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Benzo[d]thiazol-2-ylsulfonyl-based pluripotent molecules in organic synthesis

Ph.D. Thesis

Mgr. Ondřej Kováč

Supervisor: doc. RNDr. Jiří Pospíšil, Ph.D.

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Bibliografická identifikace

Jméno a příjmení autora	Mgr. Ondřej Kováč
Název práce	Benzo[d]thiazol-2-ylsulfonyl pluripotentní molekuly a jejich využití v organické syntéze
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Abstrakt	Divergentně orientovaná syntéza je dnes již nezpochybnitelných nástrojem pro medicinální chemii. Účelem tohoto přístupu je zejména umožnit přípravu strukturně rozmanitých molekul, které jsou schopny pokrýt širokou škálu biologických cílů. Cílem této práce je vývoj a aplikace nových Pluripotentních molekul (PM), které umožňují snadnou a rychlou tvorbu rozmanitých strukturních motivů. Kladen je důraz zejména na využití α-benzothiazolylsulfonyl derivátů, které lze využít k divergentní tvorbě vazby C-C, cykloadičním reakcím, Michaelovým adicím, molekulárních přesmycích, ale také v oblasti organokatalýzi. Úkolem je dosáhnout co nejsnadnějšího přístupu k tvorbě strukturně rozmanitých molekul, a tím divergentně orientované chemické knihovně látek.
Klíčová slova:	Organokatalýza, divergentně-orientovaná syntéza, olefinace, cykloadice, Michaelova adice, stereoselektivita, benzothiazolyl sulfon, pluripotentní molekula
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Abstract	Diversity oriented synthesis is now an undisputed tool for medicinal chemistry. The purpose of this approach is to enable the preparation of structurally diverse molecules that can cover a wide range of biological targets. The aim of this work is the development and application of new Pluripotent molecules (PM), that allow easy and fast generation of various structural motifs. The importance is focused on the use of α-benzothiazolylsulfonyl derivatives, which can be used for diverse C-C bond formation, cycloaddition reactions, Michael additions, molecular rearrangements, but also in the field of organocatalysis. The aim is to develop the easiest possible approach for the creation of structurally diverse molecules and thus generating a diversity-oriented chemical library.
Keywords	Organocatalysis, diversity-oriented synthesis, olefination, cycloaddition, Michael addition, stereoselectivity, benzothiazolyl sulfone, pluripotent molecule
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Prohlašuji, že předložená práce je moje vlastní původní práce, která byla vypracována za použití citované literatury.

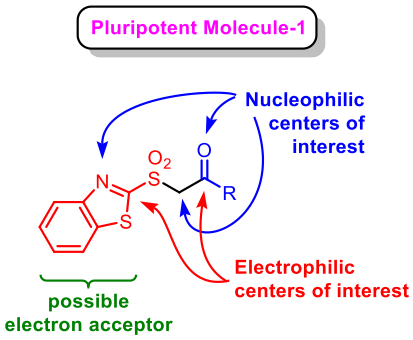
V Olomouci 05.06.2020 Mgr. Ondřej Kováč

It is my pleasure to thank people who helped me during my PhD study. First of all, I would like to thank my supervisor doc. RNDr. Jiří Pospíšil, Ph.D. for his continuous support, fruitful discussions not only about organic synthesis, creative ideas, motivation, neverending optimism and especially the wonderful opportunities that came to me thanks to him. My big thank belongs to professor Mario Waser and his research group, who created a very friendly environment for me and a wonderful opportunity to participate in his projects, which I really enjoyed. Last but not least, I would like to thank all the members of our research group, as well as the members of the Department of Organic Chemistry, for creating a friendly and inspiring work environment. Furthermore, every research needs financial support therefore I would like to acknowledge IGA_PrF_2020_012 for generous support.

Aims of the Thesis

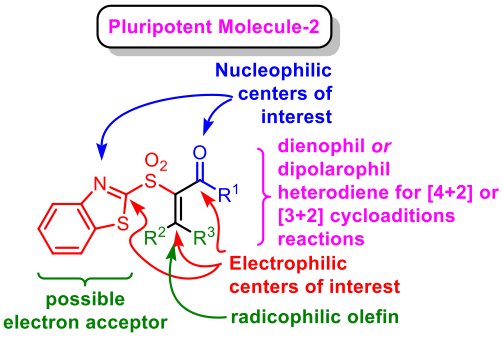
1) Preparation and application of Pluripotent Molecule 1 in context of Divergent-Oriented Synthesis.

