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**Enantioselective Strategies for the Synthesis
of Organosulfur Compounds of
Pharmacological Interest**

Tesi Doctoral

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València, Octubre de 2025

Prof. Dr. Gonzalo Blay Llinares

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Notes for the reader

The experimental results presented in this Thesis are structured into three *Parts*:

- **Part I**, which discusses Chapter 1.
- **Part II**, encompassing Chapter 2 to 4
- **Part III**, which addresses Chapter 5.

The numbering of figures, schemes and compounds follows the format ***a.b***, where ***a*** refers to the number of the corresponding *Part* and ***b*** represents the internal reference within that *Part*.

Agraïments

Qui llegisca aquests agraïments i em conega sap que, abans de començar aquesta tesi, jo ja era doctor en una altra disciplina fonamental en la vida: Doctor en Queixar-me Constantment de Tot. Per això, en un primer moment vaig pensar a començar aquests agraïments queixant-me un poc, per no trencar la rutina. Tanmateix, mentre escric aquestes línies i repasse tot el que ha suposat per a mi aquesta muntanya russa d'emocions anomenada *Tesi Doctoral*, m'adone que, per una vegada, no m'abelleix queixar-me. Que no servisca de precedent. Dit això, ací van els meus agraïments.

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Abbreviations and Symbols

$[\alpha]_D^{25}$	Specific rotation at 20 °C, sodium D line
Å	Angstrom (10^{-10} m)
Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
aq	Aqueous
AQN	Anthraquinone
Ar	Aryl
BArF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BOX	Bis(oxazoline)
^t Bu	<i>tert</i> -Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
Cbz	Benzyloxycarbonyl
CDK	Cyclin-dependent kinase
COD	1,5-Cyclooctadiene
δ	Chemical Shift
dba	Dibenzalacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DiPAMP	(Ethane-1,2-diyl)bis[(2-methoxyphenyl)(phenyl)phosphane]
DIOP	2,3- <i>O</i> -Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP	4-(<i>N,N</i> -Dimethylamino)pyridine
DMF	Dimethylformamide

DMSO	Dimethyl sulfoxide
L-DOPA	<i>L</i> -3,4-Dihydroxyphenylalanine
dr	Diastereomeric ratio
ee	Enantiomeric excess
equiv	Equivalent
ESF	Ethenesulfonyl fluoride
ESI	Electrospray ionization
Et	Ethyl
FDA	US Food and Drug Administration
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
<i>J</i>	Coupling constant
HFIP	Hexafluoroisopropanol
HMDS	Hexamethyldisilazide
Me	Methyl
MMPP	Magnesium monoperoxyphthalate
mp	Melting point
Ms	Mesyl
MS	Molecular sieves
MTBE	Methyl <i>tert</i> -butyl ether
Pent	Pentyl
NHC	<i>N</i> -Heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
Ortep	Oak Ridge thermal-ellipsoid plot program
Ph	Phenyl
PHAL	Phthalhydrazide
Pr	Propyl
<i>i</i> Pr	Isopropyl
PTC	Phase transfer catalysis

py	Pyridine
PYR	2,5-Diphenylpyrimidine
RAMBO	(<i>R,R,R</i>)-2-amino-3-methoxymethyl-2-azabicyclo[3.3.0]octane
RNA	Ribonucleic acid
rt	Room temperature
SAMP	(<i>S</i>)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine
SuFEx	Sulfur(VI) fluoride exchange
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride
TC	Thiophene-2-carboxylate
TEE	Tetraethynylethene
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
τ_{major}	Retention time for the major peak
τ_{minor}	Retention time for the minor peak
TMS	Trimethylsilyl
TOF	Time-of-flight
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	Tosyl
TS	Transition state
VANOL	3,3'-Diphenyl-2,2'-bi-(1-naphthol)
VAPOL	2,2'-Diphenyl-(4-biphenanthrol)
v/v	Volume per unit volume
w/w	Weight per unit weight
XPhos	Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane

Introduction

Molecular Chirality and its Discovery

Chirality is a geometric property which describes the impossibility of superposing an object with its mirror reflection. This concept was coined by Lord Kelvin in 1893^{[1],[2]} and nowadays IUPAC defines it as: “*The geometric property of a rigid object (or spatial arrangement of points or atoms) of being non-superposable on its mirror image; such an object has no symmetry elements of the second kind (a mirror plane, $\sigma = S_1$, a centre of inversion $I = S_2$, a rotation-reflection axis, S_{2n}).*”^[3] When referring to a pair of chiral molecules which are mirror images of each other and non-superposable, each is called an enantiomer, and they are characterized by rotating the plane of polarized light to the same extent but in opposite directions.

The quintessential example of chirality, which Lord Kelvin used in several texts to illustrate this concept, is that of human hands. Regardless of how they are rotated or positioned, it is impossible to superimpose one onto its mirror image. It is perhaps due to this illustrative example that Lord Kelvin selected the term *chirality* to describe this property, deriving it from the Greek word *χείρ* (*kheir*), which translates as “hand.”

The discovery of chirality was made possible thanks to the pioneering work of Jean-Baptiste Biot. In 1812, Biot studied the optical activity of laevorotatory and dextrorotatory quartz crystals, and later observed that certain organic substances, both liquid and in solution, were also capable of rotating the plane of linearly polarized light.^{[4]-[6]} It is also worth noting the contribution of Augustin-Jean Fresnel, who discovered circularly polarized light and hypothesized that the optical activity of a compound was due to a difference in the refractive index for left- and right-circularly polarized light. Fresnel proposed that this difference in refractive index was attributable to structural factors, thereby identifying a structural basis for optical activity.^[7]

In this context, Louis Pasteur made a fundamental discovery in 1848 while studying sodium ammonium tartrate crystals. When preparing this compound from racemic tartaric acid, he observed that it did not crystallize into a single form, but rather into a mixture of two distinct crystalline forms which were mirror images of each other. After manually separating them, Pasteur demonstrated that both types of crystals were optically active: each rotated the plane of polarized light to the same extent but in opposite directions. He also noted that an equimolar mixture of the two types of crystals exhibited no optical activity.^{[8],[9]}

By a fortunate yet meticulous observation, Pasteur not only identified for the first time the phenomenon of molecular chirality but also carried out the first documented example of a racemic resolution. This experiment marked the beginning of stereochemistry, although a structural explanation for chirality was not proposed until 1874, when Le Bel and van't Hoff independently introduced the concept of the asymmetric tetrahedral carbon atom as a chiral centre.^{[10],[11]}

At present, it is well understood that molecular chirality does not arise exclusively from the presence of an asymmetric carbon atom. In fact, there are five principal types of chirality (Figure 0.1):^[12]

- **Central chirality** is the most common type. It refers to molecules containing an atom—typically carbon, but also phosphorus, sulfur or silicon among others—bonded to four different substituents in a tetrahedral arrangement.
- **Axial chirality** occurs in systems where the spatial arrangement of substituents around an axis gives rise to chirality. A classic example is found in non-coplanar biaryls, such as BINOL, where restricted rotation around the bond connecting the two aromatic rings allows for the existence of enantiomeric forms. Axial chirality is also observed in allenes with asymmetric substitution at the terminal carbon atoms.
- **Planar chirality** manifests in certain systems where the spatial disposition of substituents within a plane leads to non-superimposable mirror images. Paradigmatic examples include substituted ferrocenes, which exhibit chirality due to the relative positioning of substituents on their cyclopentadienyl rings.
- **Helical chirality** appears in structures adopting a helical shape, where the left- or right-handed twist of the helix serves as the chiral element. Representative examples include molecules such as hexahelicenes, as well as biological macromolecules like proteins, in which α -helices are predominantly left-handed.
- **Topological chirality** refers to systems in which chirality emerges from the spatial connectivity of molecular components. This type of chirality is characteristic of mechanically interlocked molecules such as catenanes and rotaxanes, which exhibit topological enantiomers that cannot be interconverted without breaking covalent bonds.

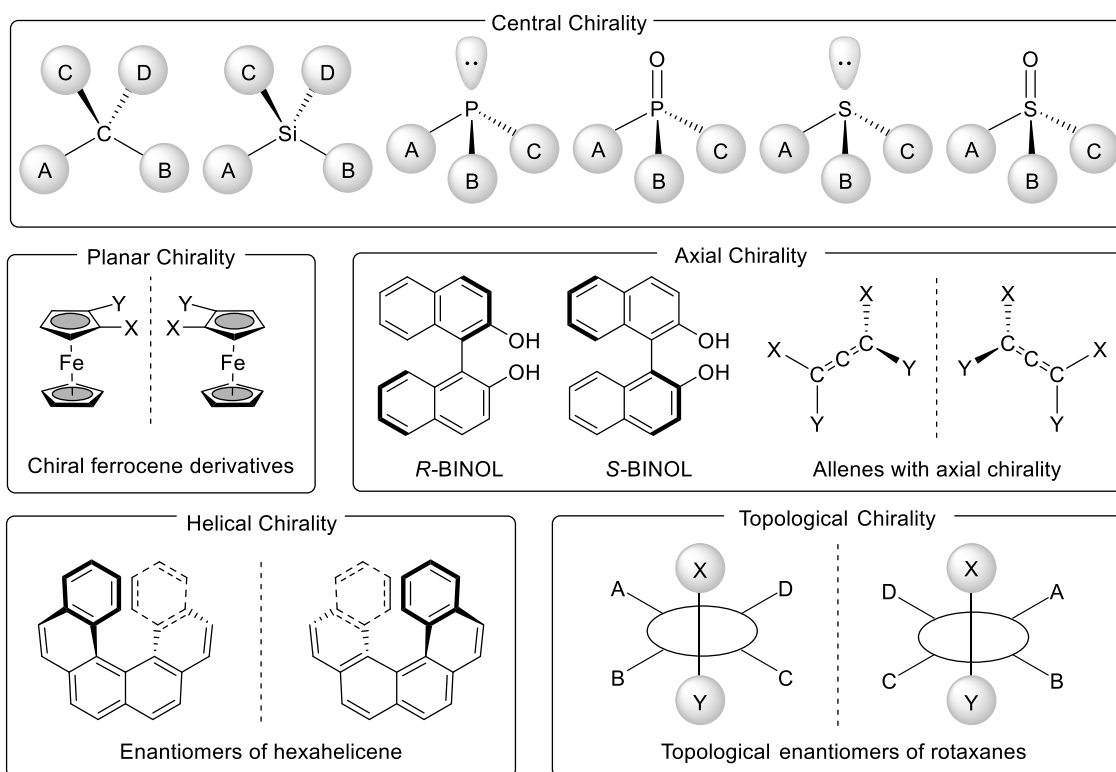


Figure 0.1- Types of chirality and examples of each type.

Biological and Pharmaceutical Implications of Chirality

Chirality is fundamentally intertwined with life and biological systems. Enzymes, for instance, are composed almost exclusively of *L*-amino acids, while the sugars found in nucleic acids exhibit *D*-configuration. This stereochemical uniformity ensures that enzymes function as highly enantioselective catalysts within biological systems; therefore, living organisms possess the ability to discriminate between enantiomers. The first experimental evidence of enantioselective biological processes was reported by Louis Pasteur in 1857, when he observed that certain microorganisms, when fed racemic tartaric acid, preferentially metabolized one of the two enantiomers, leaving the other untouched.^[13]

The ability of living organisms to discriminate between enantiomers implies that these may produce different physiological effects. One of the earliest documented examples of this phenomenon was described by Piutti in 1886, who observed that *L*-asparagine and *D*-asparagine exhibited different tastes.^[14]

This difference in behaviour within biological environments is particularly significant in the field of pharmacology. Numerous illustrative examples exist, such as ethambutol, where the (*S,S*)-enantiomer exhibits tuberculostatic activity, while the (*R,R*)-enantiomer may lead to optic neuritis and blindness.^[15] In the case of ketamine, the *S*-enantiomer is responsible for its anaesthetic action, whereas the hallucinogenic effects are primarily associated with the *R*-enantiomer.^[16] Another example is etodolac; the *S*-enantiomer exhibits anti-inflammatory activity, while the *R*-enantiomer shows gastroprotective effects (Figure 0.2).^[17]

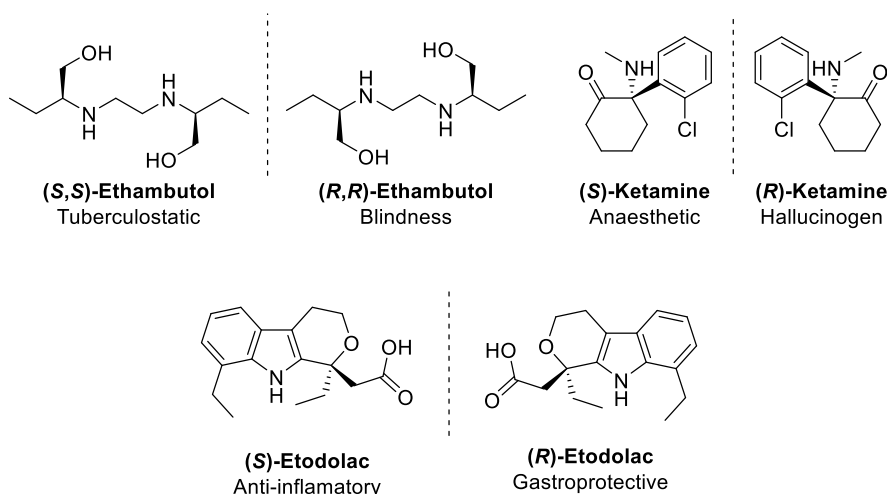


Figure 0.2- Examples of different pharmacological properties of chiral drugs.

However, the most significant case to date is that of thalidomide. This drug was marketed by the German pharmaceutical company Grünenthal in more than 46 countries, although it was never approved by the FDA for sale in the United States due to concerns about its safety. Between 1957 and 1961, it was prescribed to pregnant women as a sedative, sleep aid, and antiemetic, until McBride and Lenz independently confirmed that its use caused birth defects. It is estimated that more than 10,000 children were affected, and a significant increase in the number of miscarriages was also observed during the period of its commercialization.^[18] Subsequent research demonstrated that only the *R*-enantiomer of thalidomide possessed the desired pharmacological properties, whereas the *S*-enantiomer was responsible for the teratogenic effects.^[19] Moreover, it was shown that the

enantiomers rapidly epimerize *in vivo*^[20], meaning that even the exclusive administration of the *R*-enantiomer would not have prevented the tragedy (Figure 0.3).



Figure 0.3- Thalidomide enantiomers and its epimerization equilibrium.

If there is anything positive to be drawn from these events, it is that they exposed the existing shortcomings in the regulatory framework governing drug safety, particularly regarding chiral substances. Starting in the 1990s, the major regulatory agencies began to implement specific guidelines for the evaluation of chiral drugs, one of the most significant measures being the requirement to pharmacologically characterize each enantiomer independently. In addition, justification had to be provided for the decision to formulate a drug as a racemic mixture rather than as a single enantiomer. In cases where the racemic form was proposed, it had to be demonstrated that both enantiomers were pharmacologically and toxicologically equivalent, or alternatively, that their separation would not result in a clinically meaningful benefit. This policy was further reinforced through the introduction of specific requirements to assess *in vivo* stereochemical stability to prevent potential epimerization processes that could compromise treatment safety.^{[21],[22]}

In this context and considering that approximately 56% of currently marketed drugs consist of chiral molecules^[23], the need to develop methods for obtaining enantiomerically pure compounds becomes evident.

Asymmetric Synthesis

The branch of chemistry concerned with the synthesis of enantiomerically enriched compounds is known as Asymmetric Synthesis, and IUPAC defines it as “A *chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts.*”^[3]

Asymmetric synthesis can be divided into four main strategies: the use of the chiral pool, chiral auxiliaries, kinetic resolution of racemates, and enantioselective synthesis. It is also worth noting the classical resolutions of racemic mixtures which, although not strictly considered part of asymmetric synthesis, remain widely used in the pharmaceutical and chemical industries to obtain enantiomerically pure compounds. These include resolution by direct crystallization, separation *via* the formation and isolation of diastereomers, and separation by chiral chromatography (Figure 0.4).^[24]

The most straightforward methodology for introducing new elements of chirality is synthesis from the chiral pool, which involves the use of naturally occurring, enantiomerically pure compounds, such as amino acids, sugars, or terpenes, as starting materials for the synthesis of enantio- or diastereomerically pure products.^[25]

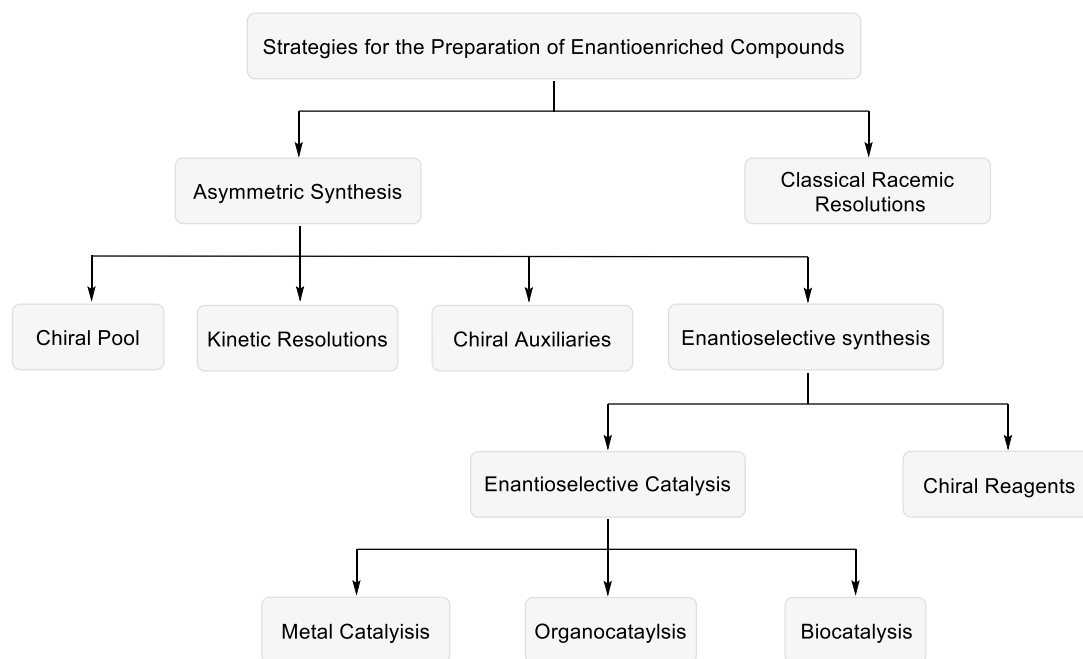


Figure 0.4- Strategies for the preparation of enantioenriched compounds.

Secondly, kinetic resolutions rely on the difference in activation energy between the diastereomeric transition states that arise when the chiral starting substrate interacts with a chiral catalyst or resolving agent. This energy difference causes one enantiomer to react significantly faster, ideally leading to a mixture composed of 50% unreacted starting material and 50% derivatized product, which can then be separated. However, as previously mentioned, the maximum theoretical yield for this process is limited to 50%, as is the case with classical resolution methods. Dynamic kinetic resolution overcomes this limitation by employing conditions under which the rate of racemization of the starting substrate exceeds the rate of reaction with the resolving agent, allowing a theoretical maximum yield of 100%.^[26]

Chiral auxiliaries are enantiomerically pure compounds that are temporarily attached to the substrate in order to induce the formation of new stereocenters through diastereoselective reactions. Once the desired transformation is complete, the auxiliary is removed to yield an enantioenriched product and, in many cases, can be recovered and reused. The main disadvantage of this approach is the need to introduce and later remove the auxiliary, thus extending the synthetic sequence by at least two steps.^[27]

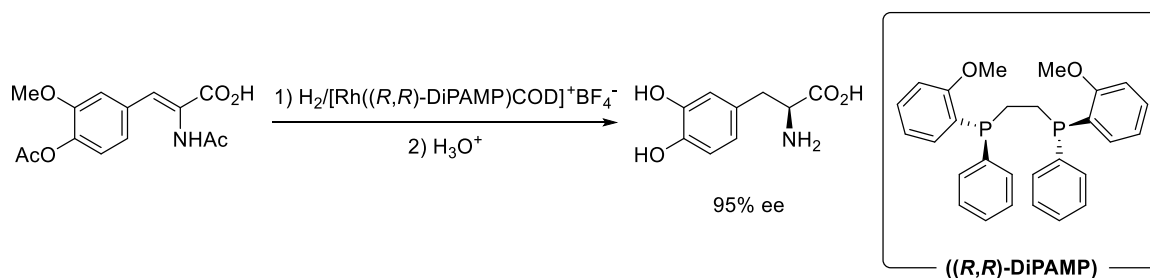
Finally, enantioselective synthesis can be divided into two categories. On one hand, the stoichiometric use of chiral reagents can induce stereoselectivity in prochiral substrates. A classic example of this approach is the use of chiral lithium amide bases.^[28] On the other hand, when chirality is induced by a catalyst, the process is referred to as enantioselective catalysis. This catalytic approach is generally preferred over the stoichiometric use of chiral reagents, as it offers superior atom economy, requires smaller amounts of chiral material, generates less waste, and reduces the energy input necessary for the reaction. These advantages align with the principles of green chemistry.^[29]

Enantioselective catalysis can be subdivided into three categories: metal catalysis, which involves the use of chiral transition metal complexes; organocatalysis, which relies on small, chiral organic molecules as catalysts; and biocatalysis, wherein chiral transformations are performed by enzymes. The research presented in this thesis focuses on the application of metal catalysis and organocatalysis.

Enantioselective Metal Catalysis

Enantioselective metal catalysis involves the use of chiral metal complexes, composed of a metal atom, responsible for the catalytic activity, coordinated to organic ligands that impart chirality to the system. This methodology rivals enzymes in efficiency and represents a clean, operationally simple, and cost-effective approach, suitable for large-scale reactions with high substrate-to-catalyst ratios and at high concentrations (up to 50% of reactant) in organic solvents. Owing to these properties, this type of catalysis is widely employed in industry, particularly in the pharmaceutical, agrochemical, flavours and fragrance sectors.^[30]

The first example of this methodology was described by Noyori in 1966, in his study of the cyclopropanation reaction between styrene and ethyl diazoacetate catalyzed by a chiral copper complex. This initial example exhibited very low enantioselectivity, which significantly limited its practical utility.^[31] Similarly, the early work of Knowles in 1968 on the enantioselective hydrogenation of olefins catalyzed by ruthenium complexes bearing chiral phosphines also led to products with poor enantioselectivity.^[32] However, his subsequent research into the development of chiral bidentate phosphines yielded outstanding results, culminating in 1974 with the rhodium-catalyzed enantioselective synthesis of *L*-DOPA, the first industrial application of enantioselective metal catalysis (Scheme 0.1).^[33]



Scheme 0.1 - *L*-DOPA synthesis via asymmetric hydrogenation.

In the years that followed, Noyori's contributions to the development of atropisomeric chiral diphosphines for asymmetric hydrogenation, together with Sharpless's pioneering work on asymmetric epoxidation and dihydroxylation, demonstrated the vast potential of asymmetric metal catalysis. The wide variety of available transition metals, with their different oxidation states, combined with the virtually unlimited number of tunable ligands, enables the design of tailor-made catalysts for specific reactions (Figure 0.5). This versatility has allowed the application of this methodology to a broad range of transformations, including asymmetric hydrogenations and oxidations, as well as cyclopropanations, Diels–Alder reactions, aldol additions, Michael additions, and alkynylations, among many others.^{[34]–[36]}

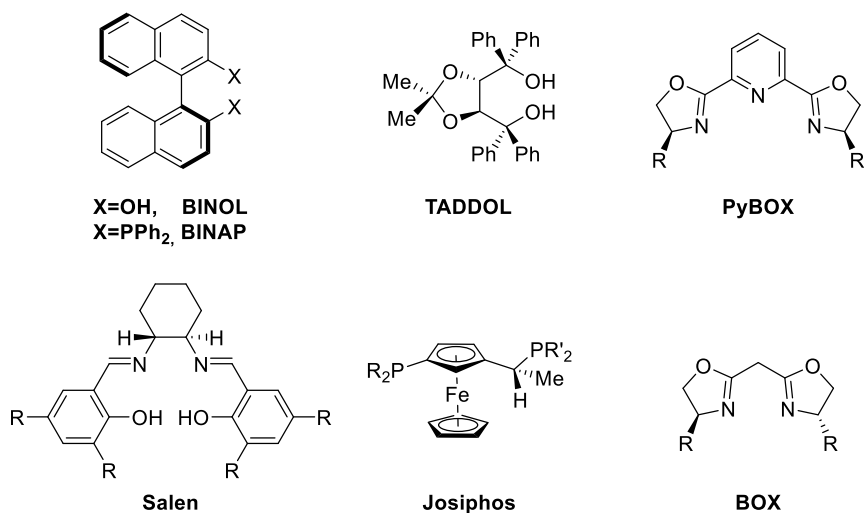


Figure 0.5.- Illustrative examples of some typical ligands used in enantioselective metal catalysis.

Given their relevance to the present work, the importance of C₂-symmetric ligands deserve particular attention. These ligands are especially attractive, as their symmetry reduces the number of possible transition states in asymmetric reactions, which is beneficial in terms of enantioselectivity.^[37] Several examples of such catalysts have been already mentioned, including DiPAMP, used by Knowles in the synthesis of *L*-DOPA; BINAP, developed by Noyori; and Salen-type ligands employed in Jacobsen's enantioselective epoxidations. Other relevant C₂-symmetric catalysts include bis(aminoalcohol)oxalamides, which have proven effective in alkynylation reactions, as will be discussed in Chapter 1 of this thesis (Figure 0.6).

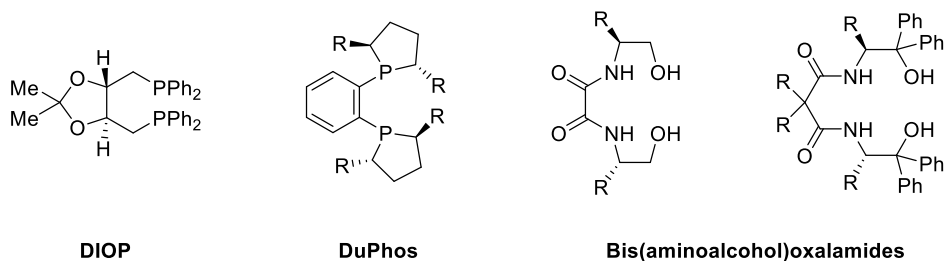


Figure 0.6- C₂-symmetric ligands.

Enantioselective Organocatalysis

Organocatalysis involves the use of small organic molecules to catalyse chemical transformations. Unlike organic ligands in transition metal complexes, the catalytic activity in organocatalysis resides entirely within the low-molecular-weight organic molecule itself. These compounds offer several advantages: they are typically stable, inexpensive, readily available from biological materials, and non-toxic. Their resistance to moisture and oxygen often eliminates the need for demanding reaction conditions such as inert atmospheres, low temperatures, or rigorously dry solvents. In addition, the absence of metal contaminants makes this methodology particularly attractive for the synthesis of compounds where metal residues are undesirable, such as pharmaceutical products.^[38]

The application of organocatalysts in asymmetric synthesis is a relatively recent area of research. Although the first documented example dates back to 1912, when Bredig and Briske reported the addition of hydrogen cyanide to benzaldehyde mediated by cinchona alkaloids, major advances were not achieved until the late 20th century. At that time, the development of the first proline-catalysed reaction by Hajos and Parrish,^[39] the work of Zhi,^[40] Denmark,^[41] and Yang^[42] on the asymmetric epoxidation of olefins catalyzed by ketones, along with the contributions of Jacobsen^[43] and Corey^[44] to the enantioselective Strecker reaction via hydrogen-bonding catalysis, demonstrated for the first time that small organic molecules could serve as effective catalysts for addressing significant challenges in chemical synthesis. Nevertheless, it was not until the groundbreaking publications by List^[45] and MacMillan^[46] in 2000, on enamine and iminium catalysis, respectively, that the field of asymmetric organocatalysis was firmly established as a discipline within organic synthesis.^[47]

Organocatalysts can be classified into two categories based on the mechanism by which they interact with the reactants (Figure 0.7).^[48] The first category is covalent catalysis, which involves the formation of catalyst–substrate adducts through covalent bond formation. Representative examples of this approach include iminium and enamine catalysis, as well as the use of *N*-heterocyclic carbenes (NHCs). The second category is non-covalent catalysis, in which the catalyst interacts with the reactants through non-covalent interactions. Examples of this type include hydrogen-bonding catalysis, where hydrogen bonds may be established directly between the catalyst and the substrate or after acid–base processes, and phase-transfer catalysis.^[38]

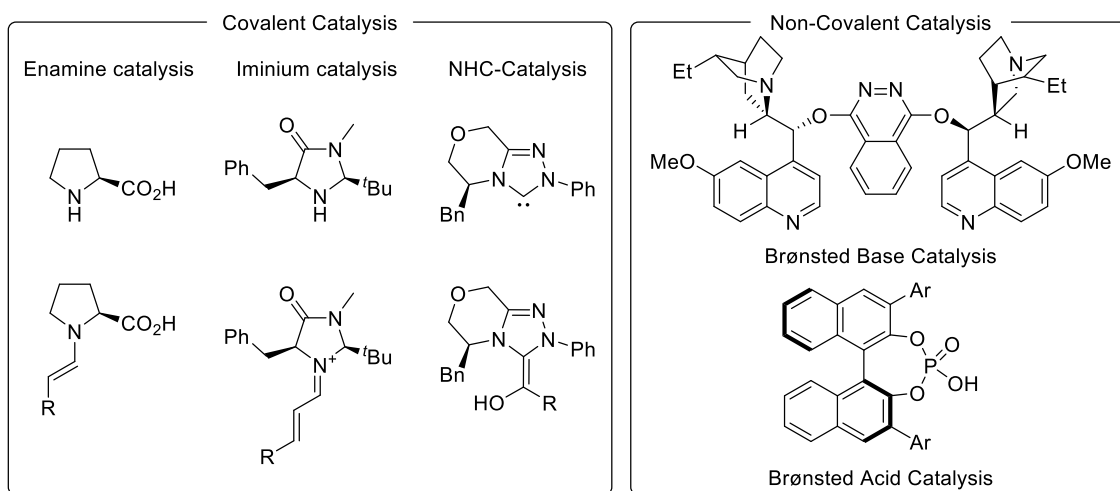


Figure 0.7- Types of organocatalysis and illustrative examples of each type.

Among these two activation modes, non-covalent catalysis is particularly relevant to the work developed in this thesis. In this context, Brønsted base catalysis stands out, in which chiral catalysts incorporating basic functional groups, such as amines, imines, amidines, or guanidines, are employed. In this type of catalysis, a pronucleophile reacts with the chiral catalyst *via* an acid–base interaction to generate an anionic species with enhanced nucleophilicity. Additionally, non-covalent interactions between the protonated catalyst and the nucleophile guide the nucleophile's approach to the electrophile in a stereoselective manner.^[49]

Catalysts that combine Brønsted bases with hydrogen-bond donor groups are referred to as bifunctional catalysts. They offer the advantage of simultaneously activating and preorienting both the nucleophile, through acid-base reactions, and the electrophile, through the formation of hydrogen bonds. This leads to the formation of an activated complex responsible for increased reactivity and chiral induction. Among these, structures derived from thioureas and squaramides are particularly noteworthy, with Takemoto's thiourea and Rawal's squaramide being the most known examples. Although the activation mechanism is analogue for both families of catalysts, they exhibit notable differences in the properties of the N–H hydrogen-bond donor groups, such as the distance between them, the angle they form, and their acidity, where pK_a values are 0.13-1.97 units higher for thioureas (Figure 0.8).^[50]

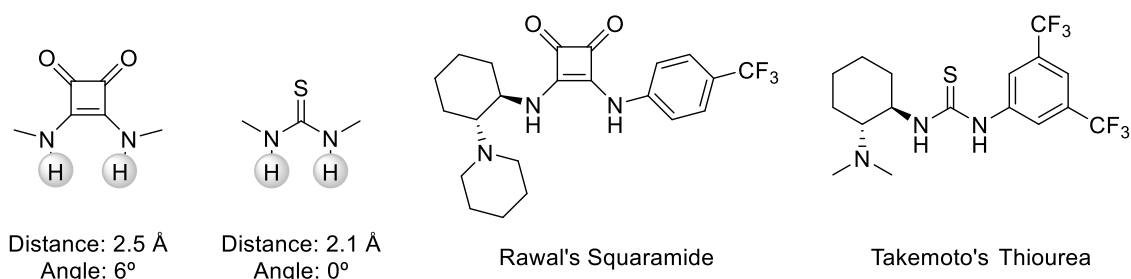


Figure 0.8- Differences between hydrogen bond donors in squaramides and thioureas. Illustrative examples of bifunctional catalysts.

The structural versatility of bifunctional catalysts has enabled the development of a wide array of chiral systems through rational modification of their chiral backbone and fine-tuning of steric and electronic features. This tunability has led to their successful application in a broad spectrum of reactions, including Mannich reactions, Michael additions, Henry reactions, Strecker reactions, desymmetrizations, and kinetic resolutions, among others.^[49]

Organosulfur Compounds: Importance and Applications

Sulfur is an essential element for life. It is found in proteinogenic amino acids such as cysteine and methionine, as well as in non-proteinogenic amino acids like taurine. It is also present in essential vitamins such as thiamine or biotin and plays a key role in metabolic processes through cofactors like coenzyme A or as part of iron-sulfur clusters in the active sites of various enzymes (Figure 0.9).

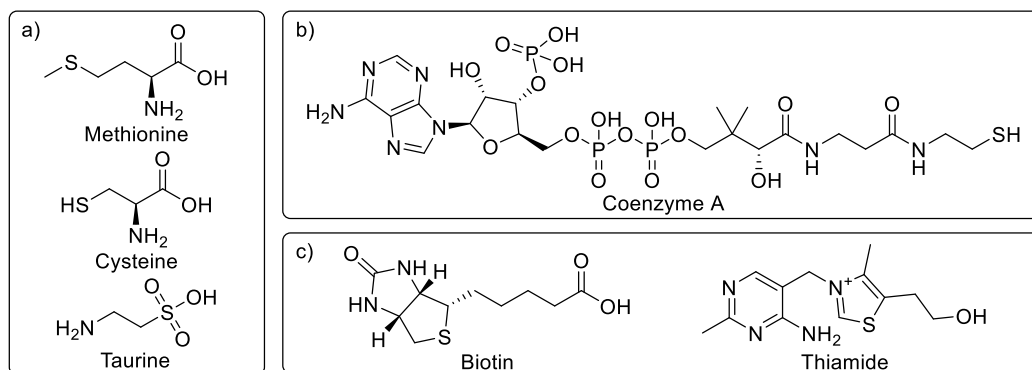


Figure 0.9- Biological organosulfur compounds: a) Amino acids. b) Cofactors. c) Vitamins.

Therefore, it is not surprising that numerous organosulfur natural products, including optically active compounds, have been isolated and identified. These molecules are of particular interest due to the broad diversity of their structures and biological activities, making them key targets in natural product-based drug discovery. Representative examples include penicillin, obtained from fungi of the *Penicillium* genus; allicin, isolated from garlic (*Allium sativum*); and compounds derived from marine organisms such as Patellamides (Figure 0.10).^{[51]-[53]}

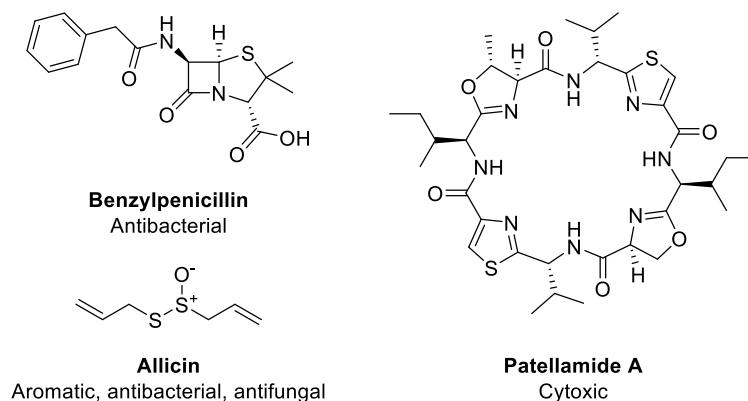


Figure 0.10- Bioactive sulfur-containing natural products.

Organosulfur compounds account for approximately 25% of all small-molecule medications currently in use, and as of 2024, sulfur is present in the structure of 30% of the top 200 small-molecule drugs by retail sales. Furthermore, between 2020 and 2024, the FDA approved 33 new sulfur-containing small-molecule medications. This clearly underscores the prominent role that sulfur plays in the development of new pharmaceuticals.^{[54],[55]}

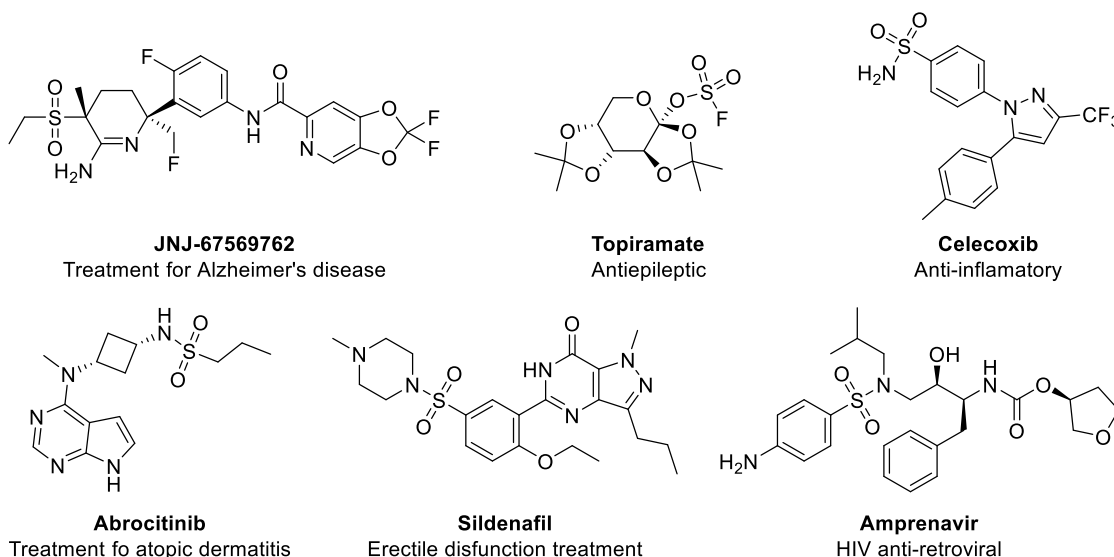


Figure 0.11-Illustrative examples of sulfur-containing drugs.

This prevalence can be attributed in part to the remarkable versatility of sulfur, which can exist in a wide variety of forms due to its multiple oxidation states and the broad range of functional groups it can adopt. These include sulfones, sulfates, sulfoxides, disulfides, thioethers, and sulfur-containing heterocycles, among others. Nevertheless, the most common forms in which sulfur appears in pharmaceuticals are as a sulfonamides and β -

sultams, which represent almost 40% of all sulfur-containing small-molecule medications.^[56]

Organosulfur compounds are used in the treatment of a wide range of diseases, including HIV, diabetes, hypertension, and erectile dysfunction, among others (Figure 0.11).^[57] However, their antibiotic activity is particularly significant considering the growing threat of bacterial resistance to antibiotics. The World Health Organization estimates that in 2019, 1.3 million deaths were directly attributable to drug-resistant infections, and projections suggest that, without effective intervention, this number could rise to as many as 10 million deaths annually by 2050. Such a scenario could trigger a global pandemic in which even common infections become life-threatening. For this reason, the development of new antibiotics will be critical in the coming decades, and organosulfur compounds may play a leading role in this field.^[58]

General Objectives

The objective of this doctoral thesis is to develop new enantioselective strategies based on asymmetric catalysis for the synthesis of organosulfur compounds of pharmacological interest. In this context, the following specific objectives have been defined for each chapter:

- **Chapter 1. Enantioselective zinc-mediated conjugate addition of terminal alkynes to saccharin-derived 1-azadienes.** This chapter explores the enantioselective conjugate alkynylation of saccharin-derived imines catalysed by metal complexes formed by zinc and chiral ligands.
- **Chapter 2. Organocatalytic enantioselective *sulfa*-Michael addition of sodium bisulfite to nitroalkenes.** This chapter explores the enantioselective addition of sodium bisulfite to *trans*- β -nitrostyrenes *via* bifunctional catalysis for the synthesis of chiral nitrosulfonic acids.
- **Chapter 3. Enantioselective construction of tetrasubstituted stereocentres *via* the organocatalytic *sulfa*-Michael addition of sodium bisulfite to β,β -disubstituted nitroalkenes.** This chapter examines the enantioselective addition of sodium bisulfite to β -CF₃- β,β -disubstituted nitroalkenes and β -nitroacrylate esters *via* bifunctional catalysis to afford chiral nitrosulfonic acids bearing a tetrasubstituted stereogenic centre.
- **Chapter 4. Organocatalytic enantioselective *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadienes.** This chapter explores the enantioselective addition of sodium bisulfite to aurone-derived imines *via* bifunctional catalysis to produce chiral benzofuran-derived sulfonic amino acids.
- **Chapter 5. Enantioselective organocatalytic addition of 3-aryloxindoles to ethenesulfonyl fluoride.** This chapter explores the enantioselective conjugate addition of 3-aryloxindoles to ethenesulfonyl fluoride catalysed by Brønsted bases to afford chiral aliphatic sulfonyl fluorides bearing a quaternary stereocentre.

Part I

Asymmetric Alkynylation of 1-Azadienes: Access to Chiral Sultams

Chapter 1. Enantioselective Zinc-Mediated Conjugate Addition of Terminal Alkynes to Saccharin-Derived 1-azadienes

Introduction

Alkynes are noteworthy compounds which exhibit remarkable versatility owing to the rich chemistry of the C-C triple bond. These moieties, orthogonal to many functional groups, can undergo a wide range of transformations, making them valuable synthetic intermediates. Representative examples of such transformations include partial or complete reductions, nucleophilic and electrophilic additions, hydrations, hydrometallations, isomerizations, and cyclotrimerizations, among others (Figure 1.1).^{[59]–[61]}

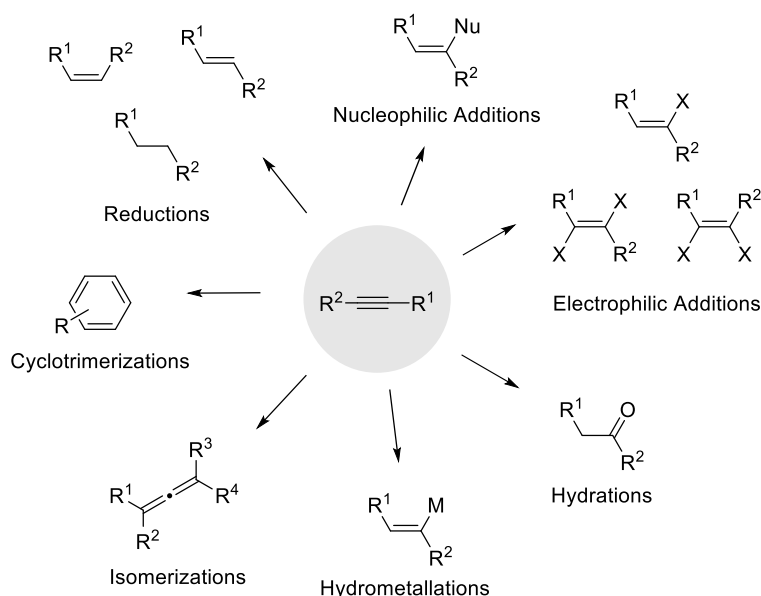


Figure 1.1- Selected examples of alkyne transformations.

In addition to their importance as synthetic intermediates, alkynes are widely found in natural products^{[62]–[64]} and other organic molecules of interest in fields such as materials science^{[65],[66]} and medicinal chemistry^{[67]–[69]} (Figure 1.2). Consequently, the development of procedures for the introduction of C-C triple bonds in organic molecules represents an important area of organic synthesis.

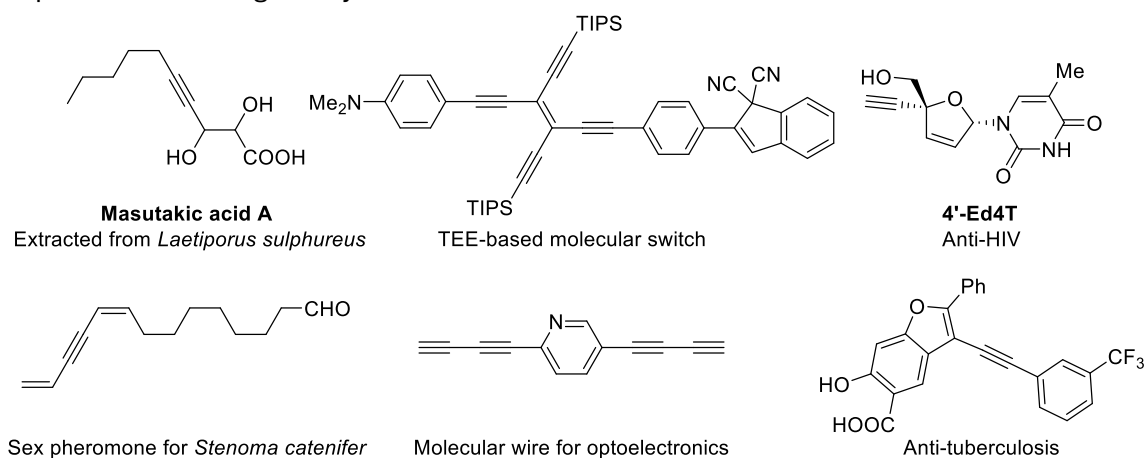
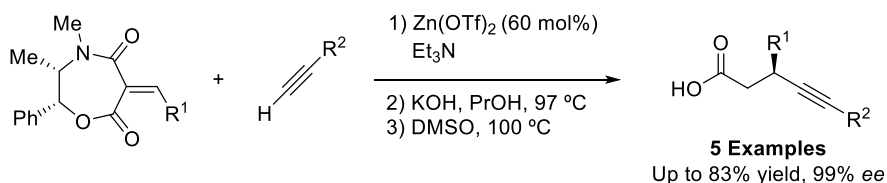


Figure 1.2- Selected alkynes with significant applications.

Among the different strategies developed, the nucleophilic addition of terminal alkynes constitutes the most direct approach for their incorporation. These methodologies rely on the exceptional acidity of the C(sp)-H bond, which can be deprotonated owing to its increased s-character compared with more saturated hydrocarbons such as alkenes or alkanes. Treatment of terminal alkynes with bases in the presence of transition metals such as Ag^I, Au^I, Cu^I, Ir^I, Pd^{II}, Rh^I, Ru^{II}, and Zn^{II} generates the corresponding metal alkynylides,^[70] which can subsequently participate in nucleophilic additions to carbon-based electrophiles. These reactions afford internal alkynes through C–C bond formation and may also generate propargylic stereocenters when prochiral electrophiles are employed. This strategy has been successfully applied to the enantioselective catalytic alkynylation of aldehydes, ketones, and imines^{[71]–[74]}

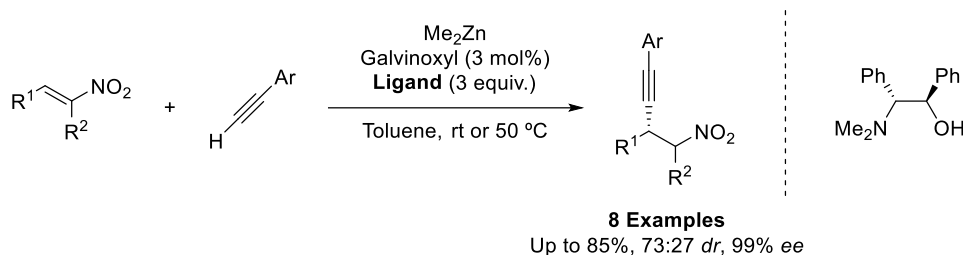
However, the 1,4-alkynylation of Michael acceptors has proven synthetically challenging, primarily due to chemoselectivity and regioselectivity issues, since alkynyllithium and alkynyl Grignard reagents typically undergo 1,2-addition. Moreover, the most commonly employed copper(I) reagents for conjugate alkyl or aryl additions struggle to promote 1,4-alkynylations due to the low nucleophilicity of copper alkynylides.^[75] As a result, their applicability is largely restricted to highly activated α,β -unsaturated systems, such as Meldrum's acid derivatives^[76], trifluoromethyl enones,^{[77],[78]} or 1,1-difluoro-1-(phenylsulfonyl)-3-en-2-ones.^[79] This limitations has been addressed by employing other softer and less reactive organometallic species than alkali metal alkynylides, among which this chapter focuses on organozinc compounds, given our group's expertise in their use for conjugate alkynylation reactions.^{[80]–[82]}

The first example of a stereoselective alkynylation of a Michael acceptor was reported by Carreira in 2004, who described the alkynylation of optically active oxazepanediones derived from ephedrine with zinc alkynylides generated *in situ* by the action of Zn(OTf)₂ and Et₃N on terminal acetylenes. The resulting adducts were obtained in good yields and excellent enantioselectivities and could be further transformed into enantioenriched β -alkynyl acids (Scheme 1.1).^[83]



Scheme 1.1- First example of a stereoselective conjugate alkynylation.

In the following year, Tomioka and co-workers reported the first enantioselective conjugate alkynylation. In this case, nitroalkenes were treated with an *in situ* generated alkynylzinc reagent prepared by treatment of terminal alkynes with dimethylzinc. The use of galvinoxyl as a radical scavenger significantly improved the reaction outcome, as dimethylzinc is known to initiate radical chain reactions.^[84] The reaction was carried out performed in the presence of stoichiometric amounts of a chiral aminoalcohol, affording the desired products in variable yields, moderate diastereoselectivities and high enantioselectivities for the major diastereomer (Scheme 1.2).^[85]



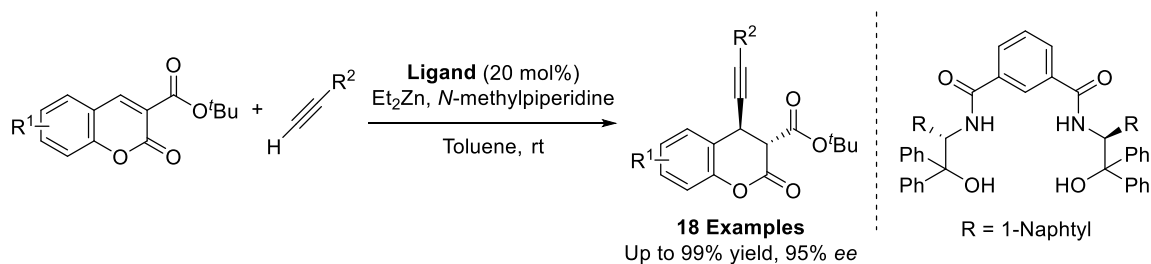
Scheme 1.2- First example of an enantioselective conjugate alkynylation, featuring nitroalkenes as electrophilic 1,4-acceptors.

It was not until 2012 when our research group developed the first catalytic asymmetric 1,4-alkynylation mediated by zinc employing catalytic amounts of a chiral ligand. In this reaction, 2-arylidene-1,3-diketones reacted with terminal alkynes in the presence of diethylzinc and (*R*)-VANOL as the chiral inducer. The alkynylation products were obtained in moderate to good yields and with high enantioselectivities, which could be further improved by crystallization to afford enantiomerically pure adducts (Scheme 1.3).^[80]



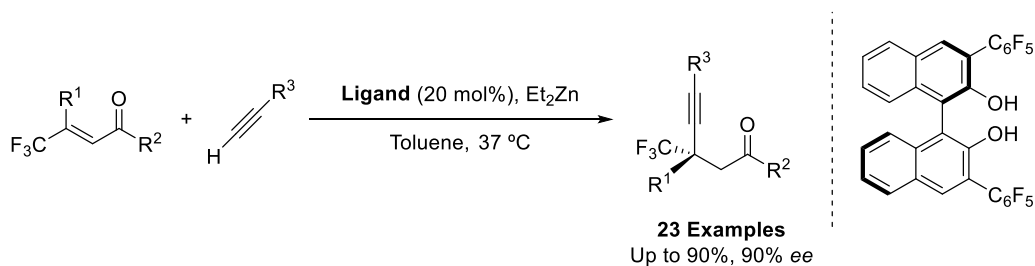
Scheme 1.3- First catalytic enantioselective 1,4-addition of terminal alkynes mediated by zinc.

One year later, our group successfully applied this methodology to the enantioselective alkynylation of 3-alkoxycarbonylcoumarins. The reaction, mediated by diethylzinc and catalytic amounts of a novel C_2 -symmetric bis-hydroxyamide ligand, delivered the alkynylated products in variable yields and moderate to excellent enantioselectivities (Scheme 1.4). Furthermore, these adducts could be transformed into valuable chiral chromanes and tetrahydrofuro[2,3-*b*]benzofurans.^[81]



Scheme 1.4- Conjugate addition of terminal alkynes to 3-alkoxycarbonylcoumarins mediated by Et_2Zn and a C_2 -symmetrical bis-hydroxyamide chiral ligand.

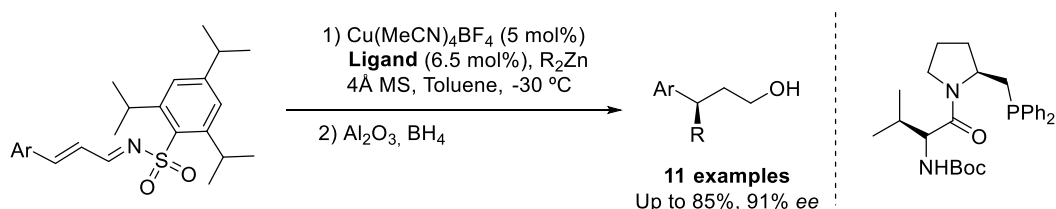
Subsequently, in 2016, our group reported the first catalytic asymmetric alkynylation of β -aryl- β -trifluoromethyl enones mediated by diethylzinc. In this case, the addition of terminal alkynes was achieved using a BINOL derivative as chiral inducer, affording the corresponding ketones bearing a trifluoromethylated propargylic quaternary stereocenter in moderate to high yields and with good to high enantiomeric excess (Scheme 1.5).^[82]



Scheme 1.5- Asymmetric 1,4-alkynylation of β -aryl- β -trifluoromethyl enones mediated by Et_2Zn and a BINOL derivative.

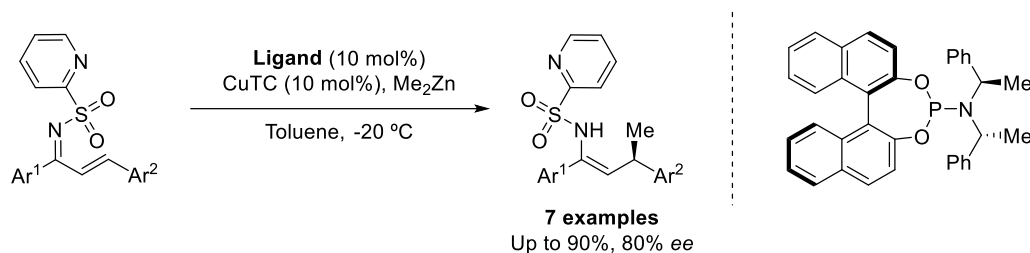
In contrast to carbonyl compounds, the asymmetric conjugate addition of organozinc reagents to α,β -unsaturated imines has been scarcely investigated. This can be attributed to the challenges associated with their application in 1,4-addition reactions, since, on the one hand, they display lower reactivity compared to their oxygenated analogues, and on the other hand, issues of regioselectivity arise due to competing 1,2- and 1,4-addition pathways. Moreover, when the 1,4-pathway takes place, the resulting imine can tautomerize to the corresponding enamine, a process that may lead to additional stereoselectivity problems due to the formation of both *E*- and *Z*-isomers. Thus, only a limited number of such reactions have been reported to date.

The first catalytic enantioselective conjugate addition of organozinc compounds to α,β -unsaturated imines was reported by Tomioka in 2005. In this work, the ethylation of unsaturated sulfonylaldimines was carried out employing diethylzinc in the presence of $\text{Cu}(\text{MeCN})_4\text{BF}_4$ and a chiral amidophosphane ligand. After hydrolysis and reduction, the corresponding β -alkylated alkanols were obtained in moderate to excellent yields and enantioselectivities (Scheme 1.6).^[86]



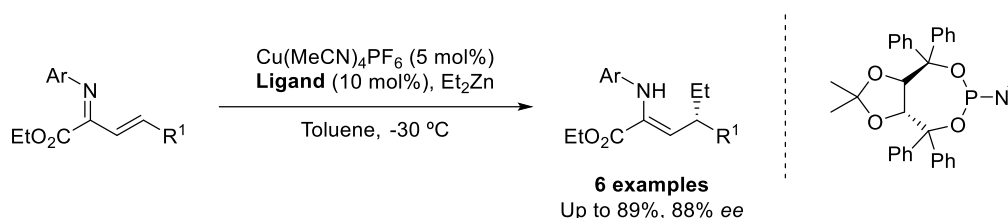
Scheme 1.6- First conjugate enantioselective addition of organozinc reagents to α,β -unsaturated imines

Simultaneously, Carretero and co-workers described the asymmetric 1,4-addition of dimethylzinc to chalcone-derived imines. The reaction was catalysed by a chiral copper(I) complex generated from CuTC and a chiral phosphoramidite ligand, affording the desired methylated (*Z*)-enamine in good yields and enantioselectivities. Remarkably, the (2-pyridyl)sulfonyl moiety proved essential for the reaction to proceed, presumably through coordination of the pyridyl nitrogen to the zinc reagent, promoting the addition process (Scheme 1.7).^[87]



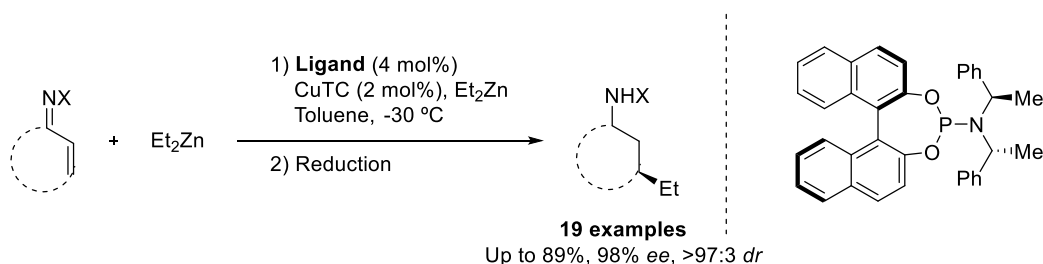
Scheme 1.7- Copper-catalysed enantioselective 1,4-addition of dimethylzinc to α,β -unsaturated imines.

The following year, Palacios and Vicario developed the copper(I)-catalysed enantioselective conjugate addition of diethylzinc to α,β -unsaturated imines derived from α -ketoesters. The use of $\text{Cu}(\text{MeCN})_4\text{PF}_6$ in combination with a TADDOL-derived phosphoramidite chiral ligand afforded α -dehydroaminoesters in high yields and moderate to good enantiomeric excesses (Scheme 1.8).^[88]



Scheme 1.8- Asymmetric conjugate ethylation of α,β -unsaturated imines derived from α -ketoesters catalysed by copper.

Later, In 2014, von Zezschwitz reported the first asymmetric conjugate addition of dialkylzinc reagents to cyclic α,β -unsaturated *N*-tosylimines. Following a subsequent reduction step, this methodology provided 3-alkylcycloalkylamines in excellent enantiomeric excesses and variable yields and diastereoselectivities. This reaction was carried out employing the same catalytic system reported by Carretero in 2005, although the reaction proceeded efficiently with much lower catalyst loadings (Scheme 1.9).^[89]



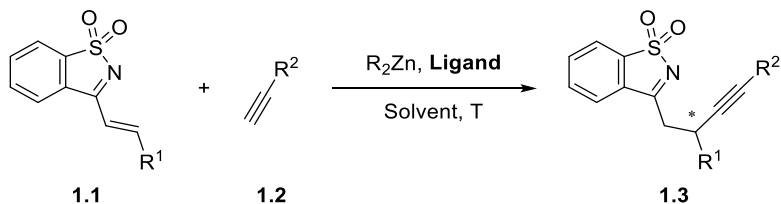
Scheme 1.9- First reported example of the asymmetric conjugate addition of dialkylzinc reagents to cyclic *N*-tosylimines.

Although zinc-mediated strategies have enabled the enantioselective addition of dialkylzinc reagents to α,β -unsaturated imines, the enantioselective alkynylation of 1-azadienes remains unexplored, with no precedents reported under any catalytic system. In this context, we propose the use of saccharin-derived 1-azadienes as electrophilic partners, which are known to participate as prochiral electrophiles in a variety of asymmetric transformations, including 1,4-arylations, formal cycloadditions, Diels-Alder reactions and cascade cyclisation reactions.^{[90]–[97]}

Considering this, the present chapter explores the enantioselective zinc-mediated 1,4-addition of terminal alkynes to saccharin-derived azadienes, affording chiral β -alkynyl *N*-sulfonyl cyclic imines bearing a propargylic stereocentre. These compounds are of considerable synthetic interest, as they serve as precursors to sulfonamides, a prominent family of molecules with a broad range of applications, which will be discussed in detail in Chapter 2.

Objectives

The main objective for this chapter is to develop an enantioselective zinc-mediated methodology for the conjugate addition of terminal alkynes to saccharin-derived azadienes **1.1**.



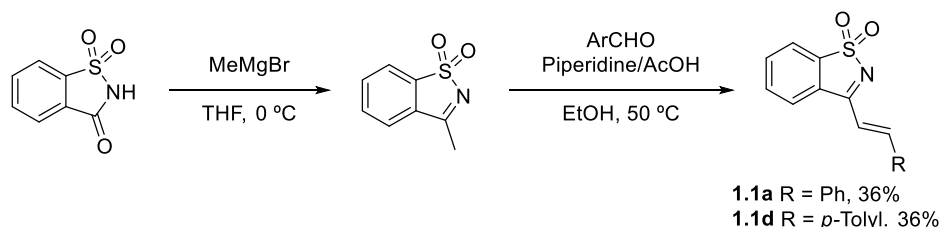
To this end, the following secondary objectives have been proposed:

1. Synthesis of the required starting materials **1.1**, bearing various substituents with different electronic and steric properties.
2. Optimization of the reaction conditions between saccharin-derived azadiene **1.1a** and acetylene **1.2a** to obtain the corresponding imine bearing a propargylic stereocentre **1.3a** with the highest yield and enantioselectivity.
3. Study of the scope of the reaction between different aromatic, aliphatic and heterocyclic saccharin-derived azadienes **1.1** and acetylenes **1.2**.
4. Applicability and synthetic transformations over the reaction products.

Results and Discussion

Synthesis of saccharin-derived azadienes **1.1**

The required saccharin-derived azadienes **1.1** were obtained following modified literature procedures *via* a two-step synthetic sequence starting from commercially available saccharin (Scheme 1.10).^{[94],[98]-[101]}



Scheme 1.10- General synthetic procedure for the synthesis of saccharine-derived azadienes **1.1**.

In the first step, the desired *N*-sulfonylimine was synthesised upon treatment of saccharine with methylmagnesium bromide, followed by a concomitant dehydration. Subsequently, the ketimine intermediate was subjected to a Knoevenagel condensation employing different aldehydes in the presence of catalytic amounts of piperidine and acetic acid, giving access to azadienes **1.1**. With the exception of compounds **1.1a** and **1.1d**, the majority of the required azadienes had already been synthesized within the research group prior to the commencement of this work. Spectroscopic data were in accordance with literature.

Optimization of the Reaction Conditions

In a first approach, a preliminary study on the enantioselective zinc-mediated conjugate addition of terminal alkynes to azadienes was carried out using chalcone-derived *N*-tosylimine **1.4a** and phenylacetylene **1.2a** as model substrates. The reaction conditions previously reported by our research group for the alkynylation of α,β -unsaturated carbonyl compounds were employed as the starting point of this investigation (Table 1.1).^[81]

Table 1.1- Preliminary study on the enantioselective alkynylation of azadiene **1.4a**.

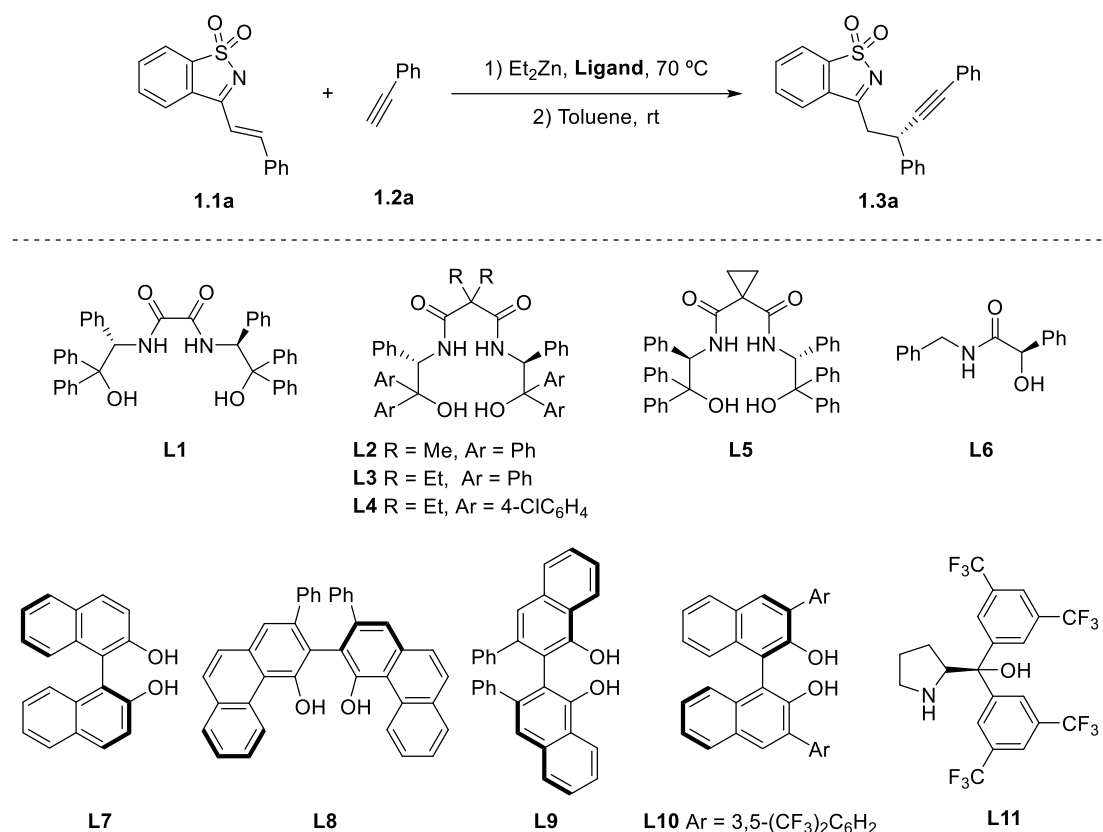
Entry ^a	Ligand	Yield (%) ^b	1.5a:1.5a' ^c	ee 1.5a (%) ^d	ee 1.5a' (%) ^d
1	L1	31	40:60	24	33
2	L2	74	80:20	22	22
3	L3	52	76:20	43	34
4	L4	45	72:28	73	75

^aReaction conditions: **1.4a** (0.125 mmol), **1.2a** (0.938 mmol), **Ligand** (20 mol%), 1.5 M Et₂Zn in toluene (0.25 mmol), in toluene (1.5 mL) at rt for 3h (see Table 1.2 for **Ligand** structure). ^bIsolated yield after column chromatography. ^cDetermined by NMR. ^dMeasured using chiral HPLC.

The reaction was evaluated in the presence of different C₂-symmetric bis(hydroxy)oxamide (Table 1, Entry 1) and bis(hydroxy)malonamide-derived chiral ligands (Table 1.1, entries 2

to 4). Although this catalytic system afforded the desired alkynylation product in fair enantioselectivities, it was consistently obtained as a mixture of imine/enamine isomers. To overcome this limitation, saccharin-derived azadienes **1.1** were selected as substrates, as the formation of the endocyclic imine is favoured according to literature reports.^[93] Thus, we started the optimization process performing a ligand screening, using azadiene **1.1a** as model substrate (Table 1.2).

Table 2.1- Chiral ligand screening for the enantioselective alkynylation of azadiene **1.1a**.



Entry ^a	Ligand	Yield (%) ^b	ee 1.3a (%) ^c
1	L1	49	10
2	L2	48	65
3	L3	50	71
4	L4	53	72
5	L5	54	30
6	L6	65	26
7	L7	22	0
8	L8	48	22
9	L9	38	45
10	L10	22	0
11	L11	29	0

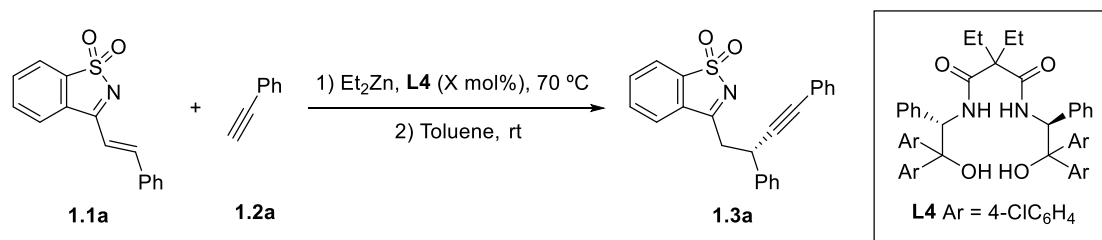
^aReaction conditions: **1.1a** (0.125 mmol), **1.2a** (0.938 mmol), **L** (20 mol%), 1.5 M Et_2Zn in toluene (0.25 mmol), in toluene (1.5 mL) at rt for 3h. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

Initially, C₂-symmetric bis(hydroxy)oxamide **L1** and bis(hydroxy)malonamide derivative **L2** (Table 1.2, entries 1 and 2) were tested, obtaining the best results with **L2**, affording compound **1.3a** in 48% yield and 65% ee. Building on this result, additional

bis(hydroxy)malonamide ligands were prepared, among which those derived from 2,2-diethylmalonic acid (**L3**) and 1,1,2-triarylaminoethanol (**L4**) displayed the best performance, with comparable efficiencies in both cases (Table 1.2, entries 3 and 4). Conversely, the cyclopropane-1,1-dicarboxylic acid derivative **L5** and mandelamide **L6** proved clearly inferior, leading to a pronounced drop in enantioselectivity (Table 2, entries 5 and 6). To further improve the outcome of the reaction, alternative catalyst families were subsequently evaluated, such as atropisomeric chiral ligands, including (*R*)-BINOL **L7**, (*S*)-VAPOL **L8**, (*R*)-VANOL **L9** and BINOL-derivative **L10**, or prolinol **L11** (Table 1.2, entries 7 to 11). In all cases, alkynylation product **1.3a** was obtained in moderate to low yields and enantioselectivities (22-48%, 0-45% ee, respectively), and therefore **L4** was selected as the optimal ligand.

With the optimal ligand in hand, further optimization of the reaction parameters was conducted, including ligand loading, stoichiometric ratio of reagents, concentration and solvent (Table 1.3). Increasing the ligand loading to 30 mol% led to a significant decrease in both yield and enantioselectivity (Table 1.3, entry 2), while decreasing it to 10 mol% resulted in only a slight reduction in performance (Table 1.3, entry 3). Thus, subsequent studies were performed with 10 mol% of **L4**.

Table 1.3- Evaluation of the ligand loading effect on the enantioselective alkynylation of **1.1a**.

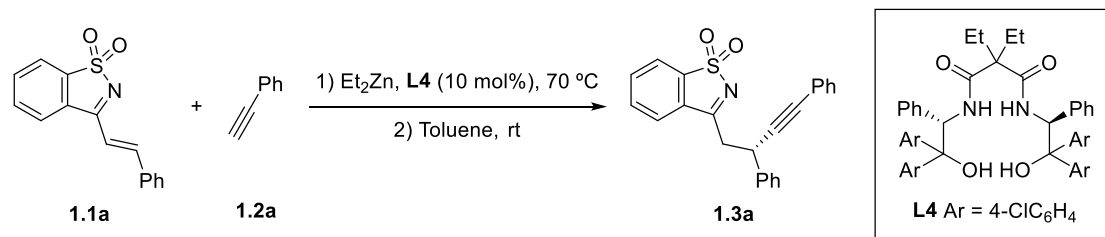


Entry ^a	L4 (X mol%)	Yield (%) ^b	ee (%) ^c
1	20	53	72
2	30	27	38
3	10	41	67

^aReaction conditions: **1.1a** (0.125 mmol), **1.2a** (0.938 mmol), 1.5 M Et_2Zn in toluene (0.25 mmol), in toluene (1.5 mL) at rt for 3h. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

The effect of the stoichiometric ratio of reagents was next examined (Table 1.4). Decreasing the amount of diethylzinc to 1.3 equivalents did not improve the reaction (Table 1.4, entry 2), whereas its increase to 4 equivalents enhanced both yield and enantioselectivity, affording **1.3a** in 53% yield and 80% ee (Table 1.4, entry 4). In contrast, the use of dimethylzinc led to a marked erosion of both parameters (Table 1.4, entry 6). The number of equivalents of phenylacetylene was also optimized, and the best outcome was obtained with 5 equivalents of **1.2a**, maintaining similar yields while slightly improving enantioselectivity to 85% ee (Table 1.4, entry 7). Thus, the optimal stoichiometry was established as 4 equivalents of diethylzinc and 5 equivalents of terminal alkyne.

Table 1.4- Evaluation of the number of equivalents of Et₂Zn and alkyne **1.2a** on the enantioselective alkynylation of **1.1a**.

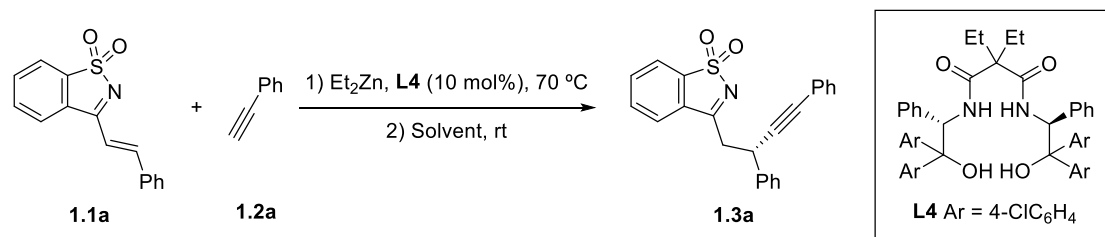


Entry ^a	Et ₂ Zn (equiv.)	1.2a (equiv.)	Yield (%) ^b	ee (%) ^c
1	2	7.5	41	67
2	1.3	7.5	52	63
3	3	7.5	50	64
4	4	7.5	53	80
5	5	7.5	43	64
6	4 ^d	7.5	50	58
7	4	5	47	85
8	4	4	38	57

^aReaction conditions: **1.1a** (0.125 mmol), **L4** (10 mol%) in toluene (1.5 mL) at rt for 3h. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC. ^dMe₂Zn was used instead of Et₂Zn.

Finally, the influence of concentration and solvent was assessed (Table 1.5). Deviations from the standard solvent volume (1.5 mL) were detrimental to the reaction outcome (Table 1.5, entries 1–3). Similarly, alternative solvents or mixtures, including toluene/1,2-dichloroethane, dichloromethane, and tetrahydrofuran, failed to improve the results (Table 1.5, entries 4–6).

Table 1.5- Effect of concentration and solvent on the enantioselective alkynylation of **1.1a**.



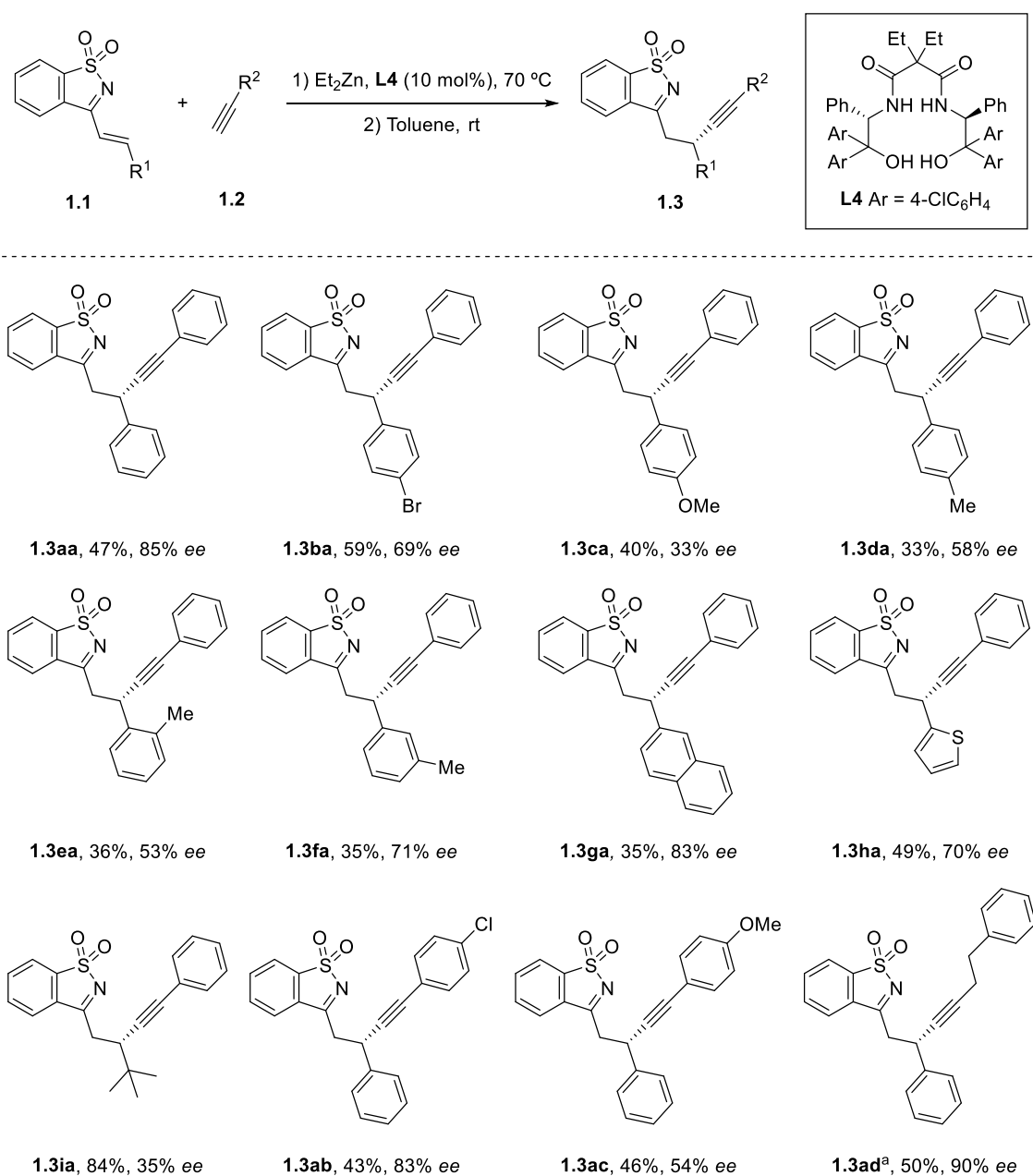
Entry ^a	Solvent	V (mL)	Yield (%) ^b	ee (%) ^c
1	Toluene	1.5	47	85
2	Toluene	2	59	59
3	Toluene	1	38	63
4	Toluene/DCE 1:2 ^d	1.5	46	41
5	Toluene/DCM 1:2 ^d	1.5	40	40
6	Toluene/THF 1:2 ^d	1.5	20	0

^aReaction conditions: **1.1a** (0.125 mmol), **1.2a** (0.625 mmol), **L4** (10 mol%). 1.5 M Et₂Zn in toluene (0.50 mmol), in solvent (X mL) at rt for 3h. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC. ^dSolvent mixtures are reported as v/v ratios.

In conclusion, the optimal reaction conditions for the model reaction between azadiene **1.1a** and phenylacetylene **1.2a** are as follows: bis(hydroxy)malonamide-derived ligand **L4** at 10 mol% loading, in 1.5 mL of toluene as solvent, using 4 equivalents of diethylzinc and 5 equivalents of alkyne **1.2a** at rt.

Scope of the Reaction with Different Azadienes **1.1** and Alkynes **1.2**

Once the optimal reaction conditions were established, we proceeded to study how different groups or substituents on azadienes **1.1** and alkynes **1.2** affected the outcome of the reaction (Scheme 1.11).



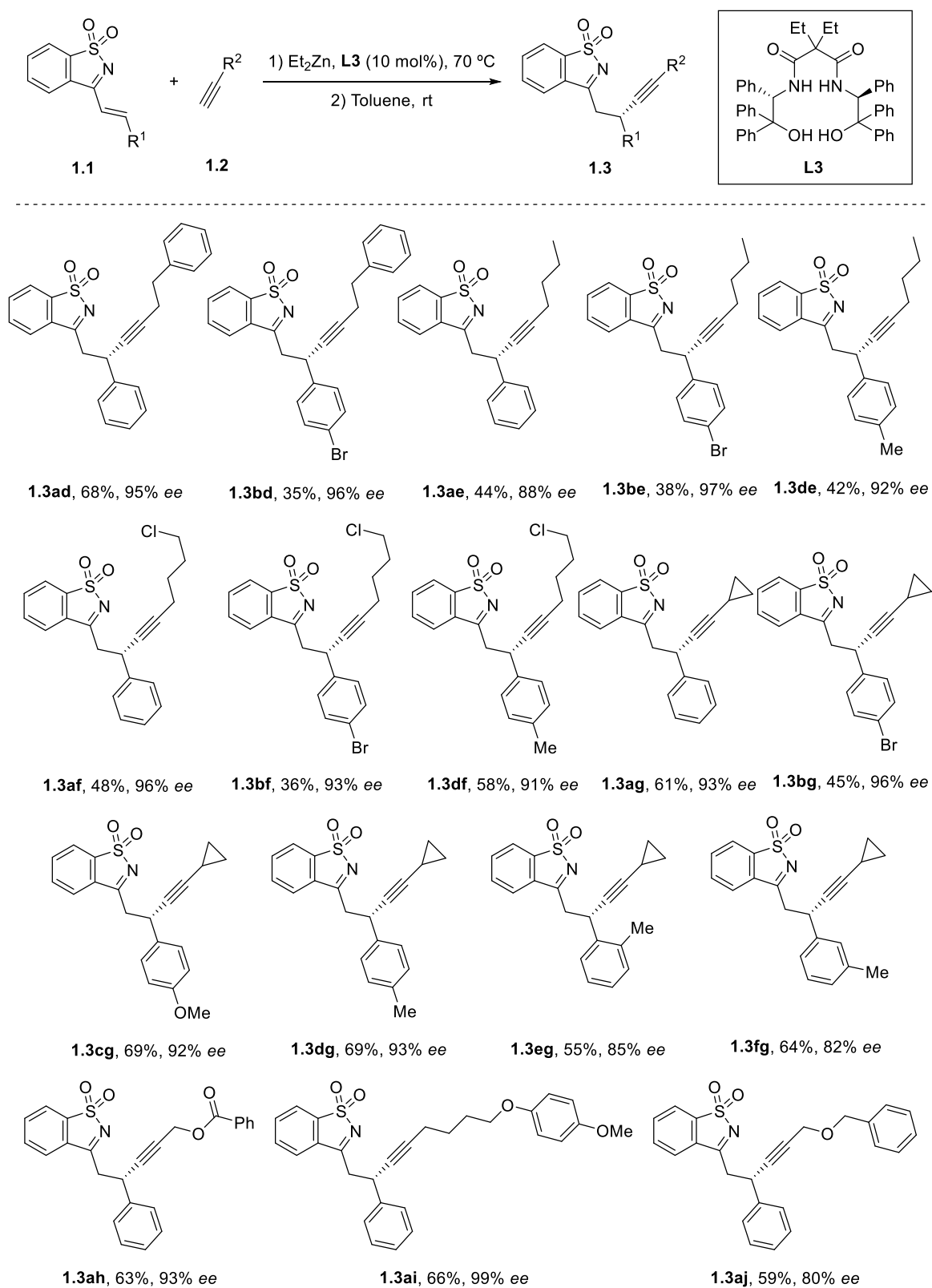
Scheme 1.11- Study of the scope of the alkynylation reaction with various saccharin-derived azadienes **1.1a**. ^a Et_2Zn (0.25 mmol, 2 equiv.).

Initially, phenylacetylene **1.2a** was reacted with a series of azadienes **1.1**. The results revealed a pronounced sensitivity to substitution on the azadiene scaffold, regardless of the electronic properties or the position of the substituents. The resulting alkynylation products **1.3aa–1.3fa** were obtained with yields and enantioselectivities varying from good to considerably diminished. Substrates featuring more extended aromatic systems or heteroaromatic rings produced adducts **1.3ga** and **1.3ha** in moderate yields and good enantioselectivities (35%, 83% ee and 49%, 70% ee, respectively).

Subsequent evaluation of different terminal alkynes focused initially on phenylacetylenes bearing substituents on the aromatic ring. The electron-deficient alkyne **1.2b** afforded product **1.3ab** in yield and enantioselectivity (43%, 83% ee) comparable to those of the parent phenylacetylene **1.2a**, whereas the electron-rich derivative **1.2c** delivered adduct **1.3ac** with a marked reduction in enantioselectivity (46%, 54% ee). Notably, the use of 4-phenyl-1-butyne **1.2d** proved highly beneficial, furnishing compound **1.3ad** with 90% ee, albeit accompanied by minor formation of a racemic ethylation byproduct, which could be suppressed by reducing the diethylzinc loading to 2 equivalents. Encouraged by this result, we extended the study to other aliphatic terminal alkynes. (Scheme 1.12).

The addition of 4-phenyl-1-butyne **1.2d** to azadiene **1.1a** was re-examined employing ligands **L3** and **L4**, which revealed that **L3** provided superior results, affording product **1.3ad** in 68% yield and 95% ee. Accordingly, subsequent studies were conducted using **L3** as the optimal ligand. Under these conditions, the *p*-bromo-substituted substrate **1.1b** was also subjected to this alkynylation procedure, affording adduct **1.3bd** with excellent enantioselectivity (96% ee). Other aliphatic alkynes, including 1-hexyne **1.2e**, 6-chloro-1-hexyne **1.2f** and cyclopropylacetylene **1.2g**, were also well tolerated, delivering the corresponding products in 44–61% yield and 88–93% ee.

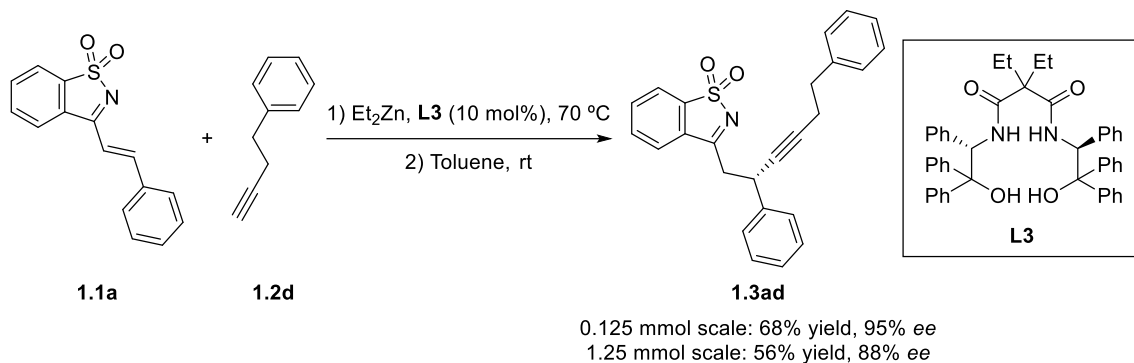
In contrast to the results observed for phenylacetylene **1.2a**, saccharin-derived azadienes **1.1** displayed a remarkable tolerance to substitution on the aryl group at the β -position of the double bond. Groups of diverse electronic character and with different substitution patterns were well accommodated, consistently affording alkynylated imines **1.3** in high enantioselectivities, particularly in the case of *para*-substituted derivatives (82–97% ee). Finally, the methodology was also successfully extended to functionalized alkynes containing ester and ether groups, yielding adducts **1.3ah–1.3aj** in 59–63% yield and 80–99% ee. Of particular note, compound **1.3ai** was obtained with complete stereocontrol.



Scheme 1.12- Study of the scope of the alkynylation reaction with various saccharin-derived azadienes **1.1a** and aliphatic terminal alkynes **1.2d** to **1.2j**.

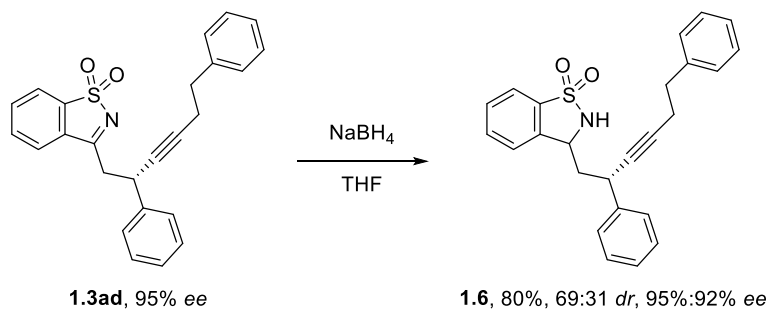
Applicability and Synthetic Transformations

The robustness of the methodology was evaluated by scaling up the reaction to 1.25 mmol. Under these conditions, the conjugate addition of 4-phenyl-1-butyne **1.2d** to saccharin-derived azadiene **1.1a** afforded alkynylation product **1.3ad** in good yield, albeit with a slight erosion of enantiomeric excess (Scheme 1.13).



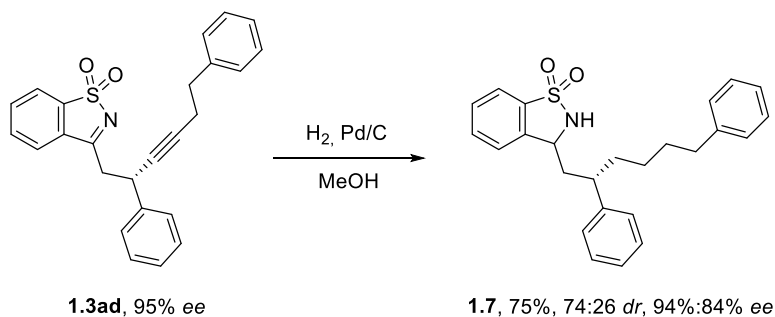
Scheme 1.13-1.25 mmol scale synthesis of alkynylated imine **1.3ad**.

To highlight the synthetic utility of the obtained adduct, compound **1.3ad** was subjected to a series of transformations. to showcase its synthetic versatility. Reduction with sodium borohydride selectively converted the imine into sulfonamide **1.6**, obtained in 80% yield as a 69:31 mixture of diastereomers, without erosion of enantioselectivity (Scheme 1.14).



Scheme 1.14- Synthesis of **1.6** via selective reduction of **1.3ad**.

In contrast, hydrogenation under Pd/C catalysis resulted in complete reduction of both the imine and the alkyne moieties, furnishing sulfonamide **1.7** in 75% yield as a 74:26 mixture of diastereomers, while preserving enantioselectivity in the major diastereomer (Scheme 1.15).



Scheme 1.15- Synthesis of **1.7** via hydrogenation of **1.3ad**.

Determination of the Absolute Configuration of Compounds **1.3**

The absolute configuration of compound **1.3bg** was determined *via* single-crystal X-ray diffraction. Analysis of the resulting crystal structure allowed the assignment of the stereogenic centre configuration as *S*, with a Flack parameter of 0.017(6) (Figure 1.3). The absolute stereochemistry of all compounds **1.3** was assigned based on the assumption of a uniform stereochemical pathway.

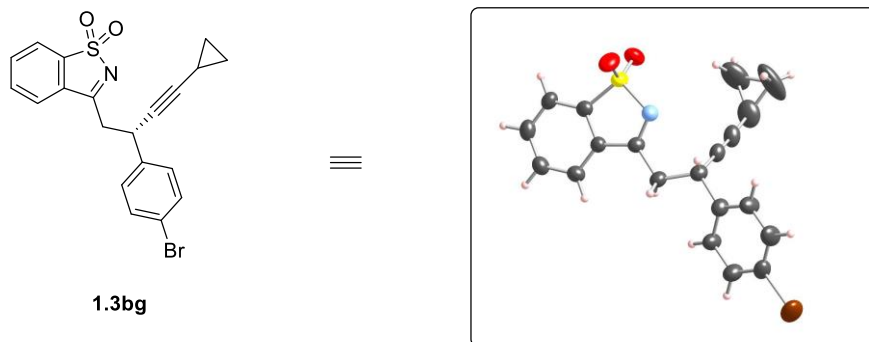


Figure 1.3- Ortep plot for the X-ray structure of compound **1.3bg**. Thermal ellipsoids drawn at the 50% probability level. Flack parameter 0.017(6).

Conclusions

The first asymmetric method for enantioselective zinc-mediated conjugate addition of terminal alkynes to saccharin-derived azadienes has been developed, employing bis(hydroxy)malonamide-derived chiral ligands **L3** and **L4**. This reaction constitutes the first reported example of the enantioselective alkynylation of azadienes.

In light of the results presented in this chapter, it can be concluded that the initially proposed objectives have been successfully achieved:

1. The required saccharin-derived azadienes **1.1**, bearing substituents with different electronic and steric properties, were synthesised in moderate yields.
2. The reaction conditions for the enantioselective alkynylation of azadienes **1.1** have been optimized as follows: bis(hydroxy)malonamide-derived chiral ligand **L4**, toluene as solvent, 4 equivalents of diethylzinc, and 5 equivalents of alkyne **1.2** at room temperature. For aliphatic alkynes, superior results were obtained with chiral ligand **L3** in combination with a reduced amount of diethylzinc (2 equivalents).
3. The addition of aryl-substituted alkynes **1.2a** to **1.2c** to saccharin-derived azadienes **1.1** was found to be sensitive to structural variations at the β -aryl substituent of the double bond, affording adducts **1.3** in moderate to low yields and modest enantioselectivities. Conversely, the use of alkyl-substituted alkynes **1.2d–1.2g** led to improved yields and higher enantioselectivities. Notably, in contrast to the behaviour observed with phenylacetylene, substitution on the azadiene scaffold was well tolerated, delivering adducts in moderate to good yields and excellent enantioselectivities in all cases. Furthermore, functionalized alkynes bearing ester and ether groups also participated successfully in the transformation.
4. The applicability of this methodology was confirmed on a 1.25 mmol scale, affording compound **1.3ad** in good yield (56%) and high enantioselectivity (88% ee). Transformations of **1.3ad** enabled access to sulfonamides featuring either an alkyne or an aliphatic moiety, depending on the reduction conditions employed. In both cases, sulfonamides **1.6** and **1.7** were obtained in high yields as a mixture of diastereomers, with full retention of enantiomeric excess in the major diastereomer.
5. The absolute configuration of the stereogenic centre was determined as *S* via single-crystal X-ray diffraction.

Part II

Asymmetric *sulfa*-Michael Addition of Sodium Bisulfite to α,β -Unsaturated Systems: Synthesis of Chiral Sulfonic Acids

Introduction: Chiral Sulfonic Acids

Sulfonic acids, especially those with optical activity, are highly relevant organosulfur compounds, as they are found in numerous natural products and pharmacologically active substances. They participate in a variety of biological processes, have been used as chiral resolving agents, and serve as valuable building blocks for the synthesis of derivatives such as sulfonamides and sulfonate esters, both of which are of considerable interest in medicinal chemistry. Representative examples include 6-gingesulfonic acid, a natural product extracted from the roots of ginger (*Zingiber officinale*) with anti-ulcer activity;^[102] pharmaceuticals, such as the antibiotic sulfobenzylpenicillin;^[103] taurine, an amino sulfonic acid found in most mammalian tissues that plays key roles in osmoregulation, immunomodulation, bile salt formation, and various metabolic processes;^[104] or camphorsulfonic acid and 1-phenylethanesulfonic acid, used as chiral resolving agents (Figure 2.1).^{[105],[106]}

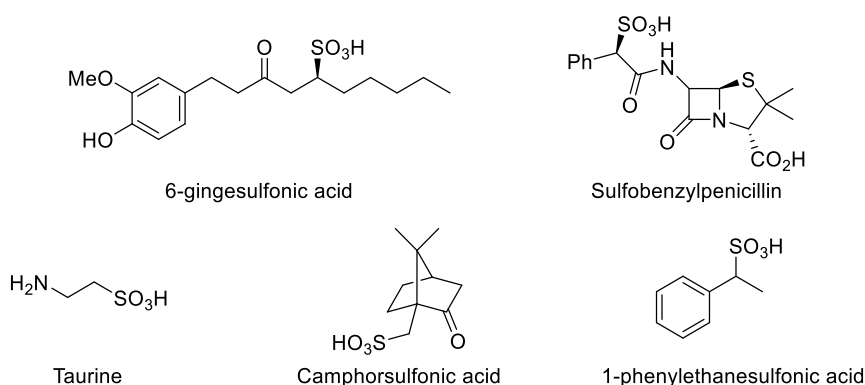
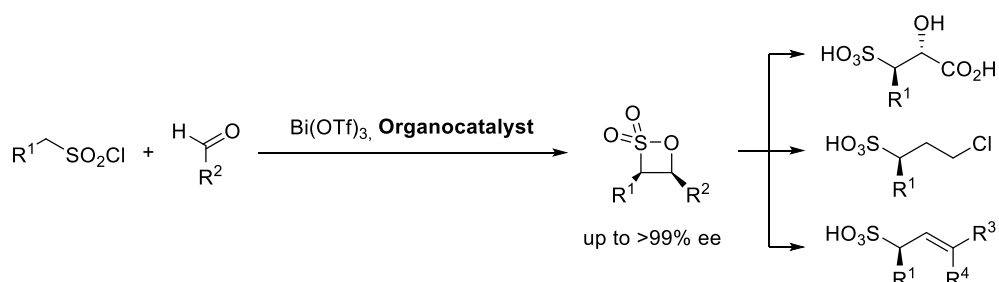
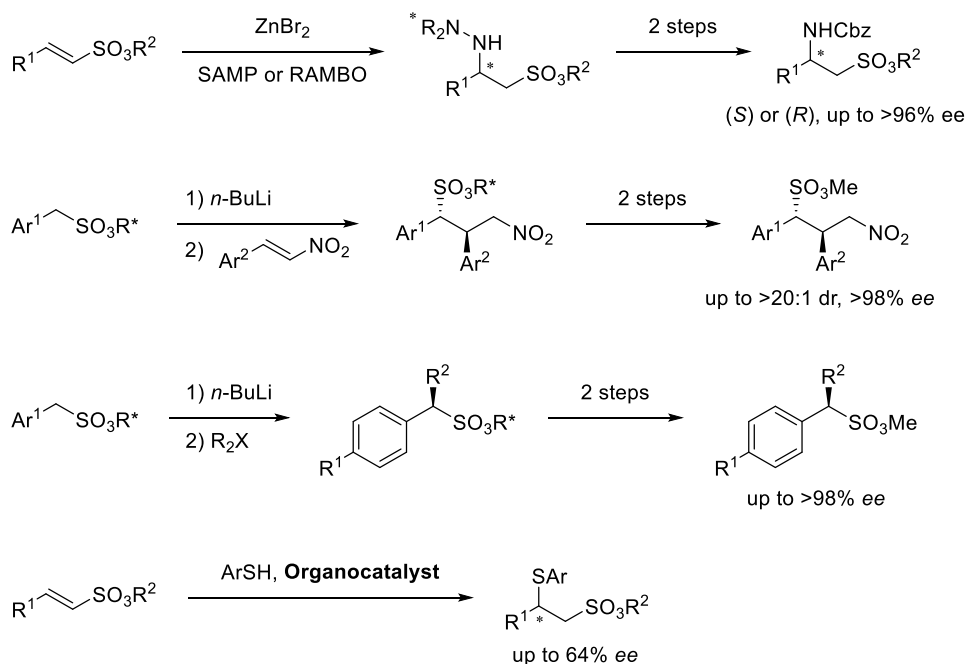


Figure 2.1- Illustrative examples of relevant sulfonic acids

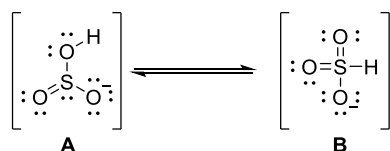
Therefore, different strategies have been reported for the enantioselective synthesis of chiral sulfonic acids and their derivatives. In earlier approaches, these compounds were obtained in enantiomerically pure form either through the resolution of racemic mixtures^[107] or *via* multistep asymmetric synthesis. Representative examples include the enantioselective synthesis of sulfonates developed by Enders *via* conjugate addition of chiral nucleophiles,^[108] the use of chiral auxiliaries^{[109]–[111]}, or enantioselective organocatalytic *sulfa*-Michael additions^[112] (Scheme 2.1, A); or the method reported by Peters for the asymmetric catalytic synthesis of β -sultones and their subsequent ring opening to yield various chiral sulfonic acids (Scheme 2.1, B).^[113]



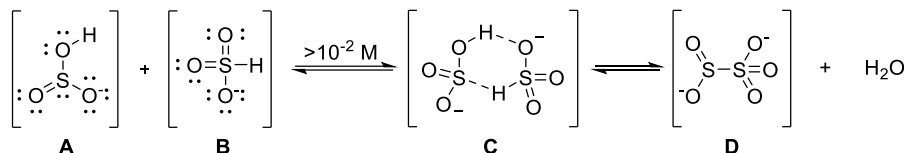
Scheme 2.1.- Multistep strategies for the enantioselective synthesis of sulfonic acids.

