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Divergent Synthesis Approaches Towards Biologically Intriguing Molecular Scaffolds

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Parts of the work described in the following can be found in the following publications.

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Abstract

The success in biological screening of small molecules is largely determined by structural and molecular properties a library represents. There is a great demand for synthetic methodologies that enable delivery of novel molecular probes and lead structures for drug discovery. We developed a synthesis strategy that grants access to a range of biologically relevant novel cyclic sulfonamide scaffolds employing easily available saccharin-derived imine substrates. In our first approach, a number of novel benzosultams were synthesized by means of annulation and addition reactions. Subsequent modification of these scaffolds yielded additional frameworks *via* ring-expansion/ring-modulation reactions which were further derivatized using synthetic handles available in the resulting small molecules. Reaction conditions were identified to obtain good diastereoselectivities for some of the reactions. The chemical transformations depicted in this work and the products formed represent promising additions to a medicinal chemist's toolbox to engage future challenges of drug discovery research as well as biological investigations. For instance, biological screening of the benzosulfonamides formed with above approaches identified antimitotic small molecules which were were found to act via modulation of cytoskeleton, in particular in a similar fashion as tubulin-binding probes. Furthermore, in a second approach exploring chemical reactivity to generate scaffold diversity, we explored potential of a new diene species as reagents in forming novel molecular scaffolds. The lack of a general and facile synthetic access to stable and acyclic, electron-deficient 1,3-butadienes had rendered their chemistry and potential in organic synthesis largely unexplored. In this work, we report an efficient and easy synthesis of stable, electron-poor 1,3-butadienes and their potential in affording new molecular scaffolds *via* intriguing cycloaddition chemistry that delivers a new class of potent hedgehog signaling pathway inhibitors.

Zusammenfassung

Der Erfolg von biologischen Screenings von kleinen Molekülen wird zum großen Teil durch strukturelle und molekulare Eigenschaften bestimmt. Es besteht seitens der Forschung nach Wirkstoffen eine große Nachfrage nach Synthesemethodologien und Strategien, die Zugriff auf molekulare Sonden und Leitstrukturen ermöglichen. Wir haben basierend auf einfach verfügbaren Saccharin-basierten Iminen eine Synthesestrategie entwickelt, die Zugriff auf eine Reihe von biologisch relevanten neuartigen zyklischen Sulfonamid-Gerüststrukturen ermöglicht. In diesem Ansatz wurde eine Reihe von neuartigen Benzosultamen mittels Annelierungs- und Additionsreaktionen synthetisiert. Weitere Modifikationen dieser Sulfonamide mittels Ringexpansionsreaktionen ermöglichten die Erschließung weiterer Gerüststrukturen, welche weiter derivatisiert wurden, um biologisch relevante Spezies zu erschließen. Darüber hinaus wurden Reaktionsbedingungen identifiziert, welche in einzelnen Fällen gute Diastereoselektivität der Reaktionen erlaubten. Die chemischen Transformationen, welche in dieser Arbeit beschrieben werden und die Produkte, welche generiert wurden, repräsentieren vielversprechende Ergänzungen zu den Werkzeugen der medizinischen Chemie, um zukünftige Herausforderungen der Wirkstoffforschung und biologische Fragestellungen anzugehen. Biologische Screenings der dargestellten Sulfonamide führten zum Beispiel zur Identifizierung von antimitotisch wirksamen Molekülen, welche über eine Modulation des Zytoskeletts wirken.
Der Wirkmechanismus schien dabei dem anderer, bekannter Tubulin-Binder zu ähneln.
In einem weiteren Ansatz wurden Studien der Reaktivität daraufhingehend untersucht, Gerüstdiversität zu erzeugen. Dafür studierten wir das Potenzial von neuartigen Dien-Spezies als Reagenzien um neuartige Gerüststrukturen zu erzeugen. Der Mangel an einem generellen synthetischen Zugang zu stabilen, azyklischen, elektronenarmen 1,3-Butadienen ließ diese und ihre Chemie größtenteils unerforscht. In dieser Arbeit beschreiben wir eine effiziente und einfache Synthese ebensolcher Spezies und untersuchen ihr Potential, um neue Gerüststrukturen über Zykloadditionen zu erschließen. Dabei entdeckten wir eine neue Klasse von Hedgehog Inhibitoren.

1. Introduction

1.1. The Need to Access Novel Molecular Scaffolds

Drug discovery has been successful at bringing therapeutic solutions to relieve humanity from disease and pain. During the last 40 years, interesting developments were observed. For instance, by the end of last century, pharma industry largely moved away from phenotypic screening methods which were used in earlier days of drug discovery to biochemical or enzyme-based screening assays and used more target-based structure designs to develop drug candidates. While compound classes like natural products, peptides or antibodies and antibody-drug conjugates are highly relevant for probing biological systems,[1–3] small molecules remain one of the best ways to modulate biological systems, due to their easily tunable bioavailability, immune response and size, which allows their structural manipulations to find selectivity in binding a target and modulating its biological functions.

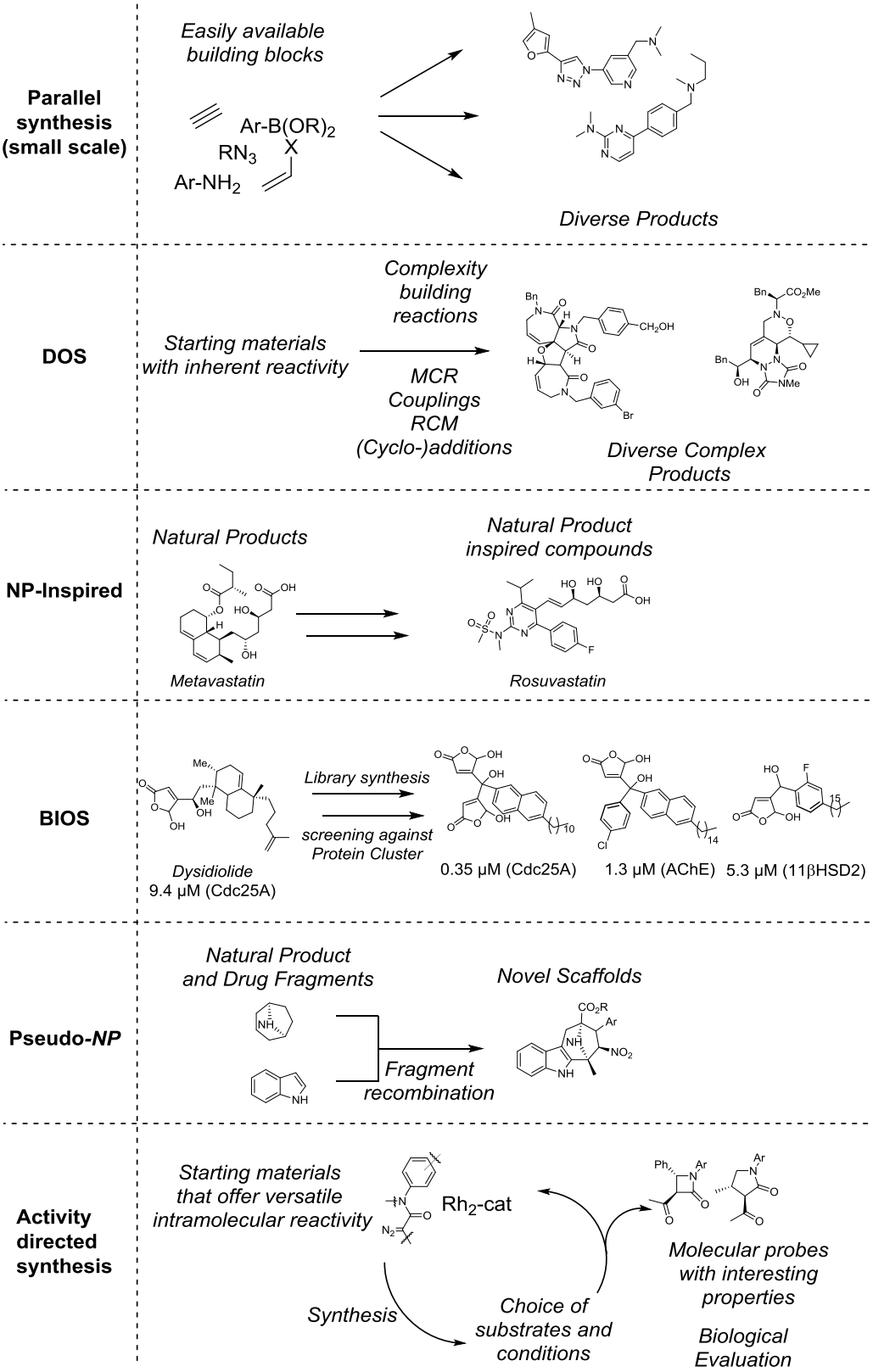
Nevertheless, some areas of medicinal chemistry have witnessed a kind of innovation stagnation. In antibiotics research for example, development of both effective & novel antibiotics as well as small molecules that elucidate novel mechanisms as targets against drug-resistant strains is moving slowly. The decline in the discovery of new antibiotics is clear from the fact that during first four years in 1980s, 16 new molecules were approved, and only four were approved during the period 2008-12.[4] Moreover, the rise of multi-drug-resistant bacteria strains is highly worrying and calls for developing novel broad-spectrum antibiotics. However, neither academia nor industry can tackle innovation challenges alone. Academic research is hampered by a lack of funding and industrial innovation in many fields is rather low due to a lack of revenue that would result from research and development in fields such as antibiotic research, given the high costs of such endeavors as well as the limited time-frames often given to industrial research projects resulting in low success rate.[5,6]

Screening of small molecule collections either in cell based or biochemical assays, provide the potential starting points and inspiration to chemical biologists and medicinal chemists for a chemical biology or medicinal chemistry program respectively. Designing probes based on biological targets requires plenty of structural information, which is not always available. However, the potential of small molecules in offering biological and therapeutically applications would remain untapped if only a limited chemical space is explored in these endeavors.

Specifically, if chemists remain focusing on selected chemotypes or use only the established synthetic strategies and methods, molecular discovery will not be able to deliver interesting novel candidates for drug discovery or small molecules as probe molecules. There is always a need for new chemotypes in medicinal chemistry or chemical biology research.

1.2 Approaches targeting novel molecular scaffolds

Structural features and molecular properties of a screening collection are key factors that determine the rate of success for any biased or unbiased screening endeavor in a biochemical or phenotypic cell-based assay respectively. During late 1990s and early 2000s, three-dimensionally flat (sp^2-carbon rich) molecules comprised a big part of compounds collections that were used for high-throughput screening (HTS). This in fact stemmed from the limited availability of reactions used in organic synthesis of these molecules that mostly included for instance, Pd-catalyzed coupling reactions in combination with heterocyclic chemistry and amide couplings etc.[7][8] Although these reaction types contributed greatly to the throughput in syntheses of molecule libraries, in particular combinatorial libraries, (Scheme 1, first row), the products were largely lacking molecular complexity in terms of sp^3 richness and presence of a number of stereogenic centers. In the lack of practical complexity generating methods that can be used in combichem type synthesis, mostly the same old synthesis methods targeting for instance, sp^2-carbon and amide-accented methodology still enable a major part of currently existing and newly synthesized molecules.
The three-dimensional complexity of a small molecule plays a significant role in selectively targeting cellular proteins and also in reducing the unspecific off-target effects. Synthetic methods offering construction of three-dimensional and more *complex* molecules, have found great attention[9][10] in recent years. These developments have provided a range of (robust) reactions targeting sp^3-sp^3 carbon bond formation – often in an asymmetric fashion – in the tool box of a chemist. Not surprising that in parallel, molecular complexity and its role in discovery and development of bioactive small molecules has got a deserving attention too in recent years.[9] Incorporation of complex molecules in screening collections, for that matter any new molecule, may reveal unexpected phenotypes and challenges to find their mode of action, cellular targets and thereby further enhancing our understanding of biological functions in both disease- and normal-state biology. Moreover, this understanding as well as identification of a bioactive new chemical entity opens up the door to drug discovery programs. Diversity oriented-synthesis (DOS) is a synthetic strategy that aims to



Scheme 1: Different approaches for synthesis of potential chemical probes 1.) Chemistry of small molecules, as often used in parallel synthesis of large numbers of compounds 2.) Diversity oriented synthesis (DOS) [17,18] 3.) Natural product inspired design of probes and drugs [16] 4.) Biology oriented synthesis (BIOS) 5.) Pseudo-natural product synthesis [19][20] 6.) Activity directed synthesis as described by Nelson *et al.* [21]

enhance structural diversity in a compound collection, while furnishing vast numbers of molecules in a few steps (Scheme 1, second row).[11,12] By the end of last century, combichem methods were the main practical aspect of DOS. However, in later years, new developments were made and different synthesis methods were used in the strategy. It has been around two decades for DOS to be in practice, but it has not lived up to its promise of flooding the databases with bioactive small molecules for various applications.

On the other hand, natural products remain an important source of bioactive small molecules in drug discovery.[13] Many previously unknown natural products are being discovered every year, and natural products have reclaimed attention of drug discovery research as a source of inspiration.[14] As natural products are not always easily accessible from natural and synthetic means, synthesis of their analogues remain a huge synthetic challenge. Natural product inspired synthesis[15][16] is a concept that tends to exploit the structural and molecular features of natural product structures and to explore their biological potential in medicinal chemistry and chemical biology. For instance, fungal natural product metavastatin was developed into a drug rotuvastatin that helps lowering cholesterol levels. (Scheme 1, third row)

Waldmann and co-workers developed biology-oriented synthesis (BIOS, Scheme 1, fourth row), wherein the core-structures of known bioactive molecules are used as starting points to build a compound collection. The main dogma of this approach was that ligand binding sites that closely resemble each other bind ligands that are structurally similar. Precisely, if a certain protein-ligand interaction is well-characterized and a different protein features a substructure which closely resembles this binding site, the ligand (e.g. a natural product) has an increased probability of binding to this protein, too. In this fashion, structural classification of natural products (SCONP) charts natural products according to their scaffold and biological activity.[22] Bioinformatic analysis of protein structures can reveal ligand-binding-site similarities and allow for target-binding hypothesis of ligands by means of forming protein structure similarity clusters (PSSC). Combination of ligand clusters on the one side and PSSC on the other side can thus serve as a hypothesis generating tool. For instance, a study by Koch *et al*. revealed similarity between ligand binding sites of cdc25a phosphatase, acetylcholine esterase and 11β-hydroxysteroid dehydrogenases type 1 and 2. Consequently, these proteins were added to a cluster. Dysidiolide is a well-known ligand for cdc25A. A compound collection based on this natural product was synthesiszed and tested on activity against other proteins of this similarity cluster. This resulted in a 143-membered compound collection with 2-3% hit-rate with compounds being active in low micromolar ranges for proteins of the cluster.[22]

The pseudo-natural product concept combines the idea originally adapted by DOS for exploring unknown chemical space with beneficial pharmacokinetic properties.These structural features can stem from synthetic and natural products alike, as long as they are biologically active molecules.[20,23] Valuable, prevalidated fragments are recombined with varying connectivity, making use of beneficial properties such as solubility and the tendency to address certain structural motives in proteins, while implementing an element of structural diversity. Narayan *et al.*[19] described such an approach by combining natural product fragments indole and tropane, which occur in molecules such as scopolamine or cocaine. One of the molecules they synthesized in this fashion was identified to inhibit molecular motor myosin and was named myokasinib.[24] Another study from Waldmann group which dealt with unprecedented recombination of fragments paved access to another pseudo natural product class i.e. chromopynones, which were shown to be inhibitors of glucose transport proteins, displaying a novel class of probes to study glucose metabolism in cancer.[25]

Nelson and co-workers developed a strategy that included facile intramolecular reaction towards different scaffolds dependent on substrate and metal catalyst. Both can be be varied to modulate outcome of the reaction. Removal of catalyst and solvent gave crude mixtures which were screened against an androgen receptor. The reaction conditions leading to active mixtures were selected and further optimized. The panel was set up for a second round of reactions and the resulting reaction mixtures analyzed. Further adjustment of reaction conditions were followed by a third cycle of reactions, allowing for evolutive improvement with androgen receptor being selection factor for reaction conditions.[21] This allowed for generation of μM-range inhibitors in three reaction cycles in an evolutive fashion. These are few representative strategies that are being explored to reach out to novel chemical space and a common aim is to deliver biologically important small molecules for academic and industrial research.[26][27] With scientists eager to find new molecules, drug repurposing, *i.e.* finding new uses for compounds that have been annotated with other activities, has become an important subject gaining attention from pharma industry as well as many academic laboratories.[28]

1.3 Considerations on Existing Approaches of Chemical Space Exploration

There is an urgent need to find new molecules that help elucidation of previously *unknown* biological mechanisms, for instance modulation or inhibition of protein-protein interactions. Strategies for the syntheses of novel molecules that may rival natural products in complexity and properties are still scarce. Even though a number of research groups are developing new synthetic methodologies and strategies, only few of them are effectively used for syntheses of compound collections.[7] This redundancy in applying similar synthetic methods in generating compound libraries has always led to a similar structural space. Lipkus and coworkers showed that a majority of synthetic small heterocyclic molecules are represented by a small fraction of known scaffolds.[29] An analysis of CAS registry from 2007 revealed that 49.6% of all heterocyclic compounds could be described by just 0.25% of all heterocyclic scaffolds. Furthermore, 51% of scaffolds that contain at least one heteroatom are only represented by single molecules, which in turn make up only 5.4% of all compounds. Moreover, some scaffolds are well represented by a number of example molecules, while other scaffolds have stayed grossly underexplored in terms of representation by molecules. Therefore, merely getting access to molecular scaffolds as singletons is not enough. Each of the scaffolds has to be represented well in a collection by a number of different decorations around the core-structure. Benzimidazoles, for instance, are featured in plethora of bioactive molecules such as antihistaminic drugs, cardiotonic agents, proton pump inhibitors and antiviral drugs, as lined out in an article by Yadav.[30]

MacLellan and Nelson analyzed different approaches for exploration of chemical space and discussed their effectiveness in achieving structural diversity.[31] An analysis of the synthetic strategies and applied methodologies showed that reactions like Ugi-multicomponent reaction and olefin metathesis are the most effective in generating diverse, complex scaffolds. Further reaction types have to be identified to augment these chemistry tools in order to effectively create complex, diverse and novel molecular scaffolds.

While the demand for unprecedented molecular frameworks is worth more efforts in developing chemical transformations, it is important to note that small structural changes can also be key to finding biologically interesting compounds. An example of this is the *magic methyl* effect[32] wherein mere introduction of methyl group in a molecule can bring much improved activity. For instance, potency of an antagonist of spingosine 1-phosphate receptor-1 ($S1P_1$, a relevant target of autoimmune disease research), increased from 4.27 µM to 4.3 nM in a $GTP\gamma^{35}s$ binding assay by just having an extra methyl group.[33] In this regard, a number of recent developments in synthetic methodologies, from C-H activation to

late stage functionalization can play a vital role in improving quality of even small focused compound collections.

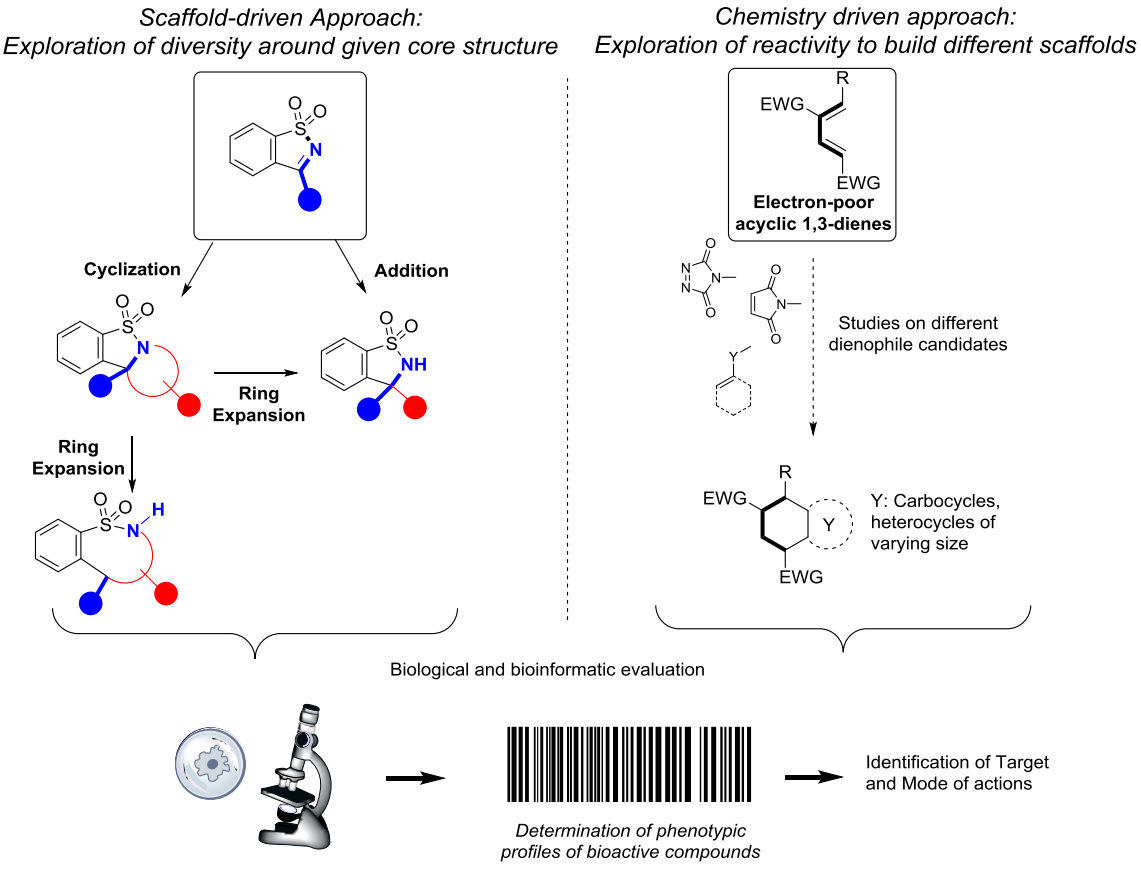
The unknown or novel compound classes have immense potential to deliver small bioactive molecules with unprecedented mechanisms of action (first-in-class). Such molecules are in particulary desired for treatment of rare diseases and infections caused by highly drug-resistant strains of bacteria and virus. Therefore, organic synthesis combined with the strength of unbiased cell based high content screenings can offer great service to discovery research. Phenotypic profiling in combination with progress made in machine learning and artificial intelligence (AI) may help elevate the means of information gain, analysis and processing[34] and eventually help medicinal chemistry and biosciences progress further.[35] Virtual screening of compound libraries is already guiding medicinal chemists in finding highly interesting molecules.[36–42] There are many opportunities wherein combination of different technologies can aid drug discovery process such as implementation of machine-assisted synthesis with sufficiently robust and feasible reaction methodology[43]The unbiased profiling and screening together with subsequent target deconvolution will also unravel the intricacies of complex biology of mammalian and other organisms and would further advance the drug discovery investigations.[44][45] These considerations underline the urgency to access underrepresented scaffolds and build compound collections around these novel scaffolds for different biological screenings.

1.4 Aims and approach followed in the present work

This work deals with the development of synthetic strategies towards new and underrepresented molecular scaffolds. Ideally, the desired scaffolds should be obtained in few steps from easily available starting materials and feature handles (functional groups) for their derivatization. In this work, different synthetic strategies were explored to afford desired compounds and eventually delivering novel biologically intriguing molecular entities. There are basically two approaches that can be employed in targeting biologically relevant and novel structural classes. First one is a structure-driven approach and intends to develop a compound collection around a core-scaffold that is already represented by bioactive synthetic or natural small molecule. The second approach is a chemistry-driven strategy. As it is said, novel chemistry often leads to novel structures, so new chemical transformations which remain underexplored are developed and explored to build a number of new frameworks. The work embodied in this thesis explore both these strategies. Chapter 2 targets synthesis of cyclic sulfonamides – scaffolds that in fact are missing in natural

products but are found in many synthetic drugs. We designed and executed a strategy that allowed access to a range of cyclic benzosulfonamides. The reactions were particularly selected so that a number of tertiary and quaternary stereogenic centers could be incorporated into sulfonamide frameworks to enhance their molecular complexity. This includes annulation reactions as well as ring-modulation reactions to transform scaffolds resulting from former reactions into additional new scaffolds. A novel sequence of branching-folding approach was thus successfully implemented to deliver biologically intriguing class of novel benzo-sulfonamides.

Access to Novel Chemical space: Two Approaches



Scheme 2: Different approaches to effectively gain access to novel, complex molecular structures.

Chapter 3 follows the chemistry-driven approach in targeting structural diversity. In this case, suitability of novel doubly electron-deficient 1,3-butadienes, i.e. dienes bearing two electron-withdrawing groups, in affording a range of cyclic scaffolds by means of cycloaddition reactions is explored. Not only does this exploration unravels the mysterious chemistry of these unprecedented dienes but also delivers uniquely functionalized small molecules which otherwise would be highly difficult to synthesize.

In both projects, biological evaluation by means of high content cell-based (phenotypical) assays were used to identify biologically intriguing small molecules as well as to get some insights into their mode of action.

2. Branching-Folding Approach to Benzosulfonamide Scaffolds

2.1 Benzosulfonamides – Relevance and Reactivity

2.1.1 Introduction: Benzosulfonamides in Drug and Probe Discovery

Small molecules supporting sulfonamide functional groups are well represented by a number of bioactive compounds, which also include a number of FDA approved marketed drugs. They were first synthesized in 1930s and were soon found to possess biological activities (Figure 1).[46] Intriguingly, natural products seem not prefer having sulfonamide groups.[47,48] While there are few rare cases of natural products bearing sulfonamides moiety, no natural products is yet known to embody a cyclic sulfonamide (or sultam)

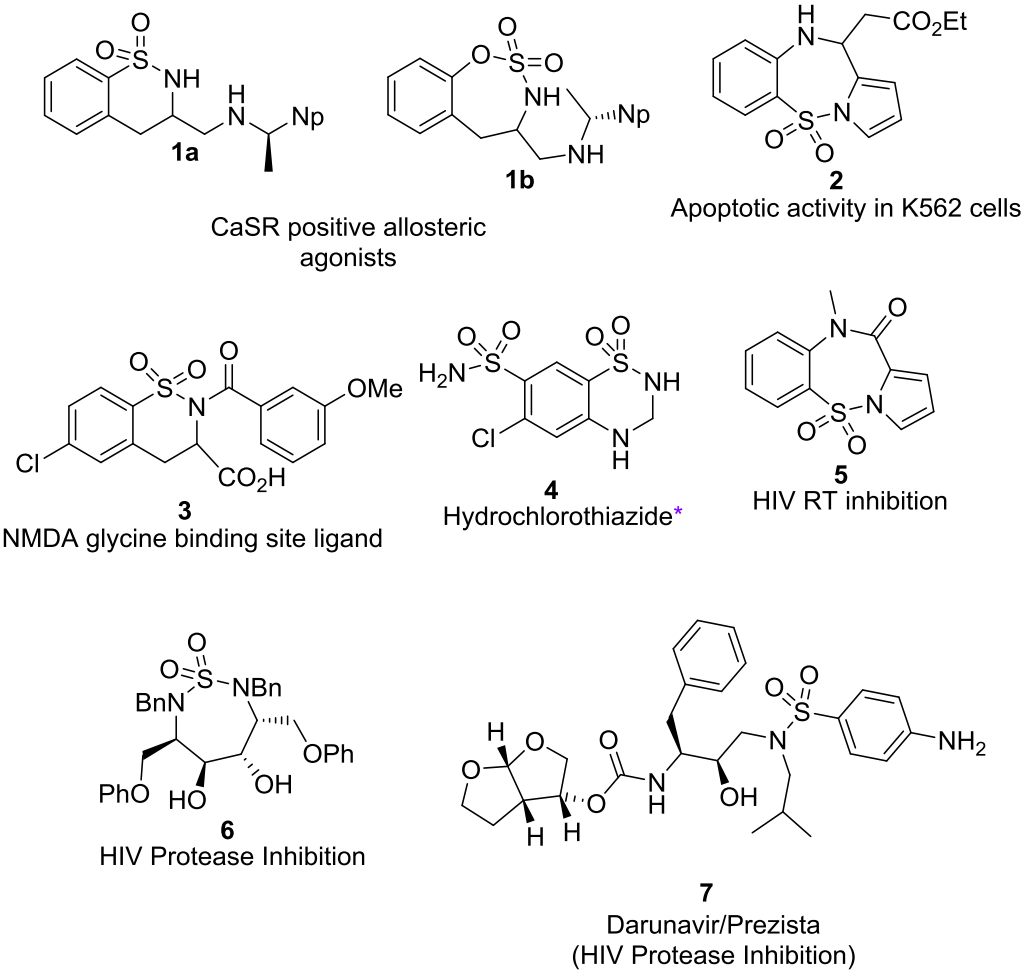


Figure 1: Different biologically relevant Sulfonamides.

Sulfonamides are well known for their inhibitory activity of metallo-enzymes such as carbonic anhydrase. [49–51] Saccharin had been widely used as a sweetener that structurally can be described as cyclic *N*-acyl-sulfonamide. Sulfapyridine is an antitbiotic found in the U.K. in the 1930s that has been used for in therapies of notable patients such as Winston

Churchill. Sulfonamide containing molecules have been reported to be positive allosteric agonists of Calcium sensing receptor (**1a** and **1b**)[52], exhibiting apoptotic activity in lung cancer cell line K562 (**2**),[53] or acting as a ligand of NMDA glycine binding site (**3**).[54] Researchers have found that sulfonamides exhibit diuretic activity which led to the development of drugs such as hydrochlorothiazide (**4**), whose activity was later revealed to be due to interaction with ion channels.[55] Sulfonamides and sulfinamides are bioisosteres for amides[56] and find applications as protease or nuclease inhibitors but also as kinase inhibitors.[49] Sulfonamide-lactam **5** and sulfamide **6** are inhibiting HIV retrotranscriptase[57] and HIV protease,[58] respectively, while Darunavir (**7**) is a marketed anti- HIV drug, acting against HIV protease.

Sulfonamides have also been found to interfere with mitosis, in particular with cytoskeleton.[59] More functions have and are being explored and reported (see following overview and references therein).[49,51–53]

2.1.2 Properties and Reactivity of Sulfonamides

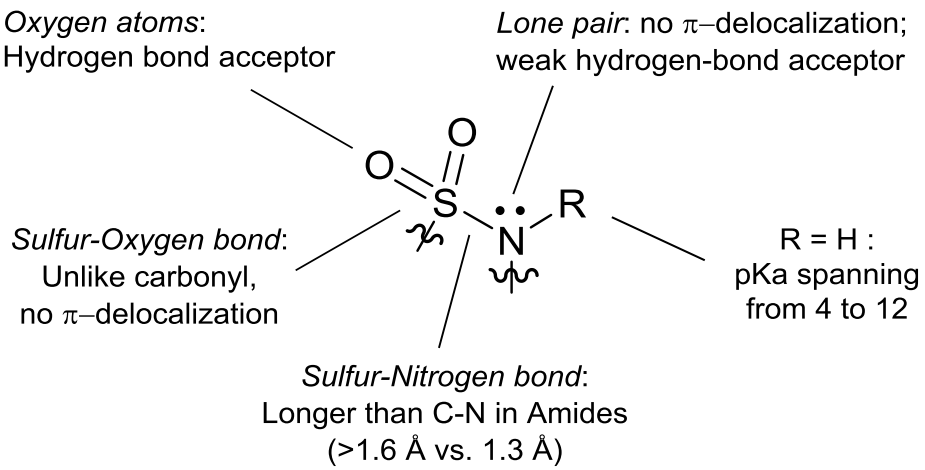
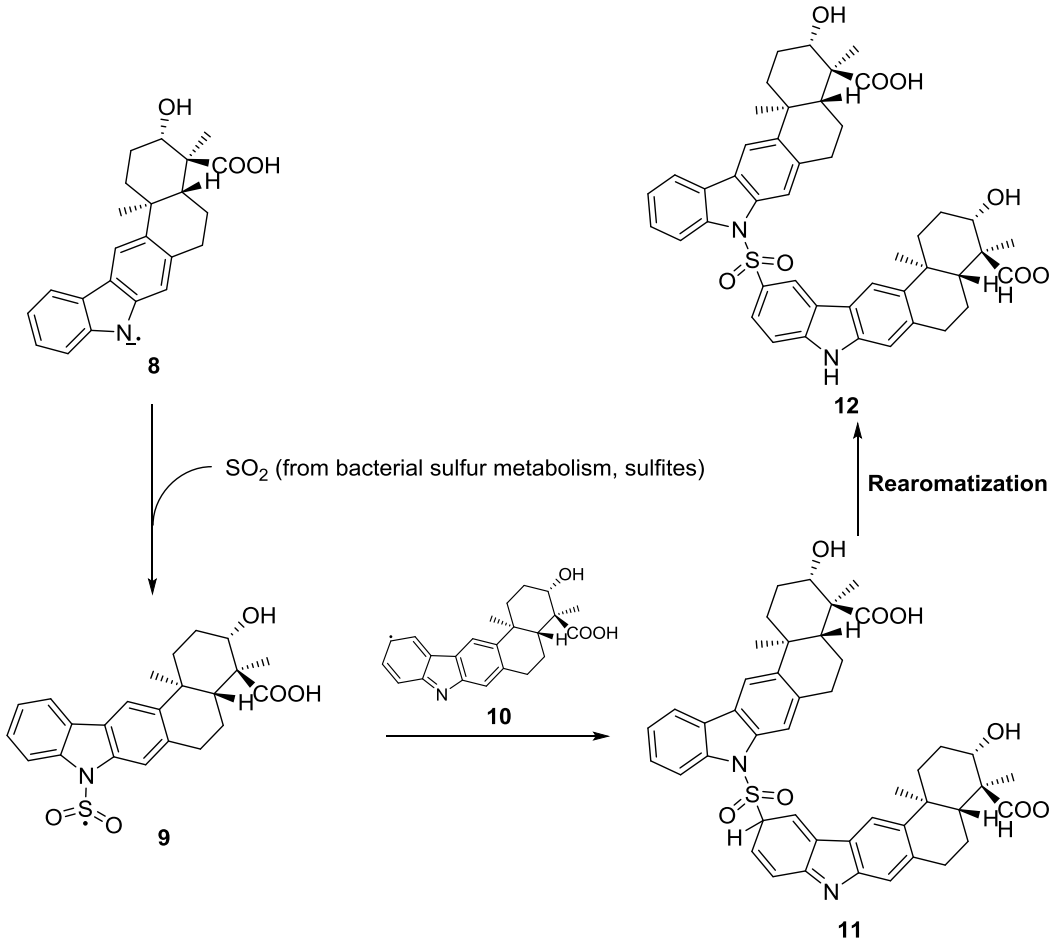


Figure 2: The sulfonamide group: stereoelectronic properties.

The special stereoelectronic properties and acidity of sulfonamides determine their contribution in host-ligand interactions (Figure 2). While amide lone pair of carbonyl moiety is delocalized by n→π interaction, this is not the case for sulfonamides. Sulfonamide nitrogen atoms are arranged in pyramidal geometry, while sulfur atoms are tetrahedral. Sulfonamide oxygen atoms can serve as hydrogen bond acceptors.[63][64] Measured pka values of sulfonamides differ vastly from amides, spanning from 4 to 12 depending on

substitutions, making them more acidic than amides. The sulfur-nitrogen bond itself (>1.6 Å) is considerably longer than carbonyl-nitrogen (~1.3 Å) bond in amides.[65] Stabilization of the stong nitrogen-sulfur bond most likely occurs by negative hyperconjugation, electrostatic interactions and - if sulfur *d*-orbitals are considered to play a role in bonding interaction - partial double bond character.[66] Participation of *d* orbitals and lone pair of nitrogen atom allow for interactions with transition metals. This manifests in the number of sulfonamide inhibitors of metalloproteins such as the zinc-protein carbonic anhydrase. Not only iron- and zinc-group elements, but also noble-metal complexes of sulfonamides are known and have been studied. Pawlikowski *et al.*, for instance, have studied behavior of sulfonamide-platinum complex that allows for C-N (and C-C) coupling via reductive elimination. Subsequent deprotection of nitrogen allows for generation of alkylamines.[67] Stable Nickel-azametallacyclobutanes from tosylaziridines have been made by Lin *et al.*[68] Oxidation leads to ring contraction, restoring aziridine by release of metal atom. Klamann *et al.* have reported nitrogen-sulfur bond cleavage of sulfonamides in 1953.[69] Among other studies, Nandi *et al.*[70] exploited this chemistry for development of a based on



Scheme 3: Radical biosynthesis mechanism of sulfadixiamicins.[47]

silica gel-based nitrogen-sulfur bond cleavage solution. Zinc dust in refluxing glacial acetic acid has been used for N-C bond cleavage for the synthesis of interesting scaffolds from indolyl tetracycles.[71,72]

Baunach *et al*. studied mechanism of sulfonamide antibiotics sulfadixiamicins (Scheme 3).[47] Thereby, amino radical of indolyl unit in xiamycin precursor **8** reacts with sulfurdioxide from sulfur metabolism of the bacteria, leading to sulfonylated radical **9**, which in turn reacts with another molecule bearing stabilized xiamycin radical in *para*-position (**10**), furnishing **11** and finally rearomatizing to sulfadixiamicin **12**. Petkowski *et al*. report in their study on occurrence of N-S bonds in biochemistry[73] that only 0.5% of natural product metabolites contain such bonds. They hypothesize that this may be due to their incompatibility with thiols - a fundamental tool of (redox) metabolism.

With nature being a poor source of sulfonamides, drug discovery has to rely on synthetic chemistry to develop and identify means to access the highly biologically relevant sulfonamide scaffolds.

2.2 Strategy and Planning

2.2.1 Branching-Folding strategy

Convinced with the idea to explore chemical transformations to build focused collections representing cyclic sulfonamide scaffolds, a number of key points in designing our strategy were considered as follows: 1) The approach should enable access to a range of diverse benzosulfonamide scaffolds and thus targeting an underexplored chemical space. 2) The *complexity-generating* reaction methodology, both in tems of ring-systems formed as well as to introduce a number of stereogenic centers on a scaffold, needs to be explored. The reactions leading to form new scaffolds would be identified and if necessary, reaction conditions would be optimized. 3) It is also important for new scaffolds to hold functional groups as synthetic handles that can be easily manipulated later to form a compound collection which can also display a preliminary SAR in a biological screening.

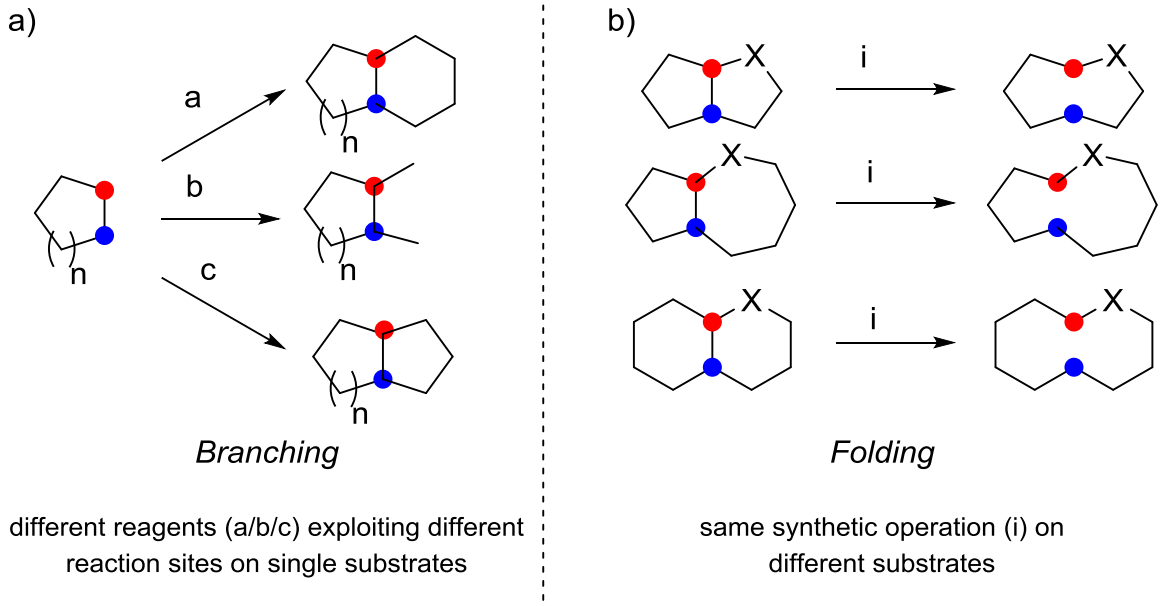


Figure 3: Branching and Folding pathways as described in DOS literature.

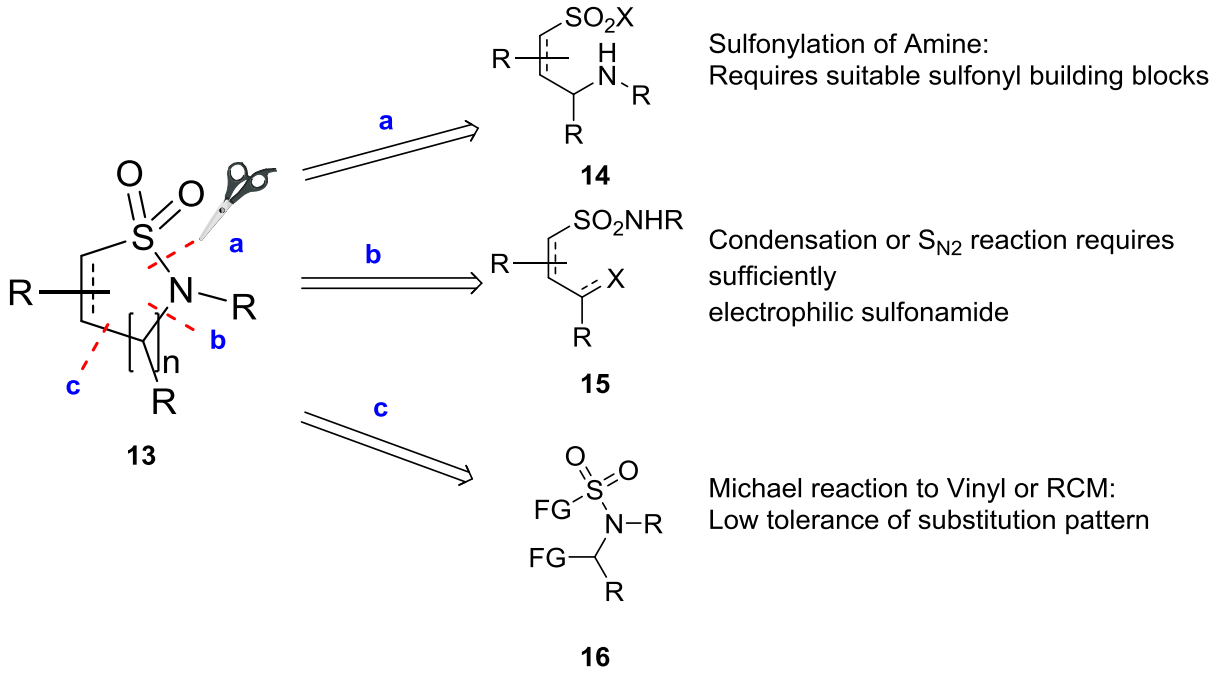
After considering different approaches, we proposed a strategy that can be described as branching-folding approach. Branching and folding pathways are terms that have been used when describing synthetic strategies in diversity oriented synthesis.[11,74–77] In branching pathways, reactive sites (highlighted blue and red, Fig. 3) react to various chemical stimuli to furnish different frameworks. This strategy is also called reagent-based, since different reagents (a-c) employed determine the reaction outcome and scaffold diversity generated (Fig. 3a). Folding pathways, in contrast, use one single type of transformation on different

substrates (Fig. 3b). This leads to congruent changes in connectivity while the product core structure can vastly differ. A notable reaction to use for this kind of strategy has been ring-closing metathesis, making use of distant olefin pairs on a variety of substrates (see also chapter 1.3 and the article by MacLellan and Nelson)[31]

Before depicting the details on how we design our strategy, let us have a look at some synthesis approaches towards benzosulfonamide small molecules.

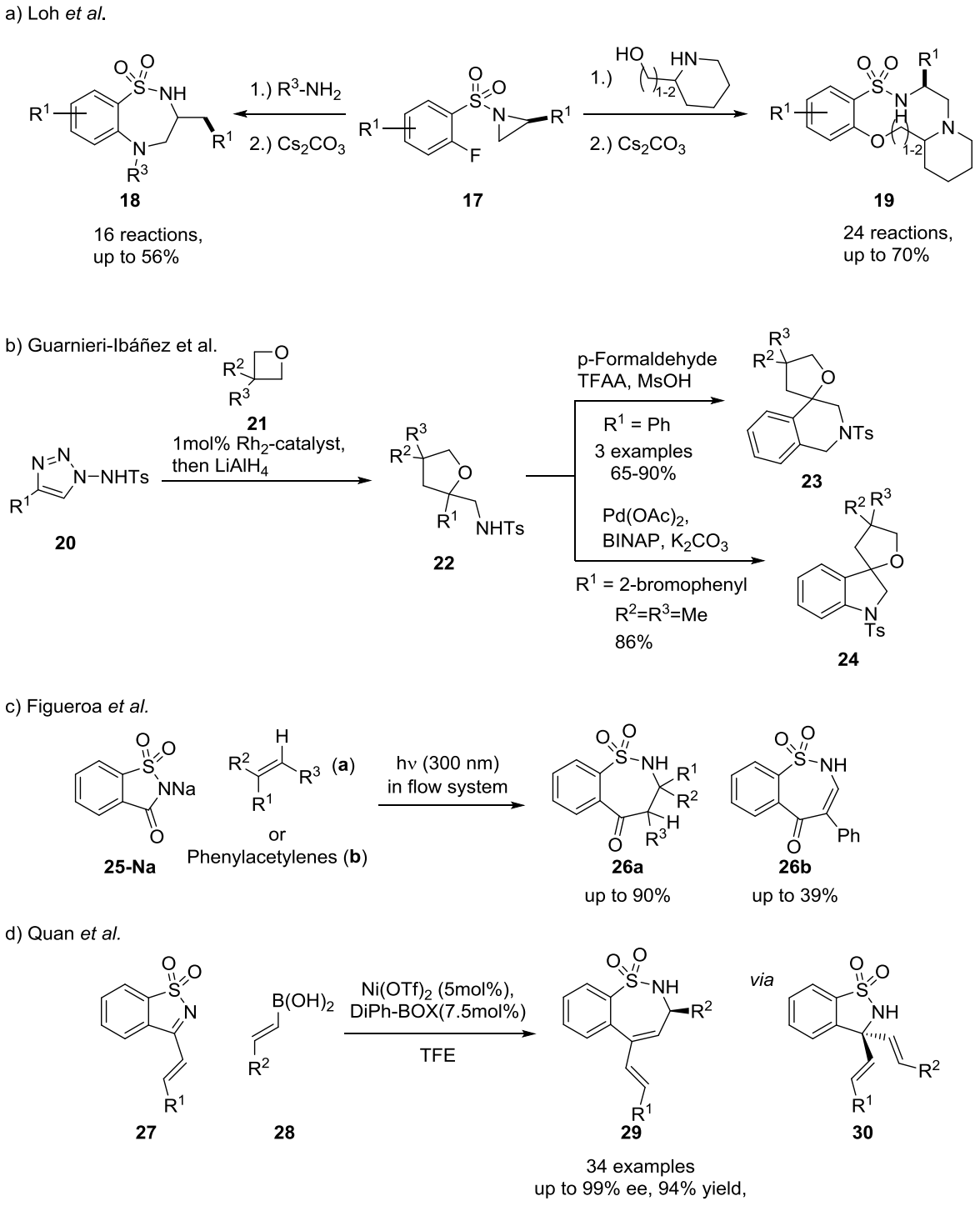
2.2.2 Synthetic approaches towards benzosulfonamides

As previously pointed out, sulfonamides are rarely found in natural product strurctures. Yet, they represent very promising structures from a medicinal chemist's perspective. In particular, cyclic benzosulfonamides which do not occur at all in naturally occurring small molecules are of particular interest. In order to synthesize cyclic sulfonamides **13**, different strategies are conceivable. Firstly, ring closing can proceed *via* sulfonylation of an amine of corresponding substrate **14** (path **a**, Scheme 4). Secondly, one could construct C-N bond via nucleophilic attack of sulfonamide nitrogen atom (**15**, path **b**, Scheme 4). Third main strategy would be the use of substituted linear sulfonamides **16** to form bonds in cyclization to build cyclic sulfonamide (path **c**, Scheme 4). In the following we show an overview of a number of approaches that have been successfully exerted.



Scheme 4: General strategies towards Cyclic sulfonamides

Hanson *et al.* studied an approach that included a chiral pool synthesis of seven-, 10 and 11 membered benzosulfonamides using an *N*-sulfonylation approach (**a,** Scheme 5).[78] Ring-opening of aziridine **17** by a primary amine or amino alcohols as nucleophiles was followed by ring closure, exploiting electron-poor nature of the ortho-fluoro benzosulfonamide. This deliv-



Scheme 5: Different approaches to cyclic sulfonamides as reported in literature.

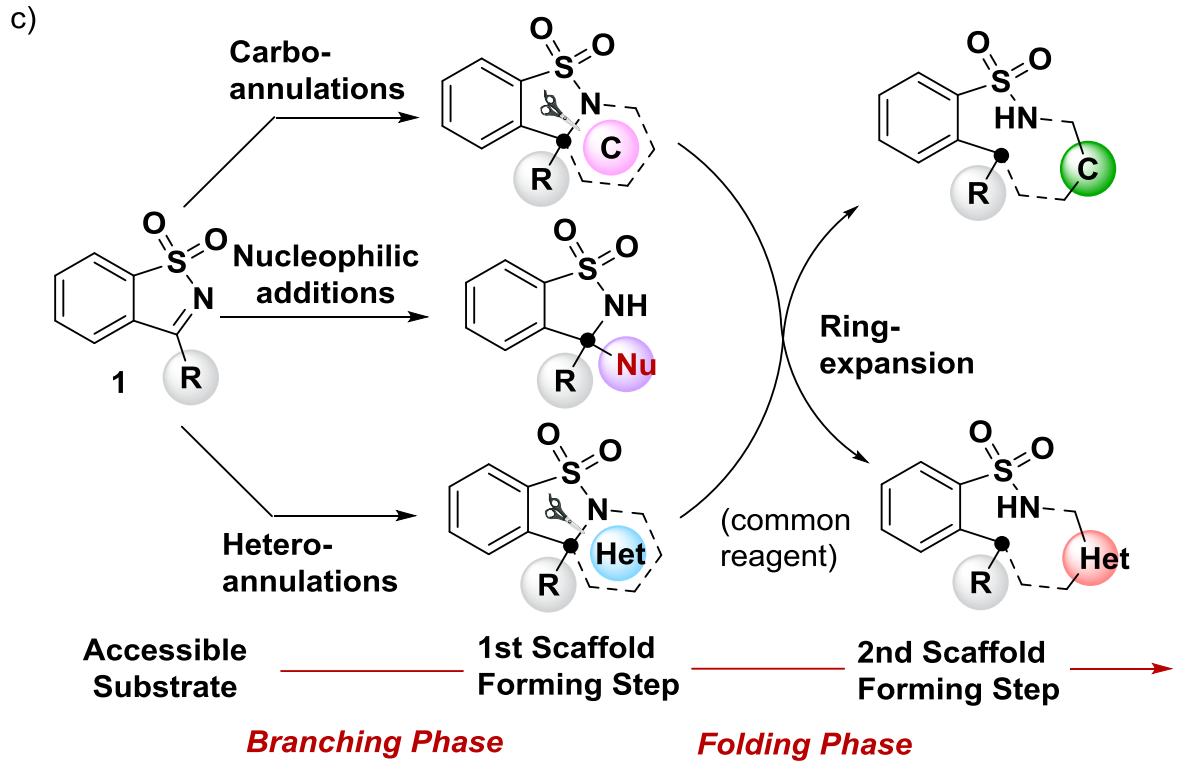
ered sultam scaffolds **18** and **19**, respectively, while retaining stereoinformation of substrates (Scheme 5). The access to different molecules, among them cyclic sulfonamides, was explored in a study using dirhodium catalyst system on triazines **20** in the presence of oxetanes **21**. (Scheme 5b).[79] Resulting tetrahydrofuran intermediate **22** could then be cyclized using amino-alkylation and hydroamination reactions to access fused spirocycles **23** and **24**, respectively.

Another interesting example was displayed in a photocatalyzed continuous flow synthesis of seven-membered sulfonamides. Saccharin sodium salt **25-a** was reacted in a flow reactor setup under light irradiation to give trisubstituted seven-membered sulfonamides **26a** with olefins (**a**) and unsaturated sulfonamides **26b** with phenylacetylenes (**b**).[80]

Ni-catalyzed alkenylations of *N*-sulfonyl ketimines **27** were exploited to synthesize seven-membered sulfonamides via a step-wise Nickel catalysis mediated mechanism that involves enantioselective addition of alkenylboronic acid **28** to give **30** which then rearranges into **29**.[81] Additional noteworthy reports leading to sulfonamides but using individual and different synthetic methods have appeared in literature.[82–85]

2.2.3 Synthetic Strategy To Access Cyclic Benzosulfonamides

Our approach relies on exploring carbo- and hetero-annulations as well as nucleophilic addition reactions on the ketimine moiety in substrate **1** (Scheme 6). Thereby, the sulfonamide group is already present in substrate and does not have to be constructed as the complexity is built up around the benzosultam core.



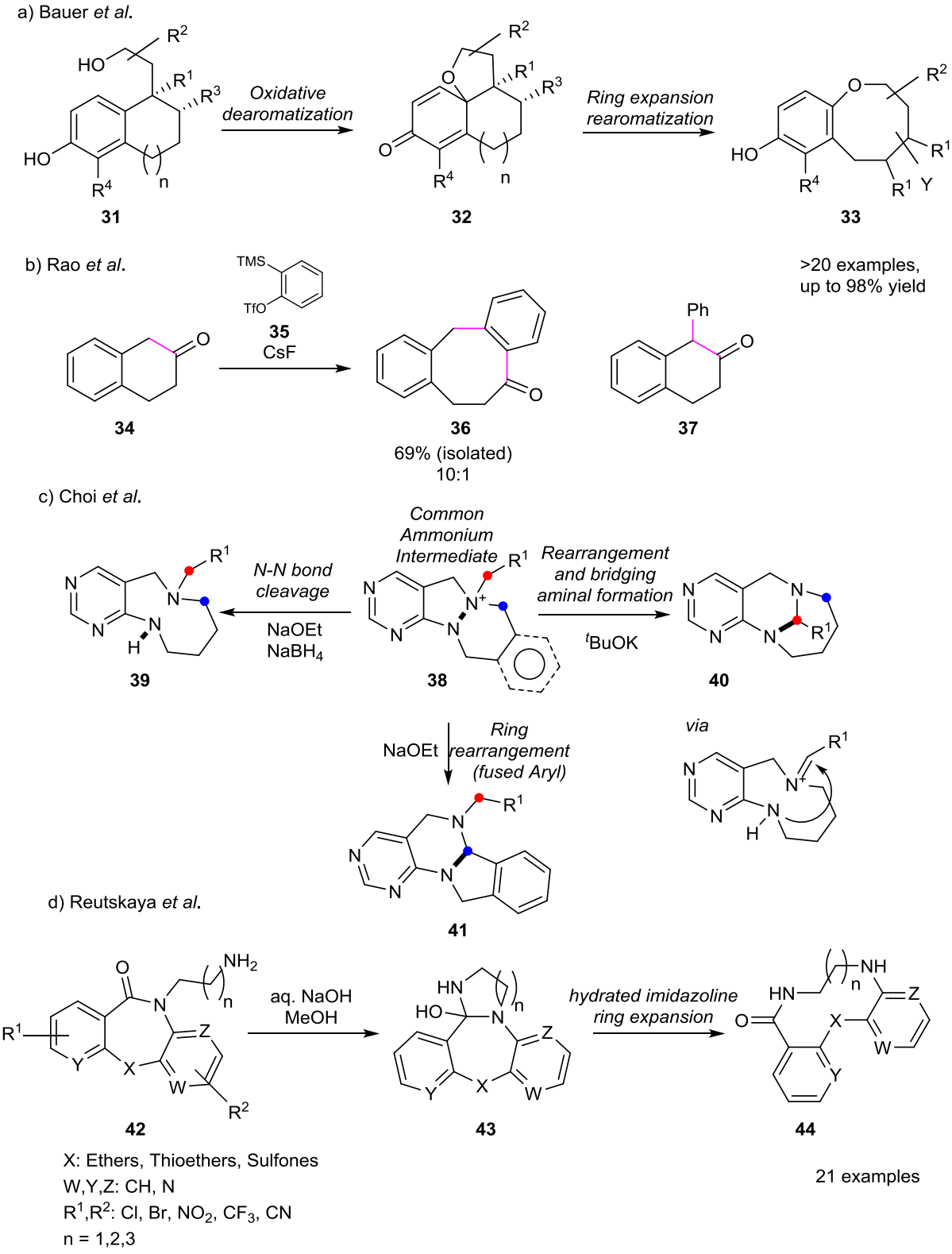
Scheme 6: Representation of synthetic plan for branching-folding strategy.

Different cyclic benzosulfonamides are constructed in this first branching phase that implies transformation of a common substrate into diverse scaffolds. The desired scaffolds must bear at least one stereocenter (highlighted with a black dot in scheme 6). This requires optimization of reaction conditions in case two stereocenters are constructed in order to achieve good diastereoselectivities. Sultams produced in first phase, are in turn used for the next ring-modulation step. We envisioned that general structure of fused benzosultams may allow scaffold transformation by, for instance ring-expansion reactions, giving access to another set of novel benzosultams. Therefore, we sought to identify methodology that can be used on all branching phase scaffolds to keep the strategy effective and modular. The inability of nature to make sultams and surprisingly underexplored synthesis to their structural diversity convinced us to develop a divergent synthesis to a range of cyclic sulfonamdies.

2.2.4 Ring Expansion Reactions

For ring expansion, bonds have to be transformed, rearranged or cleaved. Often, these bonds are carbon-carbon, carbon-nitrogen or other carbon-heteroatom bonds. In this regard, two reaction types appear to be predominant in literature: oxidative and acid-base reactions. Although they usually occur under quite harsh conditions, they do not always allow for use of a broad range of substrates or substitution pattern. Tan *et al.* have reported approaches dealing with distortion of ring structures. (Scheme 7a). Using phenolic substrate **31**, ring closure delivers oxidized ether intermediate **32**, which then undergoes ring expansion and rearomatization to give phenol-fused cycloalkane **33**.[86,87] A strategy that authors coined as *Tandem Oxidative Dearomatization-Ring Expansion Reaction* was exploited to synthesize aryl fused eight- to eleven-membered β-keto amides, which were further functionalized into amines and alcohols.[87]

Rao *et al.* reported an insertion reaction of an aryne (**35**) into 2-tetralone **34** furnishing benzo fused 8-membered rings **36** with just using fluoride as reagent (Scheme 7b). As a byproduct, functionalization at benzylic position occurred, yielding **37**.[88] This is a very interesting transformation as it does not change connectivity of existing framework but enables insertion of aryne unit into cyclic system. Choi *et al.* exploited inherent reactivity of *N-N* bond in tricyclic substrate for reactions yielding a range of very different scaffolds (Scheme 7c).[89] Nine-membered pyrimidine fused aza-heterocycle **39** was formed by using NaOEt and $NaBH_4$ as a hydride source leading to basic cleavage of nitrogen-nitrogen bond (bold) in ammonium intermediate **38**. On the other hand, treatment of **38** with a differente base, i.e. tBuOK led to an effective rearrangement *via* a shift of N-N bond to carbon connecting R^1 and nitrogen (highlighted in red) to give aminal- bridged cycle **40**. This occurred via the sequence of deprotonating amine carbon (red), cleavage of nitrogen-nitrogen bond and subsequent attack of eliminated nitrogen. If an aryl-fused substrate is selected for this reaction, 5-6 ring system can be transformed to 6-5 ring system by shift of nitrogen-nitrogen bond to benzylic carbon (blue), furnishing **41** using sodium ethoxide as a base. A strategy exploring the inherent reactivity of benzodiazepine-related substrates **42** under relatively simple reaction conditions was developed by Reutskaya and co-workers to form complex cyclic sulfonamdies. Intramolecular attack of amine in basic media leads to



Scheme 7: Different synthetic strategies employing ring-expansion as key reactions.[86,88–91]

formation of **43**, which eliminates amine to make a ring-expansion of fused imidazolidine to form medium to large membered ring system **44** (Scheme 7d).[91] In addition to these examples, there are further some reports making use of similar strategies in literature.[92–94]

With these options for scaffold generation in hand, we had to decide how modification of scaffolds that we plan to form in branching phase may be addressed. Hydrogenolysis was considered as a possible tool that may allow the folding pathway, that implies using similar reaction conditions on different substrates to form a range of diverse scaffolds. We hypothesized that an intramolecular debenzylation in this regard can furnish interesting ring-expanded/modulated scaffolds via a C-N bond cleavage. Carbon-carbon bond hydrogenolysis has been subject of research in petrochemistry in order to crack down hydrocarbon chains into smaller fragments[95,96] while carbon-nitrogen bond cleavage has been of interest as it is required to reduce amount of aminated hydrocarbons for environmental soundness.

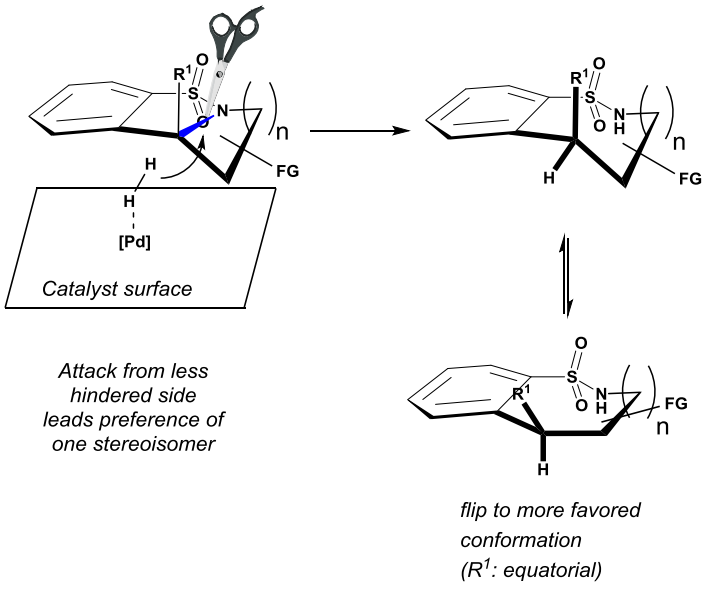


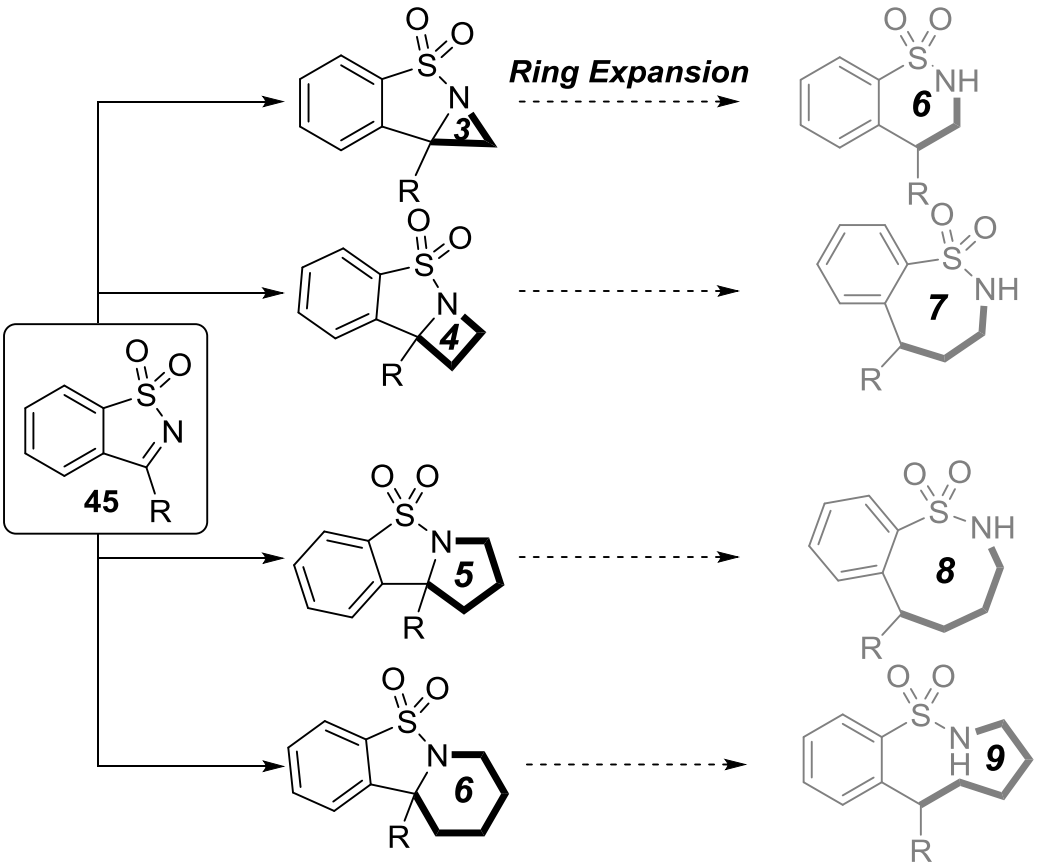
Figure 4: Hypothesis for induction of diastereoselectivity.

The tricyclic sulfonamide templates in branching phase of scaffold synthesis bear certain stereochemical features and are rather concave than flat in three-dimensional structure. Thus, from a reaction kinetics view, hydrogen donation from a more accessible site should be preferred, thus delivering a high degree of diastereoselectivity.[95,97–99] Furthermore, presence of aminohydrocarbons is problematic due to its poisoning of transition metal catalysts.[100] There are different models predicted describing mechanism of hydrogen transfer using a heterogeneous catalyst.[101] In such metal-catalyzed hydrogenation and hydrogenolysis, hydrogen adsorbs on metal catalyst and generates the reactive species on a solid support. The substrate approaches with less hindered site, allowing hydrogen to be donated to this site (Figure 4). As tricyclic benzosulfonamides take in mostly concave three-dimensonal structures, diastereoselectivity may be introduced in this fashion.

