T. Spengler, *Berichte der deutschen chemischen Gesellschaft*, **1911**, *44(3)*, 2030-2036.
[70] Yokoyama, A., T. Ohwada, K. Shudo, *The Journal of Organic Chemistry*, **1999**, *64(2)*, 611-617.
[71] Cheung, G.K., M.J. Earle, R.A. Fairhurst, H. Heaney, K.F. Shuhaibar, S.C. Eyley, F. Ince, *Synlett*, **1991**, *1991(10)*, 721-723.
[72] Kubo, A., N. Saito, N. Kawakami, Y. Matsuyama, T. Miwa, *Synthesis*, **1987**, *1987(09)*, 824-827.
[73] Singh, K., P.K. Deb, *Tetrahedron Letters*, **2000**, *41(25)*, 4977-4980.
[74] Muzalevskiy, V.M., V.G. Nenajdenko, A.V. Shastin, E.S. Balenkova, G. Haufe, *Tetrahedron*, **2009**, *65(36)*, 7553-7561.
[75] Vercauteren, J., C. Lavaud, J. Levy, G. Massiot, *The Journal of Organic Chemistry*, **1984**, *49(12)*, 2278-2279.
[76] Comins, D.L., M.M. Badawi, *Tetrahedron Letters*, **1991**, *32(26)*, 2995-2996.
[77] Youn, S.W., *Organic Preparations and Procedures International*, **2006**, *38(6)*, 505-591.
[78] Eckert, M., G. Fleischmann, R. Jira, H.M. Bolt, K. Golka, *Acetaldehyde*, in *Ullmann's Encyclopedia of Industrial Chemistry*. **2006**.
[79] Tian, Y., J. Zheng, *Chapter Six - Metabolic Activation and Toxicities of bis-Benzylisoquinoline Alkaloids*, in *Advances in Molecular Toxicology*, J.C. Fishbein and J.M. Heilman, Editors. **2017**, Elsevier. p. 241-272.
[80] Jin, H., L. Li, D. Zhong, J. Liu, X. Chen, J. Zheng, *Chemical Research in Toxicology*, **2011**, *24(12)*, 2142-2152.
[81] Tainlin, L., H. Tingyi, Z. Changqi, Y. Peipei, Z. Qiong, *Ecotoxicology and Environmental Safety*, **1982**, *6(6)*, 528-534.
[82] Iturriaga-Vásquez, P., R. Miquel, M.D. Ivorra, M.P. D'Ocon, B.K. Cassels, *Journal of Natural Products*, **2003**, *66(7)*, 954-957.
[83] Evano, G., J. Wang, A. Nitelet, *Organic Chemistry Frontiers*, **2017**, *4(12)*, 2480-2499.
[84] Ullmann, F., P. Sponagel, *Berichte der deutschen chemischen Gesellschaft*, **1905**, *38(2)*, 2211-2212.

[85] Yamada, K., M. Takeda, T. Iwakuma, *Tetrahedron Letters*, **1981**, *22(39)*, 3869-3872.
[86] Rice, K.C., *US4727146A* **1988**
[87] Asif, M.M.A., S.R. Lisa, N. Qais, *RSC Advances*, **2023**, *13(16)*, 11010-11036.
[88] Meyers, A.I., D.A. Dickman, M. Boes, *Tetrahedron*, **1987**, *43(21)*, 5095-5108.
[89] Liu, G., D.A. Cogan, J.A. Ellman, *Journal of the American Chemical Society*, **1997**, *119(41)*, 9913-9914.
[90] *Ellman Laboratory Yale University*. Outreach [08.05.2025]; Available from: https://ellman.chem.yale.edu/research/asymmetric-synthesis-amines.
[91] Mendes, J.A., P.R.R. Costa, M. Yus, F. Foubelo, C.D. Buarque, *Beilstein Journal of Organic Chemistry*, **2021**, *17*, 1096-1140.