To exploit in one-pot protocol various reactive centres present in one molecule (**PM-1**) in context of selective C-C bond formation (olefination, alkynylation, ketone/ester formation) and 5-membered heterocycle formation (pyrroles, furans, thiophenes).



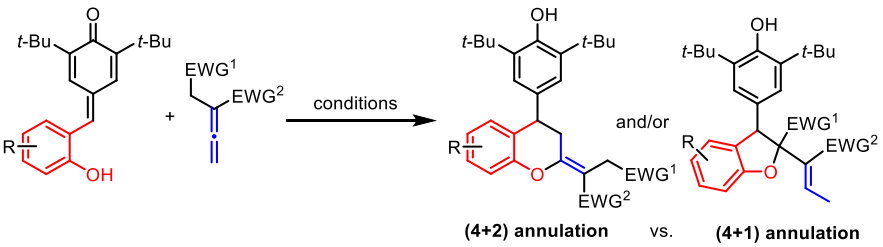
2) Preparation and application of Pluripotent Molecule 2 in context of Divergent-oriented synthesis.

To develop Pluripotent Molecule 2 (**PM-2**) synthesis and to explore its reactivity in the context of various reactions (charge-based, radical, pericyclic, rearrangements) and to apply **PM-2** in context of organocatalytic reaction using chiral amines and phosphines.



3) Exploration of *ortho*-hydroxy-*para*-Quinone methides reactivity towards allenoates.

To develop (4+2) and (4+1)-annulation reactions of above-mentioned reagents.



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List of abbreviation

ADDP	1,1-(Azodicarbonyl)dipiperidine
AIBN	Azobisisobutyronitrile
BINAP	2,2'-Bis(difenylfosfino)-1,1'-binaftyl
Bn	Benzyl
BT	Benzothiazole
BTSSBT	Dibenzothiazol-2-yl disulfide
Bz	Benzoyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density-functional theory
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DOS	Diversity oriented synthesis
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDDA	Ethylenediamine-*N,N*'-diacetic acid
EDG	Electron donating group
EWG	Electron withdrawing group
FG	Functional group
GLG	Good leaving group
HOBt	Hydroxy benzotriazole
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
IPA	Isopropyl alcohol
KHMDS	Potassium hexamethyldisilazane
LA	Lewis acid
LB	Lewis base
LC-MS	Liquid chromatography-Mass spectrometry

LDA	Lithium diisopropylamide
LG	Leaving group
LiHMDS	Lithium hexamethyldisilazane
LUMO	Lowest unoccupied molecular orbital
MBH	Morita-Baylis-Hillman
m-CPBA	*meta*-Chloroperoxybenzoic acid
Ms	Mesyl
NaHMDS	Sodium hexamethyldisalazane
NBS	*N*-bromsuccinimide
n-BuLi	*n*-butyl lithium
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
PMHS	Polymethylhydrosiloxane
PPTS	Pyridinium *p*-toluene sulfonate
PT	Phenyl-tetrazole, proton transfer
PTC	Phase transfer catalyst
p-TSA	*para*-toluene sulfonic acid
SAR	Structure and activity relationship
SET	Single electron transfer
SFC	Supercritical fluid chromatography
SM	Starting material
T.S.	Transition state
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-butyl-dimethyl silyl
TDA-1	*Tris*[2-(2-methoxyethoxy)ethyl]amine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMS	Trimethyl silyl
TOS	Target oriented synthesis
Ts	Tosyl

1 Introduction

Modern medicinal chemistry focusses on the use of small molecules, which upon interacting with bio-macromolecules may lead to the modification of biological pathways. Such small chemical entities (molecular probes) are extremely important to achieve a basic understanding of biological systems (chemical biology) and processes. The easiest way to obtain active small molecules with interesting biological properties is a screening of chemical libraries. The general rule, bigger = better, that was applied in the 90-ties and early 21st century is less and less applied nowadays. A more interesting approach is to generate diversity-oriented chemical libraries[1,2]. The word "diversity" is not limited in this context only to the atom connectivity (scaffold appendages), but it also refers to the specific distribution around and the rigidity of prepared molecular scaffolds[3].

