Review

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THE CHEMICAL RECORD

Cyclic Sulfinamides

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Dedicated to our PhD students doing their research despite all the obstacles.

Abstract: The literature on cyclic sulfinamides (put simply, sultims) published from 1989 to 2022 has been summarized and reviewed. The information is divided into two sections: the analysis of synthetic methods on the preparation of cyclic sulfinamides and the discussion of the chemical properties of cyclic sulfinamides focusing on their reactions and applications. The survey of the reaction conditions, provided in the most detailed way, and a critical view of the reaction mechanisms add an extra dimension to the text. The data presented will be useful to specialists in different areas, especially those who work in the field of synthetic organic and pharmaceutical chemistry.

Keywords: Sulfinamides, Sultims, Heterocycles, Cyclization, Asymmetric synthesis

1. Introduction

Sulfinamide fragment is an increasingly popular group in contemporary synthetic organic chemistry.[1–3] Remarkable progress has been made in the chemistry of sulfinamides while the chemistry of their cyclic congeners remains less developed. With that, cyclic sulfinamides have triggered considerable attention over the past two decades and caused the exponential growth of publications on the topic.

The sulfinamide fragment has a trigonal pyramidal shape with a non-bonding electron pair on the sulfur atom at the apex,[4,5] that led to the point chirality with the stereogenic center at the sulfur atom (Figure 1, *A*). This is also true for the cyclic representatives (Figure 1, *B*). Gratifyingly, sulfinamides do not undergo inversion or racemization upon standing, moderately high temperature, and many chemical reaction conditions, so they can be synthesized and isolated in enantiopure forms. These features allow sulfinamides to play the pivotal role of key chiral auxiliaries in modern asymmetric synthesis.[2,3,6,7] Specifically, one of the most used chiral inductors are Ellman's[8–10] and Davis'[11,12] sulfinamides (Figure 1, *C*).

It should be noted that sulfinamides may exist in two resonance forms – neutral, possessing S=O double bond, and zwitterionic (Figure 2, *A*). The graphic representation of sulfinamides also has its own peculiarities. While the racemic sulfinamides or those with undefined configuration are drawn with classic S=O double bond or arrowed S→O bond (Figure 2, *B*) their chiral forms are customary drawn with bold wedged or hashed wedged S–O bond that is implied as double bond (Figure 2, *C*). This approach seems inconsistent though it is common in the sulfinamide-related literature and is used in the present text.

A bibliometric analysis of the literature showed that the utilization of sulfinamides in asymmetric synthesis has been a hot topic for reviews. The other aspects, such as syntheses and transformations, are not sufficiently covered.[1] The only review devoted to the cyclic sulfinamides was published more than 30 years ago as a part of a book subchapter in "*Sulphinic Acids, Esters and Derivatives*" and covered the literature up to the 1988th.[13]

This review provides an overview of the literature for 1989–2022 on the synthesis, reactions, and applications of cyclic sulfinamides. The key selection criterion for the structure of compounds discussed is the presence of the carbon atom α to the sulfur one (Figure 3, *A* and *B*). Since the compounds of type ***C*** are not formally cyclic sulfinamides but rather cyclic sulfurous diamides (X=N), cyclic esters of sulfuramidous acid (X=O) or sulfuramidous *S*-acid (X=S), *etc.* (Figure 3, *C*) they are beyond the scope of present work. With that, a heteroatom may be present in the middle part of the chain attached to both ends of the sulfinamide moiety (Figure 3, *B*).

In the beginning, we would like to discuss the etymological aspects of nomenclature and trivial names for some derivatives of carboxylic, sulfonic, and sulfinic acids. Thus, the names for their amides are logical and comprehensible (Figure 4, *A*). The trivial names for intramolecular cyclic esters of the above acids are somewhat more complicated. Particularly, cyclic esters of carboxylic acids are customarily called *lactones.* This term was coined by the French chemist Jules Pelouze to name the three-membered intramolecular ester of lactic acid which he obtained in 1844.[14] Later, in 1880 the German chemist Rudolph Fittig extended the term *lactone* to all cyclic carboxylic esters.[15] As a logical consequence and a portmanteau of the words *sulfa lactone* the term *sultone* emerged for the designation of cyclic sulfonates. With that, Donald Dittmer and Michael Hoey in their pioneering review[13] used the term *sultine* for naming

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cyclic sulfinates (Figure 4, *B*). A similar etymological approach was also applied to the designation of cyclic amides. Thus, the term *lactam* is a lexical blend of the words *lactone* and *amide*. In turn, the term *sultam* arose from *sulfa lactam* and has been used for cyclic sulfonamides. Considering the cyclic sulfinamides as a separate class and following the above etymological principles we propose to name them as *sultims* (Figure 4, *C*). This term was sporadically mentioned before[16,17] and is used further in the text as a shortened title for discussed cyclic sulfinamides.

Similarly to all the above cyclic derivatives, a Greek letter prefix specifies the number of atoms in the sultim cycle. The first carbon atom after the sulfur one is labeled α, the second one is β, and so forth along said backbone – the atom chain connecting both ends of the sulfinamide moiety (Figure 5). Intriguingly, 3- and 8-membered sultims have not been known to date.

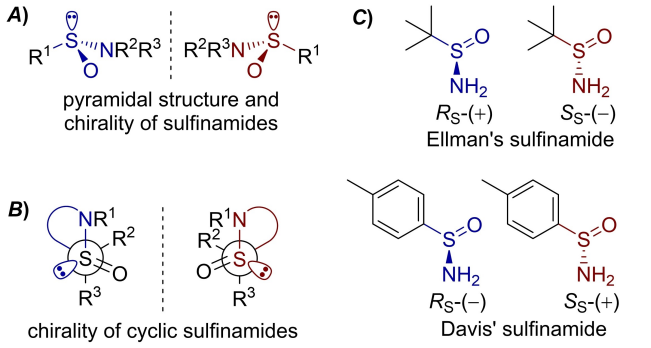

Figure 1. The structure of sulfinamides and the most known representatives.

2. Synthetic Approaches to Sultims

The discussed synthetic methods are structured according to the type of reactions. Considering the stereochemical particularities of the sulfinamide fragment it is implied that all the discussed below cyclic or linear sulfinamides (starting or target) were used or isolated as racemates with respect to the sulfur atom unless otherwise specified. As much as possible, the reaction conditions in the Schemes are provided in the most detailed way, but not always the authors of the reviewed articles reported the mechanisms and even procedures.

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Yulian M. Volovenko has been a Dean of the Faculty of Chemistry at Taras Shevchenko National University of Kyiv (Ukraine) since 2007. He received his MSc (1972), PhD (1986), and DSc (1998) degrees in organic chemistry from the same university. Yulian Volovenko is a coauthor of more than 200 papers. His research interests center around the design and synthesis of heterocyclic compounds and physical methods in organic chemistry. He has focused on the chemistry of sulfonamides since the late 1980s.

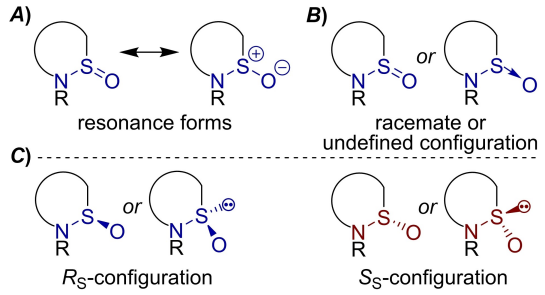


Figure 2. Resonance forms and graphic representation of cyclic sulfinamides.

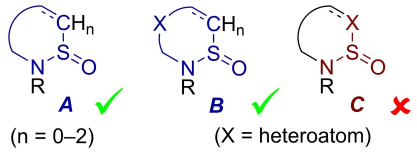


Figure 3. The selection criterion for the structure of compounds discussed.

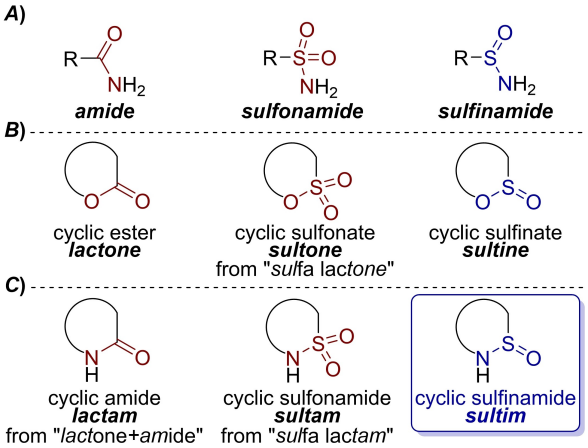


Figure 4. Structural and etymological similarity of carboxylic, sulfonic, and sulfinic acid derivatives.

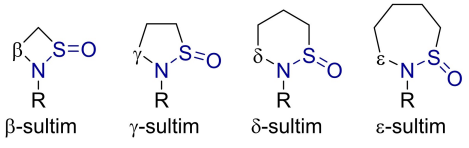


Figure 5. Trivial nomenclature for sultims depending on the ring size.

2.1. Oxidation

Historically first and the most widely used methods for the synthesis of sultims are based on converting the thiohydroxylamine moiety ($R^1S–NR^2R^3$) into the sulfinamide one ($R^1S(O)–NR^2R^3$).

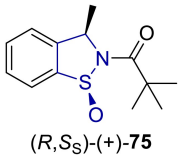


Figure 6. The structure of γ-sultim (R,S_S)-(+)-**75**.

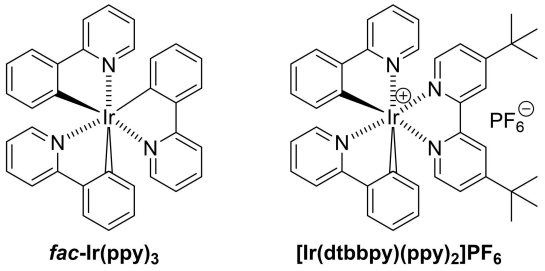
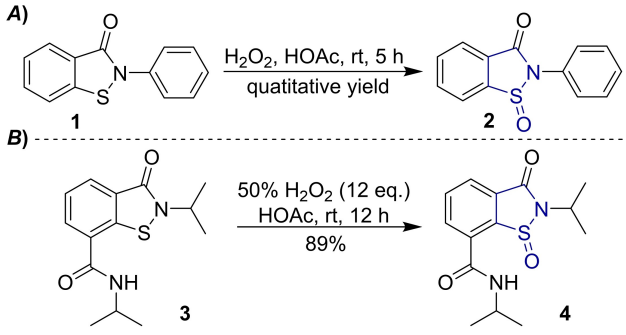


Figure 7. Ir (III) catalysts for photoinduced intramolecular homolytic substitution.

Hydrogen peroxide. H_2O_2 in HOAc media under mild conditions (rt−60 °C) is one of the most common methods for the oxidation of the thiohydroxylamines into the corresponding sulfonamides. This is also true for cyclic thiohydroxylamines which are converted into the corresponding sultims.

D. He and Z. Wang reported H_2O_2-mediated oxidation of benzofused isothiazolinone **1**. The reaction was performed in HOAc at rt and succeeded in a quantitative yield of γ-sultim **2** (Scheme 1, *A*).[18] B. Kersting and M. DeLion also chose this procedure for the preparation of γ-sultim **4** (Scheme 1, *B*).[19]

Apart from that, sultim **2** was formed during the experiments on modeling the anticancer activity of organoruthenium complex $[(\eta^6\text{-}p\text{-cymene})Ru(H_2N(CH_2)_2NH_2)Cl]PF_6$, which coordinated 2-mercaptobenzanilide, a recognized model for the active site of protein tyrosine phosphatase 1B (PTP1B). To assess the effect of coordination on the redox regulation the

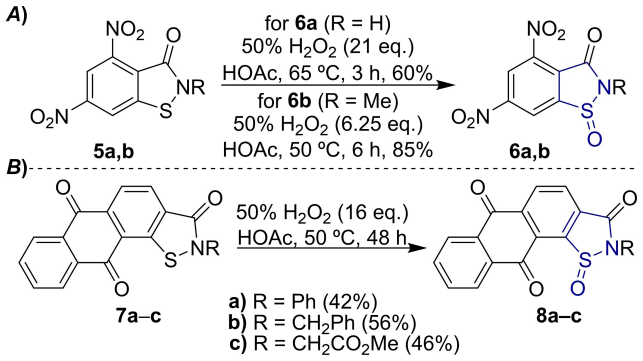


Scheme 1. Oxidation of benzofused isothiazolinones **1** and **3** with H_2O_2 at rt.

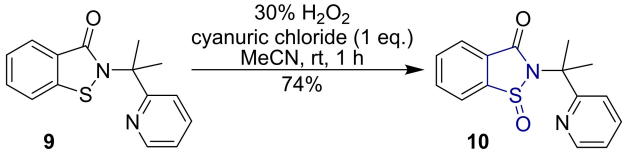
reaction with H_2O_2 was undertaken. This reaction yielded several oxidized products among which was γ-sultim **2**.[20] This method does not have the synthetic utility in terms of sultim chemistry (not shown in Scheme).

In a similar way (H_2O_2–HOAc) but at a higher temperature (50–65 °C) S. Zlotin's group obtained dinitro benzofused sultims **6** (Scheme 2, *A*)[21] as well as a series of polycyclic sultims **8** (Scheme 2, *B*).[22]

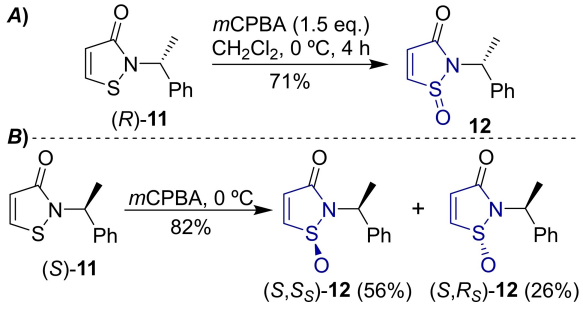
J. Wu and B.-F. Shi carried out the oxidation of benzofused isothiazolinone **9** bearing 2-pyridyl substituent in MeCN. They used H_2O_2 and an equimolar additive (towards **9**) of cyanuric chloride. Apparently, the latter was used as a known promoter for the oxidation of sulfides[23] with the aim of preventing the formation of the corresponding *N*-oxide on the pyridyl substituent. The formation of *N*-oxide on the annelated pyridine ring is demonstrated below in Scheme 88. This method allowed obtaining γ-sultim **10** in good yield without affecting the pyridine core (Scheme 3).[24]



Scheme 2. Oxidation of benzofused isothiazolinones **5** and **7** with H_2O_2 upon heating.



Scheme 3. Oxidation of benzofused isothiazolinone **9** with H_2O_2 and cyanuric chloride.



Scheme 4. Oxidation of isothiazolinones **11** with *m*CPBA at 0 °C.

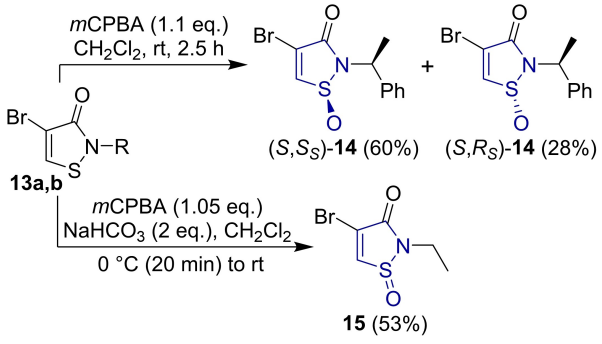
***meta*-Chloroperoxybenzoic acid (*m*CPBA).** It is customary to use either a stoichiometric equivalent or a slight excess of *m*CPBA when oxidizing the thiohydroxylamine moiety. The most common media for the reaction is CH_2Cl_2 at 0 °C or rt.

In this way, B. Touré and D. Hall converted isothiazolinone (*R*)-**11** into the corresponding γ-sultim **12** (Scheme 4, *A*).[25] Another fact of interest: the work-up procedure included column chromatography purification, which allowed for the isolation of both diastereomers: the major crystalline and the minor oily product (*ca.* 7 : 3 ratio). Unfortunately, their absolute configuration was not established. At the same time, A. Waldner subjected another stereoisomer (*S*)-**11** to the same reaction and work-up procedure but established the absolute configuration of the isolated γ-sultim (*S*)-**12** (Scheme 4, *B*).[26]

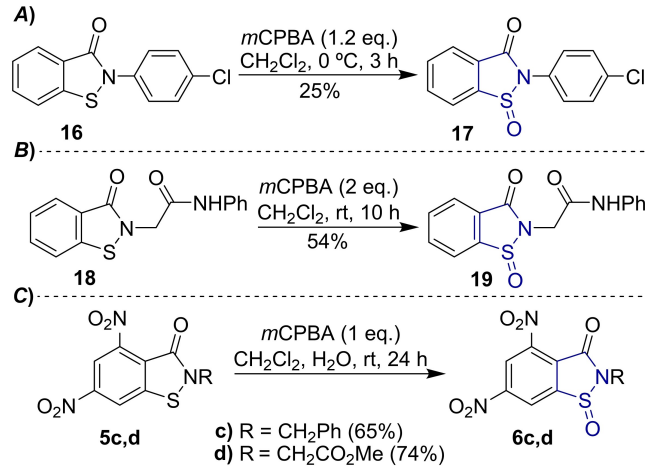
This approach was also applicable to bromo-substituted isothiazolinones **13** and may be implemented either in combination with $NaHCO_3$ or without it (Scheme 5).[27,28] Much as in the previous case, sultim **14** possessing chiral (*S*)-α-methylbenzyl substituent and an additional stereogenic center at the sulfur atom was isolated as two separate diastereoisomers. In a similar manner C. Fishwick *et al.* obtained sultim **15** as a substrate for the Stille coupling.[29]

There are a few examples of using *m*CPBA for the oxidation of endocyclic thiohydroxylamine fragments of bezofused isothiazolinones which were converted into the corresponding γ-sultims, but also not in high yield (Scheme 6, *A*,[30] *B*,[31] and *C*[32]).

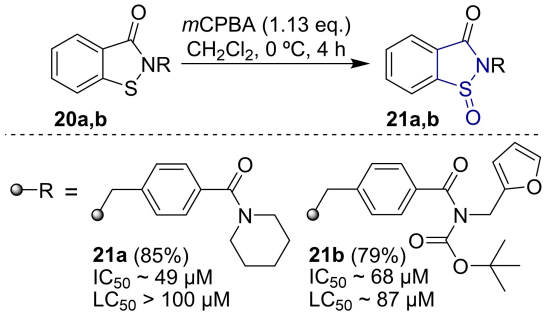
H. Yin *et al.* prepared a series of saccharin derivatives upon the look for the inhibitors of interferon-mediated inflammation. Their efforts produced a lead compound (not shown) and sultims **21** prepared *via* *m*CPBA-mediated oxidation procedure (Scheme 7).[33] The latters showed *in vitro* inhibition activity in tests with RAW 264.7 cells.



Scheme 5. Oxidation of isothiazolinones **13** with *m*CPBA at rt.



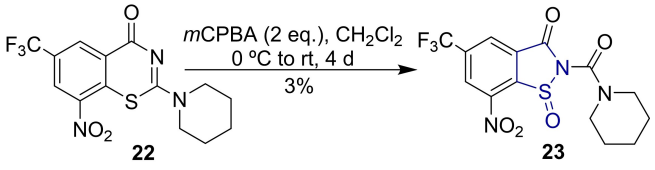
Scheme 6. Oxidation of benzofused isothiazolinones **5**, **16**, and **18** with *m*CPBA.



Scheme 7. Oxidation of benzofused isothiazolinones **20** with *m*CPBA.

R. Seidel *et al.* reported ring-contracted oxidation of benzothiazinone **22** with *m*CPBA accomplished with the formation of fused γ-sultim **23**, which was isolated after HPLC purification in a quite poor yield (Scheme 8).[34]

Chlorine and chlorinating agents. Cl_2-mediated oxidation is usually conducted by passing the chlorine flow through the reaction mixture containing a substrate dissolved or dispersed as a suspension. In so doing, the presence of water in the reaction media is obligatory since it serves as an oxygen atom source.

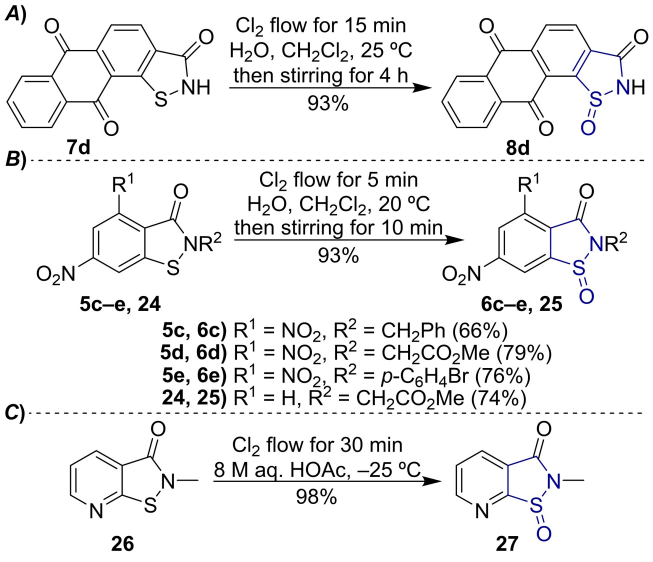


Scheme 8. Ring-contracted oxidation of benzothiazinone **22** with *m*CPBA.

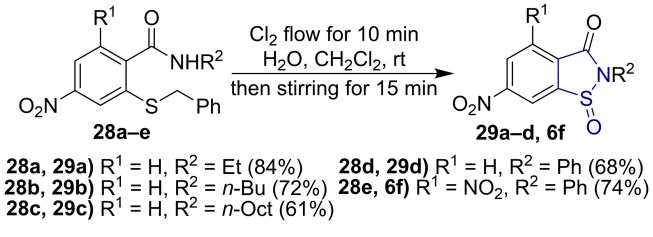
In this way, Zlotin's group converted polycyclic and benzofused isothiazolinones into the corresponding γ-sultims in three-phase media (*i. e.* suspension in CH_2Cl_2–H_2O) (Scheme 9, *A*[35] and *B*[32]). V. Martinez-Merino and colleagues obtained heterofused γ-sultim **27** in almost quantitative yield by a close method but used aqueous HOAc (Schemes 9, *C*).[36]

Further, Zlotin's group developed an approach to the synthesis of benzofused γ-sultims based on the tandem Cl_2-mediated oxidation–cyclization reaction. By this method, 2-(benzylthio)-4-nitrobenzamides **28** turned into γ-sultims **29** and **6** under the above reaction conditions (Scheme 10).[37]

The following investigation of the substrate scope for this reaction showed, that the structurally different products formed depending on the nature of the *S*-alkyl substituent. Particularly, the Cl_2-mediated oxidative cyclization of *S*–*t*-Bu substituted benzamide **30 a** was accompanied by the cleavage of the *t*-Bu group to form **29 e** whereas *S*–*n*-Bu substituted counterpart **30 b** underwent migration of the *n*-Bu group from the sulfur atom to the nitrogen one thus providing *N*-alkylated γ-sultim



Scheme 9. Cl_2-Mediated oxidation of carbo- (**5**, **7**, **24**) and heterofused (**26**) isothiazolinones.



Scheme 10. Cl_2-Mediated oxidative cyclization of 2-(benzylthio)benzamides **28**.

29b (Scheme 11, *A*). The authors proposed the mechanism for the formation of **29e** (Scheme 11, *B*) whereas the mechanism for the formation of **29b** remains unclear.[37]

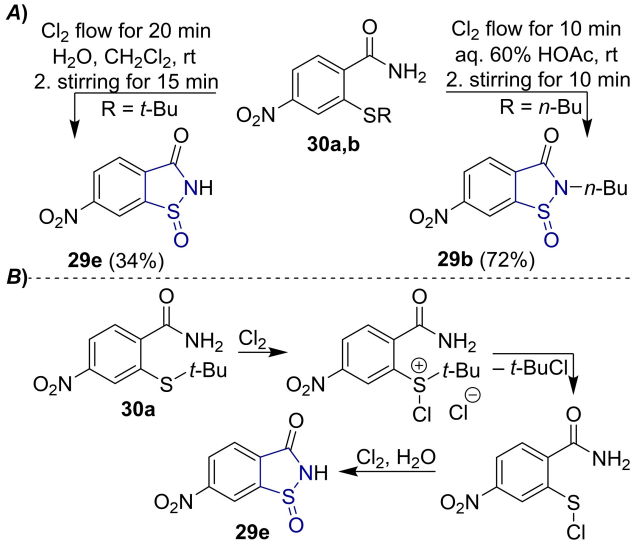
On the purpose of developing Ebsulfur[38,39] analogs S. Garneau-Tsodikova *et al.* obtained a range of benzofused isothiazolinones that differed in the structure of a substituent at the nitrogen atom as well as three *S*-oxidized counterparts (*i.e.* benzofused γ-sultims). Their method was based on *N*-chlorosuccinimide (NCS)-mediated oxidative cyclization of disulfides **32** *in situ* prepared from the corresponding acid chloride **31**. These reactions were carried out following a single-flask method and afforded sultims **33** in moderate to good yields (Scheme 12).[40] Regrettably, these *S*-oxidized Ebsulfur analogs showed neither antibacterial[40] nor antifungal[41] activity.

Finally, within a project on the design of bacterial serine protease inhibitors Z. Chen *et al.* developed the stereoselective synthesis of valuable multichiral γ-sultims with their cyclic backbones comprising predominantly of sp^3 atoms. To this end, dipeptides **34** were titrated with the appropriate amount of Cl_2 and water followed by treatment of intermediate sulfinyl chlorides **35** with pyridine. This oxidation–intramolecular sulfinylation sequence provided the corresponding sp^3-enriched γ-sultims **36** with good overall yield and excellent *dr* (Scheme 13).[42]

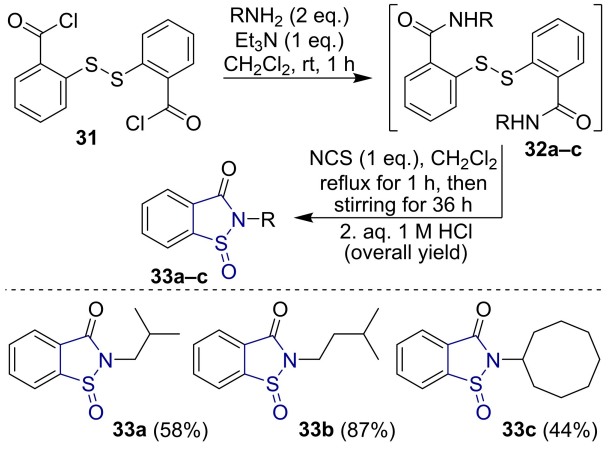
The stereoselectivity is controlled primarily by the NHCbz group, which prefers to be oriented *trans* to the oxygen atom of the emerging sulfinamide group, thus reducing steric hindrance *via* avoiding transannular 1,3-interaction in the cyclization step. The configuration of the target γ-sultims was confirmed by an X-ray diffraction study. Contrary to expectations, **36** showed weak antibacterial activity against Gram-negative bacteria (*Enterobacter cloacae* and *Moraxella catarrhalis*).