2.3 Results and Discussion

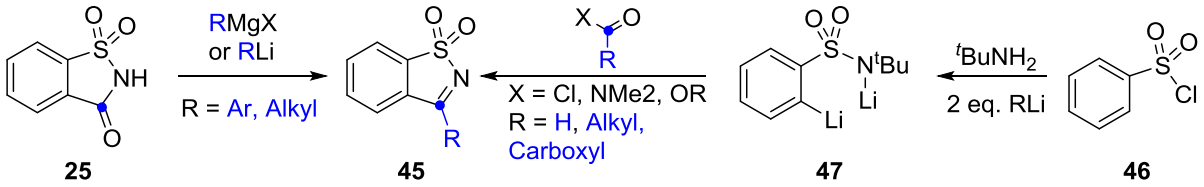
2.3.1 The Branching Phase - Synthesis of tricyclic benzosulfonamides by annulation reactions

For the first branching phase of scaffold synthesis that transform common substrates into range of different cyclic sulfoanmdies, different annulation and addition reactions on common imine substrates **45** were chosen for investigation. We realized that three- to six-membered ring-fusion to imine might be possible by direct cyclization or annulation chemistry, however, greater ring sizes between seven and nine are not as easily available by means of imine chemistry (Scheme 8).



Scheme 8: Targeted scaffolds and ring sizes. Fused three to six-membered rings (center row) are available by means of direct annulation. Ring expansion would grant access to further, interesting ring structures, including seven to nine-membered rings (right row).

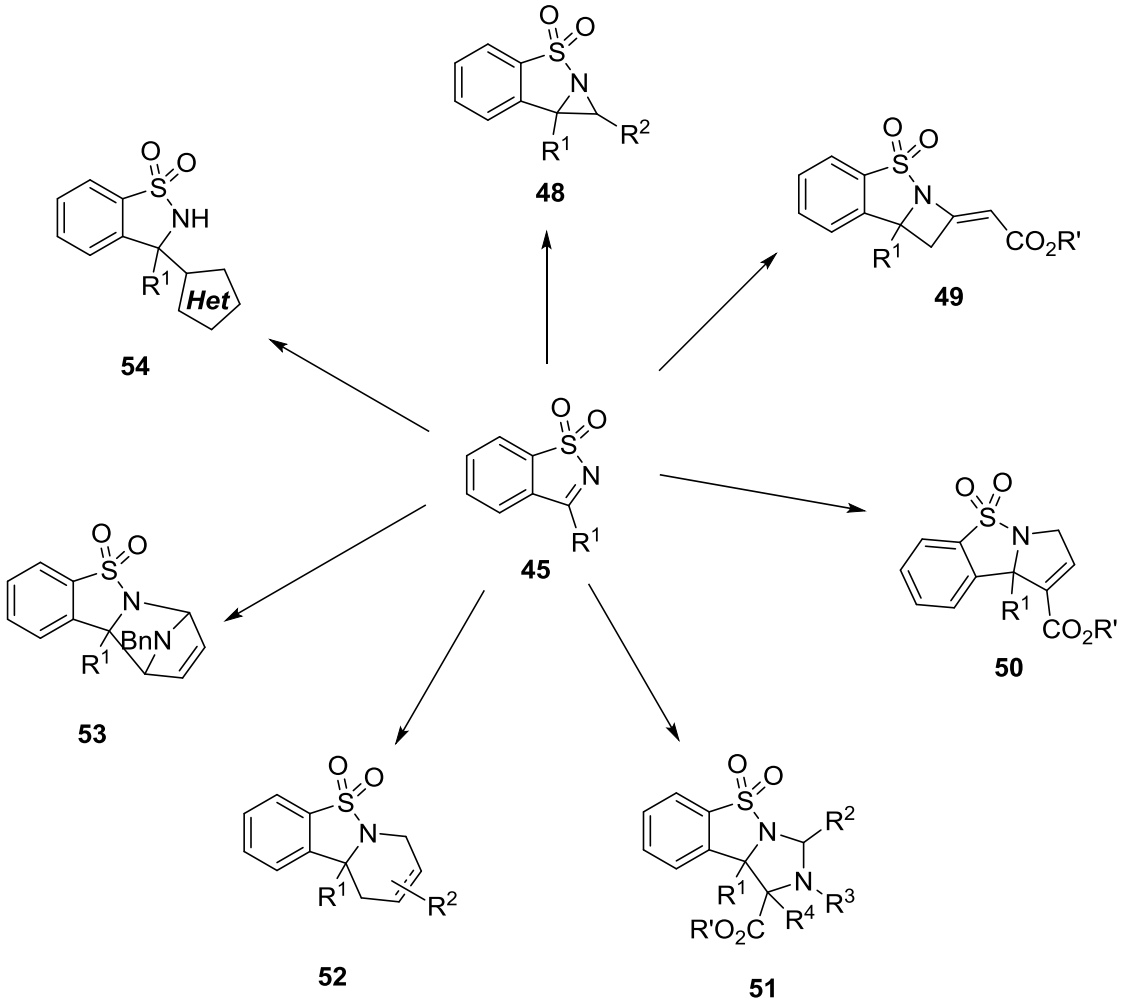
Thus, we decided to generate the smaller ring systems in a first branching phase and convert them into the larger ring systems in ring expansion or folding phase later (section 2.3.3, Scheme 8). As only few approaches mentioned above exploit the imine chemistry,[102] we selected **45** as the suitable imine candidate to generate a range of cyclic sulfonamides.



Scheme 9: Synthesis of ketimine substrates, either accessible from saccharin or from phenyl sulfonyl chloride.

Two main approaches are known for the synthesis of imine substrates (**45**). Sweetener saccharin **25** is easily available and serves as an inexpensive substrate for addition of organometallic reagents such as Grignard or organolithiums (Scheme 9). While first equivalent of base deprotonates nitrogen, second will attack carbonyl function to give hemiaminal, which can then collapse eliminating water and furnishing corresponding imine **45**. Alternatively, phenylsulfonyl chloride **46** can be turned into tert-butyl sulfonamide **47**, which then can be lithiated at amide and ortho-position to give **45**. This species can then react with activated ester-equivalents such as esters, acyl halides or amides such as DMF (to furnish aldimine) to afford ketimines **45** after elimination of water (or dimethylamine in the case of DMF). The latter approach is well suited for generation of carbonyl-derived ketimines because a range of amides, oxalates and other reactive acyl species are available to use with double-lithiated species **47**. We applied both of these previously reported approaches to synthesize different ketimines (**45-H**,[103],**45-Me**,[104] **45-Ph**,[105] **45-CO$_2$Et**,[106] **45-2-Pyr**[107]).

With these substrates in hand, a reaction planning to construct different target scaffolds was framed. Particularly, chemical reactions leading to 3 -membered ring-fusion to six-memebred ring fusion to ketimines **45** were of interest. Towards aziridines – the three membered aza-heterocycles, a handful of synthetic strategies[108][109] that can make use of imines **45** to form aziridines **48** were considered. Synthesis of azetidines **49** [110] , fused pyrrolines **50**[111] and imidazolidines **51** were planned employing dipolar annulation reactions. For the six-ring-fused benzosulfonamides, we naturally thought of using a Diels-Alder reaction strategy. There are reports about saccharin-derived ketimines **45-Me** readily reacting with Danishefsky's diene and different other (aza-)dienes to give tricyclic pyridones **52**.[112,113] We were interesting in studying and extending the scope of this reaction.. Furthermore, we were curious whether *N*-Sulfonyl ketimines would cyclize in modes to allow synthesis of frameworks such as pyrrol-fused product **53**. Furthermore, we decided to study application of Mannich-reaction using ketimines **45** as substrates. Additions of electron rich aromatic molecules such as indoles, furanes and pyrroles to carbonyl groups has been



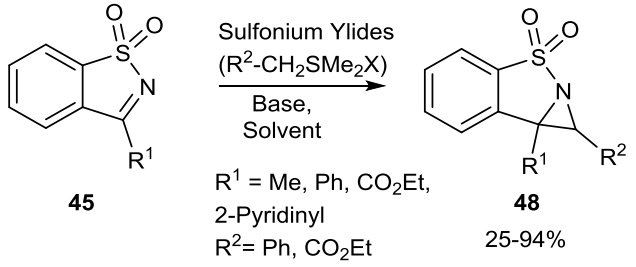
Scheme 10: Branching pathway leading to proposed scaffolds.

reported earlier to give adducts **54**.[114–117] Notably, Aldol and Mannich-type reactions are a well established and highly relevant strategy for the construction of complex frameworks.[118–120][121] With this planning, the stage was set to execute the expeirments generating the plausible scaffolds (Scheme 10) in branching phase, and for further optimization of reactions in positive cases. This will be laid out in following chapters. Attempts for the ring-expansion reactions of scaffolds formed in branching phase are described section 2.3.3.

2.3.1.1 Disubstituted saccharin-derived aziridines

We decided to utilize Aza-Corey-Chaikovsky reaction[122–126] as it is a well-documented and a promising option for synthesis of aziridines, and considering the availability of a range of chiral auxiliaries for further optimization. Sulfonium salts are commercially available, but also easily accessible by combination of organo halides and dimethyl sulfide in acetone and subsequent filtration.[127][128]

Formation of aziridine – the 3-membered aza-heterocycle- fused benzosulfonamide was commenced by the reaction of ketimines **45**, and commercially available trimethylsulfonium iodide in the presence of sodium hydride in *N,N*-dimethylformamide (DMF). The expected aziridines (**48 a-h**) were formed after 3 h (Scheme 11). Differently substituted ketimines (**45**) in combination with two sulfonium slalts i.e. phenyl and carbethoxy substituted methylidene dimethylsulfonium salt auxiliaries were chosen as diversity inducing decorations in the tricyclic benzosulfondamides (**48**). The ester group in the products can be hydrolyzed and transformed into amides, alcohols and other derivatives.

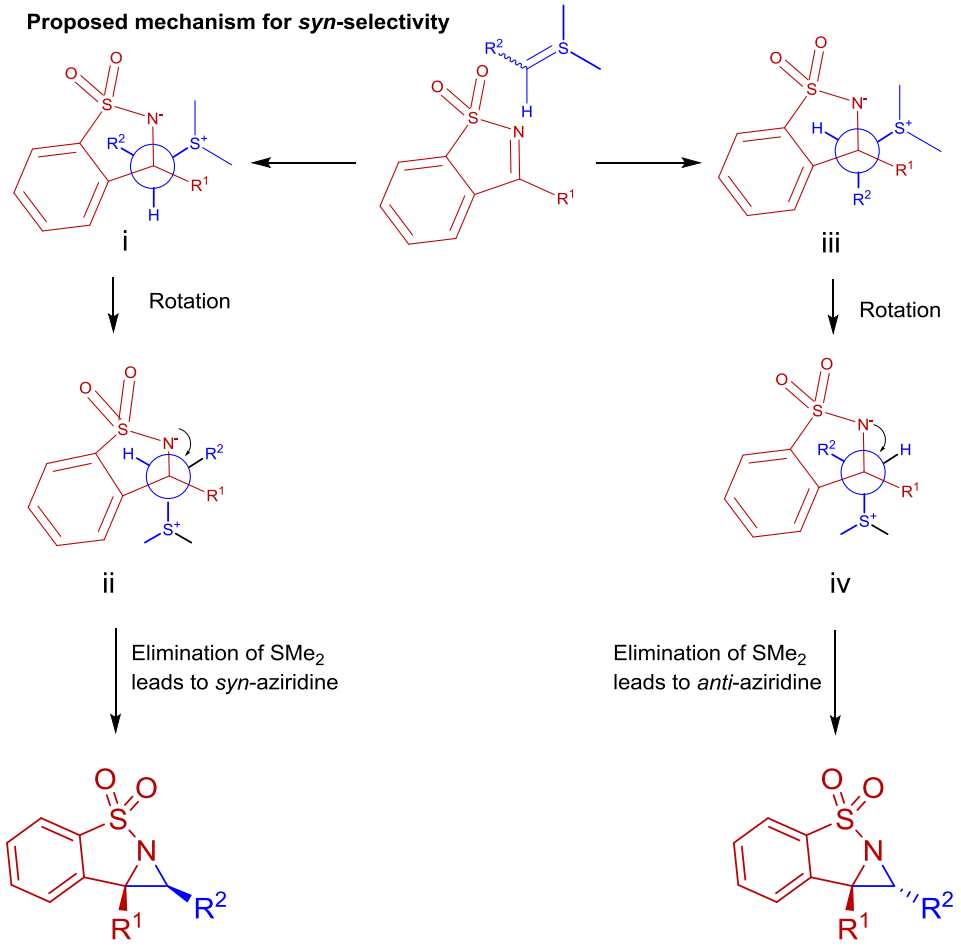


48a: 68% (R^1 = Me, R^2= Ph)
48b: 84% (R^1 = Me, R^2 = CO_2Et)
48c: 94% (R^1 = Ph, R^2 = Ph; *syn*/*anti* 1:1)
48d: 25% (R^1 = Ph, R^2 = CO_2Et)
48e: 37% (R^1 = CO_2Et, R^2 = CO_2Et)
48f: 54% (R^1 = CO_2Et, R^2= Ph)
48g: 91% (R^1 = 2-Pyr, R^2 = CO_2Et)
48h: 73% (R^1 = 2-Pyr, R^2= Ph; *syn*/*anti* 1:1)

Scheme 11: Aziridination of Ketimines **45** using *in situ* generated sulfonium ylides.

Ketimines **45-Me**, **45-2-Pyr**, **45-Ph**, **45-CO_2Et** delivered the desired aziridines successfully. Interestingly, we observed that **45-H** imine was not a suitable substrate and did not react under standard conditions, even though with no streric bulk around, it was expected to be more reactive. We found that different substrate-ylide combinations require different solvents due to solubility issue and for the reaction to proceed to completion. While reactions leading to **48c** (R^1 = R^2 = Ph) required DMF, **48e** (R^1 = R^2 = CO_2Et) was obtained employing DMSO rather in moderate yield (37%). Apart from that, acetonitrile was employed as a default solvent in the rections and the products were obtained in good to moderate yields, with exception of **48d** (DMF, 25%) and **48e**, which yielded a range of products in addition to 37% yield of desired aziridine. Varying reaction times, temperature and equivalents of sulfonium ylide could not improve the performance of these reactions. For **48c** and **48h,** the molecules bearing two neighbouring aryl groups, *syn* and *anti* isomers

were isolated in 1:1 ration in 94% and 73% combined isolated yield respectively. *Syn*-diastereomer of **48a** was obtained as major product from a mixture of 7:1 *d.r.* in 78% combined yield. The formation of byproducts with lower molecular weight in the synthesis of **48e** may be attributed to the ionic medium formed by combination of DMSO and sodium bromide and plausibly inducing decarboxylation reactions. We observed that aziridines bearing two neighbouring aryl groups (**48c** and **48h**) were obtained with poor diastereoselectivities, while most other substrates, in particular those with R^2=CO_2Et, formed a single diastereomer. For **48b** and **48d-g** we found diastereomeric ratios greater than 20:1 and only the major diastereomers were isolated.



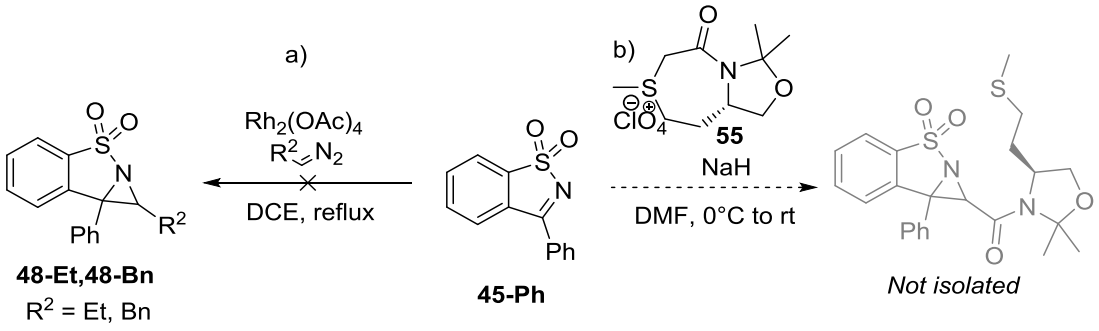
Scheme 12: Proposed mechanism of aziridination reaction, explaining preferred diastereoselectivity.

The aziridation reactions of ketimines proceeded in a mostly *syn*-selective fashion, whereas literature reports that had mostly dealt with aziridation of aldimines, reported a preferred *anti* selectivity. To explain this stereochemistry behavior, we resort to a standard model for sulfonium ylide mediated reactions of Corey and Chaikovsky. We propose that addition of sulfonyl ylides leads to formation of **i** and **iii** (Scheme 12). C-C bond rotation in betain **i**

minimizes the steric interaction between residue of ketimine and that of sulfur ylide (R^2). This leads to antiperiplanar conformation in regard to nitrogen and sulfur atoms (**ii**), allowing for *syn* product formation upon elimination of dimethyl sulfide. C-C bond rotation in betaines (**iii**) that contain neighbouring quaternary and tertiary stereocenters demands high activation energy. In case of R^2=CO_2Et, rotation of bond in **iii** would lead to electrostatic repulsion between carboxylate (**iv**) and negatively charged nitrogen atom and is thus not favoured.

In case R^1 and R^2 = Ar (i.e. **48c** and **48h**), π-stacking of aryl function (R^2), ketimine aryl function and R^1 stabilize transition state (**iii**) enabling *anti*-aziridine formation. However, in this case, betain **i** route is equally favored (low energy barrier to rotation) and therefore *syn* and *anti* products are formed in similar amounts.

Among other attempts towards aziridine formation, w also tried to adapt rhodium-carbenoid approach using diazo-compounds with diazoethane and diazoethylbenzene.[129] We proposed that these would react towards **48-Et** and **48-Bn**, allowing for chiral modification using chiral ligands with Rhodium catalyst later.[130] However, no reaction was observed as we recovered the starting material.



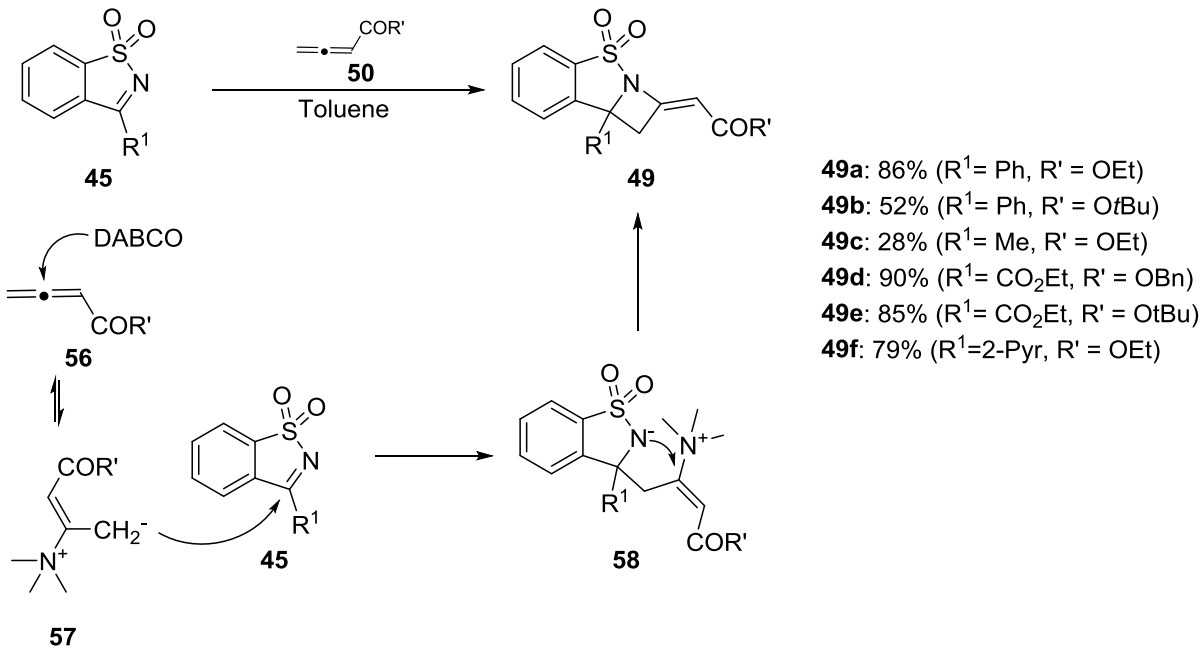
Scheme 13: Approaches for aziridination a.) Rhodium-carbenoid based approach b) methionine-derived auxiliary approach, inducing stereoselectivity through stereoinformation of auxiliary.

We also attempted some experiments with chiral sulfonium salts supporting chiral auxiliaries (Scheme 13), i.e. methionine-derived sulfonium salt **55** as studied by Sarabia *et al.*[131], but this too did not deliver the desired product. **55** is relatively easily available from methionine. Use of **55** in aziridination with **45-Ph** led to consumption of starting material and even though a product was detected in HPLC-MS analysis, we failed to isolate the desired product. Furthermore, the desired product can only be cleaved off oxazolidinyl moiety by strong lithium reagents which do not always tolerate sulfonamides based on their lewis basic nature and therefore this route was not further pursued.[69][132]

2.3.1.2 Organocatalytic reactions leading to Azetidines and Pyrrolines

2.3.1.2.1 Azetidines

After formation of a 3-membered heterocycle i.e. aziridine fused sultam, our next target was a four-membered aza-heterocycle. To this end, we used the method of Song ye *et al.*[110] wherein allene esters **56** could be used under nucleophilic catalysis using DABCO to form azetidine ring *via* zwitterionic species **58**. In this fashion, we synthesized examples **51a**, **51b** and **51f** in good yields (Scheme 14). We were pleased to observe that this zwitterionic annulation could tolerate not only aryl substation on ketimine, but also alkyl and ester function. The synthesis was further extended to examples **51c-e** that have not been reported before. Except for **51c** (28%, methyl substitution), we managed to synthesize the azetidines in good to very good yields (59-90%) and in up to gram scale.

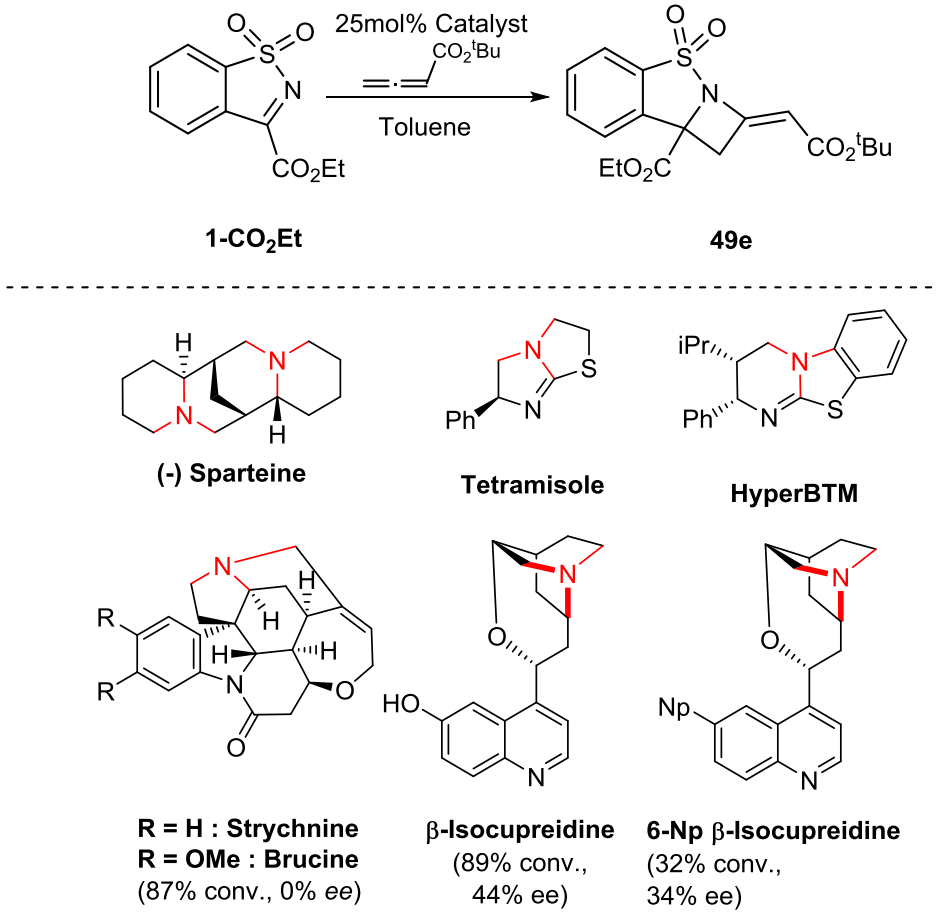


Scheme 14: Synthesis of azetidinines according to procedure of Song Ye *et al.*[110]

According to proposed mechanism,[133] allenoate is activated by addition of nucleophilic tertiary amines (here: DABCO) to give zwitterionic intermediate **57** that adds to ketimines **45** from γ-position, as α-position cannot react due to high steric demands of carboxyethyl group and ketimine residue to form interemediate of type **58**. Aza-Michael-type addition and elimination of amine catalyst then furnishes **49** as the exclusive diastereomer. It is noteworthy that aldimine substrate **45-H** did not yield the corresponding azetidine in our

hands. We assume that DABCO forms an adduct with aldimine as aldimine was partly consumed. As methyl substitution on imine delivers lower yield than aryl or carbalkoxy substituted imines, we assume that aryl or electron-withdrawing substituents are required in order for addition of zwitterionic intermediates to imine for successful reactions.

In order to make the above annulation reaction in an asymmetric fashion, we explored a handful of catalysts that may induce asymmetry and bear the feature crucial for catalytic activity i.e. the cyclic tertiary amine with increased nucleophilicity at lone pair. In scheme 15, we list a few that we thought may meet these criteria: natural products (-)-sparteine and strychnine and its analogue brucine, cinchonine-derived β-isocupreidine (β-ICD) and a derivative aswell as carbamimidothioates Hyper BTM and tetramisole, an antiparasitic drug.



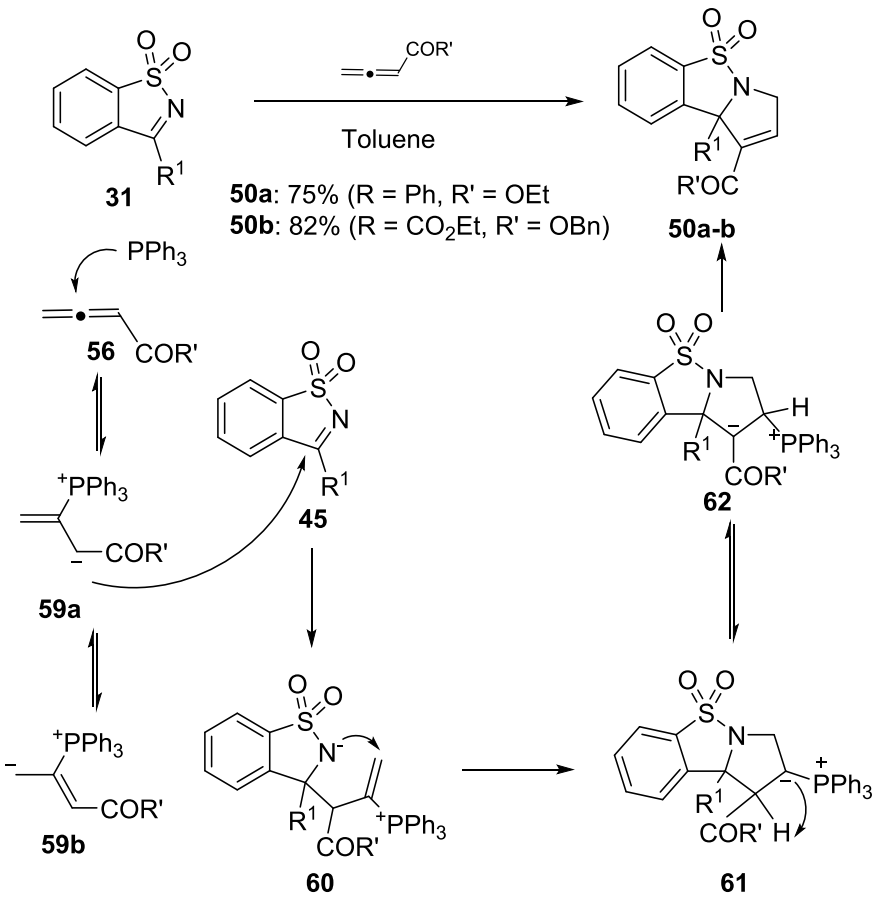
Scheme 15: Overview of attempts to achieve asymmetric induction in azetidine formation studying different chiral tertiary amines for their suitability as organocatalysts. In case of a reaction, conversion and *ee* are annotated.

We speculated that latter two compounds as may be of different stereoelectronic nature than other candidates but still worth investigating and reveal interesting reactivities. Carboxyethyl-derived ketimine **45-CO_2Et** was chosen as model substrate for this reaction.

However, we found that the only two candidates that induced conversion towards products were β-ICD and Brucine. Although significant degrees of conversion were observed (89% and 87% yields at 26 °C, respectively), β-ICD and its derivative 6-Np- β-ICD generated merely 44% *ee* and 34% ee, respectively, while brucine did not generate optically active mixture at all and therefore further optimization was not followed up. Sparteine, tetramisole and HyperBTM did not show any conversion of starting ketimine or allene, possibly due to their stereoelectronic nature (tetramisole and HyperBTM).

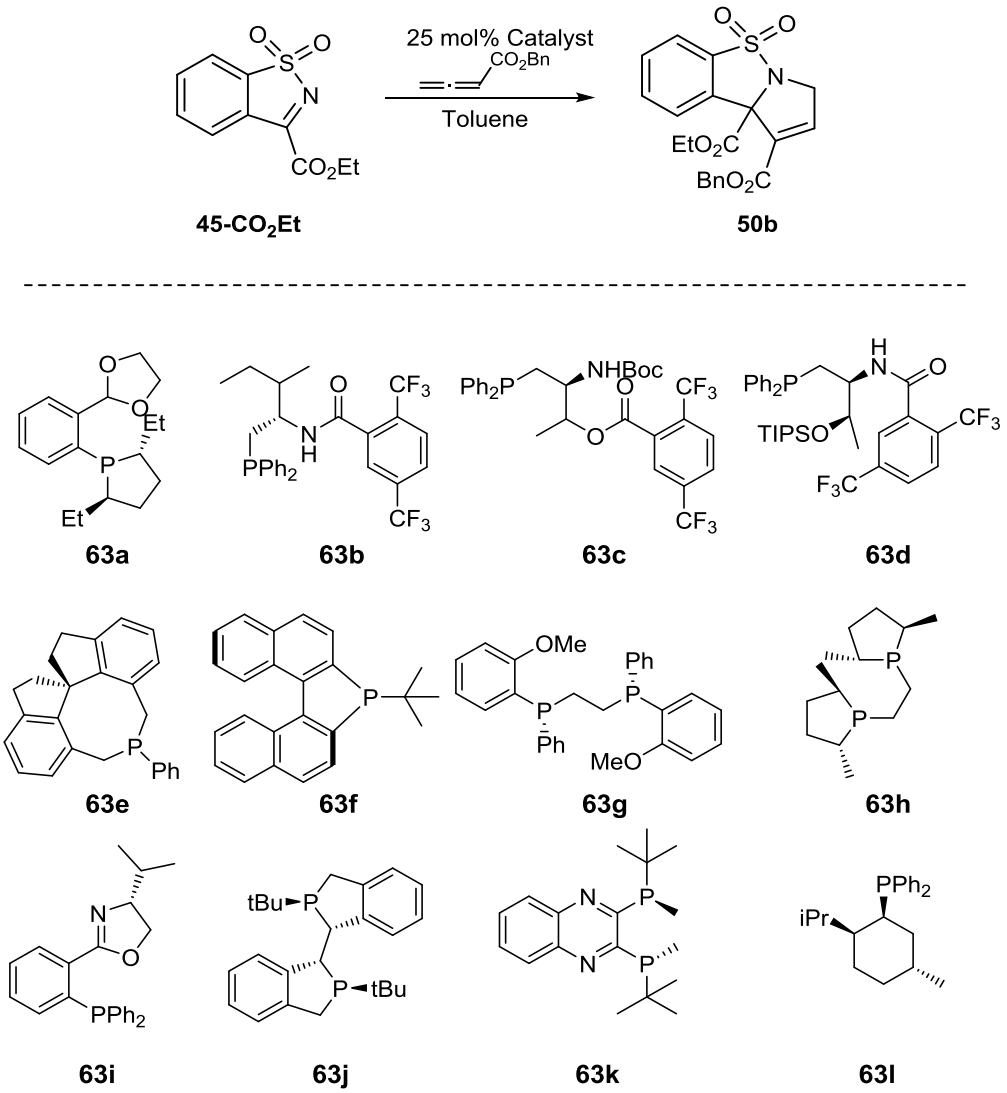
2.3.1.2.2 Pyrrolines

After successfully generating a set of aziridines, next we were interested in making frameworks with fused five-membered rings. Interestingly, in the above mentioned azetidine formation reaction catalyzed with DABCO, resorting to triphenylphosphine can deliver benzosulfonamides fused to a pyrroline ring (**50**, Scheme 16).[110]



Scheme 16: Phosphine mediated reaction of carbalkoxyallenes **56** and *N*-sulfonyl ketimines **45**.

Mechanistically, addition of phosphine catalyst to allene esters **56** generates zwitterions **59a**, which can isomerize into **59b**. However, only former species attacks ketimines **45** to give adduct **60**, which then forms phosphonium-pyrroline **61**. Acidity of carboxylic group leads to proton transfer (**62**) and subsequent elimination of phosphine, furnishing pyrrolines **50** (Scheme 16). In agreement with report by Chen *et al.*, different aryl groups on ketimine were tolerated in this annulation reaction. However, ketimines with alkyl substitutions did not afford corresponding pyrrolines. In addition to aryl substitution on ketimine, we found that **45-CO_2Et** delivered diester **50b** in 82% yield.



Scheme 17: Pyrroline formation via reactions of allenoates and ketimines using phosphine catalysis.

We performed screening experiments to develop an asymmetric variation of this transformation. As a plethora of chiral phosphines are (commercially) available, we assumed that we would have good prospects of identifying one that will mediate the reaction and furnish optically highly enriched product mixture.

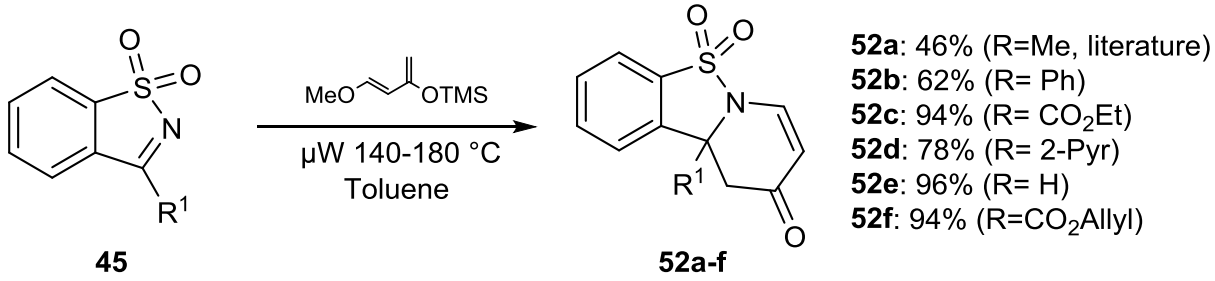
We selected a handful of phosphines for screening experiments (Scheme 17, table 2). Under conditions established for racemic variation, we found that only a handful of phosphines led to acceptable conversion of starting materials. Although phospholane **63a** (entry 2) delivered product in 51% ee, only 12% yield was observed. In contrast, isoleucine derived aminophosphine **63b** (entry 3) gave moderate yield (51%) but merely 25% ee. As reaction time (2.5 h) is rather short, it is noteworthy that even prolonged reaction time did not lead to higher conversion. We assume that extended screening experiments, studying the role of solvent and concentration effects are required to identify phosphines that mediate reaction in satisfying yields and enantiomeric excess.

Table 1: Screening conditions for [3+2] annulation leading to benzosulfonamidyl-pyrrolines. Yields were determined by ^{1}H-NMR analysis of crude reaction mixtures.

Entry	T / °C	Time / h	Yield	*ee*
1 (**PPh$_3$**)	21	2	62%	-
2 (**63a**)	0 to 22	22	12%	51%
3 (**63b**)	0	2.5	51%	25%
4 (**63c**)	0	2.5	29%	0%
5 (**63d**)	0	2.5	69%	0%
6 (**63e**)	0	2.5	81%	29%
7 (**63f**)	0 to 22	2 d	traces	-
8 (**63g**)	0	1.5	65%	0%
9 (**63h**)	0	1.5	69%	0%
10 (**63i**)	0 to 22	15	10%	0%
11 (**63j**)	0 to 22	15	52%	9%
12 (**63k**)	0 to 22	3 d	traces	-
13 (**63l**)	0 to 22	3 d	traces	-

2.3.1.3 Diels-Alder reaction towards cyclic *N*-Sulfonyl Dihydropyridones

Moving to next bigger ring, i.e. a six-memebred ring-fused benzosulfonamide, we resorted to Diels-Alder reaction approach. Infact, the reaction of Danishefsky's diene with **45-Me** has been reported earlier. Thus, decision was made to extend the substrate scope to other ketimines to obtain a set of compounds. We found that this reaction indeed allows access to a set of pyridinones (**52**). After some less successful attempts at room temperature, reactions were performed at elevated temperature using microwave irradiation and $ZnCl_2$ as a catalyst to afford the desired products in moderate to good yields (62 to 94%, Scheme 18). The reaction of each of the different substrates depicted in Scheme 18 took less than 45 min to finish. Reactions proceeded in toluene, whereas for the synthesis of **52d**, DMF addition was required to solubililize the starting ketimine. Reaction proceeded largely cleanly and only in a couple of cases rather polar impurities that could easily be separated by means of silica gel column chromatography were observed.

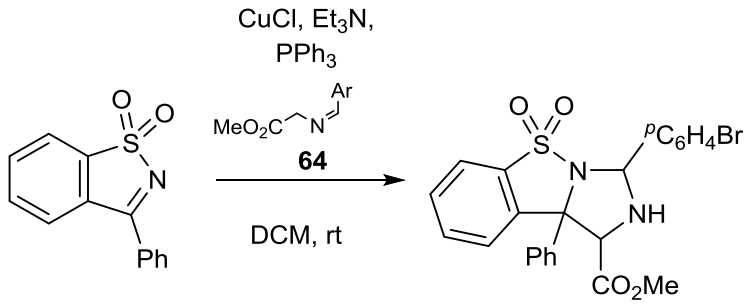


Scheme 18: Aza-Diels-Alder reaction of Danishefsky's diene with saccharin-derived ketimines.

Thus, a Diels-Alder reaction strategy easily afforded the six-memberd ring-fused benzosultam. Our findings suggest that differently substituted ketimines are well tolerated in this reaction and that carbonyl moiety can be employed for synthesis of potentially interesting molecules. For deeper investigation into this matter, see chapters 2.3.3 and 2.3.4.

2.3.1.4 Utilization of Azomethine ylides for construction of benzosultam-fused imidazolidines

In all the above examples so far, we had used different carbon-units for annulation with imine. 1-C to form aziridine, 2C-unit to form azetidine, 3C-unit for pyrroline and a 4C-unit to form pyridines. In order to bring more aza-rings fused to imine part of common substrates in branching pathway, we next targeted annulation recation of ketimines with azomethine ylides that can potentially form imidazolidine fused benzosulfoanmides. Imidazolidines are a commonly occurring fragment in natural products and other biologically active substances. To our knowledge, sultam-fused imidazolidines have not been synthesized so far. One of the most important and established synthetic strategies towards pyrrolidines and imidazolidines is [3+2] cycloaddition of azomethine ylides and olefins or imines, respectively.



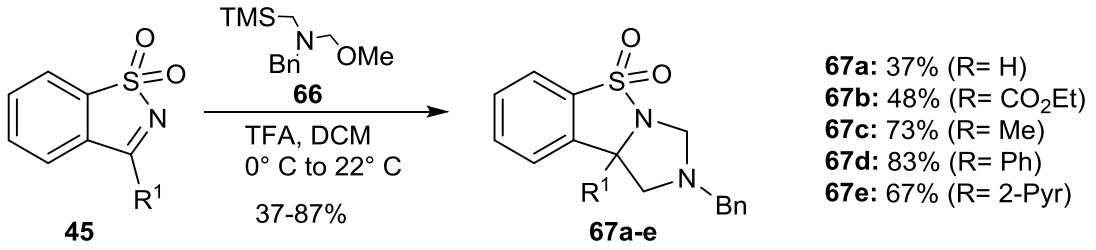
45-Ph **65**

~20-30%
Proposed structure, not isolated from complex mixture

Scheme 19: [3+2] cycloadditon using substituted benzaldehyde-derived azemethine ylides.

We employed imine **64**, easily available from glycine methyl ester and bromo-benzaldehyde as the source of azomethine ylide and observed 20-30% conversion of starting material in different attempts in the reaction with **45-Ph**. However, the reaction was not clean and a range of products, most likely diasteroisomers of **65** were obtained as a mixture (Scheme 19). We did not manage to isolate the expected product, and also recovered significant amount of starting ketimine. This inspired us to use a similar reagent whose products would not be prone to such phenomena.Motivated to find a compromise between identifying a robust reaction that would furnish stable molecules of fused imidazoline scaffold and that would not come with diastereoselectivity issues we decided to employ trimethylsilylmethyl hemiaminal **66** as source of azomethine ylide. A successful annulation of the *in situ* generated azomethine ylide would form adduct **60** with only one strereocenter and thus avoiding diastereomeric mixtures. To our satisfaction, reaction of **66** with a range of

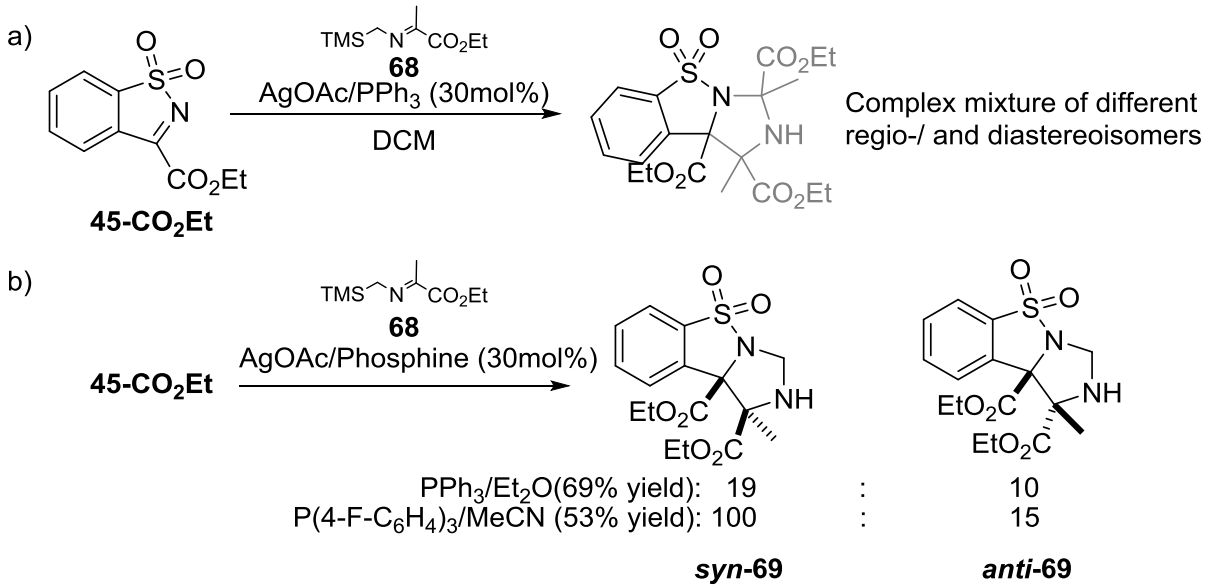
ketimines **45** supporting different substitutions and in acidic media (TFA/DCM to *in situ* generate active species) yielded imidazolidines **67** in moderate yields (Scheme 20). Reaction times ranged from 3 h to 15 h. While using **45-H** and **45-CO_2Et** delivered rather low to moderate yields (**67a** and **67b**, 37% and 48% respectively), methyl, phenyl and 2-pyridinyl substituted ketimines furnished products **67c**-**e** in good to very good yields (67% to 83%).



Scheme 20: [3+2] cycloaddition of saccharin-derived ketimines with in-situ generated azomethine ylides **66** to give imidazolidines **67a**-**e**.

These imidazolidines feature a single quaternary stereocenter each and allow orthogonal derivatization, in case such a residue R^1 is chosen to be a synthetic handle such as carboxylic ester (**67b**). For further modulation and derivatization of **67**, see section **2.3.3**.

Access to imidazolidines with a higher molecular complexity can be achieved by selection of other azomethine ylide precursors, such as pyruvate-derived azomethine ylide **68**.[134,135]



Scheme 21: Cyclization of pyruvate-derived azomethine ylides and ketimine **45-CO_2Et** furnishing disubstituted imidazolidines **69**.

We employed this pyruvate-derived **68** as ylide substrate that may offer access to more moelcular complexity by means of quaternary stereocenters and scaffolds whose ester substitution may still allow additional modifications (Scheme 21 a).[134,135] A reaction performed

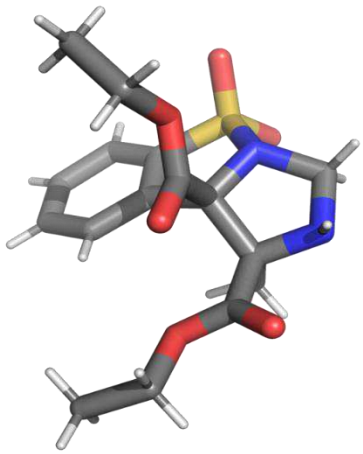


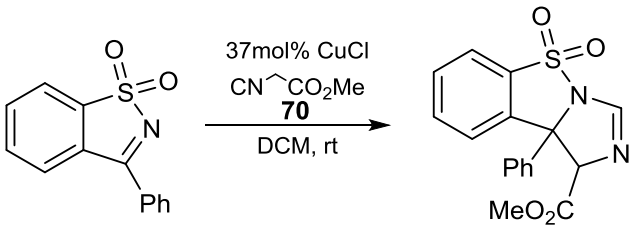
Figure 5: Crystal structure of ***syn*-69**, major product of optimized conditions of [3+2] cycloaddition.

in DCM as a solvent, although led to good conversion of starting material, however a complex mixture of products was formed.Changing the solvent to diethyl ether drasticially improved the reaction which was rather clean and delivered an almost 2:1 mixture of diastereomers in a combined yield of 69% (Scheme 21 b). The significance of solvent's role may be attributed to the Lewis basicity of ether that interacts with Lewis acid and thereby moderates its activity and selectivity and product formation.[136] Compounds formed were characterized by means of different NMR experiments (HSQC, HMBC, NOESY). X-ray diffraction of ***syn*-69** aided us to determine relative configuration (Fig. 4). This is the first report of a construction of two consecutive quaternary stereocenters on a cyclic benzosulfonamide and presents a good starting point for further studies on this reaction. Moreover, as disubstituted imidazolidines support a free amine function, further derivatization may prove useful to build a small collection. We varied phosphines and solvents in order to improve diastereomeric ratios (Table 2). While triphenylphosphine did not give a clean reaction in DCM and delivered a mere 2:1 d.r. in diethyl ether (entries 1 and 2), tricyclohexylphosphine delivered close to nodiastereomeric excess (52:42, entry 3). Electron-rich tri-o-tolylphosphine delivered relatively good d.r. in MeCN and diethyl ether (entries 4 and 5). Complex Chiral phosphines (entries 6-8) delivered negligiböe (entry 6) to moderate diastereomeric excess. Electron-deficient phosphine tri-*p*-trifluoromethylphenyl phosphine delivered low (entries 9-11) to good diastereomeric excess.

Table 2: Studies on role of Solvent and phosphine for improvement of diastereomeric ratio in synthesis of **69**. Ratios give ratio of ***syn*-69**:***anti*-69**. Ratios were determined by Proton-NMR analysis of crude reaction mixtures.

Condition #	Phosphine	Solvent	T/°C	Scale / mmol	d.r.
1	**Triphenylphosphine**	**DCM**	**-40 to 21**	**0.09**	**n.d.**
2	**Triphenylphosphine**	**Et_2O**	**21**	**0.08**	**66:34**
3	**Tricyclohexylphosphine**	**Et_2O**	**21**	**0.08**	**52:48**
4	**Tri-o-tolylphosphine**	**Et_2O**	**21**	**0.08**	**71:29**
5	**Tri-o-tolylphosphine**	**MeCN**	**21**	**0.08**	**80:20**
6	**XPhos**	**Et_2O**	**21**	**0.08**	**52:48**
7	**iPhox**	**MeCN**	**21**	**0.08**	**85:15**
8	**(*Sa*,*S*)-DTB-Bn-SIPHOX**	**MeCN**	**21**	**0.08**	**81:19**
9	**Tri(4-CF_3)-phenylphosphine**	**Et_2O**	**21**	**0.08**	**69:31**
10	**Tri(4-CF_3)-phenylphosphine**	**MeCN**	**0**	**0.08**	**86:14**
11	**Tri(4-CF_3)-phenylphosphine**	**MeCN**	**0**	**0.3**	**87:13**

The experiments show that there seems to be a definite influence of solvent. While highest d.r. values in diethyl ether are roughly around 7:3 (entries 2,4 and 9), the observed diastereomeric excess in acetonitrile is higher (entries 4 vs5 and 9 vs 10). Reaction mixture of experiment at 0.3 mmol scale was purified to furnish **69** in an isolated yield of 53% with a d.r. of 87:13.



45-Ph **71** 37%

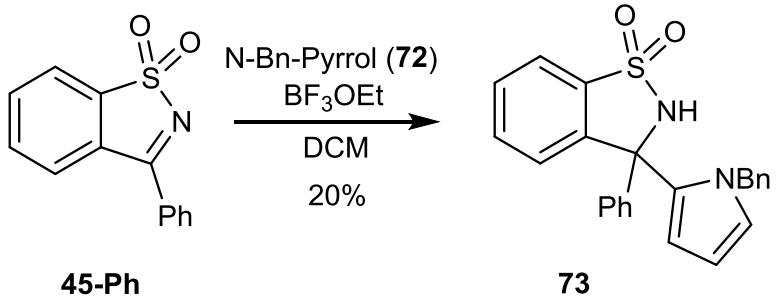
Scheme 22: Cu(I) mediated reaction of **45-Ph** with methyl isocyanoacetate **70** delivering fused imidazoline **71**.

Isonitriles have found widespread use in synthesis of diverse *N*-heterocycles.[137–142] We hypothesized that methyl isocyanoacetate **70** would react with *N*-sulfonyl ketimines **45** to give imidazoline **71**. Indeed, methyl isocyanoacetate **70** underwent reaction with **45-Ph** in the presence of 37 mol% CuCl as a Lewis acid in DCM and afforded a single diastereomer of desired imidazoline **71** in 37% isolated yield (Scheme 22). However, this reaction suffered from poor reproducibility, and we could not determine the diasteroselectivity. However, we are convinced that these initial studies may offer a valuable starting point for exploration of these highly interesting scaffolds. The isolated product proved stable at room temperature over a time span of multiple months.

2.3.2 Synthesis of structurally complex Benzosulfonamides by Mannich-type reactions

2.3.2.1 Vinylogous Addition

Although we were largely interested in building ring-fused benzosultams by cycloaddition or annulation methods with ketimines **45**, the latter imines are also substrates for addition reactions that would generate a quaternary stereogenic center. To explore suitability of ketimine substrates for Mannich-type addition reactions, we chose pyrrols as starting point as they are some of the simpler electron-rich *N*-heterocycles known for such addition reactions. However, the raction between **45-Ph** and *N*-benzyl Pyrrol **72** (Scheme 23) worked only in the presence of a Lewis acid boron trifluoride. After 15 h of the reaction, sulfonamide **73** was isolated in rather low yield of 20%.



Scheme 23: Mannich-type reaction of N-benzyl pyrrol with **45-Ph**, yielding adduct **73**.

Unfortunately, the pyrrol adduct **73** suffered from rather low stability and it turned into a brown oil and a complex mixture (NMR analysis) when kept at room temperature over more than 2 days. This is a known feature of pyrrol molecules and we decided to explore other reagents and building blocks for the addition reaction on ketimine **45**.

In the course of these investigations, studies that deal with synthesis of substituted γ-butyrolactones, a framework occurring in natural products[143] *via* Mannich-type reactions with aldimines[82,144–147] and ketimines[148–150] got our attention. All of these studies are based on transition metal catalyst systems, obtaining structurally and biologically[151–153] intriguing lactones products in good yields and stereoselectivities. Thus, we were inspired to introduce a natural product fragment to a medicinally relevant scaffold and such hybrid structures may prove highly biologically interesting. To this end, we obtained silyloxyfurane **74** *via O*-silylation *of* α-angelica lactone and studied its reactivity with **45-CO_2Et**. Notably, the resulting addition product would feature two consecutive quaternary stereocenters. In a test

experiment, we added **74** to **45-CO_2Et** in THF using 27 mol% AgOAc as activating and coordinating agent at 0 °C, furnishing desired product **75** in 5:2 d.r. (*syn*:*anti*) and in 27% yield. Even when the reaction was kept for a period of multiple hours, conversion did not increase past the point that it had reached after after 5 min of reaction time. Switching solvent to DCM led to much better performance, allowing isolated yields of 82% and d.r. of roughly 2:1.

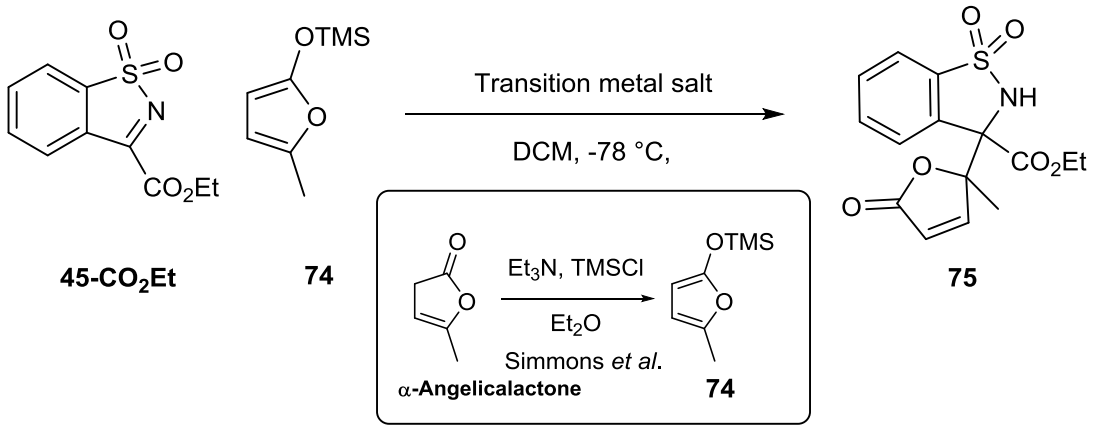


Table 3: Vinylogous addition of silyl-enol ethers **74** to sulfonyl ketimine **45-CO_2Et**. Results of reaction of silyl enol ether **74** in presence of different lewis acids. Diastereomeric ratios were determined by proton NMR analysis of crude reaction mixtures.

Entry*	R^1	Yield	d.r.	Comment
1	$Ti(O^iPr)_4$	~3%	1:2	Complex mixture
2	$Zn(OTf)_2$	3%	Not determined	Complex mixture
3	$Cu(OTf)_2$	26%	3:1	-
4	AgOAc	89%	25:2	
5	$Dy(OTf)_3$	-	Not determined	4 h reaction time, complex mixture

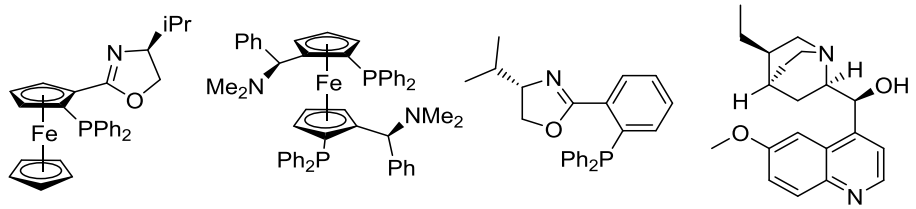
In order to optimize diastereoselectivity, we reduced the reaction temperature, and varied catalyst loading and Lewis basicity of the solvent. After some screening experiments investigating influence of different Lewis acids (table 4), we found that AgOAc performed best in terms of diastereoselectivity and cleanliness of the reaction. Hard Lewis acids such as $Ti(O^iPr)_4$, $Zn(OTf)_2$ or $Dy(OTf)_3$ led to formation of complex product mixtures, whereas lanthanide salt slowed down the reaction considerably as compared to aforementioned transition metal salts (4 h in contrast to less than 10 min). $Cu(OTf)_2$ delivered product mixture in less yield and low diastereoselectivity than the silver salt.

Table 4: Study on solvent effect and Lewis basicity of media on vinylogous addition towards **75**. Diastereomeric ratios were determined by proton NMR analysis of crude reaction mixtures.

Entry	Lewis Acid	Solvent	d.r. (*syn*:*anti*)
1	AgOAc	Toluene	11:10
2	AgOAc	Et_2O	10:24
3	AgOAc	THF	10:21
4	AgOAc	DCM +TMEDA (0.2 eq.)	10:13
5	AgOAc	DCM	93:7

As we found a clear shift in diastereoselectivity when shifting solvent from THF to DCM in initial studies, we chose to study the role of Lewis basicity by performing experiments with different solvents. Lewis acids are not only interacting with substrate but also with solvent and their activity is moderated by properties of solvent. Separate experiments on 0.2 mmol scale using 20 mol% of AgOAc showed that toluene gives almost equimolar ratio of *syn* and*anti*, whereas ethereal solvents such as diethyl ether or THF (entries 2 and 3) deliver rather similar diastereoselectivities (entries 2-3, Table 4). While DCM delivers highest diastereomeric ratio in favor of *syn*, addition of 0.2 eq. of TMEDA tipped the scales slightly in favor of *anti* product formation.

Table 5: Outcome of different reactions of silver-mediated vinylogous addition in presence of different chiral ligands. Ratios of stereoisomers were determined by chiral HPLC (see experimental part).



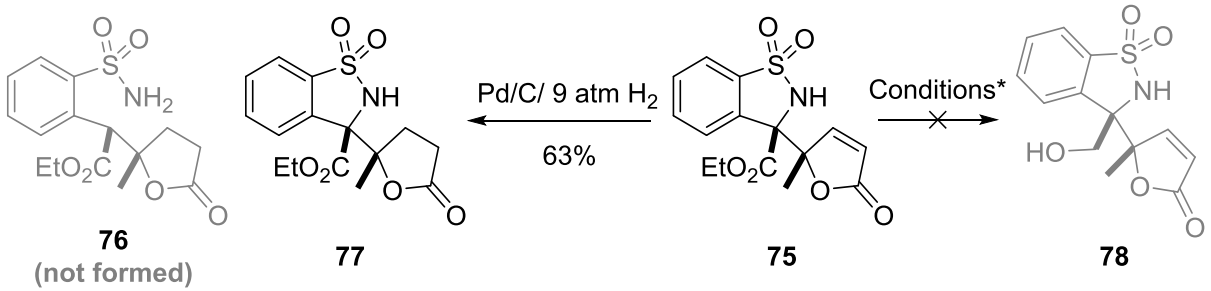
1 2 3 4

Entry	Ligand	Stereoisomeric ratio (*anti*$_1$:*syn*$_1$:*syn*$_2$:*anti*$_2$; best racemic example: 2:25:25:2)
1	1	31:35:17:18 (34% ee *syn*/26% ee *anti*)
2	2	24:23:26:27 (6% *syn*/6% *anti*)
3	3	46:36:10:10 (56% *syn*/64% *anti*)
4	4	18:30:30:23 (12% *anti*)

Further reduction of catalyst loading to 10mol% and scaling reaction up to 1 mmol delivered the product **75** in 89% yield and in a diastereomeric ratio of 86:14 (*syn*:*anti*). We were motivated to study this reaction further in terms of options for asymmetric catalysis. We executed experiments that included combination of silver acetate with different ligands (aminophosphines and cinchonine).[150] Combination of 20 mol% silver salt, corresponding ligands and ketimine at -78 °C in DCM and subsequent addition of silyl enol ether led to complete conversion of starting materials. However, analysis of product mixtures revealed a rather even distribution of stereoisomers (table 5). As far as one can come to any conclusion from these preliminary results, we assume that resulting complexes offer too much confinement and shield silver cation to effectively mediate the reaction selectively. Further research with a broader range of catalysts will pave the way to asymmetric variation of this reaction.

2.3.2.2 Modification of Benzosultam appended to a γ-butyrolactones

We found **75** to be a particular interesting molecule bearing a butyrolactone ring, along with an ester and a sulfonamide moiety. These synthetic handles can be used for further chemical modifications. When **75** was subjected to hydrogenolysis conditions, we did not detect any traces of primary sulfonamide **76** that would result from a C-N cleavage and was the expected product that would have allowed synthesis of interesting scaffolds (Scheme 24). Instead, under these reaction conditions, saturated analogue **77** was formed in good yield.

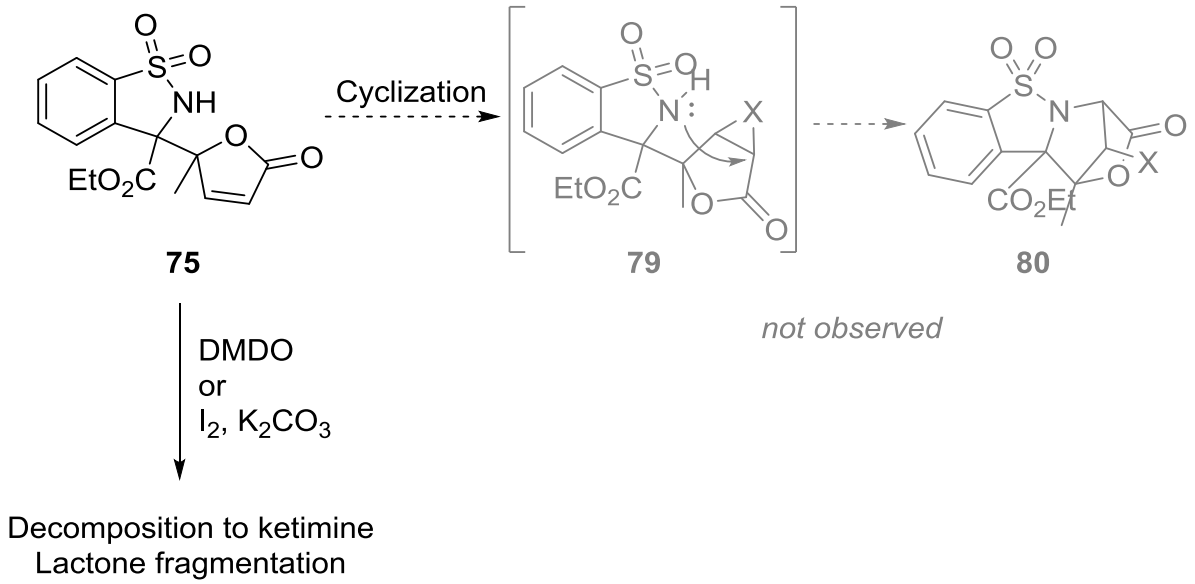


76 (not formed) **77** **75** **78**

Scheme 24: Attempts of Derivatization of Sulfonamide **75**.

Different reaction conditions were attempted for further modifications of synthetic handles available. For instance, treatment of **75** with reagents such as sodium borohydride, DIBAL-H or Lithium triethoxyborohydride ("Superhydride") did not result in selective reduction of carboxylic acid ester to give **78** but complex mixtures of molecules with rather low

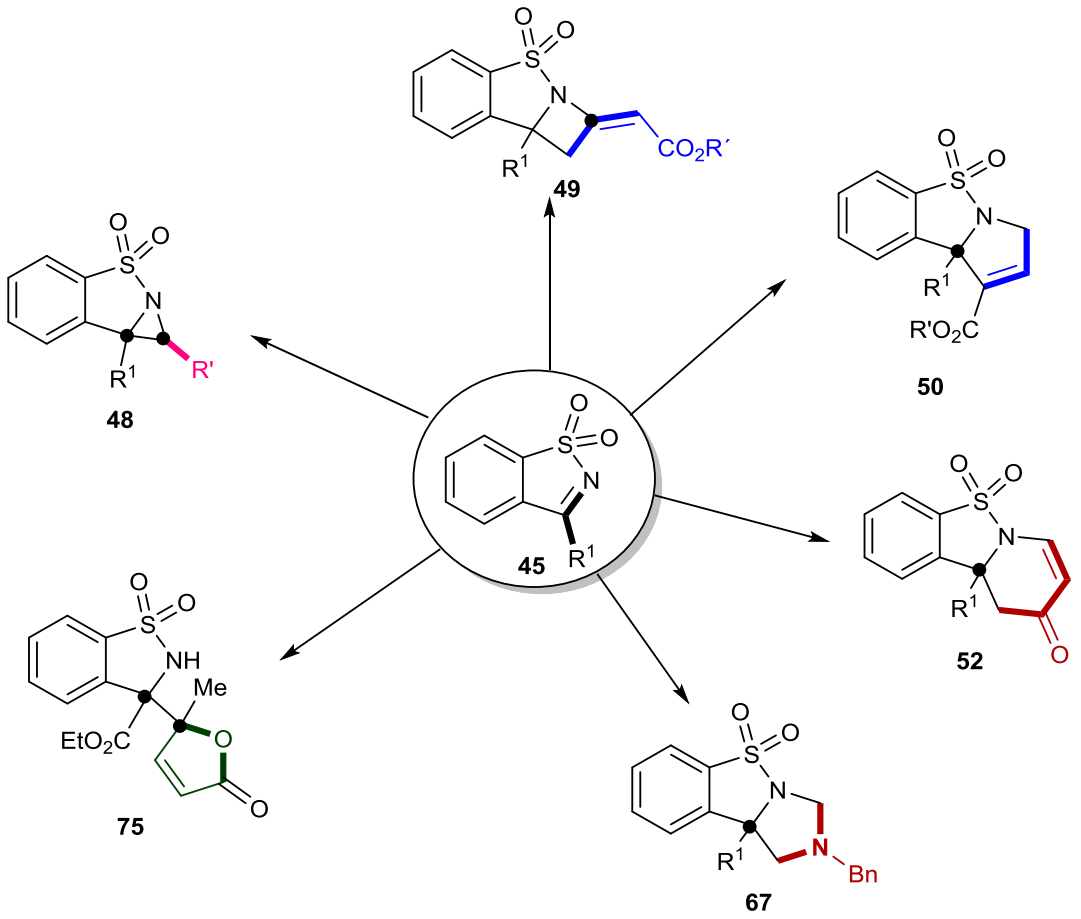
molecular weight. Hydrolysis of ester using mixtures of aq. NaOH or LiOH in aqueous THF failed, too. We assume that having two conseucutive quaternary centers takes a conformation that protects the ester from reactive reagents. Thus, a thorough study is required in order to selectively modify this functional group on a quaternary ester. Direct reduction of ester using lithium/aluminium based reagents poses a problem since cleavage of sulfonamides in presence of lithium aluminium based hydride reagents and Grignard reagents has been reported (see introductory part about sulfonamide properties).[69]



Scheme 25: Studies on test reactivity of sulfonamide-lactone **75** in order to reveal possible scaffold transformations and options for derivatization.

