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Chemistry
Master thesis

SULFENOFUNCTIONALIZATION OF DOUBLE BONDS WITH CYCLIC SULFENAMIDES AND ANIONIC CASCADE CYCLIZATION REACTION REPRESENTING FORMAL [2+2] ENOL-ALLENE CYCLOADDITION

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(permission to defend, date, signature)

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ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ad_E	addition-elimination
BINAM	1,1'-binaphthyl-2,2'-diamine
$Bu_4N^{+-}OMs$	tetrabutylammonium methanesulfonate
Cbz	benzyloxycarbonyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DME	dimethoxyethane
DMEA	dimethylethanolamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
er	enantiomeric ratio
Et	ethyl
Et_3N	triethylamine
$(Et_2N)_3PSe$	tris(diethylamino)phosphine selenide
EtOH	ethanol
$EtSO_3H$	ethanesulfonic acid
EWG	electron withdrawing group
HMPT	*tris*(dimethylamino)phosphine
KHMDS	potassium bis(trimethylsilyl)amide
KO*t*-Bu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MeOH	methanol
Ms	mesyl
MsOH	methanesulfonic acid
NaHMDS	sodium bis(trimethylsilyl)amide
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
OAc	acetyloxy
PCET	proton-coupled electron transfer
PE	petroleum ether
Ph	phenyl
PhthSPh	phenylthiophthalimide
PPh_3	triphenyl phosphine
R_f	retention factor
r.t.	room temperature

Sn_1	unimolecular substitution reaction
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
t-Bu	*tert*-butyl
t-BuOH	*tert*-butyl alcohol
t-BuOOH	*tert*-butyl hydroperoxide
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TBAI	tetrabutylammonium iodide
Ts	tosyl
$TsOH·H_2O$	*p*-toluenesulfonic acid monohydrate
TsONa	sodium *p*-toluenesulfonate

INTRODUCTION

The beginning of synthetic organic chemistry is believed to be marked by Wöhler's synthesis of urea. Since then, employing sophisticated synthetic processes myriad organic molecules were synthesized with potential applications in medicine, technology and in many other areas not only of science, but of everyday life as well.

Nevertheless, a lot of chemical structures still cannot be achieved or requires harsh conditions, thus searches for novel and simple chemical transformations in organic synthesis remain especially relevant. This study presents two new convenient methods for the synthesis of modified heterocycles. The first part of the study examines sulfenamination of alkenes using cyclic sulfenamides, while second – presents anionic cascade cyclization giving access to highly functionalized contiguous six-, five- and four-membered rings.

Saturated heterocyclic compounds are usually found in biologically active compounds or pharmaceuticals [1]. It was found that thiomorpholine derivatives possess anti-inflammatory and antioxidant activity, while similar compounds with phenyl substituents demonstrated hypocholesterolemic and hypolipidemic actions [2,3]. Employing cyclic sulfenamides and *trans*-stilbenes or styrenes a simple synthesis route has been perfected to obtain a series of corresponding thiomorpholines. Testing with symmetric alkenes led to development of methodology for macrocyclic ligands preparation, which has extensive chemistry [4].

Cascade cyclization reactions are powerful method to provide polycyclic molecules in a single synthetic operation. These reactions are widely spread in Nature, where polyisoprenoid substrates undergo cascade cyclization catalyzed by terpenoid cyclases to form various terpenes [5]. Although these cyclizations in Nature are exclusively cation induced, the studies in synthetic chemistry led to discovery not only of efficient cationic cascade cyclizations, but anionic type as well [6,7]. Notwithstanding the latter have a lot less reported examples. In the *OrentasGroup* was developed a novel anionic cascade cyclization reaction, in which the enolate is added to non-activated π-bond representing a formal [2+2] enol-allene cycloaddition. Besides the scope, the reasons of such unique cyclizations were investigated too.

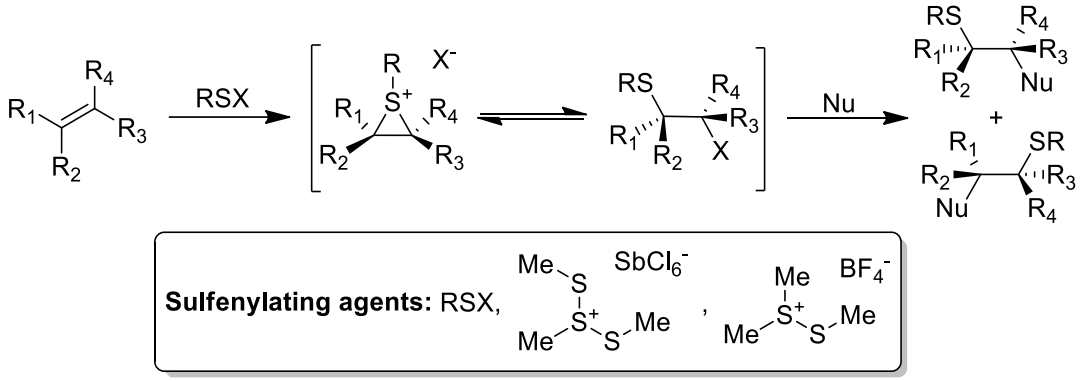
1. REVIEW OF LITERATURE PART I

1.1 Sulfenofunctionalization Reactions of Alkenes

1.1.1 General Considerations

Different biological activities of sulfur containing compounds and its transformable potential into other valuable derivatives led to the extensive exploration of these reactions [8]. The electrophilic sulfenylation of alkenes to provide sulfenofunctionalized products has been carefully studied from the middle of the 20th century primarily to examine the nature of thiiranium ions [9].

The most widely accepted Ad_E mechanism for sulfenofunctionalization of alkenes is through thiiranium intermediates, which lead to high anti-stereospecificity [9,10]. Alkenes and sulfenium ion source combination results in an $\pi \rightarrow \sigma*$ interaction, ionization of the leaving group (X) and formation of a three – membered cycle intermediate [9,11], which is confirmed by crystallographic and spectroscopic data [12] (Scheme 1). On the basis of computational transition state models and the principle of microscopic reversibility formation of thiiranium is highly favoured, in which alkene is approached collinear with S-X bond of sulfenylating reagent [13].

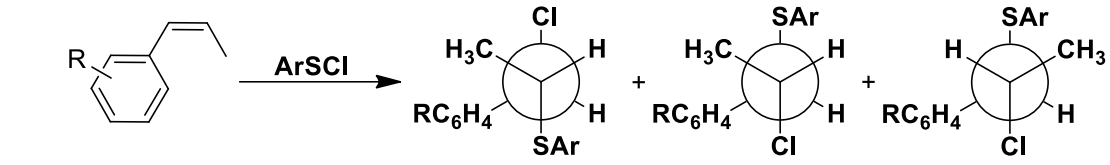


Scheme 1

These reactive intermediates can be produced using numerous of different sulfenylating agents such as disulfides, sulfenylamides, sulfenyl halides, sulfenate esters, dimethyl(methylthio)sulfonium tetrafluoroborate, methyl(bismethylthio)sulfonium hexachloroantimonate [9,14] (Scheme 1). Formed thiiranium cations further participate in nucleophilic attack by internal (X^-) or external nucleophile to provide sulfenofunctionalized product as showed in Scheme 1. A variety of different nucleophiles has been successfully employed such as thiols, alcohols, amines, nitriles, carboxylic acids, organometallic agents, aromatic rings, allylsilanes, acetals, enol ethers, silyl ketene acetals [15].

However, the nature of thiiranium species is not as simple as it may seem at first sight. The regio- and stereochemistry of the ring-opening reactions is affected by many variables such as solvent polarity, anionic counterion, temperature, reagents and additives [10]. In cases where a stabilized

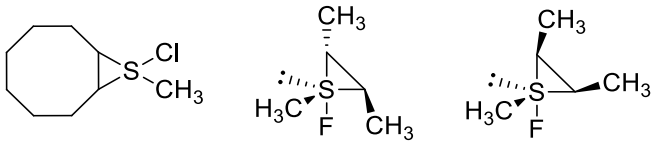
carbocation can be formed from thiiranium, loss of stereospecificity is observed due to non-selective addition [15]. For instance, cis-anethole (**1**) reaction with sulfenyl chloride shows total Markovnikov regioselectivity, but due to formation of stabilized carbeniun ion, loss of stereochemical integrity is obtained. Nevertheless, if 4-methoxy group is replaced with 3-nitro substitute (**2**) carbocation intermediate is disfavoured and stereochemical integrity is retained, in which anti-Markovnikov regioselectivity dominates (Scheme 2) [15,16].



	syn anti-Markovnikov	syn Markovnikov	anti Markovnikov
(**1**) R = 4-OMe	0 %	70 %	30 %
(**2**) R = 3-NO_2	70%	30 %	0 %

Scheme 2

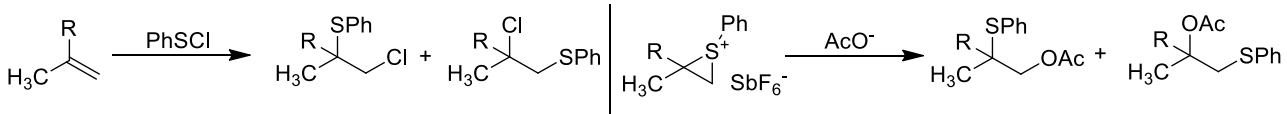
Sulfuranes or intermediate ion pairs formation is another factor that leads to different regioselectivity. There are a number of cases, in which sulfuranes are derived from thiiranium ions such as in Scheme 3 [17]. Based on computational data tetracovalent sulphur intermediates or tight ion pairs are favoured in low polarity solvents [18].



3 **4** **5**

Figure 1

Thiiranium ions have positive charge on the sulfur atom, therefore exhibit characteristics of carbocation. As a result Markovnikov type regioselectivity in the ring-opening reactions is expected. Sulfuranes, however, are uncharged molecules and carbocation character is significantly lower, thus steric effects dominate and anti-Markovnikov regioselectivity is expected [15]. For example, reaction between phenylsulfenyl chloride and alkene (**6** and **7**) gives anti-Markovnikov product, while preformed thiiranium compound (**8** and **9**) reaction with acetate – Markovnikov product (Scheme 3). Very likely the reactions of **6** and **7** go via sulfurane or tight ion pair intermediates [10,15,19].

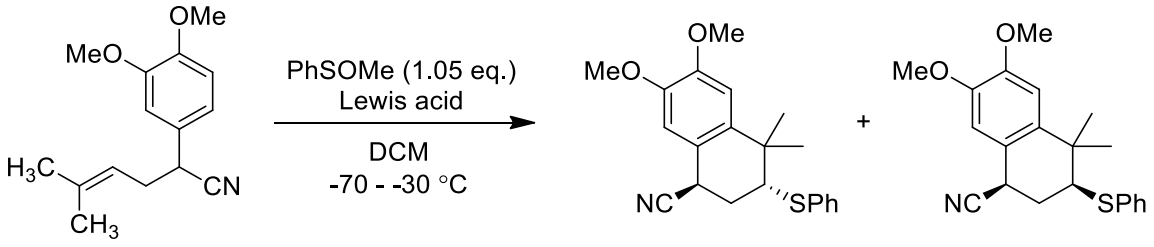


(**6**) R = H	75 %	25 %	(**8**) R = H	28 %	72 %
(**7**) R = Me	83%	17 %	(**9**) R = Me	5%	95 %

Scheme 3

1.1.2 Sulfenocyclization Reactions

So far, only intermolecular cyclization reactions were discussed. Alternatively, sulfenylating reagents can be employed for the one step synthesis of carbocycles and heterocycles. One of the first examples was reported by Livinghouse *et al.* [20]. Alkene containing electron-rich benzene in reaction with methyl benzenesulfenate under Lewis acidic conditions provided bicyclic annulations products **10a** and **10b** (Scheme 4). Reaction gave great yields with both TMSOTf and $BF_3{\cdot}CH_3NO_2$ as Lewis acid source, however the diastereoselectivity was poor.

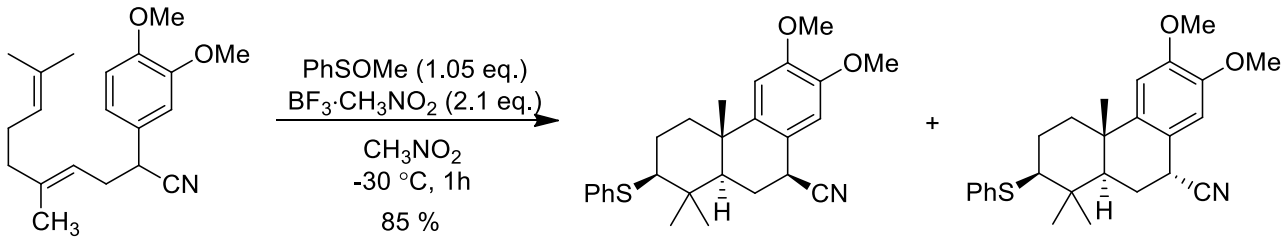


10a **10b**

Lewis acid:	**Yield:**	**10a/10b:**
TMSOTf (1 eq.)	97 %	1.25 : 1
$BF_3{\cdot}CH_3NO_2$ (2 eq.)	96.5 %	1.05 :1

Scheme 4

Shortly after that Livinghouse *et al.* expanded the scope, where under similar reaction conditions tricyclic annulations products were provided from corresponding dienes (one example showed in Scheme 5) [21]. Usually mixture of two equally distributed diastereomers is obtained.



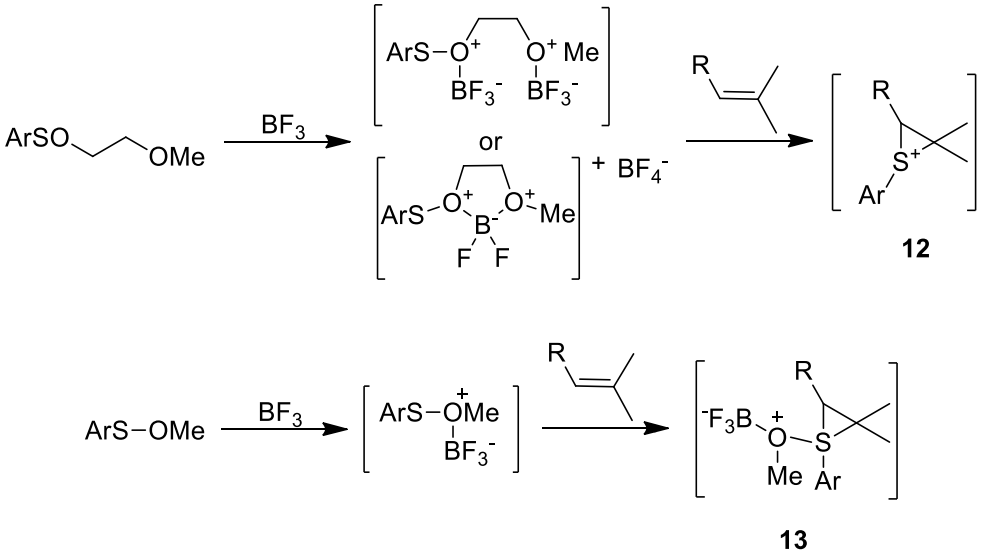
11a **11b**

11a/11b: 1 : 1

Scheme 5

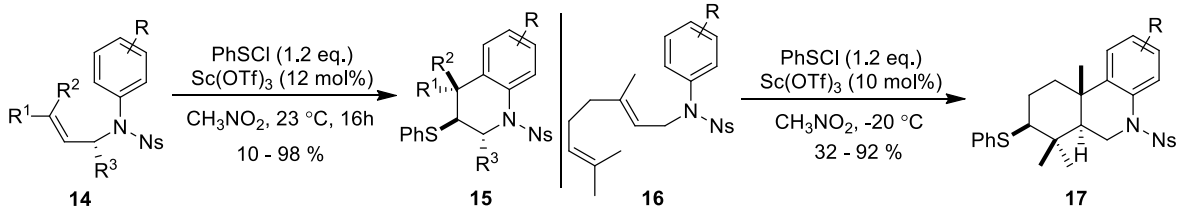
The next step Livinghouse *et al.* took was incorporation of deactivated aryldienes in cascade cyclization [22]. Firstly, standard set of conditions (discussed above) were tested, but expected products were not detected. Therefore, new sulfenium ion sources were developed, where good results gave 2-methoxyethyl 4-chlorobenzenesulfenate. These reactivity differences may have originated from the nature of the initiating species, which is determined by the degree of dissociation of the S-O bond after addition to the alkene [22]. Complexation of BF_3 with the

methoxyethoxy fragment cause rupture of S-O bond to form episulfonium (**12**), while treatment BF_3 with simple methyl ester only weaken S-O bond upon addition to substrate (**13**) (Scheme 6) [22].



Scheme 6

More recently, Shaw *et al.* reported first catalytic alkene cyclization reaction mediated by benzenesulfenyl chloride that produces nitrogen containing heterocycles (Scheme 7) [23]. Up to two rings and three stereogenic centers were formed in a single step with high stereo- and regiocontrol. Interestingly, control experiments suggested that the catalyst is a protic acid produced by adventitious moisture, where $Sc(OTf)_3$ serves as a pre-catalyst [23]. However, the scope is limited to the electron-riched arenes and alkenes.

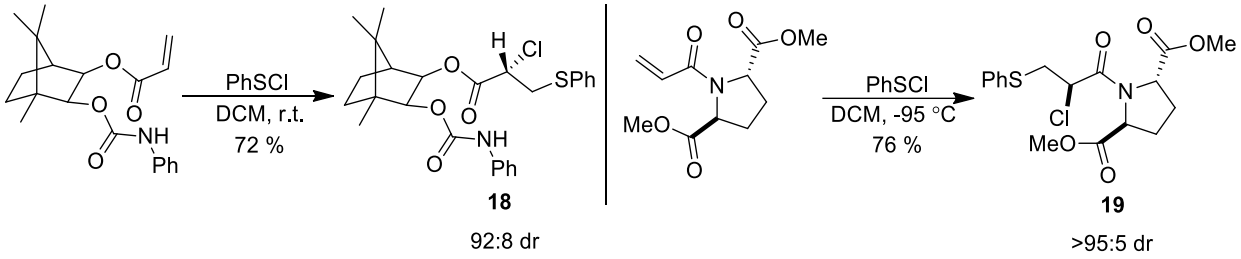


Scheme 7

1.2 Enantioselective Alkene Sulfenofunctionalizations

1.2.1 Using Chiral Substrates

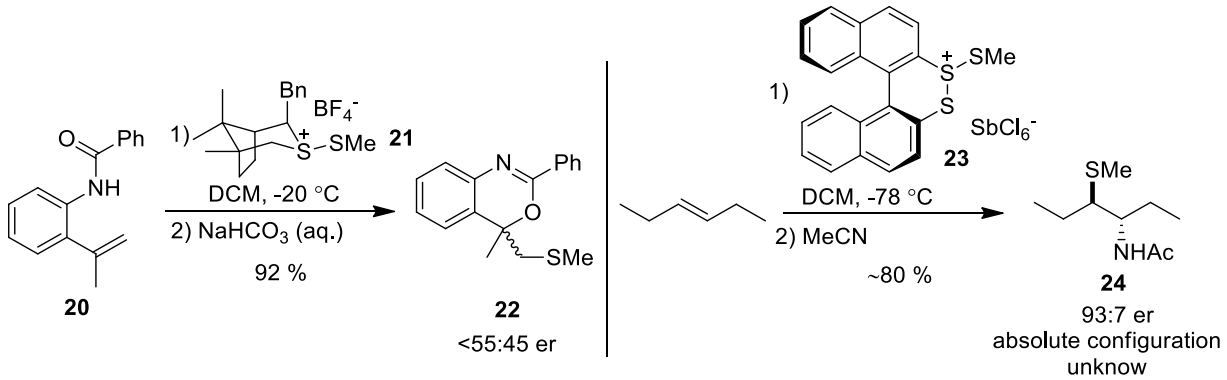
Usually sulfenofunctionalization of alkenes produces one or few new stereogenic centers, therefore interest to form them enantioselectively rises constantly. Early examples were accomplished using diastereoselective reactions of asymmetrically modified substrates. Effenberger *et al.* to provide enantioselective sulfenofunctionalized alkenes employed chiral camphor diol-derived substrate (Scheme 8, left) [24]. Chlorosulfenylation product **18** was obtained in high diastereoselectivity (92:8 dr), even at room temperature. Shortly, amide-based chiral substrates were introduced [25]. Best results were provided by *N*-acryloylpyrrolidine-2,5-dicarboxylate to give adduct **19** in high yield and diastereoselectivity (>95:5 dr) (Scheme 8, right) [11,25].



Scheme 8

1.2.2 Using Chiral Sulfenylating Reagents

Another approach for enantioselective sulfenylation uses chiral sulfenylating agents. These reactions have advantage over above described in that the substrates do not need chiral moiety, which otherwise should be introduced and after all removed. Rayner *et al.* produced benzoxazine **22** in excellent yield from treatment of alkene **20** with sulfonium salt **21** (Scheme 9, left) [11,26]. However, the enantioselectivity was poor, which may occur due to initial sulfenylation of amide followed by intramolecular *S*-methyl group transfer to alkene. Pasquato *et al.* introduced more selective sulfenylating agent – binaphtylsulfonium salt **23**, which reaction with 3-hexene and subsequent addition of acetonitrile provided acetamide **24** in high yield and enantioselectivity (93:7) (Scheme 9, right) [11,27]. Worth mentioning, the absolute configuration of major enantiomer is not established.

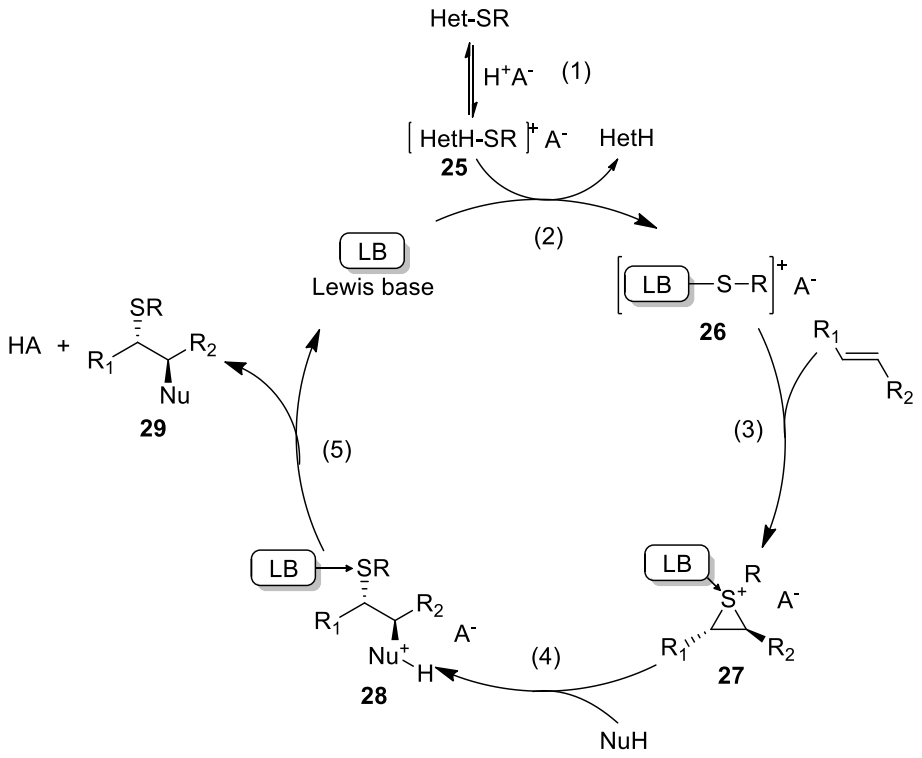


Scheme 9

1.3 Catalytic and Enantioselective Sulfenofunctionalization of Alkenes

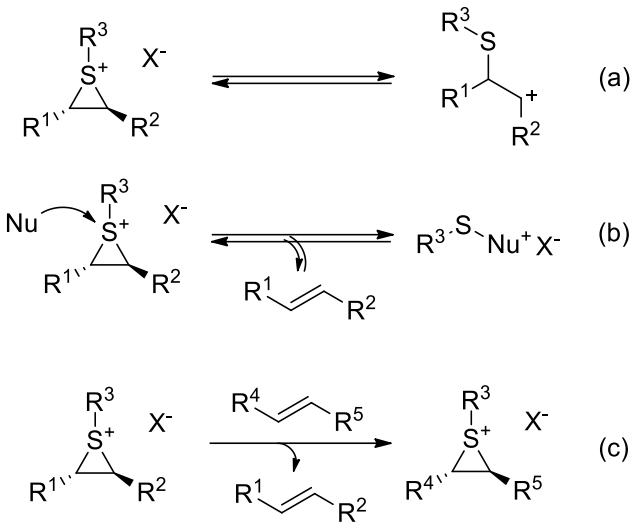
1.3.1 Mechanistic Considerations

Recently, methods for catalytic, asymmetric sulfenylation of alkenes were developed through Lewis base activation of Lewis acids, where chiral sulfenylating agents are formed *in situ* by treatment of sulfur electrophile with chiral additive [28-34]. A plausible mechanism starts with initial protonation of sulfenylating reagent with Brønsted acid (1) (Scheme 10). Subsequent sulfenylation of Lewis base generates active catalytic species **26** (2). The Lewis acidity on sulfur increases, therefore the nucleophilic attack of the alkene onto intermediate **26** occurs (3). The resulting intermediate thiiranium ion **27** is attacked by nucleophile, which leads to formation of enantioenriched product **29** and regeneration of chiral catalyst (4) [11,28-34].



Scheme 10

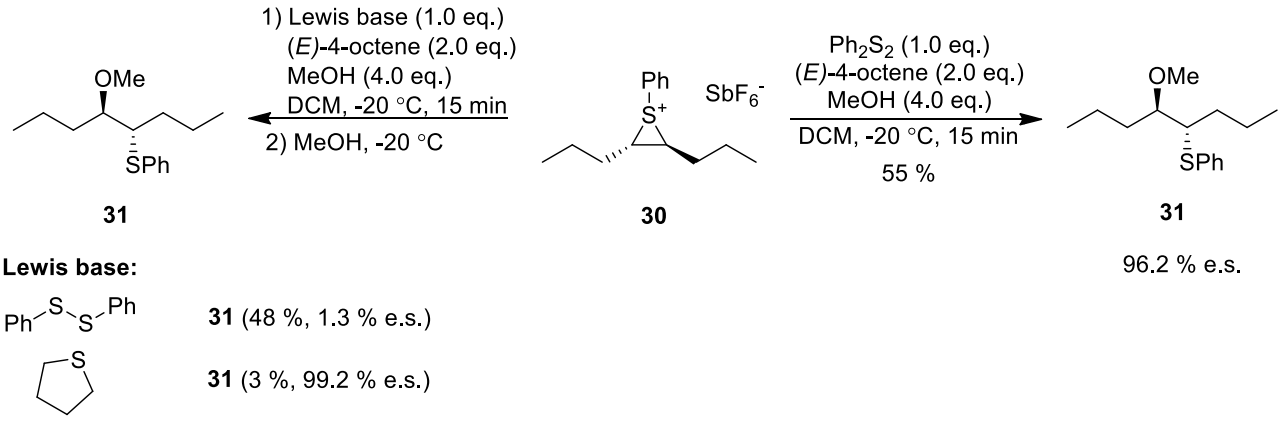
Racemization of enantiomerically enriched intermediates is common problem in the field of enantioselective reaction. Three major mechanisms are proposed that could lead to erosion of chiral thiiranium ions (Scheme 11) (11,35). The first entails racemization via open carbocation intermediate which was described in section 1.1.1. (Scheme 11, a). The second pathway involves nucleophilic attack not to a carbon, but to the sulfenyl ion and as a result new sulfenylation species is obtained (Scheme 11, b). This mechanism is more characteristic for weak nucleophiles [17a]. Lastly, direct bimolecular alkene-to-alkene transfer mechanism is encountered in racemization process.



Scheme 11

Experiments with thiiranium ion **30** in the presence of hard nucleophiles demonstrate high enantiospecificity and afford corresponding chiral thioethers [11,35]. This can be explained by the fact that unimolecular racemization process is much slower than intermolecular nucleophilic attack, therefore enantiospecificity is maintained.

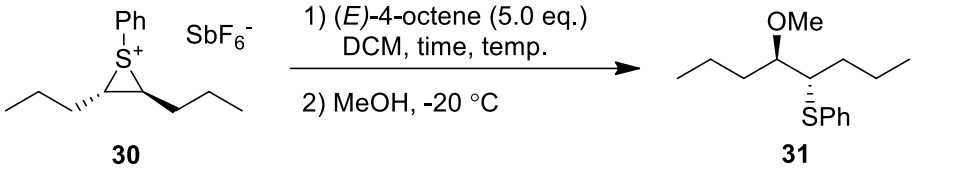
The configurational stability of thiiranium species together with various Lewis bases was investigated by Denmark and Vogler [35]. Thiiranium **30** was mixed with different Lewis bases and (*E*)-4-octene. Many of them were incompatible to provide thioether **31**, due to irreversible reaction at carbon atoms. Using thiolane, methoxy sulfide **31** was obtained in very low yield but high enantiospecificity. In comparison, using more thiophilic and weak Lewis base – phenyl disulfide full loss of enantiomeric composition was observed (Scheme 12) [11,35]. However, when methanol was present together with phenyl disulfide the configurational stability was retained (Scheme 12), suggesting that thiiranium ion capture by nucleophile is faster, than racemization process involving attack to the sulfenyl ion (Scheme 11a) [11,35].



Scheme 12

Olefin to olefin transfer is another possible racemization pathway, which influence on enantioenriched thiiranium ions was studied [35,36]. Thiiranium **30** was combined with (*E*)-4-

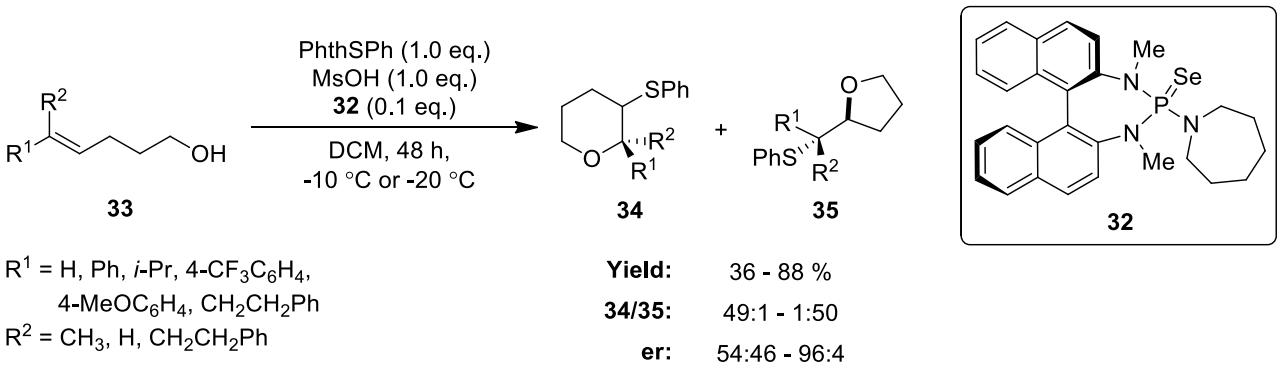
octene and after certain time methanol was added. Rapid racemization appeared at 0°C, while lowering temperature to -10 °C and -20 °C even at longer reaction time configurational stability was highly maintained, which reveals that racemization is strongly dependent on reaction temperature (Scheme 13) (11,35).