[92] Robak, M.T., M.A. Herbage, J.A. Ellman, *Chemical Reviews*, **2010**, *110(6)*, 3600-3740.
[93] Zhang, W.-Y., P.C. Hogan, C.-L. Chen, J. Niu, Z. Wang, D. Lafrance, O. Gilicky, N. Dunwoody, M. Ronn, *Organic Process Research & Development*, **2015**, *19(11)*, 1784-1795.
[94] Reynolds, M., C.T. Eary, S. Spencer, D. Juengst, B. Hache, Y. Jiang, J. Haas, S.W. Andrews, *WO2017201241* **2017**
[95] Zhang, W., S.R. Gilbertson, *Tetrahedron Letters*, **2017**, *58(23)*, 2175-2177.
[96] Colyer, J.T., N.G. Andersen, J.S. Tedrow, T.S. Soukup, M.M. Faul, *The Journal of Organic Chemistry*, **2006**, *71(18)*, 6859-6862.
[97] Kamlah, A., F. Lirk, F. Bracher, *Tetrahedron*, **2016**, *72(6)*, 837-845.
[98] Vögerl, K., D.N. Ong, F. Bracher, *Synthesis*, **2018**, *50(06)*, 1323-1330.
[99] Liu, G., D.A. Cogan, T.D. Owens, T.P. Tang, J.A. Ellman, *The Journal of Organic Chemistry*, **1999**, *64(4)*, 1278-1284.
[100] Mortimer, C.E., U. Müller, *Chemie: Das Basiswissen der Chemie; 126 Tabellen*. **2007**: Georg Thieme Verlag.
[101] Collados, J.F., E. Toledano, D. Guijarro, M. Yus, *The Journal of Organic Chemistry*, **2012**, *77(13)*, 5744-5750.
[102] Cogan, D.A., G. Liu, J. Ellman, *Tetrahedron*, **1999**, *55(29)*, 8883-8904.
[103] Quiclet-Sire, B., S.Z. Zard, *Pure and Applied Chemistry*, **2010**, *83(3)*, 519-551.
[104] Sirvent, J.A., F. Foubelo, M. Yus, *European Journal of Organic Chemistry*, **2013**, *2013(12)*, 2461-2471.
[105] Sahu, K.B., A. Maity, S. Mondal, R. Paira, P. Saha, S. Naskar, A. Hazra, S. Banerjee, N.B. Mondal, *Journal of Heterocyclic Chemistry*, **2013**, *50(S1)*, E148-E155.
[106] Reddy, Y.V., D.O. Biradar, B.J.M. Reddy, A. Rathod, M. Himabindu, B.V.S. Reddya, *Natural Product Communications*, **2017**, *12(10)*.
[107] Das, M., D.F. O'Shea, *Chemistry – A European Journal*, **2015**, *21(51)*, 18717-18723.
[108] Das, M., D.F. O'Shea, *Tetrahedron*, **2013**, *69(31)*, 6448-6460.
[109] Schütz, R., S. Schmidt, F. Bracher, *Tetrahedron*, **2020**, *76(19)*, 131150.
[110] Baxter, E.W., A.B. Reitz, *Organic Reactions*, **2004**, 1-714.
[111] Fadeyi, O.O., T.J. Senter, K.N. Hahn, C.W. Lindsley, *Chemistry – A European Journal*, **2012**, *18(19)*, 5826-5831.
[112] Senter, T.J., O.O. Fadeyi, C.W. Lindsley, *Organic Letters*, **2012**, *14(7)*, 1869-1871.
[113] Medjahdi, M., J.C. González-Gómez, F. Foubelo, M. Yus, *Heterocycles*, **2012**, *86*, 727-734.
[114] Zhang, W.-Y., C. Sun, D. Hunt, M. He, Y. Deng, Z. Zhu, C.-L. Chen, C.E. Katz, J. Niu, P.C. Hogan, X.-Y. Xiao, N. Dunwoody, M. Ronn, *Organic Process Research & Development*, **2016**, *20(2)*, 284-296.