We also wondered if an intramolecular attack of sulfonamide nitrogen on lactone moiety may be possible. Hypothetically, either epoxide or iodonium species **79** as strong electrophiles may facilitate such a nucleophilic attack and form a bridged aza-δ-lactone **80** (Scheme 25). However, DMDO and iodine in basic media led to decomposition of **75**, furnishing ketimine **45-CO_2Et** and fragments of lactone.

2.3.3 Branching Phase – Summary



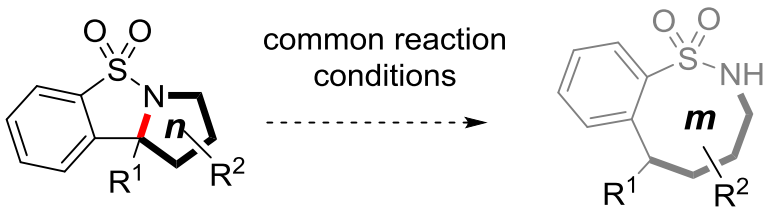
Scheme 26: Overview over scaffolds resulting from branching pathway. Utilization of imine chemistry grants access to aziridines **48**, azetidines **49**, pyrrolines **50**, 4-pyridones **52**, imidazolidines **67** and different mannich-addition products **75** bearing (defined) quaternary stereocenters.

Exploration of imine chemistry (described in chapters 2.3.1 and 2.3.2) has allowed us access to six different scaffolds with different substitution pattern and at least two potential sites of derivatization in the scaffolds formed in branching phase (Scheme 26). Based on reactivity and structural information already present in ketimine substrate **45** we gained access to six different benzosulfonamide scaffolds. While aziridines **48**, azetidines **49**, pyrrolines **50**, 4-dihydropyridones **52**, imidazolidines **67** were obtained by different cyclization reactions, Mannich-addition yielded addition **75** bearing (defined) quaternary stereocenters. We had to invest comparably little effort and ressources in adaptation and optimization of reactions. Thus, we managed to turn one type of *N*-sulfonyl-ketimine **45** into six sp^3-rich frameworks that are not only relevant themselves, but also bear potential to be further explored in ring-expansion reactions to grant access to even more distinct cyclic sulfonamide scaffolds.

2.3.4 Ring expansion reactions of tricyclic sulfonamides

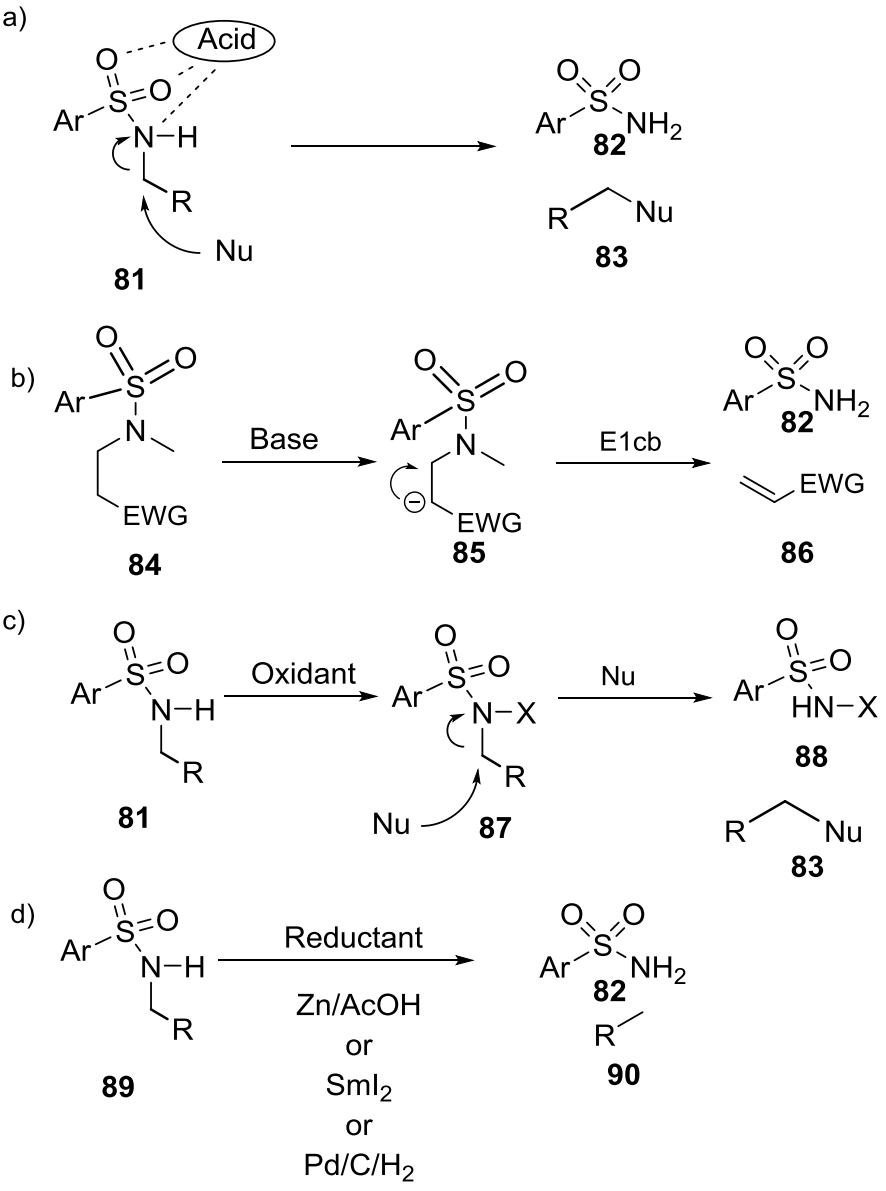
2.3.4.1 Ring expansion reactions catalyzed by palladium-based heterogeneous system

The branching phase of scaffold diversity synthesis delivered a number of tricyclic benzosulfonamides. Our next plan was to devise an easy and practical approach that can transform these scaffolds into new molecular frameworks. In particular, we targeted medium ring-sized scaffolds. The latter could be synthesized from the tricyclic sulfondmaides by a successful cleavage of C-N bond (marked red in Scheme 27). We hypothesized that under a common reaction conditions, exposing the scaffolds from branching phase might transform them into larger ring-sized benzosulfonamides. This is quite similar to what is termed as ´folding pathway´in diversity oriented synthesis approach (see chapter 2.1.1). [11,75,76][77]



Scheme 27: Principle of ring expansion reactions, transforming tricyclic benzosulfonamides into bicycles, giving rise to new interesting frameworks by cleavage of a carbon nitrogen bond (highlighted in red).

A serious challenge is posed by cleavage of carbon-nitrogen bond (highlighted in red, Scheme 27). We have considered different chemical solutions for this endeavor. Strong acids have been reported to activate sulfonamide moiety to act as leaving group which would effectively lead to ring expansion if applied to our substrate (Scheme 28, a). Sulfonamides **81** are known to be activated using rather hard transition metals such as aluminium or iron and strong Brønsted acids such as TFA, orthophosphoric acid, sulfuric acid or triflic acid. This feature has been exploited by studies that make use of sulfonamides as leaving group (**82**) in coupling reactions of for example C-nucleophiles such as malonates and affording non-sulfonamides **83**.[154–160]



Scheme 28: Different proposed mechanisms of carbon-nitrogen bond cleavage in sulfonamides.

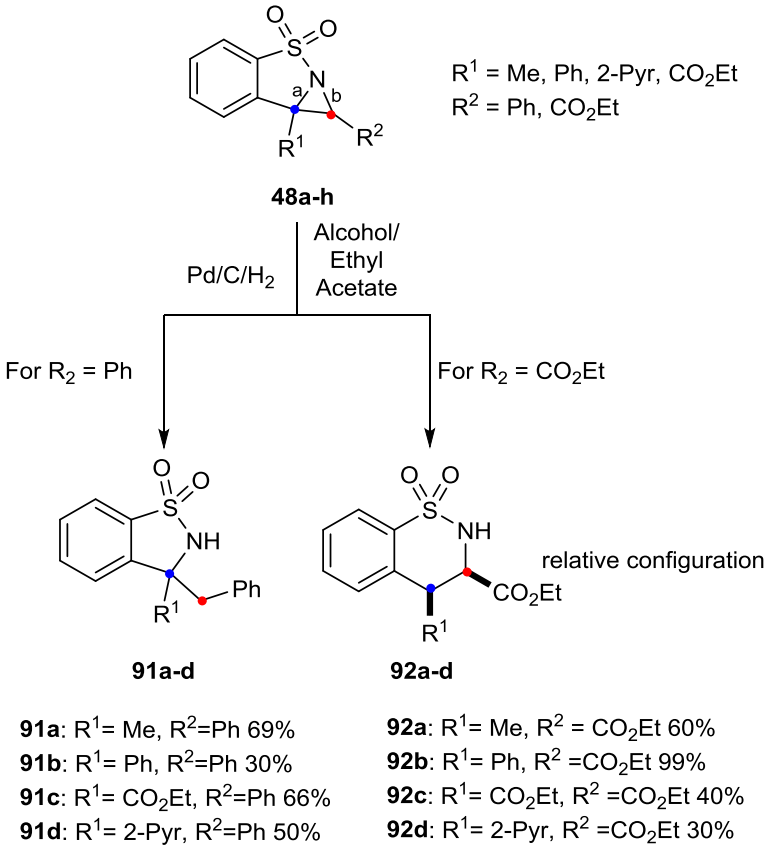
Strong, non-nucleophilic bases would deprotonate acidic position α to a carbonyl group to give enolate **85**. This may lead to elimination of sulfonamide in E1cb fashion, giving olefin **86** and sulfonamide **82**. Oxidative conditions would oxidize sulfonamide **81** nitrogen atom into species **87** and make it more prone to nucleophilic addition of nucleophiles, resulting in fragments **88** and **83** (pathway b). Some research groups have exploited C-N cleavage using Zn in acetic acid, as previously utilized in studies on lycopodium alkaloids.[161][162] Such transformations require either harsh condition or presence of transition metal catalyst. Other reductants, like SmI_2 have been reported to cleave different bonds carbon-nitrogen bonds in amines and may also be studied for our aim.[163–167]

Hydrogenation reaction could be another possibility to facilitate the desired carbon-nitrogen bond cleavage from **89** to give **82** and **90**. Pd-catalyzed heterogeneous hydrogenolysis such as in *N*-debenzylation is a simple way of C-N bond cleavage and we were curious if the C-N bond cleavage can occur in tricyclic sulfonamide scaffolds which also have the benzylic C-N bond. How and if this happens and whether it happens in all the scaffolds generated are the questions that we address in the following section.

2.3.4.2 Ring expansion of tricyclic Benzosulfonamide-aziridines

Considering the character of sulfonamides as previously laid out, we began our exploration of ring-expansion reaction by analyzing the possibility of aziridines ring opening in different conditions. It has been reported that tosyl aziridines are prone to cleavage of C-N bond,often supported by the ring-strain.[168] However, in our hands, initial screening experiments employing strong acids (TfOH, H_3PO_4, H_2SO_4, $FeCl_3$, $AlCl_3$, $ZnCl_2$, $Ti(O^iPr)_4$) as activators in DCE under refluxing condition either did not lead to any reaction or formeda complex reaction mixture.

Subjecting aziridines **48a** to 10 mol% Palladium on carbon and placing it under a hydrogen atmosphere (pathway d in Scheme 28), consumed the substrate and led to sulfonamide **91a** (Scheme 29). We applied the same reaction conditions to the other aziridines **48b-h** to get our hands on sulfonamides **91b-d** and **92a-d** in satisfying yields. While in all cases the undesired C-N bond (b) is cleaved, our studies showed that substitution at R^2 is crucial for the desired outcome of reaction i.e. C-N bond (a) cleavage. For reactions where sulfonium ylide is phenyl-substituted, it will result in a b bond cleavage from a teritary benzylic position to release cyclic strain and form **91** (Scheme 29) On the other hand, for ester substituted triazines, ring expansion by C-N cleavage (a bond) from the only *N*-benzylic position provided the ring-expanded product, i.e. benzothiazine scaffold (**92**). For **91a-d** one stereocenter is removed in C-N cleavage process (highlighted in red, Scheme 29), while **92a-d** are generated *via* hydrogenation at quarternary carbon atom (highlighted in blue) and thus the products bear two stereocenters.

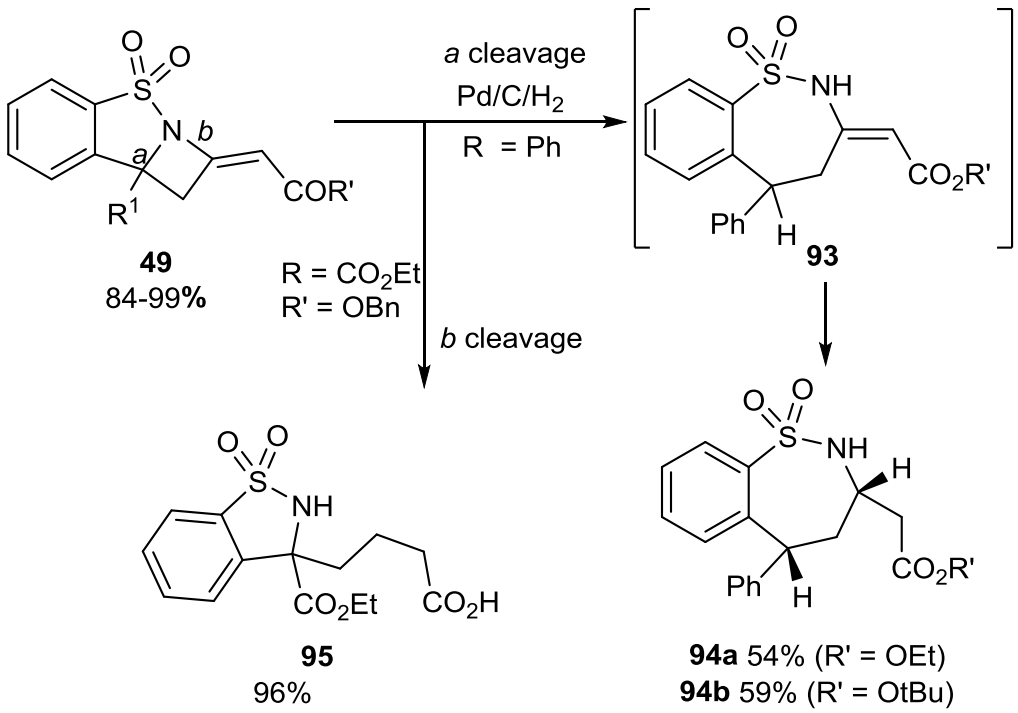


Scheme 29: Ring expansion reactions of aziridines.

It is noteworthy that for **92a-d**, only *syn* diastereomer were obtained, as characterized by NMR including NOESY experiments (see experimental part). We assume that aziridine approach reactive surface from the sterically less hindered site and thus hydrogen is donated from that site, furnishing *syn* diastereomer.

2.3.4.3 Ring expansion of azetidines: Access to seven-membered Benzosulfonamides *via* catalytic hydrogenolysis

Encouraged by ring-expansion of aziridines, we next eplored the potential of azetidiness in ring expansion under palladium catalyzed hydrogenolyiss reaction conditions. At room temperature and under 1 atm of hydrogen pressure, the reaction displayed only very low, if any, conversion happening. Increasing hydrogen pressure to 7 atm furnished a mixture of **93** and **94a** and **94b** (Scheme 30). This phenomenon implies that C-N cleavage occurs prior to saturation of *N*-sulfonyl enamide double bond. Extending the reaction time as well as an increase in temperature or addition of acid did not drive conversion towards completion, as monitored by TLC and LC-MS analysis.



Scheme 30: Hydrogenolysis of azetidines **49**, depending on substitution pattern.

As in case of aziridines, we obtained *syn* diastereomer of **94a** as the exclusive stereoisomer, as confirmed by x-ray crystal structure analysis (Fig. 6). Substitution pattern at R^1 plays a crucial role for this transformation. When employing quaternary ester **49d**, extracyclic cleavage of azetidine C-N bond takes place (*b* cleavage, Scheme 28), furnishing **95**. Benzyl ester got transformed into free acid in the course of the reaction. We concluded that ring strain is less of a driving force in this case than when using aziridine substrates. Thus, phenyl substitution, granting a *benzylic allylic* position was crucial for the desired C-N cleavage (*a* cleavage) for ring-expansiton to happen and to deliver the seven-membered benzosulfonamide scaffold **94**.

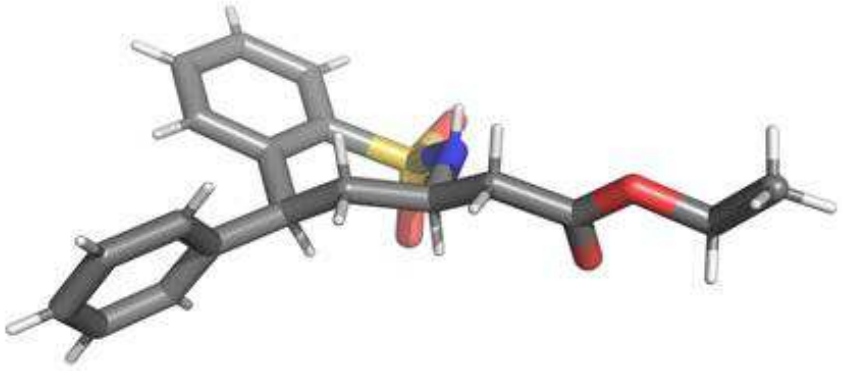


Figure 6: Three-dimensional structure of **94a** as revealed by x-ray diffraction of a single crystal.

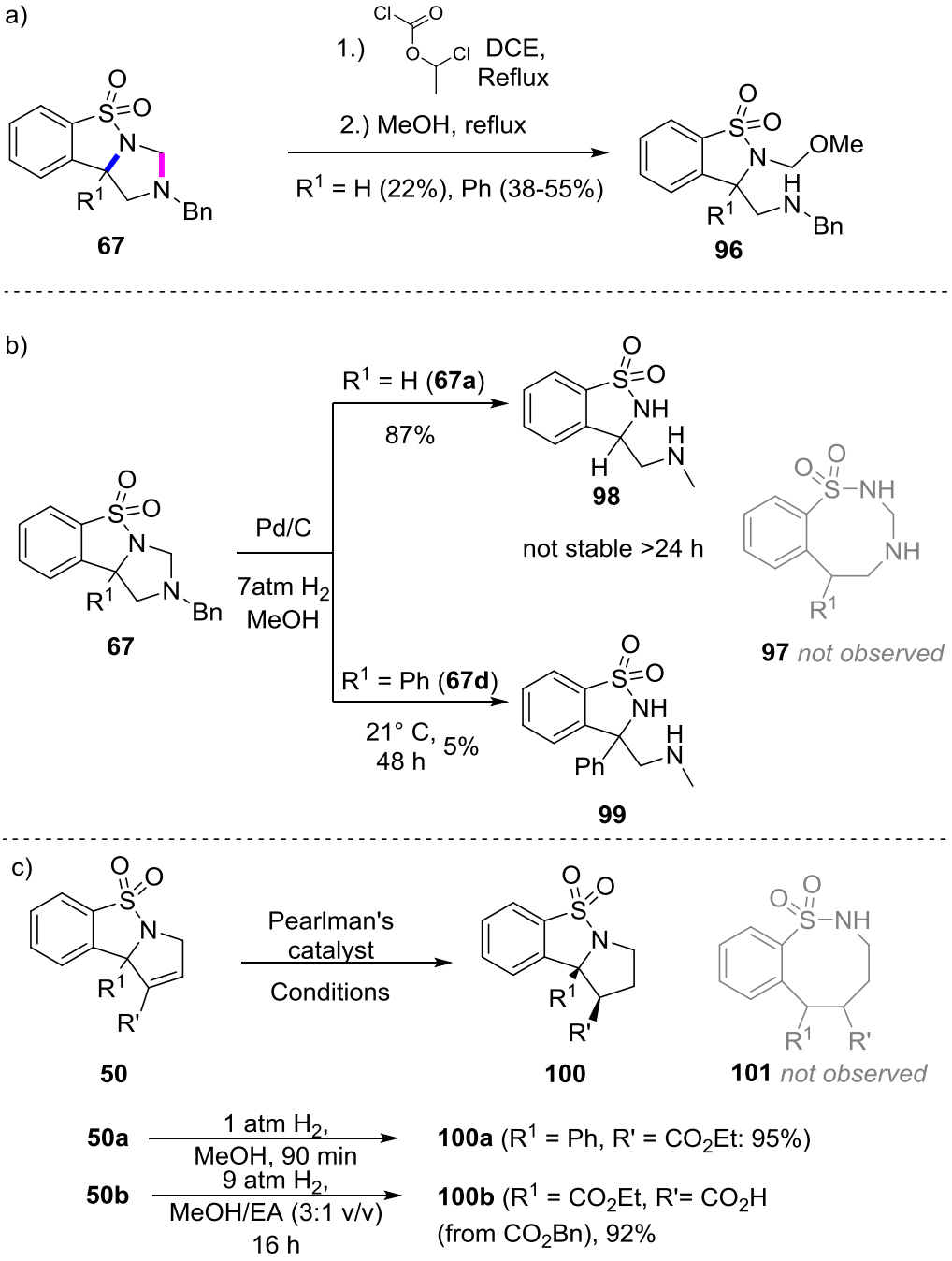
We were pleased to obtain a crystal of **94a**, which further helped corroborate the structural characterization in respect of relative stereochemical arrangement, giving *syn*-diastereomer.

2.3.4.4 Reactivity of benzosultam-fused pyrrolines and imidazolidines under palladium catalyzed hydrogenolysis

After successfully making ring-expansion of 3-membered aziridine fused benzosulfonamides and 4-membered azetidine fused sulfondmaides, we moved on to next 5-memebred pyrroline- and imidazoline-fused sulfonamides as substrates for palladium catalyzed hydrogenolysis. Inspired by the use of 1-chloroethyl chloroformate[169,170] to cleave carbon-nitrogen bonds, we sought to employ this strategy for ring-expansion on imidazoline **67** (Scheme 31 a). We applied the corresponding conditions to two different substrates **67** and observed that instead of ring-expansion, formation of hemiaminals **96** in rather low yields occurred. These entitites would require further modification such as removal of benzyl and methoxymethyl groups to be considered valuable candidates for further modification. Thus, we looked out for a different strategy.

We were curious to see whether conditions that proved useful for ring expansion of aziridines and azetidines would also cleave to give aminal or lead to the desired 8-membered ring (**97**). Thus, **67-H** was subjected to hydrogenative conditions (7 atm) in methanol (Scheme 31, b). We assumed that tandem debenzylation-ring expansion would offer a very elegant pathway towards fused eight-membered benzosultams **97** with a secondary amine available for further modifications. However, this reaction furnished **98** after stirring at room temperature overnight (Scheme 31 b). We managed to isolate and

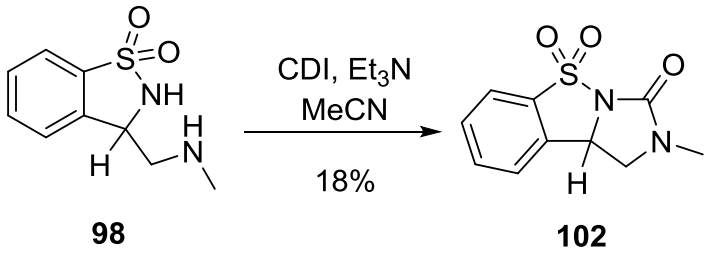
characterize this molecule but realized that prolonged incubation at room temperature (1 d) already led to decomposition into a complex mixture of products. Selecting **67-Ph** as the substrate did not make a difference with regards to regioselectivity in ring-opening and phenyl analogoue **99** was obtained in a yield as low as 5%. This left us disappointed, as we had assumed that phenyl substitution may be the key to the desired ring opening.



Scheme 31: Studies on reactivity of imidazolidines and fused pyrrolines in regards of scaffold modification. a.) Reaction of **67** under acidic conditions using 1-chloroethyl chloroformate for activation of sulfonamide moiety b.) Reactions of imidazolidines **67** under hydrogenative conditions, allowing synthesis of **98** and **99** c.) Reactivity of Transformation of benzosulfonamide-fused pyrrolines **50** under Pd-mediated heterogeneous hydrogenation conditions, furnishing **100**.

In order to avoid hemiaminals formed, pyrrolines **50** were subjected to hydrogenative conditions, using Pearlman's catalyst ($Pd(OH)_2/C$) on **50a** and **50b** (Scheme 31, c). **50a** was hydrogenated under 1 atm hydrogen pressure and afforded pyrrolidine **100a**. Formation of **100b** required enhanced pressure and prolonged reaction time. Yet, no ring-opening at all could be observed for either of the substrates. However, we were able to isolate pyrrolidines **100** as single diastereomers (*syn,* Scheme 31 c). For **100b**, we observed debenzylation of ester to give free acid, while carbethoxy group was still present, a feature that would offer opportunity for orthogonal functionalization.

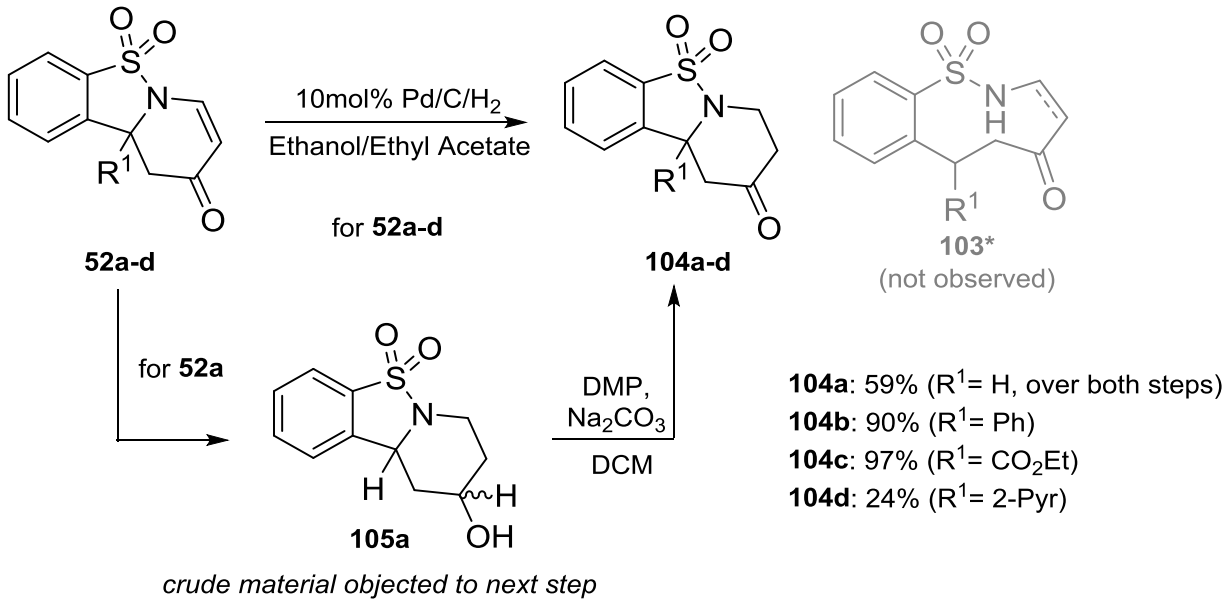
Making use of the dinucleophilic nature of **98**, we added carbonyldiimidazole (CDI) in basic media to crude reaction mixture and obtained **102** in 18% yield (over two steps) after stirring overnight in MeCN (Scheme 32). **102** Features *N*-sulfonylurea moiety, which is a structural feature that occurs in antidiabetic drugs.[171–173]



Scheme 32: Studies on reactivity of imidazolidines in regards of scaffold modification.

2.3.4.5 Ring-modulation of dihydropyridinone-fused benzosulfonamides

Based on previous results, we were doubtful whether reaction conditions that led to ring-expansion for aziridines **48** and azetidines **49** but not for fused 5-membered ring systems **50** and **67** would induce any ring-expansion in dihydropyridone-fused benzosultams **52** to form nine-membered ring systems **103** (Scheme 33). Indeed, exposure of **52** to similar hydrogenative conditions yielded corresponding tetrahydropyridinones **104** in good yields. Only in case of 2-Pyr substituted analogue, **104d** was obtained in low yield of 24%.

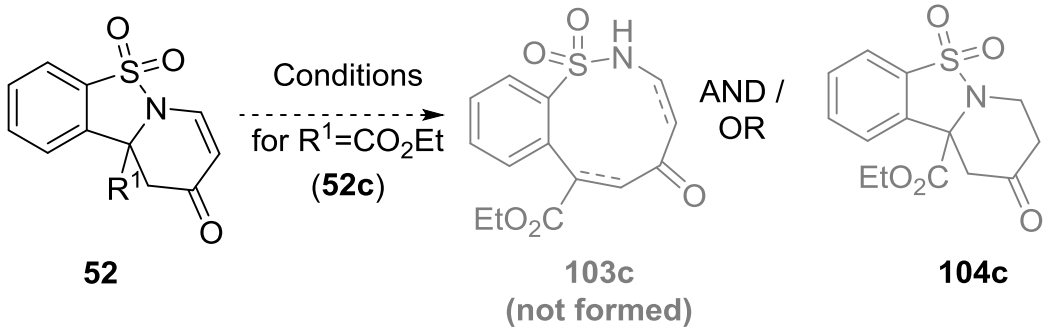


Scheme 33: Hydrogenation of tetrahydropyridones **52a-d**.

In case of aldimine derived **52a** (R^1 = H), the hydrogenation reaction yielded a mixtures of ketone **104a** and alcohol **105a**. The alcohol was subjected to DMP-mediated oxidation to yield saturated ketone (Scheme 33), furnishing **104a** in 59% over both steps.

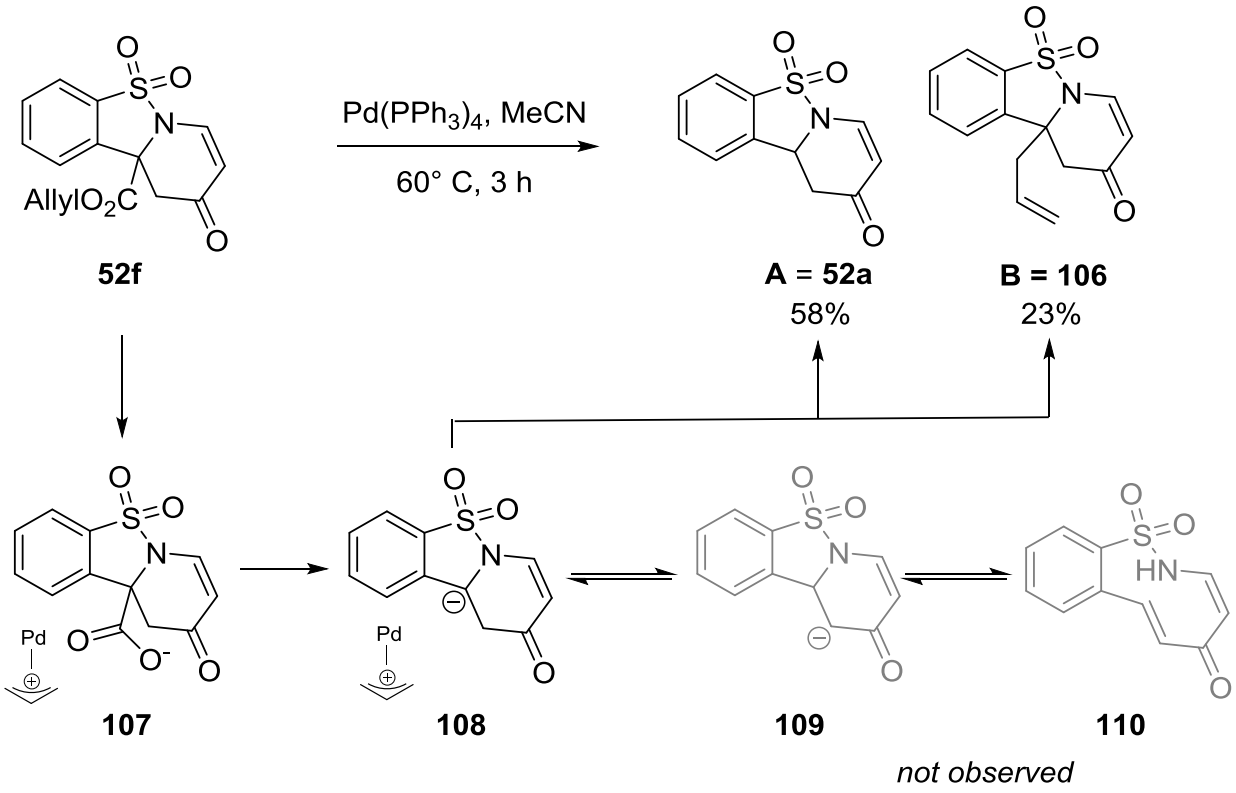
As dihydropyridinones **52** are available in moderate yields and varying substitutions, we wondered whether we would be able to identify any other mode of activation and ring expansion that would not rely strongly on ring strain and stereoelectronic properties of a phenyl substituent and would lead to formation of a postulated ring-expansion product **103**. We selected a handful of conditions (Table 7) ranging from acidic (entries 1, 2, 3, and 4[86]), basic (5,6 and 7), oxidative (2) and reductive conditions (6, 8[174], 9[175], 10) as previously discussed in chapter 2.3.4.1. to induce a ring-expansion reaction. However, none of these conditions except for 7,8 and 10 had any effect on **52c**. While a complex mixture was formed in all of these cases, we could detect presence (<10%) of ketimine when using DBU in DCM (entry 7), indicating decomposition of tricyclic benzosultam.

Table 6: Reaction conditions for ring expansion reaction. PMHS: Polymethylhydrosiloxane



Entry	Reagent	T / °C	Yield
1	2/6 M HCl (Dioxane/ H_2O 2:1)	reflux	0%
2	6 M aq. H_2SO_4 /$MeNO_2$ (1:9)	reflux	0%
3	BF_3OEt_2	0 to 21	0%
4	MgI_2/DCM	21 °C	0%
5	^tBuONa/EtOH	21 °C	0%
6	LiHMDS/THF	0 to 21	0%
7	DBU/DCM	21	decomposition: Ketimine present
8	$Cu(OTf)_2$/PMHS/THF	60	complex mixture; s.m. recovered
9	TFA/Et_3SiH/DCM	reflux	0%
10	SmI_2/THF	0 to 21	complex mixture (fragmentation)

To further explore properties of dihydropyridinone fused benzosultams **52**, we synthesized allyl-ester substituted dihydropyridone **52f**. We hypothesized that Palladium mediated deallylation occurs (**107**) and subsequent decarboxylation furnishes tertiary carbanion **108**. Then, we proposed two possible pathways: either carbanion is protonated to give **A** or attacks π-allyl complex to give allyl substituted pyridinone **B** (=**106,** Scheme 34). Alternatively, a 1,2-proton shift can occur to give enolate **109**. This species in turn would open the ring to give nine-membered benzosultam **110** – a step that is kinetically and thermodynamically disfavoured. However, we isolated **A** (=**52a**) in 58% yield and product **B** (**106**) in 23% yield and ring-expanded product was not observed.



Scheme 34: Tsuji-Trost type decarboxylation-allylation of carballyloxy-substituted benzosultam-pyridinones.

2.3.5 Synthesis of derivatives of benzosulfonamide scaffolds by functional group transformations

2.3.5.1 Synthesis of derivatives

To display the potential of our scaffolds supporting functional groups that can be used further in generating derivatives and making molecules with a range of desired molecular properties, some selected scaffolds were chosen for derivatization (Fig. 7).

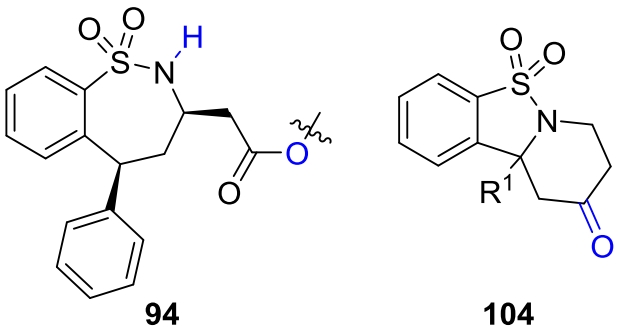


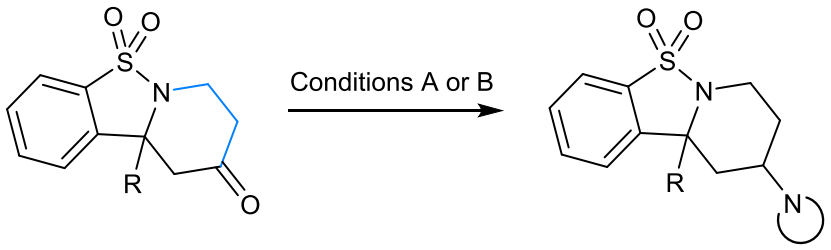
Figure 7: Selected scaffolds for synthesis of pharmaceutically relevant benzosulfonamides.

We selected fused dihydropyridinone scaffold as represented by **104a-e** and azepinone derivative as represented by **94a**. Sites for possible derivatization are highlighted in blue. As we succeeded in synthesizing **104** covering a range of substitutions, we were interested in exploiting ketone moiety for further synthesis of derivatives.

2.3.5.1.1 Synthesis of 4-aminopyridinone fused benzosulfonamides

In order to activate carbonyl group for reductive amination, π-conjugation in molecule had to be removed by reduction of the olefin (as described in chapter 2.3.3). **104a-c** were then used to synthesize different amines. We adapted two different reagents for this means; $NaBH(OEh)_3$ (condition A, Scheme 35), which features 2-ethylhexanoic acid and is a bulky variation of $NaBH(OEt)_3$ (condition B). While condition A furnished **111a** in good yield, this condition did not lead to any conversion at all for other examples. Consequently, we had to resort to condition b for **111b-e**. We found that in most cases a single diastereomer was exclusively formed. The only exception is **111c**, which features substitutions H and NH^nPr in which case we isolated *syn* and *anti* diastereomers in equimolar amounts. The lack of substituent to directing facial selectivity in this case led to daisteromeric mixture. **111b**, **111c** and **111e** were obtained as *syn* diastereomer, whereas **111f** was obtained as a *anti* diastereomer. We obtained product amines in rather low yields from these reductive

aminations, even after adding additional equivalents of reagents and stirring reagents for additional time. We generally expected higher yields as reductive amination is an established reaction type and known to deliver high yields even for ketones, especially as ketones **104** are unsubstituted at α-position.



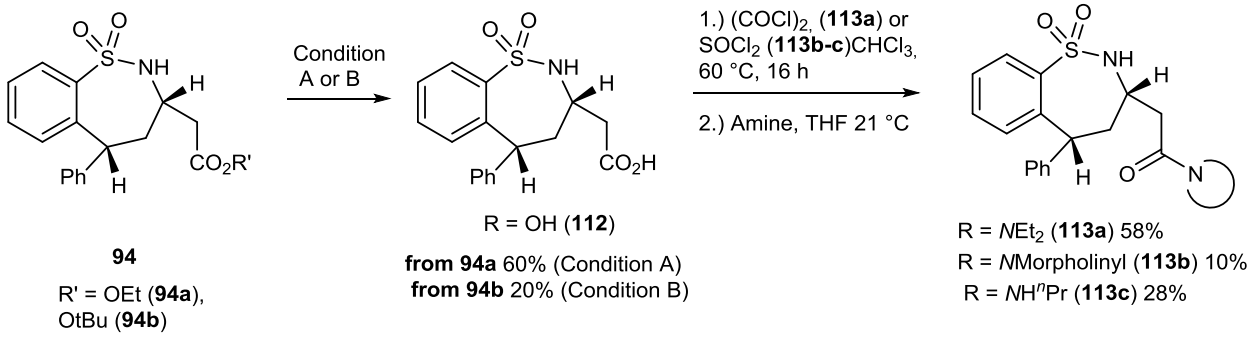
104a-c **111a-e**

111a(Condition A): R= CO_2Et, *N*-Morpholinyl 65% *syn*
111b(Condition B): R= H, *N*-Morpholinyl 34% *syn*
111c(Condition B): R= H, *N*-^{n}Pr 30% *syn*/*anti* (1:1)
111d(Condition B): R= Ph, *N*-Morpholinyl 28% *syn*
111e(Condition B): R= Ph, *N*-^{n}Pr 20% *anti*

Scheme 35: Reductive amination of **104a-d** towards amines **111a-e**. Condition A: Amine, $NaBH(OEh)_3$, EhOH 4Å MS, DCM; Condition B:, Amine, $NaBH(OAc)_3$ AcOH, 4Å MS, 1,2 DCE

2.3.5.1.2 Synthesis of amides from thiazepane-1,1 dioxide derived carboxylic acid

The seven-membered benzosulfonamides **94** showed even greater potential, as it features three different sites for modifications. Out of three sites available, we chose to modify the ester function. Aryl moieties need to be established in the substrate ketimines themseleves, and we did not wish to lose a H-bond donor in sulfonamide NH. Even though various transformations of ester group are possible, we chose to display this potential by ester hydrolysis into carboxylic acid and then synthesis of amides. In chapter 2.3.3, we described synthesis of esters **94a** and **94b**. We initially used mixtures of aqueous LiOH and THF (for solubility of substrate) to hydrolyze **94a**. However, we observed consumption of starting ester to give a complex mixture of substances that we failed to separate and characterize. Changing alkoxy base to NaOH furnished free acid **112** in 60% yield, which could be separated from, unreacted starting material by silica gel column chromatography (Scheme 36).



Scheme 36: Derivatization of **94a** and **94b**. Condition A: 0.75 M NaOH in THF/H_2O/MeCN 7.5:4:1.9, 19 h, 20 °C; Condition B: THF/1 M aq. HCl, 3:1 (v/v), 100 °C, 250 W, 45 min.

Tert-butoxy esters are usually cleaved in acidic media, releasing isobutene. Consequently, we chose acidic media for hydrolysis of **94b**. While stirring at room temperature did not induce any conversion, heating to 60 °C effected conversion to a degree that traces of product could be found. We then decided to start an experiment using microwave irradiation as the energy source. This effort proved more successful than the previous ones and we could isolate free carboxylic acid in 20% yield, as well as recovering unreacted starting material. However, we failed to induce further conversion, leading us to choose condition A, proceeding *via* **94a** to access **112**.

With **112** in hand, we sought to turn acid function into amides *via* active ester intermediate. In this regard, we combined acid with oxalyl chloride in chloroform and stirred it at 60 °C overnight. Diethylamine in THF then furnished diethylamide **113a** in 58% yield. We then repeated same reaction sequence with $SOCl_2$ instead of oxalyl chloride and morpholine and n-propylamine to furnish amides **113b** and **113c** in 10% and 28% yield, respectively.

2.3.5.2 Prediction of Molecular Properties

A compound collection needs to represent a range of molecular properties for successful screening results. These molecular properties not only determine their potential to interact with various cellular targets but also their ability to pass through plasma membrane etc. For instance, Lipinski rules of five[176,177] are generally considered for medicinally relevant small molecules that are targeted as orally available perspective drugs and takes into account the molecular weight and different measures for polarity and solubility etc..

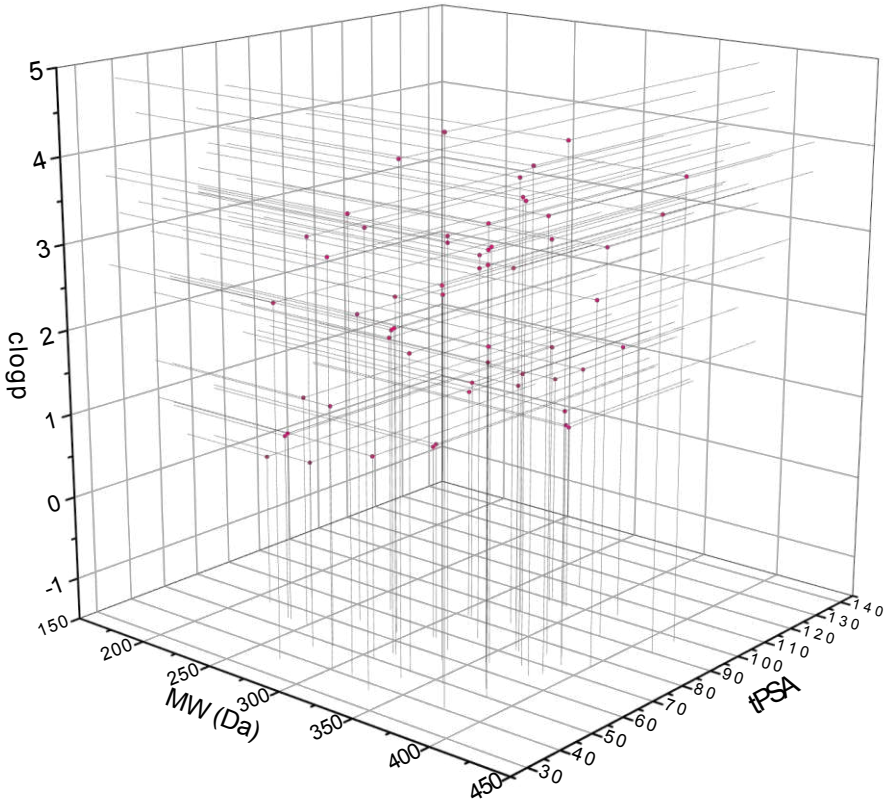


Figure 7: 3D Scatter Plot of clogp, tPSA and molweight as parameters that may be beneficial for bioavailability.

Figure 7 depicts some molecular properties of the synthesized sulfonamide compounds, i.eTopological polar surface area (^{t}PSA, should be less than 140 or 90, if availability to central nervous system is required), clogp (should be roughly between -1 and 4), both displaying a degree of how well compounds pass through plasma membrane and molecular weight, which should be generally less than 500 Da. As is clear from this figure, all of compounds do match these requirements.

2.3.5.3 Three-dimensionality: PMI Plot

Nelson's group developed the LLAMA platform which allows scientists to evaluate compounds according to their suitability for medicinal chemistry research after different parameters.[178] They also offer a principal moment of inertia (PMI) plot. Making use of this feature we could generate. Figure 8 by overlay of different compounds.

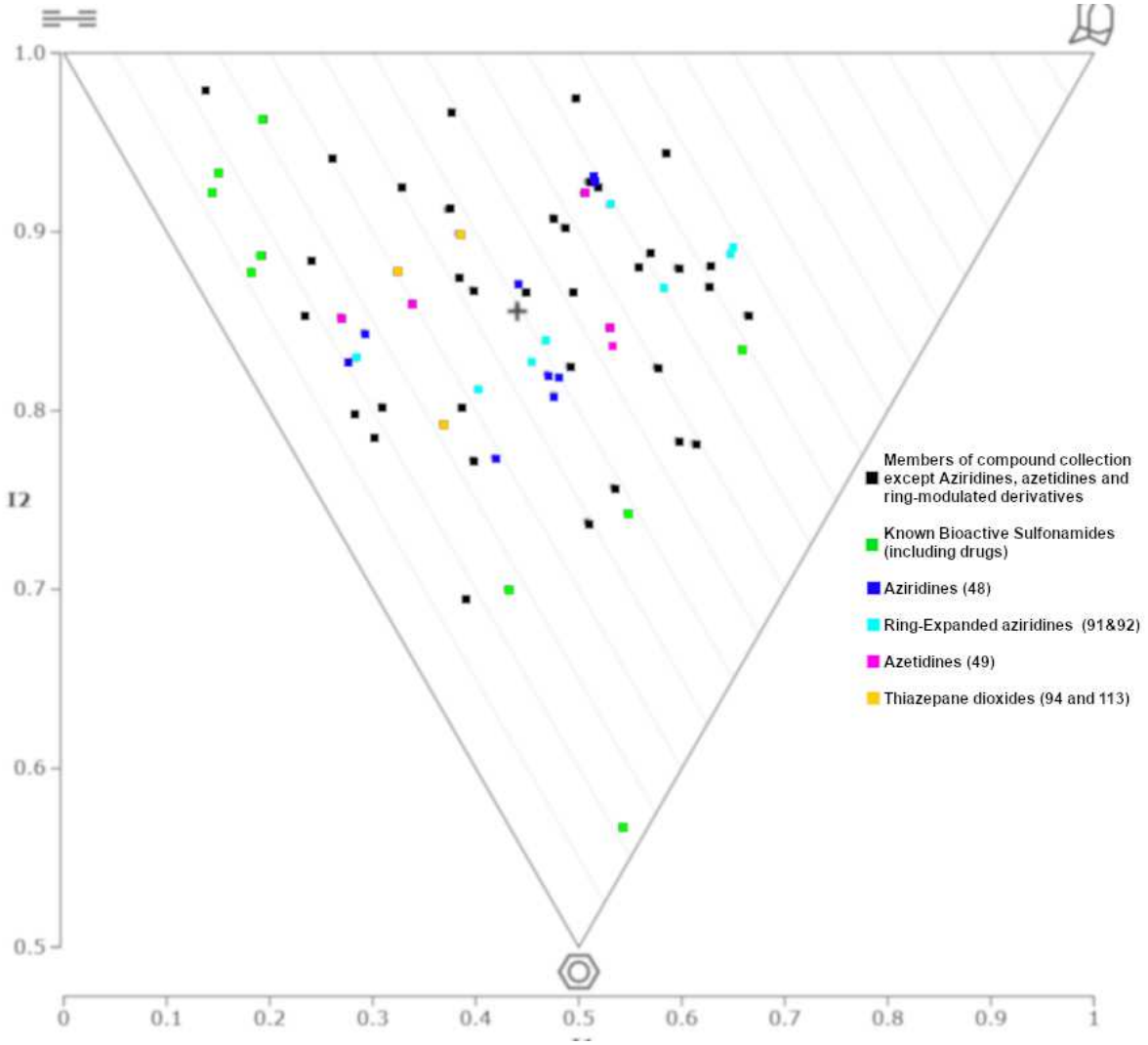


Figure 8:PMI plot of Compound collection. "+" denotes averaged center position in PMI plot.[178] Black squares show relative positions of compounds in comparison to commonly known bioactive sulfonamides (green, see also examples in Figure 1, chapter 2.1.1). Aziridines and azetidines, in particular are denoted by blue and light-blue squares, respectively. Azetidines are highlighted in margenta while their ring-expansion and derivatization products are depicted as orange squares.

Position of different members of compound collection displays, in how far its three-dimensional structure resembles either rod (top left), sphere (top right) or disk (bottom). This distribution shows that molecules synthesized occupy a rather broad portion of chemical

space when compared with known bioactive sulfonamides, which are mostly in rod-like region in the plot. We attribute this to a relatively higher amount of stereogenic centers and occurrence of a variety of different frameworks. Even though compound collection is relatively small, it covers a broad area of structure space.

2.3.6 Biological Evaluation of Benzosulfonamide Compound Collection

2.3.6.1 Unbiased cell based screening

While the aim of project was mainly to enable access to new and interesting compound classes, we made use of compound management and screening center facilities (COMAS) of Max Planck Society and their newly setup cell painting assay (CPA), a phenotypic profiling approach to identify benzosulfonamides with potential for biological applications.[179] As an image-based analysis, CPA interprets patterns in fluorescence microscopy pictures taken of cells. Dyes specific for certain organelles (hence the name cell painting) and structures are added to fixed cells (here, U2OS cells were used) that are incubated with the sample compounds. Thus, morphological changes in comparison to the DMSO-incubated cells can be encoded in parameters (579 in total) and phenotypical fingerprints of compounds can be generated, rendering compounds' effects in these experiments comparable. Induction (percentage), i.e the fraction of altered parameters of total fingerprint presents a tool to compare and establish compound profiles. Comparison to well-studied reference compounds can serve for hypothesis generation to annotate compounds with certain types of activity before going for further studies. We found that **51a** and **52b** showed altered phenotype induction values of 51% and 35% in comparison to respectively.

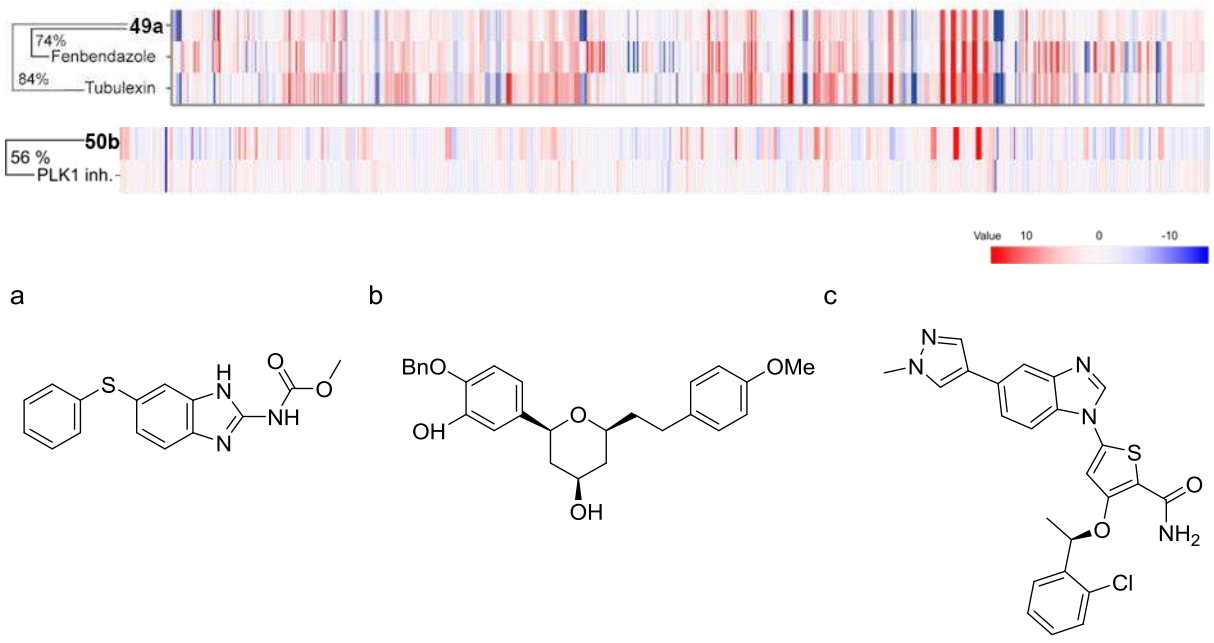


Figure 9: Fingerprint comparison of **49a** (10 µM) with fingerprints of references Fenbendazole[180] (a, 3 µM) and Tubulexin[181] (b, 50 µM) and comparison of profiles for **50b** (10 µM) with the fingerprint for a PLK1 inhibitor[182] (c, PLK1 inh. 2 µM).

Comparison with available fingerprints of reference compounds in database showed that profile of compound **49a** had great overlap with cytoskeleton-modulating agents fenbendazole[180] (74% profile similarity) and tubulexin[181] (84% profile similarity, Figure 9). Both molecules bind to tubulin and thus have a great impact on mitosis. For **50b**, CPA analysis showed that 56% similarity with polo-like kinase 1 (PLK1)[182] could be established.

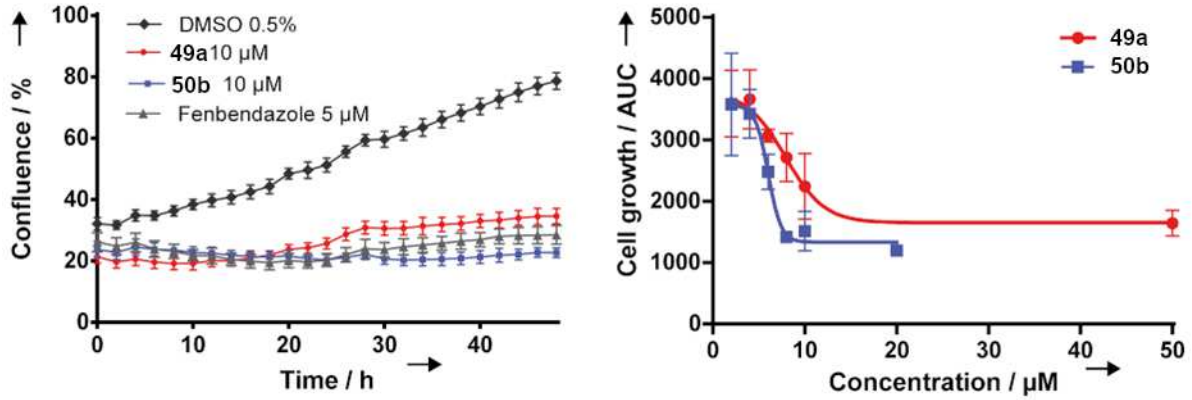


Figure 10: Dose-dependent influence growth. Left: The growth of U2OS cells was monitored for 48 h using kinetic live-cell imaging in presence of the compounds or DMSO and fenbendazole as controls. Data are mean values (N=6) ± SD and are representative of three biological replicates; right: Dose-response analyses for cell growth inhibition were carried out as described before, the area under the curve was used to determine IC50 for cell growth inhibition. IC50 (**49a**) = 7.8 ± 1.6 µM; IC50 (**50b**) = 6.0 ± 0.4 µM. Data are mean values (N=3) ± SD and are representative of two biological replicates.

This kinase serves as a switch in early mitosis, making it highly relevant for cancer research. Based on these observations we concluded that we would have to transtition from phenotypic profiling to phenotypic assay (live-cell analysis) and assess the growth of U2OS cells in order to confirm and further study influence of sulfonamides **49a** and **50b** (Fig. 11).

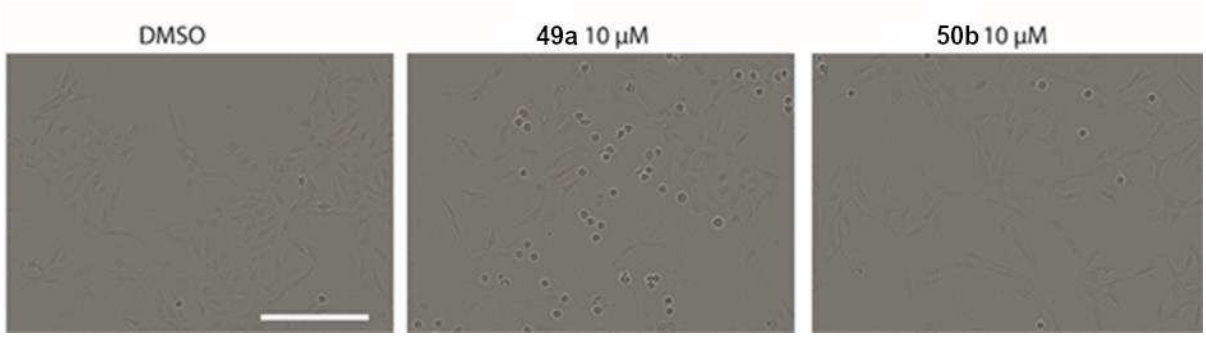


Figure 11: Benzosulfonamides **49a** and **50b** lead to accumulation of round cells. U2OS cells were treated with the compounds or DMSO followed by live-cell imaging. Images of cell after 24 h of treatment with **49a**, **50b** or DMSO as a control are shown. Scale bar: 300 µm.

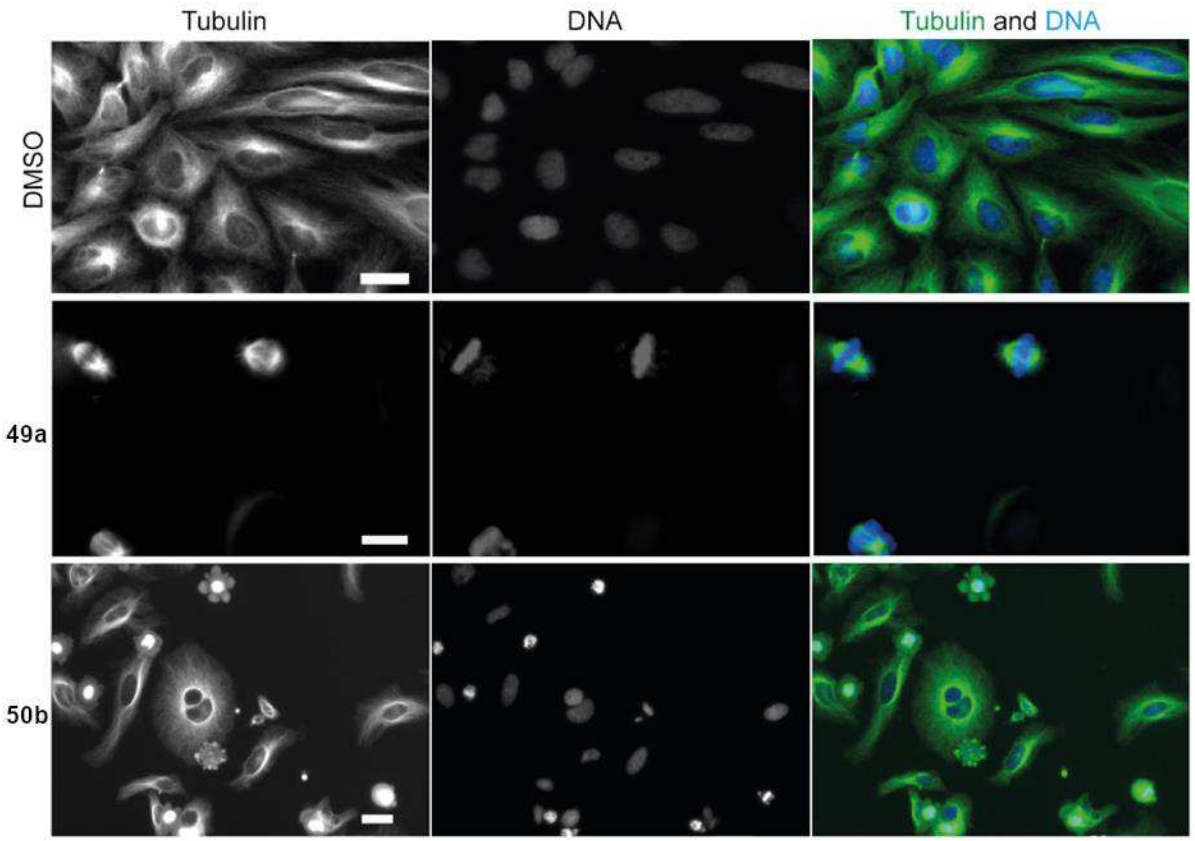


Figure 12: U2OS cells were incubated with **49a** and **50b** for a duration of 24 h prior to staining of DNA and tubulin using DAPI (blue) and anti-alpha-tubulin-FITC antibody (green). Scale bar: 20 µm.

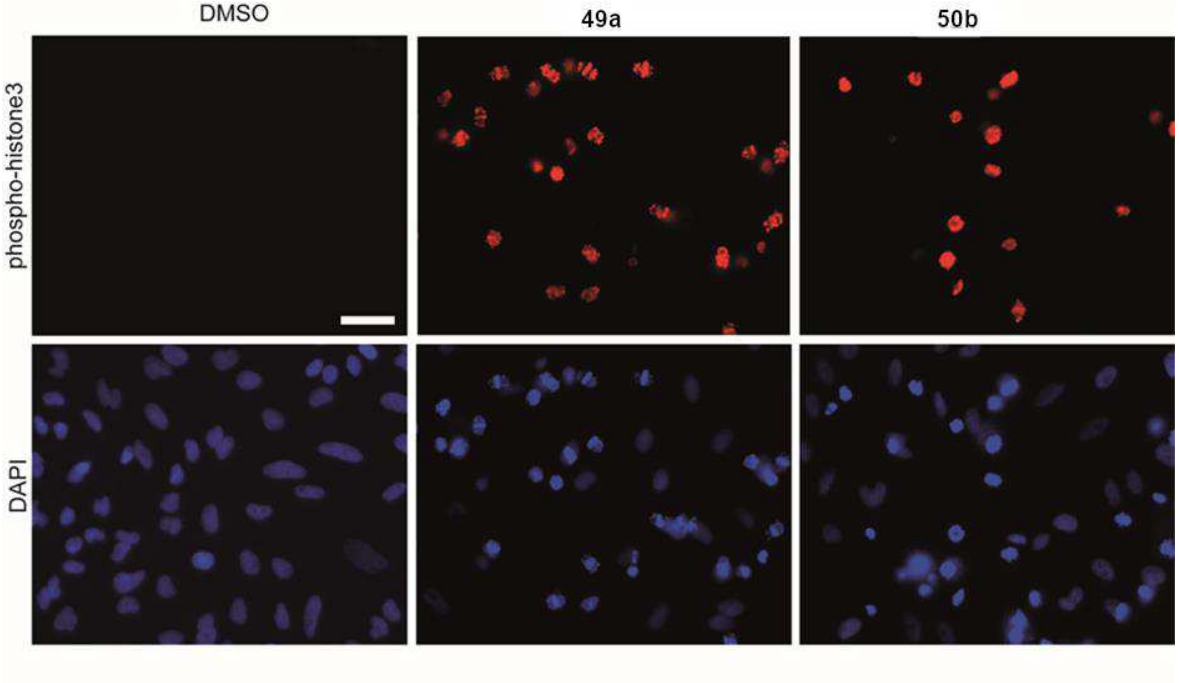


Figure 13: Benzosulfonamides **49a** and **50b** lead to accumulation of phospho-histone 3-positive cells**.** U2OS cells were treated with the compounds or DMSO for 24 h prior to staining for phospho-histone 3 as a marker for mitotic arrest and DNA using DAPI. Scale bar: 50 µm.

To our satisfaction, we could determine dose-dependent growth reduction, establishing IC_{50} values of 7.8 ± 1.6 µM (**49a**) and and 6.0 ± 0.4 µM (**50b**) (Figure 10). Studying changes in cellular morphology, there was a clear trend towards accumulation of round cells (Figure 11). In addition, presence of mitotic spindles which are clear markers of mitotic arrest was observed (Figure 12).

Mitotic arrest could also be observed by means of fluorescence microscopy (Figure 13).