Bromine and brominating agents. With an aim of obtaining isothiazolidine **38** as the key precursor for further studies, K. Gates *et al.* implemented Br_2-mediated oxidative cyclization of similar disulfide-containing dipeptide **37**. However, aside from the desired product **38**, the corresponding γ-sultim **39** and γ-sultam **40** were formed in poor yields as by-products (Scheme 14).[43]

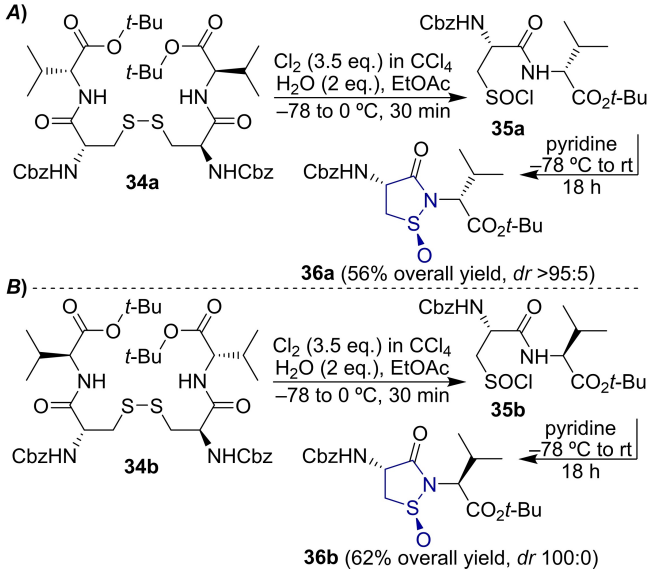
Apart from that, brominating agents such as *N*-bromosuccinimide (NBS) or dibromoisocyanuric acid (DBI) were



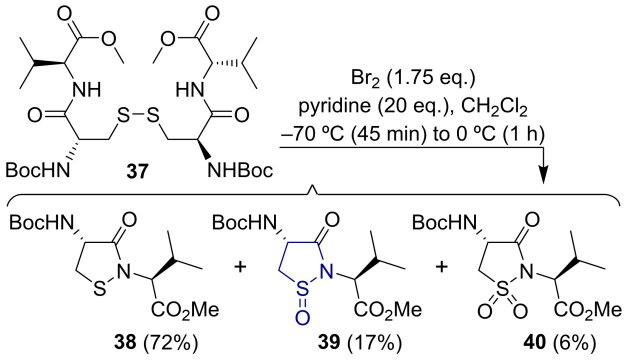
Scheme 11. Cl_2-Mediated oxidative cyclization of *S*–alkyl substituted benzamides **30**.



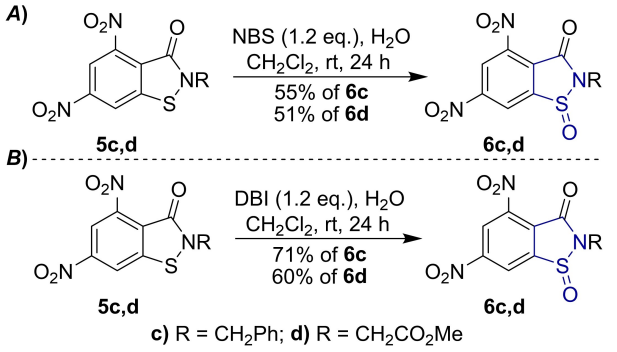
Scheme 12. One-pot amination-NCS-mediated oxidative cyclization of acid chloride **31**.



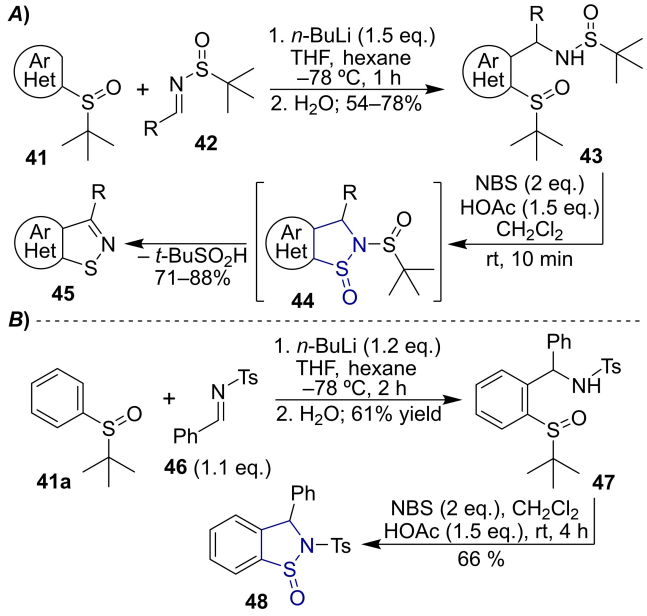
Scheme 13. Cl_2-Mediated oxidative cyclization of disulfide-containing dipeptides **34**.



Scheme 14. Br_2-Mediated oxidative cyclization of disulfide-containing dipeptide **37**.



Scheme 15. NBS and DBI-mediated oxidation of benzofused isothiazolinones **5**.



Scheme 16. Synthesis of aryl[4,5]isothiazoles **45** through the all-heteroatom Wittig-equivalent reaction (*A*) and synthesis of benzofused γ-sultim **48** (*B*).

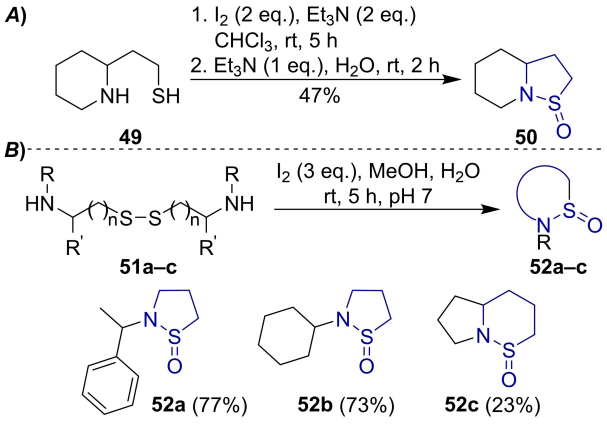
successfully used for the oxidation of bezofused isothiazolinones **5** into the corresponding γ-sultims **6** (Scheme 15).[32]

Z. Sun *et al.* developed an approach to aryl[4,5]isothiazoles starting from (het)aryl sulfoxides **41** and sulfinimines **42** through the all-heteroatom Wittig-equivalent reaction.[44] The proposed mechanism involved NBS-promoted formation of sultim-containing intermediate **44** followed by rearrangement into target fused isothiazole **45** (Scheme 16, *A*). Intending to provide evidence of the Wittig-like reaction, the authors reasoned the isolation of a more stable sulfonamide equivalent of the implied intermediate. Toward this end, the Michael adduct **47** obtained from *N*-tosylated phenylmethanimine (**46**) and lithiated (*tert*-butylsulfinyl)benzene (**41 a**) was treated with NBS that afforded expected *N*-tosylated sultim **48** in moderate yield (Scheme 16, *B*).[44]

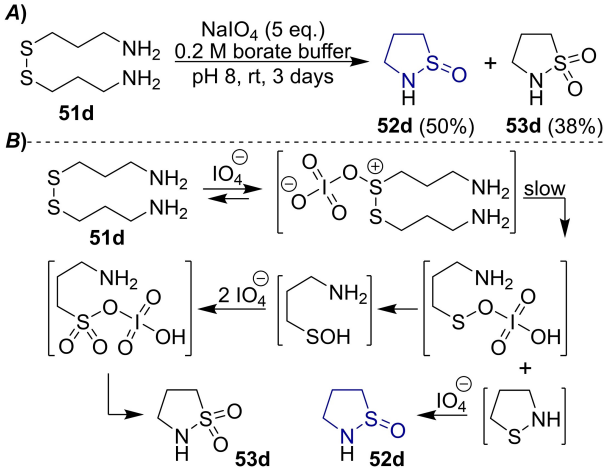
Iodine and periodates. I_2 is a rarely used reagent that has a limited use for the synthesis of sp^3-enriched sultims. It is used in stoichiometric amounts for the oxidation of either secondary amino sulfides **49** or the corresponding disulfides **51** in basic (or neutral) aqueous media at rt. Following these procedures T. Doi and K. Musker obtained γ-sultims **50**, **52 a,b** and δ-sultim **52 c** in moderate and low yields, respectively (Scheme 17).[45]

The above research group also used $NaIO_4$ in borate buffer for the oxidation of amino disulfide **51 d**. The reaction was not selective and afforded a mixture of unsubstituted γ-sultim **52 d** and γ-sultam **53 d**, which were isolated by means of column chromatography in fair yields (Scheme 18, *A*). The authors also suggested the plausible mechanism for $NaIO_4$-mediated oxidation of the above amino disulfide (Scheme 18, *B*).[46]

$NaIO_4$ has limited use. It causes oxidative ring contraction of dihydrobenzothiazines **54** in aqueous MeOH at rt. J. Szabó and colleagues assumed that the reaction proceeded *via* the formation of sulfoxide **55**, which expelled aldehyde upon hydrolysis and simultaneously cyclized into dihydroisothiazole

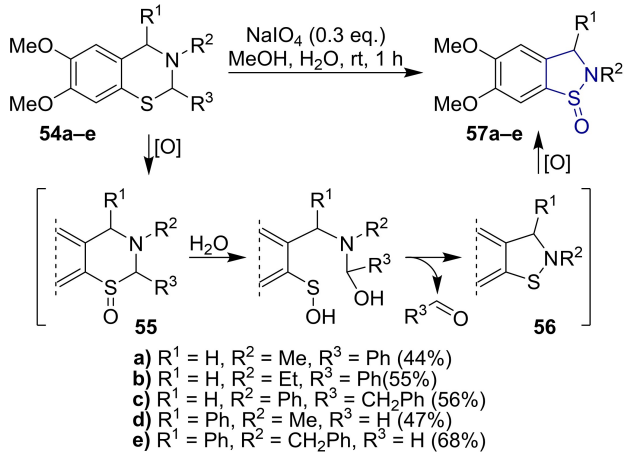


Scheme 17. Oxidative cyclization of amino sulfide **49** and amino disulfides **51** with I_2.

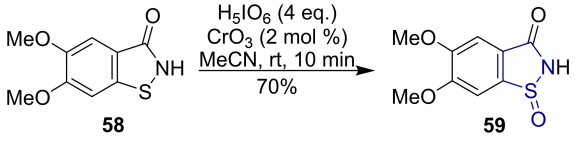


Scheme 18. Oxidative cyclization of amino disulfide **51 d** with $NaIO_4$ and a plausible mechanism for this reaction.

56. The latter was also oxidized at the sulfur atom eventually affording benzofused γ-sultim **57** (Scheme 19).[47] However, none of the suggested intermediates were detected when the oxidation had been conducted with less than a stoichiometric amount of $NaIO_4$. Instead, a mixture of sultim **57** and intact **54** was isolated.



Scheme 19. $NaIO_4$-Mediated ring contraction and oxidation of dihydrobenzothiazines **54**.



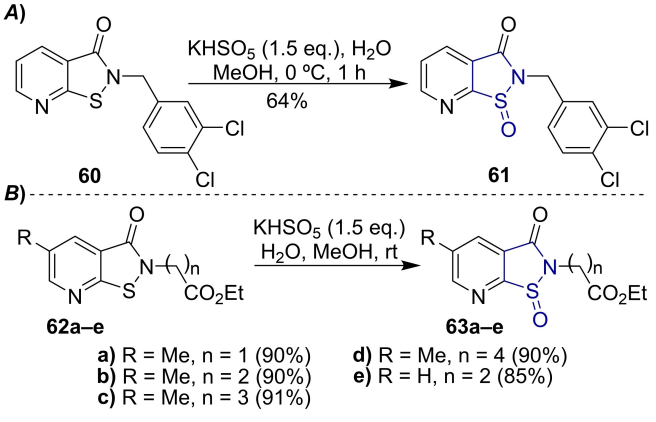
Scheme 20. H_5IO_6–CrO_3-mediated oxidation of isothiazolidinone **58**.

Another iodine (VII)-containing oxidant applied for the oxidation of the isothiazole core is H_5IO_6. Z. Tan and Y. Deng used it in combination with a catalytic amount of CrO_3 in MeCN at rt. This method allowed for the preparation of benzofused γ-sultim **59** in a short time and with moderate yield (Scheme 20).[48]

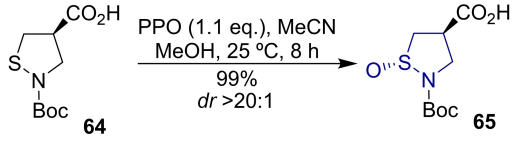
Miscellaneous oxidants. The drawbacks of conventional oxidants which may cause undesired overoxidation of the sulfur (IV) atom (inside sultim core) as well as other susceptible functionalities drove chemists to discover novel reagents and associated protocols for a more selective oxidation of sulfur (II) containing substrates providing better yields.

Treatment of pyridofused isothiazolinone **60** with $KHSO_5$ (brand name *Oxone*) in aqueous MeOH allowed W. Sippl and colleagues to obtain the racemic γ-sultim **61** without affecting the pyridine core (Scheme 21, *A*).[49] V. Merino *et al.* also used this method in the synthesis of other pyridofused γ-sultims **63** as potential herbicides (Scheme 21, *B*).[50] However, the synthetic potential of their method showed significantly better results than the plant-growth-regulating activity of the compounds synthesized.

Considering the importance of asymmetric syntheses, we would like to emphasize the phthaloyl peroxide (PPO)-mediated oxidation of chiral isothiazolidine **64** described by the group of L. Shi. This method allowed the stereoselective course of the reaction affording the corresponding γ-sultim **65** both in excellent yield and diastereoselectivity (Scheme 22).[51]



Scheme 21. *Oxone*-mediated oxidation of pyridofused isothiazolinones **60** and **62**.



Scheme 22. Diastereoselective PPO-mediated oxidation of isothiazolidine **64**.

T. Shimizu and N. Kamigata used ozone at low temperature (−20 °C) for the oxidation of benzofused isothiazolinone **66**. Notably, the work-up procedure included quite simple manipulations. The method showed unexpectedly good results and gave the corresponding γ-sultim **67** in good yield (Scheme 23).[52] The authors also obtained this sultim in optically pure form (100 % *ee*) by means of chromatographic resolution on a chiral column (not shown in Scheme).

K. Gates *et al.* oxidized a similar benzofused isothiazolinone **68a** into the corresponding γ-sultim **69a** using dimethyldioxirane (DMDO) also known as the Murray's reagent.[53] It is worth noting the mild reaction conditions, the simplicity of the work-up procedure (just ordinary evaporation), and the excellent yield (Scheme 24).[54]

In a search for inhibitors of SARS-CoV-2 main protease (M^{pro})[55] C. Schofield *et al.* devised a series of sulfur analogs of Ebselen[56,57] which has attracted attention due to the potential to treat COVID-19. Among this series were benzofused isothiazolinone **68b** and the corresponding γ-sultim **69b**. Interestingly, both compounds were obtained from the common precursor iododerivative **70** through the Cu (I)-catalyzed tandem substitution–ring-closure reaction. The procedures for the preparation of **68b** and **69b** differ only in the atmosphere, *i. e.* the presence or the absence of air (Scheme 25). Therefore it can be assumed that γ-sultim **69b** formed when **68b** was oxidized with air. Despite **69b** had been obtained in poor yield it showed some M^{pro} inhibition activity (IC_{50} ~2.9 μM).[58]

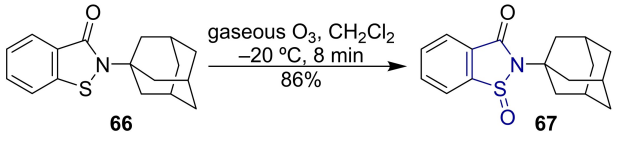
Finally, A. Nudelman and A. Hassner obtained an interesting result when exposed the fused isoxazoline **71** to the action of $LiAlH_4$ and obtained γ-sultim **72**, albeit in poor yield (Scheme 26).[59] The authors assumed that the oxidation of the sulfur atom was attributed to the action of air, which occurred during the work-up procedure upon isolation and purification steps.

2.2. Intramolecular Sulfinylation

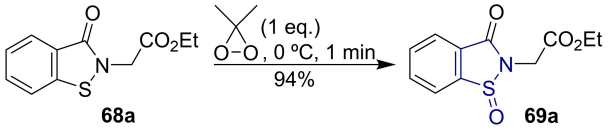
These methods are based on the intramolecular cyclization of sulfinic acid derivatives possessing an amino group. In most cases, the direct precursors for this reaction are generated *in situ* through the introduction of the sulfur (IV)-containing functionalities in the structure of the corresponding amines and amides.

W. Oppolzer *et al.* conducted intramolecular sulfinylation of amide functionality in chiral sulfinic acid **74**, obtained from amide **73**. The two-step process, namely $SOCl_2$-mediated activation and NaH-promoted cyclization succeeded in moderate overall yield. It is worth noting, that benzofused γ-sultim **75** was obtained with excellent diastereoselectivity (Scheme 27).[60]

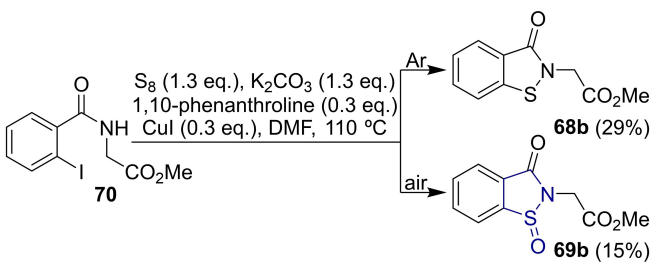
Later, this study was continued by M. Wills *et al.* This research group optimized the reaction conditions for the cyclization of amido sulfinic acid **74** and suggested using tertiary amines instead of NaH. It turned out, that the nature of the amine has an impact on the *cis*/*trans* ratio of the target product. Thus, the highest selectivity was provided with DMAP (to give exclusively *cis*-**75**) while the pyridine-mediated cyclization afforded a 6 : 4 *cis*/*trans* ratio only (Scheme 28).[61]



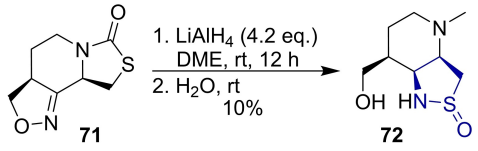
Scheme 23. O_3-mediated oxidation of benzofused isothiazolinone **71**.



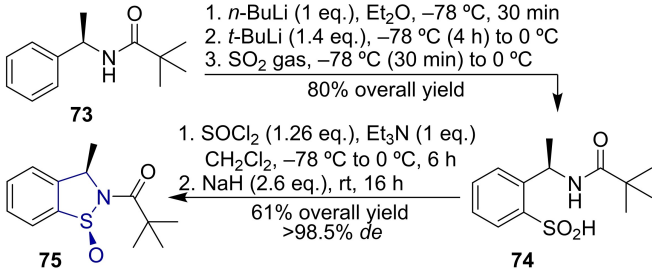
Scheme 24. DMDO-mediated oxidation of benzofused isothiazolinone **68a**.



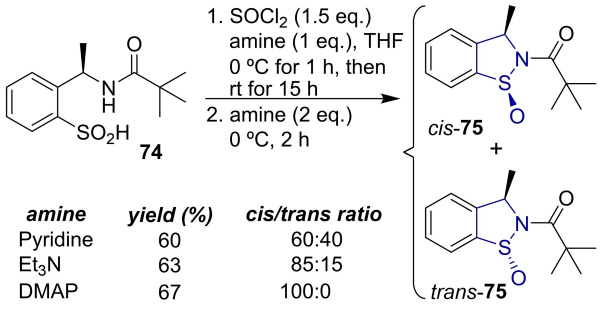
Scheme 25. Synthesis of benzofused isothiazolinone **68b** and γ-sultim **69b**.



Scheme 26. The unexpected synthesis of sp^3-enriched γ-sultim **72**.



Scheme 27. Synthesis of sulfinic acid **74** and its conversion into γ-sultim **75**.



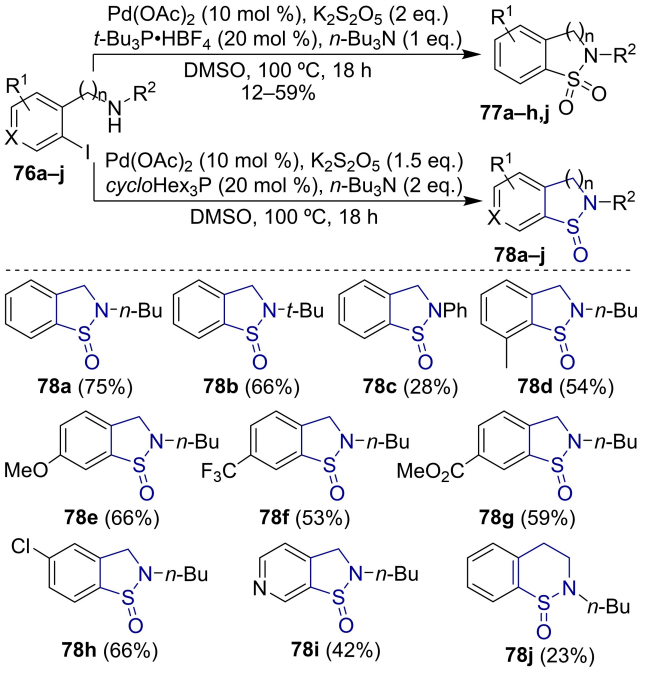
Scheme 28. Reaction conditions for the synthesis of benzofused γ-sultim **75**.

M. Wills *et al.* reported that sultim *trans*-**75** is less stable than its counterpart *cis*-**75**. The former was faster consumed in the reactions and more rapidly oxidized into the corresponding γ-sultam.[62] Besides, the researchers performed the above synthesis in an asymmetric manner and obtained (R,S_S)-(+)-**75** (Figure 6), which was used as a recoverable chiral source in the asymmetric aldol condensation.[62]

K. Manabe and coworkers used iodo(het)arenes **76** bearing alkylamino substituent at the *ortho*-position as the substrates for the coupling reaction and $K_2S_2O_5$ as a sulfur atom source (SO_2 surrogate). The reaction was catalyzed by $Pd(OAc)_2$ and was performed in DMSO media. With that, the nature of a ligand and the amount of a base were the key factors in determining the chemoselectivity. Thus, varying the reaction conditions either sultams **77** or sultims **78** can be prepared from the same precursors, catalyst, and SO_2 surrogate (Scheme 29).[63] These innovations allowed significantly improve the reaction outcome as well as expand the substrate scope: both 5- and 6-membered benzo- or pyridofused sultims can be prepared by this method. The most common substituents and functional groups in the benzene ring are also tolerated.

Another fact of interest was an attempt of creating a sultim-containing prodrug of natural antitumor antibiotic *Leinamycin* isolated from a culture broth of *Streptomyces* sp.[64,65] *Leinamycin* induces single-strand scission of plasmid DNA in the presence of thiol cofactors and thus shows potent *in vitro* antitumor activity against human tumor xenograft (such as lung, liver, ovary, prostate, and colon carcinomas). At the same time *in vivo* antitumor activity is compromised by its instability. This issue was addressed in KF2267 which acts as a prodrug providing the active form in biological media.

In pursuing this goal, Y. Kanda *et al.* alkylated *Leinamycin* with an excess of **79** thus introducing a 1,3-dioxolone trigger. In so doing, the ring opening of the spirocyclic 1-oxo-1,2-dithiolan-3-one fragment occurred against the background of the formation of the γ-sultim cycle through intramolecular sulfinylation of adjacent amide fragment. Thereafter, with the aim of improving stability the secondary hydroxyl group of the formed precursor **80** was blocked with THP protecting group

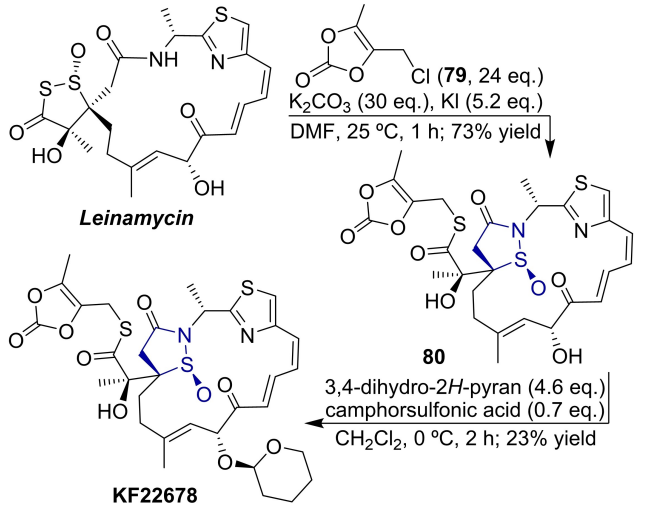


Scheme 29. Pd-Catalyzed chemoselective synthesis of sultams **77** and sultims **78** from iodo(het)arenes using $K_2S_2O_5$ as an SO_2 surrogate.

and the resulting mixture was subjected to a chromatographic separation procedure eventually affording KF2267 possessing more active (*R*)-THP fragment (Scheme 30).[66,67]

KF2267 showed significant *in vitro* antiproliferative activity against HeLa S_3 cells (IC_{50} 0.67 nM) and *in vivo* antitumor activity against mouse sarcoma 180 (optimal dose 8 mg/kg).[66]

Besides, methods based on cyclization of appropriately substituted sulfinic acids allowed for the preparation of



Scheme 30. Synthesis of KF2267 from *Leinamycin*.

extremely rare 7-membered azasultims **82** from the corresponding phenylenediamines **81** and ketene in liquid SO_2 media (Scheme 31).[68,69]

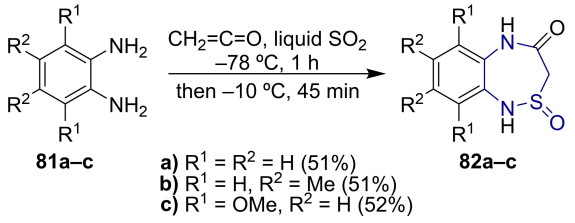
2.3. Intramolecular Homolytic Substitution

Though intramolecular homolytic substitution (S_Hi) has been extensively explored for a long period of time it has been put into practice for the sultim-directed synthesis since the mid-2000s. Nowadays it is one of the most efficient methods, featured by broad functional group tolerance, high product diversity, and excellent stereocontrol.