However, the most straightforward method for obtaining these compounds is the enantioselective addition of sodium bisulfite to unsaturated systems. Sodium bisulfite is an inexpensive and commercially available reagent whose addition to unsaturated substrates has been known since the late 19th century.^[114] Nevertheless, these reactions often required harsh conditions, namely, large excesses of sodium bisulfite, elevated temperatures, and high pressures.^[115] These severe conditions can be rationalized by considering the behaviour of the bisulfite ion in aqueous solution (Scheme 2.2).

a) pH-dependent equilibrium



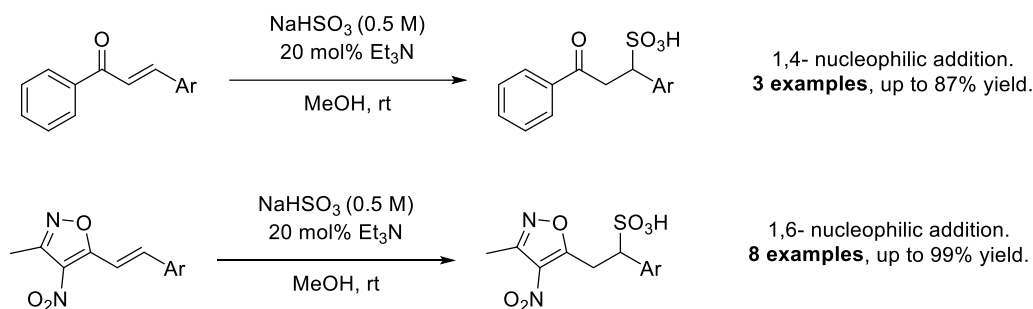
b) Concentration-dependent equilibria:



Scheme 2.2- Bisulfite equilibria in aqueous solution.

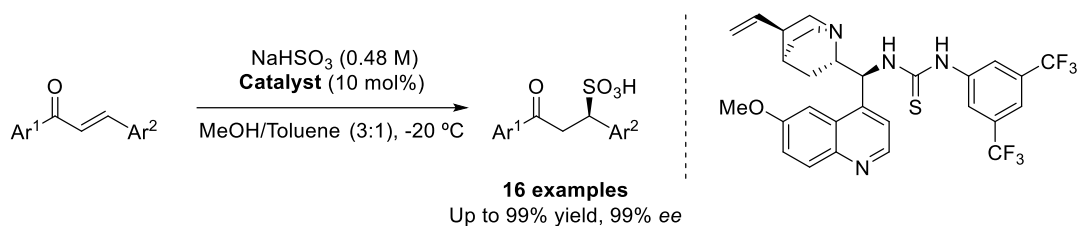
Bisulfite ion exists in equilibrium between two forms: species **A**, which is nucleophilic, and species **B**, which can be considered unreactive. This equilibrium, analogous to phosphonate–phosphite tautomerism, is pH-dependent and shifts toward the nucleophilic form **A** in the presence of base.^[116] Additionally, species **A** and **B** form at concentrations above 10^{-2} M a non-reactive dimer, species **C**, which in turn is in equilibrium with metabisulfite ion, **D**.^[117]

Based on this behaviour, in 2010 Adamo *et al.* hypothesized that, in order to successfully achieve the addition of bisulfite to electrophilic olefins, the concentration of the reactive species **A** must be maximized. To this end, they carried out the reaction at room temperature, in the presence of a catalytic organic base, and under low concentrations of sodium bisulfite. These mild reaction conditions enabled the efficient synthesis of various sulfonic acids derived from chalcones and styryl nitroisoxazoles with excellent yields (Scheme 2.3).^[118]



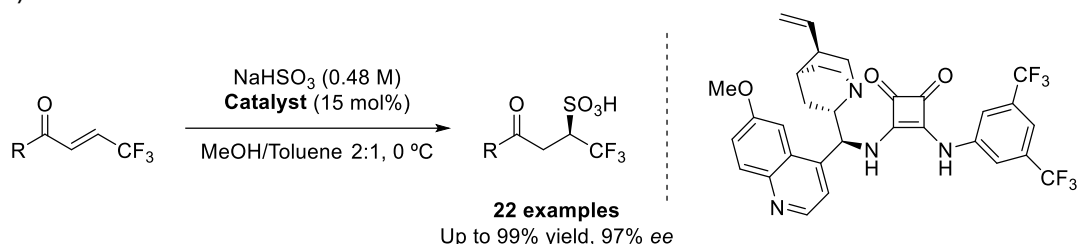
Scheme 2.3- Racemic NaHSO₃ addition to electrophilic double bonds catalysed by Et₃N.

One year later, building on the previous strategy, Adamo reported the first example of the enantioselective catalytic synthesis of chiral sulfonic acids *via* sodium bisulfite addition to chalcones, marking the first single-step synthesis of such compounds described in the literature. This methodology, catalysed by bifunctional thioureas derived from quinine, enabled the preparation of β-carbonyl sulfonic acids in excellent yields and enantioselectivities (Scheme 2.4).^[119] The same synthetic approach was also successfully extended to the synthesis of naturally occurring gingesulfonic acids.^[120]



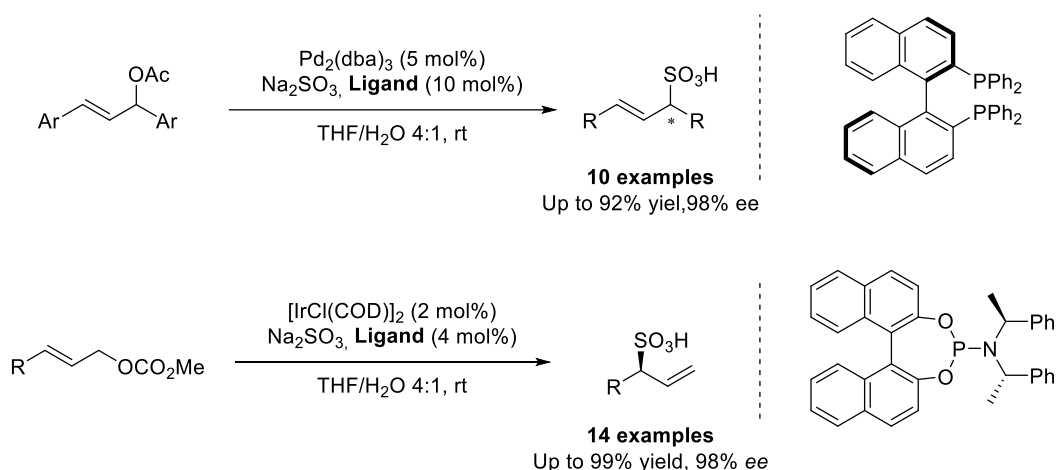
Scheme 2.4- Organocatalytic enantioselective addition of NaHSO₃ to chalcones.

Later, in 2018, Xu and Yuan successfully applied this methodology to the enantioselective synthesis of sulfonic acids derived from β -trifluoromethyl- α,β -unsaturated ketones. In this case, the reaction was catalysed by bifunctional squaramides derived from cinchona alkaloids and afforded excellent results in both yield and enantiomeric excess (Scheme 2.5).^[121]



Scheme 2.5.- Organocatalytic synthesis of chiral β -carbonyl sulfonic acids bearing a CF₃ group.

Alternatively, in 2014 Zhao and his group reported the enantioselective sulfonation of allylic acetates and carbonates with sodium sulfite using metal catalysis based on iridium and palladium chiral complexes. This strategy enabled the synthesis of the corresponding chiral allylic sulfonic acids with mixed yields and high enantiomeric excesses (Scheme 2.6).^{[122],[123]}



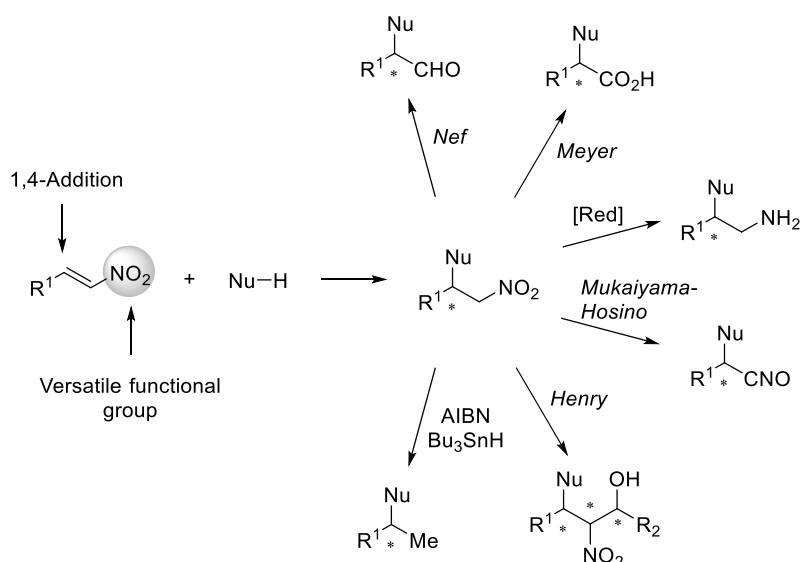
Scheme 2.6- Metal-catalysed sulfonation of allylic acetates and carbonates.

Despite the promising results reported in these studies, examples for the enantioselective addition of sodium bisulfite to electron-deficient olefins remain limited. Therefore, the identification of new electrophiles and catalytic systems capable of expanding the reaction scope is of significant interest. In the following chapters, the development of new organocatalytic asymmetric additions of sodium bisulfite to nitrostyrenes and 1-azadienes is reported.

Chapter 2. Organocatalytic Enantioselective *sulfa*-Michael Addition of Sodium Bisulfite to Nitroalkenes

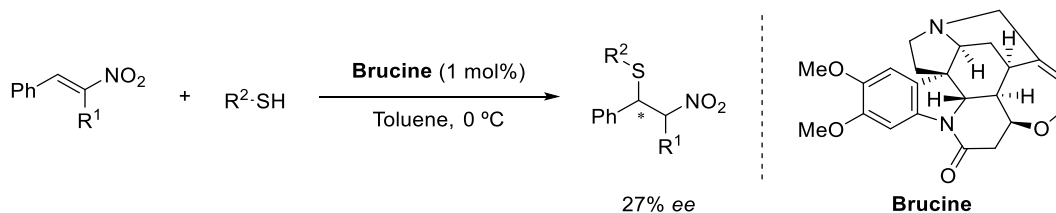
Introduction

The Michael reaction involves the 1,4-nucleophilic addition of nucleophiles to electron-deficient α,β -unsaturated systems. Since β -substituted- α,β -unsaturated systems are prochiral compounds, they have been widely employed in asymmetric synthesis for the enantioselective formation of C–C and C–X bonds (X = O, N, P, S).^[124] Among the various Michael acceptors reported, nitroalkenes stand out due to their high reactivity, caused by the strong electron-withdrawing effect of the nitro group, as well as the remarkable versatility of this functional group, which enables a broad range of synthetic transformations on the resulting adducts, affording a diverse array of enantioenriched derivatives (Scheme 2.7).^{[125]–[127]} Of particular note is the possibility of accessing chiral amines, which are of great importance to the chemical industry, especially in the fields of agrochemistry and pharmaceutical chemistry, where they are found in approximately 40% of active ingredients.^[128]



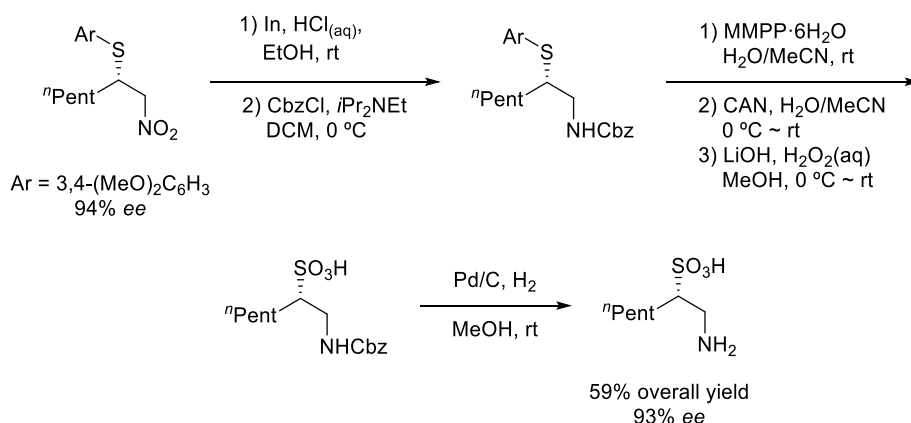
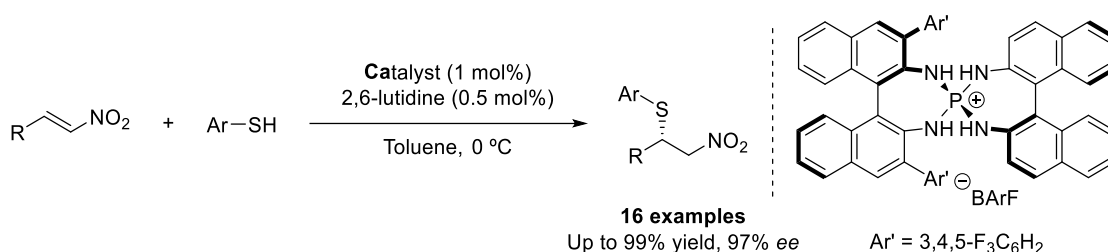
Scheme 2.7- Nitroalkenes in Michael reactions and their features.

Regarding enantioselective *sulfa*-Michael reactions with nitroalkenes, nucleophiles such as thiols and thioacids have been successfully employed, although few examples have been reported in the literature. The first of these was described by Pracejus in 1977, in which the enantioselective addition of *tert*-butylthiol to β -nitrostyrenes was studied. The reaction was catalysed by the alkaloid brucine, but the addition products were obtained with low enantioselectivity (Scheme 2.8).^[129]



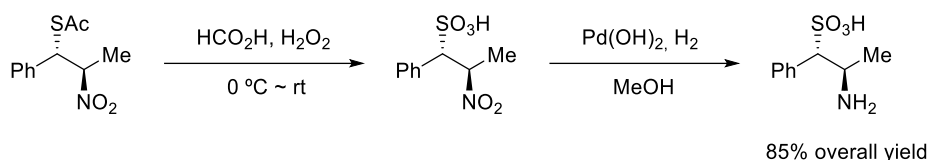
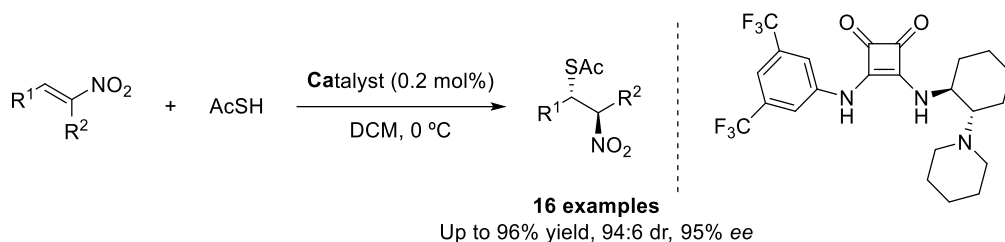
Scheme 2.8- First reported example of an asymmetric *sulfa*-Michael reaction.

Among the reported examples, the works of Ooi, Yang and Du are particularly noteworthy. In 2012, Ooi et al. developed the enantioselective catalytic synthesis of β -nitro sulfides *via* chiral ionic Brønsted acid–achiral Brønsted base synergistic catalysis. The asymmetric addition of arylthiols to both aliphatic and aromatic nitroalkenes proceeded with low catalyst loadings, affording excellent yields and enantioselectivities. Furthermore, the resulting β -nitro sulfides were converted, through a three-step synthesis, into chiral 1,2-amino sulfonic acids (Scheme 2.9).^[130]



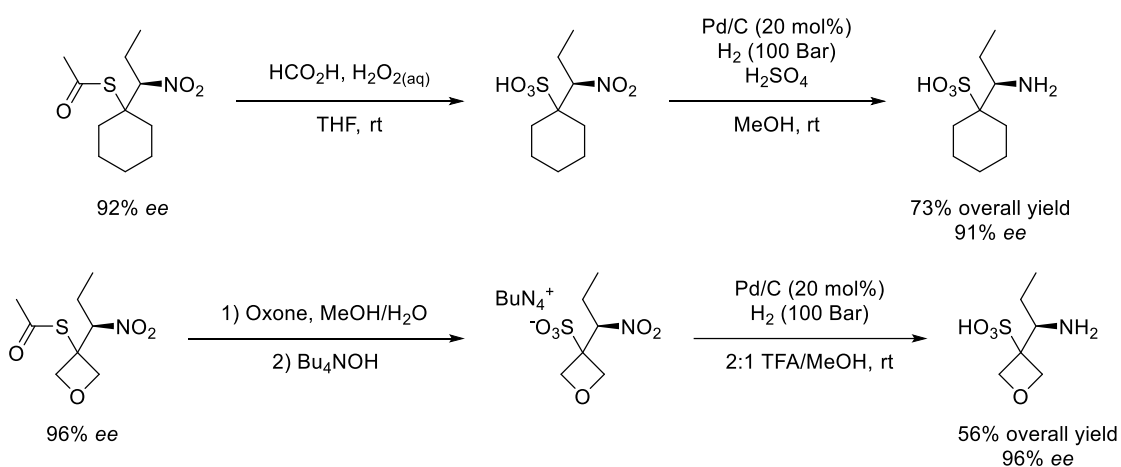
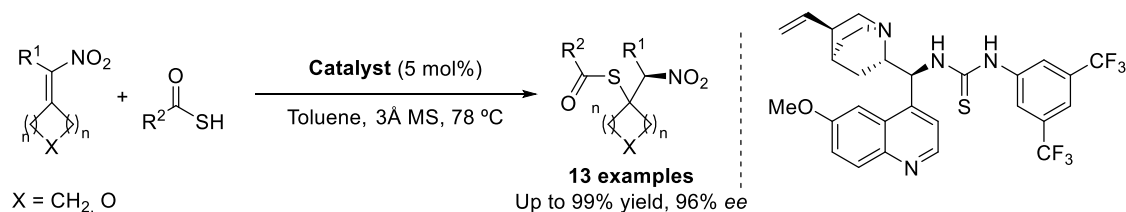
Scheme 2.9- Enantioselective synthesis of β -nitro sulfides and their oxidation to 1,2-amino sulfonic acids.

Simultaneously, Yang and Du described the enantio- and diastereoselective conjugate addition of thioacetic acid to α,β -disubstituted nitroalkenes. The reaction proceeded with a very low catalyst loading using a bifunctional squaramide derived from 1,2-cyclohexanediamine, affording the corresponding β -nitro thioesters in good yields, with high enantiomeric excesses and diastereoselectivities. These β -nitro thioesters were subsequently transformed, in a two-step sequence, into disubstituted 1,2-amino sulfonic acids (Scheme 2.10).^[131]



Scheme 2.10- Asymmetric synthesis of β-nitrothioesters and their transformation to disubstituted 1,2-amino sulfonic acids.

Finally, in 2014, Ellman and his group reported the enantioselective catalytic addition of thioacids to trisubstituted nitroalkenes. The asymmetric addition of thioacetic acid and thiobenzoic acid to nitroalkenes derived from oxetane, azetidine, cyclohexane, and oxane was catalysed by a bifunctional thiourea derived from quinine, leading to the formation of the corresponding β-nitro thioesters with excellent yields and enantioselectivities. The resulting thioesters were further transformed in a two-step sequence into 1,1,2-trisubstituted 1,2-amino sulfonic acids. However, the reduction step required harsh acidic and high-pressure conditions, likely due to the significant steric hindrance of the substrates (Scheme 2.11).^[132]



Scheme 2.11- Enantioselective synthesis of chiral cyclic β-nitro thioesters and their oxidation to trisubstituted 1,2-amino sulfonic acids.

These selected examples illustrate how asymmetric *sulfa*-Michael reactions on nitroalkenes can provide access to chiral amino sulfonic acid precursors. These amino acids are of significant interest, as they are found in natural products and used in drug discovery, catalyst and chiral auxiliary design, materials science, sensors and imaging agents, among other applications (Figure 2.2).^[133] However, the preparation of such compounds typically requires multistep routes following the initial asymmetric transformation. In this context, the direct asymmetric organocatalytic addition of sodium bisulfite to nitroalkenes is particularly appealing, as it enables the efficient synthesis of chiral β -nitrosulfonic acids, which can be converted into amino sulfonic acids through a single reduction step. Motivated by these considerations, this chapter explores the *sulfa*-Michael reaction between sodium bisulfite and *trans*- β -nitrostyrenes under organocatalytic conditions.

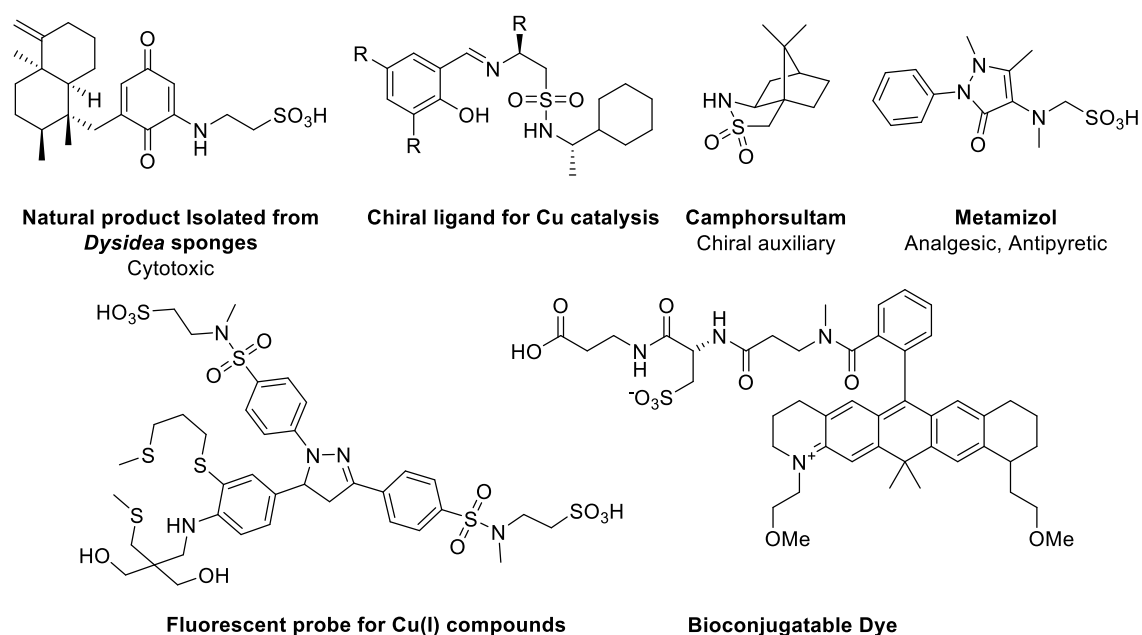
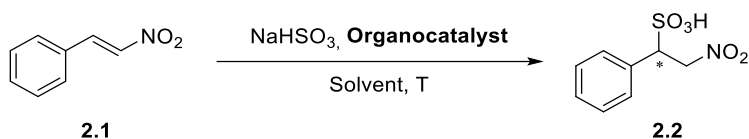


Figure 2.2- Applications of amino sulfonic acids.

Objectives

The main objective for this chapter is to develop an enantioselective organocatalytic methodology for the addition of sodium bisulfite to *trans*- β -nitrostyrenes **2.1**.



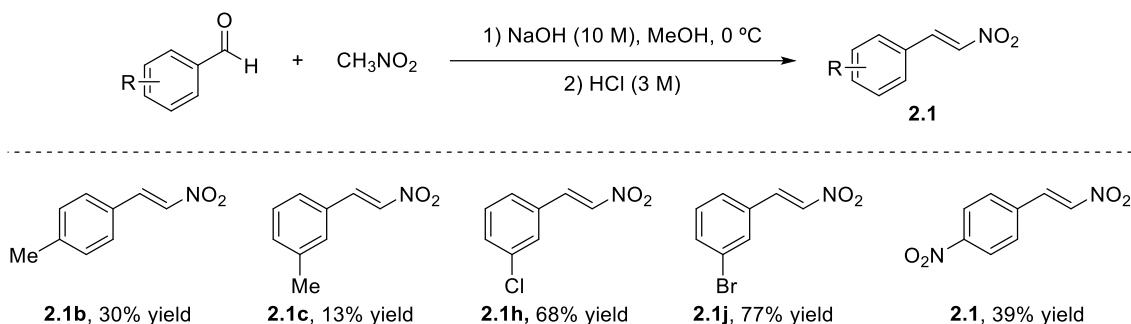
To this end, the following secondary objectives have been proposed:

1. Synthesis of the required starting materials **2.1**, bearing substituents with different electronic and steric properties.
2. Optimization of the reaction conditions between sodium bisulfite and β -nitrostyrene **2.1a** to obtain the corresponding nitrosulfonic acid **2.2a** with the highest yield and enantioselectivity.
3. Study of the scope of the reaction between sodium bisulfite and aromatic, aliphatic and heterocyclic β -nitroalkenes **2.1**.
4. Applicability and synthetic transformations over the reaction products.

Results and Discussion

Synthesis of *trans*- β -nitrostyrenes **2.1**

The required *trans*- β -nitrostyrenes **2.1** were prepared following a literature procedure reported by Crousse in 2018 (Scheme 2.12).^[134] In the first step, the corresponding aromatic aldehyde and nitromethane underwent a Henry reaction in the presence of sodium hydroxide, affording the β -nitroalcohol. This intermediate was then dehydrated under acidic conditions to give the corresponding *trans*- β -nitrostyrenes **2.1**.

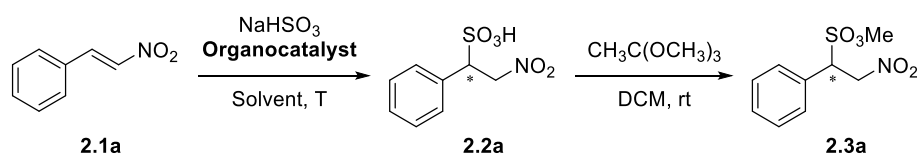


Scheme 2.12- General synthetic procedure for the synthesis of *trans*- β -nitrostyrenes **2.1**.

Most of the *trans*- β -nitrostyrenes **2.1** used in this chapter are either commercially available or had been previously prepared within the research group, therefore only products **2.1b**, **2.1c**, **2.1h**, **2.1j**, **2.1l** were synthesised. All spectroscopic data for *trans*- β -nitrostyrenes were in accordance with literature.

Optimization of the Reaction Conditions

To study the enantioselective organocatalytic addition of sodium bisulfite to *trans*- β -nitrostyrenes **2.1**, compound **2.1a** was selected as a model substrate to optimize the reaction conditions. Due to the high polarity of the resulting β -nitrosulfonic acids **2.2**, derivatization was required to determine their enantiomeric excess *via* chiral HPLC analysis. To this end, sulfonic esters **2.3** were synthesized following a reported procedure,^[121] by treatment of the corresponding β -nitrosulfonic acids with trimethyl orthoacetate (Scheme 2.13).

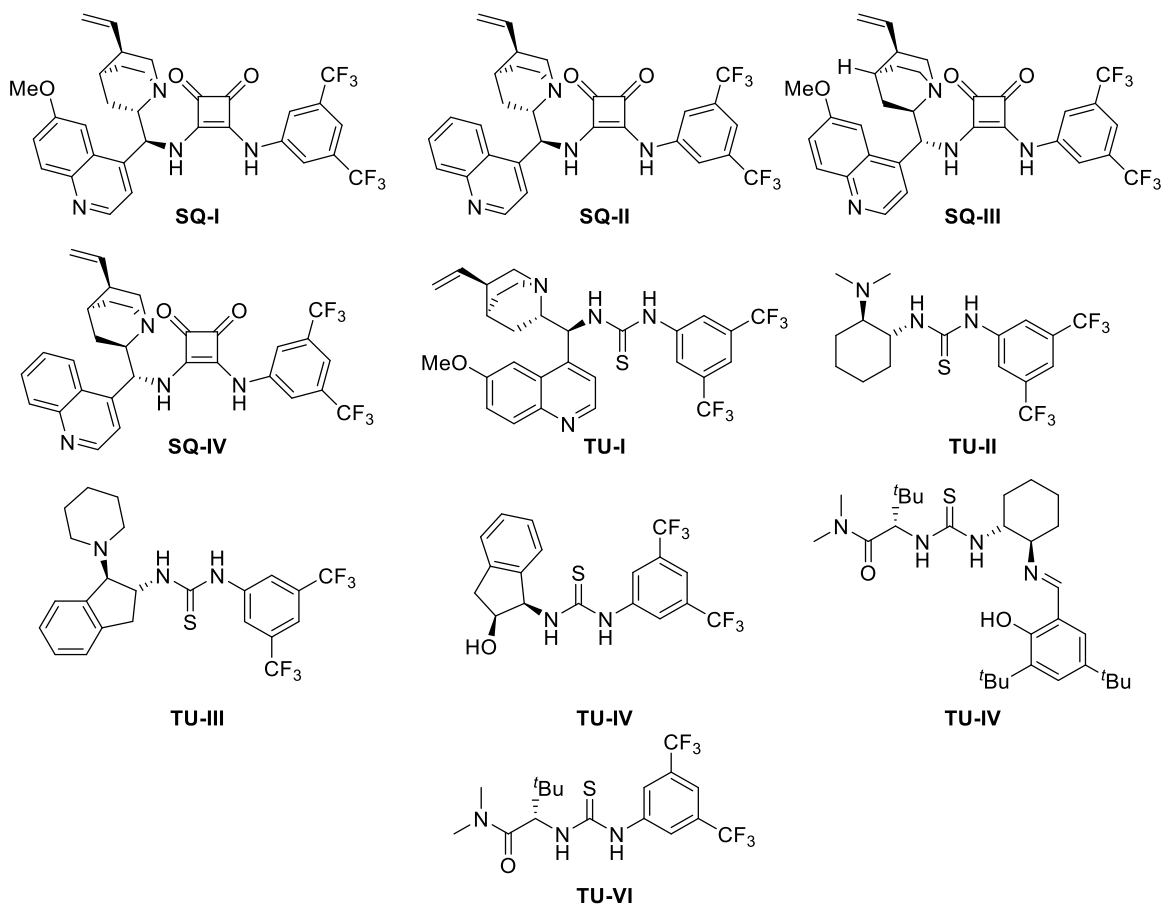
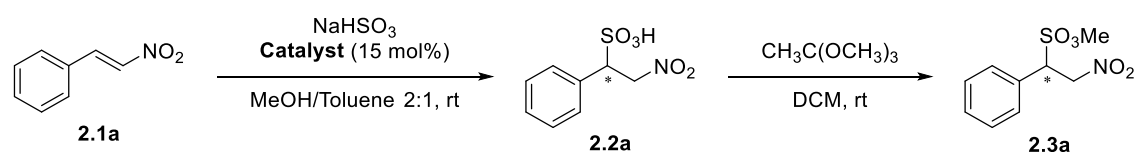


Scheme 2.13-Model reaction selected for the optimization process.

Based on the conditions described by Adamo,^[119] we started our investigation by performing a preliminary catalyst screening. To our delight, all the catalysts employed efficiently promoted the reaction, resulting in complete conversion of the starting material (Table 2.1).

Initially, squaramides **SQ-I** and **SQ-II** derived from *cinchona* alkaloids were tested, observing limited enantiomeric excess for the quinine-derived catalyst and a complete lack of enantioselectivity for its cinchonidine analogue (Table 2.1, entries 1 and 2). A similar but less pronounced effect was registered when pseudoenantiomeric catalysts **SQ-III** and **SQ-IV** were employed, but both failed to improve the outcome of the reaction (Table 2.1, entries 3 and 4).

Table 2.1-Preliminary catalyst screening for the addition of NaHSO₃ to trans-β-nitrostyrene **2.1a**.



Entry ^a	Catalyst	ee 2.3a (%) ^b
1	SQ-I	20
2	SQ-II	4
3	SQ-III	16
4	SQ-IV	14
5	TU-I	20
6	TU-II	30
7	TU-III	4
8	TU-IV	0
9	TU-V	0
10	TU-VI	2

^aReaction conditions: **2.1a** (0.2 mmol), NaHSO₃ (0.48 mmol in 0.5mL of H₂O) and **Cat.** (15 mol%) in MeOH/Toluene (2 mL, v/v, 2:1) at rt overnight. Full conversion of **2.1a** was assessed by TLC.

^bMeasured using chiral HPLC.

Considering these results, we proceeded to evaluate thiourea-based organocatalysts. We first tested the quinine-derived thiourea **TU-I**, which matched the best outcomes obtained up to that point. In addition, Takemoto's thiourea **TU-II** was also examined,^[135] yielding the best result (Table 2.1, entries 5 and 6). Encouraged by this finding, we investigated a series

of thioureas bearing different chiral moieties, but none of them provided any enantioselectivity (Table 2.1, entries 7 to 10).

After identifying the most promising catalyst, we next examined the effect of temperature on the reaction outcome (Table 2.2). When thiourea **TU-II** was used as the catalyst at -20 °C we were pleased to observe an increase of the enantiomeric excess to a 58% ee while retaining full conversion (Table 2.2, entry 2). However, lowering the temperature further resulted in diminished enantioselectivity (Table 2.2, entry 3).

Table 2.2- Study of the effect of the temperature.

Entry ^a	T (°C)	ee 2.3a (%) ^b
1	rt	30
2	-20	58
3	-40	48

^aReaction conditions: **2.1a** (0.2 mmol), NaHSO₃ (0.48 mmol in 0.5mL of H₂O) and cat. **TU-II** (15 mol%) in MeOH/Toluene (2 mL, v/v, 2:1) overnight. Full conversion of **2.1a** was assessed by TLC. ^bMeasured using chiral HPLC.

At this stage, in order to further improve the enantioselectivity, a second catalyst screening was performed at -20 °C, focusing on catalysts derived from 1,2-cyclohexanediamine (Figure 2.3).

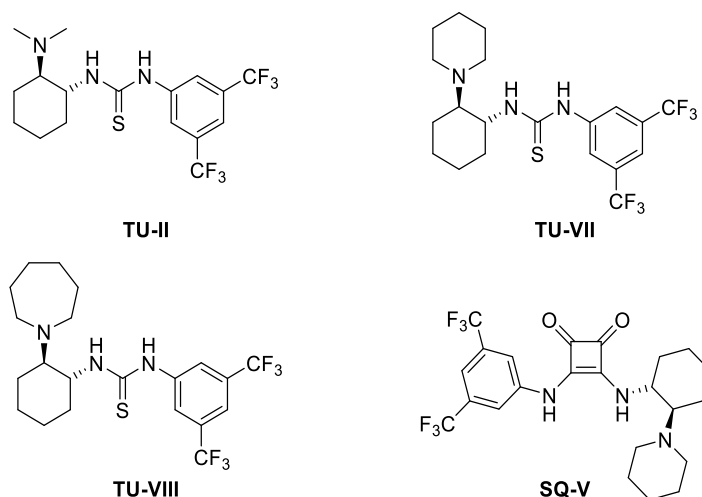


Figure 2.3- Organocatalysts examined in the second round of catalyst evaluation.

Inspired by Rawal's squaramide,^[136] thiourea **TU-VII** and squaramide **SQ-V** were evaluated, observing a significant increase in enantiomeric excess in both cases (Table 2.3, entries 2 and 3). Since thiourea **TU-VII** performed slightly better, thiourea **TU-VIII** was tested, which features an azepane ring in its structure instead of a piperidine moiety. This catalyst did not lead to an improvement in enantioselectivity (Table 2.3, entry 4), and thiourea **TU-VII** was therefore selected as the optimal catalyst for the reaction.

Table 2.3- Second catalyst screening and evaluation of co- solvent effect.

Entry ^a	Catalyst	Co-solvent	Conversion 2.1a (%) ^b	ee 2.3a (%) ^c
1	TU-II	Toluene	Full	58
2	TU-VII	Toluene	Full	88
3	SQ-V	Toluene	Full	84
4	TU-VIII	Toluene	Full	78
5	TU-VII	<i>p</i> -xylene	Full	78
6	TU-VII	<i>o</i> -xylene	Full (98% ^d)	92
7	TU-VII	Chlorobenzene	Full	91

^aReaction conditions: **2.1a** (0.2 mmol), NaHSO₃ (0.48 mmol in 0.5mL of H₂O) and **Cat.** (15 mol%) in MeOH/Co-solvent (2 mL, v/v, 2:1) at -20 °C overnight. ^bDetermined by TLC. ^cMeasured using chiral HPLC. ^dIsolated yield of **2.2a**.

Lastly, the effect of the solvent mixture over the model reaction was studied (Table 2.3, entries 5 to 7). Two families of co-solvents were examined, xylenes and chlorinated aromatic solvents. Regarding the xylenes, the use of *p*-xylene led to a significant reduction in the enantioselectivity (Table 2.5, entry 5, 78% ee). Surprisingly, the opposite effect was observed when *o*-xylene was employed (Table 2.3, entry 6), affording compound **2.2a** with a 92% enantiomeric excess. Finally, chlorobenzene did not improve the enantioselectivity (Table 2.3, entry 7, 91% ee) and *o*-xylene was thus selected as the optimal co-solvent.

In conclusion, the optimal reaction conditions for the model reaction between sodium bisulfite and *trans*- β -nitrostyrene **2.1a** are as follows: 1,2-cyclohexanediamine-derived thiourea **TU-VII** at 15 mol% loading as the catalyst, in a 2:1 (v/v) mixture of MeOH/*o*-xylene as solvent, using 2.4 equivalents of sodium bisulfite at -20 °C.

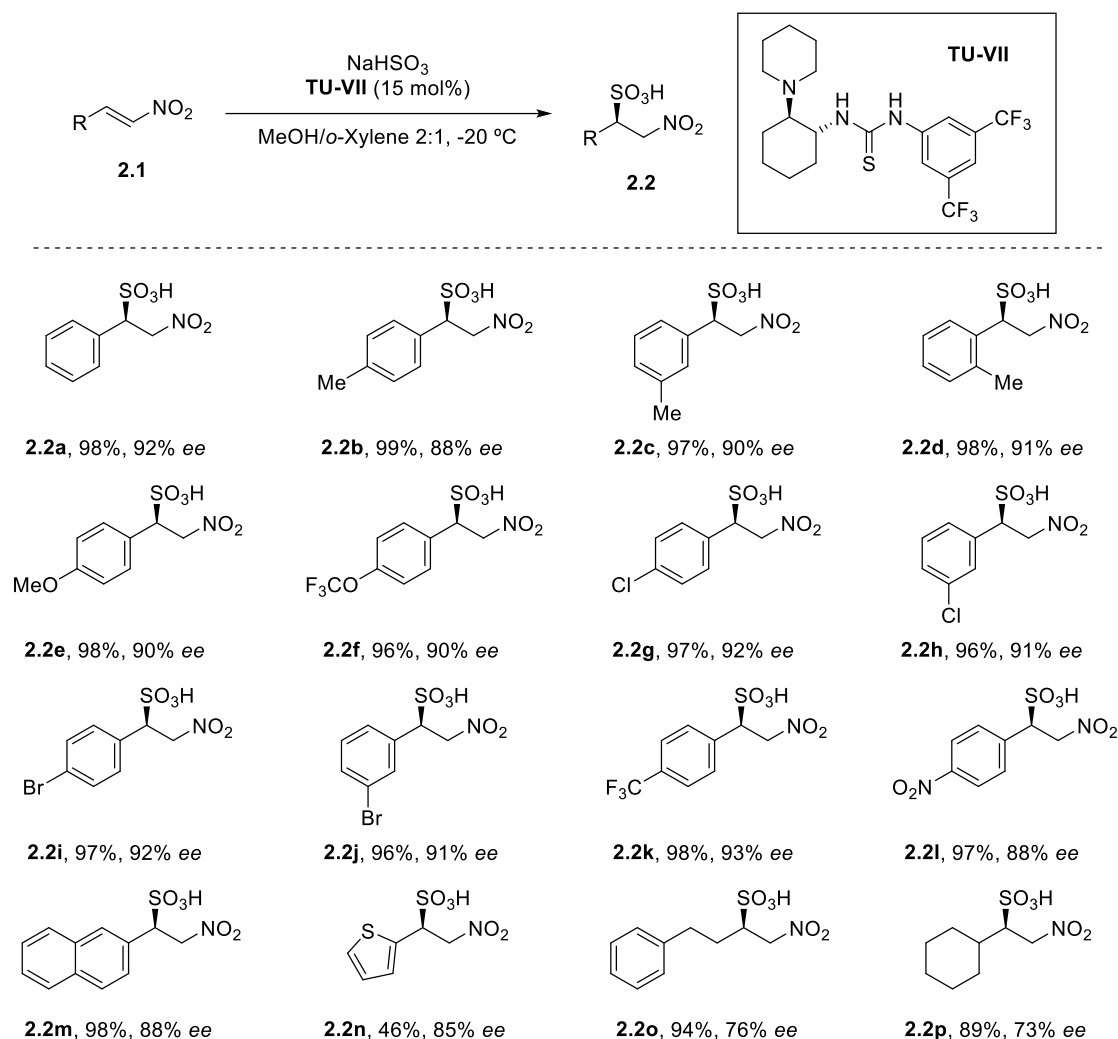
Scope of the Reaction with Different *trans*- β -nitroalkenes

Once the optimal reaction conditions were established, we proceeded to study how different groups or substituents on *trans*- β -nitroalkenes **2.1** affected the outcome of the reaction (Scheme 2.14).

First, *trans*- β -nitrostyrenes bearing electron-donating groups (Me-, MeO-) were tested. In every case, the corresponding β -nitro sulfonic acids were obtained in excellent yields ($\geq 96\%$) and high enantioselectivities (Scheme 2.14, entries **2.2b** to **2.2e**, 88-91% ee). Next, *trans*- β -nitrostyrenes bearing electron-withdrawing substituents (F₃CO-, Cl-, Br-, NO₂-) were investigated, also affording quantitative yields and excellent enantioselectivities (Scheme 2.14, entries **2.2f** to **2.2l**, 88-93% ee). Regarding the substitution pattern of the aromatic ring, the reaction tolerated substituents in the *ortho*-, *meta*-, and *para*- positions without any observable decrease in enantiomeric excess or yield, showing the robustness of this method.

On the other hand, *trans*- β -nitroalkenes bearing other aromatic and heterocyclic substituents such as 2-naphthyl and 2-thienyl groups were examined (Scheme 2.14, entries **2.2m** and **2.2n**). In both cases high enantioselectivities were achieved, although moderate yield was observed for **2.2n** (46% yield).

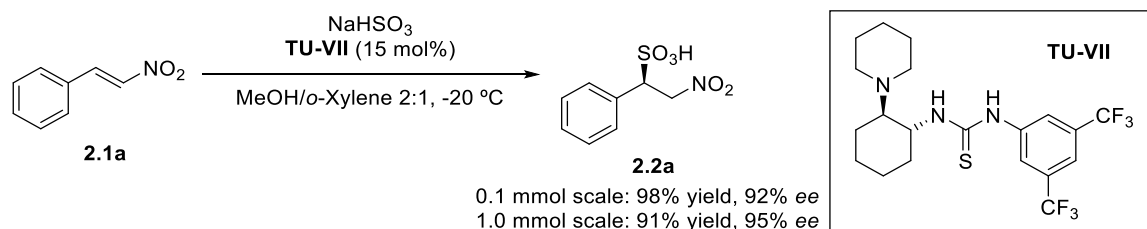
Finally, this methodology could also be applied to aliphatic *trans*- β -nitroalkenes, as demonstrated with entries **2.2o** and **2.2p**, where good results were achieved albeit with a minor enantioselectivity decrease (76% ee and 73% ee, respectively).



Scheme 2.14- Study of the scope of the reaction with various *trans*- β -nitroalkenes. Enantiomeric excesses were determined by chiral HPLC on sulfonic esters **2.3**.

Applicability and Synthetic Transformations

The reliability of the procedure was further confirmed by preparing compound **2.2a** in a 1 mmol scale. Under these conditions, the addition of sodium bisulfite to *trans*- β -nitrostyrene **2.1a** yielded an excellent enantiomeric excess (95%) in a 91% yield (Scheme 2.15).

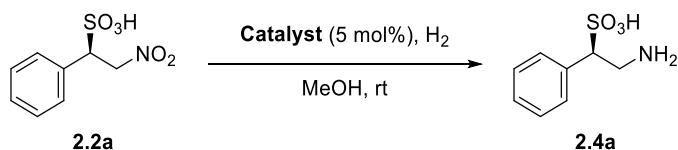


Scheme 2.15- 1 mmol scale synthesis of nitrosulfonic acid **2.2a**.

Regarding the synthetic transformations of compounds **2.2**, the reduction of the nitro group was attempted. Following reported examples in the literature,^[131] a hydrogenation reaction

was selected as a straightforward and simple methodology to obtain the corresponding taurine-derivative **2.4** (Table 2.4).

Table 2.4- Hydrogenation conditions for reduction of 1,2-nitrsulfonic acids **2.2**.



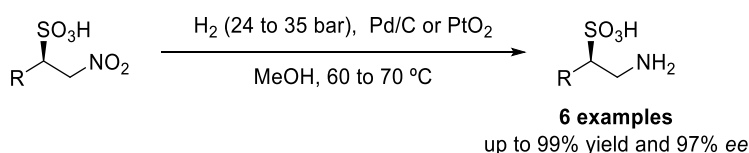
Entry ^a	Catalyst	H ₂ (bar)	t (d)	Conversion 2.2a (%) ^b
1	Pd/C (10% w/w)	1	1	< 5%
2	Pd(OH) ₂ /C, (20% w/w)	1	7	< 5%
3	PtO ₂	1	1	< 5%
4	Pd/C (10% w/w)	4	2	< 5%
5	PtO ₂	5	1	< 5%
6	PtO ₂	10	3	< 5%

^aReaction conditions: **2.2a** (0.1 mmol), H₂ and **Cat.** (5 mol%) in MeOH (1 mL) at room temperature.

^bDetermined by TLC.

Unfortunately, the use of Pd/C (10% w/w), Pd(OH)₂ (20% w/w) or PtO₂ as catalysts at room temperature and 1 bar of H₂ did not yield **2.4a** (Table 2.4, entries 1 to 3). Increasing the pressure of H₂ and reaction time (Table 2.4, entries 4 to 6) also failed to yield the desired 1,2-amino sulfonic acid.

While the manuscript for the publication of this work was being prepared for publication, Bischoff and Brière reported their research about this same reaction.^[137] In their work, they achieved the reduction of compound **2.2a** by hydrogenation using of either Pd/C or PtO₂ at high temperatures and H₂ pressures (Scheme 2.16). These harsh reaction conditions are consistent with our findings, as milder reaction conditions proved ineffective to yield the desired product.



Scheme 2.16- Bischoff and Brière reaction conditions for the reduction of nitrosulfonic acids **2.2**: H₂ (24 bar), Pd/C (10 mol%, 20% w/w), MeOH, 60 °C, 24 h or H₂ 35 bar, 5% PtO₂ (5 mol%), MeOH, 70 °C, 72 h.

Determination of the Absolute Configuration of Compounds **2.3**

The absolute configuration of methyl ester **2.3e**, prepared from nitrosulfonic acid **2.2e**, was determined *via* single-crystal X-ray diffraction. Analysis of the resulting crystal structure allowed the assignment of the stereogenic centre configuration as *R*, with a Flack parameter of 0.09(3) (Figure 2.4). The absolute stereochemistry of all **2.2** compounds was assigned based on the assumption of a uniform stereochemical pathway.

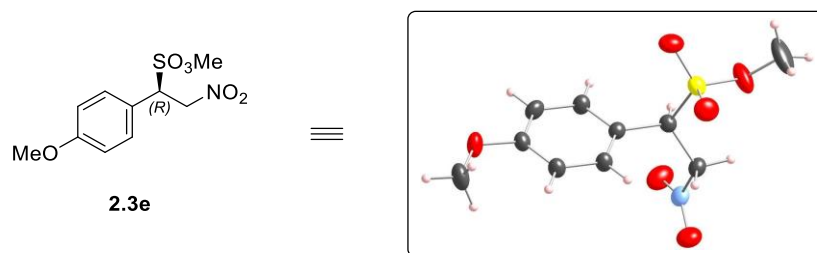
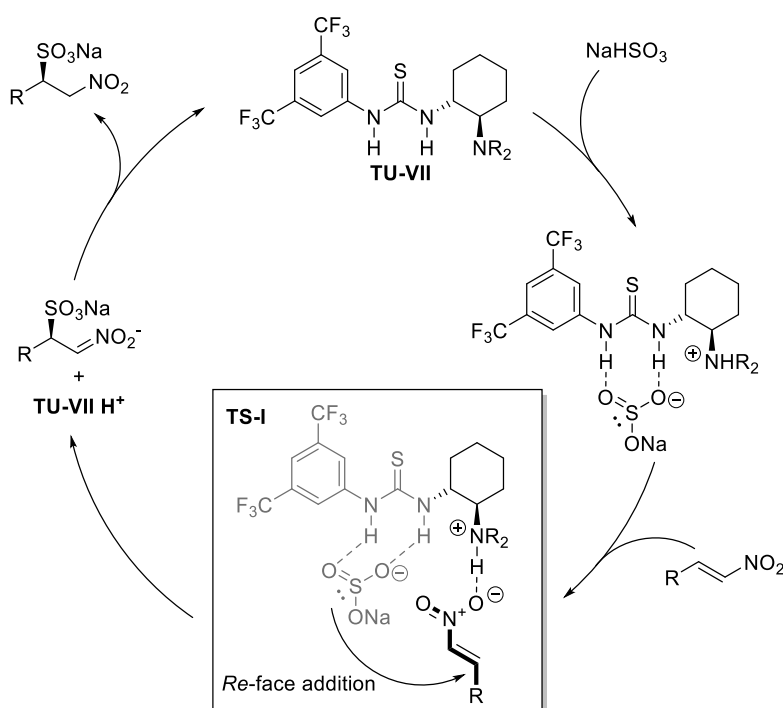


Figure 2.4- Ortep plot for the X-ray structure of compound **2.3e**. Thermal ellipsoids drawn at the 50% probability level. Flack parameter 0.09(3).

Mechanistic Proposal

Based on the theoretical mechanistic studies by Pápai and Hirschi on enantioselective Michael additions to nitroalkenes catalysed by bifunctional thiourea organocatalysts,^{[138],[139]} the *R*-configuration of compounds **2.2** and considering the previously discussed reactivity of sodium bisulfite,^[117] a catalytic cycle and stereochemical model have been proposed for the enantioselective addition of sodium bisulfite to nitroalkenes **2.1** (Scheme 2.17).



Scheme 2.17- Catalytic cycle and stereochemical pathway proposed for the asymmetric addition of sodium bisulfite to nitroalkenes **2.1**.

In the first step, catalyst **TU-VII** deprotonates sodium bisulfite to form an ion pair in which the sulfite anion is complexed through the thiourea moiety. Subsequently, a molecule of *trans*- β -nitroalkene **2.1** coordinates to the catalyst *via* hydrogen bonding between the protonated tertiary amine of the catalyst and the nitro group, orienting the *Re*-face of the alkene towards the nucleophile, as depicted in **TS-I**. The 1,4-addition of the sulfite anion affords the corresponding nitronate bearing the *R* configuration at the stereogenic centre and the protonated catalyst. Finally, a proton transfer yields the sodium *R*-sulfonate and regenerates **TU-VII**.

Conclusions

An enantioselective organocatalytic method has been developed for the 1,4-addition of sodium bisulfite to *trans*- β -nitroalkenes employing thiourea **TU-VII** as a bifunctional organocatalyst.

In view of the results presented in this chapter, it can be concluded that the initially proposed objectives have been successfully achieved:

1. The required *trans*- β -nitrostyrenes (**2.1b**, **2.1c**, **2.1h**, **2.1j** and **2.1l**), bearing substituents with different electronic and steric properties, have been synthesised with low to good yields.
2. The reaction conditions for the enantioselective organocatalytic addition of sodium bisulfite to *trans*- β -nitroalkenes **2.1** have been optimized as follows: thiourea **TU-VII** as the organocatalysts, a 2:1 (v/v) mixture of MeOH/*o*-xylene as solvent, and a reaction temperature of -20 °C. Under this conditions, excellent results have been achieved, regarding both yield (98%) and enantioselectivity (92% ee).
3. The scope of the reaction has been evaluated by analysing the effects of various substituents in *trans*- β -nitroalkenes **2.1**. Excellent results have been obtained in the presence of electron-donating and electron withdrawing-groups, regardless of the substitution pattern on the aromatic ring. Moreover, this methodology has also been successfully extended to aliphatic and heterocyclic nitroalkenes. In general, good to excellent yields (46-99%) and enantioselectivities (73-93% ee) were observed.
4. The applicability of this procedure has been demonstrated by performing the reaction at 1.0 mmol scale, retaining excellent yield (91%) and enantioselectivity (95% ee). The hydrogenation of the nitro group was attempted and, although it was not achieved in our group due to the harsh operational conditions required, a simultaneous publication on this same reaction demonstrated that this transformation is feasible, highlighting the synthetical utility of the chiral 1,2-nitro sulfonic acids **2.2** obtained in this chapter.
5. The absolute configuration of the stereogenic centre was determined as *R* via single-crystal X-ray diffraction. Based on the stereochemical outcome of the reaction and theoretical studies carried on thiourea-catalysed reactions of nitroalkenes, a catalytic cycle and stereochemical pathway consistent with the observed results have been proposed.

Chapter 3. Enantioselective Construction of Tetrasubstituted Stereocentres *via* the Organocatalytic *sulfa*-Michael Addition of Sodium Bisulfite to β,β -Disubstituted Nitroalkenes

Introduction

The construction of tetrasubstituted centres holds paramount importance in organic chemistry, owing to the widespread occurrence of both all-carbon and heteroatom-carbon stereocentres in natural products and pharmaceuticals exhibiting diverse biological activities. Representative examples include the cytotoxic and memory-enhancing Acutumine,^[140] the neuroprotective and GABA receptor modulator Bilobalide,^[141] and the antibacterial and anticancer Crinipellin B (Figure 2.5).^[142] Nevertheless, the enantioselective synthesis of compounds bearing such moieties has long been considered a significant challenge due to their steric hindrance and conformational rigidity.

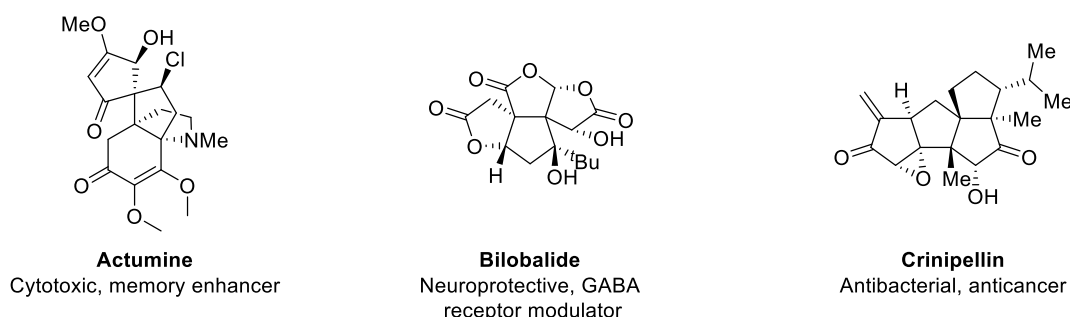


Figure 2.5- Selected bioactive natural products containing tetrasubstituted stereocentres.

Analogously to what was discussed in Chapter II of this thesis, the asymmetric Michael addition of carbon- or heteroatom-based nucleophiles to prochiral β,β -disubstituted α,β -unsaturated nitroalkenes has proven to be an efficient strategy for the synthesis of such compounds.^[143] These Michael acceptors are noteworthy due to their aforementioned versatility, which enables access to a plethora of chiral molecules including chiral amines, highlighted once again here due to their prevalence in pharmaceutical ingredients.^[128]

Regarding the use of sulfur-based nucleophiles, only a few examples of *sulfa*-Michael additions to β,β -disubstituted nitroalkenes have been reported. The most representative cases are presented below, classified according to the electrophile employed.

β -CF₃- β,β -Disubstituted Nitroalkenes as Michael Acceptors

The fluorine atom can be regarded as a bioisostere of hydrogen owing to its relatively small size (van der Waals radius of 1.47 Å), which is comparable to that of hydrogen (1.20 Å). In addition, its strong electron-withdrawing character, together with the higher stability and lipophilicity of C-F bond compared to C-H bond, allows for the substitution of hydrogen with minimal steric perturbation while remarkably modifying the properties of a compound. These changes can result in improved metabolic stability, enhanced binding affinity to target enzymes, and modulation of physicochemical properties such as pK_a, which can in return lead to improved bioavailability due to better membrane permeation.^[144]

Therefore, the introduction of fluorine atoms in bioactive compounds has become a widespread strategy in the development of new pharmaceuticals and agrochemicals. In

fact, fluorinated drugs account for approximately 20-25% of marketed pharmaceuticals, and their prevalence is even greater in agrochemicals, reaching up to 30%.^[145] Examples of fluorinated bioactive compounds include fluoxetine (Prozac), tamoxifen (Faslodex), or broflanilide (Figure 2.6).^{[146]–[148]}

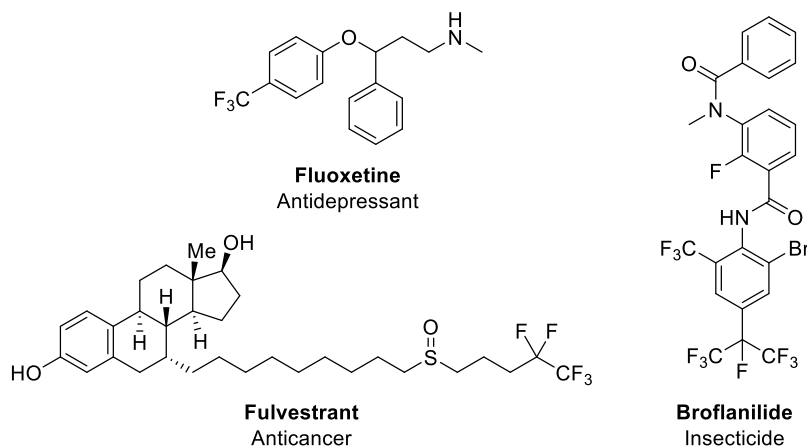
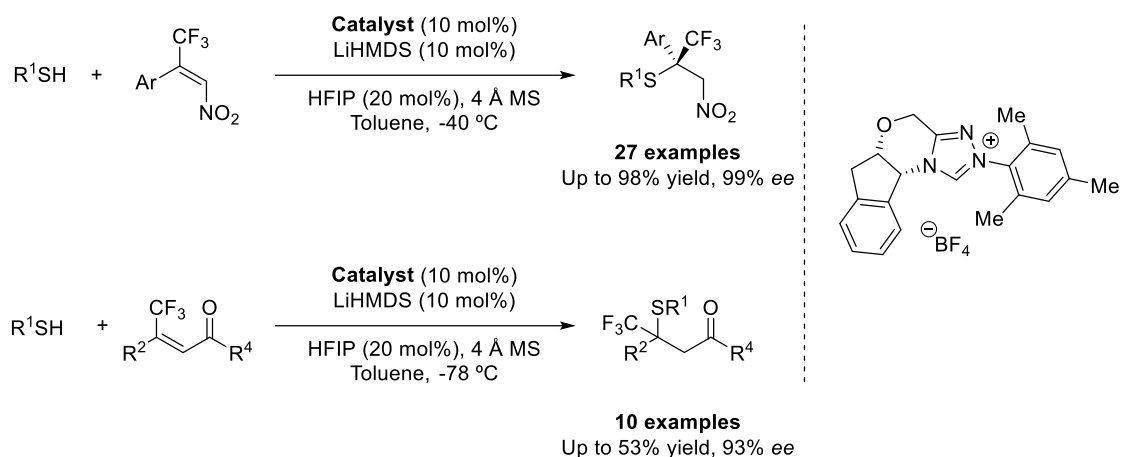


Figure 2.6- Selected examples of fluorine-containing bioactive compounds.

Regarding the synthesis of organofluorine compounds, two main strategies can be applied: the direct fluorination of a compound with nucleophilic, electrophilic or radical reactants, or the use of fluorine-containing building blocks as starting materials. The latter approach accounts for the synthesis of 90% of marketed fluorine-containing drugs.^[149]

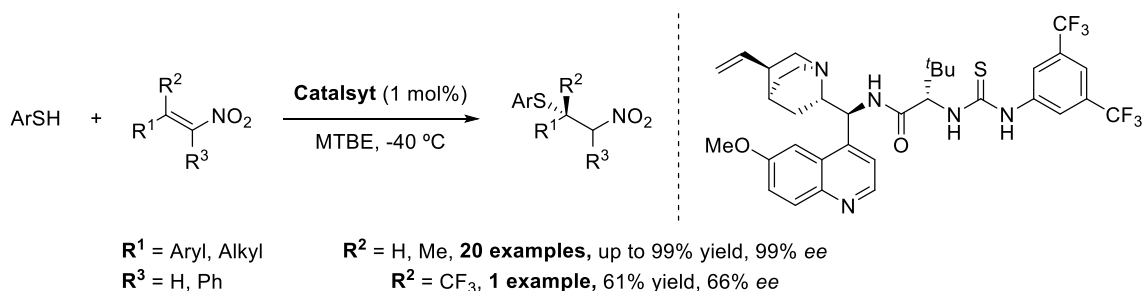
This second strategy has been applied successfully in asymmetric synthesis employing trifluoromethylated prochiral substances. In particular, the use of β -CF₃- β,β -disubstituted nitroalkenes in Michael reactions is especially appealing, as it enables the formation of tetrasubstituted stereocentres bearing a CF₃ group, a motif of growing relevance owing to its frequent occurrence in biologically active molecules as well as in compounds of interest in materials science.^[150] Regarding the use of sulfur-based nucleophiles, only two examples of *sulfa*-Michael reactions involving these substrates have been reported in the literature.

The first example of an asymmetric *sulfa*-Michael reaction involving β -CF₃- β,β -disubstituted nitroalkenes was reported by Huang's group in 2015. The addition of alkyl thiols to a broad range of the aforementioned nitroalkenes was catalysed by triazolium-based chiral *N*-heterocyclic carbene *via* non-covalent catalysis, a rather uncommon catalytic mode for this class of compounds. The corresponding chiral sulfides were obtained in all cases with good to excellent yields and excellent enantioselectivities. Moreover, this method was successfully extended to β -CF₃- β -aryl enones and simple enones with good results (Scheme 2.18).^[151]



Scheme 2.18- First asymmetric *sulfa*-Michael reaction to β -CF₃- β -disubstituted nitroalkenes.

Later, Wei *et al.* studied the enantioselective addition of arylthiols to various nitroalkene derivatives, catalysed by a cinchona alkaloid-based multifunctional thiourea. High yields and enantioselectivities were observed when β -substituted nitroalkenes or β -methyl- β , β -disubstituted nitroalkenes were employed. However, when α -CF₃- β -nitrostyrene was used, significantly lower performance was reported (Scheme 2.19).^[152]



Scheme 2.19- Enantioselective 1,4-addition of arylthiols to β -CF₃- β , β -disubstituted nitroalkenes.

α -Substituted- β -Nitroacrylates as Michael Acceptors

β -Amino acids are valuable building blocks for the synthesis of antibiotic β -lactams, such as penicillins and cephalosporins,^[153] as well as in the field of peptidomimetics for the construction of β -peptides.^[154] Moreover, they are found in various natural products and bioactive compounds, including the anticancer paclitaxel (Taxol).^[155] This family of compounds is classified depending on the substitution at the 3-aminopropionic acid core (Figure 2.6).

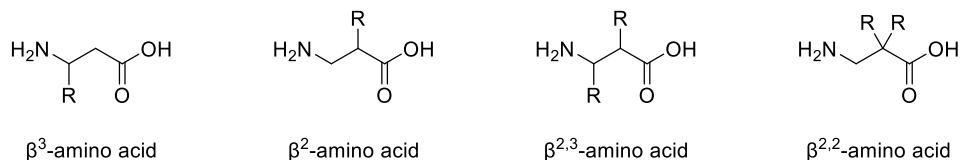


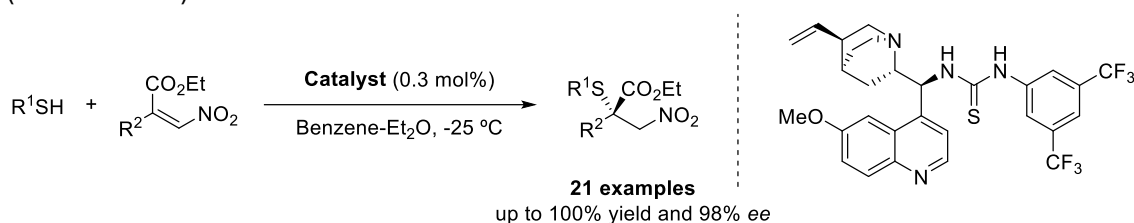
Figure 2.6- Structural classification of β -Amino acids.

While β^3 -amino acids can be readily synthesised *via* the Arndt–Eistert homologation of L- α -amino acids,^[156] the preparation of β^2 -amino acids requires stereoselective synthetic approaches.^{[157]–[160]} In this context, β -nitroacrylates are particularly noteworthy as the presence of both nitro and ester functionalities enables their enantioselective conversion into α -substituted β -nitropropionates. These intermediates can, in turn, be efficiently

transformed into β^2 -, $\beta^{2,2}$ -, $\beta^{2,3}$ - or $\beta^{2,2,3}$ amino acids, depending on the substitution pattern on the parent nitroacrylate.^[161]

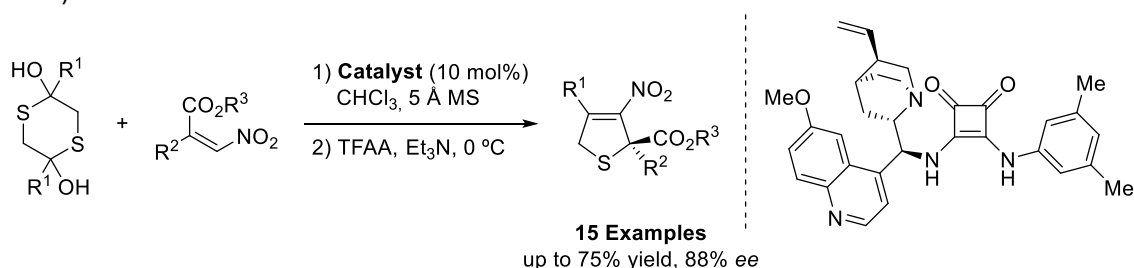
The use of α -substituted- β -nitroacrylates in *sulfa*-Michael reactions offers a straightforward route to β^2 -amino acid precursors bearing tetrasubstituted stereogenic centres directly bonded to sulfur-containing moieties. Despite the well-established relevance of organosulfur compounds, β -amino acids, and chiral molecules featuring quaternary stereocentres across various fields of chemistry, only two examples of such transformation have been reported in the literature.

In 2009, Lu *et al.* studied the enantioselective addition of arylthiols to α -substituted- β -nitroacrylates catalysed by a quinine-based thiourea. α -Sulfonylated- β -nitroesters bearing a hetero-carbon tetrasubstituted stereocenter were obtained in up to 100% yield and 98% enantiomeric excess. The synthetic utility of the process was further demonstrated through the conversion of the *sulfa*-Michael adducts into the corresponding $\beta^{2,2}$ -amino acids (Scheme 2.20).^[162]



Scheme 2.20- First enantioselective *sulfa*-Michael addition to α -substituted- β -nitroacrylates

Afterwards, Li and Xiao described an asymmetric cascade *sulfa*-Michael/aldol reaction involving the dimeric form of mercaptoacetaldehyde, 1,4-dithiane-2,5-diol, and α -substituted- β -nitroacrylates. In this synthetic methodology, the *sulfa*-Michael addition was catalysed by a quinine-derived squaramide, followed by an aldol condensation promoted by trifluoroacetic anhydride. The reaction furnished 2,5-dihydrothiophenes bearing sulfur-containing tetrasubstituted stereocentres in good yields and enantioselectivities (Scheme 2.21).^[163]

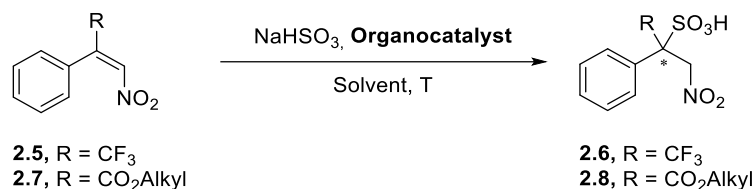


Scheme 2.21- Asymmetric cascade *sulfa*-Michael/aldol reaction involving β -nitroacrylates.

Nevertheless, the scope of sulfur-based nucleophiles employed in Michael additions to β,β -disubstituted nitroalkenes remains limited, as only thiols have been used. In this context, the direct asymmetric conjugate addition of sodium bisulfite to β,β -disubstituted nitroalkenes is particularly appealing, as it enables the efficient synthesis of chiral β -nitrosulfonic acids bearing a tetrasubstituted stereocentre, which can be converted into amino sulfonic acids through a single reduction step. Motivated by these considerations, this chapter explores the *sulfa*-Michael reaction between sodium bisulfite and β -CF₃- β,β -disubstituted nitroalkenes as well as α -substituted- β -nitroacrylates under organocatalytic conditions.

Objectives

The main objective for this chapter is to develop an enantioselective organocatalytic methodology for the construction of tetrasubstituted stereocentres *via* the addition of sodium bisulfite to β,β -disubstituted nitroalkenes **2.5** and **2.7**.



To this end, the following secondary objectives have been proposed:

1. Synthesis of the required starting materials **2.5** and **2.7**, bearing substituents with different electronic and steric properties.
2. Optimization of the reaction conditions between sodium bisulfite and β,β -disubstituted nitroalkenes **2.5a** and **2.7a** to obtain the corresponding nitrosulfonic acids **2.6a** and **2.7a** with the highest yield and enantioselectivity.
3. Study of the scope of the reaction between sodium bisulfite and different aromatic, aliphatic and heterocyclic β,β -disubstituted nitroalkenes **2.5** and **2.7**.
4. Applicability and synthetic transformations over the reaction products.

Results and Discussion

Synthesis of β -CF₃- β , β -disubstituted Nitroalkenes **2.5**

The synthesis of compounds **2.5a-p** was achieved following reported procedures through a four-step synthetic sequence starting from the corresponding aromatic aldehydes (Figure 2.7).^{[164],[165]}

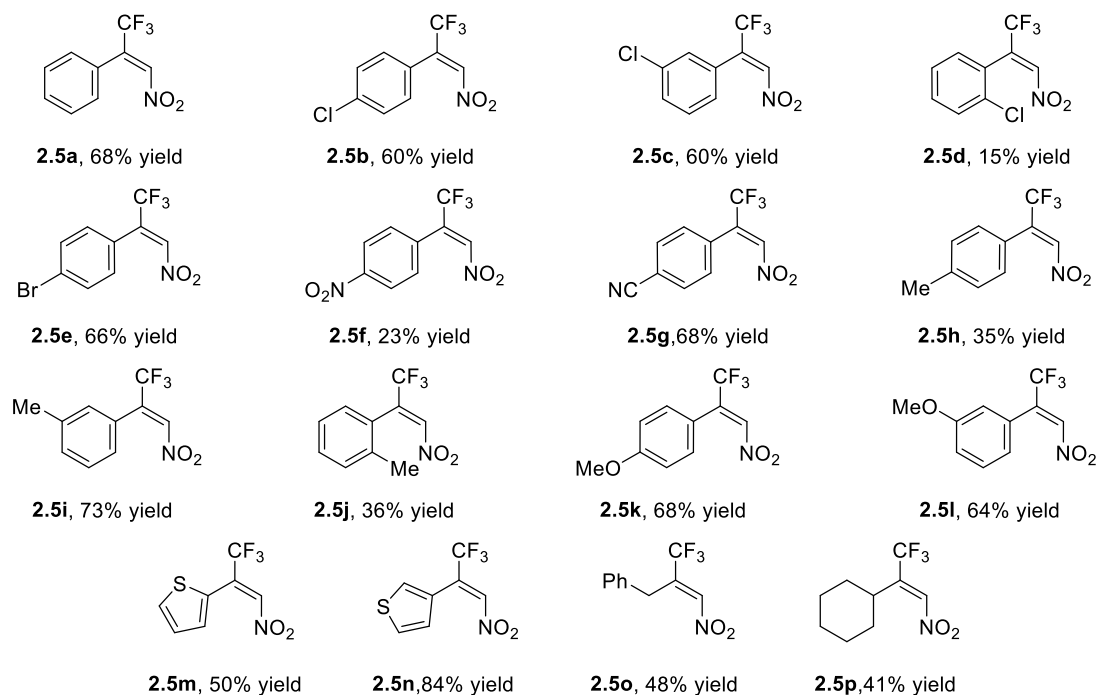
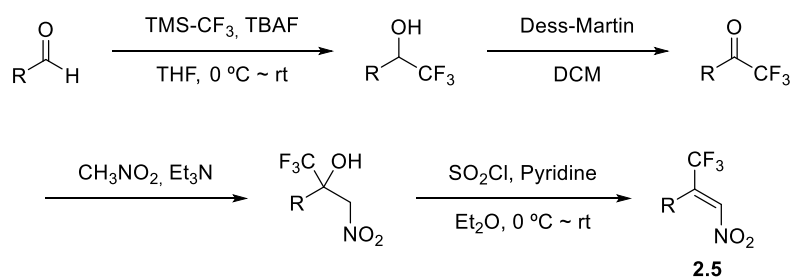


Figure 2.7- Synthesised starting materials **2.5**. Overall yields.

Initially, the appropriate aromatic aldehydes were treated with trifluoromethyl trimethylsilane in the presence of tetra-*n*-butylammonium fluoride, affording the corresponding trifluoroalcohol intermediates. In the second step, these intermediates were oxidised using Dess-Martin periodinane to yield the desired 2,2,2-trifluoromethyl acetophenones (Scheme 2.22). Most of the trifluoroketones were commercially available and their synthesis was only required for the preparation of starting materials **2.5d**, **2.5f**, **2.5g**, **2.5n**, and **2.5p**.



Scheme 2.22- Synthetic sequence for the synthesis of compounds **2.5**.

Finally, the synthesis of compounds **2.5** involved a Henry reaction between the appropriate 2,2,2-trifluoromethylacetophenones and nitromethane, affording the corresponding nitroalcohols. These intermediates were then dehydrated using thionyl chloride in the presence of a base to yield the desired nitroalkenes **2.5**. All spectroscopic data for β -CF₃- β , β -disubstituted nitroalkenes was in accordance with literature.

Synthesis of α -substituted- β -nitroacrylic Esters 2.7

α -Substituted- β -nitroacrylic esters **2.7c-l** were obtained following reported procedures^[166]–^[168] through a three-step synthetic sequence starting from ethyl α -ketoesters (Scheme 2.25, Figure 2.8). For compounds **2.7h-j**, the required α -ketoesters had to be synthesised. Compounds **2.7a** and **2.7b** were already available within our research group.

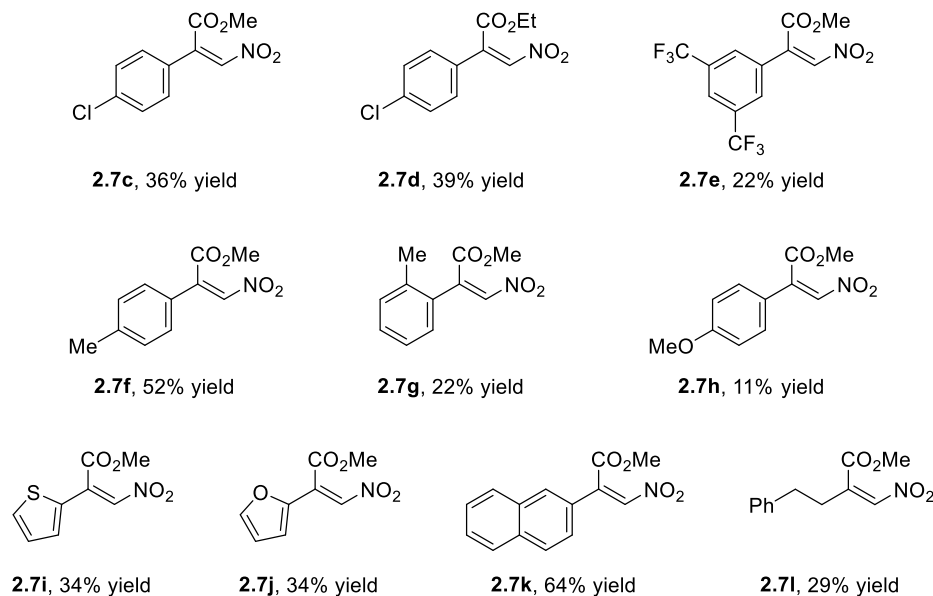
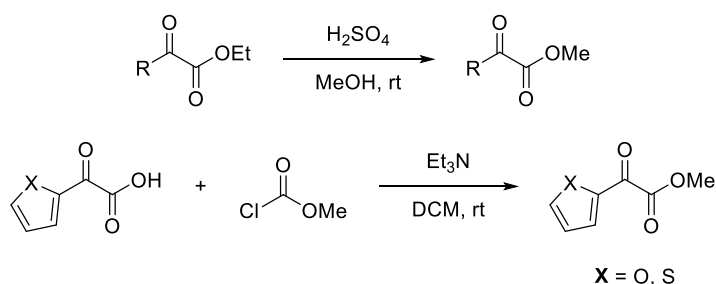


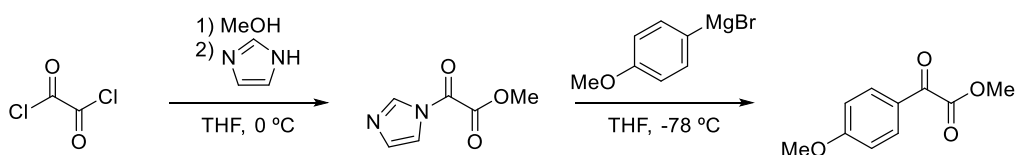
Figure 2.8- Synthesised starting materials **2.7**. Overall yields.

In a first step, the appropriate ethyl α -ketoesters were converted into the corresponding methyl α -ketoesters *via* a Fischer transesterification promoted by concentrated sulfuric acid. For heteroaromatic compounds **2.7i** and **2.7j**, the required methyl α -ketoesters were obtained through the esterification of the corresponding α -ketoacids (Scheme 2.23).^[169]



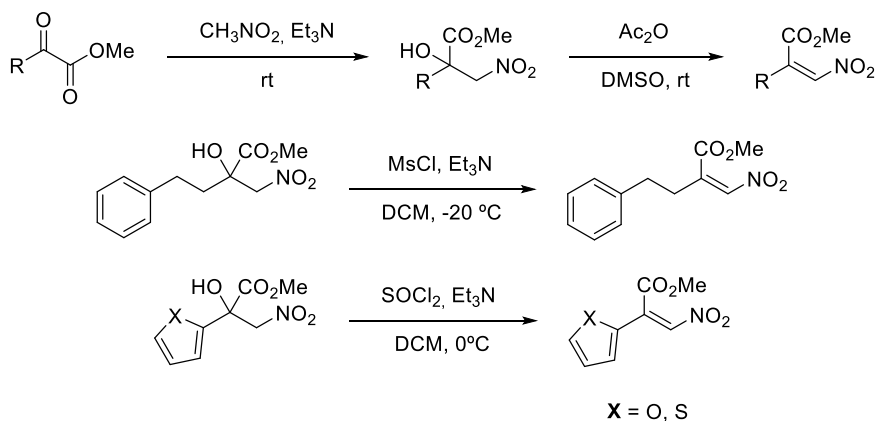
Scheme 2.23- Synthesis of methyl α -ketoesters.

In the case of compound **2.7h**, the needed α -ketoester was synthesised through a two-step procedure, starting with the transformation of oxalyl chloride into imidazolyl methyl oxalate. Subsequent addition of (4-methoxyphenyl)magnesium bromide afforded the desired methyl α -ketoester (Scheme 2.24).



Scheme 2.24- Two-step procedure for the synthesis of methyl (4-methoxyphenyl)glyoxylate.

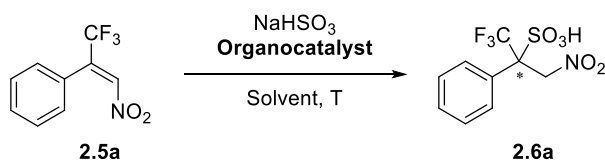
Finally, compounds **2.7** were synthesised *via* a Henry reaction between the appropriate methyl α -ketoesters and nitromethane, yielding the corresponding nitroalcohol intermediates, which were dehydrated using various reagents to yield the desired nitroacrylates **2.7** (Scheme 2.25). All spectroscopic data for α -substituted- β -nitroacrylic esters were in accordance with literature.



Scheme 2.25- Henry reaction-dehydration sequence for the preparation of compounds **2.7**.

Optimization of the Reaction Conditions

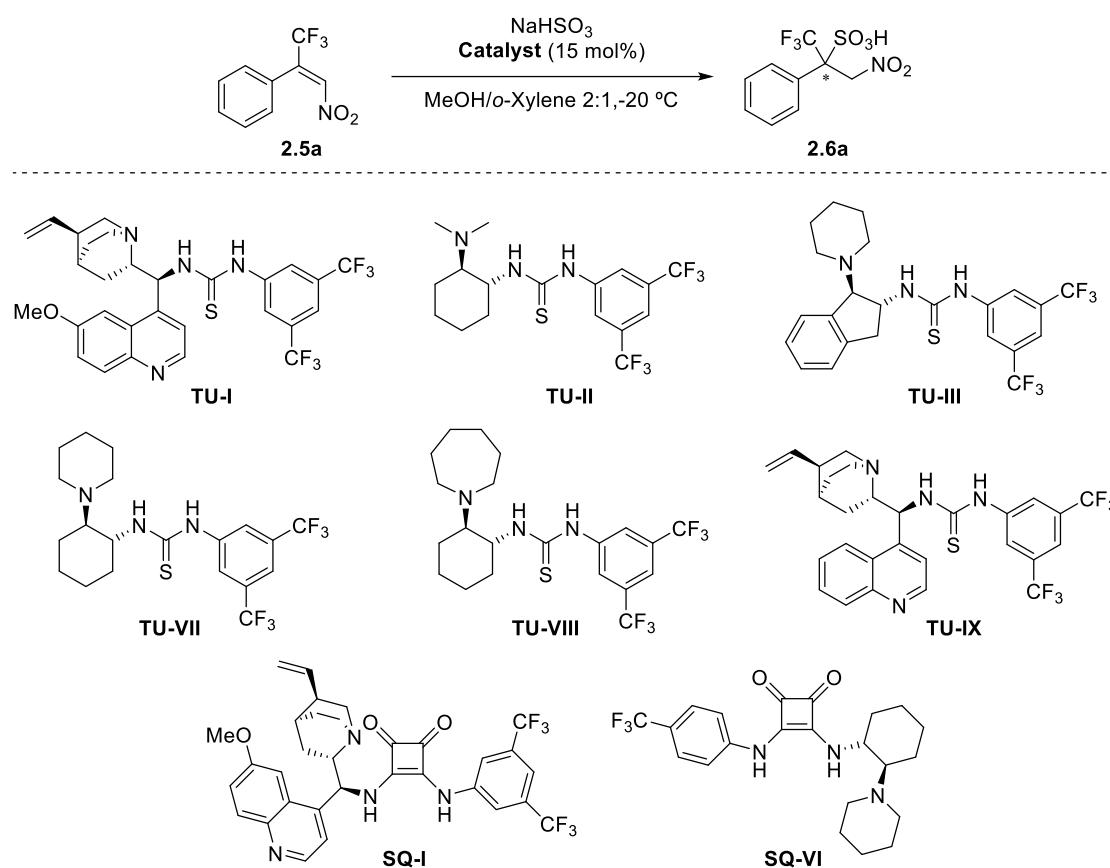
To investigate the enantioselective construction of tetrasubstituted stereocentres *via* the organocatalytic addition of sodium bisulfite to β,β -disubstituted nitroalkenes **2.5**, compound **2.5a** was selected as a model substrate to optimize the reaction conditions (Scheme 2.26).



Scheme 2.26- Model reaction selected for the optimization process.

Based on our work presented in Chapter II concerning the enantioselective addition of sodium bisulfite to *trans*- β -nitrostyrenes, we initiated our study applying those previously established reaction conditions to our model substrate **2.5a**. To our delight, catalyst **TU-VII** promoted the formation of nitrosulfonic acid **2.6a** in high enantioselectivity, albeit with moderate conversion and yield (Table 2.4, entry 1). Therefore, in order to maximise both the enantioselectivity and yield of compound **2.6a**, a catalyst screening was performed.

Table 2.4- Catalyst screening for the addition of NaHSO₃ to β,β-disubstituted nitroalkene **2.5a**.



Entry ^a	Catalyst	t (days)	Yield 2.6a (%) ^b	ee 2.6a (%) ^c
1	TU-VII	2	43	92
2	TU-I	2	70	27
3	TU-IX	3	96	47
4	TU-II	2	69	73
5	TU-VIII	3	42	88
6	TU-III	3	61	59
7	SQ-I	3	33	32
8	SQ-VI	2	44	24

^aReaction conditions: **2.5a** (0.2 mmol), NaHSO₃ (0.48 mmol in 0.5 mL of H₂O) and **Cat.** (15 mol%) in MeOH/*o*-Xylene (2 mL, v/v, 2:1) at -20 °C. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

Initially, and in line with the trend observed in Chapter II, where thiourea-based catalysts outperformed squaramides in the enantioselective addition of sodium bisulfite to *trans*-β-nitrostyrenes, the catalyst screening focused primarily in thioureas. When cinchona-alkaloid derived thioureas **TU-I** and **TU-IX** were employed, nitrosulfonic acid **2.6a** was obtained in good to excellent yields but a significant drop in enantioselectivity was observed (Table 2.4, entries 2 and 3). Therefore, chinchona-alkaloid thioureas were deemed not suitable for this transformation.

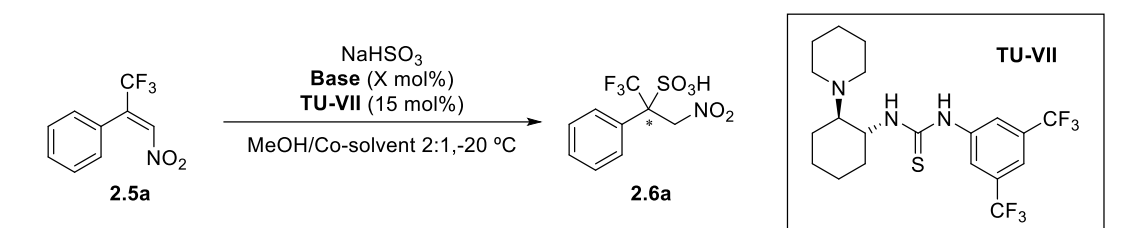
Subsequently, thioureas incorporating the 1,2-cyclohexanediamine moiety were evaluated. Takemoto's thiourea (**TU-II**) failed to improve the overall results, while the azepine-containing catalyst **TU-VIII** provided similar yield and enantioselectivity but required longer reaction times (Table 2.4, entries 4 and 5). Consequently, both catalysts

were discarded. Likewise, indane-derived thiourea **TU-III** was studied but did not offer any improvement over the best results achieved so far (Table 2.4, entry 6).

Finally, squaramide catalysts, including those derived from cinchone-alkaloid and 1,2-cyclohexanediamine, were also tested. Neither **SQ-I** nor **SQ-VI** improved on results achieved with thioureas (Table 2.4, entries 7 and 8), and therefore **TU-VII** was selected as the optimal catalyst for the reaction.

In an effort to further improve the outcome of the reaction, particularly the yield, additional optimization experiments were performed (Table 2.5).

Table 2.5- Further optimization experiments performed on the reaction between NaHSO₃ and **2.5a**.



Entry ^a	Co-solvent	Base	t (days)	Yield 2.6a (%) ^b	ee 2.6a (%) ^c
1	<i>o</i> -Xylene	-	2	43	92
2	<i>o</i> -Xylene	-	5	46	91
3	PhCF ₃	-	4	46	87
4	<i>o</i> -Xylene	Et ₃ N (5 mol%)	2	70	89
5	<i>o</i> -Xylene	Et ₃ N (2 mol%)	5	62	87

^aReaction conditions: **2.5a** (0.2 mmol), NaHSO₃ (0.48 mmol in 0.5mL of H₂O) and **TU-VII** (15 mol%) in MeOH/Cosolvent (2 mL, v/v, 2:1) at -20 °C. ^bIsolated yield after column chromatography.

^cMeasured using chiral HPLC.

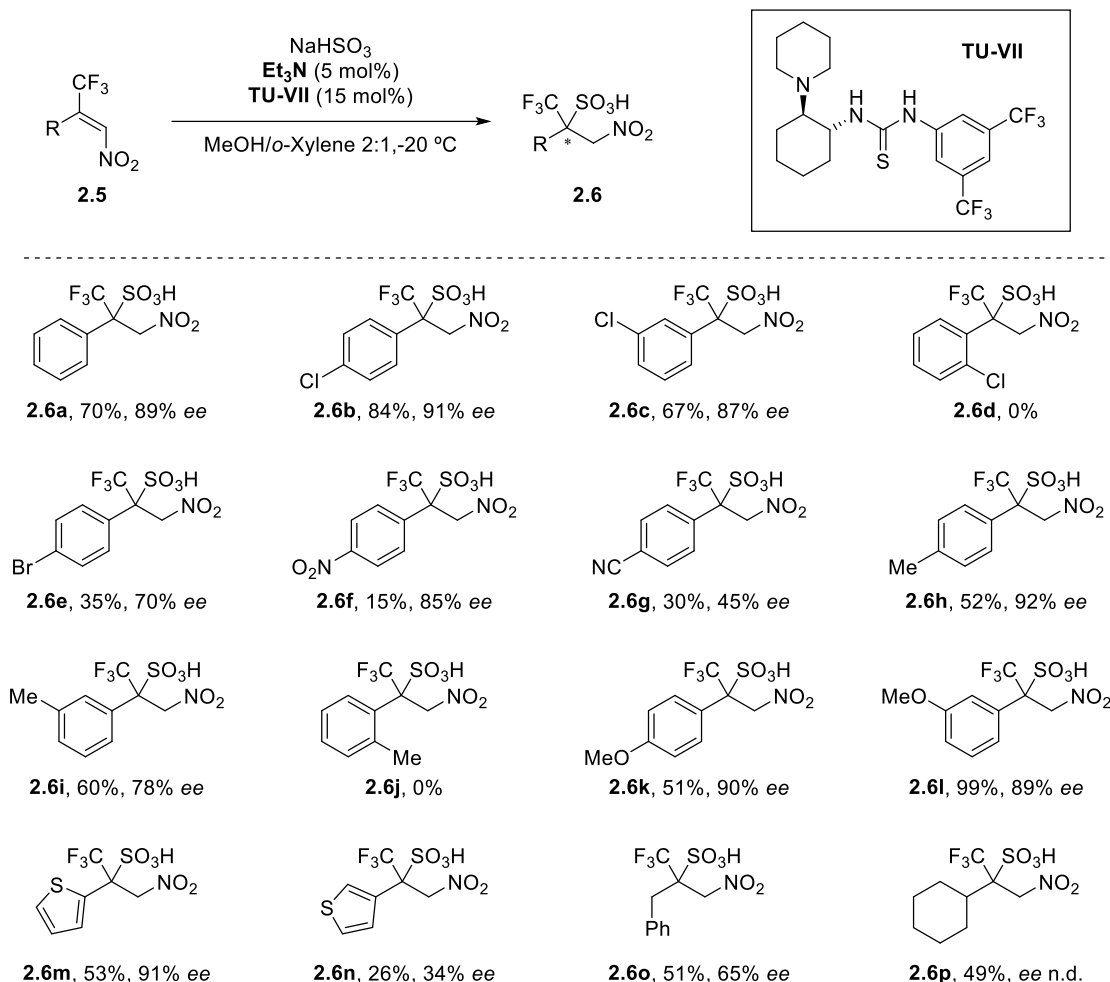
First, the effect of reaction time was investigated by extending the reaction of NaHSO₃ and **2.5a** over 5 days. However, no improvement was observed as the yield and enantiomeric excess obtained were comparable to that achieved in just 2 days (Table 2.5, entries 1 and 2). Next, a fluorinated co-solvent, α,α,α-trifluorotoluene, was tested but it did not improve the outcome of the reaction (Table 2.5, entry 3). Consequently, *o*-xylene was selected as the optimal co-solvent.

Finally, to conclude the optimization process, the use of a catalytic base was evaluated. Pleasingly, when the addition of sodium bisulfite to nitroalkene **2.5a** was performed under the optimized conditions in the presence of an additional 5 mol% of triethylamine, a notable increase in both conversion and yield was observed, while maintaining high enantioselectivity (Table 2.5, entry 5). 2 mol% of base loading required longer reaction time to achieve comparable results (Table 2.5, entry 6), thus 5 mol% triethylamine was selected as the optimal loading.

In conclusion, the optimal reaction conditions for the model reaction between sodium bisulfite and β-CF₃-β,β-disubstituted nitroalkene **2.5a** are as follows: 1,2-cyclohexanediamine-derived thiourea **TU-VII** at 15 mol% loading and 5 mol% of triethylamine as the catalytic system, in a 2:1 (v/v) mixture of MeOH/*o*-xylene as solvent, using 2.4 equivalents of sodium bisulfite, at -20 °C.

Scope of the Reaction with Different β -CF₃- β,β -disubstituted nitroalkenes

Once the optimal reaction conditions were established, we proceeded to study how different groups or substituents on β -CF₃- β,β -disubstituted nitroalkenes **2.5** affected the outcome of the reaction (Scheme 2.27).



Scheme 2.27- Study of the scope of the reaction with various β -CF₃- β,β -disubstituted nitroalkenes.

Initially, β -CF₃- β,β -disubstituted nitroalkenes bearing halogenated aromatic rings were evaluated. As anticipated, the introduction of a chlorine atom at the *para*-position enhanced the reactivity, affording product **2.6b** in 84% yield and 91% enantiomeric excess. However, substitution at the *meta*-position resulted in a moderate decrease in yield (67% yield, 87% ee for **2.6c**). This effect became even more pronounced when the chlorine atom was placed at the *ortho*-position, completely inhibiting the reaction (**2.6d**), which can be attributed to the high steric hindrance imposed by the proximity of the substituent to the reactive site. Additionally, *para*-substitution with bromine was also examined (**2.6e**), but led to a lower performance (35% yield, 70% ee).

Strong electron-withdrawing groups at the *para*-position were also tested but led to unsatisfactory outcomes. A nitro-substituted aromatic ring yielded **2.6f** with a significant drop in yield (15%) while maintaining high enantioselectivity (85% ee). Likewise, the cyano-substituted derivative **2.6g** was obtained with low yield and diminished enantioselectivity (30% yield, 45% ee), possibly due to interactions of these substituents with the catalyst, which could interfere with the stereochemical course of the reaction.

On the other hand, electron-rich aromatic rings were also examined. *Para*-substitution with a methyl group afforded compound **2.6h** in moderate yield (52%) and excellent enantioselectivity (92% ee), consistent with the reduced reactivity of electron-rich systems. The *meta*-substituted analogue **2.6i** exhibited similar yield (60%) but a notable drop in enantioselectivity (78% ee). As with halogenated substrates, *ortho*-substitution with a methyl group (**2.6j**) fully suppressed reactivity, likely due to the steric constraints near the reactive site.