[115] Brinner, K.M., J.A. Ellman, *Organic & Biomolecular Chemistry*, **2005**, *3(11)*, 2109-2113.
[116] Kurouchi, H., *Organic & Biomolecular Chemistry*, **2021**, *19(3)*, 653-658.
[117] Coates, D.A., S.J. Richards, A.J. Sanderson, *WO/2018/213056* **2018**
[118] Schwenk, R., A. Togni, *Dalton Transactions*, **2015**, *44(45)*, 19566-19575.
[119] Mukade, T., D.R. Dragoli, J.A. Ellman, *Journal of Combinatorial Chemistry*, **2003**, *5(5)*, 590-596.

[120] Brown, H.C., B.C.S. Rao, *Journal of the American Chemical Society*, **1956**, *78(21)*, 5694-5695.
[121] Zweifel, G., H.C. Brown, *Hydration of Olefins, Dienes, and Acetylenes via Hydroboration*, in *Organic Reactions*. **2011**. p. 1-54.
[122] Kudale, A.A., P. Anaspure, F. Goswami, M. Voss, *Tetrahedron Letters*, **2014**, *55(52)*, 7219-7221.
[123] Reddy, N.S.S., R.A. Babu, B.V.S. Reddy, *Synthesis*, **2016**, *48(07)*, 1079-1086.
[124] Cole, K.P., M.D. Argentine, E.W. Conder, R.K. Vaid, P. Feng, M. Jia, P. Huang, P. Liu, B. Sun, S. Tadayon, C. Zhu, R. Zhu, *Organic Process Research & Development*, **2020**, *24(10)*, 2043-2054.
[125] Hughes, D.L., *The Mitsunobu Reaction*, in *Organic Reactions*. **2004**. p. 335-656.
[126] Tsunoda, T., F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto, S. Itô, *Tetrahedron Letters*, **1996**, *37(14)*, 2463-2466.
[127] Tsunoda, T., S. Ito, *Journal of Synthetic Organic Chemistry, Japan*, **1997**, *55(7)*, 631-641.
[128] Tsunoda, T., F. Ozaki, S. Itô, *Tetrahedron Letters*, **1994**, *35(28)*, 5081-5082.
[129] Hughes, D.L., *Organic Preparations and Procedures International*, **1996**, *28(2)*, 127-164.
[130] Wyatt, P.B., *(Tributylphosphoranylidene)acetonitrile*, in *Encyclopedia of Reagents for Organic Synthesis*. **2008**.
[131] Swamy, K.C.K., N.N.B. Kumar, E. Balaraman, K.V.P.P. Kumar, *Chemical Reviews*, **2009**, *109(6)*, 2551-2651.
[132] Allenmark, S., J. Gawronski, *Chirality*, **2008**, *20(5)*, 606-608.
[133] Buesking, A.W., T.D. Baguley, J.A. Ellman, *Organic Letters*, **2011**, *13(5)*, 964-967.
[134] Xie, J.-H., P.-C. Yan, Q.-Q. Zhang, K.-X. Yuan, Q.-L. Zhou, *ACS Catalysis*, **2012**, *2(4)*, 561-564.
[135] Pelzer, A.W., M.R. Sturgeon, A.J. Yanez, G. Chupka, M.H. O'Brien, R. Katahira, R.D. Cortright, L. Woods, G.T. Beckham, L.J. Broadbelt, *ACS Sustainable Chemistry & Engineering*, **2015**, *3(7)*, 1339-1347.
[136] Evans, D.A., J.L. Katz, T.R. West, *Tetrahedron Letters*, **1998**, *39(19)*, 2937-2940.
[137] Vijayan, A., D.N. Rao, K.V. Radhakrishnan, P.Y.S. Lam, P. Das, *Synthesis*, **2020**, *53(05)*, 805-847.