Scheme 13

1.3.2 Sulfenoetherification

The first catalytic, asymmetric sulfenylation of double bonds has been achieved by Denmark *et al.* [28]. The cyclization of alkenols **33** with *N*-phenylsulfenophthalimide and MsOH as *co*-activator was investigated using different Lewis bases, where selenophosphoramide **32** showed highest enantioselectivity. Simple alkenols **33** were employed to afford tetrahydropyrans **34** and tetrahydrofurans **35 (**Scheme 14) [11,28]. However, yields, siteselectivity and enantioselectivity highly depend on the substituents. When R^1 is alkyl or aromatic, tetrahydropyrans **34** dominates due to stabilization of partial positive charge on corresponding carbon. On the other hand, more bulky substitutes in R^1 suppress *endo* transition state and tetrahydrofurans **35** proportion increases, while bulky substitute in R^2 gives almost exclusively furan **35**.



Scheme 14

Further optimization led to more enantioselective catalyst **37**, where azepanyl group is changed to diisopropylamine group [33]. Moreover, to get insight on catalytically active sulfenylating agent, X-ray crystal structure of thiophosphoramide **36** was established (crystallization attempts of analogous sulfenylating species containing selenium were unsuccessful due to disproportionation reaction). Plane defined by C(29)-N(3)-C(32) atoms is in the same direction as P(1)-S(1) bond due to anomeric stabilization. As a result, P(1)-S(1)-(S2)-phenyl moiety movement around P(1)-S(1) bond is restricted and *S*-phenyl group is oriented towards BINAM group (Figure 2) [11,33].

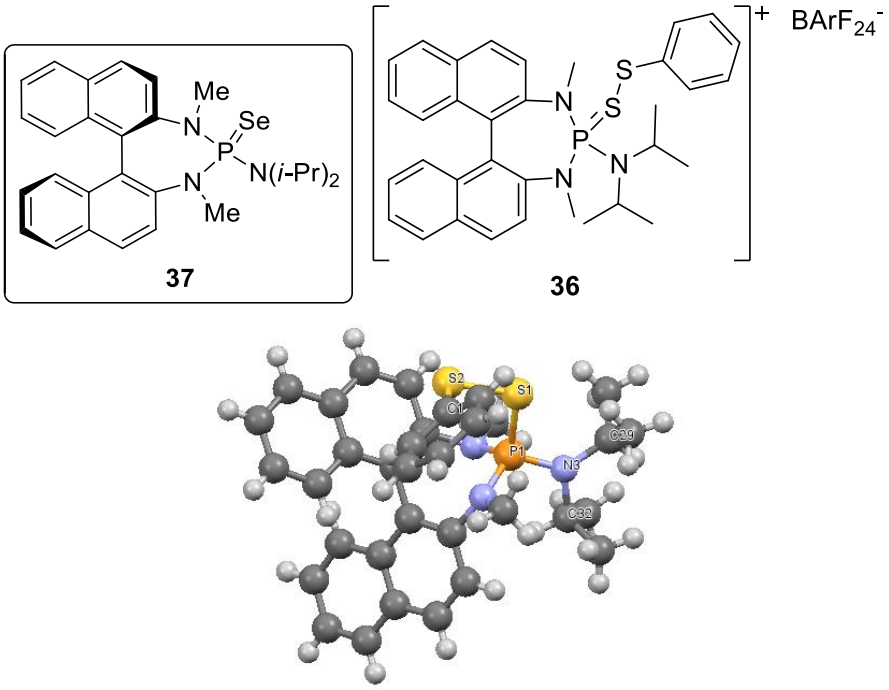
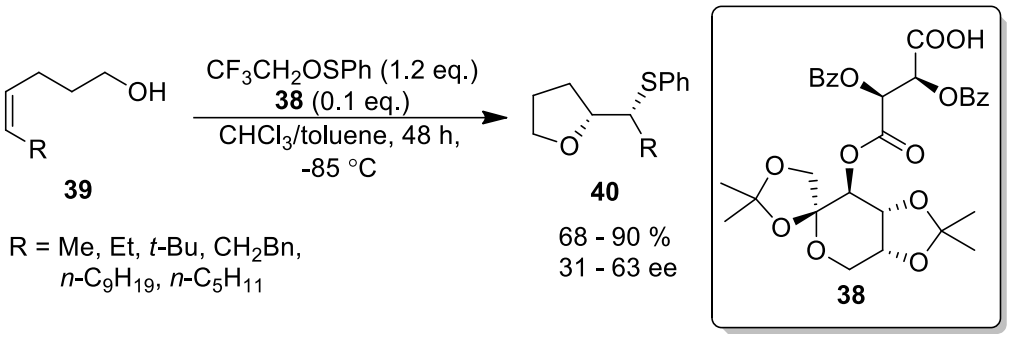


Figure 2. Chemical structure of **37**. Chemical and X-ray structures of active sulfenylating agent **36**. N(3)-P(1)-S(1)-S(2) = 175.1°, C(1)-S(2)-S(1) = 104.1° [33].

An alternative method for assymetric sulfoetherefication employs dibenzoyl *D*-tartaric acid-based catalyst **38** (Scheme 15) [37]. Enantiomerically enriched tetrahydrofurans **40** were obtained from corresponding *Z*-alkenes **39** in high yield, but moderate enantioselectivity. It is worth mentioning that the efficiency of this catalyst **38** was demosntrated for *cis*-alkenes, while BINAM based catalyst **32** – *trans*-alkenes.

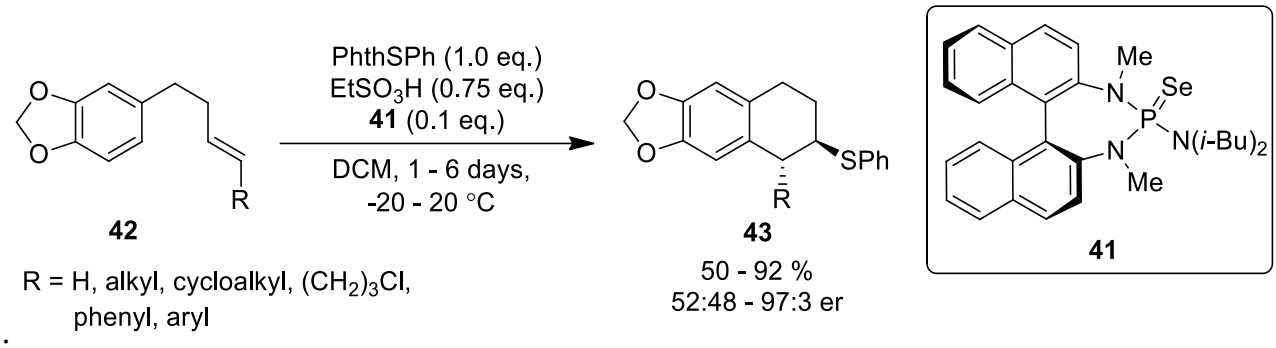


Scheme 15

1.3.3 Intramolecular Carbosulfenylation

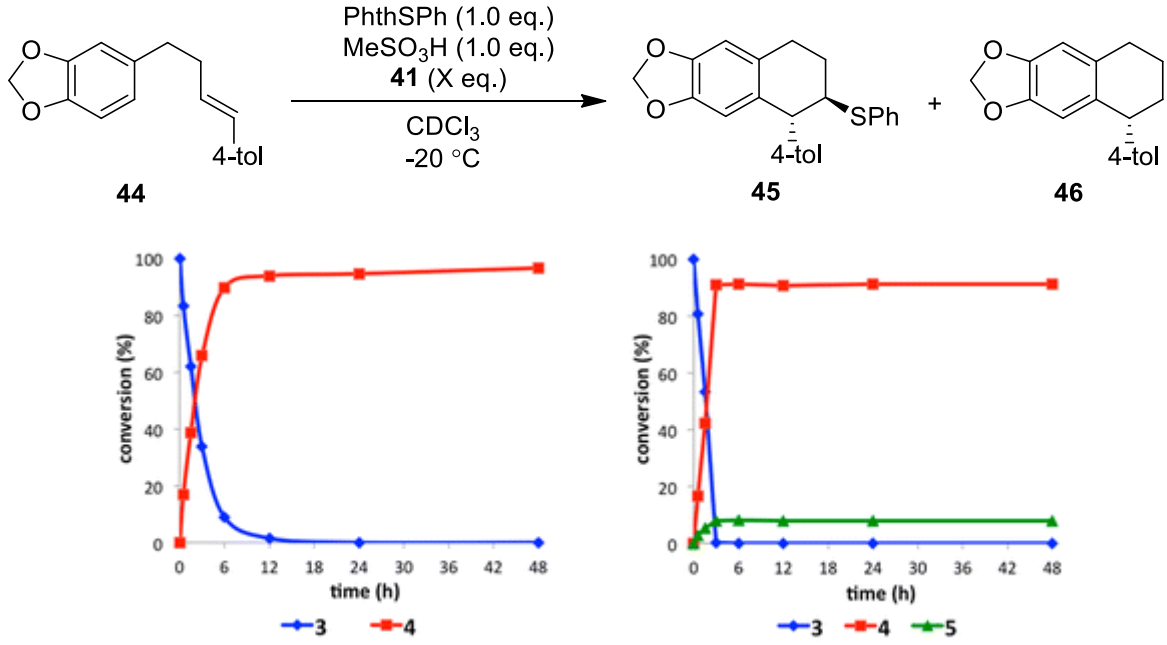
Continuing research of enantioselective sulfenofunctionalization Denmark *et al*. expanded the scope and employed various nucleophiles such as phenols [29], sulfonamides [30, 38], sulfonyl carboxamides [34], amines [39], aldehydes [40], and polyenes [41]. In addition, deep attention was paid into carbosulfenylation of alkenes, where mechanistic and kinetic aspects were investigated as well [14,31,35].

The intramolecular asymmetric carbosulfenylation of alkenes has been achieved by using chiral Lewis base **41** and $EtSO_3H$ as a *co*-catalyst (Scheme 16) [14,31]. Enantioenriched tetrahydronaphthalenes were successfully obtained in high yields and enantiomeric ratios. Cyclic, branched or electron-poor groups containing alkenes give lower enantioselectivity due to higher reactions temperature. As well, reactions with *E*-alkenes had much higher reaction rate than with *Z*-alkenes [14,31].



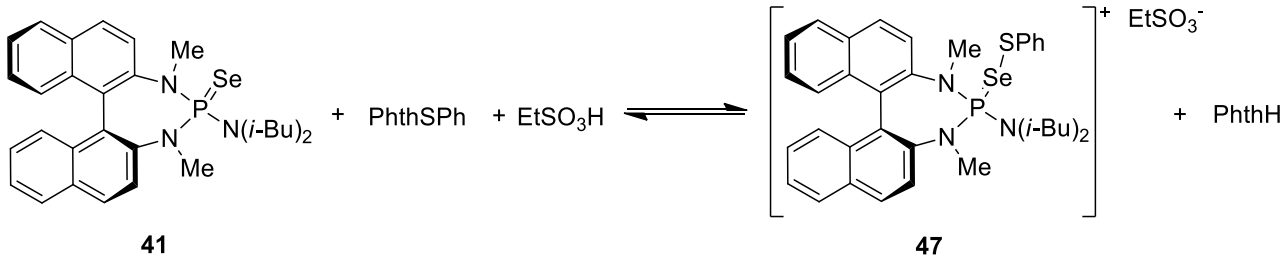
Scheme 16

Interestingly, the rate of the uncatalyzed carbosulfenylation reaction is faster (approximately two times), than catalyzed one as depicted in Scheme 17. Moreover, a proton-initiated carbocyclization produce small amount of **46** in uncatalyzed process, while it is not observed in the catalyzed reaction. Further investigations have showed that the catalytic process is overall first-order, whereas non-catalytic – overall zero order. Although, increasing acid concentration does increase reaction rate of uncatalyzed reaction [11,42]. It is assumed that acid interact with species in mixture, therefore changes the rate-determining step, overall mechanism and outcomes of both catalyzed and uncatalyzed reactions.



Scheme 17. Carbosulfenylation reactions rate profile in present (on the left) and absence (on the right) of catalyst **41**. **3** corresponds olefin **44**, **4** – product **45** and **5** – by-product **46** [42].

Composition of intermediates and their impact in carbosulfenylation reactions were further explored. Reaction between PhthSPh and MsOH (or EsOH) immediately forms corresponding salt, which suggest that uncatalyzed reaction goes via electrophile protonation [11,42]. Since the amount of catalyst **41** is non-equivalent, secondary effects that suppresses the reaction of $[PhthSPh]^+[EsO]^-$ have to exist. Titration of mixture of PhthSPh/catalyst **41** (10:1) with EsOH revealed that 4 equivalents of EsOH respect to catalyst is almost enough for full conversion to active agent **47** (Scheme 47) [11,42]. Under typical catalyzed reaction conditions 0.1 equiv $[EsO]^-$ and 0.1 equiv phthalimide are formed in respect to starting olefin, while these species are not immediately formed in corresponding uncatalyzed reaction. Worth noting that running reaction without catalyst **41**, but in the presence of Bu_4N^+ ^-OMs or phthalimide, the uncatalyzed reaction is suppressed. For example, when 0.1 equiv of Bu_4N^+ ^-OMs is used, the time of full conversion increases from 3 h to 12 h [11,42]. This effect is possibly related to aggregation of mesylate ion in dipolar aprotic solvents and additional consumption of sulfonic acids by the phthalimide protonation.



41 **47**

Scheme 18

2. RESULTS AND DISSCUSSION PART I

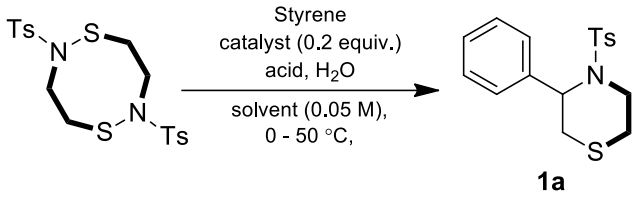
2.1 Introduction

Previously, Orentas *et al*. developed C_2-symmetric sulfenamide derivatives as electrophilic sulfur – nucleophilic nitrogen synthons [43]. In this study our aim was to investigate new routes for utilization of these sulfenamides. Therefore, after examining the literature transfer of the sulphur of 2,6-ditosyl-1,5,2,6-dithiadiazocane onto alkenes was predicted [8-42].

2.2 Sulfenofunctionalization of Styrenes

Inspired by Denmark *et al*. work initial conditions were taken as showed in Table 1 (Entry 1) following general procedure A (pg. 41). To our surprise not only sulphur was transferred onto styrene, but, as well, intramolecular nucleophilic attack by nitrogen on benzylic position occurred leading to 3-phenyl-4-tosylthiomorpholine (**1a**) in moderate yield. Addition of H_2O (4 equiv) decreased the reaction rate, but provided higher yield (Entry 2). The positive effect may be due to heterogeneous reactions conditions (H_2O does not dissolve in DCE), where acid makes hydrogen bonding cluster with water molecules. The advantage arising from MsOH hydrogen bonding clusters was showed by Xu *et al*. [44]. In our case it is believed that this cluster reduces actual acid concentration in the organic phase and suppresses side reactions by increased selectivity. Changing Brønsted acid into much stronger – TfOH has increased the reaction rate, though selectivity was lost (Entry 3). As expected, no reaction took place using a donor solvent THF instead of weakly

coordinating solvent DCE (Entry 4). Lastly, the reaction without Lewis base catalyst – $(Et_2N)_3PSe$ gave the same results (Entry 5). Notably that based on literature Lewis base catalyst may have positive effect on more sensitive substrate [42], however further optimization of reaction conditions was not attempted.



1a

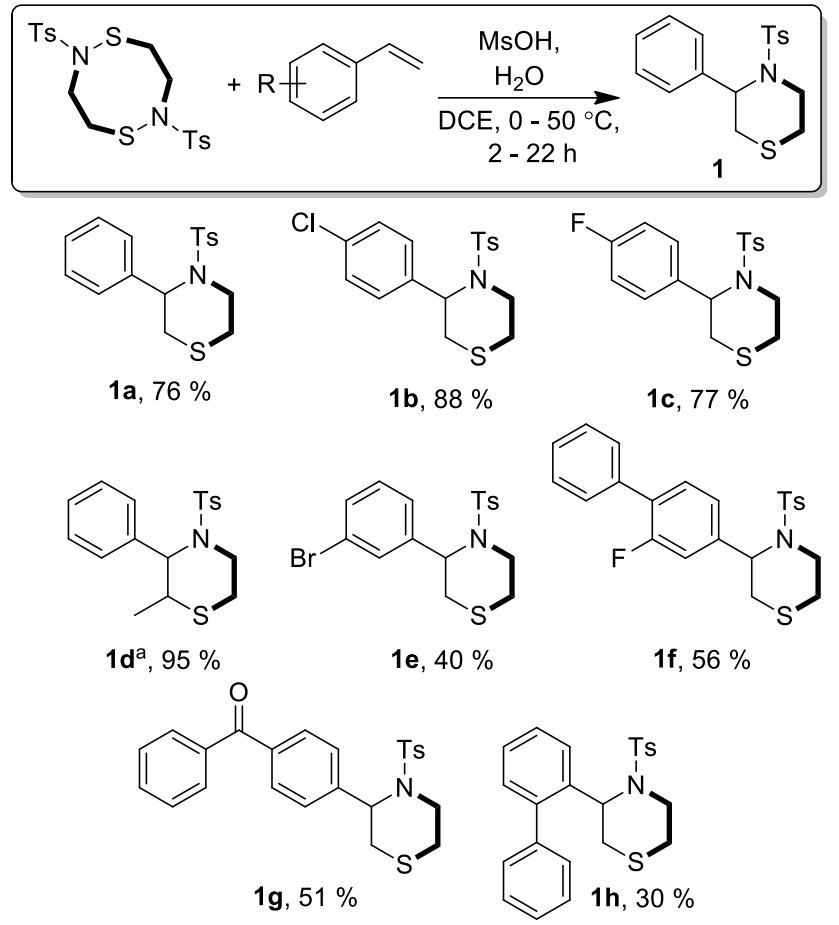
Entry[a]	Acid	Styrene (equiv.)	Catalyst	H_2O (equiv.)	Solvent	Time	Yield[c] **1a** (%)
1	MsOH[b] (2.8 equiv.)	2.3	$(Et_2N)_3PSe$	-	DCE	2 h (50 ºC)	47
2	MsOH (2.8 equiv.)	3.1	$(Et_2N)_3PSe$	4	DCE	21.5 h (50 ºC)	75
3	TfOH (2.5 equiv.)	2.3	$(Et_2N)_3PSe$	4	DCE	2h (0 ºC) + 20h (r.t.)	traces
4	MsOH (2.8 equiv.)	2.3	$(Et_2N)_3PSe$	4	THF	3.5 h (50 ºC)	-[d]
5	MsOH (2.8 equiv.)	3.0	-	4	DCE	21.5 h (50 ºC)	76

[a]Reactions were performed in the same manner as in general procedure A (pg. 41), . [b]Acid was added at r.t. [c]Isolated yield. [d]Only starting material was found on TLC, thus reaction was stopped.

Table 1. Optimization of The Reaction Conditions Between 2,6-Ditosyl-1,5,2,6-dithiadiazocane and Styrene

With the optimized conditions in hand, the scope and functional group tolerance were explored next. Following general procedure A, styrenes containing Cl or F atom in *para* position were successfully employed to provide corresponding thiomorpholines **1b** and **1c** (Figure 3). On the other hand, reaction with similar styrene having Br in *meta* position led to lower yield of product **1e** (40 %). Furthermore, reaction with *para*-phenyl substituted styrene gave higher yield, than similar substrate with *orto*-phenyl substituent, suggesting that position of substituents have effect on the yields of the reaction (Figure 3). *Trans*-*β*-methylstyrene gave excellent yield of **1d**, although it was obtained as a mixture of *E*/*Z* isomers with ratio 5:4. Finally, EWG containing styrene was utilized to give thiomorpholine **1g** in good yield.

Despite successful examples there are number of substrates that cannot be employed. Very strong EWG containing styrenes (e.g. pentafluorostyrene) gave no reaction, while substrates with EDG (e.g. 2-vinylnaphthalene, 1,2-dimethoxy-4-vinylbenzene) are too reactive and usually lead to polymerization.

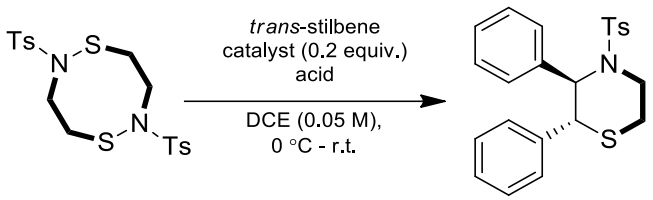


[a]Mixture of E/Z isomers. Ratio 5:4 by NMR data

Figure 3. Scope of Sulfenofunctionalization of Styrenes

2.3 Sulfenofunctionalization of Stilbenes

After successful application of 2,6-ditosyl-1,5,2,6-dithiadiazocane onto styrenes, the stilbene derivatives appeared as possible substrates as well. Taking initial conditions similar to those with styrenes 2,3-diphenyl-4-tosylthiomorpholine (**2a**) was obtained in very high yield (Table 2, Entry 1). Reaction using copolymer based acids Amberlyst 15 and Dowex WX8 instead of MsOH gave only traces of **2a** even at elevated temperature (Table 2, Entry 2). Finally, experiment without catalyst provided slightly better results (Table 2, Entry 3).



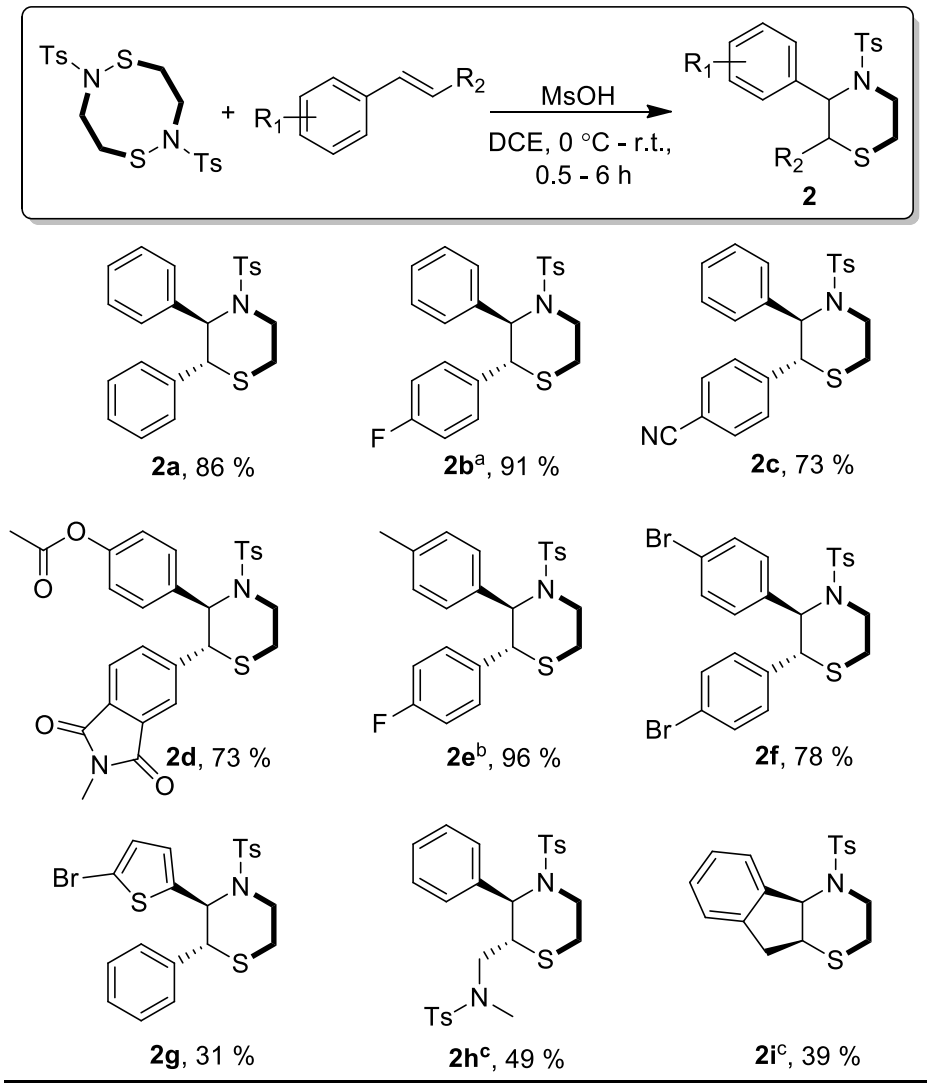
2a

Entry[a]	Acid	*trans*-Stilbene (equiv.)	Catalyst	Time	Yield[b] **2a** (%)
1	MsOH (2.8 equiv.)	2.5	$(Et_2N)_3PSe$	25 min (0 ºC) + 1.75 h (r.t.)	81
2	Amberlyst 15 (1.0 equiv. [mass]), Dovex WX8[c] (1.0 equiv. [mass])	2.6	$(Et_2N)_3PSe$	23 h (50 ºC) + 19 h (50 ºC)	traces[d]
3	MsOH (2.8 equiv.)	3.1	-	2.5 h (0 ºC)	86

[a]Reactions were performed in the same manner as in general procedure B (pg. 45). [b]Isolated yield. [c]Dovex WX8 was added to the reaction mixture after stirring at 50 ºC for 23 h. [d]Low conversion. Mainly starting material was found on TLC.

Table 2. Optimization of The Reaction Conditions Between 2,6-Ditosyl-1,5,2,6-dithiadiazocane and Stilbene

The scope and limitations were further investigated (Figure 4.). Reaction using 4-fluorostilbene afforded thiomorpholine **2b** in excellent yield, but as a mixture of two diastereomers with ratio 3.2:1, suggesting that both benzylic positions have comparable stability. Introduction of weakly EDG – methyl in other *para* position of stilbene gave similar diastereomeric ratio (3.0:1), however corresponding product **2e** was obtained in excellent yield. Stilbene with strong EWG - 4-cyanostilbene or having clearly expressed stabilized and destabilized benzylic position - (*E*)-4-(2-(2-methyl-1,3-dioxoisoindolin-5-yl)vinyl)phenyl acetate gave respectively **2c** and **2d** in high yield as solely one diastereomer. Reaction with symmetric *trans*-4,4'-dibromostilbene smoothly led to the product **2f**. Thiophene ring containing substrate provided thiomorpholine **2g** in poor yield, probably due to low stability of the stilbene under strongly acidic conditions. Moreover, *N*-cinnamyl-*N*,4-dimethylbenzenesulfonamide was successfully utilized to obtain **2h** after substituting MsOH with $TsOH{\cdot}H_2O$ and elevating temperature. Following general procedure B (pg. 45) indene was used to give tricyclic thiomorpholine **2i**. Lower yield might result from higher ring strain in intermediate imparted by cyclopentane. The reaction is not limited to 2,6-ditosyl-1,5,2,6-dithiadiazocane only. Under similar conditions to general procedure B reaction utilizing 2,6-bis(methylsulfonyl)-1,5,2,6-dithiadiazocane and *trans*-stilbene gave corresponding thiomorpholine **2j** in high yield (Figure 5.). Analogously employing dibenzyl 1,5,2,6-dithiadiazocane-2,6-dicarboxylate and *trans*-stilbene provided compound **2h**, though in much lower yield (Figure 5.). Higher stability of S-N bond in dibenzyl 1,5,2,6-dithiadiazocane-2,6-dicarboxylate may be the reason.



[a]Mixture of two diastereomers with ratio 3.2:1 by NMR data.
[b]Mixture of two diastereomers with ratio 3.0:1 by NMR data.
[c]$TsOH \cdot H_2O$, 50 ºC for 19 h.

Figure 4. Scope of Sulfenofunctionalization of Stilbenes

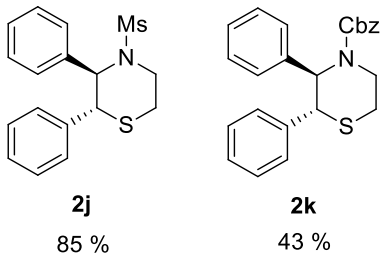


Figure 5.

Additionally, structure of thiomorpholine **2a** was indisputably confirmed by X-ray crystallography (Figure 6). Interestingly that **2a** takes a *twist-boat* conformation in a crystal, instead of a *chair*.

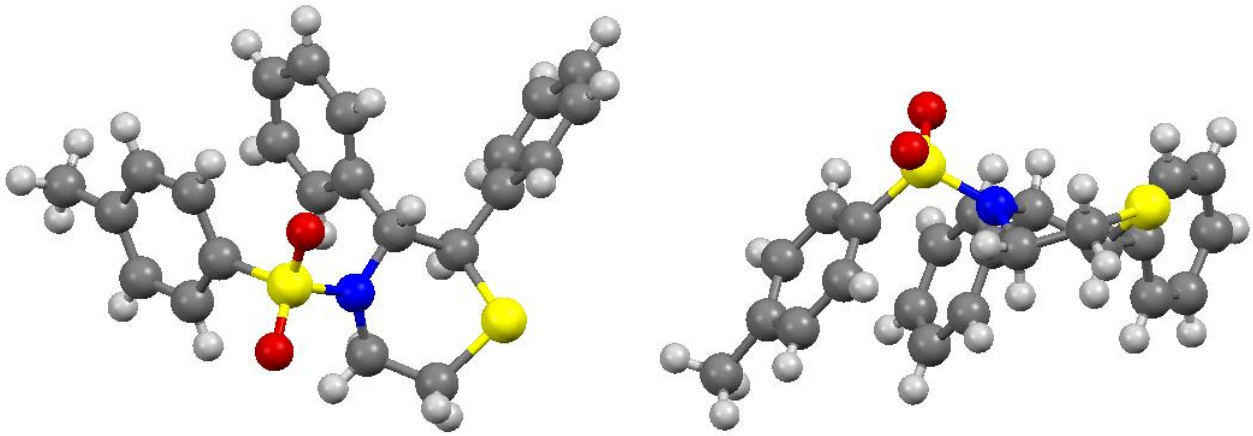
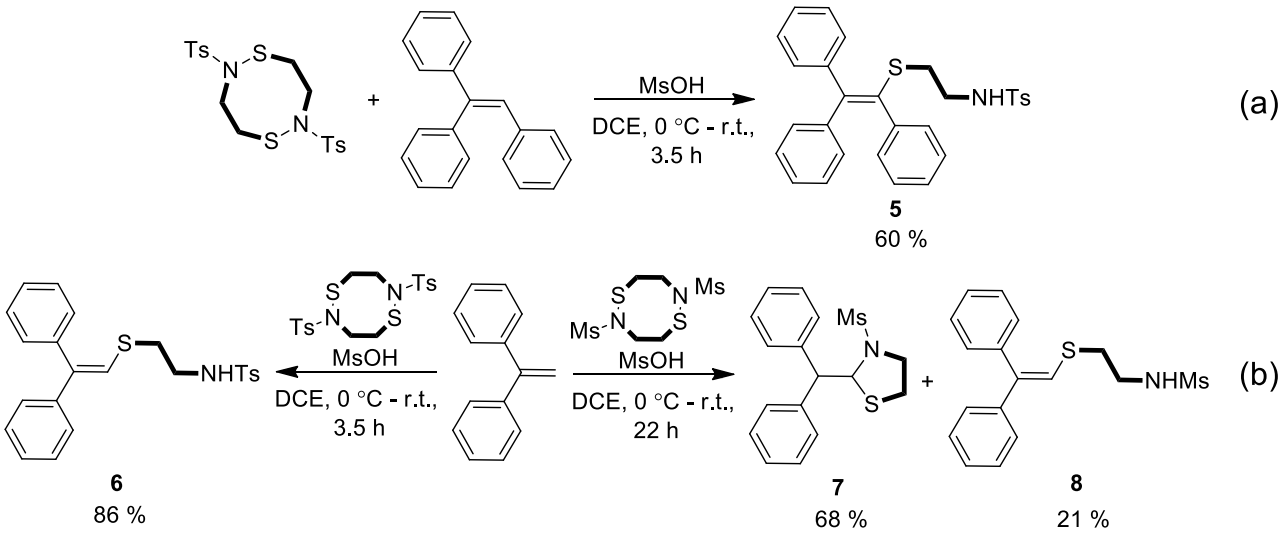


Figure 6. X-ray structure of **2a**. Blue "bubble" – nitrogen, yellow "bubble" – sulphur, red "bubble" – oxygen, grey "bubble" – carbon, light grey "bubble" – hydrogen.