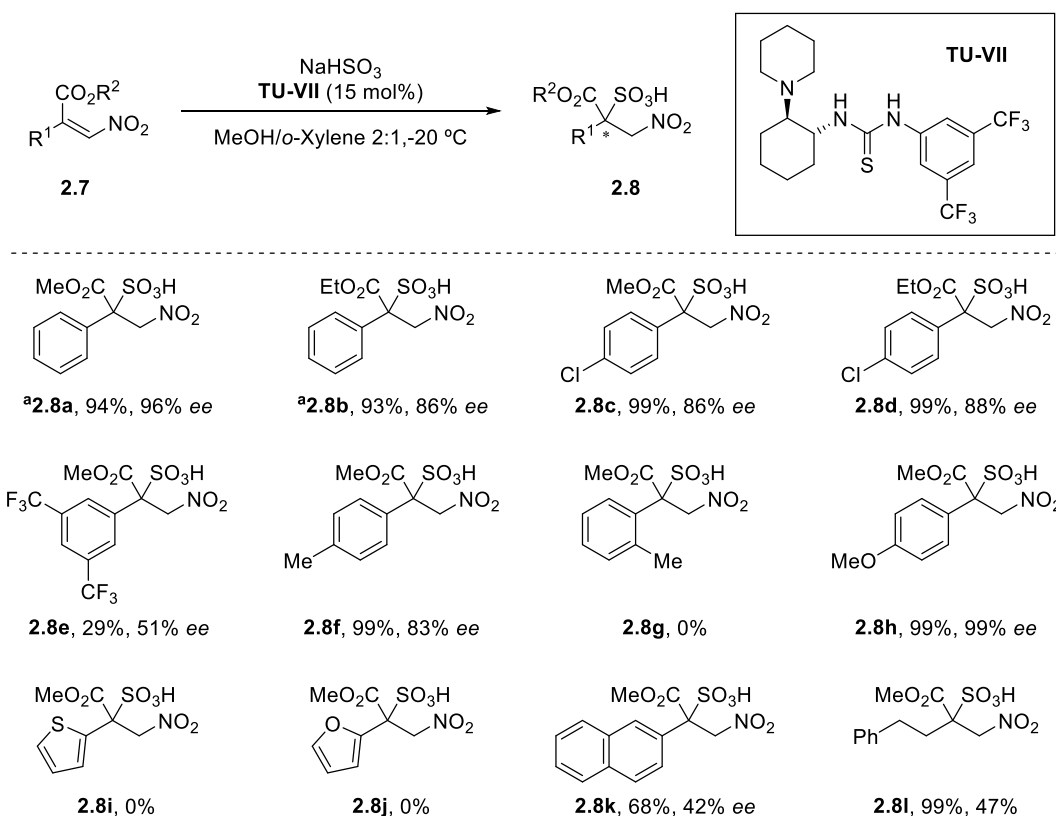
Methoxy-substituted nitroalkenes were also evaluated. When the substitution took place at the *para*- position, derivative **2.6k** was obtained with results comparable to those of the *para*-methyl analogue (51% yield, 90% ee). Interestingly, the *meta*-substituted compound **2.6l** was obtained in quantitative yield and high enantioselectivity (89% ee). This contrasting behaviour can be rationalised by considering the Hammett parameters of the methoxy group: at the *para*-position, its strong electron-donating character arises from resonance effects, whereas in the *meta*-position resonance effects are negligible and its behaviour is governed by inductive effects, effectively acting as an electron-withdrawing group.^[170]

To complete the scope of the study, substrates bearing heterocyclic and aliphatic substituents were assessed. Introduction of a 2-thienyl group (**2.6m**) resulted in moderate yield (53%) and excellent enantioselectivity (91% ee), whereas the 3-thienyl analogue **2.6n** performed poorly (26% yield, 34% ee). Finally, aliphatic substituents were tested: benzyl- and cyclohexyl-substituted nitroalkenes furnished compounds **2.6o** and **2.6p** in low to moderate yields (32% and 49%, respectively) with moderate enantiomeric excesses (65% ee for **2.6o**). The diminished stereoselectivity observed for compound **2.6o** may be attributed to the greater conformational flexibility of aliphatic moieties, potentially increasing the number of accessible transition states and thereby reducing enantioselectivity. Unfortunately, enantiomeric excess of **2.6p** was not determined, as HPLC resolution of the enantiomeric mixture could not be achieved.

Scope of the Reaction with Different α -substituted- β -nitroacrylic Esters

Once the scope of β -CF₃- β , β -disubstituted nitroalkenes had been established, we turned our attention to the enantioselective addition of sodium bisulfite to α -substituted- β -nitroacrylic esters. Remarkably, under the previously optimized conditions, the reaction proceeded efficiently even in the absence of triethylamine, affording compound **2.8a** in 94% yield and 96% enantiomeric excess. A comparable yield was achieved with the ethyl ester **2.7b**; however, the enantioselectivity was notably lower, providing **2.8b** in 93% yield and 86% ee. Considering these results, we proceeded to investigate the influence of substitution on α -substituted- β -nitroacrylic methyl esters on the outcome of the reaction (Scheme 2.28).

We first examined electron-withdrawing groups. *Para*-substitution with a chlorine atom (**2.8c**) led to quantitative yields with a slight erosion of enantioselectivity (88% ee). Additionally, the analogue ethyl ester **2.7d** was also tested, affording compound **2.8d** in comparable results (99% yield, 86% ee). When the bis(trifluoromethyl) derivative **2.7e** was employed, significantly yield and enantioselectivity were observed (29%, 51% ee), indicating a detrimental effect of strong inductive withdrawing groups on the outcome of the reaction.



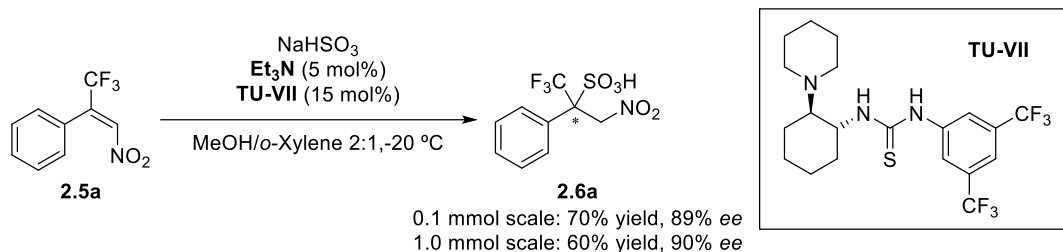
Scheme 2.28- Study of the scope of the reaction with various α -substituted- β -nitroacrylic esters. ^aEnantiomeric excess determined by HPLC after esterification with trimethyl orthoacetate.

Subsequently, the introduction of electron-donating substituents was studied. *Para*-substitution with methyl group afforded **2.8f** with quantitative yield and a good 83% enantiomeric excess. Pleasingly, *para*-substitution with a methoxy group yielded excellent results, achieving complete conversion and estereocontrol (**2.8h**). However, as previously observed in β -CF₃- β , β -disubstituted nitroalkenes, the introduction of a methyl group at the *ortho*- position completely inhibited the reaction (**2.8g**).

Moreover, substrates bearing heterocyclic and aliphatic moieties were evaluated. When thiophene and furan-containing nitroacrylates were employed, both reactions failed to afford compounds **2.8i** and **2.8j**. Instead, complex mixtures were obtained, in which no traces of the desired products were detected by ¹H NMR analysis. The 2-naphthyl derivative **2.8k** gave a moderate 68% yield and low enantiomeric excess (42%), possibly due to the bulkiness of the aromatic moiety. Similarly to the behaviour of **2.6o**, the aliphatic derivative **2.8l** showed modest enantioselectivity (47% *ee*).

Applicability and Synthetic Transformations

The robustness of the procedure was tested by preparing compound **2.6a** in a 1 mmol scale. Under these conditions, the addition of sodium bisulfite to β -CF₃- β,β -disubstituted nitroalkene **2.5a** afforded similar levels of enantioselectivity (90% ee) although with slightly lower yield (Scheme 2.29).



Scheme 2.29- 1 mmol scale synthesis of nitrosulfonic acid **2.6a**.

Regarding the synthetic transformations of compound **2.6a**, several strategies were explored. Initially, the reduction of the nitro group to the corresponding amine was investigated; however, hydrogenation conditions (Pt₂O, 5 mol%, H₂, 5 bar) as well as reducing agents such as Zn⁰/AcOH and NaBH₄ led to complex reaction mixtures that could neither be purified nor characterized. In an attempt to isolate the presumed reduction product, the crude mixtures were treated with amine-protecting reagents (CbzCl, Boc₂O) to facilitate purification, yet no products were obtained.

Additional transformations targeting the nitro group were also evaluated. An AIBN-promoted radical denitration failed to deliver satisfactory results, as no conversion was observed. Additionally, the Nef reaction was also attempted, but it resulted in complex mixtures in which no traces of the desired products were detected by ¹H NMR analysis. Finally, the conversion of the sulfonic acid into the corresponding sulfonyl chloride was studied using oxalyl chloride in the presence of catalytic DMF; however, this approach proved unsuccessful as it led to substrate decomposition.

Although the synthetic transformations of compounds **2.6** have not yet yielded the desired outcomes, the investigation remains ongoing. Moreover, transformations of compounds **2.8** remain to be explored and will be pursued in the future.

Conclusions

The first enantioselective organocatalytic method has been developed for the construction of tetrasubstituted stereocentres *via* the 1,4-addition of sodium bisulfite to β -CF₃- β,β -disubstituted nitroalkenes and α -substituted- β -nitroacrylic esters, employing thiourea **TU-VII** as a bifunctional organocatalyst. This reaction represents the first reported example of the direct addition of sodium bisulfite to β,β -disubstituted nitroalkenes.

In view of the results presented in this chapter, it can be concluded that the initially proposed objectives have been successfully achieved:

6. The required β -CF₃- β,β -disubstituted nitroalkenes (**2.5a-q**) and α -substituted- β -nitroacrylic esters (**2.7c-l**), bearing substituents with different electronic and steric properties, have been synthesised with low to good yields.
7. The reaction conditions for the enantioselective organocatalytic addition of sodium bisulfite to β -CF₃- β,β -disubstituted nitroalkenes **2.5** have been optimized as follows: thiourea **TU-VII** and triethylamine as the catalytic system, a 2:1 (v/v) mixture of MeOH/*o*-xylene as solvent, and a reaction temperature of -20 °C. Under this conditions, good yield (70%) and high enantioselectivity (89% ee) have been achieved.
8. The scope of the reaction has been evaluated by analysing the effects of various substituents in β -CF₃- β,β -disubstituted nitroalkenes **2.5**. Good results have been obtained in the presence of weak electron-donating and electron withdrawing-groups when introduced in the *para*- and *meta*- positions. In contrast, substitution at the *ortho*- position completely inhibited the reaction regardless of the nature of the substituent. Moreover, this methodology has also been extended to aliphatic and heterocyclic nitroalkenes, with mixed results.
9. The optimized reaction conditions have been also successfully applied to α -substituted- β -nitroacrylic esters **2.7**, even in the absence of triethylamine, affording excellent yield (94%) and enantiomeric excess (96%) for compound **2.8a**. The substrate scope has also been investigated, achieving good to excellent results with substituents at the *para*- or *meta*- positions, whereas substitution at the *ortho*- position resulted in complete inhibition of the reaction. Additionally, heterocyclic and aliphatic substrates have also been studied.
10. The applicability of this procedure has been demonstrated by synthesising **2.6a** at 1.0 mmol scale, retaining excellent enantioselectivity (90%) with moderate yield (60 %). Synthetic transformations of **2.6a** involving the nitro group or the sulfonic acid proved to be challenging, as complex mixtures were obtained. The investigation remains ongoing and transformations of compounds **2.8** will be pursued in the future.

Chapter 4. Organocatalytic Enantioselective *sulfa*-Michael Addition of Sodium Bisulfite to Aurone-Derived Azadienes

Introduction

Heterocycles play a central role in chemistry, particularly in the field of medicinal chemistry, due to their occurrence in many natural products and biologically active molecules. These compounds are of paramount importance in the design and discovery of new drugs, as they provide ideal scaffolds on which pharmacophores can be arranged to afford potent and selective bioactive compounds. This structural versatility is reflected in their prevalence within the pharmaceutical industry, where over 60% of top-selling drugs incorporate at least one heterocyclic moiety.^[171]

Among natural products and drugs containing heterocycles, benzofuran derivatives stand out due to their broad spectrum of biological activities, including anti-fungal, anti-alzheimer, analgesic, narcotic, anti-tubercular, antidepressant, anti-cancer, anti-viral, etc (Figure 2.9).^{[172]–[175]}

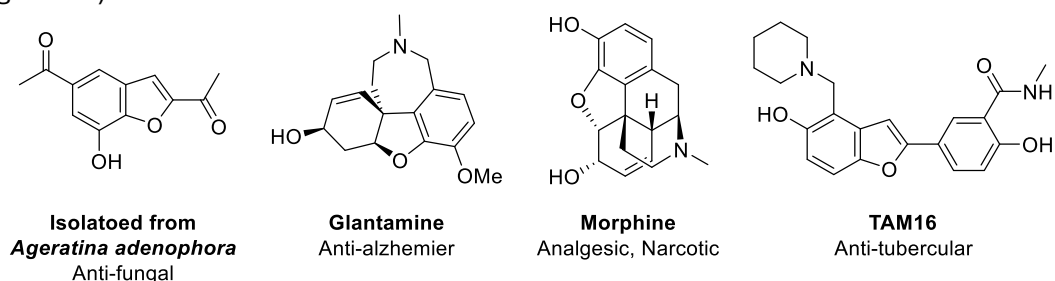


Figure 2.9- Selected examples of bioactive benzofuran derivatives.

Within this group, aurones, a small subclass of the family of flavonoids, are particularly notable as they are found across a variety of families of plants such as Anacardiaceae (cashew family), Asteraceae (daisy and sunflower family), Fabaceae (legume family), Rosaceae (rose family), Moraceae (fig family), etc.^[176] Due to their increased degree of conjugation in comparison to other flavonoids, aurones are the brightest yellow flavonoid pigments, and accordingly their primary biological role is in flower pigmentation and pollination. Nevertheless, aurones have gained increased interest in recent decades for their promising pharmacological activities, including anti-malarial, anti-virus, anti-inflammatory or anti-cancer among others (Figure 2.10).^{[177]–[180]}

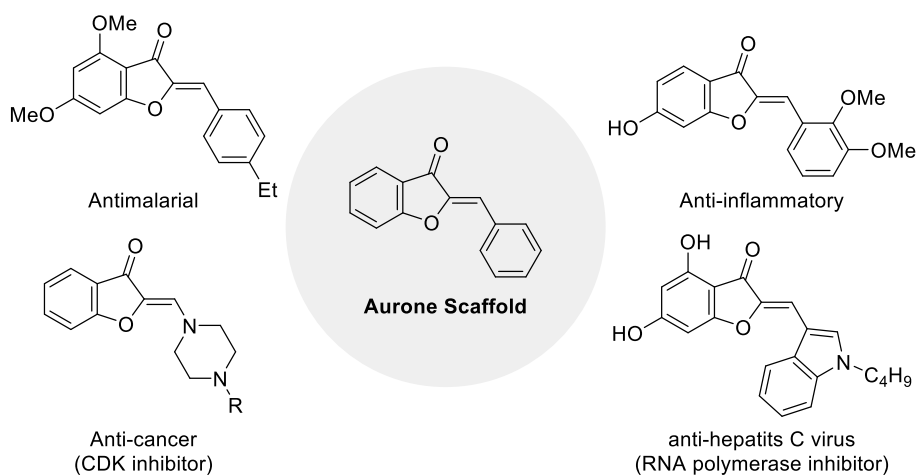
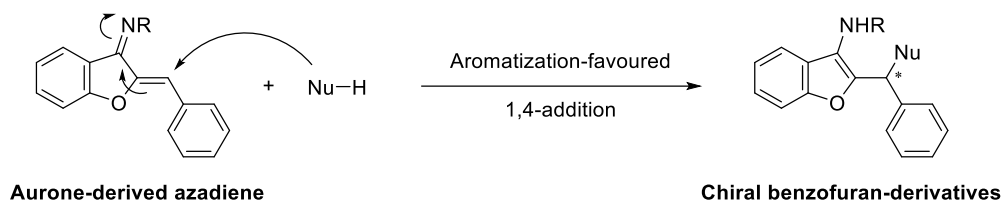


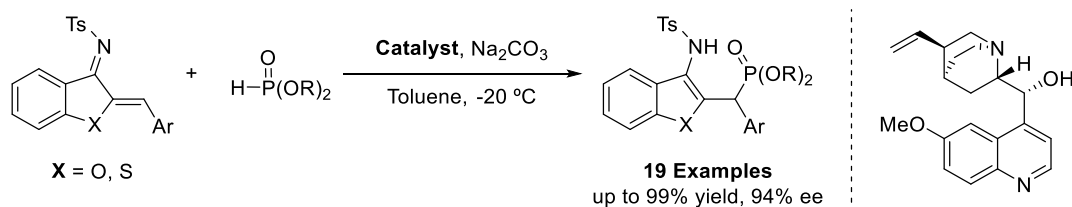
Figure 2.10- Aurone-derived bioactive compounds.

From a chemical perspective, aurones consist of a heterocyclic benzofuranone core featuring an exocyclic double bond conjugated to both a phenyl ring and a carbonyl group. Their pronounced electrophilicity has been exploited in the synthesis of chiral aurone derivatives *via* diverse asymmetric methodologies, including cycloadditions, annulations and Michael reactions.^[181] Aurones can also be easily transformed into aurone-derived azadienes, a class of compounds which are excellent Michael acceptors, as the aromatization of the benzofuran core acts as a driving force for the reaction (Scheme 2.30).



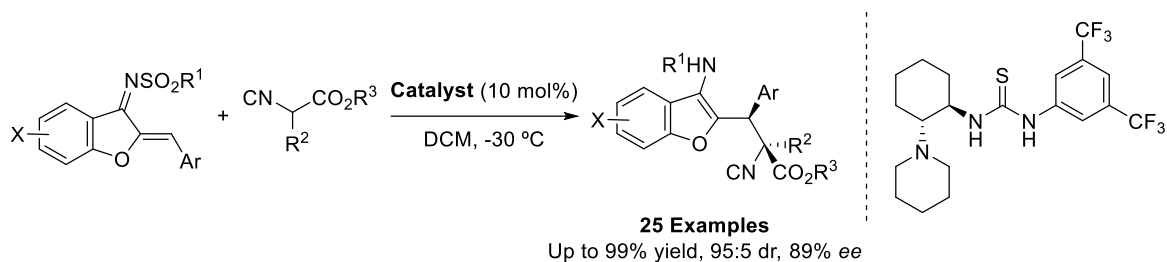
Scheme 2.30- Aurone-derived azadiene reactivity.

These azadienes have been successfully employed in the asymmetric synthesis of benzofuran derivatives bearing adjacent stereogenic carbon centres. The first enantioselective Michael addition involving aurone-derived azadienes was reported by the group of Jian and Zhou in 2018, where they studied the quinine-catalysed asymmetric addition of phosphites, affording chiral γ -aminophosphonates in excellent yields and high enantioselectivities. Remarkably, this methodology was also successfully extended to benzothiophene-derived azadienes (Scheme 2.31).^[182] Since then, similar organocatalytic approaches have been developed for the synthesis of chiral benzofuran derivatives through the addition of a variety of nucleophiles, such as γ -substituted deconjugate butenolides,^[183] rhodanines,^[184] 3-homoacyl coumarins,^[185] 5*H*-thiazol-4-ones^[186] or 3-methylbenzofuran-2(3*H*)-ones.^[187]



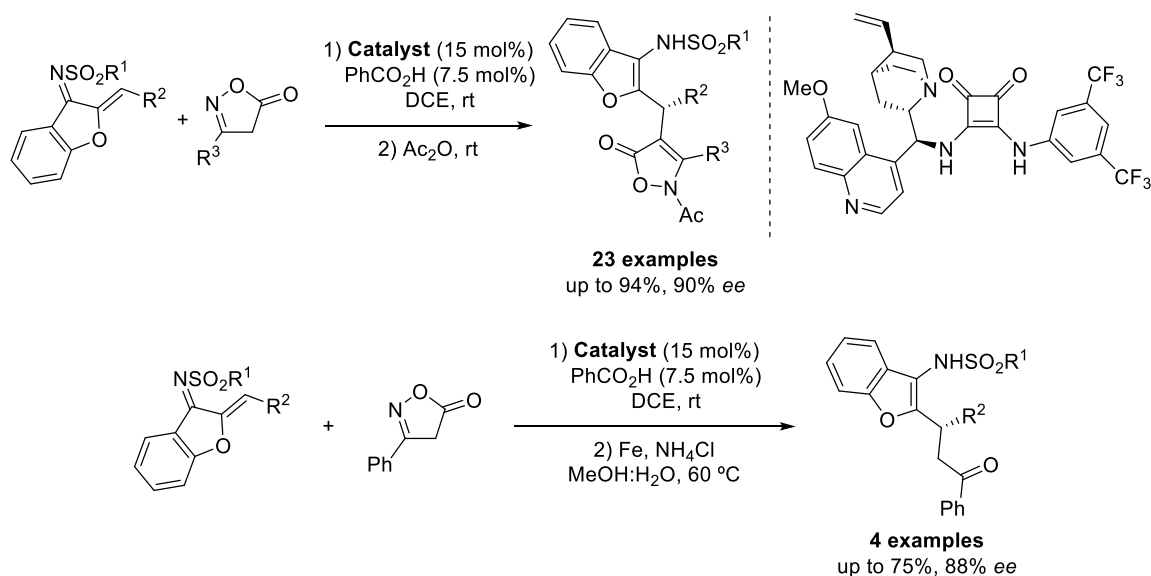
Scheme 2.31- Pioneering work of Jian and Zhou on the enantioselective Michael addition involving aurone-derived azadienes.

Recently, our research group has also contributed to the development of the functionalization of aurone-derived azadienes *via* the organocatalytic asymmetric addition of carbon nucleophiles. In 2024, we reported the synthesis of chiral α,α -disubstituted amino acids derivatives through the Michael addition of α -aryl isocyanoacetates to aurone-derived azadienes, catalysed by a bifunctional thiourea based on the 1,2-cyclohexanediamine scaffold. The resulting adducts featuring two consecutive carbon stereocentres, one of them quaternary, were obtained in high yields and stereocontrol. Moreover, the isocyanoacetates obtained could be hydrolysed to afford chiral α -aminoacids bearing a benzofuran moiety (Scheme 2.32).^[188]



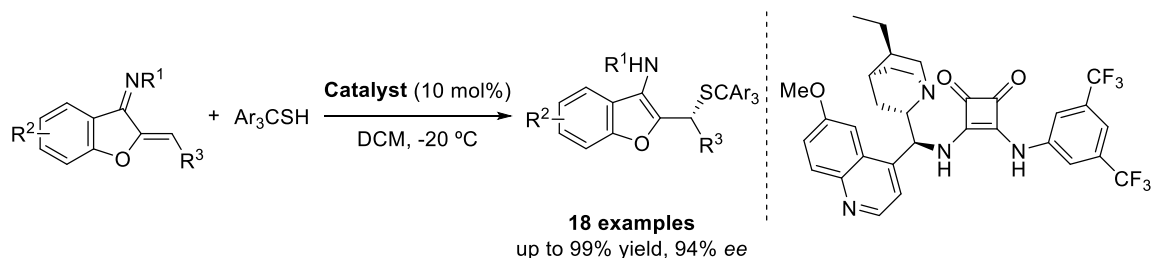
Scheme 2.32- Organocatalytic asymmetric Michael addition of chiral α,α -disubstituted amino acids derivatives.

The following year, our group explored the enantioselective conjugate addition of isoxazol-5(4*H*)-ones to aurone-derived azadienes mediated by a bifunctional squaramide catalyst derived from *Cinchona* alkaloids. The reaction provided the corresponding isoxazole-containing chiral benzofuran derivatives in high yields and enantioselectivities. In addition, these Michael adducts could be further transformed into chiral β -benzofuran-branched carbonyl compounds *via* a one-pot hydrolysis-decarboxylation of the isoxazole ring. (Scheme 2.33).^[189]



Scheme 2.33- Enantioselective 1,4-addition of isoxazol-5(4*H*)-ones to aurone-derived azadienes.

Regarding the *sulfa*-Michael addition to aurone-derived azadienes, only one example has been reported to date. In 2018, Jian and Zhou described the enantioselective addition of tritylthiols to azadienes catalyzed by dihydroquinine-derived squaramide, affording chiral organosulfur benzofuran derivatives in excellent yields and high enantiomeric excesses (Scheme 2.34).^[190]



Scheme 2.34- Asymmetric *sulfa*-Michael addition of tritylthiols to aurone-derived azadienes

However, the direct addition of sodium bisulfite to aurone-derived azadienes remain unexplored. This strategy would not only provide access to novel chiral organosulfur benzofuran derivatives but also would yield γ -amino sulfonic acids, structural analogues of the neurotransmitter γ -aminobutyric acid (GABA). These compounds have attracted attention as potential therapeutic agents for Alzheimer's disease,^[191] while the homotaurine *N*-acyl derivative Acamprosate has been marketed for over two decades as a treatment for alcohol dependence (Figure 2.11).^[192]

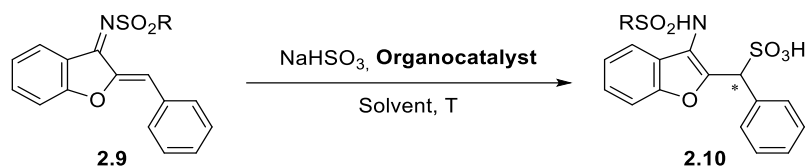


Figure 2.11- Illustrative examples of drugs containing γ -amino sulfonic acids.

Motivated by these considerations, this chapter explores the *sulfa*-Michael reaction between sodium bisulfite and aurone-derived azadienes under organocatalytic conditions.

Objectives

The main objective for this chapter is to develop an enantioselective organocatalytic methodology for the *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadienes **2.9**.



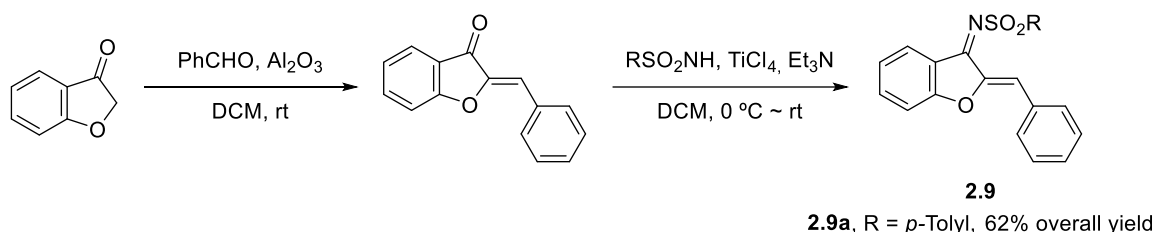
To this end, the following secondary objectives have been proposed:

1. Synthesis of the required starting materials **2.9**, bearing various protecting groups and substituents with different electronic and steric properties.
2. Optimization of the reaction conditions between sodium bisulfite and aurone-derived azadiene **2.9a** to obtain the corresponding amino sulfonic acid **2.10a** with the highest yield and enantioselectivity.
3. Study of the scope of the reaction between sodium bisulfite and different aromatic, aliphatic and heterocyclic aurone-derived azadienes **2.9**.
4. Applicability and synthetic transformations over the reaction products.

Results and Discussion

Synthesis of aurone-derived azadienes **2.9**

The required aurone-derived azadienes **2.9** were obtained following reported procedures *via* a two-step synthetic sequence starting from commercially available benzofuran-3(2*H*)-one (Scheme 2.35).^[193]

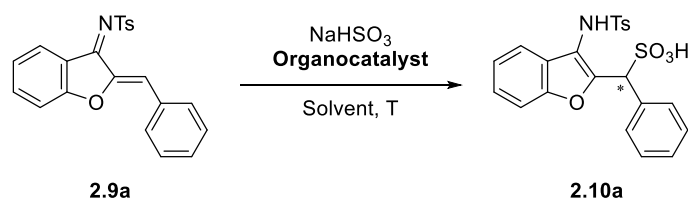


Scheme 2.35- General synthetic procedure for the synthesis of aurone-derived azadienes **2.9**.

In the first step, benzofuran-3(2*H*)-one was subjected to a crossed aldol condensation with benzaldehyde in the presence of activated basic Al_2O_3 , affording the corresponding aurone. In the second step, a condensation between aurone and the corresponding sulfonyl amines was carried out using TiCl_4 and triethylamine as base, affording the desired aurone-derived azadienes **2.9**. Most of the required azadienes had been previously prepared within the research group, therefore only product **2.9a** was synthesized. Spectroscopic data for azadiene **2.9a** were in accordance with literature.

Optimization of the Reaction Conditions

To investigate the enantioselective organocatalytic *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadienes **2.9**, compound **2.9a** was selected as a model substrate to optimize the reaction conditions (Scheme 2.36).

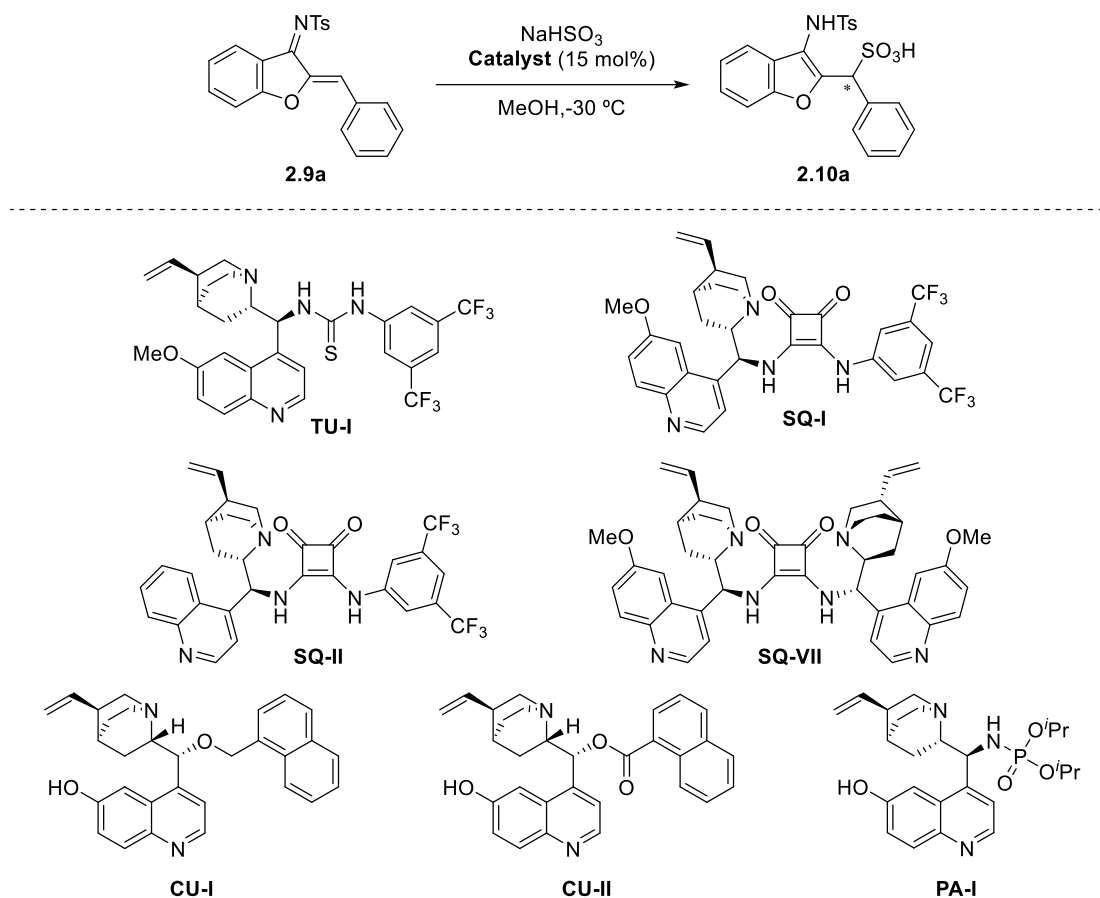


Scheme 2.36- Model reaction selected for the optimization process.

Based on our previous work presented in Chapters II and III on the enantioselective addition of sodium bisulfite to nitroalkenes, we initiated our study by applying similar reaction conditions to those previously established to our model substrate **2.9a**.

Our investigation started with a catalyst screening focused on *Cinchona* alkaloid-derived organocatalysts (Table 2.6). Initially, quinine-based catalysts **TU-I** and **SQ-I** were evaluated, both affording low levels of enantiocontrol. However, the squaramide catalyst **SQ-I** provided significantly higher yield than its thiourea analogue (Table 2.6, entries 1 and 2); consequently, thioureas were discarded for subsequent tests. Comparable enantioselectivity were obtained with cinchonidine-derived squaramide **SQ-II**, albeit with poor yields (Table 2.6, entry 3). The C_2 -symmetric squaramide **SQ-VII**, derived from quinine, afforded compound **2.10a** in high yield but with no enantioinduction (Table 6, entry 4).

Table 2.6- Screening of *Cinchona* alkaloid-derived catalysts for the addition of NaHSO₃ to aurone-derived azadiene **2.9a**.



Entry ^a	Catalyst	Yield 2.10a (%) ^b	ee 2.10a (%) ^c
1	TU-I	42	16
2	SQ-I	79	17
3	SQ-II	13	13
4	SQ-VII	77	2
5	CU-I	82	16
6	CU-II	47	2
7	PA-1	17	4

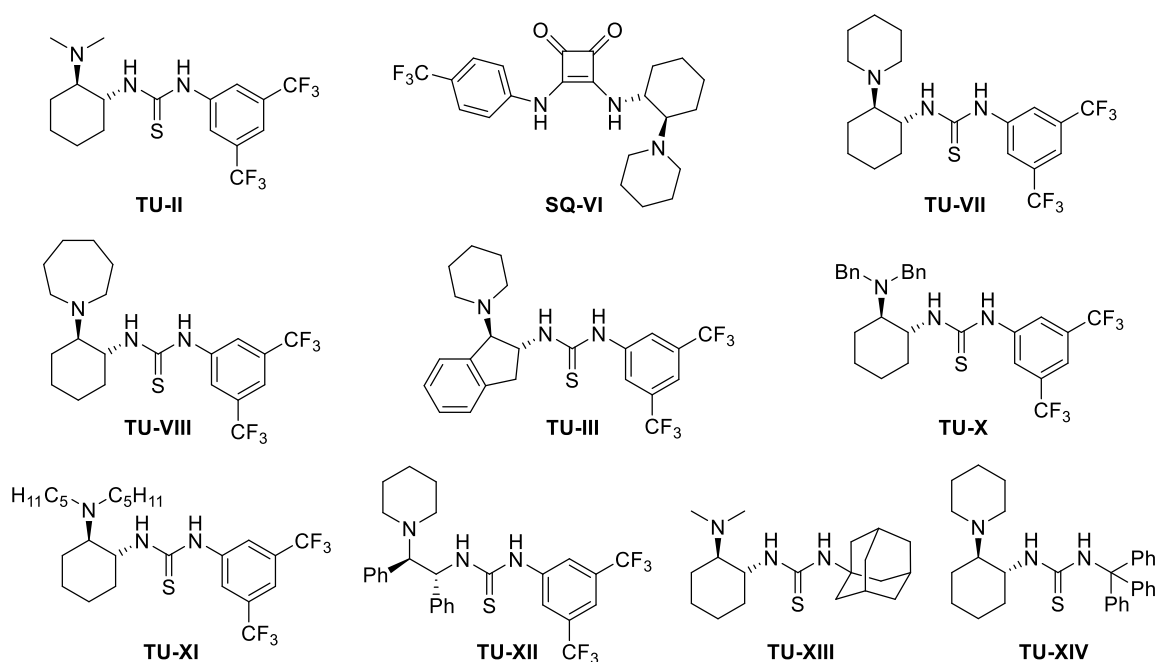
^aReaction conditions: **2.9a** (0.1 mmol), NaHSO₃ (0.25 mmol) and **Cat.** (15 mol%) in MeOH (1 mL) at -30 °C for 3 days. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

We then extended our study to other *Cinchona* alkaloid-derived scaffolds. Regarding cupreine derivatives, catalysts **CU-I** and **CU-II** also provided unsatisfactory enantioselectivities (Table 2.6, entries 5 and 6). In addition, phosphoramidate **PA-I** was also investigated, affording low yield and enantiomeric excess (Table 2.6, entry 7).

Given the unsatisfactory performance of *Cinchona* alkaloid-derived organocatalysts, we turned our attention to other chiral scaffolds (Table 2.7). First, we evaluated catalysts bearing 1,2-cyclohexanediamine motif, starting with Takemoto's and Rawal's catalysts **TU-II** and **SQ-VI**, respectively. In both cases, good yields were obtained but no enantioselectivity was observed (Table 2.7, entries 1 and 2). Notably, the use the more sterically demanding thiourea **TU-VII** led to a slightly improved enantiomeric excess of 26%, along with high yield (Table 2.7 entry 3). Encouraged by this result, we further explored this

organocatalyst family. **TU-VIII**, bearing an azepane ring, resulted in a complete loss of enantioselectivity and a marked decrease in yield (Table 2.7, entry 4). The replacement of the cycloalkyl moiety for linear substituents like benzyl or pentyl groups (**TU-X** and **TU-XI**) also failed to improve the outcome of the reaction (table 2.7 entries 5 and 6). Other chiral scaffolds, including indane-derived **TU-III** and 1,2-diphenylethane-1,2-diamine-derived **TU-XII**, did not improve the performance of **TU-VII** (Table 2.7, entries 7 and 8). In addition, substituting the aromatic ring with sterically demanding scaffolds such as adamantyl or trityl groups was also studied, but none improved our best result so far (**TU-XIII** and **TU-XIV**, Table 2.7, entries 9 and 10).

Table 2.7- Additional catalyst screening focused on non-*Cinchona* alkaloid-derived catalysts.



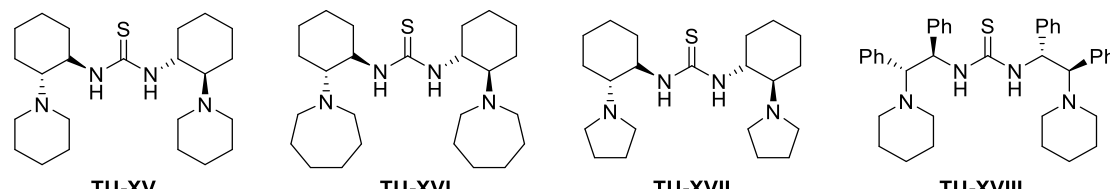
Entry ^a	Catalyst	Yield 2.10a (%) ^b	ee 2.10a (%) ^c
1	TU-II	74	0
2	SQ-VI	85	8
3	TU-VII	69	26
4	TU-VIII	34	8
5	TU-III	13	0
6	TU-X	65	0
7	TU-XI	73	5
8	TU-XII	74	12
9	TU-XIII	32	14
10	TU-XIV	30	4

^aReaction conditions: **2.9a** (0.1 mmol), NaHSO₃ (0.25 mmol) and **Cat.** (15 mol%) in MeOH (1 mL) at -30 °C for 3 days. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

In order to improve the outcome of the reaction and based on the promising performance of **TU-VII**, the novel C₂-symmetric catalyst **TU-XV**, derived from the 1,2-cyclohexanediamine scaffold, was synthesised and evaluated. This catalyst delivered a significant enhancement in enantioselectivity while affording a moderate yield (Table 2.8, entry 1). Since these were the best results obtained so far, catalysts **TU-XVI** and **TU-XVII**, bearing azepane and pyrrolidine rings respectively, were tested to investigate the influence

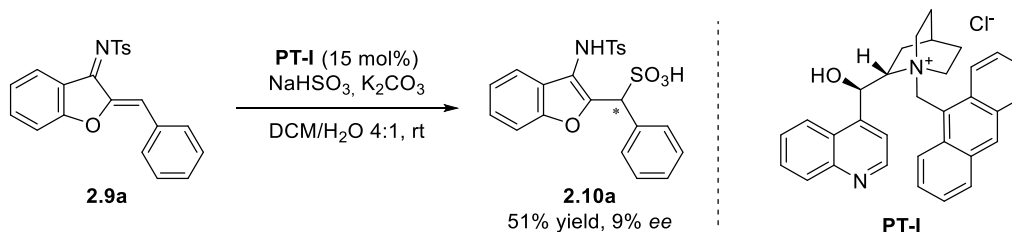
of ring size on the catalytic system. However, both led to lower enantioselectivities despite higher yields were observed (Table 2.8, entries 2 and 3). Finally, **TU-XVIII**, a C₂-symmetric catalyst based on 1,2-diphenylethane-1,2-diamine, was also synthesized and evaluated, but it underperformed in comparison to **TU-XV** (Table 2.8, entry 4).

Table 2.8- C₂-symmetric catalysts evaluated for the addition of NaHSO₃ to aurone-derived azadiene **2.9a**.

			
Entry ^a	Catalyst	Yield 2.10a (%) ^b	ee 2.10a (%) ^c
1	TU-XV	54	47
2	TU-XVI	78	22
3	TU-XVII	85	13
4	TU-XVIII	34	8

^aReaction conditions: **2.9a** (0.1 mmol), NaHSO₃ (0.25 mmol) and **Cat.** (15 mol%) in MeOH (1 mL) at -30 °C for 3 days. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

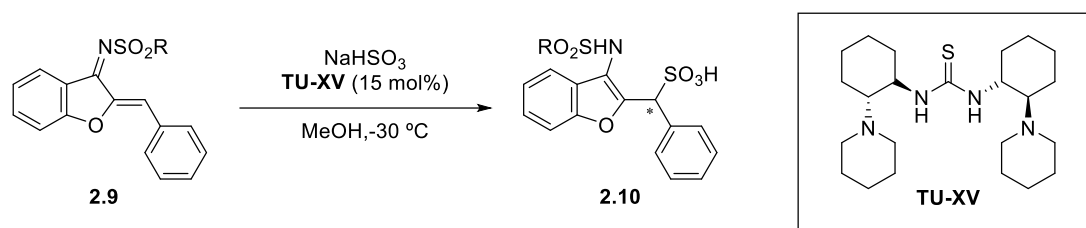
Alternatively, the addition of sodium bisulfite to azadiene **2.9a** was also conducted under phase-transfer conditions employing cinchonidine-derived catalyst **PT-I**. Unfortunately, compound **2.10a** was obtained in low enantiomeric excess and moderate yield, and this approach was therefore discarded (Scheme 2.37).



Scheme 2.37- Addition of NaHSO₃ to aurone-derived azadiene **2.9a** performed under phase-transfer conditions. Reaction conditions: **2.9a** (0.1 mmol), NaHSO₃ (0.25 mmol), K₂CO₃ (0.1 mmol) and **PT-I** (15 mol%) in DCM/H₂O (1 mL, v/v, 4:1) at rt for 3 days.

Based on these results, **TU-XV** was identified as the optimal catalyst, and we next examined the effect of the sulfonamide group on the reaction outcome (Table 2.9). When the reaction was carried out using azadiene **2.9b**, featuring an *N*-phenylsulfonyl moiety, severe erosion of both yield and enantiomeric excess was observed (Table 2.8, entry 2). Conversely, the introduction of a *para*-nitro substituent (**2.9c**) preserved enantioselectivity and slightly improved the yield (Table 2.9, entry 3). Incorporation of substituents which could potentially establish additional interactions with the catalyst, such an *ortho*-methoxy substituent or a 2-pyridyl heterocyclic ring, failed to improve the enantiocontrol of the reaction (Table 2.9, entries 4 and 5). Finally, the mesyl-containing azadiene **2.9f** afforded excellent yield but diminished enantiomeric excess (Table 2.9, entry 6). Considering these results, azadiene **2.9a** was selected as the optimal substrate, despite compound **2.9c** showing marginally better performance, due to its more convenient synthesis.

Table 2.9- Evaluation of the sulfonamide group on the addition of NaHSO₃ to aurone-derived azadienes **2.9**.



Entry ^a	R	Product	Yield (%) ^b	ee (%) ^c
1	<i>p</i> -MeC ₆ H ₄	2.10a	54	47
2	C ₆ H ₅	2.10b	26	10
3	<i>p</i> -NO ₂ C ₆ H ₄	2.10c	61	46
4	<i>o</i> -MeOC ₆ H ₄	2.10d	56	15
5	2-pyridyl	2.10e	80	38
6	Me	2.10f	90	40

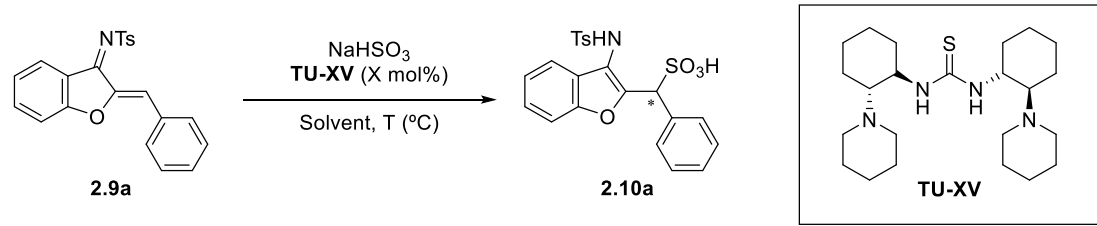
^aReaction conditions: **2.9** (0.1 mmol), NaHSO₃ (0.25 mmol) and **TU-XV** (15 mol%) in MeOH (1 mL) at -30 °C for 3 days. ^bIsolated yield after column chromatography. ^cMeasured using chiral HPLC.

To further optimize the reaction conditions, additional experiments were carried out where the influence of various parameters was evaluated, including substrate concentration, temperature, solvent, and catalyst loading (Table 2.10).

First, the effect of reactant concentration and stoichiometry ratio was evaluated, observing that variations in concentration negatively impacted enantioselectivity (Table 2.10, entries 2 and 3). Similarly, increasing the amount of sodium bisulfite to 3.5 equivalents resulted in a loss of enantioinduction (Table 2.10, entry 4). Next, the influence of the temperature was also considered, performing the reaction at higher temperatures. Unfortunately, although improved yields were obtained, enantioselectivity significantly decreased (Table 2.10, entries 5 and 6). Conversely, further lowering the reaction temperature proved unfeasible, as conducting the reaction at -30 °C already afforded moderate yield and required prolonged reaction times. In addition, reducing the temperature further could lead to solubility issues with compound **2.9a**.

Subsequently, the influence of the solvent was investigated, beginning with the evaluation of various alcohols such as ethanol, isopropanol and 2,2,2-trifluoroethanol. In all cases, poorer reaction outcomes were observed, likely due to the lower solubility of sodium bisulfite in these media (Table 2.10, entries 7 to 9). We then explored the use of co-solvent systems by combining methanol with halogenated, aromatic and ethereal solvents (Table 2.10, entries 10 to 17). Notably, a 1:1 mixture of methanol and tetrahydrofuran delivered the best results in terms of both yield and enantioselectivity (Table 2.10, entry 15). In stark contrast, performing the reaction under the solvent conditions previously used in Chapters II and III led to a complete loss of enantioselectivity, highlighting the incompatibility of water with this reaction system (Table 2.10, entry 18). Finally, catalyst loading was also studied, but both increased or decreased loadings underperformed in both cases (Table 2.10, entries 19 and 20).

Table 2.10- Further optimization experiments performed on the reaction between NaHSO₃ and **2.9a**.



Entry ^a	Solvent ^b	Yield (%) ^c	ee (%) ^d
1	MeOH	54	47
2 ^e	MeOH	83	40
3 ^f	MeOH	89	40
4 ^g	MeOH	72	40
5 ^h	MeOH	83	26
6 ⁱ	MeOH	85	20
7	EtOH	68	29
8	ⁱ PrOH	61	22
9	TFE	27	30
10	MeOH/DCM (1:1)	81	41
11	MeOH/DCE (1:1)	85	40
12	MeOH/Toluene (1:1)	80	23
13	MeOH/MTBE (1:1)	59	23
14	MeOH/1,4-dioxane (1:1)	70	22
15	MeOH/THF (1:1)	89	54
16	MeOH/THF (2:1)	78	31
17	MeOH/THF (1:2)	60	50
18	MeOH/ <i>o</i> -Xylene/H ₂ O (4:2:1.5)	66	3
19 ^j	MeOH/THF (1:1)	87	40
20 ^k	MeOH/THF (1:1)	96	46

^aReaction conditions: **2.9** (0.1 mmol), NaHSO₃ (0.25 mmol) and **TU-XV** (15 mol%), solvent (1 mL) at -30 °C for 3 days. ^bSolvent mixtures are reported as v/v ratios. ^cIsolated yield after column chromatography. ^dMeasured using chiral HPLC. ^eReaction performed using 0.5 mL of MeOH. ^fReaction performed using 2 mL of MeOH. ^gReaction performed using 3.5 equiv. of NaHSO₃. ^hPreaction performed at 0 °C. ⁱReaction performed at RT. ^jReaction performed with 10 mol% of **TU-XV**. ^kReaction performed with 20 mol% of **TU-XV**.

In conclusion, the best reaction conditions identified to date for the *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadiene **2.9a** are as follows: C₂-symmetric thiourea derived from 1,2-cyclohexanediamine **TU-XV** as catalyst at 15 mol% loading, using 1:1 (v/v) mixture of MeOH/THF as solvent, 2.5 equivalents of sodium bisulfite, and tosyl-substituted azadiene **2.9a** at -30 °C. However, these reaction conditions remain suboptimal, as the corresponding amino sulfonic acid **2.10a** was obtained in excellent yield but with only moderate enantiomeric excess (54% ee). Therefore, further investigation is necessary, as the current conditions may have reached the limitations of the catalytic system employed. A deep re-evaluation of the reaction parameters, possibly involving alternative classes of organocatalyst or different catalytic strategies, may be required to achieve higher levels of enantioinduction, which could not be performed as a part of this thesis due to time limitations; however, this study could not be undertaken as part of the present thesis due to time constraints.

Conclusions

The enantioselective *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadienes has been studied under organocatalytic conditions. This reaction represents the first example of the direct addition of sodium bisulfite to 1-azadienes.

In light of the results presented in this chapter, the following conclusions can be drawn:

1. The required aurone-derived azadiene **2.9a** has been successfully synthesised in good yield.
2. The reaction conditions for the enantioselective organocatalytic addition of sodium bisulfite to aurone-derived azadiene **2.9** have been studied. The best conditions identified are as follows: thiourea **TU-XV** as the organocatalysts, a 1:1 (v/v) mixture of MeOH/THF as solvent, tosyl-substituted azadiene **2.9a** and 2.5 equivalents of sodium bisulfite at -30 °C. Under this conditions, amino sulfonic acid **2.10a** was obtained in excellent yield (89%) but with only moderate enantiomeric excess (54% ee).
3. Further studies are required, as the current reaction conditions obtained fail to provide compound **2.10a** with satisfactory levels of enantioselectivity. A deep revision of the reaction parameters optimized, including the catalytic system, will be necessary to achieve the objectives proposed for this chapter.

Part III

Asymmetric Nucleophilic Functionalisation of Ethenesulfonyl Fluoride: Synthesis of Quaternary Chiral Sulfonyl Fluorides

Chapter 5. Enantioselective Organocatalytic Addition of 3-Aryloxindoles to Ethenesulfonyl Fluoride

Introduction

Nucleic acids, proteins, and polysaccharides are condensation polymers composed of small subunits joined by carbon–heteroatom linkages. Inspired by the biosynthetic strategies responsible for assembling such complex structures, where carbon–heteroatom bond formation is favoured over carbon–carbon bond formation, Sharpless and co-workers introduced the concept of *click chemistry* in 2001. This approach aims to provide modular and efficient synthetic strategies for constructing intermolecular linkages through a limited set of reactions that are broad in scope, high yielding, and generate only benign by-products that can be removed without the need for chromatography. Moreover, these reactions are designed to be stereospecific, operationally simple, and compatible with benign or easily removable solvents.^[194]

Several types of transformations have been identified that meet the criteria to be considered “click reactions”, including nucleophilic openings of strained rings, non-aldol carbonyl chemistry, additions to carbon–carbon multiple bonds, and cycloaddition reactions (Figure 3.1). Among these, the copper(I)-catalysed 1,3-dipolar cycloaddition between alkynes and azides to yield 1,2,3-triazoles is unequivocally the premier example of a click reaction, having found widespread application in areas such as bioconjugation, materials science, and drug discovery.^[195] The impact of click chemistry has been so significant, particularly in chemical research, biological applications, and the development of bioorthogonal chemistry, that it was recognized with the 2022 Nobel Prize in Chemistry.^[196]

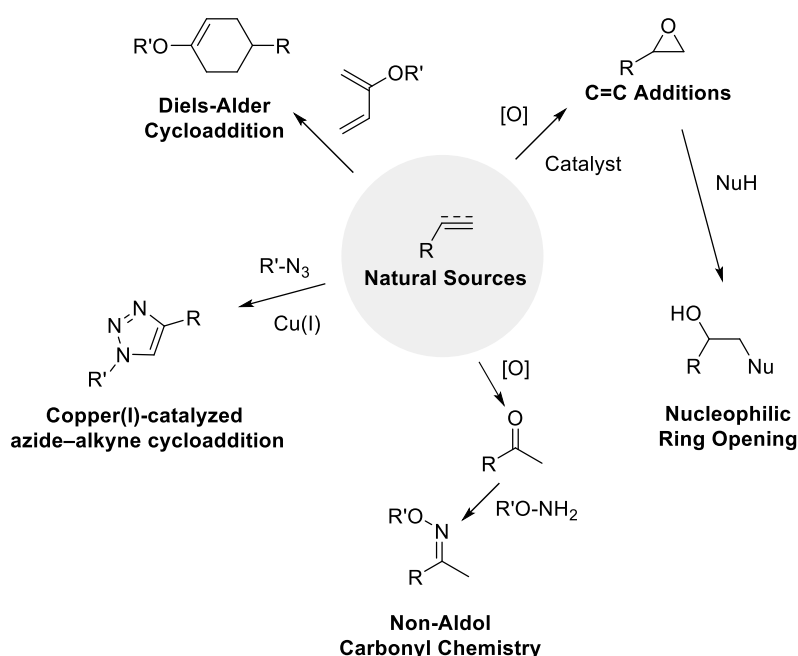
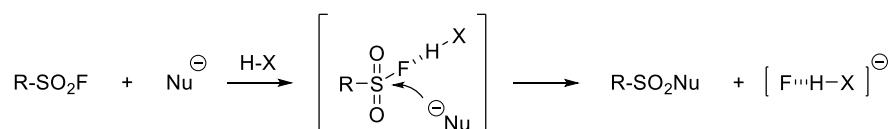


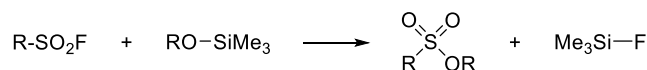
Figure 3.1- Selected examples of reactions that meet Click Chemistry criteria.

In 2014, Sharpless introduced the concept of sulfur(VI) fluoride exchange (SuFEx) *click* reactions, a family of transformations which has since emerged as an efficient and reliable tool for constructing modular intermolecular connections. Unlike chloride analogs, where halide substitution is often hindered by unwanted secondary reactions, sulfur(VI) fluorinated derivatives are reduction resistant, present high thermodynamic stability and react selectively at the sulfur atom, conferring them with high chemical passivity. However, under specific conditions, the S(VI)-F bond can be activated and readily cleaved through stabilization of the departing fluoride ion (Scheme 3.1).^[197]

a) Hydrogen bond-assisted activation:



b) Silicon-assisted activation:



Scheme 3.1- Fundamental role of fluoride stabilization in SuFEx chemistry. a) Activation through stabilization of fluoride *via* formation of hydrogen bond (~40 kcal mol⁻¹). b) Activation assisted *via* formation of silicon fluorides (Si-F ~140 kcal mol⁻¹ vs S(VI)-F 90-80 kcal mol⁻¹).

It is the combination of stability and reactivity of the S(VI)-F bond that enables the application of SuFEx reactions in click chemistry. These transformations have been successfully employed in diverse fields such as organic synthesis, medicinal chemistry, chemical biology, and materials science.^{[198]–[201]} Among the various sulfur(VI) SuFEx hubs, sulfonyl fluorides are one of the most attractive compounds due to their applications in drug development and biological applications (Figure 3.2).^{[202]–[206]}

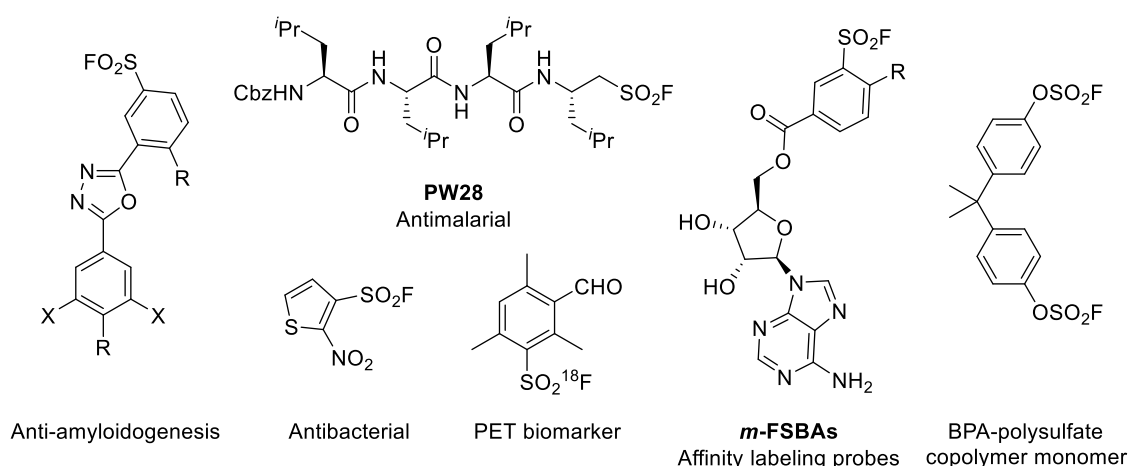
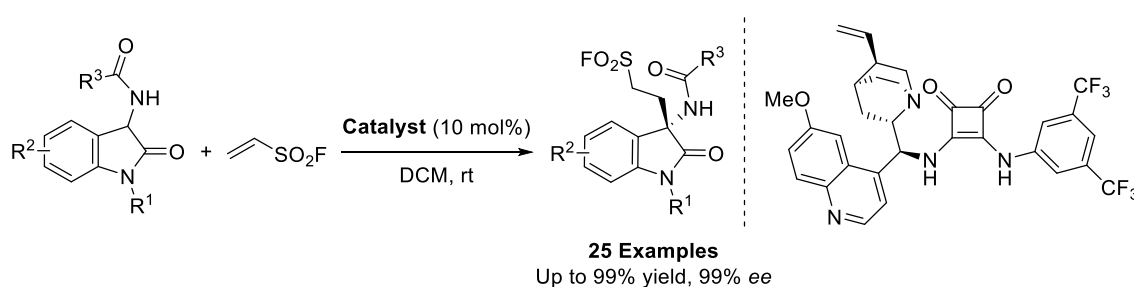


Figure 3.2- Selected molecules containing SuFEx hubs with notable applications.

The synthesis of arylsulfonyl fluorides has been extensively explored, whereas methodologies for the preparation of aliphatic sulfonyl fluorides remain scarce.^[207] In this regard, ethenesulfonyl fluoride (ESF) has emerged as highly versatile SuFEx hub due to its activated double bond, whose extraordinary Michael reactivity allows the formation of stable linkages through conjugate additions.^[208] Furthermore, ESF can be paired with prochiral nucleophiles under asymmetric conditions to afford chiral aliphatic sulfonyl

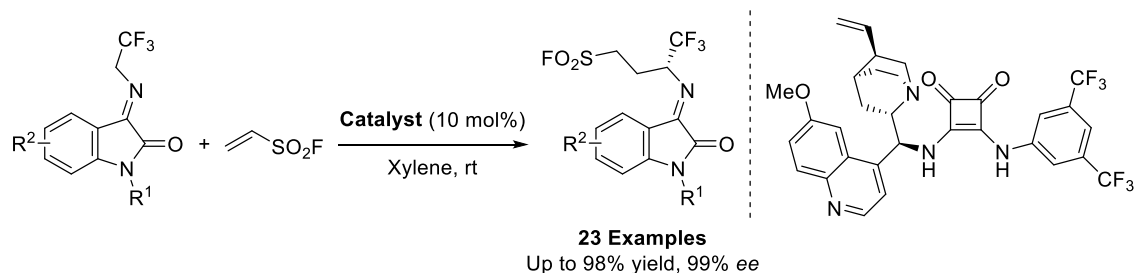
fluoride hubs, which can subsequently undergo SuFEx transformations to access a broad range of chiral sulfonamides and sulfonates, compounds whose relevance has already been discussed in previous chapters of this thesis.

Regarding the use of ESF in asymmetric organocatalysis, only a limited number of examples have been reported to date, all developed by the group of Yan. The first example of its application in enantioselective Michael additions was reported in 2019 and described the reaction between ESF and 3-amido-2-oxindoles, catalysed by a quinine-derived squaramide. The resulting tetrasubstituted adducts were obtained in excellent yields and enantioselectivities and could be subsequently transformed into spirocyclic sultams *via* an intramolecular SuFEx reaction (Scheme 3.2).^[209]



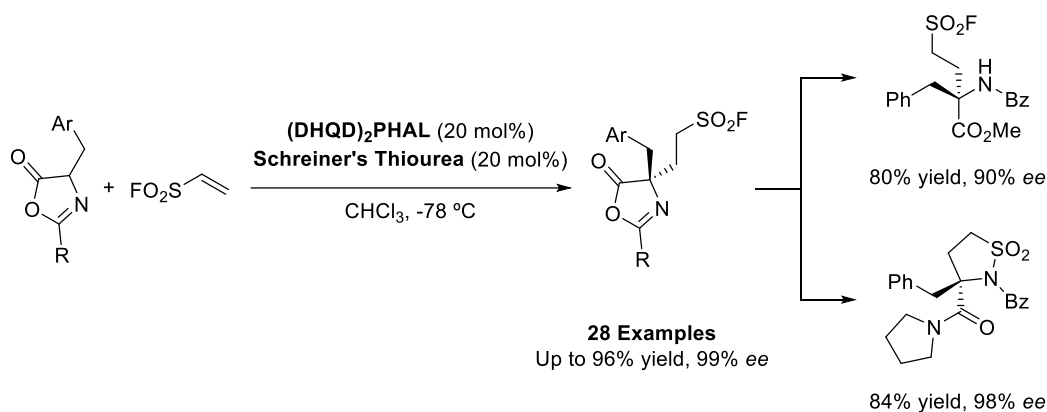
Scheme 3.2- Pioneering work of Yan on organocatalytic asymmetric Michael additions involving ESF.

Subsequently, in 2021, the enantioselective Michael addition of *N*-2,2,2-trifluoroethylisatin ketimines to ESF was reported. The reaction, carried out in the presence of a quinine-derived squaramide, afforded CF_3 -containing sulfonyl fluorides attached to isatin-derived imines with excellent results. Notably, these adducts could also be converted into chiral oxindoles bearing fluorinated sultams *via* intramolecular SuFEx cyclisation (Scheme 3.3).^[210]



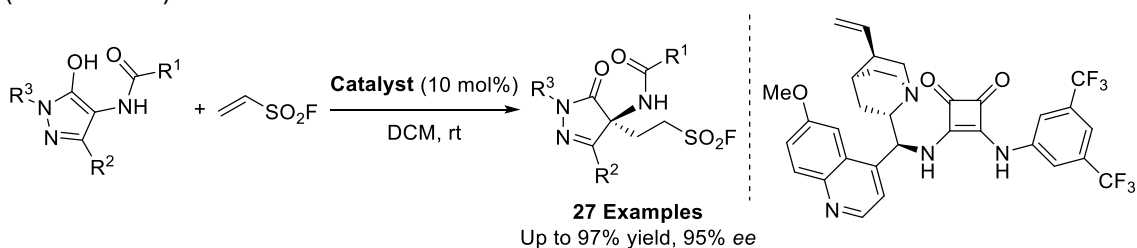
Scheme 3.3- Organocatalytic enantioselective reaction between *N*-2,2,2-trifluoroethylisatin ketimines and ESF.

Later that same year, the enantioselective conjugate addition of azlactones to ESF was disclosed. In this case, a dual catalytic system was employed: the bisdihydroquinidine adduct (DHQD)₂PHAL generated the nucleophilic enolate, while Schreiner's thiourea activated ESF through hydrogen bonding. This approach yielded tetrasubstituted azlactones with high yields and moderate to excellent enantiomeric excess. These adducts proved to be synthetically versatile as they could be readily transformed to obtain chiral tetrasubstituted sultams and α -aminoacids (Scheme 3.4).^[211]



Scheme 3.4- Asymmetric conjugate addition of azlactones to ESF *via* dual catalysis.

Additionally, 4-amido-5-hydroxypyrazoles have also been successfully employed as nucleophiles in the organocatalytic asymmetric Michael addition to ESF. Catalysed by a quinine-derived bifunctional squaramide, the reaction afforded the desired tetrasubstituted pyrazolone-derived SuFEx hubs with excellent results. The resulting adducts were also successfully transformed into sulfonamides and spirocyclic sultams (Scheme 3.5).^[212]



Scheme 3.5- Enantioselective Michael addition of 4-amido-5-hydroxypyrazoles to ESF.

To date, all reported examples have focused on the synthesis of chiral tri- and tetrasubstituted aliphatic sulfonyl fluorides. However, the enantioselective construction of all-carbon stereocentres *via* Michael additions to ESF remains unexplored. In this context, we propose the use of 3-aryl-2-oxindoles as nucleophiles. These indoline-derived heterocycles are known to participate as prochiral nucleophiles, upon treatment with suitable bases, in a variety of asymmetric transformations, including alkylations, Michael additions, Aldol and Mannich reactions.^{[213],[214]} Not only are these compounds of great synthetic utility, but they also appear in numerous natural products and pharmaceutical agents exhibiting a wide range of biological activities, such as anticancer, antibacterial, anti-inflammatory, and anti-Alzheimer's properties (Figure 3.3).^{[215]–[219]}

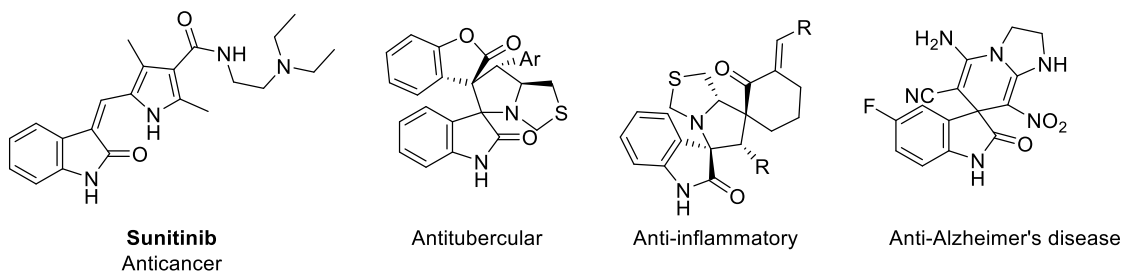
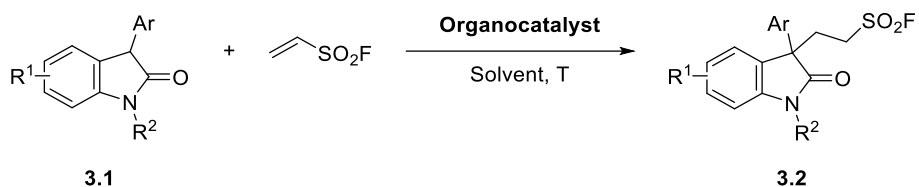


Figure 3.3- Illustrative examples of bioactive indole-containing molecules.

Motivated by these considerations, this chapter explores the enantioselective Michael addition of 3-aryl-2-oxindoles to ESF and under organocatalytic conditions.

Objectives

The main objective for this chapter is to develop an enantioselective organocatalytic methodology for the construction of quaternary stereocentres *via* the conjugate addition of 3-aryloxindoles **3.1** to ethenesulfonyl fluoride.



To this end, the following secondary objectives have been proposed:

1. Synthesis of the required starting materials **3.1**, bearing various protecting groups and substituents with different electronic and steric properties.
2. Optimization of the reaction conditions between ethenesulfonyl fluoride and 3-aryloxindole **3.1a** to obtain the corresponding sulfonyl fluoride **3.2a** with the highest yield and enantioselectivity.
3. Study of the scope of the reaction between ethenesulfonyl fluoride and different aromatic, aliphatic and heterocyclic oxindoles **3.1**.
4. Applicability and synthetic transformations over the reaction products.

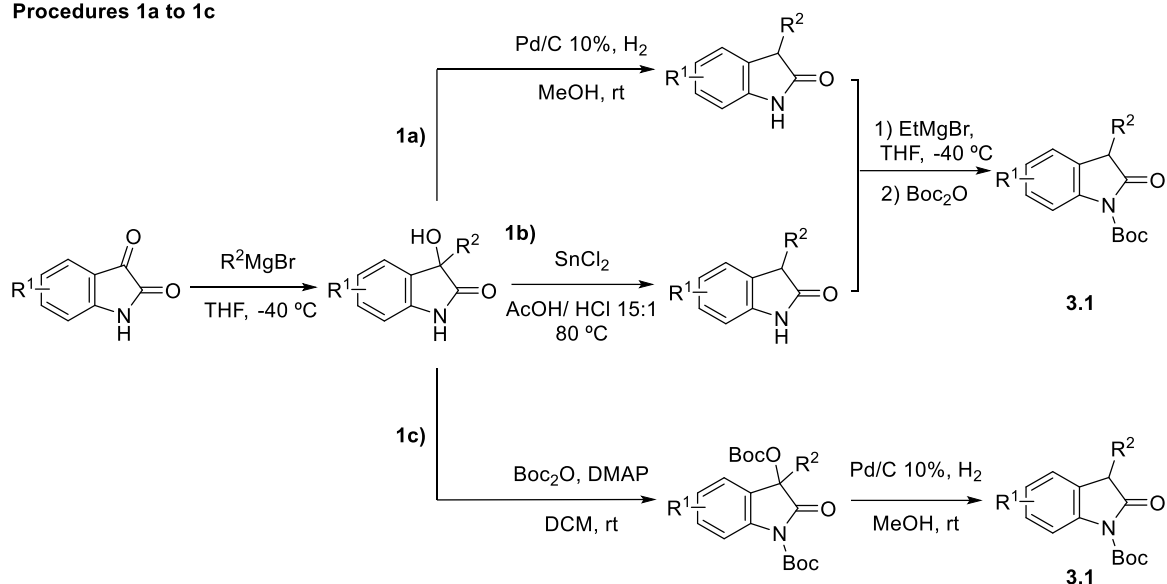
Synthesis of 3-Substituted Oxindoles 3.1

Chemical structures of 20 indole-3-carboxamide derivatives (3.1a-3.1z) are shown, along with their respective yields:

- 3.1a**, 41% yield
- 3.1b**, 15% yield
- 3.1c**, 46% yield
- 3.1d**, 26% yield
- 3.1e**, 36% yield
- 3.1f**, 29% yield
- 3.1g**, 24% yield
- 3.1h**, 11% yield
- 3.1i**, 37% yield
- 3.1j**, 13% yield
- 3.1k**, 20% yield
- 3.1l**, 26% yield
- 3.1m**, 17% yield
- 3.1n**, 26% yield
- 3.1o**, 28% yield
- 3.1p**, 19% yield
- 3.1q**, 7% yield
- 3.1r**, 16% yield
- 3.1s**, 22% yield
- 3.1t**, 14% yield
- 3.1u**, 55% yield
- 3.1v**, 78% yield
- 3.1w**, 55% yield
- 3.1x**, 13% yield
- 3.1y**, 27% yield
- 3.1z**, 9% yield

Compounds **3.1a**, **3.1b**, **3.1d**, **3.1h**, **3.1j**, **3.1l** and **3.1n** were prepared according to **Procedure 1a** (Scheme 3.7, 1a).^{[220],[221]} In this approach, the corresponding isatins were treated with Grignard reagents to yield the intermediate 3-hydroxy-3-aryloxindoles. These intermediates were subsequently hydrogenated using Pd/C to afford the corresponding 3-aryloxindoles, which were finally protected with Boc₂O using ethylmagnesium bromide as a base to afford the desired compounds **3.1**.

Procedures 1a to 1c



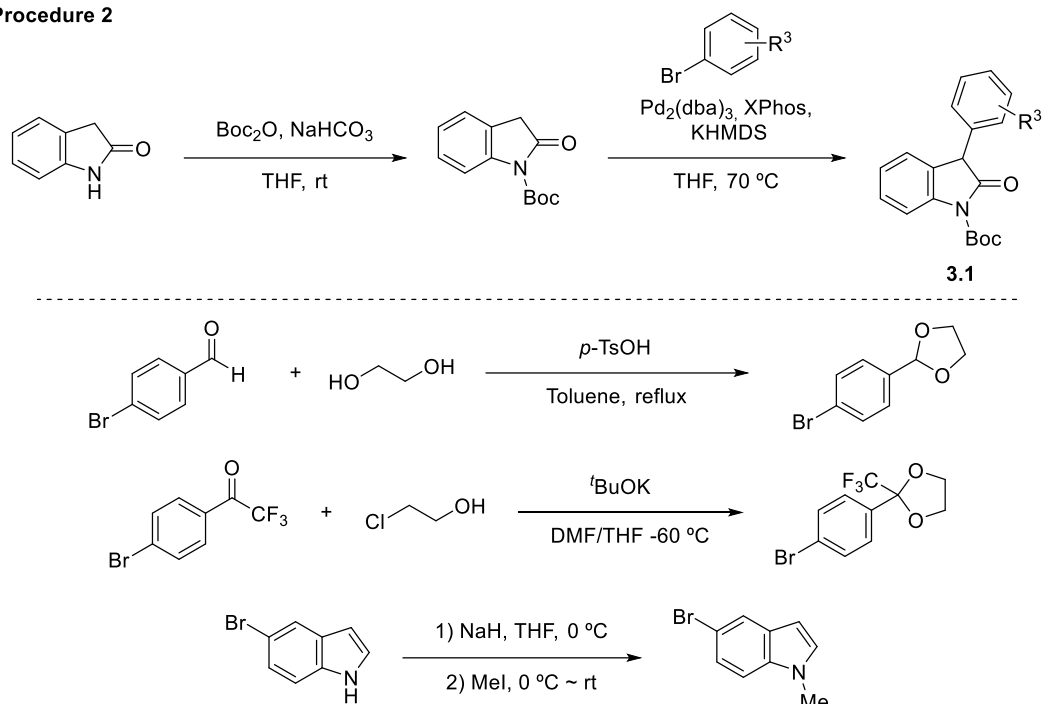
Scheme 3.7- Procedures 1a to 1c for the synthesis of the required *N*-protected 3-aryloxindoles **3.1**.

A similar approach was followed to obtain compounds **3.1c**, **3.1e**, **3.1f**, **3.1g**, **3.1i** and **3.1u**, which were synthesised following **Procedure 1b** (Scheme 3.7, 1b).^[221] After the initial Grignard reaction, the resulting alcohol intermediates were reduced using stannous chloride under acidic conditions, yielding the corresponding 3-aryloxindoles. These were then protected to afford *N*-protected 3-aryloxindoles.

For the preparation of compounds **3.1k** and **3.1w**, **Procedure 1c** was followed (Scheme 3.7, 1c).^[220] In this case, after Grignard addition, the resulting intermediates were directly protected with Boc_2O and DMAP . The corresponding *N*-Boc protected compounds were subsequently subjected to hydrogenolysis, delivering the final *N*-Boc 3-aryloxindoles.

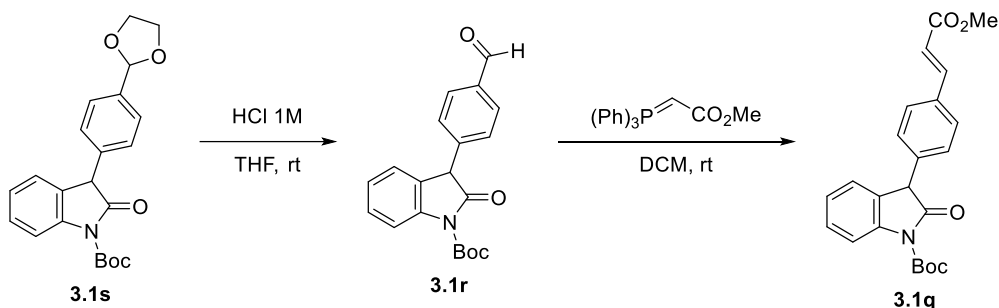
A different synthetic strategy was followed to obtain compounds **3.1m**, **3.1p**, **3.1s**, **3.1t** and **3.1v**, which were obtained *via* **Procedure 2** (Scheme 3.8).^{[222],[223]} This method involved a cross-coupling reaction between aryl bromides and potassium enolates generated *in situ* by treatment of *N*-Boc oxindole with potassium hexamethyldisilazide. For compounds **3.1s** and **3.1t**, the required aryl bromides were not commercially available and were thus synthesised through acetal-forming reactions.^{[224],[225]} In the case of compound **3.1v**, the corresponding aryl bromide was obtained via methylation of 5-bromoindole.^[226]

Procedure 2



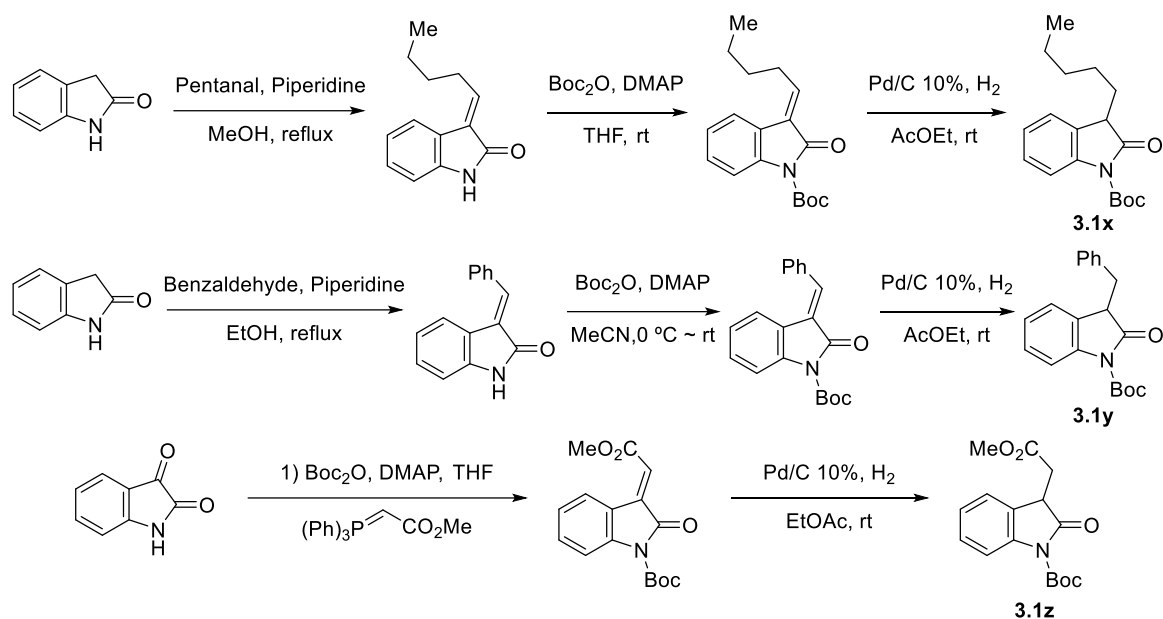
Scheme 3.8- Procedure 2 for the synthesis of the required *N*-protected 3-aryloxindoles **3.1**. Preparation of aryl bromides required for the synthesis of compounds **3.1s**, **3.1t** and **3.1v**.

Regarding carbonyl-containing 3-aryloxindoles, compound **3.1r** was obtained *via* the acid-catalysed hydrolysis of ketal **3.1s**.^[227] A subsequent Wittig reaction carried out on **3.1r** led to the formation of **3.1q** (Scheme 3.9).^[228]



Scheme 3.9- Synthesis of carbonyl-containing 3-aryloxindoles **3.1r** and **3.1q**.

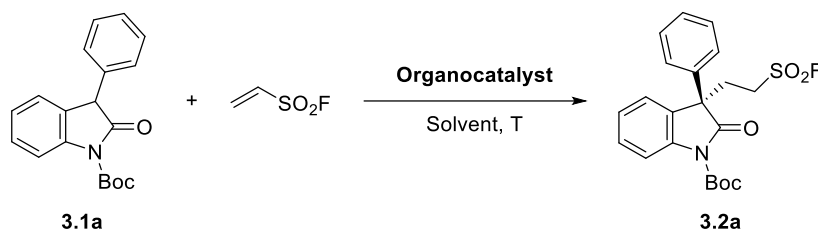
As for aliphatic derivatives, compounds **3.1x** and **3.1y** were synthesised through three-step sequences.^{[229],[230]} Initially, a Knoevenagel condensation between isatin and the corresponding aldehyde generated an oxindole derivative bearing an exocyclic double bond. This intermediate was then protected with Boc_2O and DMAP, followed by hydrogenation to yield the target *N*-Boc oxindoles. Compound **3.1z** was obtained *via* a two-step process starting with a one-pot reaction involving isatin protection followed by a Wittig reaction. The resulting olefinic oxindole intermediate was subjected to hydrogenation to afford compound **3.1z** (Scheme 3.10).^[230]



Scheme 3.10- Synthetic procedures for the obtention of aliphatic compounds **3.1x-z**.

Optimization of the Reaction Conditions

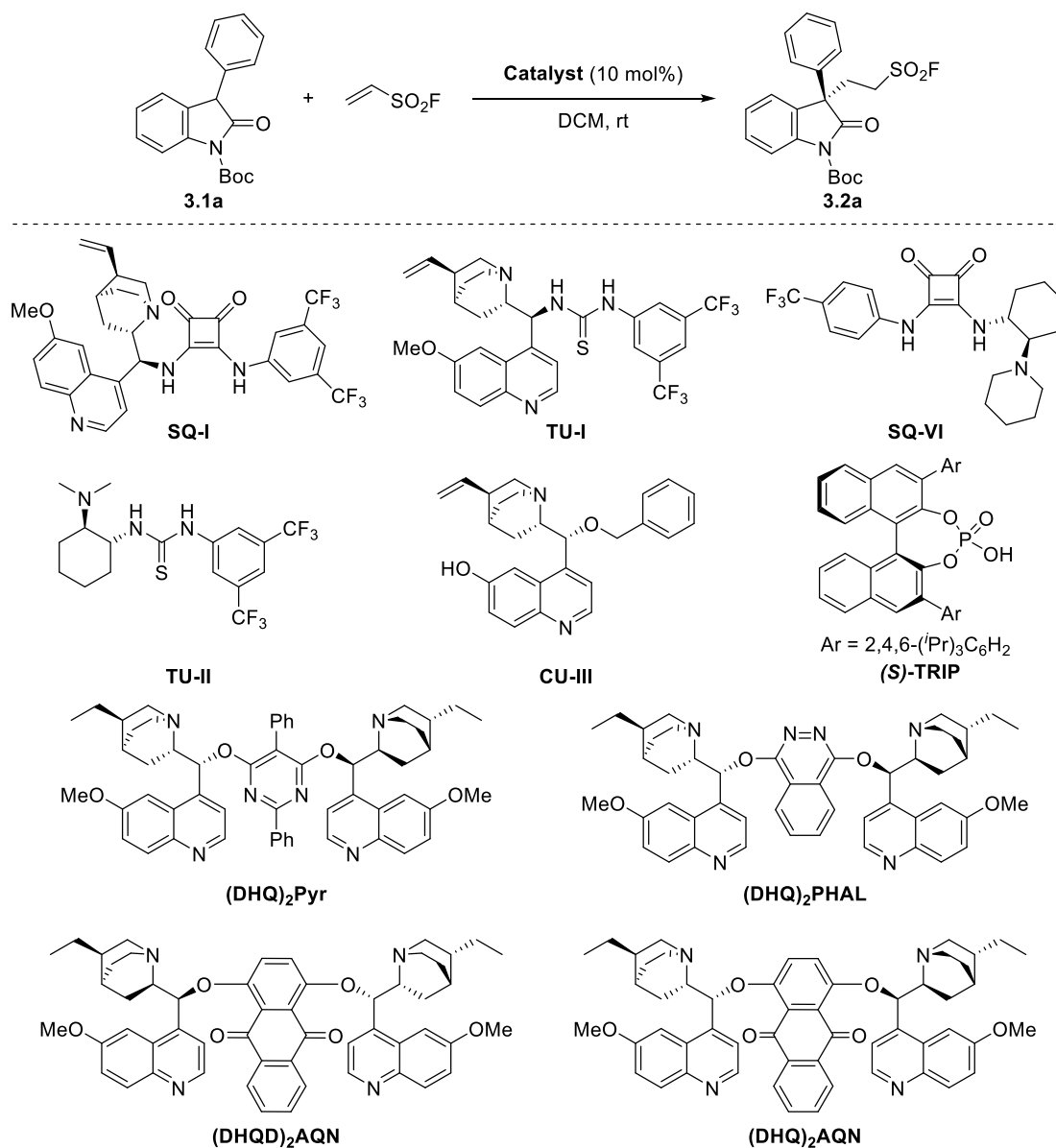
To investigate the enantioselective organocatalytic construction of quaternary stereocentres *via* the conjugate addition of 3-aryloxindoles **3.1** to ethenesulfonyl fluoride (ESF), compound **3.1a** was selected as a model substrate to optimize the reaction conditions (Scheme 3.11).



Scheme 3.11- Model reaction selected for the optimization process.

We initiated our optimization study by conducting an organocatalyst screening (Table 3.1). As a starting point, we evaluated two bifunctional catalysts derived from quinine, squaramide **SQ-I** and thiourea **TU-I**, which afforded compound **3.2a** in quantitative yields, albeit with poor enantioselectivity (Table 3.1, entries 1 and 2). Subsequently, catalysts based on *trans*-1,2-cyclohexanediamine **SQ-VI** and **TU-II** were tested, but similar results were observed, as both provided quantitative yields with low enantiomeric excesses (Table 3.1, entries 3 and 4). Cupreine **CU-III** was also evaluated but it did not improve the outcome of the reaction (Table 3.1, entry 5). In addition, a control experiment performed in the absence of the catalyst clearly demonstrated that its presence is essential for the reaction to take place, as no background reaction was observed (Table 3.1, entry 6).

Table 3.1- Catalysts evaluated for the enantioselective addition of 3-phenyloxindole 3.1a to ESF.



Entry ^a	Catalyst	t (days)	Yield 3.2a (%) ^b	ee 3.2a (%) ^c
1	SQ-I	1	99	23
2	TU-I	1	99	6
3 ^d	SQ-VI	2	99	6
4 ^d	TU-II	1	97	8
5 ^d	CU-III	2	89	17
6	-	1	0	-
7	(S)-TRIP	4	0	-
8	(DHQ)₂PHAL	1	96	31
9	(DHQ)₂PYR	1	99	67
10	(DHQ)₂AQN	1	99	63
11	(DHQD)₂AQN	1	99	75

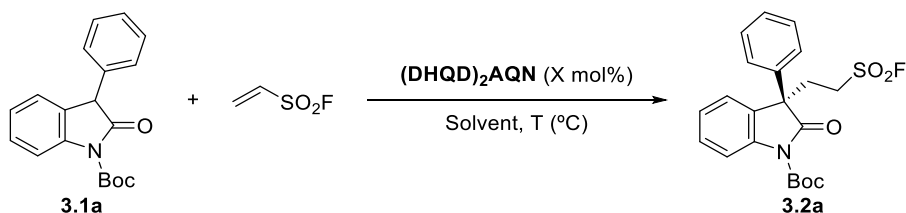
^aReaction conditions: **3.1a** (0.1 mmol), ESF (0.1 mmol) and **Cat.** (10 mol%) in DCM (1 mL) at 0 °C.

^bCrude yield after filtration through a silica pad. ^cMeasured using chiral HPLC. ^dReaction carried out at 0 °C.

Given the unsatisfactory performance of bifunctional thioureas and squaramides, alternative organocatalyst families were also explored. The chiral Brønsted acid (**S**)-TRIP was then evaluated, but it proved incapable to promote the desired reaction (Table 3.1, entry 7). We next turned our attention to chiral Brønsted bases derived from bisdihydroquinine adducts, starting with (**DHQ**)₂PHAL, (**DHQ**)₂PYR and (**DHQ**)₂AQN (Table 3.1, entries 8 to 10). All three catalysts efficiently promoted the reaction, providing **3.2a** in quantitative yields. Although the phthalazine derivative did not offer any significant improvement in enantioselectivity, the pyrimidine and anthraquinone adducts markedly improved enantioselectivity, reaching 67% and 63% ee, respectively. Finally, evaluation of the pseudoenantiomer (**DHQD**)₂AQN led to the best results, yielding compound **3.2a** in quantitative yield and 75% enantiomeric excess (Table 3.1, entry 11). Considering these results, (**DHQD**)₂AQN was selected as the optimal catalyst for further studies.

We then proceeded to optimize additional reaction parameters, including the use of additives, temperature, solvent and catalyst loading (Table 3.2). First, the reaction was conducted in the presence of a 10 mol% of Schreiner's thiourea,^[231] since its use has previously been reported to enhance enantioselectivity in bisdihydroquinidine adduct-catalyzed asymmetric conjugate additions to ESF.^[232] Unfortunately, in our reaction it proved to have no effect on the reaction outcome, as identical levels of enantioinduction were observed in its presence and absence (Table 3.2, entries 1 and 2).

Table 3.2- Further optimization experiments performed on the reaction between ESF and **3.1a**.



Entry ^a	Solvent	T (°C)	Yield 3.2a (%) ^b	ee 3.2a (%) ^c
1	DCM	rt	99	75
2 ^d	DCM	rt	97	76
3	DCM	0	99	84
4	DCM	-20	97	91
5	DCE	-20	97	89
6	Toluene	-20	95	88
7	EtOH	-20	96	73
8	EtOAc	-20	93	88
9	MTBE	-20	96	89
10	Et ₂ O	-20	99	94
11	THF	-20	97	93
12 ^f	THF	-78	95 ^e	97
13 ^g	THF	-78	99	95

^aReaction conditions: **3.1a** (0.1 mmol), ESF (0.1 mmol) and (**DHQD**)₂AQN (10 mol%) in 1 mL of solvent overnight. ^bCrude yield after filtration through a silica pad. ^cMeasured using chiral HPLC.

^dReaction carried out in the presence of 10 mol% of Schreiner's thiourea. ^eIsolated yield of **3.2a**.

^fReaction time of 3 h. ^gReaction performed with 5 mol% of catalyst loading.

Subsequent evaluation of the reaction temperature revealed a significant impact on enantioselectivity. When the reaction was performed at 0 °C and -20 °C, compound **3.2a** was obtained in quantitative yield in both cases, while the enantiomeric excess improved to 84% and 91%, respectively (Table 3.2, entries 3 and 4).

Next, we investigated the effect of the solvent at -20 °C. The use of halogenated, aromatic and polar protic solvents resulted in a slight erosion of enantioselectivity (Table 3.2, entries 5 to 7). Regarding polar aprotic solvents (table 3.2, entries 8 to 11), ether-type solvents provided the best results, affording the desired Michael adduct in quantitative yields and improved enantiomeric excesses when diethyl ether and tetrahydrofuran were used (94% and 93%, respectively). Tetrahydrofuran was chosen as the optimal solvent over diethyl ether due to its improved usability properties.

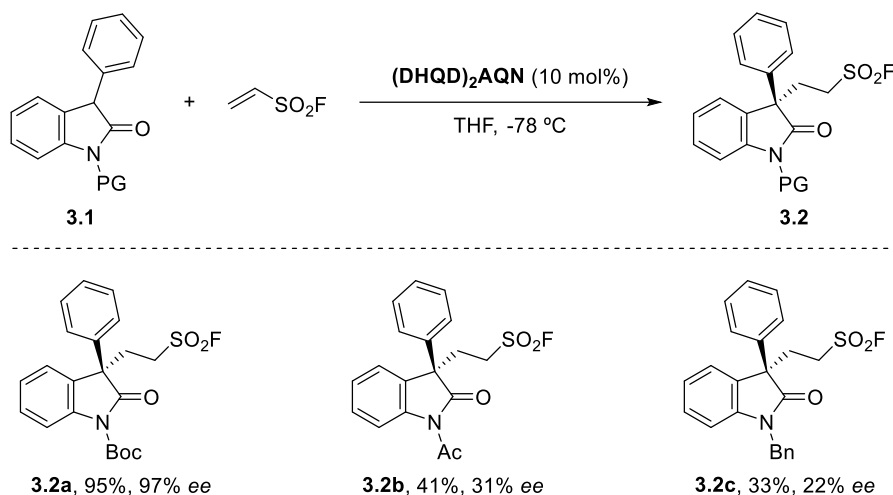
At this point, the reaction was performed at -78 °C and, to our delight, compound **3.2a** was obtained in excellent yield and enantioselectivity (Table 3.2, entry 12). Furthermore, careful monitoring of the reaction progress revealed that full conversion was achieved in under 3 hours. Under these conditions, the reaction was carried out using 5 mol% catalyst loading, observing a minimal enantioselectivity decrease while maintaining quantitative yield (Table 3.2, entry 12). Therefore, as the catalyst is commercially available and inexpensive, subsequent experiments were conducted with 10 mol% catalyst loading.

In conclusion, the optimal reaction conditions for the model reaction ESF and 3-phenyloxindole **3.1a** are as follows: bisdihydroquinidine adduct (**DHQD**)₂**AQN** as the catalyst at a 10 mol% loading, THF as solvent, and a 1:1 stoichiometric ratio of electrophile to nucleophile at -78 °C.

Scope of the Reaction with 3-substituted oxindoles

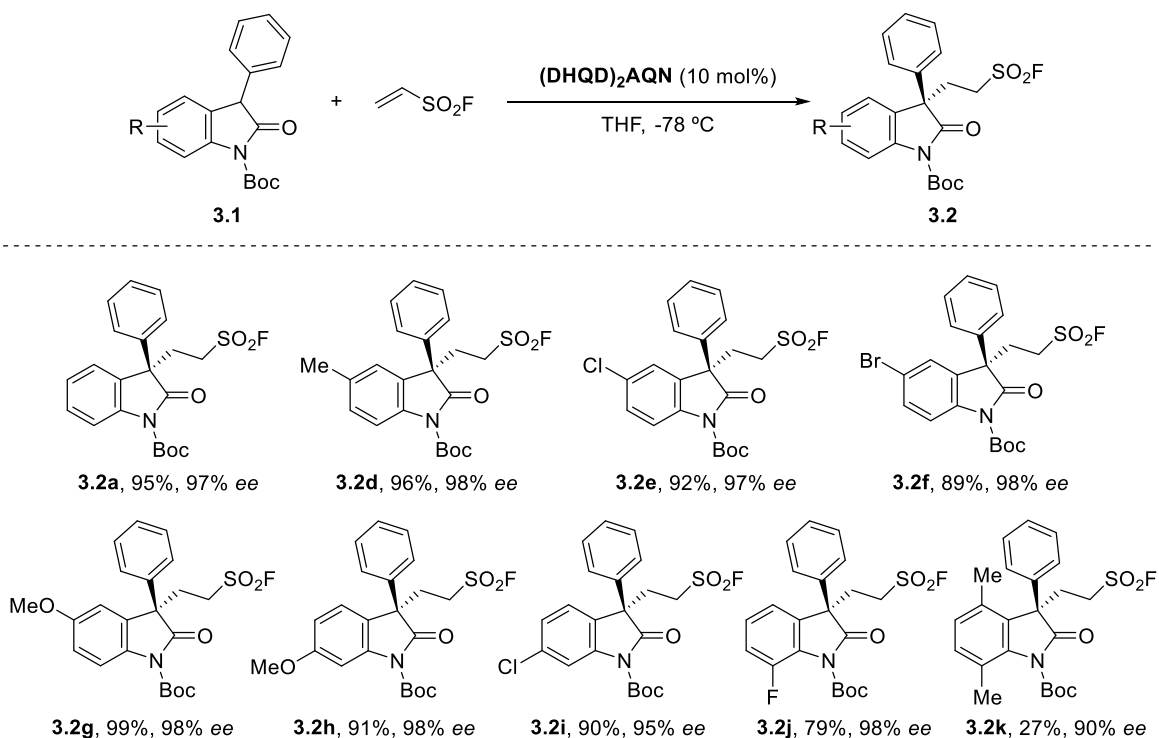
Once the optimal reaction conditions had been established, we proceeded to investigate the influence of different substituents on the 3-substituted oxindoles **3.1** on the outcome of the reaction.

We began by evaluating the effect of different protecting groups on the nitrogen atom of 3-phenyloxindole (Scheme 3.12). Both *N*-acetyl and *N*-benzyl-protected derivatives performed poorly under the optimized reaction conditions, affording compounds **3.2b** and **3.2c** in low yields and enantioselectivities. As a result, all subsequent studies were carried out employing *N*-Boc-protected oxindoles.



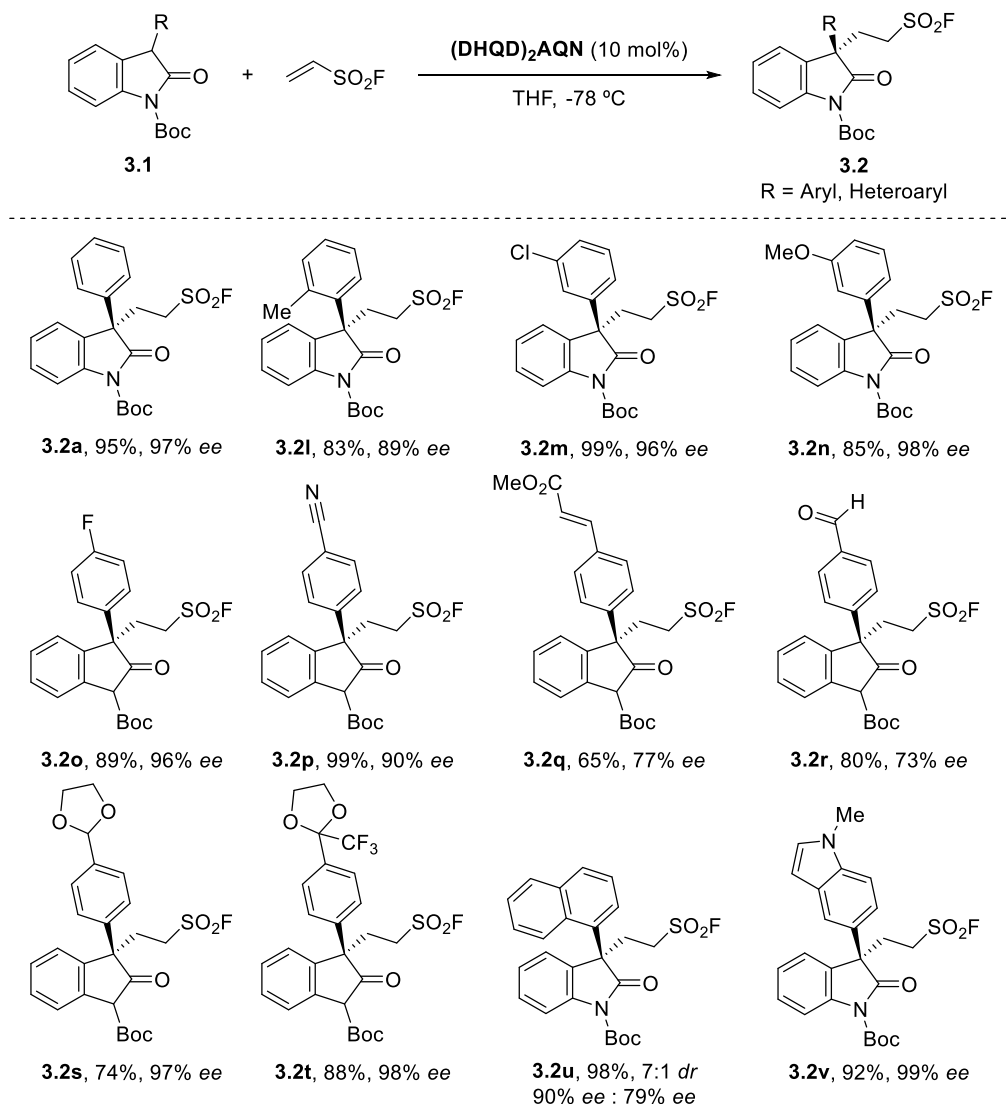
Scheme 3.12- Evaluation of the protecting group effect on the outcome of the reaction.