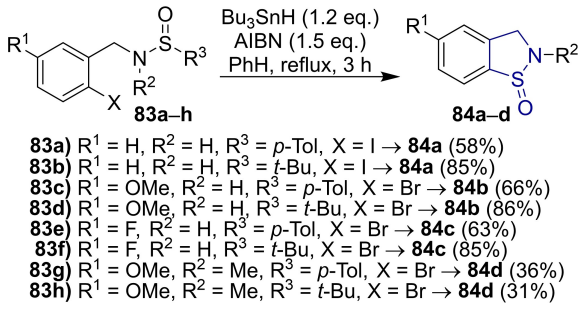
According to this strategy, the highly accessible benzyl sulfinamides **83** possessing a halogen atom at the *ortho*-position were subjected to the classical tributyltin hydride conditions (Bu_3SnH, AIBN, heat) in PhH media. Homolytic substitution at the sulfur atom was accompanied by the expulsion of *p*-Tol• or a more stable *t*-Bu• radical. In this way, L. Fensterbank *et al.* obtained a series of benzofused γ-sultims **84** in fair to good yields (selected examples are depicted in Scheme 32).[70,71]

Worthy of note, the introduction of an alkyl group on the nitrogen atom proved to be detrimental to the reaction outcome and lowered the yield of the target sultim **84d**. Apparently, this arises from the formation of the corresponding α-amino radical, which is stabilized and prone to undergo fragmentation to give intractable material.

The above research group also determined the stereochemical outcome of the reaction at the stereogenic sulfur atom.



Scheme 31. Synthesis of benzofused ε-sultims **82**.



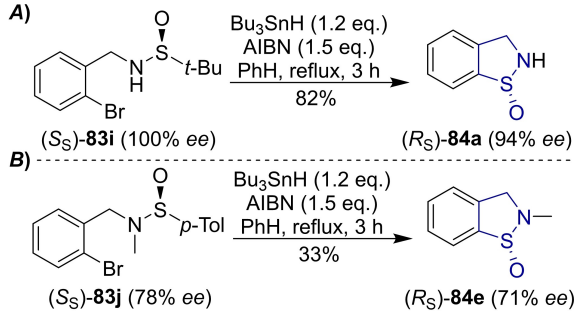
Scheme 32. Synthesis of benzofused γ-sultims **84** *via* intramolecular homolytic substitution (S_Hi).

Considering Beckwith's findings[72] on the cyclization of sulfoxides proceeded through the S_Hi mechanism and accompanied by the inversion of configuration at the sulfur atom as well as observing the inversion (without loss of enantiopurity) upon homolytic cyclization of chiral sulfinates into sultines (confirmed by independent synthesis)[70] it was decided to study the behavior of chiral sulfinamides. The experiments showed, that the intramolecular homolytic substitution in chiral sulfinamides (S_S)-**83i** and (S_S)-**83j** also proceeded with inversion of configuration and with a slight decrease of *ee* (Scheme 33).[70]

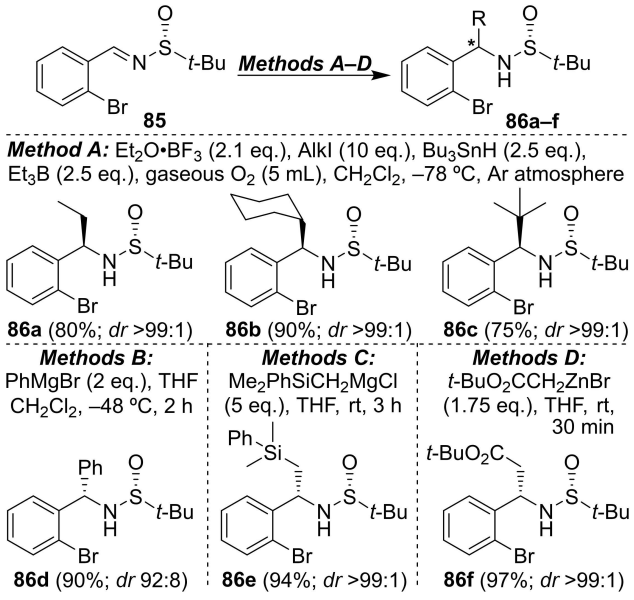
C. Maestro and M. Rodríguez-Fernández have taken this reaction to a new level and demonstrated their potential in the synthesis of enantiopure benzofused γ-sultims. Toward this end on the preliminary step, they developed the synthesis of chiral precursors **86** in four different ways. Particularly, the reduction of the C=N bond in sulfinimide **85** accompanied by the introduction of the substituent at adjacent carbon atom was performed with the complete control of the configuration under either radical reaction conditions (Scheme 34, *Method A*) or upon reaction with the Grignard or the Reformatsky reagents (Scheme 34, *Methods B–D*).[73]

With the chiral sulfinimides **86** in hand, the researchers conducted the S_Hi cyclization reaction under slightly modified conditions. It transpired that the reaction occurred with the complete inversion of the sulfur configuration, regardless of the α-carbon atom configuration of the starting sulfinamide **86** terminating with the exclusive formation of only one diastereoisomer **87**. The presence of the substituent at the α-carbon atom slowed down and hindered the pseudorotation in the hypervalent intermediate thus precluding racemization at the sulfur atom and providing enantiopure products (compare *de* and *ee* in Schemes 33 and 35). Moreover, many important functional groups (such as CO_2t-Bu) did not have any influence on the reaction course (Scheme 35).[73]

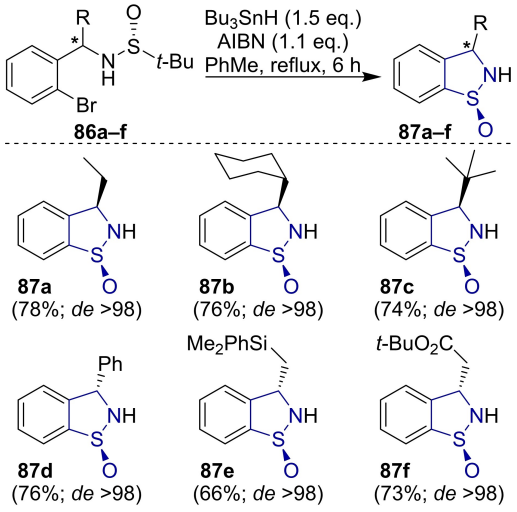
Then the S_Hi cyclization reaction was examined on the sp^3-enriched sulfinamides **88** bearing PhSe-leaving group. It turned out that the method was fully applicable and the desired γ-



Scheme 33. The fate of the sulfur stereogenic center upon S_Hi cyclization of halogenated benzyl sulfinamides **83**.

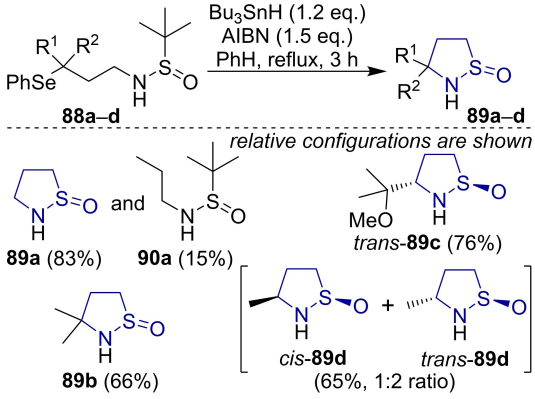


Scheme 34. Synthesis of chiral precursors for intramolecular homolytic substitution.



Scheme 35. The synthesis of chiral benzofused γ-sultims **87** *via* asymmetric intramolecular homolytic substitution.

sultims **89** were obtained in good yields. Notably, the unsubstituted γ-sultim **89a** was isolated along with its reduced by-product **90a**. With that, incoming substituents in **88c,d** were prostereogenic thus affecting the diastereoselective outcome with varying success. In this way, sulfinamide possessing bulky Me_2(MeO)C-group adjacent to PhSe resulted in exclusively *trans*-**89c**, while a small methyl group at the same position was converted into a *ca.* 1 : 2 mixture of *cis*- and *trans*-γ-sultims **89d** (Scheme 36).[70]

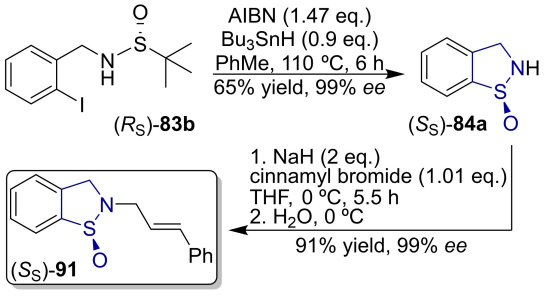


Scheme 36. Synthesis of sp^3-enriched γ-sultims **89** *via* intramolecular homolytic substitution.

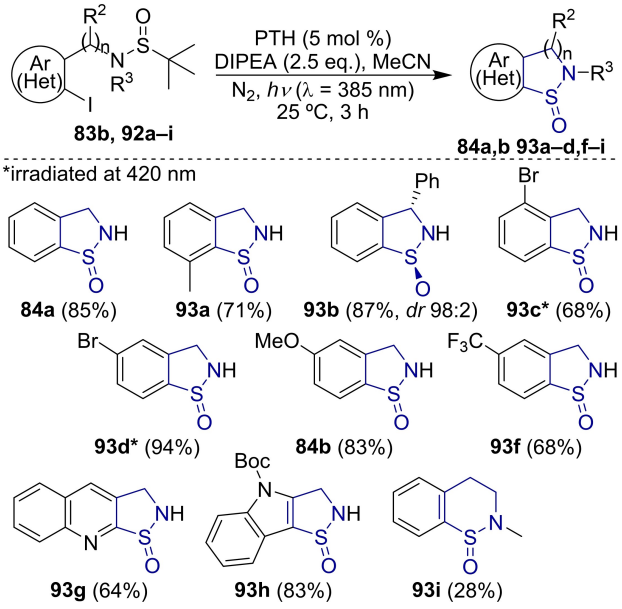
With these ideas in mind and following the above procedure Q. Zeng *et al.* designed and prepared sultim–olefin-containing chiral ligand (S_S)-**91** for the Rh-catalyzed asymmetric addition (Scheme 37).[74]

More recently, C. Maestro and J. Alemán with coworkers elegantly demonstrated the conceptual simplicity of the classical intramolecular homolytic substitution with photocatalytic approach. Their method is based on photocatalytic single-electron transfer (SET) reductive dehalogenation of aryl halides that provide access to C(sp^2)-centered radicals. In particular, the irradiation of iodinated sulfinamides **83b** and **92** with a LED lamp at 385 nm in the presence of DIPEA and 10-phenylphenothiazine (PTH) as a photocatalyst gave benzo- and heterofused sultims **84a,b** and **93** in poor to excellent yields (Scheme 38)[75]

The utilization of enantiopure starting compound **92b** resulted in chiral γ-sultim **93b** without loss of enantiopurity and with complete inversion of the configuration. Moreover, the method is tolerant to many functional groups and substituents, even bromine atoms at the benzene ring (**93c** and **93d**). In this case, a remarkable display of chemoselectivity can



Scheme 37. Synthesis of chiral ligand (S_S)-**91** for the Rh-catalyzed asymmetric addition.

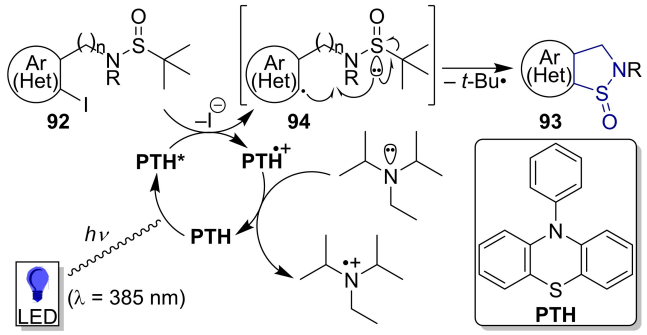


Scheme 38. Photocatalytic synthesis of fused sultims **84** and **93** *via* intramolecular homolytic substitution.

be reached by irradiation at a longer wavelength (λ = 420 nm). The method is also applicable to δ-sultim synthesis but only those of them bearing an alkyl substituent at the nitrogen atom (Scheme 38).[75]

The authors also suggested a plausible mechanism for this reaction. First, the LED irradiation drives PTH to reach a highly reducing excited state (PTH*) followed by the SET event with the aryl iodide **92**. This interaction affords aryl radical **94**, iodide anione, and the oxidized form of $PTH^{\bullet+}$. The former takes place in a concerted process on the C(sp^2) –S bond forming and the hemolytic S–C(sp^3) bond scission events involving the lone pair of the sulfur atom. These processes result in the target γ-sultim **93** formation and *t*-Bu• radical release. Lastly, the regeneration of PTH *via* sacrificial electron donation from the Hünig's base closes the photocatalytic cycle (Scheme 39).[75]

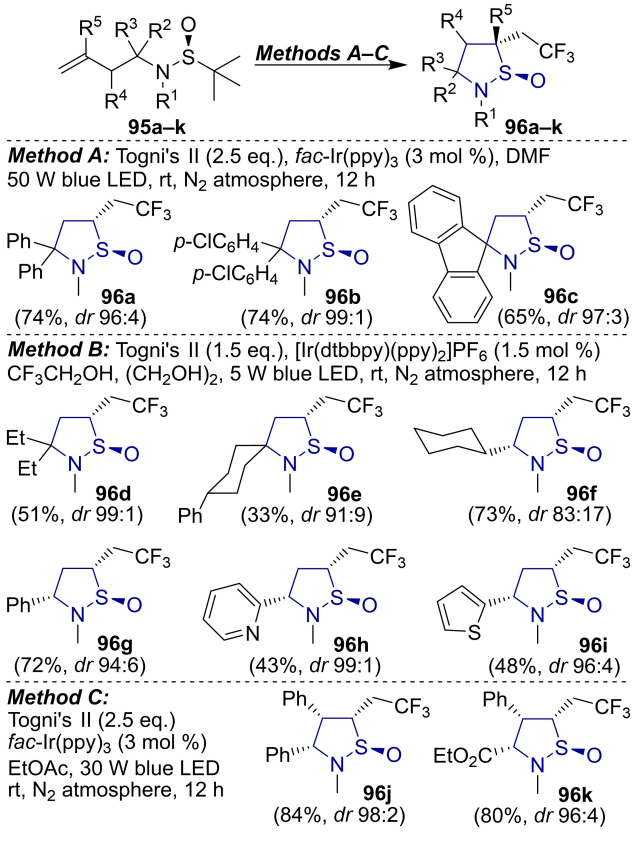
Finally, the most recent work on this reaction was devoted to the Ir (III)-catalyzed photoinduced synthesis of sp^3-enriched chiral sultims possessing up to 4 stereogenic centers. To do this, C. Zhu *et al.* used enantiopure sulfinamides **95** as direct precursors, 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni's II reagent) as $F_3C^{\bullet}$ radical source, and *fac*-Ir(ppy)$_3$ or [Ir(dtbbpy)(ppy)$_2$]PF$_6$ as visible light photoredox catalysts (Figure 7). The cyclization was performed by irradiation with a blue LED lamp at rt and afforded chiral γ-sultims **96** in fair to good yields and good stereocontrol. Again, the chirality of the sulfur atom was inverted during the radical cyclization process. Besides, the method supports structurally diverse substrates and



Scheme 39. Mechanistic proposal for PTH-catalyzed photoinduced synthesis of benzofused γ-sultims **93** proceeded through the S_Hi mechanism.

demonstrates a broad tolerance of many common functional groups (selected examples are depicted in Scheme 40).[76]

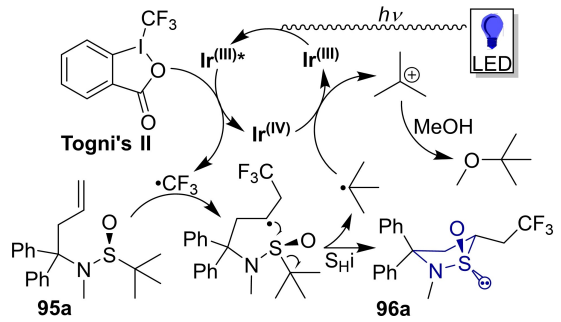
According to a plausible reaction mechanism, visible light irradiation turns Ir (III) catalyst into its excited species, which smoothly generates $F_3C^{\bullet}$ radical from the Togni's II reagent *via* the single-electron transfer (SET). The emerging radical adds to the starting unsaturated sulfinamide **95** and the formed



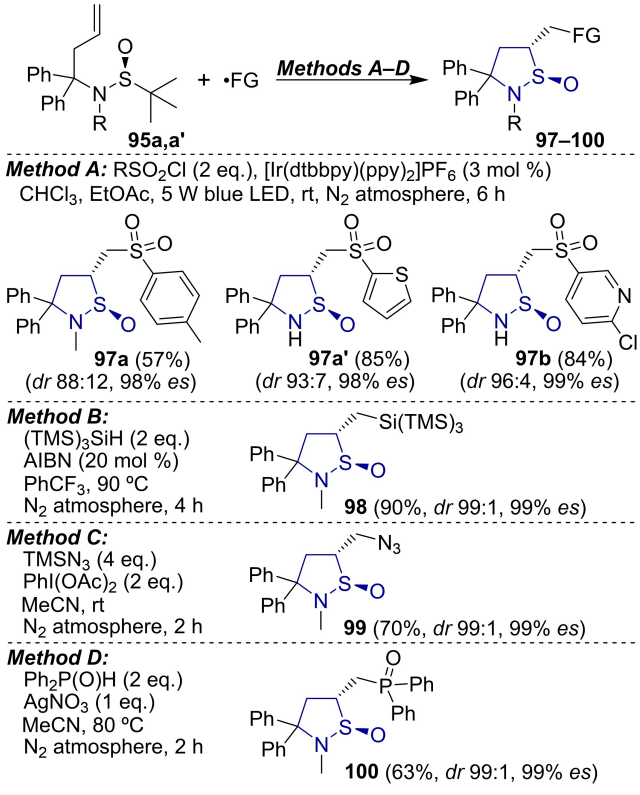
Scheme 40. Photocatalytic synthesis of sp^3-enriched chiral γ-sultims **96** *via* intramolecular homolytic substitution.

intermediate undergoes the intramolecular S_Hi cyclization to give the target γ-sultim **96** and the *t*-Bu• radical. The latter reduces Ir (IV) to Ir (III) thus perpetuating the catalytic cycle. With that, the construction of all new stereocenters of **96** is regulated mainly by the chiral sulfur atom (Scheme 41).[76]

Astonishingly, the product diversity achieved by this method can be further enhanced by exploiting various external radicals under slightly modified reaction conditions. In particular, S-, Si-, N-, and P-centered radicals were adopted and gave the appropriately functionalized γ-sultims **97–100** (Scheme 42).[76]



Scheme 41. Mechanistic proposal for Ir(III)-catalyzed photoinduced synthesis of γ-sultims **96** proceeded through the S_Hi mechanism.



Scheme 42. Photocatalytic synthesis of sultims **97–100** through the S_Hi mechanism using S-, Si-, N-, and P-centered radicals.

2.4. Transformations of Cyclic Sulfoximines

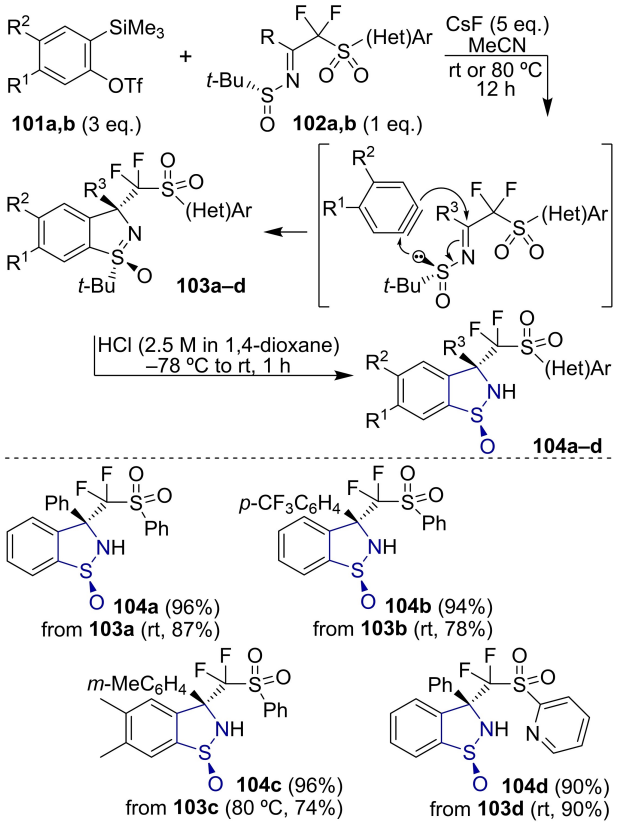
This is a group of contemporary synthetic methods that have come into practice since the late 2000s and currently are becoming increasingly popular. Cyclic sulfoximines are relatively novel and therefore not a numerous class of compounds. They can be readily prepared in a stereoselective manner starting from Ellman's or Davis' sulfinamides. *S*-Dearylation or *S*-de-*tert*butylation of cyclic sulfoximines gives the corresponding sultims with synthetically useful yields and excellent stereocontrol.

J. Hu's group discovered the stereoselective method for the synthesis of cyclic sulfoximines based on [3+2] cycloaddition between the functionalized sulfinylimines **102** obtained from Ellman's sulfinamine and generated *in situ* arynes. The subsequent acid-mediated de-*tert*butylation allowed access to optically pure benzofused γ-sultims.

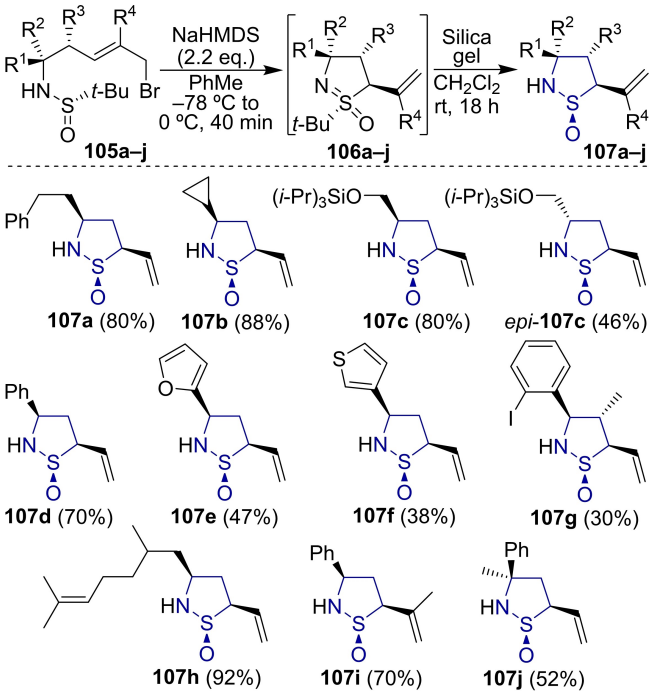
In particular, *ortho*-TMS phenyl triflates **101** were chosen as a benzyne source and CsF was used as an activator. The cycloaddition proceeded in good yields and a highly stereoselective mode (*dr* >99:1 and *er* >99:1) affording cyclic sulfoximines **103** with the retained configuration at the sulfur atom. Further treatment with the solution of HCl in 1,4-dioxane at −78 °C caused de-*tert*butylation of sulfoximines **103** thus converting them into the corresponding γ-sultims **104** with excellent yields and high stereochemical fidelity (*dr* >99:1). The configuration at the sulfur stereogenic center was also retained during the loss of *t*-Bu group (selected examples are depicted in Scheme 43).[77,78]

On the one hand, the attached (Het)ArSO_2CF_2 group facilitates the stereoselective [3+2] cycloaddition (due to its electron-withdrawing ability), and on the other hand, it serves as a good leaving group enabling β-elimination reaction for sulims **104** (see below Schemes 122 and 123).

E. Suna *et al.* developed the synthesis of unfused 5-membered cyclic sulfoximines and showed that their de-*tert*butylation can be initiated by as weak acid as silica gel. The crucial step in this synthetic approach was the intramolecular *S*-allylation of unsaturated chiral sulfinamides **105**. The reaction proceeded in completely diastereoselective mode *via* S_N2' substitution and gave densely substituted enantiopure cyclic sulfoximines **106**. The subsequent *t*-Bu-cleavage was quite facile, proceeded without loss of enantiopurity, and did not require isolation of the corresponding sulfoximines. Eventually, sp^3-enriched γ-sultims **107** were obtained in fair to good yields over the two steps one-pot process (Scheme 44).[79] Worthy of note, that the target sultims not only possess up to 4 stereogenic centers but are also decorated with synthetically useful vinyl handle.



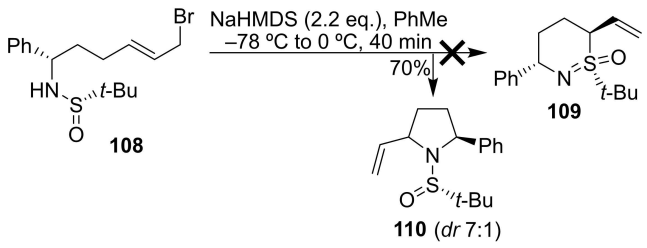
Scheme 43. The synthesis of benzofused γ-sultims **104** through the [3+2] cycloaddition-de-*tert*butylation sequence.



Scheme 44. Synthesis of enantiopure γ-sultims **107** *via* diastereoselective S_N2' cyclization-de-*tert*butylation sequence.