Nevertheless, attempts to employ more substituted alkenes were not successful. Following general procedure B (pg. 45) reaction of 2,6-ditosyl-1,5,2,6-dithiadiazocane with triphenylethylene yielded benzenesulfonamide **5** (Scheme 19, a). Similar results were obtained using 1,1-diphenylethylene, where benzenesulfonamide **6** was produced in excellent yield (Scheme 19, b). The same reaction with 2,6-bis(methylsulfonyl)-1,5,2,6-dithiadiazocane having less bulky protecting group gave a mixture of thiazolidine **7** and benzenesulfonamide **8** (Scheme 19, b). Moreover, tetraphenylethylene was not reactive at all. There are two possible explanations. First, the steric hindrance of emerging thiomorpholine is too high to complete cyclization. Second, the intermediate carbocation is so stabilized by phenyl rings that β-elimination is faster than intramolecular nucleophilic attack by benzenesulfonamide moiety.

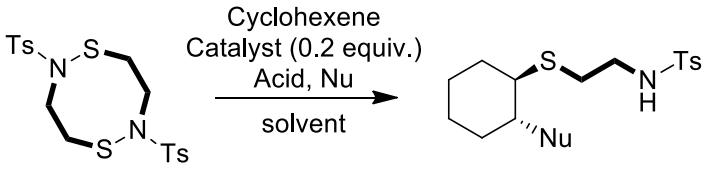


Scheme 19

In addition to these unsuccessful examples quite a few substrates were unreactive (e.g. (*E*)-4,4'-(ethene-1,2-diyl)bis(N,N-diethylbenzamide), *N*-acetyliminosilbine) or gave mixture of products (e.g. (*E*)-1-nitro-2-styrylbenzene, (*Z*)-1-(decyloxy)-4-styrylbenzene, cinnamyl(phenyl)sulfane, (*E*)-prop-1-ene-1,2-diyldibenzene, (*E*)-4-(2-(perfluorophenyl)vinyl)-1,1'-biphenyl).

2.4 Sulfenofunctionalization of Alkenes

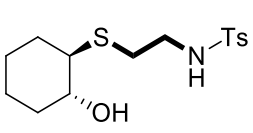
With successful sulfenofunctionalization of styrenes and stilbenes to obtain corresponding thiomorpholines our attention was next turned to non-activated alkenes. The optimization was started from similar conditions to those of styrenes and stilbenes with cyclohexene as alkene source (Table 3, Entry 1). Unexpectedly cyclohexanol **9** was formed in low yield even without source of hydroxyl group in reaction mixture. It is assumed that intermediate caught H_2O during the work up. The same outcome was observed after changing Brønsted acid into $TsOH \cdot H_2O$ (Table 3, Entry 2). Increase strength of Brønsted acid and addition of H_2O into reaction mixture led to the higher yield of **9** (Table 3, Entry 3). After reducing reaction time to 1 h, cyclohexanol derivative **9** was obtained in high yield (Table 3, Entry 4). The attempts with Lewis acid – $BF_3 \cdot Et_2O$ and TsONa or TBAI as a nucleophile were unsuccessful (Table 3, Entries 5 and 6). Adaptation of conditions of Entry 4 to ethylene glycols nucleophile gave benzenesulfonamide **3a** in moderate yield (Table 3, Entry 7). Reducing strength of Brønsted acid provided product **3a** in a higher yield (Table 3, Entry 8). Application of the similar conditions using TBAI gave mixture of products (Table 3, Entry 9). Lastly, experiment without catalyst produced benzenesulfonamide **3a** in almost the same yield (Table 3, Entry 10).



Entry[a]	Acid (equiv.)	Cyclohexene (equiv.)	Catalyst	Nu (equiv.)	Solvent (M)	Time	Yield[c] (%)
1[b]	MsOH (2.1)	2.2	$(Et_2N)_3PSe$	H_2O[d]	dry DCM (0.035 M)	6 h (0 ºC) + 46 h (r.t.)	**9** 31%
2[b]	$TsOH \cdot H_2O$ (2.2)	2.7	$(Et_2N)_3PSe$	H_2O[d]	dry DCM (0.035 M)	27 h (r.t.)	**9** 42%
3[b]	TfOH (2.6)	2.2	$(Et_2N)_3PSe$	H_2O (4)	DCE (0.05 M)	22 h (r.t.)	**9** 62%
4[b]	TfOH (2.6)	2.2	$(Et_2N)_3PSe$	H_2O (4)	DCE (0.05 M)	1 h (r.t.)	**9** 76%
5	$BF_3 \cdot Et_2O$ (10)	2.6	-	TsONa (3.0)	Dry DCM (0.05 M)	24 h (r.t.)	**9** 30%
6	$BF_3 \cdot Et_2O$ (10)	2.6	-	TBAI (2.9)	Dry DCM (0.05 M)	25 h (r.t.)	-[e]
7[b]	TfOH (2.5)	2.2	$(Et_2N)_3PSe$	Ethylene glycol (4.9)	DCE (0.05 M)	19 h (r.t.)	**3a** 45%

8[b]	MsOH (2.4)	2.2	$(Et_2N)_3PSe$	Ethylene glycol (4.8)	dry DCE (0.05 M)	25 h (r.t.) + 48 h (50 ºC)	**3a** 65%
9[b]	MsOH (2.7)	2.6	$(Et_2N)_3PSe$	TBAI (2.4)	dry DCM (0.05 M)	72 h (r.t.)	-[f]
10	MsOH (2.4)	2.2	-	Ethylene glycol (4.8)	dry DCE (0.05 M)	23 h (r.t.)	**3a** 66%

[a]Reactions were performed in the same manner as in general procedure C (pg. 51). [b]Acid was added at 0 ºC [c]Isolated yield.
[d]Additionally H_2O was not added. [e] Main product does not contain cyclohexane ring according ^1H NMR.
[f]Mixture according TLC.



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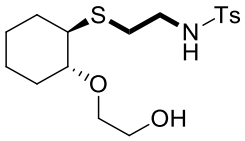
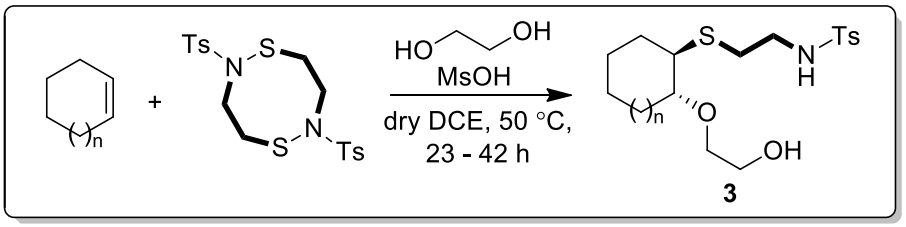


3a

Table 3. Optimization of The Reaction Conditions Between 2,6-Ditosyl-1,5,2,6-dithiadiazocane, Nucleophile and Alkene

Examination of a number of conditions employing alkenes was followed by utilization for the synthesis of heterocycles. Besides cyclohexene, using general procedure C (pg. 51) cycloheptene was utilized to provide corresponding benzenesulfonamide **3b**, though in lower yield (Figure 7). Similarly, 2-tosylisothiazolidine was used to produce product **3c** in good yield. Worth noting is that reactivity of 2-tosylisothiazolidine is much higher than 2,6-ditosyl-1,5,2,6-dithiadiazocane under these conditions.



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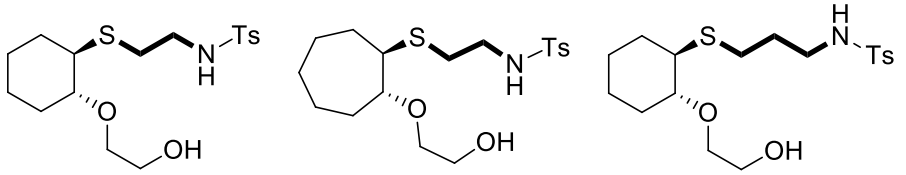


3a 66 %

3b 45 %

3c[a] 59 %

[a]2-tosylisothiazolidine was used as sulfenamide source, r.t.,1h.

Figure 7. Sulfenofunctionalization of Cyclic Alkenes

Following general procedure D (pg. 53), benzenesulfonamide **3a** was successfully cyclized to give hetero-cyclononane **4a** in high yield (Figure 8). Under same conditions substrate **3b** was utilized to

provide **4b** in slightly lower yield. Annuliation of **3c** led to hetero-cyclodecane **4c**, but in reduced yield (Figure 8).

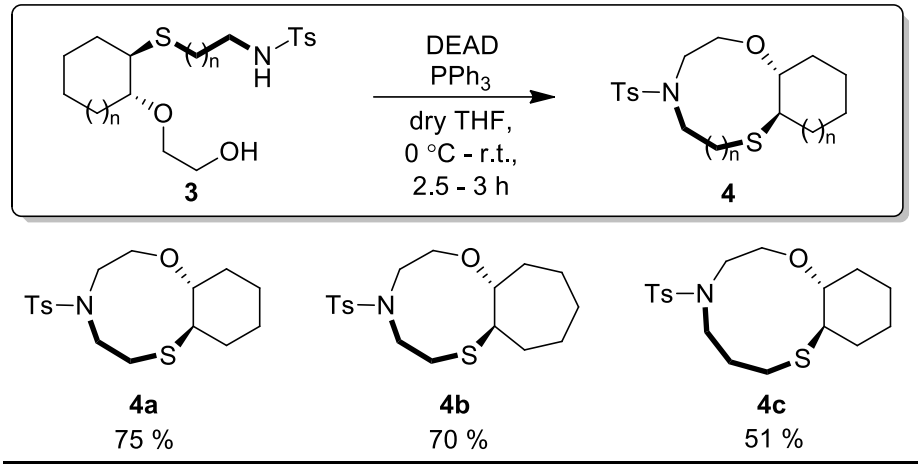
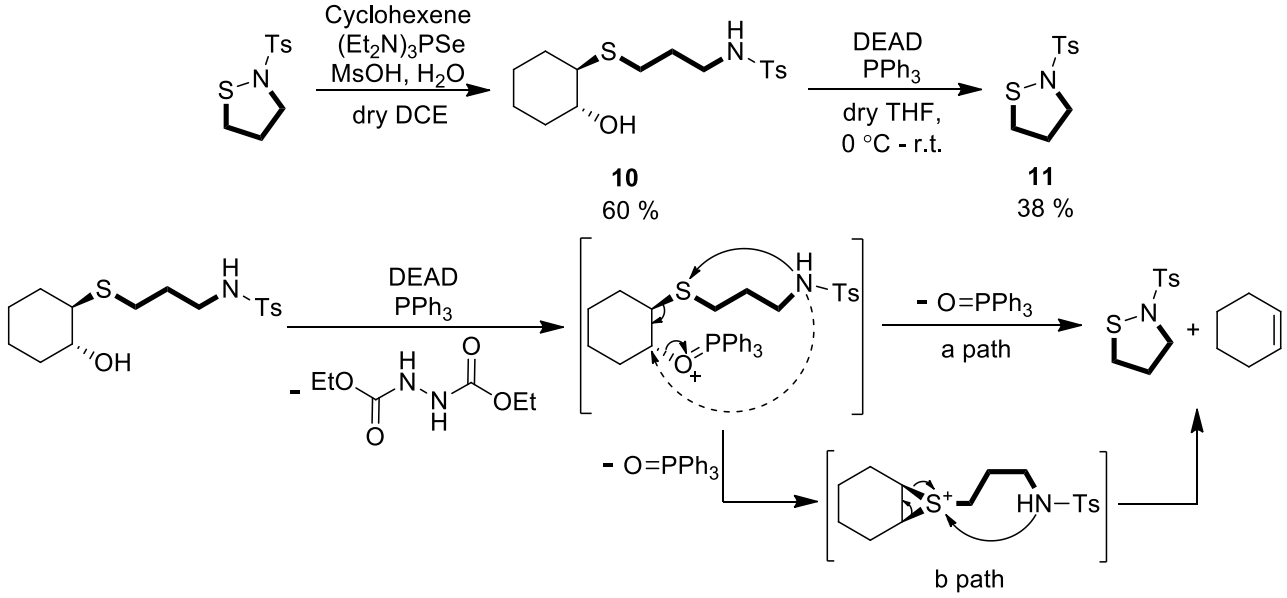


Figure 8. Annulations reactions of **3** under Mitsunobu conditions

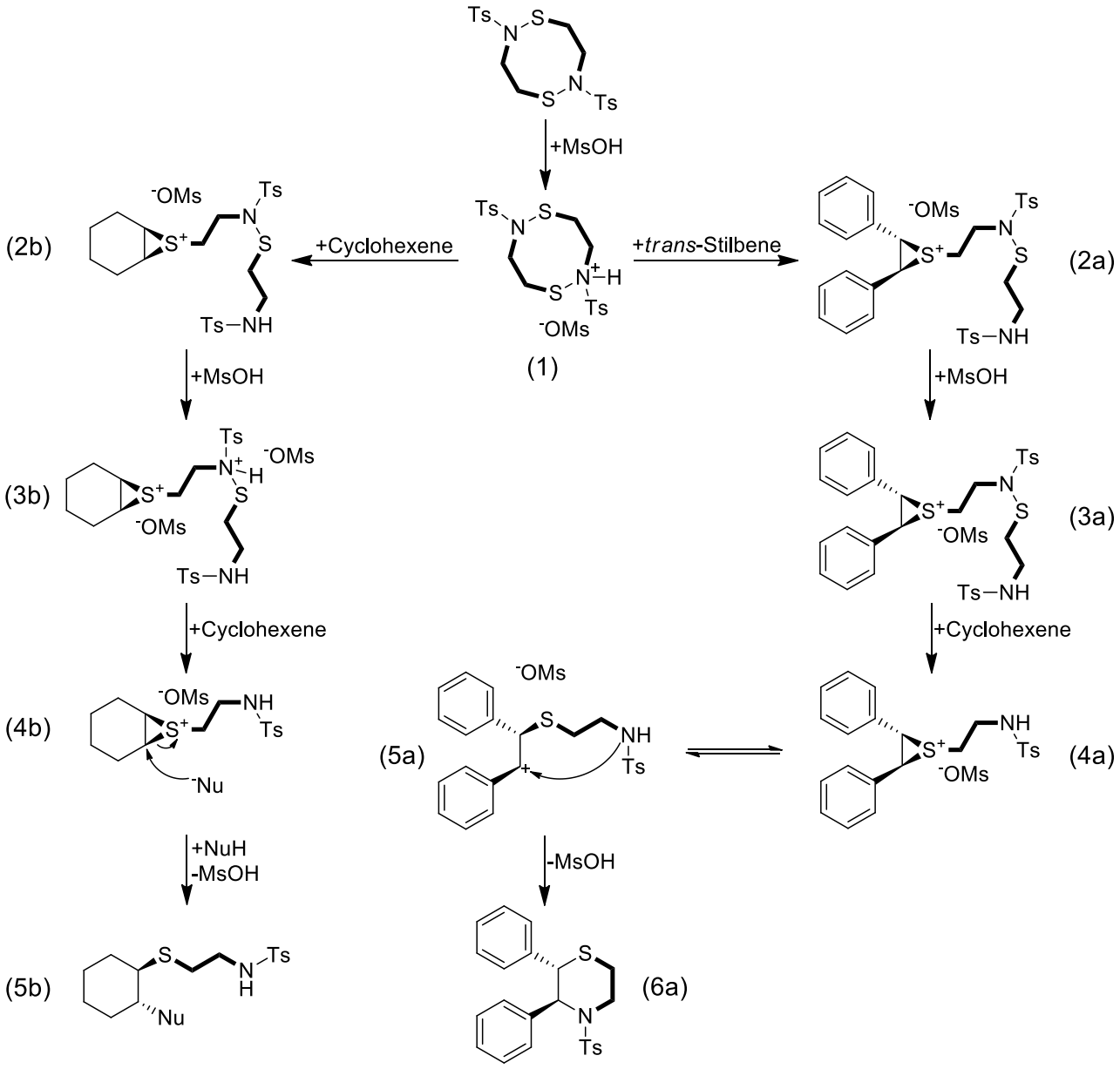
Attempts to employ cyclohexanol derivative **9** for the synthesis of corresponding thiomorpholine were ineffective under Mitsunobu conditions. Surprisingly, compound **10** prepared from 2-tosylisothiazolidine gave back starting material **11** under Mitsunobu conditions (Scheme 20). Plausible mechanism involves formation of phosphate intermediate, which further takes path a or path b (Scheme 20). In path a, the intermediate participate in intramolecular reaction, where nitrogen instead of nucleophilic substitution of phosphate directly attacks sulphur and forms 2-tosylisothiazolidine. In path b, firstly thiiranium is formed followed by nucleophilic attack onto sulphur by nitrogen.



Scheme 20

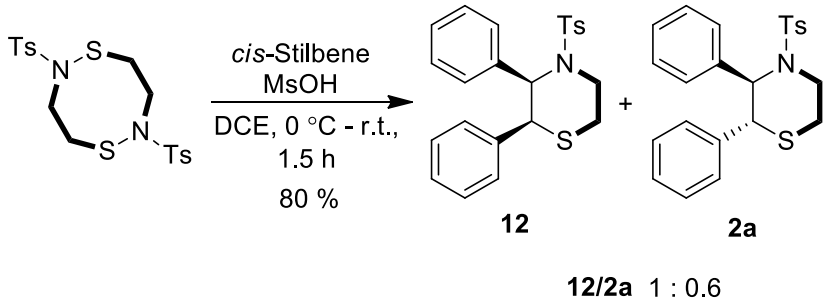
2.5 Mechanistic Considerations

On the basis of reviewed literature and obtained experimental results some mechanistic insights can be proposed. Plausible mechanism is showed in Scheme 21, however it is important to emphasize that this mechanism has nor supporting kinetics experiments nor isolated intermediates to prove it and is based solely on literature [8-42] and experimental data. First of all, 2,6-ditosyl-1,5,2,6-dithiadiazocane is protonated by MsOH to derive super-electrophilic sulphur reagent (1) (Scheme 21). The next step involves super-electrophilic sulphur transfer onto alkene to form intermediate (2a) or (2b), which are further protonated with Brønsted acid to obtain di-carbocation (3a) or (3b). Another transfer onto alkene provides thiiranium (4a) or (4b). It is likely that from alkyl substituted or deactivated alkenes derived thiiranium ions are stable, therefore due to alkyl chain shortness of sulfenamide and steric hindrance of intermediate (4b) the intramolecular nucleophilic attack cannot be afforded, which normally should be done from the opposite site to the sulphur.



Scheme 21

Nevertheless, employing external nucleophile these obstacles can be removed. Even so, formed a new C-Nu bond has to be strong enough to surpass nucleophile attack by sulphur and returning starting substrate. Thiiranium ions containing substitutes capable of stabilizing the carbocation can be treated as partially opened ring or as ring existing in equilibrium between closed (4a) and opened (5a) forms (Scheme 21). While closed form (4a) is unreactive towards intramolecular nucleophilic substitution, the opened form (5a) can freely rotate and occupy the right conformation for intramolecular reaction. It is noteworthy that even in the presence of H_2O with the examples showed in Figure 3, the intramolecular capture is faster than hydroxylation, which suggest that partially or fully opened form of thiiranium dominates. The existence of carbocation confirms experiment with *cis*-stilbene following general procedure B (Scheme 22). The product was obtained as a mixture of *cis* and *trans* isomers, which implies that the intermediate can partially rotate and occupy energetically more stable *trans* conformation.



Scheme 22

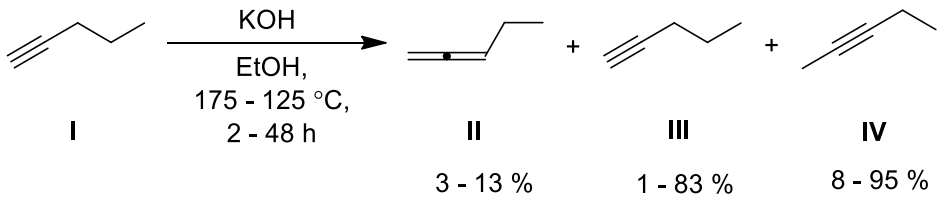
3. REVIEW OF LITERATURE PART II

3.1 Introduction

In this section it will be briefly reviewed three topics: synthesis of allenes via prototropic isomerization of alkynes, reactivity of alkali metal enolates and enolate addition to non-activated multiple bonds. All these topics are crucial and play an important role in discussing reactions presented in section 4.

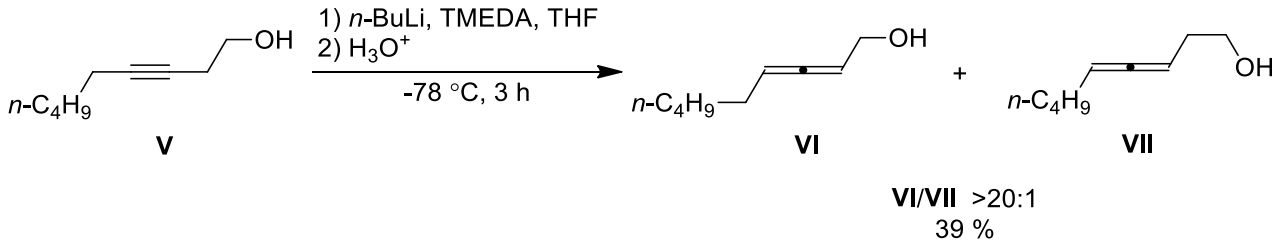
3.2 Synthesis of Allenes by Prototropic Isomerization of Alkynes

Various functional groups are tolerated in the isomerization of alkynes to allenes, thus it is useful tool in organic synthesis [45]. However, reactivities, yields and stabilities highly depend on the substituents. For example, alkyl groups containing substrates are usually in equilibrium between allenes and alkynes, where later is favoured (Scheme 23) [46]. Depending on concentration of KOH, reaction time and temperature allene **II** was obtained between 3 – 13 %. Worth noting that 1,3-pentadiene is not formed.



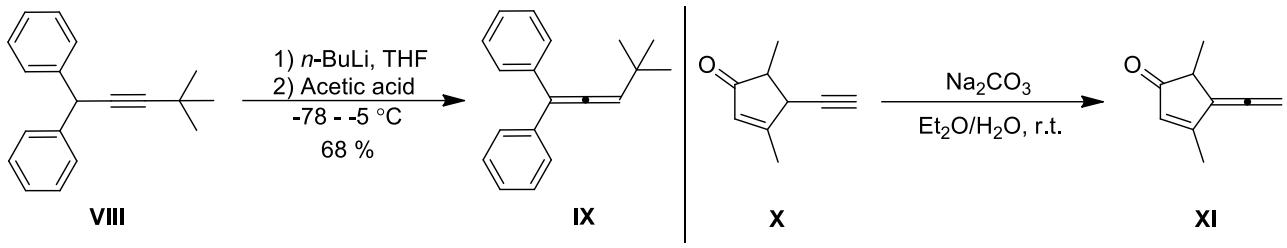
Scheme 23

When alkyne is either symmetrical or has a tertiary center substitute, the selectivity is achieved. On the other hand, allenes can be obtained in high selectivity from unsymmetrical alkynes as well. For instance, due to hydroxyl group directing effect alkynol **V** was isomerized in high favour of allene **VI** (Scheme 24) [47].



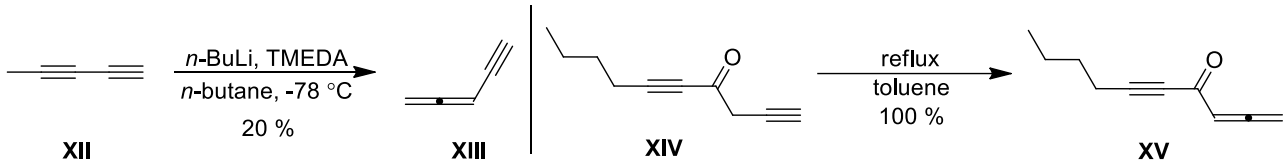
Scheme 24

The reactions where π-bond moves into conjugation with aromatic system or alkenes are favoured, thus corresponding allenes can be formed in high yields under mild conditions as showed in Scheme 25 [48,49]. Analogous alkynes containing carbonyl, sulfoxide, sulfone, phosphonate or related electron withdrawing group instead of conjugate system can be easily converted to corresponding allene using weak bases (e.g. aluminum oxide, tertiary amine, carbonate) [45].



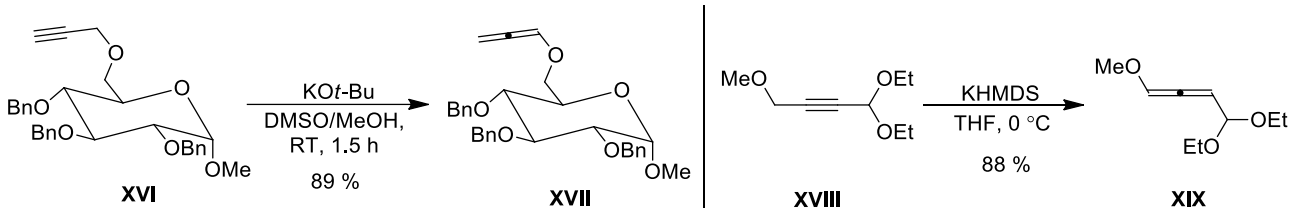
Scheme 25

However, when alkyne is already conjugated, isomerization to allene is suppressed. Reaction of 1,3-pentadiyne in presence of *n*-BuLi and TMEDA gives a small amount of corresponding allene (Scheme 26, left) [50]. As can be observed different substitutes strongly changes reactivity of alkynes towards isomerization. Therefore, it is possible to isomerize one alkyne without changing another on the same molecule. For instance, propargyl substituent on the ketone is more reactive than 1-hexynyl moiety due to conjugation increase and consequently allene **XV** was obtained quantitatively (Scheme 26, right) [51].



Scheme 26

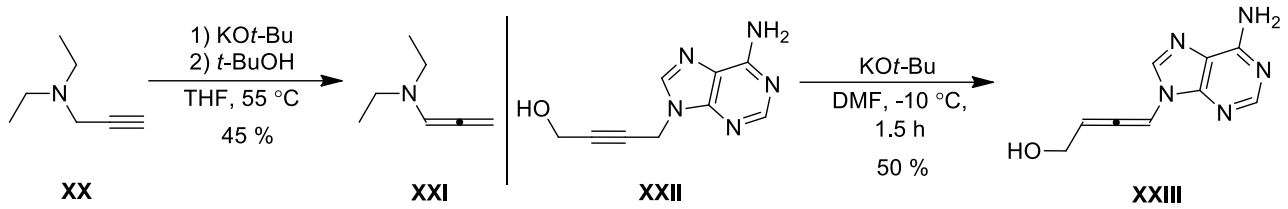
Various allenes bearing halogen [52], silyl [53], stannyl [54], phosphorus [55] substituents were successfully synthesized, but among them oxygen, nitrogen and sulphur substituents containing allenes have attracted the most attention, primarily due to potential in organic synthesis as useful intermediates [45]. Most of examples are isomerization of propargylic derivatives to corresponding allenes, where usually a strong base is needed. In the case of allenyl ether synthesis typically KO*t*-Bu is used. A wide range of allenyl ethers were obtained in high yields and selectivities such as carbohydrate moiety containing allene **XVII** (Scheme 27, left) [45,56]. Competition between ethers and acetals groups in the propargylic positions leads to disubstituted allene as showed in Scheme 27 (right), where KHMDS was used as a base [57].



Scheme 27

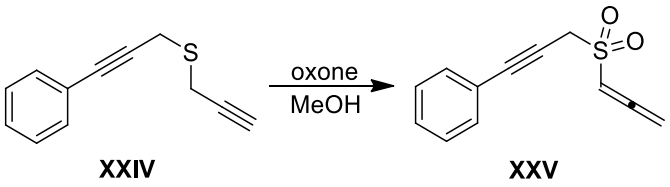
Nitrogen as substituent has similar chemical properties in these reactions as oxygen. Usually KO*t*-Bu or *n*-BuLi are used as bases followed by protonation with alcohol. Successfully both aryl and alkyl amines were utilized in isomerization reaction into allenes [45]. For example, alkil propargyl amine **XX** was isomerized into allene **XXI** in moderate yield under strong basic conditions (Scheme 28) [58]. Moreover, nucleobases can serve as suitable substituent to obtain corresponding allenes as

well. Propargyl derivative **XXII** was smoothly isomerized into allene **XXIII**, even taking in account that other propargyl position is occupied by alcohol, where competing reactions can take place [45,59]. Interesting that heterocyclic based allenes as **XXIII** have demonstrated antiretroviral effects [59,60].



Scheme 28

Propargyl thioethers in the course of isomerization into allenes shares similar properties as for propargyl alcohols and propargylamines. Typically, strong bases are used such as sodium amide, metal alcoholates and hydroxides [45]. Worth noting that oxidation of sulfur can spontaneously lead to isomerization of propargyl thioether into corresponding allene (Scheme 29) [61].