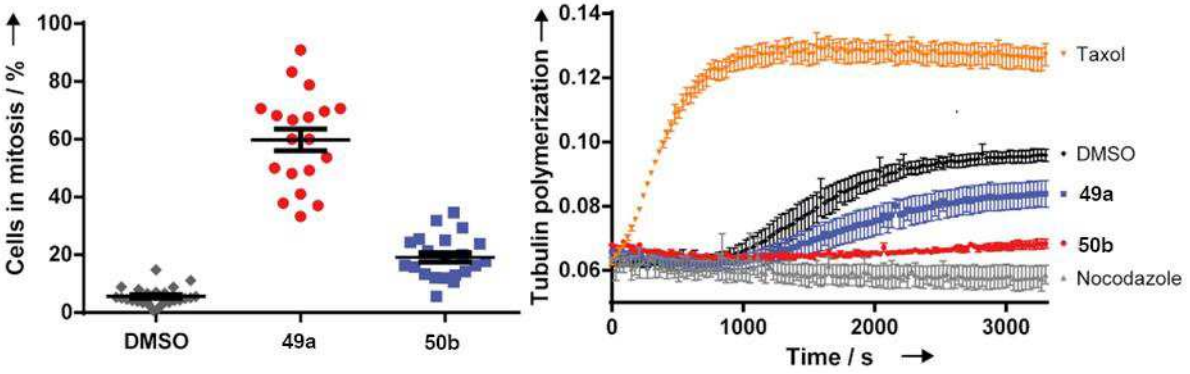


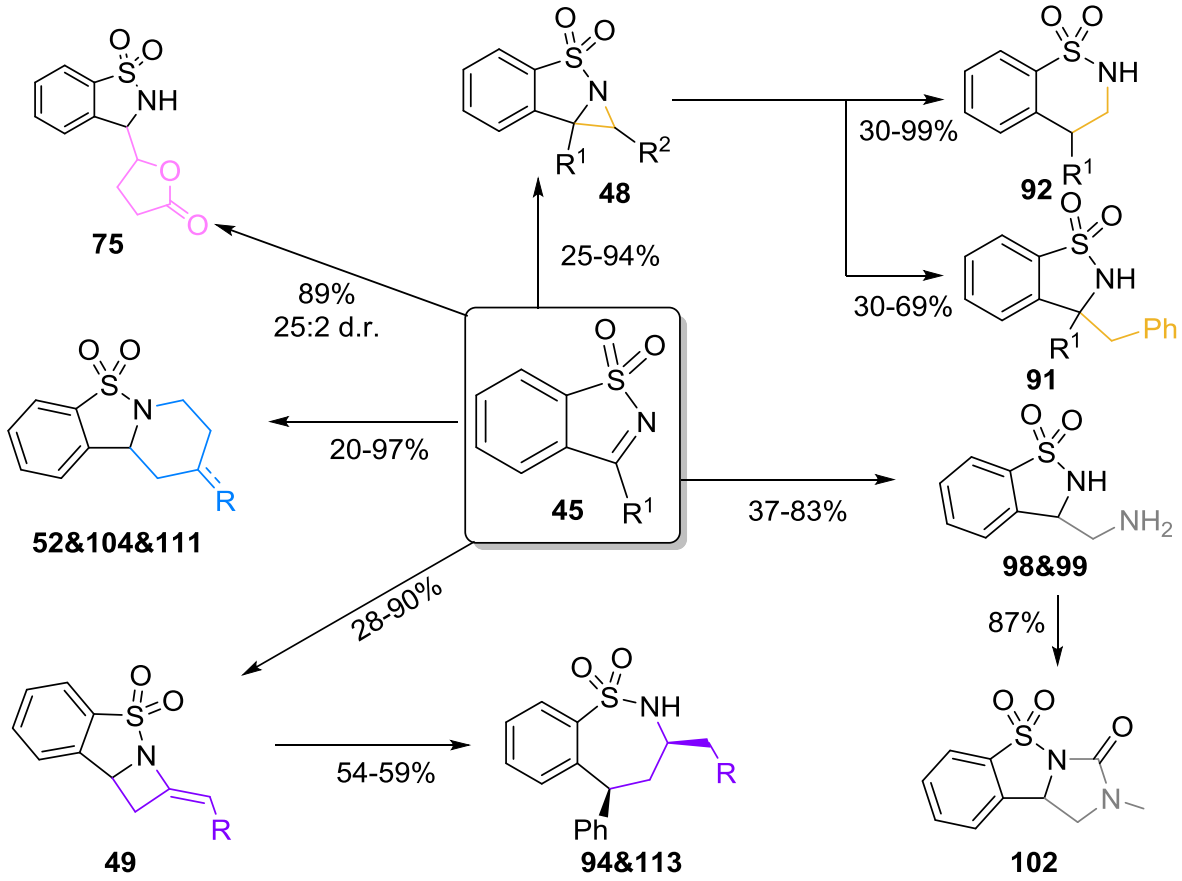
Figure 14: left: U2OS cells were treated with the compounds for 24 h prior to staining using phospho-histone 3 as mitotic arrest marker and DNA. This was followed by automated image acquisition and analysis to quantify the percentage of cells in metaphase (i.e., phospho-histone 3-positive cells). Data are mean values (N = 2) ± SD and are representative of three biological replicates; right: In vitro tubulin polymerization assay. Tubulin polymerization was initiated in presence of GTP and was monitored by means of turbidity measurement at 340 nm at 37 °C. Taxol and nocodazole were used as controls for tubulin-stabilizing and- destabilizing agents, respectively. Data are representative of three biological replicates

Phospho-histone 3 staining enabled us to determine a change of relative population of mitotic cells from 5.2 ± 2.4 % (DMSO-treated cells) to 62.5 ± 15.1 % and 19.8 ± 6.9 % in the presence of 10 µM **49a** and **50b**, respectively (Figure 14, left). We rate this a highly interesting finding as change of tubulin dynamics by small molecules leading to mitotic arrest is a relevant subject in cellular systems biology.[183] To elucidate direct effect of **49a** and **50b** on tubulin polymerization, an appropriate *in vitro* assay was employed (Figure 14, right). While **50b** did not show as much potency as **49a**, latter probe showed inhibition at 20 µM.

As there are not many microtubule-targeting probes bearing sulfonamide moiety are known, a synergistic effort of synthesis and cell painting analysis led us to identify **49a** and **50b** as interesting mitotic modulators.

2.4 Summary

This project deals with developing synthetic access to under explored but biologically intriguing cyclic benzosulfonamides. Novel benzosulfonamides were synthesized by means of different annulation and addition reactions with common substrates i.e. ketimines (**45**). Fused aziridines (**48**), azetidines (**51**), pyrrolines (**52**), imidazolines (**60**), tetrahydropyridines (**86**) and monopodal-linked lactones (**65**) were furnished from various transformations (Scheme 37). Optimization and tuning of reaction conditions led to an increase of diastereoselectivity for transformations that delivered multiple consecutive stereocenters in ensuing complex benzosulfonamides (imidazolines, aziridines, lactones).



Scheme 4: Scaffolds yielded from branching-folding pathways.

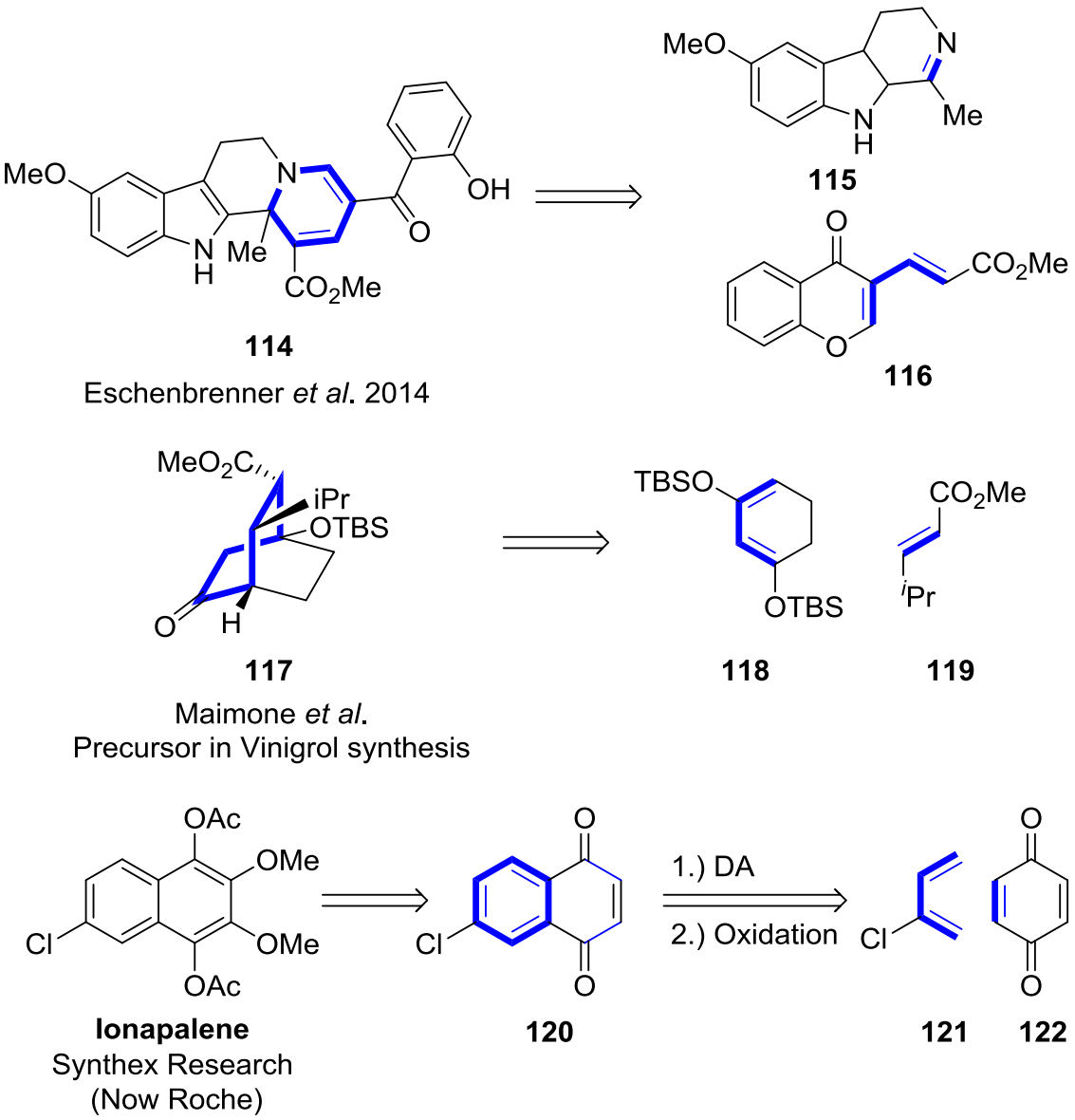
The use of heterogeneous palladium on carbon under hydrogen atmosphere conditions applied to the scaffolds formed in initial phase led to interesting transformations granting access to further ring-expanded or ring-modified scaffolds. Aziridines **48** were transformed into five-membered sultams **91** or six-membered **92** in a ring-expansion reaction. Azetidines **49** could be transformed into seven-membered sultams **94** while obtaining *syn*-

diastereomer exclusively which were then tansformed into amides **113** making use of esters as synthetic handles. The 4-pyridones **52** could be transformed into amines **104** and **111** by using reactions as hydrogenation and reductive amination. Biological evaluation of the moluecles resulting from our study was made using cell painting assay (CPA) to identify mitotic modulators **49a** and **50b** which act most likely by inflenceing the cytoskeleton dynamics.

3. Chemistry-Driven Exploration of Scaffold Diversity with *1,3* double-deficient dienes

3.1 Introduction

In the history of organic synthesis, development of a chemical reaction or new reagents have often revealed interesting oppotunities to offer new additions to chemical toolbox of medicinal chemistry. As pointed out in chapter one, access to new interesting frameworks has lots of potential for improvement and development. Most cyclic frameworks are constructed by means of cyclization and cycloaddition reactions, for instance, Diels Alder reaction being used a prominent tool due to its immense potential in a range of synthetic applications.[184–188][189] Not surprising that Diels-Alder reaction has emerged as one of the most utilized reactions in the synthesis of six-membered carbo- and heterocycles (Scheme 38). It does not only construct the molecular framework but also due to its wide toleraence ability, it introduces different functional groups as a synthetic handles for further modificaton of six-membered carbo- and heterocycle. For instance, Eschenbrenner *et al*. managed to access biologically active Centrocountins **114** by means of an inverse-electron demand aza-diels alder reaction from indole-derived imine **115** and chromone-derived diene **116** (Scheme 38).[190] In order to design synthetic routes to vinigrol, Baran and co-workeres constructed bridged frameworks using Diels-Alder reaction.[191] Bridged intermediate **117** was obtained by reaction of electron-rich diene **118** and methyl acrylate derivative **119**. A group in Syntex (which now is part of Roche) developed synthesis of Ionapalene using 2-chlorobutadiene **121** and benzoquinone **122**. Oxidation of intermediate **120** furnished aromatized Ionapalene.[192]

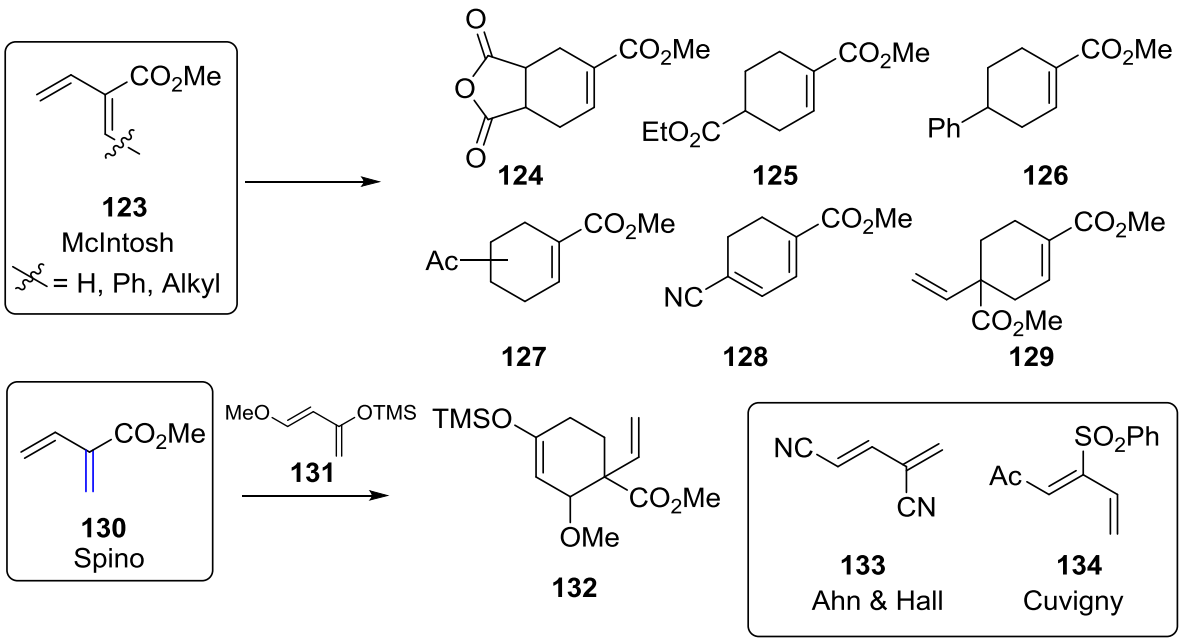


Scheme 38: Applications of Diels-Alder reaction in construction of varying frameworks.

These three examples represent only a small fraction of all applications that have been reported so far with Diels-Alder appraoch. Yet, they show that from structurally flat naphthalene-type ring to rather complex, three-dimensional structures can be accessed by means of varying combinations of dienes and dienophiles. Not only is the Diels-Alder reaction relevant for construction of frameworks in basic research and development in chemistry investigations but also feasible for large-scale synthesis and has been used by process chemists for furnishing compounds in multi-ton scale.[185]

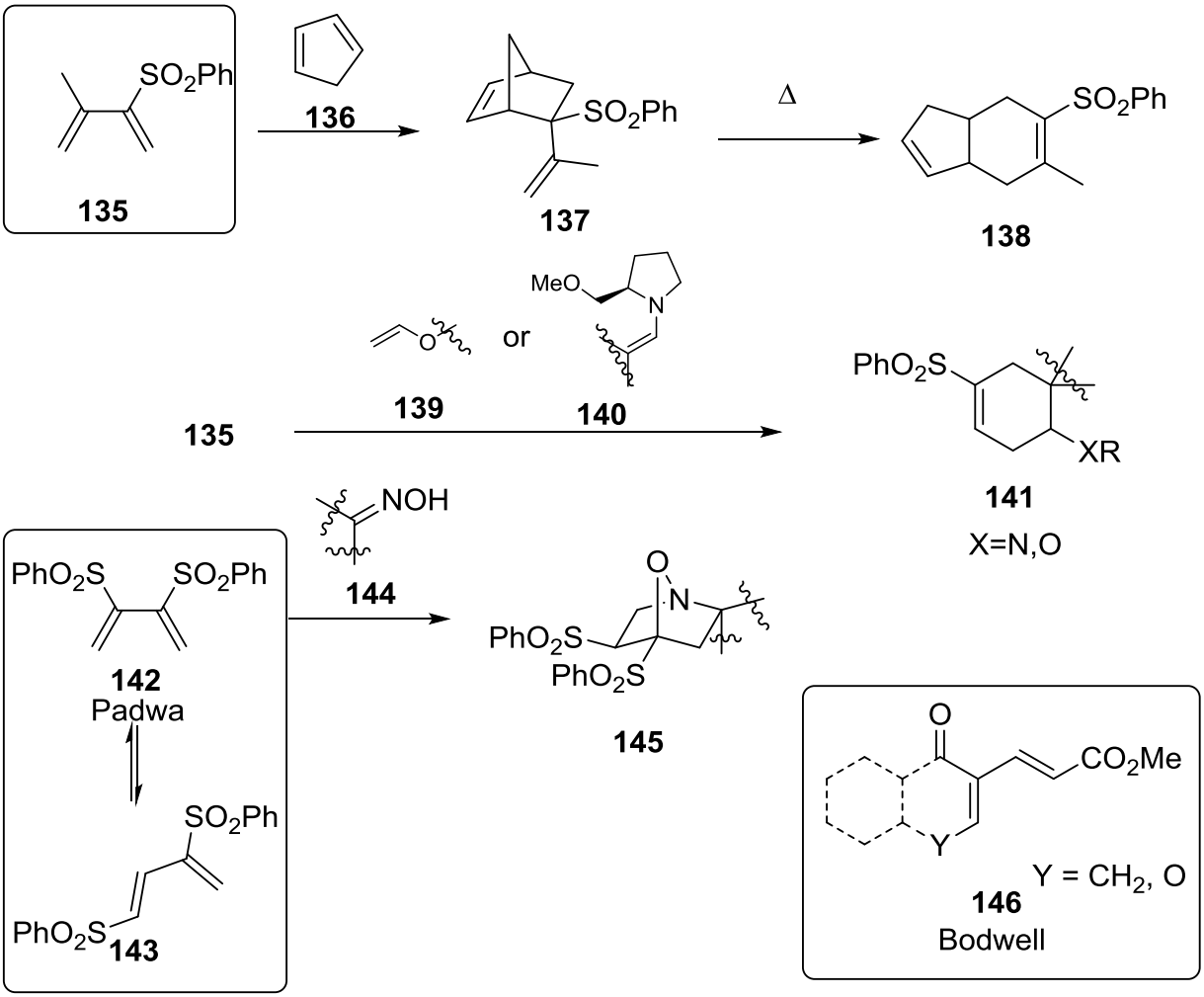
3.2 Chemistry of electron-deficient 1,3-butadienes

In a survey of literature about dienes used in organic synthesis, we realized that the vast maiority of dienes are rather electron-rich and electron-deficient dienes, in particular, acyclic dienes remain largely unexplored. As Rawal's diene,[193–195] Danishefsky's diene[196,197] and Brassard's[198] dienes have found widespread use in organic synthesis, research and development of new reagents for effective and efficient construction of scaffolds remains one of the biggest challenges for synthetic chemists. The above-mentioned dienes are electron-rich dienes as they bear electron-donating groups which raise the highest occupied molecular orbital (HOMO) of a diene closer to the lowest unoccupied molecular orbital (LUMO) of the dienophile to facilitate cycloaddition chemistry. 1,3-butadienes substituted with electron-withdrawing functional groups have been much less studied or applied in reactions as compared to their electron-rich counterparts. We attribute this to two reasons - firstly, their stability is a prime issue as they remain prone to numerous side reactions such as oligomerization as well as nucleophilic additions and secondly, it is much harder to find dienophiles which react with such species, as their LUMO have to be much lower in energy or an inverse-electron demand reaction type has to take place.



Scheme 39: Reactivity and applications of selected electron-deficient dienes.

In 1978, group of McIntosh has shown the formation of 2-carbalkoxy substituted 1,3-butadienes (**123**, Scheme 39). Their reactions with different dienophiles showed that these butadienes reacted with various *electron-deficient* dienophiles forming different frameworks such as maleic anhydride (furnishing **124**), cinnamates (to **125**), styrene (to **126**), methyl vinyl ketone (to **127**), or 1-chloro-1-cyano-ethylene (to **128**). In the absence of a dienophile or in reactions with less reactive ones, the diene gave dimer **129**.[199] Similarly, 2-carbalkoxy butadienes (**130**) were studied by group of Spino. Dienes **130** easily dimerize, but also react with electron-rich dienophiles **131** to give **132** in a cross-Diels-Alder reaction wherein **130** react in 1,4-fashion as the dienophile (Scheme 39, highlighted in blue).[200] Due to their tendency to oligomerize, electron-deficient butadienes have caught attention from polymer chemists who synthesized 1,3 dicyanobutadiene (**133**) to use as monomers.

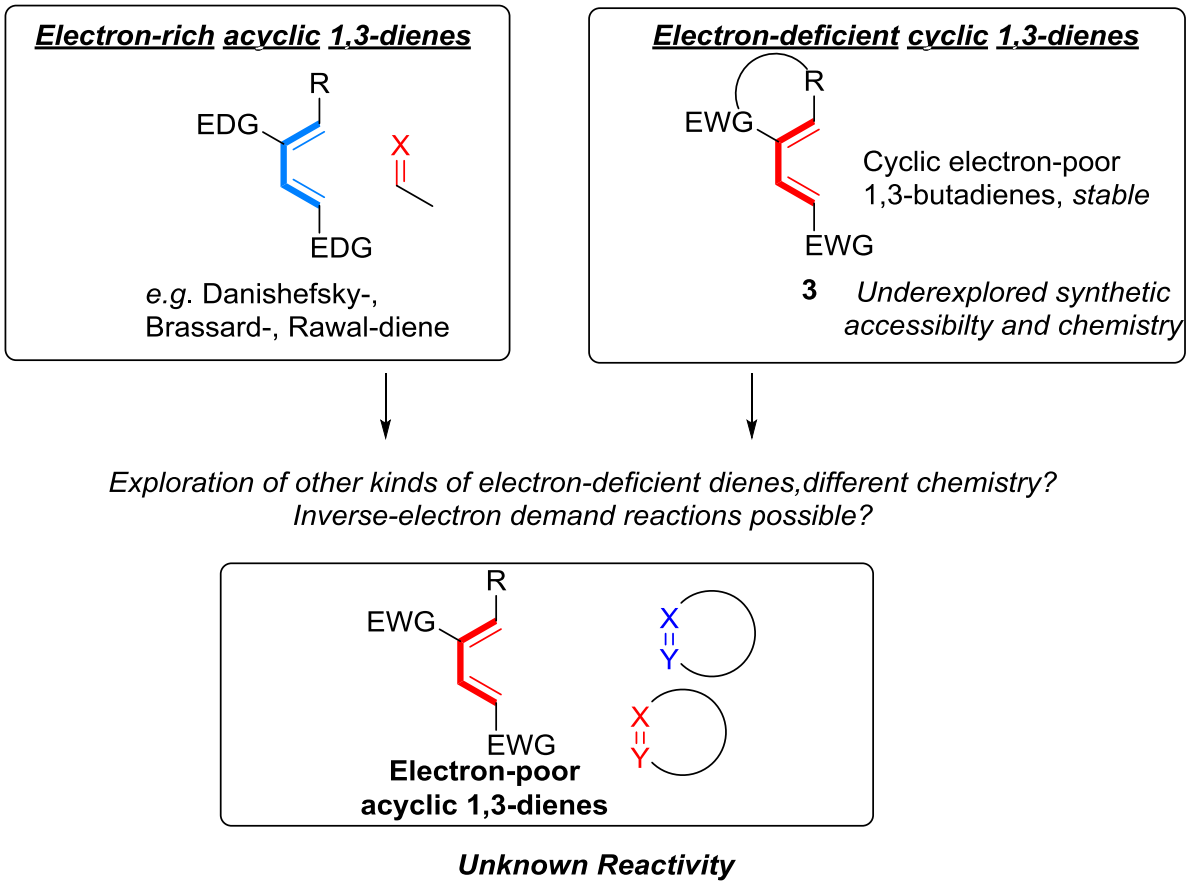


Scheme 40: Different electron-deficient dienes and examples of reactivity and transformations.

Ahn and Hall reported relative instability of these electron deficient dienes **133** in most solvents.[201] Acetyl-2-sulfonyl butadienes (**134**) feature an electron-donating and an electron withdrawing group and have been synthesized by Cuvigny *et al.*[202]

Chou and Hung studied cross- Diels-Alder reactions of 2-Sulfonyl butadienes **135** (Scheme 40).[203] They found that, with cyclopentadiene **136** electron-poor butadiene **135** acted as the dienophile to give [4+2] cycloadducts **137** which on heating at 130 °C, transformed into adduct **138**. Bäckvall and Rise reported reaction of such 2-Sulfonyl butadienes **135** with vinyl ethers (**139**) and enamines (**140**) to give cyclohexenes **141**.[204]

The Group of Padwa reported that symmetrical 2,3-sulfonyl butadienes (**142**) react with ketone oximes **144** to give bridged [4+2] adducts **145**.[205] They also reported that **142** can be transformed into 1,3-sulfonyl butadienes (**143**) which are more reactive due to lower LUMO energies.[206] In addition, **142** exists in transoid form while **143** exists in cisoid form which assists Diels-Alder reaction to proceed. The group of Bodwell has extensively worked with 1,3-electron deficient, cyclic fused dienes, including chromone and coumarine-derived fragments (**146**, see also second example in Scheme 38).



Scheme 41: Electron-rich dienes react with mostly electron-deficient dienophiles. Few examples of cyclic electron-deficient 1,3-dienes are known.

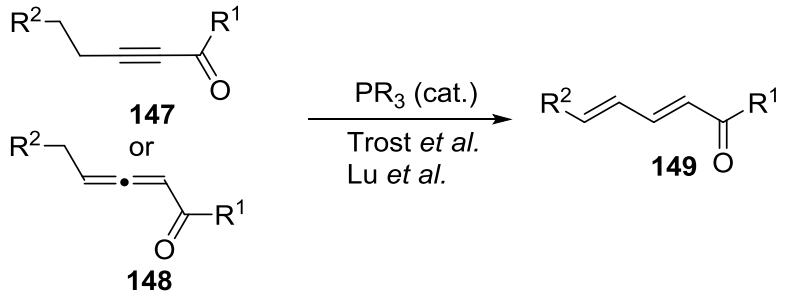
They have much better stability profiles and are suited for different inverse-electron demand Diels-Alder reactions with i.e. enamines.[207,207,208]

These reports show that electron-deficient acyclic butadienes are accessible but have some inherent reactivity that needs to be manouvered to tame these species for synthetic applications. Monosubstituted electron-deficient dienes are rather instable, just as terminally unsubstituted vinyl groups or acrylates tend to be prone to polymerization. Other examples, such as **134**, **135**, **142** and **143** feature sulfonyl groups. In case sulfonyl substitution is not desired in target structure, an extra desulfonylation step is required, rendering these dienes impractical in the eyes of chemists. These observations motivated us and ignited our curiosity about whether further variations of electron-withdrawing groups at these dienes could help with stabilization of dienes and thereby easing access to these entities. Thus, we envisioned an even higher degree of substitution of 1,3- butadiene, generating two electron-withdrawing and at least one stabilizing group (Scheme 41).

During exploration of trisubstituted electron-deficient allenes we found interesting organocatalytic isomerization to 1,3 butadienes, which will be professed in next sections. We then studied their reactivity with a particular interest in their potential for construction of cyclic frameworks.

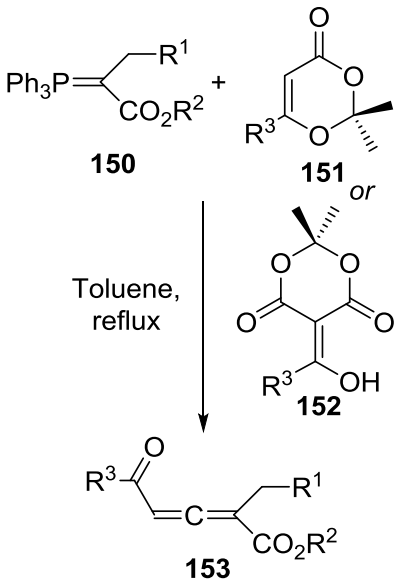
3.3 Access to doubly electron-deficient trisubstituted 1,3 butadienes

The isomerization of electron-poor acetylenes (**147**) and 1,2-butadienes or allenyl carbonyl compounds (**148**) with catalytic triphenylphosphine[209] was reported by Trost *et al.* in 1992 and constitutes an important access to electron-poor dienes **149** (Scheme 42).[210,211] These dienes are prone to oligomerization reactions much like other similar species (see chapter 3.2). Thus, reaction condition optimization, particularly fine-tuning of phosphine nucleophilicity as well as reaction temperature was required.



Scheme 42: Synthesis of electron-poor carbonyl-dienes from alkynes **147** and allenoates **148**.

As cyclic electron-poor dienes are stable (see previous chapters) we envisioned that introduction of substitutions on the butadiene with 1- and 3- position holding electron-withdrawing groups may offer stable acyclic dienes. In order to access 1,3-substituted dienes *via* phosphine isomerization route, we managed to synthesize α,γ-disubstituted allene esters by Wittig olefination of phosphoranes **150** and acetals **151** and **152** (Scheme 43).

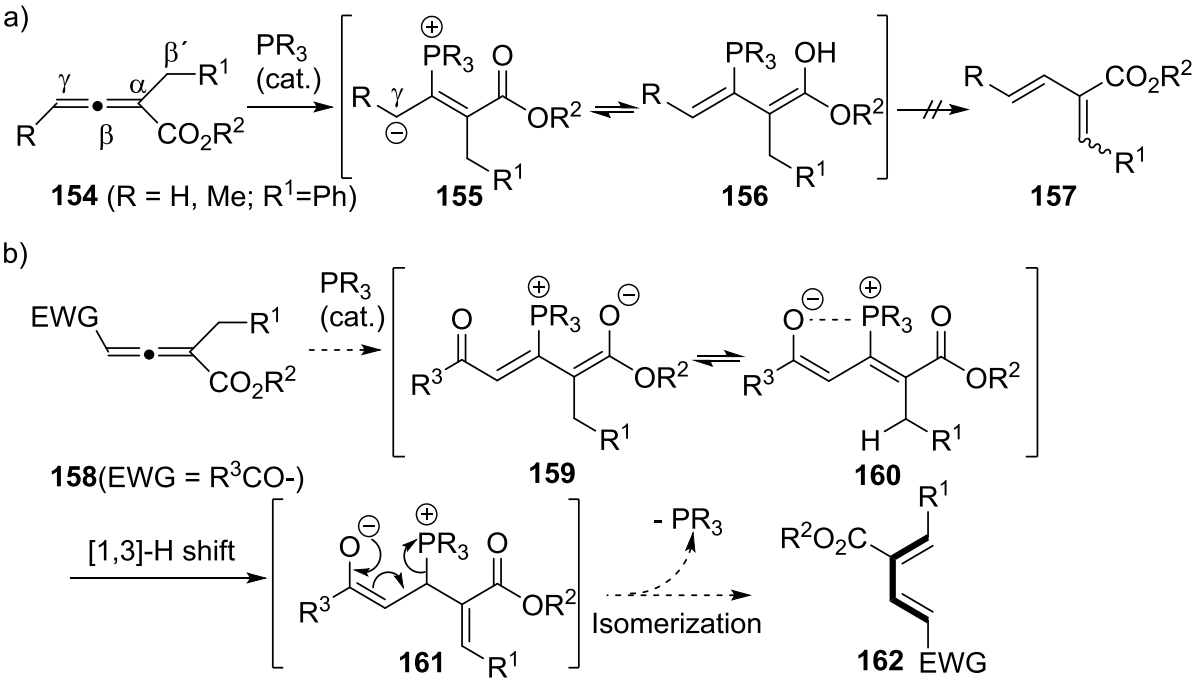


153a; R^1 = Ph, R^2 = Et, R^3 = Me, 80%
153b; R^1 = 2-Me-C_6H_4, R^2 = Et, R^3 = Me, 80%
153c; R^1 = 4-Me-C_6H_4, R^2 = Et, R^3 = Me, 80%
153d; R^1 = 3-MeO-C_6H_4, R^2 = Et, R^3 = Me, 81%
153e; R^1 = 4-CF_3-C_6H_4, R^2 = Et, R^3 = Me, 84%
153f; R^1 = 4-Br-C_6H_4, R^2 = Et, R^3 = Me, 80%
153g; R^1 = 4-NO_2-C_6H_4, R^2 = Et, R^3 = Me, 76%
153h; R^1 = H, R^2 = Et, R^3 = Me, 54%
153i; R^1 = Me, R^2 = Et, R^3 = Me, 81%
153j; R^1 = Ph, R^2 = Et, R^3 = Et, 76%
153k; R^1 = Ph, R^2 = Et, R^3 = Bn, 52%
153l; R^1 = Ph, R^2 = Et, R^3 = Ph, 62%
153m; R^1 = Ph, R^2 = ^{t}Bu, R^3 = Me, 36%

Scheme 43: Synthesis of allene esters **153**.

These acetals form the required acetyl ketenes *in situ* upon heating and allowed us to synthesize allene esters **153** in moderate to very high yields (Scheme 43). We synthesized allenes with variations at ester moiety (R^2), α-position (CH_2R^1) and on acetyl group at γ-position. The reactions performed well and could be well upscaled from hundred mg to gram scale.

Addition of Lewis bases, particularly organophosphines to allenes **154** can lead to zwitterionic species **155** (Scheme 44). We wondered whether a sufficiently acidic proton at β′ and stabilization by benzylic position would facilitate isomerization into diene **157**.



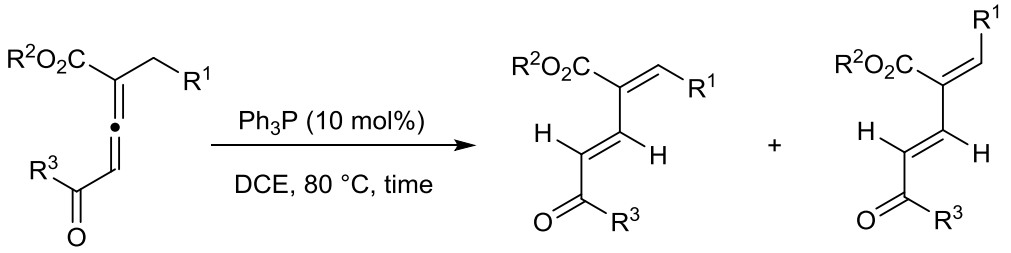
Scheme 44: Generation of disubstituted electron poor 1,3 butadienes **162** from trisubstituted allenes such as **158.** *These reactions were carried out by Dr. Xiaoyi Xin.*[212]

Thus, with a range of desired allenes in hand, their transformation into dienes was studied. The use of catalytic amounts of tributylphosphine resulted in formation of dienes as minor products and oligomerization took place as the major reaction. Less nucleophilic and reactive triphenylphosphine was then used as organocatalyst. Experiments at room temperature showed that while no oligomerization could be observed, conversion of reaction did not complete. Reaction was then performed using 10mol% of triphenylphosphine in 1,2-dichloroethane (DCE) at 80 °C. Allene ester **153a** did deliver diene as two isomers, *E,E*-**162a** and *Z,E*- **162´a** in 76 and 26%, respectively.

Mechanistically, we found that γ-substitution with an electron-withdrawing group, namely a ketone, allowed for this transformation. We postulate that zwitterionic species **159** that

might be stabilized by cyclic phosphonium enolate (**160**) allows for 1,3-hydride shift, forming enolate **161**, which in turn eliminates phosphine to give diene **162**.

Table 7: isomerization of 1,3 dicarbonyl allenoates into electron poor 1,3-butadienes. *Work has been carried out by Dr. Xiaoyi Xin and has been published in 2018.*[212]



153 (***E***, ***E***)**-162** (***Z***, ***E***)**-162´**

No	R^1	R^2	R^3	Time (h)	Yield (%) (***E***, ***E***)**-162**	Yield (%) (***Z***, ***E***)**-162´**
1	Ph	Et	Me	18	**162a**, 72	**162´a**, 26
2	2-Me-C_6H_4	Et	Me	18	**162b**, 58	**162´b**, 41
3	4-Me-C_6H_4	Et	Me	18	**162c**, 68	**162´c**, 25
4	3-MeO-C_6H_4	Et	Me	18	**162d**, 72	**162´d**, 27
5	4-CF3-C_6H_4	Et	Me	18	**162e**, 68	**162´e**, 31
6	4-Br-C_6H_4	Et	Me	18	**162f**, 67	**162´f**, 29
7	4-NO_2-C_6H_4	Et	Me	18	**162g**, 57	**162´g**, 35
8	H	Et	Me	18	**162h**, -[b]	**162´h**, -[b]
9[c]	Me	Et	Me	60	**162i**, 54	**162´i**, 24
10	Ph	Et	Et	18	**162j**, 66	**162´j**, 26
11	Ph	Et	Bn	18	**162k**, 76	**162´k**, 23
12	Ph	Et	Ph	72	**162l**, 67	**162´l**, 20
13	Ph	^{t}Bu	Me	72	**162m**, 47	**162´m**, 30

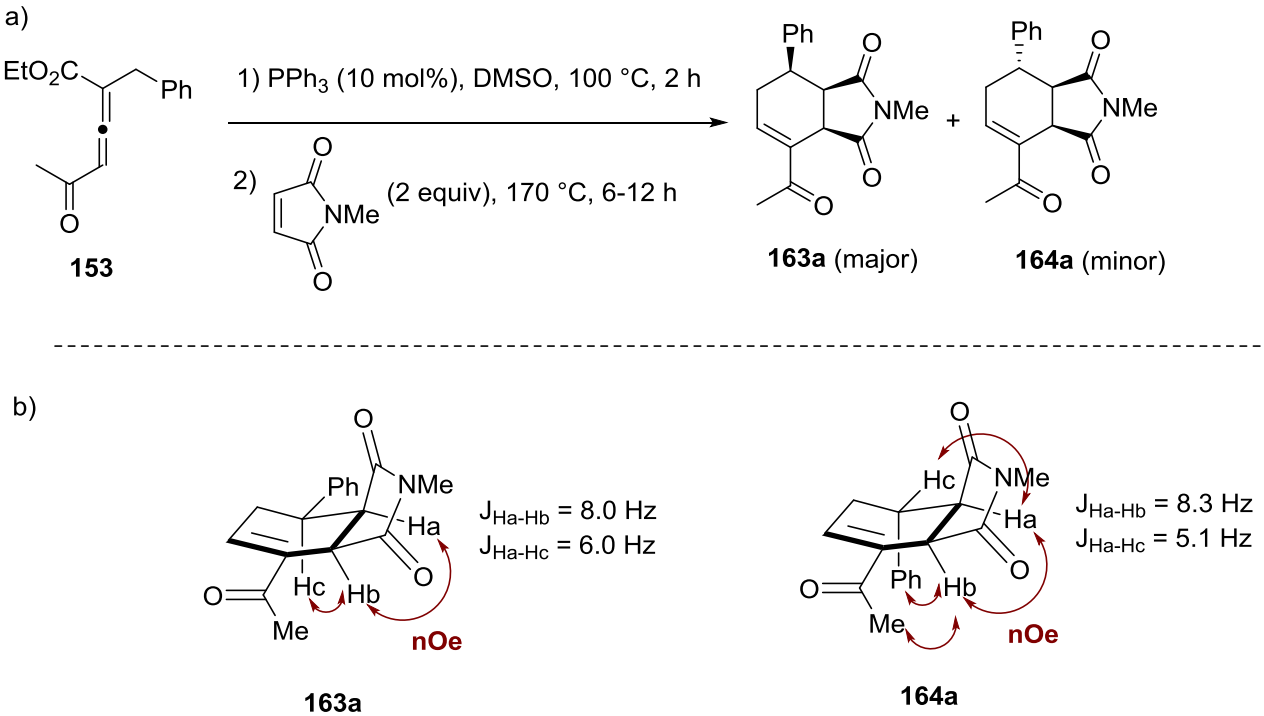
Dienes **162a/162a'** could be kept at room temperature under air for longer duration and was therefore well suitable for exploration of its reactivity.

A range of differently substituted dienes was obtained using this procedure (table 8). While different aromatic substitutions aswell as methyl group were allowed at R^1, different esters, alkyl residues at α position and ketones at R^3, were also tolerated. It may be of further interest to investigate whether different groups (i.e. CN, N_3), than ester at α position would be tolerated and result in stable dienes that may allow further diversification. The isomers

could be well separated by means of silica-gel column chromatography and diene showed high stability in the purification process. It is important to mention that even though most dienes were relatively stable, their purity at room temperature decreased when stored for longer duration at room temperature. So we preferred to store these dienes at -28 °C. With R^1 = H, the terminal diene was not formed at all.

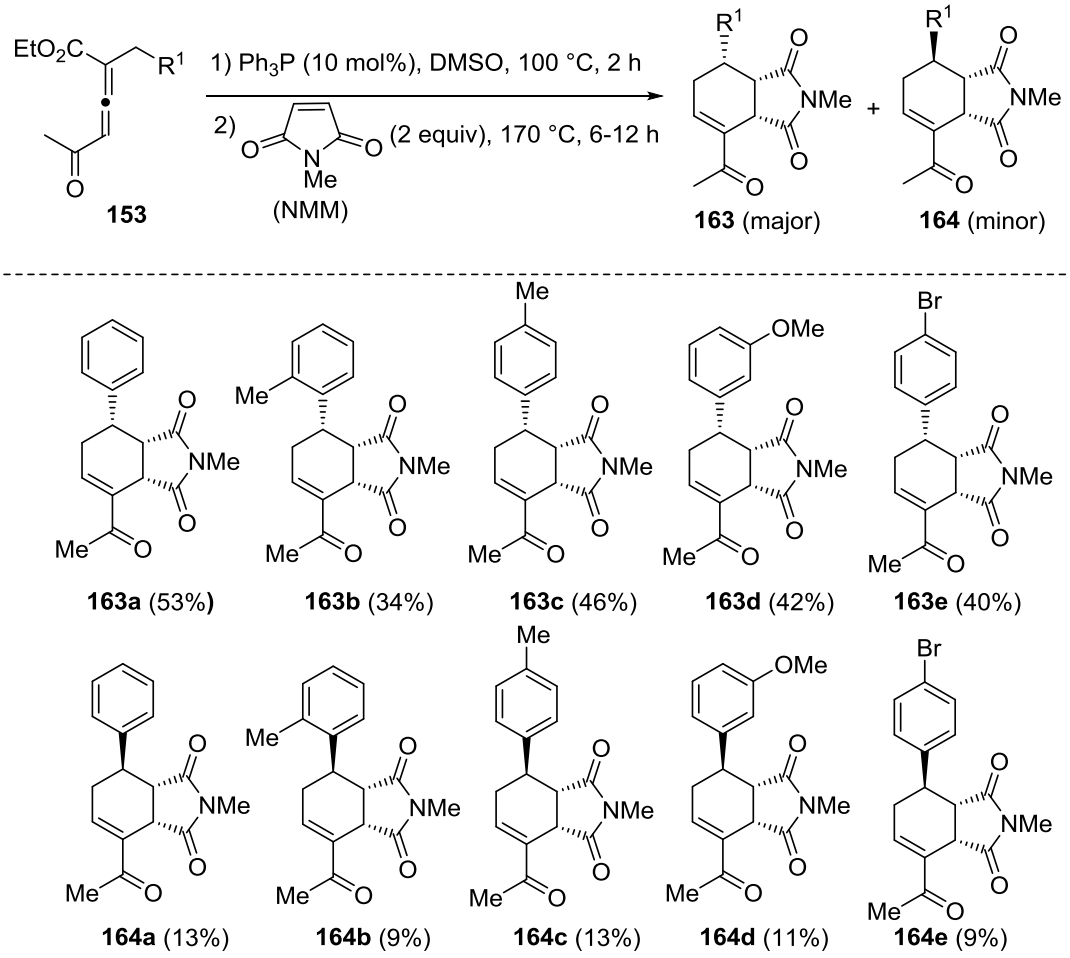
3.4 Cycloaddition reaction of 1,3 dicarbonyl dienes with maleimides and 2,3,5 triazine diones

Maleimides are among the most frequently used dienophiles for cyclization reactions.[213] Thus, we selected them as initial choice to study cycloaddition chemistry of doubly deficient dienes. The allene were transformed into dienes in toluene and the crude mixture was treated with N-methyl maleimide (NMM). Howevere, only trace amount of cycloadduct was formed. We then separately dissolved dienes **162a** and **162'a** to N-methyl maleimide (NMM) in nonpolar solvents such as toluene and *p*-xylene at room temperature or elevated temperatures (80 °C, at 150 °C and at 200 °C, under 300 W of microwave irradiation. Yet, no clean reaction was observed. Pleasingly, changing the solvent from toluene to DMSO and at 170° C, the reaction afforded a novel decarboxylated Diels-Alder adduct **163a** as the major product and the diastereomer **164a** as the minor product. The structure of the **163a** and **164a** were assigned on the basis of rigorous spectroscopic analysis, in particular, on the basis of ^{1}H and ^{13}C NMR spectra as well as 1D nOe and HMBC analysis (Scheme 45b). A one-pot procedure was then developed by transforming allene esters **153** in DMSO to dienes and then making a Diels-Alder reaction with NMM (Scheme 45a)



Scheme 45: a.) One-pot reaction for reaction of allenes with maleimides in presence of triphenyl phosphines **153**. b.) Structural elucidation using nOe and HMBC experiments.

Different allene esters supporting varying aromatic groups were used in this one-pot cascade reaction sequence to provide novel bicyclic molecular scaffolds **163** and **164** in acceptable yields (Scheme 46). The intriguing cascade reaction sequence of DA reaction-isomerization-decarboxylation poses many questions regarding its mechanism.

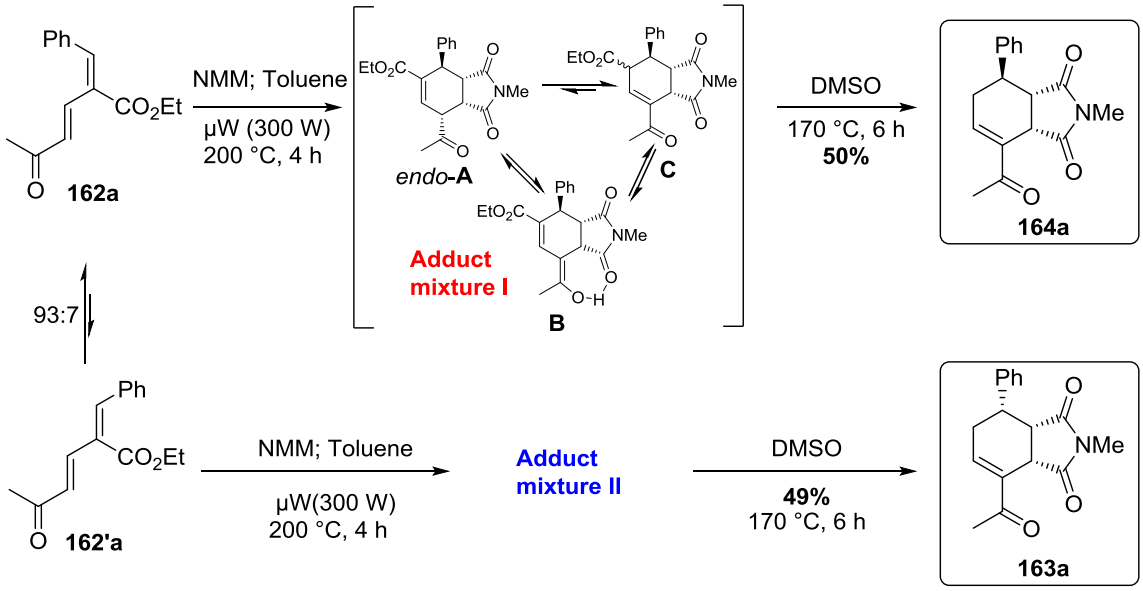


Scheme 46: Reaction scope for formation of **163** and **164** in one-pot reaction.[212] *This part of work was carried out by Dr. Xiaoyi Xin and has been published in 2018.*[212]

The decarboxylated adducts **163** and **164** are apparently derived from the *endo*-DA adducts (**163** from **162´a** and **164** from **162a** through their s-cis conformation). Importantly, as allene ester **153a** affords ca. 60:40 ratio of **162a**:**162´a** in DMSO at high temperature, (Scheme 48), **164a** should have been the major product in this cascade reaction. To get more insights into this unique chemistry of electron-poor dienes, some control reactions were planned.

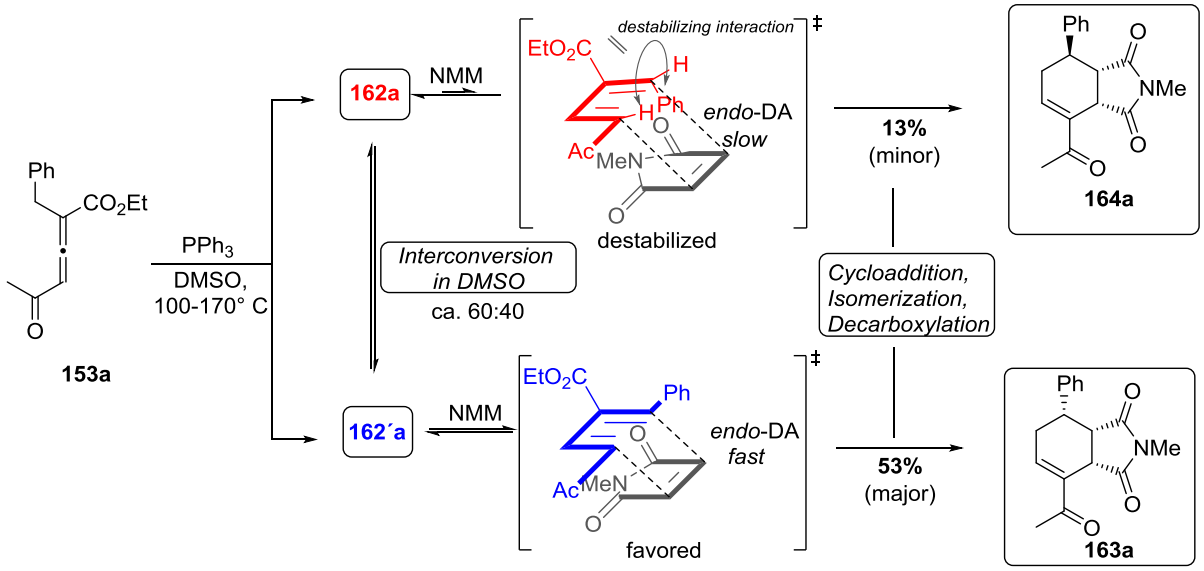
In the first case, a separate reaction of **162a** and **162´a** with NMM (2.0 eq.) was performed in deuterated DMSO for 2h and the proton NMR spectrum of the crude reaction mixtures was analyzed. Interestingly, in both the cases, **163a** was formed as the major cycloadduct. We had observed that there was substantial diene consumption in DA reaction

with NMM when performed in toluene. The DA reactions of dienes **162a** and **162a´** were thus performed again in the presence of NMM and the adduct mixtures I and II respectively were separated after a short flash column chromatorgraphy to remove the unreacted dienes and excess of NMM.



Scheme 47: Mechanistic insights into reaction of 1,3 dicarbonyl dienes with maleimides, a two-step procedure including a decarboxylative step. *This part of work was carried out by Dr. Xiaoyi Xin and has been published in 2018.*[212]

This way, we obtained inseparable mixtures of adducts (same mass, Scheme 47)). These mixtures **I** and **II** (cf. Scheme 45) were subjected to DMSO at 170 °C, and *syn* (**163**) and *anti* (**164**) isomers of fused imides could be isolated after 6 h reaction time. We assume that a decarboxylation step occurs after cycloaddition. A careful NMR analysis of the reaction mixture hinted towards the presence of major cycloaddition product (**C**) wherein olefin isomerization had already occurred along with another product with H-bonded enol moiety (**B**). *Endo*-**A** is formed at high temperatures, which reversibly transforms into two other intermediates, enolic **B** and its regioisomer **C**. We assume that the conditions (DMSO and high temperatures) are crucial, as polarization of medium is enhanced and decarboxylation of **C** is alleviated to give **164a**.



Scheme 48: One-pot reaction, generated *in situ* from allenes **153** with maleimides. Proposed selectivity for endo-Product **163a** over **164a** in reaction of in situ-generated **162'a** and **162a** from **153a** *This part of work was carried out by Dr. Xiaoyi Xin and has been published in 2018.*[212]

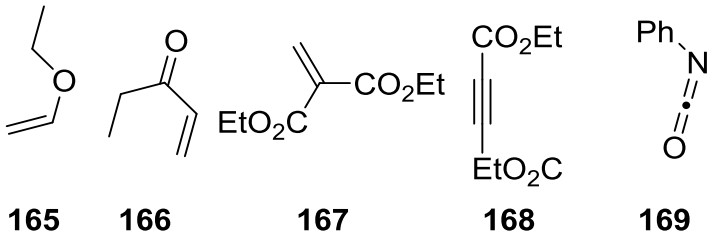
In the optimized one-pot reaction condition, first, allene is heated with DMSO with triphenylphosphine. After 2 h, NMM is added and heated six to twelve hours at 170° C to furnish adducts. Both **162** and **162'a** are in an equilibrium in reaction mixture, with **162a** being slightly favored (60:40).

Experiments for studying reaction mechanism in DMSO-d*6* clearly indicated that the rate of cycloaddition reaction was faster for *Z,E*-diene **162´a** than *E,E*-diene **162a**. While both isomers react *via* an *endo*-Diels Alder mechanism (Scheme 48), reaction of **162a** (top) is disfavoured due to sterical repulsion. The s-cis conformation of **162´a** offers relatively negligible steric repulsion to the dienophile and therefore is consumed in DA reaction much faster. This shifts the equilibrium of the diene interconversion towards *Z,E*-diene and consequently, **163a** is formed as the major product.

Ten different molecules were obtained (**163a-e** and **164a-e**, Scheme 46) in combined yields ranging from 43% to 66% per reaction. Diastereomeric ratios range from around 4:1 to 3:1 in favor of *syn*.

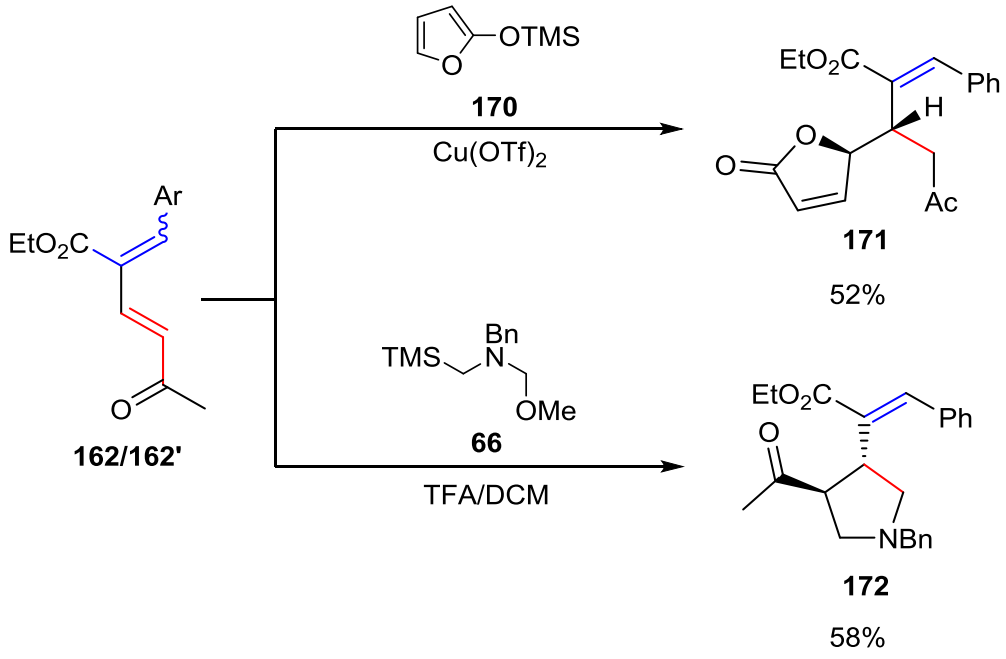
3.5 Reactivity of 1,3 dicarbonyl allenes with various dienophiles

With our findings of interesting and unexpected reactivity of electron-poor 1,3 dienes, we were curious to see how these dienes would react with other electron-rich and -poor dienophiles. We employed a range of potential dienophiles (Scheme 49 **165-169**) in cycloaddition reactions with dienes. The electron-rich dienophiles included such as ethyl vinyl ether (**165**) and deficient ones such as ethyl vinyl ketone (**166**) or 2,2-dicarbethoxyethylene (**167**), ethylene acetylene dicarboxylate (**168**) and other potential reaction partners such as isocyanate **169**.[137–142]



Scheme 49: A number of potential dienophiles that were chosen to study reactivity of dienes **162**.

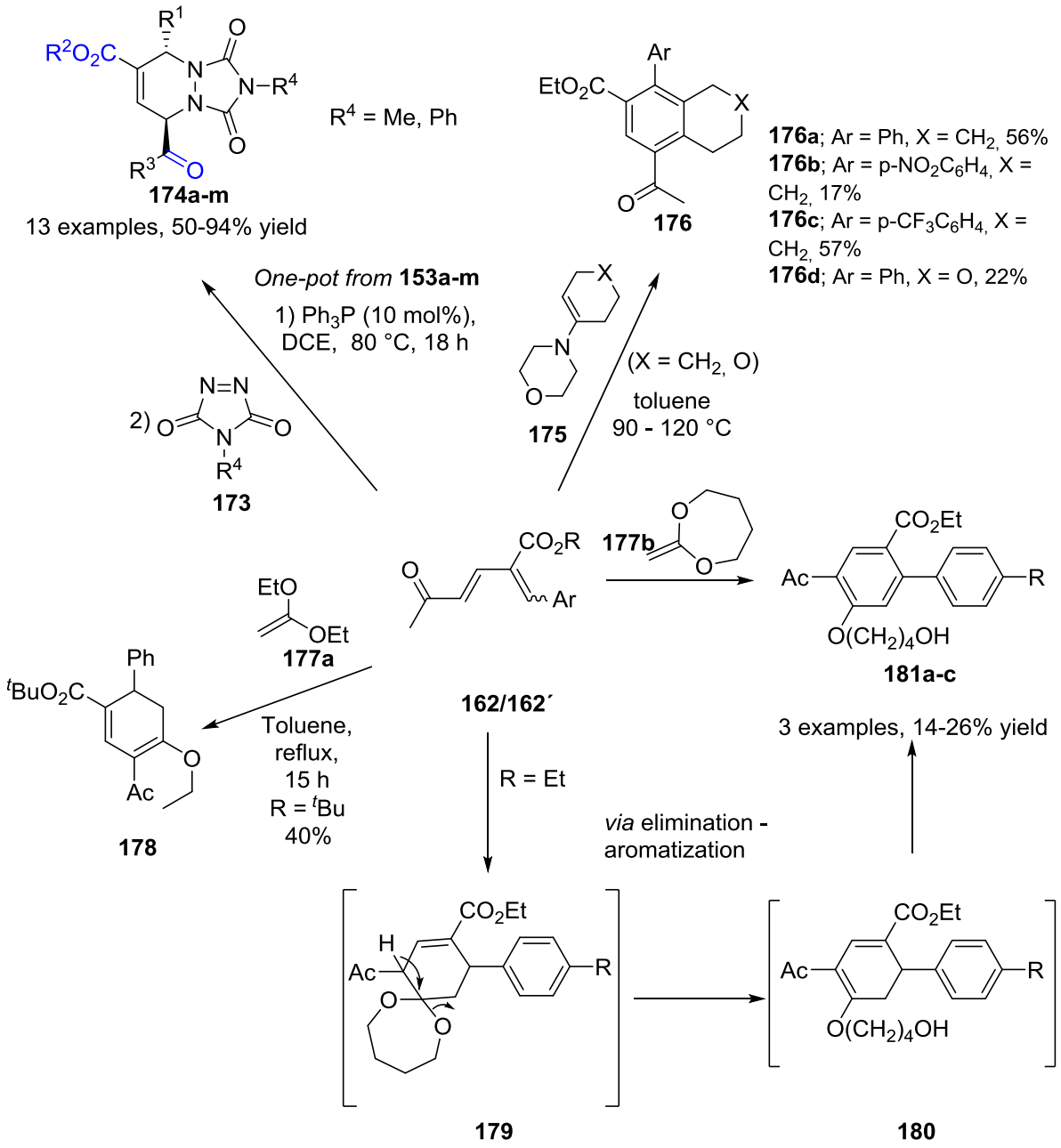
Electron-rich reagents such as **165** and related vinyl ethers did not result in any adduct formation, even after prolonged heating and microwave irradiation. To our astonishment, even electron deficient dienophiles mentioned above did not show any conversion, even



Scheme 50: Reaction of electron-poor 1,3 dicarbonyl **162**/**162'** dienes with **170** and **66** leads to adducts **171** and **172**, respectively.

after prolonged reaction time, or addition of more equivalents of reagents or performing reactions at elevated temperature.

The addition of silyl enol ether **170** or Azomethine Ylide **66** did not result in the formation of cycloadducts but instead the Michael reaction with enone moiety of diene occurred to give **171** and **172** in moderate yields (Scheme 50).



Scheme 51: Reaction of PTAD (**173**) enamines **175**, and ethylene acetals **177a** and **177b** and electron-poor dienes **162/162'**. *Synthesis of **174a-m** has been carried out by Dr. Xiaoyi Xin and has been published in 2018.*[212]

This poses an interesting phenomenon, as diene does not react as continuous π-system, furnishing 1,6-addition products. Instead, it reacts in a Michael addition at β position.

Possibly, this is due to strong delocalization of electrons in cinnamate, which deactivates this part of molecule and leaves only enone to react as an electrophile.

Electron-deficient reagent diethyl azodicarboxylate (DEAD) led to formation of complex mixtures. However, its cyclic analogue 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD, **173**) did react in a much cleaner fashion. We observed that dienes – used pure or generated *in situ* - did react with **173** to give fused urazoles **174** (Scheme 49). The reaction occurred at 80 °C in 1,2-DCE, furnishing corresponding *anti*-urazoles in moderate to good yields (Scheme 49). Under these reaction conditions, no decarboxylation as with NMM was observed. Derivatization of ester in **174** (highlighted in blue, scheme 51) proved difficult due to relative instability of urazole in presence of alkoxy bases.

Morpholine-derived enamines reacted with different dienes **175** to give tetrahydronaphtalenes **176a-c** and isochromane **176d** in low to moderate yields (scheme 51). Generally, high temperatures and long reaction times were required. However, we believe the reaction has the potential for further screening of catalytic conditions that may facilitate it at lower temperatures and whith higher efficiency.

While simple vinyl ethers did not react with dienes, ethylene acetals such as **177a** or **177b** readily reacted to give dihydronaphtalenes **178** and **181a-c**.

We assume that **181a-c** are formed *via* spirocycloadduct **179**, which collapses into dihydronaphtalene **180** which aromatizes to yield **181a-c**. Whereas different strategies towards biphenyls have been reported, these findings illustrate different means to synthesize tetrasubstituted biphenyls with synthetic handles for further derivatization. Such biaryl ring-system supporting two orthogonal electron-deficient groups as well as an electron erich moiety are otherwise difficult synthetic challenges and often require multistep and tedious synthesis.

3.6 Biological Evaluation of Hexahydrophtalimides and fused Urazoles

As previously noted, cell-based phenotypic screening strategies[214] have been shown to excel at illucidating signaling pathways such as hedgehog (Hh) pathway.[215][75] The HH pathway is a part of regulation of embryonic development, tissue regeneration, and stem cell homeostasis and its understanding is thus highly relevant for cancer research,[216] rendering probes that regulate this pathway highly demanded.[217,218]

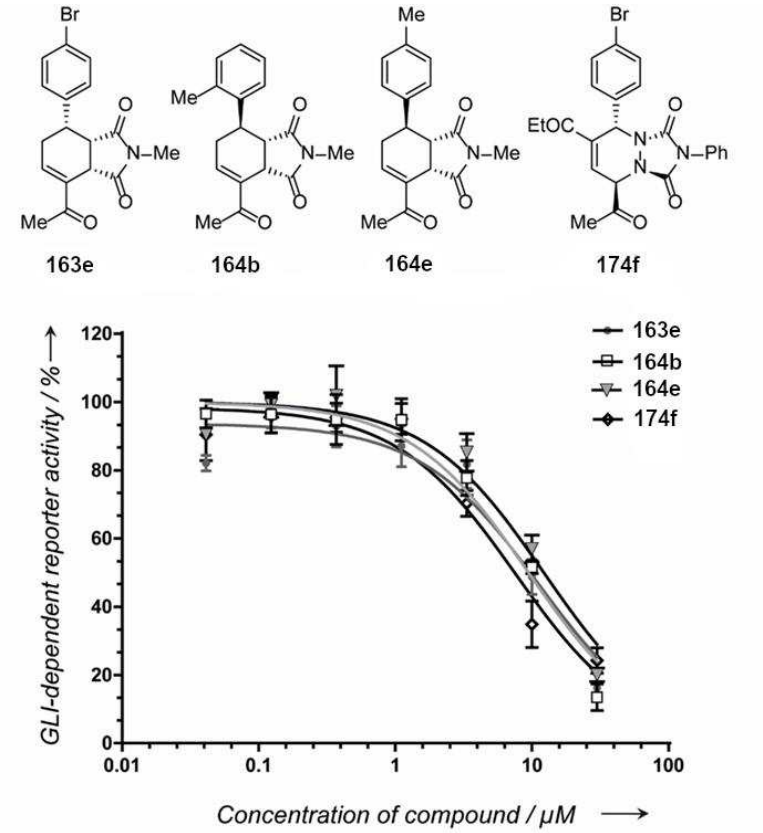


Figure 15: Perturbation by compounds **163e**, **164b**, **164c** and **174f** in GLI-dependent reporter activity, plotted in logarithmic fashion, allowing determination of IC50 values.

The cycloadducts synthesized in this project were exposed to osteoblast differentiation assay. This assay was used as a primary screening, making use of C3H10T1/2 cells to identify Hh inhibitors. Purmorphamine, a Smoothened (SMO, a GPCR, g-protein coupled receptor) agonist was employed to activate the Hh pathway, which induces the expression of the osteoblast-specific marker alkaline phosphatase.[219] Alkaline phosphatase activity can be correlated indirectly with Hh activity. [220,221] The screening identified a number of malemide cycloadducts i.e. **116e**, **117 b-c** along with **122f** as hedgehog pathway inhibitors. One important finding was that **122f** inhibits Hh dependent cell differentiation

with a IC_{50} (half-maximal inhibitory concentration) of 0.2 µM. *p*-Bromophenyl substituted *N*-methyl maleimideadduct **116e** inhibited Hh with an IC_{50} of 4.17±0.78µM. As an orthogonal tool, GLI-dependent reporter gene assay using Shh-LIGHT2 cells (Figure 15) was used to confirm the inhibition of Hh signaling. This experiment showed that **174f** inhibited the GLI-dependent luciferase expression with an IC_{50} of 7.15±1.91 µM. **163e**, **164b**, **164c** displayed IC_{50} in range of 9.5–11.2 µM (table 9).