However, the above method was applicable for the synthesis of γ-sultims only. An attempt of expanding the cyclization scope to the homologous substrate **108** resulted in the sulfinylated pyrrolidine **110** instead of the expected 6-membered sulfoximine **109** (Scheme 45).[79] This result suggests that the dominant *N*-alkylation over the *S*-alkylation is most likely determined by the kinetic preference typical for five-membered cycles.[80]

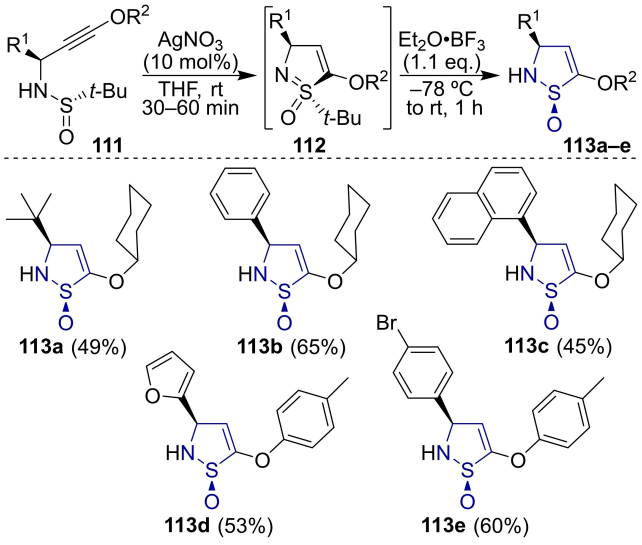
The sulfinylated alkynyl amines are other good precursors for cyclic sulfoximines and the corresponding sultims, respectively. The triple C≡C bond acts as an electrophile toward the lone pair of the sulfur (II) atom and may be activated in several ways. J.-F. Poisson *et al.* developed a one-pot procedure based on $AgNO_3$-catalyzed cycloisomerization of propargylic sulfinamides **111** leading to cyclic sulfoximines **112**, followed by $Et_2O{\cdot}BF_3$-mediated sulfur dealkylation. The method provided unsaturated γ-sultims **113** in fair yield but completely in a stereoselective manner (Scheme 46).[81]



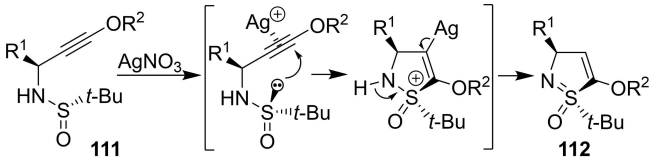
Scheme 45. A behavior of homologous substrate **108** in S_N2' cyclization protocol.

In addition to the above the authors suggested a mechanism for the $AgNO_3$-catalyzed cycloisomerization of propargylic sulfinamides **111**. According to that, the Ag^+ ion coordinates the electron-rich triple C=C bond thus enhancing its electrophilicity toward a nucleophilic attack by the sulfur atom. The subsequent protonation of the C–Ag bond (either intermolecularly or by H-shift) along with the formation of the N=S double bond gives cyclic sulfoximine **112** (Scheme 47).[81]

Another approach to cycloisomerization of propargylic sulfinamides was reported by T. Kano and K. Maruoka. According to their method, the reaction can be promoted by inorganic bases in an alcohol media. Specifically, propargylic sulfinamide **114** was treated with KOH in *n*-PrOH at 90 °C to give the corresponding cyclic sulfoximine **115**. It turned out, that the subsequent de-*tert*butylation with methanolic HCl at rt resulted in significant erosion of optical purity whereas $Et_2O{\cdot}BF_3$ in THF at 50 °C drove this reaction to



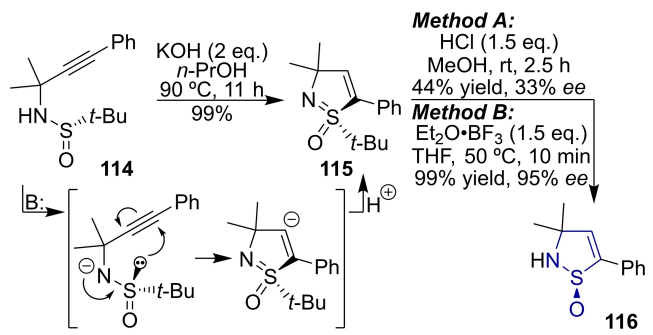
Scheme 46. Two-step one-pot conversion of sulfinylated propargyl amines **111** into γ-sultims **113**.



Scheme 47. A plausible mechanism for the $AgNO_3$-catalyzed cycloisomerization of propargylic sulfinamides **111** into cyclic sulfoximines **112**.

proceed without loss of enantiopurity affording γ-sultim **116** in almost quantitative yield (Scheme 48).[82].

Besides, the method accesses benzofused δ-sultims from the sulfinamides containing an *ortho*-phenylene spacer. Intriguingly, the base-mediated cycloisomerization is accompanied by the subsequent de-*tert*butylation even in basic media at rt. In this way, sulfinamide **117** was converted directly into sultim **118**.

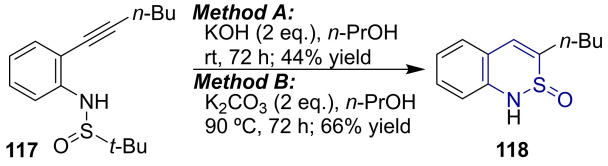


Scheme 48. Two-step method for the conversion of sulfinylated propargyl amine **114** into γ-sultim **116**.

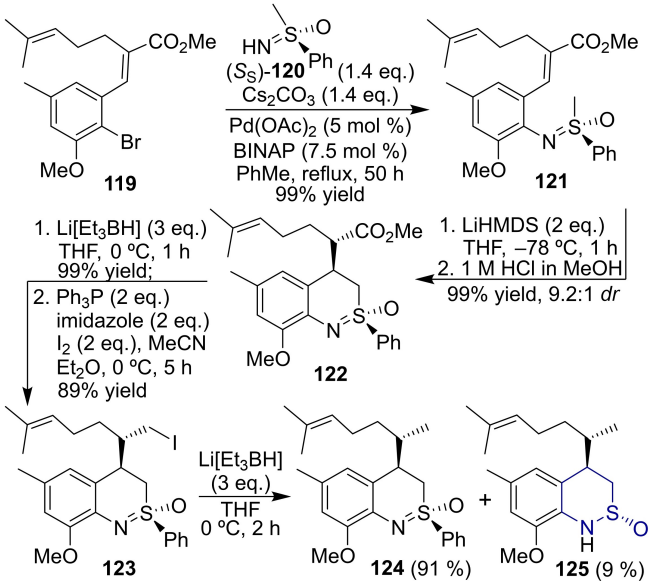
When the base was switched to K_2CO_3 and the reaction was conducted at a higher temperature (90 °C) the yield was increased by 50 % (Scheme 49).[82]

In the projected total synthesis of *seco*-pseudopteroxazol,[83] a natural product with anti-tuberculosis activity, M. Harmata and P. Zheng discovered a novel stereospecific reaction leading to chiral sultims. Thus, during optimization of the reaction conditions to improve the yield of sulfoximine **124**, a key intermediate in this synthesis, the authors found that Li[Et_3BH] not only caused reductive dehalogenation of **123** but also promoted reductive dephenylation of **124**, thereby affording sultim-based byproduct **125**, albeit in poor yield but in completely stereospecific manner (Scheme 50).[84]

The above finding underlaid further investigation of the stereospecific synthesis of enantiopure δ-sultims through the reductive dearylation of 6-membered sulfoximines. First of all, the authors optimized the reaction conditions to make dearylation the main process. This was achieved by exposure of starting benzofused sulfoximines **126** to the action of Li[Et_3BH] in refluxing THF (at different reaction times). The loss of the *S*-aryl group was accompanied by S=N bond reduction and



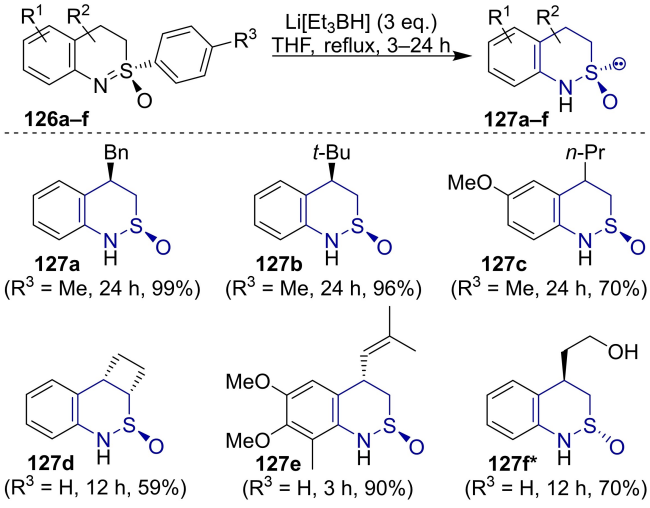
Scheme 49. Synthesis of benzofused δ-sultim **118**.



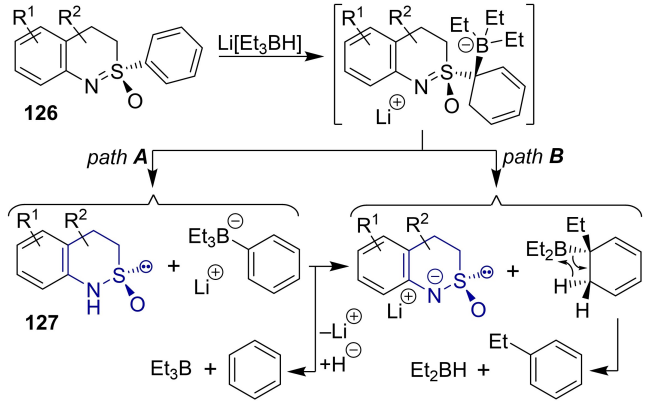
Scheme 50. Selected steps in the projected total synthesis of *seco*-pseudopteroxazol.

complete retention of the configuration at the sulfur atom. As a result, the target *NH*-unsubstituted diastereomerically (or enantiomerically) pure δ-sultims **127** were obtained in excellent yield. The reaction showed a high level of generality and a broad substrate scope even tolerating steric hindrance (Scheme 51).[85]

To gain insight into the reductive dearylation reaction mechanism, the authors analyzed the composition of the crude reaction mixture and suggested the following scheme. The reaction might start with hydride addition followed by sultim elimination and proton transfer that give benzene and Et_3B (Scheme 52, path *A*). Alternatively, the adduct would undergo ethyl group migration and subsequent deborylation that afford PhEt and Et_2BH (Scheme 52, path *B*).[85]



Scheme 51. Synthesis of benzofused δ-sultims **127** through the Li[Et_3BH]-mediated reductive dearylation of 6-membered sulfoximines **126**.



Scheme 52. Proposed mechanism for the Li[Et_3BH]-mediated reductive dearylation of benzofused sulfoximines **126**.

2.5. The [2+2]–, [3+2]–, and [4+2]-Cycloaddition Reactions (Except for the Diels–Alder Reaction)

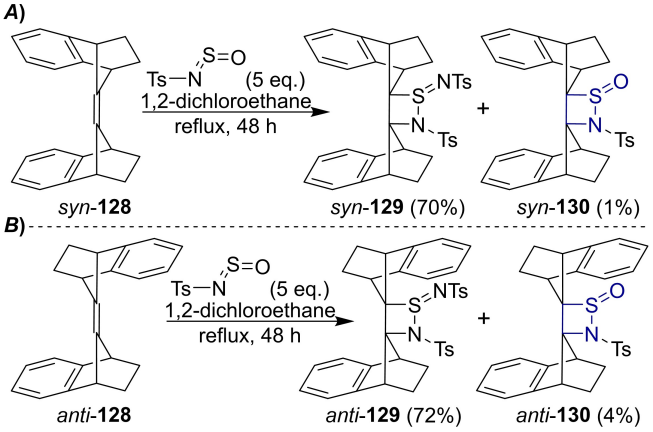
This is another group of increasingly popular methods. They have been known for several decades but have got a second wind since the 2010s when the appropriate catalysts were put into practice.

Y. Sugihara and J. Nakayama envisioned, that despite steric hindrance *syn-* and *anti*-9,9′-dibenzonorbornenylidenes (**128**) seemed to be a convenient reagent for [2+2]-cycloaddition reaction with tosyl sulfinylaniline. Indeed, this allowed construction of a 1,2-thiazetidine scaffold upon prolonged refluxing in 1,2-dichloroethane. Aside from the desired (for the above authors) products **129** the reaction also gave the corresponding β-sultims **130** as by-products in quite poor yield. Noteworthy, the yield of *anti*-products **129** and **130** was higher than that of the corresponding *syn*-counterparts (Scheme 53).[86]

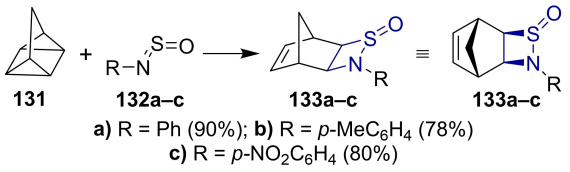
Apparently, regio- and π-face selectivity arose from both the homoconjugation interaction between the exocyclic C=C bond of the norbornenylidene fragment and the benzene ring, which resulted in the polarization of the above C=C bond and steric repulsion among the tosyl group in TsNSO and the annelated benzene ring.

Interestingly, *N*-sulfinylanilines **132** may react not only with alkenes to give the β-sultim framework. The highly strained and saturated cyclic hydrocarbons with the same empirical formula act as the masked alkenes. For instance, with an aim of annelation of the β-sultim fragment to the norbornene nucleus R. Warrener and A. Amarasekara did not use norbornadiene as an alkene component but rather its sp^3-enriched isomer quadricyclane (**131**). Unfortunately, the authors provided neither the general procedure nor the reaction conditions for the synthesis of polycyclic β-sultims **133** (Scheme 54).[87]

S. Ye *et al.* took the [2+2]-cycloaddition reaction (as applied to β-sultims) to the synthetically useful level. Specifi-



Scheme 53. Reaction of 9,9′-dibenzonorbornenylidenes **128** with TsNSO.



Scheme 54. Synthesis of norbornene-derived β-sultims **133**.

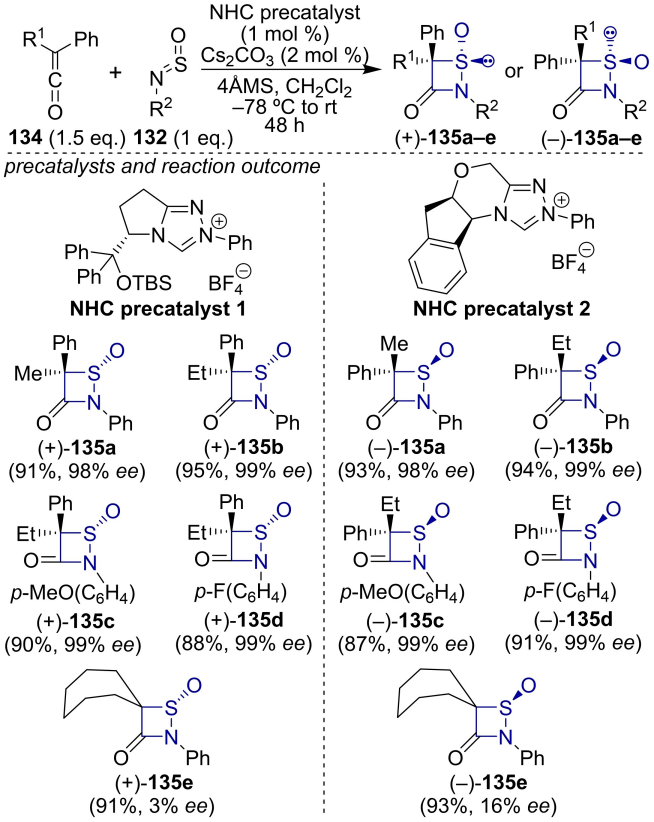
cally, they put into practice *N*-heterocyclic carbenes (NHC) as efficient catalysts in the formal [2+2]-cycloaddition reaction of ketenes and *N*-sulfinylanilines which gave the corresponding β-sultims. Moreover, the utilization of chiral NHC-precatalysts enabled the stereoselective synthesis of definite enantiomer/diastereoisomer.

After extensive efforts made to optimize the existing reaction conditions (CH_2Cl_2, −78 °C) it transpired that 4 Å molecular sieves (4ÅMS) dramatically improved the yield when had been added to the reaction mixture. Eventually, with the optimal reaction conditions and two selected chiral NHC-precatalysts in hand, the authors converted ketenes **134** and *N*-sulfinylanilines **132** into a set of chiral β-sultims **135** with excellent yields and stereoselectivity (selected examples are depicted in Scheme 55).[88]

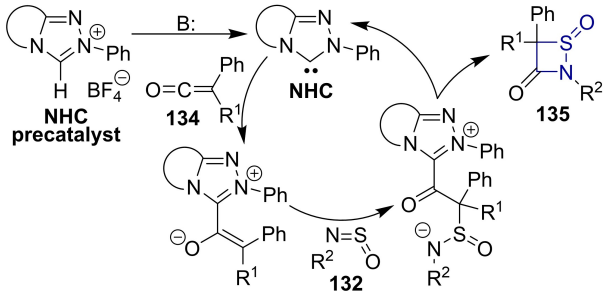
It is noteworthy, that the noncatalytic background [2+2]-cycloaddition reaction of above ketenes **134** and *N*-sulfinylanilines **132** was not observed. The crucial role of NHC catalysts was explained in the plausible reaction mechanism. According to it, the catalytic cycle is started with the addition of NHC to ketene **134** affording the corresponding enolate. The latter reacts with *N*-sulfinylaniline **132** to give the adduct, which undergoes a ring closure reaction thus liberating the target β-sultims **145** and regenerating the NHC catalyst (Scheme 56).[88]

D. Werz *et al.* in their sultam synthesis employed [3+2]- and [4+2]-cycloadditions of donor–acceptor cyclopropanes **136** and cyclobutanes **137** with *N*-sulfinylamines **132**, the double S=N bond of which acted as the 2π component. The reaction was catalyzed by the Lewis acid and $GaCl_3$ was found to be by far the most effective while −20 °C was the best temperature for combining the reagents. The scope of the [3+2]-cycloaddition was demonstrated by a broad range of γ-sultims **138** obtained in good to excellent yields and moderate to good diastereoselectivity. With that, the *cis*-diastereomer was formed as the major component (selected examples are depicted in Scheme 57).[89]

The method was also applicable toward donor–acceptor cyclobutanes (a case of [4+2]-cycloaddition) with the only difference that the final δ-sultims **139** preferred to form as *trans*-isomers (selected examples are depicted in Scheme 57).[89]



Scheme 55. NHC-catalyzed enantioselective synthesis of β-sultims **135**.

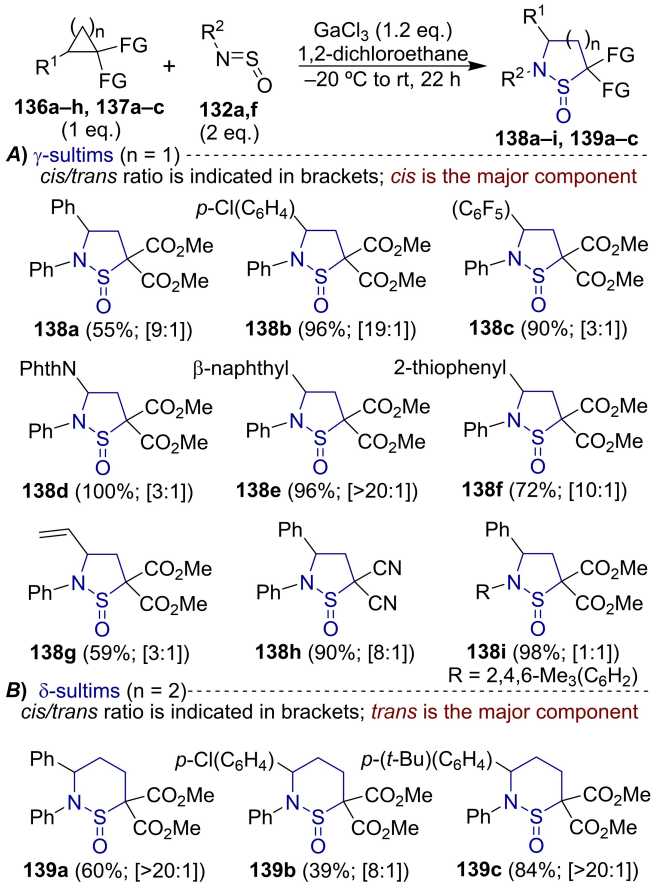


Scheme 56. Mechanistic proposal for NHC-catalyzed synthesis of β-sultims **135** through the formal [2+2]-cycloaddition.

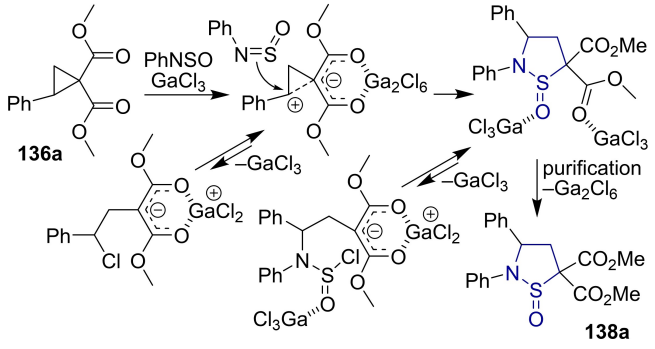
The authors also suggested a possible reaction mechanism, using the example of the formation of γ-sultim **138a** (Scheme 58).[89]

2.6. The Diels–Alder Reaction

This is the most popular method for assembling the δ-sultim framework and great progress in this field was made over the past decades. The *N*-sulfinyl group is considered as a dienophile toward conjugated dienes in the *hetero*-Diels–Alder reaction.[90]



Scheme 57. Scope of the $GaCl_3$-catalyzed [3+2]- and [4+2]-cycloaddition leading to γ-sultims **138** and δ-sultims **139**.



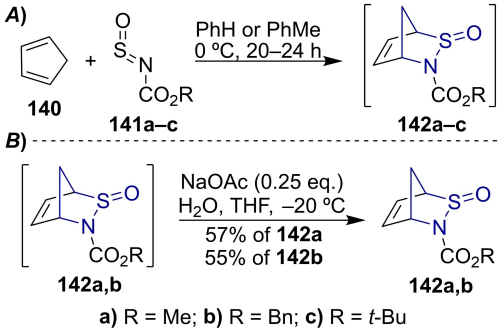
Scheme 58. Proposed mechanism for the $GaCl_3$-catalyzed [3+2]-cycloaddition leading to γ-sultims **138a**.

The electron-withdrawing substituents generally increase the reactivity of the *N*-sulfinyl group and the stereochemistry of the adducts is largely predictable on the basis of the cycloaddition mechanism. Specifically, according to the *Alder endo rule* in "normal demand" Diels–Alder scenarios the *endo*-transition state with a maximum accumulation of the double bonds is preferred thus providing *endo*-cycloaddition products despite being more sterically congested.[91]

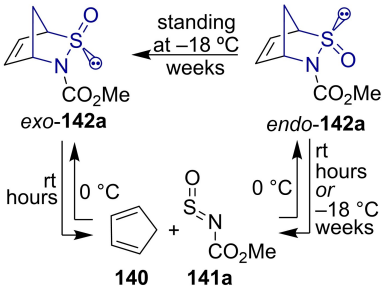
In this way, *N*-sulfinylcarbamates **141** were combined with cyclopentadiene (**140**) at 0 °C to give bridged bicyclic sultims **142** (Scheme 59, *A*).[92–95] Customarily, the obtained cycloadducts were not isolated because of their strong tendency to *retro*-Diels–Alder reaction at rt and upon attempted purification. Therefore, it was best to immediately use the crude material in subsequent chemical transformations. Nevertheless, L. Guideri and F. Ponticelli did isolate and characterized **142a,b** by treating the crude reaction mixture with an aqueous NaOAc and subsequent work-up procedure at −20 °C (Scheme 59, *B*).[95]

The stability of cycloadduct **142a** had been the subject of another research by L. Guideri and F. Ponticelli. By means of the NMR experiments, they found out that the *exo*-isomer is more thermodynamically stable and slightly dominates in the reaction mixture, although both isomers disappear at rt in a few hours since the cycloaddition reaction is reversible. With that, at −18 °C after 1 week the *endo*-adduct was mainly transformed into the starting materials and the *exo*-counterpart (Scheme 60).[95]

O. Gautun and A. Bayer focused on asymmetric *hetero*-Diels-Alder cycloaddition between *N*-protected sulfinylimines **141** and 1,3-cyclohexadiene (**143**). For this purpose, the

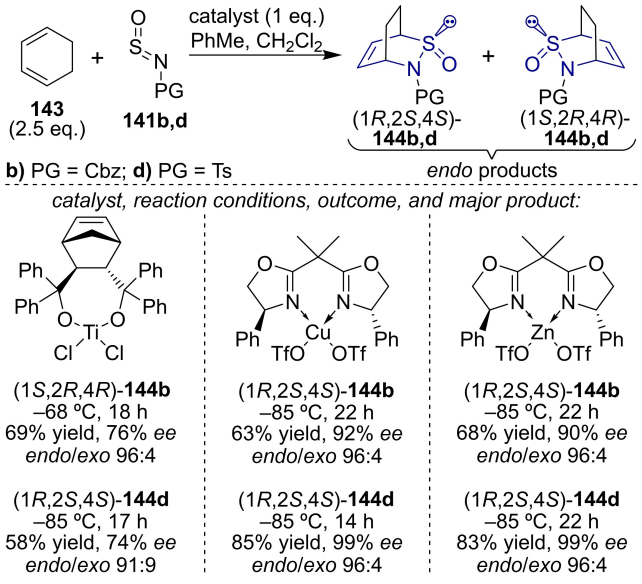


Scheme 59. Synthesis of bridged sultims **142** through the *hetero*-Diels-Alder reaction.



Scheme 60. Stability of bridged sultim **142a**.

researchers developed a series of the Lewis acid catalysts consisting of the metal species and a chiral ligand. Since the catalyst is not released from the final cycloadduct, thus inhibiting catalyst turnover, the stoichiometric amount of it is required. Wherein, Cu- and Zn-containing catalysts are superior to Ti-containing one with respect to yield and selectivity. Eventually, the method showed excellent *endo*/*exo* selectivity (> 95 : 5) and enantioselectivity (> 98 %) in the synthesis of bridged sultims **144** (selected examples are depicted in Scheme 61).[96–99]



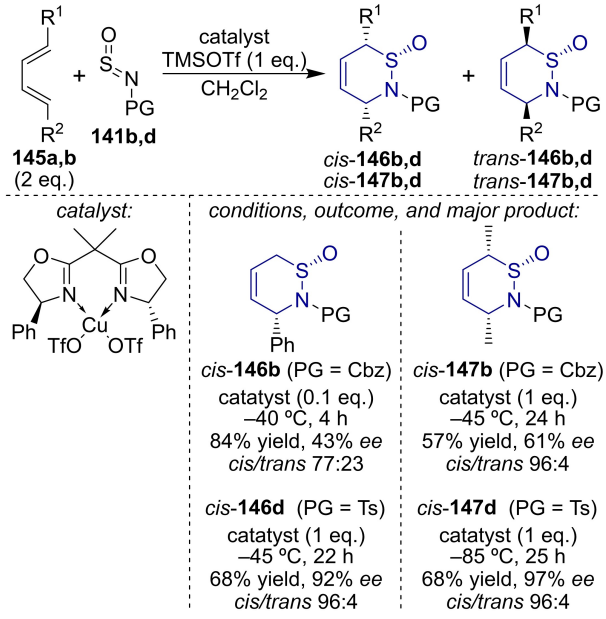
Scheme 61. Synthesis of chiral bridged sultims **150** through the Lewis acid-catalyzed asymmetric *hetero*-Diels–Alder reaction.