Scheme 29

3.3 Structure and Reactivity of Alkali Metal Enolates

Enolates bound with various metals are in different ways affected by aggregation, solvation, concentration, ligands at the metal, which lead to different reactivity and stereochemistry [62-69]. The chemistry and structures of lithium enolates are the most researched so far. X-ray structures of Li enolates analysis revealed that dimeric, tetrameric or hexameric aggregates are typically formed. Moreover, aggregation is more determined by solvent, complexing or chelating agents, than by structure of enolate itself [62-69]. The others alkali metals enolates have attracted less attention, however Williard *et al.* have successfully prepared and identified the X-ray crystal structures of lithium, sodium and potassium enolates of pinacolone. The study showed that lithium enolate aggregates as an non-solvated hexamer, sodium enolate - aggregates as tetramer solvated by pinacolone and potassium enolate – as hexamer solvated by THF (Figure 9) [64].

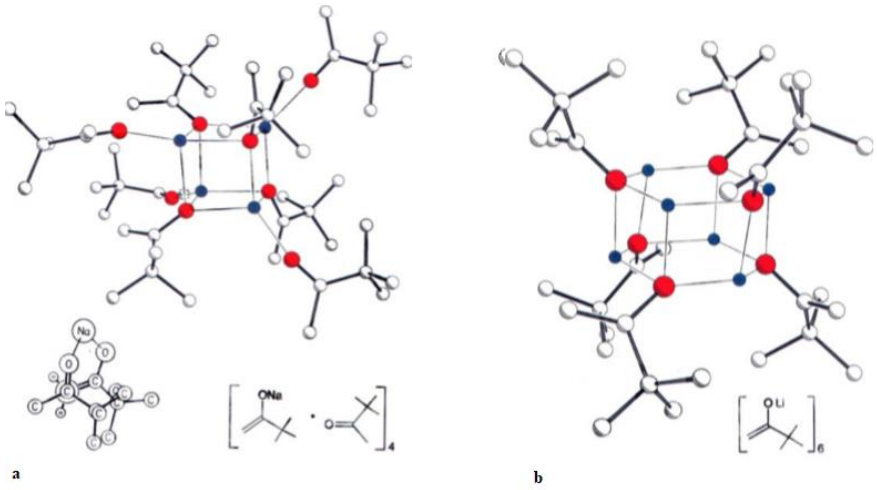
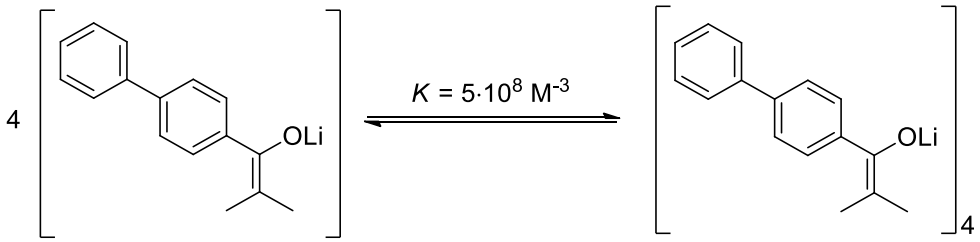


Figure 9. a) Tetrameric sodium enolate of pinacolone solvated by pinacolone. b) Hexameric lithium enolate of pinacolone structure (Copied from 63). White "bubbles" – carbon, red "bubbles" – oxygen, blue "bubbles" – metal atom.

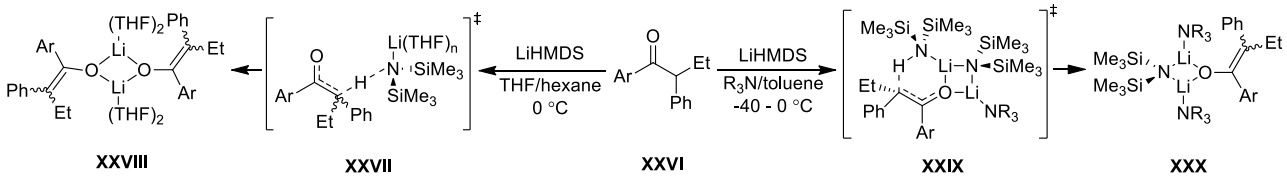
To identify aggregation of enolates in solutions is more challenging, therefore fewer examples can be found [62-69]. Studies of lithium enolates of isobutyrophenone and α-tetralone revealed *co*-existence of dimers and tetramers in polar aprotic solvents [65]. In more polar solvents such as DME dimeric structure dominates, while in less polar solvents like diethyl ether – tetrameric.
In another example Streitwieser *et al.* showed that lithium enolates of *p*-phenyl isobutyrophenone in THF exist as monomeric and tetrameric contact ion pairs, where equilibrium constant is $5 \cdot 10^8$ (Scheme 30) [65,70].



Scheme 30

Reactivities of metal enolates in solutions highly depend on the solvent polarity. In polar aprotic solvents such as DMSO or DMF reaction path usually involves free anion, especially for the large cations containing enolates. Therefore, alkylation of O position gives highest yields compared with other solvent types [62]. In polar protic solvents like methanol or water free enolate is hydrogen bonded with solvent molecules, therefore reactivity is similar to ion pair [62]. It was showed that alkylation rate of the enolate of ethyl acetoacetate in MeOH and *t*-BuOH is cation dependent, where higher rates were observed with larger cations [71]. Weakly polar solvents such as THF, diethyl ether together with non-polar solvents (alkanes, DCM) was found to have best properties for C-alkylation of enolates [62]. Typically, in non-polar solvents enolates form micelles, while in weakly polar solvents – aggregates. These assemblies can influence reactivity of enolates. Zaugg *et al.* studies have showed that the enolate made from diethyl (1-methylbutyl)malonate forms micelles in benzene and cyclohexane, which are believed to be break down into smaller aggregates after addition of small amount of DMF or HMPT [72]. As a result, reaction rate increases. In general,

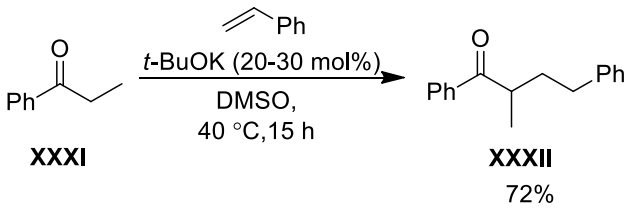
monomers are more reactive than dimers or higher aggregates [62 – 66]. However, the reaction does not necessarily go through disaggregation. Reich *et al.* conducted mechanistic studies of reaction between lithium enolate of 4-fluoroacetophenone and 4-fluorobenzaldehyde in THF [67]. Deprotonation of 4-fluoroacetophenone with LDA occurs through dimer process to provide a metastable enolate homodimer, which further dimerizes to a stable homotetramer. The spectroscopic data showed that homotetramer reaction with the aldehyde is much faster than the disaggregation of tetramer [65,67]. Recently, Collum *et al*. found that enolization of acyclic ketones in different solvents systems leads to different Z/E selectivity [69]. Enolization of ketone **XXVI** with LiHMDS in neat THF is believed to go through transition state **XXVII** leading to dimer **XXVIII** (Scheme 31). Trapping dimer gives 1:6 E/Z selectivity. Diluting THF with hexane leads to reversed selectivity (2:1 E/Z). Very high E selectivity was achieved using toluene together with Et_3N or DMEA as solvent. However, the reaction path is different leading to monomer **XXX** through cyclic transition state **XXIX** (Scheme 31). After trapping monomer **XXX** 65:1 E/Z selectivity was observed [69].



Scheme 31

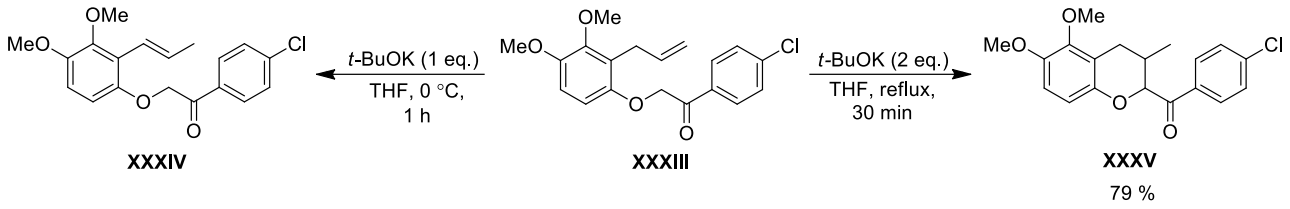
3.4 Alkali Enolates Addition to Non-Activated Multiple Bond

Addition of carbanions onto aryl-conjugated alkenes is known for decent time [6]. However, alkali enolates addition onto alkene substrates is much less studied. One of several examples was published by Knochel *et al*. [73]. Potassium enolate of ketone **XXXI** was successfully added onto styrene using catalytic amount of *t*-BuOK in DMSO (Scheme 32). The reaction temperature was found to be maintained between 38 – 41 °C in order to avoid formation of product resulting from a double addition [73].



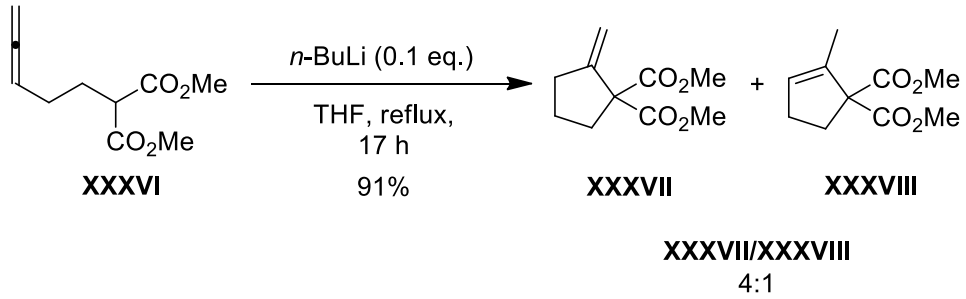
Scheme 32

In another example, Wang *et al*. found that acetophenone **XXXIII** can be cyclized into chromane **XXXV** in the presence of *t*-BuOK (2 equiv) in THF (Scheme 33) [74]. Worth noting that using only 1 equiv of *t*-BuOK and reducing temperature to 0 °C resulted only to double bond migration to provide **XXXIV** (Scheme 32). Therefore, suggested mechanism starts with double bond isomerization followed by alkali enolate addition and carbanion migration to stable potassium enolate [6,74].



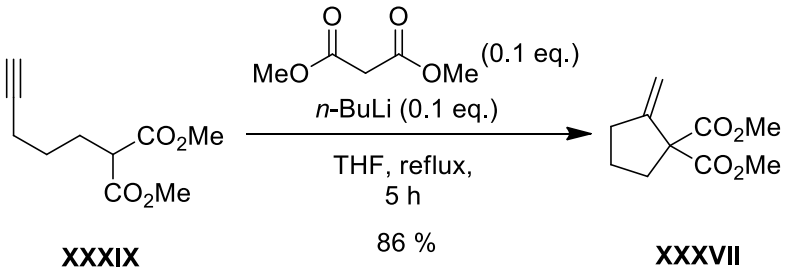
Scheme 33

The alkali enolates additions to allenes are even rarer, probably, due to uneasy preparation of latter [6]. Existing example employs allene **XXXVI** in the presence of a catalytic amount of *n*-BuLi (0.1 equiv) in THF to produce a mixture of regioisomers of cyclopentane derivatives (Scheme 34) [6,75].



Scheme 34

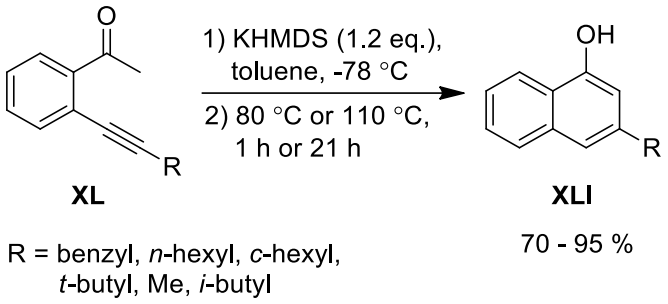
The alkali-mediated additions of enolates onto alkynes produce vinylic alkaline species, which are more stable than alkyl alkaline derivatives formed after addition of corresponding enolate onto alkenes [6]. Therefore, a wider variety of addition reactions was successfully performed utilizing alkynes. Taguchi *et al.* investigated 4-pentynylmalonate (**XXXIX**) intramolecular cyclization under basic conditions [75]. The reaction proceeded smoothly in high yield using a catalytic amount of *n*-BuLi (0.1 equiv) in THF (Scheme 35). However, the use of a stoichiometric amount of *n*-BuLi gave only low yield [75]. Furthermore, addition of dimethyl malonate as proton source improves reaction yield. These results may be explained through irreversible protonation of the highly reactive vinyl alkali intermediate leading to a thermodynamically unfavourable result [6,75].



Scheme 35

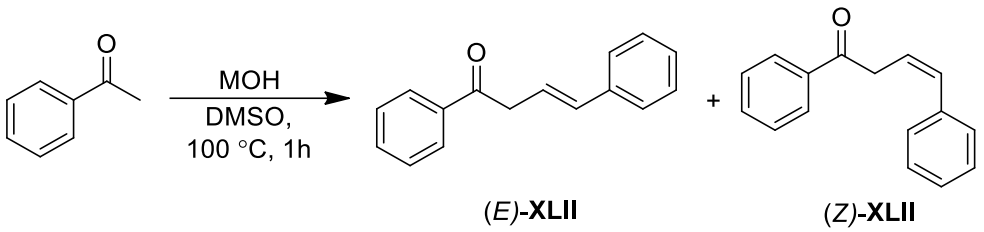
Base-mediated intramolecular cycloaromatization of *o*-alkynylacetophenones **XL** leading to 3-alkylnaphtols **XLI** was publicated by Makra *et al.* (Scheme 36) [76]. Investigation revealed that counterion plays crucial role. KH and *t*-BuOK in THF as well promoted reaction, while NaHMDS, LiHMDS and LDA were not suitable [76]. Moreover, the study with deuterated *o*-alkynylacetophenone suggested that the mechanism involves acetylene isomerization into allene

followed by 6π-electrocyclization. On the other hand, successful reaction of *o*-alkynylacetophenones **XL** containing *t*-butyl substitute demonstrates that under more harsh conditions direct attack of the enolate on the alkyne can be achieved [76].



Scheme 36

The base-catalyzed intermolecular nucleophilic addition of enolates to acetylenes might be difficult to achieve due to formation of propargylic alcohols by Favorsky reaction. However, Trofimov *et al*. reported that alkyl, aryl and alkyl hetaryl ketones can be regio- and stereoselectively utilized in vinylation reaction with acetylenes under superbasic conditions [77-80]. Vinylation of alkylarylketones with arylacetylenes was achieved using KOH in DMSO at 100 °C [77]. The conversion rate and stereochemistry are sensitive to the alkali-metal cation (Scheme 37). The highest stereoselectivity was obtained using KOH as a base, while using LiOH no reaction occurred due to lower basicity. CsOH/DMSO system gave full conversion, although *Z*/*E* selectivity was poor. Possibly, these results with CsOH come from more effective deprotonation followed by protonation with water molecule from hydrate (Scheme 37) [77]. However, increasing reaction time to 1.5 h gave solely *E* isomer, suggesting that kinetic adducts of the *Z* configuration undergo rapid isomerization to the thermodynamic products with *E* configuration [77,79]. Additionally, products have structure of substituted styrenes, which implies that conjugation in styrene is stronger than in the α,β-enone [77-80].



MOH	conversion of acetophenone, %	*E*/*Z* ratio of **XLII**
LiOH	no reaction	
NaOH	70	10:1
$KOH \cdot 0.5H_2O$	100	Only *E*
$CsOH \cdot H_2O$	100	1:1

Scheme 37

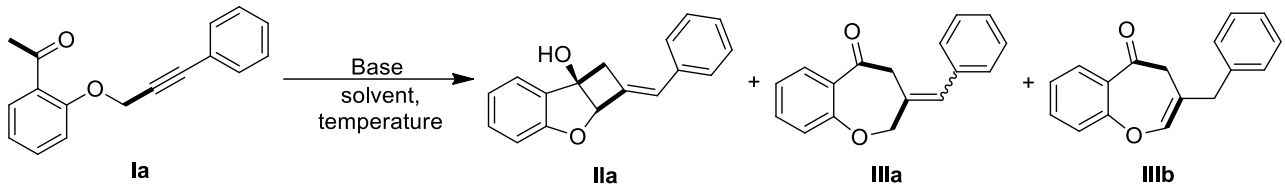
4. RESULTS AND DISSCUSSION PART II

4.1 Introduction

Investigation of 2'-(propargyloxy)acetophenone derivatives containing two relatively acidic positions, but different in nature led to the discovery of a new anionic cascade cyclization reaction. As a result, unique compounds possessing contiguous six-,five- and four-membered rings were formed. The research and development of this study was done by group of six members. Although, my main task was to examine reactivity and synthetic applicability, I contributed to the other sections as well. Experiments I performed for the topic are showed in Experimental Part II. However, to get a whole picture of research all obtained data will be discussed, but experiments which were not done by me are showed in grey colour.

4.2 Screening of Reaction Conditions

Annulation of acetophenone **Ia** through formation of allene and subsequent addition of enolate was envisaged after examination of literature [45-80]. Similar substrates to **Ia** having alkyl propargylic moiety instead of phenyl propargylic were cyclized using NaH in DMSO to give seven-membered heterocycles by Schmid *et al.* [81]. Therefore, the initial conditions were chosen similar to those reported (Table 4, Entry 1). Cyclization of **Ia** using NaH as base in dry DMSO led to formation of ketone **IIIa** in low yield, though solely *E*-stereoisomer was obtained (Table 4, Entries 1,2). Most likely mechanism involves direct addition of enolate to alkyne. Increasing the radius of counterion seven-membered ketone **IIIa** was obtained in higher yield, but in low stereoselectivity, while stereoselectivity was maintained with reduced yield using smaller counterion (Table 4, Entries 3,4). Switching solvent to less polar – THF and using NaH as a base at elevated temperature **IIIa** was obtained in good yield and moderate selectivity (Table 4, Entry 5). Using KO*t*-Bu as a base besides ketone **IIIa** the seven-membered product **IIIb** was formed (Table 4, Entry 6). Considering that there are numerous examples of propargylic ether or amine isomerization into allene induced by KO*t*-Bu, the mechanism involving enolate addition to allene is very plausible [45]. Attempts to employ weak bases in polar solvents were not successful (Table 4, Entries 7,8). Strong base, LDA, in THF gave mixture of products under very mild conditions (Table 4, Entry 9). Replacing the base with weaker one, LiHMDS, surprisingly, tricyclic tertiary alcohol **IIa** was formed in high yield and excellent diastereoselectivity (Table 4, Entry 10). Worth noting that reducing amount of LiHMDS to 1 equiv, the starting material was almost quantitatively recovered, suggesting that in the course of reaction 2 equiv of base are necessary (Table 4, Entry 11).



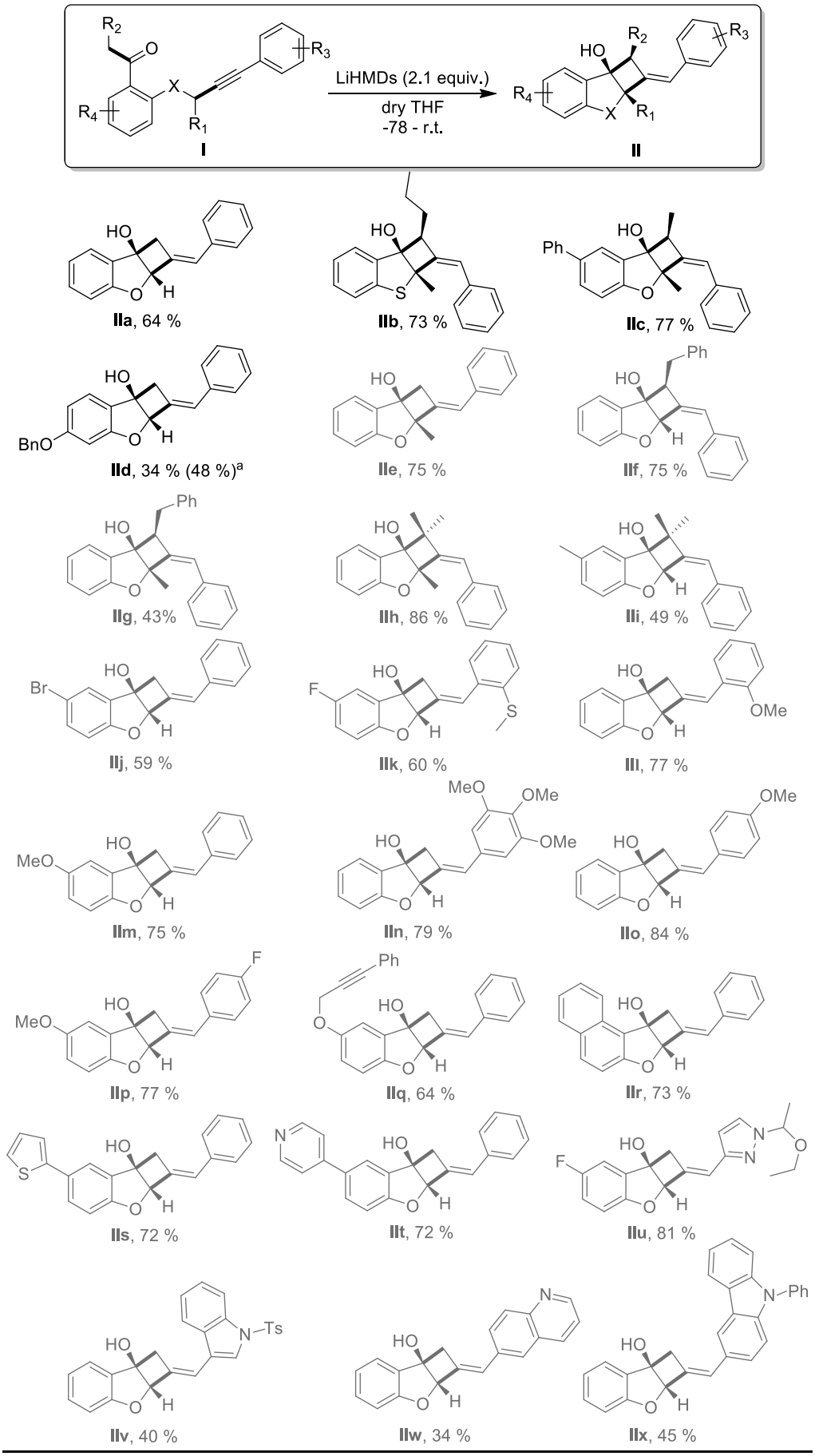
Entry[a]	Base (equiv)	Solvent	Temperature[b]	Product	Yield (%)[c]	*E*/*Z* ratio[d]
1	NaH (1.1)	DMSO	r.t.	**IIIa**	42 %	only *E*
2	NaH (3.5)	DMSO	r.t.	**IIIa**	24 %	only *E*
3	KO*t*-Bu (1.0)	DMSO	r.t	**IIIa**	66 %	1.3:1
4	*n*-BuLi (1.1)	DMSO	r.t.	**IIIa**	34 %	only *E*
5	NaH (2.9)	THF	80 °C	**IIIa**	68 %	5:1
6[d]	KO*t*-Bu (3.5)	THF	r.t.	**IIIa** **IIIb**	26 % 28 %	2.4:1
7	K_2CO_3 (3.0)	DMF	80 °C	ND[f]		
8	MeONa (2.1)	MeOH	r.t.	ND[f]		
9	LDA (2.1)	THF	-78 °C	ND[g]		
10	LiHMDS (2.1)	THF	-78 °C – -25°C	**IIa**	64 %	only *E*
11	LiHMDS (1.0)	THF	-78 °C – -25°C	**ND[f]**	almost quantitatively	

[a]General procedure for screening reaction conditions (pg 60). [b]After addition of a solution of **Ia**. [c]Isolated yield. [d]The ratio was determined by NMR. [e]Inseparable mixture. The ratios were determined by NMR. [f]Starting material was recovered. [g]Complex mixture.

Table 4. Screening of Reaction Conditions

4.3 Scope of the Reaction

Evaluation of the newly discovered reaction scope showed that various substituents on both acetophenone and aryl rings is compatible with reaction conditions (Figure 10). The reaction was also successfully applied to provide benzothiophene derivative **IIb** in high yield. Acetophenones **I** containing EDG or weakly EWG were employed to give respective products **II** in moderate to very good yields (Figure 10). Substrates with mono- or disubstituted substituents at α-position of ketone and/or at propargylic position showed that can be utilized in very high yields considering the steric hindrance. It is noteworthy that substituents at α-position led to the inversion of alkene configuration (Figure 10). Finally, acetophenones **I** with heteroaromatic moieties such as pyridine, indole or thiophene on acetophenone or aryl ring of the propargylic fragment gave good results (Figure 10).

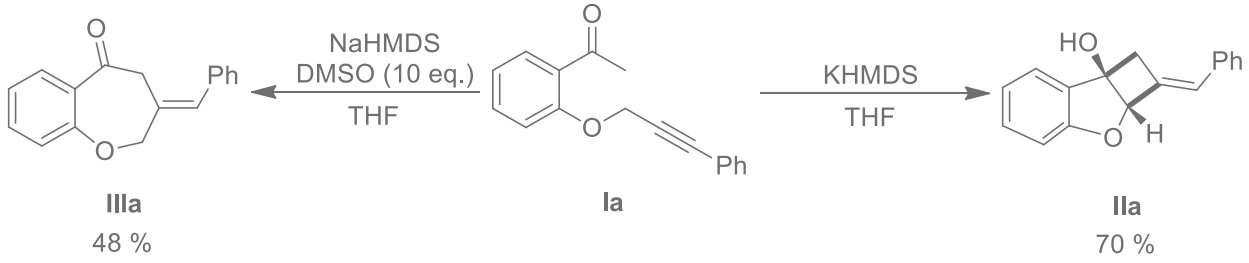


[a]Yield based on recovered starting material

Figure 10. Scope of the reaction

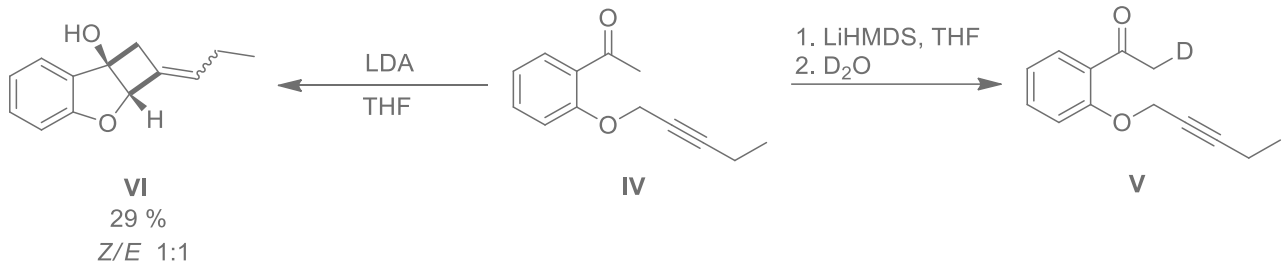
4.4 Mechanistic Considerations

After examining the reaction scope the focus was directed onto investigation of unexpected reaction route. Three main issues had to be rationalized: solvent and cation effect on the reaction outcome, unobserved proton transfer of ketone α-position and the stereochemistry of the double bond. Switching from LiHMDS to NaHMDS in THF, the reaction did not proceed. Although NaHMDS is a stronger base than LiHMDS, but the latter is much more oxophilic, therefore deprotonation of propargylic position may be facilitated by the directing effect of oxygen. However, increasing strength of sodium enolate by weakening O-Na bond with 10 equiv led to formation of seven-membered ketone **IIIa** (Scheme 38, left). Reaction using an even stronger base – KHMDS in THF gave corresponding tricyclic tertiary alcohol **IIa**, which implies that intrinsic basicity is sufficient to deprotonate propargylic position (Scheme 38, right).



Scheme 38

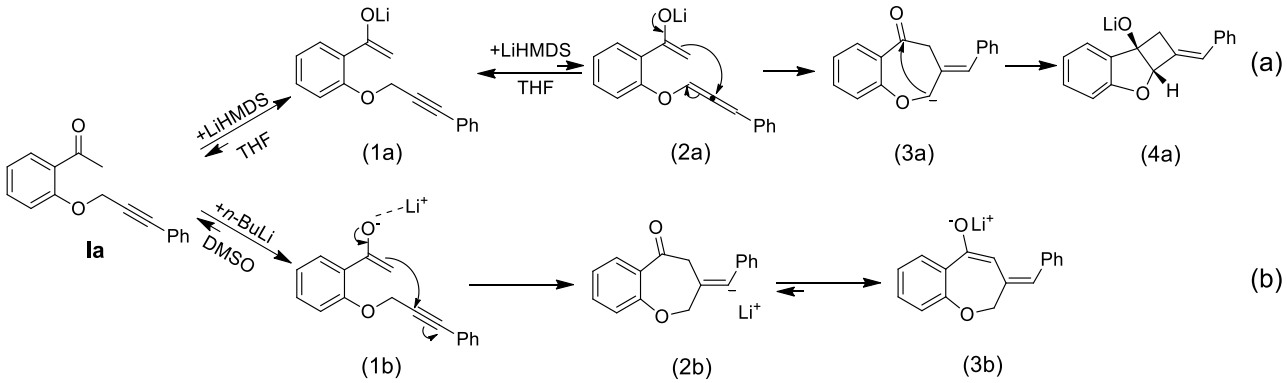
Compound **VI** with alkyl substituent on the alkyl end has less acidic propargylic position as a consequence LiHMDS was not capable to initiate deprotonation. Quenching with D_2O showed that deuterium was only incorporated in α-position of ketone (Scheme 39, right). Nevertheless, increasing base strength by changing LiHMDS into LDA gave cyclobutane derivative **VI** in low yield and as a mixture of *E/Z* isomers (Scheme 39, left).



Scheme 39

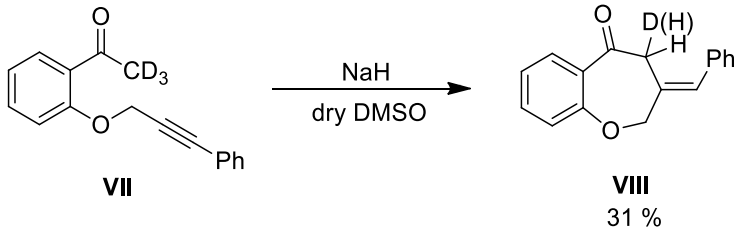
With the results from screening of reaction conditions and control experiments the plausible mechanism is showed in Scheme 40. First step in both solvents starts with enolization of acetophenone **Ia** to form intermediate (1a) or (1b). In THF lithium enolate is not nucleophilic enough for direct attack to triple bond. Based on the literature, the lithium enolates most likely exist in a form of mixed aggregates with solvent and anion [53-60]. Enolate (1a) is further isomerized into allene (2a) using second equivalent of LiHMDS followed by intramolecular addition of enolate on allene to form ketone (3a). Finally, intermediate (3a) undergoes second cyclization to provide tricyclic tertiary alcohol (4a) (Scheme 40, a). In the case of lithium enolates in DMSO, the enolates

usually exists as free ions or solvent-separated ions, thus are much more reactive than analogues in THF [62]. As a result, direct attack onto alkyne is realizable and seven-membered ketone (2b) is formed followed by isomerization into more stable cyclic enolate (3b) (Scheme 40, b).