[138] Doyle, M.G.J., R.J. Lundgren, *Chemical Communications*, **2021**, *57(22)*, 2724-2731.
[139] Subbareddy, M., *Der Pharma Chemica*, **2018**, *10(9)*, 11-14.
[140] Chen, S., H. Huang, X. Liu, J. Shen, H. Jiang, H. Liu, *Journal of Combinatorial Chemistry*, **2008**, *10(3)*, 358-360.
[141] Qiao, J.X., P.Y.S. Lam, *Synthesis*, **2011**, *2011(06)*, 829-856.
[142] Sarkate, A.P., S.S. Bahekar, V.M. Wadhai, G.N. Ghandge, P.S. Wakte, D.B. Shinde, *Synlett*, **2013**, *24(12)*, 1513-1516.
[143] Burgos, C.H., T.E. Barder, X. Huang, S.L. Buchwald, *Angewandte Chemie International Edition*, **2006**, *45(26)*, 4321-4326.
[144] Liu, Z., R.C. Larock, *Organic Letters*, **2004**, *6(1)*, 99-102.
[145] Hillmann, G., *Chemical Sciences*, **1956**, *11(7)*, 419-421.
[146] Jalalian, N., T.B. Petersen, B. Olofsson, *Chemistry – A European Journal*, **2012**, *18(44)*, 14140-14149.
[147] Boucher, M.M., M.H. Furigay, P.K. Quach, C.S. Brindle, *Organic Process Research & Development*, **2017**, *21(9)*, 1394-1403.
[148] Yoshida, Y., M. Kukita, K. Omori, T. Mino, M. Sakamoto, *Organic & Biomolecular Chemistry*, **2021**, *19(20)*, 4551-4564.
[149] Ley, S.V., M.N. Tackett, M.L. Maddess, J.C. Anderson, P.E. Brennan, M.W. Cappi, J.P. Heer, C. Helgen, M. Kori, C. Kouklovsky, S.P. Marsden, J. Norman, D.P. Osborn, M.Á. Palomero, J.B.J. Pavey, C. Pinel, L.A. Robinson, J. Schnaubelt, J.S. Scott, C.D. Spilling, H. Watanabe, K.E. Wesson, M.C. Willis, *Chemistry – A European Journal*, **2009**, *15(12)*, 2874-2914.
[150] Kadam, A., M. Nguyen, M. Kopach, P. Richardson, F. Gallou, Z.-K. Wan, W. Zhang, *Green Chemistry*, **2013**, *15(7)*, 1880-1888.

[151] Metzger, A., F.M. Piller, P. Knochel, *Chemical Communications*, **2008***(44)*, 5824-5826.
[152] Krasovskiy, A., P. Knochel, *Synthesis*, **2006***(05)*, 0890-0891.
[153] Truong, V.L., M.S. Ménard, I. Dion, *Organic Letters*, **2007**, *9(4)*, 683-685.
[154] Morita, T., S. Fuse, H. Nakamura, *Angewandte Chemie International Edition*, **2016**, *55(43)*, 13580-13584.
[155] Bailey, W.F., J.J. Patricia, *Journal of Organometallic Chemistry*, **1988**, *352(1)*, 1-46.
[156] Miyaura, N., A. Suzuki, *Journal of the Chemical Society, Chemical Communications*, **1979***(19)*, 866-867.
[157] Gómez-Ayala, S., J.A. Castrillón, A. Palma, S.M. Leal, P. Escobar, A. Bahsas, *Bioorganic & Medicinal Chemistry*, **2010**, *18(13)*, 4721-4739.
[158] Hasebein, P., B. Frehland, K. Lehmkuhl, R. Fröhlich, D. Schepmann, B. Wünsch, *Organic & Biomolecular Chemistry*, **2014**, *12(29)*, 5407-5426.
[159] Husain, S.M., R. Fröhlich, D. Schepmann, B. Wünsch, *The Journal of Organic Chemistry*, **2009**, *74(7)*, 2788-2793.