It should be noted, that contrary to bridged sultims **142** their higher homologues **144** are much more stable. They could be isolated without proceeding *retro*-Diels–Alder reaction and may be stored at rt without deterioration. Such a difference can be attributed to steric congestion in **142** caused by the hydrocarbon framework attached to the nitrogen and sulfur atoms. An introduction of additional bridged methylene moiety into the structure of **144** entails a great reduction in the internal strains and, as a consequence, increases stability.

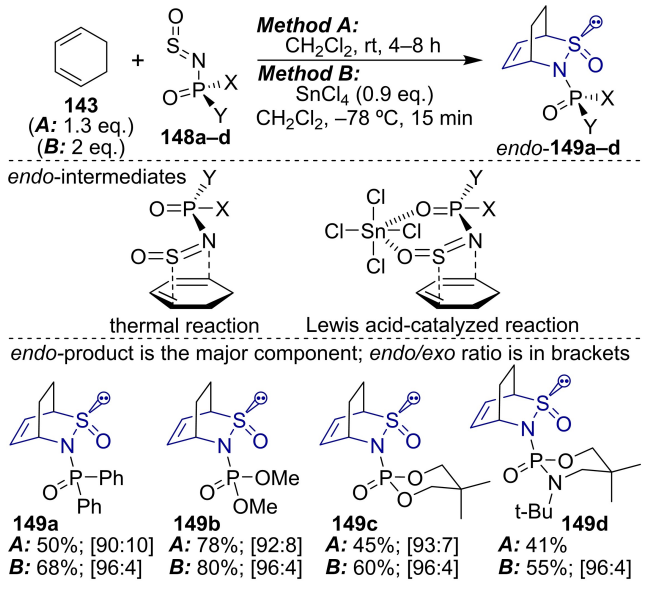
The above method also works well with acyclic dienes **145** providing monocyclic δ-sultims **146** and **147** (selected examples are depicted in Scheme 62).[100,101]

An interesting extension to the scope of the *hetero*-Diels–Alder reaction was brought in by Y. Zhang and C. Flann. They studied the behavior of *N*-sulfinyl phosphoramidates **148** as dienophiles in the reaction with 1,3-cyclohexadiene (**143**). The cycloaddition proceeded at rt with moderate yields but in a stereoselective manner. The major isomers of bridged δ-sultims **149** had *endo*-configuration at the sulfur atom. The high level of stereoselectivity may be explained by the absence of a secondary orbital interaction in the structure of the dienophile activated by the phosphor (V) atom that facilitates the formation of *endo*, *syn*-intermediate further collapsed into the corresponding *endo*-product (Scheme 63, Method *A*).[102]

These assumptions were confirmed by the Lewis acid enhancement of the reactivity and stereoselectivity that led to a



Scheme 62. Synthesis of monocyclic δ-sultims **146** and **147** through the Lewis acid-catalyzed asymmetric *hetero*-Diels–Alder reaction.



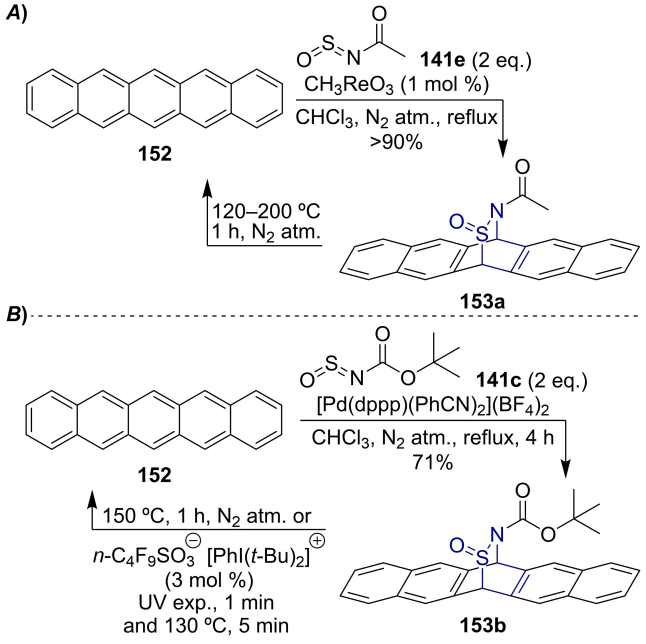
Scheme 63. Synthesis of bridged δ-sultims **149** through the Lewis acid-catalyzed *hetero*-Diels–Alder reaction.

significantly higher yield of the target products and an even higher level of stereoselectivity. With that, the reaction temperature had to be reduced to −78 °C while the reaction time shortened up to 15 min. The role of $SnCl_4$ as the Lewis acid is to form the chelates with *N*-sulfinyl phosphoramidates **148** thus endowing them with the appropriate geometry and enhancing their reactivity (*via* increasing electron-deficiency) (Scheme 63, Method *B*).[102]

The noncatalyzed method was also applicable to the reaction of acyclic dienes **150** with **148c** so that the corresponding δ-sultims **151** were obtained in moderate yields (Scheme 64).[102] However, the stereoselectivity at the sulfur atom was not determined in this case.

Surprisingly, the chemistry of sultims facilitates the development of fully "*plastic electronics*". Briefly, pentacene is the most environmentally stable organic semiconductor and its thin films exhibit high carrier mobilities which are the main requirements for high-performance organic thin film transistors (OTFTs). At the same time, pentacene is essentially insoluble in organic solvents at rt that is a great obstacle for the solution-based fabrication of the OTFTs deposited over flexible plastic substrates.

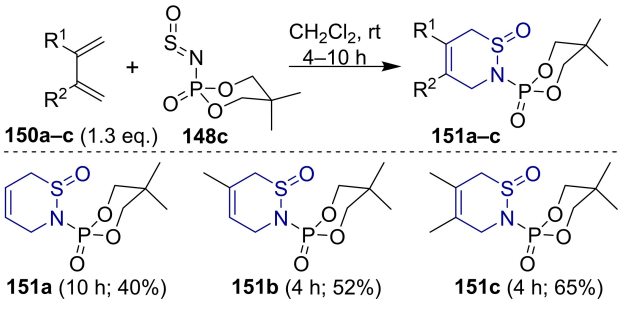
A. Afzali *et al.* solved this problem in a very original way. They showed that pentacene (**152**) readily reacted with *N*-sulfinylacetamide (**141e**) in the presence of methyltrioxorhenium (1 mol%) affording the *hetero*-Diels–Alder adduct **153a** which was highly soluble in common organic solvents. Since the reaction is reversible, heating the dried substrate with a spin-coated solution of bridged sultim **153a** resulted in the loss of *N*-sulfinylacetamide thus liberating pentacene (Scheme 65, *A*).[103] Later, the researchers suggested using **141c** as the *hetero*dienophile in a Pd-catalyzed reaction with pentacene that provided another highly soluble precursor **153b**. The main advantage of **153b** over **153a** is that the former allowed releasing pentacene under much milder conditions (150 °C *versus* 200 °C for 1 h). Moreover, photo-acid-generating compounds (PAG) as a dopant significantly reduce the conversion time. Thus, UV exposure of the dried



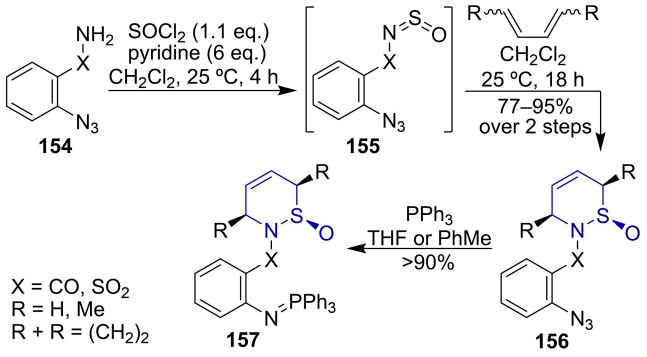
Scheme 65. Synthesis of soluble δ-sultim-based precursors **153a,b** and their conversion back into pentacene.

substrate with the coated bridged sultim **153b** for 1 min followed by heating at 130 °C for 5 min almost quantitatively regains pentacene (Scheme 65, *B*).[104]

K. Hemming *et al.* reported the synthetic access to benzodiazepines and benzothiadiazepines where the δ-sultim-containing iminophosphoranes **157** were the key precursors. According to their strategy, *ortho*-azido benzamide or sulfonamide **154** was converted into the corresponding sulfinylamine **155** whereupon the *hetero*-Diels–Alder reaction with dienes allowed assembling δ-sultim framework. Further Staudinger reaction[105–107] provided the key precursor **157** (Scheme 66).[108] The final steps of this pathway are illustrated in Scheme 121.



Scheme 64. Noncatalyzed synthesis of δ-sultims **151** through the *hetero*-Diels–Alder reaction.

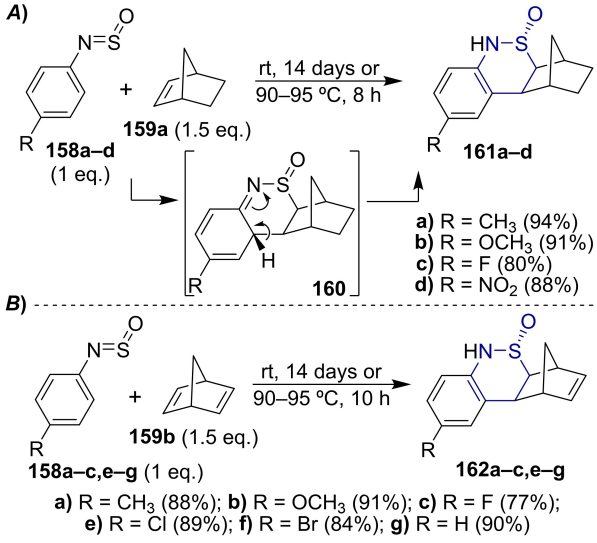


Scheme 66. Synthesis of δ-sultim-containing iminophosphoranes **157**.

V. Plemenkov *et al.* released a series of papers describing the *hetero*-Diels-Alder reaction between sulfinylamines and norbornane-derived alkenes. The former are readily available substrates prepared from anilines and $SOCl_2$ in high yields. They act as dienes in "inverse demand" Diels–Alder scenarios therefore *exo*-transition state is preferred.

Thus, sulfinylanilines **158** and norbornene (**159a**) combined edge-on to give intermediate **160**. The latter tended to renew the aromaticity of the benzene ring and therefore caused proton migration thus affording polycyclic δ-sultims **161** in high yields (Scheme 67, *A*).[109,110] The reaction is stereospecific so that the oxygen atom of the sulfinamide fragment is oriented opposite to the annelated norbornane framework.

The reaction of sulfinylanilines **158** and norbornadiene (**159b**) followed the same mechanism resulting in polycyclic δ-sultims **162** possessing an annelated norbornene framework



Scheme 67. The *hetero*-Diels–Alder reaction of *N*-sulfinylamines **158** with norbornene (**159a**) and norbornadiene (**159b**).

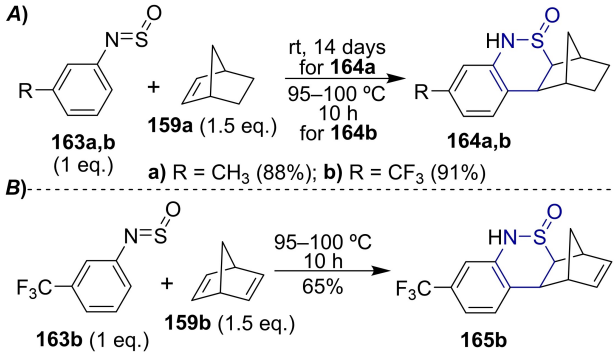
(Scheme 67, *B*).[109–111] It was carried out without solvent and the structure of the key products was confirmed by the X-ray diffraction studies.

Noteworthy, when *meta*-substituted sulfinylanilines **163** were involved in the reaction, the face [*f*] of the benzene ring took part in the cycloaddition process only. On the other hand, there was a loss of selectivity at the stereogenic sulfur center so that 1 : 1 mixture of the stereoisomers was obtained, albeit in good synthetic yields (Scheme 68, *A*).[109,112] This was also true for the reaction with norbornadiene (**159b**) (Scheme 68, *B*).[112]

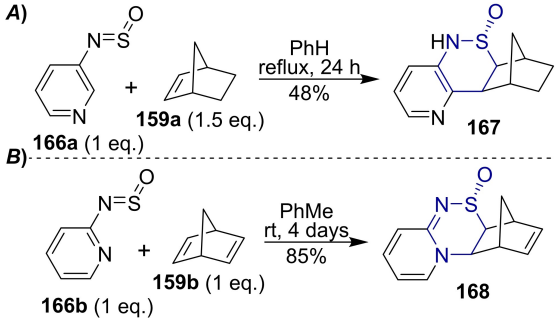
P. Hanson and S. Wren significantly expanded the substrate scope for this reaction. They studied the cycloaddition of *N*-sulfinylamino pyridines **166** to norbornene (**159a**) and norbornadiene (**159b**). Remarkably, the reaction proceeded in a stereospecific manner so that the *trans*,*exo*-adducts **167** and **168** formed only. Another interesting feature of this reaction is the regioselectivity, *i.e.* the addition to dienophiles takes place at the sulfur atom and at the carbon or nitrogen atom at the *ortho*-position to the *N*-sulfinylamino group only. In the case of β-sulfinylamino pyridine **166a** the addition takes place at the 2-carbon atom only (Scheme 69).[113]

Next, the authors studied the cycloaddition reaction with 1,4-epoxy-1,4-dihydronaphthalene (**169a**) and with dicarboxylate **169b**. It turned out, that 2-sulfinylamino pyridines **166b,e** and pyrimidine **166f** are up to 50-fold more reactive and consequently react at ambient temperature. In all cases, the reaction proceeded with an excellent level of regioselectivity but with a loss of stereoselectivity. Only the spatially crowded cycloadduct **170e** was obtained as a *trans*-isomer. Apparently, this can be explained by the fact that the bridged oxygen atom is sterically less demanding than the bridged CH_2 group (Scheme 70).[113]

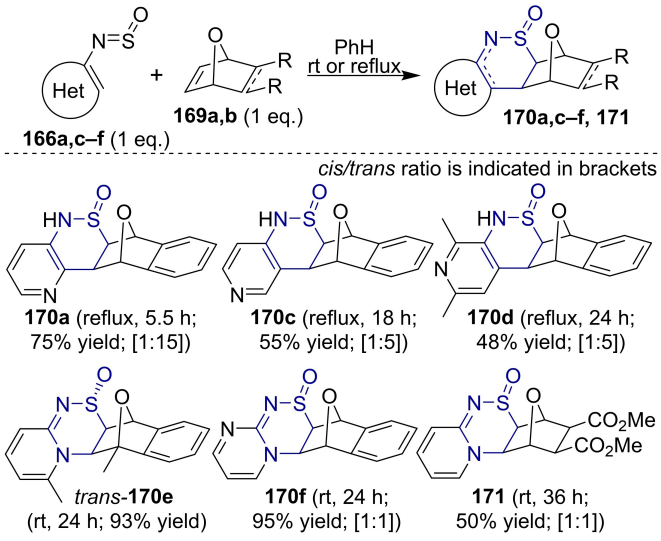
It is significant, that 2-iminopyridine chromophore endows the cycloadducts **170e,f** and **171** with a bright yellow color while the protonation of **170e** with HBF_4 produces the colorless conjugate salt **170e**•HBF_4. Treating the latter with alkali restores the color (Scheme 71).[113]



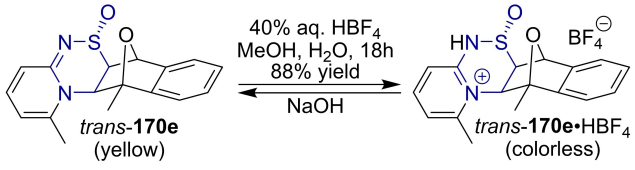
Scheme 68. The *hetero*-Diels–Alder reaction of *N*-sulfinylamines **163** with norbornene (**159a**) and norbornadiene (**159b**).



Scheme 69. The *hetero*-Diels–Alder reaction of *N*-sulfinylamines **166** with norbornene (**159a**) and norbornadiene (**159b**).



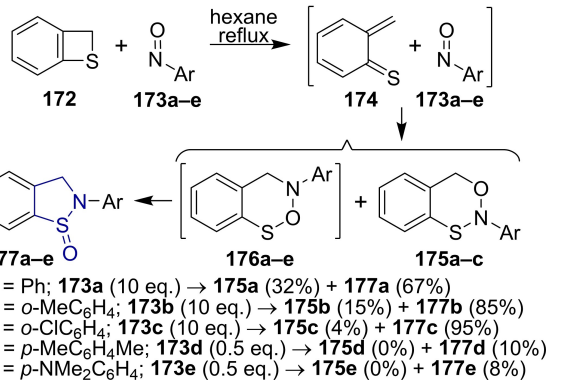
Scheme 70. The *hetero*-Diels–Alder reaction of sulfinylamino pyridines and pyrimidine **166** with epoxy-containing dienophiles **169**.



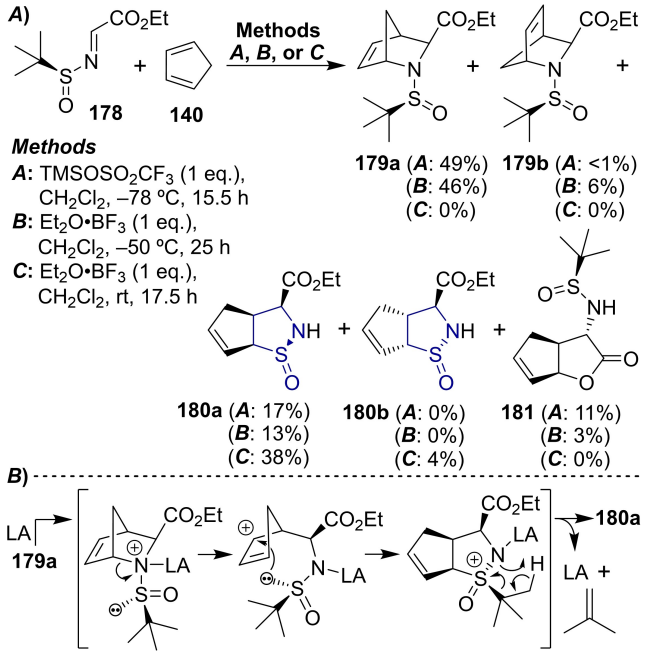
Scheme 71. Acid-base properties of **170e**.

An interesting example of the *hetero*-Diels–Alder reaction was reported by H. Meier's group. According to their method, substituted nitroso benzenes **173** acted as a dienophile whereas benzothiete **172** served as a precursor to *in situ* formed thiadiene **174**. The reaction was carried out in refluxing hexane and resulted in the formation of two regioisomeric products **175** and **176**. The latter turned out to be unstable and rearranged into benzofused γ-sultims **177** (Scheme 72).[114] The authors tested different molar ratios of the reagents but 1 : 10 (**172 : 173**) gave the best result.

Aside from target products in the direct syntheses, some sultims were obtained as by-products. Thus, the Lewis acid (LA)-catalyzed *hetero*-Diels–Alder reaction between cyclopentadiene (**140**) and *N*-sulfinyl imino ester **178** as dienophile resulted in a mixture of bridged adducts **179** and bicyclic rearrangement by-products **180** and **181** (Scheme 73, *A*).[115] Further screening the reaction conditions *via* varying the Lewis acids and the temperature gave the mixtures of different content. It was found, that the reaction at rt with $Et_2O{\bullet}BF_3$ as the Lewis acid exclusively yielded the γ-sultim by-products **180** (conditions ***C***). O. Gautun and colleagues suggested a rationale for the formation of **180a** (Scheme 73, *B*). A similar rearrangement of **179b** would give **180b**. Note, this reaction occurs through the Lewis acid-catalyzed de-*tert*butylation of intermediate cyclic sulfoximine (see Paragraph 2.4).



Scheme 72. The *hetero*-Diels–Alder reaction of substituted nitroso benzenes **173** and *in situ* generated thiadiene **174**.



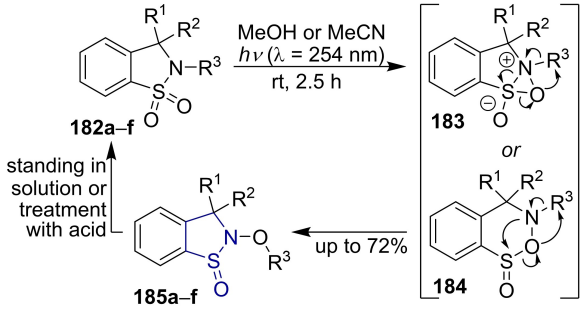
Scheme 73. Bicyclic sultims **180** obtained as by-products in the *hetero*-Diels–Alder reaction and a plausible mechanism for their formation.

2.7. Photoisomerization

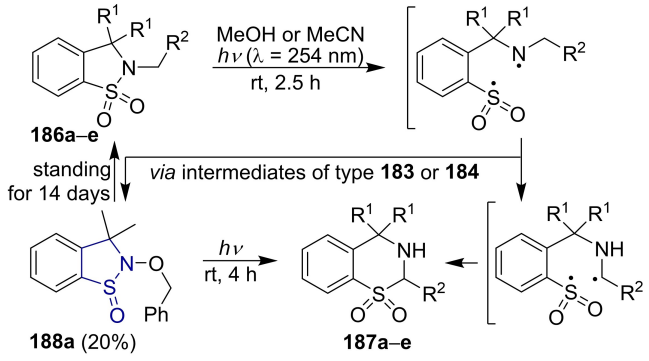
This is another example of interesting method where the valency of the sulfur atom changes from VI to IV. Actually, it can be considered as a photoinduced reduction of the sulfur (VI) atom. With that, the method has a limited substrate scope and can be applied almost only to the saccharin-like precursors.

D. Döpp and co-workers conducted UV-induced photoisomerization of benzofused isothiazole 1,1-dioxides **182** into *N*-hydroxy sulfinamides **185** with the formal oxygen shift from the sulfur atom to the nitrogen one (Scheme 74).[116–118] The authors hypothesized that the reaction proceeds *via* conceivable intermediates **183** or **184** (formed after initial S–N bond homolysis).

Importantly, the reaction took place with substrates possessing at least one alkyl or aryl substituent at the C-3 atom and either proton or MOM group or CH_2Oi-Pr substituent on the nitrogen atom. Yields tend to be higher whenever the C-3 position was disubstituted. With that, 3-monosubstituted γ-sultims **185e,f** were obtained as a *ca.* 3:7 mixtures of *cis* and *trans* isomers (at the sulfur atom) but only the major *trans*-isomers were isolated and characterized. Crystalline benzofused γ-sultims **185** are perfectly stable, but tend to revert to thermodynamically more stable γ-sultams **182** being dissolved.



Scheme 74. Photoisomerization of benzofused γ-sultams **182**.



Scheme 75. Photoisomerization of benzofused γ-sultams **186**.

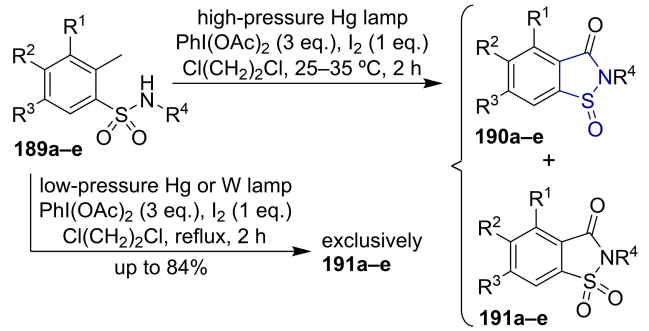
The *retro*-reaction is greatly catalyzed by the mineral acids (Scheme 74).

Later, D. Döpp and I. Elghamry utilized these reaction conditions for the synthesis of 1,3-benzothiazine 1,1-dioxides **187** through the photochemical ring expansion of benzofused γ-sultams **186**.[119] According to the renewed method, the introduction of CH_2EWG substituent at the nitrogen atom of the starting γ-sultams facilitates photoconversion into **187**. The single photoproducts were obtained in all cases, except for **186a**, which was converted into a mixture of sulfone **187a** (45% yield) and γ-sultim **188a** (20% yield). Notably, **188a** quantitatively reverted back to starting γ-sultam **186a** upon standing at rt for two weeks. Otherwise, it can be photoconverted into sulfone **187a** under the above reaction conditions (Scheme 75). That's why **188a** was not found in the photolysis mixture after **186a** had been irradiated for 6 h, while the yield of **187a** increased up to 60%.

An interesting modification of the photoisomerization reaction is the *photodeoxygenative cyclization*, as H. Togo *et al.* called it. Thus, the treatment of (*ortho*-methyl)benzenesulfonamides **189** with $PhI(OAc)_2$ and I_2 under the irradiation with a high-pressure Mercury lamp resulted in a mixture of benzofused γ-sultims **190** and saccharin derivatives **191**. Notably, the formation of γ-sultims **190** did not occur under irradiation with a low-pressure Mercury lamp or a Tungsten light bulb. In this case, the saccharin derivatives **191** were obtained exclusively (Scheme 76).[120] The mechanism for the γ-sultim formation is not clear.

2.8. Miscellaneous Methods

Apart from the above-discussed methods there were reported miscellaneous reactions which constituted useful approaches to sultims of different structures.



Scheme 76. Photodeoxygenative cyclization of sulfonamides **189**.