Scheme 40. Plausible mechanism of the reaction. (a) in THF with LiHMDS as base, (b) in DMSO with *n*-BuLi as a base

The possibility of reaction mechanism in THF through formation of (2b) and subsequent isomerization into (3a) is ruled out by the fact that reaction requires more than one equiv of LiHMDS (Table 4, Entry 11). In addition, nor intra- nor intermolecular transfer of α-proton of ketone **VIII** was recorded, suggesting that 1,3-proton transfer is slow (Scheme 41).



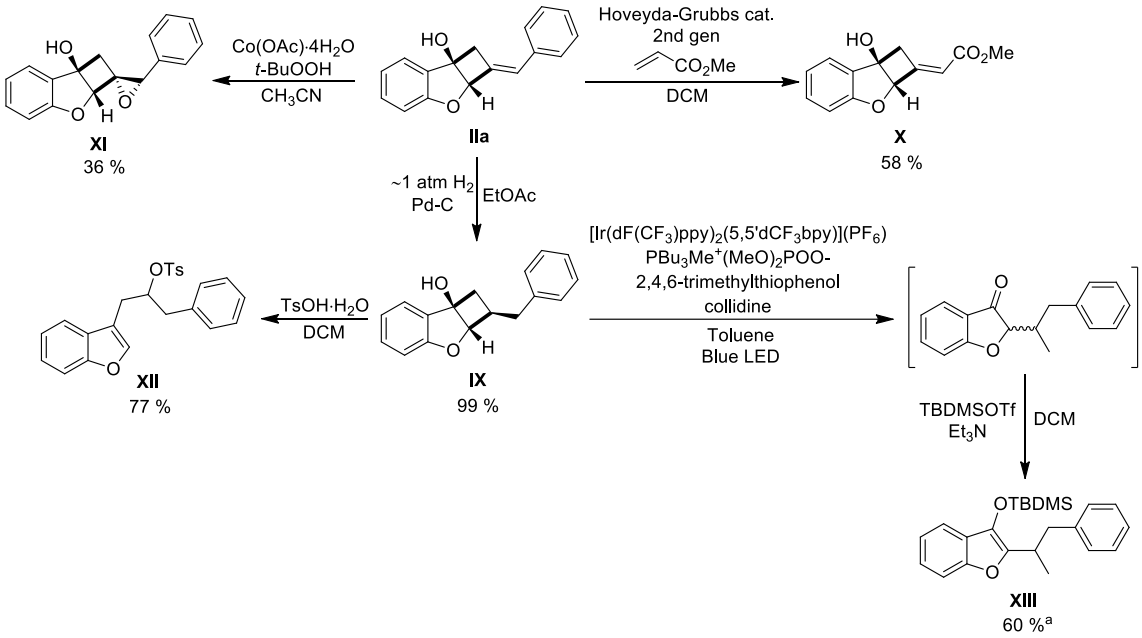
Scheme 41

While α-substituted substrates **I** gave expected stereochemistry of the alkene double bond (an addition of a nucleophile to allene from a less hindered side), non-α-substituted substrates **I** provided opposite stereochemical results (Figure 10). Theoretical calculation performed in the group revealed that Curtin-Hammet scenario (the results of reaction are determined not only by activation energies of cyclizations, but by reactants stabilization as well) may give this outcome [82].

4.5 Synthetic Applications

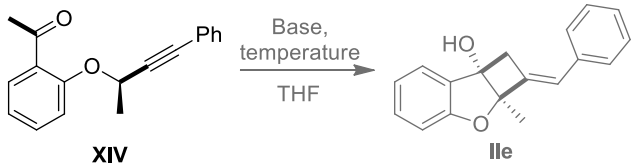
Finally, the reactivity and synthetic applicability of the compounds obtained were examined. Double bond of cyclobutane derivative **IIa** was reduced using Pd-C under H_2 atmosphere to provide **IX** in excellent yield. Moreover, compound **IIa** was successfully modified to more synthetically useful methyl acrylate derivative **X** in good yield using 2nd generation Hoveyda-Grubbs catalyst (Scheme 42). Attempts to achieve allylic oxidation were not effective. For example, using conditions similar to those reported by Clark *et al*. instead of expected allylic ketone, the epoxide derivative **XI** was formed in moderate yield (Scheme 42) [83]. Further functionalization of **IIa** by ring-opening or S_n1 type reactions did not gave desired results. Possible explanation of failing S_n1 reactions might be that tertiary carbocation cannot reach planar position due to geometric constrain

of bicyclic moiety. In addition, presence of double bond outside cyclobutane ring of **IIa** enables more paths for ring fragmentations, therefore more selective cleavage reactions of cyclobutane **IIa** were expected with hydrogenated analogues **IX**. Reaction between **IX** and $TsOH \cdot H_2O$ gave benzofuran derivative **XII** in good yield (Scheme 42). It seems that in order to avoid formation of tertiary carbocation, the cyclobutane ring undergoes cleavage to produce secondary cation followed by capture with sulfonate anion. Recently, Knowles *et al*. reported photocatalytic ring-opening reaction of cyclic alcohols enabled by proton-coupled electron transfer (PCET) [84]. Using similar conditions to those reported by Knowles *et al*. cyclobutane derivative **IX** has been tested. Unexpectedly, β-scission in cyclobutane ring resulted in the formation of primary radical rather than secondary adjacent oxygen. The intermediate was obtained as a mixture of diastereomers, therefore in reaction with TBDMSOTf it was converted into benzofuran derivative **XIII** as a racemic mixture (Scheme 42).



Scheme 42. Synthetic Applications. [a]Two steps yield.

Lastly, chirality transfer from propargylic stereogenic center was evaluated through cascade transformation using enantiomerically pure substrate **XIV** (Scheme 43). Reaction using LiHMDS as a base tricyclic tertiary alcohol **IIe** was obtained in *ee* = 37 % only. However, using more basic - KHMDS base the reaction proceeded at lower (-40 °C) temperature, therefore racemization of carbanion stereogenic center was suppressed and cyclobutane **IIe** was delivered in much higher enantioselectivity (*ee* = 80 %) (Scheme 43).



Base:	T, °C:	ee:
LiHMDS	-5 °C	37 %
KHMDS	-40 °C	80 %

Scheme 43

The absolute configuration was confirmed by X-ray crystallography after modification of **IIe** (Figure 11).

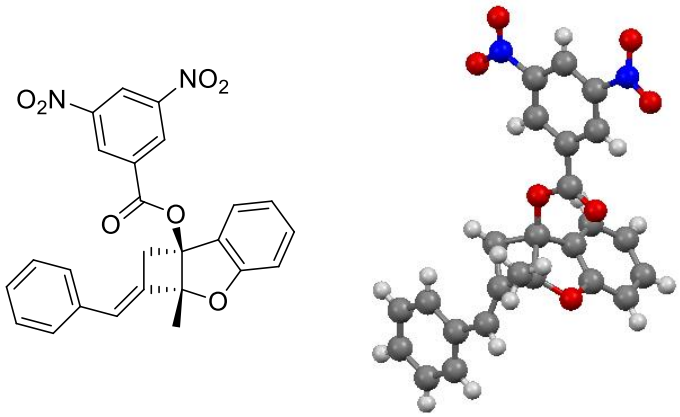
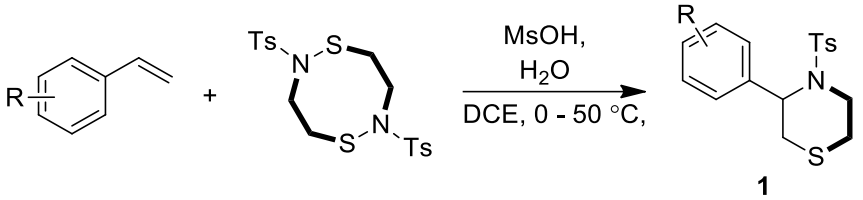


Figure 11. Chemical and X-ray structures of modified **IIe**. Blue “bubble” – nitrogen, red “bubble” – oxygen, grey “bubble” – carbon, light grey “bubble” – hydrogen.

5. EXPERIMENTAL PART

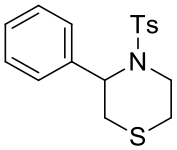
Reagents and starting material were received from commercial suppliers. Some styrene, stilbene derivatives and acetophenones **I** were prepared in the *OrentasGroup*. Preparation of 2,6-ditosyl-1,5,2,6-dithiadiazocane was reported by Orentas *et al*. [43], other cyclic sulfenamides were made in the group and are not specified in this thesis. The synthesis I made are showed below. All moisture sensitive reactions were carried out under an atmosphere of dry argon using oven-dried glassware. DCE, DCM and DMF were distilled from calcium hydride. THF and toluene were distilled from sodium/benzophenone. Reactions were monitored by TLC carried out on 0.25 mm Merck silica gel plates (60F-254). Visualization was accomplished with UV (254 nm), potassium permanganate, ninhydrin, or vanillin. Column chromatography was performed using Merck silica 60 (40−63 μm particle size). Melting points were recorded with a Gallenkamp apparatus in open capillary tubes and are not corrected. Infrared spectra were recorded on a FTIR spectrometer equipped with a diamond ATR unit. ^{1}H and ^{13}C spectra were recorded on Bruker 400 MHz spectrometer, relative to TMS using the residual solvent peaks at δ= 7.27 (^{1}H NMR) and 77.06 (^{13}C NMR) ppm in $CDCl_3$. Chemical shifts are reported in ppm, and multiplicities are indicated by br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and combinations thereof. High resolution mass spectra (HRMS) were recorded on Bruker Daltonics microTOF-II spectrometer equipped with ESI ion source

5.1 Experimental Part I



General procedure A: To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.1 mmol, 1.0 equiv.), DCE (0.05 M), corresponding styrene (2.8 eq.) and H_2O (0.01 mL, 4 equiv.) under argon atmosphere. The mixture was cooled to 0 °C and MsOH (0.020 mL, 2.7 equiv.) was added dropwise. The reaction was very slowly warmed from 0 °C to 50 °C and stirred at 50 °C till the full completion of 2,6-ditosyl-1,5,2,6-dithiadiazocane monitored by TLC. Afterwards, the reaction was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography to yield title compound **2**.

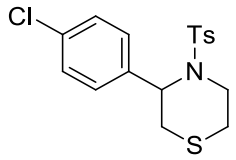
3-phenyl-4-tosylthiomorpholine (1a)



According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0519 g, 0.113 mmol, 1.0 equiv.) and styrene (0.040 mL, 0.34 mmol, 3.0 equiv.) were used. The reaction was stirred at 50 °C

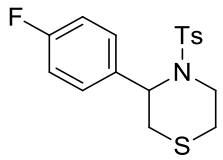
for 21.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (6:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0576 g, 76 %).
R_f = 0.40 (5:1 PE/EtOAc); m.p.: 143 – 144 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.26 (m, 7H), 5.46 (s, 1H), 4.13 – 4.00 (m, 1H), 3.31 – 3.21 (m, 1H), 3.12 (dd, *J* = 14.3, 4.0 Hz, 1H), 3.00 (d, *J* = 14.2 Hz, 1H), 2.69 (td, *J* = 13.0, 2.9 Hz, 1H), 2.44 (s, 3H), 2.21 (d, *J* = 13.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.62, 138.29, 137.38, 130.03, 128.69, 127.66, 127.43, 127.13, 54.12, 41.95, 28.58, 26.16, 21.65. FT-IR (neat) ν_{max}/cm^{-1}: 2927, 1596, 1494, 1447, 1351, 1331 (S=O), 1293, 1155 (S=O), 1089, 1045, 912, 863, 731, 689, 668 cm^{-1}.

3-(4-chlorophenyl)-4-tosylthiomorpholine (1b)



According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0520 g, 0.113 mmol, 1.0 equiv.) and 4-chlorostyrene (0.040 mL, 0.32 mmol, 2.8 equiv.) were used. The reaction was stirred at 50 °C for 18.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (15:1 → 10:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0737 g, 88 %).
R_f = 0.35 (5:1 PE/EtOAc); m.p.: 112 – 114 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.28 (m, 6H), 5.41 (t, *J* = 3.3 Hz, 1H), 4.06 (dt, *J* = 14.7, 2.9 Hz, 1H), 3.21 (ddd, *J* = 14.9, 12.5, 2.5 Hz, 1H), 3.09 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.97 – 2.90 (m, 1H), 2.67 (td, *J* = 13.1, 3.0 Hz, 1H), 2.45 (s, 3H), 2.22 (d, *J* = 14.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.86, 138.19, 136.03, 133.48, 130.14, 129.27, 128.88, 127.14, 53.66, 41.97, 28.54, 26.18, 21.71. FT-IR (neat) ν_{max}/cm^{-1}: 2925, 2915, 1724, 1597, 1494, 1424, 1328 (S=O), 1289, 1156 (S=O), 1092, 1057, 927, 875, 813, 709, 697 cm^{-1}.

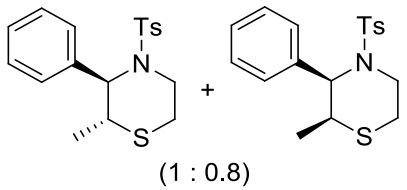
3-(4-fluorophenyl)-4-tosylthiomorpholine (1c)



According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0520 g, 0.113 mmol, 1.0 equiv.) and 4-fluorostyrene (0.040 mL, 0.32 mmol, 2.8 equiv.) were used. The reaction was stirred at 50 °C for 18.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (15:1 → 10:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0615 g, 77 %).
R_f = 0.40 (5:1 PE/EtOAc); m.p.: 81 – 82 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.02 (t, *J* = 8.7 Hz, 2H), 5.41 (s, 1H), 4.06 (dt, *J* = 14.7, 2.8 Hz, 1H), 3.22 (ddd, *J* = 14.8, 12.5, 2.5 Hz, 1H), 3.10 (dd, *J*

= 14.6, 3.6 Hz, 1H), 2.93 (d, *J* = 14.3 Hz, 1H), 2.67 (td, *J* = 13.5, 3.6 Hz, 1H), 2.45 (s, 3H), 2.23 (d, *J* = 13.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.15 (d, *J* = 246.6 Hz), 143.80, 138.24, 133.18 (d, *J* = 3.3 Hz), 130.12, 129.60 (d, *J* = 8.0 Hz), 127.14, 115.56 (d, *J* = 21.4 Hz), 53.55, 41.88, 28.65, 26.17, 21.70. FT-IR (neat) ν_{max}/cm^{-1}: 2912, 1740, 1597, 1507, 1343 (S=O), 1230, 1153 (S=O), 1093, 922, 874, 729 cm^{-1}.

(2*R,3*R**)-2-Methyl-3-phenyl-4-tosylthiomorpholine (1da) and (2*S**,3*R**)-2-methyl-3-phenyl-4-tosylthiomorpholine (1db)**

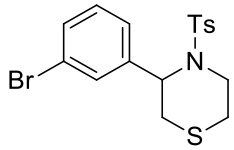


According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0515 g, 0.112 mmol, 1.0 equiv.) and *β*-methylstyrene (0.050 mL, 0.36 mmol, 3.2 equiv.) were used. The reaction was stirred at 50 °C for 2 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (6:1 PE/EtOAc) to provide mixture of compounds **2da** and **2db** as a white solid (0.0743 g, 95 %).

R_f = 0.35 (5:1 PE/EtOAc); m.p.: 76 – 78 °C

^{1}H NMR (400 MHz, $CDCl_3$, **2da**) δ 7.71 – 7.66 (m, 2H), 7.39 – 7.16 (m, 5H), 7.05 (d, *J* = 8.1 Hz, 2H), 5.16 (d, *J* = 4.3 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.51 – 3.43 (m, 1H), 3.37 – 3.22 (m, 1H), 3.09 – 2.95 (m, 1H), 2.63 (dt, *J* = 13.4, 2.4 Hz, 1H), 2.32 (s, 3H), 1.01 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, **2da**): δ 143.01, 138.77, 136.14, 130.49, 129.36, 128.00, 127.78, 127.16, 59.82, 40.93, 39.63, 28.85, 21.51, 18.59. ^{1}H NMR (400 MHz, $CDCl_3$, **2db**): δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.38 – 7.17 (m, 7H), 5.20 (d, *J* = 3.2 Hz, 1H), 3.95 (tt, *J* = 13.6, 3.1 Hz, 1H), 3.37 – 3.22 (m, 2H), 3.09 – 2.95 (m, 1H), 2.40 (s, 3H), 2.32 – 2.26 (m, 1H), 1.54 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, **2db**): δ 143.30, 137.92, 137.00, 129.62, 128.56, 128.10, 127.49, 127.18, 61.48, 41.55, 35.47, 22.66, 21.59, 20.77. FT-IR (neat) ν_{max}/cm^{-1}: 2973, 2930, 1599, 1448, 1326 (S=O), 1306, 1151 (S=O), 1085, 1047, 894, 770, 693, 668 cm^{-1}.

3-(3-bromophenyl)-4-tosylthiomorpholine (1e)



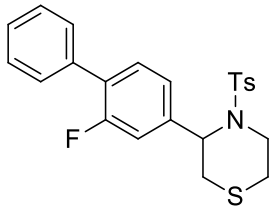
According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0518 g, 0.113 mmol, 1.0 equiv.) and 3-bromostyrene (0.045 mL, 0.33 mmol, 3.0 equiv.) were used. The reaction was stirred at 50 °C for 19 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (7:1 PE/EtOAc) to provide desired compound as a white solid (0.0374 g, 40 %).

R_f = 0.41 (5:1 PE/EtOAc); m.p.: 112 – 113 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.27 (m, 5H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.40 (s, 1H), 4.09 (d, *J* = 14.7 Hz, 1H), 3.27 – 3.18 (m, 1H), 3.10 (dd, *J* = 14.4, 4.0 Hz, 1H),

2.93 (d, *J* = 14.2 Hz, 1H), 2.70 (td, *J* = 12.9, 2.8 Hz, 1H), 2.44 (s, 3H), 2.29 – 2.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.90, 139.99, 138.01, 130.86, 130.62, 130.24, 130.14, 127.08, 126.43, 122.94, 53.75, 42.08, 28.70, 26.27, 21.69. FT-IR (neat) ν_{max}/cm^{-1}: 2921, 1596, 1565, 1337 (S=O), 1288, 1152 (S=O), 1091, 1046, 809, 756, 709, 687, 659 cm^{-1}.

3-(2-fluoro-[1,1'-biphenyl]-4-yl)-4-tosylthiomorpholine (1f)

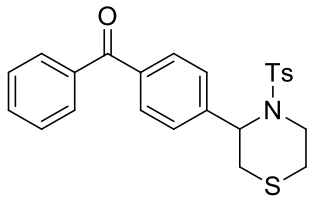


According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0507 g, 0.110 mmol, 1.0 equiv.) and 2-fluoro-4-vinyl-1,1'-biphenyl (0.0678 g, 0.332 mmol, 3.0 equiv.) were used. The reaction was stirred at 50 °C for 3 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (8:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0533 g, 56 %).

R_f = 0.53 (5:1 PE/EtOAc); m.p.: 127 – 128 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.48 – 7.32 (m, 6H), 7.17 (dd, *J* = 20.5, 10.1 Hz, 2H), 5.47 (s, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.37 – 3.25 (m, 1H), 3.14 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.98 (d, *J* = 14.3 Hz, 1H), 2.71 (td, *J* = 13.0, 3.0 Hz, 1H), 2.44 (s, 3H), 2.30 – 2.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.99 (d, *J* = 248.2 Hz), 143.86, 139.20 (d, *J* = 7.2 Hz), 138.12, 135.41 (d, *J* = 1.4 Hz), 130.94 (d, *J* = 3.9 Hz), 130.12, 129.04 (d, *J* = 3.0 Hz), 128.58, 128.11 (d, *J* = 13.6 Hz), 127.87, 127.13, 123.62 (d, *J* = 3.4 Hz), 115.68 (d, *J* = 24.7 Hz), 53.72, 42.10, 28.66, 26.21, 21.66. FT-IR (neat) ν_{max}/cm^{-1}: 2917, 1736, 1326 (S=O), 1288, 1154 (S=O), 1093, 1057, 899, 768, 720 cm^{-1}.

Phenyl(4-(4-tosylthiomorpholin-3-yl)phenyl)methanone (1g)



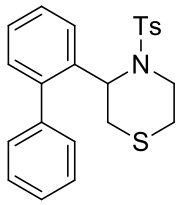
According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0510 g, 0.111 mmol, 1.0 equiv.) and phenyl(4-vinylphenyl)methanone (0.0712 g, 0.342 mmol, 3.0 equiv.) were used. The reaction was stirred at 50 °C for 18 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (4:1 PE/EtOAc) to provide desired compound as a white solid (0.0493 g, 51 %).

R_f = 0.31 (3:1 PE/EtOAc); m.p.: 114 – 115 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.72 (m, 6H), 7.61 – 7.56 (m, 1H), 7.52 – 7.44 (m, 4H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.52 (s, 1H), 4.11 (dt, *J* = 14.4, 2.5 Hz, 1H), 3.27 (ddd, *J* = 14.8, 12.6, 2.4 Hz, 1H), 3.15 (dd, *J* = 14.3, 4.0 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.71 (td, *J* = 13.0, 3.0 Hz, 1H), 2.44 (s, 3H), 2.30 – 2.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.24, 143.91, 142.38, 138.11, 137.60,

136.69, 132.62, 130.50, 130.15, 130.13, 128.43, 127.69, 127.15, 54.22, 42.20, 28.66, 26.22, 21.70. FT-IR (neat) ν_{max}/cm^{-1}: 2922, 1652 (C=O), 1597, 1321 (S=O), 1279, 1152 (S=O), 1092, 1053, 921, 880, 700, 665 cm^{-1}.

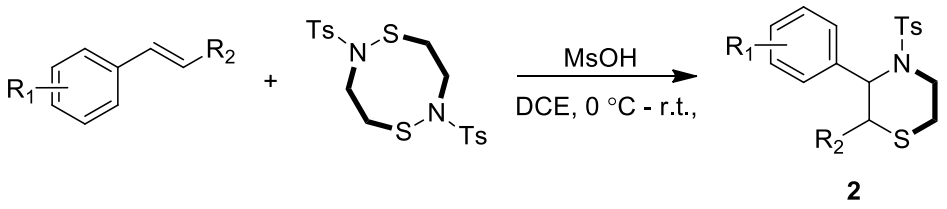
3-([1,1'-biphenyl]-2-yl)-4-tosylthiomorpholine (1h)



According to general procedure A, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0526 g, 0.114 mmol, 1.0 equiv.) and 2-vinyl-1,1'-biphenyl (0.065 mL, 0.370 mmol, 3.2 equiv.) were used. The reaction was stirred at 50 °C for 21 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 - 9:1 PE/EtOAc) to provide desired compound as a white solid (0.0283 g, 30 %).

R_f = 0.33 (10:1 PE/EtOAc); m.p.: 155 – 156 °C

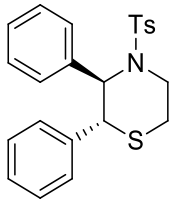
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.37 (m, 8H), 7.32 – 7.22 (m, 2H), 7.20 – 7.13 (m, 3H), 5.46 (t, *J* = 5.8 Hz, 1H), 4.17 – 4.07 (m, 1H), 3.69 (ddd, *J* = 14.8, 10.8, 4.4 Hz, 1H), 2.57 (dtd, *J* = 27.9, 14.2, 7.9 Hz, 4H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.34, 141.12, 140.57, 138.48, 137.34, 130.74, 129.56, 129.10, 128.64, 127.52, 127.43, 127.33, 127.24, 127.23, 55.53, 42.38, 31.23, 25.96, 21.62. FT-IR (neat) ν_{max}/cm^{-1}: 3055, 2922, 2852, 1597, 1475, 1442, 1339 (S=O), 1157 (S=O), 1092, 918, 758, 703 cm^{-1}.



2

General procedure B: To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.1 mmol), dry DCE (2 mL) and corresponding styrene (3.0 equiv.) under argon atmosphere. The reaction mixture was cooled to 0 °C and MsOH (0.02 mL, 2.8 equiv.) was added dropwise. After certain time, the ice bath was removed and the reaction was stirred at r.t. till the full completion of 2,6-ditosyl-1,5,2,6-dithiadiazocane monitored by TLC. Afterwards, the reaction was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography to yield title compound **1**.

(2*R,3*R**)-2,3-diphenyl-4-tosylthiomorpholine (2a)**



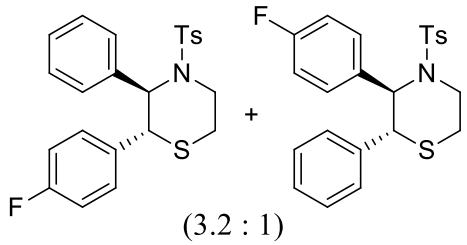
According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0511 g, 0.111 mmol, 1.0 equiv.) and *trans*-stilbene (0.0648 g, 0.351 mmol, 3.1 equiv.) were used. The reaction was stirred at 0 °C for 2.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (9:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0782 g, 86 %).

R_f = 0.42 (5:1 PE/EtOAc); m.p.: 94 – 95 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 6.7 Hz, 2H), 7.32 – 7.22 (m, 7H), 7.21 – 7.15 (m, 3H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.65 (d, *J* = 6.4 Hz, 1H), 4.31 (d, *J* = 6.3 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.62 (ddd, *J* = 14.6, 12.0, 3.7 Hz, 1H), 2.91 (td, *J* = 12.2, 5.0 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)*: δ 143.02, 139.49, 139.41, 137.40, 129.33, 128.77, 128.55, 128.36, 127.74, 127.69, 127.25, 63.42, 46.38, 41.30, 25.75, 21.58. FT-IR (neat) ν_{max}/cm^{-1}: 2956, 2920, 2855, 1723, 1492, 1450, 1336 (S=O), 1153 (S=O), 1088, 937, 754, 693, 659 cm^{-1}.

One aromatic ^{13}C has the same chemical shift as another one.

(2*R,3*R**)-2-(4-fluorophenyl)-3-phenyl-4-tosylthiomorpholine (2b)** (major)



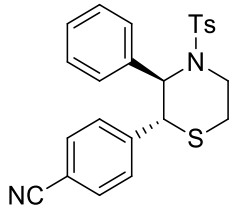
(3.2 : 1)

According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0616 g, 0.134 mmol, 1.0 equiv.) and (*E*)-1-fluoro-4-styrylbenzene (0.080 g, 0.40 mmol, 3.0 equiv.) were used. The ice bath was removed after 25 min and the reaction was stirred at r.t. for 2 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 → 6:1 PE/EtOAc) to provide desired compound as a yellowish oil (0.104 g, 91 %). Mixture of regioisomers with ratio 3.2 : 1.

R_f = 0.51 (5:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$, rr = 3.2:1, major isomer): δ 7.40 – 7.33 (m, 2H), 7.32 – 7.24 (m, 4H), 7.23 – 7.14 (m, 3H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.84 (t, *J* = 8.7 Hz, 2H), 5.57 (d, *J* = 6.9 Hz, 1H), 4.26 (d, *J* = 6.8 Hz, 1H), 4.03 (ddd, *J* = 14.5, 4.9, 2.8 Hz, 1H), 3.69 – 3.57 (m, 1H), 2.90 (td, *J* = 12.1, 5.1 Hz, 1H), 2.72 (dt, *J* = 12.6, 3.3 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, rr = 3.2:1, major isomer): δ 162.20 (d, *J* = 246.7 Hz), 143.24, 139.07, 137.41, 135.38 (d, *J* = 3.3 Hz), 129.53 (d, *J* = 8.1 Hz), 129.38, 128.82, 128.53, 127.84, 127.21, 115.13 (d, *J* = 21.4 Hz), 63.17, 46.63, 41.42, 25.98, 21.58. FT-IR (neat) ν_{max}/cm^{-1}: 2925, 1738, 1600, 1508, 1336 (S=O), 1304, 1154 (S=O), 1091, 902, 736, 660 cm^{-1}.

4-((2*R,3*R**)-3-phenyl-4-tosylthiomorpholin-2-yl)benzonitrile (2c)**

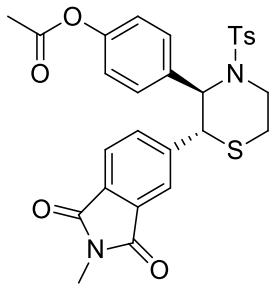


According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0503 g, 0.110 mmol, 1.0 equiv.) and (*E*)-4-styrylbenzonitrile (0.0683 g, 0.333 mmol, 3.0 equiv.) were used. The ice bath was removed after 40 min and the reaction was stirred at r.t. for 5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (8:1 → 5:1 PE/EtOAc) to provide desired compound as a white solid (0.070 g, 73 %).

R_f = 0.24 (5:1 PE/EtOAc); m.p.: 129 – 130 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.53 (m, 4H), 7.29 – 7.16 (m, 7H), 7.04 (d, *J* = 8.1 Hz, 2H), 5.61 (d, *J* = 5.3 Hz, 1H), 4.30 (d, *J* = 5.4 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.60 (ddd, *J* = 14.4, 11.9, 3.4 Hz, 1H), 2.91 (td, *J* = 12.4, 4.6 Hz, 1H), 2.68 (dt, *J* = 12.8, 2.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.51, 143.31, 138.63, 137.08, 132.42, 129.36, 129.27, 128.51, 128.04, 127.87, 127.03, 118.65, 111.44, 62.02, 45.89, 41.54, 25.26, 21.54. FT-IR (neat) ν_{max}/cm^{-1}: 2927, 2222 (C≡N), 1605, 1333 (S=O), 1155 (S=O), 1092, 1056, 910, 718, 669 cm^{-1}.

4-((2*R,3*R**)-2-(2-methyl-1,3-dioxoisoindolin-5-yl)-4-tosylthiomorpholin-3-yl)phenyl acetate (2d)**



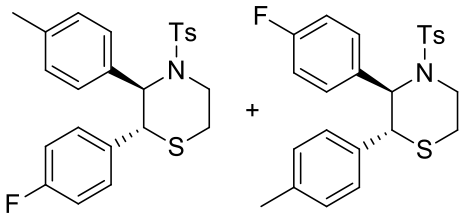
According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0511 g, 0.111 mmol, 1.0 equiv.) and (*E*)-4-(2-(2-methyl-1,3-dioxoisoindolin-5-yl)vinyl)phenyl acetate (0.106 g, 0.332 mmol, 3.0 equiv.) were used. The ice bath was removed immediately after addition and the reaction was stirred at r.t. for 3.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (50:1 → 20:1 DCM/EtOAc) to provide desired compound as a yellow solid (0.090 g, 73 %).