Regarding 3-phenyloxindoles (Scheme 3.13), the introduction of either electron-donating or electron-withdrawing groups at position 5 was well tolerated, regardless of their electronic nature. In all cases, the corresponding addition products **3.2d-3.2g** were obtained in excellent to quantitative yields and with nearly perfect enantioselectivity (89-99% yield, 97-98% ee). Substitution at position 6 was also well tolerated, as demonstrated by the excellent results achieved upon introduction of a methoxy group (**3.2h**, 99%, 98% ee) or a chlorine atom (**3.2i**, 90%, 95% ee). Additionally, fluorinated substrates were compatible with the reaction conditions, providing compound **3.2j** in 79% yield and 98% ee. To assess the impact of substitution at position 4, the 4,7-disubstituted substrate **3.1k** was tested. As expected, the increased steric hindrance near the reaction site led to a slower transformation and significantly diminished yield, although the enantioselectivity remained high (**3.2k**, 27%, 90% ee).



Scheme 3.13- Study of the scope of the reaction with different 3-phenyloxindoles.

We next turned our attention to the scope on the 3-aryl group (Scheme 3.14). The presence of a methyl group in the *ortho*-position led to a sluggish reaction due to the increased steric interference near the forming quaternary centre. Even so, product **3.2l** was obtained in high yield and enantioselectivity (83%, 89% ee). Conversely, less sterically demanding *meta*- and *para*-substituted oxindoles reacted smoothly, affording compounds **3.2m-3.2o** in excellent yields and enantiomeric excesses (85-99%, 96-98% ee).



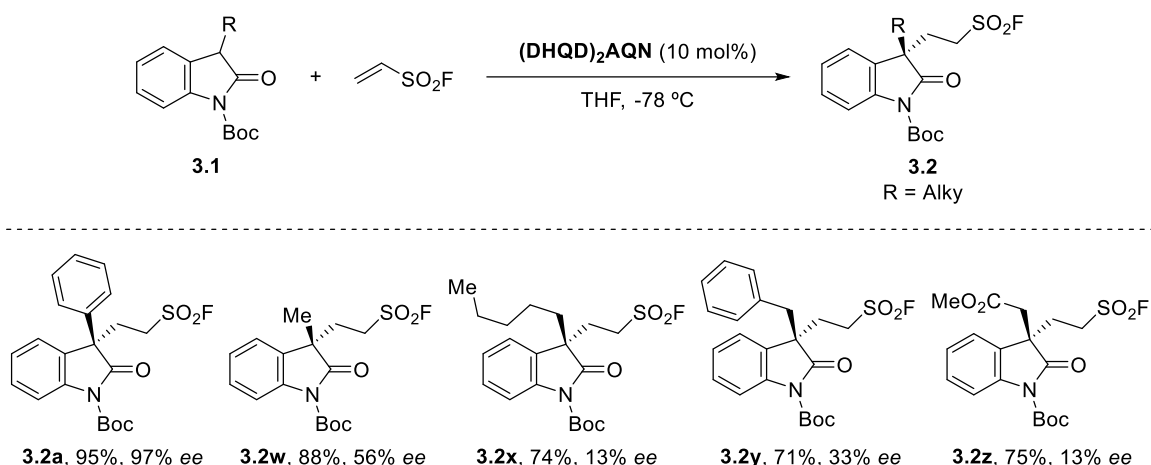
Scheme 3.14- Study of the scope of the reaction with different 3-aryloxindoles.

At this point, we explored more challenging 3-aryloxindole derivatives to assess the robustness of the methodology. The nitrile-containing substrate **3.1p** reacted efficiently, affording **3.2p** in excellent yield and with slightly decreased but still notable enantioselectivity (99%, 90% ee). We then investigated carbonyl-containing substrates, which provided adducts **3.2q** and **3.2r** in moderate to good yields (65-77%), but with a significant decrease in enantiomeric excess (73-77%). We rationalize these results due to potential additional interactions between the catalyst and the carbonyl group, which may interfere with the stereochemical pathway of the reaction and lead to reduced enantioinduction. Fortunately, this limitation could be readily circumvented by employing cyclic acetals as carbonyl surrogates, as it is demonstrated by the obtention of the

dioxolane-containing **3.2s** and trifluoromethyl ketone-derived acetal **3.2t** in good to high yields and with excellent enantioselectivities (74%, 97% ee and 88%, 98% ee, respectively).

Extended aromatic systems were also compatible with the reaction conditions, as demonstrated by the formation of 1-naphtyl derivative **3.2u** in quantitative yield as a 7:1 mixture of atropoisomers. The major diastereomer was obtained with 90% ee, while the minor one exhibited a slightly lower enantioselectivity (70% ee). Moreover, the methodology was successfully extended to heteroaromatic substrates. In particular, when the *N*-methylindole-containing oxindole **3.1v** was employed, the corresponding product **3.2v** was isolated in excellent yield and with complete regio- and enantioselectivity (92%, 99% ee).

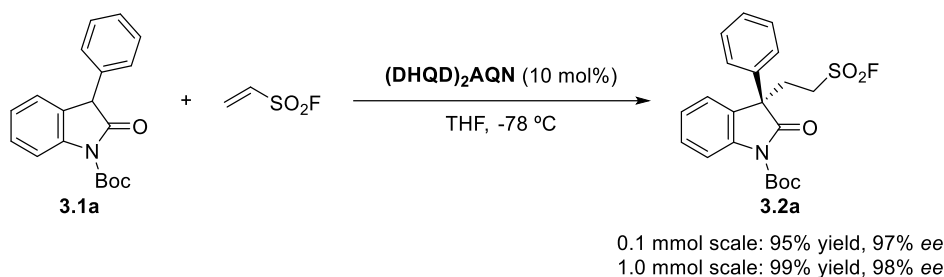
Finally, encouraged by the excellent results obtained with aryl-substituted oxindoles, we turned our attention to 3-alkyl-substituted derivatives (Scheme 3.15). As expected, this class of substrates proved more challenging due to their lower reactivity, reduced steric bulk, and greater conformational flexibility. Although 3-methyloxindole afforded **3.2w** high yield, a marked decrease in enantioselectivity was observed (56% ee). Even poorer results were obtained with substrates bearing pentyl, benzyl, or CH₂CO₂Me groups at position 3, as compounds **3.2x-3.2z** were obtained with in slightly lower yields (71-71%) and with unsatisfactory enantiomeric excesses (13-33% ee).



Scheme 3.15- Study of the scope of the reaction with different 3-alkyloxindoles.

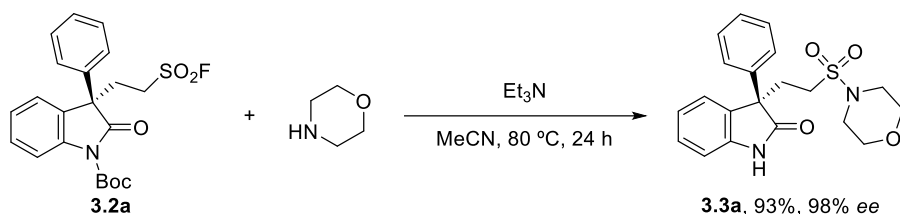
Applicability and Synthetic Transformations

The robustness of the procedure was demonstrated carrying out the synthesis of compound **3.2a** on a 1 mmol scale. Under these conditions, the addition of oxindole **3.1a** to ESF proceeded smoothly, affording the corresponding addition adduct in comparable yield and enantioselectivity (Scheme 3.16).



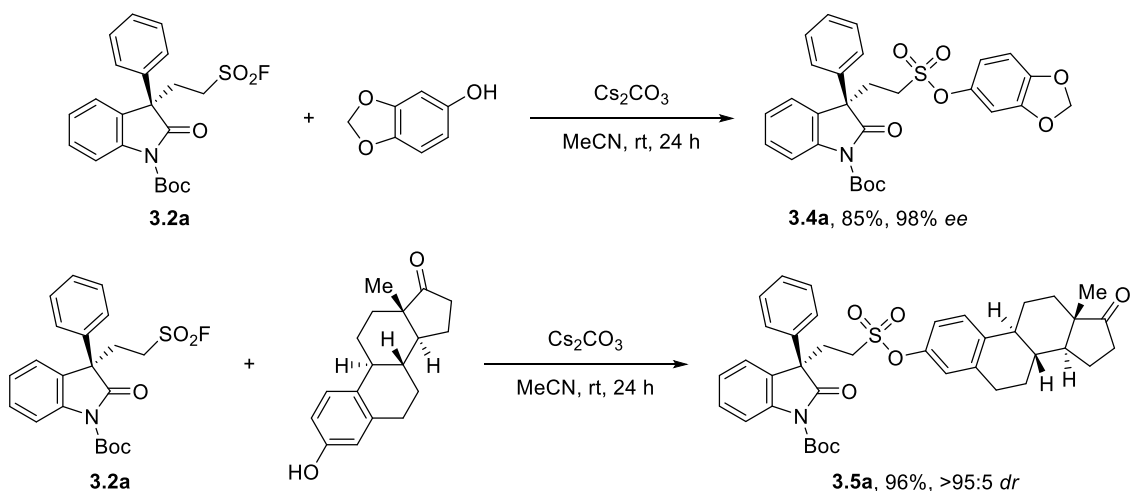
Scheme 3.16- 1 mmol scale synthesis of alkylsulfonylfluoride **3.2a**.

Subsequently, the alkylsulfonylfluoride **3.2a** was subjected to various SuFEx reactions to showcase its synthetic versatility. Treatment of **3.2a** with morpholine in the presence of triethylamine led to the efficient formation of sulfonamide **3.3a** in excellent yield and with full retention of enantioselectivity. Notably, under these reaction conditions, concomitant *N*-Boc deprotection occurred, affording free *N*-H oxindole (Scheme 3.17).



Scheme 3.17- Synthesis of sulfonamide **3.3a** via a SuFEx reaction between **3.2a** and morpholine.

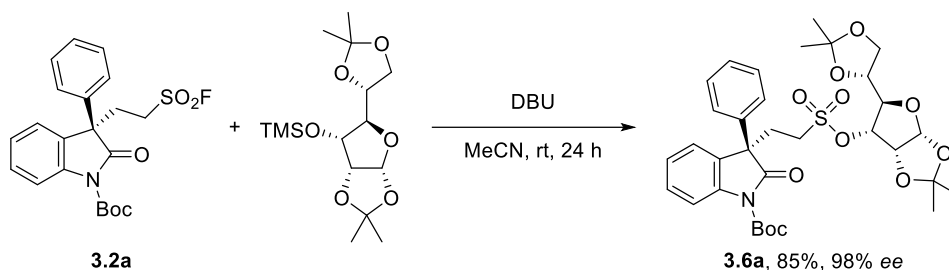
Sulfonates were also successfully synthesised, as evidenced by the formation of derivative **3.4a** upon treatment of **3.2a** with sesamol and Cs_2CO_3 . The reaction proceeded in high yield with complete preservation of the enantiomeric excess. Moreover, the method proved compatible with more complex nucleophiles, as demonstrated by the synthesis of the estrone-derived sulfonate **3.5a**, obtained in excellent yield and selectivity (Scheme 3.18).



Scheme 3.18- Synthesis of sulfonates **3.4a** and **3.5a** via SuFEx reactions of **3.2a**.

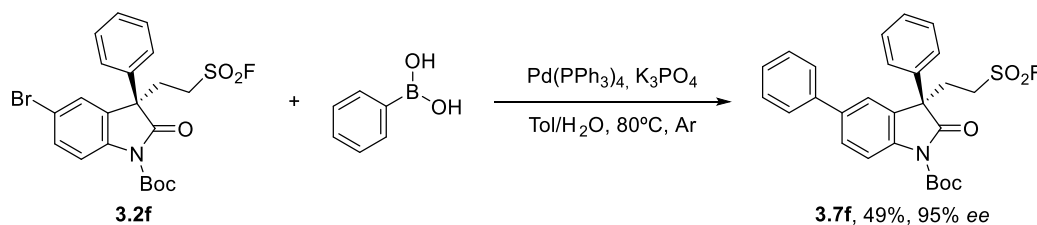
In addition, a sulfonate derived from 1,2:5,6-di-*O*-isopropylidene- α -D-allofuranose was also synthesised. In this case, a different synthetic approach was followed, wherein compound **3.2a** was reacted with the TMS-protected sugar, thus promoting the SuFEx reaction through the formation of the thermodynamically favoured TMS-F. The

corresponding sulfonate **3.6a** was obtained in high yield and with perfect diastereoselectivity (Scheme 3.19).



Scheme 3.19- Synthesis of sugar-derived sulfonate **3.6a** *via* the SuFEx reaction of **3.2a** with TMS-protected 1,2:5,6-di-O-isopropylidene-α-D-allofuranose.

Finally, the orthogonal reactivity of the -SO₂F functional group was demonstrated through a Suzuki cross-coupling of compound **3.2f**. The biaryl compound **3.7f** was obtained in a moderate yield and with full retention of enantioselectivity under non-optimized conditions (Scheme 3.20).



Scheme 3.20- Synthesis of biaryl alkylsulfonate **3.7f** *via* the Suzuki cross-coupling between aryl bromide **3.2f** and phenylboronic acid.

Determination of the Absolute Configuration of Compounds 3.2

The absolute configuration of compound **3.2e** was determined *via* single-crystal X-ray diffraction. Analysis of the resulting crystal structure allowed the assignment of the stereogenic centre configuration as *R*, with a Flack parameter of 0.02(5) (Figure 3.4). The absolute stereochemistry of all compounds **3.2** was assigned based on the assumption of a uniform stereochemical pathway.

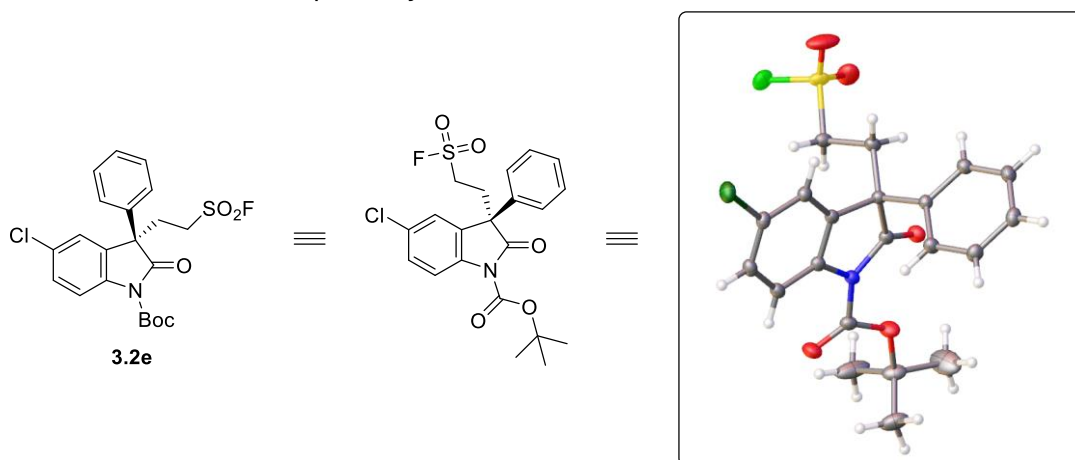


Figure 3.4- Ortep plot for the X-ray structure of compound **3.2e**. Thermal ellipsoids drawn at the 50% probability level. Flack parameter 0.02(5).

Stereochemical Proposal

Based on the outcome of the reaction, in which compounds **3.2** were obtained with *R*-configuration at the stereogenic centre, and supported by previous literature reports,^{[233],[234]} a stereochemical pathway is proposed for the enantioselective addition of oxindoles **3.1** to ESF (Figure 3.5).

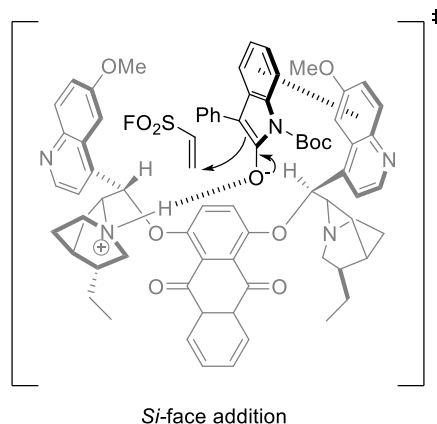


Figure 3.5- Stereochemical proposal for the asymmetric addition of oxindoles **3.1** to ESF.

Initially, the nitrogen of the quinuclidine moiety deprotonates the oxindole, generating an enolate which is stabilized within the catalytic pocket of **(DHQD)₂AQN** through hydrogen bonding and π -stacking interactions. In the resulting transition state, the *Re*-face of the oxindole is effectively shielded by the catalyst, thereby directing the approach of the electrophile from the opposite (*Si*) face, affording compounds **3.2** with *R* configuration.

Conclusions

The first enantioselective organocatalytic method has been developed for the enantioselective addition of 3-aryl-2-oxindoles to ethenesulfonyl fluoride employing bisdihydroquinidine adduct **(DHQD)₂AQN** as organocatalyst. This reaction represents the first reported example of the enantioselective construction of quaternary stereocentres through the nucleophilic functionalisation of ethenesulfonyl fluoride.

In view of the results presented in this chapter, it can be concluded that the initially proposed objectives have been successfully achieved:

1. The required 3-substituted oxindoles **3.1**, bearing substituents with different electronic and steric properties, have been synthesised with low to moderate yields.
2. The reaction conditions for the enantioselective addition of 3-substituted oxindoles **3.1** to ethenesulfonyl fluoride have been optimized as follows: bisdihydroquinidine adduct **(DHQD)₂AQN** as organocatalyst, THF as solvent, and a 1:1 stoichiometric ratio of electrophile to nucleophile at -78 °C. Under these conditions, excellent results were achieved, regarding both yield (95%) and enantioselectivity (97% ee).
3. *N*-Boc-protected oxindoles bearing electron-donating or electron-withdrawing groups at positions 5, 6, and 7, as well as at *meta*- and *para*-positions of the 3-aryl group, were well tolerated, affording the corresponding products in excellent yields and enantioselectivities. In contrast, substitution at the position 4 of the oxindole or at the *ortho*-position of the 3-aryl group was found to be detrimental, likely due to the increased steric hindrance near the reactive site. Additionally, more challenging substrates such as carbonyl-containing derivatives and extended aromatic or heterocyclic systems also participated successfully in the reaction. However, 3-alkyl-substituted oxindoles exhibited diminished reactivity and led to lower enantioselectivities.
4. The applicability of this methodology was demonstrated on a 1.0 mmol scale, furnishing compound **3.2a** in excellent yield (99%) and enantioselectivity (98% ee). Subsequent SuFEx derivatizations of **3.2a** led to the formation of a variety of sulfonamides and sulfonates (**3.3a–3.6a**) in excellent yields and with full retention of enantiomeric excess. Furthermore, the orthogonal reactivity of the –SO₂F moiety was showcased through a successful Suzuki cross-coupling reaction on compound **3.2f**.
5. The absolute configuration of the stereogenic centre was determined as *R* via single-crystal X-ray diffraction. Based on the stereochemical outcome of the reaction and previous literature reports, a stereochemical pathway consistent with the observed results has been proposed.

Experimental Part

Materials and Methods

General procedures

The progress of the reactions was monitored by thin-layer chromatography (TLC) on Merck Silica Gel 60 F-254 plates (Merck, ref. 5554). Flash chromatography was carried out using Merck silica gel 60 (particle size 0.040–0.063 mm), with the eluent pushed through the column by means of an air pump. Visualization of TLC plates was achieved either under UV light (254 or 365 nm) or after staining with a solution of cerium molybdate (10 g $\text{Ce}(\text{SO}_4)_2$ and 25 g phosphomolybdic acid in 80 mL concentrated H_2SO_4) or with potassium permanganate (1.5 g KMnO_4 , 10 g K_2CO_3 , 1.25 mL of 10% NaOH in 200 mL H_2O).

Immediately prior to use, the acidic ion-exchange resin Amberlyst@15 was conditioned by washing it with 6 M HCl (3 x 3 mL) and rinsing three times with deionized water (3 x 3 mL). Each HCl wash was allowed to remain in contact with the resin for 5 minutes.

Solvents and reagents

For routine operations, analytical grade solvents were employed. When required in anhydrous form, CH_2Cl_2 , DCE, and toluene were distilled from CaH_2 under nitrogen, while THF and diethyl ether were freshly distilled from sodium/benzophenone under nitrogen. Commercially available reagents were generally used as received without further treatment.

Melting points

Melting points were determined in open capillary tubes on a Büchi M-560 apparatus; values are uncorrected.

Nuclear magnetic resonance (NMR) spectroscopy

^1H and ^{13}C NMR spectra were obtained on Bruker Avance III 300, Bruker AV400, or Bruker Neo500 instruments operating at 300, 400, or 500 MHz for ^1H and at 75, 101, or 125 MHz for ^{13}C , respectively. ^{19}F spectra were measured at 282 MHz (Avance III 300) or 471 MHz (Neo500). Chemical shifts (δ) are given in ppm and coupling constants (J) are reported in Hz. Carbon multiplicities were assigned from DEPT and/or HSQC experiments. The residual signals of deuterated solvents were used as internal standards: δ 7.26 (^1H) and δ 77.00 (^{13}C) in CDCl_3 ; δ 2.19 (^1H) and δ 1.32 and 118.3 (^{13}C) in CD_3CN ; δ 2.50 (^1H) and δ 39.52 (^{13}C) in $\text{DMSO}-d_6$; δ 4.87 (^1H) and δ 49.00 (^{13}C) in CD_3OD .

Polarimetry

Optical rotations were determined with either a Perkin-Elmer polarimeter equipped with a sodium lamp (589 nm, D line) or a Bellingham+Stanley ADP430 polarimeter with an LED source at the same wavelength, both using 1 dm path length cells. Concentrations (c) are expressed in g per 100 mL.

High Resolution Mass spectrometry (HRMS)

Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Q-TOF Premier instrument with an electrospray source operated at a capillary voltage of 3.3 kV.

HPLC analyses

Chiral separations were performed on a Hitachi Elite LaChrom L-2130 system equipped with either a Hitachi L-4500 or a LaChrom Ultra L-2455U diode-array detector, or on an Agilent 1100 Series system fitted with a Hitachi L-4500 diode-array detector. Chiral columns from Daicel or Phenomenex were employed, using mixtures of hexane/isopropanol or heptane/ethanol, containing trifluoroacetic acid and triethylamine as eluents. Retention times (t_r) are reported in minutes.

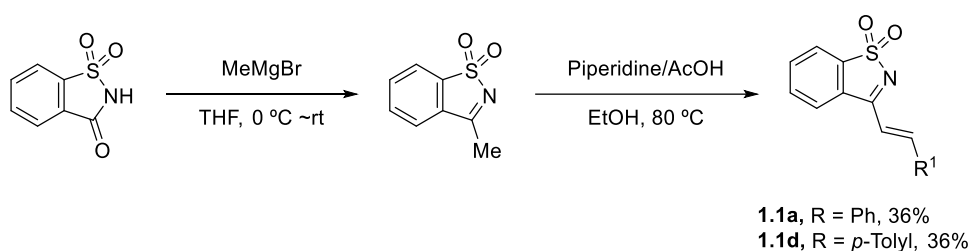
Enantioselective zinc-mediated conjugate addition of terminal alkynes to saccharin-derived azadienes

Synthesis and characterization data for saccharin-derived azadienes **1.1**

All saccharin-derived azadienes **1.1** were available at the laboratory except for compounds **1.1a** and **1.1d**.

General procedure for the synthesis of saccharin-derived azadienes.

Compounds **1.1** were prepared *via* a two-step synthesis based on modified reported procedures. Spectroscopic data for compounds **1.1a** and **1.1d** were in accordance with literature.^{[1]–[5]}



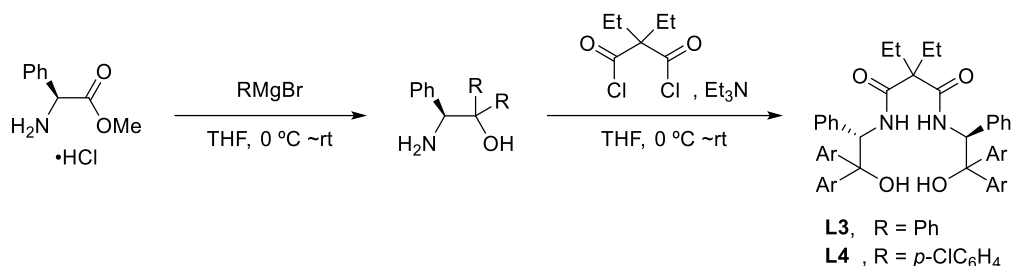
A solution of MeMgBr (3 M in diethyl ether, 62.8 mmol, 21 mL, 2.3 equiv.) was added dropwise to a stirred solution of saccharin (27.3 mmol, 5 g, 1 equiv.) in dry THF (40 mL) at 0 °C under nitrogen. The reaction was allowed to proceed overnight at ambient temperature, after which it was quenched with saturated aqueous NH₄Cl (50 mL). The aqueous layer was extracted with DCM (3 × 50 mL), and the combined organic layers were washed with brine (2 × 25 mL), dried over MgSO₄, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to afford the desired product.

3-methylbenzo[d]isothiazole 1,1-dioxide (4.3 mmol, 0.78 g, 1 equiv.) was dissolved in absolute ethanol (15 mL) and heated to 80 °C. To this solution, the corresponding aldehyde (9.6 mmol, 2.2 equiv.), piperidine (5 drops), and acetic acid (5 drops) were added in sequence. The mixture was stirred overnight, then cooled to 0 °C and filtered. The resulting solid was washed successively with cold ethanol (5 × 10 mL) and Et₂O (5 × 5 mL) to yield azadienes **1.1**. Occasionally, compounds **1.1** were obtained contaminated with a by-product of unknown structure, which was insoluble in CHCl₃. In such cases, pure products could be obtained by suspending the mixture in hot chloroform (100 mL), followed by filtration and concentration of the filtrate.

Synthesis and characterization data for ligands **L3** and **L4**

General procedure for the synthesis of bis(hydroxy)malonamide-derived ligands.

Ligands **L3** and **L4** were prepared *via* a two-step synthesis reported in the literature.^[6]



In a round bottom flask, a solution of RMgBr (3 M in Et₂O, 60 mmol, 20 mL, 6 equiv.) and Et₂O (40 mL) were introduced *via* syringe under nitrogen atmosphere. This solution was cooled down to 0 °C and (S)-2-phenylglycine methyl ester hydrochloride (10 mmol, 1.65g, 1 equiv.) was added in two portions. The resulting reaction mixture was stirred for 6 hours at room temperature, then poured into ice (ca. 35 g) and acidified with 6 M HCl (15 mL). The suspension obtained was filtered and the solid was washed with cold Et₂O (3 x 5mL). The solid was treated with 2 M NaOH in MeOH (60 mL) and concentrated *in vacuo*. The resulting crude product was stirred in a 1:1 mixture of water and DCM (100 mL) for 10 minutes, the layers were separated, and the organic layer was rinsed with water 3 x 25mL), dried over MgSO₄ and concentrated *in vacuo* to afford the desired aminoalcohol.

The corresponding aminoalcohol (1.64 mmol, 2 equiv.) and thiethylamine (1.64 mmol, 229 µL, 2 equiv.) were dissolved in dry THF (11 mL) under nitrogen atmosphere. This solution was cooled down to 0 °C and diethylmalonyl dichloride (0.82 mmol, 141 µL, 1 equiv.) was added *via* syringe. The resulting mixture was stirred at room temperature for 2 hours and then filtered. The filtrate was concentrated *in vacuo* to afford the desired bis(hydroxy)malonamide ligand.

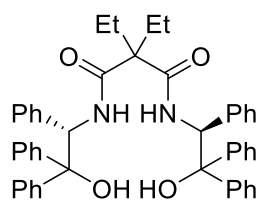
(S)-2-Amino-1,1,2-triphenylethan-1-ol

General procedure was followed using phenylmagnesium bromide (3 M in Et₂O, 60 mmol, 20 mL, 6 equiv.). White solid; 65% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.78 (m, 2H), 7.44 – 7.39 (m, 2H), 7.31 – 7.26 (m, 1H), 7.15 – 7.11 (m, 7H), 7.08 – 7.02 (m, 3H), 5.02 (s, 1H), 1.71 (br s, 2H, NH₂).

(S)-2-Amino-1,1-bis(4-chlorophenyl)-2-phenylethan-1-ol

General procedure was followed using 4-chlorophenylmagnesium bromide (3 M in Et₂O, 60 mmol, 20 mL, 6 equiv.). White solid; 62% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.70 – 7.67 (m, 2H), 7.42 – 7.39 (m, 2H), 7.19 – 7.13 (m, 5H), 7.04 (s, 4H), 4.95 (s, 1H), 1.63 (br s, 2H, NH₂).

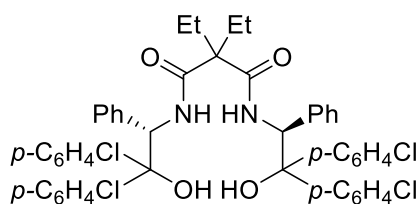
***N,N'*-Bis[(1*S*)-1,2,2-triphenyl-2-hydroxyethyl]-2,2-diethylpropanodiamide (**L3**)**



General procedure was followed using (S)-2-Amino-1,1,2-triphenylethan-1-ol (1.64 mmol, 475 mg, 2 equiv.). White solid; 58%. **Mp** 254 – 255 °C. $[\alpha]_D^{25} = -168$ ($c = 0.06$, MeOH). **¹H NMR** (300 MHz, DMSO- d_6) δ 9.02 (d, $J = 8.4$ Hz, 1H), 7.55 (d, $J = 7.1$ Hz, 2H), 7.29 – 7.21 (m, 5H), 7.11 – 7.00 (m, 8H), 6.17 (s, 1H), 5.86 (d, $J = 8.4$ Hz, 1H), 1.55 – 1.40 (m, 2H), -0.04 (t, $J = 7.0$ Hz, 3H); **¹³C NMR** (75 MHz, DMSO- d_6) δ 171.8 (C), 146.1 (C), 145.0 (C), 139.4 (C), 129.2 (2CH), 127.7 (2CH), 127.2 (2CH), 126.6 (2CH), 126.4 (CH), 126.2 (3CH), 126.1 (3CH), 79.7 (C), 59.2 (CH), 57.0 (C), 30.7 (CH₂), 8.6 (CH₃).

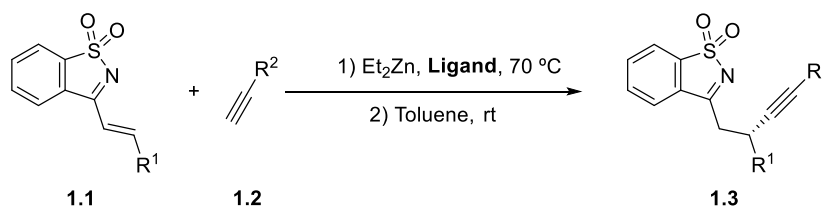
The synthesis of the opposite enantiomer of **L3**, *ent*-**L3**, required for the preparation of racemic mixtures of compounds **1.3ad-aj**, was achieved following the same general procedure used for **L3**, employing (R)-2-phenylglycine methyl ester hydrochloride as the starting material.

***N,N'*-Bis[(S)-2,2-bis(4-chlorophenyl)-2-hydroxy-1-phenylethyl]-2,2-diethylmalonamide (**L4**)**



General procedure was followed using (S)-2-Amino-1,1-bis(4-chlorophenyl)-2-phenylethan-1-ol (1.64 mmol, 590 mg, 2 equiv.). White solid; 71% yield. **Mp** 243 – 246 °C. $[\alpha]_D^{25} = -175$ ($c = 0.05$, MeOH). **¹H NMR** (300 MHz, DMSO- d_6) δ 9.05 (d, $J = 8.7$ Hz, 2H), 7.59 (d, $J = 8.7$ Hz, 4H), 7.37 (d, $J = 8.7$ Hz, 4H), 7.28 (d, $J = 8.7$ Hz, 4H), 7.16 (d, $J = 8.7$ Hz, 4H), 7.04 (s, 10H), 6.37 (s, 2H), 5.84 (d, $J = 8.7$ Hz, 2H), 1.49 (tt, $J = 15.3$, 7.0 Hz, 4H), -0.10 (t, $J = 7.2$ Hz, 3H); **¹³C NMR** (75 MHz, DMSO- d_6) δ 171.9 (C), 144.8 (C), 143.5 (C), 139.0 (C), 131.5 (C), 131.1 (C), 129.2 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 79.4 (C), 59.2 (CH), 57.1 (C), 30.8 (CH₂), 8.5 (CH₃).

Synthesis and characterization data for chiral β -alkynyl imines **1.3**



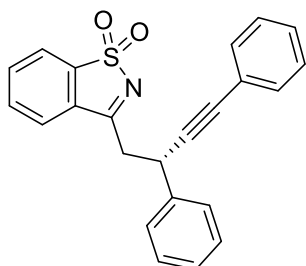
General procedure for the enantioselective addition of terminal arylacetylenes **1.2**

In a test tube, ligand **L4** (0.0125 mmol, 10.5 mg, 10 mol%) and alkyne **1.2a-d** (0.625 mmol, 5 equiv.) were dissolved in dry toluene (0.5 mL) under nitrogen. To this solution Et₂Zn (1.5 M in toluene, 0.5 mmol, 0.34 mL, 4 equiv.) was added dropwise, and the resulting mixture was stirred at 70 °C for 2 hours. After cooling to room temperature, a solution of the corresponding imine **1.1** (0.125 mmol, 1 equiv.) in dry toluene (1 mL) was added *via* syringe and the reaction mixture was stirred until the reaction was complete (TLC). The reaction was quenched with 20% NH₄Cl (1 mL), extracted with DCM (3 x 15 mL), washed with brine

(15 mL) and dried over MgSO_4 . Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane:Et₂O mixtures to afford compounds **1.3aa-ad**.

Racemic products **1.3aa-ad** were obtained following the same procedure employing *N*-benzil-2-hydroxy-2-phenylacetamide instead of **L4**.

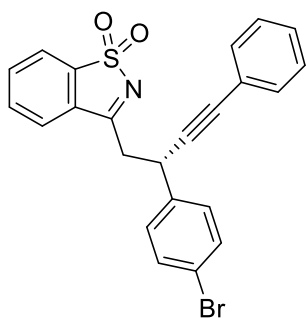
(S)-3-(2,4-diphenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3aa)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3aa** as a colourless oil (21.8 mg, 47% yield), ethylation product **1.8** was also isolated (9.3 mg, 25% yield). Compound (S)-**1.3aa** was obtained with an 85% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 29.1$ min, $\tau_{\text{minor}} = 25.8$ min. $[\alpha]_D^{25} = -2.5$ ($c = 0.80$, CHCl_3 , 87% ee). **¹H**

NMR (300 MHz, CDCl_3) δ 7.96 – 7.86 (m, 1H), 7.76 – 7.58 (m, 2H), 7.57 – 7.49 (m, 2H), 7.43 – 7.26 (m, 8H), 4.65 (dd, $J = 8.4, 6.3$ Hz, 1H), 3.55 (dd, $J = 15.3, 8.4$ Hz, 1H), 3.41 (dd, $J = 15.4, 6.3$ Hz, 1H); **¹³C NMR** (75 MHz, CDCl_3) δ 173.7 (C=N), 156.0 (C), 153.5 (C), 140.0 (C), 133.9 (CH), 133.7 (CH), 131.8 (CH), 131.4 (C), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 124.3 (CH), 122.9 (CH), 122.7 (CH), 89.0 (C), 85.2 (C), 39.9 (CH_2), 36.1 (CH); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{23}\text{H}_{17}\text{NO}_2\text{S}+\text{H}]^+$: 372.4615; found: 372.4620.

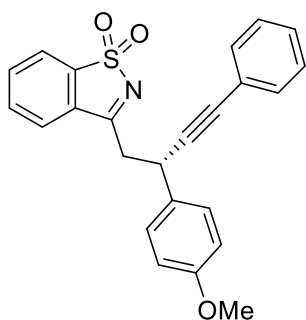
(S)-3-(2-(4-Bromophenyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.1ba)



General procedure was followed using **1.1b** (0.125 mmol, 43.5 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ba** as a yellow solid (33.2 mg, 59% yield). Compound (S)-**1.3ba** was obtained with an 69% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1.5 mL/min]: $\tau_{\text{major}} = 21.7$ min, $\tau_{\text{minor}} = 35.1$ min. **Mp** 174 – 176 °C. $[\alpha]_D^{25} = 1.3$ ($c = 0.80$, CHCl_3 , 69% ee). **¹H NMR** (300 MHz, CDCl_3) δ 7.87 – 7.81 (m, 1H), 7.71 – 7.53 (m, 3H), 7.46 – 7.39 (m, 2H), 7.39 – 7.33 (m, 2H), 7.31

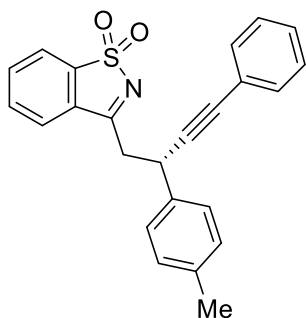
– 7.24 (m, 2H), 7.25 – 7.18 (m, 3H), 4.57 (dd, $J = 7.9, 6.5$ Hz, 1H), 3.47 (dd, $J = 15.8, 8.0$ Hz, 1H), 3.32 (dd, $J = 15.8, 6.5$ Hz, 1H); **¹³C NMR** (75 MHz, CDCl_3) δ 173.3 (C), 139.9 (C), 139.0 (C), 133.9 (CH), 133.8 (CH), 132.2 (CH), 131.8 (CH), 131.2 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 124.2 (CH), 122.7 (CH), 122.6 (C), 121.8 (C), 88.5 (C), 85.3 (C), 39.6 (CH_2), 35.3 (CH); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{23}\text{H}_{16}\text{BrNO}_2\text{S}+\text{H}]^+$: 450.0158; found: 450.0160.

(S)-3-(2-(4-Methoxyphenyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole (1.3ca)



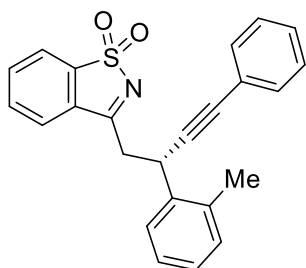
General procedure was followed using **1.1c** (0.125 mmol, 37.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ca** as a colourless oil (20.1 mg, 40% yield). Compound (S)-**1.3ca** was obtained with a 33% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1.5 mL/min]: $\tau_{\text{major}} = 25.5$ min, $\tau_{\text{minor}} = 18.7$ min. $[\alpha]_D^{25} = -27.5$ (*c* = 0.90, CHCl₃, 33% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.97 – 7.86 (m, 1H), 7.75 – 7.57 (m, 3H), 7.49 – 7.40 (m, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.23 (m, 3H), 6.94 – 6.85 (m, 2H), 4.60 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.79 (s, 3H), 3.52 (dd, *J* = 15.3, 8.2 Hz, 1H), 3.38 (dd, *J* = 15.3, 6.5 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.7 (C), 159.1 (C), 139.8 (C), 133.8 (CH), 133.5 (CH), 131.9 (C), 131.7 (CH), 131.3 (C), 128.6 (CH), 128.2 (CH), 124.3 (CH), 122.8 (C), 122.5 (CH), 114.3 (CH), 89.3 (C), 84.8 (C), 55.4 (CH₃), 39.9 (CH₂), 35.2 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₉NO₃S+H]⁺: 402.1158; found: 402.1158.

(S)-3-(2-(4-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole (1.3da)



General procedure was followed using **1.1d** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3da** as a yellow solid (16.0 mg, 33% yield). Compound (S)-**1.3da** was obtained with a 58% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1.5 mL/min]: $\tau_{\text{major}} = 17.0$ min, $\tau_{\text{minor}} = 13.4$ min. **Mp** 143 – 145 °C. $[\alpha]_D^{25} = -5.3$ (*c* = 0.60, CHCl₃, 58% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.84 (m, 1H), 7.77 – 7.59 (m, 3H), 7.47 – 7.38 (m, 2H), 7.37 – 7.22 (m, 5H), 7.21 – 7.11 (m, 2H), 4.61 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.52 (dd, *J* = 15.3, 8.4 Hz, 1H), 3.39 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.34 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.7 (C), 139.9 (C), 137.5 (C), 137.0 (C), 133.8 (CH), 133.6 (CH), 131.7 (CH), 131.4 (C), 129.7 (CH), 128.3 (CH), 128.3 (CH), 127.5 (CH), 124.4 (CH), 123.0 (C), 122.6 (CH), 89.3 (C), 84.9 (C), 39.9 (CH₂), 35.7 (CH), 21.2 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₉NO₂S+H]⁺: 386.1209; found: 386.1208.

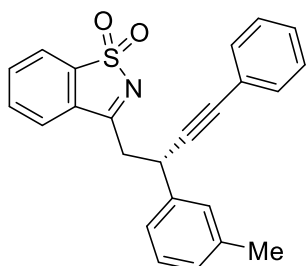
(S)-3-(2-(2-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole (1.3ea)



General procedure was followed using **1.1e** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ea** as a yellow oil (17.3 mg, 36% yield). Compound (S)-**1.3ea** was obtained with a 53% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 11.9$ min, $\tau_{\text{minor}} = 15.2$ min. $[\alpha]_D^{25} = -11.6$ (*c* = 0.90, CHCl₃, 53% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.87 (m, 1H), 7.80 – 7.59 (m, 4H), 7.32 – 7.26 (m, 3H), 7.26 – 7.18 (m, 5H), 4.80 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.51 (dd, *J* = 15.2, 9.2 Hz, 1H), 3.34 (dd, *J* = 15.2, 5.3 Hz, 1H), 2.49 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.9 (C), 139.9 (C), 138.2 (C), 135.3 (C), 133.9 (CH), 133.7 (CH), 131.7 (CH), 131.5 (C),

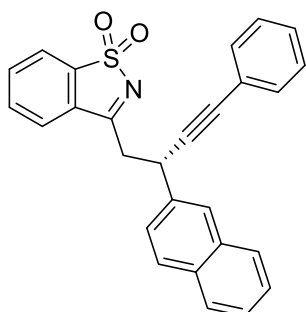
131.1 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 124.5 (CH), 122.9 (C), 122.7 (CH), 89.4 (C), 84.7 (C), 38.3 (CH₂), 32.9 (CH), 19.5 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₉NO₂S + H]⁺: 386.1209; found: 386.1213.

(S)-3-(2-(3-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole (1.3fa)



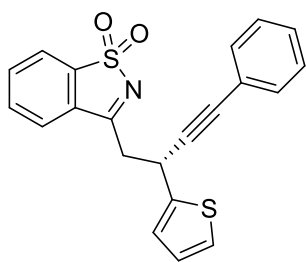
General procedure was followed using **1.1f** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3fa** as yellow oil (16.8 mg, 35% yield). Compound (S)-**1.3fa** was obtained with an 71% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 20.9 min, τ_{minor} = 18.0 min. $[\alpha]_D^{25}$ = -5.1 (*c* = 0.50, CHCl₃, 71% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.76 – 7.58 (m, 3H), 7.36 – 7.30 (m, 4H), 7.29 – 7.22 (m, 4H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.60 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.53 (dd, *J* = 15.2, 8.6 Hz, 1H), 3.39 (dd, *J* = 15.2, 6.2 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.7 (C), 140.0 (C), 139.9 (C), 138.9 (C), 133.8 (CH), 133.6 (CH), 131.8 (CH), 131.5 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 124.6 (CH), 124.4 (CH), 123.0 (C), 122.7 (CH), 89.1 (C), 85.1 (C), 39.9 (CH₂), 36.1 (CH), 21.6 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₉NO₂S + H]⁺: 386.1209; found: 386.1214.

(S)-3-(2-(Naphthalen-2-yl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ga)



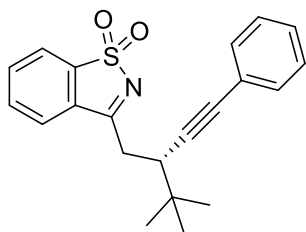
General procedure was followed using **1.1g** (0.125 mmol, 39.9 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ga** as a yellow oil (18.5 mg, 35% yield). Compound (S)-**1.3ga** was obtained with an 83% enantiomeric excess determined by HPLC using a Chiralcel AS-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 53.7 min, τ_{minor} = 60.9 min. $[\alpha]_D^{25}$ = 1.8 (*c* = 0.50, CHCl₃, 83% ee). **¹H NMR** (300 MHz, CDCl₃) δ 8.01 – 7.96 (m, 1H), 7.93 – 7.78 (m, 4H), 7.74 – 7.58 (m, 4H), 7.52 – 7.45 (m, 2H), 7.40 – 7.33 (m, 2H), 7.28 (q, *J* = 3.1 Hz, 3H), 4.83 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.63 (dd, *J* = 15.5, 8.4 Hz, 1H), 3.49 (dd, *J* = 15.4, 6.2 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.7 (C), 140.0 (C), 137.3 (C), 133.8 (CH), 133.7 (CH), 133.6 (C), 132.9 (CH), 131.8 (CH), 131.4 (C), 129.0 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 126.3 (CH), 125.5 (CH), 124.3 (CH), 122.9 (C), 122.8 (C), 122.7 (CH), 89.0 (C), 85.4 (C), 39.8 (CH₂), 36.2 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₇H₁₉NO₂S + H]⁺: 422.1209; found: 422.1209.

(R)-3-(4-Phenyl-2-(thiophen-2-yl)but-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ha)



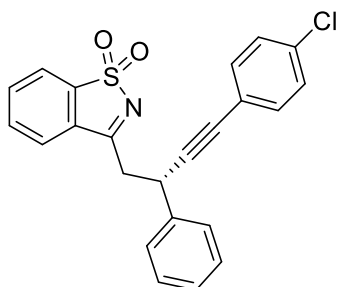
General procedure was followed using **1.1h** (0.125 mmol, 34.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ha** as yellow oil (23.1 mg, 49% yield). Compound (*R*)-**1.3ha** was obtained with a 70% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 31.9$ min, $\tau_{\text{minor}} = 27.7$ min. $[\alpha]_D^{25} = 3.5$ ($c = 1.0$, CHCl₃, 70% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.95 – 7.89 (m, 1H), 7.80 – 7.60 (m, 3H), 7.41 – 7.32 (m, 2H), 7.32 – 7.25 (m, 3H), 7.25 – 7.19 (m, 1H), 7.17 – 7.09 (m, 1H), 6.98 – 6.90 (m, 1H), 4.97 (dd, $J = 7.5, 6.5$ Hz, 1H), 3.62 (dd, $J = 15.8, 7.7$ Hz, 1H), 3.52 (dd, $J = 15.8, 6.7$ Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.2 (C), 143.2 (C), 139.9 (C), 134.0 (CH), 133.8 (CH), 131.8 (CH), 131.3 (C), 128.6 (CH), 128.4 (CH), 127.2 (CH), 125.7 (CH), 125.0 (CH), 124.3 (CH), 122.7 (CH), 122.6 (C), 88.5 (C), 84.6 (C), 40.1 (CH₂), 31.1 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₅NO₂S₂+NH₄]⁺: 395.0882; found: 395.0880.

(S)-3-(2-(tert-Butyl)-4-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ia)



General procedure was followed using **1.1i** (0.125 mmol, 31.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ia** as a white solid (37.0 mg, 84% yield). Compound (*S*)-**1.3ia** was obtained with a 35% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 14.0$ min, $\tau_{\text{minor}} = 9.0$ min. **Mp** 90–93 °C. $[\alpha]_D^{25} = -40.5$ ($c = 1.0$, CHCl₃, 35% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.95 – 7.88 (m, 1H), 7.81 – 7.59 (m, 3H), 7.24 – 7.14 (m, 5H), 3.24 – 3.06 (m, 3H), 1.18 (s, 9H); **¹³C NMR** (75 MHz, CDCl₃) δ 175.8 (C), 140.0 (C), 133.8 (CH), 133.5 (CH), 131.7 (C), 131.6 (CH), 128.2 (CH), 128.0 (CH), 124.6 (CH), 123.2 (C), 122.6 (CH), 89.6 (C), 85.3 (C), 42.2 (CH), 34.4 (C), 32.1 (CH₂), 27.5 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₁H₂₁NO₂S₂+H]⁺: 352.1366; found: 352.1370.

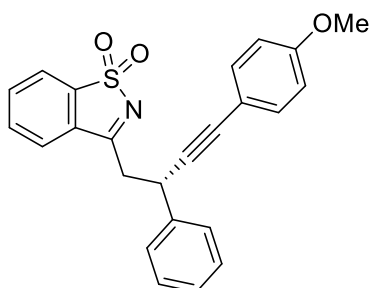
(S)-3-(4-(4-Chlorophenyl)-2-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ab)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ab** as a brown solid (21.8 mg, 43% yield). Compound (*S*)-**1.3ab** was obtained with an 83% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 26.9$ min, $\tau_{\text{minor}} = 32.7$ min. **Mp** 113–116 °C. $[\alpha]_D^{25} = -1.9$ ($c = 0.80$, CHCl₃, 83% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.84 (m, 2H), 7.76 – 7.56 (m, 5H), 7.54 – 7.48 (m, 3H), 7.43 – 7.33 (m, 3H), 7.33 – 7.20 (m, 5H), 4.64 (dd, $J = 8.5, 6.1$ Hz, 1H), 3.53 (dd, $J = 15.6, 8.5$ Hz, 1H), 3.40 (dd, $J = 15.5, 6.1$ Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.5 (C), 139.9 (C), 139.8 (C), 134.4 (C), 133.9 (CH), 133.7 (CH), 133.0 (CH), 131.3 (C), 129.2 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH),

124.2 (CH), 122.7 (CH), 121.4 (C), 90.0 (C), 84.0 (CH), 39.7 (CH₂), 36.0 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₃H₁₆ClNO₂S+H]⁺: 406.0663; found: 406.0662.

(S)-3-(4-(4-Methoxyphenyl)-2-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ac)



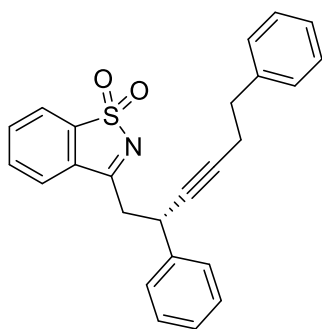
General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ac** as colourless oil (23.1 mg, 46% yield). Compound (S)-**1.3ac** was obtained with an 54% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 44.8 min, τ_{minor} = 28.8 min. $[\alpha]_D^{25}$ = -3.5 (c = 0.90, CHCl₃, 54% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.94 – 7.86 (m, 1H), 7.74 – 7.65 (m, 1H), 7.65 – 7.58 (m, 2H), 7.56 – 7.50 (m, 2H), 7.42 – 7.32 (m, 3H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 4.62 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.78 (s, 3H), 3.53 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.39 (dd, *J* = 15.2, 6.2 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.7 (C), 159.6 (C), 140.1 (C), 139.8 (C), 133.7 (CH), 133.5 (CH), 133.1 (CH), 131.3 (C), 129.0 (CH), 127.7 (CH), 127.5 (CH), 124.3 (CH), 122.5 (CH), 114.9 (C), 113.9 (CH), 87.4 (C), 85.0 (C), 55.3 (CH), 39.9 (CH₂), 36.1 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₄H₁₉NO₂S+NH₄]⁺: 419.1424; found: 419.1424.

General procedure for the enantioselective addition of terminal alkylacetylenes 1.2

In a test tube, ligand **L3** (0.0125 mmol, 9.0 mg, 10 mol%) and alkyne **1.2d-j** (0.625 mmol, 5 equiv.) were dissolved in dry toluene (0.5 mL) under nitrogen. To this solution Et₂Zn (1.5 M in toluene, 0.25 mmol, 0.17 mL, 2 equiv.) was added dropwise, and the resulting mixture was stirred at 70 °C for 2 hours. After cooling to room temperature, a solution of the corresponding imine **1.1** (0.125 mmol, 1 equiv.) in dry toluene (1 mL) was added *via* syringe and the reaction mixture was stirred until the reaction was complete (TLC). The reaction was quenched with 20% NH₄Cl (1 mL), extracted with DCM (3 x 15 mL), washed with brine (15 mL) and dried over MgSO₄. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane:Et₂O mixtures to afford compounds **1.3ad-aj**.

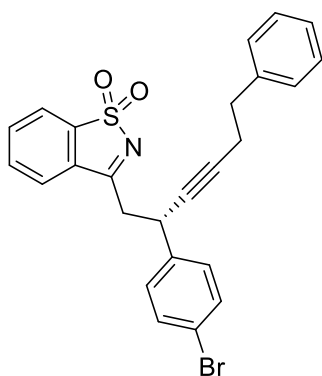
Racemic mixtures of compounds **1.3ad-aj** were prepared by mixing equal amounts of enantiomeric compounds **1.3** obtained in separated reactions with **L3** and *ent*-**L3**.

(S)-3-(2,6-Diphenylhex-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ad)



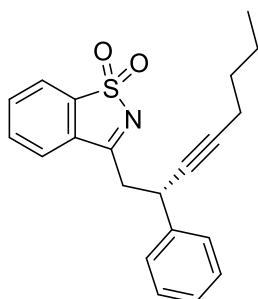
General procedure was followed using **1.1a** (0.125 mmol, 3.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ad** as a colourless oil (34.0 mg, 68% yield). Compound (S)-**1.3ad** was obtained with a 95% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 29.5$ min, $\tau_{\text{minor}} = 24.7$ min. $[\alpha]_D^{25} = 6.2$ (*c* = 1.0, CHCl₃, 95% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 – 7.87 (m, 1H), 7.74 – 7.61 (m, 2H), 7.51 – 7.49 (m, 1H), 7.40 – 7.04 (m, 10H), 4.36 (ddt, *J* = 8.4, 6.2, 2.3 Hz, 1H), 3.40 (dd, *J* = 15.0, 8.6 Hz, 1H), 3.27 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.55 – 2.35 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.9 (C), 140.5 (C), 139.9 (C), 133.7 (CH), 133.6 (CH), 131.5 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 127.6 (CH), 126.3 (CH), 124.3 (CH), 122.6 (CH), 84.7 (C), 80.5 (C), 40.1 (CH₂), 35.6 (CH), 35.0 (CH₂), 21.0 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₁NO₂S+H]⁺: 400.1366; found: 400.1363.

(S)-3-(2-(4-Bromophenyl)-6-phenylhex-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3bd)



General procedure was followed using **1.1b** (0.125 mmol, 43.5 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3bd** as a colourless oil (21.0 mg, 35% yield). Compound (S)-**1.3bd** was obtained with a 96% enantiomeric excess determined by HPLC using a Chiralcel AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 18.6$ min, $\tau_{\text{minor}} = 21.8$ min. $[\alpha]_D^{25} = 4.3$ (*c* = 1.0, CHCl₃, 96% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.92 – 7.90 (m, 1H), 7.73 (td, *J* = 7.4, 1.2 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.44 – 7.40 (m, 2H), 7.28 – 7.15 (m, 7H), 4.34 (ddt, *J* = 8.4, 6.4, 2.2 Hz, 1H), 3.32 (dd, *J* = 15.7, 8.1 Hz, 1H), 3.20 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.48 – 2.42 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.3 (C), 140.5 (C), 139.7 (C), 139.4 (C), 133.6 (CH), 133.6 (CH), 131.8 (CH), 131.8 (C), 129.2 (CH), 128.5 (CH), 128.3 (CH), 126.2 (CH), 124.0 (CH), 122.6 (CH), 121.3 (C), 84.8 (C), 80.0 (C), 39.7 (CH₂), 34.8 (CH₂), 34.6 (CH), 20.7 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₀BrNO₂S+H]⁺: 478.0471; found: 478.0473.

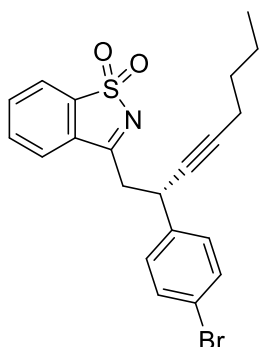
(S)-3-(2-Phenyl-oct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ae)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ae** as yellow solid (19.3 mg, 44% yield). Compound (S)-**1.3ae** was obtained with an 88% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 26.2$ min, $\tau_{\text{minor}} = 22.7$ min. **Mp** 91 – 93 °C. $[\alpha]_D^{25} = 4.7$ (*c* = 0.95, CHCl₃, 88% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 – 7.89 (m, 1H), 7.69 (dtd, *J* = 16.8, 7.3, 1.2 Hz, 2H),

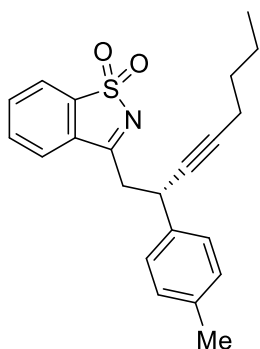
7.60 – 7.57 (m, 1H), 7.47 – 7.43 (m, 2H), 7.36 – 7.30 (m, 2H), 7.27 – 7.22 (m, 1H), 4.39 (ddt, J = 8.5, 6.2, 2.3 Hz, 1H), 3.40 (dd, J = 15.0, 8.6 Hz, 1H), 3.27 (dd, J = 15.0, 6.2 Hz, 1H), 2.13 (td, J = 6.9, 2.2 Hz, 2H), 1.46 – 1.21 (m, 4H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.8 (C), 140.6 (C), 139.8 (C), 133.6 (CH), 133.4 (CH), 131.5 (C), 128.8 (CH), 127.4 (CH), 127.4 (CH), 124.2 (CH), 122.5 (CH), 85.5 (C), 79.4 (C), 40.0 (CH_2), 35.6 (CH), 30.7 (CH_2), 21.9 (CH_2), 18.4 (CH_2), 13.5 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{21}\text{NO}_2\text{S}+\text{H}]^+$: 352.1366; found: 352.1363.

(S)-3-(2-(4-Bromophenyl)oct-3-yn-1-yl)benzo[d]isothiazole (1.3be)



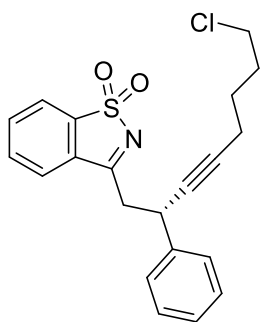
General procedure was followed using **1.1b** (0.125 mmol, 43.5mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3be** as a yellow solid (20.4 mg, 38% yield). Compound (*S*-**1.3be**) was obtained with a 97% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 26.6 min, τ_{minor} = 24.1 min. **Mp** 152 – 155 °C. $[\alpha]_D^{25}$ = 7.2 (c = 0.98, CHCl_3 , 97% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.92 – 7.89 (m, 1H), 7.71 (dtd, J = 16.1, 7.4, 1.3 Hz, 2H), 7.60 – 7.58 (m, 1H), 7.48 – 7.43 (m, 2H), 7.36 – 7.31 (m, 2H), 4.37 (ddt, J = 8.6, 6.4, 2.3 Hz, 1H), 3.38 (dd, J = 15.4, 8.1 Hz, 1H), 3.24 (dd, J = 15.4, 6.5 Hz, 1H), 2.13 (td, J = 6.9, 2.3 Hz, 2H), 1.43 – 1.23 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.6 (C), 139.9 (C), 139.8 (C), 133.8 (CH), 133.7 (CH), 132.0 (CH), 131.4 (C), 129.4 (C), 124.3 (CH), 122.7 (CH), 121.5 (C), 85.9 (C), 79.1 (C), 39.9 (CH_2), 35.0 (CH), 30.8 (CH_2), 22.0 (CH_2), 18.5 (CH_2), 13.7 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{20}\text{BrNO}_2\text{S}+\text{H}]^+$: 430.0471; found: 430.0473.

(S)-3-(2-(4-Tolyl)oct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3de)



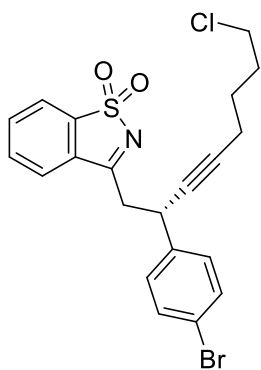
General procedure was followed using **1.1d** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3de** as a yellow solid (19.2 mg, 42% yield). Compound (*S*-**1.3de**) was obtained with a 92% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 0.7 mL/min]: τ_{major} = 18.3 min, τ_{minor} = 16.35 min. **Mp** 131 – 135 °C. $[\alpha]_D^{25}$ = 1.61 (c = 0.99, CHCl_3 , 92% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.91 – 7.88 (m, 1H), 7.69 (dtd, J = 16.0, 7.3, 1.3 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.35 – 7.32 (m, 2H), 7.15 – 7.13 (m, 2H), 4.35 (ddt, J = 8.5, 6.1, 2.3 Hz, 1H), 3.38 (dd, J = 15.0, 8.6 Hz, 1H), 3.25 (dd, J = 15.0, 6.2 Hz, 1H), 2.32 (s, 3H), 2.11 (td, J = 6.9, 2.2 Hz, 2H), 1.42 – 1.23 (m, 4H), 0.83 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.1 (C), 140.0 (C), 137.8 (C), 137.3 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 129.6 (CH), 127.4 (CH), 124.4 (CH), 122.6 (CH), 85.4 (C), 79.7 (C), 40.2 (CH_2), 35.4 (CH), 30.8 (CH_2), 22.0 (CH_2), 21.2 (CH_3), 18.5 (CH_2), 13.7 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{23}\text{NO}_2\text{S}+\text{H}]^+$: 366.1522; found: 366.1523.

(S)-3-(8-Chloro-2-phenyloct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3af)



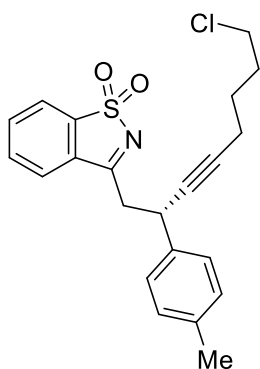
General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3af** as a colourless oil (22.3 mg, 48% yield). Compound (S)-**1.3af** was obtained with a 96% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 34.7$ min, $\tau_{\text{minor}} = 32.1$ min. $[\alpha]_D^{25} = -2.4$ ($c = 0.98$, CHCl_3 , 96% ee). **¹H NMR** (300 MHz, CDCl_3) δ 7.92–7.90 (m, 1H), 7.70 (dtd, $J = 16.8, 7.4, 1.3$ Hz, 2H), 7.60–7.56 (m, 1H), 7.47–7.43 (m, 2H), 7.37–7.31 (m, 2H), 7.29–7.23 (m, 1H), 4.40 (ddt, $J = 8.4, 5.3, 2.3$ Hz, 1H), 3.50 (td, $J = 6.5, 2.1$ Hz, 2H), 3.40 (dd, $J = 15.3, 8.9$ Hz, 1H), 3.27 (dd, $J = 15.3, 5.9$ Hz, 1H), 2.19 (td, $J = 6.8, 2.2$ Hz, 2H), 1.83–1.74 (m, 2H), 1.61–1.51 (m, 2H); **¹³C NMR** (75 MHz, CDCl_3) δ 173.8 (C), 140.5 (C), 140.0 (C), 133.8 (CH), 133.7 (CH), 131.5 (C), 129.0 (CH), 127.7 (CH), 127.5 (CH), 124.3 (CH), 122.7 (CH), 84.7 (C), 80.3 (C), 44.8 (CH_2), 40.1 (CH_2), 35.6 (CH), 31.5 (CH_2), 25.8 (CH_2), 18.2 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{20}\text{ClNO}_2\text{S}+\text{H}]^+$: 386.0976; found: 386.0976.

(S)-3-(2-(4-Bromophenyl)-8-chlorooct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3bf)



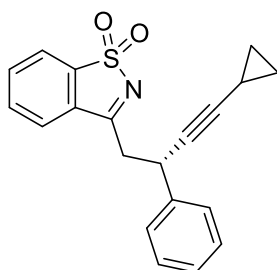
General procedure was followed using **1.1b** (0.125 mmol, 43.5 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3bf** as a yellow solid (20.3 mg, 36% yield). Compound (S)-**1.3bf** was obtained with a 93% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 21.3$ min, $\tau_{\text{minor}} = 17.7$ min. **Mp** 116–119 °C. $[\alpha]_D^{25} = 4.7$ ($c = 1.0$, CHCl_3 , 93% ee). **¹H NMR** (300 MHz, CDCl_3) δ 7.93–7.90 (m, 1H), 7.72 (dtd, $J = 15.9, 7.4, 1.3$ Hz, 2H), 7.61–7.57 (m, 1H), 7.49–7.44 (m, 2H), 7.36–7.31 (m, 2H), 4.38 (ddt, $J = 8.4, 6.0, 2.3$ Hz, 1H), 3.49 (td, $J = 6.5, 1.8$ Hz, 2H), 3.39 (dd, $J = 15.7, 8.5$ Hz, 1H), 3.25 (dd, $J = 15.7, 6.2$ Hz, 1H), 2.19 (td, $J = 6.8, 2.2$ Hz, 2H), 1.83–1.73 (m, 2H), 1.61–1.51 (m, 2H); **¹³C NMR** (75 MHz, CDCl_3) δ 173.5 (C), 139.9 (C), 139.6 (C), 133.9 (CH), 133.8 (CH), 132.1 (CH), 131.3 (C), 129.3 (CH), 124.2 (CH), 122.8 (CH), 121.6 (C), 84.9 (C), 79.9 (C), 44.7 (CH_2), 39.8 (CH_2), 34.9 (CH), 31.5 (CH_2), 25.8 (CH_2), 18.1 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{19}\text{BrClNO}_2\text{S}+\text{H}]^+$: 464.0081; found: 464.0079.

(S)-3-(8-Chloro-2-(4-tolyl)oct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3df)



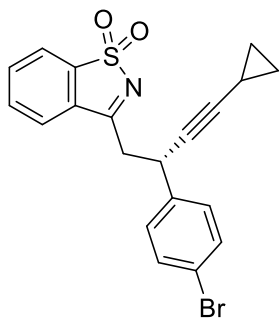
General procedure was followed using **1.1d** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3df** as a yellow solid (28.0 mg, 58% yield). Compound (S)-**1.3df** was obtained with a 91% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 32.5$ min, $\tau_{\text{minor}} = 29.7$ min. **Mp** 85 – 89 °C. $[\alpha]_D^{25} = -3.5$ (*c* = 0.95, CHCl₃, 91% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.92 – 7.89 (m, 1H), 7.70 (dtd, *J* = 16.0, 7.4, 1.3 Hz, 2H), 7.61 – 7.58 (m, 1H), 7.35 – 7.31 (m, 2H), 7.17 – 7.13 (m, 2H), 4.36 (dtd, *J* = 8.5, 5.5, 2.4 Hz, 1H), 3.49 (td, *J* = 6.5, 2.2 Hz, 2H), 3.38 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.25 (dd, *J* = 15.2, 5.9 Hz, 1H), 2.33 (s, 3H), 2.18 (td, *J* = 6.7, 1.9 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.60 – 1.50 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.9 (C), 139.9 (C), 137.6 (C), 137.4 (C), 133.8 (CH), 133.6 (CH), 131.5 (C), 129.7 (CH), 127.4 (CH), 124.3 (CH), 122.7 (CH), 84.4 (C), 80.5 (C), 44.8 (CH₂), 40.1 (CH₂), 35.2 (CH), 31.5 (CH₂), 25.8 (CH₂), 21.2 (CH₃), 18.2 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₂H₂₂ClNO₂S+H]⁺: 400.1133; found: 400.1132.

(S)-3-(4-Cyclopropyl-2-phenylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ag)



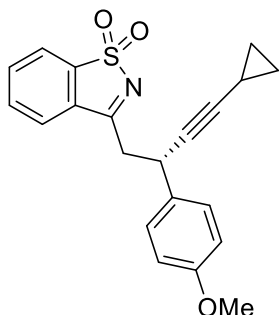
General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ag** as colourless oil (25.6 mg, 61% yield). Compound (S)-**1.3ag** was obtained with a 93% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 28.7$ min, $\tau_{\text{minor}} = 34.3$ min. $[\alpha]_D^{25} = 6.6$ (*c* = 0.98, CHCl₃, 93% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 – 7.88 (m, 1H), 7.69 (dtd, *J* = 16.9, 7.4, 1.2 Hz, 2H), 7.59 – 7.56 (m, 1H), 7.45 – 7.41 (m, 2H), 7.36 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 4.34 (ddd, *J* = 8.3, 6.2, 1.8 Hz, 1H), 3.38 (dd, *J* = 14.9, 8.5 Hz, 1H), 3.26 (dd, *J* = 14.9, 6.3 Hz, 1H), 1.17 (ttd, *J* = 8.2, 5.0, 1.8 Hz, 1H), 0.70 – 0.61 (m, 2H), 0.60 – 0.47 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.9 (C), 140.6 (C), 139.9 (C), 133.7 (CH), 133.6 (CH), 131.5 (C), 128.9 (CH), 127.6 (CH), 127.5 (CH), 124.4 (CH), 122.6 (CH), 88.7 (C), 74.7 (C), 40.1 (CH₂), 35.7 (C), 8.2 (CH₂), 8.2 (CH₂), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₀H₁₇NO₂S+H]⁺: 336.1053; found: 336.1055.

(S)-3-(2-(4-bromophenyl)-4-cyclopropylbut-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3bg)



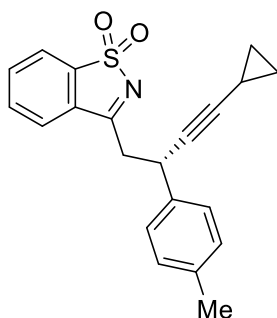
General procedure was followed using **1.1b** (0.125 mmol, 43.5 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3bg** as a yellow solid (23.3 mg, 45% yield). Compound (S)-**1.3bg** was obtained with a 96% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 20.0$ min, $\tau_{\text{minor}} = 16.7$ min. **Mp** 119 – 121 °C. $[\alpha]_D^{25} = 6.3$ (*c* = 1.0, CHCl₃, 96% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.92 – 7.89 (m, 1H), 7.71 (dtd, *J* = 16.1, 7.4, 1.2 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.47 – 7.43 (m, 2H), 7.34 – 7.29 (m, 2H), 4.33 (ddd, *J* = 8.2, 6.5, 1.8 Hz, 1H), 3.36 (dd, *J* = 15.3, 8.2 Hz, 1H), 3.24 (dd, *J* = 15.3, 6.5 Hz, 1H), 1.17 (ttt, *J* = 8.2, 5.0, 1.8 Hz, 1H), 0.71 – 0.67 (m, 2H), 0.59 – 0.48 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.5 (C), 139.9 (C), 139.6 (C), 133.8 (CH), 133.7 (CH), 132.0 (CH), 131.4 (C), 129.4 (CH), 124.3 (CH), 122.7 (CH), 121.5 (C), 89.0 (C), 74.3 (C), 39.8 (CH₂), 35.0 (CH), 8.3 (CH₂), 8.2 (CH₂), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₀H₁₆BrNO₂S+H]⁺: 414.0158; found: 414.0154.

(S)-3-(4-Cyclopropyl-2-(4-methoxyphenyl)but-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3cg)



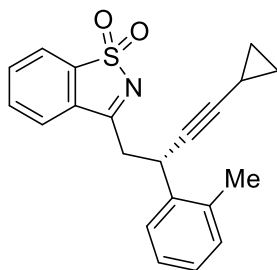
General procedure was followed using **1.1c** (0.125 mmol, 37.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3cg** as a yellow solid (31.5 mg, 69% yield). Compound (S)-**1.3cg** was obtained with a 92% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 22.0$ min, $\tau_{\text{minor}} = 19.3$ min. **Mp** 112 – 115 °C. $[\alpha]_D^{25} = 7.5$ (*c* = 1.0, CHCl₃, 92% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 – 7.88 (m, 1H), 7.69 (dtd, *J* = 16.0, 7.4, 1.3 Hz, 2H), 7.59 – 7.56 (m, 1H), 7.37 – 7.32 (m, 2H), 6.87 – 6.82 (m, 2H), 4.30 (ddd, *J* = 8.2, 6.4, 1.8 Hz, 1H), 3.78 (s, 3H), 3.35 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.24 (dd, *J* = 14.9, 6.5 Hz, 1H), 1.16 (ttt, *J* = 8.2, 5.0, 1.8 Hz, 1H), 0.69 – 0.62 (m, 2H), 0.59 – 0.46 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 174.0 (C), 159.1 (C), 139.9 (C), 133.7 (CH), 133.5 (CH), 132.7 (C), 131.6 (C), 128.6 (CH), 124.5 (CH), 122.6 (CH), 114.3 (CH), 88.5 (C), 75.1 (C), 55.5 (CH₃), 40.3 (CH₂), 35.0 (CH), 8.2 (CH₂), 8.2 (CH₂), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₁H₁₉NO₃S+H]⁺: 366.1158; found: 366.1159.

(S)-3-(4-Cyclopropyl-2-(4-tolyl)but-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3dg)



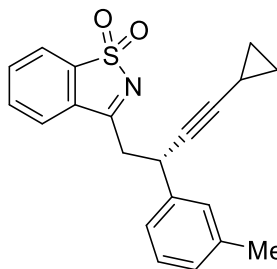
General procedure was followed using **1.1d** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3dg** as yellow solid (31.0 mg, 69% yield). Compound (S)-**1.3dg** was obtained with a 93% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 16.5$ min, $\tau_{\text{minor}} = 14.4$ min. **Mp** 104 – 107 °C. $[\alpha]_D^{25} = 1.3$ (*c* = 1.0, CHCl₃, 93% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.92 – 7.89 (m, 1H), 7.69 (dtd, *J* = 16.2, 7.3, 1.3 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.34 – 7.30 (m, 2H), 7.15 – 7.12 (m, 2H), 4.30 (ddd, *J* = 8.3, 6.2, 1.7 Hz, 1H), 3.35 (dd, *J* = 14.9, 8.5 Hz, 1H), 3.24 (dd, *J* = 14.9, 6.3 Hz, 1H), 2.32 (s, 3H), 1.17 (ttd, *J* = 8.2, 5.0, 1.8 Hz, 1H), 0.70 – 0.61 (m, 2H), 0.58 – 0.45 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 174.0 (C), 139.9 (C), 137.6 (C), 137.3 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 129.6 (CH), 127.4 (CH), 124.5 (CH), 122.6 (CH), 88.5 (C), 74.9 (C), 40.2 (CH₂), 35.4 (CH), 21.2 (CH₃), 8.2 (CH₂), 8.2 (CH₂), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₁H₁₉NO₂S + H]⁺: 350.1209; found: 350.1212.

(S)-3-(4-Cyclopropyl-2-(2-tolyl)but-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3eg)



General procedure was followed using **1.1e** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3eg** as a yellow solid (24.0 mg, 55% yield). Compound (S)-**1.3eg** was obtained with an 85% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 1.05$ min, $\tau_{\text{minor}} = 9.9$ min. **Mp** 143 – 146 °C. $[\alpha]_D^{25} = -17.8$ (*c* = 1.0, CHCl₃, 85% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.93 – 7.90 (m, 1H), 7.71 (dtd, *J* = 14.2, 7.3, 1.4 Hz, 2H), 7.65 – 7.61 (m, 1H), 7.59 – 7.56 (m, 1H), 7.25 – 7.14 (m, 3H), 4.50 (ddd, *J* = 9.3, 5.3, 1.8 Hz, 1H), 3.34 (dd, *J* = 14.7, 9.3 Hz, 1H), 3.19 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.42 (s, 3H), 1.13 (ttd, *J* = 8.2, 5.0, 1.8 Hz, 1H), 0.67 – 0.58 (m, 2H), 0.56 – 0.42 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 174.1 (C), 140.0 (C), 138.8 (C), 135.1 (C), 133.7 (CH), 133.6 (CH), 131.6 (C), 131.0 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 124.6 (CH), 122.6 (CH), 88.2 (C), 75.0 (C), 38.6 (CH₂), 32.5 (CH), 19.4 (CH₃), 8.2 (CH₂), 8.1 (CH₂), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₁H₁₉NO₂S + H]⁺: 350.1209; found: 350.1212.

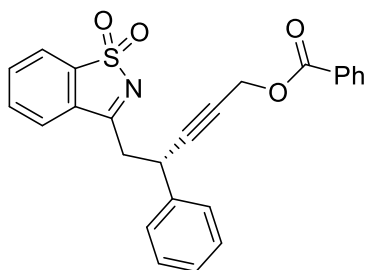
(S)-3-(4-Cyclopropyl-2-(3-tolyl)but-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3fg)



General procedure was followed using **1.1f** (0.125 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3fg** as yellow oil (28.0 mg, 64% yield). Compound (S)-**1.3fg** was obtained with an 82% enantiomeric excess determined by HPLC using a Chiralpak AY-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 46.0$ min, $\tau_{\text{minor}} = 43.8$ min. $[\alpha]_D^{25} = 11.2$ (*c* = 1.0, CHCl₃, 82% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.91 – 7.89 (m, 1H), 7.69 (dtd, *J* = 21.7, 7.4, 1.1 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.23 – 7.21 (m, 3H), 7.07 – 7.04 (m, 1H), 4.29 (ddd, *J* = 8.5, 6.2, 1.8

Hz, 1H), 3.36 (dd, $J = 14.8, 8.8$ Hz, 1H), 3.25 (dd, $J = 14.8, 6.1$ Hz, 1H), 2.32 (s, 3H), 1.17 (ttd, $J = 8.3, 5.0, 1.8$ Hz, 1H), 0.69 – 0.64 (m, 2H), 0.58 – 0.47 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 174.0 (C), 140.5 (C), 139.9 (C), 138.7 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 124.5 (CH), 124.4 (CH), 122.6 (CH), 88.7 (C), 74.8 (C), 40.1 (CH_2), 35.8 (CH), 21.5 (CH_3), 8.2 (CH_2), 8.2 (CH_2), -0.4 (CH); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{19}\text{NO}_2\text{S}+\text{H}]^+$: 350.1209; found: 350.1211.

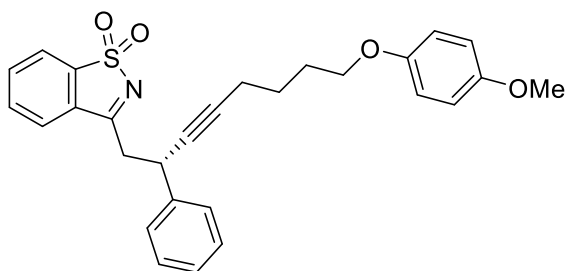
(S)-5-(1,1-Dioxidobenzo[d]isothiazol-3-yl)-4-phenylpent-2-yn-1-yl benzoate (1.3ah)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ah** as a colourless oil (34 mg, 63% yield). Compound (S)-**1.3ah** was obtained with a 93% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 56.5$ min, $\tau_{\text{minor}} = 46.8$ min. $[\alpha]_D^{25} = 15.6$ ($c = 1.0$, CHCl_3 , 93% ee). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ

8.04 – 8.02 (m, 2H), 7.86 – 7.83 (m, 1H), 7.66 – 7.55 (m, 4H), 7.47 – 7.41 (m, 4H), 7.36 – 7.23 (m, 3H), 4.90 (dd, $J = 2.1, 1.5$ Hz, 2H), 4.53 – 4.47 (m, 1H), 3.49 (dd, $J = 15.7, 8.2$ Hz, 1H), 3.33 (dd, $J = 15.7, 6.4$ Hz, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 173.5 (C), 166.0 (C), 139.8 (C), 139.4 (C), 133.9 (CH), 133.7 (CH), 133.4 (CH), 131.3 (C), 130.0 (CH), 129.7 (C), 129.1 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 124.2 (CH), 122.6 (CH), 86.8 (C), 78.8 (C), 53.0 (CH_2), 39.5 (CH_2), 35.3 (CH); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{25}\text{H}_{19}\text{NO}_4\text{S}+\text{H}]^+$: 430.1108; found: 430.1104.

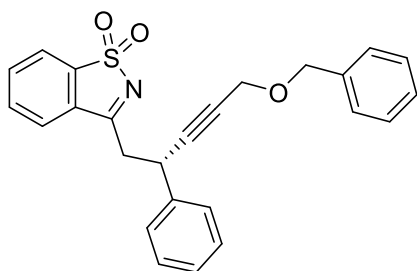
(S)-3-(8-(4-Methoxyphenoxy)-2-phenyloct-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3ai)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3ai** as a colourless oil (39.3 mg, 66% yield). Compound (S)-**1.3ai** was obtained with a 99% enantiomeric excess determined by HPLC using a Chiralpak OD-H column [*n*-

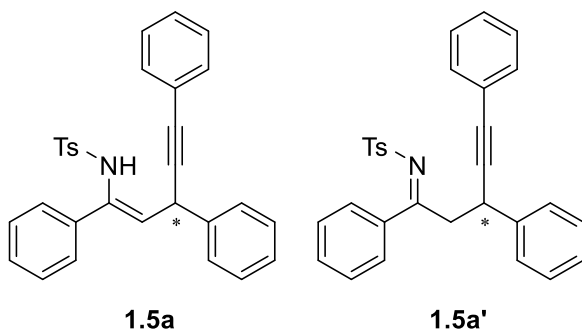
hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 38.7$ min, $\tau_{\text{minor}} = 48.1$ min. $[\alpha]_D^{25} = 10.3$ ($c = 0.96$, CHCl_3 , 99% ee). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.89 – 7.86 (m, 1H), 7.68 – 7.64 (m, 2H), 7.58 – 7.56 (m, 1H), 7.47 – 7.44 (m, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.22 (m, 1H), 6.81 (s, 4H), 4.40 – 4.37 (m, 1H), 3.86 (td, $J = 6.3, 2.2$ Hz, 2H), 3.76 (s, 3H), 3.39 (dd, $J = 15.1, 8.7$ Hz, 1H), 3.27 (dd, $J = 15.1, 6.1$ Hz, 1H), 2.21 (td, $J = 7.1, 2.3$ Hz, 2H), 1.79 – 1.71 (m, 2H), 1.63 – 1.55 (m, 4H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 173.1 (C), 153.8 (C), 153.3 (C), 140.6 (C), 139.9 (C), 133.8 (CH), 133.6 (CH), 131.5 (C), 129.9 (CH), 127.7 (CH), 127.5 (CH), 124.4 (CH), 122.6 (CH), 115.5 (CH), 114.8 (CH), 85.1 (C), 80.0 (C), 68.0 (CH_2), 55.9 (CH_3), 40.1 (CH_2), 35.7 (CH), 28.5 (CH_2), 25.3 (CH_2), 18.6 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{28}\text{H}_{27}\text{NO}_4\text{S}+\text{H}]^+$: 474.1734; found: 474.1732.

(S)-3-(5-(Benzyloxy)-2-phenylpent-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (1.3aj)



General procedure was followed using **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **1.3aj** as a colourless oil (30.7 mg, 59% yield). Compound (S)-**1.3aj** was obtained with a 80% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 45.4$ min, $\tau_{\text{minor}} = 26.9$ min. $[\alpha]_D^{25} = 0.38$ (c = 0.65, CHCl₃, 80% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.89 – 7.86 (m, 1H), 7.72 – 7.61 (m, 2H), 7.58 – 7.55 (m, 1H), 7.49 – 7.45 (m, 2H), 7.37 – 7.27 (m, 8H), 4.52 (d, *J* = 1.9 Hz, 2H), 4.17 (d, *J* = 2.0 Hz, 2H), 3.48 (dd, *J* = 15.9, 8.5 Hz, 1H), 3.32 (dd, *J* = 15.8, 6.1 Hz, 1H); **¹³C NMR** (75 MHz, CDCl₃) δ 173.5 (C), 139.9 (C), 139.8 (C), 137.6 (C), 133.9 (CH), 133.7 (CH), 131.3 (C), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.90 (CH), 127.85 (CH), 127.6 (CH), 124.2 (CH), 122.7 (CH), 86.3 (C), 80.7 (C), 71.6 (CH₂), 57.6 (CH₃), 39.7 (CH₂), 35.3 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₁NO₃S+H]⁺: 416.1315; found: 416.1312.

4-Methyl-N-(1,3,5-triphenylpent-1-en-4-yn-1-yl)benzenesulfonamide (1.5a) and 4-Methyl-N-(1,3,5-triphenylpent-4-yn-1-ylidene)benzenesulfonamide (1.5a')



General procedure was followed using **1.4a** (0.125 mmol, 45.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography, affording the addition product 72:28 as a mixture of enamine **1.5a**/imine **1.5a'** (24.5 mg, 43% yield).

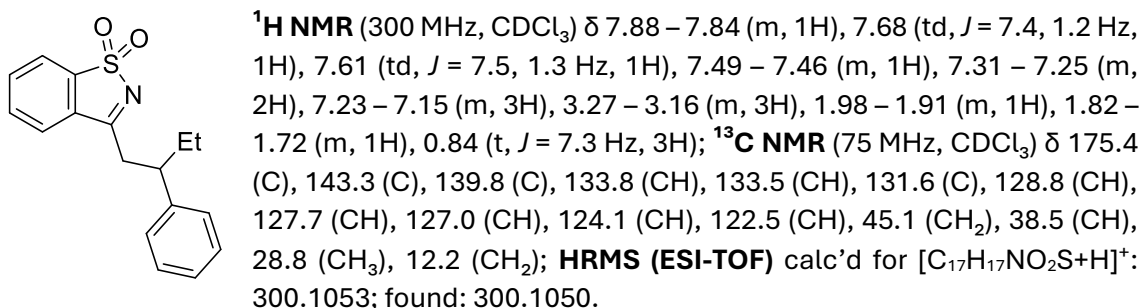
Enamine 1.5a: Compound **1.5a** was obtained as a brown solid with a 73% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10), 1 mL/min]: $\tau_{\text{major}} = 14.2$ min, $\tau_{\text{minor}} = 17.5$ min. **Mp** 45 – 50 °C. $[\alpha]_D^{25} = 7.6$ (c = 1.0, CHCl₃, 73% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7.31 (m, 3H), 7.25 – 7.07 (m, 5H), 6.80 (s, 1H), 5.51 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.35 (d, *J* = 8.1 Hz, 1H), 2.30 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 143.9 (C), 139.6 (C), 136.9 (C), 136.8 (C), 135.7 (C), 131.8 (CH), 129.7 (CH), 128.8 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 124.2 (CH), 122.8 (C), 87.6 (C), 84.8 (C), 35.7 (CH), 21.6 (CH₃).

Imine 1.5a': Compound **1.5a'** was obtained as an oil with a 75% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10), 1 mL/min]: $\tau_{\text{major}} = 28.3$ min, $\tau_{\text{minor}} = 22.9$ min. **¹H NMR** (300 MHz, CDCl₃) δ 7.94 (d, *J* = 8.1 Hz, 4H), 7.61 (bd, *J* = 7.4 Hz, 2H), 7.55 – 7.47 (m, 1H), 7.43 – 7.29 (m, 7H), 7.23 – 7.16 (m, 3H), 7.08 (bd, *J* = 6.5 Hz, 2H), 4.75 (s, 1H), 3.96 (s, 1H), 3.82 (s, 1H), 2.44 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 180.5 (C), 143.7 (C), 140.5 (C), 138.5 (C), 137.7 (C), 132.9 (CH), 131.5 (CH), 129.5 (CH),

129.1 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 123.0 (C), 89.2 (C), 85.9 (C), 41.4 (CH₂), 37.3 (CH), 21.6 (CH₃).

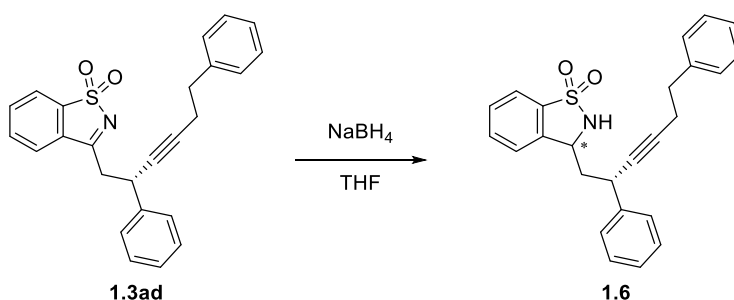
3-(2-Phenylbutyl)benzo[d]isothiazole 1,1-dioxide (1.8)

In some cases, the formation of the conjugate ethylation product **1.8** was observed:



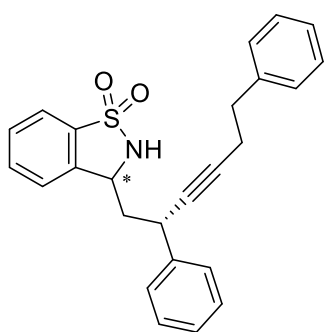
Synthetic transformations of compound 1.3ad

General procedure for the synthesis of compound 1.6



In a round bottom flask, compound **1.3ad** (0.05 mmol, 20 mg, 1 equiv.) was dissolved in dry THF (1 mL) at room temperature under nitrogen atmosphere. To this solution, NaBH₄ (0.2 mmol, 8 mg, 4 equiv.) was added, and the resulting mixture was stirred for 1 hour. The reaction was quenched with HCl 1 M (1 mL), extracted with DCM (3 x 10 mL), dried over MgSO₄. Solvents were moved *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures to yield the desired sulfonamide **1.6**.

3-((S)-2,6-Diphenylhex-3-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (1.6)



The crude product was purified by silica gel column chromatography affording pure **1.6** as colourless oil (16.0 mg, 80% yield, 69:31 *dr*).

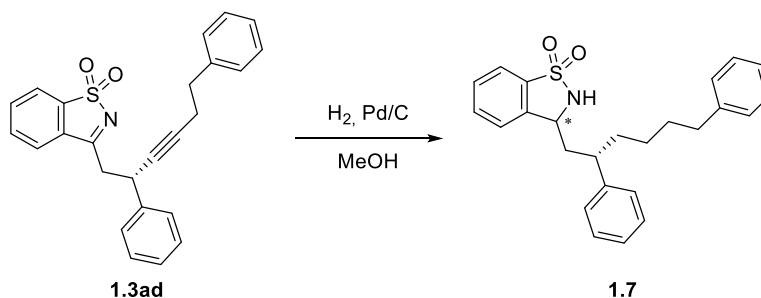
Major diastereomer: Compound was obtained with a 95% enantiomeric excess determined by HPLC using a Lux Cellulose 4 column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 36.5 min, τ_{minor} = 24.1 min. [α]_D²⁵ = 11.1 (c = 0.70, CHCl₃, 95% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.78 – 7.75 (m, 1H), 7.59

(td, *J* = 7.5, 1.3 Hz, 1H), 7.52 (td, *J* = 7.4, 1.2 Hz, 1H), 7.35 – 7.19 (m, 11H), 4.80 (d, *J* = 4.6 Hz,

1H), 4.55 (dt, $J = 9.4, 4.6$ Hz, 1H), 3.90 – 3.85 (m, 1H), 2.86 (t, $J = 7.3$ Hz, 2H), 2.59 (td, $J = 7.3, 2.2$ Hz, 2H), 2.26 – 2.18 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 140.7 (C), 140.7 (C), 140.2 (C), 135.6 (C), 133.1 (CH), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 127.5 (CH), 127.5 (CH), 126.4 (CH), 124.6 (CH), 121.6 (CH), 84.9 (C), 81.5 (C), 56.3 (CH), 44.8 (CH_2), 35.8 (CH), 35.1 (CH_2), 20.9 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{25}\text{H}_{23}\text{NO}_2\text{S}+\text{H}]^+$: 402.1522; found: 402.1530.

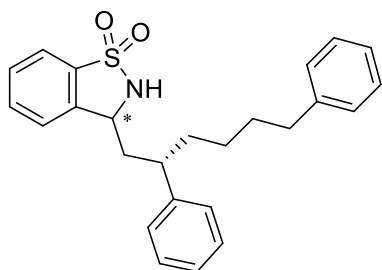
Minor diastereomer: Compound was obtained with a 92% enantiomeric excess determined by HPLC using a Chiralcel OD-H column [n -hexane/ i -PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 13.1$ min, $\tau_{\text{minor}} = 27.6$ min. $[\alpha]_D^{25} = -11.7$ ($c = 0.30$, CHCl_3 , 92% ee). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.78 – 7.75 (m, 1H), 7.58 (td, $J = 7.5, 1.3$ Hz, 1H), 7.53 – 7.48 (m, 1H), 7.32 – 7.15 (m, 11H), 4.77 (d, $J = 6.0$ Hz, 1H), 4.69 – 4.64 (m, 1H), 3.95 – 3.90 (m, 1H), 2.89 (t, $J = 6.9$ Hz, 2H), 2.66 (td, $J = 7.0, 2.1$ Hz, 2H), 2.03 – 1.97 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 141.0 (C), 140.8 (C), 140.6 (C), 136.7 (C), 133.1 (CH), 129.4 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.4 (CH), 127.2 (CH), 126.6 (CH), 124.3 (CH), 121.5 (CH), 85.3 (C), 80.8 (C), 56.5 (CH), 45.0 (CH_2), 35.6 (CH), 35.0 (CH_2), 20.7 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{25}\text{H}_{23}\text{NO}_2\text{S}+\text{H}]^+$: 402.1522; found: 402.1530.

General procedure for the synthesis of compound 1.7



In a round bottom flask, a solution of compound **1.3ad** (0.05 mmol, 20 mg, 1 equiv.) in MeOH (1 mL) was stirred at room temperature under hydrogen atmosphere in the presence of 10% Pd/C. After 30 minutes, the suspension was filtered through a short Celite® pad and rinsed with EtOAc. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures to yield the desired sulfonamide **1.7**.

3-((S)-2,6-Diphenylhexyl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (1.7)



The crude product was purified by silica gel column chromatography affording pure **1.7** as colourless oil (15.3 mg, 75% yield, 74:26 *dr*).

Major diastereomer: Compound was obtained with a 94% enantiomeric excess determined by HPLC using a Lux Cellulose 4 column [n -hexane/ i -PrOH (80:20), 1 mL/min]:

$\tau_{\text{major}} = 21.4$ min, $\tau_{\text{minor}} = 25.7$ min. $[\alpha]_D^{25} = -26.7$ ($c = 0.80$, CHCl_3 , 94% ee). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.74 – 7.71 (m, 1H), 7.54 (td, $J = 7.5, 1.4$ Hz, 1H), 7.47 (t, $J = 7.1$ Hz, 1H), 7.33 – 7.10 (m, 11H), 4.67 – 4.61 (m, 1H), 4.23 (d, $J = 4.2$ Hz, 1H), 2.88 – 2.78 (m, 1H), 2.56 – 2.50 (m, 2H), 2.29 (ddd, $J = 14.4, 5.7, 4.2$ Hz, 1H), 2.10 (dt, $J = 14.6,$

9.0 Hz, 1H), 1.74 – 1.54 (m, 4H), 1.29 – 1.18 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 144.0 (C), 142.6 (C), 140.4 (C), 135.4 (C), 133.0 (CH), 129.4 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 125.8 (CH), 124.4 (CH), 121.5 (CH), 57.1 (CH), 44.0 (CH), 43.6 (CH₂), 36.6 (CH₂), 35.9 (CH₂), 31.5 (CH₂), 27.0 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₇NO₂S + H]⁺: 406.1835; found: 406.1841.

Minor diastereomer: Compound was obtained with an 84% enantiomeric excess determined by HPLC using a Lux Cellulose 4 column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 17.8 min, τ_{minor} = 14.7 min. [α]_D²⁵ = 41.3 (c = 0.30, CHCl₃, 84% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.75 – 7.72 (m, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.40 – 7.34 (m, 2H), 7.29 – 7.22 (m, 6H), 7.18 – 7.09 (m, 3H), 4.55 (d, *J* = 6.0 Hz, 1H), 4.22 (ddd, *J* = 11.1, 5.9, 3.0 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.55 – 2.49 (m, 2H), 2.15 – 2.02 (m, 2H), 1.69 – 1.53 (m, 4H), 1.28 – 1.23 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 143.5 (C), 142.7 (C), 141.3 (C), 135.7 (C), 133.2 (CH), 129.3 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 125.8 (CH), 124.2 (CH), 121.5 (CH), 56.1 (CH), 43.6 (CH), 43.5 (CH₂), 37.3 (CH₂), 35.9 (CH₂), 31.5 (CH₂), 27.3 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₇NO₂S + H]⁺: 406.1835; found: 406.1841.

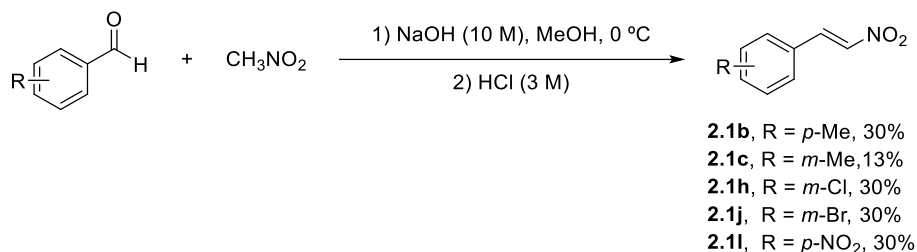
Enantioselective zinc-mediated conjugate addition of terminal alkynes to saccharin-derived azadienes

Synthesis and characterization data for *trans*- β -nitrostyrenes **2.1**

All *trans*- β -nitrostyrenes **2.1** were available at the laboratory except for compounds **2.1b**, **2.1c**, **2.1h**, **2.1j** and **2.1l**.

General procedure for the synthesis of *trans*- β -nitrostyrenes **2.1**

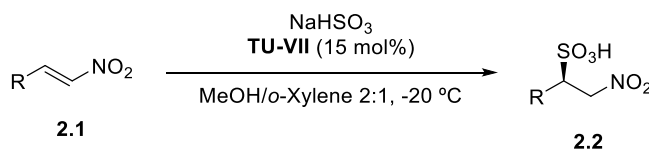
Compounds **2.1** were prepared based on modified reported procedures. Spectroscopic data for compounds **2.1b**, **2.1c**, **2.1h**, **2.1j** and **2.1l** were in accordance with literature.^{[7]–[9]}



The corresponding aldehyde (8 mmol, 1 equiv.) and nitromethane (8 mmol, 0.45 mL, 1 equiv.) were dissolved in MeOH (6 mL) at 0 °C. To this solution, NaOH 10 M (8 mmol, 0.8 mL, 1 equiv.) was added dropwise and stirred for 1 hour. The solution was acidified with HCl 4 M (5 mL), extracted with DCM (3 x 25 mL) and the combined organic layers were dried over MgSO₄. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane:Et₂O mixtures as eluent to afford the desired product.

In some cases, spontaneous dehydration of the intermediate nitroalcohol was not observed. Therefore, a solution of the nitroalcohol in DCM (30 mL) was treated with acetic anhydride (1 equiv.) and DMAP (5 mol%) for 24h at room temperature. Next, saturated NaHCO₃ was added until no gas evolution was observed, and the organic phase was rinsed with brine. The aqueous phase was extracted with DCM (30 mL), the combined organic layers were dried over MgSO₄, and solvents were removed *in vacuo*. Recrystallization of the crude product with ethanol yielded *trans*- β -nitrostyrenes **2.1**.