The change in the library contents constitution is a consequence of the biological target-based screening approach. In late 90-ties and early decade of 21st century, constituted chemical libraries were mostly screened against known biological targets (e.g. targeted proteins/enzymes were crystallized/computed active sites were known with high level of accuracy). Thus, focused libraries that were screened against such targets readily generated "hits" and virtually "fed" scientists with leading compounds. At the end of the first decade of the 21st century, the situation has changed dramatically. New diseases/targets with unknown active site or mode of action were selected as drug targets. Unfortunately, in this case, focused libraries proved to be useless and the results obtained by screening were truly disappointing[4]. As a reaction to such situation, Schreiber[5] proposed and developed a novel approach of library generation. He suggested that newly constituted libraries should be composed of structurally *different* scaffolds. To achieve such goal, two different approaches to build up chemical libraries were proposed: (1) to use already structurally different compounds and to further modify them with the same chemical transformations, and (2) to develop synthetic methods that would have inherently encoded new molecular scaffold formation while applied to the same type of the substrate. And ideally to combine these two approaches. Applying such an approach, further on renamed as Divergent oriented synthesis (DOS), with limitation of 2 to 5 synthetic steps, should furnish desired structural diversity in newly constituted chemical libraries.

One of the aims of our research group is to develop novel synthetic strategies that would allow the preparation of diverse molecular scaffolds in a short, simple, and efficient manner from readily available starting materials. The key step of our strategy is the design of highly functionalized intermediate that would allow us to transform it into highly stereo and scaffold-diverse products. The key intermediate in these transformations referred to as **Pluripotent Molecule** (**PM**), is the *key* in reaching to our main goal = Scaffolds Diversity.

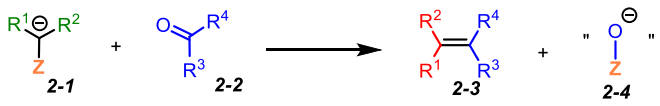
2 Theoretical part

2.1 Introduction to the olefination methods

The formation of multiple bonds C=C has always been one of the most important and challenging tasks in synthetic organic chemistry since alkenes (olefins) are omnipresent in biologically active substances[6]. Besides, olefins are very useful as a starting material, especially if they are considered as functional groups, for subsequent synthetic transformations.

Carbon-Carbon olefinic bonds are thus often created as the last functional group when synthesis of complex biologically active compounds is planned and performed. Therefore, the demand for controlling stereoselectivity of such transformations and requirements for milder reaction conditions triggered and still triggers the development of new synthetic protocols and methods. Many of those olefination methods follow a similar retrosynthetic pattern. It divides C=C bond to two parts where one fragment (***2-1***) hosts carbanion (ylide) species with carbanion stabilized with adjacent anion-stabilizing group Z, and the second fragment (***2-2***) is terminated with an electrophilic carbonyl group (aldehydes, ketones, or derivatives of carboxylic acid). The driving force of such transformations is the formation of new oxygen-heteroatom (O-Z) bond-containing species ***2-4*** where the O-Z is stronger than it was in the original O-C bond in the carbonyl group of ***2-2***. In general, the whole sequence proceeds in several fundamental steps and lead to the formation of a double bond between coupling partners (***2-3***) and oxidized form of activating group (***2-4***). Several most commonly employed olefination methods based on this principle are shown in Table 1.[7–11]

Table 1 – Overview of olefination methods.