R_f = 0.31 (100:1 $CHCl_3$/MeOH); m.p.: 191 – 192 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.76 (s, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.60 (d, *J* = 5.3 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.07 (dt, *J* = 14.1, 4.0 Hz, 1H), 3.59 (ddd, *J* = 14.5, 11.7, 3.3 Hz, 1H), 3.18 (s, 3H), 2.95 (td, *J* = 12.4, 11.9, 4.5 Hz, 1H), 2.72 (dt, *J* = 12.6, 2.9 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.19, 168.08, 168.07, 150.46, 147.11, 143.43, 137.20, 135.95, 133.85, 132.86, 131.40, 129.54, 129.17, 126.94, 123.52, 123.43, 121.70, 61.94, 45.69, 41.56, 25.51, 24.15, 21.54,

21.26. FT-IR (neat) ν_{max}/cm^{-1}: 2954, 2925, 2855, 1768 (C=O), 1737 (C=O), 1714 (C=O), 1506, 1379, 1336, 1224, 1160 (S=O), 1014, 908, 741, 695 cm^{-1}.

(2*R,3*R**)-2-(4-fluorophenyl)-3-(p-tolyl)-4-tosylthiomorpholine (2e)** (major)



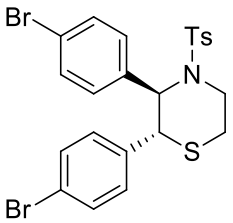
(3.0 : 1)

According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0503 g, 0.110 mmol, 1.0 equiv.) and (*E*)-1-fluoro-4-(4-methylstyryl)benzene (0.0698 g, 0.329 mmol, 3.0 equiv.) were used. The reaction was stirred at 0 °C for 1.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.0935 g, 96 %). Mixture of regioisomers with ratio 3.0 : 1.

R_f = 0.42 (5:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$, rr = 3.0:1, major isomer) δ 7.42 – 7.13 (m, 5H), 7.12 – 6.91 (m, 7H), 5.61 – 5.43 (m, 1H), 4.27 (d, *J* = 5.6 Hz, 1H), 4.01 (d, *J* = 13.1 Hz, 1H), 3.59 (t, *J* = 11.5 Hz, 1H), 2.94 – 2.80 (m, 1H), 2.68 (t, *J* = 13.3 Hz, 1H), 2.33 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, rr = 3.0:1, major isomer): δ 162.08 (d, *J* = 246.6 Hz), 142.98, 137.45 (d, *J* = 3.6 Hz), 136.13, 135.35, 135.32, 130.11 (d, *J* = 8.1 Hz), 129.23, 128.98, 127.63, 127.08, 115.48 (d, *J* = 21.4 Hz), 63.31, 45.55, 41.31, 25.72, 21.50, 21.09. FT-IR (neat) ν_{max}/cm^{-1}: 2927, 1740, 1601, 1508, 1334 (S=O), 1224, 1154 (S=O), 1092, 930, 740, 660 cm^{-1}.

(2*R,3*R**)-2,3-bis(4-bromophenyl)-4-tosylthiomorpholine (2f)**



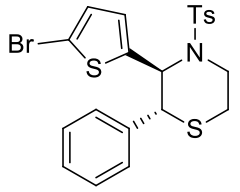
According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0512 g, 0.111 mmol, 1.0 equiv.) and 4,4'- dibromostilbene (0.116 g, 0.334 mmol, 3.0 equiv.) were used. The ice bath was removed after 30 min and the reaction was stirred at r.t. for 3 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as a white solid (0.0988 g, 78 %).

R_f = 0.36 (5:1 PE/EtOAc); m.p.: 162 – 163 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.22 (m, 6H), 7.09 (t, *J* = 8.8 Hz, 4H), 5.49 (d, *J* = 6.1 Hz, 1H), 4.21 (d, *J* = 6.2 Hz, 1H), 4.05 (ddd, *J* = 14.3, 4.5, 3.1 Hz, 1H), 3.58 (ddd, *J* = 14.6, 11.7, 3.6 Hz, 1H), 2.87 (td, *J* = 12.2, 4.8 Hz, 1H), 2.68 (dt, *J* = 12.7, 3.1 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.43, 138.22, 138.05, 137.29, 131.92, 131.50,

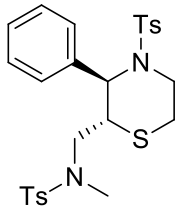
130.17, 129.60, 129.45, 126.98, 121.93, 121.82, 62.72, 45.43, 41.59, 25.64, 21.63. FT-IR (neat) ν_{max}/cm^{-1}: 2927, 1740, 1597, 1490, 1329 (S=O), 1290, 1148 (S=O), 1008, 905, 893, 796, 694, 666 cm^{-1}.

(2*R,3*S**)-3-(5-bromothiophen-2-yl)-2-phenyl-4-tosylthiomorpholine (2g)**



According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0507 g, 0.110 mmol, 1.0 equiv.) and (*E*)-2-bromo-5-styrylthiophene (0.0886 g, 0.334 mmol, 3.0 equiv.) were used. The reaction was stirred at 0 °C for 30 min. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 PE/EtOAc) to provide desired compound as brownish oil (0.0335 g, 31 %).
R_f = 0.19 (10:1 PE/EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.15 (m, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 – 6.98 (m, 2H), 6.67 (d, *J* = 3.6 Hz, 1H), 6.32 (d, *J* = 3.6 Hz, 1H), 5.75 (d, *J* = 3.2 Hz, 1H), 4.46 (d, *J* = 3.2 Hz, 1H), 4.17 – 4.03 (m, 1H), 3.27 – 3.03 (m, 2H), 2.76 (d, *J* = 13.5 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.59, 137.38, 136.83, 135.79, 130.30, 129.43, 128.51, 128.05, 127.99, 127.84, 127.20, 113.31, 59.53, 51.44, 42.11, 29.29, 21.59. FT-IR (neat) ν_{max}/cm^{-1}: 2925, 2901, 1597, 1434, 1348 (S=O), 1286, 1163 (S=O), 1087, 893, 800, 702, 665, 607 cm^{-1}.

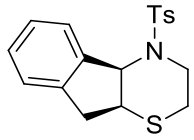
***N*,4-Dimethyl-*N*-(((2*R**,3*R**)-3-phenyl-4-tosylthiomorpholin-2-yl)methyl)benzenesulfonamide (2h)**



According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0514 g, 0.112 mmol, 1.0 equiv.) and *N*-cinnamyl-*N*,4-dimethylbenzenesulfonamide (0.102 g, 0.339 mmol, 3.0 equiv.) were used. The ice bath was removed after 20 min and the reaction was stirred at r.t. for 4.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (3:1 PE/EtOAc) to provide desired compound as a white solid (0.0578 g, 49 %).
R_f = 0.27 (3:1 PE/EtOAc); m.p.: 138 – 139 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.27 (m, 2H), 7.25 – 7.21 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 1H), 3.92 (dt, *J* = 13.5, 2.6 Hz, 1H), 3.59 – 3.48 (m, 2H), 3.42 – 3.34 (m, 1H), 3.29 (td, *J* = 14.0, 13.3, 2.4 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.95 (s, 3H), 2.45 (s, 3H), 2.38 (s, 3H), 2.25 (d, *J* = 13.7 Hz, 1H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 143.74, 143.60, 137.80, 137.01, 133.89, 129.88, 129.68, 128.51, 127.95, 127.77, 127.56, 127.28, 55.93, 53.51, 41.65, 41.58, 38.24, 22.37, 21.64, 21.57. FT-IR (neat) ν_{max}/cm^{-1}: 2922, 1740, 1598, 1496, 1446, 1331 (S=O), 1157 (S=O), 1094, 1059, 925, 887, 772, 728, 653 cm^{-1}.

(4a*R,9a*S**)-4-Tosyl-2,3,4,4a,9,9a-hexahydroindeno[2,1-b][1,4]thiazine (2i)**

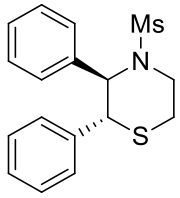


To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0515 g, 0.112 mmol, 1.0 equiv.), dry DCE (2 mL) and indene (0.040 mL,0.34 mmol, 3.0 equiv.) under argon atmosphere. The mixture was cooled to 0 °C and $TsOH{\cdot}H_2O$ (0.0742 g, 0.382 mmol, 3.4 equiv.) was added in one portion. The reaction was very slowly warmed to 50 °C and stirred at 50 °C for 19 h. Afterwards, the reaction mixture was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography (10:1 PE/EtOAc) to yield title compound as a yellowish solid (0.0305 g, 39 %).

R_f = 0.26 (10:1 PE/EtOAc); m.p.: 140 – 141 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.19 (m, 3H), 7.02 (d, *J* = 6.9 Hz, 1H), 5.65 (d, *J* = 4.8 Hz, 1H), 4.17 (d, *J* = 14.4 Hz, 1H), 3.79 (t, *J* = 5.3 Hz, 1H), 3.25 – 3.13 (m, 2H), 2.72 – 2.58 (m, 2H), 2.49 (s, 3H), 2.11 (d, *J* = 13.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.81, 140.29, 138.43, 138.30, 130.12, 128.12, 127.28, 127.22, 125.76, 124.01, 60.99, 41.12, 39.57, 37.28, 25.29, 21.71. FT-IR (neat) ν_{max}/cm^{-1}: 2915, 2850, 1725, 1596, 1437, 1342 (S=O), 1285, 1158 (S=O), 1092, 929, 809, 756, 658 cm^{-1}.

(2*R,3*R**)-4-(methylsulfonyl)-2,3-diphenylthiomorpholine (2j)**



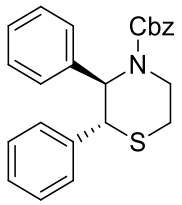
According to general procedure B, 2,6-bis(methylsulfonyl)-1,5,2,6-dithiadiazocane (0.047 g, 0.15 mmol, 1.0 equiv.) and *trans*-stilbene (0.083 g, 0.44 mmol, 2.9 equiv.) were used. The reaction was stirred at r.t. for 3.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.087 g, 85 %).

R_f = 0.39 (3:1 PE/EtOAc); m.p.: 82 – 83 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 13.3, 7.3 Hz, 4H), 7.37 – 7.24 (m, 6H), 5.57 (d, *J* = 5.8 Hz, 1H), 4.40 (d, *J* = 5.8 Hz, 1H), 4.08 (ddd, *J* = 14.2, 4.5, 2.8 Hz, 1H), 3.65 (ddd, *J* = 14.6, 12.0, 3.5 Hz, 1H), 3.09 (td, *J* = 12.3, 4.9 Hz, 1H), 2.78 (dt, *J* = 12.8, 3.0 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.53, 139.00, 128.86, 128.78, 128.46, 128.24, 127.93, 127.82, 62.86, 45.41,

41.21, 40.38, 25.86. FT-IR (neat) ν_{max}/cm^{-1}: 2930, 1723, 1494, 1450, 1325 (S=O), 1144 (S=O), 1059, 921, 902,877, 778, 749, 733, 698 cm^{-1}.

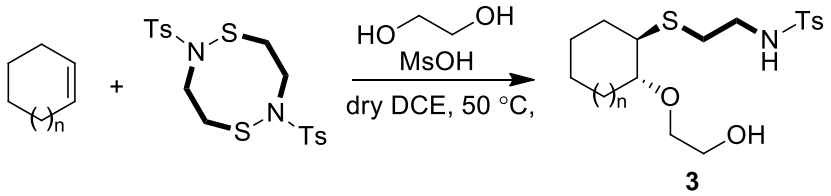
(2*R,3*R**)-Benzyl 2,3-diphenylthiomorpholine-4-carboxylate (2k)**



According to general procedure B, dibenzyl 1,5,2,6-dithiadiazocane-2,6-dicarboxylate (0.0442 g, 0.105 mmol, 1.0 equiv.) and *trans*-stilbene (0.0595 g, 0.317 mmol, 3.0 equiv.) were used. The ice bath was removed after 25 min and the reaction was stirred at r.t. for 25 h.. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 → 9:1 PE/EtOAc) to provide desired compound as yellowish solid (0.0356 g, 43 %).

R_f = 0.34 (10:1 PE/EtOAc) m.p.: 89 – 90 °C

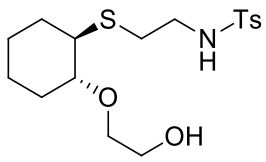
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.35 (m, 2H), 7.34 – 7.23 (m, 9H), 7.22 – 7.13 (m, 4H), 5.70 (d, *J* = 7.1 Hz, 1H), 5.20 – 5.07 (m, 2H), 4.58 – 4.48 (m, 1H), 4.42 (d, *J* = 7.1 Hz, 1H), 3.50 (ddd, *J* = 14.1, 12.5, 4.0 Hz, 1H), 3.08 (td, *J* = 12.2, 5.3 Hz, 1H), 2.84 – 2.73 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 156.20, 140.29, 139.66, 136.53, 128.65, 128.52, 128.51, 128.48, 128.04, 127.82, 127.71, 127.50, 126.90, 67.57, 62.20, 45.59, 39.50, 26.00. FT-IR (neat) ν_{max}/cm^{-1}: 2945, 2930, 1695 (C=O), 1451, 1413, 1289, 1219, 1166, 730, 693 cm^{-1}.



3

General procedure C: To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2,6-ditosyl-1,5,2,6-dithiadiazocane (1.0 equiv.), DCE (0.05 M), alkene (2.2 - 2.5 equiv.), ethylene glycol (4.8 equiv.) and MsOH (2.4 - 2.7 equiv.) at r.t. under argon atmosphere. The reaction was stirred at 50 °C till the full completion of 2,6-ditosyl-1,5,2,6-dithiadiazocane monitored by TLC. Afterwards, the reaction was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography to yield title compound **3**.

***N*-(2-(((1*R**,2*R**)-2-(2-hydroxyethoxy)cyclohexyl)thio)ethyl)-4-methylbenzenesulfonamide (3a)**



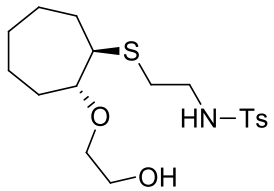
According to general procedure C, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.102 g, 0.224 mmol, 1.0 equiv.), cyclohexene (0.050 mL, 0.49 mmol, 2.2 equiv.), ethylene glycol (0.060 mL, 1.1 mmol, 4.8 equiv.) and MsOH (0.035 mL, 0.54 mmol, 2.4 equiv.) were used. The reaction was stirred at 50 °C

for 23 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (1:1 PE/EtOAc) to provide desired compound as colourless oil (0.111 g, 66 %).

R_f = 0.33 (1:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.72 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.04 (t, *J* = 6.1 Hz, 1H), 3.81 – 3.68 (m, 3H), 3.55 – 3.48 (m, 1H), 3.27 – 3.10 (m, 2H), 3.09 – 3.03 (m, 1H), 2.88 (t, *J* = 5.6 Hz, 1H), 2.76 – 2.61 (m, 2H), 2.44 – 2.37 (m, 4H), 2.19 – 2.10 (m, 1H), 2.03 – 1.95 (m, 1H), 1.77 – 1.63 (m, 2H), 1.36 – 1.12 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.49, 137.50, 129.85, 127.22, 82.39, 70.27, 62.00, 50.29, 43.05, 33.97, 32.23, 31.89, 26.06, 24.18, 21.65. FT-IR (neat) ν_{max}/cm^{-1}: 3485 (O-H), 3281 (N-H), 2931, 2859, 1598, 1447, 1324 (S=O), 1154 (S=O), 1092, 1065, 814, 658 cm^{-1}.

_N_-(2-(((1_R_*,2_R_*)-2-(2-hydroxyethoxy)cycloheptyl)thio)ethyl)-4-methylbenzenesulfonamide (3b)

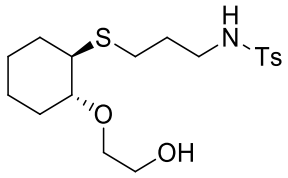


According to general procedure C, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0512 g, 0.111 mmol, 1.0 equiv.), cycloheptene (0.035 mL, 0.28 mmol, 2.5 equiv.), ethylene glycol (0.030 mL, 0.54 mmol, 4.8 equiv.) and MsOH (0.020 mL, 0.31 mmol, 2.7 equiv.) were used. The reaction was stirred at 50 ºC for 42 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (1:1 PE/EtOAc) to provide desired compound as colourless oil (0.0389 g, 45 %).

R_f = 0.45 (1:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.99 (t, *J* = 6.2 Hz, 1H), 3.82 – 3.66 (m, 3H), 3.43 (ddt, *J* = 8.8, 6.0, 2.7 Hz, 1H), 3.27 (dt, *J* = 8.5, 5.0 Hz, 1H), 3.16 (qd, *J* = 6.2, 2.2 Hz, 2H), 3.04 – 2.86 (m, 1H), 2.68 – 2.57 (m, 3H), 2.41 (s, 3H), 1.89 – 1.79 (m, 1H), 1.79 – 1.70 (m, 2H), 1.69 – 1.50 (m, 4H), 1.47 – 1.30 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.47, 137.38, 129.83, 127.20, 85.20, 70.45, 61.93, 52.24, 42.69, 32.62, 31.58, 30.57, 28.99, 26.41, 22.65, 21.62. FT-IR (neat) ν_{max}/cm^{-1}: 3481 (O-H), 3259 (N-H), 2927, 2858, 1598, 1454, 1323 (S=O), 1155 (S=O), 1093, 1062, 887, 814, 658 cm^{-1}.

_N_-(3-(((1_R_*,2_R_*)-2-(2-hydroxyethoxy)cyclohexyl)thio)propyl)-4-methylbenzenesulfonamide (3c)

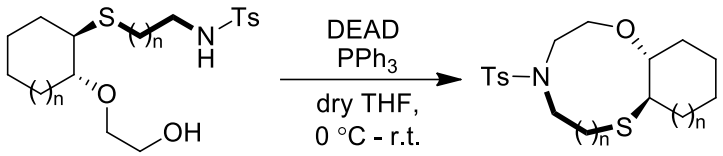


According to general procedure C, 2-tosylisothiazolidine (0.0759 g, 0.312 mmol, 1.0 equiv.), cyclohexene (0.035 mL, 0.34 mmol, 1.1 equiv.), ethylene glycol (0.045 mL, 0.80 mmol, 2.5 equiv.)

and MsOH (0.025 mL, 0.31 mmol, 1.2 equiv.) were used. The reaction was stirred at r.t. for 1 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (1:1 PE/EtOAc) to provide desired compound as colourless oil (0.0714 g, 59 %).

R_f = 0.36 (1:1 PE/EtOAc)

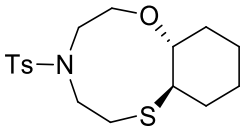
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.35 (t, *J* = 5.6 Hz, 1H), 3.80 – 3.70 (m, 3H), 3.54 – 3.47 (m, 1H), 3.15 – 3.07 (m, 1H), 3.07 – 2.93 (m, 3H), 2.69 (t, *J* = 6.9 Hz, 2H), 2.52 (ddd, *J* = 11.6, 9.7, 4.1 Hz, 1H), 2.42 (s, 3H), 2.17 – 2.07 (m, 1H), 2.06 – 1.98 (m, 1H), 1.80 – 1.65 (m, 4H), 1.37 – 1.17 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.41, 137.26, 129.82, 127.21, 82.64, 70.27, 62.17, 49.45, 42.14, 32.71, 31.86, 29.38, 28.55, 25.87, 24.16, 21.64. FT-IR (neat) ν_{max}/cm^{-1}: 3449 (O-H), 3274 (N-H), 2927, 2858, 1598, 1447, 1323 (S=O), 1155 (S=O), 1093, 1062, 954, 814, 661 cm^{-1}.



3 **4**

General procedure D: Compound **3** (1.0 equiv.) was dissolved in dry THF (0.03 M) under argon atmosphere. The solution was cooled to 0 °C and PPh_3 (1.5 equiv.) followed by dropwise addition of DEAD (1.5 equiv.). After certain time, the ice bath was removed and the reaction was stirred at r.t. till the full completion of compound **3** monitored by TLC. Afterwards, the reaction was diluted with DCM, concentrated on silica gel and purified by column chromatography to yield title compound **4**.

(7a*R,11a*R**)-4-tosyldecahydro-2H-benzo[b][1,4,7]oxathiazonine (4a)**

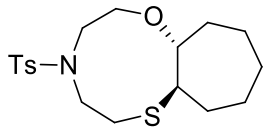


According to general procedure D, compound **3a** (0.1074 g, 0.288 mmol, 1.0 equiv.), PPh_3 (0.1194 g, 0.455 mmol, 1.5 equiv.) and DEAD (0.075 mL, 0.43 mmol, 1.5 equiv.) were used. The ice bath was removed immediate after addition and the reaction was stirred at r.t. for 3 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (10:1 → 5:1 PE/EtOAc) to provide desired compound as a white solid (0.0767 g, 75 %).

R_f = 0.31 (5:1 PE/EtOAc); m.p.: 159 – 160 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.07 – 3.92 (m, 2H), 3.64 – 3.50 (m, 2H), 3.30 – 3.17 (m, 2H), 3.04 (t, *J* = 5.2 Hz, 2H), 2.87 (ddd, *J* = 14.6, 8.2, 4.2 Hz, 1H), 2.50 – 2.40 (m, 4H), 2.04 – 1.95 (m, 2H), 1.76 – 1.61 (m, 2H), 1.35 – 1.12 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.39, 135.95, 129.78, 127.34, 87.29, 71.90, 51.41, 51.25, 51.04, 33.94, 33.80, 32.80, 26.28, 24.70, 21.60. FT-IR (neat) ν_{max}/cm^{-1}: 2918, 2855, 1725, 1597, 1446, 1316 (S=O), 1149 (S=O), 1122 (C-O), 1052, 948, 812, 709, 676 cm^{-1}.

(7a*R,12a*R**)-4-tosyldodecahydrocyclohepta[b][1,4,7]oxathiazonine (4b)**

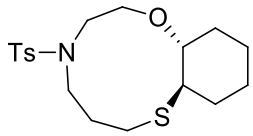


According to general procedure D, compound **3b** (0.0354 g, 0.0913 mmol, 1.0 equiv.), PPh_3 (0.0522 g, 0.140 mmol, 1.5 equiv.) and DEAD (0.025 mL, 0.14 mmol, 1.5 equiv.) were used. The ice bath was removed after 30 min and the reaction was stirred at r.t. for 2 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as a white solid (0.0236 g, 70 %).

R_f = 0.28 (5:1 PE/EtOAc); m.p.: 134 – 135 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 3.92 – 3.84 (m, 1H), 3.83 – 3.73 (m, 2H), 3.66 – 3.59 (m, 1H), 3.45 (d, *J* = 15.0 Hz, 1H), 3.26 – 3.16 (m, 1H), 3.08 – 2.97 (m, 2H), 2.88 – 2.76 (m, 2H), 2.41 (s, 3H), 1.81 – 1.41 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.44, 135.86, 129.81, 127.40, 91.82, 69.55, 52.57, 52.43, 51.23, 33.13, 32.99, 31.54, 29.11, 27.27, 22.94, 21.62. FT-IR (neat) ν_{max}/cm^{-1}: 2926, 2852, 1444, 1329 (S=O), 1149 (S=O), 1100, 1057, 959, 908, 812, 710, 697, 674 cm^{-1}.

(8a*R,12a*R**)-4-tosyldodecahydrobenzo[b][1,4,8]oxathiazecine (4c)**

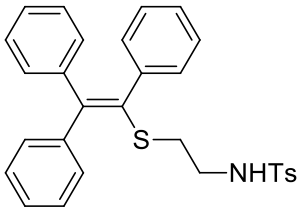


According to general procedure D, compound **3c** (0.0466 g, 0.120 mmol, 1.0 equiv.), PPh_3 (0.0701 g, 0.188 mmol, 1.5 equiv.) and DEAD (0.030 mL, 0.18 mmol, 1.5 equiv.) were used. The ice bath was removed after 30 min and the reaction was stirred at r.t. for 2.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (7:1 PE/EtOAc) to provide desired compound as a white solid (0.0226 g, 51 %).

R_f = 0.37 (5:1 PE/EtOAc); m.p.: 108 – 109 °C

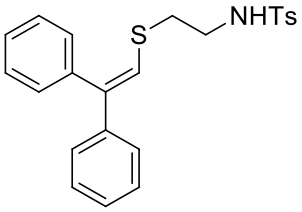
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.97 (ddd, *J* = 11.3, 5.3, 2.5 Hz, 1H), 3.63 (ddd, *J* = 11.2, 7.6, 2.4 Hz, 1H), 3.39 – 3.11 (m, 6H), 2.96 (ddd, *J* = 13.1, 6.3, 5.0 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.42 (s, 3H), 2.20 (dddd, *J* = 14.5, 11.2, 9.7, 4.9 Hz, 1H), 2.13 – 2.05 (m, 1H), 2.03 – 1.96 (m, 1H), 1.77 – 1.62 (m, 3H), 1.31 – 1.16 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.42, 135.26, 129.78, 127.55, 84.78, 68.83, 51.83, 49.56, 48.02, 33.36, 32.37, 29.63, 28.29, 26.45, 24.58, 21.63. FT-IR (neat) ν_{max}/cm^{-1}: 2945, 2924, 2855, 1740, 1461, 1336 (S=O), 1152 (S=O), 1086, 1035, 811, 715, 699 cm^{-1}.

4-Methyl-*N*-(2-((1,2,2-triphenylvinyl)thio)ethyl)benzenesulfonamide (5)



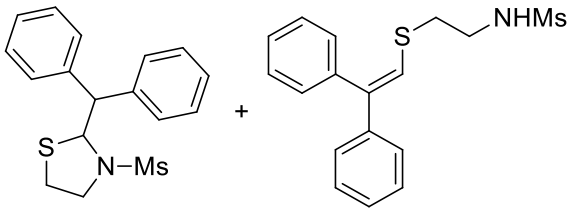
According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0520 g, 0.113 mmol, 1.0 equiv.) and triphenylethylene (0.0938 g, 0.366 mmol, 3.2 equiv.) were used. The ice bath was removed after 30 min and the reaction was stirred at r.t. for 3 h.. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide title compound as a white solid (0.0672 g, 60 %).
R_f = 0.27 (5:1 PE/EtOAc); m.p.: 168 – 169 °C
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.36 – 7.24 (m, 5H), 7.24 – 7.14 (m, 5H), 7.07 – 6.97 (m, 3H), 6.87 (dd, *J* = 6.6, 3.0 Hz, 2H), 4.65 (t, *J* = 6.0 Hz, 1H), 2.96 (q, *J* = 6.3 Hz, 2H), 2.43 (s, 3H), 2.32 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.29, 143.63, 143.52, 141.88, 138.12, 137.11, 133.87, 130.67, 130.30, 129.83, 129.34, 128.68, 128.42, 127.73, 127.68, 127.35, 127.18, 126.61, 42.42, 31.73, 21.65. FT-IR (neat) ν_{max}/cm^{-1}: 3236 (N-H), 2924, 1741, 1596, 1437, 1321 (S=O), 1153 (S=O), 1059, 904, 812, 747, 694 cm^{-1}.

***N*-(2-((2,2-diphenylvinyl)thio)ethyl)-4-methylbenzenesulfonamide (6)**



According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0512 g, 0.111 mmol, 1.0 equiv.) and ethene-1,1-diyldibenzene (0.060 mL, 0.33 mmol, 2.9 equiv.) were used. The reaction was stirred at 0 °C. for 2.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide compound as a yellowish solid (0.079 g, 86 %).
R_f = 0.29 (5:1 PE/EtOAc)
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.38 (dt, *J* = 15.0, 6.9 Hz, 3H), 7.32 – 7.21 (m, 7H), 7.17 – 7.09 (m, 2H), 6.35 (s, 1H), 4.88 (br, 1H), 3.21 (q, *J* = 6.3 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.81, 141.44, 141.09, 139.21, 136.86, 129.95, 129.69, 128.52, 128.42, 127.96, 127.39, 127.22, 127.19, 123.45, 42.80, 34.64, 21.65.

2-Benzhydryl-3-(methylsulfonyl)thiazolidine (7) and
***N*-(2-((2,2-diphenylvinyl)thio)ethyl)methanesulfonamide (8)**



According to general procedure B, 2,6-bis(methylsulfonyl)-1,5,2,6-dithiadiazocane (0.0495 g, 0.161 mmol, 1.0 equiv.) and ethene-1,1-diyldibenzene (0.090 mL, 0.49 mmol, 3.0 equiv.) were used. The ice bath was removed after 15 min and the reaction was stirred at r.t. for 22 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide compound **7** as a white solid (0.0728 g, 68 %) and compound **8** as colourless solid (0.0224 g, 21 %).

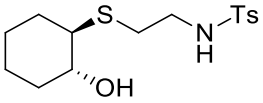
R_f = 0.37 (2:1 PE/EtOAc); m.p.: 176 – 177 °C (**7**)

^{1}H NMR (400 MHz, $CDCl_3$, **7**): δ 7.41 – 7.18 (m, 10H), 6.05 (d, *J* = 10.4 Hz, 1H), 4.26 (ddd, *J* = 12.8, 6.0, 1.7 Hz, 1H), 4.13 (d, *J* = 10.4 Hz, 1H), 3.33 (ddd, *J* = 12.8, 10.5, 6.1 Hz, 1H), 3.02 – 2.88 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, **7**): δ 142.19, 140.54, 128.83, 128.79, 128.72, 128.64, 127.35, 127.29, 69.36, 60.20, 50.32, 40.24, 33.72. FT-IR (neat, **7**) ν_{max}/cm^{-1}: 3059, 2955, 2927, 1726, 1497, 1450, 1320 (S=O), 1144 (S=O), 1034, 960, 795, 741, 705 cm^{-1}.

R_f = 0.34 (1:1 PE/EtOAc); m.p.: 97 – 98 °C (**8**)

^{1}H NMR (400 MHz, $CDCl_3$, **8**): δ 7.43 – 7.38 (m, 2H), 7.37 – 7.33 (m, 1H), 7.30 – 7.24 (m, 5H), 7.23 – 7.18 (m, 2H), 6.51 (s, 1H), 4.81 (br, 1H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.98 – 2.91 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$, **8**): δ 141.44, 141.24, 139.25, 129.74, 128.54, 128.48, 127.98, 127.45, 127.21, 123.67, 43.14, 40.95, 35.47. FT-IR (neat, **8**) ν_{max}/cm^{-1}: 3271 (N-H), 2927, 1725, 1496, 1443, 1305 (S=O), 1289, 1132 (S=O), 1077, 971, 773, 750, 696 cm^{-1}.

***N*-(2-(((1*R**,2*R**)-2-hydroxycyclohexyl)thio)ethyl)-4-methylbenzenesulfonamide (9)**



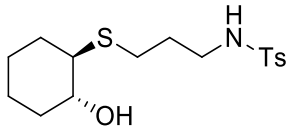
To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0511 g, 0.111 mmol, 1.0 equiv.), DCE (2 mL), cyclohexene (0.025 mL, 0.28 mmol, 2.5 equiv.), $(Et_2N)_3PSe$ (0.008 mL, 0.02 mmol, 0.2 equiv.) and H_2O (0.01 mL, 0.5 mmol, 4 equiv.) under argon atmosphere. The mixture was cooled to 0 °C and TfOH (0.025 mL, 0.28 mmol, 2.5 equiv.) was added dropwise. The ice bath was removed and the mixture was stirred at r.t. for 1 h. Afterwards, the reaction mixture was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography (3:2 PE/EtOAc) to provide desired compound as a yellowish solid (0.0557 g, 76 %).