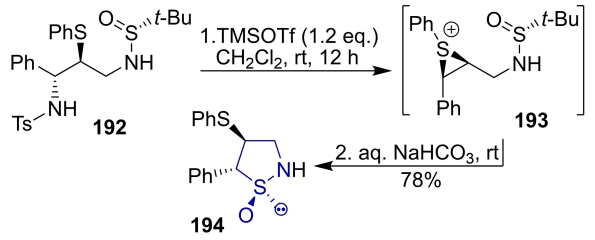
The reported by C.-D. Lu cyclization of *tert*-butylsulfinamide **192** into sp^3-enriched γ-sultim **194** under the polar conditions may be an alternative to the intramolecular homolytic substitution (see Paragraph 2.3). Particularly, treatment of **192** with the Lewis acid TMSOTf resulted in the displacement of the TosNH group by the adjacent SPh thus forming a three-membered episulfonium ion intermediate **193**. The latter underwent rearrangement through the thiiranium ring opening and γ-sultim ring closure accompanied by the inversion of the configuration at the stereogenic sulfur (IV) atom. Eventually, sp^3-enriched γ-sultim **194** possessing three chiral centers was isolated in good yield (Scheme 77).[121] To our knowledge, it has been the first and the only example of this reaction.

Another interesting reaction involving quaternized sulfur (IV) atom was reported by K. Okuma's group. They found that treatment of methyl morpholino(*N*-aryl) sulfoxonium salts **195** with the bases led to benzofused γ-sultims **196** as the rearrangement and methylene-shift products. The reactions were done under several conditions, but the best outcome was achieved with *t*-BuOK as a base in *t*-BuOH media (Scheme 78, *A*). On the other hand, the decrease in the yield of resulting γ-sultims **196c,d** could be attributed to the nature of the starting diaminosulfoxonium salts **195c,d** or to the steric hindrance (Scheme 78, *B* and *C*).[122,123]

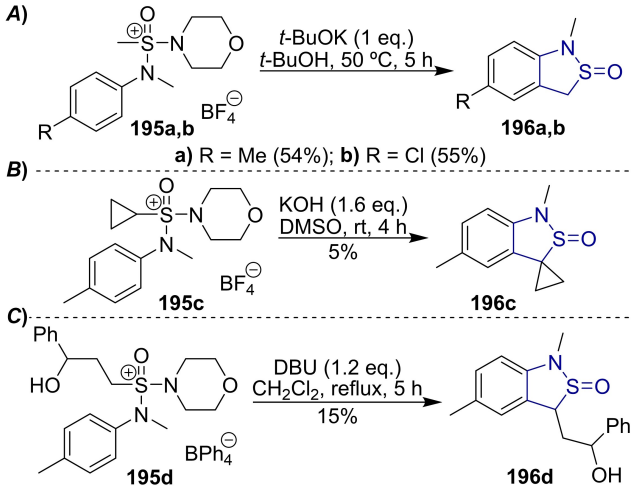
The authors also proposed a mechanism for the formation of benzofused γ-sultims **196**. According to their assumption, the treatment of diaminosulfoxonium salts **195** with a base give the corresponding sulfoxonium ylide which undergoes [2,3]-sigmatropic rearrangement accompanied by the *ortho*-substitution. The subsequent action of another equivalent of a base leads to the rearomatization followed by intramolecular transamination resulting in γ-sultims **196** (Scheme 79).[122]

P. Stanetty and T. Emerschitz constructed benzofused γ-sultim framework through directed *ortho*-metalation of *N*-*tert*-butyl benzenesulfinamide (**197**). Since the sulfinamide functionality is the potent *ortho*-directing group, the lithiation of **197** afforded the corresponding *ortho*-carboanion, which upon treatment with DMF as an electrophile afforded hydroxyl bearing γ-sultim **198** in good yield (Scheme 80).[124]

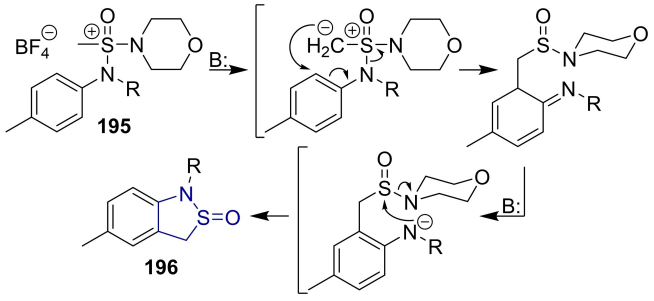
Research group of F. Davis devised $SnCl_4$-promoted imino ene reaction of enantiopure *N*-sulfinyl imino ester (*R*)-(−)-**178** and allyl benzene that provided γ-sultims **199** and **200** (Scheme 81).[125] The relative configuration of the major isomer **199** was determined by an X-Ray diffraction study. The authors speculate that γ-sultim **199** might result from the rearrangement of **201**, which was detected in a crude reaction mixture but could not be isolated. It is worth noting, that other Lewis acids either failed to give any reaction ($Et_2O^{\bullet}BF_3$, $ZnCl_2$, $Ti(OEt)_4$, and YTf_3) or resulted in decomposition (Me_3Al, Me_2AlCl).



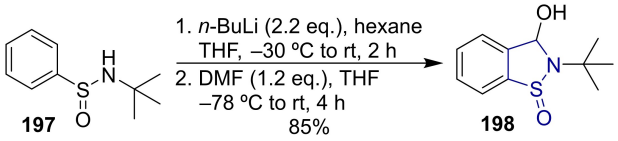
Scheme 77. Synthesis of γ-sultim **194** *via* formation and ring-opening of episulfonium ion intermediate **193**.



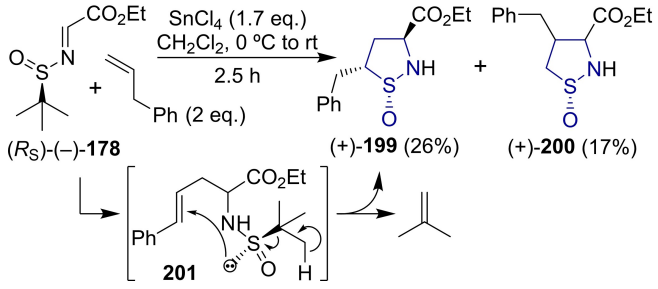
Scheme 78. Synthesis of benzofused γ-sultims **196** through the base-mediated rearrangement of diaminosulfoxonium salts **195**.



Scheme 79. A plausible mechanism for the formation of γ-sultims **196** through the base-mediated rearrangement of diaminosulfoxonium salts **195**.



Scheme 80. Synthesis of benzofused γ-sultim **198** through the *ortho*-metalation strategy.



Scheme 81. Synthesis of γ-sultims **199** and **200** *via* $SnCl_4$-promoted imino ene reaction.

C. Chapuis *et al.* studied the reduction of camphor-derived cyclic sulfinimides **202** into the corresponding sultims. The main feature of this reaction was its stereospecific course. Thus, the reduction of (+)-**202** with $NaBH_4$ in MeOH at rt cleanly afforded camphor-derived sultim (−)-**203**. With that, the diastereoisomeric (−)-**202**[126] also gave exclusively the same sultim (−)-**203** being subjected to similar reductive conditions. This suggests that the reaction is accompanied by competitive epimerization at the sulfur atom. Worth noting, that the target camphor-derived γ-sultim **203** is considered as an analogue of Oppolzer's camphorsultam[127] – one of the most commonly used chiral auxiliaries (Scheme 82).[128]

Sulfonamides are generally quite resistant to reduction and often remain inert to the action of strong reducing agents. However, the course of the reaction may be changed when several functional groups are crowded together in close vicinity, especially when located at a suitable distance and in a suitable orientation. The following reactions support this assertion and present rare examples of sulfonamide group reduction.

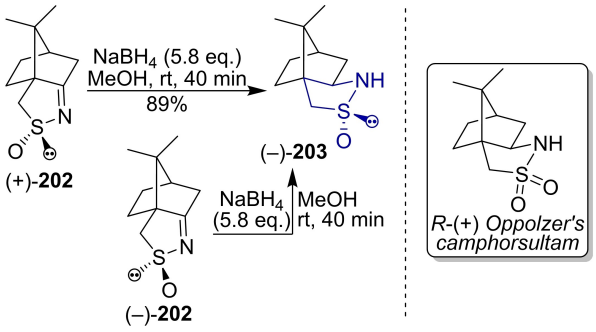
F. Carvalho and R. Herrmann focused on the Pt (II)-catalyzed cascade isomerization of camphorsultam derivatives **204** leading to rare tricyclic sultim framework **206** possessing a nine-membered carbocycle. Thus, $[PtCl_2(PhCN)_2]$ initiates the cyclization of bisalkynyl hydroxy camphorsultam derivatives **204** accompanied by the three-carbon ring enlargement in a single step. Remarkably, in the course of the reaction, the sulfonamide group was reduced to the sulfinamide one, while nearby alkynyl carbon was oxidized into the carbonyl group. The proposed mechanism implies the formation of intermediate **205** (Scheme 83).[129–131]

Sulfonamide reduction under oxidizing conditions in the above camphorsultam derivative **204b** looks even more puzzling! Thus, the reaction with Br_2 initialized another cascade reaction eventually affording the mixture of bisbrominated polycyclic sultims **208** and **209**. The reaction with I_2, apparently, proceeded in a similar way with the only difference that the bisiodinated product underwent hydrolysis (because of the low energy value for the C–I bond) thus affording ketone **210** (Scheme 84).[132]

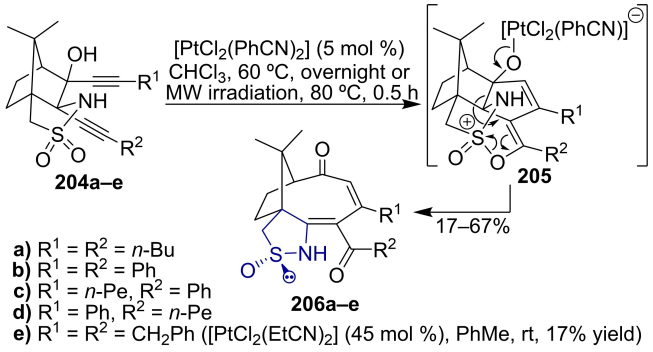
Another puzzling case is the reaction of **204b** with protic acids, namely CF_3CO_2H and HCl. Considering the protonation as an electrophilic attack it initiated the annulation reaction followed by sulfonamide reduction and the carbonyl group formation. At the same time, strong acidic media caused the inversion of the configuration at the sulfur atom, thus leading to thermodynamically more stable counterparts **211** (Scheme 84).[132]

According to a plausible mechanism the reaction proceeds *via* the formation of the key intermediate **207** stabilized by the transfer of the positive charge to the sulfur atom. The existence of the endocyclic C–O bond should greatly facilitate the sulfonamide reduction through the attack of a nucleophile thus initiating the S–O bond cleavage. The latter occurs in stereoselective mode leading to the *S*-configuration of the sulfur atom. The presence of a secondary NH group is essential for the sulfonamide reduction step. Otherwise (if the nitrogen atom is blocked by an alkyl substituent) only the annulation of the five-membered ring to the bornane skeleton is observed.[132]

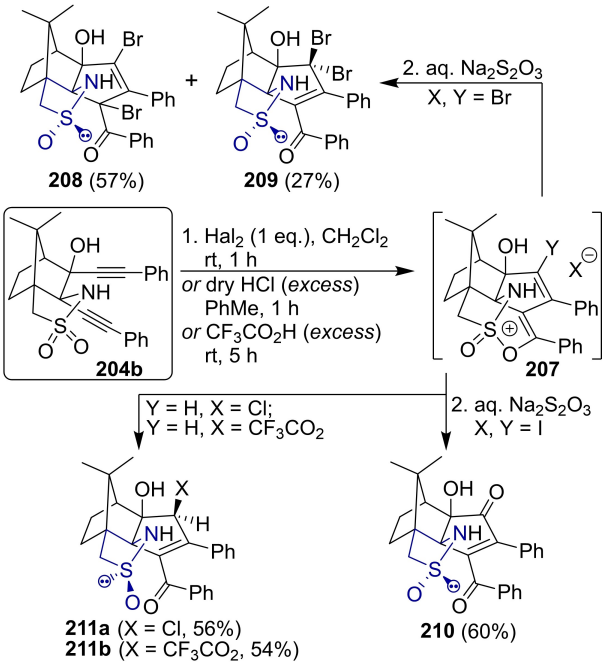
Finally, as a logical continuation of our research program on the synthesis of sultams[133–139] and sultones[140,141] through the CSIC (*Carbanion-mediated Sulfonate (or Sulfonamide)*



Scheme 82. Reduction of camphor-derived cyclic sulfinimides **202**.

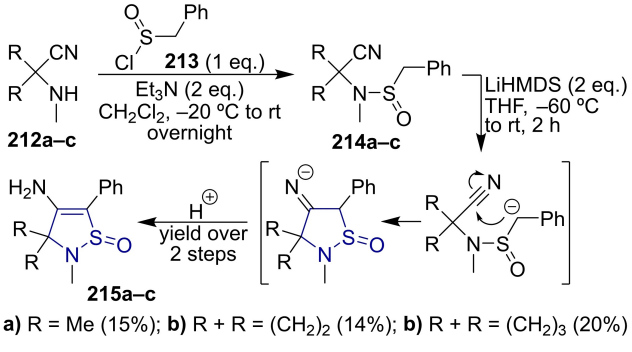


Scheme 83. Pt (II)-catalyzed cascade reaction (annelation-Sulphur reduction-ring enlargement) of sultam **204** leading to sultims **206**.



Scheme 84. Unusual reduction of sulfonamide group in **204b** under oxidizing reaction conditions.

Intermolecular Coupling and Intramolecular Cyclization)[142–146] reaction strategy we turned our attention to functionalized sulfinamides as the potential substrates. Bringing these ideas to life our remarkable PhD student Y. Chuchvera performed the LiHMDS-mediated cyclization of sulfinylated Strecker amines **214** into the corresponding β-enamino-γ-sultims **215**, albeit in poor yield (Scheme 85). To the best of our knowledge, this reaction set the precedent in the chemistry of cyclic sulfinamides.



Scheme 85. Synthesis of γ-sultims **215** through the CSIC reaction strategy.

3. Reactions and Applications of Sultims

In many cases discussed above sultims were prepared not as the target compounds but also as intermediate products or precursors with an aim of involving them in further transformations. Therefore the discussion of the reactivity and synthetic modifications of the sultim scaffold as well as its application constitutes another important part of the present review.

3.1. Oxidation

Oxidation is the first thing that comes to mind when discussing the reactivity of sultims. Indeed, many of them were prepared with a view of obtaining the corresponding sultams.

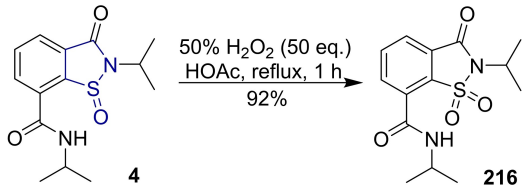
H_2O_2 oxidizes sultims into the corresponding sultams under harsher reaction conditions than those applied for the oxidation of the thiohydroxylamine fragment (see Paragraph 2.1): either higher temperature or significantly increased reaction time is required against the background of a large excess of the oxidizer.

In this way benzofused γ-sultim **4** (also obtained through the oxidation with H_2O_2 *via* Scheme 1) was converted into the corresponding γ-sultam **216** in refluxing HOAc (Scheme 86).[19]

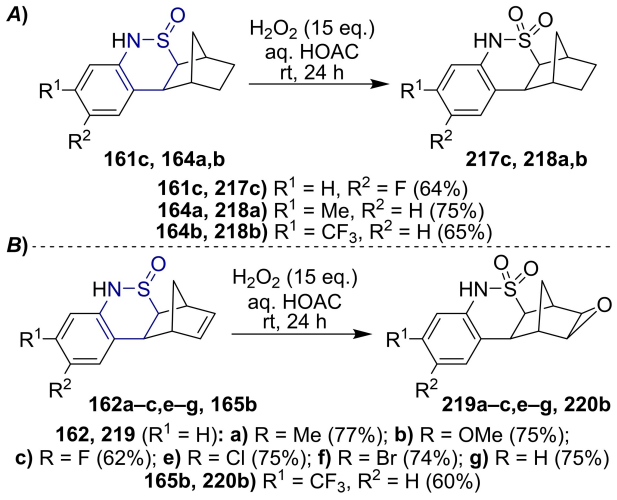
The polycyclic δ-sultims **161** and **164** (prepared *via* Schemes 67 and 68) were oxidized into the corresponding δ-sultams **217**, **218** in the same media at rt upon standing for 24 h (Scheme 70, *A*).[109,110,112] The annelated norbornene framework of δ-sultims **162** and **165** was stereoselectively epoxidated under the above reaction conditions thus providing functionalized δ-sultams **219**, **220** (Scheme 87, *B*).[110–112]

The oxidation of δ-sultim **170a** possessing an annelated pyridine nucleus (prepared *via* Scheme 70) at rt affected both centers prone to oxidation with H_2O_2 so that the corresponding *N*-oxide of pyridoannelated δ-sultam **221** was isolated in good yield (Scheme 88).[113]

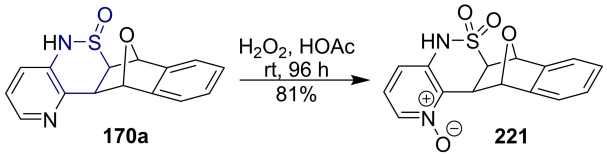
Apparently, NaClO acts more selectively so that the pyridine core remains intact. An example can be the oxidation of **61** (prepared *via* Scheme 21) in two-phase media leading to the corresponding γ-sultam **222**, albeit in poor yield (Scheme 89).[49]



Scheme 86. Oxidation of benzofused γ-sultim **4** with H_2O_2 in refluxing HOAc.



Scheme 87. Oxidation of δ-sultims **161**, **164**, **162**, and **165** with H_2O_2 in HOAc at rt.

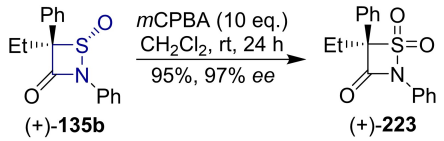


Scheme 88. Oxidation of pyridoannelated δ-sultim **170a** with H_2O_2.

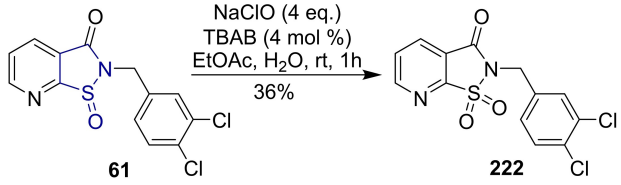
*m*CPBA is another commonly used reagent for the oxidation of sultims into the corresponding sultams. The undoubted advantage of this reagent is its selectivity so that the only sulfur (IV) atom is affected by being surrounded by ordinary functional groups and substituents. Particularly, this method allowed oxidizing such a fragile compound as β-sultim **135** (prepared *via* Scheme 55) in excellent yield (Scheme 90).[88]

γ-Sultim **199** (prepared *via* Scheme 81) was oxidized by *m*CPBA into the corresponding γ-sultam **224** in excellent yield. The latter was subjected to the Raney Ni-catalyzed reductive desulfonylation to give amino acids **225** isolated by virtue of preparative chromatography (Scheme 91).[125]

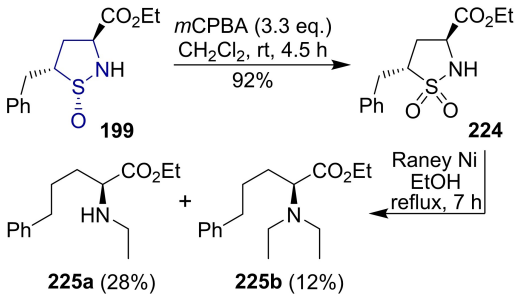
It should be emphasized, that γ-sultams of type **224** are considered as *sulfa*isosteres of pyroglutamic acid[133] and have been used in the development of peptidosulfonamides and for generating abzymes.[147–152]



Scheme 90. Oxidation of β-sultim (+)-**135** with *m*CPBA.



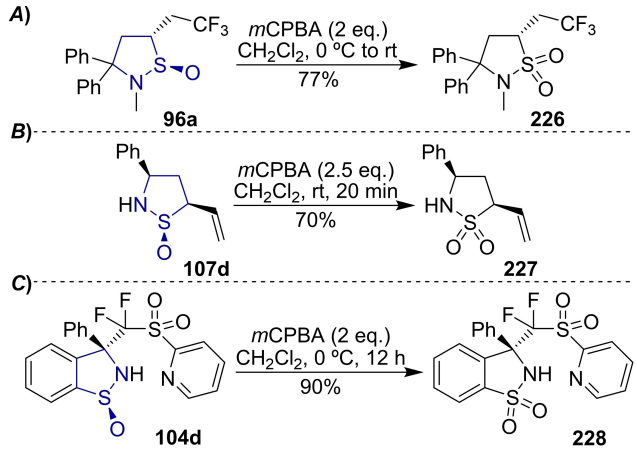
Scheme 89. Oxidation of pyridoannelated γ-sultim **61** with NaClO.



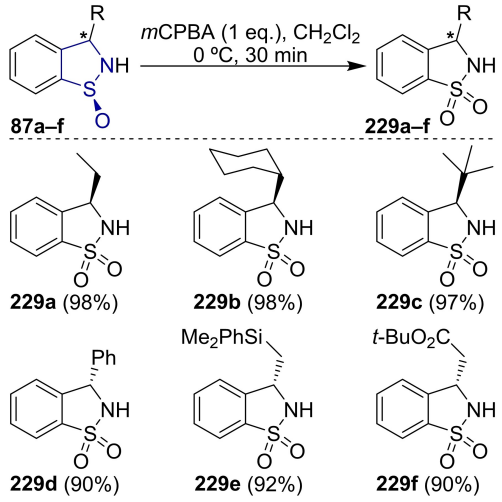
Scheme 91. Oxidation of γ-sultim **199** with *m*CPBA and subsequent desulfonylation of γ-sultam **224** into amino acids **225a,b**.

There are some other ordinary examples of oxidation of γ-sultims with *m*CPBA. Interestingly, while sp^3-enriched γ-sultims **96a** (prepared *via* Scheme 40) and **107d** (prepared *via* Scheme 44) were oxidized at rt, their bezofused congener **104d** (prepared *via* Scheme 43) required lower (0 °C) temperature (Scheme 92, *A*,[76] *B*,[79] and *C*[78]). Under these conditions, the pyridine ring of γ-sultam **228** remained intact.

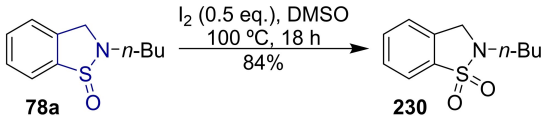
A series of chiral benzofused γ-sultims **87** (prepared *via* Scheme 35) was also oxidized with *m*CPBA in CH_2Cl_2 media at 0 °C. The reaction proceeded in excellent yields with complete retention of stereochemistry at the C-3 carbon atom thus providing chiral γ-sultams **229** (Scheme 93).[73] The



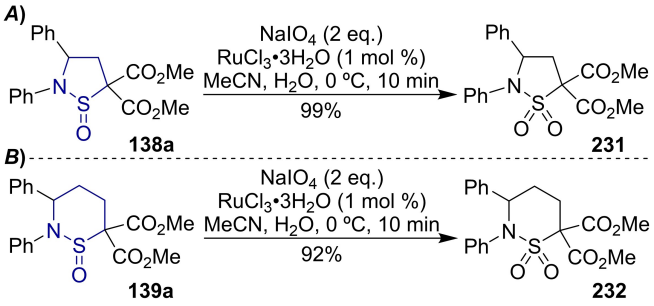
Scheme 92. Oxidation of γ-sultims **96a**, **107d**, and **104d** with *m*CPBA.



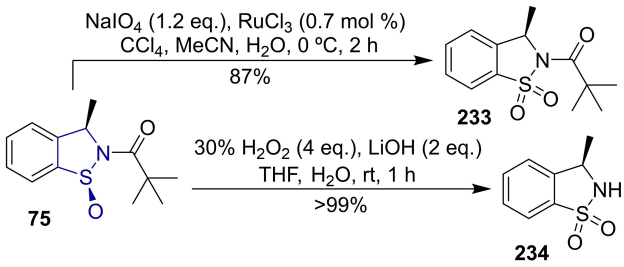
Scheme 93. Oxidation of benzofused γ-sultims **87** with *m*CPBA.



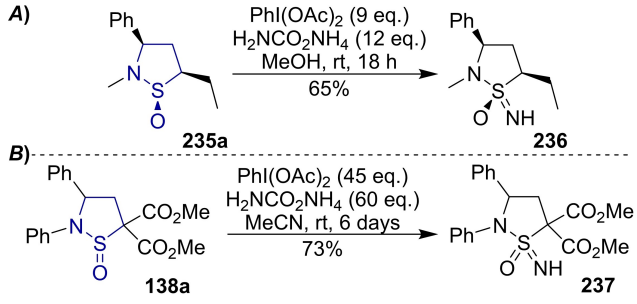
Scheme 94. Oxidation of benzofused γ-sultim **78a** with I_2.



Scheme 95. Oxidation of sultims **138a** and **139a** with $NaIO_4$–$RuCl_3$.



Scheme 96. Oxidation of benzofused γ-sultim **75** with $NaIO_4$–$RuCl_3$ and H_2O_2–LiOH.



Scheme 97. Conversion of γ-sultims **235a** and **138a** into cyclic sulfonimidamide **236** and **237**.

synthetic value of the latters is conditioned by the presence of unsubstituted endocyclic NH-functionality.

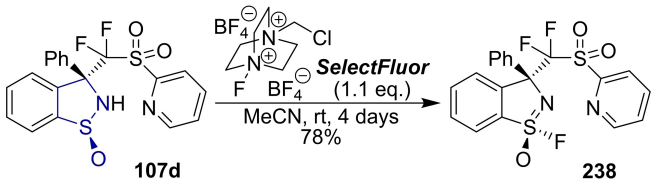
Despite the reported synthesis of sultims via I_2-mediated oxidation of amino (di)sulfides (see Paragraph 2.1, Scheme 17) and I_2-mediated oxidation of sultim **78a** (prepared *via* Scheme 29) performed within mechanistic studies for their formation (Scheme 94),[63] it might be expected that sultims are susceptible to iodine in basic media since this reaction conditions are used for deprotection of *tert*-butanesulfinyl and *p*-toluenesulfinyl amines (not shown in Scheme).[153]

$NaIO_4$ in combination with a catalytic amount of the soluble Ruthenium (III) salts gives excellent preparative yields of the corresponding sultams upon oxidation of the corresponding sultims. The method works well both for γ- and δ-sultims as shown in the example of **138a** and **139a** (prepared *via* Scheme 57) (Scheme 95).[89]

Chiral γ-sultim **75** (prepared *via* Scheme 27) was also oxidized into the corresponding benzofused γ-sultam **233** using $NaIO_4$ and $RuCl_3$ as a catalyst. Alternatively, the combination of H_2O_2 and LiOH allowed one-pot sulfur oxidation and nitrogen deprotection to give *N*-unsubstituted γ-sultam **234** in almost quantitative yield (Scheme 96).[60]

Finally, other vivid examples of sultims' synthetic utility were provided by the reaction with $PhI(OAc)_2$ in the presence of ammonium carbamate and by treatment with *SelectFluor*. The former reaction led to the formation of increasingly more popular cyclic sulfonimidamides, a representative of a not numerous but quite interesting class of compounds. In this way, sp^3-enriched γ-sultims **235a** (prepared *via* Scheme 106, see below) and **138a** (prepared *via* Scheme 57) were converted into the corresponding sulfonimidamides **236** and **237** with configurational retention at the sulfur atom (Scheme 97, *A*[79] and *B*[89]).