Table 8: IC50 values of the selected compounds that show significant biological activity.

Compound*	Mean IC_{50}* [µM] (osteogenesis)	Mean IC_{50}** [µM] (GLI reporter gene assay)
174f	0.2 ± 0.0	7.2 ± 1.9
163e	4.2 ± 0.8	11.2 ± 2.1
164b	6.8 ± 1.3	9.5 ± 0.1
164c	4.1 ± 1.1	11.5 ± 1.4

*: Racemic moelcules; **: Mean IC_{50} values ± standard deviation (n = 3)

A competition experiment with BODIPY-cyclopamine in HEK293T cells ectopically expressing SMO was used to test the SMO-binding of the molecules.We hypothesized that compound **174f** may bind to SMO heptahelical bundle as BODIPY fluorescence was significantly reduced after this compounds addition (Figure 16).[222] A clear displacement could not be observed for carbocycles **163e**, **164b**, and **164c** and therefore they may have a different, potentially new unknown mode of action.[223][224]

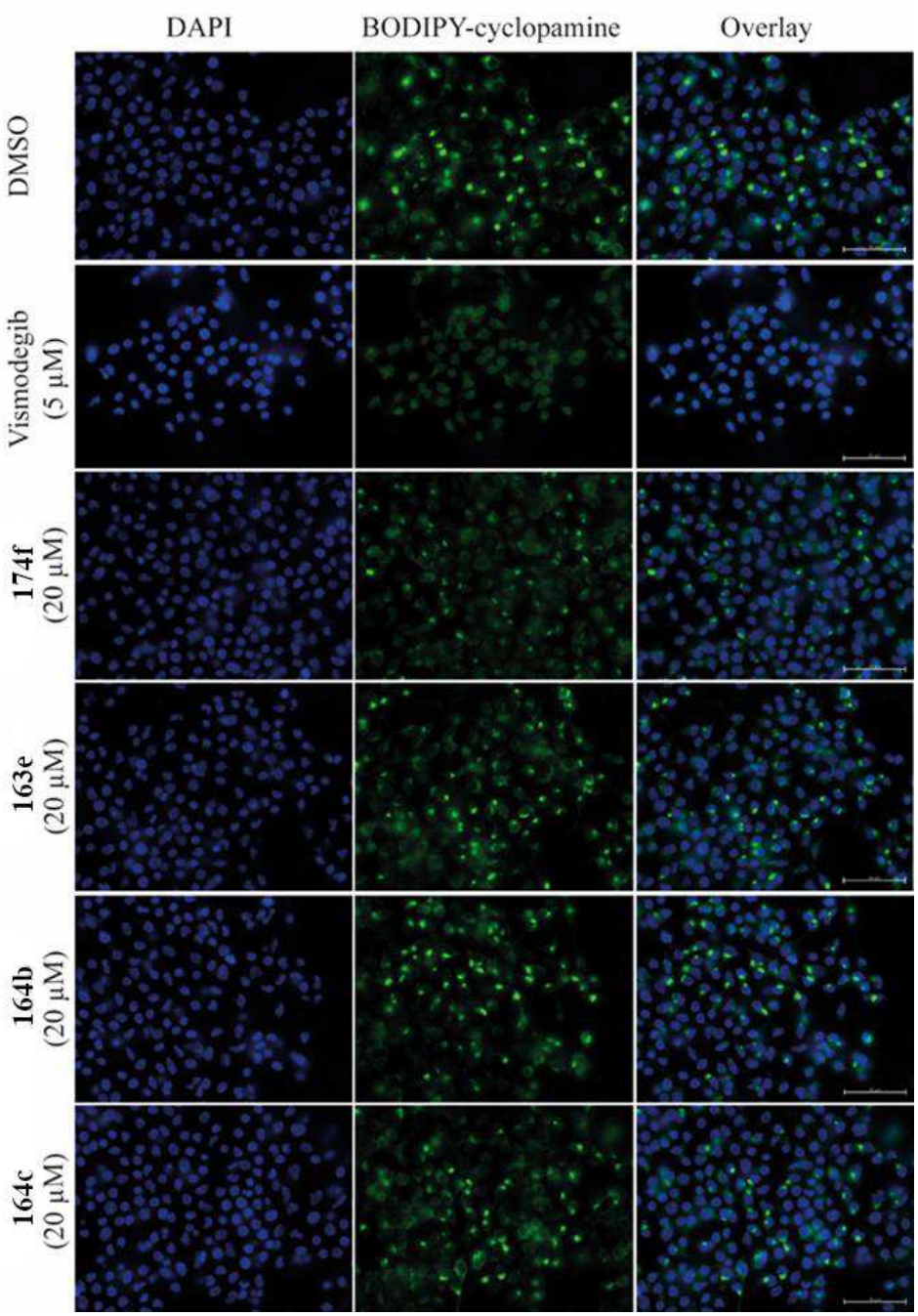
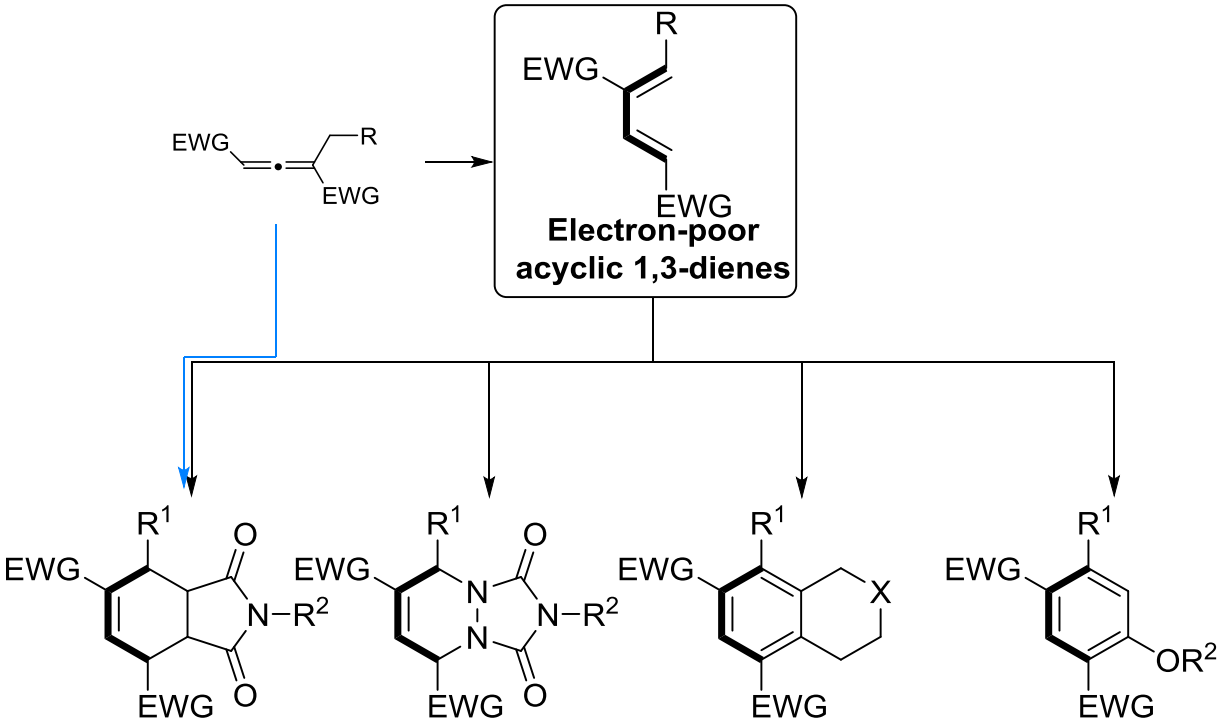


Figure 16: Activity of compounds **163e**, **164b**, **164c**, **174f** in comparison with vismodegib and DMSO.

3.7 Summary

Trisubstituted allenes were transformed into novel doubly deficient 1,3-butadienes **162**. The potential of dienes **162** in different cyclization/cycloaddition reactions was explored (Scheme 52). While the cycloaddition reaction of dienes with PTAD delivered the novel bicyclic triazolines **174**, a cascade reaction sequence of Diels-Alder reaction, isomerization and decarboxylation of the cycloadduct formed with *N*-methylmaleimide afforded stereoselective access to novel bicyclic scaffolds **163** and **164**.



Scheme 52: 1,3-double deficient dienes for generation of multisubstituted fused scaffolds.

In addition, enamines and ethylene acetals were also identified as potential candidates for cycloaddition chemistry of electron-poor dienes **162/162'** and affording highly substituted aromatics, tetrahydronaphtalenes **176a-c** and chromane **176d** and paving the way to discovery of more potential reaction partners. Another interesting find was that, *N*-methylmaleimide adducts **163e**, **164e**, **164b** as well as the bicyclic triazolindione, **174f** showed inhibition of the Hedgehog signalling pathway. This finding of interesting probes for hedgehog pathways as well as potential of this class of 1,3 double-deficient dienes present promising starting points for further studies, chemically, biologically and as well as for chemical biology research.

4. Experimental Part

4.1. General Information

All commercially available compounds were used as provided without further purification unless otherwise noted. Solvents were purchased from Fisher, VWR and Acros in laboratory, reagent and anhydrous grade, as labelled by corresponding companies. If no additional information regarding treatment is given, the solvents were used directly from the container. Reagents were purchased from Alfa Aesar, Sigma Aldrich and VWR respectively. If it is stated, that a reaction was carried out under an Argon atmosphere, standard Schlenk techniques were used. Column chromatography was performed using silica gel (Acros, particle size 0.035-0.070 mm).

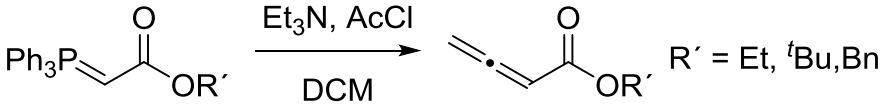
^{1}H, ^{13}C, ^{19}F and other NMR experiments were recorded on a Agilent Technologies DD2 (500 MHz),Bruker Biospin AVANCE HD-III Nanobay (400 MHz) Bruker Biospin AVANCE NEO (500 MHz) or Bruker Biospin AVANCE HDX-III (500 and 700 MHz machines available), Bruker Biospin AVANCE HD-III (600 MHz) using Chloroform-*d* (Chloroform-d), CD_2Cl_2, $(CD_3)_2CO$, CD_3CN or $(CD_3)_2SO$ as solvent at room temperature. ^{1}H and ^{13}C-NMR spectra were calibrated to the solvent signals of Chloroform-*d* (7.26 and 77.16 ppm), CD_2Cl_2 (5.32 and 53.84 ppm), CD_3CN (1.94 and 1.32/118.26 ppm) or $(CD_3)_2SO$ (2.50 and 39.52 ppm).[225] The abbreviations *s*, *d*, *t*, *q* and *m* stand for singlet, doublet, triplet, quartet and multiplet in that order. High resolution mass spectra (HRMS) were recorded on a *LTQ Orbitrap* mass spectrometer coupled to an *Accela HPLC*-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm; Ionization method: electron spray ionization). Preparative HPLC was performed using a 1260 Infinity II system by Agilent Technologies and Nucleodur C18 Gravity VP10/125 5 µm or Nucleodur C18 gravity VP21/125 5 µm columns by Macherey-Nagel.

4.2 Scaffold Diversity Synthesis of Benzosulfonamides

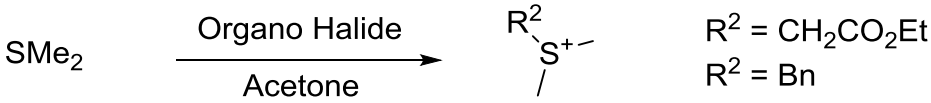
4.2.1 Branching Pathway

4.2.1.1 Synthesis of Ketimines (45), Allenes and sulfonium Salts

45-Ph,[105] **45-CO_2Et**,[106] **45-H**,[103] **45-Me**[104], **45-2-Pyr**[107] were synthesized according to procedures previously reported in literature. Spectral data were in accordance with reported ones.

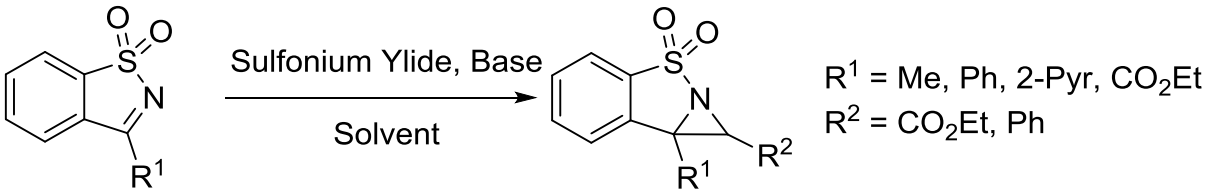


Allenes **50-OEt**, **50-OtBu** and **50-OBn** were synthesized according to reported literature procedures;[226][227] with recorded spectral data matching previously reported ones.



Sulfonium salts (carbethoxy)methyl dimethylsulfonium bromide and benzyl dimethylsulfonium bromide were synthesized and handled according to reported literature procedures; with recorded spectral data matching previously reported ones.[127][128]

4.2.1.2 Synthesis of Aziridines 48a-48h



General Reaction Scheme

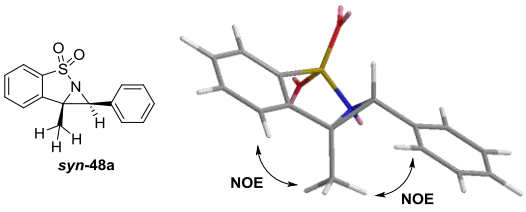
Aziridines were synthesized according to general scheme depicted above. Observed diastereoselectivity (*syn* in most examples) or lack of it in cases of **48c** and **48h** can be

described and established as described below. See also chapter 2.3.1.1, referring to general considerations of sulfur ylide mediated aziridination.[228]

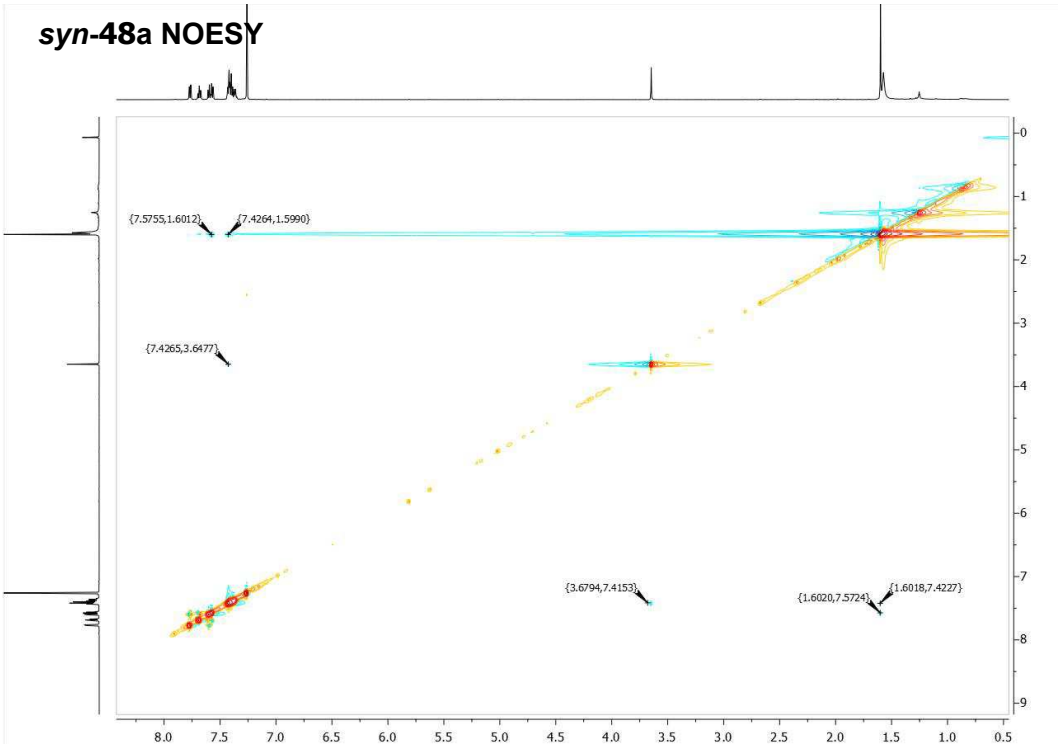
(±)-7b-methyl-1-phenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (2a)

Benzyl dimethylsulfonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol) and 3-methylbenzo[d]isothiazole 1,1-dioxide **45-Me** (1.0 eq., 21.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 h at ambient temperature. Then, an additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was concentrated and objected to silica gel column chromatography (7% to 14% EA/CyH) to yield 22 mg (0.08 mmol, 68%) of ***syn*-48a** and 3 mg (0.01 mmol, 9%) of ***anti*-48a**.

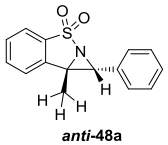
***syn*-48a**

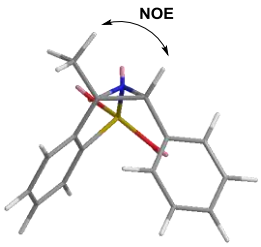


^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (dt, *J* = 7.6, 0.9 Hz, 1H), 7.69 (td, *J* = 7.6, 1.2 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.45 – 7.34 (m, 5H), 3.65 (s, 1H), 1.60 (s, 3H); **^{13}C NMR** (126 MHz, Chloroform-d) δ 141.2, 133.8, 133.7, 132.6, 130.3, 128.8, 128.7, 127.7, 124.3, 123.66, 61.6, 56.9, 13.1; **HMRS (ESI):** Calculated for C_{15} H_{14} O_2 N S = $[M+H]^+$: 272.07398, found: 272.07328

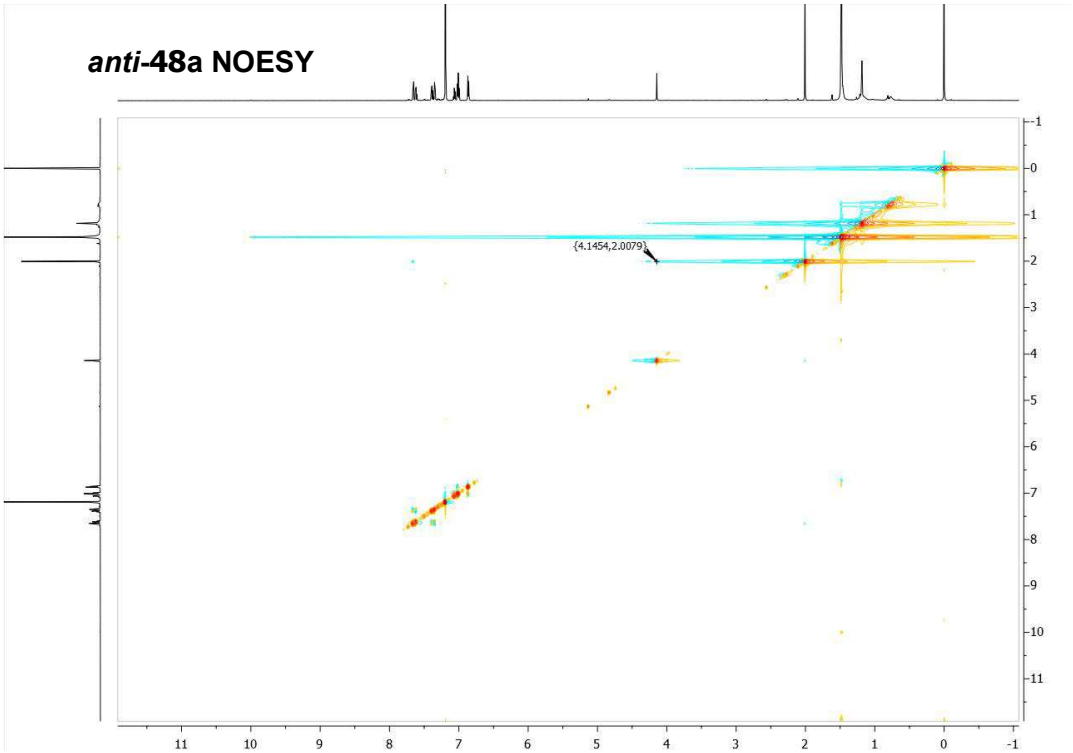


***anti*-48a**

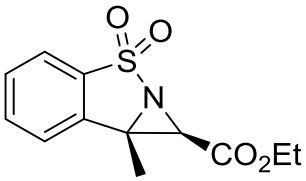




^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.73 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.68 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 7.46 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.41 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.10 – 7.06 (m, 2H), 6.93 (dq, *J* = 7.3, 1.2 Hz, 2H), 4.21 (s, 1H), 2.07 (s, 3H); **^{13}C NMR** (151 MHz, Chloroform-d) δ 137.7, 137.4, 133.4, 131.0, 130.4, 128.5, 128.3, 127.9, 125.6, 122.6, 62.2, 55.1, 19.7; **HMRS (ESI):** Calculated for C_{15} H_{14} O_2 N S = $[M+H]^+$: 272.07398, found: 272.07359



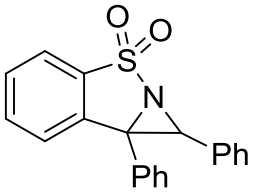
(±)-7b-methyl-1-carbethoxy-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide (48b)



(Carbethoxymethyl)dimethylsulfonium bromide (1.2 eq., 99 mg, 0.43 mmol, Potassium carbonate (2.0 eq., 99.0 mg, 0.72 mmol) and 3-methylbenzo[d]isothiazole 1,1-dioxide **45-Me** (1.0 eq., 65.0 mg, 0.36 mmol) were combined in Acetonitrile (1.3 ml). The reaction was concentrated and objected to silica gel column chromatography (15% to 21% EA/CyH) to yield 81.0 mg (0.30 mmol, 84%) of product aziridine.

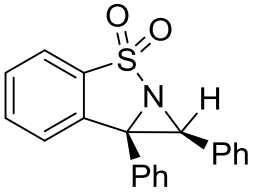
R_f (30% EA/CyH) = 0.55; **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.74 – 7.64 (m, 2H), 7.61 – 7.54 (m, 2H), 4.28 (m, 2H), 3.15 (s, 1H), 1.91 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 164.0, 139.2, 134.0, 133.2, 130.7, 124.9, 123.3, 62.4, 55.5, 53.9, 14.1, 13.3.
HMRS (ESI): Calculated for C_{12} H_{14} O_4 N S = $[M+H]^+$: 268.06381, found: 268.06385

(±)-1,7b-diphenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide(48c)



Benzyl dimethylsulfonium bromide (2.25 eq., 112.0 mg, 0.48 mmol was combined with Potassium carbonate (2.50., 74.0 mg, 0.53 mmol) in an oven-dried schlenk tube with a magnetic stirring bar and solved in 2.28 ml DMF. After 10 min. Ketimine **45-Ph** (1.0 eq., 52.0 mg, 0.21 mmol mg) was added to the mixture. The reaction was stirred at ambient temperature overnight. After completion of conversion (TLC analysis), the reaction was quenched by adding saturated aqueous ammonium chloride solution (4 ml). 2 ml Ethyl Acetate were added and layers were separated. The aqueous layer was extracted twice more with 2 ml each. Combined organic layers were washed with water three times (10 ml each) and brine once. Concentration delivered crude material, which was objected to silica gel column chromatography (3:2 Ethyl acetate / Cyclohexane (v/v)) to deliver 67 mg (0.20 mmol, 94%) of aziridine.

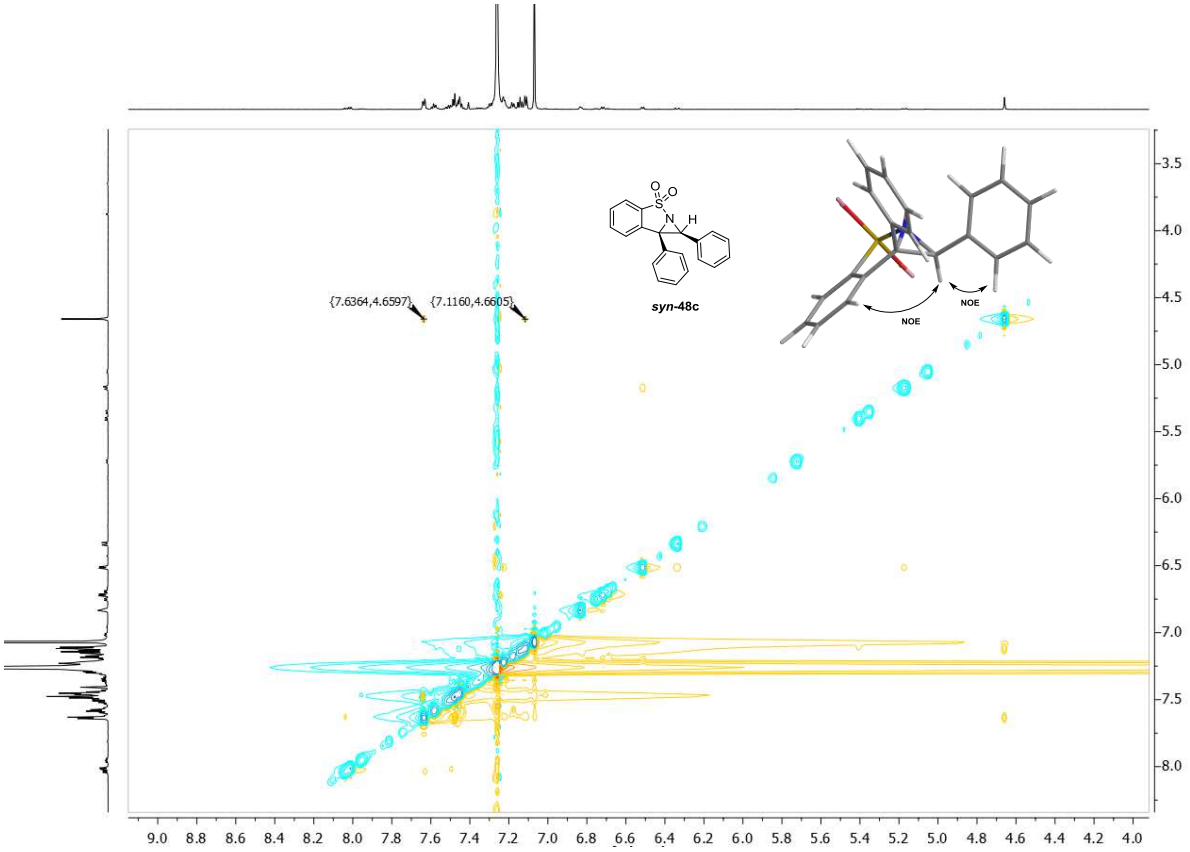
***Syn*-48c**



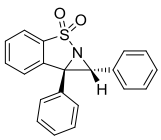
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 2H), 7.61 – 7.56 (m, 1H), 7.52 – 7.41 (m, 6H), 7.20 – 7.09 (m, 5H), 4.65 (s, 1H).

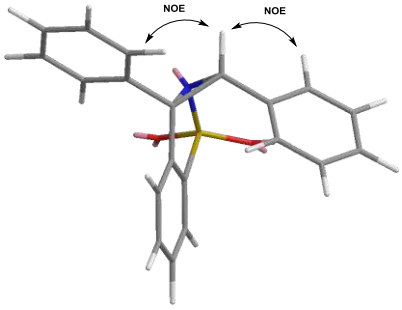
^{13}C NMR (126 MHz, Chloroform-d) δ 137.3, 136.7, 135.1, 133.2, 131.0, 130.4, 129.5, 129.1, 128.5, 128.5, 128.0, 127.9, 127.1, 122.2, 60.7, 60.2.

HMRS (ESI): Calculated for C_{20} H_{16} O_2 N S = $[M+H]^+$: 334.08963, found: 334.09003



***anti*-48c**

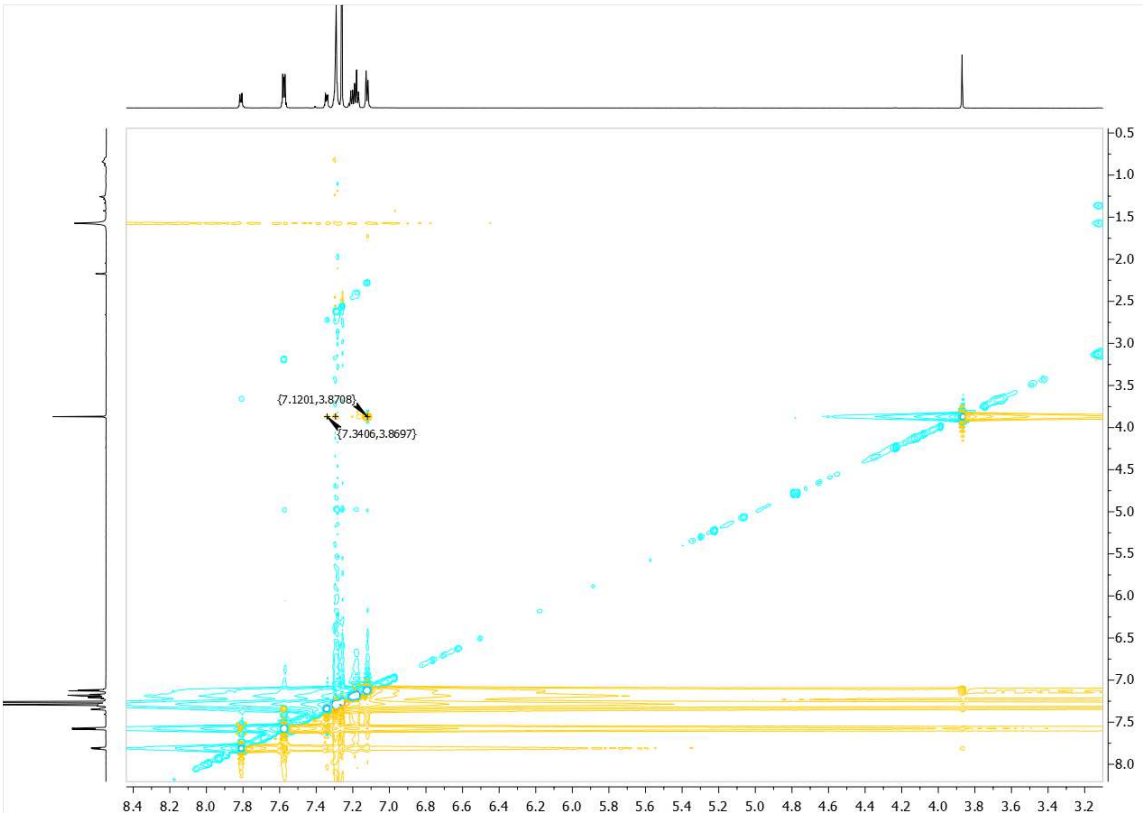




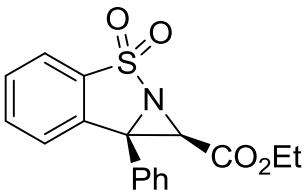
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.83 – 7.80 (m, 1H), 7.59 – 7.56 (m, 2H), 7.36 – 7.33 (m, 1H), 7.31 – 7.27 (m, 5H), 7.23 – 7.16 (m, 3H), 7.12 (d, *J* = 7.7 Hz, 2H), 3.87 (s, 1H).

^{13}C NMR (176 MHz, Chloroform-d) δ 140.6, 133.6, 133.2, 132.6, 130.9, 130.3, 129.3, 129.0, 128.8, 128.7, 128.3, 127.8, 125.6, 123.5, 62.4, 62.3.

HMRS (ESI): Calculated for C_{20} H_{16} O_2 N S = $[M+H]^+$: 334.08963, found: 334.09043



(±)-Ethyl 7b-phenyl-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-1-carboxylate 3,3-dioxide (48d)



To (Carbethoxymethyl)dimethylsulfonium bromide (121 mg, 0.53 mmol, 1.35 eq.) was added sodium hydride (24 mg ,60 wt.% in paraffin oil, 1.55 eq.) in 3.8 ml *N,N*-DMF. The mixture was stirred for 5 min at ambient temperature and 3-(phenyl)- 1,2 benzothiazole 1,1-dioxide **45-Ph** (1.0 eq., 95 mg, 0.39 mmol) was added in one portion. The reaction was stirred for 10 h at ambient temperature. The reaction mixture was poured into 50 ml of saturated aqueous ammonium chloride solution and extracted with 10 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography

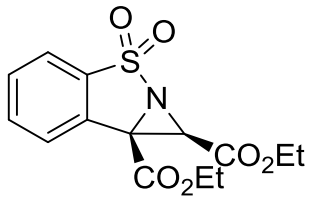
(Ethyl Acetate/Cyclohexane 15-25%) furnished 32 mg (0.10 mmol, 25%) of desired aziridine.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 1H), 7.61 – 7.58 (m, 2H), 7.53 (dq, *J* = 5.1, 2.9 Hz, 2H), 7.46 – 7.40 (m, 4H), 4.10 – 3.96 (m, 2H), 3.50 (s, 1H), 0.96 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 163.4, 138.4, 133.8, 132.7, 130.8, 130., 129.5, 129.0, 128.1, 126.0, 123.3, 62.1, 58.7, 56.6, 13.7.

HMRS (ESI): Calculated for C_{17} H_{16} O_4 N S = $[M+H]^+$: 330.07946, found: 330.07993

(±)-Diethyl azirino[1,2-b]benzo[d]isothiazole-1,7b(1H)-dicarboxylate 3,3-dioxide(48e)



(Carbethoxymethyl)dimethylsulfonium bromide (2.0 eq., 105 mg, 0.46 mmol) and Potassium carbonate (3.0 eq., 95.3 mg, 0.69 mmol) were combined in dry DMSO (2.3 ml) in a flame-dried 10 ml schlenk tubed equipped with a magnetic stirring bar under an Argon atmosphere. The mixture was stirred for 10 min and Ketimine **45-CO_2Et** (1.0 eq., 55 mg, 230.0 µmol) was added as a solid. The reaction was then monitored via TLC.

After 3 h, starting material had been consumed and the reaction mixture was quenched with 2 ml saturated aqueous ammonium chloride solution and the resulting mixture was poured into 40 ml water in a separation funnel.

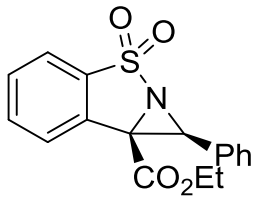
The mixture was extracted with Ethyl acetate (5 times with 9 ml each). Combined organic layers were washed with water and brine and dried over anhydrous sodium sulfate. Concentration delivered crude product. Objection to silica gel column chromatography (16 to 30% EA/CyH) furnished 28 mg aziridine (0.09 mmol, 37% yield).

R_f = 0.31 (30%EA/CyH); **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.93 – 7.89 (m, 1H), 7.73 – 7.67 (m, 2H), 7.66 – 7.60 (m, 1H), 4.33 (qd, *J* = 7.1, 5.9 Hz, 2H), 4.24 (qd, *J* = 7.2, 0.6 Hz, 2H), 3.26 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 162.8, 162.7, 134.1, 132.9, 132.8, 131.6, 126.4, 123.4, 63.3, 62.8, 55.3, 53.8, 13.9, 13.9.

HMRS (ESI): Calculated for C_{14} H_{16} O_6 N S = $[M+H]^+$: 326.06928, found: 326.06938
Calculated for C_{14} H_{15} O_6 N Na S = $[M+Na]^+$: 348.05123, found: 348.05129

Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide (48f)



To 3-carbethoxy 1,2 benzothiazole 1,1-dioxide **1-CO_2Et** (1.0 eq., 24 mg, 0.10 mmol) in 0.8 ml Acetonitrile was added 2.1 eq. (benzyl)dimethylsulfonium bromide (49.1 mg, 0.21 mmol) and Potassium carbonate (2.05 eq., 28.4 mg, 0.21 mmol). The reaction was stirred for 14 h at ambient temperature.

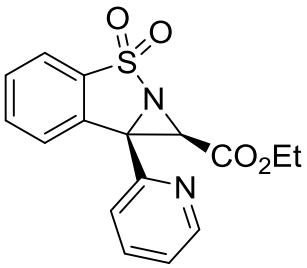
The reaction mixture was poured into 10 ml of saturated aqueous ammonium chloride solution and extracted with 5 ml Ethyl acetate (3 times). Combined organic layers were washed with water and brine (each 15 ml), dried over anhydrous sodium sulfate and concentrated. Objection to silica gel column chromatography (11% to 29% EA/CyH) furnished 18 mg (0.05 mmol, 54%) aziridine.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.78 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.73 (td, *J* = 7.7, 1.2 Hz, 10H), 7.65 (td, *J* = 7.6, 1.1 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.39 – 7.35 (m, 3H), 4.16 – 4.01 (m, 2H), 3.80 (s, 1H), 1.02 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 163.4, 134.7, 133.8, 133.2, 131.0, 130.9, 129.3, 128.4, 127.6, 126.5, 123.4, 62.5, 61.7, 57.7, 13.8.

HMRS (ESI): Calculated for C_{17} H_{16} O_4 N S = $[M+H]^+$: 330.07946, found: 330.07982

(±)-Ethyl 7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole-1-carboxylate 3,3-dioxide (48g)

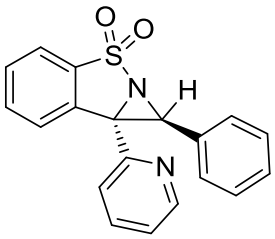


(Carbethoxymethyl)dimethylsulfonium bromide (1.37 eq., 108 mg, 0.47 mmol), Potassium carbonate (2.0 eq., 95 mg ,0.69 mmol) and 3-methylbenzo[*d*]isothiazole 1,1-dioxide **45-Me** (1.0 eq., 84.0 mg, 0.34 mmol) were combined in Acetonitrile (1.275 ml). The reaction was concentrated and objected to silica gel column chromatography (18% to 36% EA/CyH) to yield 103 mg (0.31 mmol, 91%) of product aziridine.

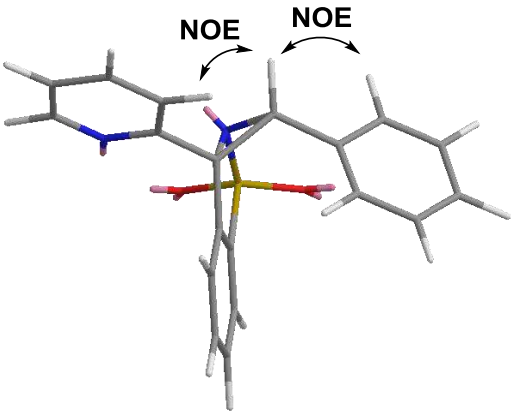
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (ddd, *J* = 4.9, 1.7, 1.0 Hz, 1H), 8.04 – 7.98 (m, 1H), 7.77 – 7.67 (m, 3H), 7.59 (pd, *J* = 7.4, 1.4 Hz, 1H), 7.31 (ddd, *J* = 7.2, 4.9, 1.6 Hz, 1H), 4.10 – 3.92 (m, 1H), 3.48 (s, 1H), 1.00 (t, *J* = 7.1 Hz, 2H).
^{13}C NMR (101 MHz, Chloroform-d) δ 163.2, 151.7, 149.5, 137.8, 137.3, 134.0, 133.0, 131.1, 127.3, 124.2, 124.1, 123.3, 62.3, 56.8, 27.1, 14.0.
HMRS (ESI): Calculated for C_{16} H_{15} O_4 N_2 S = $[M+H]^+$: 331.07470, found: 331.07463

(±)-1-Phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-*b*]benzo[*d*]isothiazole 3,3-dioxide (48h)

Benzyldimethylsulfonium bromide (1.4 eq., 100.0 mg, 0.43 mmol), Potassium carbonate (2.0 eq., 32.8 mg, 0.24 mmol) and 2-Pyridinyl Ketimine **45-2-Pyr** (1.0 eq., 29.0 mg, 0.12 mmol) were combined in Acetonitrile (970 µl). The reaction was stirred for 10 hours at ambient temperature. Then, additional 2.2 eq (157 mg, 0.68 mmol) of sulfonium salt were added to the mixture and the reaction stirred for 30 additional hours at ambient temperature. The reaction was stopped by concentration using a rotary evaporator and objected to silica gel column chromatography to yield 29 mg (0.09 mmol, 73%) of a 1:1 mixture of diastereomers.



anti-48h

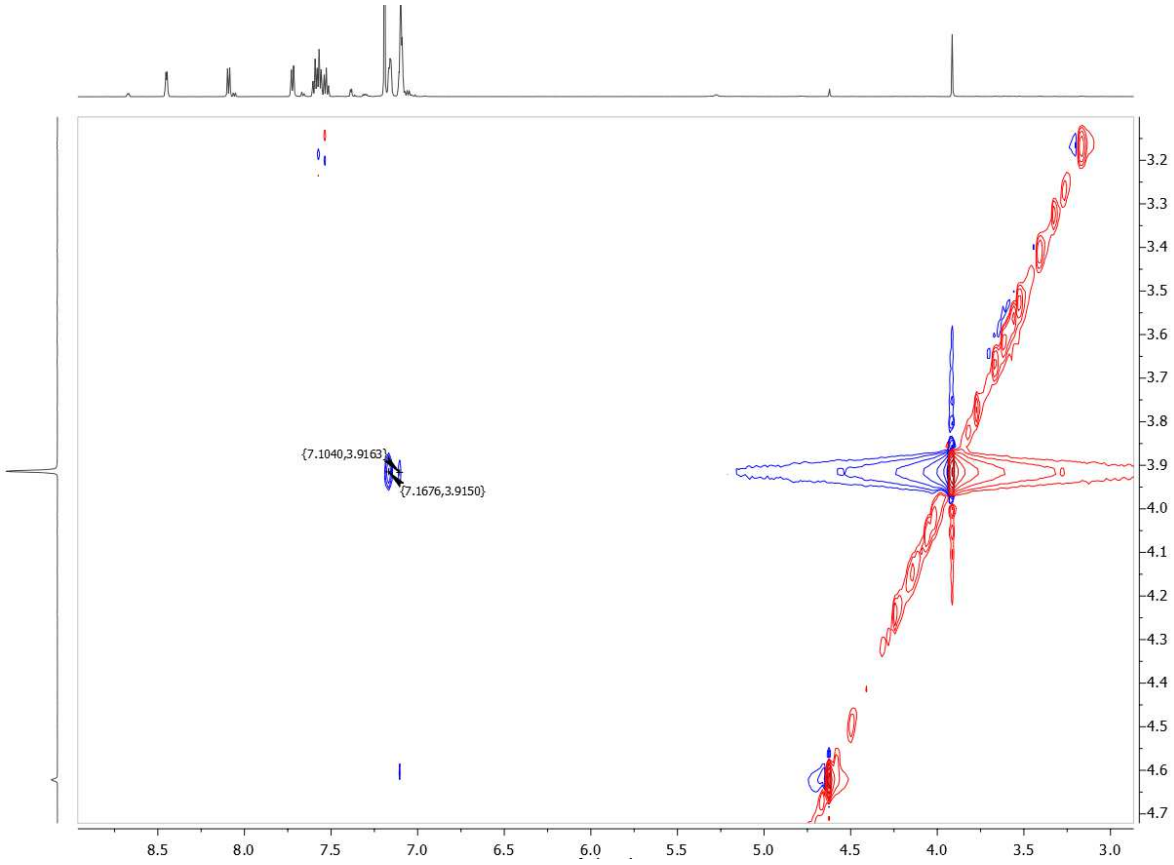


***anti*-48h**

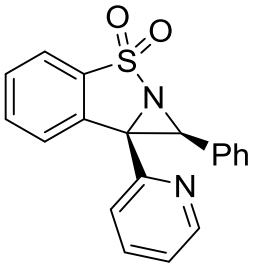
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.53 – 8.50 (m, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.69 – 7.55 (m, 5H), 7.23 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.16 (tt, *J* = 4.8, 2.7 Hz, 5H), 3.98 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 151.5, 149.5, 138.7, 136.7, 133.5, 133.1, 131.9, 130.3, 128.5, 128.2, 127.4, 126.7, 123.8, 123.7, 123.2, 62.9, 61.3.

HMRS (ESI): Calculated for C_{19} H_{15} O_2 N_2 S = $[M+H]^+$: 335.08487 found: 335.08570 Calculated for C_{19} H_{15} O_2 N_2 Na S = $[M+Na]^+$: 357.06682 found: 357.06777



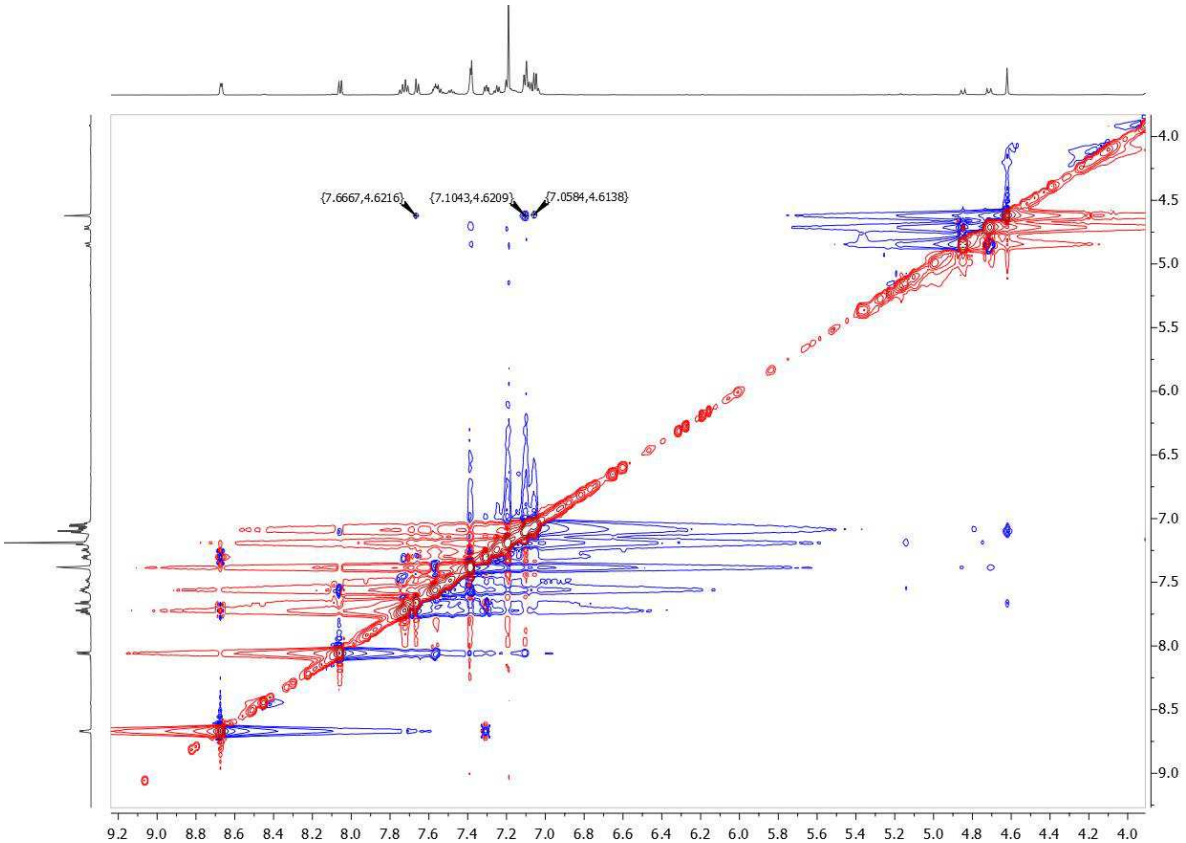
***syn*-48h**



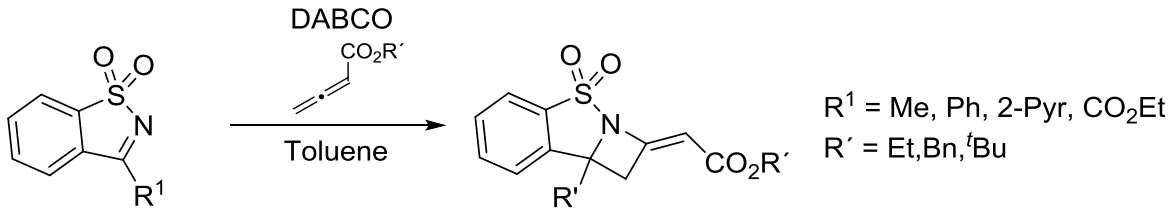
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.74 (dt, *J* = 5.0, 1.3 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.79 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.64 (td, *J* = 4.9, 2.6 Hz, 1H), 7.38 (ddd, *J* = 7.6, 4.9, 1.3 Hz, 1H), 7.20 – 7.07 (m, 5H), 4.70 (s, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 154.8, 149.8, 137.6, 137.1, 135.7, 133.3, 131.1, 130.5, 128.6, 128.1, 127.9, 124.1, 122.6, 122.3, 61.9, 59.4.

HMRS (ESI): Calculated for C_{19} H_{15} O_2 N_2 S = $[M+H]^+$: 335.08487, found: 335.08470



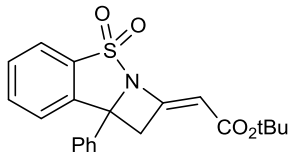
4.2.1.3 Synthesis of Azetidines



General Reaction Scheme

Azetidines **49a and 49b** were synthesized according to the procedure of Ye *et al.*[110] and results were in accordance with the reported yields and spectral data. For azetidines **49c-e**, same conditions with corresponding substrates and allenes were used.

(±)-tert-butyl (*E*)-2-(4,4-dioxido-8b-phenyl-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]- isothiazol-2-ylidene)acetate (49b)



Yield: 742 mg, 52% (3.7 mmol scale)

^{1}H NMR (400 MHz, Chloroform-d) δ 7.80 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 3H), 7.46 – 7.38 (m, 3H), 7.37 – 7.31 (m, 1H), 5.85 (t, *J* = 2.4 Hz, 1H), 4.01 (dd, *J* = 17.0, 2.4 Hz, 1H), 3.73 (dd, *J* = 17.0, 2.4 Hz, 1H), 1.42 (s, 9H).

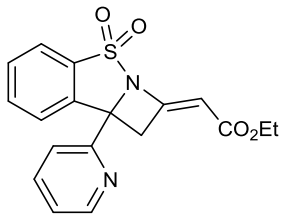
^{13}C NMR (176 MHz, Chloroform-d) δ 165.7, 154.9, 143.3, 139.4, 136.5, 134.3, 130.2, 129.1, 128.8, 125.8, 125.0, 122.4, 106.8, 80.7, 77.1, 43.3, 28.4.

HMRS (ESI): Calculated for C_{21} H_{22} O_4 N S = $[M+H]^+$: = 384.12641, found: 384.12632

Calculated for C_{21} H_{22} O_4 N Na S = $[M+Na]^+$: = 406.10835, found: 406.10802

Calculated for C_{21} H_{22} O_4 N K S = $[M+K]^+$: = 422.08229, found: 422.08188

(±)-Ethyl (*E*)-2-(4,4-dioxido-8b-(pyridin-2-yl)-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]-isothiazol-2-ylidene)acetate (49c)[110]

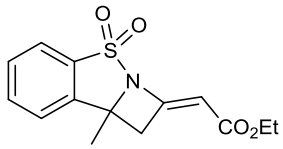


^{1}H NMR (400 MHz, Chloroform-d) δ 8.66 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.87 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.75 – 7.72 (m, 1H), 7.72 – 7.69 (m, 1H), 7.66 (ddd, *J* = 7.8, 4.7, 1.1 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.26 (ddd, *J* = 7.2, 4.9, 1.5 Hz, 1H), 5.96 (t, *J* = 2.3 Hz, 1H), 4.09 (ddd, *J* = 17.7, 8.9, 2.9 Hz, 3H), 3.74 (dd, *J* = 17.4, 2.4 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 166.0, 157.6, 156.1, 149.5, 141.6, 137.4, 136.2, 134.3, 130.3, 125.9, 123.3, 121.8, 120.3, 105.1, 76.0, 60.2, 42.9, 14.3.

HMRS (ESI): Calculated for C_{18} H_{17} O_4 N_2 S = $[M+H]^+$: = 357.09035, found: 357.09011

(±)-ethyl(*E*)-2-(8b-methyl-4,4-dioxido-1,8b-dihydro-2H-azeto[1,2-b]benzo[d]isothiazol-2-ylidene)acetate (**49d**)



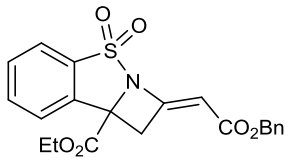
Yield: 28% (0.12 mmol scale, 10 mg)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.9 Hz, 1H), 7.72 – 7.67 (m, 1H), 7.58 (t, *J* = 7.6 Hz, 0H), 7.44 (d, *J* = 7.8 Hz, 1H), 5.87 (t, *J* = 2.3 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.53 (dd, *J* = 17.1, 2.3 Hz, 1H), 3.35 (dd, *J* = 17.1, 2.3 Hz, 1H), 1.90 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 4H).

^{13}C NMR (126 MHz, Chloroform-d) δ 166.4, 156.0, 143.9, 137.2, 134.3, 130.1, 123.8, 122.3, 104.4, 73.6, 60.2, 42.6, 25.7, 14.4

HMRS (ESI): Calculated for C_{14} H_{16} O_4 N S = $[M+H]^+$: = 294.07946, found: 294.07974

(±)-Ethyl (*E*)-2-(2-(benzyloxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-isothiazole-8b-carboxylate 4,4-dioxide (**49e**)



Yield: 90% (0.34 mmol scale, 140 mg)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.80 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.77 – 7.62 (m, 3H), 7.35 – 7.30 (m, 5H), 5.96 (t, *J* = 2.3 Hz, 1H), 5.09 (d, *J* = 2.0 Hz, 2H), 4.36 – 4.23 (m, 2H), 4.02 – 3.95 (m, 1H), 3.50 (dd, *J* = 17.3, 2.3 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 9H).

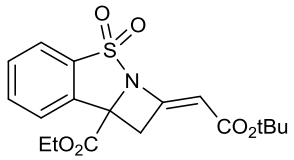
^{13}C NMR (126 MHz, Chloroform-d) δ 167.5, 165.8, 155.5, 137.2, 137.2, 135.8, 134.5, 131.2, 128.7, 128.4, 128.4, 125.3, 122.4, 104.9, 72.4, 66.3, 63.4, 40.9, 14.1.

HMRS (ESI): Calculated for C_{21} H_{20} O_6 N S = $[M+H]^+$: = 414.10058, found: 414.09967

Calculated for C_{21} H_{19} O_6 N Na S = $[M+Na]^+$: = 436.08253, found: 436.08153

Calculated for C_{21} H_{19} O_6 N K S = $[M+K]^+$: = 452.05647, found: 452.05550

(±)-Ethyl (*E*)-2-(2-(tert-butoxy)-2-oxoethylidene)-1,2-dihydro-8bH-azeto[1,2-b]benzo[d]-isothiazole-8b-carboxylate 4,4-dioxide (**49f**)



Yield: 85% (70 µmol scale, 27 mg)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.77 – 7.64 (m, 3H), 5.82 (t, *J* = 2.2 Hz, 1H), 4.37 – 4.23 (m, 2H), 3.96 (dd, *J* = 17.2, 2.2 Hz, 1H), 3.46 (dd, *J* = 17.2, 2.2 Hz, 1H), 1.41 (s, 9H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 167.6, 165.1, 153.6, 137.3, 137.2, 134.3, 131.1, 125.1, 122.3, 107.1, 80.8, 72.4, 63.2, 40.7, 28.2, 14.0.

HMRS (ESI): Calculated for C_{14} H_{13} O_6 N S = $[M-^{t}Bu+H]^+$: = 324.05636, found: 324.05687

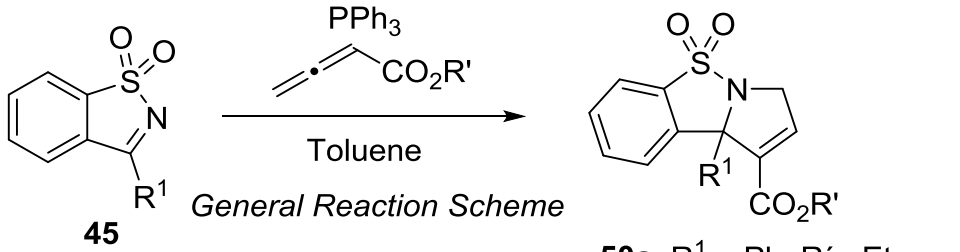
Screening experiments to test asymmetric induction (see 2.3.1.2.1)

The experiments were performed in similar fashion as racemic variations, with the difference that 25% of corresponding catalysts were added to reaction prior to addition of allene. Furthermore, reactions were performed at 0° C.

Reaction with organocatalyst β-ICD: conversion: 89% , major enantiomer: t_R= 38 min; minor enantiomer: t_R= 43 min; ee= 44%; Eluents: 30% DCM:EtOH (100:2 v/v) in Isohexane, flow rate 0.5 ml/min, chiralpak IA)

Reaction with organocatalyst 6-Np-β-ICD: conversion: 32% , major enantiomer: t_R= 38 min; minor enantiomer: t_R= 43 min; ee= 34%; Eluents: 30% DCM:EtOH (100:2 v/v) in Isohexane, flow rate 0.5 ml/min, chiralpak IA)

4.2.1.4 Synthesis of fused Pyrrolines by Phosphine Catalysis

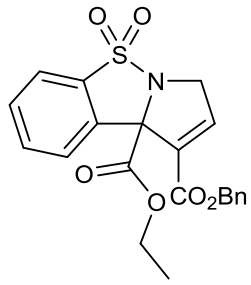


50a; R^1 = Ph, R´= Et

50b; R^1 = CO_2Et. R´= Bn

Pyrroline **50a** was synthesized according to the procedure reported by Chen *et al.*[110]

(±)-1-Benzyl 9b-ethyl benzo[d]pyrrolo[1,2-b]isothiazole-1,9b(3H)-dicarboxylate 5,5-dioxide(50b)



Ketimine substrate **45-CO_2Et** (1.0 eq., 90 mg, 0.38 mmol) and PPh_3 (0.35 eq., 34.5 mg, 0.13 mmol) were combined in dry Toluene (6 ml) in an oven-dried Schlenk tube under an Argon atmosphere. Benzyloxyallene (1.70 eq., 93.5 mg, 0.64 mmol) was added and the reaction was stirred at same temperature and monitored by TLC. After completion of

conversion (5 h), the reaction mixture was concentrated under reduced pressure. Crude reaction mixtures were subjected to silica gel column chromatography (12% to 16% EA/CyH) to give product **50b** in 82% yield (0.31 mmol, 128 mg).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.03 – 7.93 (m, 1H), 7.81 – 7.74 (m, 1H), 7.64 – 7.53 (m, 2H), 7.43 – 7.31 (m, 5H), 7.01 (t, *J* = 2.3 Hz, 1H), 5.29 (d, *J* = 12.2 Hz, 1H), 5.24 (d, *J* = 12.2 Hz, 1H), 4.87 (d, *J* = 18.2 Hz, 1H), 4.38 (d, *J* = 18.2 Hz, 1H), 4.21 (qd, *J* = 7.1, 4.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 167.9, 161.8, 141.7, 136.5, 135.2, 135.1, 133.6, 133.4, 130.6, 128.8, 128.8, 128.5, 127.5, 121.4, 80.9, 67.3, 63.0, 54.8, 13.9.

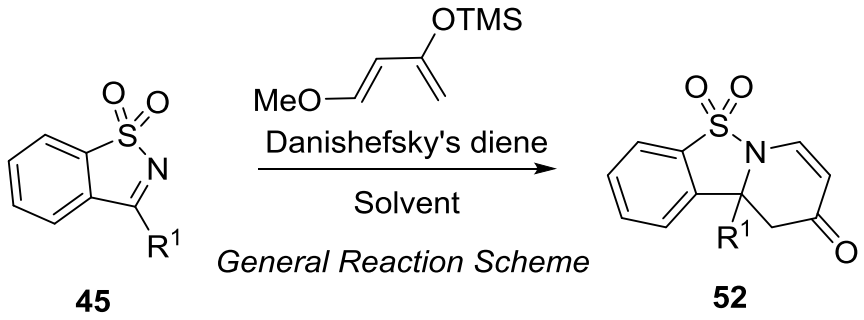
HMRS (ESI): Calculated for $C_{21}H_{20}O_6NS$ = $[M+H]^+$: = 414.10058, found: 414.10013
Calculated for $C_{21}H_{19}O_6NNaS$ = $[M+H]^+$: = 436.08253, found: 436.08184
Calculated for $C_{21}H_{19}O_6NKS$ = $[M+H]^+$: = 452.05593, found: 452.05647

Screening experiments to test asymmetric induction (see 2.3.1.2.2)
The experiments were performed in similar fashion as racemic variations, with the difference that 25% of corresponding catalysts were added to reaction prior to addition of allene. Furthermore, reactions were performed at 0° C and stopped after 150 min. Reaction mixtures were filtered over pads of silica gel, concentrated and analyzed by proton NMR and chiral HPLC. Results were added to table 2.

Eluents of chiral HPLC-analysis: 30% DCM:EtOH (100:2 v/v) in Isohexane, flow rate 0.5 ml/min, chiralpak IC)

Reaction with phospholane 63a (entry 2): yield: 12%, major enantiomer: t_R= 60 min; minor enantiomer: t_R= 64 min; ee= 51%
Reaction with aminophosphine 63b (entry 3): yield: 51%, major enantiomer: t_R= 60 min; minor enantiomer: t_R= 64 min; ee= 25%
Reaction with 63c (entry 6): yield: 81%, major enantiomer: t_R= 60 min; minor enantiomer: t_R= 64 min; ee= 29%
Reaction with 63j (Duanphos) (entry 11): yield: 52%, major enantiomer: t_R= 60 min; minor enantiomer: t_R= 64 min; ee= 9%

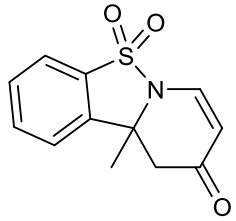
4.1.5 Diels-Alder reaction of Ketimines with Danishefsky's diene



General procedure:

To a solution of Ketimine **45** (1.0 eq) in Toluene or *N,N*-DMF in a 35 ml microwave tube equipped with a magnetic stirring bar, Danishefsky's diene was added, the vessel was flushed with Argon, closed and heated in a microwave at corresponding maximum temperature at 250 W for 45 min. After reaction, 8 ml of saturated aqueous NH_4Cl solution was added and the mixture was extracted with Ethyl acetate (three times 5 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated using a rotary evaporator. The crude material was objected to silica gel flash chromatography.

(±)-10a-methyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (52a)



Conditions:

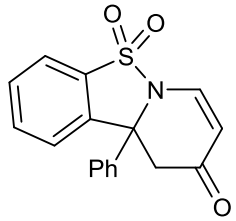
Ketimine **45-Me** (1.0 eq., 200.0 mg, 1.10 mmol) in 5 ml *Toluene* (to give 0.22 M solution)
Danishefsky's diene (1.25 eq., 267 µl, 1.38 mmol)
Conditions: 140 °C (250 W) for 30 min
Silica gel flash chromatography (EA/ CyH 22%-34%) to furnish 19 mg of Sulfonamide (7% yield, 0.08 mmol)

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.76 (t, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 5.58 (d, *J* = 7.9 Hz, 1H), 2.88 (d, *J* = 15.7 Hz, 1H), 2.81 (d, *J* = 15.7 Hz, 1H), 1.71 (s, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 190.7, 141.3, 136.7, 134.6, 133.2, 130.4, 130.3, 122.8, 122.1, 106.9, 64.1, 47.3, 24.3.

HMRS (ESI): Calculated for $C_{12}H_{12}O_3NS = [M+H]^+$: = 250.05324 found: 250.05298

(±)-10a-phenyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (52b)



Conditions:

Ketimine **45-Ph** (1.0 eq., 400 mg, 1.64 mmol) in 3.5 ml Toluene (to give a 0.45 M solution), Danishefsky's diene (1.25 eq., 398 µl, 2.06 mmol),

Conditions: 180 °C (250 W) for 45 min,

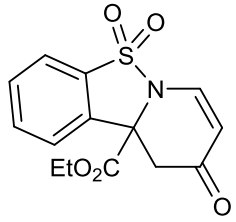
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 315 mg of sulfonamide (62%, 1.01 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.88 (m, 1H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.48 (m, 3H), 7.39 – 7.28 (m, 7H), 5.53 (dd, *J* = 7.8, 1.1 Hz, 2H), 3.66 (dd, *J* = 16.1, 1.1 Hz, 1H), 3.05 (d, *J* = 16.1 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-d) δ 190.4, 140.5, 137.9, 136.8, 134.8, 132.2, 130.4, 129.5, 129.3, 126.3, 124.2, 122.1, 109.9, 69.3, 46.4.

HMRS (ESI): Calculated for $C_{17}H_{14}O_3NS = [M+H]^+$: = 312.06889, found: 312.06872

(±)-10a-ethyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide-carbon dioxide (52c)



Conditions:

Ketimine **45-CO_2Et** (1.0 eq., 248 mg, 1.00 mmol) in 3.4 ml Toluene (0.29 M),

Danishefsky's diene (1.4 eq., 271 µl, 1.40 mmol),

Conditions: 140 °C (250 W) for 45 min,

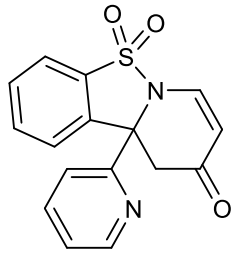
Silica gel flash chromatography (EA/ CyH 20%-34%) to furnish 290 mg of desired sulfonamide (94%, 0.94 mmol)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.74 – 7.62 (m, 3H), 5.58 (d, *J* = 8.0 Hz, 1H), 4.28 – 4.12 (m, 2H), 3.61 (d, *J* = 16.1 Hz, 1H), 2.83 (d, *J* = 16.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 194.8, 169.8, 164.2, 137.1, 135.7, 133.7, 130.8, 124.3, 122.0, 104.9, 65.6, 63.5, 58.0, 14.1.