Synthesis and characterization data for chiral β -nitro sulfonic acids **2.2**



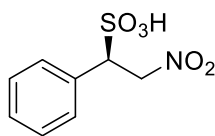
General procedure for the enantioselective addition of NaHSO₃ to *trans*- β -nitrostyrenes

In a test tube, catalyst **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%) and the nitroalkene **2.1** (0.2 mmol, 1 equiv.) were dissolved in a MeOH/*o*-xylene mixture (2 mL, v/v, 2:1), and the solution was stirred at -20 °C for 10 minutes. Then, NaHSO₃ (0.48 mmol, 50.0 mg, 2.4 equiv.) in 0.5 mL of H₂O was added and the reaction was vigorously stirred overnight or until the reaction was complete (TLC). The mixture was filtered through a Celite® pad, rinsed with H₂O, and

solvents were removed *in vacuo*. The crude product was dissolved in 3 mL of a THF/H₂O mixture (v/v, 2:1), passed through a plug of freshly conditioned acidic ion-exchange resin Amberlyst@15 and rinsed with water (3 x 3 mL). The resulting aqueous solution was concentrated *in vacuo* and dried under high vacuum in the presence of P₂O₅. Crude products were purified by silica gel column chromatography using DCM/MeOH mixtures to afford compounds **2.2**.

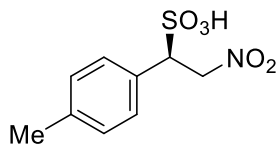
Racemic products **2.2** were obtained following the same procedure employing 3 drops of Et₃N instead of **TU-VII** at room temperature for 2 hours.

(*R*)-2-Nitro-1-phenylethane-1-sulfonic acid (**2.2a**)



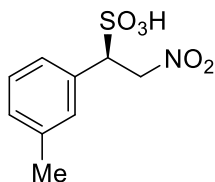
General procedure was followed using **2.1a** (0.2 mmol, 29.8 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2a** as a white solid (45.5 mg, 98% yield). **Mp** 88 – 92 °C. $[\alpha]_D^{25} = 5.7$ (*c* = 0.49, MeOH, 92% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.49 – 7.45 (m, 2H), 7.37 – 7.32 (m, 3H), 5.29 (dd, *J* = 13.6, 5.1 Hz, 1H), 5.06 (dd, *J* = 13.6, 10.0 Hz, 1H), 4.75 (dd, *J* = 10.0, 5.1 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 135.2 (C), 130.5 (CH), 129.5 (CH), 129.4 (CH), 77.5 (CH₂), 65.0 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₉NO₅S+NH₄]⁺: 249.0540; found: 249.0529.

(*R*)-2-Nitro-1-(4-tolyl)ethane-1-sulfonic acid (**2.2b**)



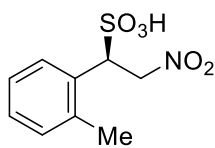
General procedure was followed using **2.1b** (0.2 mmol, 32.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2b** as a light brown oil (48.7 mg, 99% yield). $[\alpha]_D^{25} = 5.4$ (*c* = 0.99, MeOH, 88% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.38 – 7.29 (m, 2H), 7.20 – 7.11 (m, 2H), 5.26 (dd, *J* = 13.5, 5.2 Hz, 1H), 5.02 (dd, *J* = 13.5, 10.0 Hz, 1H), 4.70 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.32 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 139.3 (C), 132.0 (C), 130.2 (CH), 130.0 (CH), 77.5 (CH₂), 64.6 (CH), 21.1 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₁NO₅S+NH₄]⁺: 263.0696; found: 263.0703.

(*R*)-2-Nitro-1-(3-tolyl)ethane-1-sulfonic acid (**2.2c**)



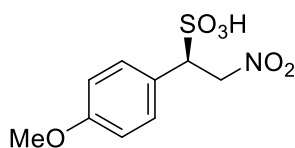
General procedure was followed using **2.1c** (0.2 mmol, 32.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2c** as light brown oil (47.8 mg, 97% yield). $[\alpha]_D^{25} = 3.6$ (*c* = 0.95, MeOH, 90% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.31 – 7.17 (m, 3H), 7.15 – 7.09 (m, 1H), 5.26 (dd, *J* = 13.6, 5.2 Hz, 1H), 5.03 (dd, *J* = 13.5, 10.0 Hz, 1H), 4.70 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.34 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 139.1 (C), 135.0 (C), 131.0 (CH), 130.0 (CH), 129.3 (CH), 127.4 (CH), 77.5 (CH₂), 64.9 (CH), 21.4 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₁NO₅S+NH₄]⁺: 263.0696; found: 263.0659.

(R)-2-Nitro-1-(2-tolyl)ethane-1-sulfonic acid (2.2d)



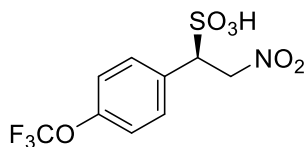
General procedure was followed using **2.1d** (0.2 mmol, 32.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2d** as light brown oil (48.0 mg, 98% yield). $[\alpha]_D^{25} = -20.4$ ($c = 1.1$, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.33–7.27 (m, 1H), 7.01–6.93 (m, 3H), 5.09 (dd, $J = 12.9, 4.5$ Hz, 1H), 4.96 (dd, $J = 9.7, 4.5$ Hz, 1H), 4.85 (dd, $J = 12.9, 9.7$ Hz, 1H), 2.27 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 139.7 (C), 133.6 (C), 131.6 (CH), 129.2 (CH), 128.3 (CH), 127.2 (CH), 77.7 (CH₂), 59.9 (CH), 20.1 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₁NO₅S+NH₄]⁺: 263.0696; found: 263.0670.

(R)-1-(4-Methoxyphenyl)-2-nitroethane-1-sulfonic acid (2.2e)



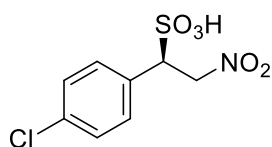
General procedure was followed using **2.1e** (0.2 mmol, 35.8 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2e** as light brown oil (51.1 mg, 98% yield). $[\alpha]_D^{25} = 10.6$ ($c = 0.50$, MeOH, 92% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.39 (d, $J = 8.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 5.27 (dd, $J = 13.4, 5.1$ Hz, 1H), 5.01 (dd, $J = 13.4, 10.2$ Hz, 1H), 4.75 (dd, $J = 10.2, 5.1$ Hz, 1H), 3.78 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 161.3 (C), 131.6 (CH), 127.0 (C), 115.0 (CH), 77.7 (CH₂), 64.4 (CH), 55.8 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₁NO₆S+NH₄]⁺: 279.0645; found: 279.0637.

(R)-2-nitro-1-(4-(trifluoromethoxy)phenyl)ethane-1-sulfonic acid (2.2f)



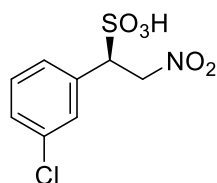
General procedure was followed using **2.1f** (0.2 mmol, 46.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2f** as light brown oil (60.7 mg, 96% yield). $[\alpha]_D^{25} = -5.3$ ($c = 1.8$, MeOH, 90% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.58 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 5.30 (dd, $J = 13.8, 5.3$ Hz, 1H), 5.08 (dd, $J = 13.8, 9.8$ Hz, 1H), 4.81 (dd, $J = 9.8, 5.3$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 150.6 (q, $J = 3.5$ Hz, C), 134.7 (C), 132.3 (CH), 122.1 (CH), 121.0 (q, $J = 256.0$ Hz, C), 77.3 (CH₂), 64.2 (CH); **¹⁹F NMR** (282 MHz, CD₃OD) δ -59.4. **HRMS (ESI-TOF)** calc'd for [C₉H₈F₃NO₆S+NH₄]⁺: 333.0363; found: 333.0367.

(R)-1-(4-Chlorophenyl)-2-nitroethane-1-sulfonic acid (2.2g)



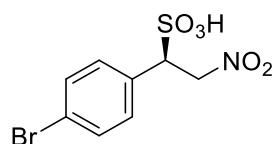
General procedure was followed using **2.1g** (0.2 mmol, 36.7 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2g** as light brown oil (51.7 mg, 97% yield). $[\alpha]_D^{25} = 4.3$ ($c = 0.90$, MeOH, 92% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.37 (d, $J = 8.6$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 2H), 5.20 (dd, $J = 13.7, 5.0$ Hz, 1H), 4.96 (dd, $J = 13.7, 10.0$ Hz, 1H), 4.67 (dd, $J = 10.0, 5.0$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 135.4 (C), 134.2 (C), 132.1 (CH), 129.6 (CH), 77.4 (CH₂), 75.2 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₈ClNO₅S+NH₄]⁺: 283.0150; found: 283.0141.

(R)-1-(3-Chlorophenyl)-2-nitroethane-1-sulfonic acid (2.2h)



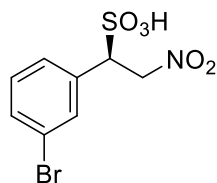
General procedure was followed using **2.1h** (0.2 mmol, 36.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2h** as light brown oil (51.2 mg, 96% yield). $[\alpha]_D^{25} = -2.1$ ($c = 1.3$, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.36 (s, 1H), 7.27–7.17 (m, 3H), 5.14 (dd, $J = 13.7, 4.8$ Hz, 1H), 4.99 (dd, $J = 13.7, 9.9$ Hz, 1H), 4.68 (dd, $J = 9.9, 4.8$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 137.7 (C), 135.3 (C), 131.0 (CH), 130.5 (CH), 129.6 (CH), 129.0 (CH), 77.4 (CH₂), 63.7 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₈ClNO₅S+NH₄]⁺: 283.0150; found: 283.0143.

(R)-1-(4-Bromophenyl)-2-nitroethane-1-sulfonic acid (2.2i)



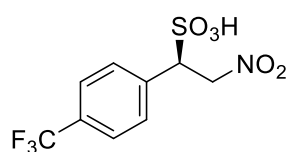
General procedure was followed using **2.1i** (0.2 mmol, 45.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2i** as light brown oil (60.5 mg, 97% yield). $[\alpha]_D^{25} = -9.8$ ($c = 2.3$, MeOH, 92% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.50 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 5.29 (dd, $J = 13.7, 5.2$ Hz, 1H), 5.05 (dd, $J = 13.7, 9.9$ Hz, 1H), 4.75 (dd, $J = 9.9, 5.2$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 134.6 (C), 132.6 (CH), 132.4 (CH), 123.4 (C), 77.2 (CH₂), 64.3 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₈BrNO₅S+NH₄]⁺: 326.9645; found: 326.9653.

(R)-1-(3-Bromophenyl)-2-nitroethane-1-sulfonic acid (2.2j)



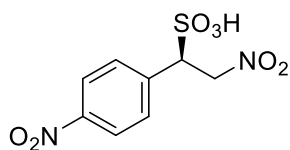
General procedure was followed using **2.1j** (0.2 mmol, 45.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2j** as white solid (58.8 mg, 95% yield). **Mp** 93 – 96 °C. $[\alpha]_D^{25} = 3.1$ ($c = 1.0$, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.60 (t, $J = 1.9$ Hz, 1H), 7.41 (ddd, $J = 7.9, 2.0, 1.1$ Hz, 1H), 7.39 (m, 1H), 7.20 (t, $J = 7.9$ Hz, 1H), 5.22 (dd, $J = 13.8, 5.1$ Hz, 1H), 4.99 (dd, $J = 13.8, 10.0$ Hz, 1H), 4.68 (dd, $J = 10.0, 5.1$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 137.9 (C), 133.4 (CH), 132.6 (CH), 131.3 (CH), 129.4 (CH), 123.3 (C), 77.3 (CH₂), 64.3 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₈BrNO₅S+NH₄]⁺: 326.9645; found: 326.9659.

(R)-2-Nitro-1-(4-(trifluoromethyl)phenyl)ethane-1-sulfonic acid (2.2k)



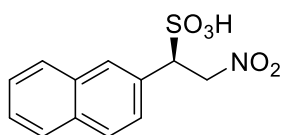
General procedure was followed using **2.1k** (0.2 mmol, 43.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2k** as light brown oil (58.6 mg, 98% yield). $[\alpha]_D^{25} = 1.9$ ($c = 1.3$, MeOH, 93% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.52 (d, $J = 8.7$ Hz, 2H), 7.48 (d, $J = 8.7$ Hz, 2H), 5.27 (dd, $J = 13.9, 5.2$ Hz, 1H), 5.01 (dd, $J = 13.9, 9.9$ Hz, 1H), 4.75 (dd, $J = 9.9, 5.2$ Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 140.0 (C), 131.5 (q, $J = 32.3$ Hz, C), 131.3 (CH), 126.4 (q, $J = 3.8$ Hz, CH), 125.8 (q, $J = 271.0$ Hz, C), 77.2 (CH₂), 64.6 (CH); **¹⁹F NMR** (282 MHz, CD₃OD) δ -64.1; **HRMS (ESI-TOF)** calc'd for [C₉H₈F₃NO₅S+NH₄]⁺: 317.0414; found: 317.0422.

(R)-2-Nitro-1-(4-nitrophenyl)ethane-1-sulfonic acid (2.2l)



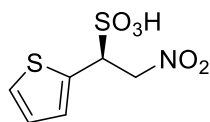
General procedure was followed using **2.1l** (0.2 mmol, 38.8 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2l** as brown solid (53.7 mg, 97% yield). **Mp** 110 °C (dec.). $[\alpha]_D^{25} = -3.5$ ($c = 1.0$, MeOH, 88% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.12 (d, $J = 8.8$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 2H), 5.26 (dd, $J = 14.0$, 5.0 Hz, 1H), 4.96 (dd, $J = 14.0$, 10.0 Hz, 1H), 4.67 (dd, $J = 10.0$, 5.0 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 149.3 (C), 143.0 (C), 131.8 (CH), 124.4 (CH), 77.0 (CH₂), 64.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₈H₈N₂O₇S+NH₄]⁺: 294.0390; found: 294.0382.

(R)-1-(Naphthalen-2-yl)-2-nitroethane-1-sulfonic acid (2.2m)



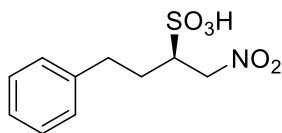
General procedure was followed using **2.1m** (0.2 mmol, 39.8 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2m** as light brown solid (55.3 mg, 98% yield). **Mp** 90 – 93 °C. $[\alpha]_D^{25} = 40.8$ ($c = 1.1$, MeOH, 88% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.25 (d, $J = 8.6$ Hz, 1H), 7.81–7.76 (m, 2H), 7.72 (dd, $J = 7.4$, 1.1 Hz, 1H), 7.50 (ddd, $J = 8.5$, 7.0, 1.5 Hz, 1H), 7.43 (d, $J = 7.4$, 1.0 Hz, 1H), 7.41 (dd, $J = 8.0$, 1.2 Hz, 2H), 5.79 (dd, $J = 9.4$, 5.4 Hz, 1H), 5.42 (dd, $J = 13.9$, 5.4 Hz, 1H), 5.17 (dd, $J = 13.9$, 9.4 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 135.6 (C), 134.1 (C), 131.5 (C), 130.0 (CH), 129.9 (CH), 127.6 (CH), 126.9 (CH), 126.8 (CH), 126.3 (CH), 124.7 (CH), 78.0 (CH₂), 58.5 (CH); **HRMS (ESI-TOF)** calc'd for [C₁₂H₁₁NO₅S+NH₄]⁺: 299.0696; found: 299.0691.

(S)-2-Nitro-1-(thiophen-2-yl)ethane-1-sulfonic acid (2.2n)



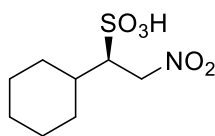
General procedure was followed using **2.1n** (0.2 mmol, 31.0 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2n** as a light brown oil (21.8 mg, 46% yield). $[\alpha]_D^{25} = 11.0$ ($c = 0.94$, MeOH, 85% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.38 (dd, $J = 5.2$, 1.2 Hz, 1H), 7.16 (ddd, $J = 3.6$, 1.3, 0.5 Hz, 1H), 6.99 (dd, $J = 5.2$, 3.6 Hz, 1H), 5.30 (dd, $J = 12.8$, 4.2 Hz, 1H), 5.04 (dd, $J = 10.0$, 4.2 Hz, 1H), 4.94 (dd, $J = 12.8$, 10.0 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 136.4 (C), 129.1 (CH), 127.6 (CH), 127.1 (CH), 78.4 (CH₂), 60.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₆H₇NO₅S₂+NH₄]⁺: 255.0104; found: 255.0110.

(R)-1-Nitro-4-phenylbutane-2-sulfonic acid (2.2o)



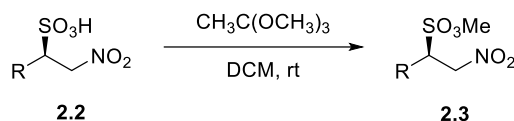
General procedure was followed using **2.1o** (0.2 mmol, 35.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2o** as light brown solid (48.8 mg, 94% yield). **Mp** 100 – 104 °C. $[\alpha]_D^{25} = 2.3$ ($c = 1.6$, MeOH, 76% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.17–7.02 (m, 5H), 4.76 (m, 1H), 4.52 (dd, $J = 13.9$, 6.2 Hz, 1H), 3.48 (p, $J = 6.5$ Hz, 1H), 2.72 (t, $J = 7.6$ Hz, 2H), 2.17 (ddt, $J = 14.3$, 8.5, 7.1 Hz, 1H), 1.77 (ddt, $J = 14.3$, 8.5, 7.1 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 141.1 (C), 128.1 (CH), 128.0 (CH), 125.7 (CH), 75.3 (CH₂), 57.2 (CH), 32.5 (CH₂), 30.5 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₃NO₅S+NH₄]⁺: 277.0853; found: 277.0849.

(*R*)-1-Cyclohexyl-2-nitroethane-1-sulfonic acid (**2.2p**)



General procedure was followed using **2.1p** (0.2 mmol, 31.0 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.2p** as a light brown oil (42.3 mg, 89% yield). $[\alpha]_D^{25} = -11.4$ ($c = 0.86$, MeOH, 73% ee). $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 4.68 (dd, $J = 14.2, 7.4$ Hz, 1H), 5.06 (dd, $J = 14.2, 5.0$ Hz, 1H), 3.41 (ddd, $J = 7.4, 5.0, 2.9$ Hz, 1H), 2.04–1.92 (m, 2H), 1.66–1.50 (m, 4H), 1.25–0.90 (m, 5H); $^{13}\text{C NMR}$ (75 MHz, CD_3OD) δ 74.6 (CH_2), 64.5 (CH), 39.5 (CH), 32.8 (CH_2), 29.4 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 27.4 (CH_2); **HRMS (ESI-TOF)** calc'd for $[\text{C}_8\text{H}_{15}\text{NO}_5\text{S}+\text{NH}_4]^+$: 255.1009; found: 255.1016.

Synthesis and characterization data for chiral β -nitro sulfonic esters **2.3**



General procedure for the synthesis of β -nitro sulfonic esters **2.3**

The crude sulfonic acid **2.1** (0.1 mmol, 1 equiv.) obtained after filtration through Amberlyst@15 was dissolved in DCM (1 mL) at room temperature, and trimethyl orthoacetate (0.5 mL, 3.9 mmol, 39 equiv.) was added. The reaction mixture was stirred for 2 hours, solvents were removed *in vacuo* and solvent traces were removed in high vacuum to yield β -nitro sulfonic esters **2.3**.

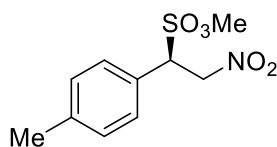
Note: Crude esterification products could not be purified by silica gel column chromatography due to decomposition issues. This behaviour was also observed to some extent when compounds **2.3** were analysed by HPLC.

Methyl (*R*)-2-nitro-1-phenylethane-1-sulfonate (**2.3a**)



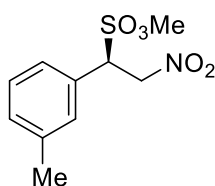
General procedure was followed using **2.2a** (0.1 mmol, 23.1 mg, 1 equiv.). Compound (*R*)-**2.3a** was obtained as a white solid with a 92% enantiomeric excess determined by HPLC using a Chiralpak AY-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 22.2$ min, $\tau_{\text{minor}} = 21.0$ min. **Mp** 108–113 °C. $[\alpha]_D^{25} = 13.4$ ($c = 0.48$, CHCl_3 , 92% ee). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.46 (br s, 5H), 5.27 (dd, $J = 13.5, 5.3$ Hz, 1H), 5.16 (dd, $J = 8.4, 5.3$ Hz, 1H), 5.03 (dd, $J = 13.5, 8.4$ Hz, 1H), 3.76 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 130.6 (CH), 129.7 (CH), 129.5 (CH), 128.5 (C), 74.2 (CH_2), 63.4 (CH), 58.0 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_9\text{H}_{11}\text{NO}_5\text{S}+\text{NH}_4]^+$: 263.0696; found: 263.0701.

Methyl (*R*)-2-nitro-1-(4-tolyl)ethane-1-sulfonate (**2.3b**)



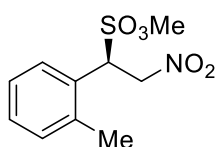
General procedure was followed using **2.2b** (0.1 mmol, 24.5 mg, 1 equiv.). Compound (*R*)-**2.3b** was obtained as a light brown oil with an 88% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 35.7$ min, $\tau_{\text{minor}} = 23.4$ min. $[\alpha]_D^{25} = -10.0$ ($c = 1.0$, CHCl₃, 88% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.38–7.30 (m, 2H), 7.29–7.20 (m, 2H), 5.25 (dd, $J = 13.4, 5.2$ Hz, 1H), 5.12 (dd, $J = 8.6, 5.2$ Hz, 1H), 5.00 (dd, $J = 13.4, 8.6$ Hz, 1H), 3.75 (s, 3H), 2.37 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 140.8 (C), 130.3 (CH), 129.3 (CH), 125.3 (C), 72.2 (CH₂), 64.7 (CH), 57.9 (CH₃), 21.4 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₃NO₅S + NH₄]⁺: 277.0853; found: 277.0845.

Methyl (*R*)-2-nitro-1-(3-tolyl)ethane-1-sulfonate (**2.3c**)



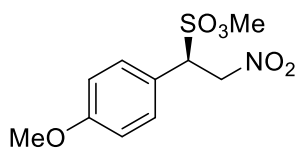
General procedure was followed using **2.2c** (0.1 mmol, 24.5 mg, 1 equiv.). Compound (*R*)-**2.3c** was obtained as a light brown oil with a 90% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 39.6$ min, $\tau_{\text{minor}} = 22.4$ min. $[\alpha]_D^{25} = -59$ ($c = 0.98$, CHCl₃, 90% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.39–7.29 (m, 1H), 7.28–7.21 (m, 3H), 5.25 (dd, $J = 13.5, 5.2$ Hz, 1H), 5.12 (dd, $J = 8.4, 5.2$ Hz, 1H), 5.00 (dd, $J = 13.5, 8.4$ Hz, 1H), 3.77 (s, 3H), 2.38 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 139.5 (C), 131.3 (CH), 130.1 (CH), 129.4 (CH), 128.3 (C), 126.4 (C), 74.2 (CH₂), 63.4 (CH), 57.9 (CH₃), 21.5 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₃NO₅S + NH₄]⁺: 277.0853; found: 277.0861.

Methyl (*R*)-2-nitro-1-(2-tolyl)ethane-1-sulfonate (**2.3d**)



General procedure was followed using **2.2d** (0.1 mmol, 24.5 mg, 1 equiv.). Compound (*R*)-**2.3d** was obtained as a light brown oil with a 91% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 16.8$ min, $\tau_{\text{minor}} = 18.6$ min. $[\alpha]_D^{25} = 9.9$ ($c = 1.1$, CHCl₃, 91% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.44–7.42 (m, 1H), 7.35–7.27 (m, 3H), 5.54 (dd, $J = 8.7, 5.5$ Hz, 1H), 5.28 (dd, $J = 14.4, 5.5$ Hz, 1H), 5.03 (dd, $J = 14.3, 8.8$ Hz, 1H), 3.73 (s, 3H), 2.52 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 138.8 (CH), 131.7 (CH), 130.4 (CH), 127.6 (C), 127.2 (CH), 127.1 (C), 74.5 (CH₂), 58.7 (CH), 57.9 (CH₃), 19.8 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₃NO₅S + NH₄]⁺: 277.0853; found: 277.0850.

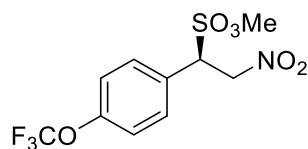
Methyl (*R*)-1-(4-methoxyphenyl)-2-nitroethane-1-sulfonate (**2.3e**)



General procedure was followed using **2.2e** (0.1 mmol, 26.1 mg, 1 equiv.). Compound (*R*)-**2.3e** was obtained as a light brown solid with a 90% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 34.1$ min, $\tau_{\text{minor}} = 28.5$ min. **mp** 88–89 °C. $[\alpha]_D^{25} = -10.6$ ($c = 0.50$, CHCl₃, 90% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.37 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 5.24 (dd, $J = 13.3, 5.1$ Hz, 1H), 5.11 (dd, $J = 8.7, 5.1$ Hz, 1H), 4.75 (dd, $J = 13.3, 8.7$ Hz, 1H), 3.82 (s, 3H), 3.76 (s,

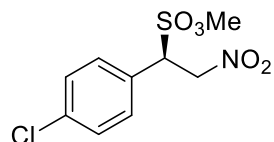
3H); ^{13}C NMR (75 MHz, CDCl_3) δ 161.2 (C), 130.8 (CH), 120.0 (CH), 115.0 (C), 74.3 (CH_2), 63.0 (CH), 58.0 (CH_3), 55.6 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_{10}\text{H}_{13}\text{NO}_6\text{S}+\text{NH}_4]^+$: 293.0802; found: 293.0792.

Methyl (*R*)-2-nitro-1-(4-(trifluoromethoxy)phenyl)ethane-1-sulfonate (**2.3f**)



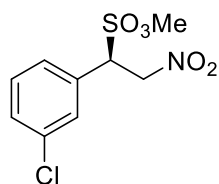
General procedure was followed using **2.2f** (0.1 mmol, 31.5 mg, 1 equiv.). Compound (*R*)-**2.3f** was obtained as a light brown solid with a 90% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 12.8$ min, $\tau_{\text{minor}} = 15.1$ min. **Mp** 79–82 °C. $[\alpha]_D^{25} = -9.2$ ($c = 0.50$, CHCl_3 , 90% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.51 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 5.27 (dd, $J = 13.7$, 5.3 Hz, 1H), 5.17 (dd, $J = 8.5$, 5.3 Hz, 1H), 4.99 (dd, $J = 13.7$, 8.5 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 150.5 (q, $J = 1.9$ Hz, C), 130.9 (CH), 126.8 (C), 121.6 (CH), 120.2 (q, $J = 258.8$ Hz, C), 73.8 (CH_2), 62.2 (CH), 57.5 (CH_3); ^{19}F NMR (282 MHz, CDCl_3) δ -57.8; **HRMS (ESI-TOF)** calc'd for $[\text{C}_{10}\text{H}_{10}\text{F}_3\text{NO}_5\text{S}+\text{NH}_4]^+$: 347.0519; found: 347.0522.

Methyl (*R*)-1-(4-chlorophenyl)-2-nitroethane-1-sulfonate (**2.3g**)



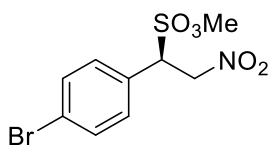
General procedure was followed using **2.2g** (0.1 mmol, 26.6 mg, 1 equiv.). Compound (*R*)-**2.3g** was obtained as a light brown solid with a 92% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 27.7$ min, $\tau_{\text{minor}} = 18.0$ min. **Mp** 104–107 °C. $[\alpha]_D^{25} = -14.2$ ($c = 0.50$, CHCl_3 , 92% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.44 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H), 5.25 (dd, $J = 13.6$, 5.1 Hz, 1H), 5.13 (dd, $J = 8.8$, 5.1 Hz, 1H), 4.98 (dd, $J = 13.6$, 8.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 137.0 (C), 130.8 (CH), 130.0 (CH), 127.0 (C), 74.0 (CH_2), 62.7 (CH), 57.9 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_9\text{H}_{10}\text{ClNO}_5\text{S}+\text{NH}_4]^+$: 297.0306; found: 297.0303.

Methyl (*R*)-1-(3-chlorophenyl)-2-nitroethane-1-sulfonate (**2.3h**)



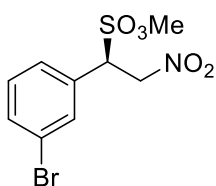
General procedure was followed using **2.2h** (0.1 mmol, 26.6 mg, 1 equiv.). Compound (*R*)-**2.3h** was obtained as a light brown solid with a 91% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 23.9$ min, $\tau_{\text{minor}} = 15.6$ min. **Mp** 70–72 °C. $[\alpha]_D^{25} = -13.9$ ($c = 1.1$, CHCl_3 , 91% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.46–7.42 (m, 2H), 7.41–7.34 (m, 2H), 5.25 (dd, $J = 13.8$, 5.2 Hz, 1H), 5.12 (dd, $J = 8.6$, 5.2 Hz, 1H), 5.03 (dd, $J = 13.8$, 8.6 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.6 (C), 130.9 (C, CH), 130.5 (C), 129.7 (CH), 127.6 (CH), 74.0 (CH_2), 62.8 (CH), 57.9 (CH_3); **HRMS (ESI-TOF)** calc'd for $[\text{C}_9\text{H}_{10}\text{ClNO}_5\text{S}+\text{NH}_4]^+$: 297.0306; found: 297.0314.

Methyl (*R*)-1-(4-bromophenyl)-2-nitroethane-1-sulfonate (**2.3i**)



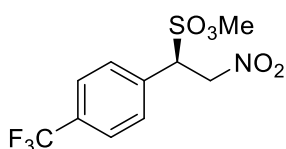
General procedure was followed using **2.2i** (0.1 mmol, 31.0 mg, 1 equiv.). Compound (*R*)-**2.3i** was obtained as a white solid with a 92% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 29.9$ min, $\tau_{\text{minor}} = 20.4$ min. **Mp** 81 – 83 °C. $[\alpha]_D^{25} = -12.0$ (*c* = 0.50, CHCl₃, 92% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.25 (dd, *J* = 13.6, 5.1 Hz, 1H), 5.12 (dd, *J* = 8.8, 5.1 Hz, 1H), 4.98 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.81 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 133.0 (CH), 131.0 (CH), 127.6 (C), 125.2 (C), 74.0 (CH₂), 62.8 (CH), 57.9 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₀BrNO₅S+NH₄]⁺: 340.9801; found: 340.9812.

Methyl (*R*)-1-(3-bromophenyl)-2-nitroethane-1-sulfonate (**2.3j**)



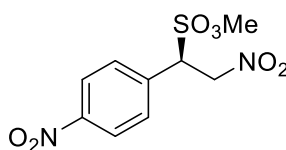
General procedure was followed using **2.2j** (0.1 mmol, 32.4 mg, 1 equiv.). Compound (*R*)-**2.3j** was obtained as a white solid with a 91% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 31.2$ min, $\tau_{\text{minor}} = 20.1$ min. **Mp** 85 – 88 °C. $[\alpha]_D^{25} = -10.9$ (*c* = 1.1, CHCl₃, 91% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.62 – 7.58 (m, 2H), 7.41 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.36 – 7.30 (m, 1H), 5.25 (dd, *J* = 13.8, 5.2 Hz, 1H), 5.11 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.98 (dd, *J* = 13.8, 8.6 Hz, 1H), 3.83 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 133.8 (CH), 132.5 (CH), 131.1 (CH), 130.8 (C), 128.1 (CH), 123.6 (C), 74.0 (CH₂), 62.7 (CH), 58.0 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₉H₁₀BrNO₅S+NH₄]⁺: 340.9801; found: 340.9798.

Methyl (*R*)-2-nitro-1-(4-(trifluoromethyl)phenyl)ethane-1-sulfonate (**2.3k**)



General procedure was followed using **2.2k** (0.1 mmol, 29.9 mg, 1 equiv.). Compound (*R*)-**2.3k** was obtained as a light brown solid with a 93% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 21.1$ min, $\tau_{\text{minor}} = 13.2$ min. **Mp** 85 – 88 °C. $[\alpha]_D^{25} = -6.8$ (*c* = 0.50, CHCl₃, 93% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 5.29 (dd, *J* = 13.5, 5.2 Hz, 1H), 5.22 (dd, *J* = 8.3, 5.2 Hz, 1H), 5.03 (dd, *J* = 13.5, 8.3 Hz, 1H), 3.85 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 137.3 (C), 132.8 (q, *J* = 29.0 Hz, C), 130.0 (CH), 126.6 (q, *J* = 3.7 Hz, CH), 123.6 (q, *J* = 272.6 Hz, C), 73.8 (CH₂), 62.7 (CH), 57.8 (CH₃); **¹⁹F NMR** (282 MHz, CDCl₃) δ -63.1.; **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₅S+NH₄]⁺: 331.0570; found: 331.0568.

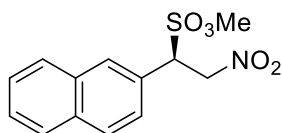
Methyl (*R*)-2-nitro-1-(4-nitrophenyl)ethane-1-sulfonate (**2.3l**)



General procedure was followed using **2.2l** (0.1 mmol, 27.6 mg, 1 equiv.). Compound (*R*)-**2.3l** was obtained as a brown solid with an 88% enantiomeric excess determined by HPLC using a Chiralpak AY-H column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 51.6$ min, $\tau_{\text{minor}} = 49.1$ min. **Mp** 89 – 92 °C. $[\alpha]_D^{25} = -12.0$ (*c* = 0.60, CHCl₃, 88% ee). **¹H NMR** (300

MHz, CDCl₃) δ 8.32 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 5.31 (dd, *J* = 12.5, 5.1 Hz, 1H), 5.28 (dd, *J* = 7.3, 5.1 Hz, 1H), 5.05 (dd, *J* = 12.5, 7.3 Hz, 1H), 3.89 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 135.5 (C), 130.7 (CH), 130.0 (C), 124.7 (CH), 73.7 (CH₂), 62.5 (CH), 57.8 (CH₃); HRMS (ESI-TOF) calc'd for [C₉H₁₁N₂O₇S+NH₄]⁺: 308.0547; found: 308.0539.

Methyl (*R*)-1-(naphthalen-2-yl)-2-nitroethane-1-sulfonate (2.3m)



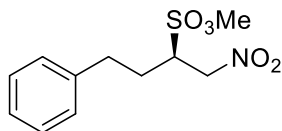
General procedure was followed using **2.2m** (0.1 mmol, 29.1 mg, 1 equiv.). Compound (*R*)-**2.3m** was obtained as a light brown oil with an 88% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: τ_{major} = 42.1 min, τ_{minor} = 27.3 min. [α]_D²⁵ = -10.0 (c = 1.0, CHCl₃, 88% ee). ¹H NMR (300 MHz, CDCl₃) δ 8.19–8.13 (m, 1H), 8.02–7.91 (m, 3H), 7.77–7.50 (m, 3H), 6.20 (m, 1H), 5.46 (dd, *J* = 14.4, 6.1 Hz, 1H), 5.13 (dd, *J* = 14.4, 7.7 Hz, 1H), 3.67 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 136.2 (C), 134.1 (C), 132.6 (C), 131.1 (CH), 129.4 (CH), 127.9 (CH), 126.7 (CH), 125.2 (CH), 123.0 (CH), 122.0 (CH), 74.7 (CH₂), 57.8 (CH), 57.3 (CH₃); HRMS (ESI-TOF) calc'd for [C₁₃H₁₃NO₅S+NH₄]⁺: 313.0853; found: 313.0861.

Methyl (*S*)-2-nitro-1-(thiophen-2-yl)ethane-1-sulfonate (2.3n)



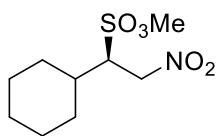
General procedure was followed using **2.2n** (0.09 mmol, 21.8 mg, 1 equiv.). Compound (*S*)-**2.3n** was obtained as a light brown oil with an 85% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: τ_{major} = 43.2 min, τ_{minor} = 29.0 min. [α]_D²⁵ = -4.3 (c = 0.45, CHCl₃, 85% ee). ¹H NMR (300 MHz, CDCl₃) δ 7.45 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.27 (ddd, *J* = 3.7, 1.2, 0.6 Hz, 1H), 7.08 (dd, *J* = 5.2, 3.7 Hz, 1H), 5.46 (dd, *J* = 8.9, 5.3 Hz, 1H), 5.26 (dd, *J* = 14.1, 5.3 Hz, 1H), 4.98 (dd, *J* = 14.1, 8.9 Hz, 1H), 3.83 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 130.2 (CH), 129.3 (C), 128.6 (CH), 127.8 (CH), 74.9 (CH₂), 59.1 (CH), 58.3 (CH₃); HRMS (ESI-TOF) calc'd for [C₇H₉NO₅S₂+NH₄]⁺: 269.0260; found: 269.0267.

Methyl (*R*)-1-nitro-4-phenylbutane-2-sulfonate (2.3o)



General procedure was followed using **2.2o** (0.1 mmol, 25.9 mg, 1 equiv.). Compound (*R*)-**2.3o** was obtained as a light brown oil with a 76% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10), 1 mL/min]: τ_{major} = 40.1 min, τ_{minor} = 36.1 min. [α]_D²⁵ = 5.3 (c = 1.0, CHCl₃, 76% ee). ¹H NMR (300 MHz, CDCl₃) δ 7.24–7.09 (m, 5H), 4.79 (dd, *J* = 14.6, 6.7 Hz, 1H), 4.43 (dd, *J* = 14.6, 5.7 Hz, 1H), 4.10 (ddd, *J* = 6.7, 5.7, 2.5 Hz, 1H), 3.78 (s, 3H), 2.78 (m, 2H), 2.33 (dddd, *J* = 14.6, 8.9, 6.8, 5.7 Hz, 1H), 1.77 (dddd, *J* = 14.6, 8.9, 6.9, 5.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 139.1 (C), 129.1 (CH), 128.6 (CH), 127.1 (CH), 73.7 (CH₂), 57.0 (CH), 56.4 (CH₃), 32.4 (CH₂), 29.4 (CH₂); HRMS (ESI-TOF) calc'd for [C₁₁H₁₅NO₅S+NH₄]⁺: 291.1009; found: 291.1013.

Methyl (*R*)-1-cyclohexyl-2-nitroethane-1-sulfonate (2.3p)



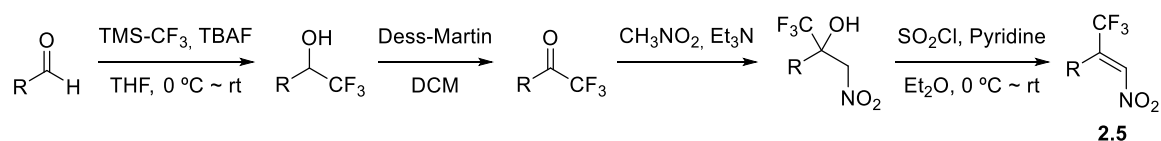
General procedure was followed using **2.2p** (0.1 mmol, 23.7 mg, 1 equiv.). Compound (*R*)-**2.3p** was obtained as a Dlight brown oil with a 73% enantiomeric excess determined by HPLC using a Chiralpak AY-H column [*n*-hexane/*i*-PrOH (95:05), 1 mL/min]: τ_{major} = 40.2 min, τ_{minor} = 30.3 min. $[\alpha]_D^{25}$ = -5.4 (c = 0.80, CHCl₃, 73% ee). **¹H NMR** (300 MHz, CDCl₃) δ 4.86 (dd, *J* = 15.0, 7.5 Hz, 1H), 4.60 (dd, *J* = 15.0, 4.1 Hz, 1H), 3.99 – 3.94 (m, 1H), 3.88 (s, 3H), 2.21 (tq, *J* = 11.9, 3.2 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.86 – 1.66 (m, 4H), 1.38 – 1.40 (m, 5H); **¹³C NMR** (75 MHz, CDCl₃) δ 72.0 (CH₂), 62.7 (CH), 56.4 (CH₃), 37.6 (CH), 31.2 (CH₂), 28.7 (CH₂), 26.5 (CH₂), 26.2 (CH₂), 25.9 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₉H₁₇NO₅S+NH₄]⁺: 269.1166; found: 269.1163.

Enantioselective Construction of Tetrasubstituted Stereocentres *via* the Organocatalytic *sulfa*-Michael Addition of Sodium Bisulfite to β,β -Disubstituted Nitroalkenes

Synthesis and characterization data for Nitroalkenes 2.5

General procedure for the synthesis of β -CF₃- β,β -disubstituted Nitroalkenes 2.5

Compounds **2.5** were prepared *via* a four-step synthesis based on modified reported procedures. Most of the trifluoroketones were commercially available and their synthesis was only required for the preparation of **2.5d**, **2.5f**, **2.5g**, **2.5n** and **2.5p**. Spectroscopic data for compounds **2.5** was in accordance with literature.^{[10]–[15]} Compounds **2.5d**, **2.5f**, **2.5g** are new compounds and have been fully characterized.



In a round bottom flask, the corresponding aldehyde (10 mmol, 1 equiv.) and TMS-CF₃ (12 mmol, 1.8 mL, 1.2 equiv.) were dissolved in dry THF (10 mL) at 0 °C. To this solution, TBAF (1M in THF, 0.08 mmol, 8 μ L, 0.8 mol%) was added dropwise and the resulting mixture was stirred at room temperature for 1 hour. Solvents were removed *in vacuo* and the resulting residue was dissolved in THF (5 mL) and treated with HCl 4 M (5 mL). The solution was stirred at room temperature for 1 hour and then was diluted with water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were rinsed with brine, dried over MgSO₄ and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired trifluoromethylcarbinol.

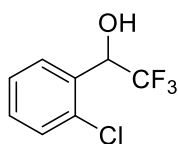
In a round bottom flask, Dess-Martin periodinane (13 mmol, 5.6 g, 1.3 equiv.) was suspended in DCM (20 mL) at 0 °C. To this mixture, trifluoromethylcarbinol (10 mmol, 1 equiv.) was added dropwise, and the resulting solution was stirred at room temperature overnight. The reaction was filtered through silica, and the filtrate was poured over a mixture of saturated Na₂S₂O₃/NaHCO₃ (20 mL, v/v, 5:1). The aqueous layer was extracted with DCM (2 x 50 mL) and the combined organic layers were washed with water, brine and dried over MgSO₄. Solvents were removed *in vacuo* to afford the crude trifluoroketone, which was used without any further purification.

To a solution of the corresponding trifluoroketone (10 mmol, 1 equiv.) in nitromethane (20 mL), triethylamine (15 mmol, 2 mL, 1.5 equiv.) was added and the resulting solution was stirred at room temperature overnight. The reaction was diluted with EtOAc (20 mL), quenched with HCl 1M (20 mL), and the organic layer was washed with water and brine and dried over MgSO₄. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired nitroalcohol.

A solution of the required nitroalcohol (10 mmol, 1 equiv.) in Et₂O (40 mL) was cooled to 0 °C under nitrogen atmosphere and treated sequentially with thionyl chloride (15 mmol, 1.1 mL, 1.5 equiv.) and pyridine (20 mmol, 1.6 mL, 2 equiv.) The resulting mixture was stirred at room temperature for 3 hours. The reaction was diluted with Et₂O (60 mL), washed with

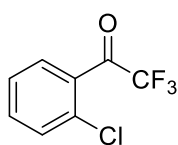
water (2 x 50 mL) and brine, and solvents were removed *in vacuo*. The resulting residue was purified by silica gel column chromatography using hexane/Et₂O mixtures as eluent to afford the desired β -CF₃- β,β -disubstituted nitroalkene.

1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-ol



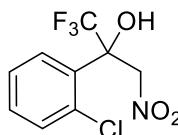
General procedure was followed using 2-chlorobenzaldehyde (10 mmol, 1.4 g, 1 equiv.). Colourless oil, 63% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.74 – 7.63 (m, 1H), 7.54 – 7.36 (m, 1H), 7.40 – 7.29 (m, 2H), 5.65 (qd, *J* = 6.4, 5.0 Hz, 1H), 2.82 (d, *J* = 5.0 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ –78.3.

1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-one



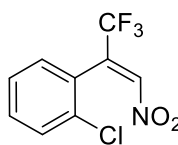
General procedure was followed using 1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-ol (6.3 mmol, 1.3 g, 1 equiv.). Yellow liquid, 99% yield. Crude 1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-one was used without purification.

2-(2-chlorophenyl)-1,1,1-trifluoro-3-nitropropan-2-ol



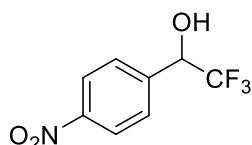
General procedure was followed using 1-(2-chlorophenyl)-2,2,2-trifluoroethan-1-one (6.3 mmol, 1.3 g, 1 equiv.). White solid, 44% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.18 – 7.73 (m, 1H), 7.47 – 7.41 (m, 1H), 7.41 – 7.33 (m, 2H), 6.00 (d, *J* = 14.5 Hz, 1H), 5.10 (d, *J* = 14.5 Hz, 1H), 4.75 (d, *J* = 0.7 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ –77.6.

(E)-1-chloro-2-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzene (2.5d)



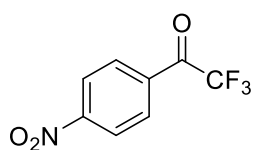
General procedure was followed using 2-(2-chlorophenyl)-1,1,1-trifluoro-3-nitropropan-2-ol (2.8 mmol, 750 mg, 1 equiv.). Yellow liquid, 72% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.64 (q, *J* = 1.4 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.44 (td, *J* = 7.6, 1.8 Hz, 1H), 7.37 (td, *J* = 7.5, 1.5 Hz, 1H), 7.31 – 7.24 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 141.8 (bs, CH), 134.4 (q, *J* = 33.0 Hz, C), 133.6 (C), 131.7 (CH), 130.1 (CH), 129.5 (CH), 127.2 (CH), 126.5 (C), 121.7 (q, *J* = 276.3 Hz, CF₃); ¹⁹F NMR (282 MHz, CDCl₃) δ –67.3;

2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-ol



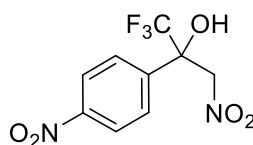
General procedure was followed using 4-nitrobenzaldehyde (10 mmol, 1.5 g, 1 equiv.). Yellow solid, 92% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.70 (dt, *J* = 9.0, 0.7 Hz, 2H), 5.19 (qd, *J* = 6.4, 4.0 Hz, 1H), 2.85 (d, *J* = 4.3 Hz, 1H); ¹⁹F NMR (282 MHz, CDCl₃) δ –78.7.

2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-one



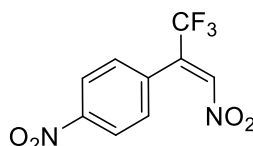
General procedure was followed using 2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-ol (9.2 mmol, 2.0 g, 1 equiv.). The crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent, affording the title compound as a yellow solid in 82% yield. $^1\text{H NMR}$ (300 MHz, CD_3OD) δ 8.47–8.29 (m, 2H), 8.10–7.82 (m, 2H); $^{19}\text{F NMR}$ (282 MHz, CD_3OD) δ –84.8.

1,1,1-trifluoro-3-nitro-2-(4-nitrophenyl)propan-2-ol



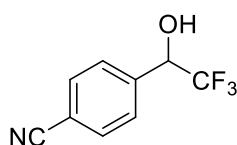
General procedure was followed using 2,2,2-trifluoro-1-(4-nitrophenyl)ethan-1-one (7.6 mmol, 1.7 g, 1 equiv.). Yellow solid, 47% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.37–8.26 (m, 2H), 7.88–7.78 (m, 2H), 5.14 (d, J = 13.7 Hz, 1H), 5.07 (d, J = 13.7 Hz, 1H), 4.82 (s, 1H); $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ –78.8.

(E)-1-nitro-4-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzene (2.5f)



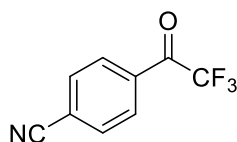
General procedure was followed using 1,1,1-trifluoro-3-nitro-2-(4-nitrophenyl)propan-2-ol (4.7 mmol, 1.2 g, 1 equiv.). Yellow solid, 50 % yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.42–8.31 (m, 2H), 7.62 (q, J = 1.4 Hz, 1H), 7.57–7.46 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 149.2 (C), 141.2 (q, J = 6.6, 6.1 Hz, C), 134.7 (q, J = 32.7 Hz, C), 133.3 (C), 129.8 (CH), 124.2 (CH), 121.5 (q, J = 275.9 Hz, CF_3); $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ –66.9.

4-(2,2,2-trifluoro-1-hydroxyethyl)benzonitrile



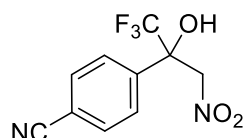
General procedure was followed using 4-formylbenzonitrile (15 mmol, 2 g, 1 equiv.). White solid, 90% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.76–7.68 (m, 2H), 7.67–7.58 (m, 2H), 5.11 (qd, J = 6.5, 4.5 Hz, 1H), 3.05 (d, J = 4.5 Hz, 1H); $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ –78.7.

4-(2,2,2-trifluoroacetyl)benzonitrile



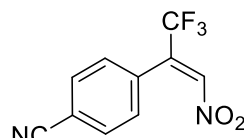
General procedure was followed using 4-(2,2,2-trifluoro-1-hydroxyethyl)benzonitrile (14 mmol, 2.8 g, 1 equiv.). Yellow solid, 93% yield. Crude 4-(2,2,2-trifluoroacetyl)benzonitrile was used without purification.

4-(1,1,1-trifluoro-2-hydroxy-3-nitropropan-2-yl)benzonitrile



General procedure was followed using 4-(2,2,2-trifluoroacetyl)benzonitrile (12.75 mmol, 2.8 g, 1 equiv.). White solid, 70% yield. $^1\text{H NMR}$ (300 MHz, CD_3CN) δ 8.31–7.49 (m, 4H), 5.55 (s, 1H), 5.37 (dd, J = 13.3, 0.6 Hz, 1H), 5.13 (d, J = 13.3 Hz, 1H); $^{19}\text{F NMR}$ (282 MHz, CD_3CN) δ –78.9.

(*E*)-4-(3,3,3-trifluoro-1-nitroprop-1-en-2-yl)benzonitrile (2.5g)

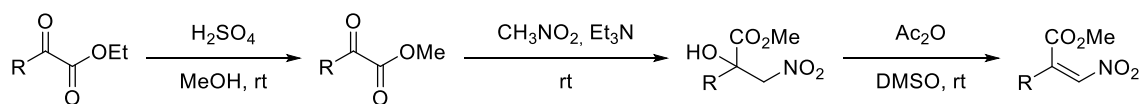


General procedure was followed using 4-(1,1,1-trifluoro-2-hydroxy-3-nitropropan-2-yl)benzonitrile (3.8 mmol, 1.0 g, 1 equiv.). Yellow solid, 68% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.92–7.72 (m, 2H), 7.59 (q, J = 1.4 Hz, 1H), 7.53–7.37 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 140.9 (bs, CH), 134.9 (q, J = 32.7 Hz, C), 132.8 (CH), 131.5 (C), 129.3 (CH), 121.5 (q, J = 276.1 Hz, CF_3), 117.8 (C), 114.9 (C). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ –66.9.

Synthesis and characterization data for nitroacrylic esters 2.7

General procedure for the synthesis of α -substituted- β -nitroacrylic esters 2.7

Compounds **2.7** were prepared *via* a three-step synthesis based on modified reported procedures. Spectroscopic data for compounds **2.7** was in accordance with literature.^{[16]–[20]} Compounds **2.7e**, **2.7g**, **2.7j** are new compounds and have been fully characterized.



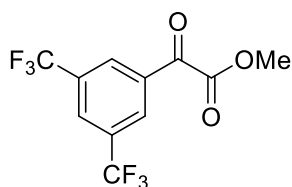
In a round bottom flask, the required ethyl α -ketoester (5 mmol, 1 equiv.) was dissolved in MeOH (50 mL). To this solution, concentrated H_2SO_4 (5 mL) was added, and the reaction mixture was stirred at room temperature until the reaction was complete (TLC). Solvents were removed *in vacuo* and the residue was dissolved in EtOAc (70 mL), washed with saturated NaHCO_3 (2 x 20 mL), water and brine. The organic layer was dried over MgSO_4 , concentrated under vacuum, and the crude product was used without any further purification.

A solution of the corresponding α -ketoester (5 mmol, 1 equiv.) in nitromethane (20 mL) was treated with triethylamine (7.5 mmol, 0.96 mL, 1.5 equiv.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (20 mL) and washed with HCl 1 M (3 x 20 mL), water and brine. The combined organic layers were dried over MgSO_4 , solvents were removed *in vacuo*, and the residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired β -nitro- α -hydroxyester.

In a round bottom flask, β -nitro- α -hydroxyesters (2 mmol, 1 equiv.) was dissolved in anhydrous DMSO (7 mL) under nitrogen atmosphere. To this solution, acetic anhydride (6 mmol, 0.57 mL, 3 equiv.) was added and the resulting mixture was stirred at room temperature overnight. The reaction was diluted with water (70 mL) and extracted three

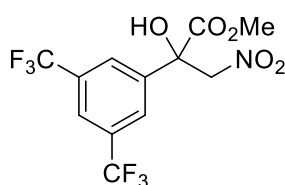
times with EtOAc (3 x 50 mL). The combined organic layers were washed with saturated NaHCO₃ (2 x 25 mL) and brine and were dried over MgSO₄. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford compounds **2.7**.

methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate



General procedure was followed using ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate (5 mmol, 1.6 g, 1 equiv.). Colourless oil, 99% yield. Crude methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate was used without purification

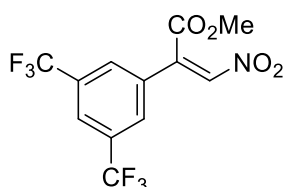
methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-3-nitropropanoate



MHz, CDCl₃) δ -63.4.

General procedure was followed using methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoacetate (5 mmol, 1.5 g, 1 equiv.). White solid, 73% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.19–8.09 (m, 2H), 7.99–7.85 (m, 1H), 5.27 (dd, *J* = 14.2, 1.0 Hz, 1H), 4.68 (d, *J* = 14.2 Hz, 1H), 4.43 (d, *J* = 0.9 Hz, 1H), 3.98 (s, 3H); ¹⁹F NMR (282

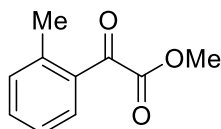
methyl (Z)-2-(3,5-bis(trifluoromethyl)phenyl)-3-nitroacrylate (2.7e)



¹³C NMR (75 MHz, CDCl₃) δ 164.1 (C), 139.8 (C), 137.6 (CH), 133.4 (q, *J* = 34.2 Hz, C), 132.1 (C), 127.9–127.4 (m, CH), 125.6–125.2 (m, CH), 122.7 (q, *J* = 273.3 Hz, CF₃), 54.2 (CH₃). ¹⁹F NMR (282 MHz, CDCl₃) δ -63.6.

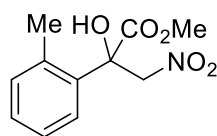
General procedure was followed using methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-3-nitropropanoate (3.6 mmol, 1.3 g, 1 equiv.). Yellow oil, 30% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.09–8.00 (m, 1H), 7.98–7.91 (m, 2H), 7.36 (s, 1H), 4.02 (s, 3H). ¹³C

methyl 2-oxo-2-(o-tolyl)acetate



General procedure was followed using ethyl 2-oxo-2-(o-tolyl)acetate (5 mmol, 0.88 g, 1 equiv.). Colourless oil, 99% yield. methyl 2-oxo-2-(o-tolyl)acetate was used without purification

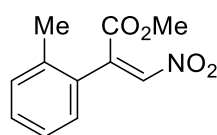
methyl 2-hydroxy-3-nitro-2-(*o*-tolyl)propanoate



(s, 3H).

General procedure was followed using methyl 2-hydroxy-3-nitro-2-(*o*-tolyl)propanoate (5 mmol, 1.5 g, 1 equiv.). White solid, 43% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.30–7.24 (m, 1H), 7.24–7.17 (m, 3H), 5.33 (dd, *J* = 13.3, 0.8 Hz, 1H), 4.99 (d, *J* = 13.2 Hz, 1H), 4.24 (d, *J* = 0.7 Hz, 1H), 3.91

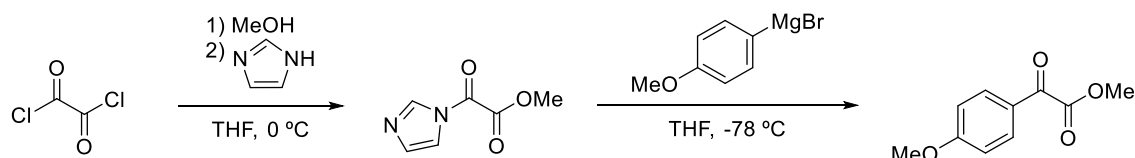
methyl (Z)-3-nitro-2-(*o*-tolyl)acrylate (2.7g)



136.6 (C), 131.4 (CH), 130.6 (CH), 130.0 (C), 128.9 (CH), 126.6 (CH), 53.5 (CH₃), 20.2 (CH₃).

General procedure was followed using methyl 2-hydroxy-3-nitro-2-(*o*-tolyl)propanoate (2.2 mmol, 520 mg, 1 equiv.). Yellow oil, 22% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.42–7.18 (m, 4H), 7.00 (s, 1H), 3.90 (s, 3H), 2.41 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 165.2 (C), 142.6 (C), 138.2 (CH),

Regarding the synthesis of compound **2.7j**, the required ethyl α-ketoester was not available and therefore had to be synthesised following a modified literature procedure.^[17]

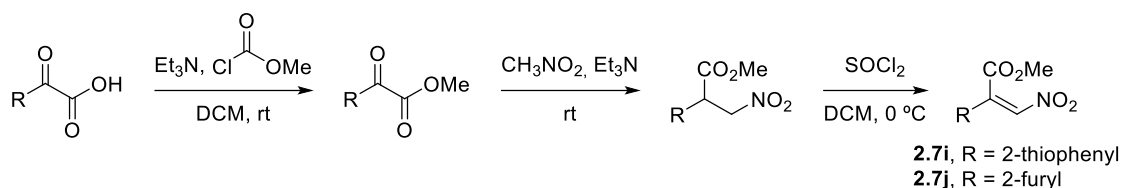


In a round bottom flask, oxalyl chloride (16 mmol, 2.8 mL, 1 equiv.) was dissolved in dry THF (50 mL) and cooled to 0 °C under nitrogen atmosphere. MeOH (16 mmol, 1.3 mL, 1 equiv.) was added, and the solution was stirred for 1 hour. Subsequently, a solution of imidazole (48 mmol, 6.5 g, 3 equiv.) in THF (10 mL) was added, and the reaction mixture was stirred for an additional 1 hour at 0 °C. The reaction was filtered through a Celite® pad and the filtrate was concentrated *in vacuo* to afford the crude methyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate, which was used without any further purification.

The crude methyl 2-(1*H*-imidazol-1-yl)-2-oxoacetate (4 mmol, 620 mg, 1 equiv) was dissolved in dry THF (30 mL) and cooled to -78 °C under nitrogen atmosphere. To this solution, (4-methoxyphenyl) magnesium bromide (1 M in Et₂O, 10 mmol, 10 mL, 2.5 equiv.) was added dropwise and the resulting mixture was stirred for 0.5 hours at -78 °C and it was allowed to reach room temperature. The reaction was quenched with saturated NH₄Cl (20 mL), extracted with EtOAc (4 x 25 mL) and the combined organic layers were rinsed with brine and dried over MgSO₄. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford methyl 2-(4-methoxyphenyl)-2-oxoacetate as a colourless oil in 20% yield.

Synthesis of heteroaromatic compounds **2.7i** and **2.7j**.

Substrates **2.7i** and **2.7j** and **3.1z** were prepared following modified reported procedures.^{[18],[21]}

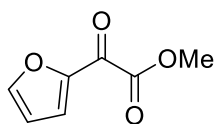


The corresponding 2-oxoacetic acid (19 mmol, 1 equiv.) was dissolved in dry DCM (20 mL) under nitrogen atmosphere. To this solution, triethylamine (19 mmol, 2.7 mL, 1 equiv.) and methyl chloroformate (19 mmol, 1.5 mL, 1 equiv.) were sequentially added and the reaction was stirred for 30 minutes. The reaction was quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 and solvents were removed *in vacuo*. The residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired heteroaromatic methyl α -ketoester

A solution of the corresponding α -ketoester (5 mmol, 1 equiv.) in nitromethane (20 mL) was treated with triethylamine (7.5 mmol, 0.96 mL, 1.5 equiv.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (20 mL) and washed with HCl 1 M (3 x 20 mL), water and brine. The combined organic layers were dried over MgSO_4 , solvents were removed *in vacuo*, and the residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired β -nitro- α -hydroxyester.

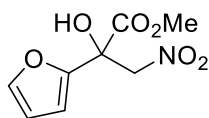
In a round bottom flask, the required β -nitro- α -hydroxyester (2 mmol, 1 equiv.) was dissolved in DCM (10 mL) and cooled to 0° C under nitrogen atmosphere. To this solution, triethylamine (6 mmol, 0.83 mL, 3 equiv.) and thionyl chloride (6 mmol, 0.43 mL, 3 equiv.) were added dropwise. The mixture was stirred at 0 °C until the reaction was complete (TLC). Solvents were evaporated *in vacuo* and the residue was purified by silica gel column chromatography using hexane/ Et_2O mixtures as eluents to afford the desired heteroaromatic β -nitroacrylic esters.

methyl 2-(furan-2-yl)-2-oxoacetate



General procedure was followed using 2-(furan-2-yl)-2-oxoacetic acid (14 mmol, 2.0 g, 1 equiv.). Yellow liquid, 82% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.75 (dd, J = 1.7, 0.8 Hz, 1H), 7.71 (dd, J = 3.7, 0.8 Hz, 1H), 6.61 (dd, J = 3.7, 1.7 Hz, 1H), 3.93 (s, 3H).

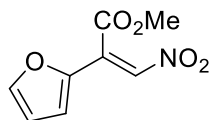
methyl 2-(furan-2-yl)-2-hydroxy-3-nitropropanoate



General procedure was followed using methyl 2-(furan-2-yl)-2-oxoacetate (11.5 mmol, 1.8 g, 1 equiv.). Yellow solid, 60% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.42 (dd, J = 1.8, 0.9 Hz, 1H), 6.43 (dd, J = 3.4, 0.9 Hz,

1H), 6.39 (dd, $J = 3.4, 1.8$ Hz, 1H), 5.25 (d, $J = 14.2$ Hz, 1H), 4.90 (d, $J = 14.2$ Hz, 1H), 4.24 (bs, 1H), 3.92 (s, 3H).

methyl (Z)-2-(furan-2-yl)-3-nitroacrylate (**2.7j**)



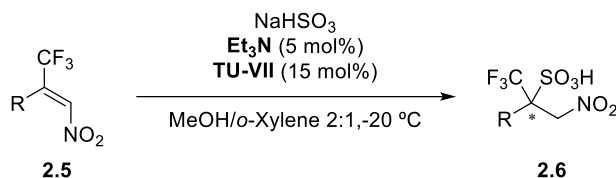
General procedure was followed using methyl 2-(furan-2-yl)-2-hydroxy-3-nitropropanoate (6.8 mmol, 1.5 g, 1 equiv.). Yellow solid, 69% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.59 (dd, $J = 1.8, 0.7$ Hz, 1H), 7.42 (s, 1H), 6.79 (dd, $J = 3.6, 0.7$ Hz, 1H), 6.57 (dd, $J = 3.6, 1.8$ Hz, 1H), 3.96 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 163.5 (C), 147.3 (CH), 144.8 (C), 131.7 (C), 130.8 (CH), 119.2 (CH), 113.5 (CH), 53.6 (CH₃).

Synthesis and characterization data for chiral β -nitro sulfonic acids **2.6** and **2.7**

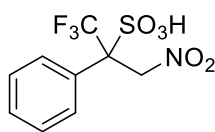
General procedure for the enantioselective addition of NaHSO₃ to β -CF₃- β,β -disubstituted Nitroalkenes **2.5**



In a test tube, catalyst **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%), β -CF₃- β,β -disubstituted nitroalkene **2.5** (0.2 mmol, 1 equiv.) and triethylamine (0.01 mmol, 1.4 μ L, 5 mol%) were dissolved in a MeOH/*o*-xylene mixture (2 mL, v/v, 2:1), and the solution was stirred at -20 °C for 10 minutes. Then, NaHSO₃ (0.48 mmol, 50.0 mg, 2.4 equiv.) in 0.5 mL of H₂O was added and the reaction was vigorously stirred until the reaction was complete (TLC). The mixture was filtered through a Celite® pad, rinsed with H₂O, and solvents were removed *in vacuo*. The crude product was dissolved in 3 mL of a THF/H₂O mixture (v/v, 2:1), passed through a plug of freshly conditioned acidic ion-exchange resin Amberlyst®15 and rinsed with water (3 x 3 mL). The resulting aqueous solution was concentrated *in vacuo* and dried under high vacuum in the presence of P₂O₅. Crude products were purified by silica gel column chromatography using DCM/MeOH mixtures to afford compounds **2.6**.

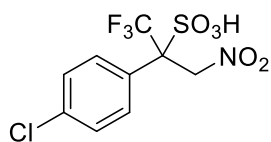
Racemic products **2.6** were obtained following the same procedure employing 3 drops of Et₃N instead of **TU-VII** at room temperature.

1,1,1-trifluoro-3-nitro-2-phenylpropane-2-sulfonic acid (**2.6a**)



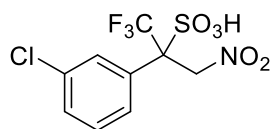
General procedure was followed using **2.5a** (0.2 mmol, 43.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6a** as a deliquescent white solid (41.7 mg, 70% yield). Compound **2.6a** was obtained with an 89% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 5.5$ min, $\tau_{\text{minor}} = 7.8$ min. $[\alpha]_D^{25} = -49.4$ (*c* = 0.70, MeOH, 89% ee). **¹H NMR** (500 MHz, CD₃OD) δ 7.80 – 7.68 (m, 2H), 7.41 – 7.29 (m, 3H), 5.89 (dq, *J* = 14.2, 1.9 Hz, 1H), 5.48 (d, *J* = 14.2 Hz, 1H). **¹³C NMR** (126 MHz, CD₃OD) δ 130.27 (C), 128.9 (q, *J* = 1.9 Hz, CH), 128.0 (CH), 127.3 (CH), 124.7 (d, *J* = 285.1 Hz, CF₃), 74.66 (q, *J* = 2.4 Hz, CH₂), 71.70 (q, *J* = 25.0 Hz, C). **¹⁹F NMR** (282 MHz, CD₃OD) δ -58.5. **HRMS (ESI-TOF)** calc'd for [C₉H₈F₃NO₅S+NH₄]⁺: 317.4014; found: 317.0409.

2-(4-chlorophenyl)-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (**2.6b**)



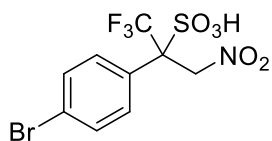
General procedure was followed using **2.5b** (0.2 mmol, 50.3 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6b** as a deliquescent white solid (56.4 mg, 85% yield). Compound **2.6b** was obtained with a 91% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 6.2$ min, $\tau_{\text{minor}} = 5.2$ min. $[\alpha]_D^{25} = -73.2$ (*c* = 0.94, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.01 – 7.51 (m, 2H), 7.46 – 7.17 (m, 2H), 5.83 (dq, *J* = 14.2, 1.9 Hz, 1H), 5.42 (d, *J* = 14.2 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 135.5 (C), 132.0 (q, *J* = 2.3 Hz, CH), 130.6 (C), 128.7 (CH), 126.0 (q, *J* = 283.5 Hz, CF₃), 75.9 (q, *J* = 2.3 Hz, C), 72.8 (CH₂); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.9. **HRMS (ESI-TOF)** calc'd for [C₉H₇ClF₃NO₅S+NH₄]⁺: 351.0024; found: 351.0017.

2-(3-chlorophenyl)-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (**2.6c**)



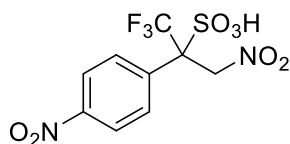
General procedure was followed using **2.5c** (0.2 mmol, 50.3 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6c** as a deliquescent white solid (44.9 mg, 67% yield). Compound **2.6c** was obtained with an 87% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 5.4$ min, $\tau_{\text{minor}} = 4.7$ min. $[\alpha]_D^{25} = -66.5$ (*c* = 1.0, MeOH, 87% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.77 (s, 1H), 7.72 – 7.58 (m, 1H), 7.49 – 7.17 (m, 2H), 5.88 (dq, *J* = 14.3, 1.9 Hz, 1H), 5.47 (d, *J* = 14.3 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 134.5 (C), 134.0 (C), 130.5 (q, *J* = 2.0 Hz, CH), 130.0 (CH), 129.5 (CH), 128.7 (q, *J* = 1.9 Hz, CH), 125.9 (q, *J* = 285.3 Hz, CF₃), 75.9 (q, *J* = 2.6 Hz, CH₂), 72.7 (q, *J* = 25.1 Hz, C); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.9. **HRMS (ESI-TOF)** calc'd for [C₉H₇ClF₃NO₅S+NH₄]⁺: 351.0024; found: 351.0017.

2-(4-bromophenyl)-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (2.6e)



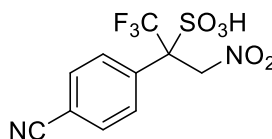
General procedure was followed using **2.5e** (0.2 mmol, 59.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6e** as a deliquescent white solid (26.5 mg, 35% yield). Compound **2.6e** was obtained with an 70% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 6.7$ min, $\tau_{\text{minor}} = 5.4$ min. $[\alpha]_D^{25} = -54.3$ (*c* = 0.44, MeOH, 70% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.71 – 7.61 (m, 2H), 7.58 – 7.48 (m, 2H), 5.86 (dq, *J* = 14.2, 1.9 Hz, 1H), 5.46 (d, *J* = 14.3 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 132.3 (q, *J* = 2.0 Hz, CH), 131.7 (CH), 131.1 (C), 125.9 (q, *J* = 285.3 Hz, CF₃), 123.6 (C), 75.8 (q, *J* = 2.6 Hz, CH₂), 72.7 (q, *J* = 25.6 Hz, C); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.9. **HRMS (ESI-TOF)** calc'd for [C₉H₇BrF₃NO₅S+NH₄]⁺: 394.9519; found: 394.9515.

1,1,1-trifluoro-3-nitro-2-(4-nitrophenyl)propane-2-sulfonic acid (2.6f)



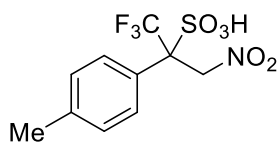
General procedure was followed using **2.5f** (0.2 mmol, 52.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6f** as a deliquescent white solid (10.4 mg, 15% yield). Compound **2.6f** was obtained with an 85% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 9.2$ min, $\tau_{\text{minor}} = 6.4$ min. $[\alpha]_D^{25} = -51.4$ (*c* = 0.52, MeOH, 85% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.32 – 8.18 (m, 2H), 8.08 – 7.94 (m, 2H), 6.00 (dd, *J* = 14.5, 2.0 Hz, 1H), 5.50 (d, *J* = 14.5 Hz, 1H); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.9. **¹³C NMR** (75 MHz, CD₃OD) δ 148.9 (C), 139.3 (C), 131.6 (q, *J* = 2.0 Hz, CH), 125.8 (q, *J* = 285.6 Hz, CF₃), 123.4 (CH), 75.9 (CH₂), 72.9 (q, *J* = 25.3 Hz, C).

2-(4-cyanophenyl)-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (2.6g)



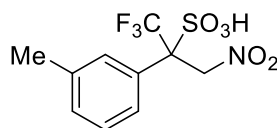
General procedure was followed using **2.5g** (0.2 mmol, 48.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6g** as a deliquescent white solid (19.5 mg, 30% yield). Compound **2.6g** was obtained with an 45% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 8.4$ min, $\tau_{\text{minor}} = 5.6$ min. $[\alpha]_D^{25} = -33.8$ (*c* = 0.33, MeOH, 45% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.99 – 7.89 (m, 2H), 7.80 – 7.69 (m, 2H), 5.95 (dq, *J* = 14.5, 2.0 Hz, 1H), 5.48 (d, *J* = 14.5 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 137.6 (C), 132.3 (CH), 131.3 (q, *J* = 1.9 Hz, CH), 125.9 (q, *J* = 285.1 Hz, CF₃), 119.4 (C), 113.0 (C), 75.7 (q, *J* = 2.3 Hz, CH₂), 72.9 (q, *J* = 25.3 Hz, C); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.8. **HRMS (ESI-TOF)** calc'd for [C₁₀H₇F₃N₂O₅S+NH₄]⁺: 342.0366; found: 342.0357.

1,1,1-trifluoro-3-nitro-2-(p-tolyl)propane-2-sulfonic acid (**2.6h**)



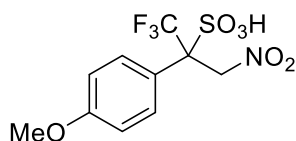
General procedure was followed using **2.5h** (0.2 mmol, 46.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6h** as a deliquescent white solid (30.9 mg, 52% yield). Compound **2.6h** was obtained with a 92% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 4.9$ min, $\tau_{\text{minor}} = 4.4$ min. $[\alpha]_D^{25} = -63.5$ ($c = 1.0$, MeOH, 92% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.60 (d, $J = 8.2$ Hz, 2H), 7.20 – 7.17 (m, 2H), 5.84 (dq, $J = 14.1$, 1.9 Hz, 1H), 5.45 (d, $J = 14.1$ Hz, 1H), 2.35 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 139.4 (C), 130.2 (q, $J = 1.8$ Hz, CH), 129.3 (CH), 128.6 (C), 126.2 (q, $J = 285.2$ Hz, CF₃), 76.11 (q, $J = 2.1$ Hz, CH₂), 72.93 (q, $J = 24.9$ Hz, C), 21.0 (CH₃); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.6. **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₅S+NH₄]⁺: 331.0570; found: 331.0562.

1,1,1-trifluoro-3-nitro-2-(m-tolyl)propane-2-sulfonic acid (**2.6i**)



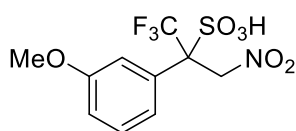
General procedure was followed using **2.5i** (0.2 mmol, 46.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6i** as a deliquescent white solid (37.3 mg, 60% yield). Compound **2.6i** was obtained with a 78% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 5.0$ min, $\tau_{\text{minor}} = 4.5$ min. $[\alpha]_D^{25} = -65.4$ ($c = 0.93$, MeOH, 78% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.56 (s, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.26 (t, $J = 7.7$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 1H), 5.88 (dq, $J = 14.2$, 1.9 Hz, 1H), 5.47 (d, $J = 14.2$ Hz, 1H), 2.37 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 138.3 (C), 131.4 (C), 130.8 (q, $J = 1.8$ Hz, CH), 130.0 (CH), 128.5 (CH), 127.3 (q, $J = 1.7$ Hz, CH), 126.1 (q, $J = 285.1$ Hz, CF₃), 76.1 (q, $J = 2.1$ Hz, CH₂), 73.1 (q, $J = 25.1$ Hz, C), 21.7 (CH₃); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.3. **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₅S+NH₄]⁺: 331.0570; found: 331.0560.

1,1,1-trifluoro-2-(4-methoxyphenyl)-3-nitropropane-2-sulfonic acid (**2.6k**)



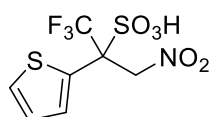
General procedure was followed using **2.5k** (0.2 mmol, 49.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6k** as a deliquescent white solid (33.3 mg, 51% yield). Compound **2.6k** was obtained with a 91% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 7.1$ min, $\tau_{\text{minor}} = 6.3$ min. $[\alpha]_D^{25} = -52.0$ ($c = 0.95$, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.65 (dd, $J = 9.2$, 1.0 Hz, 2H), 7.19 – 6.70 (m, 2H), 5.82 (dq, $J = 14.0$, 1.8 Hz, 1H), 5.45 (d, $J = 14.0$ Hz, 1H), 3.81 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 159.7 (C), 130.2 (q, $J = 1.9$ Hz, CH), 124.8 (q, $J = 285.2$ Hz, CF₃), 121.9 (C), 112.7 (CH), 74.7 (q, $J = 2.2$ Hz, CH₂), 71.3 (q, $J = 25.3$ Hz, C), 54.3 (CH₃); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.7. **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₆S+NH₄]⁺: 347.0519; found: 347.0510.

1,1,1-trifluoro-2-(3-methoxyphenyl)-3-nitropropane-2-sulfonic acid (**2.6l**)



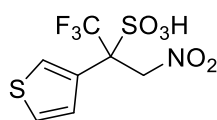
General procedure was followed using **2.5l** (0.2 mmol, 49.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6l** as a deliquescent white solid (65.0 mg, 99% yield). Compound **2.6l** was obtained with an 89% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (80:20:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 21.0$ min, $\tau_{\text{minor}} = 16.2$ min. $[\alpha]_D^{25} = -42.8$ (*c* = 1.1, MeOH, 89% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.34–7.24 (m, 3H), 7.00–6.89 (m, 1H), 5.86 (dq, *J* = 14.2, 1.9 Hz, 1H), 5.48 (d, *J* = 14.2 Hz, 1H), 3.81 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 160.4 (C), 132.9 (C), 129.5 (CH), 125.9 (q, *J* = 274.5 Hz, CF₃), 122.52 (q, *J* = 2.0 Hz, CH), 116.89 (q, *J* = 1.7 Hz, CH), 114.6 (CH), 76.22 (q, *J* = 2.3 Hz, CH₂), 73.01 (q, *J* = 25.0 Hz, C), 55.7 (CH₃); **¹⁹F NMR** (282 MHz, CD₃OD) δ -62.4. **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₆S+NH₄]⁺: 347.0519; found: 347.0511.

1,1,1-trifluoro-3-nitro-2-(thiophen-2-yl)propane-2-sulfonic acid (**2.6m**)



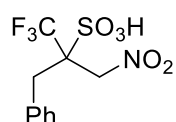
General procedure was followed using **2.5m** (0.2 mmol, 44.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6m** as a deliquescent white solid (32.4 mg, 53% yield). Compound **2.6m** was obtained with a 91% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 10.3$ min, $\tau_{\text{minor}} = 9.5$ min. $[\alpha]_D^{25} = -66.0$ (*c* = 0.98, MeOH, 91% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.49 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.43 (dt, *J* = 3.8, 1.0 Hz, 1H), 7.03 (dd, *J* = 5.2, 3.8 Hz, 1H), 5.57 (dq, *J* = 13.2, 1.4 Hz, 1H), 5.45 (d, *J* = 13.2 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 133.4 (C), 130.9 (q, *J* = 1.7 Hz, CH), 127.9 (CH), 126.8 (CH), 121.7 (q, *J* = 285.0 Hz, CF₃), 78.2 (q, *J* = 1.4 Hz, CH₂), 70.9 (q, *J* = 26.6 Hz, CH₃); **¹⁹F NMR** (282 MHz, CD₃OD) δ -65.5. **HRMS (ESI-TOF)** calc'd for [C₇H₆F₃NO₅S₂+NH₄]⁺: 332.9978; found: 332.9978.

1,1,1-trifluoro-3-nitro-2-(thiophen-3-yl)propane-2-sulfonic acid (**2.6n**)



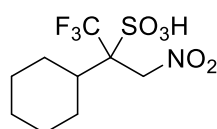
General procedure was followed using **2.5n** (0.2 mmol, 44.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6n** as a deliquescent white solid (16.0 mg, 26% yield). Compound **2.6n** was obtained with an 34% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 6.0$ min, $\tau_{\text{minor}} = 5.0$ min. $[\alpha]_D^{25} = -3.0$ (*c* = 0.57, MeOH, 34% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.68 (ddq, *J* = 3.4, 1.8, 1.0 Hz, 1H), 7.43 (ddq, *J* = 5.2, 1.7, 0.9 Hz, 1H), 7.37 (dd, *J* = 5.2, 2.9 Hz, 1H), 5.68 (dd, *J* = 13.2, 1.5 Hz, 1H), 5.41 (d, *J* = 13.2 Hz, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 131.40 (C), 129.87 (q, *J* = 1.7 Hz, CH), 127.29 (q, *J* = 1.9 Hz, CH), 125.78 (q, *J* = 284.6 Hz, CF₃), 124.96 (CH), 77.27 (q, *J* = 1.8 Hz, CH₂), 70.70 (q, *J* = 26.0 Hz, C); **¹⁹F NMR** (282 MHz, CD₃OD) δ -65.3. **HRMS (ESI-TOF)** calc'd for [C₇H₆F₃NO₅S₂+NH₄]⁺: 332.9978; found: 332.9977.

2-benzyl-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (**2.6o**)



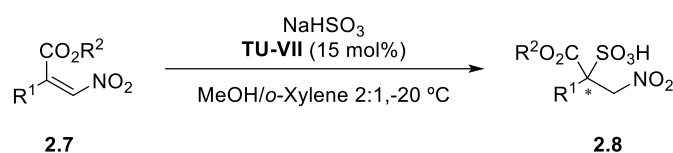
General procedure was followed using **2.5o** (0.2 mmol, 46.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6o** as a deliquescent white solid (32.1 mg, 51% yield). Compound **2.6o** was obtained with an 65% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 4.9$ min, $\tau_{\text{minor}} = 4.5$ min. $[\alpha]_D^{25} = 3.7$ ($c = 0.53$, MeOH, 65% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.66–7.47 (m, 2H), 7.40–7.14 (m, 3H), 4.99 (d, $J = 12.7$ Hz, 1H), 4.91 (d, $J = 12.7$ Hz, 1H), 3.67 (d, $J = 14.4$ Hz, 1H), 3.56 (d, $J = 14.4$ Hz, 1H); **¹⁹F NMR** (282 MHz, CD₃OD) δ –67.0. **¹³C NMR** (75 MHz, CD₃OD) δ 135.5 (C), 132.6 (CH), 129.1 (CH), 128.2 (CH), 125.9 (q, $J = 285.1$ Hz, CF₃), 75.0 (q, $J = 1.8$ Hz, CH₂), 68.9 (q, $J = 23.3$ Hz, C), 35.3 (q, $J = 1.5$ Hz, CH₂). **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀F₃NO₅S+NH₄]⁺: 331.0570; found: 331.0562.

2-cyclohexyl-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (**2.6p**)



General procedure was followed using **2.5p** (0.2 mmol, 44.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.6p** as a deliquescent white solid (29.5 mg, 48% yield). Enantiomeric excess of compound **2.6p** could not be determined, as HPLC resolution of the enantiomeric mixture was not achieved. $[\alpha]_D^{25} = -0.75$ ($c = 0.98$, MeOH). **¹H NMR** (300 MHz, CD₃OD) δ 5.20 (dq, $J = 12.5, 1.3$ Hz, 1H), 5.04 (d, $J = 12.4$ Hz, 1H), 2.30–2.06 (m, 2H), 1.97–1.60 (m, 6H), 1.42–1.15 (m, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 126.35 (q, $J = 286.3$ Hz, CF₃), 75.94 (q, $J = 2.3$ Hz, CH₂), 71.80 (q, $J = 23.0$ Hz, C), 40.90 (CH), 29.75 (CH₂), 29.27 (q, $J = 2.0$ Hz, CH₂), 28.60 (CH₂), 28.50 (CH₂), 27.37 (CH₂); **¹⁹F NMR** (282 MHz, CD₃OD) δ –63.5. **HRMS (ESI-TOF)** calc'd for [C₉H₁₄F₃NO₅S+NH₄]⁺: 323.0883; found: 323.0883.

General procedure for the enantioselective addition of NaHSO₃ to α -substituted- β -nitroacrylic esters **2.7**



In a test tube, catalyst **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%) and α -substituted- β -nitroacrylic ester **2.7** (0.2 mmol, 1 equiv.) were dissolved in a MeOH/*o*-xylene mixture (2 mL, v/v, 2:1), and the solution was stirred at -20 °C for 10 minutes. Then, NaHSO₃ (0.48 mmol, 50.0 mg, 2.4 equiv.) in 0.5 mL of H₂O was added and the reaction was vigorously stirred until the reaction was complete (TLC). The mixture was filtered through a Celite® pad, rinsed with H₂O, and solvents were removed *in vacuo*. The crude product was dissolved in 3 mL of a THF/H₂O mixture (v/v, 2:1), passed through a plug of freshly conditioned acidic ion-exchange resin Amberlyst®15 and rinsed with water (3 x 3 mL). The resulting aqueous solution was concentrated *in vacuo* and dried under high vacuum in the presence of P₂O₅. Crude products were purified by silica gel column chromatography using DCM/MeOH mixtures to afford compounds **2.8**.

Racemic products **2.8** were obtained following the same procedure employing 3 drops of Et₃N instead of **TU-VII** at room temperature.

1-methoxy-3-nitro-1-oxo-2-phenylpropane-2-sulfonic acid (**2.8a**)



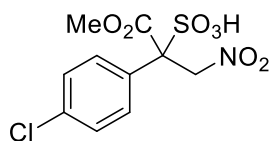
General procedure was followed using **2.7a** (0.2 mmol, 42 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8a** as a deliquescent white solid (54.0 mg, 94% yield). Compound **2.8a** was obtained with a 96% enantiomeric excess determined by HPLC after esterification with trimethyl orthoacetate, using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 34.0$ min, $\tau_{\text{minor}} = 38.0$ min $[\alpha]_D^{25} = -25.6$ (*c* = 1.0, MeOH, 96% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.80–7.65 (m, 2H), 7.38–7.23 (m, 3H), 5.72 (d, *J* = 15.6 Hz, 1H), 5.48 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H). **¹³C NMR** (75 MHz, CD₃OD) δ 169.9 (C), 135.3 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 78.7 (CH₂), 74.3 (C), 53.6 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₁NO₇S+NH₄]⁺: 307.0594; found: 307.0594.

1-ethoxy-3-nitro-1-oxo-2-phenylpropane-2-sulfonic acid (**2.8b**)



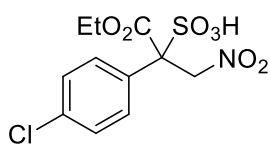
General procedure was followed using **2.7b** (0.2 mmol, 44.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8b** as a deliquescent white solid (56.4 mg, 93% yield). Compound **2.8b** was obtained with an 86% enantiomeric excess determined by HPLC after esterification with trimethyl orthoacetate, using a Chiralpak IC column [*n*-hexane/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 35.7$ min, $\tau_{\text{minor}} = 23.4$ min. $[\alpha]_D^{25} = -22.1$ (*c* = 0.67, MeOH, 86% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.91 – 7.60 (m, 2H, Ar), 7.49 – 7.13 (m, 3H, Ar), 5.72 (d, *J* = 15.6 Hz, 1H, CH₂), 5.48 (d, *J* = 15.6 Hz, 1H, CH₂), 4.34 (qd, *J* = 7.1, 1.3 Hz, 2H, CH₂), 1.30 (t, *J* = 7.1 Hz, 3H, CH₃); **¹³C NMR** (75 MHz, CD₃OD) δ 169.3 (C), 135.4 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 78.6 (CH₂), 74.2 (C), 63.5 (CH₂), 14.1 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₁H₁₃NO₇S+Na]⁺: 321.0751; found: 321.0744.

2-(4-chlorophenyl)-1-methoxy-3-nitro-1-oxopropane-2-sulfonic acid (**2.8c**)



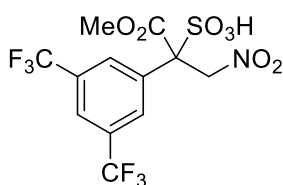
General procedure was followed using **2.7c** (0.2 mmol, 48.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8c** as a deliquescent white solid (63.9 mg, 99% yield). Compound **2.8c** was obtained with an 86% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 0.5 mL/min]: $\tau_{\text{major}} = 62.3$ min, $\tau_{\text{minor}} = 76.9$ min. $[\alpha]_D^{25} = -23.2$ (*c* = 1.0, MeOH, 86% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.76 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 5.72 (d, *J* = 15.9 Hz, 1H), 5.48 (d, *J* = 15.9 Hz, 1H), 3.85 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 169.5 (C), 134.9 (C), 134.3 (C), 131.5 (CH), 128.7 (CH), 78.4 (CH₂), 73.9 (C), 53.7 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₀H₁₀ClNO₇S+NH₄]⁺: 341.0205; found: 341.0207.

2-(4-chlorophenyl)-1-ethoxy-3-nitro-1-oxopropane-2-sulfonic acid (**2.8d**)



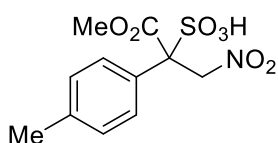
General procedure was followed using **2.7d** (0.2 mmol, 51.0 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8d** as a deliquescent white solid (66.0 mg, 99% yield). Compound **2.8d** was obtained with an 88% enantiomeric excess determined by HPLC using a Lux i-Amylose 1 column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 9.3$ min, $\tau_{\text{minor}} = 7.2$ min. $[\alpha]_D^{25} = -14.5$ ($c = 1.1$, MeOH, 88% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.81 – 7.63 (m, 2H), 7.46 – 7.28 (m, 2H), 5.72 (d, $J = 15.8$ Hz, 1H), 5.49 (d, $J = 15.8$ Hz, 1H), 4.34 (qd, $J = 7.2, 2.3$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 169.1 (C), 134.9 (C), 134.2 (C), 131.5 (CH), 128.7 (CH), 78.3 (CH₂), 73.6 (C), 63.8 (CH₂), 14.0 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₁H₁₂ClNO₇S+NH₄]⁺: 355.0361; found: 355.0364.

2-(3,5-bis(trifluoromethyl)phenyl)-1,1,1-trifluoro-3-nitropropane-2-sulfonic acid (**2.8e**)



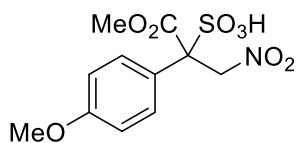
General procedure was followed using **2.7e** (0.2 mmol, 68.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8e** as a deliquescent white solid (25.0 mg, 29% yield). Compound **2.8e** was obtained with an 51% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (80:20:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 14.2$ min, $\tau_{\text{minor}} = 13.4$ min. $[\alpha]_D^{25} = -5.0$ ($c = 0.42$, MeOH, 50% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.48 – 8.40 (m, 2H), 7.97 – 7.88 (m, 1H), 5.82 (d, $J = 16.3$ Hz, 1H), 5.67 (d, $J = 16.3$ Hz, 1H), 3.88 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 168.6 (C), 139.0 (C), 131.8 (q, $J = 33.1$ Hz, C), 130.9 – 130.6 (m, CH), 124.9 (q, $J = 271.7$ Hz, CF₃), 122.7 – 121.9 (m, CH), 78.0 (CH₂), 73.7 (q, $J = 4.8$ Hz, C), 53.9 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₂H₉F₆NO₇S+NH₄]⁺: 443.0342; found: 443.0340.

1-methoxy-3-nitro-1-oxo-2-(*p*-tolyl)propane-2-sulfonic acid (**2.8f**)



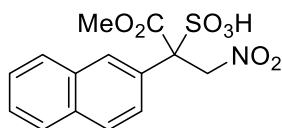
General procedure was followed using **2.7f** (0.2 mmol, 44.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8f** as a deliquescent white solid (60 mg, 99% yield). Compound **2.8f** was obtained with an 83% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 24.0$ min, $\tau_{\text{minor}} = 31.7$ min. $[\alpha]_D^{25} = -21.6$ ($c = 0.96$, MeOH, 83% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.59 (d, $J = 8.5$ Hz, 2H), 7.15 (d, $J = 8.5$ Hz, 2H), 5.70 (d, $J = 15.5$ Hz, 1H), 5.45 (d, $J = 15.5$ Hz, 1H), 3.85 (s, 3H), 2.32 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 170.2 (C), 138.9 (C), 132.2 (C), 129.6 (CH), 129.4 (CH), 78.6 (CH₂), 74.0 (C), 53.6 (CH₃), 21.0 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₁H₁₃NO₇S+NH₄]⁺: 321.0751; found: 321.0743.

1,1,1-trifluoro-2-(4-methoxyphenyl)-3-nitropropane-2-sulfonic acid (**2.8h**)



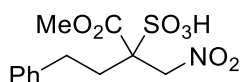
General procedure was followed using **2.7h** (0.2 mmol, 47.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8h** as a deliquescent white solid (63.9 mg, 99% yield). Compound **2.8h** was obtained with a >99% enantiomeric excess determined by HPLC using a Lux i-Amylose-1 column [*n*-hexane/*i*-PrOH (90:10), 0.7 mL/min]: $\tau_{\text{major}} = 39.7$ min, $\tau_{\text{minor}} = \text{n.d.}$ $[\alpha]_D^{25} = -22.0$ ($c = 1.0$, MeOH, >99% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.65 (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 9.2$ Hz, 2H), 5.70 (d, $J = 15.6$ Hz, 1H), 5.43 (d, $J = 15.6$ Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 169.5 (C), 160.5 (C), 130.8 (CH), 127.0 (C), 113.9 (CH), 78.5 (CH₂), 74.1 (C), 55.6 (CH₃), 53.3 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₁H₁₃NO₈S+NH₄]⁺: 337.0700; found: 337.0701.

1-methoxy-2-(naphthalen-2-yl)-3-nitro-1-oxopropane-2-sulfonic acid (**2.8k**)



General procedure was followed using **2.7k** (0.2 mmol, 51.4 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8k** as a deliquescent white solid (46.3 mg, 68% yield). Compound **2.8k** was obtained with an 42% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 21.6$ min, $\tau_{\text{minor}} = 26.9$ min. $[\alpha]_D^{25} = -13.2$ ($c = 0.77$, MeOH, 42% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.17 (d, $J = 2.1$ Hz, 1H), 7.97 – 7.77 (m, 4H), 7.53 – 7.40 (m, 2H), 5.83 (d, $J = 15.5$ Hz, 1H), 5.66 (d, $J = 15.5$ Hz, 1H), 3.91 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 170.3 (C), 134.2 (C), 132.6 (C), 132.6 (C), 129.5 (CH), 128.9 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.4 (CH), 127.1 (CH), 78.6 (CH₂), 74.3 (C), 53.8 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₁₄H₁₃NO₇S+NH₄]⁺: 357.0751; found: 357.0743.

1-methoxy-2-(nitromethyl)-1-oxo-4-phenylbutane-2-sulfonic acid (**2.8l**)



General procedure was followed using **2.7l** (0.2 mmol, 47.0 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.8l** as a deliquescent white solid (62.8 mg, 99% yield). Compound **2.8l** was obtained with an 47% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20), 1.5 mL/min]: $\tau_{\text{major}} = 6.9$ min, $\tau_{\text{minor}} = 14.7$ min. $[\alpha]_D^{25} = -8.8$ ($c = 0.88$, MeOH, 47% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.29 – 7.10 (m, 5H), 5.42 (d, $J = 15.0$ Hz, 1H), 5.02 (d, $J = 15.0$ Hz, 1H), 3.78 (s, 3H), 3.18 – 3.03 (m, 1H), 2.73 – 2.55 (m, 2H), 2.49 – 2.34 (m, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 170.8 (C), 143.3 (C), 129.4 (CH), 129.4 (CH), 127.0 (CH), 76.7 (CH₂), 70.1 (C), 53.5 (CH₃), 35.0 (CH₂), 31.9 (CH₂). **HRMS (ESI-TOF)** calc'd for [C₁₂H₁₅NO₇S+NH₄]⁺: 335.0907; found: 335.0899.

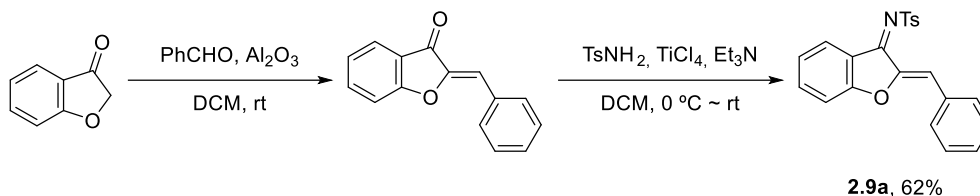
Organocatalytic Enantioselective *sulfa*-Michael Addition of Sodium Bisulfite to Aurone-Derived Azadienes

Synthesis and characterization data for aurone-derived azadienes **2.9**

All aurone-derived azadienes **2.9** were available at the laboratory except for compound **2.9a**.

General procedure for the synthesis of aurone-derived azadiene **2.9a**

Compound **2.9a** was prepared *via* a two-step synthesis based on a modified reported procedure. Spectroscopic data for compound **2.9a** was in accordance with literature.^[22]



In a round bottom flask, benzofuran-3(2*H*)-one (22.4 mmol, 3.0 g, 1 equiv.) and benzaldehyde (26.9 mmol, 2.75 mL, 1.2 equiv.) were dissolved in DCM (220 mL) at room temperature. To this solution, basic alumina (134.4 mmol, 13.7 g, 6 equiv., activated by heating at 130 °C in oven for 2 h) was added and the resulting mixture was stirred for 7 hours. The reaction mixture was filtered, solvents were removed *in vacuo*, and the crude product was recrystallized employing DCM/hexane mixtures to obtain the desired aurone.

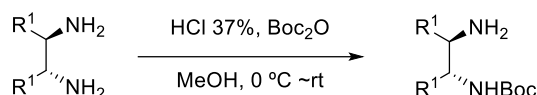
Aurone (6.75 mmol, 1.5g, 1 equiv.) and *p*-tosylamine (10.1 mmol, 1.7 g, 1.5 equiv.) were dissolved in DCM (60 mL) under nitrogen atmosphere at 0 °C. To this solution, triethylamine (13.5 mmol, 1.9 mL, 2.0 equiv.) and TiCl₄ (1 M in toluene, 8.1 mmol, 8.1 mL, 1.2 equiv.) were sequentially added, and the resulting mixture was stirred at room temperature for 24 hours. The reaction was quenched with 30 mL of H₂O, layers were separated and the aqueous phase was extracted with DCM (3 x 60 mL)- The combined organic layers were dried over MgSO₄, solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using hexane:EtOAc mixtures to afford aurone-derived azadiene **2.9a**.

Synthesis and characterization data for catalysts TU-XII and XV to XVIII

General procedure for the synthesis of thiourea-derived catalysts TU-XII and XV to XVIII

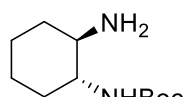
Organocatalysts **TU-XII** and **TU-XV** to **TU-XVIII** were prepared *via* a four-step synthesis based on modified reported procedures.^{[23],[24]}

Diamine monoprotection



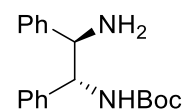
In a round bottom flask, HCl 37% (44.2 mmol, 3.7 mL, 1 equiv.) was dissolved in MeOH (35 mL) at 0 °C. To this mixture, a solution of the corresponding diamine (44.2 mmol, 1 equiv.) dissolved in MeOH (50 mL) was added dropwise. The reaction was allowed to reach room temperature, a solution of Boc₂O (44.2 mmol, 9.6g, 1 equiv.) in MeOH (50 mL) was added dropwise for 2 hours, and the reaction was stirred for 12 hours. Solvents were removed *in vacuo* and the residue was dissolved in 100 mL of water and washed with Et₂O (3 x 200 mL). The aqueous layer was basified with NaOH 2.5 M (150 mL), extracted with DCM (4 x 400 mL), and the combined organic layers were dried over MgSO₄. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using DCM:MeOH mixtures to afford the desired mono-Boc protected diamines.

tert-butyl ((1*R*,2*R*)-2-aminocyclohexyl)carbamate



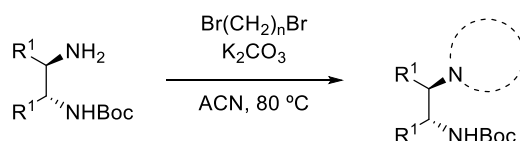
General procedure was followed using (1*R*,2*R*)-cyclohexane-1,2-diamine (44.2 mmol, 5.0 g, 1 equiv.). Brown solid; 80% yield. ¹H NMR (300 MHz, CDCl₃) δ 4.42 (m, 1H), 3.13 (m, 1H), 2.31 (td, *J* = 10.3, 3.9 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.75 – 1.66 (m, 2H), 1.45 (s, 9H), 1.31 – 0.97 (m, 3H).

tert-butyl ((1*R*,2*R*)-2-amino-1,2-diphenylethyl)carbamate



General procedure was followed using (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (44.2 mmol, 9.4 g, 1 equiv.). White solid; 69% yield. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.17 (m, 10H), 5.79 (d, *J* = 7.8 Hz, 1H), 4.31 (d, *J* = 7.6 Hz, 1H), 1.33 (s, 9H).