The reaction with *SelectFluor*[154] at rt turned benzofused γ-sultim **107d** (prepared *via* Scheme 43) into sulfonimidoyl fluoride **238** formed as a sole diastereoisomer in good yield (Scheme 98).[78]



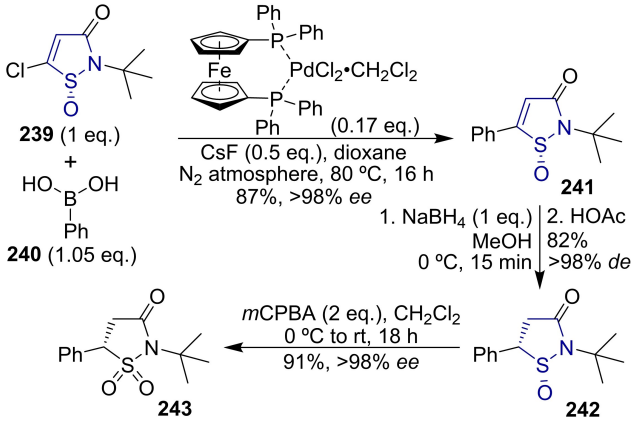
Scheme 98. Oxidation of benzofused γ-sultim **107 d** with *SelectFluor*.

3.2. Reduction

The reduction of the sultim framework is the rarely used transformation because of the susceptible sulfur (IV) atom. However, there are a few examples of reduction of unsaturated sultims without affecting the sulfinamide fragment as well as reactions providing sulfur (II)-containing products and desulfurized ones.

A. Combs *et al.* extensively studied potent protein tyrosine phosphatase 1B (PTP1B) inhibitors possessing γ-sultam core.[155–157] In their research the authors utilized γ-sultim precursors that allowed for the preparation of the target compounds with strictly defined configuration in high yield and excellent stereoselectivity.

In detail, the synthesis of pTyr mimetic commenced from the Suzuki coupling between enantiopure unsaturated γ-sultim **239** (>98% *ee*) and phenylboronic acid (**240**) that gave the corresponding phehylketosultim **241** without loss in stereochemical integrity. The key reaction in this sequence was the reduction with $NaBH_4$ that succeeded with excellent regiochemical and stereochemical control and afforded only one diastereomer **242** thus demonstrating that the chiral induction from the sulfinamide moiety was absolute. Finally, **243**, a direct precursor to pTyr mimetic, was achieved through the *m*CPBA oxidation of **242** with excellent yield and stereocontrol (Scheme 99).[158]



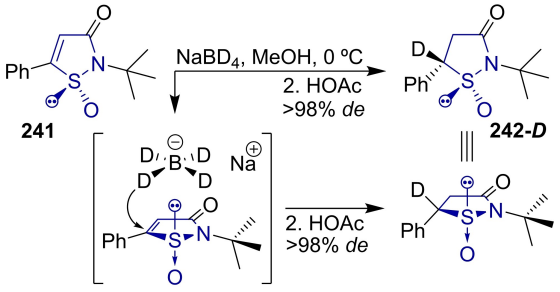
Scheme 99. Selected steps in the synthesis of pTyr mimetic.

With the object of a more detailed study of the key reaction, the reduction of **241** with $NaBD_4$ was performed. NMR analysis of the reduced product ***242-D*** showed, that the deuteride addition occurred to the C-5 carbon atom (*i.e.* α to the sulfinamide fragment) only. Therefore, the close proximity of intramolecular chiral auxiliary (*i.e.* the sulfur (IV) atom) compels hydride/deuteride anion to attack the C-5 carbon atom on the opposite face of the γ-sultim framework compared to that of the Oxygen of sulfinamide thus causing the high degree of stereochemical control (Scheme 100).[158]

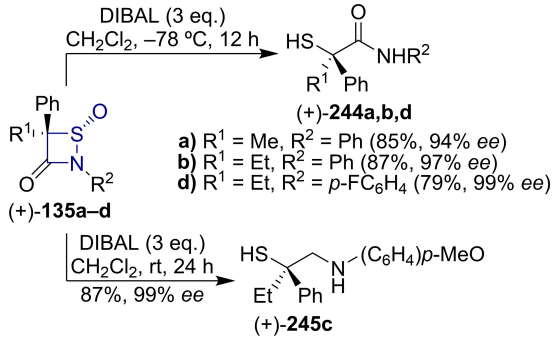
Treatment of β-sultims **135** (prepared *via* Scheme 55) with $(i\text{-Bu})_2AlH$ (DIBAL) resulted in ring-opening products possessing the SH group. In particular, the reaction at low temperature (−78 °C) gave mercapto amides **244**, whereas the elevated temperature (rt) caused the exhaustive reduction thus affording mercapto amine **245**. Both processes succeeded with good yields and excellent enantioselectivity (Scheme 101).[88]

With the aim of establishing the structure of tricyclic δ-sultim **173** (prepared *via* Scheme 69), it was hydrogenated with the Raney Ni in refluxing aqueous dioxane. This led to desulfurization and the formation of the corresponding amine **246** (Scheme 102).[113]

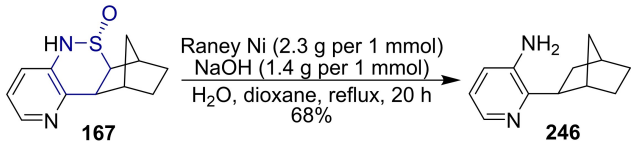
There is a noteworthy example of the reduction of exocyclic C=C bond without affecting the saturated γ-sultim core. This was achieved by exploiting the *in situ* generated 2-nitrobenzene-



Scheme 100. Proposed mechanism for stereoselective reduction of unsaturated γ-sultim **241** with $NaBD_4$.



Scheme 101. Reduction of β-sultims **135** with DIBAL.



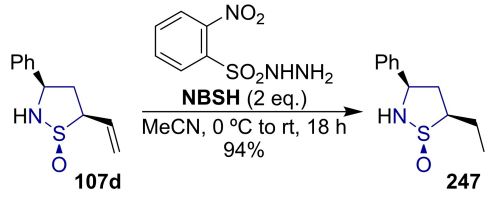
Scheme 102. Raney Ni-mediated desulfurization of sultim δ-**167**.

sulfonylhydrazide (NBSH) as a reducing agent. The method allowed converting the vinyl group of γ-sultim **107 d** (prepared *via* Scheme 44) into the ethyl substituent with high yield (Scheme 103).[79]

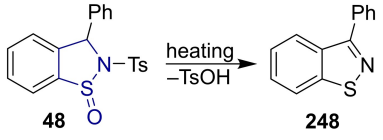
3.3. Deoxygenation and Dehydration

The tendency of sultims to deoxygenation was mentioned in passing above when discussing the mechanism for the formation of aryl[4,5]isothiazoles **45** through the all-heteroatom Wittig-equivalent reaction (see above Scheme 16). This important feature of sultims' behavior was additionally demonstrated by the following examples.

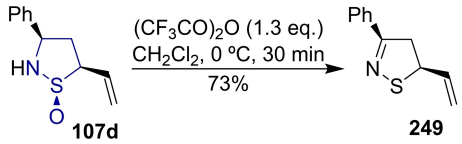
Z. Sun *et al.* reported on the elimination of TsOH upon heating of *N*-tosylated benzofused γ-sultim **48** (prepared *via* Scheme 16) that terminated with the formation of isothiazole **248** and change in the valency of the sulfur atom from IV to II (Scheme 104).[44] However, the authors gave neither protocol nor yield for this reaction.



Scheme 103. NBSH-mediated reduction of vinyl group of γ-sultim **107 d**.



Scheme 104. Conversion of *N*-tosylated benzofused γ-sultim **48** into isothiazole **248**.



Scheme 105. TFAA-mediated dehydration of γ-sultim **107 d**.

The classic dehydration was exemplified by the treatment of γ-sultim **107 d** (prepared *via* Scheme 44) with $(CF_3CO)_2O$ in CH_2Cl_2 media at 0 °C. The loss of water was accompanied by the formation of dihydroisothiazole **249** in good yield (Scheme 105).[79]

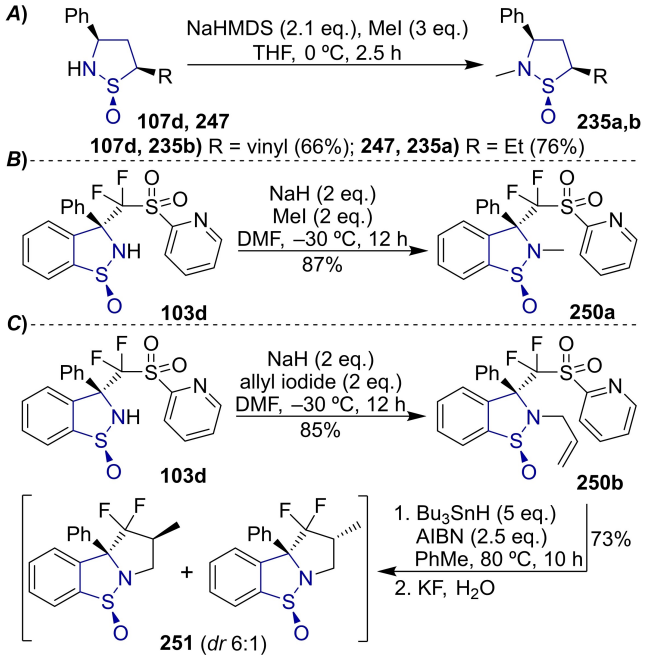
One more example of a similar transformation involving tricyclic δ-sultim **299** is outlined in Scheme 128 (see below).

3.4. Alkylation of Endocyclic *NH*-Group

N-Unsubstituted sultims possess two nucleophilic centers, *i. e.* a nitrogen atom and a sulfur one. The endocyclic *NH*-group is significantly more reactive toward alkylating agents therefore exclusively *N*-alkylated products form in the alkylation step. The reaction is promoted by strong bases and is conducted at reduced temperatures because of the fragility of the sultim framework and its susceptibility toward electrophiles.

In this way, γ-sultims **107 d** (prepared *via* Scheme 44), **247** (prepared *via* Scheme 103), and **103 d** (prepared *via* Scheme 43) were alkylated in good yields using either MeI or AllI and NaHMDS or NaH as a base at low temperature (Scheme 106, *A*[79] and *B*, *C*[78]).

Moreover, the *N*-allylated γ-sultim **250 b** underwent intramolecular radical S_Hi cyclization under the standard reaction conditions affording tricyclic γ-sultim **251** as a *ca.* 6 : 1 mixture of epimers (Scheme 106, *C*).[78]



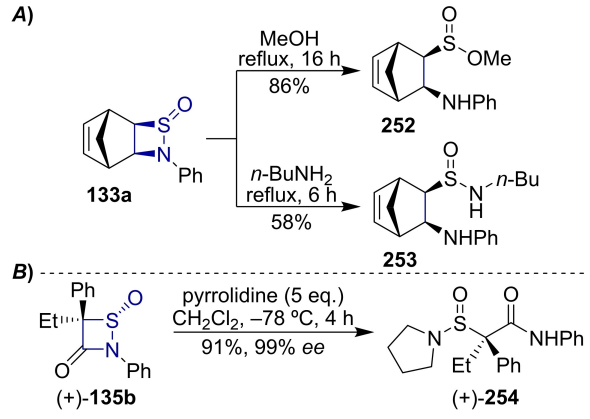
Scheme 106. Alkylation of -unsubstituted γ-sultims **107 d**, **247**, and **103 d**. The intramolecular radical S_Hi cyclization of *N*-allylated γ-sultim **250 d**.

3.5. Interaction with Nucleophiles

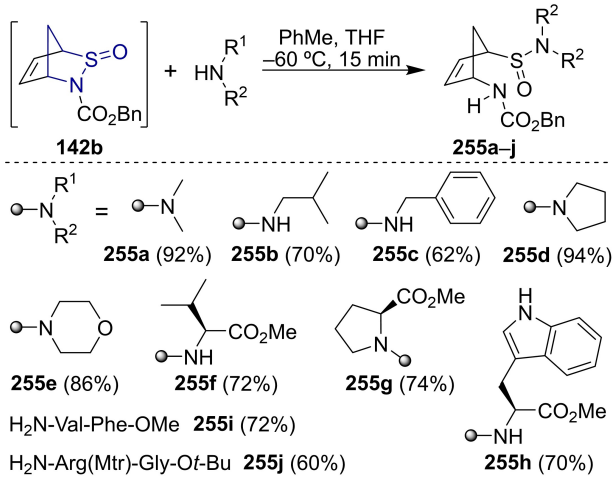
This type of reaction almost always leads to ring-opening products through the cleavage of the endocyclic S–N bond. Depending on the stability of the sultim framework and nucleophilicity of the reagent the reaction is performed under different conditions. In general, sultims are quite susceptible to the action of nucleophiles, which is underlaid in many synthetic methods in preparative organic chemistry, especially asymmetric ones.

For instance, alcoholysis and aminolysis of β-sultims **133a** (prepared *via* Scheme 54) and **135b** (prepared *via* Scheme 55) led to ring-opened sulfinate **252** and sulfinamides **253**, **254** (Scheme 107, *A*[87] and *B*[88]).

Interestingly, *N*-nucleophiles attack the sulfur atom so that the adjacent endocyclic nitrogen atom acts as a leaving group. Apparently, this arises from the lower nucleophilicity of the latter caused by the attached protecting group (CO_2Me, Boc, or Cbz) bearing carbonyl functionality.



Scheme 107. Alcoholysis and aminolysis of β-sultims **133a** and **135b**.



Scheme 108. The reaction of bridged sultim **142b** with *N*-nucleophiles.

G. Papandrea and F. Ponticelli conducted the reaction of bridged sultim **142b** (prepared *via* Scheme 59) not only with a series of primary and secondary amines (Scheme 108, compounds **255a–e**) but also with amino acid esters (compounds **255f–h**) and even dipeptides (compounds **255i,j**).[94,159]

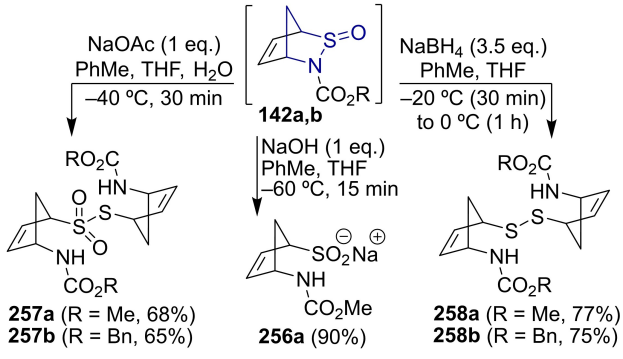
Worth to note, that sulfinamides **255i,j** could be readily oxidized with *m*CPBA to give the corresponding sulfonamides in good yields (not shown in Scheme) thus providing an easy-to-handle procedure for the synthesis and purification of peptidosulfonamides applicable to a wide range of substrates.[159]

In a similar way, bridged sultim **142a** (prepared *via* Scheme 59) smoothly reacted with NaOH to give the corresponding *N*-protected γ-amino sulfinate **256a** in excellent yield (Scheme 109).[94]

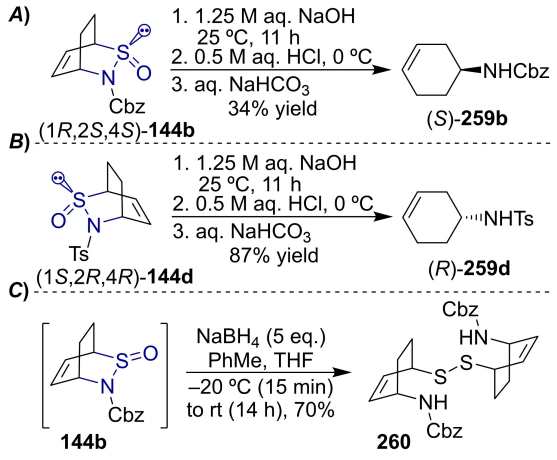
Quite interesting the behavior of bridged sultims **142a,b** towards NaOAc. As it was mentioned above, the treatment of the crude reaction mixture with a quarter equivalent of NaOAc at −20 °C allowed for the isolation of pure **142a,b** (Scheme 59). With that, a stoichiometric amount of NaOAc at a lower temperature (−40 °C) induced S–N bond cleavage accompanied by the disproportionation reaction of the sulfur atom thus affording thiosulfonates **257a,b** (Scheme 109).[95]

On the other hand, the reduction of sultims **142a,b** with the excess of $NaBH_4$ at −20 °C also proceeded *via* the S–N bond rupture and resulted in disulfides **258a,b** (Scheme 109).[95]

The reaction of the higher homologues **144** (prepared *via* Scheme 61) with aqueous NaOH was conducted at a significantly higher temperature (25 °C versus −60 °C) therefore apart from S–N bond rupture it was accompanied by the rearrangement to give carbamate **259b** and tosylate **259d** (Scheme 110, *A* and *B*).[96,97] The crude **144b** was also converted into dimer **260** upon the action of $NaBH_4$ with the only difference (as



Scheme 109. Ring-opening reactions of bridged sultims **142a,b** with NaOH, NaOAc, and $NaBH_4$.



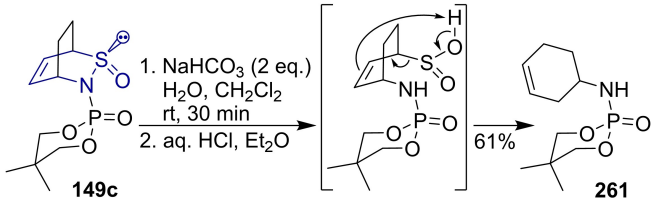
Scheme 110. Ring-opening reactions of bridged sultims **144b,d** with NaOH and $NaBH_4$.

compared to **258b**, Scheme 109) that it needed a higher temperature and more time (Scheme 110, *C*).[95]

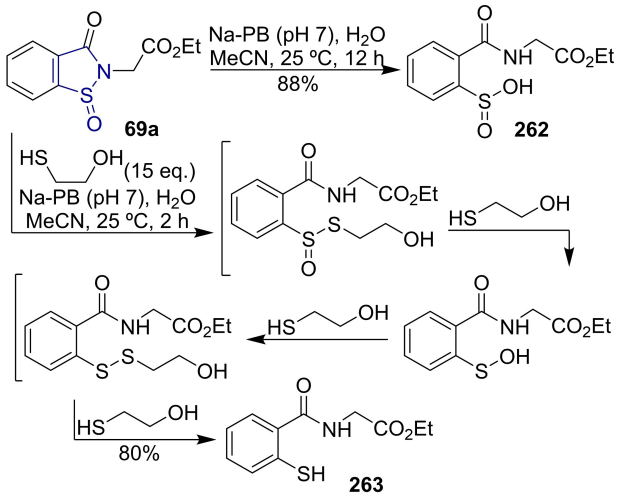
A similar reactivity was observed for bridged δ-sultim **149c** possessing *N*-phosphoramidate functionality (prepared *via* Scheme 63). Its treatment with aqueous $NaHCO_3$ at rt resulted in the hydrolysis of the S–N bond followed by sigmatropic rearrangement accomplished by the loss of SO_2 and phosphoramidate **261** formation (Scheme 111).[102]

As it was shown, sultims are less stable compared to the corresponding sultams and undergo hydrolysis at milder conditions. Thus, benzofused γ-sultim **69a** (prepared *via* Scheme 24) was converted into amido sulfinic acid **262** in neutral MeCN–water media containing sodium phosphate buffer (Na–PB, pH 7) at 25 °C within 12 h. Worth taking into account the impact of the amide nature of the nitrogen atom that greatly facilitates ring-opening reactions. Next, when treated with an excess of 2-mercaptoethanol the starting γ-sultim **69a** disappeared in 5 minutes, but the formation of final sulfide **263** took more time. Ultimately, after 2 h it was isolated in good yield. The mechanism for its formation is also proposed (Scheme 112).[54]

A tendency of sultims to ring opening upon the action of nucleophiles was used for the activation of γ-sultim-containing



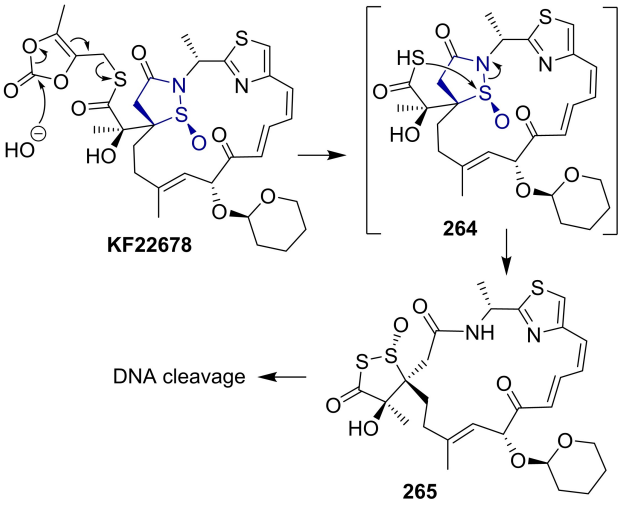
Scheme 111. The ring-opening reaction of bridged sultim **149c** with $NaHCO_3$.



Scheme 112. Hydrolysis of benzofused γ-sultim **69a** and its reaction with 2-mercaptoethanol.

prodrug KF22678 (prepared *via* Scheme 30) in biological media. In this way, the 1,3-dioxolone trigger is either enzymatically or chemically hydrolyzes and thus liberates thioacyl fragment which attacks the sulfur (IV) atom of γ-sultim core in interim **264**. This leads to the ring opening of the γ-sultim ring and regains the spirocyclic dithiolanone fragment thus converting the biologically active form **265** (Scheme 113).[66]

There were reported ring-opening reactions of optically pure benzofused γ-sultim (+)-**75** (prepared *via* Scheme 28) accomplished by the inversion of configuration at the sulfur atom. The nucleophilic attack of MeOLi on the sulfur atom resulted in the corresponding sulfinate methyl ester (−)-**266** (as a 2 : 1 mixture of diastereomers) while the treatment with



Scheme 113. A plausible activation pathway for KF22678.

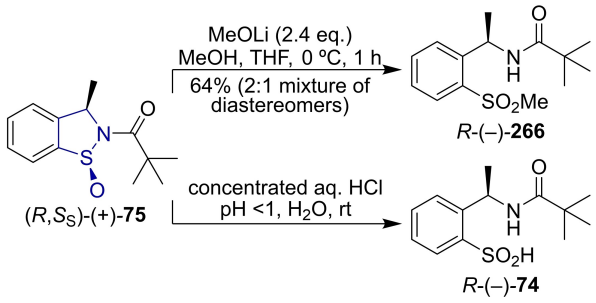
concentrated aq. HCl gave sulfinic acid (−)-**74** (Scheme 114).[62]

Finally, the interaction of sultims with the Grignard reagents is another noteworthy transformation.

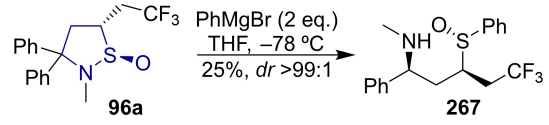
Under these conditions sp^3-enriched γ-sultim **96a** (prepared *via* Scheme 40) underwent ring-opening through the cleavage of the N–S bond when reacting with PhMgBr. This led to the linear chiral amino sulfoxide **267** obtained in low yield but with excellent diastereoselectivity (Scheme 115).[76]

T. Shimizu and N. Kamigata involved benzofused γ-sultim **67** (prepared *via* Scheme 23) in the reaction with MeMgCl and isolated ring-opening product – the corresponding sulfoxide **268** (Scheme 116, *A*).[52] At the same time, M. Wills *et al.* studied in detail the behavior of *cis*-**75** (prepared *via* Scheme 28) towards alkyl lithiums and the Grignard reagents. The authors found out that the reaction was accompanied by the inversion of configuration at the sulfur atom (Scheme 116, *B*).[61]

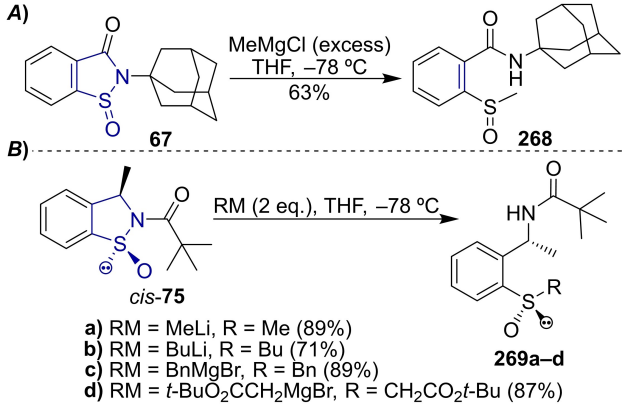
M. Wills' group also developed the methodology for asymmetric aldol condensation in which the sulfoxide auxiliary can be recovered and reused. According to their procedure, optically pure benzofused γ-sultim (+)-**75** (prepared *via* Scheme 28, Figure 6) reacted with the Grignard reagent *t*-BuO_2CCH_2MgBr to give the open chain product (−)-**270** with the inversed configuration at the sulfur atom. The subsequent reaction with the aldehydes was carried out in the presence of *t*-BuMgBr as a base and at a low temperature (−78 °C) thus affording the single diastereomer of chiral product **271**. The reductive cleavage of the C–S bond with the Al/Hg amalgam provided the target chiral β-hydroxy ester **272** with different levels of chemical yield and enantiomeric excess. In turn, another product of this reaction – thiol (−)-**273** was oxidized with $NaIO_4$ into the corresponding sulfinic acid (−)-**74**. Finally, the subsequent stereoselective cyclization (−)-**74** proceeded with respect to an existing asymmetric center and recovered the chiral sultim (+)-**75** (Scheme 117).[62]



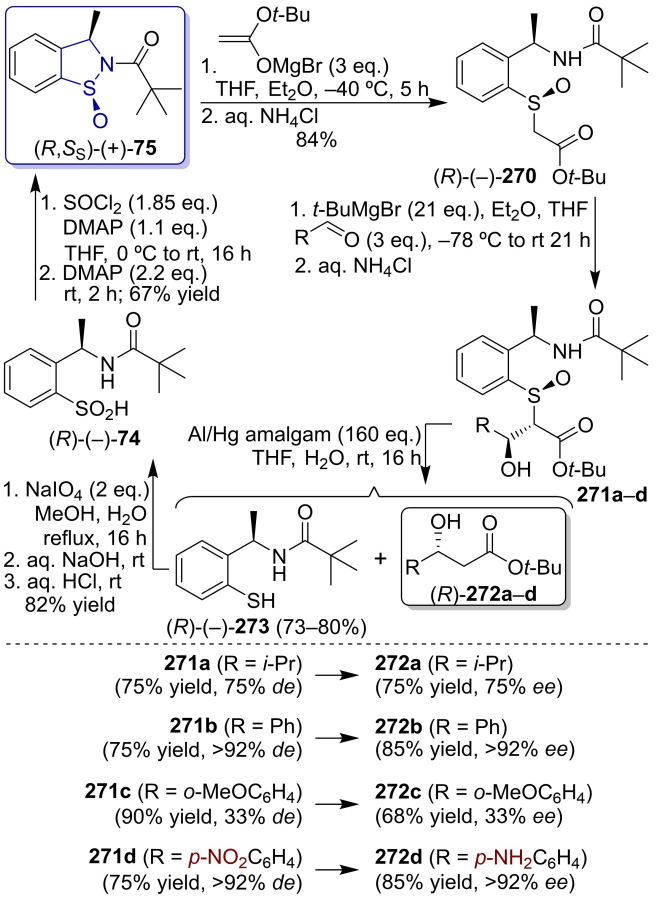
Scheme 114. Ring-opening reactions of benzofused γ-sultim (*R*,S_S)-(+)-**75**.