HMRS (ESI): Calculated for C_{14} H_{14} O_5 N S = $[M+H]^+$: = 308.05872, found: 308.05897

(±)-10a-(pyridin-2-yl)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (52d)



Conditions:

Ketimine **45-2-Pyr** (1.0 eq., 240 mg, 0.98 mmol) in 4 ml Toluene:N,N DMF 7:1 (v/v, as Ketimine is not soluble in neat toluene, to give 0.25 M solution)

Danishefsky's diene (1.5 eq., 285 µl, 1.47 mmol)

Conditions: 140 °C (250 W) for 45 min

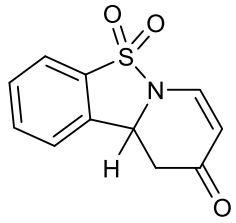
Silica gel flash chromatography (EA/ CyH 20%-32%) to furnish 238 mg of Sulfonamide (78%, 0.76 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.70 – 7.58 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 1H), 5.52 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.23 (dd, *J* = 15.7, 1.1 Hz, 1H), 2.93 (d, *J* = 15.7 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 190.6, 156.6, 150.0, 139.0, 137.7, 136.5, 134.7, 132.1, 130.5, 125.0, 123.6, 121.7, 119.8, 109.7, 69.8, 46.1.

HMRS (ESI): Calculated for C_{17} H_{16} O_3 N_2 S = $[M+H]^+$: = 313.06414 found: 316.06401

(±)-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (52e)



Conditions:

Ketimine **45-H** (1.0 eq., 148 mg, 0.89 mmol) in 3 ml *Toluene* (to give 0.30 M solution)

Danishefsky's diene (1.4 eq., 240 µl, 1.24 mmol)

Conditions: 140 °C (250 W) for 30 min

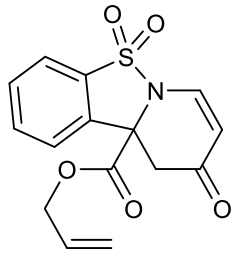
Silica gel flash chromatography (EA/ CyH 18%-26%) to furnish 200 mg of Sulfonamide (96%, 0.85 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.76 (td, *J* = 7.6, 1.1 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 5.58 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.35 (dd, *J* = 15.2, 4.3 Hz, 1H), 3.06 (ddd, *J* = 16.0, 4.3, 1.1 Hz, 1H), 2.72 (dd, *J* = 16.0, 15.2 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 190.8, 138.1, 134.8, 134.4, 134.2, 130.6, 123.7, 122.1, 108.4, 57.3, 41.1.

HMRS (ESI): Calculated for C_{11} H_{10} O_3 N S = $[M+H]^+$: = 236.03759 found: 236.03744

Allyl 9-oxo-9,10-dihydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (52f)



Conditions:

Ketimine **45-CO_2Allyl** (1.0 eq., 60.0 mg, 0.24 mmol) in 2 ml *N,N*-DMF (to give 0.12 M solution)

Danyshevsky's diene (1.25 eq., 58 µl, 0.30 mmol)

Conditions: 140 °C (250 W) for 30 min

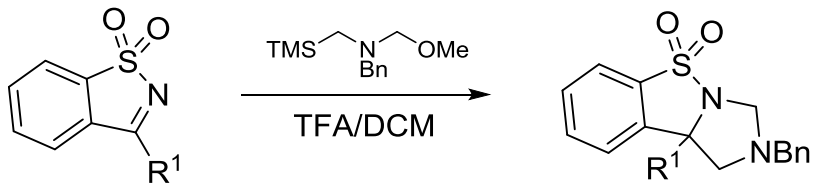
Silica gel flash chromatography (EA/ CyH 20%-35%) to furnish 72 mg (94%, 0.23 mmol,) sulfonamide

^{1}H NMR (500 MHz, Chloroform-d) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.77 (td, *J* = 7.6, 1.2 Hz, 1H), 7.72 – 7.61 (m, 3H), 5.80 – 5.70 (m, 1H), 5.56 (d, *J* = 8.0 Hz, 1H), 5.25 – 5.15 (m, 2H), 4.66 – 4.56 (m, 2H), 3.61 (dd, *J* = 16.2, 1.1 Hz, 1H), 2.83 (d, *J* = 16.2 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 189.1, 167.5, 137.6, 134.8, 133.5, 133.3, 131.5, 130.3, 124.1, 122.2, 119.6, 108.4, 68.3, 67.9, 44.2.

HMRS (ESI): Calculated for $C_{15}H_{14}O_5NS = [M+H]^+$: = 320.05872, found: 320.05849

4.1.6 [3+2] Cycloaddition of Ketimines with Azomethine ylides 66

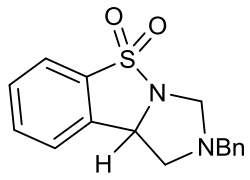


General Reaction Scheme

General procedure for synthesis of fused imidazolidines 67a-e

N-(Methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **66** (82.0 µl, 0.30 mmol) and corresponding imine **45** (0.10 mmol) were combined in CH_2Cl_2 (0.7 mL) in an oven-dried Schlenk tube and a mixture of TFA and CH_2Cl_2 (10% v/v in 36 µl DCM, 0.5 eq.) was added *via* syringe. The resultant mixture was stirred at 0° C (ice-water bath) for 1 h. The crude reaction mixture was purified by flash chromatography on silica gel (EtOAc/Petroleum Ether) to afford corresponding tricyclic sulfonamides.

(±)-2-benzyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (67a)



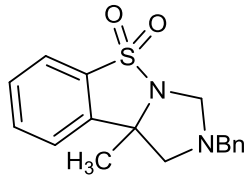
Yield: 37%, 11 mg, 0.04 mmol

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.63 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.33 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.18 (d, *J* = 7.2 Hz, 1H), 5.07 (dd, *J* = 7.0, 2.8 Hz, 1H), 4.74 (d, *J* = 8.6 Hz, 1H), 3.87 (d, *J* = 8.6 Hz, 1H), 3.60 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 13.2 Hz, 1H), 3.22 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.17 (dd, *J* = 10.5, 7.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 139.9, 137.3, 136.2, 133.4, 129.6, 128.5, 128.5, 127.5, 123.8, 121.6, 71.0, 63.2, 58.0, 57.2.

HMRS (ESI): Calculated for $C_{16}H_{17}O_2N_2S = [M+H]^+$: = 301.10053, found: 301.10053

(±)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (67b)



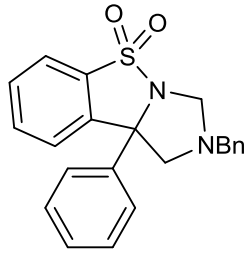
Yield: 73%, 23 mg, 0.07 mmol

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.75 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 (td, *J* = 7.6, 1.0 Hz, 1H), 7.31 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.27 – 7.21 (m, 3H), 7.11 (dd, *J* = 7.9, 1.7 Hz, 2H), 4.75 (dd, *J* = 8.6, 1.1 Hz, 1H), 3.83 (d, *J* = 8.6 Hz, 1H), 3.57 – 3.44 (m, 2H), 3.38 (dd, *J* = 10.0, 1.2 Hz, 1H), 2.78 (d, *J* = 10.0 Hz, 1H), 1.71 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 145.0, 137.3, 136.0, 133.6, 129.3, 128.5, 128.5, 127.5, 122.9, 121.4, 72.1, 71.1. 65.3, 56.7, 27.3.

HMRS (ESI): Calculated for $C_{17}H_{19}O_2N_2S = [M+H]^+$: = 315.11618, found: 315.11605

(±)-2-benzyl-9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (67c)



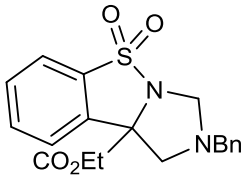
Yield: 83%, 73 mg, 0.19 mmol

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 7.7 Hz 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.45 (d, *J* = 8.5, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.32 – 7.22 (m, 4H), 7.14 (d, *J* = 6.8 Hz, 2H), 4.98 (d, *J* = 9.0 Hz, 1H), 3.92 (d, *J* = 8.9 Hz, 1H), 3.84 (d, *J* = 10.1 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 2H), 3.50 (d, *J* = 13.2 Hz, 2H), 3.30 (d, *J* = 10.2 Hz, 2H).

^{13}C NMR (126 MHz, Chloroform-d) δ 144.0, 142.7, 137.7, 135.4, 133.8, 129.7, 129.0, 128.7, 128.6, 128.2, 127.7, 125.9, 124.3, 121.3, 77.4, 71.6, 66.4, 56.7

HMRS (ESI): Calculated for $C_{22}H_{21}O_2N_2S = [M+H]^+$: = 377.13183, found: 377.13178

(±)-2-benzyl-9b-methyl-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (67d)



Yield: 48%, 18 mg, 0.05 mmol

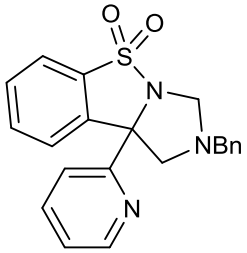
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 – 7.70 (m, 1H), 7.63 – 7.51 (m, 3H), 7.24 – 7.16 (m, 3H), 7.08 – 7.04 (m, 2H), 4.76 (dd, *J* = 9.1, 0.5 Hz, 1H), 4.18 (tq, *J* = 7.1, 3.6 Hz, 2H), 4.01 (d, *J* = 9.1 Hz, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 3.41 (d, *J* = 0.7 Hz, 2H), 3.39 (s, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 169.7, 138.2, 137.1, 135.7, 133.7, 130.6, 128.6, 128.6, 127.7, 124.7, 121.7, 75.2, 72.1, 63.0, 62.7, 57.2, 14.0.

HMRS (ESI): Calculated for $C_{19}H_{21}O_4N_2S$ = $[M+H]^+$: = 373.12165, found: 373.12118

Calculated for $C_{19}H_{20}O_4N_2NaS$ = $[M+H]^+$: = 395.10360, found: 395.10346

(±)-2-benzyl-9b-(pyridin-2-yl)-1,2,3,9b-tetrahydrobenzo[d]imidazo[1,5-b]isothiazole 5,5-dioxide (67e)



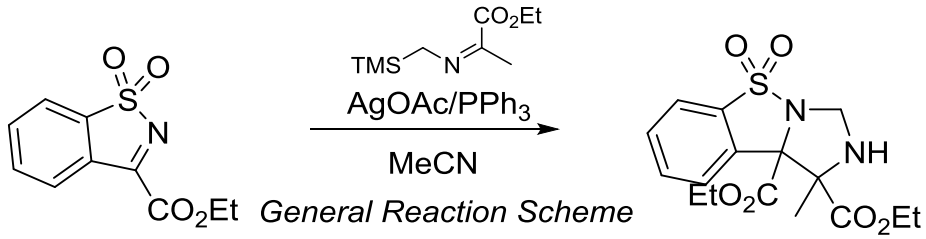
Yield: 67%, 28 mg, 74 µmol

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.57 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.95 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.85 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.72 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.65 (td, *J* = 7.8, 1.8 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.50 (td, *J* = 7.5, 1.1 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.18 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.14 – 7.09 (m, 2H), 4.96 (dd, *J* = 9.0, 1.3 Hz, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.88 (dd, *J* = 11.0, 1.3 Hz, 1H), 3.58 (d, *J* = 13.3 Hz, 1H), 3.46 (d, *J* = 13.3 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 161.0, 149.5, 142.8, 137.5, 137.4, 134.7, 133.6, 129.7, 128.7, 128.5, 127.5, 125.3, 122.8, 121.1, 120.2, 77.4, 72.0, 65.7, 57.1.

HMRS (ESI): Calculated for $C_{21}H_{20}O_2N_3S$ = $[M+H]^+$: = 378.12707, found: 378.12685

4.1.7 Reaction of Pyruvate derived α-silyl imines with Ketimines



General Reaction Scheme

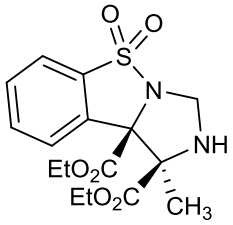
(±)-diethyl-1-methyl-2,3-dihydrobenzo[d]imidazo[1,5-b]isothiazole-1,9b(1H)-dicarboxylate 5,5-dioxide (69)

Condition A *(affording ~ 1:1 d.r.)*

To a solution of ketimine **45-CO_2Et** (19 mg, 80 µmol, 1.0 eq.) in 500 µl dry Et_2O was added silylimine **68** (365.470 µl, 90 mg per ml in diethyl ether solution, 158.83 µmol, 2.0 eq.) followed by the addition of AgOAc (30mol%, 4.0 mg, 23.82 µmol) and PPh_3 (30mol%, 6.3 mg, 23.82 µmol). The reaction was stirred at 21° C and monitored *via* TLC for completion. The reaction mixture was then quenched by the addition of brine and transferred to a separation funnel. EA was added and layers were separated. The aqueous layer was extracted twice more with EA. Combined organic layers were washed with water and brine once more each and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was objected to silica gel column chromatography (25% to 27% to 29% to 32% to 39% EA/CyH, 1 CV each) to elute two products ***syn*-69** and ***anti*-69** in 38% (11 mg, 0.03 mmol) and 31% (9 mg, 0.02 mmol) yield, respectively.

Optimized Condition B *(affording 100:15 d.r.)*

$AgNO_3$ (20mol%, 9.9 mg, 58.5 µmol) and tri(4-trifluoromethylphenyl)phosphine (20mol% 27 mg, 58.5 µmol,) were combined in 1.84 ml dry MeCN at 0 °C. Ketimine **45-CO_2Et** (70 mg, 293 µmol, 1.0 eq.) and silylimine **68** (2.0 eq., 585.16 µl, 585.16 µmol, 1 mM in diethyl ether) were subsequently added. The reaction was stirred at 0° C for 2 h and monitored *via* TLC for completion. HCl (20 µl) was added to the reaction mixture and stirred for 20 more minutes. The reaction mixture was then quenched by the addition of 50 µl 1 M aq. HCl. The mixture was concentrated and redissolved in Chloroform/Ethanol (9:1) and passed through a short pad of silica gel. The crude material was then analyzed by proton NMR to show a diastereomeric ratio of 100:15 in favor of ***syn*-69**. Objection to silica gel column chromatography (using gradient 25% to 27% to 29% to 32% to 39% EA/CyH) then furnished 57 mg (154.7 µmol, 53% combined yield) of fused imidazoline.



***syn*-69**

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.96 (d, J= 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.69 (td, *J* = 7.6 Hz, 1H), 7.64 (td, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 8.5 Hz, 1H), 4.59 (d, *J* = 8.5 Hz, 1H), 4.33 (qd, *J* = 7.2, 3.2 Hz, 2H), 4.18 (tq, *J* = 7.1, 3.6 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.95 (s, 3H).

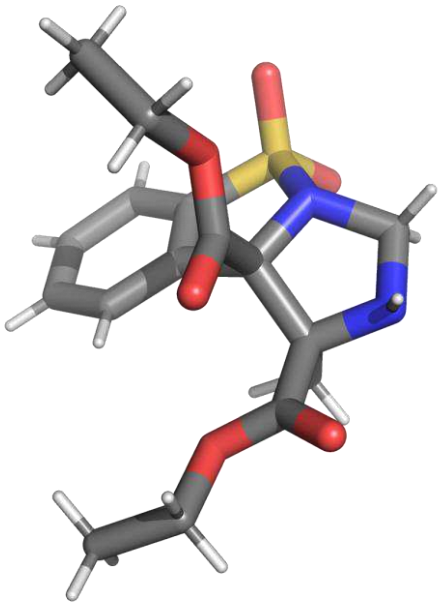
^{13}C NMR (126 MHz, Chloroform-d) δ 171.3, 136.6, 133.3, 133.3, 131.1, 127.4, 121.4, 80.4, 72.0, 63.2, 62.8, 62.7, 20.2, 14.2, 14.0.

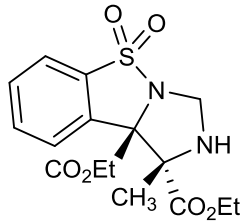
HMRS (ESI): Calculated for $C_{16}H_{21}O_6N_2S$ = $[M+H]^+$: = 369.11148, found: 369.11103

Calculated for $C_{16}H_{20}O_6N_2NaS$ = $[M+H]^+$: = 391.09343, found: 391.09237

Calculated for $C_{16}H_{20}O_6N_2KS$ = $[M+H]^+$: = 407.06737, found: 407.06662

Xray Deposition number at the Cambridge Crystallographic Data Centre: CCDC 1910465





***anti*-69**

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.3 Hz, 1H), 7.63 – 7.56 (m, 2H), 5.14 (d, *J* = 9.8 Hz, 1H), 4.43 (d, *J* = 9.8 Hz, 1H), 4.30 (qd, *J* = 7.2, 1.6 Hz, 2H), 3.83 – 3.74 (m, 1H), 3.72 – 3.63 (m, 1H), 1.63 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 169.4, 168.1, 135.6, 133.2, 132.6, 130.8, 127.4, 120.9, 80.4, 74.7, 65.2, 62.9, 62.1, 20.2, 14.1, 13.5.

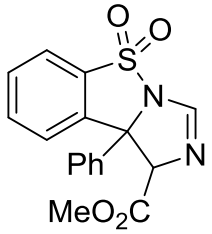
HMRS (ESI): Calculated for $C_{16}H_{21}O_6N_2S$ = $[M+H]^+$: = 369.11148, found: 369.11134

Calculated for $C_{16}H_{20}O_6N_2NaS$ = $[M+H]^+$: = 391.09343, found: 391.09284

Calculated for $C_{16}H_{20}O_6N_2KS$ = $[M+H]^+$: = 407.06737, found: 407.06702

4.2.1.8 Studies on Reaction of Ketimines with methyl isocyanoacetate

Methyl 9b-phenyl-1,9b-dihydrobenzo[d]imidazo[1,5-b]isothiazole-1-carboxylate 5,5-dioxide (71)



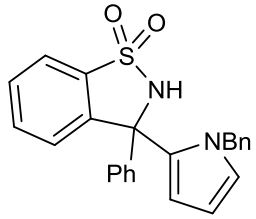
To a stirred solution of 3-phenylbenzo[d]isothiazole 1,1-dioxide **45-Ph** (1.0 eq., 40 mg, 0.16 mmol) and Cu (I) Chloride (0.37 eq., 6.0 mg, 0.06 mmol) in dry DCM (1.6 ml) ,Methyl Isocyanoacetate (**70**, 1.10 eq., 18 mg, 0.18 mmol) was added under an Argon atmosphere at rt. The reaction mixture was stirred at rt for 4 h. After complete conversion of starting material (U-HPLC/ TLC analysis), sat. aq. sodium chloride solution was added (3 ml) and the layers were separated. The aq. layer was extracted 3 more times with DCM (5 ml each).

Combined organic layers were washed with brine (10 ml, once), dried over sodium sulfate and the solvent was evaporated.
Silica gel column chromatography delivered the Imidazoline in 37% yield (21 mg, 61.3 µmol)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (dt, *J* = 7.9, 0.8 Hz, 1H), 7.81 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.75 (ddd, *J* = 7.8, 1.2, 0.6 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.55 – 7.49 (m, 2H), 7.35 – 7.27 (m, 3H), 5.47 (d, *J* = 1.8 Hz, 1H), 3.23 (d, *J* = 0.7 Hz, 3H).
^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.65, 153.93, 143.23, 135.11, 134.75, 134.16, 131.07, 128.88, 128.52, 126.97, 125.45, 122.59, 82.88, 82.82, 52.43.
HMRS (ESI): Calculated for C_{17} H_{15} O_4 N_2 S = $[M+H]^+$: 343.07470, found: 343.07515

4.2.1.9 Addition of N-Benzyl Pyrrol (72) to 45-Ph.

3-(1-benzyl-1H-pyrrol-2-yl)-3-phenyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (73)



15 mol% of BF_3OEt (4.870 µl, 39.46 µmol) were added to a mixture of 3-phenyl 1,2 benzothiazol 1,1 dioxide (**45-Ph**, 1.0 eq., 64 mg, 0.26 mmol) and *N*-benzylpyrrole (1.0 eq., 41.4 mg, 0.26 mmol) at 0° C. The reaction was allowed to come to ambient temperature and stirred overnight. Then, it was quenched by addition of saturated aqueous sodium bicarbonate solution. The mixture was transferred to a separatory funnel and layers were saturated. Aqueous layer was extracted twice with 10 ml ethyl acetate each and combined organic layers were washed with brine (15 ml) and dried over anhydrous sodium sulfate. Concentration and silica gel column chromatography (15 to 25% EA/CyH) furnished 11 mg product of product **73** (10%, 27.47 µmol).

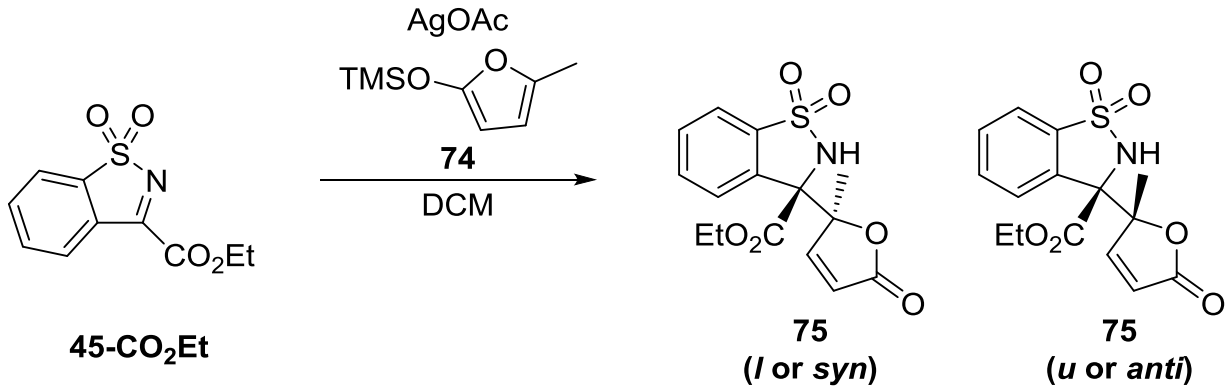
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.80 – 7.72 (m, 1H), 7.60 – 7.41 (m, 5H), 7.40 – 7.27 (m, 5H), 6.84 (d, *J* = 6.7 Hz, 2H), 6.73 (dd, *J* = 2.7, 1.9 Hz, 1H), 6.12 (dd, *J* = 3.7, 2.9

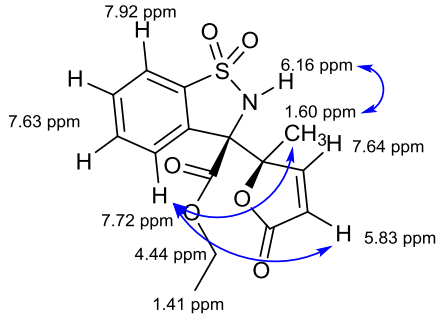
Hz, 1H), 5.86 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.81 (d, *J* = 16.2 Hz, 1H), 4.75 – 4.70 (m, 1H), 4.66 (t, *J* = 14.0 Hz, 1H).

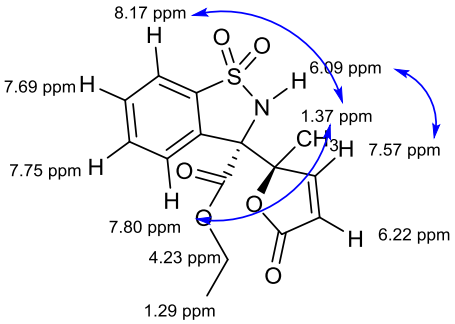
^{13}C NMR (176 MHz, Chloroform-*d*) δ 142.5, 142.5, 137.5, 134.1, 133.1, 132.3, 129.8, 129.3, 129.2, 128.5, 128.3, 127.1, 126.7, 126.3, 125.9, 121.5, 112.7, 107.3, 68.2, 51.5, 29.9.

HMRS (ESI): Calculated for $C_{24}H_{22}O_2N_2S$ = $[M+H]^+$: = 401.13183, found: 401.13061

4.2.2 Vinylogous Addition of Silyl Enol Ether 74 to Ketimines







The proposed structures were based on evaluation of 1D –NOE NMR experiments(see below).

To 239 mg (1.0 eq, 1.00 mmol) of 3-carbethoxy 1,2 benzothiazole 1,1 dioxide (**45-CO_2Et**) and AgOAc in dry DCM (3.7 ml) under an Argon atmosphere in an oven-dried Schlenk flask, Silyl Enol Ether **74** (1.6 eq, 312 µl, 1.60 mmol) was added at -78°C (Acetone-dry ice bath). The reaction was stirred at same temperature and monitored by TLC. After completion of reaction (10 min), sat. aqueous $NaHCO_3$ solution was added and stirred for 5 min at 0 °C, then transferred to a separation funnel and 8 ml of Ethyl acetate were added. Layers were separated and the aqueous layer was extracted two more times (8 ml Ethyl Acetate each). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified using silica gel flash column

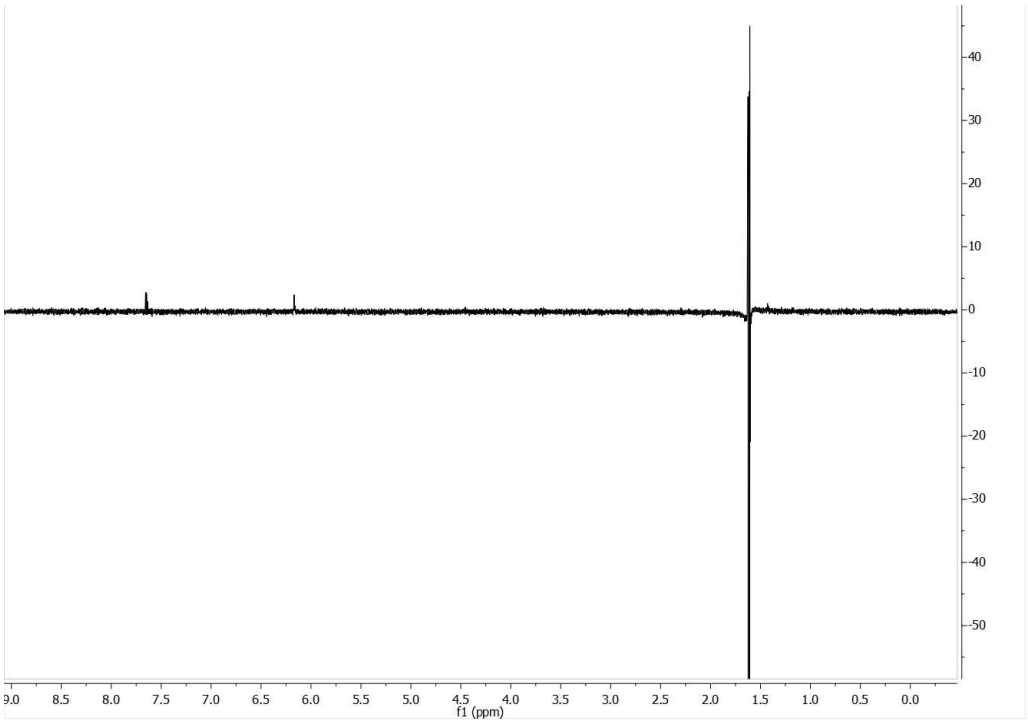
chromatography (22% EA/CyH to 35% EA/CyH) to yield product in 89% yield (300 mg, 0.89 mmol) and 86:14 d.r. .

(±)Ethyl-3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (*l* or *syn* 75)

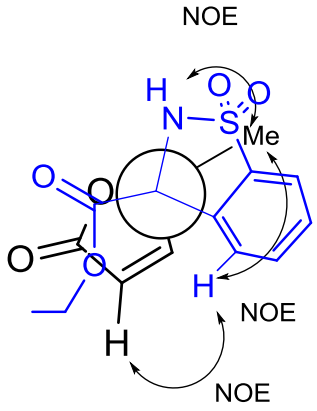
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.91 (m, 1H), 7.74 – 7.71 (m, 1H), 7.67 – 7.61 (m, 3H), 6.15 (s, 1H), 5.84 (d, *J* = 5.7 Hz, 1H), 4.52 – 4.39 (m, 2H), 1.61 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, Chloroform-d) δ 171.8, 167.9, 157.6, 135.8, 133.9, 132.2, 131.6, 127.5, 123.1, 121.7, 89.6, 71.6, 64.9, 20.8, 14.2; **HMRS (ESI)**: Calculated for $C_{15}H_{16}O_6$ N S = $[M+H]^+$: = 338.06928, found: 338.06994

Calculated for C_{15} H_{15} O_6 N Na S = $[M+H]^+$: = 360.05123, found: 360.05266

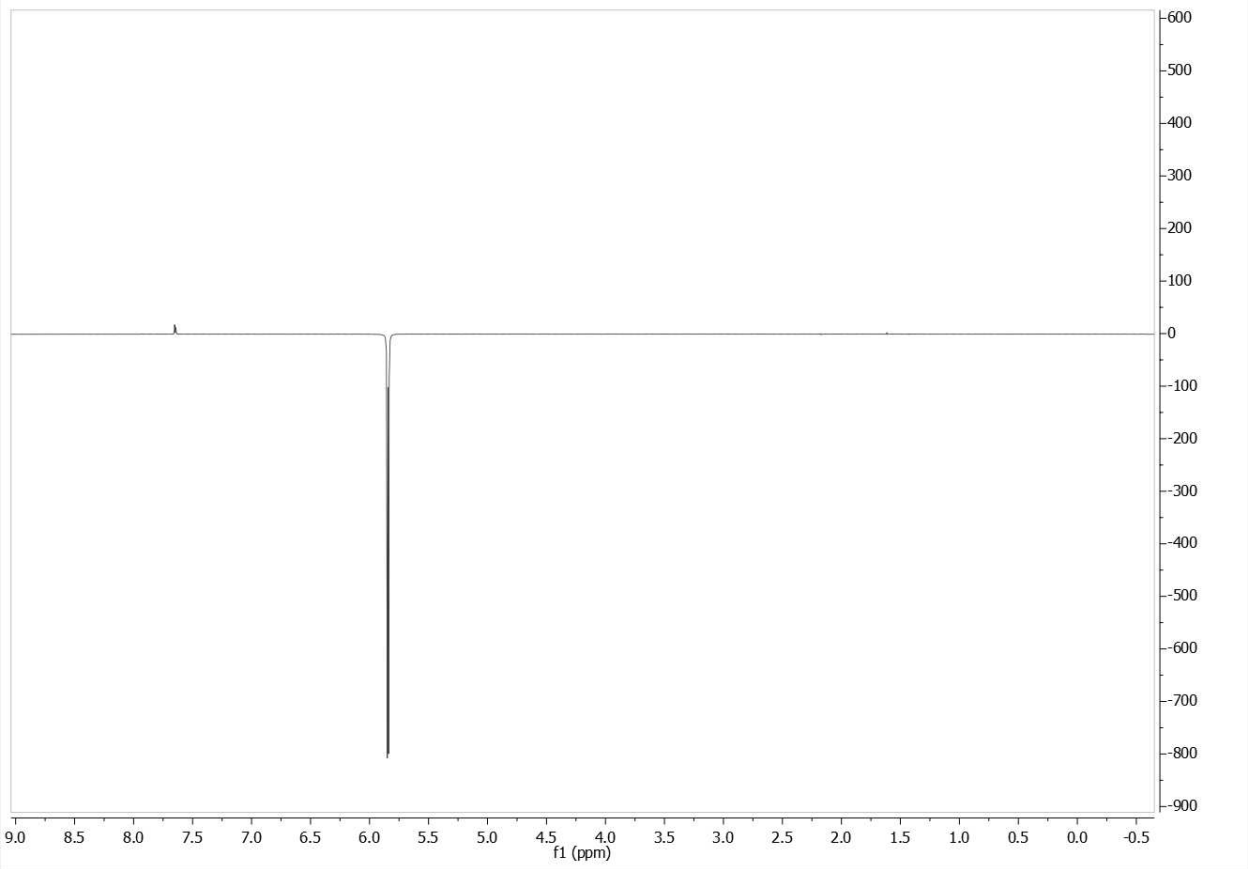
***l*-75 1D NOE-experiments**



Irradiation of methyl group (1.6 ppm) shows NOE with sulfonamide amine N-H (6.15 ppm) and aromatic proton at ~7.6 ppm.



***syn*-75 or *I*-75**



Irradiation of lactone proton in α carbonyl position (5.8 ppm) shows NOE to aromatic proton at roughly 7.6 ppm. Both observations lead us to conclude that we this is in fact diastereomer in conformation depicted in structure below.

(±)-Ethyl-3-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (*anti or I*-75)

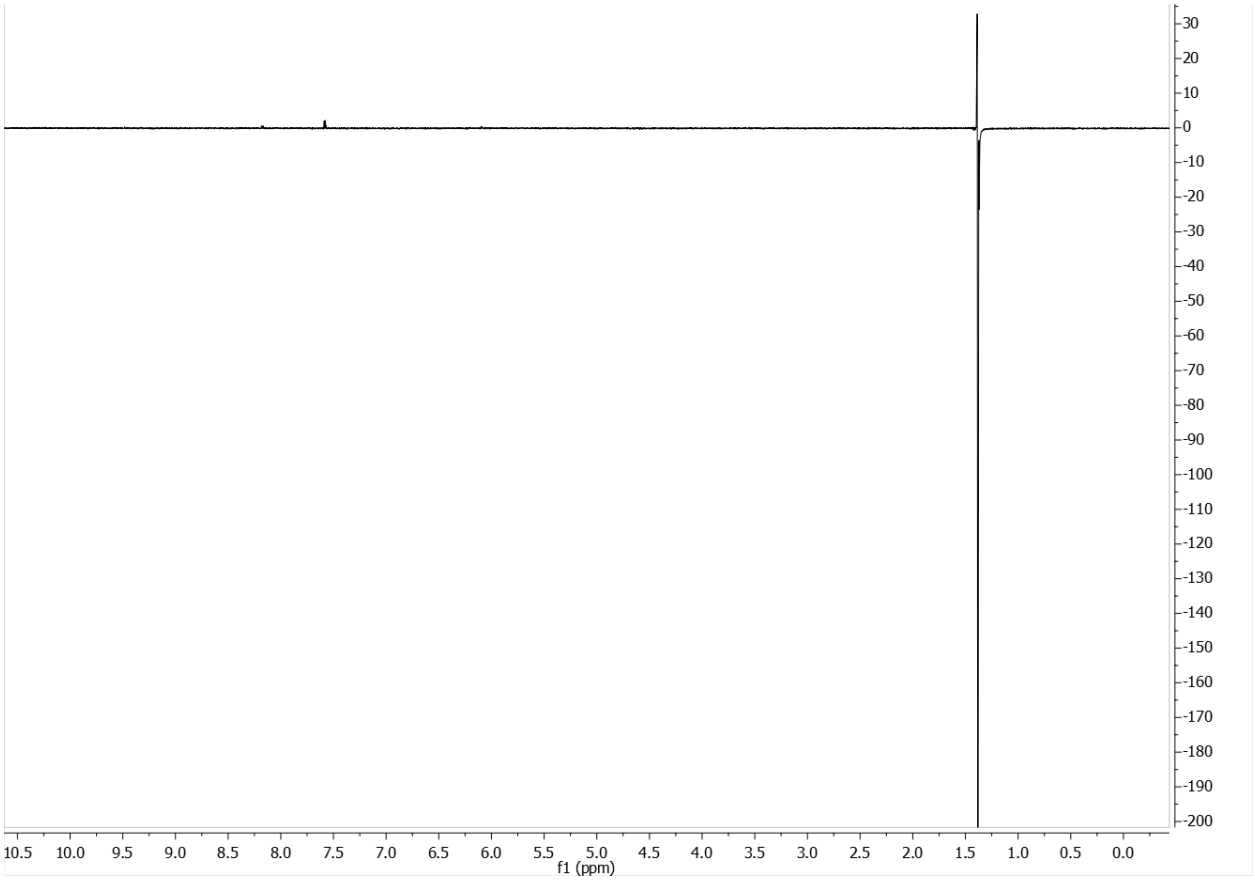
^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.75 (td, *J* = 7.6, 1.3 Hz, 1H), 7.69 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 (d, *J* = 5.7 Hz, 1H), 6.20 (d, *J* = 5.6 Hz, 1H), 6.09 (s, 1H), 4.29 – 4.16 (m, 2H), 1.37 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 171.1, 167.7, 157.7, 136.3, 133.9, 132.4, 131.6, 128.7, 123.3, 121.6, 90.4, 72.0, 60.5, 19.6, 13.9.

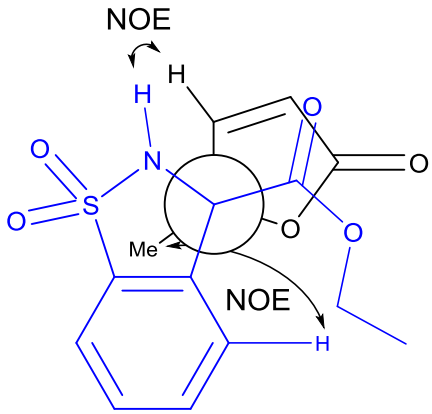
HMRS (ESI): Calculated for $C_{15}H_{16}O_6NS$ = $[M+H]^+$: = 338.06928, found: 338.06966

Calculated for $C_{15}H_{15}O_6NNaS$ = $[M+H]^+$: = 360.05123, found: 360.05123

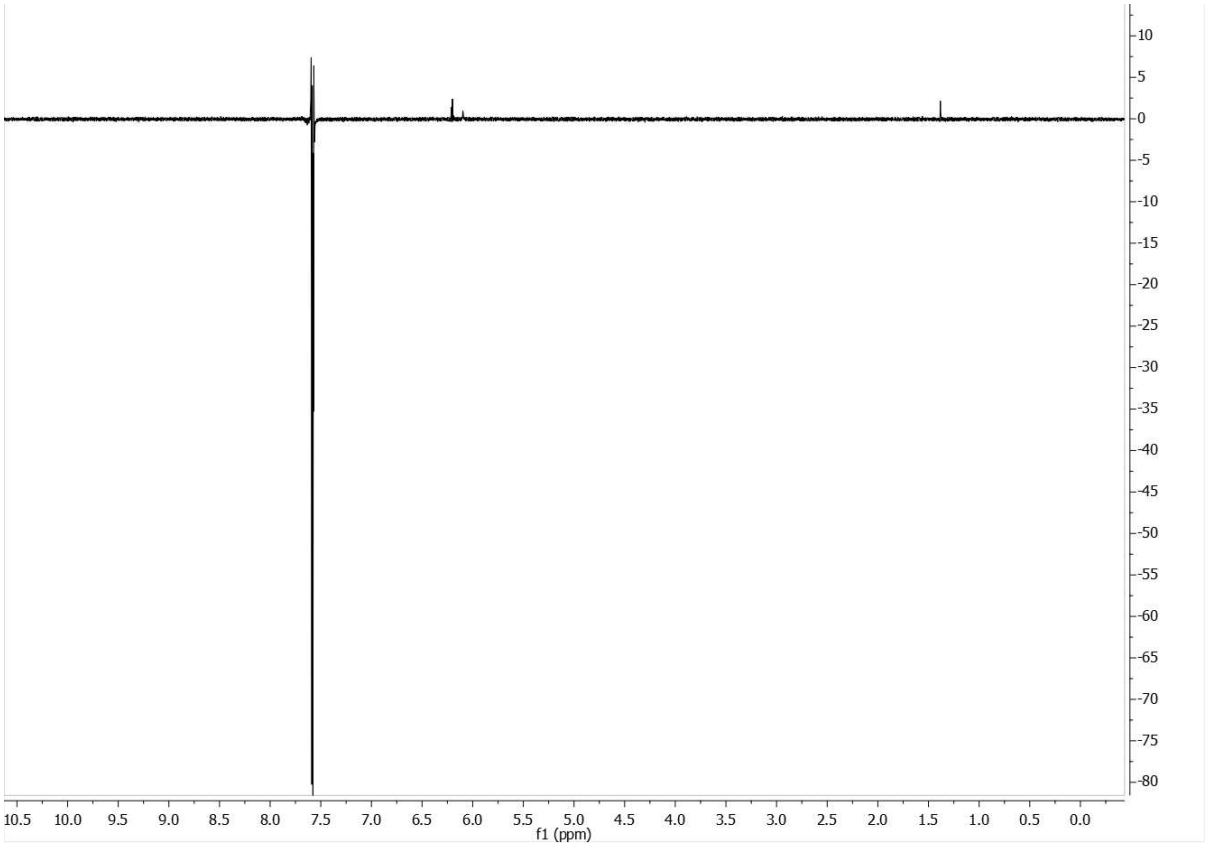
***anti-* or *l*-75a 1D NOE-experiments**

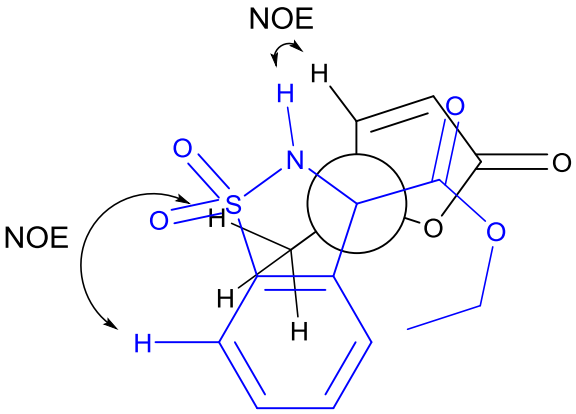


Aromatic proton shows weak NOE of methyl group (1.4 ppm) with aromatic proton at 7.8 ppm, hinting towards conformation depicted below.

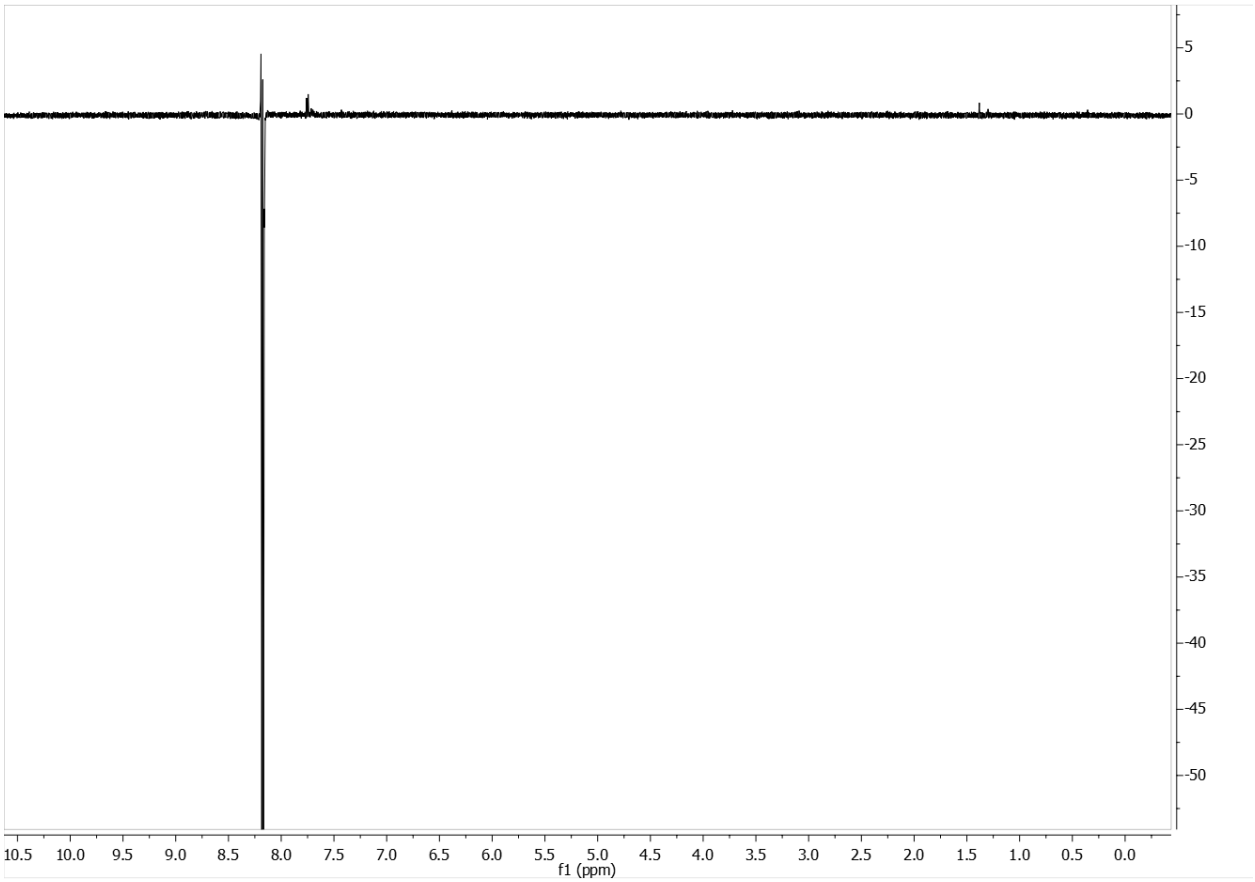


***anti*-75 or *u*-75**

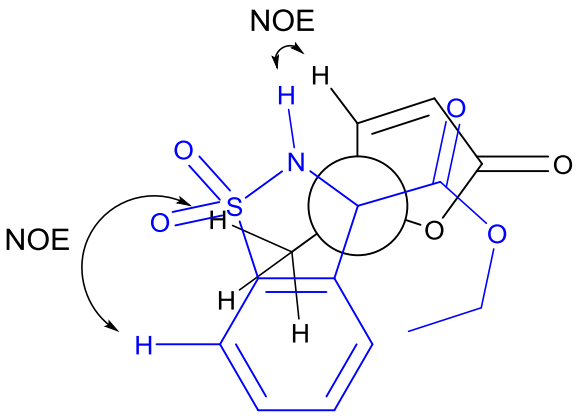




***anti*-75 or *u*-75**



Irradiation of 7' (8.15 ppm) shows NOE with not only neighbouring aromatic proton (~7.6 ppm) but also weak effect with methyl group (1.37 ppm).



***anti*-75 or *u*-75**

4.2.2.1 Screening conditions for improvement of diastereomeric ratio of 75

Screening conditions to improve d.r. of vinylogous addition to ketimines (see also table 4).

Diastereomeric ratios were determined by 1H-NMR measurements of crude reaction mixtures.

Condition #	Catalyst	Solvent	d.r. (*syn*:*anti*)
1	**$Ti(O^iPr)_4$**	**DCM**	**1:2**
2	**$Zn(OTf)_2$**	**DCM**	**n.d. Complex mixture**
3	**$Cu(OTf)_2$**	**DCM**	**3:1**
4	**$Dy(OTf)_3$**	**DCM**	**n.d. – Complex mixture**
5	**AgOAc**	**Et_2O**	**2:1 (f2:f1)**
6	**AgOAc**	**THF**	**10:13**
7	**AgOAc**	**DCM +TMEDA**	**10:6.8**
8	**AgOAc**	**DCM**	**93:7**

Screening experiments to test asymmetric induction (see 2.3.2.1, table 6)

The experiments were performed in similar fashion as racemic variations, with the difference that 20mol% of corresponding ligands were added to reaction after addition of metal but prior to addition of silyl enol ether. Reactions were stopped after 5 min, objected to aqueous workup like racemic version (see above). Concentration delivered crude reaction mixtures which were analyzed by chiral HPLC analysis and are corroborated in table 6.

Eluents: 30% ^{i}PrOH in Isohexane, flow rate 0.5 ml/min, chiralpak IA

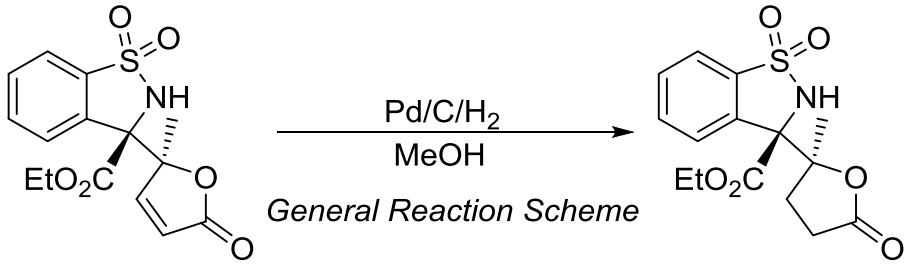
Reaction with ligand 1: stereoisomer *anti*$_1$: t_R= 14.0 min; *syn*$_1$: t_R= 15.1 min; *syn*$_2$: t_R= 18.5 min; *anti*$_2$: t_R= 20.9 min; ee= 34% for *syn*-diasteromer; 26% for *anti*-diastereomer

Reaction with ligand 2: stereoisomer *anti*$_1$: t_R= 14.0 min; *syn*$_1$: t_R= 15.1 min; *syn*$_2$: t_R= 18.5 min; *anti*$_2$: t_R= 20.9 min; ee= 6% for *syn*-diasteromer; 6% for *anti*-diastereomer

Reaction with ligand 3: stereoisomer *anti*$_1$: t_R= 14.0 min; *syn*$_1$: t_R= 15.1 min; *syn*$_2$: t_R= 18.5 min; *anti*$_2$: t_R= 20.9 min; ee= 56% for *syn*-diasteromer; 64% for *anti*-diastereomer

Reaction with ligand 4: stereoisomer *anti*$_1$: t_R= 14.0 min; *syn*$_1$: t_R= 15.1 min; *syn*$_2$: t_R= 18.5 min; *anti*$_2$: t_R= 20.9 min; ee= 12% for *anti*-diastereomer

(±)-3-ethyl-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)-5-methyldihydrofuran-2(3H)-one-carbon dioxide (*syn or l*-77)



Sulfonamide ***syn*-75** (62 mg, 183.8 µmol) and Pd on Carbon (10 wt.%, 22.5 mg, 21.14 µmol) were dissolved in EtOH (1.4 ml) in a 10 ml Schlenk tube and stirred at ambient temperature (21 °C). The vessel was evacuated and refilled with hydrogen. This was repeated two times. The mixture was allowed to come to ambient temperature and stirred under an hydrogen atmosphere for 3 h. Then, reaction mixture was filtered over celite, concentrated and objected to silica gel column chromatography (25% to 35% EA/CyH) to yield 39 mg (0.11 mmol, 63%) of product sulfonamide and recover 28 mg (0.07 mmol, 37%) of starting material.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.02 – 7.99 (m, 1H), 7.81 – 7.78 (m, 1H), 7.69 – 7.65 (m, 2H), 6.05 (s, 1H), 4.44 – 4.32 (m, 2H), 2.51 – 2.45 (m, 1H), 2.16 – 2.11 (m, 1H), 2.07 – 1.98 (m, 2H), 1.52 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 175.9, 168.4, 136.4, 133.7, 132.4, 131.4, 128.3, 121.7, 87.4, 72.7, 64.4, 29.8, 28.0, 23.8, 14.0.

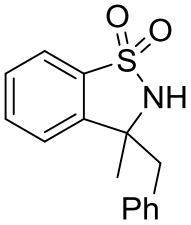
HMRS (ESI): Calculated for $C_{15}H_{18}O_6NS$ = $[M+H]^+$: = 340.08493, found: 340.08524

Calculated for $C_{15}H_{17}O_6NNaS$ = $[M+H]^+$: = 362.06688, found: 362.06717

4.2.3 Folding Pathway

4.2.3.1 Hydrogenolysis of Aziridines

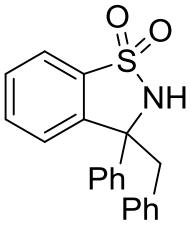
(±)-4-methyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (91a)



Sulfonamide **48a** (1.0 eq., 20 mg, 73.71 µmol) and Palladium on carbon (10 wt.%, 0.1 eq., 7.8 mg, 0.01 mmol) were dissolved in 750 µl of a 3:1 (v/v) Ethanol/Ethyl Acetate Mixture in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 16 h. Then it was filtered using a syringe filter and concentrated under reduced pressure to give 22 mg (0.08 mmol, 69%) of sulfonamide **91a**.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.65 (td, *J* = 7.6, 1.1 Hz, 1H), 7.54 (td, *J* = 7.6, 1.0 Hz, 1H), 7.36 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.23 – 7.18 (m, 2H), 4.69 (s, 1H), 3.18 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 1.57 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 144.9, 135.5, 135.3, 133.3, 130.9, 129.5, 128.6, 127.5, 123.5, 121.6, 63.6, 47.8, 26.7.
HMRS (ESI): Calculated for C_{15} H_{15} O_2 N S = $[M+H]^+$: C_{15} H_{16} O_2 N S = 274.08963, found: 274.08965

(±)-3-benzyl-3-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (91b)



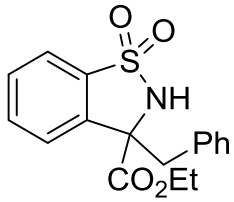
Sulfonamide **48c** (1.0 eq., 20 mg, 0.06 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 6.4 mg, 0.01 mmol) were dissolved in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for 4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 6 mg (0.02 mmol, 30% yield) of product **91b**.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 3H), 7.63 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, *J* = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.59 (d, *J* = 14.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.2, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6

HMRS (ESI): Calculated for C_{20} H_{18} O_2 N S = $[M+H]^+$: C_{15} H_{16} O_2 N S = 336.10528, found: 336.10549

(±)-Ethyl 3-benzyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (91c)



Ethyl 1-phenylazirino[1,2-b]benzo[d]isothiazole-7b(1H)-carboxylate 3,3-dioxide **48f** (1.0 eq., 23 mg, 69.83 µmol) was combined with Palladium on Carbon(10 wt.%, 0.1 eq., 7.4 mg, 0.01 mmol) in a 10 ml Schlenk tube and dissolved in 700 µl of a Ethanol/Ethyl acetate mixture (5:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen

atmosphere. The reaction was monitored via TLC. After completion of conversion, reaction mixture was filtered using a syringe filter and concentrated to give 12 mg sulfonamide product **91c** (0.04 mmol, 66%).

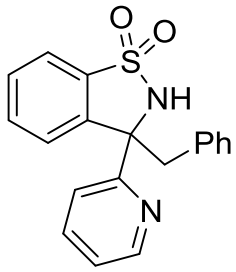
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.74 – 7.66 (m, 3H), 7.63 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.52 (ddd, *J* = 8.5, 7.7, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.15 (m, 3H), 6.94 (dt, *J* = 6.6, 1.6 Hz, 2H), 4.88 (s, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.59 (d, *J* = 14.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 143.6, 141.8, 134.7, 134.5, 133.3, 130.6, 129.6, 129.1, 128.8, 128.4, 127.8, 126.4, 125.0, 121.7, 68.8, 46.6,

HMRS (ESI): Calculated for C_{17} H_{18} O_4 N S = $[M+H]^+$: = 332.09511, found: 332.09535

Calculated for C_{17} H_{17} O_4 N Na S = $[M+H]^+$: = 354.07705, found: 354.07723

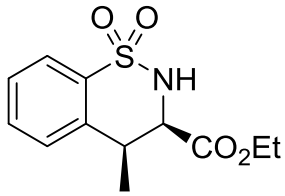
(±)-3-benzyl-3-(pyridin-2-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide(91d)



1-phenyl-7b-(pyridin-2-yl)-1,7b-dihydroazirino[1,2-b]benzo[d]isothiazole 3,3-dioxide **48h** (1.0 eq., 10 mg, 29.90 µmoll) was combined with Pd/C (10 wt.%; 0.15 eq., 4.7 mg, 4.49 µmol) and dissolved in 500 µl Ethanol/Ethyl Acetate (2:1) in a 10 ml round bottom flask equipped with a magnetic stirring bar and a septum. The mixture was carefully evacuated and refilled with hydrogen (using a hydrogen-filled balloon). This procedure was repeated twice and the reaction was stirred under an hydrogen atmosphere at 21 °C and monitored by TLC. After 15 h, the reaction mixture was filtered. Concentration delivered crude reaction mixture. Silica gel column chromatography yielded 5 mg (0.01 mmol, 50%) of product sulfonamide **91d**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.97 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.73 (d, *J* = 7.76 Hz), 7.70 –7.61 (m, 2H), 7.53 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.22 (ddd, *J* = 7.3, 4.8, 1.2 Hz, 1H), 7.20 – 7.13 (m, 3H), 6.99 – 6.94 (m, 2H), 5.83 (s, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 3.44 (d, *J* = 13.8 Hz, 1H).
^{13}C NMR (126 MHz, Chloroform-d) δ 158.9, 148.9, 142.5, 137.5, 135.2, 134.5, 133.4, 130.5, 129.8, 128.7, 127.6, 125.5, 123.1, 121.4, 121.0, 69.5, 46.9.
HMRS (ESI): Calculated for C_{19} H_{17} O_2 N2 S = $[M+H]^+$: = 337.10053, found: 337.10054

(±)- 4-methyl-3-carbethoxy-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (92a)



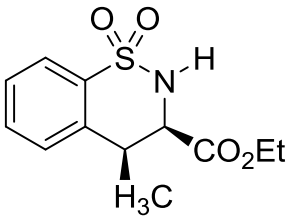
Sulfonamide **48b** (1.0 eq., 40 mg, 0.15 mmol) and Palladium on carbon (10 wt.%, 0.1 eq., 8.0 mg, 0.05 mmol) were dissolved in 1 ml Ethanol in a 10 ml tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reaction was left stirring at 21 °C under an hydrogen atmosphere for

4 h. Then, it was filtered using a syringe filter and concentrated under reduced pressure to give 24 mg (0.09 mmol, 60% yield) product.

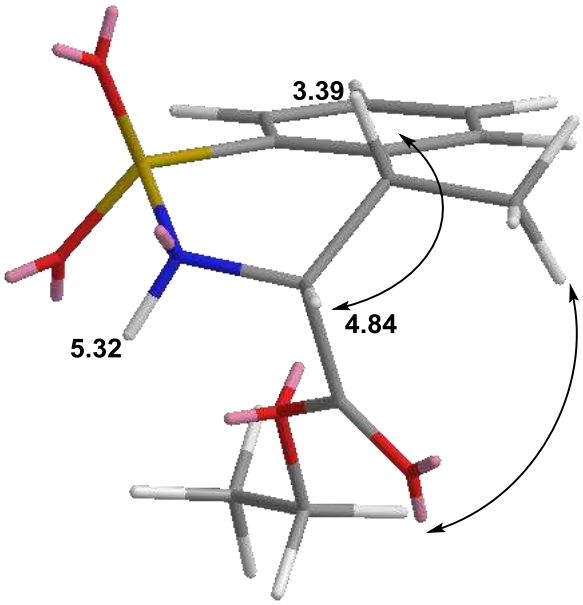
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.81 (dq, *J* = 7.9, 1.4 Hz, 1H), 7.50 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.41 (tq, *J* = 7.6, 1.2 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.36 – 5.27 (m, 1H), 4.84 (ddd, *J* = 10.4, 3.7, 1.0 Hz, 1H), 4.32 (qt, *J* = 7.2, 1.2 Hz, 2H), 3.39 (qd, *J* = 7.2, 3.7 Hz, 1H), 1.35 (td, *J* = 7.2, 1.2 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 168.3, 139.2, 136.4, 132.6, 129.4, 128.2, 124.1, 62.4, 57.8, 34.7, 17.5, 14.2.

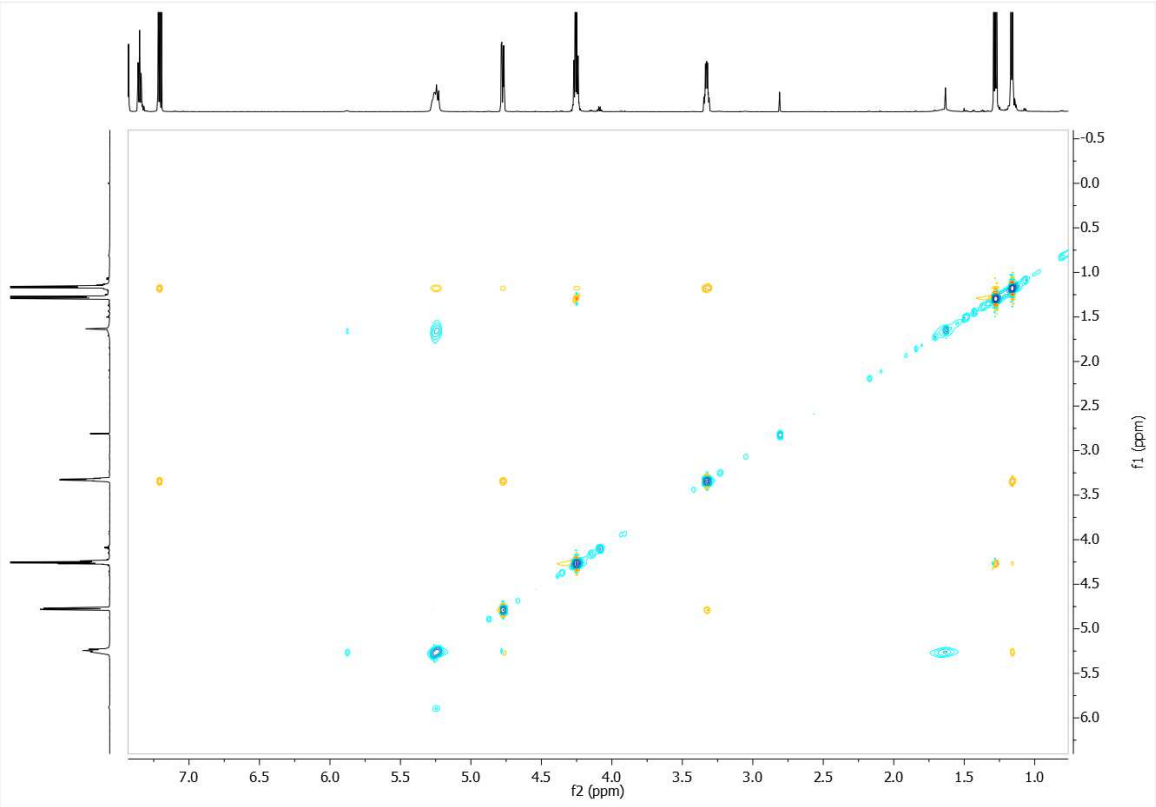
HMRS (ESI): Calculated for C_{12} H_{16} O_4 N S $[M+H]^+$: = 270.07946, found: 270.07923



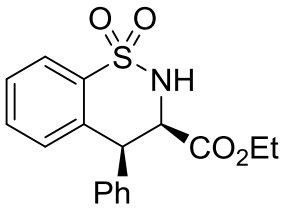
92a



NOESY



(±)-*syn*- 4-Phenyl-3-carbethoxy-3,4-dihydro-2H-benzo[e][1,2]thiazine 1,1-dioxide (92b)



Sulfonamide **48d** (1.0 eq., 17 mg, 51.61 µmol) was combined with Pd/C (10 wt.%, 4.4 mg, 4.13 µmol) in a 10 ml Schlenk tube and dissolved in 500 µl of a Ethanol/Ethyl acetate mixture (2:1 v/v). The reaction vessel was carefully evacuated under stirring and refilled with hydrogen. This was repeated twice and the reaction was allowed to stir at 21 °C under an hydrogen atmosphere. After completion of conversion, the reaction mixture was filtered using a syringe filter and concentrated to give 16 mg (0.05 mmol, quantitative) of desired product.

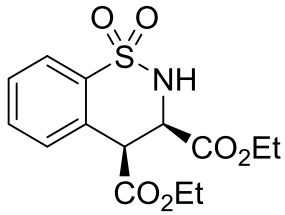
^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.95 – 7.90 (m, 1H), 7.49 – 7.41 (m, 2H), 7.31 – 7.22 (m, 3H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.96 (dd, *J* = 7.3, 2.2 Hz, 2H), 5.11 (d, *J* = 11.7 Hz, 1H),

5.04 (dd, *J* = 11.7, 3.8 Hz [syn], 1H), 4.58 (d, *J* = 3.8 Hz [syn], 1H), 4.15 – 4.03 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 167.1, 137.4, 137.2, 136.7, 132.9, 130.9, 129.2, 129.0, 128.9, 128.4, 124.3, 62.3, 58.8, 46.0, 14.1.

HMRS (ESI): Calculated for C_{17} H_{18} O_4 N S = $[M+H]^+$: = 332.09511, found: 332.09556

(±)-*syn*- Diethyl 3,4-dihydro-2H-benzo[e][1,2]thiazine-3,4-dicarboxylate 1,1-dioxide (92c)



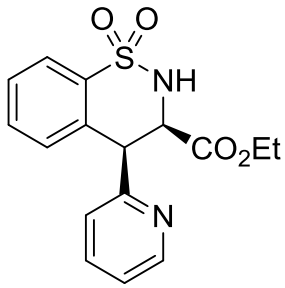
Sulfonamide **48e** (1.0 eq., 20 mg, 61.47 µmol) and Palladium on carbon (10 wt.%, 0.1 eq., 6.5 mg, 0.01 mmol) were dissolved in 650 µl of a 3:1 Ethanol/Ethyl Acetate (v/v) mixture in a 10 ml Schlenk tube equipped with a stirring bar. The vessel was evacuated and refilled with hydrogen using a balloon. This was repeated twice and the reeaction was left stirring at 21 °C under an hydrogen atmosphere. After completion of conversion, filtration using a syringe filter and concentration delivered desired 8 mg (0.02 mmol, 40% yield) of desired sulfonamide as one diastereomer.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.87 (m, 1H), 7.60 – 7.48 (m, 3H), 5.84 (d, *J* = 12.4 Hz, 1H), 4.85 (dd, *J* = 12.4, 3.9 Hz [syn], 1H), 4.31 (qd, *J* = 7.1, 1.1 Hz, 2H), 4.27 (d, *J* = 3.9 Hz [syn], 1H), 4.17 (qd, *J* = 7.1, 3.3 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 170.8, 168.1, 137.3, 132.8, 130.8, 130.7, 129.9, 125.1, 63.0, 62.8, 56.5, 44.8, 14.4, 14.3.

HMRS (ESI): Calculated for C_{14} H_{18} O_6 N S = $[M+H]^+$: = 328.08493, found: 328.08529

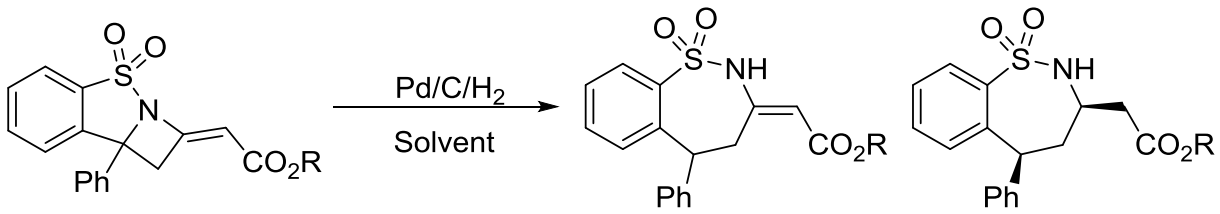
(±)-Ethyl (*syn*)-C4-(pyridin-2-yl)phenylalaninate 1,1-dioxide (92d)



Palladium on carbon (0.1 eq., 6.4 mg, 6.05 µmol) and Sulfonamide **48g** (1.0 eq., 20 mg, 60.54 µmol) were combined in 600 µl Ethanol/Ethyl Acetate (3:1 v/v) in a 10 ml Schlenk tube equipped with a magnetic stirring bar. The vessel was evacuated and refilled with hydrogen. This procedure was repeated 2 times. The mixture was kept stirring for 4 h. Then, it was filtered using a syringe filter and concentrated to give product 6 mg sulfonamide (0.02 mmol, 30%).