[160] Berney, D., T. Jauner, *Helvetica Chimica Acta*, **1976**, *59(2)*, 623-626.
[161] Clark, M.T., J. Chang, S.S. Navran, H. Akbar, A. Mukhopadhyay, H. Amin, D.R. Feller, D.D. Miller, *Journal of Medicinal Chemistry*, **1986**, *29(2)*, 181-185.
[162] Meyers, A.I., R.H. Hutchings, *Tetrahedron*, **1993**, *49(9)*, 1807-1820.
[163] Lewis, F.D., G. Dasharatha Reddy, *Tetrahedron Letters*, **1992**, *33(30)*, 4249-4252.
[164] Meyers, A.I., *Tetrahedron*, **1992**, *48(13)*, 2589-2612.
[165] Melpolder, J.B., R.F. Heck, *The Journal of Organic Chemistry*, **1976**, *41(2)*, 265-272.
[166] Calò, V., A. Nacci, A. Monopoli, V. Ferola, *The Journal of Organic Chemistry*, **2007**, *72(7)*, 2596-2601.
[167] Colbon, P., J. Ruan, M. Purdie, K. Mulholland, J. Xiao, *Organic Letters*, **2011**, *13(20)*, 5456-5459.
[168] Chernyshev, V.M., O.V. Khazipov, D.B. Eremin, E.A. Denisova, V.P. Ananikov, *Coordination Chemistry Reviews*, **2021**, *437*, 213860.
[169] Shang, Y., X. Jie, K. Jonnada, S.N. Zafar, W. Su, *Nature Communications*, **2017**, *8(1)*, 2273.
[170] Legault, C.Y., Y. Garcia, C.A. Merlic, K.N. Houk, *Journal of the American Chemical Society*, **2007**, *129(42)*, 12664-12665.
[171] Anton-Torrecillas, C., J.C. Gonzalez-Gomez, *Organic & Biomolecular Chemistry*, **2014**, *12(36)*, 7018-7025.
[172] Tang, R.-J., T. Milcent, B. Crousse, *The Journal of Organic Chemistry*, **2018**, *83(2)*, 930-938.
[173] Gao, W., Q. Li, J. Chen, Z. Wang, C. Hua, *Molecules*, **2013**, *18(12)*, 15613-15623.
[174] Hathaway, B.A., W.K. L., M.E. and McGill, *Synthetic Communications*, **2007**, *37(21)*, 3855-3860.
[175] Castanet, A.-S., F. Colobert, P.-E. Broutin, *Tetrahedron Letters*, **2002**, *43(29)*, 5047-5048.
[176] Ogata, T., T. Kimachi, K.-i. Yamada, Y. Yamamoto, K. Tomioka, *Heterocycles*, **2012**, *86*, 469-485.
[177] Yin, Q., Z. Li, J. He, Y. Lai, Q. Zhang, H. Sun, *The Journal of Organic Chemistry*, **2025**, *90(9)*, 3501-3506.
[178] Kobayashi, T., T. Hosoya, S. Yoshida, *Bulletin of the Chemical Society of Japan*, **2021**, *94(7)*, 1823-1832.
[179] Kobayashi, T., T. Hosoya, S. Yoshida, *Chemistry Letters*, **2020**, *49(7)*, 809-812.
[180] Chen, J., Y. Zhang, L. Yang, X. Zhang, J. Liu, L. Li, H. Zhang, *Tetrahedron*, **2007**, *63(20)*, 4266-4270.
[181] Alonso, F., I.P. Beletskaya, M. Yus, *Chemical Reviews*, **2002**, *102(11)*, 4009-4092.
[182] Fjelbye, K., N. Svenstrup, A. Püschl, *Synthesis*, **2015**, *47(20)*, 3231-3240.
[183] Panossian, A., F.R. Leroux, *Chimia*, **2016**, *70(43)*, 1-2.