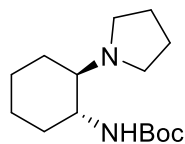
Mono-Boc protected tertiary amine synthesis



To a mixture of mono-Boc protected diamine (9.6 mmol, 1 equiv.) and K₂CO₃ (49 mmol, 6.77 g, 5 equiv.) in dry MeCN (20 mL) under nitrogen atmosphere, the corresponding dihalide (14.4 mmol, 1.5 equiv.) was added. The resulting mixture was stirred overnight at reflux and

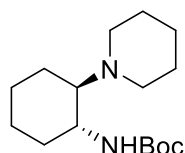
then filtered. The filtrate was concentrated under vacuum and the crude product was purified by silica gel column chromatography using DCM:MeOH mixtures to obtain the mono-Boc protected tertiary amines.

tert-butyl ((1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexyl)carbamate



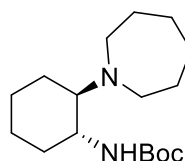
General procedure was followed using 1,4-dichlorobutane (14.4 mmol, 1.6 mL, 1.5 equiv.). Brown oil; 64% yield. **¹H NMR** (400 MHz, CDCl₃) δ 1.35 – 1.10 (m, 4H), 1.43 (s, 9H), 1.64 – 1.55 (m, 1H), 1.84 – 1.65 (m, *J* = 17.1 Hz, 6H), 2.32 (br d, *J* = 10.1 Hz, 1H), 2.47 (br t, *J* = 8.0 Hz, 1H), 2.58 (br s, 2H), 2.66 (br d, *J* = 5.7 Hz, 2H), 3.31 (br, 1H), 5.24 (br s, 1H).

tert-butyl ((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)carbamate



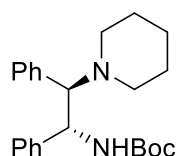
General procedure was followed using 1,5-dibromopentane (14.4 mmol, 2.0 mL, 1.5 equiv.). Brown solid; 75% yield. **¹H NMR** (300 MHz, CDCl₃) δ 5.36 (m, 1H), 3.20 (m, 1H), 2.57 (m, 1H), 2.42 (d, *J* = 11.7 Hz, 1H), 2.12 (m, 3H), 1.85 – 1.74 (m, 8H), 1.64 (m, 2H), 1.54 (s, 9H), 1.26 – 1.01 (m, 4H).

tert-butyl ((1*R*,2*R*)-2-(azepan-1-yl)cyclohexyl)carbamate



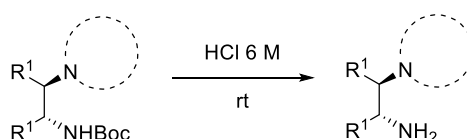
General procedure was followed using 1,6-dibromohexane (14.4 mmol, 2.4 mL, 1.5 equiv.). Brown solid, 42% yield. **¹H NMR** (300 MHz, CDCl₃) δ 5.43 (s, 1H), 3.13 (tt, *J* = 10.6, 3.6 Hz, 1H), 2.71 (d, *J* = 12.9 Hz, 2H), 2.49 – 2.38 (m, 3H), 2.21 (td, *J* = 11.8, 11.4, 3.9 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.56 (m, 9H), 1.44 (s, 9H), 1.31 – 0.90 (m, 4H).

tert-butyl ((1*R*,2*R*)-1,2-diphenyl-2-(piperidin-1-yl)ethyl)carbamate



General procedure was followed using 1,5-dibromopentane (14.4 mmol, 2.0 mL, 1.5 equiv.). White solid; 96% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.34 – 7.19 (m, 3H), 7.19 – 7.09 (m, 7H), 6.49 – 6.42 (s, 1H), 4.95 (d, *J* = 9.3 Hz, 1H), 3.62 (d, *J* = 10.9 Hz, 1H), 2.50 (m, 2H), 2.32 (m, 2H), 1.75 – 1.57 (m, 6H), 1.41 (s, 9H).

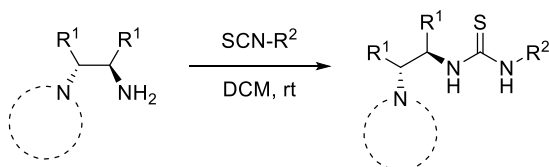
Mono-Boc protected tertiary amine deprotection



In a round bottom flask, the corresponding mono-Boc protected tertiary amine (7.5 mmol, 1 equiv.) was introduced, HCl 6 M (55 mmol, 9 mL, 7.2 equiv.) was added dropwise, and the resulting mixture was stirred overnight. The reaction mixture was rinsed twice with Et₂O (2

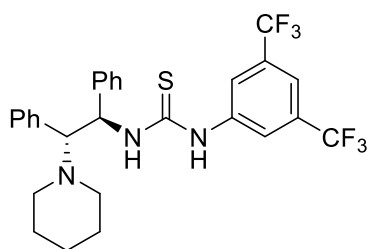
x 15 mL), the aqueous layer was basified with NaOH until pH > 10 (ca. 10 pearls) and extracted four times with DCM (4 x 80 mL). The combined organic layers were rinsed with brine, dried over MgSO₄ and solvents were removed *in vacuo* to afford the crude product, which was used in the next step without further purification.

Synthesis of thiourea-derived organocatalysts



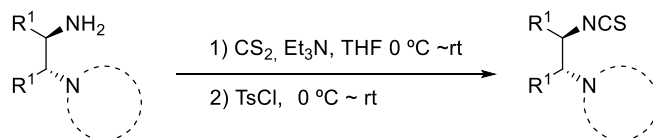
To a solution of the corresponding amine (1.3 mmol, 1.1 equiv.) in DCM (12 mL) under nitrogen atmosphere, isothiocyanate (1.18 mmol, 1 equiv.) was added, and the resulting solution was stirred overnight at room temperature. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using DCM:MeOH mixtures to obtain the desired organocatalyst.

1-(3,5-bis(trifluoromethyl)phenyl)-3-((1R,2R)-1,2-diphenyl-2-(piperidin-1-yl)ethyl)thiourea (TU-XII)



General procedure was followed using phenyl isothiocyanate (1.15 mmol, 135 μ L, 1 equiv.) and (1R,2R)-1,2-diphenyl-2-(piperidin-1-yl)ethan-1-amine (1.3 mmol, 365 mg 1.1 equiv.). White solid; 93% yield. **Mp** 195–198 °C. **¹H NMR** (300 MHz, CDCl₃) δ 8.11 (s, 1H), 7.75 (s, 2H), 7.67 (s, 1H), 7.33 – 7.11 (m, 9H), 7.05 (dd, *J* = 6.5, 2.8 Hz, 2H), 5.16 (s, 1H), 3.70 (d, *J* = 10.8 Hz, 1H), 2.44 (s, 2H), 2.26 (s, 2H), 1.47 (s, 4H), 1.27 (m, 2H); **¹³C NMR** (75 MHz, CDCl₃) δ 181.3 (C), 139.7 (C), 132.3 (C), 132.2 (C), 129.8 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 124.2 (CH), 123.0 (q, *J* = 273 Hz, C), 119.2 (CH), 75.4 (CH), 58.7 (CH), 26.44 (CH₂), 24.1 (CH₂), 24.0 (CH₂); **¹⁹F NMR** (282 MHz, CDCl₃) δ –63.5 (s, 6F); **HRMS (ESI-TOF)** calc'd for [C₂₈H₂₇F₆N₃S+H]⁺: 552.1903; found: 552.1919.

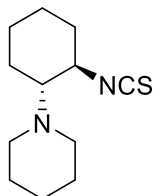
Regarding the synthesis of C₂-symmetric **TU-XV** to **TU-XVIII**, the required isothiocyanates were prepared following a modified reported procedure.^[25]



In a round bottom flask, the corresponding amine (2.5 mmol, 1 equiv.) was dissolved in dry THF (30 mL) at 0 °C under nitrogen atmosphere. To this solution, Et₃N (2.25 mL, 8.25 mmol, 3.3 equiv.) and CS₂ (138 μ L, 2.5 mmol, 1 equiv.) were added sequentially and the reaction mixture was stirred at room temperature for 1 hour. Next, the reaction was cooled to 0 °C,

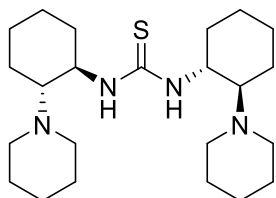
TsCl (0.52 g, 2.75 mmol, 1.1 equiv.) was added and the reaction was stirred at room temperature for 2 hours. The reaction mixture was diluted with DCM (50 mL), treated with saturated aqueous NaHCO₃ (50 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were dried over MgSO₄, solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane:EtOAc mixtures to afford the isothiocyanate.

1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)piperidine



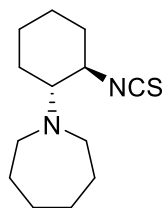
General procedure was followed using (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexan-1-amine (2.5 mmol, 456 mg, 1 equiv.). Brown solid; 84% yield. **¹H NMR** (300 MHz, CDCl₃) δ 3.76 (td, *J* = 7.4, 3.6 Hz, 1H), 2.70 (t, *J* = 6.3 Hz, 4H), 2.53 (td, *J* = 7.4, 3.2 Hz, 1H), 2.27–2.05 (m, 2H), 1.83–1.69 (m, 8H), 1.65–1.30 (m, 4H).

1,3-bis((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)thiourea (TU-XV)



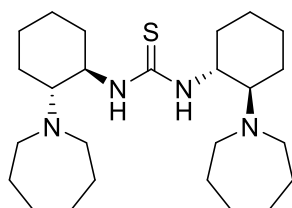
General procedure was followed using 1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)piperidine (1.15 mmol, 264 mg, 1 equiv.) and (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexan-1-amine (1.3 mmol, 236 mg 1.1 equiv.). Yellow solid; 33% yield. **Mp** 125–127 °C. **¹H NMR** (300 MHz, CDCl₃) δ 6.78 (m, 2H), 3.62 (m, 2H), 2.61 (m, 6H), 2.37 (m, 6H), 2.03–1.84 (m, 2H), 1.84–1.75 (m, 2H), 1.68 (m, 3H), 1.57–1.46 (m, 6H), 1.45–1.35 (m, 5H), 1.19 (m, 8H); **¹³C NMR** (75 MHz, CDCl₃) δ 182.0 (C), 67.8 (CH), 54.6 (CH), 49.1 (CH₂), 34.9 (CH₂), 32.6 (CH₂), 26.9 (CH₂), 26.5 (CH₂), 25.9 (CH₂), 25.5 (CH₂), 25.1 (CH₂), 25.0 (CH₂), 24.6 (CH₂), 24.5 (CH₂), 23.3 (CH₂), 22.6 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₃H₄₂N₄S+H]⁺: 407.3182; found: 407.3203.

1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)azepane



General procedure was followed using (1*R*,2*R*)-2-(azepan-1-yl)cyclohexan-1-amine (2.5 mmol, 490 mg, 1 equiv.). Brown solid; 92%. **¹H NMR** (300 MHz, CDCl₃) δ 3.49 (td, *J* = 11.1, 4.2 Hz, 1H), 2.74 (m, 2H), 2.61 (m, 2H), 2.50 (td, *J* = 10.7, 3.6 Hz, 1H), 2.20–2.04 (m, 1H), 1.84 (m, 1H), 1.76–1.53 (m, 1H), 1.46 (qd, *J* = 12.8, 3.7 Hz, 1H), 1.31–1.01 (m, 3H).

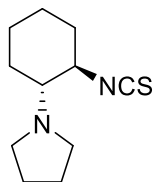
1,3-bis((1*R*,2*R*)-2-(azepan-1-yl)cyclohexyl)thiourea (TU-XVI)



General procedure was followed using 1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)azepane (1.15 mmol, 281 mg, 1 equiv.) and (1*R*,2*R*)-2-(azepan-1-yl)cyclohexan-1-amine (1.3 mmol, 255 mg 1.1 equiv.). Brown oil, 91% yield. **¹H NMR** (300 MHz, CDCl₃) δ 6.73 (s, 2H), 3.44 (m, 2H), 2.72 (d, *J* = 13.0 Hz, 6H), 2.46 (d, *J* = 12.7 Hz, 6H), 1.92–1.77 (m, 5H), 1.59 (m, 16H), 1.40–0.87 (m, 10H); **¹³C NMR** (75 MHz, CDCl₃) δ 181.7 (C), 69.0 (CH₂), 55.4 (CH₂), 50.7 (CH₂), 32.4 (CH₂), 29.8 (CH₂),

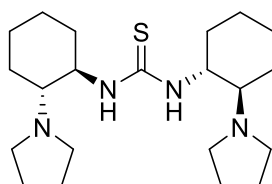
26.9 (CH₂), 25.6 (CH₂), 24.6 (CH₂), 23.9 (CH₂); **HRMS (ESI-TOF)** calcd for [C₂₅H₄₆N₄S+H]⁺: 435.3516; found: 435.3502.

1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)pyrrolidine



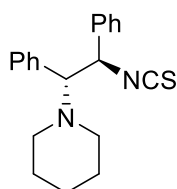
General procedure was followed using (1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexan-1-amine (2.5 mmol, 420 mg, 1 equiv.). Brown solid; 64% yield. **¹H NMR** (300 MHz, CDCl₃) δ 3.73 (td, *J* = 7.6, 3.8 Hz, 1H), 2.62 (t, *J* = 6.3 Hz, 4H), 2.52 (td, *J* = 7.7, 3.4 Hz, 1H), 2.16 – 2.01 (m, 1H), 1.93 – 1.53 (m, 8H), 1.50 – 1.20 (m, 3H).

1,3-bis((1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexyl)thiourea (TU-XVII)



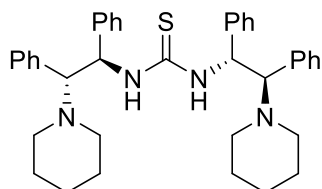
General procedure was followed using 1-((1*R*,2*R*)-2-isothiocyanatocyclohexyl)pyrrolidine (1.15 mmol, 248 mg, 1 equiv.) and (1*R*,2*R*)-2-(pyrrolidin-1-yl)cyclohexan-1-amine (1.3 mmol, 219 mg 1.1 equiv.). Brown solid; 45% yield. **Mp** 113 – 116 °C. **¹H NMR** (300 MHz, CDCl₃) δ 6.67 (s, 2H), 3.72 (m, 2H), 2.59 (m, 8H), 2.38 (m, 2H), 1.87 – 1.53 (m, 8H), 1.43 – 1.07 (m, 8H); **¹³C NMR** (75 MHz, CDCl₃) δ 181.8 (C), 62.6 (CH), 56.0 (CH), 48.2 (CH₂), 31.4 (CH₂), 24.1 (CH₂), 23.9 (CH₂), 23.8 (CH₂), 23.4 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₂₁H₃₈N₄S+H]⁺: 379.2890; found: 379.2875.

1-((1*R*,2*R*)-2-isothiocyanato-1,2-diphenylethyl)piperidine



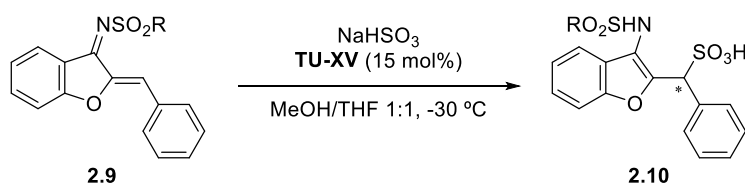
General procedure was followed using (1*R*,2*R*)-1,2-diphenyl-2-(piperidin-1-yl)ethan-1-amine (2.5 mmol, 700 mg, 1 equiv.) White solid; 69% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.05 (m, 6H), 6.98 (d, *J* = 7.4 Hz, 2H), 5.25 (d, *J* = 10.2 Hz, 1H), 3.84 (d, *J* = 10.1 Hz, 1H), 2.60 – 2.46 (m, 2H), 2.45 – 2.32 (m, 2H), 1.77 – 1.63 (m, 4H), 1.37 (q, *J* = 5.8, 5.4 Hz, 2H).

1,3-bis((1*R*,2*R*)-1,2-diphenyl-2-(piperidin-1-yl)ethyl)thiourea (TU-XVIII)



General procedure was followed using 1-((1*R*,2*R*)-2-isothiocyanato-1,2-diphenylethyl)piperidine (1.15 mmol, 370 mg, 1 equiv.) and (1*R*,2*R*)-1,2-diphenyl-2-(piperidin-1-yl)ethan-1-amine (1.3 mmol, 365 mg 1.1 equiv.). White solid; 97% yield. **Mp** 165 – 167 °C. **¹H NMR** (300 MHz, CDCl₃) δ 7.41 – 6.81 (m, 20H), 5.23 (s, 2H), 3.46 (m, 2H), 2.48 (m, 4H), 2.29 (m, 4H), 1.82 – 1.66 (m, 9H), 1.43 (s, 4H); **¹³C NMR** (75 MHz, CDCl₃) δ 180.2 (C), 133.2 (2C), 129.8 (CH), 127.9 (CH), 127.9 (CH), 127.7 (C), 75.4 (CH), 58.0 (CH), 50.0 (CH₂), 26.8 (CH₂), 24.5 (CH₂); **HRMS (ESI-TOF)** calc'd for [C₃₉H₄₆N₄S+H]⁺: 603.3516; found: 603.3497.

Synthesis and characterization data for chiral amino sulfonic acids **2.10**

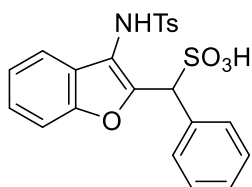


General procedure for the enantioselective addition of NaHSO₃ to aurone-derived azadienes

In a test tube, catalyst **TU-XV** (0.015 mmol, 6.1 mg, 15 mol%), the aurone-derived azadiene **2.9** (0.1 mmol, 1 equiv.) and NaHSO₃ (0.25 mmol, 26.2 mg, 2.5 equiv.) were dissolved in a MeOH/THF mixture (1 mL, v/v, 1:1) under nitrogen atmosphere, and the mixture was stirred at -30 °C until completion (TLC) or for up to 72 hours if no further progress was observed. Solvents were removed *in vacuo* and the crude product was dissolved in 3 mL of a THF/H₂O mixture (v/v, 2:1), passed through a plug of freshly conditioned acidic ion-exchange resin Amberlyst@15 and rinsed with water (3 x 3 mL). The resulting aqueous solution was concentrated *in vacuo* and dried under high vacuum in the presence of P₂O₅. Crude products were purified by silica gel column chromatography using DCM/MeOH mixtures to afford compounds **2.10**.

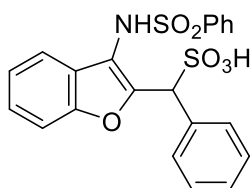
Racemic products **2.10** were obtained following the same procedure employing 3 drops of Et₃N instead of **TU-XV** at room temperature for 24 hours.

(3-((4-methylphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methanesulfonic acid (**2.10a**)



General procedure was followed using **2.9a** (0.1 mmol, 37.5 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10a** as yellow solid (40.6 mg, 88% yield). Compound **2.10a** was obtained with a 54% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 7.9$ min, $\tau_{\text{minor}} = 11.9$ min. **Mp** 225 – 227 °C. $[\alpha]_D^{25} = 11.8$ (*c* = 0.75, MeOH, 54% ee). **¹H NMR** (300 MHz, CD₃OD) δ 7.54 (d, *J* = 6.6 Hz, 2H), 7.52 – 7.27 (m, 4H), 7.26 – 7.12 (m, 7H), 5.11 (s, 1H), 2.35 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 154.9 (C), 149.6 (C), 145.2 (C), 138.1 (C), 135.0 (C), 131.4 (CH), 130.8 (CH), 128.8 (CH), 128.8 (CH), 128.4 (CH), 127.2 (C), 125.8 (CH), 123.9 (CH), 121.1 (CH), 117.6 (C), 112.3 (CH), 64.1 (CH), 21.5 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₂H₁₉NO₆S₂+NH₄]⁺: 475.0992; found: 475.0979.

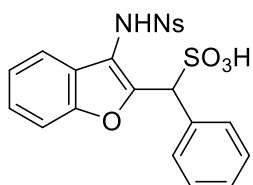
phenyl(3-(phenylsulfonamido)benzofuran-2-yl)methanesulfonic acid (**2.10b**)



General procedure was followed using **2.9b** (0.1 mmol, 36.1 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10b** as a yellow solid (11.4 mg, 26% yield). Compound **2.10b** was obtained with a 10% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 7.2$ min, $\tau_{\text{minor}} = 9.8$ min. **Mp** 205 –

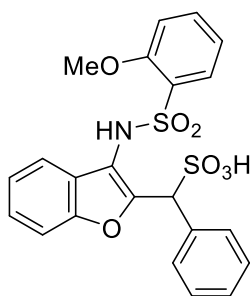
207 °C. **¹H NMR** (300 MHz, CD₃OD) δ 7.68 (dd, *J*₁ = 8.4 Hz, *J*₂ = 1.2 Hz, 2H), 7.60 – 7.44 (m, 3H), 7.39 (ddd, *J*₁ = 9.7 Hz, *J*₂ = 6.2 Hz, *J*₃ = 2.5 Hz, 3H), 7.33 – 7.16 (m, 5H), 7.08 (td, *J*₁ = 7.6 Hz, *J*₂ = 0.9 Hz, 1H), 5.22 (s, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 155.2 (C), 150.3 (C), 141.6 (C), 135.5 (C), 134.5 (CH), 131.8 (CH), 130.6 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 127.4 (C), 126.1 (CH), 124.2 (CH), 121.1 (CH), 117.8 (C), 112.7 (CH), 64.5 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₁H₁₇NO₆S₂+NH₄]⁺: 461.0836; found: 461.0808.

(3-((4-nitrophenyl)sulfonamido)benzofuran-2-yl)(phenyl)methanesulfonic acid (2.10c)



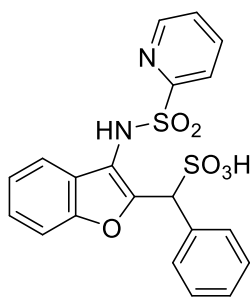
General procedure was followed using **2.9c** (0.1 mmol, 40.6 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10c** as a yellow solid (30.1 mg, 88% yield). Compound **2.10c** was obtained with a 54% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: τ_{major} = 6.45 min, τ_{minor} = 8.31 min. **Mp** 223 – 225 °C. [α]_D²⁵ = -4.0 (c = 0.62, MeOH, 54% ee). **¹H NMR** (300 MHz, CD₃OD) δ 8.11 – 8.01 (m, 2H), 7.84 – 7.73 (m, 2H), 7.56 – 7.46 (m, 2H), 7.45 – 7.39 (m, 2H), 7.27 (ddd, *J*₁ = 8.5 Hz, *J*₂ = 7.3 Hz, *J*₃ = 1.3 Hz, 1H), 7.21 – 7.12 (m, 4H), 5.24 (s, 1H); **¹³C NMR** (75 MHz, CD₃OD) δ 155.1 (C), 151.5 (C), 149.7 (C), 146.9 (C), 135.6 (C), 131.2 (CH), 129.7 (CH), 129.0 (CH), 128.9 (CH), 127.2 (C), 126.1 (CH), 125.4 (CH), 124.2 (CH), 121.4 (CH), 118.2 (C), 112.7 (CH), 63.9 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₁H₁₆O₈S₂+NH₄]⁺: 506.0686; found: 506.0660.

(3-((2-methoxyphenyl)sulfonamido)benzofuran-2-yl)(phenyl)methanesulfonic acid (2.10d)



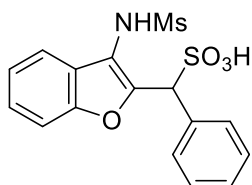
General procedure was followed using **2.9d** (0.1 mmol, 39.1 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10d** as a yellow solid (26.5 mg, 54% yield). Compound **2.10d** was obtained with a 15% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: τ_{major} = 8.3 min, τ_{minor} = 7.1 min. **Mp** 224 – 227 °C. **¹H NMR** (300 MHz, CD₃OD) δ 7.68 – 7.55 (m, 3H), 7.40 – 7.32 (m, 3H), 7.31 – 7.21 (m, 5H), 7.20 – 7.13 (m, 1H), 6.94 (td, *J*₁ = 7.7 Hz, *J*₂ = 0.9 Hz, 1H), 5.19 (s, 1H), 4.05 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 157.9 (C), 156.6 (C), 154.5 (C), 149.1 (C), 148.6 (C), 136.0 (CH), 134.5 (C), 131.0 (CH), 130.9 (CH), 128.5 (CH), 128.4 (CH), 128.4 (CH), 125.3 (CH), 123.6 (CH), 120.9 (CH), 120.9 (CH), 117.3 (C), 113.4 (CH), 111.9 (CH), 63.9 (CH), 56.6 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₂₂H₁₉NO₇S₂+NH₄]⁺: 491.0941; found: 491.017.

phenyl(3-(pyridine-2-sulfonamido)benzofuran-2-yl)methanesulfonic acid (2.10e)



General procedure was followed using **2.9e** (0.1 mmol, 36.2 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10e** as a white solid (35.1 mg, 80% yield). Compound **2.10e** was obtained with a 38% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 9.0$ min, $\tau_{\text{minor}} = 12.1$ min. **Mp** 250–253 °C. **¹H NMR** (DMSO-*d*₆, 300 MHz) δ 8.70 (d, *J* = 4.6 Hz, 1H), 7.95–7.68 (m, 2H), 7.59–7.44 (m, 4H), 7.39–7.23 (m, 4H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 5.52 (s, 1H); **¹³C NMR** (75 MHz, DMSO-*d*₆) δ 155.3 (C), 151.6 (C), 151.3 (CH), 140.1 (CH), 135.8 (C), 131.7 (CH), 129.9 (C), 129.2 (CH), 129.1 (CH), 124.5 (CH), 112.5 (CH), 64.4 (CH); **HRMS (ESI-TOF)** calc'd for [C₂₀H₁₆NO₆S₂+H]⁺: 445.0523; found: 445.0498. Some ¹³C NMR signals were not observed due to the low concentration of the sample, as compound **2.10e** is insoluble in most commercial deuterated solvents and only barely soluble in DMSO.

(3-(methylsulfonamido)benzofuran-2-yl)(phenyl)methanesulfonic acid (2.10f)



General procedure was followed using **2.9f** (0.1 mmol, 29.9 mg, 1 equiv.). The crude product was purified by silica gel column chromatography affording pure **2.10f** as a yellow solid (33.4 mg, 90% yield). Compound **2.10f** was obtained with a 40% enantiomeric excess determined by HPLC using a Chiralpak IE column [*n*-heptane/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]: $\tau_{\text{major}} = 7.3$ min, $\tau_{\text{minor}} = 9.0$ min. **Mp** 205–207 °C. $[\alpha]_D^{25} = -23.6$ (*c* = 0.46, MeOH, 40% ee). **¹H NMR** (CD₃OD, 300 MHz) δ 7.85 (dd, *J*₁ = 1.8 Hz, *J*₂ = 6.6 Hz, 2H), 7.71 (dd, *J*₁ = 0.9 Hz, *J*₂ = 7.2 Hz, 1H), 7.52 (dd, *J*₁ = 7.2 Hz, *J*₂ = 0.9 Hz, 1H), 7.35–7.25 (m, 5H), 5.77 (s, 1H), 2.98 (s, 3H); **¹³C NMR** (75 MHz, CD₃OD) δ 155.0 (C), 150.4 (C), 135.9 (C), 131.5 (CH), 129.1 (CH), 128.9 (CH), 127.2 (C), 126.0 (CH), 124.2 (CH), 121.0 (CH), 117.7 (C), 112.6 (CH), 64.0 (CH), 40.2 (CH₃); **HRMS (ESI-TOF)** calc'd for [C₁₆H₁₅NO₆S₂+NH₄]⁺: 399.0679; found: 399.0658.

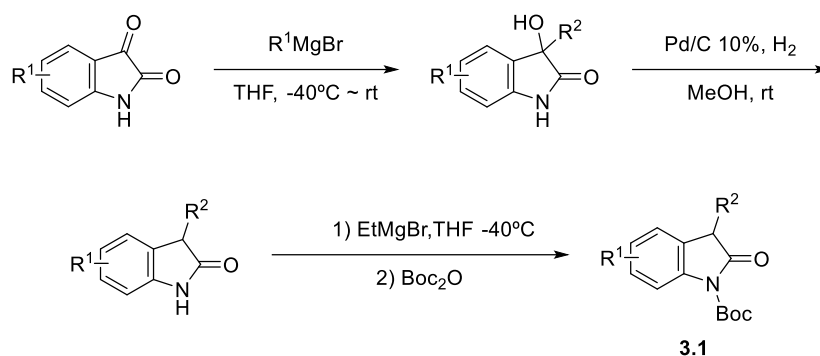
Enantioselective Addition of 3-Aryloxindoles to Ethenesulfonyl Fluoride

Synthesis and characterization data for 3-Substituted Oxindoles 3.1

General procedures for the synthesis of 3-Substituted Oxindoles

Compounds **3.1** were prepared *via* various multi-step syntheses following modified reported procedures.

Procedure 1.a^{[26],[27]}

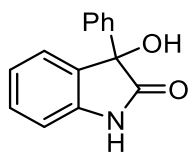


A septum-sealed flask equipped with a stirring bar was charged with the corresponding isatin (1.0 equiv.) under nitrogen atmosphere. Dry THF (15 mL) was added, and the resulting solution was cooled to $-40^\circ C$. A solution of R^1MgBr (3 M in Et_2O , 2.0 equiv.) was then added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction was cooled to $0^\circ C$, diluted with Et_2O (25 mL) and quenched with HCl 1 M (15 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL), and the combined organic phases were washed with water, brine and dried over $MgSO_4$. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using DCM:EtOAc mixtures as eluent to yield the desired 3-substituted 3-hydroxyl-2-oxindole.

3-substituted 3-hydroxyl-2-oxindole intermediate (1.0 equiv.) was dissolved in MeOH (30 mL), and 10% Pd/C (10 mol%) was added. The suspension was stirred overnight under hydrogen atmosphere (balloon) at room temperature. The mixture was filtered through Celite®, concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to give the corresponding product.

3-substituted oxindole (1.0 equiv.) was dissolved in dry THF (7.5 mL) under nitrogen atmosphere and cooled to $-40^\circ C$. $EtMgBr$ (3 M in Et_2O , 1.2 equiv.) was added dropwise, and the mixture was stirred for 30 min. Subsequently, Boc_2O (1.5 equiv.) was added, and the reaction was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc (50 mL), quenched with saturated NH_4Cl (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to afford the desired N-Boc protected 3-substituted oxindole.

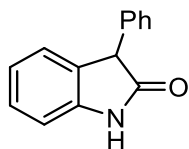
3-hydroxy-3-phenylindolin-2-one



0.9 Hz, 1H).

General procedure was followed using isatin (3.4 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.8 mmol, 2.3 mL, 2 equiv.). Orange solid, 78% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.42 – 7.24 (m, 6H), 7.17 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.04 (td, *J* = 7.5, 1.1 Hz, 1H), 6.97 (dt, *J* = 7.8,

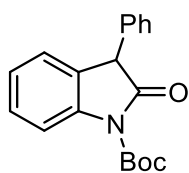
3-phenylindolin-2-one



1H).

General procedure was followed using 3-hydroxy-3-phenylindolin-2-one (2.4 mmol, 304 mg, 1 equiv.) White solid, 75% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.85 (bs, 1H), 7.41 – 7.25 (m, 3H), 7.30 – 7.17 (m, 3H), 7.18 – 7.08 (m, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 (dd, *J* = 7.7, 1.0 Hz, 1H), 4.64 (s,

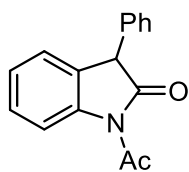
tert-butyl 2-oxo-3-phenylindoline-1-carboxylate (3.1a)



115.3 (CH), 84.6 (C), 52.7 (CH), 28.2 (CH₃). Signal at 128.8 corresponds to 2 overlapping aromatic CH singlets.

General procedure was followed using 3-phenylindolin-2-one (1.4 mmol, 201 mg, 1 equiv.). White solid, 70% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.90 (m, 1H), 7.41 – 7.29 (m, 4H), 7.22 – 7.14 (m, 4H), 4.73 (s, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.1 (C), 149.5 (C), 140.6 (C), 136.4 (C), 129.1 (CH), 128.8 (CH), 128.0 (CH), 127.6 (C), 125.2 (CH), 124.7 (CH),

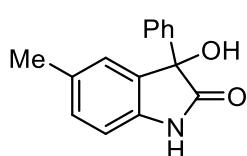
1-acetyl-3-phenylindolin-2-one (3.1b)



125.1 (CH), 116.9 (CH), 52.8 (CH), 26.8 (CH₃).

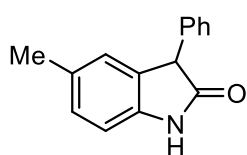
General procedure was followed using 3-phenylindolin-2-one (1.4 mmol, 210 mg, 1 equiv.) and Ac₂O (2.2 mmol, 1.1 mL, 1.5 equiv.) instead of Boc₂O. White solid, 26% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.31 (ddt, *J* = 8.2, 1.1, 0.6 Hz, 1H), 7.43 – 7.31 (m, 4H), 7.23 – 7.16 (m, 4H), 4.79 (d, *J* = 0.5 Hz, 1H), 2.66 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 176.6 (C), 171.2 (C),

3-hydroxy-5-methyl-3-phenylindolin-2-one



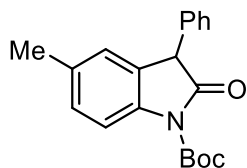
General procedure was followed using 5-methylisatin (3.1 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 64% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.40 – 7.34 (m, 2H), 7.34 – 7.22 (m, 3H), 7.10 (ddd, *J* = 7.9, 1.7, 0.7 Hz, 01), 7.01 – 6.94 (m, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 2.27 (s, 3H).

5-methyl-3-phenylindolin-2-one



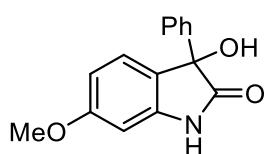
General procedure was followed using 3-hydroxy-5-methyl-3-phenylindolin-2-one (2.0 mmol, 240 mg, 1 equiv.). White solid, 67% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.40 – 7.21 (m, 3H), 7.21 – 7.10 (m, 2H), 7.06 (ddt, J = 7.8, 1.6, 0.8 Hz, 1H), 6.91 – 6.80 (m, 2H), 4.62 (s, 1H), 2.25 (s, 3H).

tert-butyl 5-methyl-2-oxo-3-phenylindoline-1-carboxylate (3.1d)



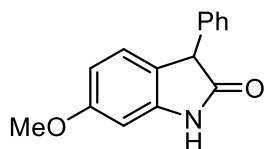
General procedure was followed using 5-methyl-3-phenylindolin-2-one (1.3 mmol, 240 mg, 1 equiv.). White solid, 60% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.80 (d, J = 8.3 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.22 – 7.13 (m, 3H), 6.98 – 6.93 (m, 1H), 4.69 (s, 1H), 2.32 (s, 3H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.3 (C), 149.6 (C), 138.2 (C), 136.6 (C), 134.4 (C), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.0 (CH), 127.6 (C), 125.7 (CH), 115.0 (CH), 84.4 (C), 52.8 (CH), 28.2 (CH₃), 21.2 (CH₃).

3-hydroxy-6-methoxy-3-phenylindolin-2-one



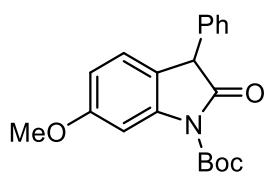
General procedure was followed using 6-methoxyisatin (2.8 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 44% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.40 – 7.34 (m, 2H), 7.33 – 7.22 (m, 3H), 7.10 – 7.03 (m, 1H), 6.62 – 6.54 (m, 2H), 3.80 (s, 3H).

6-methoxy-3-phenylindolin-2-one



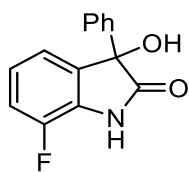
General procedure was followed using 3-hydroxy-6-methoxy-3-phenylindolin-2-one (1.3 mmol, 320 mg, 1 equiv.). Yellow solid, 54% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.60 (bs, 1H), 7.40 – 7.28 (m, 3H), 7.25 – 7.18 (m, 2H), 7.01 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.54 (s, 1H), 4.58 (s, 1H), 3.80 (s, 3H).

tert-butyl 6-methoxy-2-oxo-3-phenylindoline-1-carboxylate (3.1h)



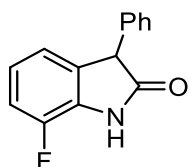
General procedure was followed using 6-methoxy-3-phenylindolin-2-one (0.7 mmol, 160 mg, 1 equiv.). Yellow solid, 48% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.58 (d, J = 2.4 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.22 – 7.16 (m, 2H), 7.05 (dd, J = 8.3, 1.0 Hz, 1H), 6.71 (dd, J = 8.3, 2.4 Hz, 1H), 4.67 (s, 1H), 3.86 (s, 3H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.6 (C), 160.2 (C), 149.5 (C), 141.6 (C), 136.8 (C), 129.0 (CH), 128.7 (CH), 127.9 (CH), 125.7 (CH), 119.2 (C), 110.5 (CH), 101.9 (CH), 84.5 (C), 55.7 (CH₃), 52.2 (CH), 28.2 (CH₃).

7-fluoro-3-hydroxy-3-phenylindolin-2-one



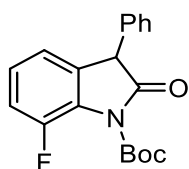
General procedure was followed using 7-fluoroisatin (3.0 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.0 mmol, 2.0 mL, 2 equiv.). Orange solid, 60% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.49 – 7.23 (m, 5H), 7.19 – 6.86 (m, 3H).

7-fluoro-3-phenylindolin-2-one



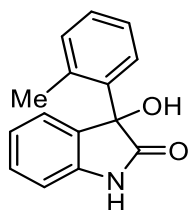
General procedure was followed using 7-fluoro-3-hydroxy-3-phenylindolin-2-one (1.8 mmol, 430 mg, 1 equiv.). White solid, 37% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.48 (bs, 1H), 7.40 – 7.27 (m, 3H), 7.24 – 7.18 (m, 2H), 7.08 – 6.89 (m, 3H), 4.68 (s, 1H).

tert-butyl 7-fluoro-2-oxo-3-phenylindoline-1-carboxylate (3.1i)



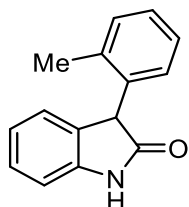
General procedure was followed using 7-fluoro-3-phenylindolin-2-one (1.1 mmol, 270 mg, 1 equiv.). White solid, 59% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.40 – 7.29 (m, 3H), 7.23 – 7.17 (m, 2H), 7.15 – 7.06 (m, 2H), 6.99 – 6.92 (m, 1H), 4.77 (s, 1H), 1.61 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.3 (C), 148.6 (d, J = 251.2 Hz, C), 147.7 (C), 135.6 (C), 130.7 (d, J = 2.1 Hz, C), 129.0 (CH), 128.6 (CH), 128.1 (CH), 127.35 (d, J = 9.5 Hz, C), 125.6 (d, J = 7.0 Hz, CH), 120.9 (d, J = 3.6 Hz, CH), 116.9 (d, J = 20.5 Hz, CH), 85.1 (C), 52.8 (d, J = 1.8 Hz, CH), 27.7 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ -120.2.

3-hydroxy-3-(o-tolyl)indolin-2-one



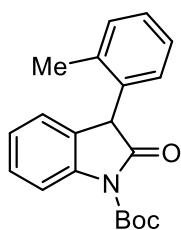
General procedure was followed using isatin (3.4 mmol, 500 mg, 1 equiv.) and 2-methylphenylmagnesium bromide (2M in Et₂O, 6.0 mmol, 3.4 mL, 2 equiv.). Orange solid, 55% yield. **¹H NMR** (300 MHz, CD₃OD) δ 8.01 (dd, J = 7.8, 1.2 Hz, 1H), 7.35 – 7.25 (m, 2H), 7.20 (td, J = 7.4, 1.4 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 7.01 – 6.87 (m, 3H), 1.85 (s, 3H).

3-(o-tolyl)indolin-2-one



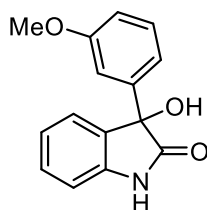
General procedure was followed using 3-hydroxy-3-(o-tolyl)indolin-2-one (1.9 mmol, 445 mg, 1 equiv.). White solid, 73% yield. **¹H NMR** (300 MHz, CDCl₃) δ 9.15 (bs, 1H), 7.33 – 7.09 (m, 4H), 7.07 – 6.82 (m, 4H), 4.87 (bs, 1H), 2.36 (bs, 3H).

tert-butyl 2-oxo-3-(o-tolyl)indoline-1-carboxylate (3.1l)



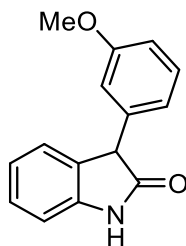
General procedure was followed using 3-(o-tolyl)indolin-2-one (1.5 mmol, 310 mg, 1 equiv.). White solid, 64% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.96 – 7.88 (m, 1H), 7.35 (dddd, *J* = 8.3, 7.4, 1.5, 0.9 Hz, 1H), 7.25 – 7.16 (m, 2H), 7.15 – 7.01 (m, 3H), 6.87 (bs, 1H), 4.99 (s, 1H), 2.40 (bs, 3H), 1.64 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.1 (C), 149.6 (C), 140.5 (C), 137.5 (C), 135.3 (C), 131.2 (CH), 128.6 (CH), 128.1 (C), 128.1 (CH), 126.5 (CH), 124.8 (CH), 124.7 (CH), 115.2 (CH), 84.5 (C), 50.5 (bs, CH), 28.2 (CH₃), 20.0 (CH₃). A ¹³C NMR aromatic CH signal was not detected, presumably due to the presence of rotamers.

3-hydroxy-3-(3-methoxyphenyl)indolin-2-one



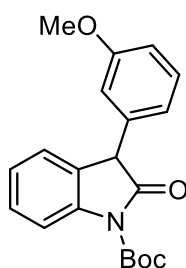
General procedure was followed using isatin (3.4 mmol, 500 mg, 1 equiv.) and 3-methoxyphenylmagnesium bromide (1M in Et₂O, 6.0 mmol, 6.8 mL, 2 equiv.). Orange solid, 41% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.61 – 7.51 (m, 1H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.13 – 6.91 (m, 3H), 6.89 – 6.76 (m, 1H), 3.77 (s, 3H).

3-(3-methoxyphenyl)indolin-2-one



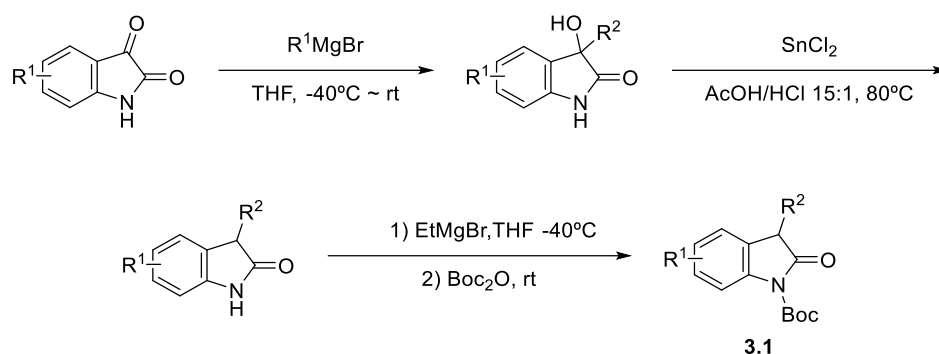
General procedure was followed using 3-hydroxy-3-(3-methoxyphenyl)indolin-2-one (1.26 mmol, 320 mg, 1 equiv.). White solid, 78% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.98 (bs, 1H), 7.32 – 7.22 (m, 2H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.80 – 6.76 (m, 1H), 4.63 (s, 3H), 3.79 (s, 3H).

tert-butyl 3-(3-methoxyphenyl)-2-oxoindoline-1-carboxylate (3.1n)



General procedure was followed using 3-(3-methoxyphenyl)indolin-2-one (1.0 mmol, 220 mg, 1 equiv.). White solid, 81% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.30 (m, 1H), 7.31 – 7.20 (m, 1H), 7.21 – 7.13 (m, 2H), 6.84 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.77 – 6.69 (m, 1H), 4.69 (s, 1H), 3.77 (s, 3H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.8 (C), 159.9 (C), 149.4 (C), 140.5 (C), 137.7 (C), 129.9 (CH), 128.7 (CH), 127.3 (C), 125.1 (CH), 124.6 (CH), 121.0 (CH), 115.1 (CH), 114.6 (CH), 113.2 (CH), 84.4 (C), 55.3 (CH₃), 52.5 (CH), 28.1 (CH₃).

Procedure 1.b^[27]

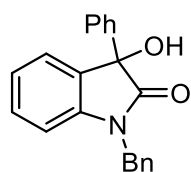


A septum-sealed flask equipped with a stirring bar was charged with the corresponding isatin (1.0 equiv.) under nitrogen atmosphere. Dry THF (15 mL) was added, and the resulting solution was cooled to -40°C . A solution of R^1MgBr (3 M in Et_2O , 2.0 equiv.) was then added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction was cooled to 0°C , diluted with Et_2O (25 mL) and quenched with HCl 1 M (15 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL), and the combined organic phases were washed with water, brine and dried over MgSO_4 . Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using DCM:EtOAc mixtures as eluent to yield the desired 3-substituted 3-hydroxyl-2-oxindole.

3-substituted 3-hydroxyl-2-oxindole intermediate (1.0 equiv.) was suspended in AcOH/HCl (15 mL, 15:1, v/v) and heated to 80°C . SnCl_2 (2.0 equiv.) was added, and the mixture was stirred for 1.5 h. The reaction was then diluted with EtOAc (50 mL), quenched with saturated NaHCO_3 (50 mL) followed by $\text{Na}_2\text{CO}_3(\text{s})$ until neutral pH was reached, and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with NaOH 0.1 M (30 mL) and brine, dried over MgSO_4 , and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to give the corresponding product.

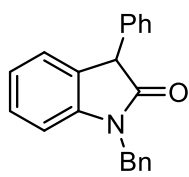
3-substituted oxindole (1.0 equiv.) was dissolved in dry THF (7.5 mL) under nitrogen atmosphere and cooled to -40°C . EtMgBr (3 M in Et_2O , 1.2 equiv.) was added dropwise, and the mixture was stirred for 30 min. Subsequently, Boc_2O (1.5 equiv.) was added, and the reaction was allowed to stir overnight at room temperature. The mixture was diluted with EtOAc (50 mL), quenched with saturated NH_4Cl (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to afford the desired *N*-Boc protected 3-substituted oxindole.

1-benzyl-3-hydroxy-3-phenylindolin-2-one



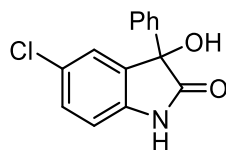
General procedure was followed using *N*-benzylisatin (2.1 mmol, 500 mg, 1 equiv.), which had previously been synthesized within the research group, and phenylmagnesium bromide (3M in Et_2O , 6.2 mmol, 2.1 mL, 2 equiv.). White solid, 61% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.45 – 7.39 (m, 2H), 7.38 – 7.24 (m, 9H), 7.22 (dd, J = 7.8, 1.3 Hz, 1H), 7.04 (td, J = 7.6, 0.9 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 5.05 (d, J = 15.7 Hz, 1H), 4.83 (d, J = 15.7 Hz, 1H).

1-benzyl-3-phenylindolin-2-one (3.1c)



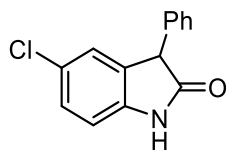
General procedure was followed using 1-benzyl-3-hydroxy-3-phenylindolin-2-one (1.3 mmol, 400 mg, 1 equiv.). Yellow solid, 75% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.41 – 7.28 (m, 8H), 7.27 – 7.22 (m, 3H), 7.21 – 7.16 (m, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.73 (s, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 176.2 (C), 143.7 (C), 136.9 (C), 136.0 (C), 129.1 (CH), 129.0 (C), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 125.3 (CH), 122.9 (CH), 109.3 (CH), 52.2 (CH), 44.1 (CH₂).

5-chloro-3-hydroxy-3-phenylindolin-2-one



General procedure was followed using 5-chloroisatin (2.8 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 72% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.40 – 7.23 (m, 6H), 7.13 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H).

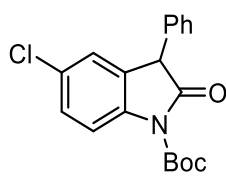
5-chloro-3-phenylindolin-2-one



1H).

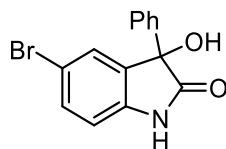
General procedure was followed using 5-chloro-3-hydroxy-3-phenylindolin-2-one (1.9 mmol, 514 mg, 1 equiv.). White solid, 73% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.46 (bs, 1H), 7.44 – 7.29 (m, 3H), 7.25 – 7.17 (m, 3H), 7.13 – 7.08 (m, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.62 (s,

tert-butyl 5-chloro-2-oxo-3-phenylindoline-1-carboxylate (3.1e)



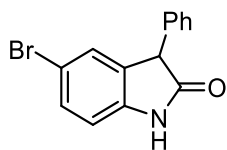
General procedure was followed using 5-chloro-3-phenylindolin-2-one (1.4 mmol, 340 mg, 1 equiv.). White solid, 69% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.89 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.21 – 7.15 (m, 2H), 7.14 (dd, *J* = 2.3, 1.2 Hz, 1H), 4.70 (s, 1H), 1.62 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.3 (C), 149.3 (C), 139.1 (C), 135.7 (C), 130.2 (C), 129.3 (C), 129.2 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 125.4 (CH), 116.5 (CH), 84.9 (C), 52.6 (CH), 28.2 (CH₃).

5-bromo-3-hydroxy-3-phenylindolin-2-one



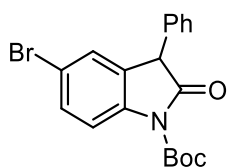
General procedure was followed using 5-bromoisatin (2.2 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 60% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.44 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.26 (d, *J* = 2.0 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H).

5-bromo-3-phenylindolin-2-one



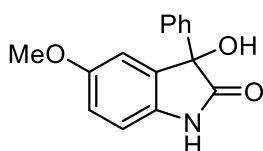
General procedure was followed using 5-bromo-3-hydroxy-3-phenylindolin-2-one (1.3 mmol, 304 mg, 1 equiv.) White solid, 92% yield. **¹H NMR** (300 MHz, CDCl₃) δ 9.03 (bs, 1H), 7.44 – 7.28 (m, 4H), 7.26 – 7.14 (m, 3H), 6.81 (d, *J* = 8.3 Hz, 1H), 4.63 (s, 1H).

tert-butyl 5-bromo-2-oxo-3-phenylindoline-1-carboxylate (3.1f)



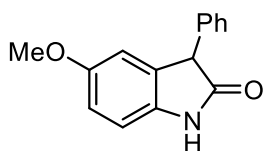
General procedure was followed using 5-bromo-3-phenylindolin-2-one (1.2 mmol, 350 mg, 1 equiv.). White solid, 52% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.84 (d, *J* = 8.7 Hz, 1H), 7.49 (ddd, *J* = 8.7, 2.2, 0.9 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.28 (dd, *J* = 2.1, 1.2 Hz, 1H), 7.21 – 7.10 (m, 2H), 4.71 (s, 1H), 1.62 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.2 (C), 149.3 (C), 139.7 (C), 135.7 (C), 131.8 (CH), 129.7 (C), 129.2 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 117.7 (C), 116.9 (CH), 85.0 (C), 52.5 (CH), 28.2 (CH₃).

3-hydroxy-5-methoxy-3-phenylindolin-2-one



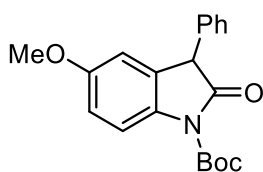
General procedure was followed using 5-methoxyisatin (2.8 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 60% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.55 – 7.47 (m, 2H), 7.44 – 7.31 (m, 3H), 6.99 (dd, *J* = 8.3, 0.6 Hz, 1H), 6.95 – 6.85 (m, 2H), 3.80 (s, 3H).

5-methoxy-3-phenylindolin-2-one



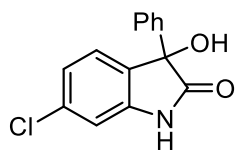
General procedure was followed using 3-hydroxy-5-methoxy-3-phenylindolin-2-one (1.9 mmol, 480 mg, 1 equiv.). Yellow solid, 54% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.32 (bs, 1H), 7.39 – 7.29 (m, 3H), 7.25 – 7.18 (m, 2H), 6.89 – 6.68 (m, 3H), 4.61 (s, 1H), 3.74 (s, 3H).

tert-butyl 5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (3.1g)



General procedure was followed using 5-methoxy-3-phenylindolin-2-one (1.0 mmol, 240 mg, 1 equiv.). Yellow solid, 67% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.85 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.24 – 7.16 (m, 2H), 6.89 (ddd, *J* = 9.0, 2.7, 0.8 Hz, 1H), 6.72 (dd, *J* = 2.6, 1.0 Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 1.62 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.1 (C), 157.1 (C), 149.6 (C), 136.4 (C), 134.0 (C), 129.1 (CH), 128.8 (CH), 128.8 (C), 128.0 (CH), 116.2 (CH), 113.8 (CH), 111.2 (CH), 84.3 (C), 55.8 (CH₃), 53.0 (CH), 28.2 (CH₃).

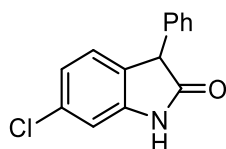
6-chloro-3-hydroxy-3-phenylindolin-2-one



6.97 (m, 2H).

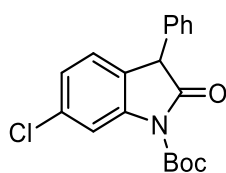
General procedure was followed using 6-chloroisatin (2.8 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 61% yield. **¹H NMR** (300 MHz, CD₃OD) δ 7.43 – 7.36 (m, 2H), 7.35 – 7.20 (m, 3H), 7.17 – 7.08 (m, 1H), 7.03 –

6-chloro-3-phenylindolin-2-one



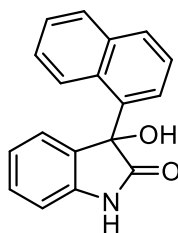
General procedure was followed using 6-chloro-3-hydroxy-3-phenylindolin-2-one (1.6 mmol, 440 mg, 1 equiv.). White solid, 73% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.58 (bs, 1H), 7.34 (dddt, J = 6.9, 5.1, 3.4, 1.7 Hz, 3H), 7.23 – 7.16 (m, 2H), 7.09 – 6.98 (m, 2H), 6.96 (d, J = 1.7 Hz, 1H), 4.60 (s, 1H).

tert-butyl 6-chloro-2-oxo-3-phenylindoline-1-carboxylate (3.1i)



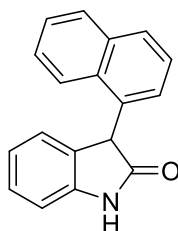
General procedure was followed using 6-chloro-3-phenylindolin-2-one (1.4 mmol, 330 mg, 1 equiv.). White solid, 77% yield. **¹H NMR** (300 MHz, CDCl₃) δ 8.02 (d, J = 1.9 Hz, 1H), 7.34 (dtd, J = 6.6, 5.2, 1.5 Hz, 3H), 7.17 (dt, J = 8.0, 2.0 Hz, 3H), 7.08 (dd, J = 8.0, 0.9 Hz, 1H), 4.69 (s, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.5 (C), 149.3 (C), 141.5 (C), 135.9 (C), 134.6 (C), 129.2 (CH), 128.7 (CH), 128.2 (CH), 126.0 (CH), 125.9 (C), 124.8 (CH), 116.0 (CH), 85.1 (C), 52.3 (CH), 28.2 (CH₃).

3-hydroxy-3-(naphthalen-1-yl)indolin-2-one



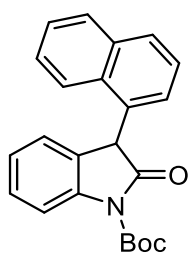
General procedure was followed using isatin (3.4 mmol, 500 mg, 1 equiv.). The required Grignard reagent was prepared *in situ* following a reported procedure.^[28] Orange solid, 93% yield. **¹H NMR** (300 MHz, CD₃OD) δ 8.11 (d, J = 7.3 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.66 (d, J = 7.7 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.37 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.33 – 7.18 (m, 2H), 7.07 (d, J = 7.8 Hz, 1H), 6.94 (dtd, J = 14.8, 7.4, 1.0 Hz, 2H).

3-(naphthalen-1-yl)indolin-2-one



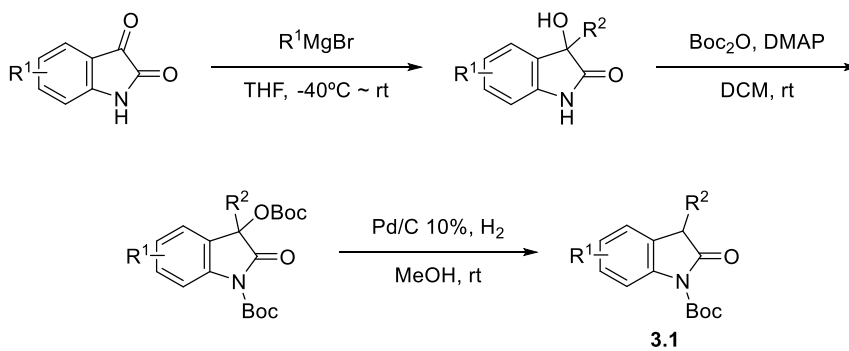
General procedure was followed using 3-hydroxy-3-(naphthalen-1-yl)indolin-2-one (3.1 mmol, 870 mg, 1 equiv.). White solid, 73% yield. Crude 3-hydroxy-3-(naphthalen-1-yl)indolin-2-one was used without purification.

tert-butyl 3-(naphthalen-1-yl)-2-oxindoline-1-carboxylate (3.1u)



General procedure was followed using 3-(naphthalen-1-yl)indolin-2-one (3.1 mmol, 800 mg, 1 equiv.). White solid, 59% yield, isolated as a mixture of rotamers. Signals for the major rotamer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.00 (d, $J = 8.2$ Hz, 1H), 7.90 (d, $J = 7.9$ Hz, 1H), 7.83 (d, $J = 8.3$ Hz, 1H), 7.77 – 7.32 (m, 5H), 7.21 – 6.95 (m, 3H), 5.62 (bs, 1H), 1.64 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 173.9 (C), 149.7 (C), 134.4 (C), 129.1 (C), 129.0 (CH), 128.7 (CH), 128.3 (C), 127.0 (C), 126.9 (CH), 126.1 (CH), 125.5 (CH), 124.8 (CH), 124.1 (C), 115.3 (CH), 84.6 (C), 48.2 (bs, CH), 28.2 (CH_3). Broad signals were observed for $^1\text{H NMR}$ and four $^{13}\text{C NMR}$ aromatic CH signals were not detected due to the presence of rotamers.

Procedure 1.c^[26]



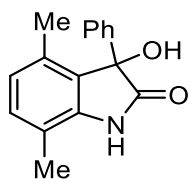
A septum-sealed flask equipped with a stirring bar was charged with the corresponding isatin (1.0 equiv.) under nitrogen atmosphere. Dry THF (15 mL) was added, and the resulting solution was cooled to -40°C . A solution of R^1MgBr (3 M in Et_2O , 2.0 equiv.) was then added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction was cooled to 0°C , diluted with Et_2O (25 mL) and quenched with HCl 1 M (15 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL), and the combined organic phases were washed with water, brine and dried over MgSO_4 . Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using DCM:EtOAc mixtures as eluent to yield the desired 3-substituted 3-hydroxyl-2-oxindole.

3-substituted 3-hydroxyl-2-oxindole intermediate (1.0 equiv.) and DMAP (10 mol%) were dissolved in DCM (20 mL) under nitrogen atmosphere. Boc_2O (2.0 equiv.) was added at room temperature, and the mixture was stirred overnight. The reaction mixture was then diluted with EtOAc (50 mL), quenched with saturated NH_4Cl (25 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed successively with water and brine, dried over MgSO_4 , and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to furnish the desired compound.

3-substituted oxindole (1.0 equiv.) was dissolved in MeOH (20 mL), and 10% Pd/C (10 mol%) was added. The suspension was stirred under hydrogen atmosphere (balloon) at room temperature overnight. After completion, the reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated *in vacuo*. The resulting residue was

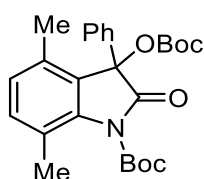
purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to yield the desired *N*-Boc protected 3-substituted oxindole.

3-hydroxy-4,7-dimethyl-3-phenylindolin-2-one



General procedure was followed using 4,7-dimethylisatin (2.9 mmol, 500 mg, 1 equiv.) and phenylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 46% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.25 (bs, 1H), 7.40 – 7.21 (m, 5H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 2.21 (s, 3H), 2.03 (s, 3H).

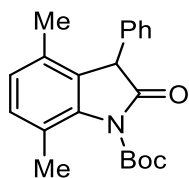
tert-butyl carboxylate



3-((*tert*-butoxycarbonyl)oxy)-4,7-dimethyl-2-oxo-3-phenylindoline-1-

General procedure was followed using 3-hydroxy-4,7-dimethyl-3-phenylindolin-2-one (1.5 mmol, 330 mg, 1 equiv.) White solid, 84% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.36 – 7.21 (m, 5H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 2.27 (s, 3H), 2.03 (s, 3H), 1.56 (s, 9H), 1.40 (s, 9H).

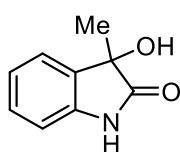
4,7-dimethyl-3-phenylindolin-2-one (3.1k)



General procedure was followed using *tert*-butyl 3-((*tert*-butoxycarbonyl)oxy)-4,7-dimethyl-2-oxo-3-phenylindoline-1-carboxylate (1.3 mmol, 450 mg, 1 equiv.). White solid, 51% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.35 – 7.26 (m, 3H), 7.16 – 7.11 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 4.61 (s, 1H), 2.26 (s, 3H), 1.92 (s, 3H), 1.59 (s, 9H).

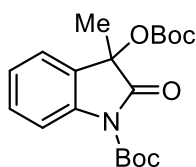
¹³C NMR (75 MHz, CDCl₃) δ 175.0 (C), 149.7 (C), 139.2 (C), 135.8 (C), 132.5 (C), 131.7 (CH), 129.1 (CH), 128.4 (CH), 127.9 (CH), 126.9 (C), 126.1 (CH), 120.7 (C), 84.9 (C), 52.5 (CH), 27.9 (CH₃), 19.4 (CH₃), 18.5 (CH₃).

3-hydroxy-3-methylindolin-2-one



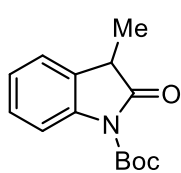
General procedure was followed using isatin (3.4 mmol, 500 mg, 1 equiv.) and methylmagnesium bromide (3M in Et₂O, 6.2 mmol, 2.1 mL, 2 equiv.). Orange solid, 81% yield. ¹H NMR (300 MHz, CD₃OD) δ 7.3 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 7.2 (td, *J* = 7.7, 1.3 Hz, 1H), 7.0 (td, *J* = 7.5, 1.0 Hz, 1H), 6.9 (dt, *J* = 7.8, 0.9 Hz, 1H), 1.5 (s, 3H).

tert-Butyl 3-((*tert*-butoxycarbonyl)oxy)-3-methyl-2-oxoindoline-1-carboxylate



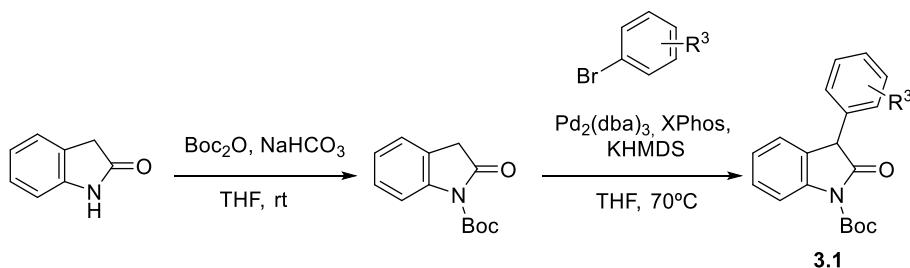
General procedure was followed using 3-hydroxy-3-methylindolin-2-one (2.8 mmol, 450 mg, 1 equiv.). Orange solid, 91% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.9 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.4 – 7.3 (m, 2H), 7.2 (td, *J* = 7.5, 1.0 Hz, 1H), 1.6 (s, 9H), 1.6 (s, 3H), 1.3 (s, 9H).

tert-butyl 2-oxo-3-methylindoline-1-carboxylate (3.1w)



General procedure was followed using tert-Butyl 3-((tert-butoxycarbonyl)oxy)-3-methyl-2-oxoindoline-1-carboxylate (2.6 mmol, 930 mg, 1 equiv.). White solid, 75% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.8 (ddt, $J = 8.2, 1.1, 0.6$ Hz, 1H), 7.3 – 7.3 (m, 1H), 7.3 – 7.2 (m, 1H), 7.2 (td, $J = 7.4, 1.1$ Hz, 1H), 3.6 – 3.5 (m, 1H), 1.6 (s, 9H), 1.5 (d, $J = 7.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 177.0 (C), 149.5 (C), 139.9 (C), 129.5 (C), 128.2 (CH), 124.5 (CH), 123.6 (CH), 115.1 (CH), 84.4 (C), 41.2 (CH), 28.2 (CH_3), 16.1 (CH_3).

Procedure 2^{[29],[30]}

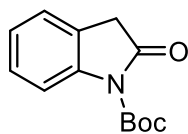


In a round bottom flask, 2-oxindole (37.5 mmol, 5.0 g, 1 equiv.) was dissolved in THF (280 mL). To this solution, Boc_2O (94 mmol, 20.5g, 2.5 equiv.) and NaHCO_3 (323 mmol, 28.2 g, 8.6 equiv.) were then added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered, and the solid was washed with THF. The filtrates were combined, concentrated under reduced pressure, and the crude residue was purified by silica gel column chromatography using hexane:EtOAc mixtures as eluent to furnish the corresponding *N*-Boc oxindole.

In a screw-cap tube, *N*-Boc oxindole (0.5 mmol, 117 mg, 1 equiv.), $\text{Pd}(\text{dba})_2$ (0.01 mmol, 6 mg, 2 mol%), and XPhos (0.14 mmol, 67 mg, 30 mol%) were introduced under nitrogen atmosphere. Anhydrous, degassed THF (0.8 mL) and aryl bromide (0.55 mmol, 1.1 equiv.) were added sequentially. The mixture was heated to 70 °C, after which KHMDS (0.5 M in toluene, 0.55 mmol, 1.1 mL, 1.1 equiv.) was added. After 30 minutes, the reaction was quenched with saturated NH_4Cl (2 mL), diluted with water (20 mL) and DCM (20 mL), and extracted with DCM (3 x 20 mL). The combined organic layers were washed with water and brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to provide the desired *N*-Boc-3-aryloxindole.

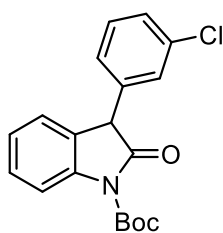
Regarding the synthesis of compounds **3.1s**, **3.1t**, and **3.1v**, the required aryl bromides were not commercially available and therefore had to be synthesised

tert-butyl 2-oxoindoline-1-carboxylate



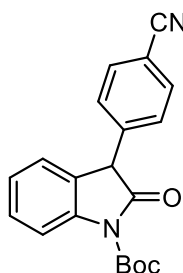
General procedure was followed using 2-oxindole (37.5 mmol, 5.0 g, 1 equiv.). White solid, 38% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.86 – 7.74 (m, 1H), 7.34 – 7.23 (m, 2H), 7.14 (td, $J = 7.5, 1.0$ Hz, 1H), 3.66 (s, 1H), 1.65 (s, 4H).

tert-butyl 3-(3-chlorophenyl)-2-oxoindoline-1-carboxylate (3.1m)



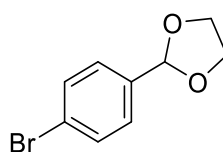
General procedure was followed using 1-bromo-3-chlorobenzene (0.55 mmol, 67 μ L, 1.1 equiv.). White solid, 45% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.94 (d, J = 8.2 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.24 (m, 2H), 7.22 – 7.08 (m, 4H), 4.70 (s, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.4 (C), 149.4 (C), 140.6 (C), 138.2 (C), 134.9 (C), 130.3 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 127.2 (CH), 126.7 (C), 125.2 (CH), 124.9 (CH), 115.4 (CH), 84.8 (C), 52.2 (CH), 28.2 (CH₃).

tert-butyl 3-(4-cyanophenyl)-2-oxoindoline-1-carboxylate (3.1p)



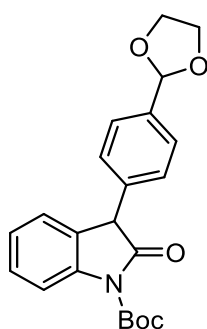
General procedure was followed using 4-bromobenzonitrile (0.55 mmol, 100 mg, 1.1 equiv.). Yellow solid, 50% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.95 (d, J = 8.3 Hz, 1H), 7.74 – 7.61 (m, 2H), 7.44 – 7.37 (m, 1H), 7.37 – 7.31 (m, 2H), 7.21 (td, J = 7.5, 0.9 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 4.79 (s, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.2 (C), 149.6 (C), 141.9 (C), 141.2 (C), 133.2 (CH), 130.1 (CH), 129.9 (CH), 126.4 (C), 125.6 (CH), 125.5 (CH), 119.0 (C), 116.0 (CH), 112.5 (C), 85.5 (C), 52.9 (CH), 28.6 (CH₃).

2-(4-bromophenyl)-1,3-dioxolane



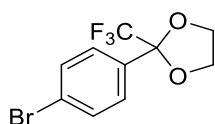
A literature procedure was carried out.^[31] A mixture of ethylene glycol (58 mmol, 3.6g, 2.0 equiv.), 4-bromobenzaldehyde (29 mmol, 5.3 g, 1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (0.9 mmol, 5.1 mg, 3 mol%) in dry toluene (40 mL) was refluxed in a round-bottom flask equipped with a Dean-Stark trap overnight. The reaction mixture was cooled down to room temperature, diluted with Et₂O (40 mL), quenched with saturated NaHCO₃ (40 mL) and extracted with Et₂O (3 x 40 mL). The combined organic layers were dried over MgSO₄ and solvents were removed *in vacuo*. The residue obtained was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford 2-(4-bromophenyl)-1,3-dioxolane as a white solid in 49% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.58 – 7.47 (m, 2H), 7.42 – 7.29 (m, 2H), 5.77 (s, 1H), 4.16 – 4.07 (m, 2H), 4.07 – 3.97 (m, 2H).

tert-butyl 3-(4-(1,3-dioxolan-2-yl)phenyl)-2-oxoindoline-1-carboxylate (3.1s)



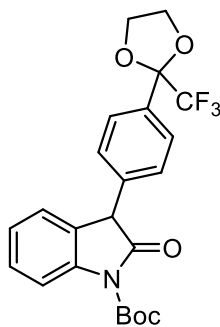
General procedure was followed using 2-(4-bromophenyl)-1,3-dioxolane (0.55 mmol, 130 mg, 1.1 equiv.). Yellow solid, 59% yield. **¹H NMR** (300 MHz, CDCl₃) δ 7.92 (dq, J = 8.1, 0.7 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.36 (dddd, J = 8.1, 7.1, 2.0, 0.9 Hz, 1H), 7.24 – 7.08 (m, 14), 5.81 (s, 1H), 4.74 (s, 1H), 4.13 – 4.06 (m, 2H), 4.06 – 3.98 (m, 2H), 1.62 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 173.8 (C), 149.5 (C), 140.6 (C), 137.9 (C), 137.3 (C), 129.2 (CH), 128.8 (CH), 127.4 (C), 127.1 (CH), 125.2 (CH), 124.8 (CH), 115.3 (CH), 103.5 (CH), 84.6 (C), 65.4 (CH₂), 52.5 (CH), 28.2 (CH₃).

2-(4-bromophenyl)-2-(trifluoromethyl)-1,3-dioxolane



A literature procedure was carried out.^[32] A solution of 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (2.0 mmol, 500 mg, 1.0 equiv.) and 2-chloroethanol (14.8 mmol, 0.99 mL, 7.5 equiv.) in a mixture of DMF/THF (6 mL, v/v, 2:1) under argon atmosphere was cooled to -60 °C. To this mixture, a solution of *t*-BuOK (14.8 mmol, 1.7 g, 7.5 equiv.) in DMF (3 mL) was added dropwise for 30 minutes and then stirred for 1.5 h. The reaction was quenched with saturated NH₄Cl (50 mL), rinsed with brine (30 mL) and water (30 mL), and then extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with water (70 mL) four times to remove the remaining DMF, dried over MgSO₄ and solvents were removed *in vacuo* to afford the 2-(4-bromophenyl)-2-(trifluoromethyl)-1,3-dioxolane as a white solid, which was used without any further purification.

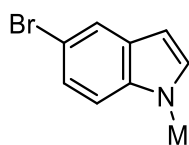
tert-butyl carboxylate (3.1t)



2-oxo-3-(4-(2-(trifluoromethyl)-1,3-dioxolan-2-yl)phenyl)indoline-1-

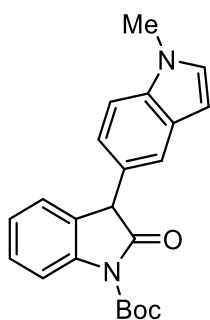
General procedure was followed using 2-(4-bromophenyl)-2-(trifluoromethyl)-1,3-dioxolane (0.55 mmol, 163 mg, 1.1 equiv.). White solid, 37% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.42 – 7.34 (m, 1H), 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 2H), 4.75 (s, 1H), 4.32 – 4.23 (m, 2H), 4.09 – 4.00 (m, 2H), 1.63 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 173.7 (C), 144.9 (C), 140.7 (C), 137.9 (C), 134.5 (C), 129.0 (CH), 128.5 (CH), 127.7 (CH), 127.1 (C), 125.3 (CH), 124.8 (CH), 115.4 (CH), 84.7 (C), 66.9 (CH₂), 52.4 (CH), 28.2 (CH₃). CF₃ and ketal quadruplet signals were not detected due to both low signal intensity and its coupling with fluorine nuclei. ¹⁹F NMR (282 MHz, CDCl₃) δ -82.1.

5-bromo-1-methyl-1*H*-indole



A literature procedure was carried out.^[33] In a round bottom flask, 5-bromoindole (8 mmol, 1.6 g, 1.0 equiv.) was dissolved in dry THF (20 mL) under nitrogen atmosphere. To this solution, NaH (60% suspension in mineral oil, 9.6 mmol, 384 mg, 1.2 equiv.) was added at 0 °C. The mixture was stirred for 15 minutes and then a solution of iodomethane (8 mmol, 1.14g, 1.0 equiv.) in THF (5 mL) was added at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH₄Cl (10 mL), extracted three times with EtOAc (3 x 20mL) and the combined organic layers were dried over MgSO₄. Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired product as a white solid in 92% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.75 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.30 (ddd, *J* = 8.7, 1.9, 0.4 Hz, 1H), 7.19 (dt, *J* = 8.7, 0.7 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.42 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.78 (s, 3H).

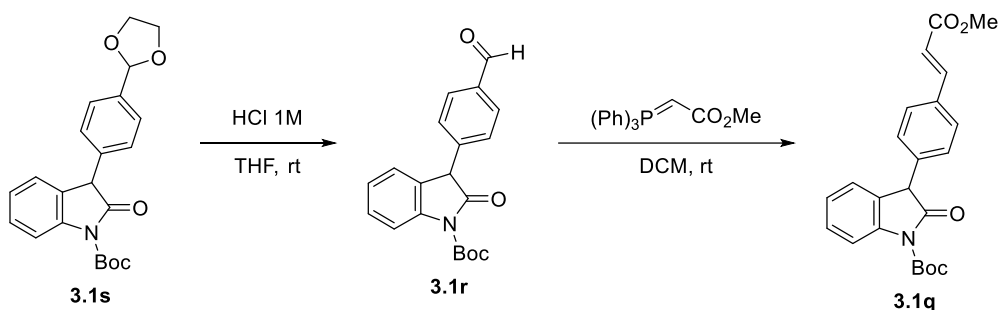
tert-butyl 3-(1-methyl-1*H*-indol-5-yl)-2-oxoindoline-1-carboxylate (3.1v)



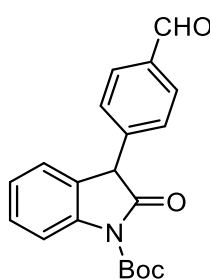
General procedure was followed using 5-bromo-1-methyl-1*H*-indole (0.55 mmol, 115 mg, 1.1 equiv.). Brown solid, 78 % yield. **¹H NMR** (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.41 (s, 1H), 7.39 – 7.33 (m, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.13 (m, 2H), 7.04 (dt, *J* = 5.8, 2.0 Hz, 2H), 6.42 (d, *J* = 3.1 Hz, 1H), 4.81 (s, 1H), 3.77 (s, 3H), 1.63 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) δ 174.8 (C), 149.7 (C), 140.6 (C), 136.5 (C), 129.6 (CH), 128.9 (C), 128.7 (C), 128.5 (CH), 127.4 (C), 125.3 (CH), 124.7 (CH), 122.3 (CH), 121.1 (CH), 115.1 (CH), 109.9 (CH), 101.2 (CH), 84.3 (C), 52.9 (CH), 33.0 (CH₃), 28.2 (CH₃).

Synthesis of carbonyl-containing 3-aryloxindoles 3.1r and 3.1q

Substrates **3.1r** and **3.1q** were prepared following modified reported procedures. ^{[34],[35]}



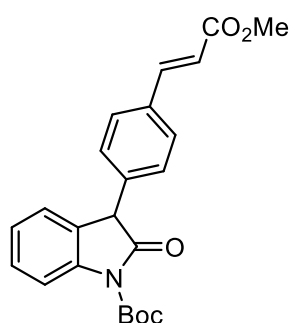
tert-butyl 3-(4-formylphenyl)-2-oxoindoline-1-carboxylate (3.1r)



A solution of compound **3.1s** (4.6 mmol, 1.8 g, 1.0 equiv.) in THF (70 mL) was treated with HCl 1 M (70 mL) and stirred at room temperature for 4 h. The reaction mixture was then diluted with DCM (150 mL), neutralized with saturated NaHCO₃ (100 mL), and extracted three times with DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford product compound

3.1r as a yellow solid in 70% yield. **¹H NMR** (300 MHz, CDCl₃) δ 10.01 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.45 – 7.34 (m, 3H), 7.23 – 7.10 (m, 2H), 4.82 (s, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 191.8, 173.1 (C), 149.3 (C), 143.0 (C), 140.7 (C), 136.1 (C), 130.4 (CH), 129.6 (CH), 129.3 (CH), 126.5 (C), 125.2 (CH), 125.0 (CH), 115.5 (CH), 84.9 (C), 52.7 (CH), 28.2 (CH₃).

**tert-butyl
carboxylate (3.1q)**

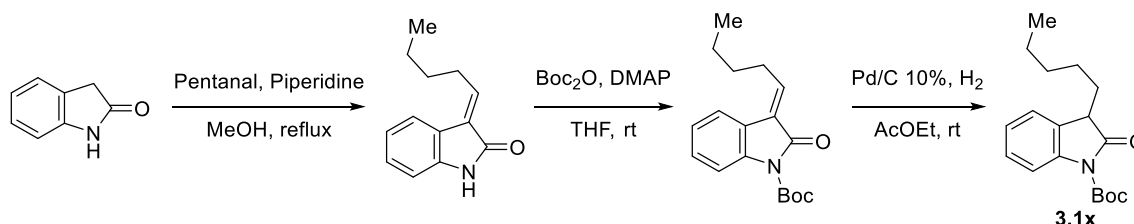


Compound **3.1r** (0.89 mmol, 300 mg, 1.0 equiv.) was dissolved in DCM (5 mL), and methyl 2-(triphenylphosphoranylidene)acetate (1.3 mmol, 435 mg, 2.2 equiv.) was added in a single portion. The resulting mixture was stirred overnight at room temperature. The reaction was diluted with DCM (50 mL) and quenched with saturated NH_4Cl (25 mL). The aqueous phase was extracted three times with DCM (3 x 50 mL), and the combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*.

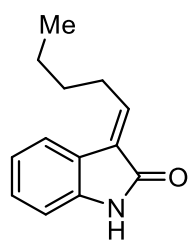
The crude residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford compound **3.1q** as a yellow oil in 45% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.93 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 16.1 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.38 (tdd, J = 7.0, 2.4, 0.9 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.20 – 7.12 (m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 4.75 (s, 1H), 3.80 (s, 3H), 1.63 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 173.6 (C), 167.5 (C), 149.1 (C), 144.3 (CH), 140.1 (C), 138.6 (C), 134.2 (C), 129.4 (CH), 129.0 (CH), 128.7 (CH), 126.7 (C), 125.2 (CH), 124.9 (CH), 118.3 (CH), 115.4

Synthesis of aliphatic 3-substituted oxindoles 3.1x, 3.1y and 3.1z

Substrates **3.1x**, **3.1y** and **3.1z** were prepared following modified reported procedures.^{[36],[37]}

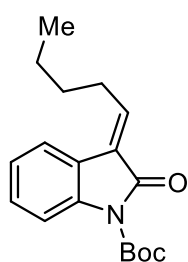


3-pentyldeneindolin-2-one



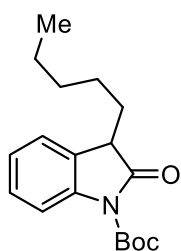
In a dry round bottom flask, 2-oxindole (7.5 mmol, 1.0g, 1.0 equiv.) and pentanal (7.5 mmol, 0.8 mL, 1.0 equiv.) were dissolved in MeOH (40 mL). Piperidine (7.5 mmol, 0.74 mL, 1.0 equiv.) was added, and the mixture was heated to reflux overnight. Solvents were removed *in vacuo* and the resulting residue was purified by silica gel column chromatography using DCM/EtOAc mixtures as eluent to afford the desired compound as a yellow solid in 40% yield as a 2.3:1 mixture of diastereomers. Major diastereomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.16 (bs, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.88 (dt, J = 7.8, 0.9 Hz, 1H), 2.69 (q, J = 7.5 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.53 – 1.40 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). Minor diastereomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.93 (bs, 1H), 7.38 (dt, J = 7.5, 0.7 Hz, 1H), 7.19 (td, J = 7.7, 1.2 Hz, 1H), 6.99 (td, J = 7.6, 1.0 Hz, 1H), 6.89 (td, J = 7.9, 0.7 Hz, 1H), 6.83 (dt, J = 7.8, 0.8 Hz, 1H), 3.01 (q, J = 7.6 Hz, 2H), 1.67 – 1.49 (m, 2H), 1.48 – 1.36 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

tert-butyl 2-oxo-3-pentylideneindoline-1-carboxylate

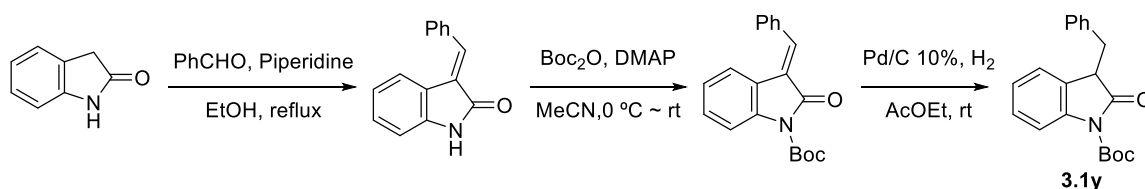


3-pentylideneindolin-2-one (3.0 mmol, 600 mg, 1.0 equiv.) and DMAP (0.15 mmol, 18 mg, 5 mol%) were charged in a round bottom flask and dissolved in dry THF (15 mL) under nitrogen atmosphere. Boc_2O was added (3.3 mmol, 720 mg, 1.1 equiv.) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (50 mL), washed with saturated NH_4Cl (25 mL) and extracted with DCM (3 x 50 mL). The combined organic layers were washed with water, brine, dried over MgSO_4 and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatograph using hexane/EtOAc mixtures as eluent to afford the desired compound as a yellow oil in 45% as 2.3:1 mixture of diastereomers. Major diastereomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.91 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.60 (dt, $J = 7.5, 0.9$ Hz, 1H), 7.37 – 7.24 (m, 1H), 7.16 (td, $J = 7.6, 1.1$ Hz, 1H), 7.13 – 7.05 (m, 1H), 2.68 (q, $J = 7.5$ Hz, 2H), 1.65 (s, 9H), 1.62 – 1.52 (m, 2H), 1.52 – 1.38 (m, 2H), 1.02 – 0.83 (m, 3H). Minor diastereomer: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.83 (dd, $J = 8.2, 0.9$ Hz, 1H), 7.42 (dd, $J = 7.5, 1.4$ Hz, 1H), 7.32 – 7.24 (m, 1H), 7.14 (dd, $J = 3.0, 1.0$ Hz, 1H), 6.92 (t, $J = 7.8$ Hz, 1H), 3.00 (q, $J = 7.5$ Hz, 1H), 1.66 (s, 9H), 1.64 – 1.49 (m, 2H), 1.54 – 1.36 (m, 2H), 0.95 (td, $J = 7.2, 3.6$ Hz, 3H).

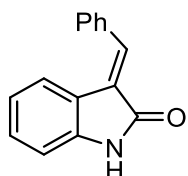
tert-butyl 2-oxo-3-pentylindoline-1-carboxylate (3.1x)



tert-butyl 2-oxo-3-pentylideneindoline-1-carboxylate (1.4 mmol, 410 mg, 1 equiv.) was dissolved in EtOAc (10 mL) and 10% Pd/C (0.04 mmol, 45 mg, 3 mol%) was added. The resulting suspension was stirred under hydrogen atmosphere (balloon) overnight at room temperature. The reaction mixture was filtered through Celite®, concentrated *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/Et₂O mixtures as eluent to afford the desired product as a colourless oil in 73% yield. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.8 (ddt, $J = 8.2, 1.1, 0.5$ Hz, 1H), 7.4 – 7.3 (m, 1H), 7.3 – 7.2 (m, 1H), 7.1 (td, $J = 7.4, 1.1$ Hz, 1H), 3.5 (t, $J = 5.9$ Hz, 1H), 2.0 (td, $J = 7.9, 5.9$ Hz, 2H), 1.6 (s, 9H), 1.4 – 1.2 (m, 6H), 1.0 – 0.7 (m, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 176.5 (C), 149.5 (C), 140.3 (C), 128.3 (C), 128.1 (CH), 124.3 (CH), 123.8 (CH), 115.0 (CH), 84.3 (C), 46.2 (CH), 31.9 (CH₂), 31.4 (CH₂), 28.3 (CH₃), 25.5 (CH₂), 22.5 (CH₂), 14.1 (CH₃).



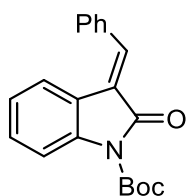
3-benzylideneindolin-2-one



In a dry round bottom flask, 2-oxindole (3.8 mmol, 0.5g, 1.0 equiv.) was dissolved in EtOH (5 mL). To this solution, benzaldehyde (4.5 mmol, 0.46 mL, 1.1 equiv.) and piperidine (7.5 mmol, 0.75 mL, 2.0 equiv.) were sequentially added, and the mixture was heated to reflux for 2.5 h. After

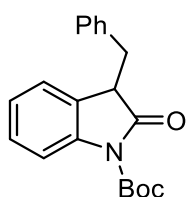
cooling to 0 °C, the precipitate formed is filtered and washed with cold EtOH. The crude was obtained as a yellow solid in 32% yield, which was used without any further purification. ¹H NMR (300 MHz, CDCl₃) δ 8.72 (bs, 1H), 7.85 (s, 1H), 7.72 – 7.60 (m, 3H), 7.54 – 7.39 (m, 3H), 7.22 (td, *J* = 7.7, 1.0 Hz, 1H), 7.00 – 6.74 (m, 2H).

tert-butyl 3-benzylidene-2-oxoindoline-1-carboxylate

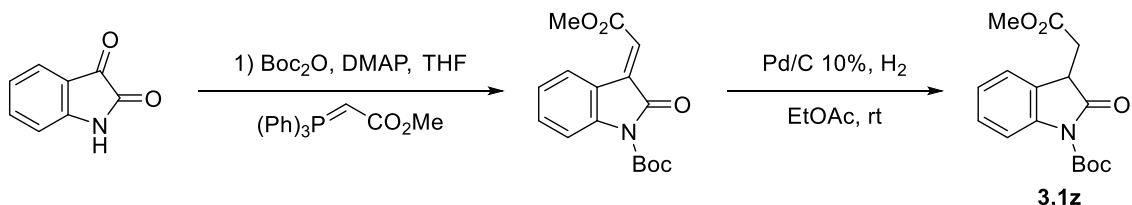


3-benzylideneindolin-2-one (1.1 mmol, 240 mg, 1.0 equiv.) was dissolved in MeCN (7 mL) and cooled to 0°C. To this solution, DMAP (0.11 mmol, 13 mg, 10 mol%) and Boc₂O (1.2 mmol, 260 mg, 1.1 equiv.) were added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was then cooled to 0°C and quenched with saturated NH₄Cl (50 mL) and extracted three times with EtOAc (3 x 50 mL). The combined organic layers were washed with HCl 0.5 M (50 mL) and saturated NaHCO₃ (50 mL), dried over MgSO₄ and concentrated under vacuum. The crude product was obtained as a yellow solid in 99% yield, which was used without any further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 7.71 – 7.58 (m, 3H), 7.51 – 7.41 (m, 3H), 7.36 – 7.27 (m, 1H), 6.98 (td, *J* = 7.7, 1.0 Hz, 1H), 1.67 (s, 9H).

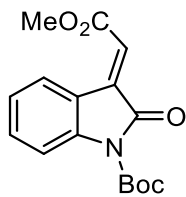
tert-butyl 3-benzyl-2-oxoindoline-1-carboxylate (3.1y)



tert-butyl 3-benzylidene-2-oxoindoline-1-carboxylate (1.0 mmol, 314 mg, 1 equiv.) was dissolved in EtOAc (10 mL) and 10% Pd/C (0.15 mmol, 167 mg, 15 mol%) was added. The resulting suspension was stirred under hydrogen atmosphere (balloon) overnight at room temperature. The reaction mixture was filtered through Celite®, concentrated *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired product as a yellow solid in an 85% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, *J* = 8.2 Hz, 1H), 7.30 – 7.20 (m, 4H), 7.18 – 7.12 (m, 2H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 3.82 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.51 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.95 (dd, *J* = 13.7, 9.1 Hz, 1H), 1.63 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 175.6 (C), 149.3 (C), 140.1 (C), 137.5 (C), 129.6 (CH), 128.6 (CH), 128.3 (CH), 127.3 (C), 127.0 (CH), 124.5 (CH), 124.0 (CH), 115.0 (CH), 84.4 (C), 47.7 (CH), 37.8 (CH₂), 28.2 (CH₃).



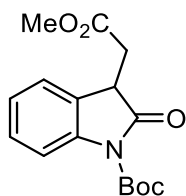
tert-butyl 3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate



Isatin (3.40 mmol, 500 mg, 1.0 equiv.) and DMAP (0.34 mmol, 42 mg, 10 mol%) were dissolved in dry THF (5 mL) under nitrogen atmosphere, and the solution was cooled to 0 °C. To this mixture, Boc₂O (4.1 mmol, 890 mg, 1.2 equiv.) in dry THF (3 mL) was added dropwise and the reaction was stirred for 2h. In another flask, methyl (triphenylphosphoranylidene) acetate (3.4 mmol, 1.1 g, 1.0 equiv.) was dissolved in THF (12 mL) under nitrogen

atmosphere at 0° C. The previously prepared *N*-Boc protected isatin solution was added dropwise and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water (50 mL), extracted with EtOAc (3 x 30 mL), and the combined organic layers were dried over MgSO₂. Solvents were removed *in vacuo* and the resulting residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired product as a yellow solid in 71% yield. ¹H NMR (300 MHz, CDCl₃) δ 8.72 – 8.62 (m, 1H), 7.91 (ddd, *J* = 8.3, 1.1, 0.6 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.5, 1.4 Hz, 1H), 7.19 (td, *J* = 7.7, 1.1 Hz, 1H), 6.91 (s, 1H), 3.87 (s, 3H), 1.65 (s, 9H).

***tert*-butyl 3-(2-methoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (3.1z)**



tert-butyl 3-(2-methoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (2.3 mmol, 740 mg, 1equiv.) was dissolved in EtOAc (30 mL) and 10% Pd/C (0.36 mmol, 400 mg, 15 mol%) was added. The resulting suspension was stirred under hydrogen atmosphere (balloon) overnight at room temperature. The reaction mixture was filtered through Celite®, concentrated *in vacuo* and purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the desired product as a colourless oil in 33% yield. ¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.35 – 7.26 (m, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H), 4.02 – 3.80 (m, 1H), 3.66 (s, 3H), 3.08 (dd, *J* = 17.1, 4.5 Hz, 1H), 2.89 (dd, *J* = 17.1, 7.4 Hz, 1H), 1.63 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 175.2

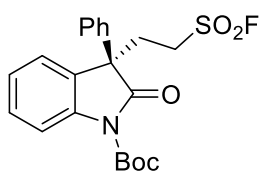
Synthesis and characterization data for chiral sulfonyl fluorides 3.2

General procedure for the enantioselective synthesis of products 2a-2z

In a screw cap tube, 3-substituted oxindole **3.1** (0.1 mmol, 1.0 equiv.) and (DHQD)₂AQN (0.01 mmol, 8.6 mg, 0.1 equiv.) were dissolved in anhydrous THF (1 mL). The resulting solution was cooled at -78 °C under nitrogen atmosphere. To this solution, ESF (0.1 mmol, 8.3 μL, 1.0 equiv.) was added and the resulting mixture was stirred at -78 °C until the reaction was complete (TLC). Solvents were removed *in vacuo* and the crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford compound **3.2**.

Racemic products **3.2** were obtained following the same procedure employing triethylamine (0.1 mmol, 13.9 μL, 1.0 equiv.) instead of (DHQD)₂AQN at room temperature.

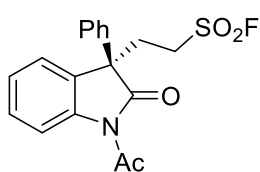
***tert*-butyl (*R*)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.2a)**



General procedure was followed using **3.1a** (0.1 mmol, 30.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2a** as a white solid (39.8 mg, 95% yield). Compound (*R*)-**3.2a** was obtained with a 97% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: τ_{major} = 6.8 min, τ_{minor} = 5.8 min. [α]_D²⁵ = 26.1 (c = 0.63, CHCl₃, 97% ee). ¹H NMR (300 MHz, CDCl₃) δ 7.97 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.2, 6.3, 2.7 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.30 – 7.26 (m, 2H), 3.38 – 3.14 (m, 2H), 3.07 (ddd, *J* =

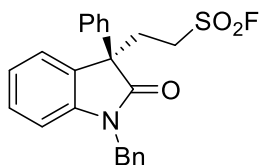
13.4, 12.0, 4.7 Hz, 1H), 2.71 (ddd, J = 13.3, 12.4, 3.7 Hz, 1H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.4 (C), 148.9 (C), 139.7 (C), 137.6 (C), 129.8 (CH), 129.3 (CH), 128.7 (C), 128.6 (CH), 126.8 (CH), 125.4 (CH), 124.5 (CH), 116.0 (CH), 85.4 (C), 55.1 (C), 47.00 (d, J = 18.1 Hz, CH_2), 31.5 (CH_2), 28.2 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.8. HRMS (ESI-TOF) calc'd for $[\text{C}_{21}\text{H}_{22}\text{FNO}_5\text{S}+\text{Na}]^+$: 442,1095; found: 442,1086.

(R)-2-(1-acetyl-2-oxo-3-phenylindolin-3-yl)ethane-1-sulfonyl fluoride (3.2b)



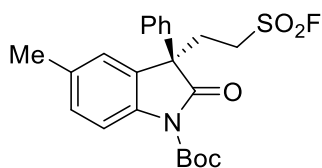
General procedure was followed using **3.1b** (0.1 mmol, 25.1 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2b** as a white solid (14.7 mg, 41% yield). Compound (*R*)-**3.2b** was obtained with a 31% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: τ_{major} = 12.0 min, τ_{minor} = 8.3 min. $[\alpha]_D^{25}$ = 10.6 (c = 0.24, CHCl_3 , 31% ee). ^1H NMR (300 MHz, CDCl_3) δ 8.39 – 8.31 (m, 1H), 7.46 (ddd, J = 8.2, 7.4, 1.6 Hz, 1H), 7.42 – 7.20 (m, 7H), 3.44 – 2.96 (m, 3H), 2.76 (ddd, J = 13.2, 11.7, 3.7 Hz, 1H), 2.66 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 177.9 (C), 170.8 (C), 140.1 (C), 137.4 (C), 130.0 (CH), 129.5 (CH), 128.8 (CH), 128.8 (C), 126.7 (CH), 126.2 (CH), 124.4 (CH), 117.6 (CH), 55.3 (C), 47.0 (d, J = 18.4 Hz, CH_2), 31.3 (CH_2), 26.8 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.9. HRMS (ESI-TOF) calc'd for $[\text{C}_{18}\text{H}_{16}\text{FNO}_4\text{S}+\text{H}]^+$: 362.0857; found: 362.0857.