R_f = 0.45 (1:1 PE/EtOAc); m.p.: 56 – 57 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.53 (br, 1H), 3.34 – 3.23 (m, 1H), 3.22 – 3.03 (m, 2H), 2.75 – 2.62 (m, 2H), 2.42 (s, 3H), 2.30 (ddd, *J* = 12.3, 10.2, 4.0 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.98 – 1.89 (m, 1H), 1.77 – 1.63 (m, 2H), 1.37 – 1.15 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.64, 137.06, 129.89, 127.23, 73.28, 53.23, 43.16, 34.56,

33.37, 30.82, 26.27, 24.45, 21.65. FT-IR (neat) ν_{max}/cm^{-1}: 3315 (O-H), 2933, 2852, 1597, 1412, 1318 (S=O), 1153 (S=O), 1095, 1073, 813, 659 cm^{-1}.

_N_-(3-(((1_R_*,2_R_*)-2-hydroxycyclohexyl)thio)propyl)-4-methylbenzenesulfonamide (10)

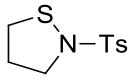


To an oven-dried reaction tube equipped with a magnetic stir bar were subsequently added 2-tosylisothiazolidine (0.0494 g, 0.203 mmol, 1.0 equiv.), dry DCE (2 mL), cyclohexene (0.040 mL, 0.39 mmol, 1.9 equiv.), $(Et_2N)_3PSe$ (0.008 mL, 0.02 mmol, 0.1 equiv.), H_2O (0.01 mL, 0.5 mmol, 2 equiv.) and MsOH (0.020 mL, 0.31 mmol, 1.5 equiv.) under argon atmosphere. The mixture was stirred at r.t. for 3 h. Afterwards, the reaction was quenched with Et_3N (0.05 mL), diluted with DCM, concentrated on silica gel and purified by column chromatography (2:1 PE/EtOAc) to provide desired compound as a colourless oil (0.0421 g, 60 %)

R_f = 0.31 (2:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 5.30 (t, *J* = 6.2 Hz, 1H), 3.28 (td, *J* = 9.9, 4.7 Hz, 1H), 3.09 – 2.90 (m, 3H), 2.64 – 2.54 (m, 2H), 2.41 (s, 3H), 2.34 (ddd, *J* = 12.2, 10.0, 3.9 Hz, 1H), 2.10 – 1.96 (m, 2H), 1.75 – 1.67 (m, 3H), 1.38 – 1.19 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.52, 137.00, 129.84, 127.17, 72.82, 53.20, 42.03, 34.26, 32.96, 29.79, 27.21, 26.31, 24.49, 21.62.

2-tosylisothiazolidine (11)

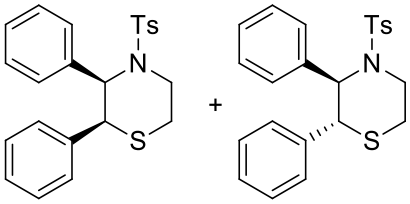


Compound **10** (0.0395 g, 0.115 mmol, 1.0 equiv.) was dissolved in dry THF (3 mL) under argon atmosphere followed by PPh_3 (0.0477 g, 0.182 mmol, 1.5 equiv.) addition. The solution was cooled to 0 °C and DEAD (0.030 mL, 0.17 mmol, 1.5 equiv.) was added dropwise. The mixture was stirred at r.t. for 23 h. Due to not full conversion PPh_3 (0.0290 g, 0.110 mmol, 1.0 equiv) and DEAD (0.020 mL, 0.110 mmol, 1.0 equiv.) were additionally added and the mixture was stirred at r.t. for 1.5 h. Afterwards, the reaction was diluted with DCM, concentrated on silica gel and purified by column chromatography (5:1 PE/EtOAc) to yield compound **11** as a yellowish solid (0.0107 g, 38 %)

R_f = 0.46 (3:1 PE/EtOAc); m.p.: 68 – 69 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.70 (t, *J* = 6.9 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.45 (s, 3H), 1.79 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.63, 129.77, 128.84, 127.20, 54.58, 34.56, 28.54, 21.78. FT-IR (neat) ν_{max}/cm^{-1}: 3275, 2953, 1595, 1338 (S=O), 1151 (S=O), 1085, 1050, 813, 800, 675 cm^{-1}.

(2*S,3*R**)-2,3-diphenyl-4-tosylthiomorpholine (12) and (2*R**,3*R**)-2,3-diphenyl-4-tosylthiomorpholine (2a)**



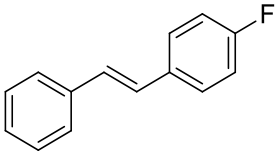
According to general procedure B, 2,6-ditosyl-1,5,2,6-dithiadiazocane (0.0518 g, 0.113 mmol, 1.0 equiv.) and *cis*-stilbene (0.065 mL, 0.350 mmol, 3.1 equiv.) were used. After 30 min the ice bath was removed and the reaction was stirred at r.t. for 1 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (7:1 PE/EtOAc) to provide desired compound as yellowish solid (0.0745 g, 80 %). Mixture of cis/trans isomers with ratio 1 : 0.6.

R_f = 0.39 (5:1 PE/EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$, **12**) δ 7.45 – 6.93 (m, 14H), 5.45 (d, *J* = 3.6 Hz, 1H), 4.57 (d, *J* = 3.7 Hz, 1H), 4.11 (d, *J* = 13.6 Hz, 1H), 3.41 (t, *J* = 12.7 Hz, 1H), 3.20 – 3.06 (m, 1H), 2.81 (d, *J* = 13.6 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, **12**): δ 143.11, 139.28, 137.99, 136.63, 135.96, 130.52, 129.36, 128.26, 128.15, 127.64, 127.62, 127.19, 60.58, 50.65, 46.36, 29.48, 21.51. ^{1}H NMR (400 MHz, $CDCl_3$, **2a**): δ 7.45 – 6.93 (m, 14H), 5.65 (d, *J* = 6.4 Hz, 1H), 4.31 (d, *J* = 6.3 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.62 (ddd, *J* = 14.6, 12.0, 3.7 Hz, 1H), 2.91 (td, *J* = 12.2, 5.0 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, **2a**)*: δ 143.02, 139.49, 139.41, 137.40, 129.33, 128.77, 128.55, 128.36, 127.74, 127.69, 127.25, 63.42, 46.38, 41.30, 25.75, 21.58. FT-IR (neat) ν_{max}/cm^{-1}: 3029, 2922, 2904, 1599, 1492, 1345 (S=O), 1297, 1152 (S=O), 1091, 903, 750, 695, 656.

***One aromatic ^{13}C has the same chemical shift as another one.*

(*E*)-1-fluoro-4-styrylbenzene (13)

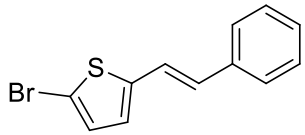


A title compound was synthesized via modified literature procedure [85]. A mixture of 1-fluoro-4-(phenylethynyl)benzene (0.486 g, 2.48 mmol, 1.0 equiv.) and $Na_2S{\cdot}xH_2O$ (0.492 g, 60 %, 3.7 mmol, 1.5 equiv.) in DMF (10 mL) was placed in sealed vial equipped with a magnetic stir bar. The mixture was stirred at 140 °C for 14 h. Afterwards, the reaction was poured into H_2O (50 mL) and extracted three times with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (100:1 PE/EtOAc) to provide desired compound as a white solid (0.0862 g, 18 %).

^{1}H NMR is in accordance with literature [85].

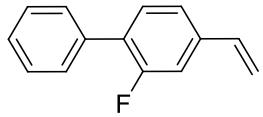
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.45 (m, 4H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.15 – 6.99 (m, 4H).

(*E*)-2-bromo-5-styrylthiophene (14)



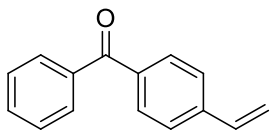
A title compound was synthesized via modified literature procedure [86]. A reaction tube was charged with 1,4-benzoquinone (0.649 g, 6.00 mmol, 2.0 equiv.), $Pd(OAc)_2$ (0.0704 g, 0.313 mmol, 0.10 equiv.), AcOH (6 mL), DMSO (6 mL), 2-bromothiophene (0.60 mL, 6.0 mmol, 2.0 equiv.) and *trans*-styrene (0.345 mL, 3.00 mmol, 1.0 equiv.). The mixture was stirred at r.t. for 21 h. Afterwards, the reaction was diluted with sat. $NaHCO_3$ (25 mL), extracted once with Et_2O (60 mL) and once with EtOAc (60 mL). The combined organic layers were washed once with 1M NaOH (20 mL), once with brine (20 mL), dried over Na_2SO_4, filtered, dried over Na_2SO_4, concentrated on silica gel and purified by column chromatography (9:1 PE/EtOAc) to provide desired compound as orange solid (0.348 g, 44 %).
^{1}H NMR is in accordance with literature [87].
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.43 (m, 2H), 7.37 – 7.33 (m, 2H), 7.29 – 7.24 (m, 1H), 7.11 (dd, *J* = 16.1, 0.6 Hz, 1H), 6.96 (d, *J* = 3.8 Hz, 1H), 6.85 – 6.79 (m, 2H).

2-Fluoro-4-vinyl-1,1'-biphenyl (15)



A title compound was synthesized via modified literature procedure [88]. 4-bromo-2-fluoro-1,1'-biphenyl (0.594 g, 2.36 mmol, 1.0 equiv.), potassium vinyltrifluoroborate (0.360 g, 2.60 mmol, 1.1 equiv.), PPh_3 (0.0384 g, 0.146 mmol, 0.06 equiv.) and Cs_2CO_3 (2.31 g, 7.09 mmol, 3.0 equiv.) were suspended in sparged by argon THF/H_2O (5 mL, 9:1) under argon atmosphere. To this mixture $PdCl_2$ (0.0184 g, 0.103 mmol, 0.04 equiv.) was added in one portion and the reaction was stirred at 90 °C for 15 h. Afterwards, the reaction mixture was cooled to r.t., diluted with H_2O (6 mL) and extracted twice with DCM (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (PE → 50:1 PE/DCM) to provide desired compound as colourless oil (0.379 g, 81 %).
^{1}H NMR is in accordance with literature [89].
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.54 (m, 2H), 7.49 – 7.36 (m, 4H), 7.28 – 7.20 (m, 2H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.81 (d, *J* = 17.6 Hz, 1H), 5.34 (d, *J* = 10.9 Hz, 1H).

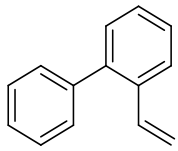
Phenyl(4-vinylphenyl)methanone (16)



A title compound was synthesized via modified literature procedure [88]. 4-Bromobenzophenone (0.270 g, 1.00 mmol, 1.0 equiv.), potassium vinyltrifluoroborate (0.160 g, 1.16 mmol, 1.1 equiv.),

PPh_3 (0.0286 g, 0.109 mmol, 0.1 equiv.) and $CsCO_3$ (1.00 g, 3.08 mmol, 3.0 equiv.) were suspended in sparged by argon THF/H_2O (2 mL, 9:1) under argon atmosphere. To this mixture $PdCl_2$ (0.0043 g, 0.024 mmol, 0.02 equiv.) was added in one portion and the reaction was stirred at 85 °C for 15 h. Afterwards, the reaction was cooled to r.t., diluted with H_2O (6 mL) and extracted twice with DCM (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (1:1 PE/DCM) to provide desired compound as colourless oil (0.202 g, 97 %).
^{1}H NMR is in accordance with literature [90].
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 – 7.74 (m, 4H), 7.61 – 7.56 (m, 1H), 7.53 – 7.46 (m, 4H), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.90 (dd, *J* = 17.6, 0.7 Hz, 1H), 5.41 (dd, *J* = 10.9, 0.7 Hz, 1H).

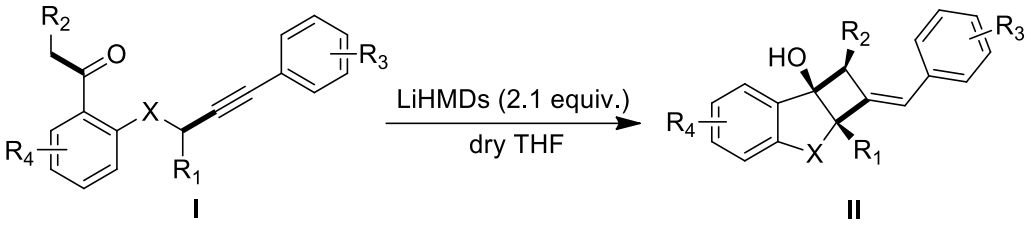
2-vinyl-1,1'-biphenyl (17)



A title compound was synthesized via modified literature procedure [88]. 2-bromo-1,1'-biphenyl (0.40 mL, 2.2 mmmol, 1.0 equiv.), potassium vinyltrifluoroborate (0.331 g, 2.40 mmol, 1.1 equiv.), PPh_3 (0.0465 g, 0.177 mmol, 0.08 equiv.) and $CsCO_3$ (2.04g, 6.25 mmol, 2.8 equiv.) were suspended in sparged by argon THF/H_2O (5 mL, 9:1) under argon atmosphere. To this mixture $PdCl_2$ (0.011 g, 0.063 mmol, 0.03 equiv.) and the reaction was stirred at 85 °C for 17 h. Afterwards, the reaction mixture was diluted with H_2O (6 mL) and extracted twice with DCM (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (PE) to provide desired compound as colourless liquid (0.38 g, 95 %)
^{1}H NMR is in accordance with literature [91].
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 – 7.65 (m, 1H), 7.51 – 7.31 (m, 8H), 6.73 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.72 (dd, *J* = 17.5, 1.3 Hz, 1H), 5.20 (dd, *J* = 11.0, 1.3 Hz, 1H).

5.2 Experimental Part II

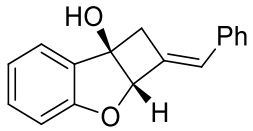
General procedure for screening reaction conditions: To an oven-dried reaction flask equipped with a magnetic stir bar was added dry corresponding solvent under argon atmosphere (for entries 9 - 11 the solvent was cooled to -78 °C). To this a base was added dropwise or in one portion. (for entries 1,2,5 the base solution was pre-heated for 1h at 60 °C). Then, a solution of compound **Ia** (1.0 equiv.) in dry corresponding solvent was added dropwise. The reaction mixture was stirred at temperature specified in Table 4 till full consumption of starting material or till conversion of **Ia** stopped. The reaction was monitored by TLC. Afterwards, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography to provide compound or compounds as showed in Table 4.



X = O, S

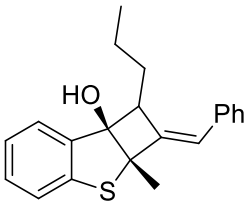
General procedure E: To an oven-dried reaction flask equipped with a magnetic stir bar was added dry THF under argon atmosphere and the solvent was cooled to -78 ºC. To this LiHMDS (2.1 equiv.) was added dropwise. Then, a solution of compound **I** (1.0 equiv.) in dry THF was added dropwise followed by rinsing with dry THF. The cooling was stopped and the solution was very slowly warmed from -78 ºC to certain temperature within a period of time as specified. Afterwards, the reaction was quenched with sat. NH_4Cl (10 mL) and extracted twice with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography to provide desired compound **II**.

(2a*S,7b*R**,*E*)-2-benzylidene-1,2,2a,7b-tetrahydrocyclobuta[b]benzofuran-7b-ol (IIa)**



According to general procedure E, to an oven-dried reaction flask equipped with a magnetic stir bar was added dry THF (8 mL) under argon atmosphere and the solvent was cooled to -78 ºC. To this LiHMDS (4.2 mL, 1M, 4.2 mmol, 2.1 eq.) was added dropwise. Then, a solution of 1-(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)ethanone (0.494 g, 1.97 mmol, 1.0 eq.) in dry THF (7 mL) was added dropwise followed by rinsing with dry THF (1 mL). The cooling was stopped and the solution was very slowly warmed from -78 ºC to -25 ºC over 2.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.314 g, 64 %).
R_f = 0.32 (5:1 PE/EtOAc); m.p.: 138 – 141 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.18 (m, 6H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.72 – 6.67 (m, 1H), 5.43 (s, 1H), 3.47 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.30, 136.52, 133.61, 130.72, 130.59, 128.61, 128.30, 128.02, 127.56, 124.72, 121.83, 111.68, 90.04, 80.25, 43.81. HRMS (ESI) calc. for $C_{17}H_{15}O_2$ (M+H): 251.1072; Found: 251.1060.

(2a*S,7b*R**,*E**)-2-benzylidene-2a-methyl-1-propyl-1,2,2a,7b-tetrahydrobenzo[b]cyclobuta[d]thiophen-7b-ol (IIb)**

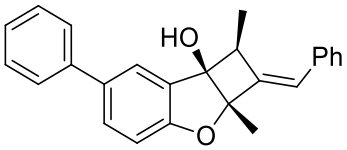


According to general procedure E, to an oven-dried reaction tube equipped with a magnetic stir bar was added dry THF (6 mL) under argon atmosphere and the solution was cooled to -78 ºC. To this LiHMDS (1.2 mL, 1M, 1.2 mmol, 2.1 eq.) was added dropwise. Then, a solution of 1-(2-((5-phenylpent-4-yn-2-yl)thio)phenyl)pentan-1-one (0.176 g, 0.546 mmol, 1.0 eq.) in dry THF (4 mL) was added dropwise followed by rinsing with dry THF (1 mL). The solution was very slowly warmed from -78 ºC to 5 ºC over 5.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (40:1 PE/EtOAc) to provide desired compound as a yellowish solid (0.129 g, 73 %).

R_f = 0.24 (40:1 PE/EtOAc); m.p.: 75 – 77 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.30 – 7.26 (m, 1H), 7.25 – 7.18 (m, 2H), 7.15 – 7.08 (m, 2H), 6.25 (d, *J* = 2.3 Hz, 1H), 3.34 (ddd, *J* = 8.6, 5.9, 2.2 Hz, 1H), 2.21 (s, 1H), 2.01 – 1.89 (m, 1H), 1.71 – 1.57 (m, 5H), 1.54 – 1.42 (m, 1H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.64, 143.43, 141.29, 136.33, 129.51, 128.82, 128.42, 126.97, 125.04, 124.68, 123.88, 122.01, 87.64, 64.56, 55.41, 31.84, 21.79, 20.39, 14.44. HRMS (ESI) calc. for $C_{21}H_{23}OS$ (M+H): 323.1464; Found: 323.1465.

(1*S,2a*S**,7b*R**,*E*)-2-benzylidene-1,2a-dimethyl-6-phenyl-1,2,2a,7b-tetrahydrocyclobuta[b]benzofuran-7b-ol (IIc)**



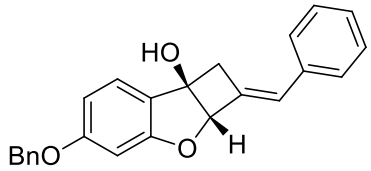
According to general procedure E, to an oven-dried reaction tube equipped with a magnetic stir bar was added dry THF (6 mL) under argon atmosphere. The solvent was cooled to -78 ºC and LiHMDS (0.530 mL, 1M, 0.530 mmol, 2.1 eq.) was added dropwise. To this a solution of 1-(4-((4-phenylbut-3-yn-2-yl)oxy)-[1,1'-biphenyl]-3-yl)propan-1-one (**Ic**) (0.0887 g, 0.250 mmol, 1.0 eq.) in dry THF (4 mL) was added dropwise followed by rinsing with dry THF (1 mL). The solution was very slowly warmed from -78 ºC to 5 ºC over 4.5 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (20:1 PE/EtOAc) to provide desired compound as colourless oil (0.0678 g, 77 %).

R_f = 0.36 (10:1 PE/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.65 (m, 3H), 7.60 – 7.55 (m, 2H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (dt, *J* = 15.0, 7.6 Hz, 4H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 1.8 Hz, 1H), 3.36 (qd, *J* = 7.4, 1.8 Hz, 1H), 2.26 (s, 1H), 1.75 (s, 3H), 1.45 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.62, 144.97, 141.05, 135.83, 135.20, 132.91, 129.45, 128.88, 128.63, 128.62, 128.57, 127.44, 126.89, 126.86, 123.26, 111.31, 93.86,

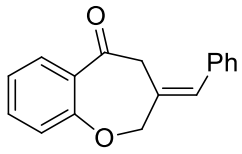
80.01, 48.01, 16.69, 15.52. FT-IR (neat) ν_{max}/cm^{-1}: 3538 (O-H), 3029, 2972, 2928, 1613, 1473, 1250, 1082, 1036, 886, 762, 732, 694 cm^{-1}. HRMS (ESI) calc. for $C_{25}H_{23}O_2$ (M+H): 355.1698; Found: 355.1690.

(2a*S,7b*R**,*E*)-2-benzylidene-5-(benzyloxy)-1,2,2a,7b-tetrahydrocyclobuta[b]benzofuran-7b-ol (IId)**



According to general procedure E, to an oven-dried reaction tube equipped with a magnetic stir bar was added dry THF (6 mL) under argon atmosphere. The solvent was cooled to -78 ºC and LiHMDS (0.520 mL, 1M, 0.530 mmol, 2.1 eq.) was added dropwise. To this a solution of compound 1 (0.0883 g, 0.248 mmol, 1.0 eq.) in dry THF (4 mL) was added dropwise followed by rinsing with dry THF (1 mL). The solution was very slowly warmed from -78 ºC to 10 ºC over 7 h. Then, the reaction was moved to r.t. and stirred at r.t. for 15 h. Afterwards, the mixture was subjected to the workup procedure outlined in general procedure and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as white solid (0.0295 g, 33 %). Recovered starting material: (0.0266 g, 30 %). Yield based on recovered starting material: 48 %.
R_f = 0.27 (5:1 PE/EtOAc); m.p.: 140 -141 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 3H), 7.25 – 7.14 (m, 5H), 7.13 – 7.07 (m, 3H), 6.59 – 6.54 (m, 1H), 6.47 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 5.33 (s, 1H), 4.90 (s, 2H), 3.32 (d, *J* = 2.3 Hz, 2H), 2.39 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.87, 161.42, 136.82, 136.55, 133.83, 128.73, 128.60, 128.18, 128.15, 128.01, 127.57, 127.54, 125.04, 123.05, 109.20, 98.24, 91.03, 79.91, 70.39, 43.67. FT-IR (neat) ν_{max}/cm^{-1}: 3272 (O-H), 3029, 2950, 1617, 1594, 1496, 1272, 1259, 1148, 1102, 1080, 1029, 819, 689 cm^{-1}.

(*E*)-3-benzylidene-3,4-dihydrobenzo[b]oxepin-5(2H)-one (IIIa)

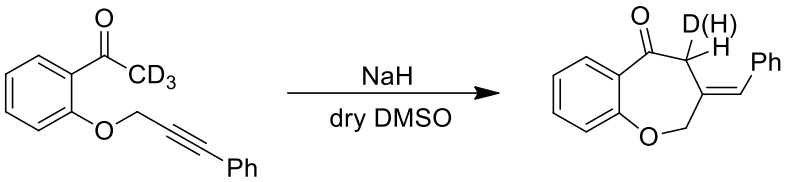


NaH (0.0327 g, 60 %, 0.818 mmol, 2.9 eq.) was suspended in dry THF (3 mL) under argon atmosphere. To this a solution of 1-(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)ethanone (0.070 g, 0.28 mmol, 1.0 eq.) in dry THF (3 mL) was added dropwise followed by rinsing with dry THF (1mL). The reaction mixture was stirred at 60 ºC for 20 h. Afterwards, the reaction was quenched with saturated NH_4Cl (15 mL) and was extracted twice with EtOAc (75 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (20:1 PE/EtOAc) to provide compound **IIIa** as yellowish oil (0.0474 g, 68 %). oil. Product was obtained as a mixture of cis/trans (1:5) isomers.
R_f = 0.48 (10:1 PE/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$, trans/cis 5:1, trans): δ 7.82 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1H), 7.30 – 7.04 (m, 7H), 6.38 (s, 1H), 4.74 (s, 2H), 3.76 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, trans/cis 5:1, trans): δ 196.57, 160.68, 135.63, 134.93, 132.58, 130.07, 128.75, 128.70, 128.68, 128.58, 127.53, 124.07, 122.23, 78.41, 46.14. ^{1}H NMR (400 MHz, $CDCl_3$, trans/cis 5:1, cis): δ 7.87 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.30 – 7.04 (m, 4H), 7.02 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 2H), 6.48 (s, 1H), 4.90 (d, *J* = 2.1 Hz, 2H), 3.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, trans/cis 5:1, cis)*: δ 195.43, 161.20, 136.13, 135.17, 133.25, 129.43, 129.25, 129.02, 128.45, 127.40, 124.50, 122.62, 73.41, 52.02. HRMS (ESI) calc. for $C_{17}H_{15}O_2$ (M+H): 251.1066; Found: 251.1065.

**One aromatic ^{13}C has the same chemical shift as trans isomers.*

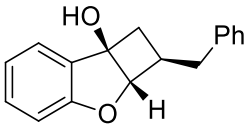
Compound VIII



VII **VIII**

NaH (0.0167 g, 60%, 0.417 mmol, 3.2 eq.) was suspended in dry DMSO (2 mL) under argon atmosphere. The mixture was heated at 60 ºC for 1 h, cooled to r.t. and a solution of compound **X** (0.0324 g, 0.128 mmol, 1.0 eq.) in dry DMSO (0.5 mL) was added dropwise followed by rinsing with dry DMSO (0.5 mL). The reaction was stirred at r.t. for 15 min. Afterwards, the reaction was diluted with saturated NH_4Cl (6 mL) and extracted twice with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (30:1 PE/EtOAc) to provide compound **VIII** as yellowish oil (0.010 g, 31 %)
R_f = 0.37 (20:1 PE/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.52 (td, *J* = 8.1, 1.7 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.22 (m, 3H), 7.21 – 7.14 (m, 2H), 6.49 (s, 1H), 4.85 (s, 2H), 3.88 – 3.81 (m, 1.15H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.64, 160.74, 135.68, 134.98, 132.60, 130.12, 129.47, 128.78, 128.73, 128.63, 127.57, 124.13, 122.28, 78.46, 46.19, 46.09, 45.89, 45.69. HRMS (ESI) calc. for $C_{17}H_{14}DO_2$ (M+H): 252.1135; Found: 252.1127.

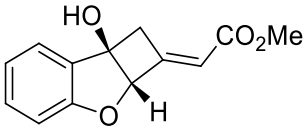
(2*R,2a*S**,7b*R**)-2-benzyl-1,2,2a,7b-tetrahydrocyclobuta[b]benzofuran-7b-ol (IX)**



Compound **IIa** (0.149 g, 0.595 mmol, 1.0 eq.) was dissolved in EtOAc (25 mL) under argon atmosphere. The reaction flask was evacuated, backfilled with argon and Pd-C (0.028 g, 10 %, 60-65 % wet) was added. The flask was evacuated and backfilled with H_2. The last step was repeated once more and the mixture was stirred at r.t. under H_2 atmosphere for 18 h. Afterwards, the mixture was filtered through celite pad and thoroughly washed with EtOAc. The filtrate was concentrated on silica gel and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as colourless oil (0.148 g, 99 %).

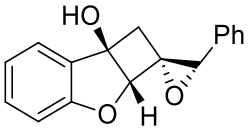
R_f = 0.28 (5:1 PE/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.22 – 7.18 (m, 1H), 7.14 – 7.08 (m, 2H), 7.03 (td, *J* = 7.4, 0.8 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 5.10 (d, *J* = 7.9 Hz, 1H), 3.00 – 2.89 (m, 1H), 2.80 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.67 (ddd, *J* = 12.2, 10.9, 1.1 Hz, 1H), 2.34 – 2.24 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.07, 140.61, 132.64, 130.80, 128.75, 128.43, 126.05, 124.21, 121.72, 110.62, 87.01, 80.05, 38.15, 34.78, 33.11. FT-IR (neat) ν_{max}/cm^{-1}: 3379 (O-H), 3027, 2934, 1596, 1462, 1233, 1101, 1030, 752, 697 cm^{-1}. HRMS (ESI) calc. for $C_{17}H_{17}O_2$ (M+H): 253.1229; Found: 253.1230.

(*E*)-methyl 2-((2a*S,7b*R**)-7b-hydroxy-1,7b-dihydrocyclobuta[b]benzofuran-2(2aH)-ylidene)acetate (X)**



A title compound was synthesized via modified literature procedure [92]. Compound **IIa** (0.102 g, 0.410 mmol, 1.0 eq.) and Hoveyda-Grubbs cat. 2nd gen. (0.014 g, 0.021 mmol, 0.05 eq.) were suspended in dry DCM (6 mL). Methyl acrylate (0.220 mL, 2.44 mmol, 6.0 eq.) was added and the reaction was stirred at 40 ºC for 28 h. Afterwards, the reaction mixture was concentrated on silica gel and purified by column chromatography (5:1 PE/EtOAc) to provide desired compound as yellowish solid (0.0547 g, 58 %).
R_f = 0.31 (3:1 PE/EtOAc); m.p.: 91 – 92 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 3.66 (s, 4H), 3.41 (dd, *J* = 18.3, 2.7 Hz, 1H), 2.62 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.27, 161.16, 155.15, 130.92, 129.80, 124.93, 122.32, 118.51, 111.69, 88.75, 79.82, 51.52, 44.62. FT-IR (neat) ν_{max}/cm^{-1}: 3396 (O-H), 2951, 2920, 2850, 1699 (C=O), 1655, 1462, 1284, 1193, 1101, 1030, 838, 754 cm^{-1}. HRMS (ESI) calc. for $C_{13}H_{13}O_4$ (M+H): 233.0814; Found: 233.0808.