Scheme 115. Reaction of γ-sultim **96a** with PhMgBr.



Scheme 116. The reaction of benzofused γ-sultims **67** and *cis*-**75** with metal-organic compounds.



Scheme 117. The use of benzofused γ-sultim (*R*,S_S)-(+)-**75** as a recoverable chiral auxiliary in the asymmetric aldol condensation.

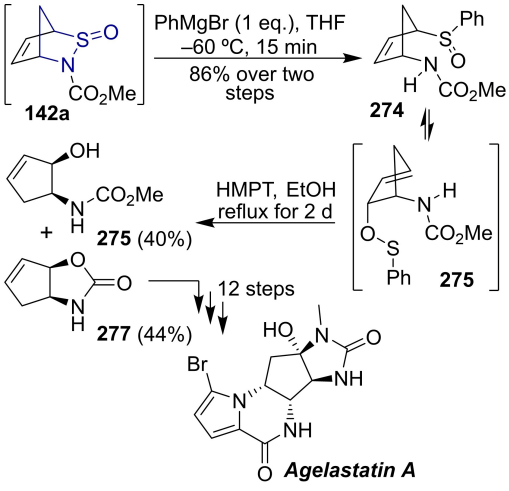
S. Weinreb's group commenced the synthesis of cytotoxic marine alkaloid *Agelastatin A*[160] (against leukemia and epithelial tumor lines) and its analogues from the *hetero*-Diels–Alder reaction.[92,93] The resulting bridged bicyclic sultim **142a** (prepared *via* Scheme 59, *A*) reacted with PhMgBr to form ring-opened allylic sulfoxide **274** *via* S–N bond rupture. Notably, the valence of the sulfur atom remained unchanged. The subsequent [2,3]-sigmatropic rearrangement *via* the formation of interim sulfenate ester **275** afforded a *ca.* 1 : 1.1 mixture of carbamate **276** and desired oxazolidinone **277**. The latter was eventually converted into the target marine alkaloid *Agelastatin A* in 12 steps (Scheme 118).[93]

To assign the absolute configuration of (1*R*,2*S*,4*S*)-**144b** (prepared *via* Scheme 61) by chemical correlation with the known carbamate (3a*S*,7a*R*)-**281**, the former was treated with PhMgBr to give sulfoxide **278**, which was subjected to $(MeO)_3P$-mediated [2,3]-sigmatropic rearrangement followed by intramolecular interesterification and Rh-catalyzed hydrogenation eventually affording known (3a*S*,7a*R*)-**281** with definite configuration (Scheme 119).[96,97]

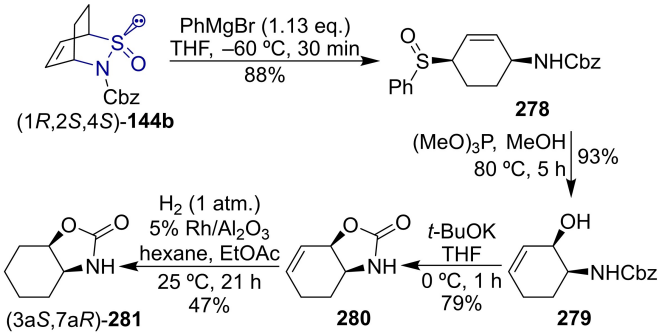
For a similar purpose – to determine the enantiomeric excess of the δ-sultims *cis*-**146a,b** (formed *via* Scheme 62), the reaction with the Grignard reagent PhMgBr was carried out (Scheme 120).[101]

The above-mentioned reliable synthesis of benzodiazepines and benzothiadiazepines developed by K. Hemming relies upon the transformations of the key precursor – δ-sultim-containing iminophosphoranes **157** (prepared *via* Scheme 66). The latters reacted with PhMgBr to afford the allylic sulfoxide **283**. In this case [2,3]-sigmatropic rearrangement was also induced by epy treatment with $(MeO)_3P$ that delivered interim sulfenate ester **284** and thereafter alcohol **285**. Finally, Dess–Martin oxidation of **285** followed by intramolecular *aza*-Wittig reaction[161] with **286** gave desired fused diazepines (X=CO) and 7-membered *aza*sultams (X = SO_2) **287** (Scheme 121).[108]

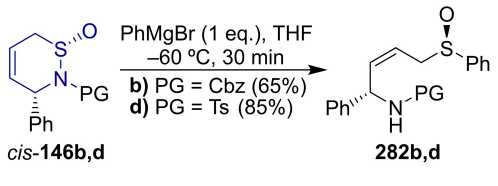
The nucleofugality of the $PhSO_2CF_2^-$ anion allows its abstracting from the benzofuzed γ-sultims **104** (prepared *via* Scheme 43) under base-mediated conditions. Hence, the treat-



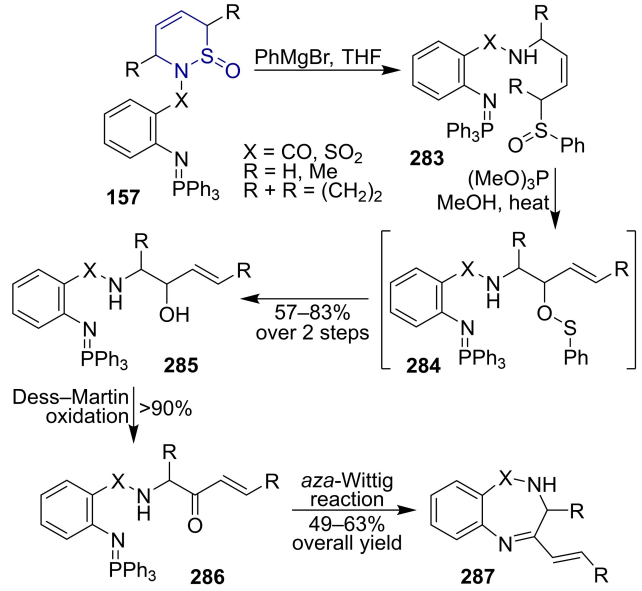
Scheme 118. Selected steps in the total synthesis of *Agelastatin A*.



Scheme 119. Assigning the absolute configuration of (1*R*,2*S*,4*S*)-**144b** by chemical correlation with known (3a*S*,7a*R*)-**281**.



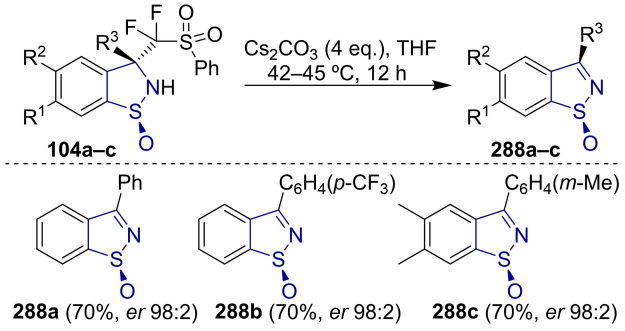
Scheme 120. The ring-opening reaction of δ-sultims *cis*-**146a,b** with PhMgBr.



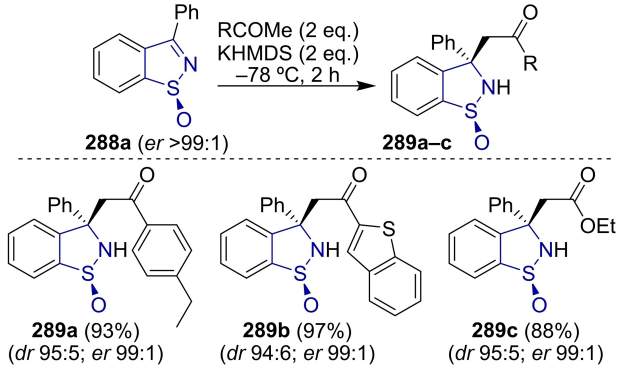
Scheme 121. Synthesis of benzodiazepines and benzothiadiazepines **287** starting from δ-sultim-containing iminophosphoranes **157**.

ment of **104** with Cs_2CO_3 in THF media at 42–45 °C induced β-elimination thus delivering cyclic sulfinimides **288** in good yields and high enantioselectivity (Scheme 122).[77]

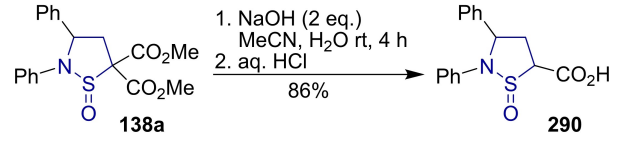
These cyclic sulfinimides **288** are considered as good Michael acceptors therefore they are prone to act in the addition reactions with other nucleophiles. This was exemplified by the addition of enolate anions to enantioenriched **288a** (*er* was improved after a single recrystallization) in the presence of KHMDS as a base at −78 °C. The reaction succeeded with the formation of chiral γ-sultims **289** with good yields, high enantioselectivity, and the retention of the absolute configuration at the sulfur atom (Scheme 123).[77] Such elimination–addition reaction would be synthetically valuable since it corresponds to a formal nucleophilic substitution of the $PhSO_2CF_2^-$ anion.



Scheme 122. Synthesis of benzofuzed cyclic sulfinimides **288**.



Scheme 123. The addition of enolate aniones to cyclic sulfinimide **288a** through the Michael reaction.



Scheme 124. Synthesis of γ-sultim-derived carboxylic acid **290**.

There is also an example when a sultim ring tolerated the action of as strong a nucleophile as an alkali. Thus, NaOH-mediated saponification of the diester **138a** (prepared *via* Scheme 57) followed by decarboxylation upon acidification with aq. HCl did not affect the sultim ring thus providing acid **290** (Scheme 124).[89]

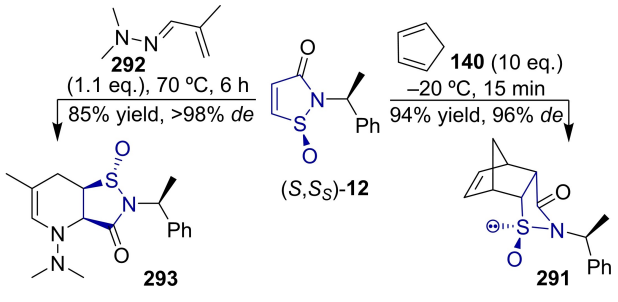
3.6. The Diels–Alder Reaction

Unsaturated sultims found the practical application both as dienophiles and dienes in the Diels–Alder reaction. Sultim-based dienophiles are interesting in terms of chiral induction in cycloaddition. In detail, the steric discrimination between the oxygen atom and the lone pair on the sulfur one is quite sufficient for the excellent diastereoselectivity upon reaction with dienes. Another noteworthy feature is the nature of activating EWG: unlike the acrylate-based and related dienophiles with strong mesomeric effect, the sulfinamide functionality activates the C=C-bond by its inductive effect only.[26]

In this way, A. Waldner demonstrated the application of unsaturated γ-sultim (*S*,S_S)-**12** (prepared *via* Scheme 4, *B*) as a highly efficient homochiral dienophile. The cycloaddition reaction of with *carbo*- and *aza*dienes succeeded both in stereo and regiospecific manner affording fused γ-sultims **291** and **293** in good yields and excellent *de* (Scheme 125).[26]

Apart from that, *N*-sulfinyl dienophiles of type **12** (see Scheme 4) are less reactive than the corresponding sulfone counterparts. This leads to significantly better regioselectivity and *endo*-diastereoselectivity. Besides, the Diels–Alder reaction with sulfone analogues often accompanies by the formed cycle aromatization and SO_2 extrusion. Therefore, desired but unachieved by this reaction sultam-derived cycloadducts can be obtained through the oxidation of sultim-derived cycloadducts.[162]

Brominated unsaturated γ-sultims (*S*)-**14a** and **15** (prepared *via* Scheme 5) were involved in Pd-catalyzed coupling with vinyltributyltin (so-called the Stille coupling)[29] to obtain valuable diene species **294**. Indeed, this methodology led to the intermediate formation of desired compounds, but the



Scheme 125. Cycloaddition reaction of unsaturated γ-sultim (*S*,S_S)-**12** with cyclopentadiene **140** and azadiene **292**.

applied reaction conditions induced the subsequent dimerization so that the corresponding dimers *exo*-**295** were isolated (Scheme 126).[27,28]

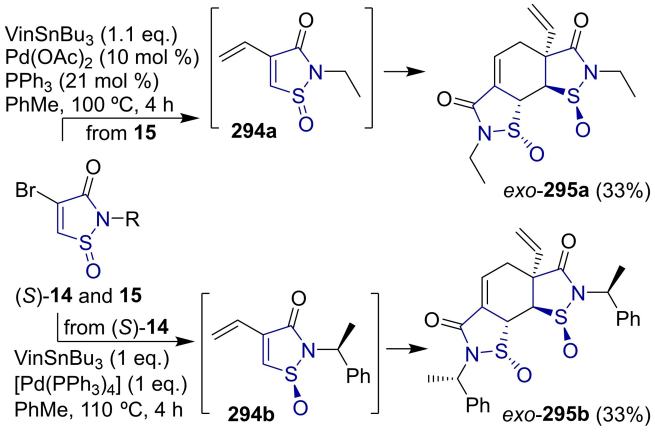
Intriguingly, an alternative stereoisomer of the above Diels–Alder dimer was obtained upon *m*CPBA-mediated oxidation of 4-vinylisothiazolinone **296**. The interim vinyl γ-sultim **294a** underwent dimerization thus affording *endo*-**295a**. The absence of the Pd-catalyst in the reaction media led to reversed facial selectivity. To further investigate the reaction mode *N*-phenyl maleimide (**297**) was added to trap *in situ* formed **294a** and the corresponding cycloadduct *endo*-**298** was isolated in fair yield (Scheme 127).[27]

Finally, sultims may serve not only as the direct reagents for the Diels–Alder reaction (dienes and dienophiles) but also as precursors for them. H. Shimizu *et al.* reported the dehydration reaction of *NH*-unsubstituted polycyclic δ-sultim **299** upon treatment with TFAA and $LiBF_4$ at rt. Thus *in situ* generated 1,2-thiazinylium salt **300** reacted with dienes across the N=S bond to form the cycloadducts **301** bearing the bridgehead sulfur and nitrogen atoms. Further treatment of **301b** with strong bases triggered rearrangement within the amino sulfonium ylide framework to give **302** which oxidized into polycyclic pyrrole derivative **303** upon workup procedures (Scheme 128).[163]

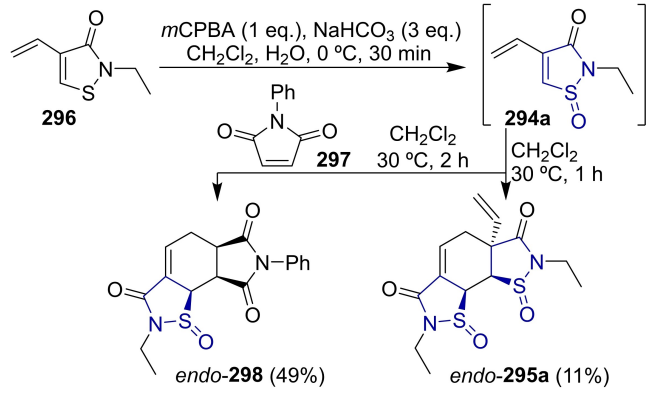
3.7. Miscellaneous Reactions and Application of Sultims

The steric hindrance of β-sultims leads to facile cleavage of the S–N bond that in combination with steric congestion becomes a driving force in their prone to ring-opening and rearrangement reactions. Thus, heating the norbornene-derived β-sultim **133a** (prepared *via* Scheme 54) yielded a pair of stereoisomeric products **304**, differed only by the configuration at the sulfur atom (Scheme 129).[87]

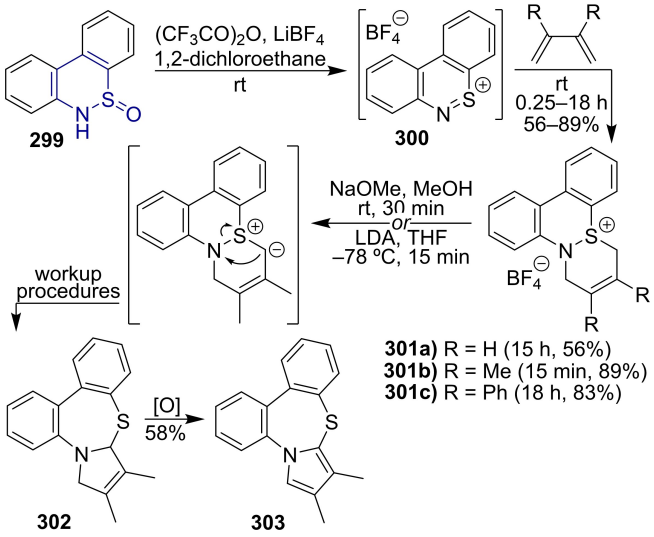
Unsaturated γ-sultim **12** (prepared *via* Scheme 4, *A*) was used as a starting material in the total synthesis of (−)-methyl dihydropalustramate (a degradation product of alkaloid palustrine)[164] *via* the three-component *hetero*[4+2]-cycloaddi-



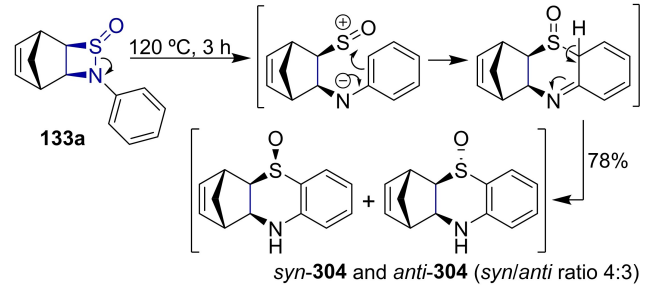
Scheme 126. Pd-catalyzed coupling route to the Diels–Alder dimers *exo*-**295a,b**.



Scheme 127. Oxidative route to the Diels–Alder dimer *endo*-**295a** and adduct *endo*-**298**.

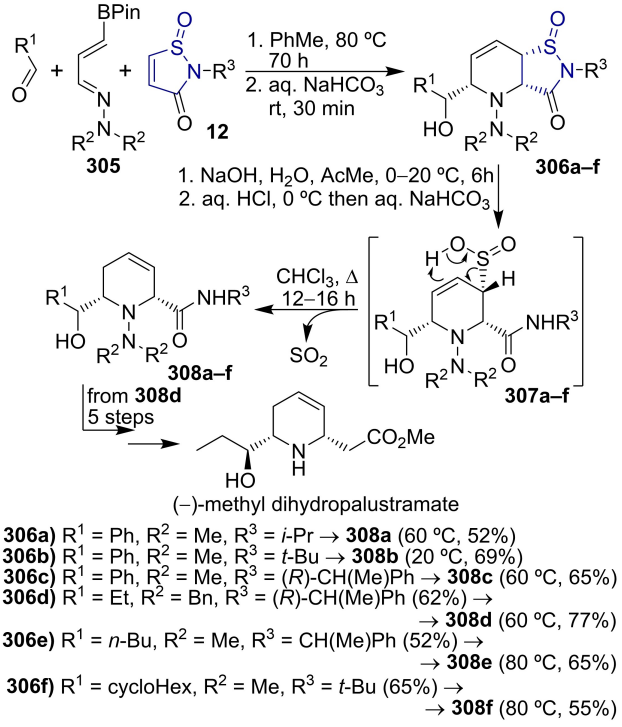


Scheme 128. Reactions of polycyclic δ-sultim **299**.

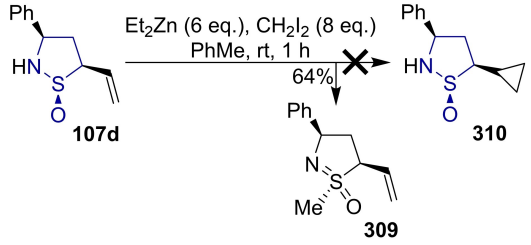


Scheme 129. Thermo-induced isomerization of β-sultim **133a**.

tion-allylboration-*retro*-sulfinyl-ene reaction strategy. Thus, the reaction between unsaturated γ-sultim **12**, boronic diene **305**, and aldehydes resulted in cycloadducts **306** (also sultims) isolated as single regio- and diastereomers in good yields. This three-component reaction showed a broad substrate scope towards *aza*diene and aldehyde components. Then, cycloadducts **306** were saponified to the corresponding sulfinic acid **307** and subjected to *retro*-sulfinyl-ene reaction accompanied by SO_2 extrusion and double bond migration to give **308** (selected examples are depicted in Scheme 130).[25,165] In general, this reaction sequence is a great synthetic tool to access 2,6-disubstituted piperidine units. Eventually, the target (−)-methyl dihydropalustramate was reached in 5 steps from **308 d**.[25]



Scheme 130. Three-component sequential aza[4 + 2]cycloaddition—allylboration–*retro*-sulfinyl-ene reaction and the selected steps in total synthesis of (−)-methyl dihydropalustramate.



Scheme 131. The behavior of γ-sultim **107 d** under the Simmons – Smith cyclopropanation conditions.

An unprecedented reaction was observed when sultim **107 d** (prepared *via* Scheme 44) was involved in the Simmons – Smith cyclopropanation.[166] As a result, cyclic sulfoximine **309** was isolated in fair yield rather than expected sultim **310** decorated with the cyclopropyl substituent (Scheme 131).[79]

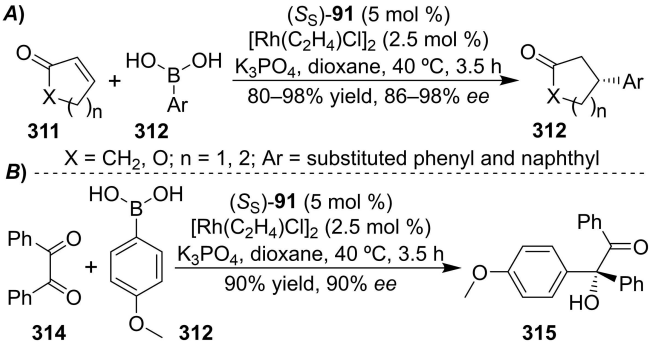
The abovementioned chiral γ-sultim–olefin ligand (S_S)-**91** (prepared *via* Scheme 37) was used as a chiral auxiliary for the highly enantioselective Rh-catalyzed asymmetric 1,4-addition of α,β-unsaturated cyclic ketones **311** to aryl boronic acids **312** (Scheme 51, *A*).[74]

The method showed a broad substrate scope in terms of α,β-unsaturated ketones (5- and 6-membered carbocyclic and heterocyclic), and boronic acid (halogenated, alkylated, alkoxylated phenyl and naphthyl boronic acids) components, thus making it appropriate for the application in diversity-oriented synthesis.[167] Moreover, the reaction conditions turned out to be applicable for stereoselective 1,2-addition of aryl boronic acid to benzil (**314**) that proceeded both with excellent yield and *ee* (Scheme 132, *B*).[74]

4. Summary and Outlook

Cyclic sulfinamides (put simply, *sultims*) are an increasingly popular class of compounds that attracts more and more attention because of their unique stereochemical profile and reactivity. Specifically, the presence of the stereogenic center at the sulfur (IV) atom and the intermediate value of its valence enable a range of reactions that can be proceeded in a stereospecific manner. In this regard, cyclic sulfinamides are much more interesting and have greater synthetic potential than the corresponding sulfonamides.

The chemical space of cyclic sulfinamides is mostly limited to 5- and 6-membered representatives. With that, the number of sp^3-enriched sultims has increased only in the last two decades, when new synthetic methods were discovered and put into practice. Moreover, special attention was paid to developing the protocols for asymmetric synthesis. Thus, *N*-heterocyclic



Scheme 132. Application of sultim–olefin chiral ligand (S_S)-**91** for Rh-catalyzed asymmetric additions.

carbene catalysts allowed the preparation of chiral 4-membered sultims through the formal [2+2] cycloaddition reaction. Methods based on radical S_Hi substitution at the sulfur (IV) atom and transformations of cyclic sulfoximines opened up a new avenue for the synthesis of enantiopure 5- and 6-membered sultims with the highest level of stereoselectivity. Finally, chiral Lewis acid catalysts enabled asymmetric *hetero*-Diels-Alder cycloaddition that gave access to chiral bridged and monocyclic 6-membered sultims.

Despite cyclic sulfinamides being underappreciated as structural fragments in drug discovery and medicinal chemistry they have been established as a convenient synthetic platform for many medicinally acknowledged and chiral compounds as well as valuable building blocks.[168–171] For instance, some chiral sultams are not always accessible from the precursors possessing sulfur (VI) atom but can be readily prepared from the corresponding sultims.

We hope this timely review stimulates ongoing research on sulfinamide chemistry and contributes to the development of novel synthetic procedures thus expanding and complicating the chemical space and the area of applications of cyclic sulfinamides.

Acknowledgements

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