(R)-2-(1-benzyl-2-oxo-3-phenylindolin-3-yl)ethane-1-sulfonyl fluoride (3.2c)



General procedure was followed using **3.1c** (0.1 mmol, 29.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2c** as a yellow oil (14.3 mg, 33% yield). Compound (*R*)-**3.2c** was obtained with a 22% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: τ_{major} = 12.2 min, τ_{minor} = 11.3 min. $[\alpha]_D^{25}$ = -12.6 (c = 0.25, CHCl_3 , 22% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.41 – 7.16 (m, 12H), 7.09 (td, J = 7.6, 1.1 Hz, 1H), 6.84 (dd, J = 8.2, 1.1 Hz, 1H), 4.98 (d, J = 15.5 Hz, 1H), 4.86 (d, J = 15.5 Hz, 1H), 3.38 – 3.12 (m, 2H), 3.01 (ddd, J = 13.5, 12.0, 5.0 Hz, 1H), 2.68 (ddd, J = 13.5, 11.8, 4.7 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 177.1 (C), 142.5 (C), 137.7 (C), 135.6 (C), 130.5 (C), 129.3 (CH), 129.3 (CH), 129.1 (CH), 128.3 (CH), 128.1 (CH), 127.4 (CH), 126.7 (CH), 124.6 (CH), 123.6 (CH), 110.2 (CH), 54.6 (C), 46.8 (d, J = 18.0 Hz, CH_2), 44.2 (CH_2), 31.1 (CH_2). ^{19}F NMR (282 MHz, CDCl_3) δ 52.6. HRMS (ESI-TOF) calc'd for $[\text{C}_{23}\text{H}_{20}\text{FNO}_3\text{F}+\text{H}]^+$: 410.1221; found: 410.1229.

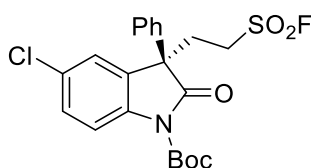
tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-5-methyl-2-oxo-3-phenylindoline-1-carboxylate (3.2d)



General procedure was followed using **3.1d** (0.1 mmol, 32.3 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2d** as a colourless oil (41.4 mg, 96% yield). Compound (*R*)-**3.2d** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: τ_{major} = 7.9 min, τ_{minor} = 6.6 min.

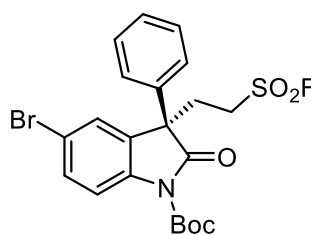
$[\alpha]_D^{25} = 34.2$ ($c = 0.77$, CHCl_3 , 98% ee). **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 7.83 (d, $J = 8.4$ Hz, 1H), 7.41 – 7.28 (m, 5H), 7.22 (ddd, $J = 8.5, 1.9, 0.8$ Hz, 1H), 7.06 (dd, $J = 1.7, 1.0$ Hz, 1H), 3.44 – 3.14 (m, 2H), 3.06 (ddd, $J = 13.3, 11.8, 5.0$ Hz, 1H), 2.69 (ddd, $J = 13.4, 12.3, 4.1$ Hz, 1H), 2.40 (s, 3H), 1.64 (s, 9H). **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 175.5 (C), 149.0 (C), 137.8 (C), 137.3 (C), 135.3 (C), 130.3 (CH), 129.3 (CH), 128.7 (C), 128.5 (CH), 126.8 (CH), 124.9 (CH), 115.7 (CH), 85.2 (C), 55.2 (C), 47.0 (d, $J = 18.1$ Hz, CH_2), 31.4 (CH_2), 28.2 (CH_3), 21.3 (CH_3). **$^{19}\text{F NMR}$** (282 MHz, CDCl_3) δ 52.8. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_5\text{S}+\text{NH}_4]^+$: 451.1697; found: 451.1695.

tert-butyl (R)-5-chloro-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.2e)



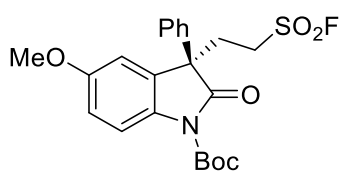
General procedure was followed using **3.1e** (0.1 mmol, 34.4 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2e** as a white solid (41.7 mg, 92% yield). Compound (*R*)-**3.2e** was obtained with a 97% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 11.3$ min, $\tau_{\text{minor}} = 5.98$ min. $[\alpha]_D^{25} = 39.0$ ($c = 0.70$, CHCl_3 , 95% ee); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 7.93 (d, $J = 8.8$ Hz, 1H), 7.43 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.24 (d, $J = 2.2$ Hz, 1H), 3.37 – 3.21 (m, 2H), 3.05 (ddd, $J = 13.7, 9.7, 7.2$ Hz, 1H), 2.68 (ddd, $J = 13.7, 9.6, 7.1$ Hz, 1H), 1.64 (s, 9H). **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 174.7 (C), 148.7 (C), 138.1 (C), 136.8 (C), 130.9 (C), 130.8 (C), 129.8 (CH), 129.6 (CH), 128.8 (CH), 126.6 (CH), 124.6 (CH), 117.2 (CH), 85.8 (C), 55.1 (C), 46.8 (d, $J = 18.3$ Hz, CH_2), 31.2 (CH_2), 28.2 (CH_3). **$^{19}\text{F NMR}$** (282 MHz, CDCl_3) δ 52.9. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{21}\text{ClFNO}_5\text{S}+\text{H}]^+$: 453.0886; found: 453.0875.

tert-butyl (R)-5-bromo-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.2f)



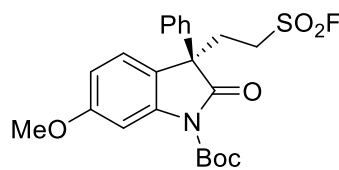
General procedure was followed using **3.1f** (0.1 mmol, 38.8 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2f** as a colourless oil (44.2 mg, 89% yield). Compound (*R*)-**3.2f** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 13.2$ min, $\tau_{\text{minor}} = 6.0$ min. $[\alpha]_D^{25} = 41.5$ ($c = 0.74$, CHCl_3 , 98% ee); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 7.87 (d, $J = 8.8$ Hz, 1H), 7.55 (dd, $J = 8.7, 2.1$ Hz, 1H), 7.45 – 7.17 (m, 6H), 3.45 – 3.21 (m, 2H), 3.14 – 2.88 (m, 1H), 2.68 (ddd, $J = 13.7, 9.5, 7.1$ Hz, 1H), 1.64 (s, 9H). **$^{13}\text{C NMR}$** (75 MHz, CDCl_3) δ 174.6 (C), 148.7 (C), 138.6 (C), 136.8 (C), 132.7 (CH), 131.2 (C), 129.6 (CH), 128.8 (CH), 127.4 (CH), 126.6 (CH), 118.4 (C), 117.6 (CH), 85.8 (C), 55.1 (C), 46.8 (d, $J = 18.3$ Hz, CH_2), 31.2 (CH_2), 28.2 (CH_3). **$^{19}\text{F NMR}$** (282 MHz, CDCl_3) δ 52.9. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{21}\text{BrFNO}_5\text{S}+\text{NH}_4]^+$: 515.0648; found: 515.0648.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-5-methoxy-2-oxo-3-phenylindoline-1-carboxylate (3.2g)



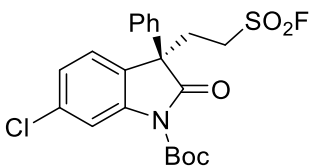
General procedure was followed using **3.1g** (0.1 mmol, 33.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2g** as a yellow oil (45.0 mg, 99% yield). Compound (R)-**3.2g** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 8.2$ min, $\tau_{\text{minor}} = 7.5$ min. $[\alpha]_D^{25} = -3.2$ ($c = 0.75$, CHCl_3 , 98% ee). **¹H NMR** (300 MHz, CDCl_3) δ 7.89 (d, $J = 9.0$ Hz, 1H), 7.43 – 7.25 (m, 5H), 6.94 (dd, $J = 9.0$, 2.7 Hz, 1H), 6.79 (d, $J = 2.6$ Hz, 1H), 3.82 (s, 3H), 3.48 – 3.14 (m, 2H), 3.08 (ddd, $J = 13.4$, 12.0, 4.6 Hz, 1H), 2.68 (td, $J = 12.8$, 3.6 Hz, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl_3) δ 175.4 (C), 157.5 (C), 149.0 (C), 137.6 (C), 132.9 (C), 130.0 (C), 129.3 (CH), 128.6 (CH), 126.8 (CH), 117.0 (CH), 114.2 (CH), 110.8 (CH), 85.2 (C), 55.9 (CH₃), 55.4 (C), 47.0 (d, $J = 18.1$ Hz, CH₂), 31.3 (CH₂), 28.2 (CH₃). **¹⁹F NMR** (282 MHz, CDCl_3) δ 52.8. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_6\text{S} + \text{NH}_4]^+$: 467.1647; found: 467.1641.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-6-methoxy-2-oxo-3-phenylindoline-1-carboxylate (3.2h)



General procedure was followed using **3.1h** (0.1 mmol, 33.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2h** as a white solid (40.7 mg, 91% yield). Compound (R)-**3.2h** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 19.4$ min, $\tau_{\text{minor}} = 7.7$ min. Colourless Oil; $[\alpha]_D^{25} = 7.5$ ($c = 0.67$, CHCl_3 , 98% ee); **¹H NMR** (300 MHz, CDCl_3) δ 7.60 (d, $J = 2.4$ Hz, 1H), 7.41 – 7.29 (m, 5H), 7.16 (d, $J = 8.4$ Hz, 1H), 6.82 (dd, $J = 8.4$, 2.4 Hz, 1H), 3.87 (s, 3H), 3.37 – 3.10 (m, 2H), 3.04 (ddd, $J = 13.4$, 12.0, 4.8 Hz, 1H), 2.79 – 2.58 (m, 1H), 1.64 (s, 9H). **¹³C NMR** (75 MHz, CDCl_3) δ 175.8 (C), 160.8 (C), 148.9 (C), 140.8 (C), 138.0 (C), 129.3 (CH), 128.5 (CH), 126.8 (CH), 125.2 (CH), 120.0 (C), 111.0 (CH), 102.6 (CH), 85.3 (C), 55.8 (CH₃), 54.7 (C), 47.1 (d, $J = 18.0$ Hz, CH₂), 31.7 (CH₂), 28.2 (CH₃). **¹⁹F NMR** (282 MHz, CDCl_3) δ 52.8. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_6\text{S} + \text{NH}_4]^+$: 467.1647; found: 467.1645.

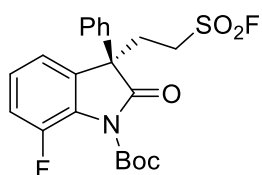
tert-butyl (R)-6-chloro-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.2i)



General procedure was followed using **3.1i** (0.1 mmol, 34.4 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2i** as a white solid (41.0 mg, 90% yield). Compound (R)-**3.2i** was obtained with a 95% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 13.60$ min, $\tau_{\text{minor}} = 6.0$ min. $[\alpha]_D^{25} = 18.3$ ($c = 0.68$, CHCl_3 , 95% ee). **¹H NMR** (300 MHz, CDCl_3) δ 7.96 (d, $J = 1.9$ Hz, 1H), 7.37 – 7.15 (m, 6H), 7.11 (d, $J = 8.1$ Hz, 1H), 3.30 – 3.03 (m, 2H), 2.95 (ddd, $J = 13.6$, 11.5, 5.3 Hz, 1H), 2.59 (ddd, $J = 13.6$, 12.0, 4.4 Hz, 1H), 1.55 (s, 9H). **¹³C NMR** (75 MHz, CDCl_3) δ 174.9 (C), 148.7 (C), 140.6 (C), 137.0 (C), 135.6 (C), 129.5 (CH), 128.8 (CH), 127.1 (C), 126.7 (CH),

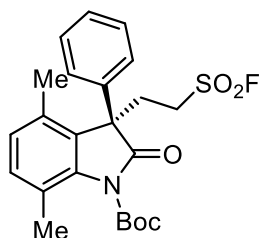
125.5 (CH), 125.4 (CH), 116.8 (CH), 85.9 (C), 54.9 (C), 46.9 (d, $J = 18.5$ Hz, CH₂), 31.3 (CH₂), 28.1 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.9. **HRMS (ESI-TOF)** calc'd for [C₂₁H₂₁ClFNO₅S+NH₄]⁺: 471.1151; found: 471.1150.

tert-butyl (R)-7-fluoro-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.2j)



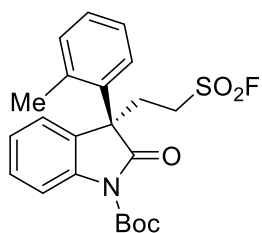
General procedure was followed using **3.1j** (0.1 mmol, 32.7 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2j** as a colourless oil (34.3 mg, 76% yield). Compound (*R*)-**3.2j** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.5 mL/min]: $\tau_{\text{major}} = 9.8$ min, $\tau_{\text{minor}} = 7.6$ min. $[\alpha]_D^{25} = 15.9$ ($c = 0.50$, CHCl₃, 98% ee); **¹H NMR** (300 MHz, CDCl₃) δ 7.45 – 7.29 (m, 5H), 7.29 – 7.22 (m, 1H), 7.18 (ddd, $J = 10.8, 8.4, 1.3$ Hz, 1H), 7.08 (dd, $J = 7.3, 1.4$ Hz, 1H), 3.41 – 3.16 (m, 2H), 3.06 (ddd, $J = 13.6, 11.2, 5.6$ Hz, 1H), 2.71 (ddd, $J = 13.6, 11.7, 4.8$ Hz, 1H), 1.61 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.9 (C), 148.9 (d, $J = 252.7$ Hz, C), 147.2 (C), 136.9 (C), 132.3 (d, $J = 1.9$ Hz, C), 129.5 (CH), 128.8 (CH), 126.6 (CH), 126.6 (d, $J = 9.8$ Hz, C), 126.4 (d, $J = 7.0$ Hz, CH), 120.3 (d, $J = 3.7$ Hz, CH), 118.0 (d, $J = 20.5$ Hz, CH), 86.1 (C), 55.6 (d, $J = 1.4$ Hz, C), 46.7 (d, $J = 18.3$ Hz, CH₂), 31.3 (CH₂), 27.8 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.9, -119.0. **HRMS (ESI-TOF)** calc'd for [C₂₁H₂₁F₂NO₅S+NH₄]⁺: 455.1447; found: 455.1445.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-4,7-dimethyl-2-oxo-3-phenylindoline-1-carboxylate (3.2k)



General procedure was followed using **3.1k** (0.1 mmol, 33.7 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2k** as a white solid (12.0 mg, 27% yield). Compound (*R*)-**3.2k** was obtained with a 90% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 5.1$ min, $\tau_{\text{minor}} = 5.5$ min. $[\alpha]_D^{25} = 40.0$ ($c = 0.03$, CHCl₃, 90% ee); **¹H NMR** (300 MHz, CDCl₃) δ 7.39 – 7.27 (m, 3H), 7.24 – 7.04 (m, 3H), 6.95 (d, $J = 7.9$ Hz, 1H), 3.37 – 3.09 (m, 1H), 2.97 – 2.77 (m, 2H), 2.27 (s, 3H), 2.00 (s, 3H), 1.59 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 176.1 (C), 149.2 (C), 138.9 (C), 137.1 (C), 132.8 (CH), 132.6 (C), 129.3 (CH), 128.4 (CH), 127.6 (CH), 127.2 (C), 126.5 (CH), 121.4 (C), 85.8 (C), 56.0 (C), 47.1 (d, $J = 18.3$ Hz, CH₂), 28.2 (CH₂), 27.8 (CH₃), 19.3 (CH₃), 18.1 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.8. **HRMS (ESI-TOF)** calc'd for [C₂₃H₂₆FNO₅S+NH₄]⁺: 465.1854; found: 465.1832.

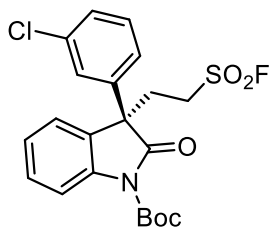
tert-butyl (*R*)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-(*o*-tolyl)indoline-1-carboxylate (3.2l**)**



General procedure was followed using **3.1l** (0.1 mmol, 32.3 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2l** as a white solid (35.5 mg, 83% yield). Compound (*R*)-**3.2l** was obtained with a 89% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 7.3$ min, $\tau_{\text{minor}} = 8.5$ min.

$[\alpha]_D^{25} = -79.3$ ($c = 0.30$, CHCl_3 , 89% ee); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.89 (d, $J = 8.2$ Hz, 1H), 7.56 – 7.47 (m, 1H), 7.36 (tdd, $J = 7.9, 3.2, 1.5$ Hz, 2H), 7.26 (dd, $J = 14.9, 1.3$ Hz, 1H), 7.20 – 7.07 (m, 2H), 6.88 (dd, $J = 7.6, 1.4$ Hz, 1H), 3.65 – 3.32 (m, 2H), 3.07 (ddd, $J = 13.8, 12.2, 4.0$ Hz, 1H), 2.54 (ddd, $J = 13.8, 12.5, 4.5$ Hz, 1H), 1.79 (s, 3H), 1.68 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 175.8 (C), 149.1 (C), 139.1 (C), 137.3 (C), 135.3 (C), 133.1 (CH), 130.3 (C), 129.4 (CH), 128.7 (CH), 126.8 (CH), 126.5 (CH), 125.7 (CH), 123.6 (CH), 115.3 (CH), 85.5 (C), 54.7 (C), 46.4 (d, $J = 17.7$ Hz, CH_2), 31.9 (CH_2), 28.3 (CH_3), 20.1 (CH_3). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ 53.0. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_5\text{S} + \text{NH}_4]^+$: 451.1697; found: 451.1685.

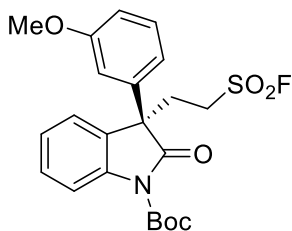
tert-butyl (*R*)-3-(3-chlorophenyl)-3-(2-(fluorosulfonyl)ethyl)-2-oxoindoline-1-carboxylate (3.2m**)**



General procedure was followed using **3.1m** (0.1 mmol, 34.4 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2m** as a colourless oil (45.0 mg, 99% yield). Compound (*R*)-**3.2m** was obtained with a 96% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 7.7$ min, $\tau_{\text{minor}} = 6.1$ min.

$[\alpha]_D^{25} = 45.4$ ($c = 0.76$, CHCl_3 , 96% ee); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.98 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.46 (ddd, $J = 8.2, 7.3, 1.7$ Hz, 1H), 7.37 – 7.17 (m, 6H), 3.36 – 3.22 (m, 1H), 3.18 – 2.94 (m, 2H), 2.79 – 2.52 (m, 1H), 1.64 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 174.7 (C), 148.8 (C), 139.8 (C), 139.6 (C), 135.3 (C), 130.5 (CH), 130.1 (CH), 128.9 (CH), 127.7 (C), 127.2 (CH), 125.6 (CH), 125.1 (CH), 124.5 (CH), 116.2 (CH), 85.6 (C), 54.9 (C), 46.9 (d, $J = 18.4$ Hz, CH_2), 31.6 (CH_2), 28.2 (CH_3). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ 52.9. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{21}\text{ClFNO}_5\text{S} + \text{NH}_4]^+$: 471.1151; found: 471.1153.

tert-butyl (*R*)-3-(2-(fluorosulfonyl)ethyl)-3-(3-methoxyphenyl)-2-oxoindoline-1-carboxylate (3.2n**)**

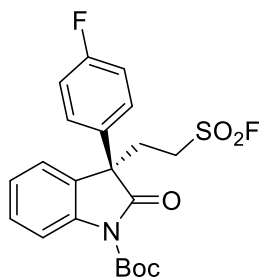


General procedure was followed using **3.1n** (0.1 mmol, 33.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2n** as a colourless oil (38.3 mg, 85% yield). Compound (*R*)-**3.2n** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak OD-H column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 9.1$ min, $\tau_{\text{minor}} = 6.39$ min.

$[\alpha]_D^{25} = 26.2$ ($c = 0.64$, CHCl_3 , 98% ee); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.95 (dd, $J = 8.2, 1.0$ Hz, 1H), 7.50 – 7.35 (m, 1H), 7.34 – 7.22 (m, 3H), 6.96 – 6.87 (m, 1H), 6.87 – 6.81 (m, 2H), 3.77 (s, 3H), 3.41 – 3.13 (m, 2H), 3.03 (ddd, $J = 13.5$,

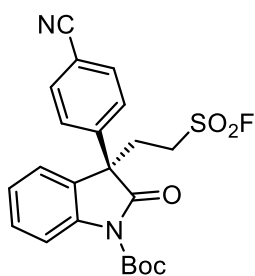
11.9, 5.0 Hz, 1H), 2.70 (ddd, $J = 13.5, 12.4, 4.0$ Hz, 1H), 1.64 (s, 9H). **^{13}C NMR** (75 MHz, CDCl_3) δ 175.2 (C), 160.2 (C), 148.9 (C), 139.7 (C), 139.0 (C), 130.3 (CH), 129.8 (CH), 128.6 (C), 125.4 (CH), 124.5 (CH), 119.0 (CH), 115.9 (CH), 113.4 (CH), 113.3 (CH), 85.4 (C), 55.4 (CH_3), 55.0 (C), 47.0 (d, $J = 18.1$ Hz, CH_2), 31.4 (CH_2), 28.2 (CH_3). **^{19}F NMR** (282 MHz, CDCl_3) δ 52.7. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_6\text{S}+\text{Na}]^+$: 472.1201; found: 472.1187.

tert-butyl (R)-3-(4-fluorophenyl)-3-(2-(fluorosulfonyl)ethyl)-2-oxoindoline-1-carboxylate (3.2o)



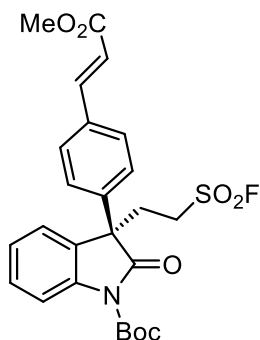
General procedure was followed using **3.1o** (0.1 mmol, 32.7 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2o** as a white solid (38.7 mg, 89% yield). Compound (*R*)-**3.2o** was obtained with a 96% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 8.0$ min, $\tau_{\text{minor}} = 6.4$ min. $[\alpha]_D^{25} = 47.4$ ($c = 0.65$, CHCl_3 , 96% ee); **^1H NMR** (300 MHz, CDCl_3) δ 7.97 (dt, $J = 8.2, 0.9$ Hz, 1H), 7.45 (ddd, $J = 8.2, 7.3, 1.7$ Hz, 1H), 7.38 – 7.21 (m, 4H), 7.11 – 6.95 (m, 2H), 3.39 – 3.20 (m, 1H), 3.20 – 2.94 (m, 2H), 2.68 (td, $J = 12.5, 2.7$ Hz, 1H), 1.64 (s, 9H). **^{13}C NMR** (75 MHz, CDCl_3) δ 175.1 (C), 162.6 (d, $J = 248.9$ Hz, C), 148.7 (C), 139.7 (C), 133.2 (d, $J = 3.3$ Hz, C), 129.9 (CH), 128.7 (d, $J = 8.2$ Hz, CH), 128.1 (C), 125.4 (CH), 124.4 (CH), 116.3 (CH), 116.0 (d, $J = 2.9$ Hz, CH), 85.4 (C), 54.5 (C), 46.8 (d, $J = 18.3$ Hz, CH_2), 31.6 (CH_2), 28.1 (CH_3). **^{19}F NMR** (282 MHz, CDCl_3) δ 52.9, -113.7. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{21}\text{H}_{21}\text{F}_2\text{NO}_5\text{S}+\text{NH}_4]^+$: 455.1447; found: 455.1439.

tert-butyl (R)-3-(4-cyanophenyl)-3-(2-(fluorosulfonyl)ethyl)-2-oxoindoline-1-carboxylate (3.2p)



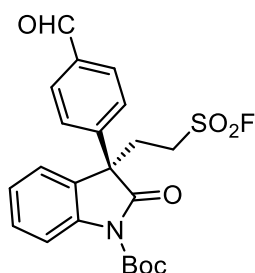
General procedure was followed using **3.1p** (0.1 mmol, 33.4 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2p** as a yellow oil (44.1 mg, 99% yield). Compound (*R*)-**3.2p** was obtained with a 90% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1.0 mL/min]: $\tau_{\text{major}} = 28.0$ min, $\tau_{\text{minor}} = 23.20$ min. $[\alpha]_D^{25} = 37.3$ ($c = 0.64$, CHCl_3 , 90% ee); **^1H NMR** (300 MHz, CDCl_3) δ 7.99 (dt, $J = 8.3, 0.8$ Hz, 1H), 7.70 – 7.59 (m, 2H), 7.54 – 7.42 (m, 3H), 7.34 (td, $J = 7.5, 1.1$ Hz, 1H), 7.28 – 7.22 (m, 1H), 3.37 – 3.18 (m, 1H), 3.16 – 2.96 (m, 2H), 2.77 – 2.63 (m, 1H), 1.63 (s, 9H). **^{13}C NMR** (75 MHz, CDCl_3) δ 174.3 (C), 148.6 (C), 142.7 (C), 139.9 (C), 133.0 (CH), 130.4 (CH), 127.8 (CH), 127.0 (C), 125.8 (CH), 124.5 (CH), 118.2 (C), 116.3 (CH), 112.7 (C), 85.9 (C), 55.3 (C), 46.8 (d, $J = 18.8$ Hz, CH_2), 31.5 (CH_2), 28.1 (CH_3). **^{19}F NMR** (282 MHz, CDCl_3) δ 53.1. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{22}\text{H}_{21}\text{FN}_2\text{O}_5\text{S}+\text{NH}_4]^+$: 462.1493; found: 462.1489.

(*R*)-tert-butyl (R,E)-3-(2-(fluorosulfonyl)ethyl)-3-(4-(3-methoxy-3-oxoprop-1-en-1-yl)phenyl)-2-oxoindoline-1-carboxylate (3.2q)



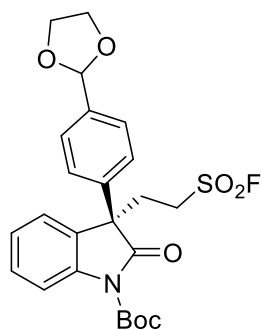
General procedure was followed using **3.1q** (0.1 mmol, 39.3 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2q** as a yellow oil (32.5 mg, 65% yield). Compound (*R*)-**3.2q** was obtained with a 77% enantiomeric excess determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 27.9$ min, $\tau_{\text{minor}} = 15.9$ min. $[\alpha]_D^{25} = 15.1$ (*c* = 0.40, CHCl₃, 77% ee); **¹H NMR** (300 MHz, CDCl₃) δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 16.0 Hz, 1H), 7.54 – 7.41 (m, 3H), 7.39 – 7.32 (m, 2H), 7.34 – 7.21 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 3.38 – 2.99 (m, 3H), 2.70 (td, *J* = 12.6, 2.8 Hz, 1H), 1.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 174.9 (C), 167.3 (C), 148.8 (C), 143.6 (CH), 139.8 (C), 139.5 (C), 134.7 (C), 130.0 (CH), 128.8 (CH), 128.1 (C), 127.4 (CH), 125.5 (CH), 124.5 (CH), 119.1 (CH), 116.1 (CH), 85.6 (C), 55.1 (C), 51.9 (CH₃), 46.9 (d, *J* = 18.2 Hz, CH₂), 31.4 (CH₂), 28.2 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.9. **HRMS (ESI-TOF)** calc'd for [C₂₅H₂₆FNO₇S+NH₄]⁺: 521.1752; found: 521.1745.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-3-(4-formylphenyl)-2-oxoindoline-1-carboxylate (3.2r)



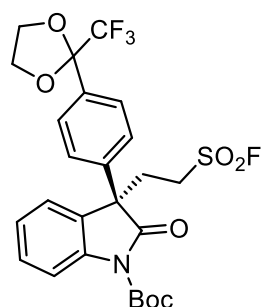
General procedure was followed using **3.1r** (0.1 mmol, 33.7 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2r** as a yellow oil (35.9 mg, 80% yield). Compound (*R*)-**3.2r** was obtained with a 73% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (95:5), 1.0 mL/min]: $\tau_{\text{major}} = 24.9$ min, $\tau_{\text{minor}} = 26.4$ min. $[\alpha]_D^{25} = 5.3$ (*c* = 0.60, CHCl₃, 73% ee); **¹H NMR** (300 MHz, CDCl₃) δ 10.01 (s, 1H), 8.02 – 7.96 (m, 1H), 7.93 – 7.82 (m, 2H), 7.56 – 7.43 (m, 3H), 7.33 (td, *J* = 7.5, 1.1 Hz, 1H), 7.29 – 7.23 (m, 1H), 3.38 – 3.03 (m, 3H), 2.83 – 2.66 (m, 1H), 1.64 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 191.5 (C), 174.6 (C), 148.7 (C), 144.0 (C), 139.8 (C), 136.2 (C), 130.4 (CH), 130.2 (CH), 127.7 (CH), 127.7 (C), 125.7 (CH), 124.5 (C), 116.2 (CH), 85.7 (C), 55.4 (C), 46.8 (d, *J* = 18.5 Hz, CH₂), 31.4 (CH₂), 28.1 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 53.0. **HRMS (ESI-TOF)** calc'd for [C₂₂H₂₂FNO₆S+NH₄]⁺: 465.1490; found: 465.1483.

tert-butyl (*R*)-3-(4-(1,3-dioxolan-2-yl)phenyl)-3-(2-(fluorosulfonyl)ethyl)-2-oxoindoline-1-carboxylate (3.2s**)**



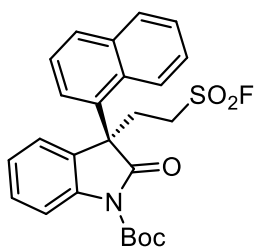
General procedure was followed using **3.1s** (0.1 mmol, 38.1 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2s** as a yellow oil (36.5 mg, 74% yield). Compound (*R*)-**3.2s** was obtained with a 97% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 20.3$ min, $\tau_{\text{minor}} = 17.3$ min. $[\alpha]_D^{25} = 19.4$ ($c = 0.67$, CHCl_3 , 97% ee); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.96 (dt, $J = 8.2, 0.8$ Hz, 1H), 7.50 – 7.39 (m, 3H), 7.37 – 7.30 (m, 2H), 7.29 – 7.20 (m, 2H), 5.79 (s, 1H), 4.09 (ddd, $J = 7.1, 5.9, 3.7$ Hz, 2H), 4.05 – 3.93 (m, 2H), 3.46 – 3.12 (m, 2H), 3.06 (ddd, $J = 13.4, 11.9, 4.8$ Hz, 1H), 2.80 – 2.62 (m, 1H), 1.63 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 175.1 (C), 148.8 (C), 139.6 (C), 138.4 (C), 138.3 (C), 129.7 (CH), 128.4 (C), 127.3 (CH), 126.8 (CH), 125.3 (CH), 124.4 (CH), 115.9 (CH), 103.0 (CH), 85.3 (C), 65.4 (CH_2), 54.9 (C), 46.8 (d, $J = 18.3$ Hz, CH_2), 31.2 (CH_2), 28.1 (CH_3). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ 52.8. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{24}\text{H}_{26}\text{FNO}_6\text{S} + \text{NH}_4]^+$: 509.1752; found: 509.1746.

tert-butyl (*R*)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-(4-(2-(trifluoromethyl)-1,3-dioxolan-2-yl) phenyl)indoline-1-carboxylate (3.2t**)**



General procedure was followed using **3.1t** (0.1 mmol, 44.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2t** as a white solid (49.1 mg, 88% yield). Compound (*R*)-**3.2t** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 8.4$ min, $\tau_{\text{minor}} = 6.5$ min. $[\alpha]_D^{25} = 26.4$ ($c = 0.82$, CHCl_3 , 98% ee); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.95 – 7.80 (m, 1H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.37 (ddd, $J = 8.2, 6.8, 2.1$ Hz, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.14 (m, 2H), 4.25 – 4.10 (m, 2H), 4.03 – 3.91 (m, 2H), 3.31 – 2.91 (m, 3H), 2.63 (td, $J = 12.6, 3.0$ Hz, 1H), 1.56 (s, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 175.1 (C), 148.8 (C), 139.8 (C), 139.1 (C), 135.2 (C), 129.9 (CH), 128.2 (C), 127.9 (CH), 126.6 (CH), 125.5 (CH), 124.6 (CH), 122.8 (q, $J = 288.5$ Hz, CF_3), 116.1 (CH), 104.5 (q, $J = 32.3$ Hz, C), 85.5 (C), 67.0 (CH_2), 55.0 (C), 46.9 (d, $J = 18.2$ Hz, CH_2), 31.5 (CH_2), 28.2 (CH_3). $^{19}\text{F NMR}$ (282 MHz, CDCl_3) δ 52.8, -82.1. **HRMS (ESI-TOF)** calc'd for $[\text{C}_{25}\text{H}_{25}\text{F}_4\text{NO}_7\text{S} + \text{NH}_4]^+$: 577.1626; found: 577.1636.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-3-(naphthalen-1-yl)indoline-1-carboxylate (3.2u)

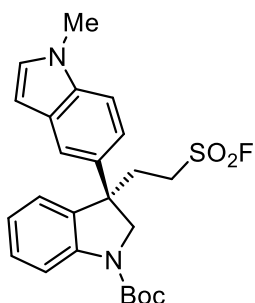


General procedure was followed using **3.1u** (0.1 mmol, 35.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2u** as a colourless oil (46.1 mg, 96% yield, 7:1 diastereomeric ratio determined by ^1H NMR). Compound (*R*)-**3.2u** was obtained with a 90% enantiomeric excess for the major diastereomer and 79% for the minor diastereomer, both determined by HPLC using a Chiralpak AD column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]. $[\alpha]_D^{25} = -61.4$ ($c = 0.77$, CHCl_3 , 7:1 dr, 90/79% ee). **HRMS (ESI-TOF)** calc'd for $[\text{C}_{25}\text{H}_{24}\text{FNO}_5\text{S} + \text{NH}_4]^+$: 487.1697; found: 487.1697.

Major diastereomer: $\tau_{\text{major}} = 8.9$ min, $\tau_{\text{minor}} = 5.9$ min. ^1H NMR (300 MHz, CDCl_3) δ 8.05 (d, $J = 8.2$ Hz, 1H), 7.95 – 7.77 (m, 2H), 7.76 – 7.66 (m, 1H), 7.58 (t, $J = 7.8$ Hz, 1H), 7.48 – 7.33 (m, 2H), 7.36 – 7.20 (m, 1H), 7.16 – 7.01 (m, 2H), 6.88 (dd, $J = 7.6, 1.4$ Hz, 1H), 3.73 – 3.56 (m, 1H), 3.54 – 3.32 (m, 1H), 3.29 – 3.11 (m, 1H), 2.89 – 2.60 (m, 1H), 1.70 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.9 (C), 149.2 (C), 138.5 (C), 135.0 (C), 132.5 (C), 131.7 (C), 131.0 (C), 130.3 (CH), 129.7 (CH), 129.6 (CH), 127.0 (CH), 126.0 (CH), 125.8 (CH), 125.8 (CH), 125.1 (CH), 123.5 (CH), 123.2 (CH), 115.9 (CH), 85.6 (C), 55.0 (C), 46.5 (d, $J = 17.9$ Hz, CH_2), 32.5 (CH_2), 28.2 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 53.2.

Minor diastereomer: $\tau_{\text{major}} = 6.9$ min, $\tau_{\text{minor}} = 5.2$ min ^1H NMR (300 MHz, CDCl_3) δ 8.13 (d, $J = 1.9$ Hz, 1H), 7.95 – 7.80 (m, 2H), 7.72 (td, $J = 7.5, 1.2$ Hz, 1H), 7.58 (t, $J = 7.8$ Hz, 1H), 7.48 – 7.33 (m, 2H), 7.36 – 7.20 (m, 1H), 7.16 – 7.01 (m, 2H), 6.79 (d, $J = 8.1$ Hz, 1H), 3.73 – 3.56 (m, 1H), 3.54 – 3.32 (m, 1H), 3.29 – 3.11 (m, 1H), 2.89 – 2.60 (m, 1H), 1.70 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.4 (C), 149.0 (C), 138.5 (C), 135.3 (C), 131.8 (C), 130.9 (C), 130.5 (CH), 130.1 (CH), 129.8 (CH), 127.2 (CH), 126.1 (CH), 125.8 (CH), 124.4 (CH), 122.9 (CH), 116.7 (CH), 86.2 (C), 54.7 (C), 46.3 (d, $J = 17.7$ Hz, CH_2), 32.3 (CH_2), 28.2 (CH_3). 2 ^{19}F NMR (282 MHz, CDCl_3) δ 53.3. Two ^{13}C NMR signals were not detected due to low intensity of the minor diastereomer signals and overlapping with major diastereomer signals.

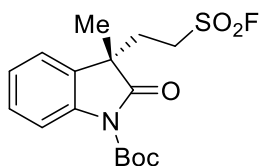
tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-3-(1-methyl-1H-indol-5-yl)indoline-1-carboxylate (3.2v)



General procedure was followed using **3.1v** (0.1 mmol, 36.2 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2v** as a brown oil (42.1 mg, 92% yield). Compound (*R*)-**3.2v** was obtained with a 99% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 14.8$ min, $\tau_{\text{minor}} = 12.2$ min. $[\alpha]_D^{25} = 11.5$ ($c = 0.70$, CHCl_3 , 99% ee); ^1H NMR (300 MHz, CDCl_3) δ 8.01 – 7.94 (m, 1H), 7.49 (dd, $J = 2.0, 0.7$ Hz, 1H), 7.43 (ddd, $J = 8.2, 6.7, 2.3$ Hz, 1H), 7.36 – 7.28 (m, 3H), 7.27 – 7.22 (m, 1H), 7.06 (d, $J = 3.1$ Hz, 1H), 6.44 (dd, $J = 3.1, 0.8$ Hz, 1H), 3.77 (s, 3H), 3.44 – 3.22 (m, 2H), 3.13 (ddd, $J = 13.5, 11.5, 5.3$ Hz, 1H), 2.78 (ddd, $J = 13.4, 12.0, 4.3$ Hz, 1H), 1.64 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 176.0 (C), 149.1 (C), 139.6 (C), 136.3 (C), 130.0 (CH), 129.6 (C), 129.3 (CH), 128.6 (C), 128.2 (C), 125.1 (CH), 124.5 (CH), 120.0 (CH), 119.3 (CH), 115.8 (CH), 110.1 (CH), 101.4 (CH), 85.0 (C), 55.0 (C),

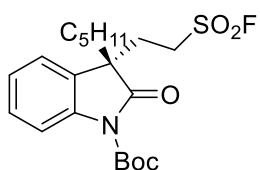
47.1 (d, $J = 17.8$ Hz CH_2), 32.9 (CH_3), 31.6 (CH_2), 28.1 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.7. HRMS (ESI-TOF) calc'd for $[\text{C}_{24}\text{H}_{25}\text{FN}_2\text{O}_5\text{S}+\text{NH}_4]^+$: 490.1806; found: 490.1795.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-3-methyl-2-oxoindoline-1-carboxylate (3.2w)



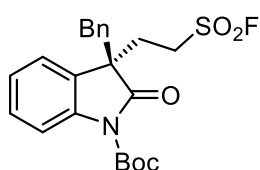
General procedure was followed using **3.1w** (0.1 mmol, 24.7 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2w** as a colourless oil (31.3 mg, 88% yield). Compound (*R*)-**3.2w** was obtained with a 56% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 10.5$ min, $\tau_{\text{minor}} = 10.0$ min. $[\alpha]_D^{25} = 11.9$ ($c = 0.52$, CHCl_3 , 56% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.92 – 7.83 (m, 1H), 7.36 (ddd, $J = 8.1$, 6.1, 2.9 Hz, 1H), 7.23 (td, $J = 4.3$, 2.5 Hz, 2H), 3.34 – 3.02 (m, 2H), 2.54 (ddd, $J = 13.6$, 12.4, 4.9 Hz, 1H), 2.30 (td, $J = 13.3$, 4.0 Hz, 1H), 1.66 (s, 9H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 177.3 (C), 149.0 (C), 139.0 (C), 130.4 (C), 129.3 (CH), 125.4 (CH), 122.5 (CH), 115.7 (CH), 85.2 (C), 47.1 (C), 46.7 (d, $J = 18.2$ Hz, CH_2), 31.8 (CH_2), 28.2 (CH_3), 24.5 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.5. HRMS (ESI-TOF) calc'd for $[\text{C}_{16}\text{H}_{20}\text{FNO}_5\text{S}+\text{H}]^+$: 358.1119; found: 358.1117.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-pentylindoline-1-carboxylate (3.2x)



General procedure was followed using **3.1x** (0.1 mmol, 30.3 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2x** as a colourless oil (30.6 mg, 74% yield). Compound (*R*)-**3.2x** was obtained with a 13% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 6.2$ min, $\tau_{\text{minor}} = 5.3$ min. $[\alpha]_D^{25} = 47.8$ ($c = 0.48$, CHCl_3 , 13% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.87 (dt, $J = 8.2$, 0.8 Hz, 1H), 7.37 (ddd, $J = 8.2$, 7.4, 1.6 Hz, 1H), 7.26 (dd, $J = 7.4$, 1.1 Hz, 1H), 7.23 – 7.13 (m, 1H), 3.22 (dddd, $J = 14.2$, 12.9, 4.8, 3.4 Hz, 1H), 3.05 (dddd, $J = 14.3$, 12.5, 5.7, 3.8 Hz, 1H), 2.54 (ddd, $J = 13.5$, 12.5, 4.8 Hz, 1H), 2.30 (td, $J = 13.2$, 3.8 Hz, 1H), 2.04 – 1.88 (m, 1H), 1.84 – 1.69 (m, 1H), 1.66 (s, 9H), 1.30 – 0.98 (m, 5H), 0.96 – 0.84 (m, 1H), 0.83 – 0.69 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 177.1 (C), 148.9 (C), 139.8 (C), 129.3 (CH), 128.8 (C), 125.4 (CH), 122.6 (CH), 115.6 (CH), 85.2 (C), 51.6 (C), 46.6 (d, $J = 18.1$ Hz, CH_2), 38.6 (CH_2), 31.7 (CH_2), 31.3 (CH_2), 28.2 (CH_3), 23.6 (CH_2), 22.3 (CH_2), 14.0 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.5. HRMS (ESI-TOF) calc'd for $[\text{C}_{20}\text{H}_{28}\text{FNO}_5\text{S}+\text{NH}_4]^+$: 431.2010; found: 431.1992.

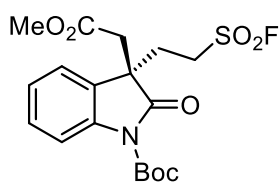
tert-butyl (S)-3-benzyl-3-(2-(fluorosulfonyl)ethyl)-2-oxoindoline-1-carboxylate (3.2y)



General procedure was followed using **3.1y** (0.1 mmol, 32.3 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2y** as a yellow solid (30.6 mg, 71% yield). Compound (*R*)-**3.2y** was obtained with a 30% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 8.2$ min, $\tau_{\text{minor}} = 7.2$ min. $[\alpha]_D^{25} = -3.1$ ($c = 0.51$, CHCl_3 , 31% ee). ^1H NMR (300 MHz, CDCl_3) δ 7.67 – 7.56 (m, 1H), 7.37 – 6.94 (m, 6H), 6.78

(dt, $J = 6.7, 1.6$ Hz, 2H), 3.32 – 3.16 (m, 2H), 3.09 – 2.90 (m, 2H), 2.76 (td, $J = 13.0, 4.6$ Hz, 1H), 2.47 (td, $J = 13.1, 3.5$ Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 176.3 (C), 148.3 (C), 139.8 (C), 133.6 (C), 129.8 (CH), 129.4 (CH), 127.9 (CH), 127.3 (CH), 127.1 (C), 124.8 (CH), 123.1 (CH), 115.3 (CH), 84.7 (C), 53.3 (C), 46.7 (d, $J = 18.3$ Hz, CH_2), 45.4 (CH_2), 29.9 (CH_3), 28.0 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.6. HRMS (ESI-TOF) calc'd for $[\text{C}_{22}\text{H}_{24}\text{FNO}_5\text{S}+\text{NH}_4]^+$: 451.1697; found: 451.1690.

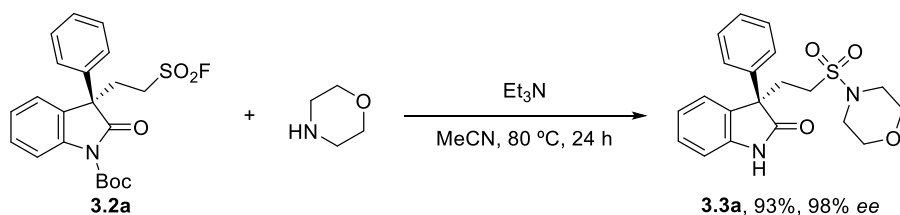
tert-butyl (S)-3-(2-(fluorosulfonyl)ethyl)-3-(2-methoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (3.2z)



General procedure was followed using **3.1z** (0.1 mmol, 30.6 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2z** as a colourless oil (32.1 mg, 75% yield). Compound (*R*)-**3.2z** was obtained with a 13% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 14.5$ min, $\tau_{\text{minor}} = 25.7$ min. $[\alpha]_D^{25} = -4.7$ ($c = 0.54$, CHCl_3 , 13% ee); ^1H NMR (300 MHz, CDCl_3) δ 7.89 (dt, $J = 8.2, 0.8$ Hz, 1H), 7.38 (ddd, $J = 8.2, 5.1, 4.0$ Hz, 1H), 7.23 – 7.19 (m, 2H), 3.50 (s, 3H), 3.33 – 3.15 (m, 1H), 3.13 – 2.97 (m, 2H), 2.91 (d, $J = 16.4$ Hz, 1H), 2.52 (ddd, $J = 13.5, 12.5, 4.8$ Hz, 1H), 2.33 (td, $J = 13.2, 3.8$ Hz, 1H), 1.66 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 176.1 (C), 169.2 (C), 148.9 (C), 140.2 (C), 129.8 (CH), 127.6 (C), 125.3 (CH), 122.5 (CH), 115.8 (CH), 85.2 (C), 52.2 (CH_3), 48.4 (C), 46.0 (d, $J = 18.5$ Hz), 41.4 (CH_2), 31.5 (CH_2), 28.2 (CH_3). ^{19}F NMR (282 MHz, CDCl_3) δ 52.9. HRMS (ESI-TOF) calc'd for $[\text{C}_{18}\text{H}_{22}\text{FNO}_7\text{S}+\text{NH}_4]^+$: 433.1439; found: 433.1430.

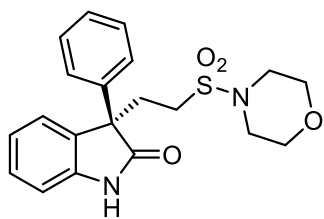
Synthetic transformations of compounds 3.2

General procedure for the synthesis of compound 3.3a



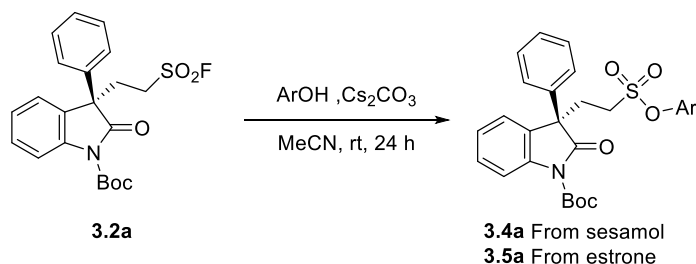
A modified literature procedure was carried out.^[38] In a screw cap tube, **3.2a** (0.1 mmol, 41.9 mg, 1.0 equiv.) and morpholine (0.2 mmol, 17.3 μL , 2.0 equiv.) were dissolved in 1 mL of anhydrous MeCN under N_2 atmosphere at room temperature. To this solution Et_3N was added (0.2 mmol, 27.9 μL , 0.2 equiv.) and the resulting mixture was stirred at 80°C overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford compound **3.3a**.

(*R*)-tert-butyl 3-(2-(morpholinosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.3a)



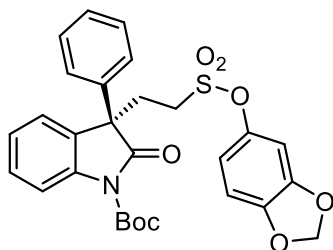
The crude product was purified by silica gel column chromatography affording pure **3.3a** as a white solid (35.8 mg, 93% yield). Compound (*R*)-**3.3a** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 65.3$ min, $\tau_{\text{minor}} = 61.2$ min. $[\alpha]_D^{25} = 34.5$ (*c* = 0.60, CHCl₃, 98% ee); **¹H NMR** (300 MHz, CDCl₃) δ 8.85 (s, 1H), 7.43 – 7.27 (m, 6H), 7.21 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 3.78 – 3.64 (m, 4H), 3.27 – 3.14 (m, 4H), 2.99 – 2.71 (m, 3H), 2.70 – 2.54 (m, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 179.9 (C), 140.6 (C), 138.3 (C), 131.5 (C), 129.1 (CH), 129.1 (CH), 128.1 (CH), 126.8 (CH), 124.9 (CH), 123.4 (CH), 110.8 (CH), 66.6 (CH₂), 45.9 (CH₂), 45.1 (CH₂), 30.7 (CH₂). **HRMS (ESI-TOF)** calc'd for [C₂₀H₂₂N₂O₄S+H]⁺: 387.1373; found: 387.1377.

General procedure for the synthesis of compounds 3.4a and 3.5a



A modified literature procedure was carried out.^[38] In a screw cap tube, **3.2a** (0.1 mmol, 41.9 mg, 1.0 equiv.), the corresponding phenol (0.1 mmol, 1.0 equiv.) and Cs₂CO₃ (0.1 mmol, 32.6 mg, 1.0 equiv.) were dissolved in 1 mL of anhydrous MeCN at room temperature. The resulting mixture was stirred at rt overnight. Solvents were removed *in vacuo* and the resulting residue was purified by silica gel column chromatography employing hexane/EtOAc mixtures as eluent to afford the desired sulfonates.

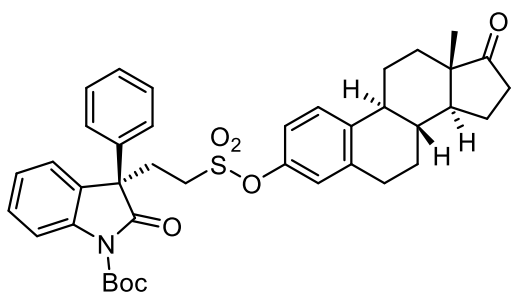
(*R*)-tert-butyl 3-(2-((benzo[d][1,3]dioxol-5-yloxy)sulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.4a)



General procedure was followed using sesamol (0.1 mmol, 13.8 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.4a** as a colourless oil (45.6 mg, 85% yield). Compound (*R*)-**3.4a** was obtained with a 98% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (80:20), 1.0 mL/min]: $\tau_{\text{major}} = 34.8$ min, $\tau_{\text{minor}} = 18.11$ min. $[\alpha]_D^{25} = 33.0$ (*c* = 0.76, CHCl₃, 98% ee); **¹H NMR** (300 MHz, CDCl₃) δ 7.87 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.29 – 7.24 (m, 4H), 7.24 – 7.16 (m, 3H), 6.70 – 6.63 (m, 2H), 6.61 – 6.53 (m, 1H), 5.91 (s, 2H), 3.17 – 2.97 (m, 2H), 2.96 – 2.82 (m, 1H), 2.78 – 2.62 (m, 1H), 1.55 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 175.6 (C), 149.0 (C), 148.4 (C), 146.8 (C), 143.0 (C), 139.8 (C), 138.0

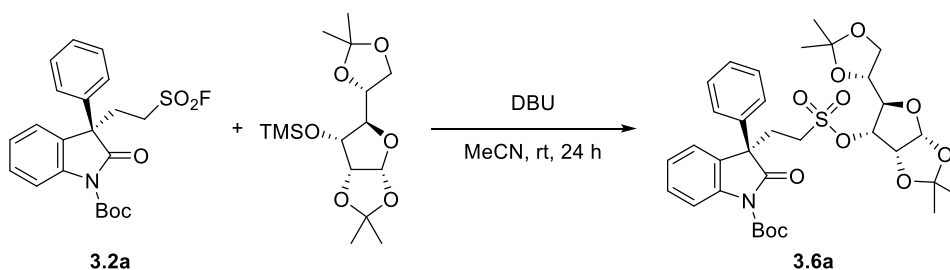
(C), 129.6 (CH), 129.2 (CH), 129.0 (C), 128.4 (CH), 126.9 (CH), 125.2 (CH), 124.7 (CH), 115.8 (CH), 115.0 (CH), 108.2 (CH), 104.4 (CH), 102.2 (CH₂), 85.2 (C), 55.3 (C), 46.2 (CH₂), 31.9 (CH₂), 28.2 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₂₈H₂₇NO₈S+NH₄]⁺: 555.1796; found: 555.1798.

tert-butyl (R)-3-(2-((((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)sulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (3.5a)



General procedure was followed using estrone (0.1 mmol, 27.0 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.5a** as a colourless oil (64.2 mg, 96% yield). Compound **3.5a** was obtained with a >20:1 diastereomeric ratio, determined by ¹H NMR. [α]_D²⁵ = 78.9 (c = 1.07, CHCl₃, >20:1 dr). **¹H NMR** (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.41 (dq, *J* = 8.2, 4.1 Hz, 1H), 7.35 (d, *J* = 4.3 Hz, 4H), 7.33 – 7.22 (m, 4H), 7.02 – 6.93 (m, 2H), 3.22 – 3.09 (m, 2H), 3.02 – 2.87 (m, 3H), 2.80 (td, *J* = 13.8, 13.2, 3.6 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.39 (dq, *J* = 12.2, 3.4, 2.9 Hz, 1H), 2.27 (td, *J* = 10.8, 4.4 Hz, 1H), 2.15 (dt, *J* = 18.9, 8.9 Hz, 1H), 2.09 – 1.93 (m, 3H), 1.63 (s, 9H), 1.59 – 1.39 (m, 6H), 0.91 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 220.7 (C), 175.7 (C), 149.0 (C), 147.0 (C), 139.8 (C), 139.2 (C), 139.0 (C), 138.1 (C), 129.5 (CH), 129.2 (CH), 129.0 (C), 128.4 (CH), 127.0 (CH), 126.9 (CH), 125.2 (CH), 124.7 (CH), 122.1 (CH), 119.3 (CH), 115.8 (CH), 85.2 (C), 55.4 (C), 50.5 (CH), 48.0 (C), 46.3 (CH₂), 44.2 (CH), 38.0 (CH), 36.0 (CH₂), 31.9 (CH₂), 31.6 (CH₂), 29.4 (CH₂), 28.2 (CH₃), 26.3 (CH₂), 25.8 (CH₂), 21.7 (CH₂), 13.9 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₃₉H₄₃NO₇S+NH₄]⁺: 687.3099; found: 687.3095.

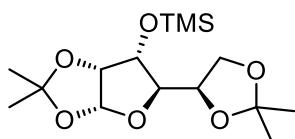
General procedure for the synthesis of compound 3.6a



A modified literature procedure was carried out.^[38] In a screw cap tube, **3.2a** (0.1 mmol, 41.9 mg, 1.0 equiv.) and the TMS-protected 1,2:5,6-di-O-isopropylidene- α -D-allofuranose (0.11 mmol, 36.6 mg, 1.1 equiv.) were dissolved in 1 mL of dry MeCN under N₂ atmosphere. To this solution, DBU (0.02 mmol, 3.0 μ L, 0.2 equiv.) was added and the mixture was stirred at rt overnight to achieve full conversion. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford product **3.6a**.

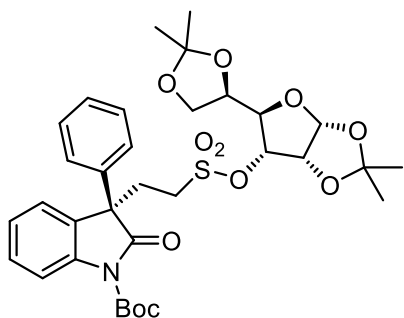
The required TMS-protected 1,2:5,6-di-O-isopropylidene- α -D-allofuranose was not commercially available and therefore had to be synthesized.

(((3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)trimethylsilane



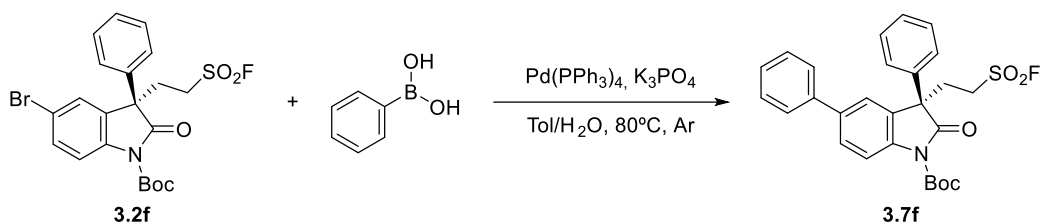
A literature procedure was carried out.^[39] In a flask, 1,2:5,6-di-O-isopropylidene- α -D-allofuranose (1.0 mmol, 300 mg, 1.0 equiv.) was dissolved in pyridine (10 mL) under nitrogen atmosphere. To this solution, TMSCl (1.2 mmol, 152 μ L, 1.2 equiv.) was added at 0 °C and the resulting mixture was stirred overnight at rt. The solution was diluted with EtOAc (20 mL), washed with water (3 x 20 mL) and the organic layer was dried over MgSO₄. Solvents were removed *in vacuo* and the resulting crude product was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford the title compound as a white solid in 17% yield. **¹H NMR** (300 MHz, CDCl₃) δ 5.75 (d, *J* = 3.7 Hz, 1H), 4.49 – 4.42 (m, 1H), 4.36 (td, *J* = 7.1, 2.9 Hz, 1H), 4.11 – 4.03 (m, 2H), 4.00 (s, 1H), 3.98 (d, *J* = 1.0 Hz, 1H), 1.57 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 0.19 (s, 9H).

***tert*-butyl (*R*)-3-(2-(((3a*R*,5*R*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)sulfonyl)ethyl)-2-oxo-3-phenylindolin-1 carboxylate (**3.6a**)**



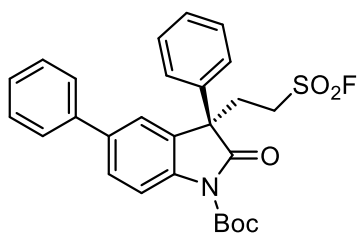
The crude product was purified by silica gel column chromatography affording pure **3.6a** as a white solid (50.0 mg, 76% yield). Compound **3.6a** was obtained with a >20:1 diastereomeric ratio, determined by ¹H NMR. [α]_D²⁵ = 39.5 (*c* = 0.83, CHCl₃, >20:1 dr); **¹H NMR** (300 MHz, CDCl₃) δ 7.93 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.39 (ddd, *J* = 8.2, 5.5, 3.5 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.30 – 7.22 (m, 3H), 5.82 – 5.75 (m, 1H), 4.80 – 4.69 (m, 2H), 4.33 – 4.21 (m, 1H), 4.15 – 4.07 (m, 1H), 4.03 (dd, *J* = 8.7, 6.8 Hz, 1H), 3.87 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.24 – 2.99 (m, 3H), 2.73 (td, *J* = 9.9, 2.5 Hz, 1H), 1.63 (s, 9H), 1.53 (s, 3H), 1.35 (s, 6H), 1.28 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 175.6 (C), 149.0 (C), 139.7 (C), 138.2 (C), 129.5 (C), 129.4 (CH), 129.1 (CH), 128.3 (CH), 126.9 (CH), 125.1 (CH), 124.6 (CH), 115.7 (CH), 113.8 (C), 110.3 (C), 104.0 (CH), 85.1 (C), 78.0 (CH), 76.7 (CH), 74.8 (CH), 65.6 (CH₂), 55.3 (C), 47.7 (CH₂), 31.4 (CH₂), 28.2 (CH₃), 26.8 (CH₃), 26.8 (CH₃), 26.2 (CH₃), 25.0 (CH₃). **HRMS (ESI-TOF)** calc'd for [C₃₃H₄₁NO₁₁S+NH₄]⁺: 677.2739; found: 677.2751.

General procedure for the synthesis of compound **3.7f**



A modified literature procedure was carried out.^[40] In a screw cap tube, **3.2f** (0.075 mmol, 37.6 mg, 1.0 equiv.) was dissolved in 1 mL of a degasified mixture of Tol/H₂O (1.2 mL, v/v, 10:3) under argon atmosphere at room temperature. To this solution, phenylboronic acid (0.11 mmol, 13.8 mg, 1.5 equiv.), Pd(Ph₃)₄ (0.004 mmol, 4.4 mg, 5 mol%) and K₃PO₄ (0.19 mmol, 40.0 mg, 2.5 equiv.) were added. The resulting mixture was stirred at 80 °C for 4 hours. The crude reaction mixture was diluted with toluene (10 mL), washed three times with water (3 x 5 mL) and brine, and the organic layer was dried over MgSO₄. Solvents were removed *in vacuo* and the resulting residue was purified by silica gel column chromatography using hexane/EtOAc mixtures as eluent to afford compound **3.7f**.

tert-butyl (R)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3,5-diphenylindoline-1-carboxylate (3.7f)



The crude product was purified by silica gel column chromatography affording pure **3.7f** as a white solid (24.2 mg, 49% yield). Compound (*R*)-**3.7f** was obtained with a 95% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (90:10), 1.0 mL/min]: τ_{major} = 8.2 min, τ_{minor} = 7.2 min. $[\alpha]_D^{25}$ = 77.4 (*c* = 0.40, CHCl₃, 95% ee); **¹H NMR** (300 MHz, CDCl₃) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* =

8.5, 1.9 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.51 – 7.43 (m, 3H), 7.42 – 7.31 (m, 6H), 3.43 – 3.23 (m, 2H), 3.21 – 3.03 (m, 1H), 2.77 (ddd, *J* = 13.5, 11.5, 4.8 Hz, 1H), 1.66 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 175.4 (C), 148.9 (C), 139.9 (C), 138.9 (C), 138.8 (C), 137.5 (C), 129.4 (CH), 129.4 (C), 129.2 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.1 (CH), 126.8 (CH), 123.0 (CH), 116.3 (CH), 85.5 (C), 55.3 (C), 47.02 (d, *J* = 18.2 Hz, CH₂), 31.5 (CH₂), 28.2 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.8. **HRMS (ESI-TOF)** calc'd for [C₂₇H₂₆FO₅S+NH₄]⁺: 513.1854; found: 513.1835.

General Conclusions

1. Five new methods have been developed for the enantioselective synthesis of organosulfur compounds through the nucleophilic functionalization of organosulfur substrates and the addition of sodium bisulfite to electron-deficient alkenes.
2. The enantioselective conjugate addition of terminal alkynes to saccharin-derived imines has been developed *via* metal catalysis using zinc complexes formed in situ with chiral bis(hydroxy)malonamide ligands. This methodology represents the first example of enantioselective conjugate alkynylation of α,β -unsaturated imines. Optimal reaction conditions for aryl-substituted alkynes were achieved with ligand **L4**, while ligand **L3** proved more effective for alkyl-substituted alkynes. aryl-substituted alkynes afforded adducts **1.3** with moderate to low yields and modest enantioselectivities, whereas alkyl-substituted alkynes provided higher yields and enantioselectivities. Synthetic transformations of compound **1.3ad** afforded sulfonamides **1.6** and **1.7** in high yields with complete retention of enantioselectivity. Single-crystal X-ray diffraction confirmed the **S** configuration of the stereogenic centre.
3. The enantioselective *sulfa*-Michael addition of sodium bisulfite to *trans*- β -nitrostyrenes was developed using a bifunctional thiourea organocatalyst derived from *trans*-1,2-diaminocyclohexane. This methodology demonstrated high robustness, tolerating both electron-donating and electron-withdrawing substituents at any position of the aromatic ring. Aliphatic and heterocyclic nitroalkenes were also successfully employed. Although nitro group hydrogenation was not achieved in this work, a simultaneous study has confirmed the feasibility of this transformation, highlighting the synthetic utility of the obtained chiral nitrosulfonic acids. The absolute stereochemistry was established as *R* by single-crystal X-ray diffraction, and a catalytic cycle consistent with the observed stereochemistry was proposed.
4. The enantioselective construction of tetrasubstituted stereogenic centres has been developed *via* the 1,4-addition of sodium bisulfite to β -CF₃- β,β -disubstituted nitroalkenes and α -substituted β -nitroacrylate esters, catalysed by a bifunctional thiourea organocatalyst derived from *trans*-1,2-diaminocyclohexane. This represents the first example of an enantioselective *sulfa*-Michael addition of sodium bisulfite to β,β -disubstituted nitroalkenes. The method exhibited high robustness, tolerating *para*- and *meta*-substituents regardless of their electronic nature; however, *ortho*-substitution completely inhibited the reaction. Synthetic transformations of the resulting products have proven challenging and are currently under investigation.
5. The enantioselective *sulfa*-Michael addition of sodium bisulfite to aurone-derived azadienes was investigated using a C₂-symmetric bifunctional thiourea organocatalyst derived from *trans*-1,2-diaminocyclohexane. This represents the first example of enantioselective *sulfa*-Michael addition of sodium bisulfite to α,β -unsaturated imines. Optimization studies enabled the preparation of the

corresponding γ -sulfonic amino acids in excellent yields, although the enantioselectivity remained suboptimal. Therefore, a comprehensive reassessment of the optimized reaction parameters will be required, including the exploration of alternative classes of organocatalysts or different catalytic strategies.

6. The enantioselective conjugate addition of 3-aryloxindoles to ethenesulfonyl fluoride has been developed using the bisdihydroquinidine adduct **(DHQD)₂AQN** as the catalyst. This represents the first example of the asymmetric construction of quaternary stereocentres *via* nucleophilic functionalization of ethenesulfonyl fluoride. Optimal results were achieved with *N*-Boc-protected oxindoles substituted at positions 5, 6, and 7 of the oxindole core, as well as at the *meta*- and *para*- positions of the 3-aryl group, whereas substitution at position 4 of the oxindole or *ortho*- of the 3-aryl group reduced enantioselectivity due to steric hindrance. More complex derivatives bearing carbonyl groups, extended aromatic systems, and heterocycles were also successfully employed, although 3-alkyl-substituted oxindoles afforded lower yields and enantiomeric excesses. Synthetic transformations of compounds **3.2a** enabled the preparation of chiral sulfonamides and sulfones with excellent results *via* SuFEx reactions, and the orthogonal reactivity of the SO₂F group was demonstrated through a Suzuki cross-coupling using a brominated derivative. The absolute stereochemistry was established as *R* by single-crystal X-ray diffraction, and a stereochemical model consistent with the observed outcomes was proposed.

Resum en Valencià

Introducció

Quiralitat, rellevància i síntesi asimètrica

La quiralitat es la propietat geomètrica d'aquells objectes que no són superposables amb la seua imatge especular.^[3] Quan es fa referència a un parell de molècules quirals que són imatges especulars l'una de l'altra i no superposables, cadascuna s'anomena enantiòmer.

La quiralitat esta intrínsecament relacionada amb la vida i els éssers vius, ja que, per exemple, els enzims estan formats quasi exclusivament per *L*-aminoàcids i els glúcids que formen part dels àcids nucleics presenten únicament configuració *D*. Es aquesta uniformitat estereoquímica dels sistemes biològics el que provoca que els enzims actuen com a catalitzadors altament enantioselectius i que siguen capaços de discriminar entre enantiòmers. Aquest efecte provoca que els dos enantiòmers d'una molècula quiral puguen mostrar efectes fisiològics diferents, fet d'especial rellevància en el disseny de fàrmacs, on són ben coneguts diversos exemples de medicaments on un enantiòmer presenta els efectes terapèutics desitjats mentre que l'enantiòmer contrari provoca greus efectes secundaris.^{[15]-[18]}

En aquest context, la necessitat de desenvolupar mètodes per obtenir substàncies enantiomèricament pures o enantioenriquides es evident. La síntesi asimètrica és la branca de la química que s'ocupa d'aquest camp i és definida per la IUPAC com *“Una reacció química (o una seqüència de reaccions) en la qual un o més elements nous de quiralitat es formen en una molècula i que produeix els productes estereomèrics (enantiomèrics o diastereomèrics) en proporcions desiguals”*.^[3] Aquesta disciplina es pot dividir en quatre estratègies sintètiques: l'ús de la *“chiral pool”*, l'ús d'auxiliars quirals, resolucions cinètiques de mesclures racèmiques i la síntesi enantioselectiva.

D'entre aquestes metodologies, aquest treball es centra en la síntesi enantioselectiva, i més concretament en la catàlisi asimètrica. En aquesta estratègia, substrats proquirals reaccionen en presència de catalitzadors quirals, responsables de la enantioinducció. En concret, en aquesta tesi s'han utilitzat dues aproximacions: l'organocatàlisi, basada en l'ús de molècules orgàniques quirals de baix pes molecular com a catalitzadors, i la catàlisi metàl·lica, que empra catalitzadors quirals formats per complexos quirals de metalls de transició.

Compostos organosulfurats: Importància i aplicacions

Els compostos organosulfurats tenen un paper essencial en la biologia i en la química mèdica. El sofre està present en aminoàcids com la cisteïna i la metionina, en vitamines com la tiamina i la biotina, i en cofactors com la coenzim A (Figura 4.1). S'han aïllat i estudiat nombrosos productes naturals que contenen sofre i que presenten activitats biològiques rellevants, com ara la penicil·lina, l'al·licina o les patelamides.^{[51]-[53]}

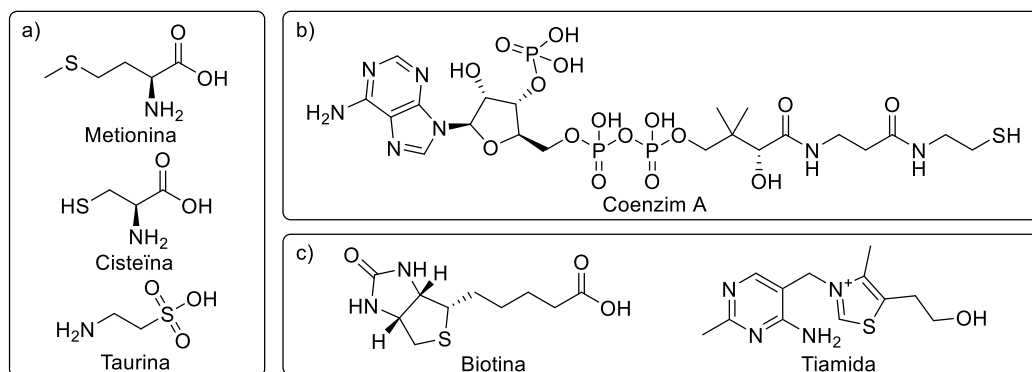


Figura 4.1- Compostos organosulfurats biològics: a) Aminoàcids. b) Cofactors. c) Vitamines.

Aproximadament el 25 % dels fàrmacs de baix pes molecular i el 30 % dels més venuts al 2024 contenen sofre. A més a més, entre 2020 i 2024 es van aprovar 33 nous fàrmacs d'aquest tipus.^{[54],[55]} La prevalença del sofre es pot atribuir a la seua versatilitat, ja que presenta múltiples estats d'oxidació i pot formar part de un gran nombre de grups funcionals (sulfones, sulfòxids, tioèters, etc.), sent las sulfonamides i β -sultames els més comuns en fàrmacs.^[56]

Els compostos organosulfurats s'utilitzen en el tractament del VIH, la diabetis, la hipertensió i la disfunció erèctil, entre altres (Figura 4.2),^[57] i la seua activitat antibiòtica adquireix una importància especial davant l'augment de la resistència bacteriana. L'OMS estima que el 2019 es van produir 1,3 milions de morts per infeccions resistents, xifra que podria ascendir a 10 milions anuals l'any 2050. El desenvolupament de nous antibiòtics serà, per tant, crucial, i els compostos sulfurats podrien exercir un paper protagonista en aquest repte.^[58]

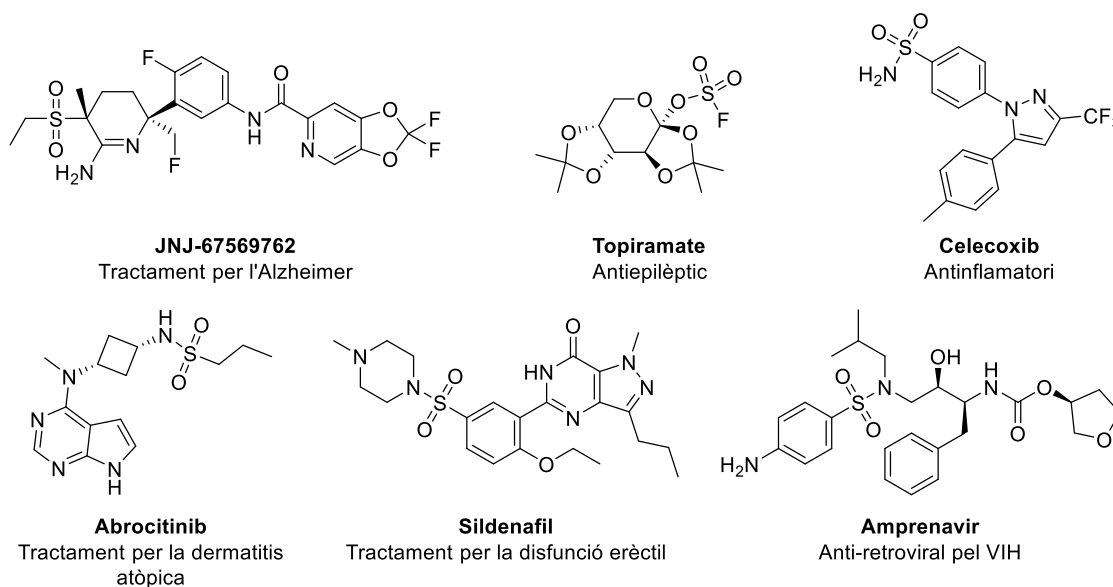


Figura 4.2-Exemples representatius de fàrmacs organosulfurats.

Objectius

L'objectiu d'aquesta tesi doctoral és el desenvolupament de noves estratègies enantioselectives basades en la catàlisi asimètrica per la síntesi de compostos organosulfurats d'interès farmacològic. En aquest context, per a cada capítol s'han establert els objectius específics següents:

- **Capítol 1: Adició conjugada enantioselectiva mediada per zinc d'alquins terminals a 1-azadiens derivats de la sacarina.** En aquest capítol s'estudia l'alquilació conjugada enantioselectiva d'imines derivades de la sacarina catalitzada per complexos metàl·lics formats per zinc i lligands quirals.
- **Capítol 2: Adició enantioselectiva organocatalítica sulfa-Michael de bisulfit de sodi a nitroalquens.** En aquest capítol s'investiga l'adició enantioselectiva de bisulfit de sodi a *trans*- β -nitroestirens mitjançant catàlisi bifuncional per a sintetitzar àcids nitrosulfònics quirals.
- **Capítol 3: Construcció enantioselectiva de centres estereogènics tetrasubstituïts mitjançant l'adició sulfa-Michael organocatalítica de bisulfit de sodi a nitroalquens β,β -disubstituïts.** En aquest capítol s'explora l'adició enantioselectiva de bisulfit de sodi a nitroalquens β -CF₃- β,β -disubstituïts i a esters β -nitroacrílics mitjançant catàlisi bifuncional per obtenir àcids nitrosulfònics quirals que incorporen un centre estereogènic tetrasubstituït a la seua estructura.
- **Capítol 4: Adició enantioselectiva organocatalítica sulfa-Michael de bisulfit de sodi a 1-azadiens derivats d'aurona.** En aquest capítol s'estudia l'adició enantioselectiva de bisulfit de sodi a imines derivades d'aurona mitjançant catàlisi bifuncional per obtenir aminoàcids sulfònics quirals derivats de benzofurà.
- **Capítol 5: Adició organocatalítica enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil.** En aquest capítol s'investiga l'adició conjugada enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil catalitzada per bases de Brønsted per obtenir fluorurs de sulfonil alifàtics quirals que incorporen un estereocentre quaternari a la seua estructura.

Resultats Principals

Capítol 1. Adició conjugada enantioselectiva mediada per zinc d'alquins terminals a 1-azadiens derivats de la sacarina

Els alquins són compostos químicament versàtils, ja que poden ser transformats en un gran nombre de grups funcionals. Addicionalment, aquests compostos han demostrat ser altament rellevants als camps de la química mèdica, biològica i en ciències dels materials (Figura 4.3). Conseqüentment, el desenvolupament de metodologies enantioselectives per a introduir aquest grup en molècules orgàniques és d'especial interès, destacant entre elles l'adició conjugada d'alquins terminals a sistemes conjugats, ja que constitueix una de les vies més directes per la seva incorporació. En aquest context, els 1-azadiens emergeixen com a acceptor 1,4 interessants, ja que l'alquiniació d'aquests substrats dona lloc a β -alquini imines que contenen un estereocentre propargílic, compostos d'interès sintètic per la seva utilitat com a precursors de sulfonamides quirals.

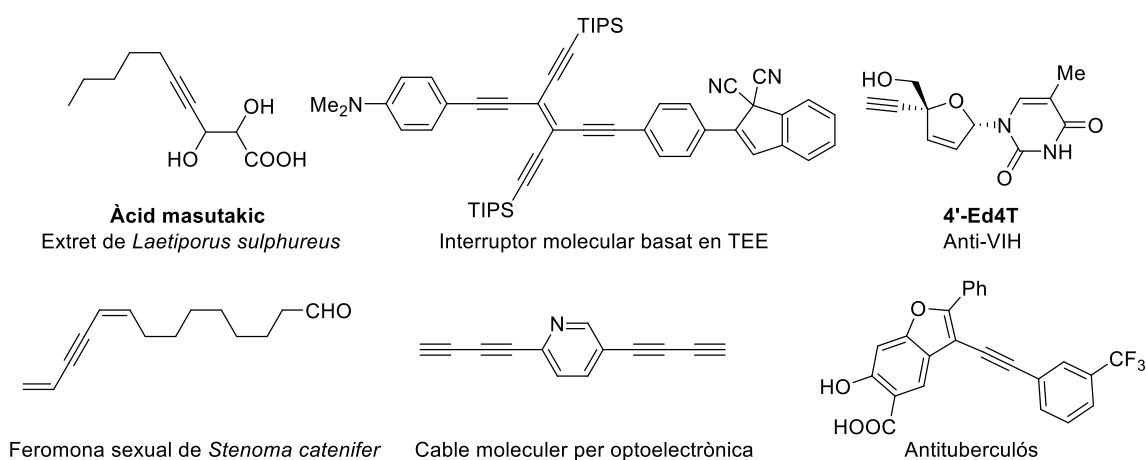
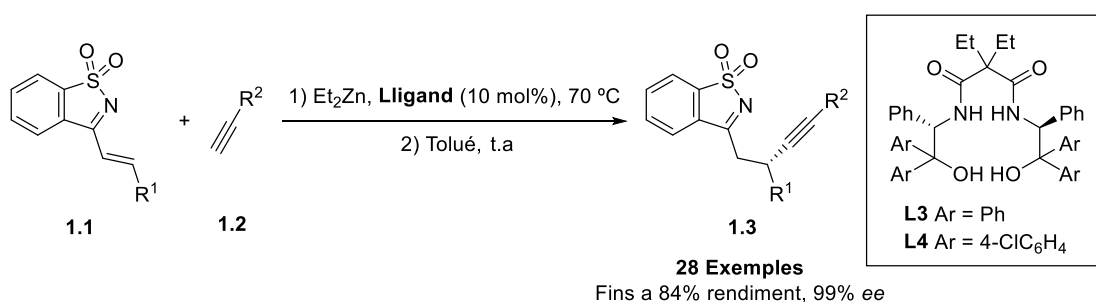


Figura 4.3- Exemples seleccionats d'alquins amb aplicacions rellevants.

S'ha desenvolupat l'alquiniació enantioselectiva mediada per zinc d'imines derivades de la sacarina per obtenir β -alquini imines que incorporen un estereocentre propargílic. La reacció va ser catalitzada per un complex metàl·lic de zinc, utilitzant el lligand **L4** quan es van emprar alquins terminals aromàtics i el lligand **L3** per alquins terminals alifàtics. (Esquema 4.1)

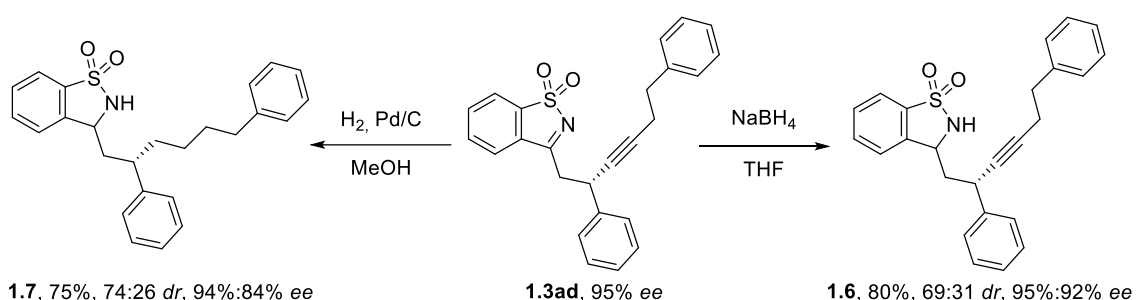


Esquema 4.1- Alquiniació enantioselectiva de 1-azadiens derivats de la sacarina.

S'ha avaluat l'abast i les limitacions de la reacció assatjant diferents alquins aromàtics i imines derivades de la sacarina. Es va observar que la reacció és altament sensible a les modificacions estructurals del substituent β -aril del doble enllaç de la imina, donant lloc a rendiments baixos i enantioselectivitats moderades. En canvi, l'ús d'alquins terminals

alifàtics va conduir a l'obtenció de millors rendiments i enantioselectivitats excel·lents. A diferència del cas dels alquins aromàtics, la introducció de substituents en la imina va ser ben tolerada. Addicionalment, l'ús d'alquins alifàtics i funcionalitzats també va conduir a resultats satisfactoris.

Finalment, la versatilitat sintètica dels productes obtinguts es va avaluar mitjançant diferents transformacions sintètiques, que van permetre l'obtenció de sulfonamides que incorporen substituents alquínics o alifàtics, en funció de les condicions de reducció emprades. En ambdós casos, els productes es van obtenir amb alts rendiments com a mescles de diastereòmers, amb retenció completa de la enantioselectivitat pel diastereòmer majoritari (Esquema 4.2).



Esquema 4.2- Síntesi de sulfonamides quirals mitjançant reducció selectiva de la imina i la reducció total tant de l'amina com de l'alquí.

Capítol 2. Adició enantioselectiva organocatalítica *sulfa*-Michael de bisulfit de sodi a nitroalquens.

Els àcids sulfònics i els seus derivats, especialment aquells amb activitat òptica, són compostos d'alt interès ja que es troben en un gran nombre de compostos farmacològicament actius i en compostos biològics d'alta rellevància, i s'han utilitzat com a agents de resolució quiral (Figura 4.4). Tot i que existeixen mètodes per la seva síntesi, aquests impliquen tradicionalment processos complexos amb diverses etapes. Recentment, s'ha desenvolupat l'adició enantioselectiva *sulfa*-Michael de bisulfit de sodi a alquens deficients en electrons; no obstant això, la seva aplicació s'ha limitat a compostos carbonílics insaturats. En aquest context, l'ús de nitroalquens com a acceptors de Michael resulta especialment interessant, ja que els àcids nitrosulfònics quirals obtinguts són precursors d'aminoàcids sulfònics.

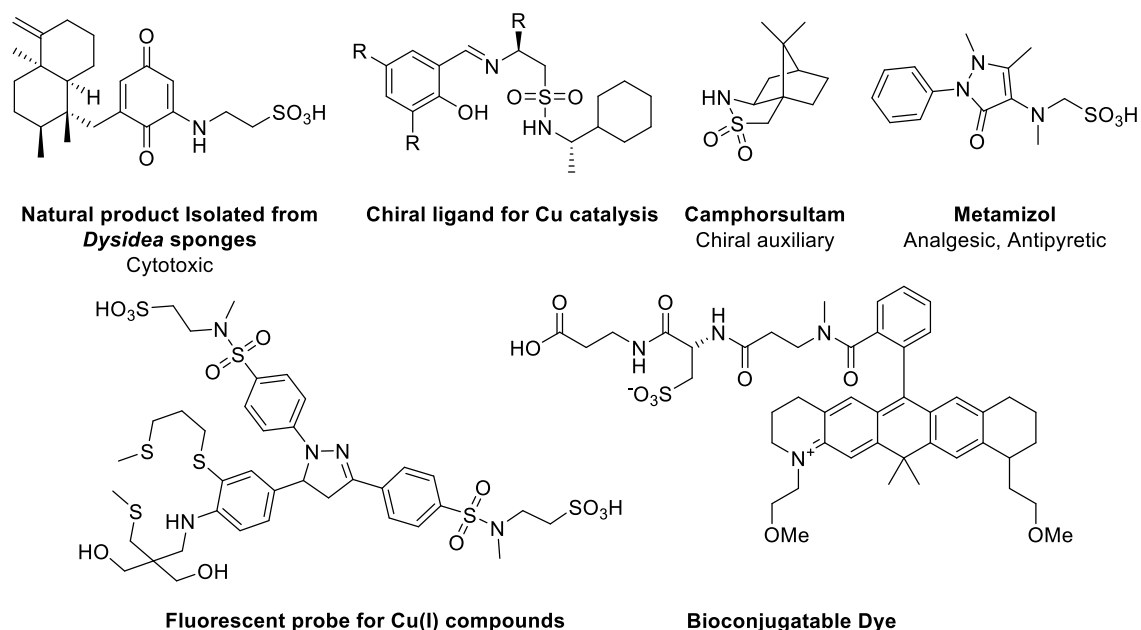
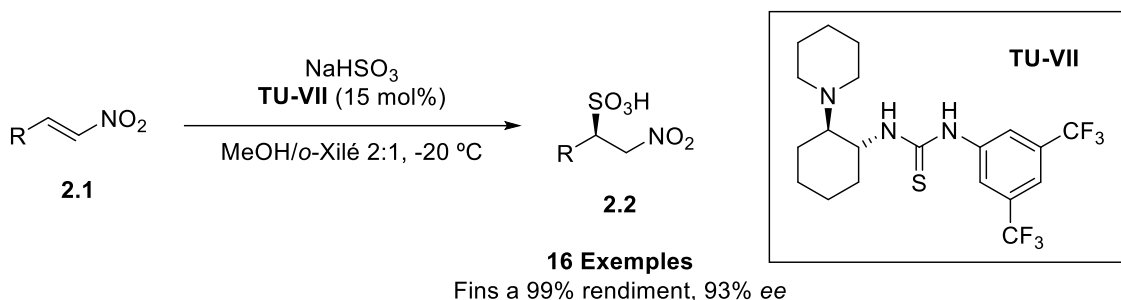


Figura 4.4- Exemples d'àcids sulfònics i dels seus derivats amb aplicacions rellevants.

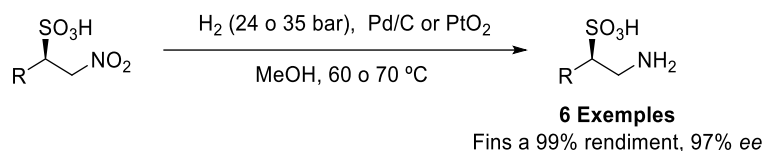
S'ha dut a terme l'addició enantioselectiva de bisulfit de sodi a *trans*- β -nitroestirens per obtenir àcids nitrosulfònics quirals. La reacció va ser organocatalitzada per una tiourea quiral derivada del *trans*-1,2-diaminociclohexà (Esquema 4.3)



Esquema 4.3- Addició enantioselectiva de bisulfit de sodi a *trans*- β -nitroestirens.

Es van avaluar l'abast i limitacions de la reacció assatjant diferents *trans*- β -nitroestirens, obtenint-se els corresponents àcids nitrosulfònics amb excel·lents rendiments i enantioselectivitats, tant en presència de substituents donadors d'electrons com atractors d'electrons, independentment de la seva posició en l'anell aromàtic. Addicionalment, aquesta metodologia s'ha estès amb èxit a nitroalquens heterocíclics i alifàtics, en els quals es van mantindre els rendiments quantitatius, encara que es va observar una lleugera erosió de l'excés enantiomèric.

L'aplicabilitat d'aquest procediment es va demostrar portant a terme la reacció a escala de 1.0 mmol, mantenint-se els excel·lents resultats previs. Finalment, la versatilitat sintètica dels productes obtinguts es va avaluar mitjançant la hidrogenació del grup nitro; tot i que aquesta transformació no es va aconseguir en el nostre grup degut a les dràstiques condicions experimentals requerides, una publicació simultània sobre aquesta mateixa reacció va demostrar que la transformació és factible (Esquema 4.4).^[137]



Esquema 4.4 Condicions de reacció descrites per Bischoff i Brière per la reducció dels àcids nitrosulfònics **2.2**: H₂ (24 bar), Pd/C (10 mol%, 20% w/w), MeOH, 60 °C, 24 h o H₂ (35 bar), 5% PtO₂ (5 mol%), MeOH, 70 °C, 72 h.

Capítol 3. Construcció enantioselectiva de centres estereogènics tetra substituïts mitjançant l'adició *sulfa*-Michael organocatalítica de bisulfit de sodi a nitroalquens β,β-disubstituïts.

La construcció de centres estereogènics tetrasubstituïts és un camp d'alt interès en síntesi degut a la presència d'aquestes estructures en nombrosos productes naturals i compostos d'interès farmacològic (Figura 4.5). En aquest context, l'ús de nitroalquens β,β-disubstituïts permet l'obtenció àcids nitrosulfònics quirals que contenen un centre estereogènic tetrasubstituït directament unit al grup sulfònic. Addicionalment, l'ús d'aquests substrats possibilita la introducció de grups fluorats, de gran rellevància en el desenvolupament de fàrmacs, així com de grups èster en la molècula final, donant lloc a valuosos precursors de β-aminoàcids sulfònics.

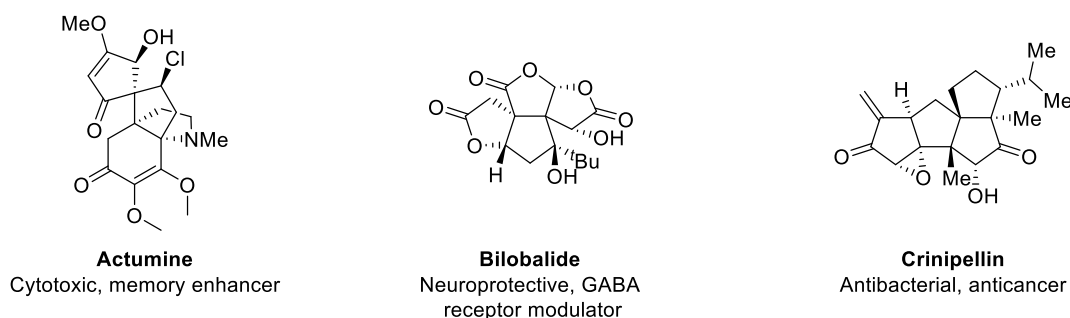
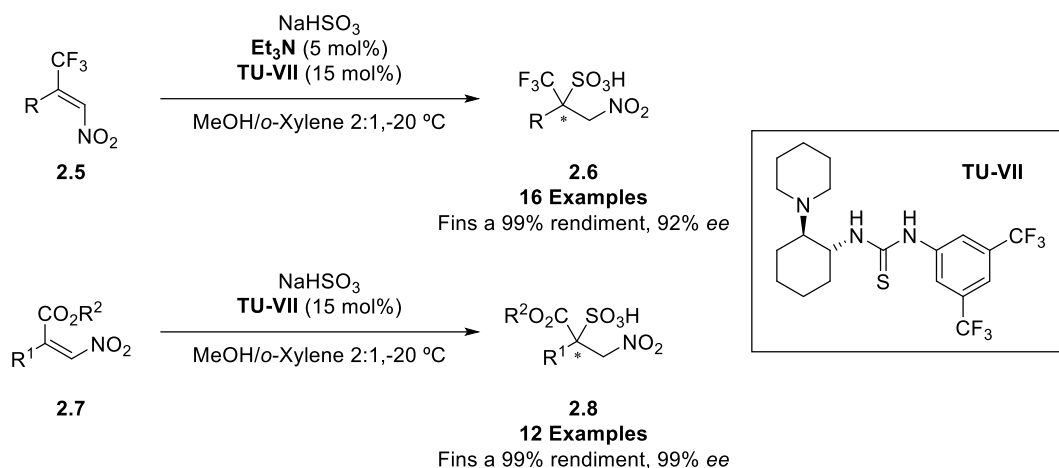


Figura 4.5- Exemples de productes naturals amb activitat biològica que presenten centres estereogènics tetrasubstituïts en la seva estructura.

S'ha estudiat la reacció d'adició enantioselectiva de bisulfit de sodi a nitroalquens β-CF₃-β,β-disubstituïts i èsters β-nitroacrílics per obtenir àcids nitrosulfònics quirals que presenten un estereocèntr tetrasubstituït en la seua estructura. La reacció va ser organocatalitzada per una tiourea quiral derivada del *trans*-1,2-diaminociclohexà (Esquema 4.5)



Esquema 4.5- Adició enantioselectiva de bisulfit de sodi a nitroalquens β,β-disubstituïts

Es van avaluar l'abast i limitacions de la reacció assatjant, en primer lloc, diferents nitroalquens β-CF₃-β,β-disubstituïts. S'obtingueren bons resultats en presència de grups donadors i atractors d'electrons quan aquests es van introduir en les posicions *para* i *meta* de l'anell aromàtic. No obstant això, la substitució en la posició *orto* va inhibir completament la reacció, independentment de la naturalesa del substituent, possiblement degut a l'elevat impediment estèric que imposen els substituents en aquesta posició per la seva proximitat al lloc de reacció. A més, aquesta metodologia també s'ha estès a nitroalquens alifàtics i heterocíclics.

Per altra banda, l'estudi de la reacció emprant diferents èsters β-nitroacrílics com a acceptors de Michael ha conduït a l'obtenció d'excel·lents resultats amb substituents en les posicions *para* o *meta*, mentre que la substitució en la posició *orto* va inhibir completament la reacció. També es van estudiar substrats heterocíclics i alifàtics.

L'aplicabilitat d'aquest procediment es va demostrar sintetitzant el compost **2.6a** a escala de 1.0 mmol, mantenint-se els excel·lents resultats previs. Finalment, la versatilitat sintètica del producte **2.6a** es va avaluar mitjançant diferents transformacions que, malauradament, van donar lloc a mesclures complexes o la descomposició del producte de partida. La investigació continua oberta i en el futur s'investigaran les transformacions sintètiques dels compostos **2.8**.

Capítol 4. Adició enantioselectiva organocatalítica sulfa-Michael de bisulfit de sodi a 1-azadiens derivats d'aurona

Els heterocicles són fonamentals en la química mèdica degut a la seva presència en un gran nombre de productes naturals i en molècules bioactives. En concret, els derivats de benzofurà destaquen per estar presents en nombrosos fàrmacs amb un ampli ventall d'efectes fisiològics. (Figura 4.6). En aquest context, els 1-azadiens derivats de les auronas, una subclasse de la família dels flavonoides, són especialment interessants, ja que són excel·lents acceptors de Michael i permeten l'obtenció de derivats de benzofurà quirals. Concretament, l'adició de bisulfut de sodi als azadiens derivats de l'aurona permet obtenir γ -aminoàcids sulfònics quirals derivats del nucli de benzofurà.

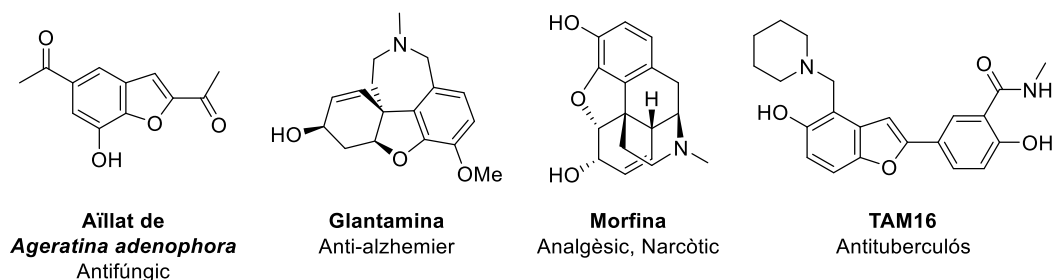
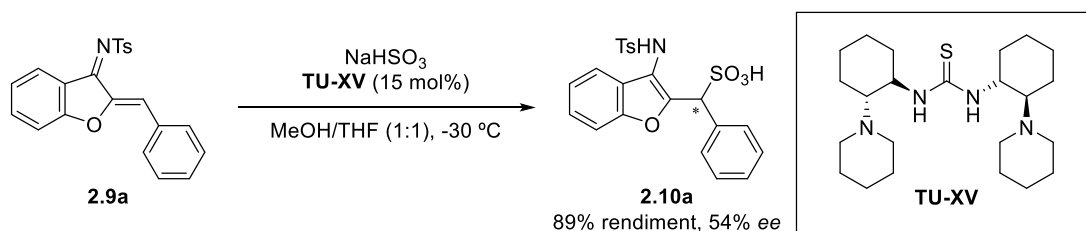


Figura 4.6- Exemples de benzofurans amb activitat biològica.

S'ha estudiat la reacció d'adició enantioselectiva de bisulfit de sodi a 1-azadiens derivats de l'aurona però obtenir γ -aminoàcids sulfònics. Després d'un ampli estudi per optimitzar les condicions de reacció, on s'avaluaren diferents famílies d'organocatalitzadors, sulfonamides, dissolvents, concentracions de reactius i temperatures, malauradament els resultats obtinguts no van ser satisfactoris (Esquema 4.6).



Esquema 4.6- Adició enantioselectiva de bisulfit de sodi a 1-azadiens derivats de l'aurona.

Conseqüentment, resulta necessari aprofundir en la recerca, ja que les condicions de reacció actuals podrien haver assolit les limitacions del sistema catalític utilitzat i no permeten obtenir el compost **2.10a** amb nivells satisfactoris d'enantioselectivitat. Serà necessari dur a terme una revisió exhaustiva dels paràmetres de reacció optimitzats, incloent-hi la possibilitat d'emprar classes alternatives d'organocatalitzadors o diferents estratègies catalítiques.

Capítol 5. Adició organocatalítica enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil.

Degut a la combinació d'estabilitat i reactivitat de l'enllaç S(VI)-F, els fluorurs de sulfonil són compostos d'alt interès en el camp de la química *Click*. A més, aquests compostos han demostrat ser altament rellevants per les seues aplicacions biològiques i per el desenvolupament de nous fàrmacs (Figura 4.7). No obstant això, encara que els mètodes per a la síntesi de fluorurs de sulfonil aromàtics han estat àmpliament estudiats, es disposa de pocs procediments per a la síntesi de fluorurs de sulfonil alifàtics, sent especialment escassos els exemples de síntesi enantioselectiva. Una via per accedir a fluorurs de sulfonil alifàtics quirals és mitjançant l'addició conjugada enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil.