[184] Sealy, J.M., A.P. Truong, L. Tso, G.D. Probst, J. Aquino, R.K. Hom, B.M. Jagodzinska, D. Dressen, D.W.G. Wone, L. Brogley, V. John, J.S. Tung, M.A. Pleiss, J.A. Tucker, A.W. Konradi, M.S. Dappen, G. Toth, H. Pan, L. Ruslim, J. Miller, M.P.

Bova, S. Sinha, K.P. Quinn, J.-M. Sauer, *Bioorganic & Medicinal Chemistry Letters*, **2009**, *19(22)*, 6386-6391.
[185] Ueda, T., H. Konishi, K. Manabe, *Angewandte Chemie International Edition*, **2013**, *52(33)*, 8611-8615.
[186] Ma, Y.-R., X.-J. Lv, Q. Dong, Y.-C. Ming, Y.-K. Liu, *Organic Letters*, **2023**, *25(32)*, 5929-5934.
[187] Rosenblum, S.B., T. Huynh, A. Afonso, H.R. Davis, N. Yumibe, J.W. Clader, D.A. Burnett, *Journal of Medicinal Chemistry*, **1998**, *41(6)*, 973-980.
[188] Knochel, P., *Organomagnesium and Organozinc Chemistry*, in *Organometallics in Synthesis*. **2013**. p. 223-372.
[189] Bosco, M., R. Dalpozzo, G. Bartoli, G. Palmieri, M. Petrini, *Journal of the Chemical Society, Perkin Transactions 2*, **1991***(5)*, 657-663.
[190] Kuduk, S.D., R.M. DiPardo, R.K. Chang, C. Ng, M.G. Bock, *Tetrahedron Letters*, **2004**, *45(35)*, 6641-6643.
[191] Hagelin, H., B. Hedman, I. Orabona, T. Åkermark, B. Åkermark, C.A. Klug, *Journal of Molecular Catalysis A: Chemical*, **2000**, *164(1)*, 137-146.
[192] Wrackmeyer, B., C. Bihlmayer, K. Shahid, W. Milius, *Chemical Sciences*, **2009**, *64(4)*, 399-402.
[193] Gottlieb, H.E., V. Kotlyar, A. Nudelman, *Journal of organic chemistry*, **1997**, *62(21)*, 7512-7515.
[194] Sun, C., B. Potter, J.P. Morken, *Journal of the American Chemical Society*, **2014**, *136(18)*, 6534-6537.
[195] Fan, R., D. Pu, F. Wen, Y. Ye, X. Wang, *The Journal of Organic Chemistry*, **2008**, *73(9)*, 3623-3625.
[196] Adepu, R., B. Prasad, M.A. Ashfaq, N.Z. Ehtesham, M. Pal, *RSC Advances*, **2014**, *4(90)*, 49324-49328.
[197] Thaima, T., A.C. Willis, S.G. Pyne, *Tetrahedron*, **2019**, *75(36)*, 130476.
[198] Gremmen, C., M.J. Wanner, G.-J. Koomen, *Tetrahedron Letters*, **2001**, *42(50)*, 8885-8888.
[199] Okano, K., H. Tokuyama, T. Fukuyama, *Journal of the American Chemical Society*, **2006**, *128(22)*, 7136-7137.
[200] Battula, S.R.K., G.V. Subbareddy, I.E. Chakravarthy, V. Saravanan, *RSC Advances*, **2016**, *6(61)*, 55710-55714.
[201] Fustero, S., I. Ibáñez, P. Barrio, M.A. Maestro, S. Catalán, *Organic Letters*, **2013**, *15(4)*, 832-835.
[202] Moorthy, J.N., K. Senapati, S. Kumar, *The Journal of Organic Chemistry*, **2009**, *74(16)*, 6287-6290.
[203] Kobayashi, S., K. Okimoto, Y. Imakura, *Chemical & Pharmaceutical Bulletin*, **1982**, *30(5)*, 1567-1573.