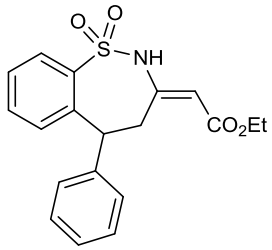
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.95 – 7.89 (m, 1H), 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H), 7.18 (ddd, *J* = 7.7, 4.9, 1.1 Hz, 1H), 5.12 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.56 (d, *J* = 4.1 Hz, 1H), 4.06 (qd, *J* = 7.1, 2.5 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 168.0, 159.2, 149.9, 137.7, 137.1, 136.1, 132.4, 130.0, 128.8, 124.9, 123.3, 123.2, 62.0, 58.9, 45.6, 14.1.
HMRS (ESI): Calculated for C_{16} H_{17} O_4 N_2 S = $[M+H]^+$: = 333.09035, found: 333.09018

4.2.3.2 Hydrogenolysis of Azetidines 49



General Reaction Scheme

(±)-Ethyl (E)-2-(1,1-dioxido-5-phenyl-4,5-dihydrobenzo[f][1,2]thiazepin-3(2H)-ylidene)-acetate (93a)

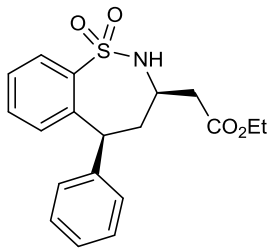


Sulfonamide **51a** (1.0 eq., 350 mg, 0.98 mmol) was dissolved in 10 ml Ethyl acetate and 83 mg (10wt.% Pd/C, 8 mol%., 78 µmol) and charged with 8 atm hydrogen in a high pressure cylinder and was stirred for 60 h at 21 °C. Eight drops of glacial AcOH were added and the reaction was placed again under 7.5 atm of hydrogen and stirred at that temperature. After 20 h, almost no conversion could be determined and another 6 mol% of Pd/C were added (by that time, it contained 141 mg, 0.14 eq.,0.13 mmol of Pd/C in total). It was stirred for 18 additional hours. As no further conversion (TLC, U-HPLC-MS analysis) could be observed, reaction mixture was filtered over celite and concentrated. Silica gel column chromatography (12% to 15% EA/CyH) yielded Products **93a** and **94a** in 49% (173mg, 0.48 mmol) and 51% (179 mg, 0.50 mmol) yield.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 11.02 (s, 1H), 7.38 (td, *J* = 7.5, 1.6 Hz, 1H), 7.34 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29 (td, *J* = 7.3, 6.6, 1.2 Hz, 2H), 7.24 – 7.21 (m, 1H), 7.18 – 7.15 (m, 2H), 7.14 (dt, *J* = 7.6, 1.0 Hz, 1H), 4.93 (s, 1H), 4.59 (dd, *J* = 10.0, 5.2 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.73 (t, *J* = 12.6 Hz, 1H), 3.24 – 3.17 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (176 MHz, Chloroform-d) δ 168.9, 152.2, 144.4, 139.4, 139.3, 134.1, 132.7, 129.1, 128.3, 127.3, 127.0, 125.8, 96.4, 60.3, 50.8, 38.4, 14.3.
HMRS (ESI): Calculated for $C_{19}H_{20}O_4NS = [M+H]^+$: = 358.11076, found: 358.11134

Calculated for $C_{19}H_{19}O_4NNaS$ = $[M+H]^+$: = 380.09270, found: 380.09279

(±)-Ethyl-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5tetrahydrobenzo-[f][1,2]thiazepin-3-yl)acetate (94a)

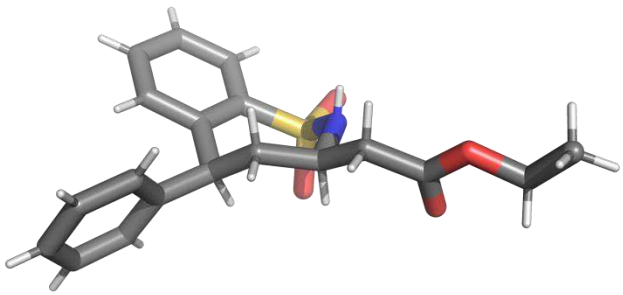


^{1}H NMR (400 MHz, Chloroform-d) δ 8.09 – 8.04 (m, 1H), 7.45 – 7.37 (m, 2H), 7.34-7.27 (m, 3H), 7.25 – 7.22 (m, 2H), 6.66 – 6.61 (m, 1H), 6.67 – 6.59 (m, 1H), 5.40 (d, *J* = 9.6 Hz, 1H), 5.11 (dd, *J* = 5.8, 2.5 Hz, 1H), 4.41 – 4.31 (m, 1H), 4.21 – 4.08 (m, 2H), 2.79 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.59 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.31-2.25 (m, 2H), 1.28 – 1.24 (t, *J* = 7.04 Hz, 3H).

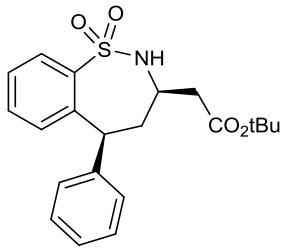
^{13}C NMR (101 MHz, Chloroform-d) δ 171.7, 143.4, 142.8, 141.2, 132.8, 129.7, 129.2, 129.1, 127.8, 127.4, 126.8, 61.4, 53.3, 46.6, 39.7, 39.1, 14.3.

HMRS (ESI): Calculated for $C_{19}H_{22}O_4NS$ = $[M+H]^+$: = 360.12641, found: 360.12695

Xray Deposition number at the Cambridge Crystallographic Data Centre: CCDC 1910510



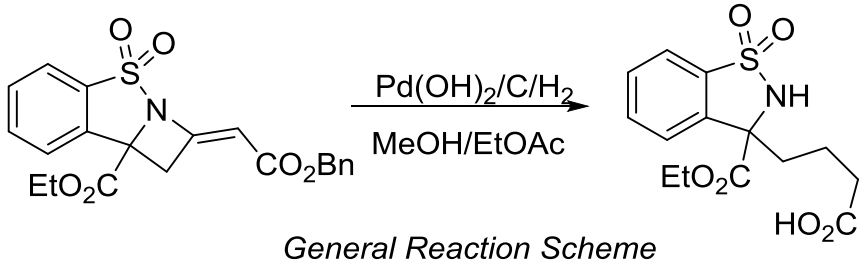
(±)-Tert-butyl 2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetate (94b)



59% yield (0.64 mmol, 274 mg)

^{1}H NMR (600 MHz, Chloroform-d) δ 8.10 – 8.06 (m, 1H), 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 1H), 7.33 – 7.30 (m, 2H), 7.28 – 7.26 (m, 2H), 6.67 – 6.64 (m, 1H), 5.50 (d, *J* = 9.5 Hz, 1H), 5.13 (d, *J* = 9.9 Hz, 1H), 4.37 – 4.30 (m, 1H), 2.76 (dd, *J* = 16.7, 4.7 Hz, 1H), 2.51 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.36 – 2.25 (m, 2H), 1.46 (s, 9H).
^{13}C NMR (151 MHz, Chloroform-d) δ 171.0, 143.3, 142.7, 141.0, 132.5, 129.4, 129.0, 128.9, 127.6, 127.1, 126.6, 53.3, 46.5, 40.4, 38.8, 28.1, 26.9.
HMRS (ESI): Calculated for C_{21} H_{26} O_4 N Na S = $[M+Na]^+$: = 411.14748, found: 411.14993

(±)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid (95)



General Reaction Scheme

Pearlman's catalyst (20wt%., 9mol%, 7.2 mg, 0.01 mmol) and **51d** (1.0 eq.,50 mg, 0.12 mmol) were dissolved in a 3:1 (v/v) Methanol/Ethyl Acetate Mixture (1.250) in a 10 ml tube equipped with a stirring bar. The vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 2 h. Then, reaction mixture was filtered to furnish 37 mg (0.11 mmol, 93% yield) of (+)-4-(3-(ethoxycarbonyl)-1,1-dioxido-2,3-dihydrobenzo[d]isothiazol-3-yl)butanoic acid **95**.

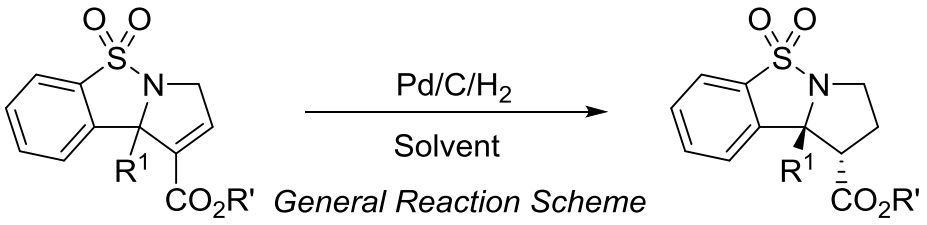
^{1}H NMR (700 MHz, Chloroform-d) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.7 Hz), 7.60 (dd, *J* = 11.1, 3.9 Hz, 1H), 5.83 (s, 1H), 4.37 – 4.28 (m, 2H), 2.43 (dt,

J = 16.7, 7.0 Hz, 1H), 2.36 (dt, *J* = 16.7, 7.3 Hz, 1H), 2.29 (ddd, *J* = 13.7, 11.5, 4.8 Hz, 1H), 2.05 (ddd, *J* = 13.7, 11.7, 4.8 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (176 MHz, Chloroform-d) δ 178.3, 169.9, 137.9, 135.4, 133.6, 130.6, 124.9, 121.5, 69.0, 63.8, 39.3, 33.1, 19.7, 14.1.

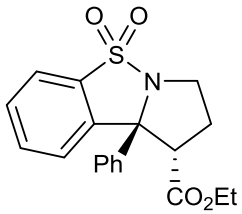
HMRS (ESI): Calculated for $C_{14}H_{18}O_6NS$ = $[M+H]^+$: = 328.08493, found: 328.08477

4.2.3.3 Synthesis of fused Pyrrolines by Reduction



General Reaction Scheme

(±)-Ethyl 9b-phenyl-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylate 5,5-dioxide (**100a**)



To 23 mg Pyrroline **50a** (1.0 eq., 0.06 mmol) in 1.5 ml of a Methanol/Ethyl Acetate Mixture (5:1) was added 3.2 mg Pearlman's Catalyst (20wt.%, 4mol%, 2.26 µmol,) in a Schlenk tube. The mixture was cooled to 0°C, degassed and refilled with hydrogen, again degassed, once more refilled with hydrogen using a balloon and stirred at rt.

After 40 min, TLC (Ethyl Acetate/CyH 1:3) showed complete conversion of starting material (r*f*= 0.33) to a product (r*f* = 0.24). The mixture was filtered through a syringe filter and the solvent was removed under reduced pressure to obtain crude product, which was purified using silica gel column chromatography (14%-20% EA/CH) to yield **100a** in 95% yield (22 mg, 0.06 mmol).

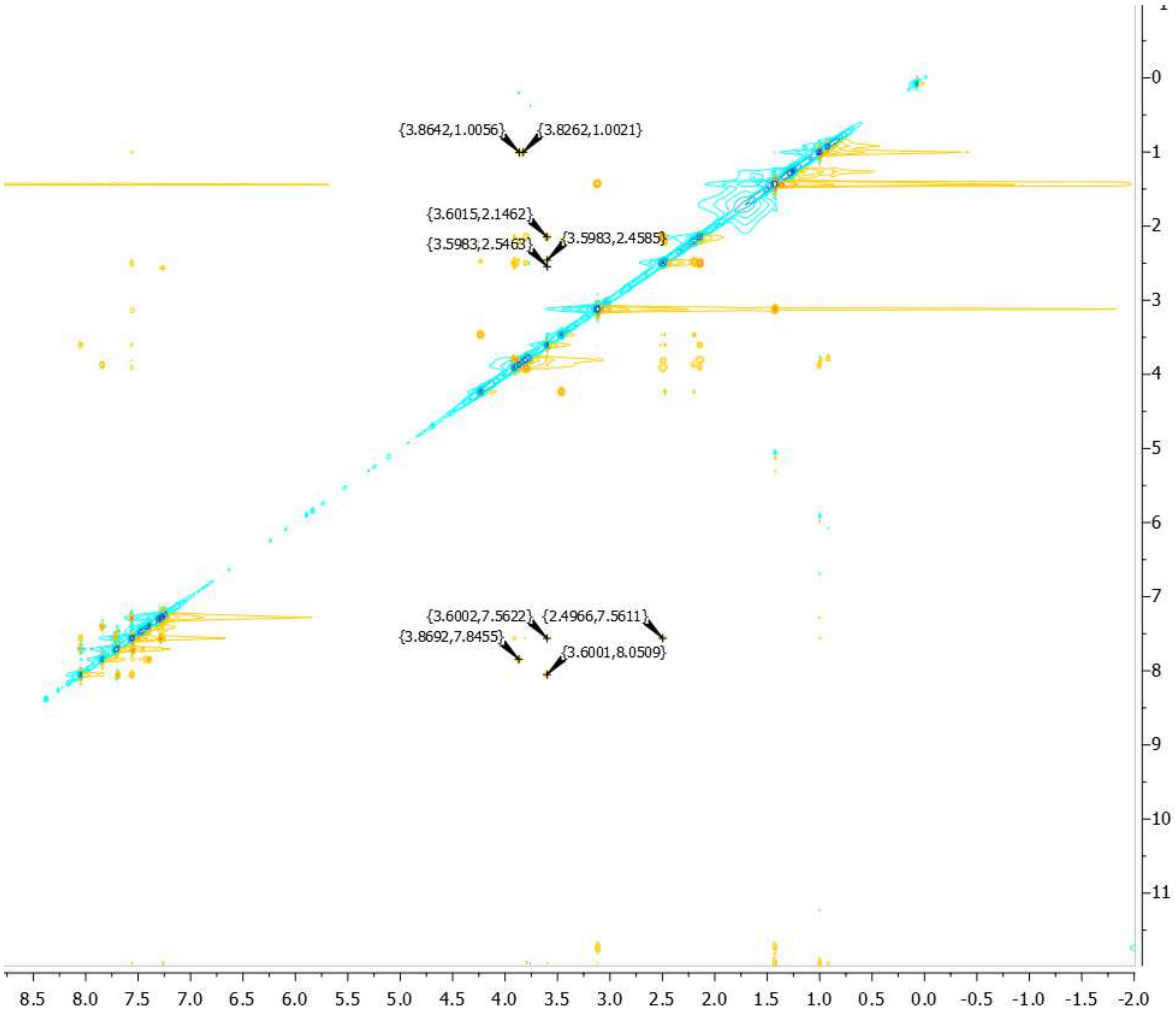
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.59 – 7.53 (m, 3H), 7.33– 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 3.94-3.73 (m, 4H), 3.60 (t, *J* =7.6 Hz, 1H), 2.49 (m, 1H), 2.15 (m, 1H), 1.0 (t, *J* = 7.1 Hz, 3H).

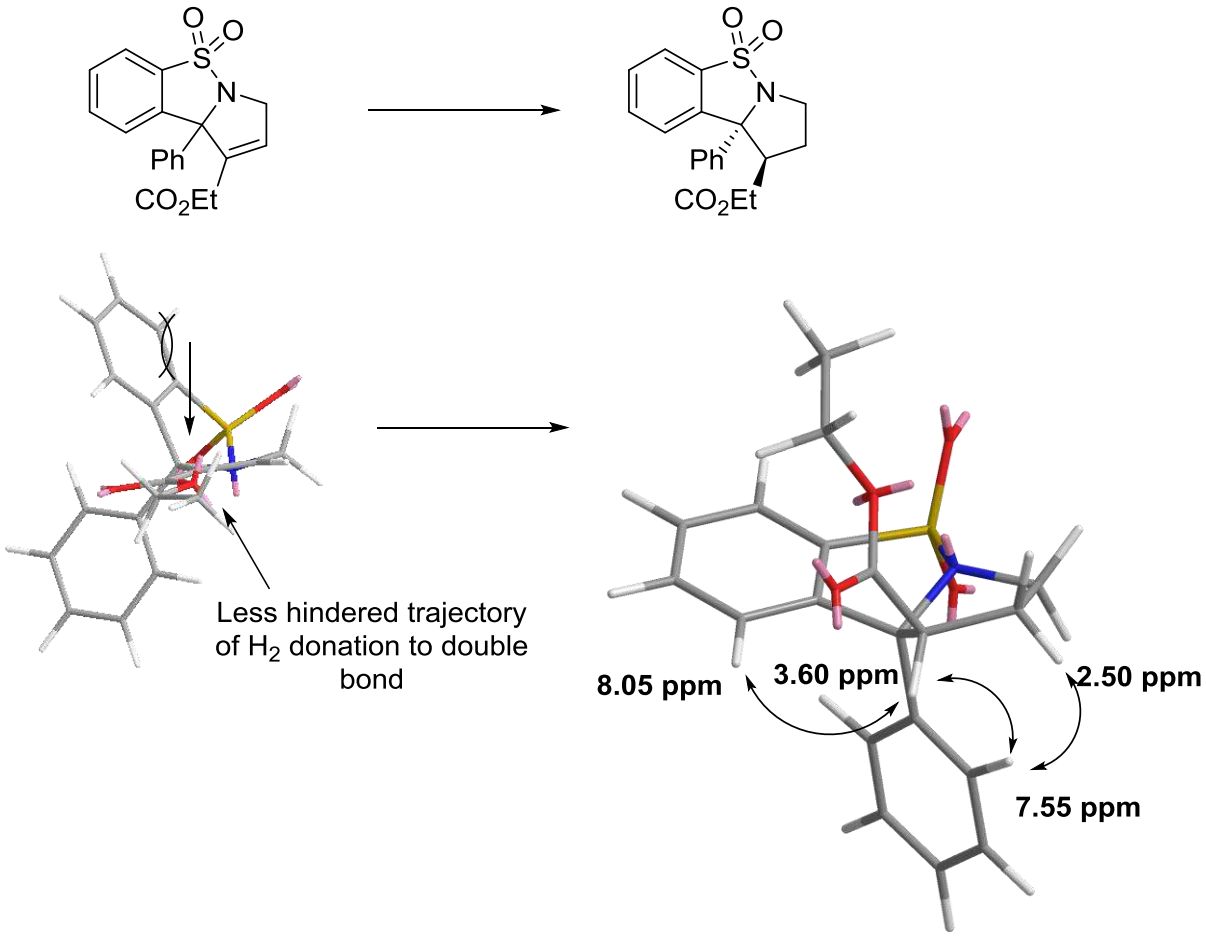
^{13}C NMR (151 MHz, Chloroform-d) δ 170.2, 143.6, 139.1, 135.9, 133.1, 129.7, 128.2, 128.1, 126.8, 125.6, 121.7, 78.2, 61.3, 56.7, 48.4, 28.9, 13.7

HMRS (ESI): Calculated for $C_{19}H_{20}O_4NS$ = $[M+H]^+$: = 358.11076, found: 358.11092

Calculated for $C_{19}H_{19}O_4NNaS$ = $[M+H]^+$: = 380.09270, found: 380.09282

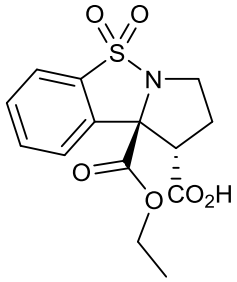
100a NOESY


{3.8642,1.0056}
{3.8262,1.0021}
{3.6015,2.1462}
{3.5983,2.5463}
{3.5983,2.4585}
{3.6002,7.5622}
{2.4966,7.5611}
{3.8692,7.8455}
{3.6001,8.0509}
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
0 1 2 3 4 5 6 7 8 9 10 11



Structure of lowest energy conformation of substrate hints that addition leading to anti-pyrrolidine may be preferred, as the most probable structure (deduced via NOE interactions) suggests.

(±)-9b-(ethoxycarbonyl)-1,2,3,9b-tetrahydrobenzo[d]pyrrolo[1,2-b]isothiazole-1-carboxylic acid 5,5-dioxide (100b)



Structure assigned in analogy to **100a**.

Pearlman's catalyst (10mol%, 8.4 mg, 0,01 mmol) and **50b** (1.0 eq., 50.0 mg, 0.12 mmol) were dissolved in a 3:1 Methanol/Ethyl Acetate (3:1 v/v) mixture in a 10 ml glass tube equipped with a stirring bar. The open vessel was placed in a high-pressure reactor, which was then sealed and charged with Hydrogen (9 atm). The reactor was placed on a stirring plate and left there for 3 h. Then, reaction mixture was filtered using a syringe filter. Concentration of filtrate delivered **100b** in 92% yield (36 mg, 0.11 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.65 Hz, 1H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.21 (m, 2H), 3.89 (dt, *J* = 10.7, 7.6 Hz, 1H), 3.68 (ddd, *J* = 10.7, 7.6, 4.6 Hz, 1H), 3.27 (t, *J* = 8.4 Hz, 1H), 2.67 (m, 1H), 2.42 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 2H).

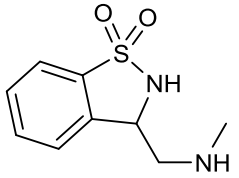
^{13}C NMR (126 MHz, Chloroform-d) δ 175.7, 168.7, 136.7, 135.1, 133.7, 130.9, 126.4, 121.5, 63.0, 60.6, 53.7, 46.5, 30.1, 13.9.

HMRS (ESI): Calculated for $C_{14}H_{16}O_6NS = [M+H]^+$: = 326.06928, found: 326.06963

Calculated for $C_{14}H_{15}O_6NNaS = [M+H]^+$: = 348.05123, found: 348.05164

4.2.3.4 Ring modulation reaction of cycloadduct 60a

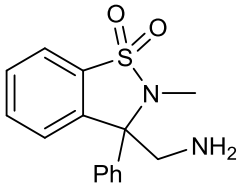
(±)-3-(aminomethyl)-2-methyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (98)



Sulfonamide **67a** (1.0 eq., 55 mg, 0.18 mmol) was dissolved in 1.8 ml in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.%, 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, whichw as charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. Purification by preparative HPLC (C18, 10% to 50% MeCN/H_2O (+0.1% v/v TFA))) delivered unstable Product **98** in 87% yield (34 mg, 0.16 mmol).

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.75 – 7.73 (d, J = 8.1 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.57 (t, J = 7.9 Hz, 2H), 4.77 (dd, J = 8.8, 4.9 Hz, 1H), 2.70 (dd, J = 12.6, 4.9 Hz, 1H), 2.54 (dd, J = 12.6, 8.8 Hz, 1H), 2.28 (s, 3H).
^{13}C NMR (126 MHz, CD_3CN) δ 139.8, 136.6, 133.6, 130.2, 125.7, 121.3, 118.0, 64.1, 55.8, 45.4.
HMRS (ESI): Calculated for $C_9H_{13}O_2N_2S = [M+H]^+$: = 213.06922, found: 213.06943

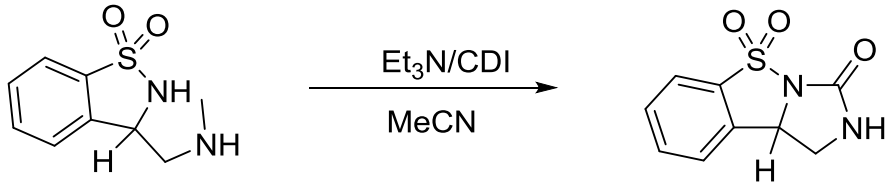
3-(aminomethyl)-2-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (99)



A solution of sulfonamide **67c** (1.0 eq., 115 mg, 305.5 µmol) and $Pd(OH)_2/C$ (20wt.%, 0.2 eq. 42.9 mg) in 3.5 ml MeOH (0.087 M) in a Schlenk flask equipped with a magnetic stirring bar was evacuated and refilled with hydrogen. The evacuation-hydrogen refilling was repeated twice. The reaction vessel was kept stirring with a balloon filled with hydrogen for 48 h at 21 °C. Then, reaction mixture was filtered through celite, concentrated and the residue purified by silica gel column chromatography. Product (5 mg, corresponds to 6% of proposed product) was analyzed by NMR.

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 7.74 (dt, *J* = 7.8, 1.0 Hz, 0H), 7.71 – 7.66 (m, 1H), 7.62 – 7.56 (m, 1H), 7.40 – 7.34 (m, 1H), 7.32 – 7.27 (m, 0H), 3.43 (d, *J* = 12.8 Hz, 0H), 3.21 (dd, *J* = 12.8, 1.1 Hz, 0H), 2.28 (s, 1H).

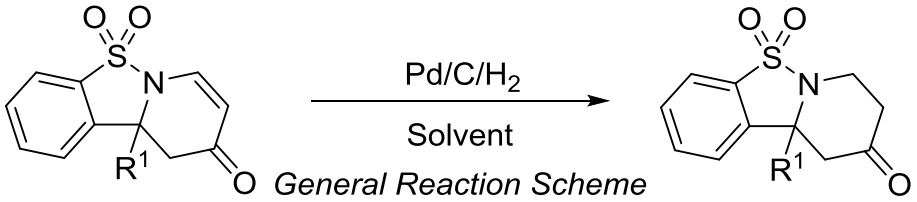
(±)-2-methyl-1,9b-dihydrobenzo[d]imidazo[1,5-b]isothiazol-3(2H)-one 5,5-dioxide (102)



Crude sulfonamide **98** (1.0 eq.,33 mg, 109.86 µmol) was dissolved in 1.0 ml MeOH in a 10 ml glass vial equipped with a magnetic stirring bar. Pd/C (10 wt.% , 0.1 eq., 19.5 mg, 0.02 mmol) was added and the open vial was placed in a high-pressure reactor, which was charged with 7 atm of hydrogen. The reactor was placed on a stirring plate and the reaction was stirred at ambient temperature for 16 h. Then, it was filtered over celite and concentrated. It was dissolved in 2 ml dry acetonitrile and triethylamine (2.30 eq., 35 µl, 252.7 µmol) and CDI (1.15 eq., 20.5 mg, 0.13 mmol) were added and the reaction stirred at 21° C for 16 h. Then, it was stopped by addition of 1 M aqueous HCl (50 µl) and concentrated. The residue was purified by preparative HPLC (C18, 10% to 60% MeCN/H_2O (+0.1% v/v TFA)) to yield 6 mg (23%, 0.03 mmol) of **102**.

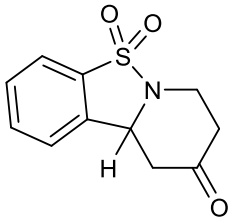
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 7.8, 1H), 7.71 (td, *J* = 7.6, 1.0 Hz, 1H), 7.62 (t, *J* = 7.7, 1H), 7.42 (dq, *J* = 7.8, 0.7 Hz, 1H), 5.40 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.01 (t, *J* = 9.3 Hz, 1H), 3.67 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.89 (s, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 152.5, 136.9, 135.3, 132.9, 129.5, 122.5, 121.2, 53.9, 49.3, 29.9.
HMRS (ESI): Calculated for $C_{10}H_{11}O_3N_2S = [M+H]^+$: = 239.04849, found: 239.04863
Calculated for $C_{10}H_{11}O_3N_2NaS = [M+Na]^+$: = 261.03043, found: 261.03012

4.2.3.5 Synthesis of tetrahydropyridones 104a-d



General Reaction Scheme

(±)-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one-5,5-dioxide (104a)

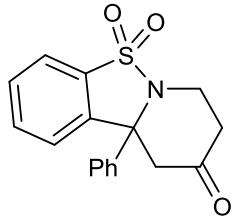


Enamide **52a** (1.0 eq., 195 mg, 0.83 mmol) was combined with Pd/C (10wt% , 0.1 eq., 88 mg, 82.89 µmol) and dissolved in 16 ml EtOH/Ethyl Acetate 1:1 (v/v). The mixture was stirred in a high-pressure reactor 18 h under 8 atm of hydrogen pressure. Then, reaction mixture was filtered over celite and concentrated. The main component of reaction mixture was alcohol **105a**. Crude reaction mixture was dissolved in 22 ml DCM and solid sodium bicarbonate (6.25 eq., 435 mg, 0.01 mol) was added. The reaction mixture was cooled down to 0° C (ice-water bath) and DMP (2.5 eq., 879 mg, 2.07 mmol) was carefully added portionwise over 10 min under a stream of Argon. The reaction was monitored via TLC. After completion of conversion (3 h) 50 ml of aqueous sodium thiosulfate solution was added and the reaction mixture was transferred to a separation funnel. Layers were separated and the aqueous layer was extracted twice more with 40 ml DCM each. Combined organic layers were washed with brine (25 ml each) and dried over anhydrous sodium sulfate. Concentration delivered crude product ,which was objected to silica gel flash column chromatography (29% to 35% EA/CyH) to yield tetrahydropyridin-4one **104a** in 59% yield (117 mg, 0.49 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.85 (m, 1H), 7.67 (td, *J* = 7.6, 1.3 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.41 – 7.34 (m, 1H), 4.66 (dd, *J* = 12.0, 3.7 Hz, 1H), 4.19 (ddd, *J* = 13.3, 7.3, 2.1 Hz, 1H), 3.40 (ddd, *J* = 13.2, 12.0, 3.7 Hz, 1H), 2.97 (ddd, *J* = 14.1, 3.7, 1.7 Hz, 1H), 2.83 (dddd, *J* = 14.8, 12.0, 7.3, 0.8 Hz, 1H), 2.63 – 2.54 (m, 2H).
^{13}C NMR (126 MHz, Chloroform-d) δ 204.4, 136.6, 134.5, 133.3, 129.9, 123.3, 121.6, 58.1, 45.9, 39.4, 38.4.

HMRS (ESI): Calculated for $C_{11}\,H_{12}\,O_3\,N\,S$ = $[M+H]^+$: = 238.05324 found: 238.05324

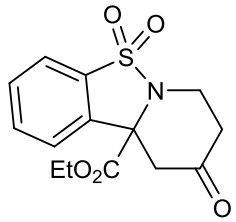
(±)-10a-phenyl-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (104b)



Tricyclic sulfonamide **52b** (307 mg, 986.01 µmol) and Pd on Carbon (10 wt%,74 mg, 69.02 µmol) were dissolved in Ethanol (18 ml) in a 100 ml Schlenk flask equipped with a magnetic stirring bar. The mixture stirred at ambient temperature with a balloon filled with hydrogen attached. The reaction was monitored by TLC. After 3 h, TLC analysis had implicated complete conversion of starting material and the mixture was filtered over celite and solvent was evaporated under reduced pressure to give crude reaction product, which was purified by silica gel column chromatography (18% to 32% EA/CyH) to give product sulfonamide **104b** in 90% yield (278 mg, 0.89 mmol).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.89 (m, 1H), 7.59 – 7.51 (m, 2H), 7.44 – 7.29 (m, 6H), 7.03 – 6.98 (m, 1H), 4.18 (ddd, *J* = 14.7, 7.6, 1.5 Hz, 1H), 3.55 (dd, *J* = 14.4, 1.6 Hz, 1H), 3.13 (ddd, *J* = 14.7, 12.3, 3.8 Hz, 1H), 2.96 – 2.84 (m, 3H), 2.34 – 2.25 (m, 1H).
^{13}C NMR (101 MHz, Chloroform-d) δ 204.5, 142.8, 137.8, 133.8, 132.7, 129.8, 129.5, 129.1, 127.5, 124.0, 121.8, 69.1, 49.6, 39.1, 36.1.
HMRS (ESI): Calculated for $C_{17}\,H_{16}\,O_3\,N_2\,S$ = $[M+H]^+$: = 314.08454, found: 314.08470

(±)-ethyl 9-oxo-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (104c)

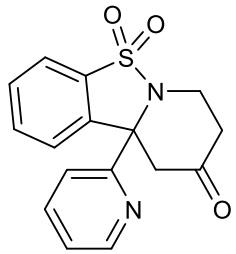


Sulfonyl enamide **52c** (1.0 eq., 150 mg, 0.49 mmol) was dissolved in 9ml EtOH and 26 mg (5mol%, 10wt.%content ,24.40 µmol) of Pd/C was added to the mixture. The reaction vessel (35 ml tube containing magnetic stirring bar) was placed in a high-pressure reactor

that was charged with 7 bars of hydrogen and placed on a stirring plate. The reaction was stirred at 20° C and monitored by TLC. The crude reaction mixture was filtered over celite, concentrated and the residue objected to silica gel flash column chromatography (25 to 28 to 32 % EA/CyH) to yield tetrahydropyridin-4one **104c** in 97% yield (146 mg 0.47 mmol).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.85 (m, 1H), 7.73 – 7.63 (m, 2H), 7.58 – 7.53 (m, 1H), 4.30 – 4.17 (m, 3H), 3.62 (ddd, *J* = 14.0, 11.6, 4.1 Hz, 1H), 3.36 (dd, *J* = 14.4, 1.6 Hz, 1H), 2.76 (dddd, *J* = 15.0, 11.6, 7.6, 0.7 Hz, 1H), 2.62 (dd, *J* = 14.5, 0.7 Hz, 1H), 2.51 (ddt, *J* = 15.0, 4.0, 1.9 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 202.7, 168.1, 135.9, 133.7, 133.5, 130.8, 123.8, 121.9, 68.3, 63.5, 48.9, 38.8, 37.1, 14.1.
HMRS (ESI): Calculated for $C_{14}H_{16}O_5NS = [M+H]^+$: = 310.07437 found: 310.07468

(±)-10a-(pyridin-2-yl)-7,8,10,10a-tetrahydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (104d)

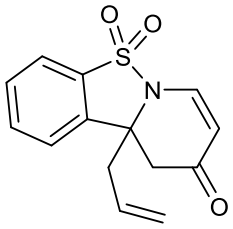


Sulfonamide **52d** (1.0 eq., 220 mg, 704.35 µmol) and Pd/C (0.12 eq., 90 mg, 84.52 µmol) were combined in a 35 ml reaction tube equipped with a magnetic stirring bar. 7 ml of Ethyl Acetate/EtOH (15:7 v/v) were added and the vessel was placed in a high-pressure reactor. The reactor was charged with 7 atm of hydrogen pressure and stirred for 16 h at 22 °C. Then reaction mixture was filtered over celite and concentrated. Silica gel column chromatography (19 to 23% EA/CyH) delivered desired product **104d** in 24% yield (54 mg, 0.17 mmol) and recovered starting material **52d**. Corresponding alcohol or other side products could not be detected.
^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.67 – 8.62 (m, 1H), 7.92 – 7.88 (m, 1H), 7.65 (td, *J* = 7.7, 1.8 Hz, 1H), 7.60 – 7.59 (m, 2H), 7.31 (ddt, *J* = 10.2, 8.0, 0.8 Hz, 2H), 7.26 – 7.24 (m, 1H), 4.20 (ddd, *J* = 14.3, 7.4, 2.4 Hz, 1H), 4.00 (dd, *J* = 14.5, 1.6 Hz, 1H), 3.25 (ddd, *J* = 14.3, 11.4, 4.1 Hz, 1H), 2.80 (dddd, *J* = 15.4, 11.4, 7.4, 0.8 Hz, 1H), 2.70 (dd, *J* = 14.4, 0.8 Hz, 1H), 2.38 (dddd, *J* = 15.4, 4.0, 2.4, 1.5 Hz, 1H).

^{13}C NMR (176 MHz, Chloroform-d) δ 201.8, 155.4, 147.3, 138.8, 135.9, 131.8, 130.9, 128.1, 122.1, 121.6, 119.7, 119.3, 67.7, 47.2, 36.6, 34.3.

HMRS (ESI): Calculated for $C_{16}H_{15}O_3N_2S$ = $[M+H]^+$: = 315.07979 found: 315.07962

10a-allyl-10,10a-dihydro-9H-benzo[4,5]isothiazolo[2,3-a]pyridin-9-one 5,5-dioxide (106)

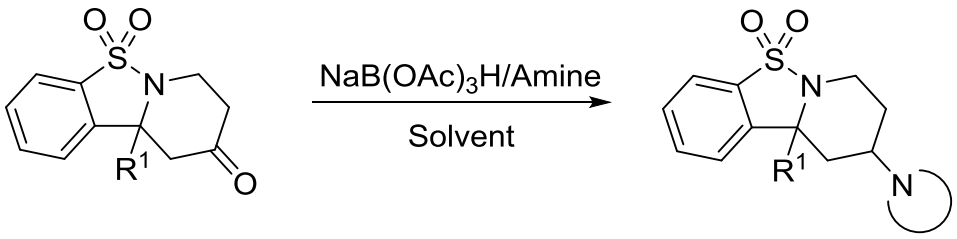


Sulfonamide **52e** (~85% purity, 141 mg, 0.38 mmmol) and Tetrakis triphenylphosphine palladium (6mol%, 26 mg, 0.02 mmol) were combined in dry MeCN (3.2 ml, 0.1 M) in a 25 ml oven-dried schlenk tube under an argon atmosphere equipped with a magnetic stirring bar. The reaction mixture was heated at 80 °C overnight. U-HPLC and TLC analysis showed conversion of the starting material. The mixture was allowed to cool down to ambient temperature (20 °C). The reaction mixture was quenched by the addition of saturated aqueous sodium bicarbonate solution and transferred to a separation funnel. 4 ml of ethyl Acetate were added and layers were separated. The aqueous layer was extracted twice more (4 ml Ethyl acetate each) and the combined organic layers were washed with water and brine (once each 10 ml), dried over anhydrous sodium sulfate and concentrated using a rotary evaporator. The crude material was objected to silica gel flash chromatography. (EA/ CyH 26%-33%), furnishing products **52a** (51 mg, 0.22 mmol, 58%) and **106** (24 mg, 0.09 mmol, 23%). **106** turned out to be rather unstable at room temperature and quickly decomposed, which left us without a suitable sample for HR-MS measurements.

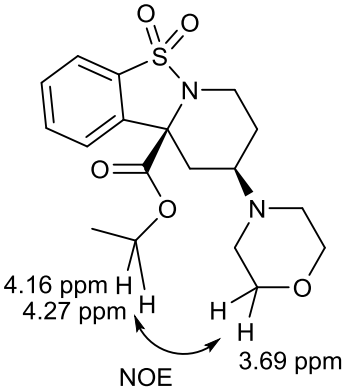
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (ddd, *J* = 7.8, 0.7 Hz, 1H), 7.77 – 7.68 (m, 2H), 7.65 (td, *J* = 7.6, 1.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.39 (dt, *J* = 7.9, 0.8 Hz, 2H), 5.61 – 5.50 (m, 2H), 5.15 – 5.10 (m, 1H), 5.02 (dq, *J* = 16.9, 1.3 Hz, 1H), 2.98 (dd, *J* = 16.0, 1.1 Hz, 1H), 2.87 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.80 (d, *J* = 16.0 Hz, 1H), 2.71 (ddt, *J* = 14.2, 7.6, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*$_3$) δ 190.6, 139.2, 137.0, 134.3, 133.5, 130.4, 129.7, 123.4, 122.1, 122.0, 107.6, 66.6, 45.7, 40.6.

4.2.3.6 Synthesis of tricyclic sulfonamides 111a-e via reductive amination



(±)-Ethyl 9-morpholino-7,8,9,10-tetrahydro-10aH-benzo[4,5]isothiazolo[2,3-a]pyridine-10a-carboxylate 5,5-dioxide (111a)



Morpholine (1.2 eq., 6.7 µl, 0.08 mmol) was added dropwise via syringe to a solution of **104c** (1.0 eq., 20 mg, 64.7 µmol) with 2-Ethylhexanoic acid (1.25 eq., 12.9 µl, 0.08 mmol) in DCM (0.6 ml) and stirred for 20 min. Then, in situ generated $NaBH(OEh)_3$ (1.25 eq., 12.9 µl, 0.08 mmol) was added and the reaction stirred overnight. Then, solvents were removed and the residue purified by silica gel column chromatography (30% to 45% EA/CyH) to yield 16 mg (0.04 mmol, 65%) of amine product.

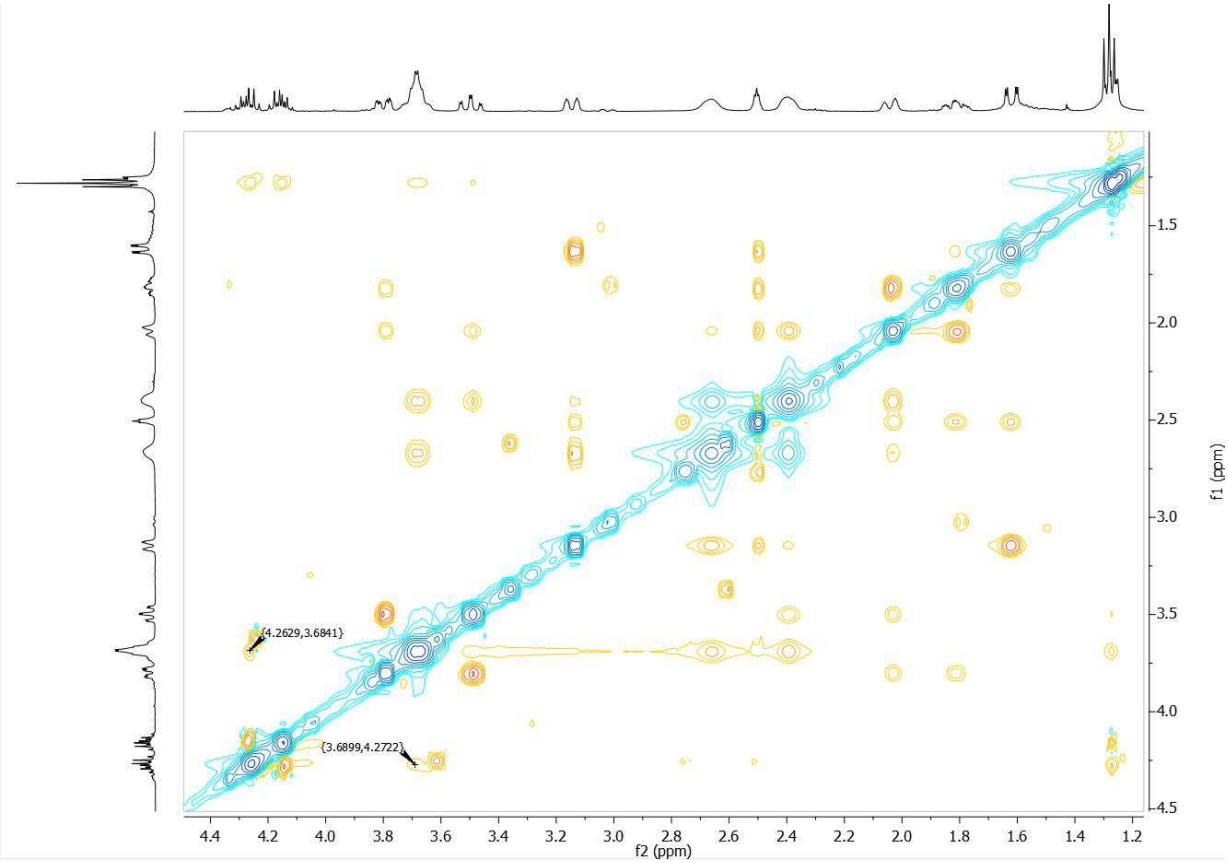
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.66 – 7.54 (m, 2H), 4.27 (dq, *J* = 10.8, 7.3 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.80 (ddd, *J* = 14.0, 4.9, 2.0 Hz, 1H), 3.75 – 3.62 (m, 4H), 3.50 (td, *J* = 13.7, 2.6 Hz, 1H), 3.15 (ddd, *J* = 14.2, 3.3, 2.0 Hz, 1H), 2.66 (s, 2H), 2.50 (p, *J* = 3.1 Hz, 1H), 2.40 (s, 2H), 2.04 (dt, *J* = 15.1, 2.6 Hz, 1H), 1.88 – 1.75 (m, 1H), 1.65 – 1.58 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-d) δ 170.4, 137.5, 133.3, 133.2, 130.2, 124.4, 121.5, 67.1, 64.2, 62.5, 56.7, 51.4, 36.6, 33.9, 25.5, 14.1.

HMRS (ESI): Calculated for $C_{18}H_{25}O_5N_2S = [M+H]^+$: = 381.14787 found: 381.14779

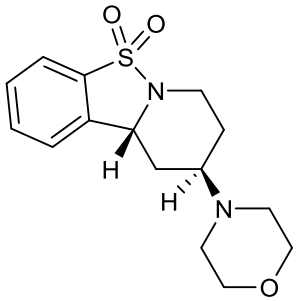
Calculated for $C_{18}H_{24}O_5N_2NaS = [M+H]^+$: = 403.12981 found: 403.12960

Calculated for $C_{18}H_{24}O_5N_2KS = [M+H]^+$: = 419.10375 found: 419.10375



NOE experiment shows NOE between Morpholine H and CH_2-group of ethyl ester.

(±)-9-morpholino-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (111b)



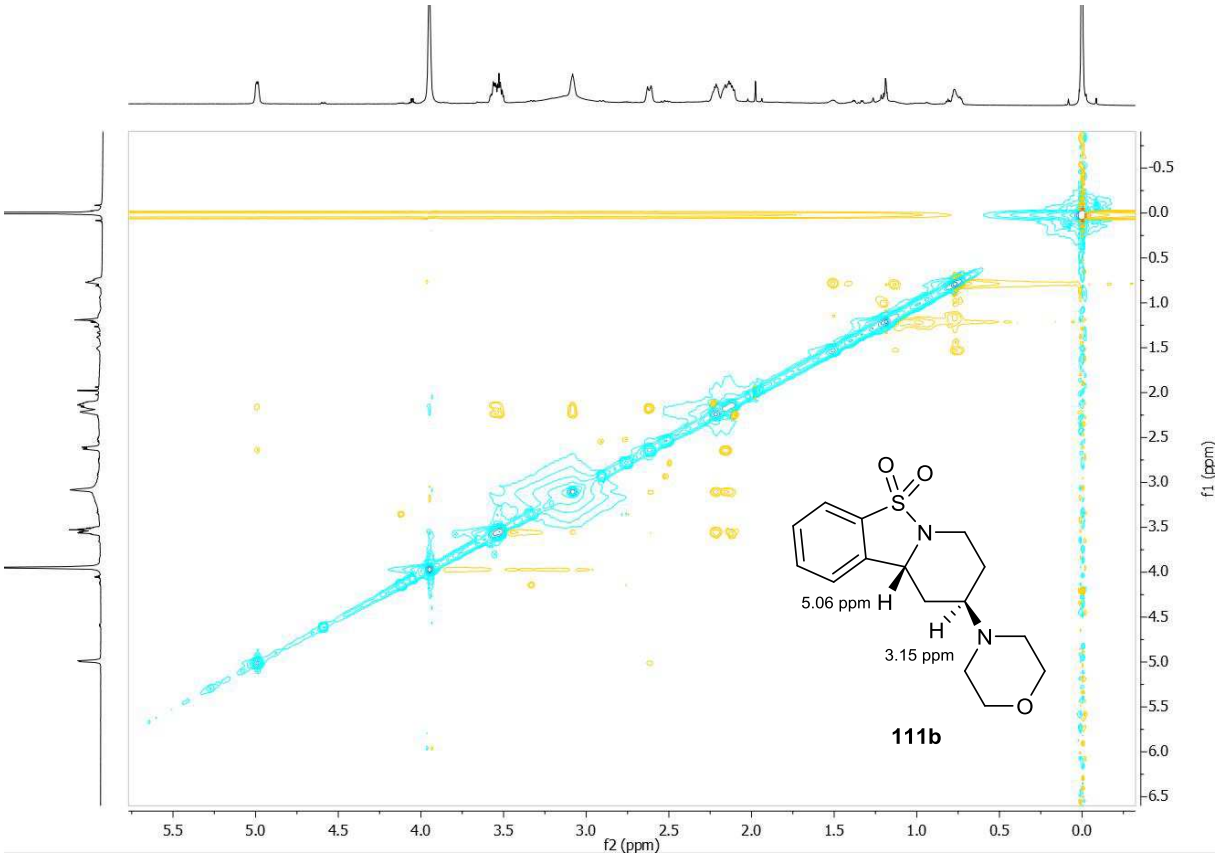
104a (1.0 eq., 16 mg, 67.43 µmol), morpholine (1.25 eq., 145 µl, 84.3 µmol, as 5% v/v solution in 1,2-DCE) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a two-necked round bottom flask under an Argon atmosphere and stirred for 12 h at ambient temperature. Then, sodium triacetoxyborohydride (1.4 eq., 20 mg, 94.40 µmol) and glacial acetic acid (1.05 eq., 4 µl, 70.80 µmol) were added and the reaction stirred at ambient temperature overnight. Then, it was concentrated in vacuo and the residue purified

(C18, 10% to 38% MeCN/H_2O (+0.1% v/v TFA)) yield 7.0 mg (0.02 mmol, 34%) of product sulfonamide.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 5.06 (dd, *J* = 9.4, 4.1 Hz, 1H), 4.02 (d, *J* = 4.7 Hz, 4H), 3.61 (ddt, *J* = 25.0, 13.2, 7.3 Hz, 2H), 3.33 – 2.99 (m, 6H), 2.69 (dt, *J* = 14.2, 5.3 Hz, 1H), 2.28 (h, *J* = 5.6, 4.3 Hz, 1H), 2.25 – 2.15 (m, 3H).

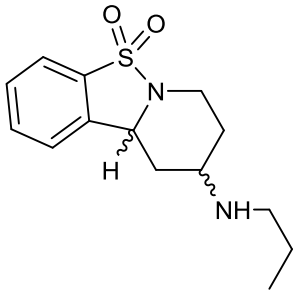
^{13}C NMR (176 MHz, Chloroform-d) δ 137.5, 134.8, 133.6, 130.0, 124.2, 122.1, 64.3, 60.1, 54.5, 50.4, 36.9, 29.6, 23.3.

HMRS (ESI): Calculated for $C_{15}H_{21}O_3N_2S$ = $[M+H]^+$: = 381.12674 found: 381.12676



In NOESY experiment, no NOE between benzylic proton and the other tertiary proton can be established. For the other amines, in contrast, such an NOE could be found. Consequently, we suggest that we isolated above depicted stereoisomer.

(±)-9-(propylamino)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (111c)



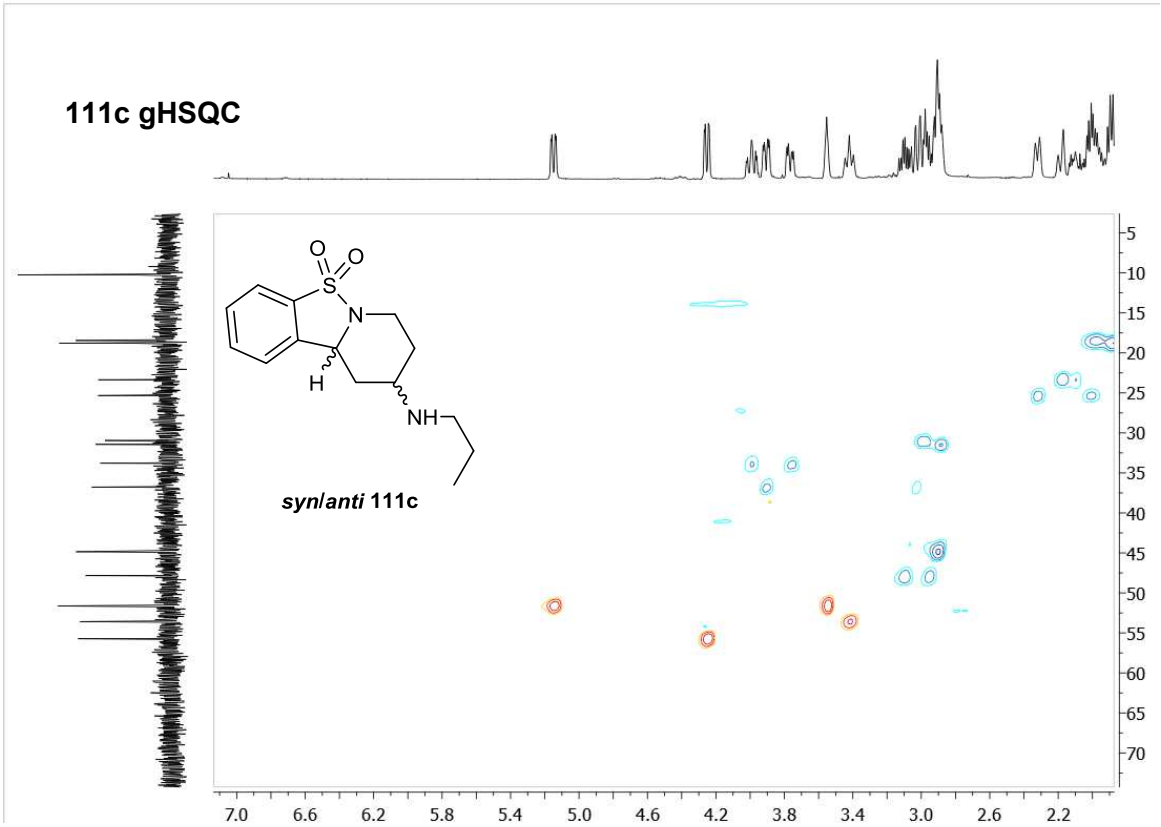
104a (1.0 eq., 28 mg, 110.93 µmol), *n*-propylamine (1.25 eq., 11 µl, 138.66 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (800 µl) in a 10 ml oven-dried Schlenk tube under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 33 mg, 155.30 µmol) and glacial acetic acid (1.05 eq., 6.6 µl, 116.47 µmol) were added and the reaction stirred at ambient temperature overnight. The reaction was concentrated and the crude reaction material was purified by preparative HPLC (C18, 3% to 7% MeCN/H_2O (+0.1% v/v TFA)) Lyophilization then delivered product amine **111c** (9.4 mg, 0.03 mmol, 30%) and alcohol side product **105a** (11 mg, 0.05 mmol, 41%).

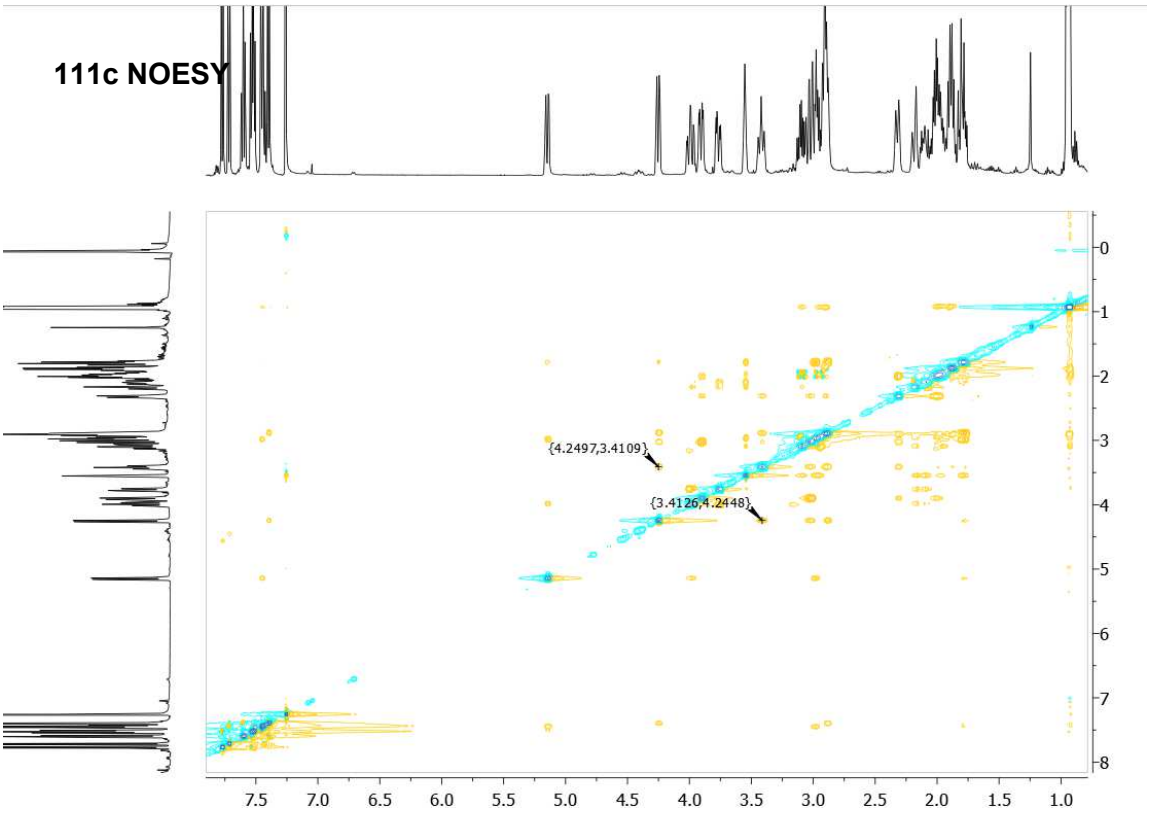
Mixture of diastereomers, ~10:9 syn:anti (see NOESY)

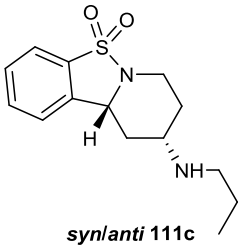
^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 7.7 Hz, 1H, *major*), 7.72 (d, *J* = 7.7 Hz, 1H, *minor*), 7.60 (td, *J* = 7.6, 1.1 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.47 – 7.38 (m, 3H), 5.15 (dd, *J* = 12.2, 3.1 Hz, 1H, minor), 4.25 (dd, *J* = 11.7, 2.9 Hz, 1H, major), 3.99 (ddd, *J* = 14.4, 12.8, 3.4 Hz, 1H), 3.91 (ddd, *J* = 13.5, 4.9, 2.0 Hz, 1H), 3.77 (ddd, *J* = 14.2, 5.6, 2.2 Hz, 1H), 3.55 (t, *J* = 3.5 Hz, 1H, minor), 3.42 (tt, *J* = 12.1, 3.6 Hz, 1H, major), 3.14 – 2.86 (m, 7H), 2.32 (d, *J* = 12.5 Hz, 1H, major), 2.19 (d, *J* = 14.9 Hz, 1H), 2.10 (ddd, *J* = 18.7, 9.2, 4.2 Hz, 1H), 2.06 (s, 0H), 1.89 (q, *J* = 7.8 Hz, 2H), 1.81 (dd, *J* = 13.5, 10.0 Hz, 1H), 0.94 (td, *J* = 7.4, 3.5 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-d) δ 137.3, 136.4, 134.9, 134.6, 133.3, 133.2, 129.9, 129.6, 123.9, 123.4, 121.6, 121.4, 56.9, 54.8, 52.8, 49.0, 46.0, 37.9, 35.0, 32.6, 32.1, 26.5, 24.5, 20.0, 19.6, 11.4, 11.4.

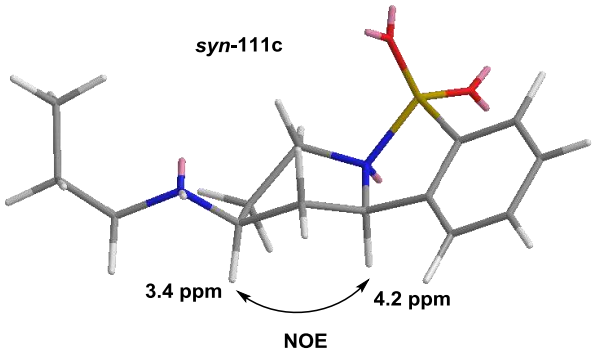
HMRS (ESI): Calculated for $C_{14}H_{21}O_2N_2S$ = $[M+H]^+$: = 281.13183 found: 281.13189


111c gHSQC
O
O
S
N
H
NH
syn/anti 111c
5
10
15
20
25
30
35
40
45
50
55
60
65
70
7.0
6.6
6.2
5.8
5.4
5.0
4.6
4.2
3.8
3.4
3.0
2.6
2.2

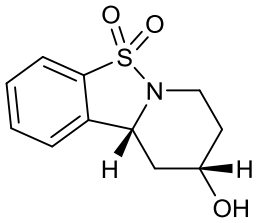

111c NOESY
{4.2497,3.4109}
{3.4126,4.2448}
0
1
2
3
4
5
6
7
8
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0



syn/*anti* 111c



(±)-9-hydroxy-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (*syn*-105a)



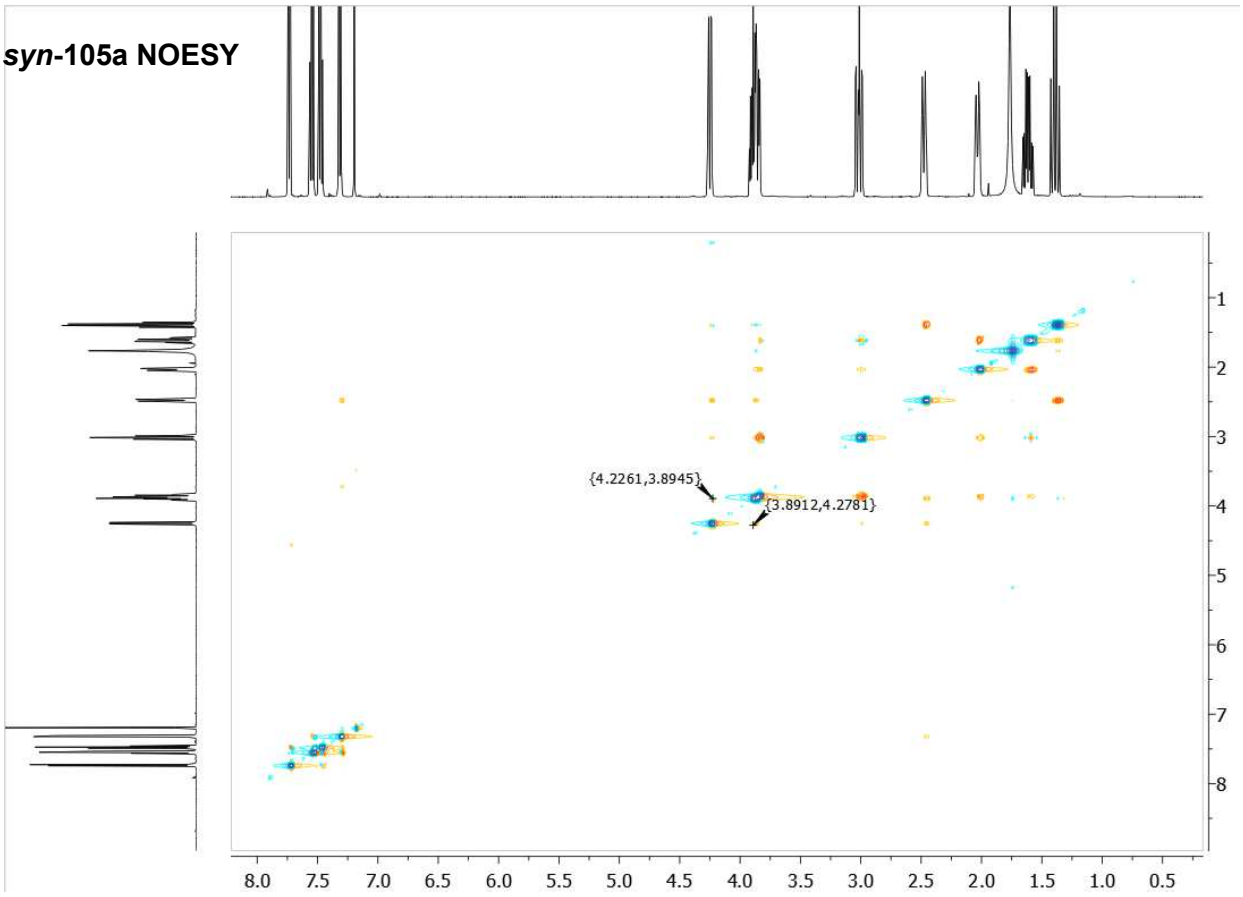
rel. stereochemistry

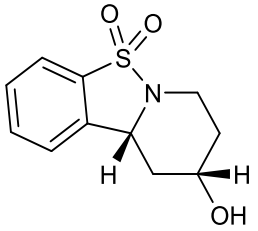
This product was isolated from reductive amination reaction towards **111c** in significant amount (see procedure above). Only by preparative HPLC, the product mixture could be purified and we found quite some amount of alcohol ***syn*-105a**.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.61 (td, *J* = 7.6, 1.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.0 Hz, 1H), 4.31 (dd, *J* = 11.9, 3.1 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.08 (td, *J* = 13.1, 3.0 Hz, 1H), 2.54 (dddd, *J* = 12.2, 4.6, 3.2, 1.8 Hz, 1H), 2.10 (dq, *J* = 12.5, 2.4 Hz, 1H), 1.68 (tdd, *J* = 12.7, 11.2, 5.1 Hz, 1H), 1.45 (q, *J* = 11.8 Hz, 1H).

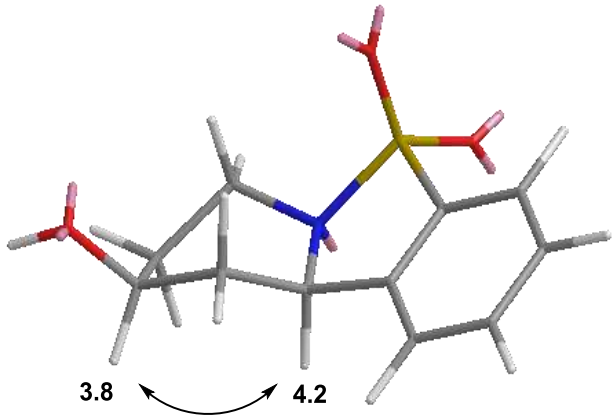
^{13}C NMR (126 MHz, Chloroform-d) δ 137.5, 135.2, 132.9, 129.5, 123.1, 121.6, 68.4, 57.5, 39.2, 37.9, 33.4.