(2*R*,2a*R*,3'*S*,7b*R*)-3'-phenyl-2a,7b-dihydro-1H-spiro[cyclobuta[b]benzofuran-2,2'-oxiran]-7b-ol (XI)



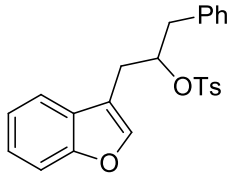
A title compound was synthesized via modified literature procedure [83]. Compound **IIa** (0.0351 g, 0.140 mmol, 1.0 eq.) was dissolved in dry CH_3CN (2 mL) under argon atmosphere. $Co(OAc)_2{\cdot}4H_2O$ (0.0034 g, 0.013 mmol, 0.1 eq.) was added followed by dropwise addition of *t*-BuOOH (0.12 mL, 70% in H_2O, 0.87 mmol, 6.2 eq.). The reaction was stirred at 50 ºC for 40 h. Additionally $Co(OAc)_2{\cdot}4H_2O$ (0.0038 g, 0.015 mmol, 0.1 eq.) was added followed by dropwise addition of *t*-BuOOH (0.12 mL, 70% in H_2O, 0.87 mmol, 6.2 eq.) and the mixture was further stirred at 50 ºC for 23 h. Afterwards, the reaction was poured into sat. Na_2SO_3 (5 mL)/H_2O(5 mL) and extracted twice with EtOAc (30 mL). The combined organic layers were washed once with satturated $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, concentrated on silica gel and purified by

column chromatography (6:1 PE/EtOAc) to provide desired compound **XI** as yellowish solid (0.0134 g, 36 %)

R_f = 0.27 (5:1 PE/EtOAc); m.p.: 99 – 100 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 2H), 7.22 – 7.18 (m, 3H), 6.99 – 6.93 (m, 2H), 6.81 – 6.75 (m, 2H), 5.21 (s, 1H), 4.00 (s, 1H), 2.90 (d, *J* = 13.2 Hz, 1H), 2.49 (br, 1H), 2.34 (dd, *J* = 13.2, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.66, 134.90, 131.00, 130.30, 128.34, 128.03, 125.78, 125.07, 122.15, 111.63, 91.23, 75.59, 64.55, 57.92, 38.49. FT-IR (neat) ν_{max}/cm^{-1}: 3182 (O-H), 2920, 2850, 1707, 1608, 1595, 1462, 1228, 1202, 1041, 1027, 900, 753, 696 cm^{-1}.

1-(benzofuran-3-yl)-3-phenylpropan-2-yl 4-methylbenzenesulfonate (XII)

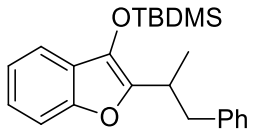


Compound **IX** (0.0254 g, 0.100 mmol, 1.0 eq.) was dissolved in DCM (2 mL) under argon atmosphere. The solution was cooled to 0 ºC in an ice bath and $TsOH{\cdot}H_2O$ (0.0216 g, 0.111 mmol, 1.1 eq.) was added in one portion. The ice bath was removed and the mixture was stirred at r.t. for 4 days. Afterwards, the reaction was quenched with Et_3N (0.05 mL), concentrated on silica gel and purified by column chromatography (25:1 PE/EtOAc) to provide compound **XII** as yellowish oil (0.0313 g, 77 %).

R_f = 0.44 (10:1 PE/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 3H), 7.33 (s, 1H), 7.30 – 7.23 (m, 5H), 7.19 – 7.11 (m, 3H), 6.94 (d, *J* = 8.1 Hz, 2H), 4.85 (p, *J* = 6.4 Hz, 1H), 3.13 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.05 – 2.92 (m, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.24, 144.19, 142.91, 136.21, 133.00, 129.72, 129.37, 128.71, 127.61, 127.39, 126.96, 124.30, 122.61, 119.55, 114.98, 111.49, 82.68, 41.06, 28.42, 21.67. HRMS (ESI) calc. for $C_{24}H_{25}NO_4S$ ($M+NH_2$): 424.1588; Found: 424.1580.

***tert*-Butyldimethyl((2-(1-phenylpropan-2-yl)benzofuran-3-yl)oxy)silane (XIII)**



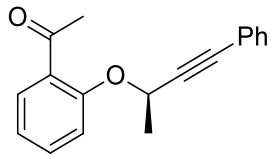
A title compound was synthesized via modified literature procedure [84]. Compound **IX** (0.0262 g, 0.103 mmol, 1.0 eq.) and $[Ir(dF(CF_3)ppy)_2(5,5'dCF_3bpy)](PF_6)$ (0.0035 g, 0.003 mmol, 0.03 eq.) were dissolved in dry toluene (2 mL) under argon atmosphere. To this solution $PBu_3Me^+(MeO)_2POO^-$ (0.01 mL, 0.03 mmol, 0.3 eq.) and 2,4,6-trimethylthiophenol (0.06 mL, 0.06 mmol, 0.6 eq.) were added. The reaction was irradiated with blue LED (450 nm, 29 V) at r.t. for 4.5 h. Afterwards, the reaction was concentrated on silica gel and purified by column chromatography (50:1 PE/EtOAC) to provide intermediate as a mixture of diastereomers, which was used further as it is. The intermediate was dissolved in dry DCM (2 mL) under argon atmosphere and the solution was cooled to 0 ºC. Et_3N (0.020 mL, 0.14 mmol, 1.4 eq.) was added followed by slow addition of TBDMSOTf (0.030 mL, 0.13 mmol, 1.2 eq). The mixture was warmed to r.t. and stirred at r.t. for 20 h. Afterwards, the reaction was diluted with DCM, poured into saturated $NaHCO_3$ (10 mL) and

extracted two times with DCM (30 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (100:1 Heptane/EtOAc) to provide compound **XIII** as yellowish oil (0.0229 g, 60 %)

R_f = 0.31 (100:1 Heptane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 11.7, 8.0 Hz, 2H), 7.25 – 7.09 (m, 7H), 3.31 (dp, *J* = 14.2, 7.0 Hz, 1H), 3.11 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.88 (dd, *J* = 13.4, 7.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 0.09 (d, *J* = 14.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 152.22, 147.19, 140.45, 132.56, 129.15, 128.39, 126.14, 125.16, 123.33, 121.98, 118.31, 111.31, 41.61, 32.62, 25.88, 18.86, 18.25, -4.09, -4.25. HRMS (ESI) calc. for $C_{23}H_{31}O_2Si$ (M+H): 367.2093; Found: 367.2093.

(*R*)-1-(2-((4-phenylbut-3-yn-2-yl)oxy)phenyl)ethanone (XIV)

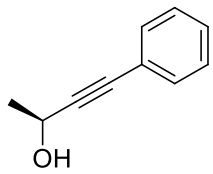


2'-Hydroxyacetophenone (0.250 mL, 2.00 mmol, 1.3 eq.) and (*S*)-4-phenylbut-3-yn-2-ol (**XV**) (0.215 g, 1.47 mmol, 1.0 eq.) were dissolved in dry toluene (10 mL) under argon atmosphere. The mixture was cooled to 0 ºC and PPh_3 (0.462 g, 1.76 mmol, 1.2 eq.) was added followed by dropwise addition of DEAD (0.300 mL, 1.71 mmol, 1.3 eq.). The mixture was stirred at 0 ºC for 1 h. Afterwards, the reaction was concentrated on silica gel and purified by column chromatography (20:1 PE/EtOAc) to provide desired compound as colourless oil (0.328 g, 84 %). Enantiomeric excess: 96 %.

R_f = 0.33 (20:1 PE/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.48 (ddd, *J* = 8.5, 7.3, 1.8 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.32 – 7.23 (m, 4H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 2.68 (s, 3H), 1.82 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.05, 157.00, 133.49, 131.83, 130.46, 129.41, 128.84, 128.43, 122.18, 121.40, 114.61, 87.61, 86.53, 65.31, 32.25, 22.48. FT-IR (neat) ν_{max}/cm^{-1}: 2990, 2238 (C≡C), 1672 (C=O), 1596, 1480, 1291, 1228, 1084, 941, 753, 690 cm^{-1}. HRMS (ESI) calc. for $C_{18}H_{17}O_2$ (M+H): 265.1229; Found: 265.1225.

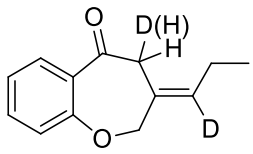
(*S*)-4-phenylbut-3-yn-2-ol (XV)



A title compound was synthesized via modified literature procedure [94]. $Pd(PPh_3)_2Cl_2$ (0.0295 g, 0.0420 mmol, 0.01 eq.) and CuI (0.0193 g, 0.0993 mmol, 0.02 eq.) were suspended in sparged by argon Et_3N (10 mL) under argon atmosphere followed by dropwise addition of iodobenzene (0.500 mL, 4.38 mmol, 1.2 eq.). The reaction mixture was stirred for 5 min and (*S*)-(-)-3-butyn-2-ol (0.300 mL, 3.71 mmol, 1.0 eq.) was added. The reaction was stirred at r.t. for 20 h. Afterwards, the reaction was diluted with saturated $NaHCO_3$ (15 mL) and extracted three times with EtOAc (50

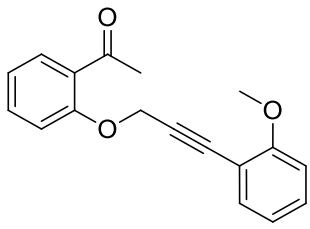
mL). The combined organic layers were washed once with brine (15 mL), dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (7:1 → 6:1 PE/EtOAc) to provide desired compound as dark brown oil (0.501 g, 92 %).
^{1}H NMR is in accordance with literature [95]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.39 (m, 2H), 7.34 – 7.28 (m, 3H), 4.76 (q, *J* = 6.6 Hz, 1H), 1.93 (br, 1H), 1.56 (d, *J* = 6.6 Hz, 3H).

Compound XVI



NaH (0.011 g, 60 %, 0.27 mmol, 2.6 eq.) was suspended in dry *d6*-DMSO (1.0 mL) under argon atmosphere. The mixture was heated at 60 ºC for 1 h, cooled to r.t. and a solution of 1-(2-(pent-2-yn-1-yloxy)phenyl)ethanone (0.0215 g, 0.106 mmol, 1.0 eq.) in dry *d6*-DMSO (0.25 mL) was added dropwise followed by rinsing with dry *d6*-DMSO (0.25 mL). The reaction mixture was stirred at r.t. for 4.5 h. Afterwards, the reaction was diluted with saturated NH_4Cl (5 mL) and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (20:1 PE/EtOAc) to provide compound **IX** as yellowish oil (0.0084 g, 39 %).
R_f = 0.48 (10:1 PE/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.17 – 7.12 (m, 1H), 7.09 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.63 (s, 2H), 3.66 – 3.59 (m, 1.12H), 2.07 (q, *J* = 7.5 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.99, 160.39, 134.69, 132.14, 132.02, 131.79, 131.56, 130.03, 129.48, 129.21, 123.76, 122.18, 77.92, 44.97, 44.87, 44.67, 44.48, 21.06, 13.84. FT-IR (neat) ν_{max}/cm^{-1}: 3341, 2971, 2934, 1629, 1598 (C=O), 1476, 1454, 1308, 1037, 761 cm^{-1}.

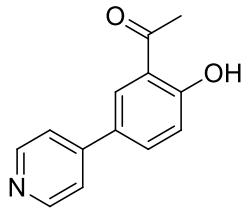
1-(2-((3-(2-methoxyphenyl)prop-2-yn-1-yl)oxy)phenyl)ethanone (XVII)



A title compound was synthesized via modified literature procedure [96]. To a stirred mixture of 1-(2-(prop-2-ynyloxy)phenyl)ethanone (0.139 g, 0.798 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol, 0.03 eq.) and CuI (0.011 g, 0.057mmol, 0.07 eq.) in dry THF (3 mL) under argon atmosphere was dropwise added a mixture of sparged by argon Et_3N (3 mL), 2-iodoanisole (0.390 g, 1.66 mmol, 2.0 eq.) in dry THF (1.5 mL) followed by rinsing with dry THF (0.5 mL). Afterwards, the reaction was quenched with sat. NH_4Cl (5 mL) and extracted twice with EtOAc (50 mL). The combined organic layers were washed once with brine (10 mL), dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (10:1→8:1 PE/EtOAc) to provide title compound as darkish oil (0.155 g, 69 %).

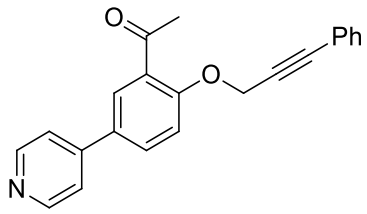
R_f = 0.28 (10:1 PE/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.37 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.93 – 6.84 (m, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 2.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.98, 160.40, 157.36, 133.87, 133.57, 130.55, 130.50, 129.17, 121.47, 120.59, 113.68, 111.33, 110.82, 87.36, 84.38, 57.58, 55.89, 32.20. HRMS (ESI) calc. for $C_{18}H_{17}O_3$ (M+H): 281.1178; Found: 281.1169.

1-(2-hydroxy-5-(pyridin-4-yl)phenyl)ethanone (XVIII)



5-Bromo-2-hydroacetophenone (0.501 g, 2.28 mmol, 1.0 eq.), pyridine-4-boronic acid hydrate (0.395 g, 3.05 mmol, 1.3 eq.), K_2CO_3 (1.59 g, 11.5 mmol, 5.0 eq.) and $Pd(PPh_3)$ (0.140 g, 0.121 mmol, 0.05 eq.) were suspended in sparged by argon dioxane/water (10:1, 20 mL) under argon atmosphere. The reaction was stirred at 105 ºC for 19 h. Afterwards, the reaction mixture was diluted with H_2O (25 mL) and extracted three times with DCM (60 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (2:1:0.05 EtOAc/PE/Et_3N) to provide desired compound as slightly yellow solid (0.358 g, 74%).
R_f = 0.32 (2:1:0.05 EtOAc/PE/Et_3N); m.p.: 102 – 103 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.66 (d, *J* = 6.2 Hz, 2H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.37, 163.12, 150.43, 146.99, 134.85, 129.15, 129.07, 121.04, 119.96, 119.49, 26.74. FT-IR (neat) ν_{max}/cm^{-1}: 3430 (O-H), 2995, 2683, 2047, 1629 (C=O), 1598, 1513, 1476, 1369, 1306, 1256, 1216, 1025, 964, 852, 816, 754 cm^{-1}. HRMS (ESI) calc. for $C_{13}H_{12}NO_2$ (M+H): 214.0868; Found: 214.0869.

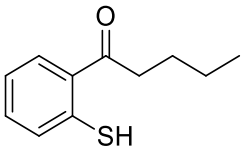
1-(2-((3-phenylprop-2-yn-1-yl)oxy)-5-(pyridin-4-yl)phenyl)ethanone (XIX)



1-(2-hydroxy-5-(pyridin-4-yl)phenyl)ethanone (**XVIII**) (0.206 g, 0.966 mmol, 1.0 eq.) and 3-phenylpropargyl alcohol (0.140 mL, 1.12 mmol, 1.1 eq.) were dissolved in dry toluene (9 mL) under argon atmosphere. The solution was cooled to 0 ºC and PPh_3 (0.316g, 1.20 mmol, 1.2 eq.) was added followed by dropwise addition of DEAD (0.200 mL, 1.14 mmol, 1.1 eq.). The mixture was stirred at 0 ºC for 7.5 h, slowly warmed to r.t. and stirred overnight at r.t. Afterwards, the reaction mixture was diluted with DCM, concentrated on silica gel and purified by column

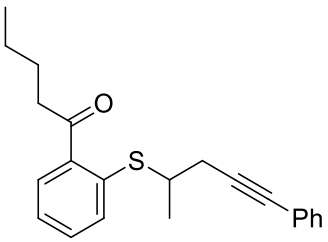
chromatography (100:1:2 $CHCl_3$/MeOH/AcOH) to provide desired compound as white solid (0.221 g, 72 %).
R_f = 0.29 (1:1:0.05 PE/EtOAc/Et_3N); m.p.: 104 – 106 ºC
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (br, 2H), 8.11 – 8.05 (m, 1H), 7.83 – 7.74 (m, 1H), 7.57 – 7.47 (m, 2H), 7.46 – 7.41 (m, 2H), 7.37 – 7.27 (m, 4H), 5.10 (s, 2H), 2.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.27, 157.87, 150.35, 131.93, 131.81, 131.24, 129.51, 129.29, 129.17, 128.55, 121.92, 121.37, 121.29, 114.16, 88.33, 82.85, 57.43, 32.21. FT-IR (neat) ν_{max}/cm^{-1}: 3058, 2919, 2232 (C≡C), 1665 (C=O), 1595, 1461, 1375, 1268, 1220, 1020, 770, 693 cm^{-1}. HRMS (ESI) calc. for $C_{22}H_{18}NO_2$ (M+H): 328.1338; Found: 328.1338.

1-(2-mercaptophenyl)pentan-1-one (XX)



Thiosalycilic acid (2.057 g, 13.08 mmol, 1.0 eq.) was dissolved in dry THF (60 mL) under argon atmosphere. The solution was cooled to 0 ºC and n-BuLi (21 mL, 2.5 M, 52 mmol, 4.0 eq.) in hexane was added dropwise over 50 min. After 40 min, the ice bath was removed and the mixture was stirred at r.t. for 5 h. Afterwards, the reaction was cooled to 0 ºC, diluted with saturated $NaHCO_3$ (15 mL) and extracted three times with EtOAC (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (100:1→80:1 PE/EtOAc) to provide desired compound as yellowish solid (1.638 g, 65 %).
^{1}H NMR is in accordance with literature [97].
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.19 (ddd, *J* = 8.5, 5.5, 3.0 Hz, 1H), 4.34 (s, 1H), 3.01 – 2.90 (m, 2H), 1.72 (p, *J* = 7.5 Hz, 2H), 1.41 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

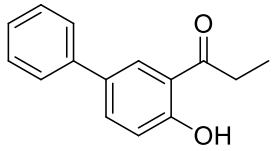
1-(2-((5-phenylpent-4-yn-2-yl)thio)phenyl)pentan-1-one (XXI)



1-(2-mercaptophenyl)pentan-1-one (**XX**) (0.402 g, 2.07 mmol, 1.0 eq.) was dissolved in dry toluene (15 mL) followed by 4-phenyl-3-butyn-2-ol (0.370 mL, 2.46 mmol, 1.2 eq) under argon atmosphere. The solution was cooled to 0 ºC and PPh_3 (0.826 g, 3.15 mmol, 1.5 eq.) was added followed by dropwise addition of DEAD (0.540 mL, 3.08 mmol, 1.5 eq.). The mixture was stirred at 0 ºC for 1.5 h. Afterwards, the reaction was concentrated on silica gel and purified by column chromatography (60:1 PE/EtOAc) to provide desired compound as yellowish oil (0.185 g, 28 %).
R_f = 0.40 (40:1 PE/EtOAc).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.46 (td, *J* = 7.7, 1.5 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.21 (m, 4H), 4.22 (q, *J* = 7.0 Hz, 1H), 2.99 – 2.89 (m, 2H), 1.77 – 1.62 (m,

5H), 1.39 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 203.12, 138.39, 137.64, 131.77, 131.48, 129.99, 129.28, 128.30, 128.21, 125.44, 123.15, 90.23, 83.45, 40.87, 32.37, 26.53, 22.56, 21.18, 14.07. FT-IR (neat) ν_{max}/cm^{-1}: 2956, 2929, 1670 (C=O), 1490, 1460, 1442, 1195, 1071, 1002, 969, 754, 690 cm^{-1}. HRMS (ESI) calc. for $C_{20}H_{21}OS$ (M+H): 323.1464; Found: 323.1465.

1-(4-hydroxy-[1,1'-biphenyl]-3-yl)propan-1-one (XXII)

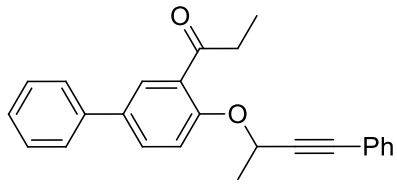


5'-Bromo-2'-hydroxypropiophenone (0.304 g, 1.26 mmol, 1.0 eq.), K_2CO_3 (0.699 g, 5.06 mmol, 4.0 eq.) and phenylboronic acid (0.190 g, 1.53 mmol, 1.2 eq.) were suspended in sparged by argon toluene (6.5 mL) and EtOH/H_2O (3.9 mL, 2:1) under argon atmosphere. To this mixture $Pd(PPh_3)_4$ (0.084 g, 0.073 mmol, 0.05 eq.) was added and the reaction was stirred at 100 ºC for 18 h. Afterwards, the mixture was diluted with H_2O (15mL) and extracted twice with EtOAc (50 mL). The combined organic layers were washed once with brine (15mL), dried over Na_2SO_4, filtered, concentrated on silica gel and purified by column chromatography (3:1 PE/DCM) to provide desired compound as a yellowish solid (0.247 g, 87 %).

R_f = 0.43 (1:1 PE/DCM); m.p.: 89 – 90 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.37 (s, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 3.12 (q, *J* = 7.3 Hz, 2H), 1.28 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.29, 161.95, 140.21, 135.16, 132.41, 129.07, 128.29, 127.32, 126.85, 119.43, 119.10, 31.79, 8.36. FT-IR (neat) ν_{max}/cm^{-1}: 3744 (O-H), 3241, 2983, 2939, 2907, 1635 (C=O), 1479, 1374, 1358, 1267, 1194, 964, 774, 759, 699 cm^{-1}.

1-(4-((4-phenylbut-3-yn-2-yl)oxy)-[1,1'-biphenyl]-3-yl)propan-1-one (Ic)



1-(4-ydroxy-[1,1'-biphenyl]-3-yl)propan-1-one (**XXII**) **(**0.120 g, 0.529 mmol, 1.0 eq.) was dissolved in dry toluene (4 mL) under argon atmosphere followed by 4-phenyl-3-butyn-2-ol (0.10 mL, 0.667 mmol, 1.2 eq.). The solution was cooled to 0 ºC and PPh_3 (0.191 g, 0.730 mmol, 1.3 eq.) was added followed by dropwise addition of DEAD (0.12 mL, 0.686 mmol, 1.3 eq.). The mixture was stirred at 0 ºC for 50 min. Afterwards, the reaction was diluted with DCM, concentrated on silica gel and purified by column chromatography (40:1 PE/EtOAc) to provide desired compound as colourless oil (0.175 g, 94 %).

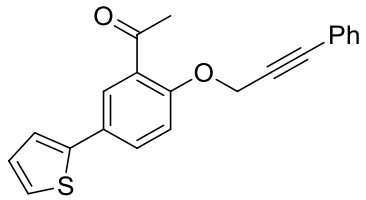
R_f = 0.25 (40:1 PE/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.46 – 7.38 (m, 4H), 7.36 – 7.27 (m, 5H), 5.23 (q, *J* = 6.5 Hz, 1H), 3.19 – 3.02

(m, 2H), 1.84 (d, *J* = 6.5 Hz, 3H), 1.23 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)*: δ 203.70, 155.96, 140.01, 134.48, 131.85, 131.34, 129.82, 128.92, 128.85, 128.45, 127.24, 126.90, 122.20, 114.97, 87.64, 86.62, 65.43, 37.33, 22.49, 8.80. FT-IR (neat) ν_{max}/cm^{-1}: 2986, 2937, 1674 (C=O), 1604, 1479, 1267, 1235, 1083, 1034, 942, 755, 690 cm^{-1}. HRMS (ESI) calc. for $C_{25}H_{23}O_2$ (M+H): 355.1698; Found: 355.1697.

**One aromatic ^{13}C has the same chemical shift as another one.*

1-(2-((3-phenylprop-2-yn-1-yl)oxy)-5-(thiophen-2-yl)phenyl)ethanone (XXIII)



1-(2-hydroxy-5-(thiophen-2-yl)phenyl)ethanone (0.0778 g, 0.356 mmol, 1.0 eq.) and 3-phenylpropargyl bromide (0.080 mL, 0.57 mmol, 1.6 eq.) were dissolved in dry DMF (2 mL) under argon atmosphere. The mixture was cooled to 0 ºC and K_2CO_3 (0.0730 g, 0.528 mmol, 1.5 eq.) was added in one portion. After 0.5 h the ice bath was removed and the reaction mixture was stirred at r.t. for 6 h. Afterwards, the reaction was diluted with H_2O (10 mL) and extracted three times with DCM (50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated on silica and purified by column chromatography (10:1 PE/EtOAc) to provide desired compound greenish solid (0.114 g, 96 %).

R_f = 0.39 (10:1 PE/EtOAc); 80 – 82 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 2.5 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.29 – 7.23 (m, 3H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.06 (s, 2H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.55, 156.49, 143.18, 131.93, 130.84, 129.45, 129.08, 128.52, 128.32, 128.19, 127.97, 124.77, 123.12, 122.04, 114.05, 88.13, 83.13, 57.47, 32.17. HRMS (ESI) calc. for $C_{21}H_{17}O_2S$ (M+H): 333.0949; Found: 333.0944.

CONCLUSIONS

- Single step reaction using 2,6-ditosyl-1,5,2,6-dithiadiazocane as sulfenamide source and MsOH as strong Brønsted acid with various styrenes and stilbenes provided corresponding thiomorpholine derivatives. In the case of stilbenes, it was demonstrated, that Ms- or Cbz-protecting group containing sulfenamides can be utilized too.

- Attempts to employ more phenyl substituted alkenes to obtain desired thiomorpholines were unsuccessful. These alkenes were unreactive, gave uncyclized or thiazolidine derivatives.

- During investigation of the scope it was observed, that those strongly withdrawing groups having styrenes or stilbenes were unreactive, while substrates with strongly donating groups had tendency for polymerization.

- Alkenes with alkyl substituents failed to produce thiomorpholine derivatives, however additionally using ethylene glycol led to prepare macrocyclic ligand type products in two steps.

- Based on the literature together with observed reactivity difference between alkyl substituted alkenes and styrenes or stilbenes, the plausible mechanism involves thiiranium intermediates, where derived from alkyl alkenes are stable, while obtained from stilbenes or styrenes exist in equilibrium with open form and therefore the intramolecular nucleophilic attack is facilitated.

- In the *OrentasGroup* was developed a novel cascade cyclization reaction. Utilizing acetophenone substrates containing phenyl propargyl alcohol substituent in the presence of LiHMDS, molecular scaffolds possessing contiguous six-, five- and four membered rings with excellent diastereoselectivity were synthesized.

- The study of the scope demonstrated that the reaction is compatible with various substituents on both acetophenone and aryl ring of propargylic moiety.

- Mechanistic studies suggest triple bond isomerization into allene followed by lithium enolate addition and subsequent intramolecular anion attack to ketone. In addition, the reaction outcome highly depends on solvent, base, base cation and pK_a of propargylic position.

- Investigation of synthetic applicability of the obtained products revealed that cyclobutane moiety is prone to fragmentation under acidic conditions. Nevertheless, the product or its derivative was successfully utilized in metathesis, photocatalytic ring-opening reaction enabled by proton-coupled electron transfer and epoxidation reactions.

SANTRAUKA

VILNIAUS UNIVERSITETAS
CHEMIJOS IR GEOMOKSLŲ FAKULTETAS

ARMINAS JURYS

Alkenų sulfenofunkcionalizavimo reakcijos naudojant ciklinius sulfenamidus ir formali [2+2] enolių-alenų cikloprisijungimo anijoninė kaskadinė reakcija

Nors nuo organinės sintezės pradžios yra sukurta begalė metodų, o junginių skirtingų tiek struktūra tiek cheminėmis savybėmis dar daugiau, tačiau nepaisant to, vis dar labai daug junginių negalima gauti esamais sintezės būdais arba reikalingos ilgos procedūros su brangiais reagentais. Šiame darbe pristatomi du nauji sintezės metodai gauti modifikuotus heterociklus.

Sotūs heterocikliniai junginiai yra dažnai randami biologiškai aktyvių junginių struktūrose [1]. Atlikti tyrimai parodė, kad kai kurie tiomorfolino dariniai pasižymi priešuždegiminiu, hipocholesteroleminiu ar hipolipideminiu poveikiu [2,3]. Šiuo darbu pristatomas nesudėtingas metodas gauti tiomorfolino darinius panaudojant ciklinius sulfenamidus reakcijoje su stirenais ar stilbenais. Iš tyrinėtų reakcijos sąlygų geriausi rezultatai buvo gauti naudojant 2,6-ditozil-1,5,2,6-ditiadiazokaną, MsOH ir atitinkamą stireną ar stilbeną 1,2-dichloretane. Nurodytas metodas sėkmingiausiai suderinamas su silpnai deaktyvuojančius arba silpnai aktyvuojančius pakaitus turinčiais substratais. Bandymai panaudoti alkil pakeistus alkenus gauti tiomorfolinams nebuvo sėkmingi, tačiau modifikavus metodiką buvo susintetinti makrociklinių ligandų dariniai, turintys platų pritaikymą chemijoje [4].

Tinkamai parinkus sąlygas domino ciklizacijos reakcijos yra puikus metodas norint gauti policiklinius jungnius su gera išeiga ir aukštu stereoselektyvumu. Šios reakcijos plačiai paplitusios gamtoje, kur poliizoprenoidai katalizuojant terpenoidų ciklazėms yra verčiami į terpenus [5]. Tiek gamtoje tiek sintetinėje chemijoje daugiausiai žinomos katijoninės domino reakcijos, o anijoninės yra žymiai retesnės [6,7]. *OrentasGroup* grupėje buvo išrastas naujas anijoninės domino ciklizacijos metodas gauti policiklinius junginius, turinčius sujungtus šešianarį, penkianarį ir keturnarį ciklus, iš aciklinių darinių. Reakcijoje naudojami acetofenono dariniai turintys fenil propargil alkoholio pakaitus ir LiHMDS tetrahydrofurane. Metodas suderinamas su įvairiais substratais, turinčiais pakaitus tiek ant acetofenono tiek ant fenil propargilo fragmento. Gautas policiklinis darinys buvo sėkmingai panaudotas metastezės ir fotokatalinėje žiedo atidarymo reakcijoje.

SUMMARY

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Sulfenofunctionalization of Double Bonds with Cyclic Sulfenamides and Anionic Cascade Cyclization Reaction Representing Formal [2+2] enol-allene Cycloaddition

Although so far a lot of different organic molecules were synthesized using sophisticated synthetic processes, however plenty chemical structures still cannot be achieved or requires harsh conditions. This master thesis presents two new convenient methods for the synthesis of modified heterocycles.

Saturated heterocycles compounds are usually found in substances having biological activity [1]. For example, it was found that some thiomorpholine derivatives possess anti-inflammatory, hypocholesterolemic or hypolipidemic activity [2,3]. This study presents simple one-pot synthesis to provide thiomorpholine derivatives employing cyclic sulfenamides and *trans*-stilbenes or styrenes. The highest results from optimization reaction conditions were obtained using 2,6-ditosyl-1,5,2,6-dithiadiazocane, MsOH and corresponding *trans*-stilbene or styrene in 1,2-dichloroethane. The method is best compatible with substrates having weakly electron withdrawing or weakly activating substituents. Attempts to employ alkenes with alkyl substitutes were not successful to obtain thiomorpholines. However, after changing synthesis route these alkenes were utilized to prepare macrocyclic ligands, which have a wide range of uses in chemistry [4].

Cascade cyclization reactions are powerful method to provide polycyclic molecules in a single synthetic operation. These reactions are widely spread in Nature, where polyisoprenoid substrates undergo cascade cyclization catalyzed by terpenoid cyclases to form various terpenes [5]. Both in Nature and in synthetic chemistry the cationic cascade cyclizations are much more known than anionic type [6,7]. In the *OrentasGroup* was developed a novel anionic cascade cyclization reaction. Utilizing acetophenone substrates containing phenyl propargyl alcohol substituent in the presence of LiHMDS, molecular scaffolds possessing contiguous six-, five- and four membered rings with excellent diastereoselectivity were synthesized. The study of the scope demonstrated that the reaction is compatible with various substituents on both acetophenone and aryl ring of propargylic moiety. The obtained polycyclic compounds were successfully utilized in metathesis and photocatalytic ring-opening enabled by proton-coupled electron transfer reactions.

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