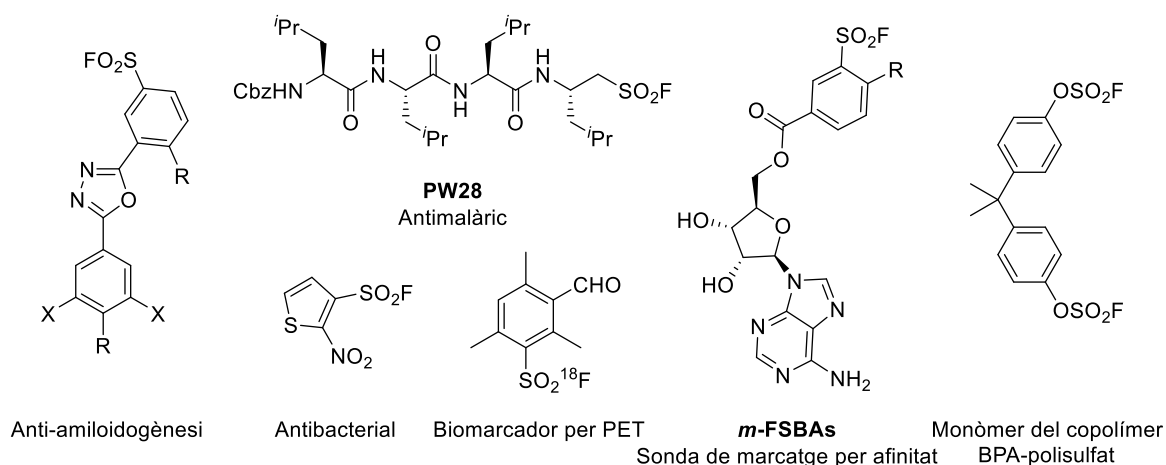
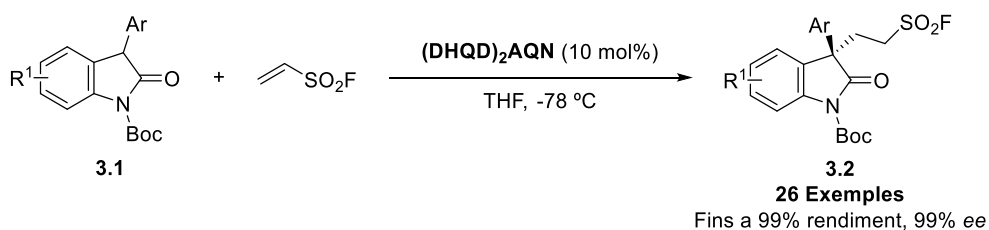


Figura 4.7- Exemples seleccionats de fluorurs de sulfonil amb aplicacions rellevants.

S'ha descrit la reacció d'addició enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil per obtenir fluorurs de sulfonil quirals que incorporen un estereocentre quaternari unit a un esquelet d'oxindole. La reacció va ser organocatalitzada per l'adducte de bisdihidroquinidina (**(DHQD)₂AQN**) (Esquema 4.7).

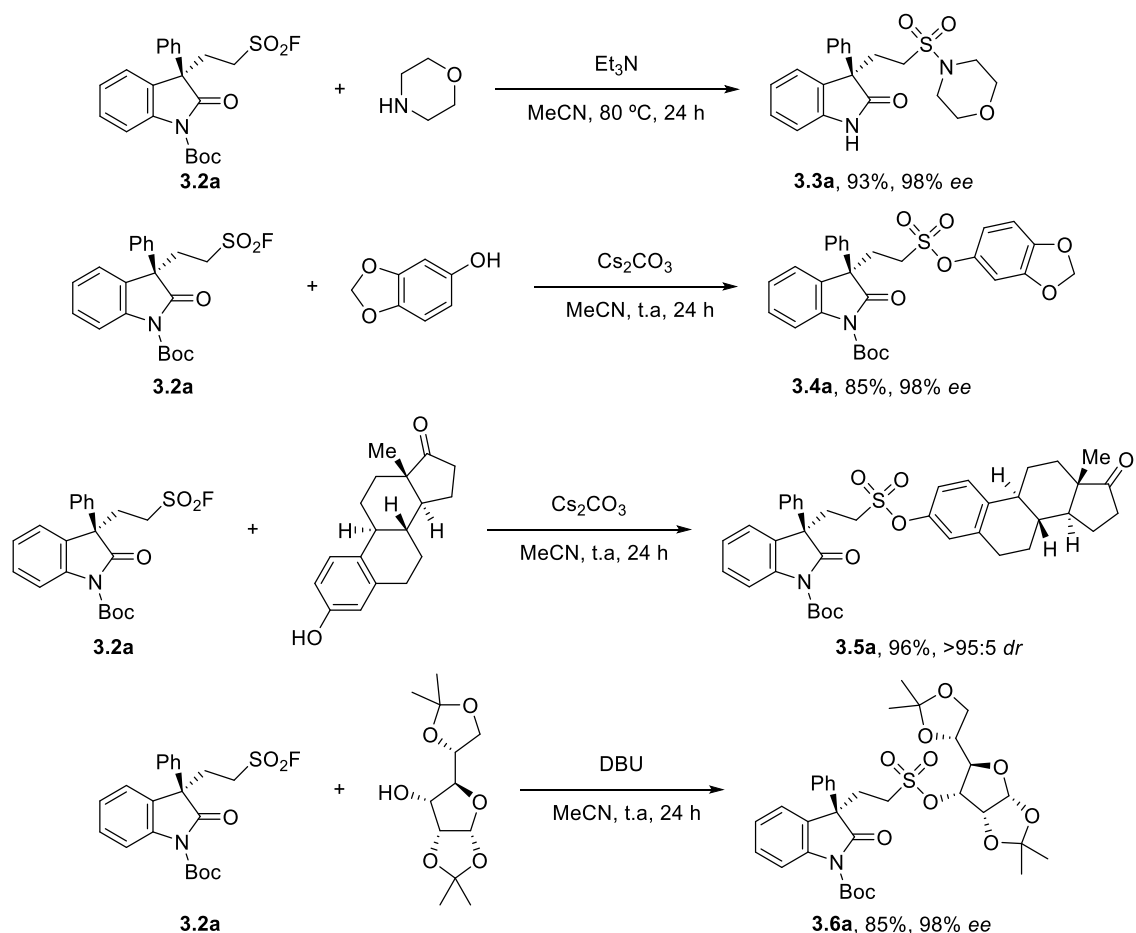


Esquema 4.7- Addició enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil.

Es van avaluar l'abast i limitacions de la reacció assatjant diferents 3-ariloxindoles, obtenint-se resultats excel·lents en tots els casos, excepte quan es van introduir substituents en la posició 4 del anell d'oxindole o en la posició *orto* de l'anell aromàtic en posició 3 de l'oxindole, on es va observar un descens de la enantioselectivitat. Aquest efecte es pot justificar per l'elevat impediment estèric que imposen els substituents en aquestes posicions degut a la seua proximitat al lloc de reacció. Addicionalment, es van assatjar oxindoles més complexes, com derivats carbonílics i heterocíclics, els quals van ser tolerats per la reacció, donant lloc a resultats excel·lents. No obstant això, l'ús de 3-

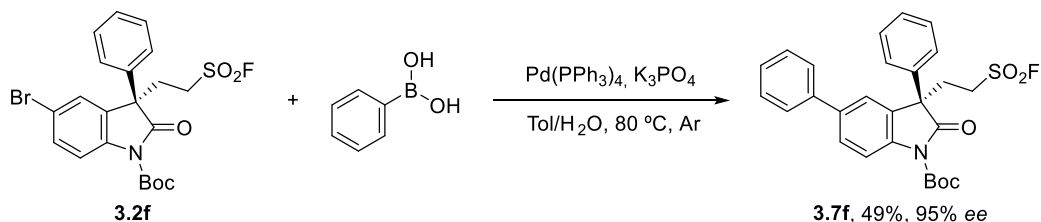
alquiloxindoles va conduir a resultats desfavorables, amb baixos rendiments i enantioselectivitats.

Finalment, la versatilitat sintètica dels productes obtinguts es va avaluar mitjançant diferents transformacions sintètiques. En primer lloc, es van dur a terme diverses reaccions SuFEx sobre el fluorur de sulfonil, obtenint diferents sulfonamides i sulfonats amb excel·lents rendiments i amb total retenció de l'enantioselectivitat (Esquema 4.8).



Esquema 4.8- Síntesi de sulfonamides i sulfonats mitjançant reaccions SuFEx.

Addicionalment, es va estudiar la reactivitat ortogonal del grup SO_2F mitjançant un acoblament creuat de Suzuki utilitzant un derivat bromat, obtenint el producte d'acoblament amb un rendiment i excés enantiomèric satisfactoris (Esquema 4.9).



Esquema 4.9- Reacció d'acoblament creuada de Suzuki a partir del derivat bromat 3.2f

Metodologia Experimental

Procediments generals

El progrés de la reacció es va monitoritzar per cromatografia de capa fina (CCF) utilitzant plaques de sílice Merck Silica Gel 60 F-254 (Merck, ref. 5554). La cromatografia per columna es va dur a terme utilitzant sílice Merck Silica Gel 60 (grandària de partícula 0,040–0,063 mm), fent passar l'eluent a través de la columna per mitjà d'una bomba d'aire. La visualització de les plaques de CCF es va realitzar bé sota llum ultraviolada (254 o 365 nm), bé després de revelar-les amb una solució de molibdat de ceri (10 g de $\text{Ce}(\text{SO}_4)_2$ i 25 g d'àcid fosfomolibdic en 80 mL d' H_2SO_4 concentrat) o amb permanganat de potassi (1,5 g de KMnO_4 , 10 g de K_2CO_3 , 1,25 mL d'una solució de NaOH al 10% en 200 mL d' H_2O).

Immediatament abans del seu ús, la resina d'intercanvi iònic àcida Amberlyst®15 es va condicionar rentant-la amb HCl 6 M (3×3 mL) i amb aigua desionitzada (3×3 mL). Cada rentat amb HCl es va deixar en contacte amb la resina durant 5 minuts.

Dissolvents i reactius

Per a les operacions rutinàries, es van emprar dissolvents de grau analític. Quan es requerien en forma anhidra, CH_2Cl_2 , DCE i tolué es van destil·lar a partir de CaH_2 sota atmosfera de nitrogen, mentre que el THF i el Et_2O es van destil·lar recentment a partir de sodi/benzofenona també sota nitrogen. Els reactius disponibles comercialment es van utilitzar generalment tal com es van rebre, sense cap tractament addicional.

Punts de fusió

Els punts de fusió es van determinar en tubs capil·lars oberts utilitzant un aparell Büchi M-560; els valors indicats no estan corregits.

Espectroscòpia de ressonància magnètica nuclear (RMN)

Els espectres de RMN de ^1H i ^{13}C es van obtenir en instruments Bruker Avance III 300, Bruker AV400 o Bruker Neo500, operant a 300, 400 o 500 MHz per a ^1H i a 75, 101 o 125 MHz per a ^{13}C , respectivament. Els espectres de ^{19}F es van mesurar a 282 MHz (Avance III 300) o 471 MHz (Neo500). Els desplaçaments químics (δ) s'expressen en ppm i les constants de acoblament (J) s'indiquen en Hz. Les multiplicats dels senyals de carboni es van assignar mitjançant experiments DEPT i/o HSQC. Els senyals residuals dels dissolvents deuterats es van utilitzar com a estàndards interns: δ 7,26 (^1H) i δ 77,00 (^{13}C) en CDCl_3 ; δ 2,19 (^1H) i δ 1,32 i 118,3 (^{13}C) en CD_3CN ; δ 2,50 (^1H) i δ 39,52 (^{13}C) en $\text{DMSO}-d_6$; δ 4,87 (^1H) i δ 49,00 (^{13}C) en CD_3OD .

Polarimetria

Les rotacions òptiques es van determinar amb un polarímetre Perkin-Elmer equipat amb una làmpada de sodi (589 nm, línia D) o amb un polarímetre Bellingham+Stanley ADP430 amb una font LED a la mateixa longitud d'ona, emprant en tots dos casos cèl·lules d'1 dm de longitud òptica. Les concentracions (c) s'expressen en g per 100 mL.

Espectrometria de masses d'alta resolució (HRMS)

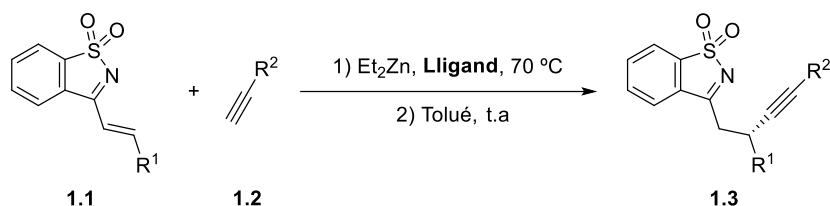
Els espectres de masses per ionització per electrospray (ESI-MS) es van enregistrar en un instrument Waters Q-TOF Premier amb una font d'electrospray operant a un voltatge capil·lar de 3,3 kV.

Anàlisis per HPLC

Les separacions quirals es van realitzar en un sistema Hitachi Elite LaChrom L-2130 equipat amb un detector de diodes Hitachi L-4500 o LaChrom Ultra L-2455U, o bé en un sistema Agilent 1100 Series equipat amb un detector de diodes Hitachi L-4500. Es van emprar columnes quirals de Daicel o Phenomenex, utilitzant mescles d'hexà/isopropanol o heptà/etanol que contenen àcid trifluoroacètic i trietilamina com a eluents. Els temps de retenció (t_r) s'indiquen en minuts.

Síntesi i caracterització de les β -alquínil imines 1.3

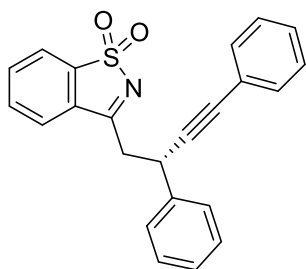
Procediment general per l'addició enantioselectiva d'arilacetilens terminals 1.2.



En un tub d'assaig, el lligand **L4** (0,0125 mmol, 10,5 mg, 10 mol %) i l'alquí **1.2a-d** (0,625 mmol, 5 equiv.) es van dissoldre en tolué sec (0,5 mL) sota atmosfera de nitrogen. A aquesta solució s'hi va afegir gota a gota Et₂Zn (1,5 M en tolué, 0,5 mmol, 0,34 mL, 4 equiv.), i la mescla resultant es va agitar a 70 °C durant 2 hores. Després de refredar-la a temperatura ambient, es va afegir mitjançant xeringa una solució de la imina corresponent **1.1** (0,125 mmol, 1 equivalent) en tolué sec (1 mL), i la mescla de reacció es va agitar fins a la seua completa finalització.

La reacció es va neutralitzar amb una solució de NH₄Cl al 20 % (1 mL), es va extraure amb DCM (3 × 15 mL), es va rentar amb salmorra (15 mL) i es va assecar sobre MgSO₄. Els dissolvents es van eliminar *in vacuo* i el producte cru resultant es va purificar per cromatografia de columna sobre gel de sílice utilitzant mescles d'hexà:Et₂O, per obtenir els compostos **1.3aa-ad**.

1,1-diòxid de (S)-3-(2,4-difenilbut-3-in-1-il)benzo[d]isotiazole (1.3aa)



El procediment general es va seguir utilitzant **1.1a** (0.125 mmol, 33.7 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **1.3aa** com un oli incolor (21.8 mg, 47% rendiment). També es va aïllar el producte d'etilació **1.8** (9.3 mg, 25% rendiment). El compost (S)-**1.3aa** es va obtenir amb un excés enantiomèric del 85%, determinat per HPLC utilitzant una columna Chiralcel OD-H [*n*-hexà/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 29.1$ min, $\tau_{\text{minor}} = 25.8$ min.

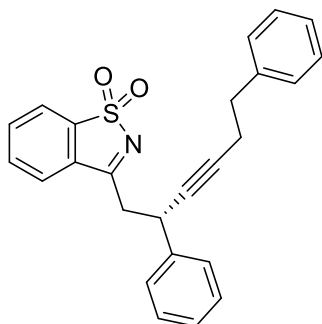
$[\alpha]_D^{25} = -2.5$ ($c = 0.80$, CHCl₃, 87% ee). **¹H RMN** (300 MHz, CDCl₃) δ 7.96 – 7.86 (m, 1H), 7.76 – 7.58 (m, 2H), 7.57 – 7.49 (m, 2H), 7.43 – 7.26 (m, 8H), 4.65 (dd, $J = 8.4, 6.3$ Hz, 1H), 3.55 (dd, $J = 15.3, 8.4$ Hz, 1H), 3.41 (dd, $J = 15.4, 6.3$ Hz, 1H); **¹³C RMN** (75 MHz, CDCl₃) δ 173.7 (C=N), 156.0 (C), 153.5 (C), 140.0 (C), 133.9 (CH), 133.7 (CH), 131.8 (CH), 131.4 (C), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 124.3 (CH), 122.9 (CH), 122.7 (CH), 89.0 (C), 85.2 (C), 39.9 (CH₂), 36.1 (CH); **HRMS (ESI-TOF)** calculada per [C₂₃H₁₇NO₂S+H]⁺: 372.4615; trobada: 372.4620.

Procediment general per l'adició enantioselectiva d'alquilacetilens terminals 1.2.

En un tub d'assaig, el lligand **34** (0,0125 mmol, 9.0 mg, 10 mol %) i l'alquí **1.2d-j** (0,625 mmol, 5 equiv.) es van dissoldre en tolué sec (0,5 mL) sota atmosfera de nitrogen. A aquesta solució s'hi va afegir gota a gota Et_2Zn (1,5 M en tolué, 0,5 mmol, 0,34 mL, 4 equiv.), i la mescla resultant es va agitar a 70 °C durant 2 hores. Després de refredar-la a temperatura ambient, es va afegir mitjançant xeringa una solució de la imina corresponent **1.1** (0,125 mmol, 1 equivalent) en tolué sec (1 mL), i la mescla de reacció es va agitar fins a la seua completa finalització.

La reacció es va neutralitzar amb una solució de NH_4Cl al 20 % (1 mL), es va extraure amb DCM (3×15 mL), es va rentar amb salmorra (15 mL) i es va assecat sobre MgSO_4 . Els dissolvents es van eliminar *in vacuo* i el producte cru resultant es va purificar per cromatografia de columna sobre gel de sílice utilitzant mescles d'hexà:Et₂O per obtenir els compostos **1.3ad-aj**.

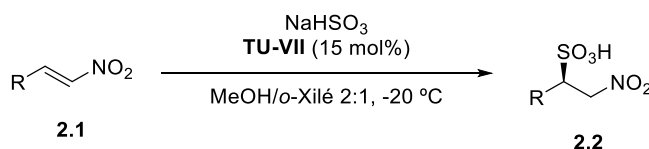
1,1-diòxid de (S)-3-(2,6-difenilhex-3-in-1-il)benzo[d]isotiazole (1.3ad)



El procediment general es va seguir utilitzant **1.1a** (0.125 mmol, 3.7 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **1.3ad** com un oli incolor (34.0 mg, 68% rendiment). El compost (S)-**1.3ad** es va obtenir amb un excés enantiomèric del 95%, determinat per HPLC utilitzant una columna Chiralcel OD-H [*n*-hexà/*i*-PrOH (80:20), 1 mL/min]: $\tau_{\text{major}} = 29.5$ min, $\tau_{\text{minor}} = 24.7$ min. $[\alpha]_D^{25} = 6.2$ ($c = 1.0$, CHCl_3 , 95% ee). **¹H RMN** (300 MHz, CDCl_3) δ 7.91 – 7.87 (m, 1H), 7.74 – 7.61 (m, 2H), 7.51 – 7.49 (m, 1H), 7.40 – 7.04 (m, 10H), 4.36 (ddt, $J = 8.4, 6.2, 2.3$ Hz, 1H), 3.40 (dd, $J = 15.0, 8.6$ Hz, 1H), 3.27 (dd, $J = 15.0, 8.6$ Hz, 1H), 2.74 (t, $J = 7.4$ Hz, 2H), 2.55 – 2.35 (m, 2H); **¹³C RMN** (75 MHz, CDCl_3) δ 173.9 (C), 140.5 (C), 139.9 (C), 133.7 (CH), 133.6 (CH), 131.5 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 127.6 (CH), 126.3 (CH), 124.3 (CH), 122.6 (CH), 84.7 (C), 80.5 (C), 40.1 (CH_2), 35.6 (CH), 35.0 (CH_2), 21.0 (CH_2); **HRMS (ESI-TOF)** calculada per $[\text{C}_{25}\text{H}_{21}\text{NO}_2\text{S}+\text{H}]^+$: 400.1366; trobada: 400.1363.

Síntesi i caracterització dels àcids β -nitro sulfònics 2.2

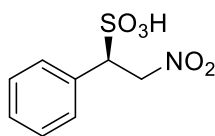
Procediment general per l'adició enantioselectiva de bisulfit de sodi a *trans*- β -nitroestirens



En un tub d'assaig, el catalitzador **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%) i el nitroalquí **2.1** (0.2 mmol, 1 equiv.) es van dissoldre en una mescla de MeOH/*o*-xilé (2 mL, v/v, 2:1), i la dissolució resultant es va agitar a -20 °C 10 minuts. Posteriorment, es va afegir el NaHSO_3 (0.48 mmol, 50.0 mg, 2.4 equiv.) dissolt en 0.5 mL d'aigua i la reacció es va agitar vigorosament tota la nit o fins que la reacció es va completar (CCF). La mescla de reacció es va filtrar a través de Celite®, es va rentar amb aigua i els dissolvents es van eliminar *in*

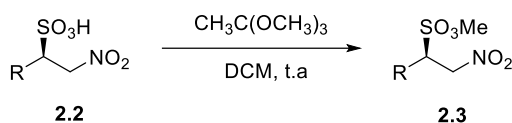
vacuo. El producte cru es va dissoldre en 3 mL d'una mescla de THF/H₂O (v/v, 2:1), es va fer passar a través de resina àcida d'intercanvi iònic Amberlyst®15 recentment condicionada i es va rentar amb aigua (3 x 3 mL). La solució aquosa resultant es va concentrar *in vacuo* i es va assecat sota alt buit en presència de P₂O₅. Els productes crus es van purificar per cromatografia de columna sobre gel de sílice utilitzant mescles de DCM/MeOH per obtenir els compostos **2.2**.

Àcid (*R*)-2-nitro-1-feniletan-1-sulfònic (**2.2a**)



El procediment general es va seguir utilitzant **2.1a** (0.2 mmol, 29.8 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **2.2a** com un sòlid blanc (45.5 mg, 98% rendiment). **Pf** 88 – 92 °C. $[\alpha]_D^{25} = 5.7$ (*c* = 0.49, MeOH, 92% ee). **¹H RMN** (300 MHz, CD₃OD) δ 7.49 – 7.45 (m, 2H), 7.37 – 7.32 (m, 3H), 5.29 (dd, *J* = 13.6, 5.1 Hz, 1H), 5.06 (dd, *J* = 13.6, 10.0 Hz, 1H), 4.75 (dd, *J* = 10.0, 5.1 Hz, 1H); **¹³C RMN** (75 MHz, CD₃OD) δ 135.2 (C), 130.5 (CH), 129.5 (CH), 129.4 (CH), 77.5 (CH₂), 65.0 (CH); **HRMS (ESI-TOF)** calculada per [C₈H₉NO₅S+NH₄]⁺: 249.0540; trobada: 249.0529.

Procediment general per la síntesi dels esters β-nitrosulfònics **2.3**



L'àcid sulfònic cru **2.1** (0.1 mmol, 1 equiv.) obtingut després de la filtració a través d'Amberlyst@15 es va dissoldre en DCM (1 mL) a temperatura ambient. A continuació, es va afegir l'ortoacetat de trimetil (0.5 mL, 3.9 mmol, 39 equiv.) i la reacció es va agitar durant 2 hores. Els dissolvents es van evaporar *in vacuo* i les traces de dissolvents es van eliminar sota alt buit per obtenir el esters β-nitro sulfònics **2.3**.

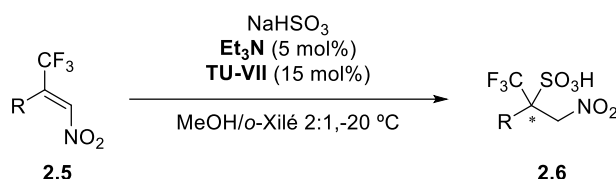
(*R*)-2-nitro-1-feniletan-1-sulfonat de metil (**2.3a**)



El procediment general es va seguir utilitzant **2.2a** (0.1 mmol, 23.1 mg, 1 equiv.). El compost (*R*)-**2.3a** es va obtenir com un sòlid blanc amb un 92% d'excés enantiomèric, determinat per HPLC utilitzant una columna Chiralpak AY-H [*n*-hexà/*i*-PrOH (80:20), 1 mL/min]: τ_{major} = 22.2 min, τ_{minor} = 21.0 min. **Pf** 108 – 113 °C. $[\alpha]_D^{25} = 13.4$ (*c* = 0.48, CHCl₃, 92% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.46 (br s, 5H), 5.27 (dd, *J* = 13.5, 5.3 Hz, 1H), 5.16 (dd, *J* = 8.4, 5.3 Hz, 1H), 5.03 (dd, *J* = 13.5, 8.4 Hz, 1H), 3.76 (s, 3H); **¹³C NMR** (75 MHz, CDCl₃) δ 130.6 (CH), 129.7 (CH), 129.5 (CH), 128.5 (C), 74.2 (CH₂), 63.4 (CH), 58.0 (CH₃); **HRMS (ESI-TOF)** calculada per [C₉H₁₁NO₅S+NH₄]⁺: 263.0696; trobada: 263.0701.

Síntesi i caracterització dels àcids β -nitrosulfònics tetrasubstituïts **2.6** i **2.8**

Procediment general per l'addició enantioselectiva de bisulfit de sodi a nitroalquens β -CF₃- β , β -disubstituïts.



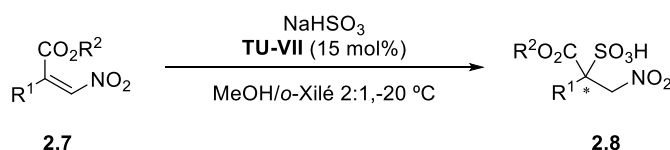
En un tub d'assaig, el catalitzador **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%), el nitroalquè β -CF₃- β , β -disubstituït **2.5** (0.2 mmol, 1 equiv.) i la trietilamina (0.01 mmol, 1.4 μ L, 5 mol%) es van dissoldre en una mescla de MeOH/*o*-xilè (2 mL, v/v, 2:1), i la dissolució resultant es va agitar a -20 °C 10 minuts. Posteriorment, es va afegir el NaHSO₃ (0.48 mmol, 50.0 mg, 2.4 equiv.) dissolt en 0.5 mL d'aigua i la reacció es va agitar vigorosament fins que la reacció es va completar (CCF). La mescla de reacció es va filtrar a través de Celite®, es va rentar amb aigua i els dissolvents es van eliminar *in vacuo*. El producte cru es va dissoldre en 3 mL d'una mescla de THF/H₂O (v/v, 2:1), es va fer passar a través de resina àcida d'intercanvi iònic Amberlyst®15 recentment condicionada i es va rentar amb aigua (3 x 3 mL). La solució aquosa resultant es va concentrar *in vacuo* i es va assecar sota alt buit en presència de P₂O₅. Els productes crus es van purificar per cromatografia de columna sobre gel de sílice utilitzant mesclures de DCM/MeOH per obtenir els compostos **2.6**.

Àcid 1,1,1-trifluoro-3-nitro-2-fenilpropan-2-sulfònic (**2.6a**)



El procediment general es va seguir utilitzant **2.5a** (0.2 mmol, 43.4 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **2.6a** com un sòlid blanc deliquescents (41.7 mg, 70% rendiment). El compost **2.6a** es va obtenir amb un excés enantiomèric del 89%, determinat per HPLC utilitzant una columna Lux i-Amylose 1 [*n*-hexà/*i*-PrOH (70:30), 1 mL/min]: $\tau_{\text{major}} = 5.5$ min, $\tau_{\text{minor}} = 7.8$ min. $[\alpha]_D^{25} = -49.4$ ($c = 0.70$, MeOH, 89% ee). **¹H RMN** (500 MHz, CD₃OD) δ 7.80 – 7.68 (m, 2H), 7.41 – 7.29 (m, 3H), 5.89 (dq, $J = 14.2$, 1.9 Hz, 1H), 5.48 (d, $J = 14.2$ Hz, 1H). **¹³C NMR** (126 MHz, CD₃OD) δ 130.27 (C), 128.9 (q, $J = 1.9$ Hz, CH), 128.0 (CH), 127.3 (CH), 124.7 (d, $J = 285.1$ Hz, CF₃), 74.66 (q, $J = 2.4$ Hz, CH₂), 71.70 (q, $J = 25.0$ Hz, C). **¹⁹F RMN** (282 MHz, CD₃OD) δ -58.5. **HRMS (ESI-TOF)** calculada per [C₉H₈F₃NO₅S+NH₄]⁺: 317.4014; trobada: 317.0409.

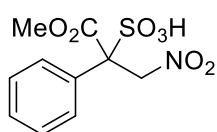
Procediment general per l'addició enantioselectiva de bisulfit de sodi a èsters β -nitroacrílics.



En un tub d'assaig, el catalitzador **TU-VII** (0.03 mmol, 14.0 mg, 15 mol%) i l'èster β -nitroacrílic **2.7** (0.2 mmol, 1 equiv.) es van dissoldre en una mescla de MeOH/*o*-xilè (2 mL,

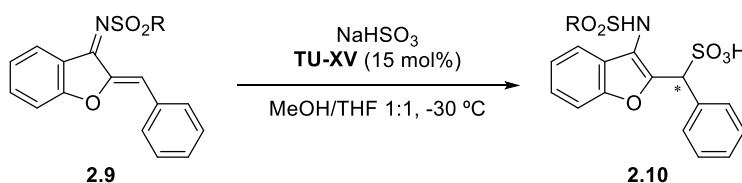
v/v, 2:1), i la dissolució resultant es va agitar a -20 °C 10 minuts. Posteriorment, es va afegir el NaHSO₃ (0.48 mmol, 50.0 mg, 2.4 equiv.) dissolt en 0.5 mL d'aigua i la reacció es va agitar vigorosament fins que la reacció es va completar (CCF). La mescla de reacció es va filtrar a través de Celite®, es va rentar amb aigua i els dissolvents es van eliminar *in vacuo*. El producte cru es va dissoldre en 3 mL d'una mescla de THF/H₂O (v/v, 2:1), es va fer passar a través de resina àcida d'intercanvi iònic Amberlyst®15 recentment condicionada i es va rentar amb aigua (3 x 3 mL). La solució aquosa resultant es va concentrar *in vacuo* i es va assecar sota alt buit en presència de P₂O₅. Els productes crus es van purificar per cromatografia de columna sobre gel de sílice utilitzant mescles de DCM/MeOH per obtenir els compostos **2.8**.

Àcid 1-metoxi-3-nitro-1-oxo-2-fenilpropan-2-sulfònic (**2.8a**)



El procediment general es va seguir utilitzant **2.7a** (0.2 mmol, 42 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **2.8a** com un sòlid blanc deliquescents (54.0 mg, 94% rendiment). El compost **2.8a** es va obtenir amb un excés enantiomèric del 96%, determinat per HPLC després d'esterificar amb ortoacetat de trimetil, utilitzant una columna Chiralpak IC [*n*-hexà/*i*-PrOH (85:15), 1 mL/min]: $\tau_{\text{major}} = 34.0$ min, $\tau_{\text{minor}} = 38.0$ min [$\alpha]_D^{25} = -25.6$ ($c = 1.0$, MeOH, 96% ee). **¹H RMN** (300 MHz, CD₃OD) δ 7.80–7.65 (m, 2H), 7.38–7.23 (m, 3H), 5.72 (d, $J = 15.6$ Hz, 1H), 5.48 (d, $J = 15.6$ Hz, 1H), 3.86 (s, 3H). **¹³C RMN** (75 MHz, CD₃OD) δ 169.9 (C), 135.3 (C), 129.7 (CH), 128.9 (CH), 128.7 (CH), 78.7 (CH₂), 74.3 (C), 53.6 (CH₃). **HRMS (ESI-TOF)** calculada per [C₁₀H₁₁NO₇S+NH₄]⁺: 307.0594; trobada: 307.0594.

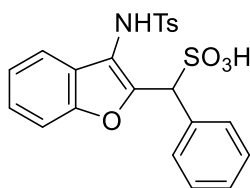
Síntesi i caracterització dels aminoàcids sulfònics **2.10**



Procediment general per l'addició enantioselectiva de bisulfid de sodi a azadiens derivats de l'aurona.

En un tub d'assaig, el catalitzador **TU-XV** (0.015 mmol, 6.1 mg, 15 mol%), l'azadien **2.9** (0.1 mmol, 1 equiv.) i el NaHSO₃ (0.25 mmol, 26.2 mg, 2.5 equiv.) es van dissoldre en una mescla de MeOH/THF (1 mL, v/v, 1:1) sota atmosfera de nitrogen, i la mescla resultant es va agitar a -30 °C fins que la reacció es va completar (CCF) o fins un màxim de 72 hores si no s'observava cap progrés addicional. Els dissolvents es van eliminar *in vacuo* i el producte cru es va dissoldre en 3 mL d'una mescla de THF/H₂O (v/v, 2:1), es va fer passar a través de resina àcida d'intercanvi iònic Amberlyst®15 recentment condicionada i es va rentar amb aigua (3 x 3 mL). La solució aquosa resultant es va concentrar *in vacuo* i es va assecar sota alt buit en presència de P₂O₅. Els productes crus es van purificar per cromatografia de columna sobre gel de sílice utilitzant mescles de DCM/MeOH per obtenir els compostos **2.10**.

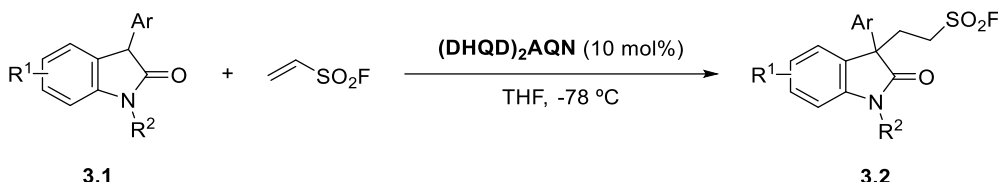
Àcid (3-((4-metilfenil)sulfonamido)benzofuran-2-il)(fenil)metansulfònic (**2.10a**)



El procediment general es va seguir utilitzant **2.9a** (0.1 mmol, 37.5 mg, 1 equiv.). El producte cru es va purificar per cromatografia de columna, obtenint el compost pur **2.10a** com un sòlid groc (40.6 mg, 88% rendiment). El compost **2.10a** es va obtenir amb un excés enantiomèric del 54% determinat per HPLC utilitzant una columna Chiralpak IE [*n*-heptà/EtOH/Et₃N/TFA (90:10:0.3:0.1), 1 mL/min]:

$\tau_{\text{major}} = 7.9$ min, $\tau_{\text{minor}} = 11.9$ min. **Pf** 225 – 227 °C. $[\alpha]_D^{25} = 11.8$ (*c* = 0.75, MeOH, 54% ee). **¹H RMN** (300 MHz, CD₃OD) δ 7.54 (d, *J* = 6.6 Hz, 2H), 7.52 – 7.27 (m, 4H), 7.26 – 7.12 (m, 7H), 5.11 (s, 1H), 2.35 (s, 3H); **¹³C RMN** (75 MHz, CD₃OD) δ 154.9 (C), 149.6 (C), 145.2 (C), 138.1 (C), 135.0 (C), 131.4 (CH), 130.8 (CH), 128.8 (CH), 128.8 (CH), 128.4 (CH), 127.2 (C), 125.8 (CH), 123.9 (CH), 121.1 (CH), 117.6 (C), 112.3 (CH), 64.1 (CH), 21.5 (CH₃); **HRMS (ESI-TOF)** calculada [C₂₂H₁₉NO₆S₂+NH₄]⁺: 475.0992; trobada: 475.0979.

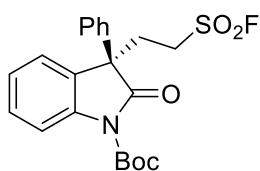
Síntesi i caracterització dels fluorurs de sulfonil **3.2**



Procediment general per l'adició enantioselectiva de 3-ariloxindoles a fluorur d'etensulfonil.

En un tub amb tap de rosca, l'oxindole **3.1** (0.1 mmol, 1.0 equiv.) i (DHQD)₂AQN (0.01 mmol, 8.6 mg, 0.1 equiv.) es van dissoldre en THF anhidre (1 mL). La dissolució resultant es va refredar a -78 °C sota atmosfera de nitrogen. A aquesta dissolució es va afegir, ESF (0.1 mmol, 8.3 µL, 1.0 equiv.) i la mescla resultant es va agitar a -78 °C fins que la reacció es va completar (CCF). Els dissolvents es van eliminar *in vacuo* i el producte cru es va purificar per cromatografia de columna sobre gel de sílice utilitzant mescles d'hexà/EtOAc com a eluent per obtenir els compostos **3.2**.

tert-butyl (*R*)-3-(2-(fluorosulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate (**3.2a**)



General procedure was followed using **3.1a** (0.1 mmol, 30.9 mg, 1.0 equiv.). The crude product was purified by silica gel column chromatography affording pure **3.2a** as a white solid (39.8 mg, 95% yield). Compound (*R*)-**3.2a** was obtained with a 97% enantiomeric excess determined by HPLC using a Chiralpak IC column [*n*-

hexane/*i*-PrOH (90:10), 1.0 mL/min]: $\tau_{\text{major}} = 6.8$ min, $\tau_{\text{minor}} = 5.8$ min. $[\alpha]_D^{25} = 26.1$ (*c* = 0.63, CHCl₃, 97% ee). **¹H NMR** (300 MHz, CDCl₃) δ 7.97 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.2, 6.3, 2.7 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.30 – 7.26 (m, 2H), 3.38 – 3.14 (m, 2H), 3.07 (ddd, *J* = 13.4, 12.0, 4.7 Hz, 1H), 2.71 (ddd, *J* = 13.3, 12.4, 3.7 Hz, 1H), 1.64 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 175.4 (C), 148.9 (C), 139.7 (C), 137.6 (C), 129.8 (CH), 129.3 (CH), 128.7 (C), 128.6 (CH), 126.8 (CH), 125.4 (CH), 124.5 (CH), 116.0 (CH), 85.4 (C), 55.1 (C), 47.00 (d, *J* = 18.1 Hz, CH₂), 31.5 (CH₂), 28.2 (CH₃). **¹⁹F NMR** (282 MHz, CDCl₃) δ 52.8. **HRMS (ESI-TOF)** calc'd for [C₂₁H₂₂FNO₅S+Na]⁺: 442,1095; found: 442,1086.

Conclusions

1. S'han desenvolupat cinc nous mètodes per a la síntesi enantioselectiva de compostos organosulfurats mitjançant la funcionalització nucleofílica de substrats organosulfurats i mitjançant l'adició de bisulfit de sodi a alquens deficients en electrons.
2. S'ha desenvolupat l'adició conjugada enantioselectiva mediada per zinc d'alquins terminals a imines derivades de la sacarina, mitjançant catàlisi metàl·lica per complexos de zinc i lligands quirals de tipus bis(hidroximetil)malonamida. Aquesta metodologia representa el primer exemple d'alquilació conjugada enantioselectiva de imines α,β -insaturades. Les condicions òptimes de reacció per als alquins aromàtics es van establir amb el lligand **L4**, mentre que el lligand **L3** va demostrar ser més eficaç per a alquins alifàtics. Els alquins aromàtics van donar lloc als adductes **1.3** amb rendiments moderats o baixos i enantioselectivitats modestes, mentre que els alquins alifàtics van donar proporcionar rendiments i enantioselectivitats superiors. Les transformacions sintètiques del compost **1.3ad** van proporcionar les sulfonamides **1.6** i **1.7** amb alts rendiments i total retenció de l'enantioselectivitat. Finalment, la difracció de raigs X en monocristall va confirmar la configuració S del centre estereogènic.
3. S'ha desenvolupat l'adició enantioselectiva *sulfa*-Michael de bisulfit de sodi a *trans*- β -nitroestirens, catalitzada per un organocatalitzador bifuncional de tipus tiourea derivat del *trans*-1,2-diaminociclohexà. Aquesta metodologia va mostrar una elevada robustesa, tolerant la introducció de substituents tant donadors com acceptors d'electrons en qualsevol posició de l'anell aromàtic. Addicionalment, també es van assatjar amb èxit nitroalquens alifàtics i heterocíclics. Respecte a les transformacions sintètiques, tot i que la hidrogenació del grup nitro no es va aconseguir en aquest treball, estudis paral·lels publicats han confirmat la viabilitat d'aquesta transformació, posant de relleu la utilitat sintètica dels àcids nitrosulfònics quirals obtinguts. L'estereoquímica absoluta es va establir com a *R* mitjançant difracció de raigs X en monocristall i es va proposar un cicle catalític coherent amb la estereoquímica observada.
4. S'ha desenvolupat un mètode enantioselectiu per a la construcció de centres estereogènics tetrasubstituïts mitjançant l'adició 1,4 de bisulfit de sodi a nitroalquens β -CF₃- β,β -disubstituïts i èsters α -substituïts- β -nitroacrílics, catalitzada per un organocatalitzador bifuncional de tipus tiourea derivat del *trans*-1,2-diaminociclohexà. Aquesta metodologia constitueix el primer exemple d'adició enantioselectiva *sulfa*-Michael de bisulfit de sodi a nitroalquens β,β -disubstituïts. La metodologia va mostrar una elevada robustesa, tolerant la introducció de substituents en posició *para* i *meta* independentment del seu caràcter electrònic. No obstant, la substitució en posició *orto* va inhibir completament la reacció. Les transformacions sintètiques dels productes obtinguts han resultat complexes i es troben en estudi.
5. S'ha estudiat l'adició enantioselectiva *sulfa*-Michael de bisulfit de sodi a azadiens derivats de l'aurona, catalitzada per un organocatalitzador bifuncional de tipus

tiourea amb simetria C_2 derivat del *trans*-1,2-diaminociclohexà. Aquesta reacció representa el primer exemple d'adició enantioselectiva *sulfa*-Michael de bisulfit de sodi a imines α,β -insaturades. L'estudi d'optimització va permetre obtenir els corresponents γ -aminoàcids sulfònics amb rendiments excel·lents, però amb nivells d'enantioselectivitat no satisfactoris. Consequentment, serà necessari dur a terme una revisió exhaustiva dels paràmetres de reacció optimitzats, incloent-hi l'exploració de classes alternatives d'organocatalitzadors o estratègies catalítiques diferents.

6. S'ha desenvolupat un mètode enantioselectiu per a l'adició conjugada de 3-ariloxindoles a fluorur d'etensulfonil, catalitzada per l'aducte de bisdihidroquinidina **(DHQD)₂AQN**. Aquesta metodologia constitueix el primer exemple de la construcció asimètrica d'estereocentres quaternaris mitjançant la funcionalització nucleofílica del fluorur d'etensulfonil. Els millors resultats es van obtenir amb *N*-Boc oxindoles substituïts en les posicions 5, 6 i 7 de nucli d'oxindole, així com en les posicions *meta* i *para* del grup 3-aril, mentre que la introducció de substituents a la posició 4 o *orto* del grup 3-aril va reduir l'enantioselectivitat degut a efectes estèrics. També es van utilitzar amb èxit derivats més complexos amb grups carbonil, sistemes aromàtics ampliat i heterocíclics, encara que els oxindoles amb substituents alquílics en posició 3 van proporcionar rendiments i excessos enantiomèrics inferiors. Les transformacions sintètiques dels compostos **3.2a** van permetre obtenir sulfonamides i sulfonats quirals amb excel·lents resultats mitjançant reaccions SuFEx i es va demostrar la reactivitat ortogonal del grup SO_2F mitjançant un acoblament creuat de Suzuki emprant un derivat bromat. L'estereoquímica absoluta es va establir com a *R* mitjançant difracció de raigs X en monocristall i es va proposar un model estereoquímic coherent amb els resultats observats.

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List of Publications

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Enantioselective zinc-mediated conjugate alkynylation of saccharin-derived 1-aza-butadienes†

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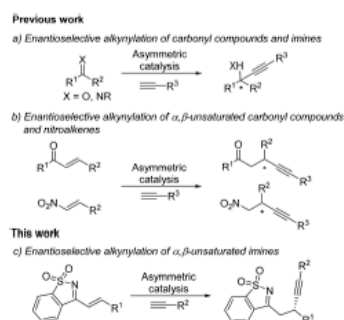
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The enantioselective 1,4-alkynylation of conjugated imines derived from saccharin with aryl- and alkyl-substituted terminal alkynes has been achieved. The reaction mediated by diethylzinc in the presence of a catalytic amount of a bis(hydroxyl)malonamide chiral ligand provides the corresponding imines bearing a propargylic stereocenter with moderate yields and fair to excellent enantioselectivities.

The C–C triple bond is present in the structures of many natural products and other organic compounds of interest in biochemistry and material science.¹ Furthermore, alkynes are versatile building blocks in synthetic organic chemistry that can undergo a broad range of transformation providing access to different functional groups and structural motifs.² Accordingly, the development of procedures to introduce a C–C triple bond in organic molecules is an important goal for many synthetic chemists. Among the different methodologies developed, those that exploit the acidic character of terminal alkynes are especially appealing. Thus, deprotonation of terminal alkynes with stoichiometric or catalytic amounts of base (in the presence of metal catalyst) provides nucleophilic metal alkynylides, which can react with carbon-based electrophiles to give internal alkynes with concomitant formation of a new C–C bond and, sometimes, of a new propargylic stereogenic center. In this context, considerable efforts have been devoted to the enantioselective alkynylation of carbonyl compounds³ and imines⁴ to give propargylic alcohols and amines, respectively (Scheme 1a). On the other hand, the enantioselective alkynylation of electrophilic C–C double bonds conjugated with electron-withdrawing groups has constituted a bigger challenge

due to their lower electrophilicity and regioselectivity issues.⁵ Nevertheless, considerable success has been obtained in the enantioselective alkynylation of conjugated carbonyl compounds⁶ and nitroalkenes⁷ under a variety of metal catalysis (Scheme 1b). However, despite these advances some limitations still remain. For instance, most of the reported procedures are appropriate for aryl- or trialkylsilyl-acetylenes but provide low enantioselectivities with alkyl-substituted alkynes.⁵ Furthermore, developing conditions for the regio- and enantioselective alkynylation of other 1,4-acceptors, besides conjugated carbonyls and nitroalkenes, would be highly desirable.

Recently, α,β -unsaturated imines (1-aza-butadienes), the nitrogen analogues of enones, have been explored as Michael acceptors in enantioselective reactions.^{8,9} However, although a synthesis of pyridines and pyrroles involving the copper-catalyzed conjugate addition of alkyl propiolates to *N*-sulfonyl *aza*-dienes has been reported,¹⁰ there are no literature precedents on the enantioselective conjugate alkynylation of α,β -unsaturated imines to give chiral β -alkynyl imines bearing a propargylic stereocenter. Here, we describe our results on this elusive reaction (Scheme 1c), with



Scheme 1 Enantioselective addition of terminal alkynes.

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† Electronic supplementary information (ESI) available. CCDC 1992564. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc04221h

Enantioselective Addition of Sodium Bisulfite to Nitroalkenes. A Convenient Approach to Chiral Sulfonic Acids

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An enantioselective organocatalytic addition of sodium bisulfite to (E)-nitroalkenes has been developed by using a chiral bifunctional organocatalyst. The present methodology provides a variety of chiral β -nitroethanesulfonic acid compounds (17 examples) with excellent results: up to 99% yield and excellent enantioselectivity (up to 96% ee). The reaction tolerates (hetero)aryl and alkyl substituents on the β -nitroalkenes, and β , β -disubstituted nitroalkenes.

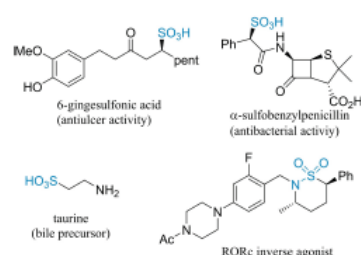


Figure 1. Examples of chiral sulfonic acid derivatives with biological and pharmacological activity.

Organosulfur compounds,^[1] including optically active ones,^[2] are of great importance in organic chemistry due to their occurrence in nature and their pharmaceutical applications. Among them, chiral sulfonic acids and their derivatives have shown remarkable significance and application in the areas of natural product and pharmaceutical chemistry. Examples include the antitumor compound 6-gingesulfonic acid, isolated from *Zingiberis* rhizome,^[3] the antibacterial α -sulfobenzylpenicillin,^[4] or taurine,^[5] a β -amino sulfonic acid precursor of the bile (Figure 1). Similarly, sulfonates and sulfamides have become important pharmacophores in medicinal molecules with a broad spectrum of biological activities, such as antiviral, antibacterial, antitumor and so forth. Among the pool of sulfonamides, sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties, even though they do not occur in nature. Chiral non benzo-fused sultams can be found, for instance in RORc inverse agonists as potential treatments of inflammatory diseases (Figure 1).^[6]

As a result, the pursuit of new catalytic strategies that enable the effective synthesis of sulfur-containing organic molecules with the introduction of chiral information is an important goal in modern synthetic organic chemistry. Thus, the development of enantioselective carbon-sulfur (C–S) bond forming reactions constitute an important field in organic synthesis.^[7]

In this context, the enantioselective addition of sulfur nucleophiles to carbon-carbon double bonds via sulfa-Michael reaction represent a powerful and straightforward strategy for the chiral synthesis of new C–S bonds. This strategy has been mainly approached via enantioselective organocatalysis,^[8] providing access to valuable sulfur-containing compounds using thiols,^[9] thioacids^[10] as well as 1,4-dithiane-2,5-diol^[11] as nucleophiles for the enantioselective sulfa-Michael addition.

On the other hand, nucleophilic addition of sodium bisulfite, a cheap and readily available chemical, has been used for the direct synthesis of sulfonic acids and their salts upon addition to electrophilic double bonds, including conjugated carbonyl compounds^[12] and nitroalkenes.^[13] Particularly, Adamo has reported the non-enantioselective amine-catalyzed addition of sodium bisulfite to nitrostyrene to give the corresponding nitrosulfonic acid under mild conditions.^[12d] Despite this, the enantioselective versions of these or related reactions involving nucleophilic sodium bisulfite remain almost unexplored. In 2011, Adamo described the organocatalytic enantioselective addition of sodium bisulfite to chalcones catalyzed by an aminothiurea bifunctional catalyst to give β -carbonyl sulfonic acids in high yields and enantioselectivities (Scheme 1).^[14] More recently, the enantioselective sulfa-Michael addition of sodium

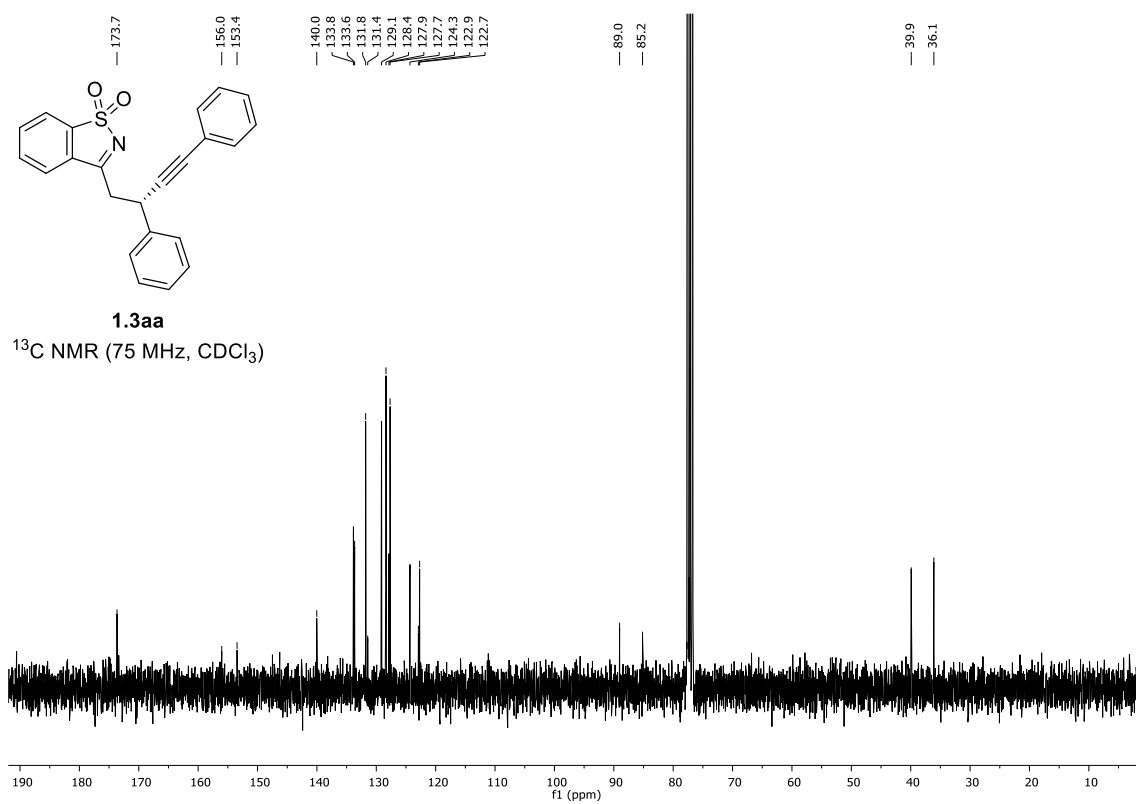
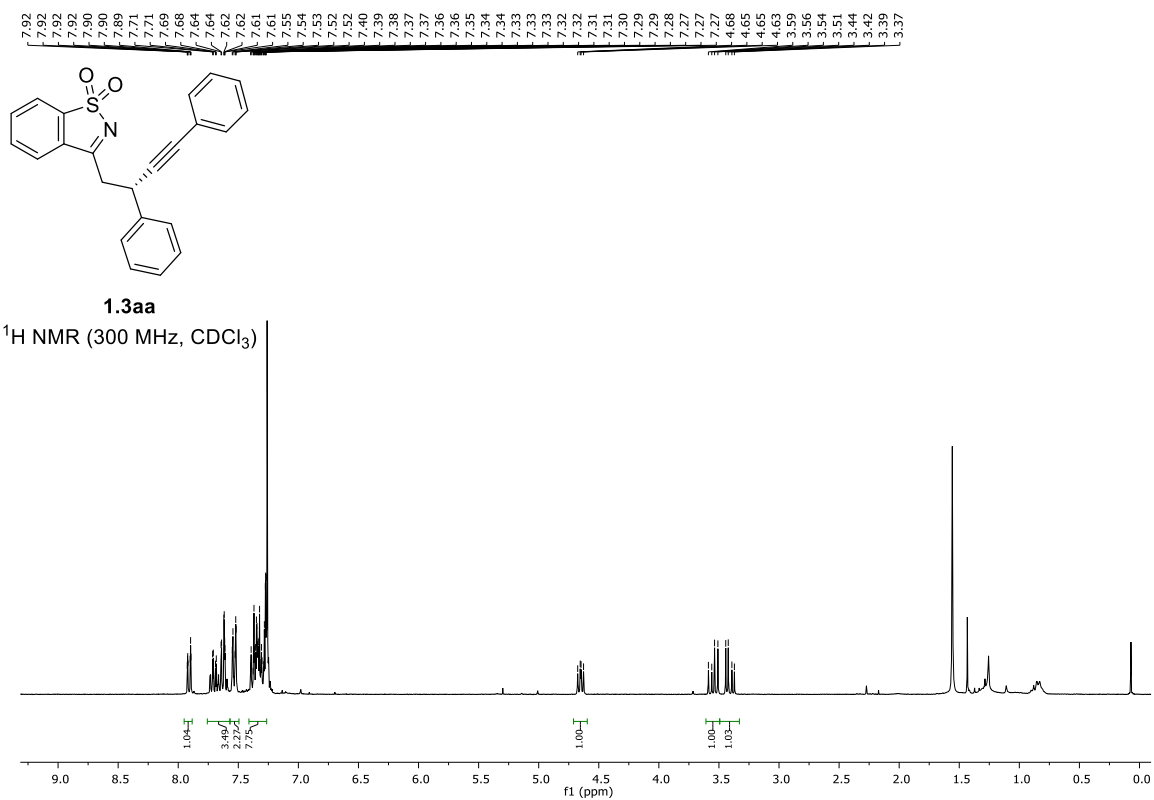
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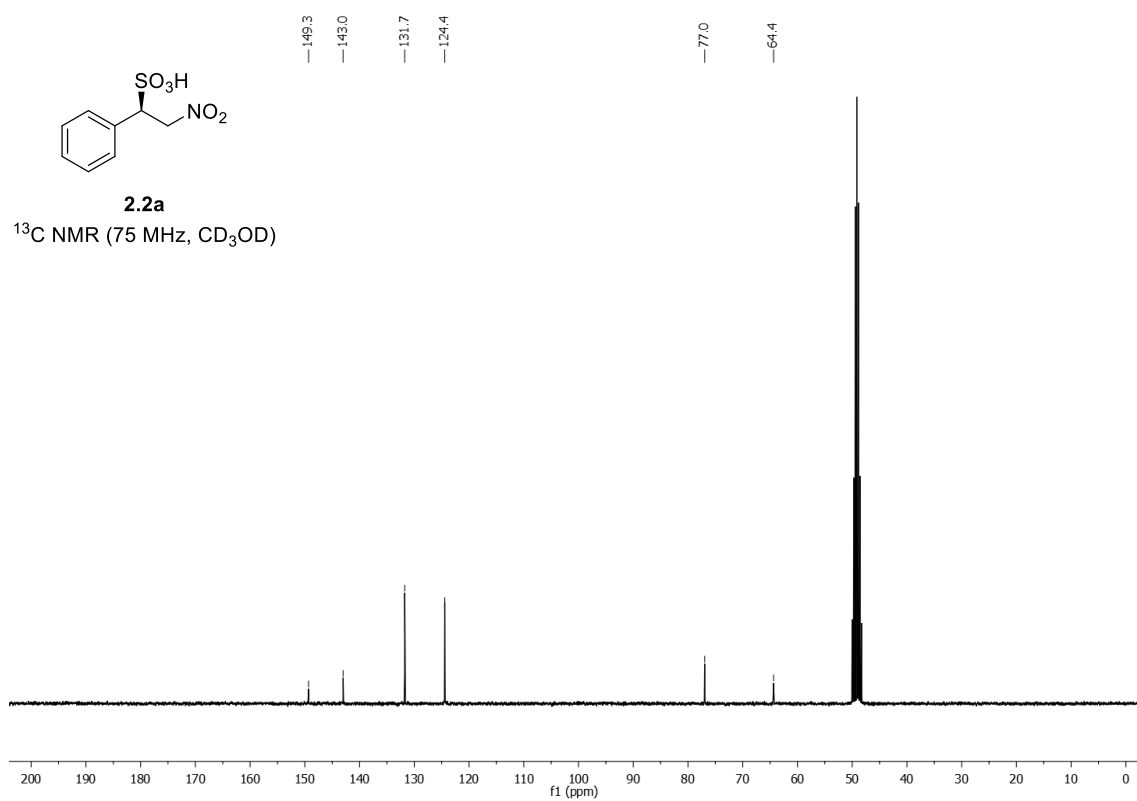
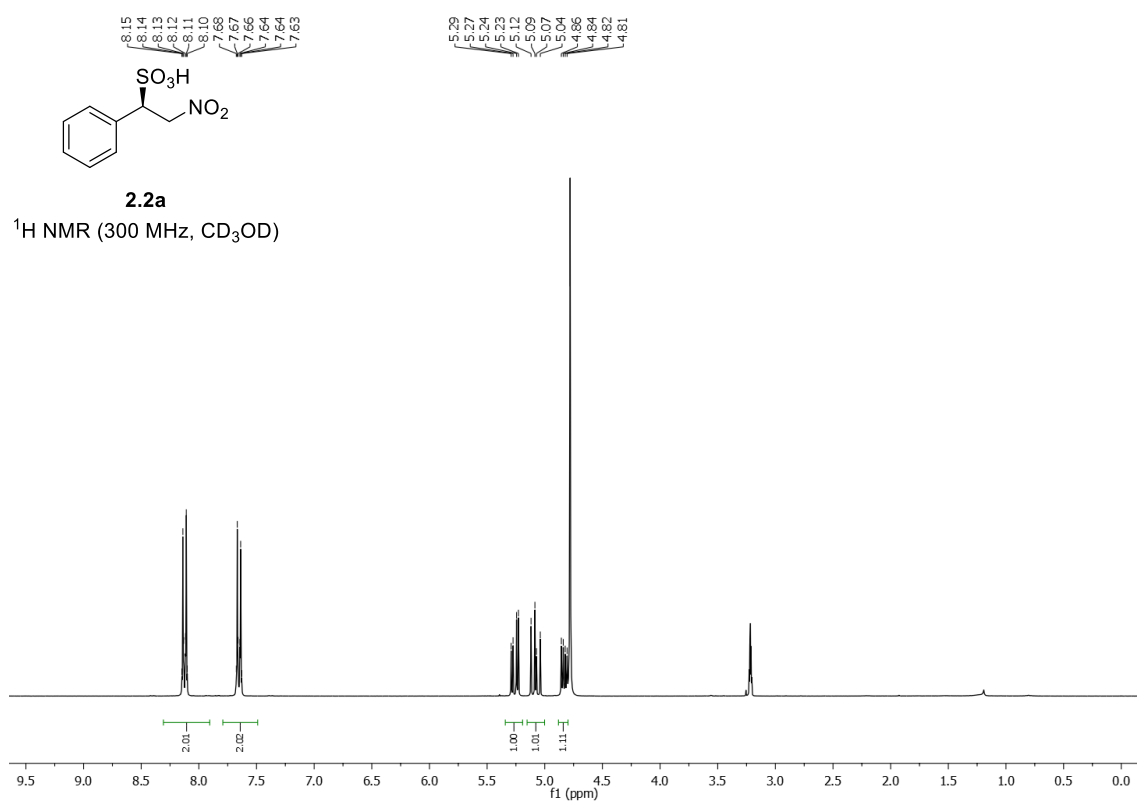
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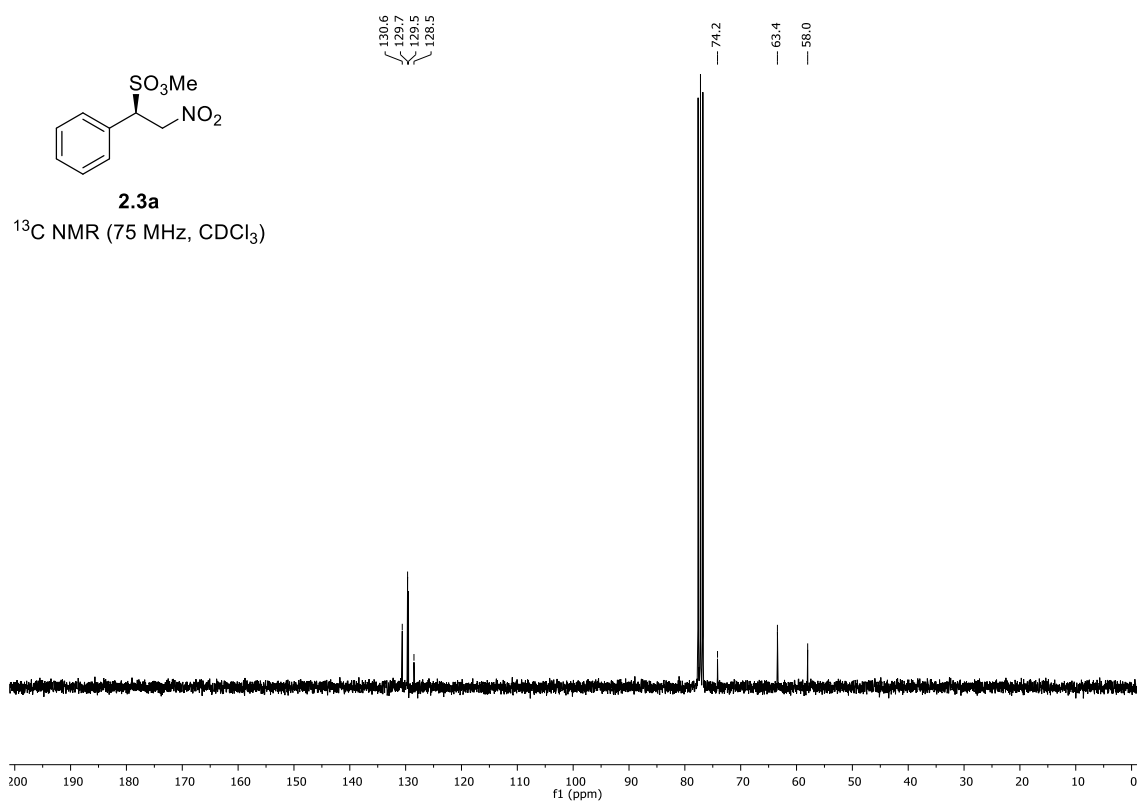
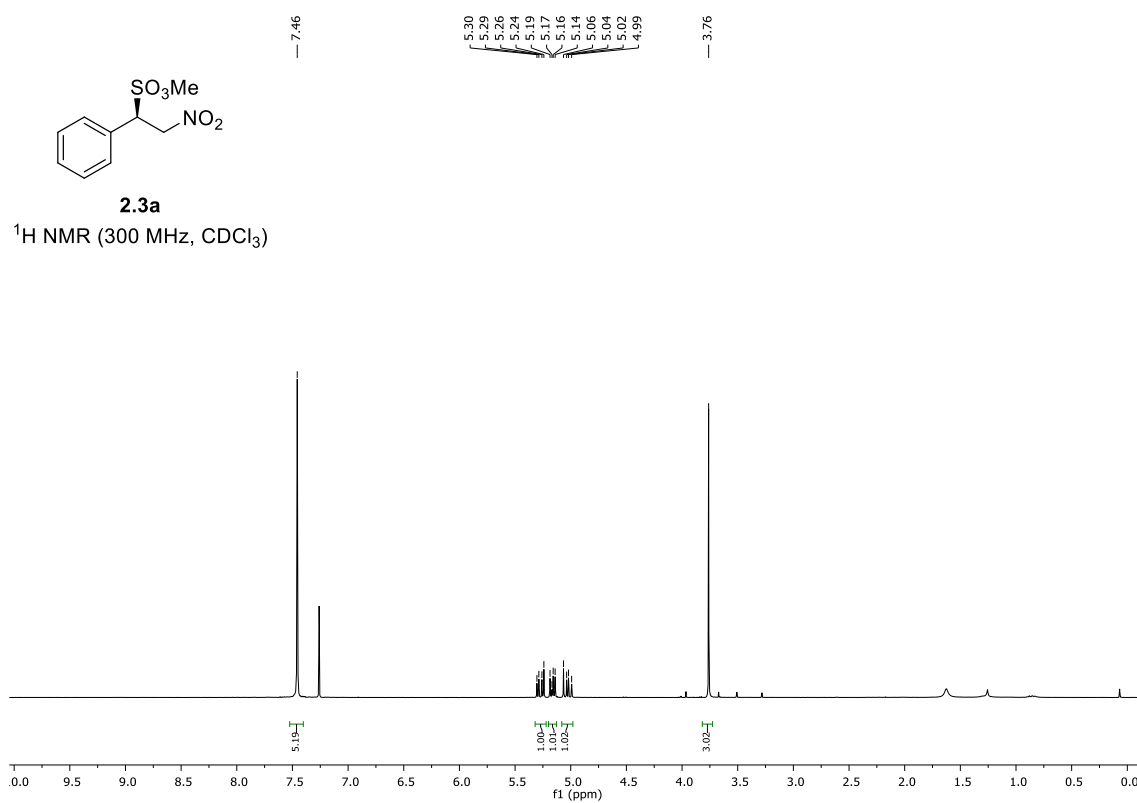
Supporting information for this article is available on the WWW under <https://doi.org/10.1002/ejoc.202101064>

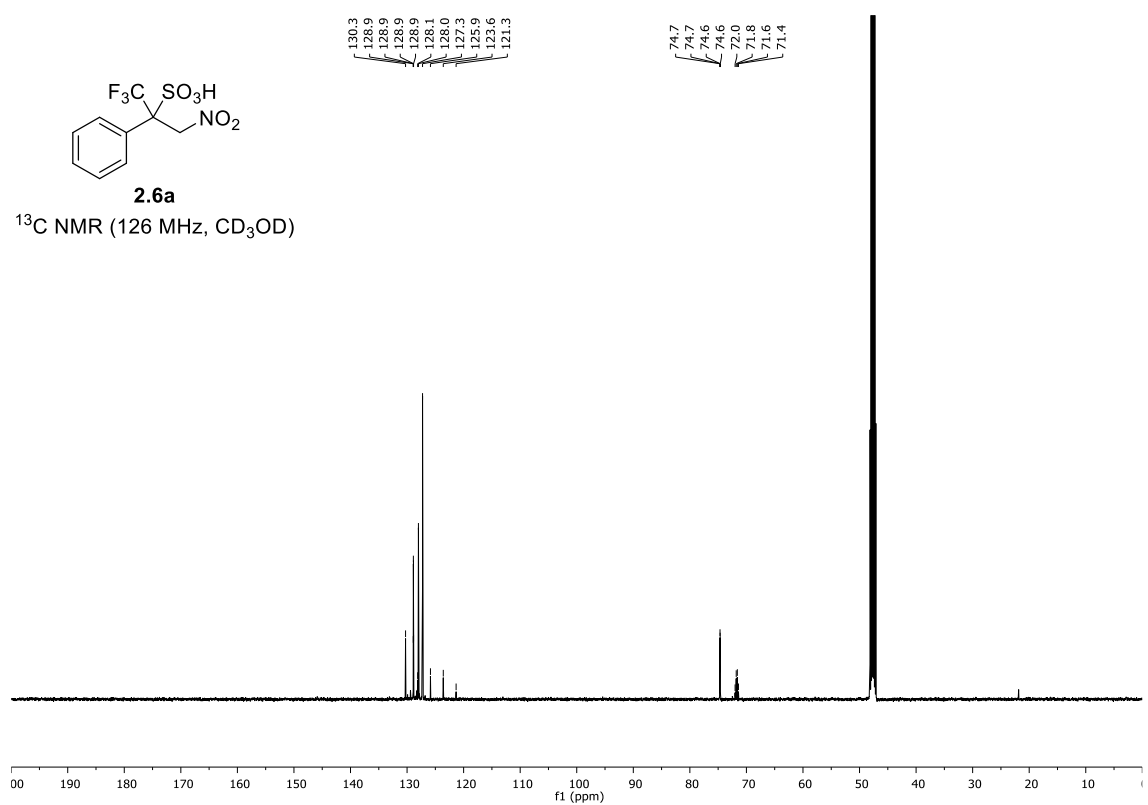
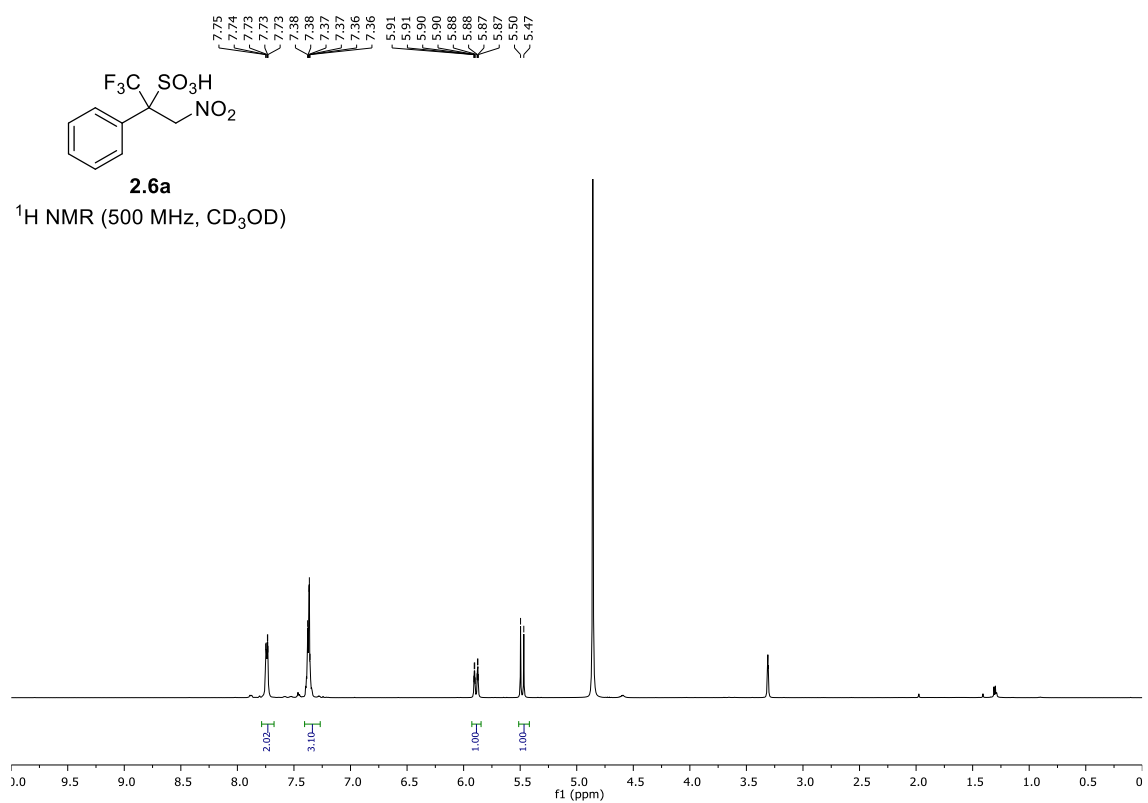
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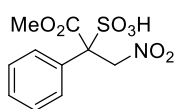
Annex I: Selected NMR Spectra





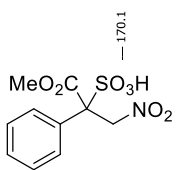
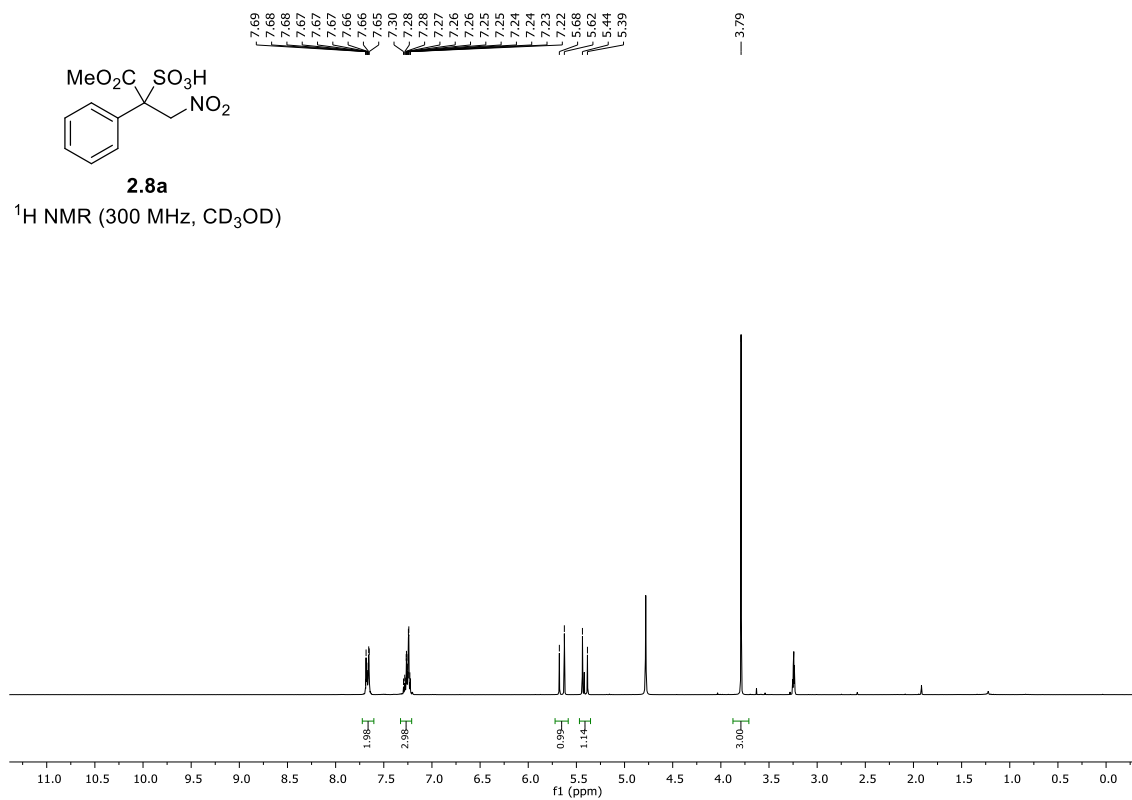






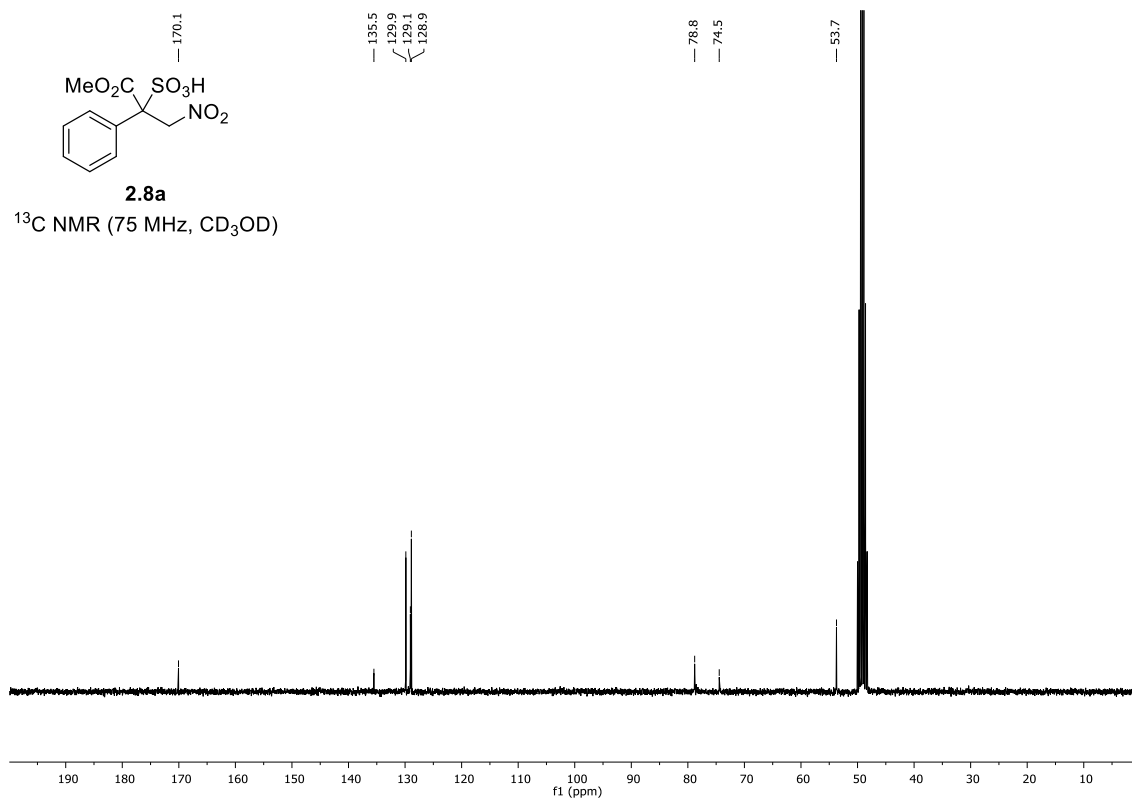
2.8a

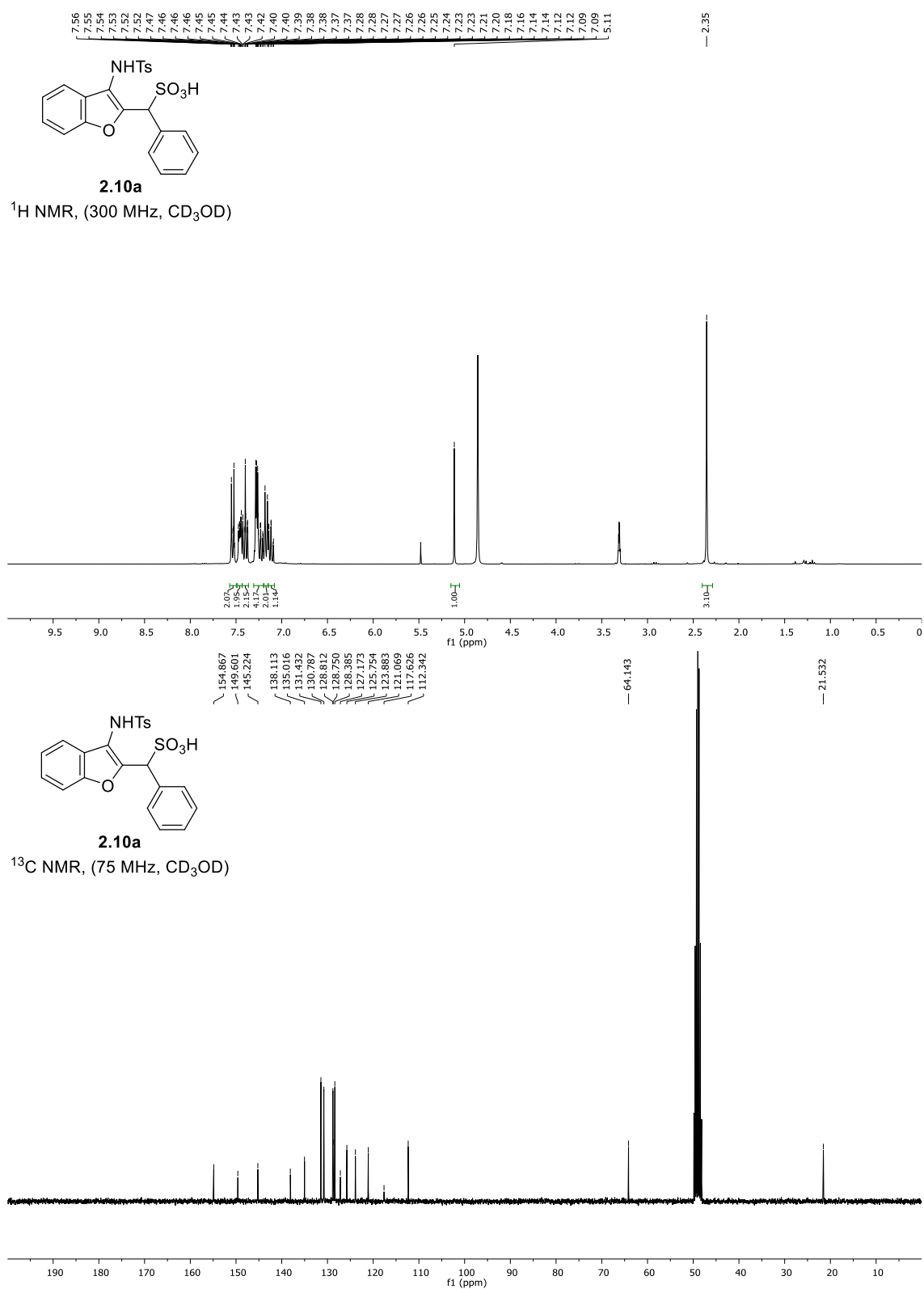
¹H NMR (300 MHz, CD₃OD)

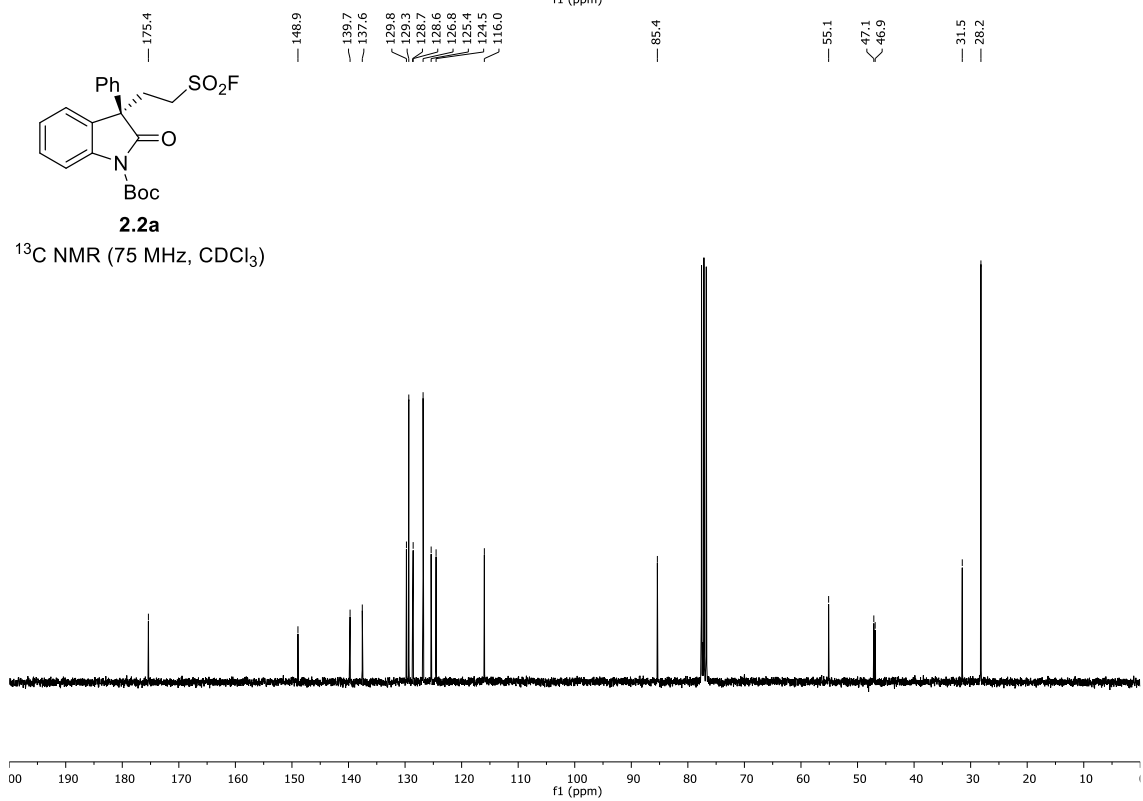
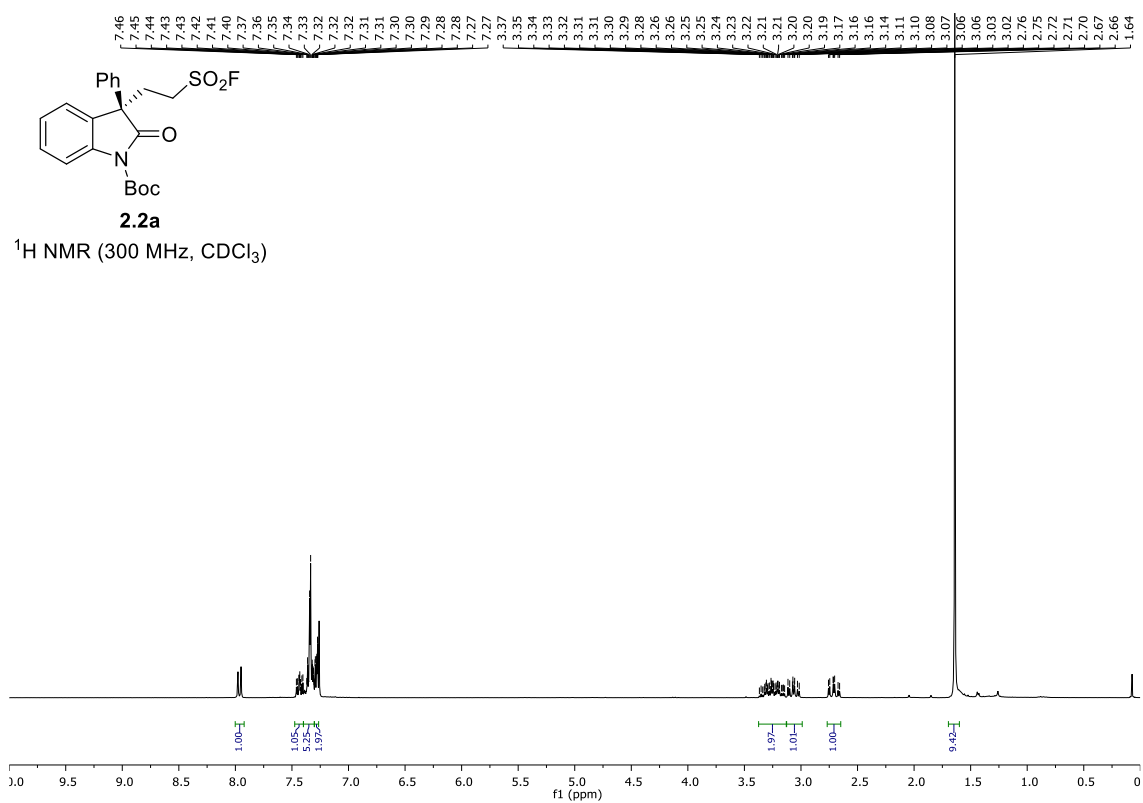


2.8a

¹³C NMR (75 MHz, CD₃OD)

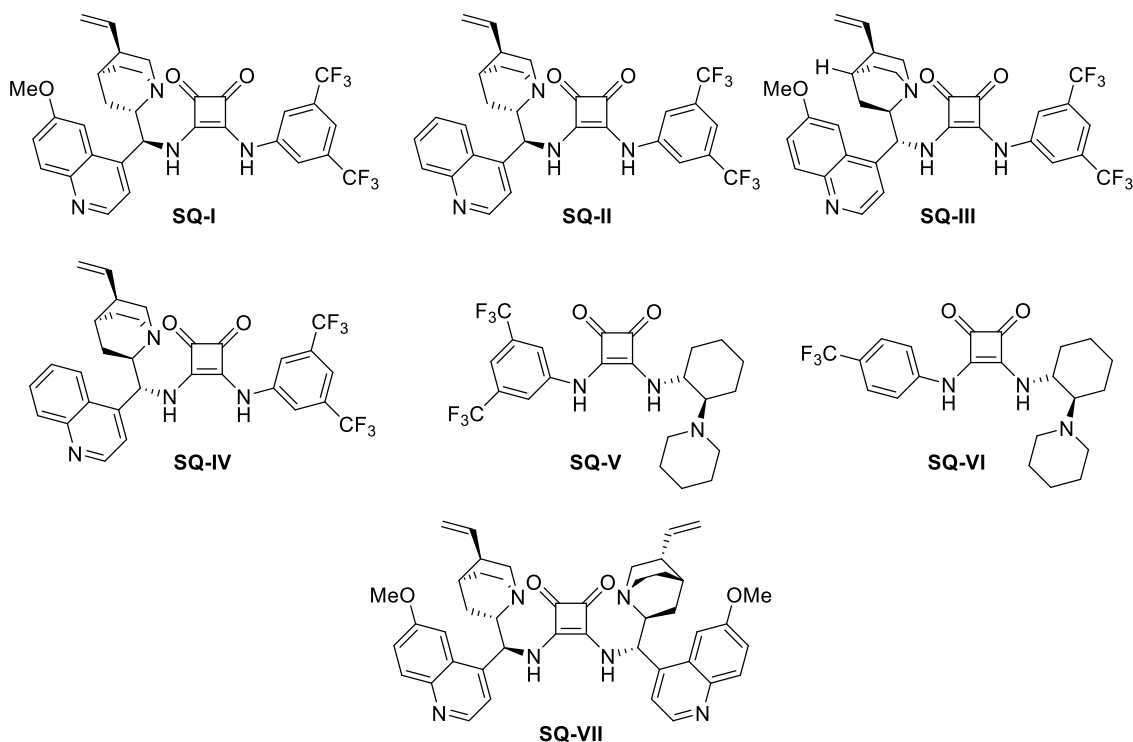




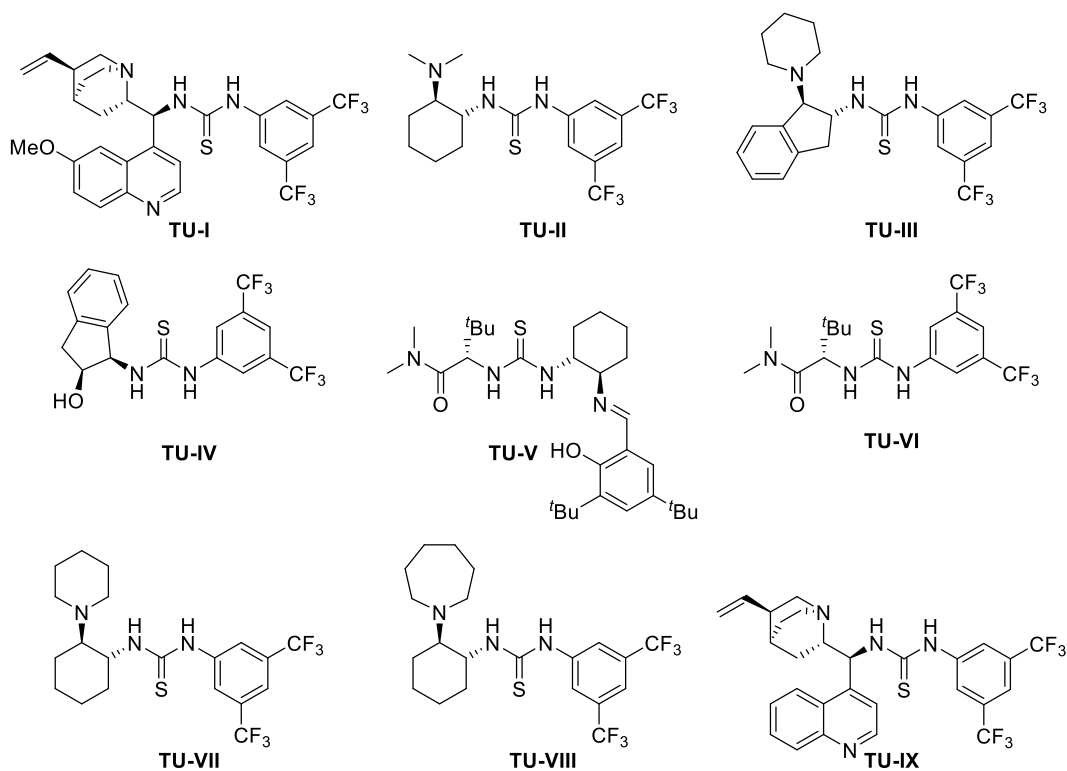


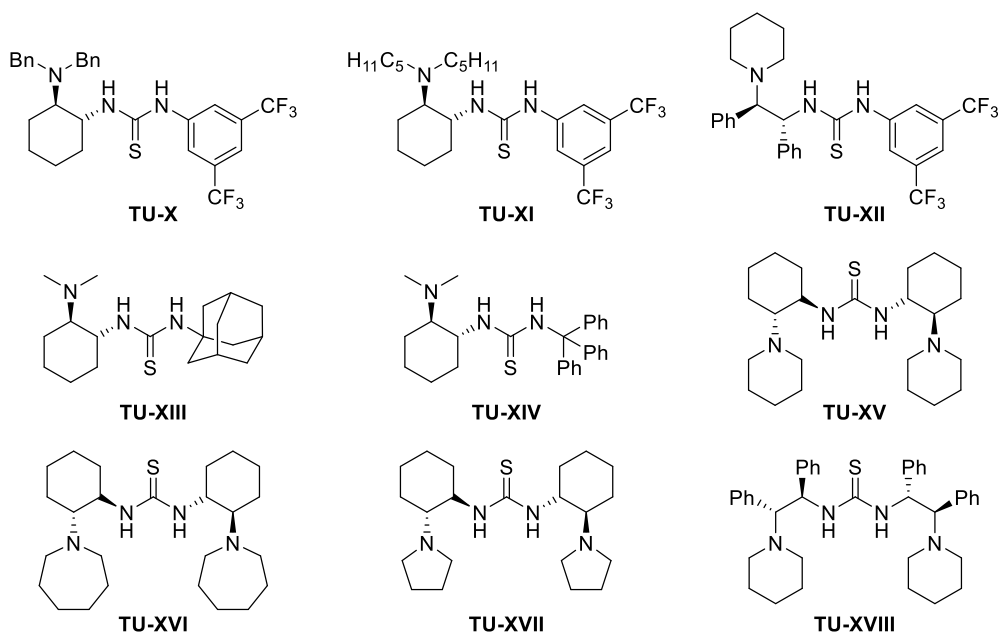
Annex II: Structures of Chiral Ligands and Organocatalysts

Bifunctional Squaramides

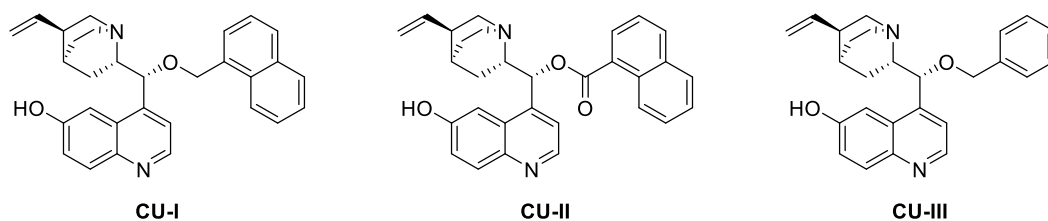


Bifunctional Thioureas

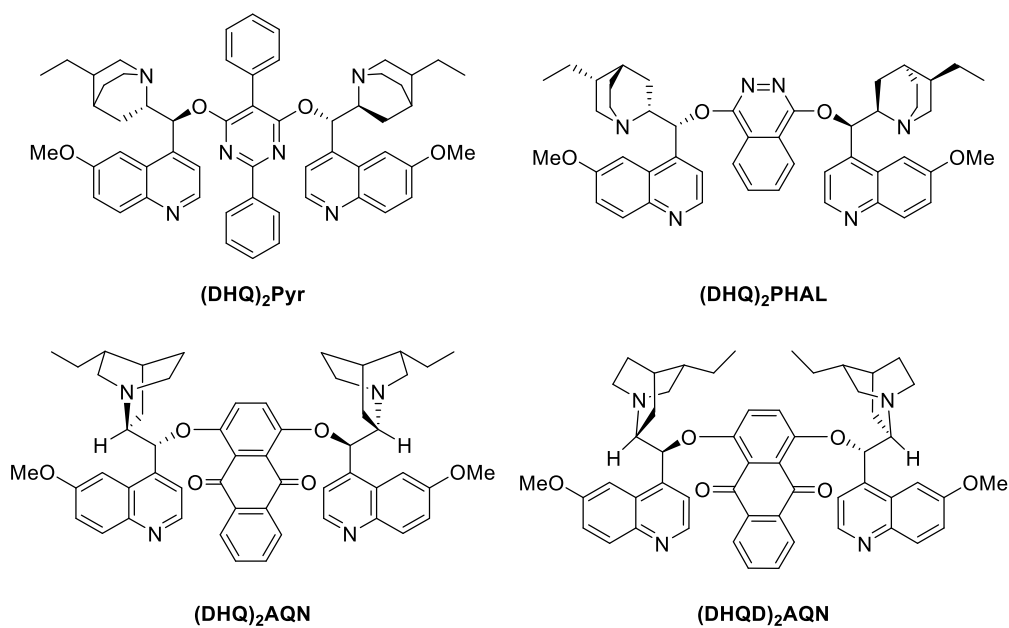




Cupreines



Brønsted Bases



Other Cinchona Alkaloid-derived Organocatalysts