HMRS (ESI): Calculated for $C_{11}H_{14}O_3NS = [M+H]^+$: = 240.06889 found: 240.06871


syn-105a NOESY
{4.2261,3.8945}
{3.8912,4.2781}
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8

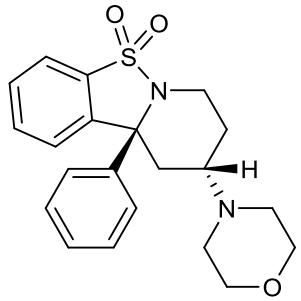

O
O
S
N
H
H
OH

syn-105a


3.8
4.2

NOE

(±)-9-morpholino-10a-phenyl-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (111d)

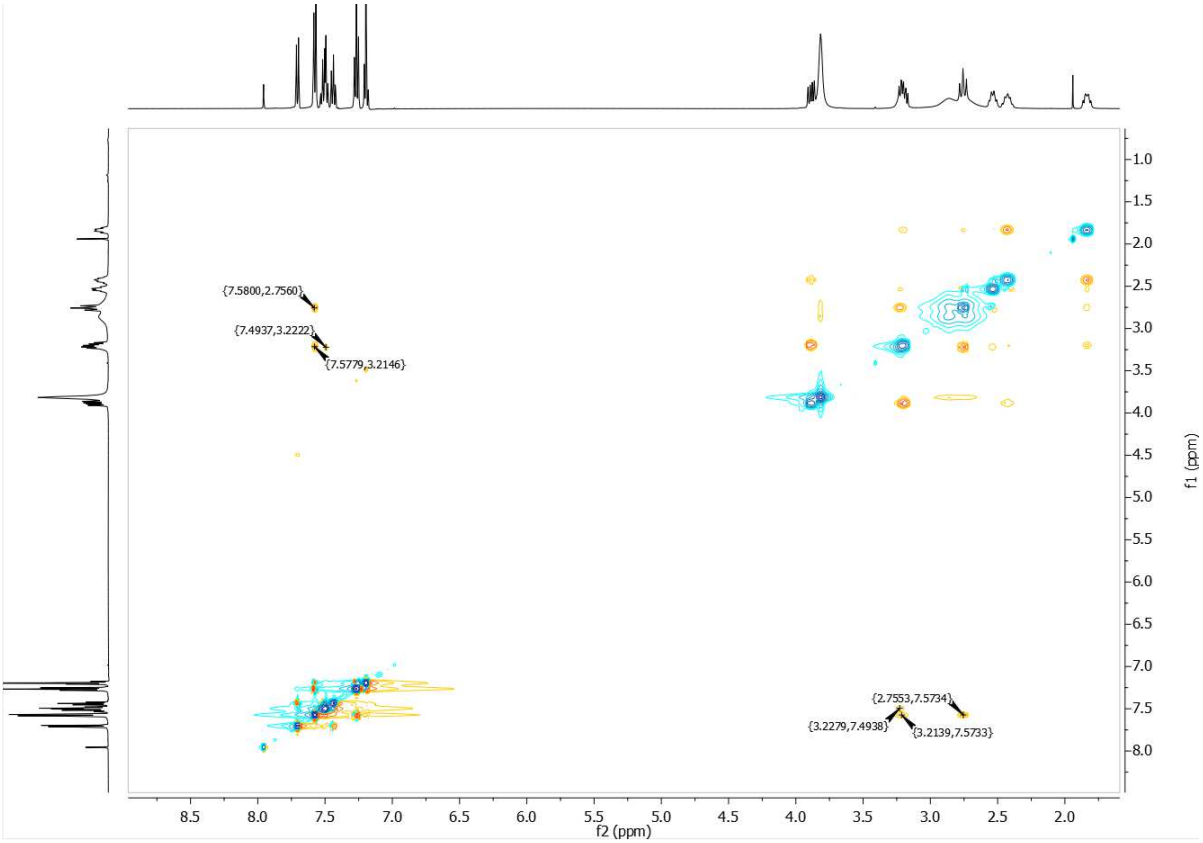


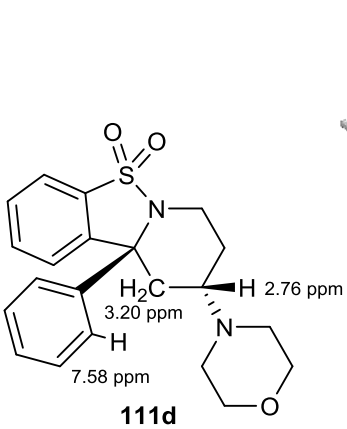
104b (1.0 eq., 25 mg, 71.8 µmol), morpholine (1.25 eq., 8 µl, 89.8 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.5 µmol) and glacial acetic acid (1.05 eq., 4.3 µl, 75.4 µmol) were added and the reaction stirred at ambient temperature. After 16 h additional 2.3 eq. of morpholine (14 µl, 165.14 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 6 h of additional stirring, the reaction was quenched by addition of 3 ml sat. aq. ammonium chloride solution. The mixture was transferred to a separation funnel, diluted with water (15 ml) and extracted with 3 x 4 ml ethyl acetate. Combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Concentration yielded crude product which was purified by preparative HPLC (10 to 38% Acetonitrile/water (+0.1 % HCOOH).) Lyophilization then delivered product **111d** (7.7 mg, 0.02 mmol, 28%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.54 – 7.47 (m, 2H), 7.44 (ddd, *J* = 8.1, 6.8, 1.5 Hz, 1H), 7.27 (dd, *J* = 8.5, 6.9 Hz, 2H), 7.20 (d, *J* = 6.2 Hz, 2H), 3.89 (ddd, *J* = 15.4, 8.6, 1.4 Hz, 1H), 3.82 (s, 4H), 3.20 (ddd, *J* = 15.3, 9.9, 7.3 Hz, 1H), 2.97 – 2.59 (m, 2H), 2.54 (tdd, *J* = 12.0, 8.4, 2.5 Hz, 1H), 2.43 (dq, *J* = 16.6, 8.5, 7.8 Hz, 1H), 1.84 (dt, *J* = 12.5, 8.3 Hz, 1H).

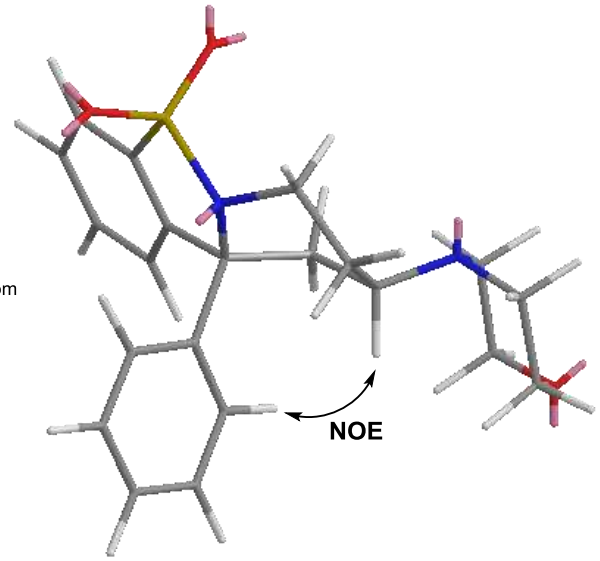
^{13}C NMR (126 MHz, Chloroform-d) δ 142.7, 141.4, 134.1, 132.6, 129.9, 129.1, 128.3, 125.3, 124.6, 121.4, 69.0, 64.6, 57.9, 49.6, 35.3, 35.2, 23.4.

HMRS (ESI): Calculated for C_{21} H_{25} O_3 N_2 S = $[M+H]^+$: = 385.15804 found: 385.15842

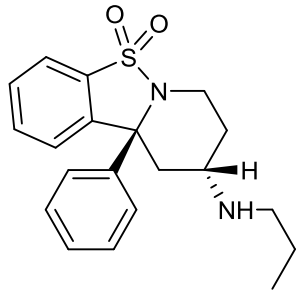

{7.5800,2.7560}
{7.4937,3.2222}
{7.5779,3.2146}
{2.7553,7.5734}
{3.2279,7.4938}
{3.2139,7.5733}
f2 (ppm)
f1 (ppm)


O
O
S
N
H2C
H 2.76 ppm
3.20 ppm
H
7.58 ppm
N
O

111d

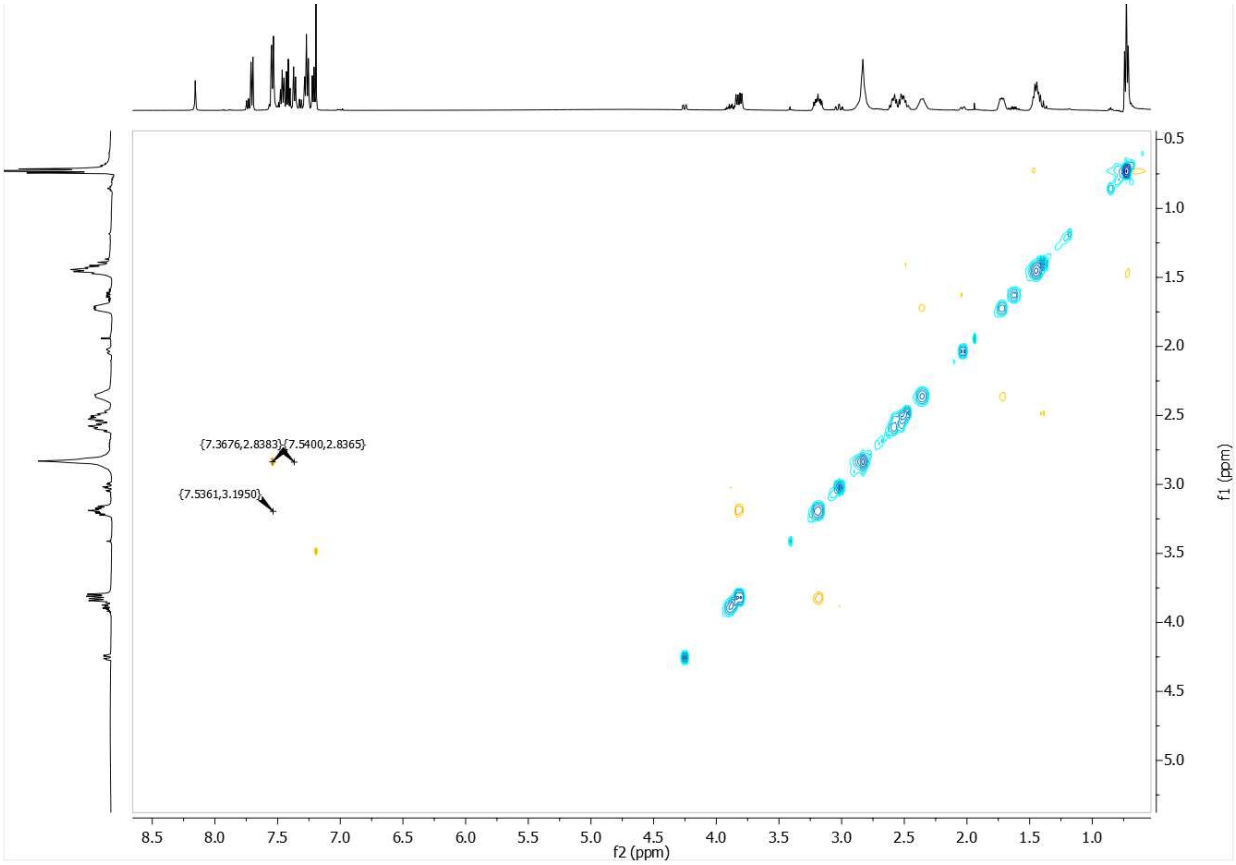

NOE

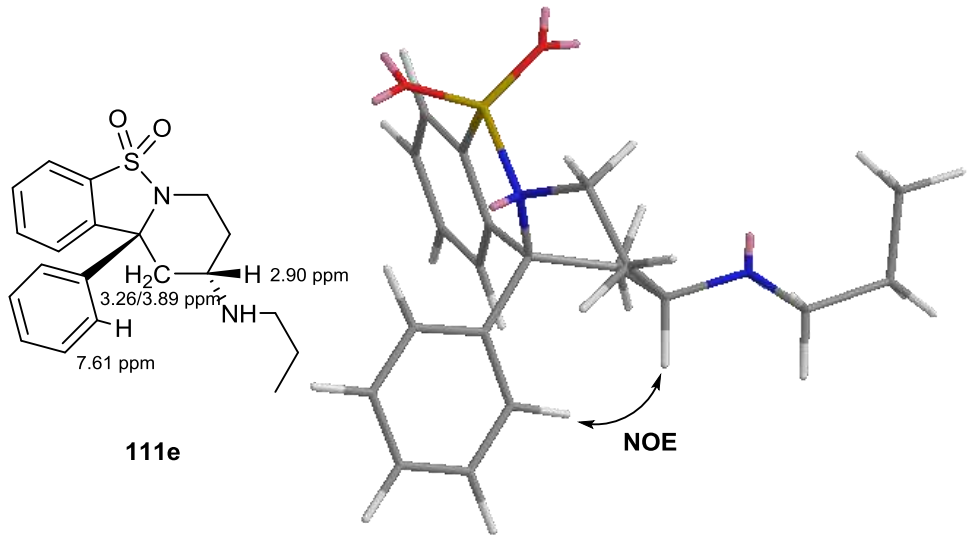
(±)-10a-phenyl-9-(propylamino)-8,9,10,10a-tetrahydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridine 5,5-dioxide (111e)



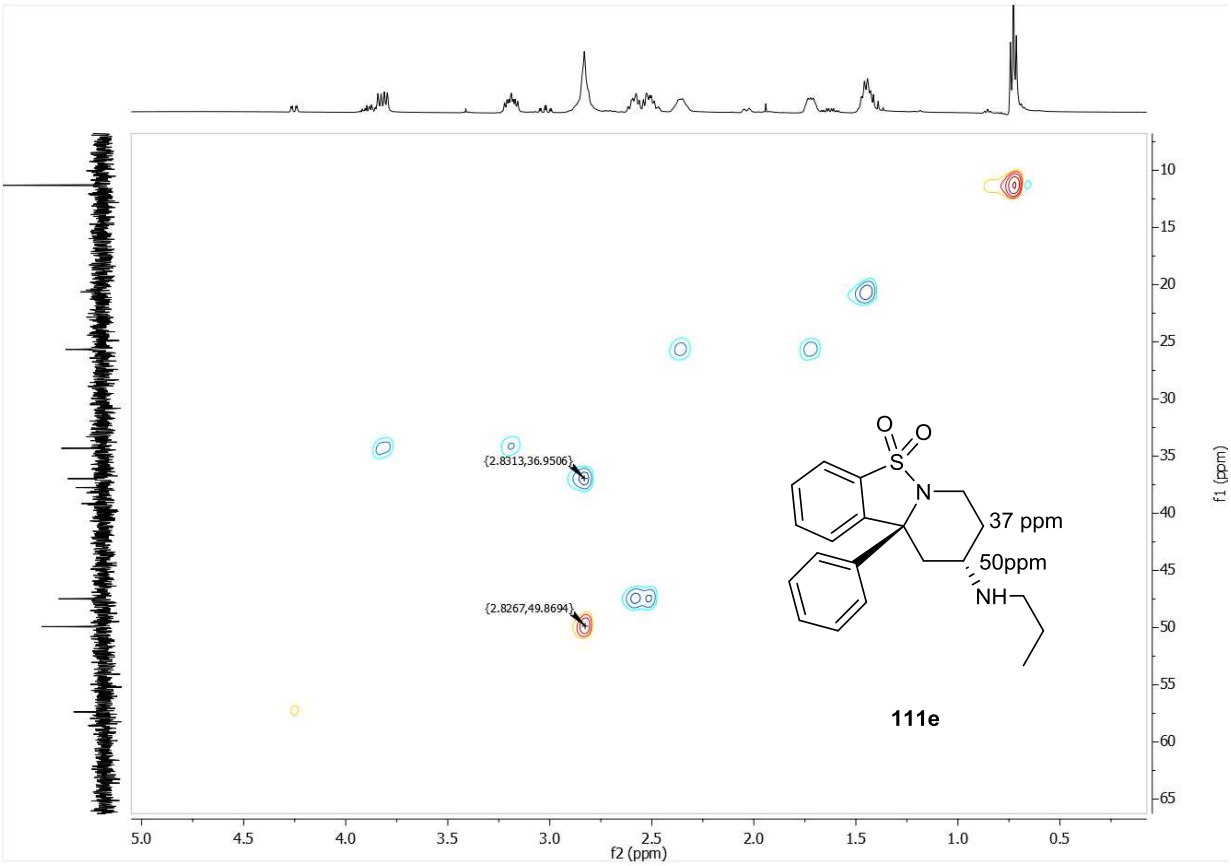
104b (1.0 eq., 25 mg, 71.80 µmol), n-propylamine (1.25 eq., 7.43 µl, 89.75 µmol) and powdered 4 A molecular sieves were combined in dry 1,2 DCE (600 µl) in a two-necked round bottom flask under an Argon atmosphere and sodium triacetoxyborohydride (1.4 eq., 21 mg, 100.52 µmol) and glacial acetic acid (1.05 eq., 4.312 µl, 75.39 µmol) were added and the reaction stirred at ambient temperature. After 16 h, additional 2.5 eq. of n-propylamine (15 µl, 179.50 µmol) and an additional 1.4 eq. of sodium acetoxyborohydride (21 mg, 100.52 µmol) were added to the mixture. After 1 d of additional stirring, reaction was concentrated under reduced pressure and the residue was purified by preparative HPLC (C18, 10% to 38% MeCN/H_2O (+0.1% v/v TFA)) to yield 5 mg (20%, 14.03 µmol) of product amine **111e**.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.53 (td, *J* = 7.6, 1.5 Hz, 1H), 7.48 (td, *J* = 7.5, 1.0 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.30 – 3.21 (m, 1H), 2.90 (q, *J* = 9.7, 8.2 Hz, 3H), 2.70 – 2.51 (m, 2H), 2.48 – 2.36 (m, 1H), 1.78 (dd, *J* = 13.3, 6.6 Hz, 1H), 1.56 – 1.43 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 142.1, 133.8, 132.5, 129.8, 129.3 (3 C), 128.5, 125.4, 124.5, 121.5, 57.5, 50.0, 47.6, 37.9, 37.1, 34.4, 25.8, 11.4.
HMRS (ESI): Calculated for C_{20} H_{25} O_2 N_2 S = $[M+H]^+$: = 357.16313 found: 357.16270

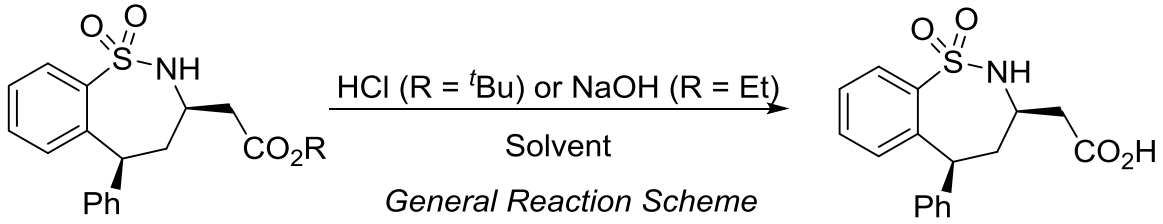

{7.3676,2.8383} {7.5400,2.8365}
{7.5361,3.1950}
f2 (ppm)
f1 (ppm)


H2C
H 2.90 ppm
3.26/3.89 ppm
NH
H
7.61 ppm
NOE

111e


{2.8313,36.9506}
{2.8267,49.8694}
O
O
S
N
37 ppm
50ppm
NH
111e
f2 (ppm)
f1 (ppm)

4.2.3.7 Hydrolysis of Esters 94



General Reaction Scheme

(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)acetic acid (112)

By hydrolysis from Ethyl Ester 94a

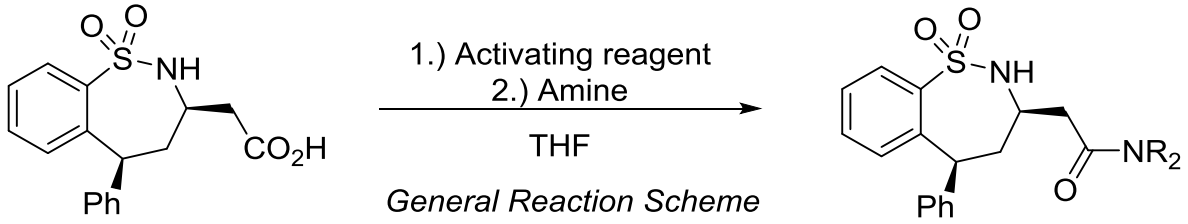
Sulfonamide **94a** (1.0 eq. 252 mg, 701.09 µmol) was dissolved in 9.16 ml THF/MeCN 4:1 v/v mixture. Then, 2.92 ml water and aqueous 2 M NaOH (974 µl) was added to the solution. The resulting mixture was stirred at ambient temperature stirred for 19 hours. The reaction was quenched by addition of 1 M HCl (2.103 ml, 2.10 mmol) and concentrated under reduced pressure. Silica gel column chromatography (20% to 40% EA/CyH to 10% EtOH/EA) delivered 217 mg (0.65 mmol, 93%) free acid **112** as a white solid.

By hydrolysis of tert-butyl ester 94b

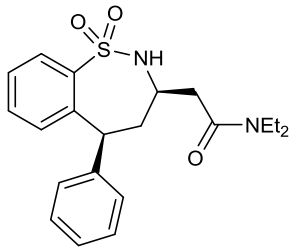
Tert-butyl ester **94b** (1.0 eq., 145 mg, 374.20 µmol) was dissolved in 3.2 ml THF/1 M aq. HCl (3:1 v/v) in a 30 ml microwave tube. The vessel was sealed and irradiated at 100 °C/250 W for 45 min using a microwave synthesizer. The reaction was quenched by addition of aqueous 2 M NaOH and extracted using Ethyl acetate (3 x 5 ml). Concentration and silica gel column chromatography (20% to 40% to 10% EtOH/EA) delivered free acid (24 mg, 0.07 mmol, 19%) delivered free acid **112** (24 mg, 0.07 mmol, 19%) and allowed recovery of unreacted starting material **94b** (81 mg, 0.21 mmol, 56%).

^{1}H NMR (500 MHz, Acetonitrile-d_3) δ 7.99 – 7.95 (m, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.29 – 7.25 (m, 2H), 6.63 – 6.59 (m, 1H), 5.51 (d, J = 9.9 Hz, 1H), 5.05 (d, J = 10.6 Hz, 1H), 4.36-4.27 (m, 1H), 2.59 (dd, J = 16.1, 5.6 Hz, 1H), 2.51 (dd, J = 16.1, 7.8 Hz, 1H), 2.32 (d, J = 14.0, 1.5 Hz,1H), 2.08 (dd, J = 14.0, 2.4 Hz, 1H).
^{13}C NMR (126 MHz, CD_3CN) δ 172.3, 144.5, 143.9, 142.3, 133.5, 130.1, 129.8, 129.8, 128.1, 127.9, 127.5, 54.4, 47.3, 40.2, 40.1.
HMRS (ESI): Calculated for $C_{17}H_{18}O_4NS$ = $[M+H]^+$: = 332.09511, found: 332.09543

4.2.3.8 Synthesis of Amides 113a-c



(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-N,N-diethylacetamide (113a)



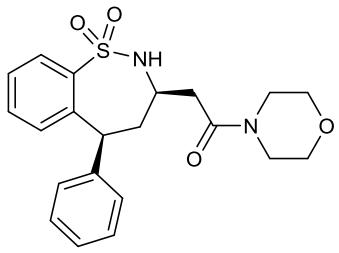
To a solution of 40 mg of carboxylic acid **112** (1.0 eq.,120.70 µmol) in chloroform (0.9 ml) was added oxalyl chloride (1.15 eq., 238 µl, 5% solution in DCM). The vial was heated gently and dissolved after a few minutes. It was then heated at 60 °C overnight. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess oxalyl chloride. Then, the reaction mixture was redissolved in THF (0.9 ml) and diethylamine (4.0 eq., 50 µl, 483 µmol) was added dropwise at 0 °C. After completion of conversion, reaction mixture was concentrated under reduced pressure, dried *in vacuo* and purified by preparative HPLC (C18, 25% to 80% MeCN/H_2O (+0.1% v/v HCOOH)) to yield 27 mg of **113a** (0.07 mmol, 58%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.08 – 8.02 (m, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.31 (m, 1H), 7.27 – 7.23 (m, 4H), 6.64 – 6.59 (m, 1H), 5.09 (d, *J* = 10.8 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.38 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.32-3.20 (m, 3H), 2.80 (dd, *J* = 16.7, 4.5 Hz, 1H), 2.68 – 2.58 (m, 2H), 2.14 (ddd, *J* = 13.9, 2.3, 1.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, Chloroform-d) δ 170.0, 143.8, 142.8, 141.3, 132.5, 129.5, 129.1, 129.0, 127.9, 127.2, 126.6, 54.0, 46.9, 42.3, 40.5, 38.7, 37.3, 14.3, 13.1.

HMRS (ESI): Calculated for C_{21} H_{27} O_3 N S = $[M+H]^+$: = 387.17369, found: 387.17375
Calculated for C_{21} H_{26} O_3 N Na S = $[M+H]^+$: = 409.15563, found: 409.15560

(±)-2-((*syn*)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-1-morpholinoethan-1-one (113b)



To a solution of acid **112** (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in $CHCl_3$). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h. The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. morpholine (29 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (7.49 µmol, 10% yield) of product sulfonamide **113b**.

Purification by preparative HPLC (C18, 35% to 90% MeCN/H_2O (+0.1% v/v TFA))

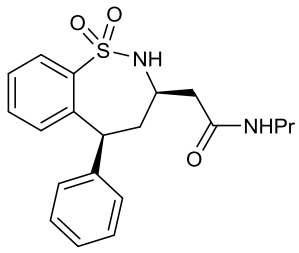
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.02 (m, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.23 (m, 4H), 6.65 – 6.61 (m, 1H), 6.17 (d, *J* = 9.6 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 4.37 (m, 1H), 3.77 – 3.61 (m, 5H), 3.53 – 3.40 (m, 3H), 2.79 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.70 – 2.55 (m, 2H), 2.16 (d, *J* = 12.7 Hz, 1H).

^{13}C NMR (176 MHz, Chloroform-d) δ 167.3, 141.6, 140.7, 139.2, 130.5, 127.5, 127.1, 127.0, 125.8, 125.2, 124.6, 64.8, 64.5, 51.7, 45.0, 44.0, 39.8, 36.9, 35.4.

HMRS (ESI): Calculated for $C_{21}H_{25}O_4N_2S = [M+H]^+$: = 401.15218, found: 401.15295

Calculated for $C_{21}H_{24}O_4N_2NaS = [M+H]^+$: = 423.13490 found: 423.13396

(±)-2-((syn)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,2]thiazepin-3-yl)-N-propylacetamide (113c)



To a solution of acid **112** (1.0 eq., 25 mg, 76 µmol) in chloroform (1 ml) was added thionyl chloride (1.20 eq., 7.5 µl, 90 µmol, as 5% solution in $CHCl_3$). The vial was heated gently and dissolved after a few minutes. It was then heated at 40° C for 16 h . The reaction was allowed to cool to room temperature and then concentrated under reduced pressure to remove any excess thionyl chloride. Crude acyl chloride was then dissolved in 500 µl THF in an oven-dried Schlenk tube equipped with a magnetic stirring bar under Argon atmosphere. Then, 5.0 eq. n-propylamine (28 µl, 0.34 mmol) was added and the reaction was kept stirring overnight. Then, it was concentrated, dried and purified by preparative HPLC to deliver 14 mg (0.04 mmol, 50% yield) of product sulfonamide **113c**.

Purification by preparative HPLC (C18, 35% to 90% MeCN/H_2O (+0.1% v/v TFA))

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 5.5, 2.0 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 7.24 (ddd, *J* = 8.0, 3.5, 2.0 Hz, 3H), 6.63 – 6.58 (m, 1H), 6.31 (s, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 5.09 (d, *J* = 10.6 Hz, 1H), 4.30 (s, 1H), 3.23 – 3.13 (m, 2H), 2.76 (dd, *J* = 15.6, 4.3 Hz, 1H), 2.41 – 2.32 (m, 2H), 2.23 – 2.17 (m, 1H), 1.52 (h, *J* = 7.1 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 170.8, 143.6, 142.6, 141.2, 132.5, 129.5, 129.1, 127.8, 127.2, 126.7, 53.7, 46.5, 41.4, 40.5, 38.7, 22.9, 11.5

HMRS (ESI): Calculated for $C_{20}H_{25}O_3N_2S = [M+H]^+$: = 373.15804, found: 373.15774

Calculated for $C_{20}H_{24}O_3N_2NaS = [M+H]^+$: = 395.13998 found: 395.13907

4.2.4. Biological Evaluation

4.2.4.1 Experimental section - Biology

Reagents

DAPI (4',6-Diamidin-2-phenylindol, #10236276001), anti-tubulin FITC (Cat# F2168;) and Hoechst 33342 (Cat. No. B2261-25mg) were purchased from Sigma Aldrich. Anti-phospho-histone3 antibody was obtained from Abcam (Cat# ab5176). Tubulin purified from porcine brain was purchased from Cytoskeleton, Inc **(**#T240). Human bone osteosarcoma epithelial c*ells* U2OS were obtained from CLS (Cat# 300364; RRID: CVCL_0042). DMEM, sodium pyruvate and non-essential amino acid obtained from PAN Biotech, and fetal bovine serum (FBS) was purchased from Gibco. Mito Tracker Deep Red (Cat. No. M22426), Phalloidin (A12381), Concanavalin A (Cat. No. C11252), WGA-Alexa594 conjugate (Cat. No. W11262) and µl/ml SYTO 14 solution (Cat. No. S7576) were obtained from Thermo Fisher Scientific.

Cell culture

U2OS cells were maintained in DMEM medium supplemented with 10 % fetal bovine serum (FBS) at 37 °C and 5% CO_2 in a humidified atmosphere. Cells were regularly assayed for mycoplasma contamination and were always confirmed to be free of mycoplasma.

Cell painting assay

The cell painting assay[179] was carried out as described by and Bray *et al*. [229] with some modifications.[230] Initially, 5 µl U2OS medium were added to each well of a 384-well plate (PerkinElmer CellCarrier-384 Ultra). Subsequently, 1600 U2OS cells were seeded per well in 20 µl medium. The plate was incubated for 10 min at the room temperature prior to incubation for 4 h at 37 °C. Compounds were then added with the Echo 520 acoustic dispenser (Labcyte) and cells were incubation for 20 h at 37 °C. Subsequently, mitochondria were stained with Mito Tracker Deep Red for 30 min in the dark at 37 °C. Cells were fixed using 3.7 % formaldehyde (in PBS) for 20 min in the dark at 37 °C prior to permeabilization Triton X-100 for 15 min 37 °C in the dark. After three washing steps, cells were stained with Alexa Fluor 594 Phalloidin, Concanavalin A Alexa Fluor 488, Hoechst 33342, WGA-Alexa594 conjugate and SYTO 14. The plate was incubated for 30 min at 37 °C in the dark and washed three times with PBS. After the final washing step, the PBS was not aspirated. The plates were sealed and centrifuged for 1 min at 500 rpm.

The plates were prepared in triplicates with shifted layouts to reduce plate effects and imaged using a Micro XL High-Content Screening System (Molecular Devices) in 5 channels (DAPI: Ex350-400/ Em410-480; FITC: Ex470-500/ Em510-540; Spectrum Gold: Ex520-545/ Em560-585; TxRed: Ex535-585/ Em600-650; Cy5: Ex605-650/ Em670-715) with 9 sites per well and 20x magnification (binning 2).

The generated images were processed with the CellProfiler package (https://cellprofiler.org/) on a computing cluster of the Max Planck Society to extract 1716 cell features (parameters).

Further analysis was performed with custom Python (https://www.python.org/) scripts using the Pandas (https://pandas.pydata.org/) and Dask (https://dask.org/) data processing libraries (separate publication to follow).

In a first step, the data was aggregated as overall medians per well.

A subset of highly reproducible parameters was determined using the procedure described by Woehrmann *et al.* [231] in the following way:

Two biological repeats of one plate containing reference compounds were analysed. For every parameter, its full profile over each whole plate was calculated. If the profiles from the two repeats showed a similarity >= 0.8 (see below), the parameter was added to the set.

This was only done once and resulted in a set of 579 parameters that was used for all further analyses.

Z-scores were then calculated for each parameter as how many times the MAD of the controls the measured value deviates from the median of the controls:

$$z - score = \frac{value_{meas.} - Median_{Controls}}{MAD_{Controls}}$$

The phenotypic compound profile is then the list of z-scores of all parameters for one compound.

In addition to the phenotypic profile, an induction value was determined for each compound as the fraction of significantly changed parameters, in percent:

$$Induction\ [\%] = \frac{number\ of\ parameters\ with\ abs.\ \ values > 3}{total\ number\ of\ parameters}$$

Similarities of phenotypic profiles were calculated from the correlation distances between two profiles (https://docs.scipy.org/doc/scipy/reference/generated/scipy.spatial.distance.correlation.html ; Similarity = 1 - Correlation Distance) and the compounds with the most similar profiles were determined from a set of 3000 reference compounds that was also measured in the assay.

4.2.4.2 Immunocytochemistry

U2OS cells were seeded per well in a 96-well plate and incubated overnight. Cells were treated with compounds or DMSO as a control for 24 hours. Cells were then fixed using 3.7% paraformaldehyde in phosphate-buffered saline. PBS and permeabilized with 0.1% Triton X-100 (in PBS) prior to staining with DAPI to visualize DNA and anti-tubulin-FITC antibody or anti-phosphor-Histone3 antibody antibodies overnight at 4 C°. Images were acquired using Observer Z1 (Carl Zeiss, Germany) using 20X and 40 X objectives (LD Plan-Neofluar). Automated image analysis to quantify the percentage of phospho-histone3-positive cells was performed using the DAPI stain to assess the total number of cells and the software MetaMorph.

In vitro tubulin polymerization assay:

In vitro tubulin polymerization assay was performed as described previously.[181] Briefly, porcine α/β-tubulin was diluted in a general buffer containing 80 mM PIPES (pH 6.9), 2 mM $MgCl_2$ and 0.5 mM EGTA. Next, 10 µM of α/β-tubulin was added to a solution containing $MgCl_2$ and glutamate with a final concentration of 0.88 µM and 0.8 mM, respectively, and added to a 96-well plate. Afterwards, compounds at a final concentration 20 µM were added to the tubulin solution and incubated at room temperature for 20 min. The plate was then incubated on ice for another 20 min prior to addition of GTP to a final concentration of 500 µM. Tubulin polymerization was monitored for 60 min by means of turbidity measurements at 340 nm.

Real-time live-cell analysis

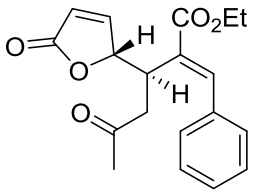
Cell growth was monitored by means of real-time live-cell analysis using the IncuCyte S3 (Essen Bioscience). For this, 4000 U2OS cells were seeded per well in 96-well plate and incubated overnight. The medium was then exchanged for fresh medium that contained the

compounds or DMSO as a control. Cells were incubated for 48 h and cell growth were imaged every two hours using in the bright-field mode. Cell confluence was quantified as a measure of cell growth using the IncuCyte S3 2019A software.

4.3 Chemistry-Driven Exploration of 1,3-Dicarbonyl Dienes

4.3.1 Synthesis of Adducts 119 and 120

Ethyl 2-benzylidene-5-oxo-3-(5-oxo-2,5-dihydrofuran-2-yl)hexanoate (171)

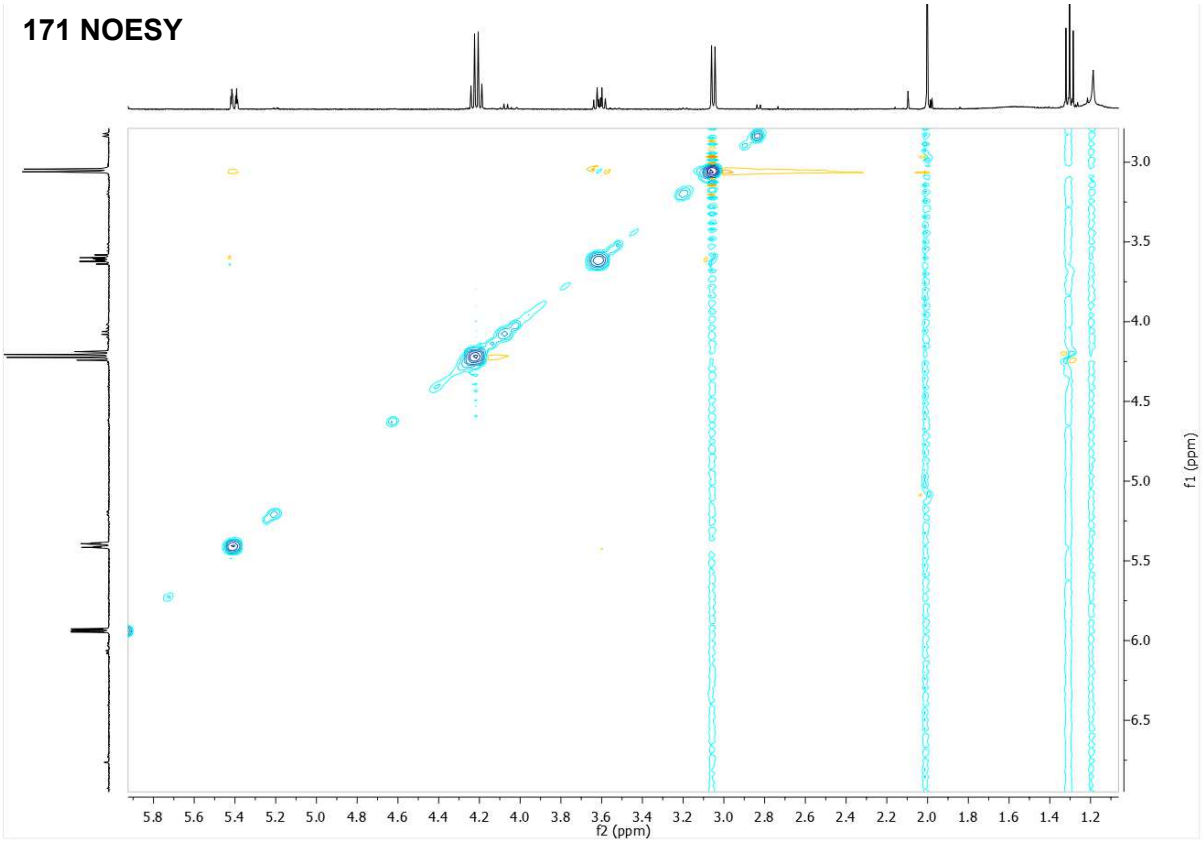


Diene **162a** (1.0 eq., 20 mg, 81.87 µmol) and $Cu(OTf)_2$ were dissolved in 0.9 ml dry DCE in an oven-dried 10 ml Schlenk tube under an Argon atmosphere. The reaction mixture was cooled to 0° C (ice-water bath). Then, silyl ether **170** (1.5 eq., 21 µl, 0.12 mmol) was added using a microsyringe. The reaction was stirred and monitored by means of TLC. After 1 min, the reaction took a light blue-greenish color. After 3 h, ice bath was removed and reaction was allowed to warm to 21 °C (room temperature). 2 h later, 33 µl (2.4 eq., 0.19 mmol) of additional Silyloxyfuran (**170**) were added and the reaction allowed to stir at 21° C overnight. Then, the reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (5 ml) and transferred to a separatory funnel. Layers were separated and the aqeous layer extracted twice with 5 ml DCM each. Combined organic layers were washed with brine (15 ml) and dried over anhydrous sodium sulfate. Concentration delivered crude reaction material which was objected to silica gel column chromatography (15% to 35% EA/CyH in 5% steps) to furnish 14 mg (52%, 0.04 mmol) of substituted lactone **171**.

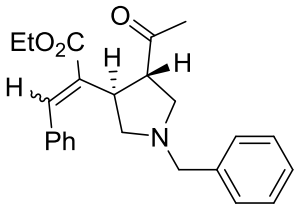
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (s, 1H), 7.40 – 7.31 (m, 7H), 6.00 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.47 (ddd, *J* = 9.4 (hints to *anti*), 2.0, 1.5 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.68 (dt, *J* = 9.4(hints to *anti*), 6.7 Hz, 1H), 3.11 (s, 1H), 2.07 (s, 4H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 206.5, 172.6, 167.2, 155.6, 144.5, 134.6, 129.6, 129.1, 128.9, 128.8, 121.8, 84.3, 61.4, 44.5, 38.6, 30.4, 14.4.

HRMS (ESI): calculated for $C_{19}H_{21}O_5N$ = $[M+H]^+$: 329.13835, found: 329.13835.
calculated for $C_{19}H_{20}O_5N$ Na = $[M+Na]^+$: 351.12029, found: 351.12019.
calculated for $C_{19}H_{20}O_5N$ K = $[M+K]^+$: 367.09423, found: 367.09419.



Ethyl 2-(4-acetyl-1-benzylpyrrolidin-3-yl)-3-phenylacrylate (172)



In a 10 ml oven-dried Schlenk tube under an Argon atmosphere to substituted Diene **162a/162a'** (1.0 eq., 20.000 mg, 81.87 µmol) in 0.9 ml dry DCM was added TFA (0.35 eq., 22 µl, 0.03 mmol, 10% v/v in DCM,) at 0°C. Then, N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine **66** (1.50 eq., 31 µl, 0.12 mmol) was added using a microsyringe.The reaction was stirred at the same temperature and monitored by TLC. After 3 h, reaction was quenched by addition of 2 ml saturated aqueous sodium bicarbonate solution and the resulting mixture transferred to a separatory funnel. Layers were separated and aqueous layer extracted twice more with 5 ml DCM each. Combined organic layers were washed with 10 ml brine and dried over anhydrous sodium sulfate. concentration delivered

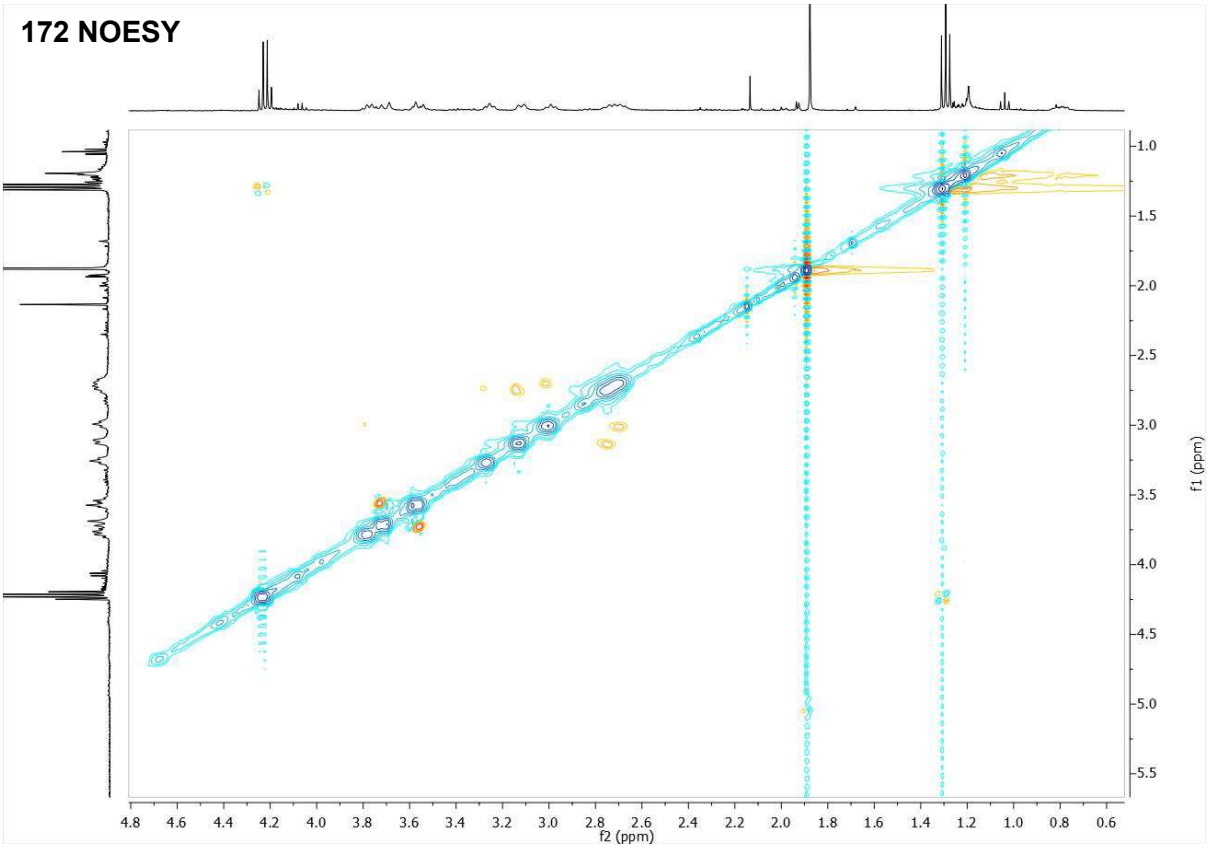
crude reaction material which was objected to silica gel column chromatography (15% to 30% EA/CyH) to furnish 18 mg (58%, 47.7 µmol) of **172**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 (s, 1H), 7.41 – 7.27 (m, 9H), 7.25 – 7.20 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (ddd, *J* = 9.6, 7.9, 6.7 Hz, 1H), 3.73 (d, *J* = 13.0 Hz, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.30 (ddd, *J* = 9.0, 6.6, 2.7 Hz, 1H), 3.15 (dd, *J* = 9.4, 2.6 Hz, 1H), 3.02 (t, *J* = 4.4 Hz, 1H), 2.77 (t, *J* = 9.0 Hz, 1H), 2.71 (t, *J* = 9.2 Hz 1H), 1.94 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (126 MHz, Chloroform-d) δ 208.8, 167.2, 142.7, 138.9, 135.2, 132.4, 128.8, 128.8, 128.7, 128.7, 128.6, 128.4, 128.3, 127.1, 60.5, 59.9, 59.1, 56.0, 55.5, 39.3, 27.9, 14.4.

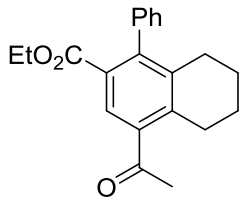
HRMS (ESI): calculated for $C_{24}H_{28}O_3N$ = $[M+H]^+$: 378.20637, found: 378.20598.

calculated for $C_{24}H_{27}O_3N$ Na = $[M+Na]^+$: 400.18731, found: 400.18789.



4.3.2 Synthesis of 176a-d

Ethyl 4-acetyl-1-phenyl-5,6,7,8-tetrahydronaphthalene-2-carboxylate (176a):

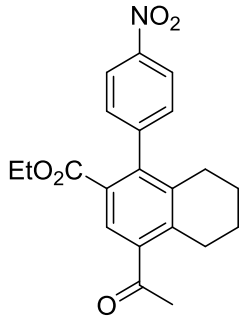


124a

Ethyl (*E*)-2-((*E*)-benzylidene)-5-oxohex-3-enoate **162a** (48.9 mg, 0.2 mmol, 1.0 eq.), and 4-(cyclohex-1-en-1-yl)morpholine (25.1 mg, 0.15 mmol, 1.5 eq.) were combined in dry toluene (1 mL) in an oven-dried Schlenk tube under an argon atmosphere. The mixture was stirred at reflux for 12 h. The mixture was directly purified using flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1, v/v) to give **176a** as colorless liquid (17.9 mg, 56%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (s, 1H), 7.42 – 7.34 (m, 3H), 7.16 – 7.06 (m, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 6.3 Hz, 2H), 2.62 (s, 3H), 2.40 (t, *J* = 6.4 Hz, 2H), 1.75 – 1.63 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H);
^{13}C NMR (101 MHz, chloroform-d) δ 202.4, 168.0, 144.9, 140.9, 140.1, 138.2, 138.0, 129.0, 128.5, 128.1, 127.2, 127.1, 60.9, 30.4, 29.3, 28.6, 22.5, 22.4, 13.7;
HRMS (ESI): calculated for $C_{21}H_{23}O_3$ = $[M+H]^+$: 323.16417, found: 323.16469.

Ethyl 4-acetyl-1-(4-nitrophenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (176b):



Ethyl (*E*)-2-((*Z*)-4-nitrobenzylidene)-5-oxohex-3-enoate **162´g** (24 mg, 82.00 µmol, 1.0 eq.) and 1-(cyclohex-1-en-1-yl)piperidine (27 mg, 0.16 mmol, 2.0 eq.) were combined in dry toluene (0.8 mL) in an oven-dried 10 ml Schlenk tube under an argon atmosphere. The vessel was sealed with a glass stopper and stirred at 120 °C. The reaction was monitored by

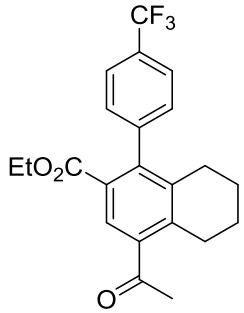
means of TLC. After 4 h, TLC analysis indicated full conversion of starting diene. The reaction was allowed to cool down to room temperature and quenched by the addition of 1 mL saturated aqueous sodium chloride solution. The mixture was transferred to a separation funnel and layers were separated. The aqueous phase was extracted with ethyl acetate three times (3 ml each). Combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous sodium sulfate. Concentration delivered crude product that was objected to silica gel column chromatography (8% to 12% ethyl acetate/cyclohexane) to give **176b** as a yellow oil in 17% yield.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.30 – 8.27 (m, 2H), 8.06 (s, 1H), 7.32 – 7.28 (m, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.03 (t, *J* = 6.3 Hz, 2H), 2.63 (s, 3H), 2.29 (t, *J* = 6.4 Hz, 2H), 1.75 – 1.71 (m, 2H), 1.69 – 1.65 (m, 2H), 1.01 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (176 MHz, Chloroform-d) δ 202.3, 166.6, 147.8, 147.2, 143.0, 141.6, 139.1, 137.6, 129.5, 127.6, 127.5, 123.6, 61.3, 30.5, 29.4, 28.5, 22.4, 22.2, 13.9;

HRMS (ESI): calculated for $C_{21}H_{22}NO_5$: $[M+H]^+$: 368.14925, found: 368.14937.

Ethyl 4-acetyl-1-(4-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (176c):



Ethyl (*E*)-5-oxo-2-((*E*)-4-(trifluoromethyl)benzylidene)hex-3-enoate **162e** (23 mg, 72.05 µmol, 1.0 eq.) and 1-(cyclohex-1-en-1-yl)piperidine (60 mg, 0.36 mmol, 5.0 eq.) were combined in dry toluene (0.7 mL) in an oven-dried 10 mL Schlenk tube under an argon atmosphere. The vessel was sealed with a glass stopper and stirred at 120 °C. The reaction was monitored by means of TLC. After 12 h, TLC indicated full conversion of starting diene. The reaction was allowed to cool down to room temperature and quenched by the addition of 1 mL saturated aqueous sodium chloride solution. The mixture was transferred to a separation funnel and layers were separated. The aqueous phase was extracted with ethyl acetate three times (3 ml each). Combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over anhydrous sodium sulfate. Concentration delivered crude

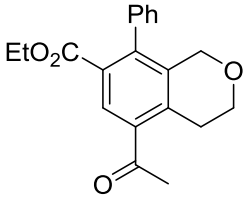
product that was objected to silica gel column chromatography (3% to 11% ethyl acetate/cyclohexane) to yield **176c** as a colorless oil in 57% yield.

^{1}H NMR (700 MHz, CD_2Cl_2) δ 7.99 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 3.96 (q, *J* = 7.2 Hz, 2H), 2.99 (t, *J* = 6.4 Hz, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 1.72 (qd, *J* = 6.2, 3.1 Hz, 2H), 1.66 (qd, *J* = 6.2, 3.1 Hz, 2H), 0.91 (t, *J* = 7.1 Hz, 3H);

NMR (176 MHz, CD_2Cl_2) δ 202.6, 167.3, 143.6, 141.2, 139.2, 138.2, 129.5, 129.4 (q, *J* = 32.3 Hz), 128.6, 127.8, 127.4, 125.3 (q, *J* = 3.7 Hz), 124.9 (q, *J* = 271.8 Hz), 61.3, 30.6, 29.6, 28.7, 22.8, 22.6, 13.7;

HRMS (ESI): calculated for $C_{22}H_{22}F_3O_3$: $[M+H]^+$: 391.15156, found: 391.15170.

Ethyl 5-acetyl-8-phenylisochromane-7-carboxylate (176d)



Ethyl (*E*)-2-((*E*)-benzylidene)-5-oxohex-3-enoate **162a** (150.0 mg, 0.61 mmol, 1.0 eq.) and 4-(3,6-dihydro-2*H*-pyran-4-yl)morpholine (416.2 mg, 2.46 mmol, 4.0 eq.) were combined in dry toluene (6 mL) in an oven-dried 10 ml Schlenk tube under an argon atmosphere. The vessel was sealed with a glass stopper and heated at 90 °C for 20 h. The reaction was allowed to cool down to room temperature and quenched by the addition of 3 mL saturated aqueous ammonium chloride solution. The mixture was transferred to a separation funnel and 10 mL of water as well as 6 mL of ethyl acetate were added. Layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 6 mL). Combined organic layers were washed with brine (10 mL) and dried over anhydrous magnesium sulfate. Filtration, concentration and objection to silica gel column chromatography (10 to 13 to 16 % ethyl acetate/cyclohexane) yielded 43 mg of **176d** (22% yield) as an orange oil.

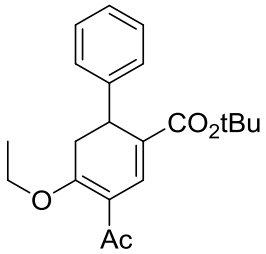
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (s, 1H), 7.41 – 7.36 (m, 3H), 7.14 – 7.09 (m, 2H), 4.40 (q, *J* = 1.1 Hz, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.87 (t, *J* = 5.8 Hz, 2H), 3.24 – 3.18 (m, 2H), 2.66 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (126 MHz, Chloroform-d) δ 200.7, 167.4, 142.8, 138.2, 137.9, 136.1, 135.7, 129.3, 129.2, 128.3, 127.8, 125.4, 67.9, 64.6, 61.1, 29.9, 28.0, 13.7;

HRMS (ESI): calculated for $C_{20}H_{21}O_4$ = $[M+H]^+$: 325.14344, found: 325.14368.

4.3.3 Synthesis of Compounds 178 and 181a-c

tert-butyl 4-acetyl-5-ethoxy-1,6-dihydro-[1,1'-biphenyl]-2-carboxylate (178)

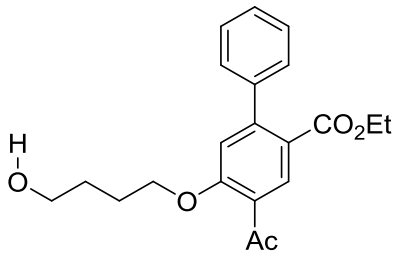


126

162m/162´m (1.0 eq., 348 µl as 0.19M toluene solution, 66 µmol) and freshly prepared 1,1 diethoxyethylene **177a** (2.0 eq., 26 mg in 60% content, 0.13 mmol; prepared according to procedure by E. Nandanan *et al.*, *J. Med. Chem.,* **2000***, 43,* 829 ff.) were combined with 200 µl dry toluene in an oven-dried 10 ml tube equipped with magnetic stirring bar under an Argon atmosphere. The vessel was sealed with a glass stopper and heated at 130° C for 15 h. The reaction was monitored via TLC. After completion, solution was concentrated and purified by silica gel column chromatography (8% to 18% EA/CyH). Then, product fraction (which contained an impurity) was further purified by preparative HPLC (30% to 95% water(+0.1 % HCOOH)/MeCN (+0.1% HCOOH). Concentration delivered 9 mg (0.03 mmol, 40% yield) of **178** as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.85 (s, 1H), 7.26 – 7.24 (m, 2H), 7.21 – 7.18 (m, 3H), 4.12 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.09 – 4.03 (m, 2H), 3.06 (dd, *J* = 17.4, 9.8 Hz, 1H), 2.90 (dd, *J* = 17.4, 2.2 Hz, 1H), 2.43 (s, 3H), 1.40 (s, 9H), 1.29 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (176 MHz, Chloroform-d) δ 195.1, 169.1, 166.2, 142.0, 134.4, 128.8, 127.1, 127.0, 123.4, 114.8, 80.3, 64.9, 37.9, 33.7, 32.5, 28.3, 15.2.
HRMS (ESI): calculated for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.19039, found: 343.19039 ;
calculated for $C_{21}H_{26}O_4Na$ $[M+Na]^+$: 365.17233, found: 365.17240

4-acetyl-5-(4-hydroxybutoxy)-[1,1'-biphenyl]-2-yl propionate(181a)



162a/162a´ (1.0 eq., 50.0 mg, 0.20 mmol, in 360 µl toluene) and 2-methylene-1,3-dioxepane **177b** (2.0 eq., 46.7 mg, 409.36 µmol, in 400 µl toluene; purchased from Activate Scientific) were combined in an oven-dried 10 ml Schlenk tube under an Argon atmosphere. The vessel was sealed with a glass stopper and heated at 120° C for 15 h.

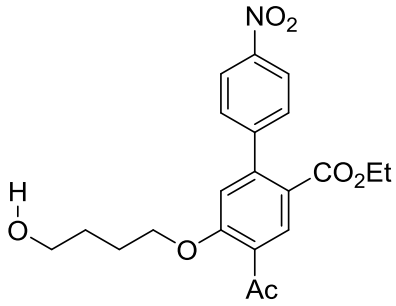
Then, 3 additional equivalents of 2-methylene-1,3-dioxepane were added and the reaction was stirred for 3 further hours at 120° C. Then, as no further conversion could be detected by means of TLC, the reaction was quenched by addition of 3 ml sat. aq. sodium chloride solution and the mixture transferred to a separation funnel. Layers were separated and the aqueous layer was extracted twice more with 3 ml ethyl acetate each. Combined organic layers were washed with brine. Crude reaction material was dried over anhydrous sodium sulfate. Evaporation yielded crude reaction mass which was purified by preparative HPLC (35% to 95% water(+0.1 % HCOOH)/MeCN (+0.1% HCOOH). Lyophilization of product fractions delivered 12 mg (0.03 mmol, 16.5% yield) of product **181a** as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.32 (s, 1H), 7.42 - 7.38 (m, 3H), 7.32 - 7.28 (m, 2H), 6.88 (s, 1H), 4.17 (t, J = 6.3 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.75 (t, J = 6.3 Hz, 2H), 2.66 (s, 3H), 2.02 - 1.95 (m, 2H), 1.77 (dt, J = 13.4, 6.3 Hz, 2H), 1.05 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 198.5, 167.2, 159.9, 149.0, 141.1, 133.5, 128.2, 128.2, 127.9, 126.7, 123.2, 114.9, 69.0, 62.4, 61.0, 32.0, 29.5, 25.8, 13.9.

HRMS (ESI): calculated for $C_{21}H_{25}O_5$ = $[M+H]^+$: 357.16965, found: 357.16998.

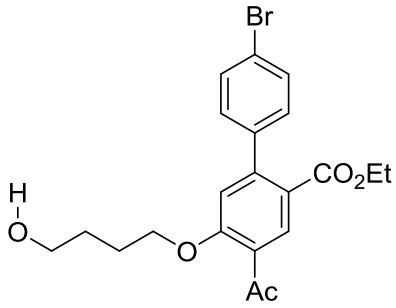
4-acetyl-5-(4-hydroxybutoxy)-4'-nitro-[1,1'-biphenyl]-2-yl propionate(181b)



162g/162g´ (1.0 eq., 20.0 mg, 69.14 µmol) and 2-methylene-1,3-dioxepane **177b** (5.0 eq., 271 µl, 15% v/v in toluene) in 400 µl toluene were combined in an oven-dried 10 ml tube equipped with a rubber septum under an Argon atmosphere. The vessel was sealed with a glass stopper and heated at 130° C for 12 h. The reaction was quenched by addition of 3 ml sat. aq. sodium chloride solution and the mixture transferred to a sepraration funnel. Layers were separated and the aqueous layer was extracted twice more with 3 ml ethyl acetate each. Combined organic layers were washed with brine. The organic solution was dried over anhydrous sodium sulfate. The crude reaction mixture was purified by preparative HPLC (25% to 75% water(+0.1 % HCOOH)/MeCN (+0.1% HCOOH). Concentration delivered 4 mg (10 µmol, 14% yield) of product **181b** as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.41 (s, 1H), 8.30 - 8.25 (m, 2H), 7.48 - 7.43 (m, 2H), 6.82 (s, 1H), 4.21 - 4.10 (m, 4H), 3.75 (t, J = 6.2 Hz, 2H), 2.68 (s, 3H), 2.01 (dt, J = 14.6, 6.5 Hz, 2H), 1.83 - 1.73 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, Chloroform-d) δ 198.2, 165.9, 160.0, 147.9, 147.3, 146.8, 133.9, 129.1, 127.6, 123.3, 122.1, 114.6, 69.1, 62.2, 61.2, 31.9, 29.2, 25.7, 14.0.
HRMS (ESI): calculated for $C_{21}H_{24}O_7N$ = $[M+H]^+$: 402.15473, found: 402.15468.

4-Acetyl-4'-bromo-5-(4-hydroxybutoxy)-[1,1'-biphenyl]-2-yl propionate (181c)



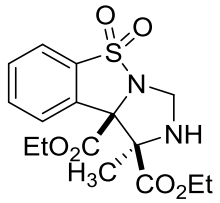
162f/162f´ (1.0 eq., 28.0 mg, 86.64 µmol) and 2-methylene-1,3-dioxepane **177b** (5.0 eq., 340 µl, 15% v/v in toluene) in 400 µl toluene were combined in an oven-dried 10 ml tube equipped with a rubber septum under an Argon atmosphere. The vessel was sealed with a glass stopper and heated at 130° C for 12 h. The reaction was quenched by addition of 3 ml sat. aq. sodium chloride solution and the mixture transferred to a sepraration funnel. Layers were separated and the aqueous layer was extracted twice more with 3 ml ethyl acetate each. Combined organic layers were washed with brine. The organic solution was dried over anhydrous sodium sulfate. The crude reaction mixture was purified by preparative HPLC (25% to 75% water (+0.1 % HCOOH)/MeCN (+0.1% HCOOH). Concentration delivered 5 mg (10 µmol, 13% yield) each of two products) as colorless oils, out of which one quickly transformed into **181c** upon storage in Chloroform-d.

^{1}H NMR (400 MHz, Chloroform-d) δ 8.27 (s, 1H), 7.50 - 7.43 (m, 2H), 7.13 - 7.07 (m, 2H), 6.75 (s, 1H), 4.13 - 4.01 (m, 4H), 3.68 (t, J = 6.2 Hz, 2H), 2.59 (s, 3H), 1.98 - 1.88 (m, 2H), 1.75 - 1.67 (m, 2H), 1.05 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 199.0, 184.7, 166.4, 141.4, 133.3, 132.0, 131.3, 129.9, 128.8, 122.7, 121.0, 108.0, 63.0, 60.9, 42.6, 37.9, 30.0, 20.2, 14.4.

HRMS (ESI): calculated for $C_{21}H_{24}O_5Br$ = [M+H]+: 435.08016, found: 435.07970.
calculated for $C_{21}H_{24}O_5{}^{81}Br$ = [M+H]+: 437.07812, found: 437.07766.

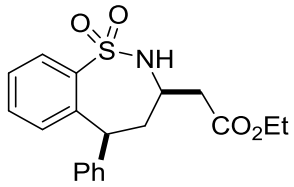
4.4 X-Ray Data of compounds *syn*-69 and 86a



***syn*-69**

Crystal data and structure refinement for syn-69a.

Identification code	C0076_0m
Empirical formula	$C_{16}H_{20}N_2O_6S$
Formula weight	368.40
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	7.7558(3)
b/Å	10.0904(4)
c/Å	22.1316(10)
α/°	90
β/°	98.937(2)
γ/°	90
Volume/Å^3	1710.97(12)
Z	4
ρ_{calc}g/cm^3	1.430
μ/mm^{-1}	0.225
F(000)	776.0
Crystal size/mm^3	0.937 × 0.388 × 0.274
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.494 to 77.996
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 17, -39 ≤ l ≤ 39
Reflections collected	83416
Independent reflections	9831 [R_{int} = 0.0298, R_{sigma} = 0.0188]
Data/restraints/parameters	9831/0/234
Goodness-of-fit on F^2	1.094
Final R indexes [I>=2σ (I)]	R_1 = 0.0294, wR_2 = 0.0828
Final R indexes [all data]	R_1 = 0.0317, wR_2 = 0.0848
Largest diff. peak/hole / e Å^{-3}	0.68/-0.43



94a

Crystal data and structure refinement for 94a.

Identification code	pbca
Empirical formula	$C_{19}H_{21}NO_4S$
Formula weight	359.43
Temperature/K	100
Crystal system	orthorhombic
Space group	Pbca
a/Å	16.4445(14)
b/Å	9.7793(8)
c/Å	21.9616(18)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	3531.8(5)
Z	8
ρ_{calc}g/cm^3	1.352
μ/mm^{-1}	0.207
F(000)	1520.0
Crystal size/mm^3	0.277 × 0.116 × 0.059
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.104 to 53.998
Index ranges	-21 ≤ h ≤ 21, -12 ≤ k ≤ 12, -28 ≤ l ≤ 28
Reflections collected	82730
Independent reflections	3852 [R_{int} = 0.0453, R_{sigma} = 0.0160]
Data/restraints/parameters	3852/0/251
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0417, wR_2 = 0.0946
Final R indexes [all data]	R_1 = 0.0493, wR_2 = 0.0985
Largest diff. peak/hole / e Å^{-3}	0.49/-0.50

5. References

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6. Appendix

6.1 Abbreviations

2-Pyr	2-pyridinyl
Ac	acetyl
Ar	aryl
BIOS	biology-oriented synthesis
Bn	benzyl
COMAS	Compound Management and Screening Center
DA	Diels Alder
DCE	1,2-dichloroethane
DCM	dichloromethane
DMSO	dimethyl sulfoxide
DMF	*N,N*-dimethylformamide
DOS	diversity-oriented synthesis
d.r.	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
Eh	2-ethylhexanoyl
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
Hh	hedgehog
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	half-maximal inhibitory concentration
*i*Pr	*iso*-propyl
J	coupling constants
Me	methyl
MOM	methoxymethyl
NMR	nuclear magnetic resonance
NP	natural product
nOe	nuclear Overhauser effect
Nu	nucleophile
Ph	phenyl
PMB	*para*-methoxy benzyl
ppm	parts per million
R*f*	retention factor
rt	room temperature
SAR	structure activity relationship
SCONP	structural classification of natural product
s.m.	starting material

SMO	smoothened
*t*Bu	*tert*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*para*-tosyl

Eidesstattliche Versicherung (Affidavit)

Zimmermann, Stefan
Name, Vorname
(Surname, first name)

129391
Matrikel-Nr.
(Enrolment number)

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6.3 Curriculum Vitae

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"Cascade Synthesis Strategies targeting biologically intriguing indole polycycles" M. G. Ciulla, **S. Zimmermann**, K. Kumar Org. Biomol. Chem. , **2019**, *17* , 413

"Unravelling Synthesis and Chemistry of Stable, Acyclic and Double-Deficient 1,3-Butadienes: An endo-selective Diels-Alder Route to Hedgehog Pathway Inhibitors" K. Kumar, X. Xin, **S. Zimmermann**, J. Flegel, F. Otte, L. Knauer, C. Strohmann, and S. Ziegler Chem. Eur. J., **2019**, *25*, 2717

"A Scaffold Diversity Synthesis of Biologically Intriguing Cyclic Sulfonamides" K. Kumar, **S. Zimmermann**, M. Akbarzadeh, F. Otte, C. Strohmann, M. Sankar, S. Ziegler, A. Pahl, and S. Sievers, Chem. Eur. J., **2019**, accepted author manuscript (doi.org/10.1002/chem.201904175)