Activating unit Z	Olefination method	Lit. reviews
$PhSO_2$	Julia-Lythgoe	Ref. [12]
$HetSO_2$	Julia-Kocienski	Ref. [12]
R_3P^+	Wittig	Ref. [8]
$R_2P(=O)$	Wittig-Horner	Ref. [8]
$(RO)_2P(=O)$	Horner-Wodsworth-Emmons (HWE)	Ref. [9]
R_3Si	Peterson	Ref. [10]
ArS(=O)(=NMe)	Johnson	Ref. [11]
Het= heteroaryl		

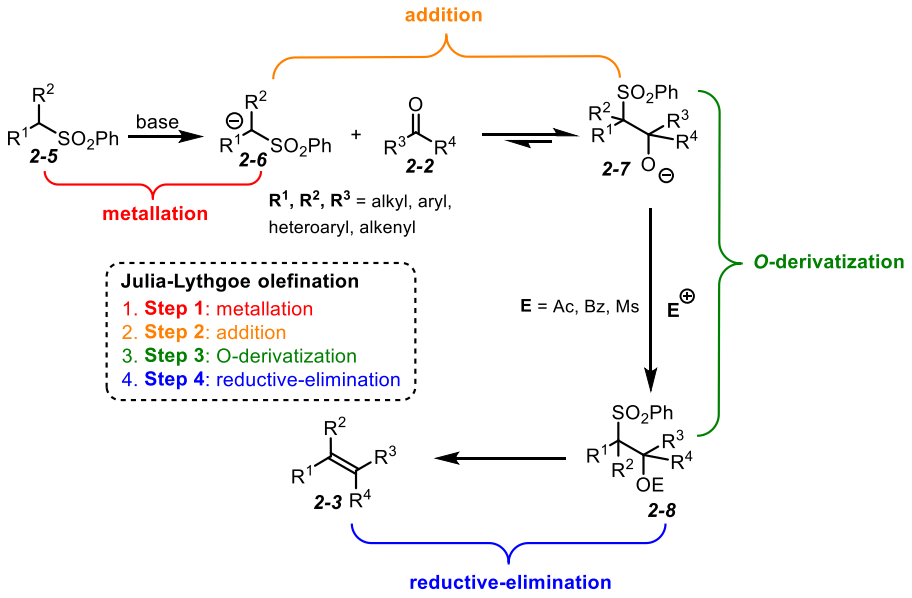
The second most commonly used approach emerged relatively recently and is referred to as metathesis-based approach. The method starts from the two olefins and generates, in general, one new *more complex* C=C bond, and one *less complex* C=C bond.[13] The "olefin exchange" is promoted

with the help of transition metals and it is a catalytic process. However, it creates "olefin from olefin" and therefore it will not be covered in my manuscript.

My Thesis will mainly focus on the olefination methods that exploit the rich chemistry of sulfur. This group of reactions includes mainly Julia-Lythgoe[14] and Julia-Kocienski[15] olefination. The key features of these transformations as the influence reagents/reaction conditions on olefination stereoselectivity, advantages and disadvantages of both methods, and some applications will be discussed. At the end of this introductory chapter, a contribution of our research group to the development of this field will be discussed.

2.2 Julia-Lythgoe olefination

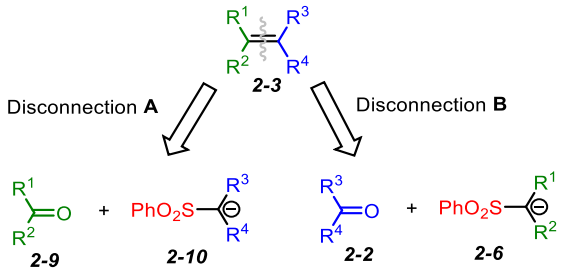
The classical Julia olefination reaction, also known as Julia-Lythgoe olefination, was first described by Mark Julia and Paris in 1973.[14] The reaction was further studied and optimized by Kocienski and Lythgoe[16] (introduction of the *O*-derivatization of generated β-hydroxy sulfone ***2-7***) and consist from three-step protocol that is in general carried out as a two-pot procedure (Scheme 1). Mechanistically the "classical" Julia-Lythgoe olefination can be divided into 4 elementary steps. The first step includes α-metalation of phenyl sulfones ***2-5*** (R^1, R^2 = alkyl, aryl, heteroaryl) to generate the corresponding carbanion ***2-6***. Next, the addition of ***2-6*** to the carbonyl group ***2-2*** generates β-hydroxy sulfone ***2-7***. Final fourth step, reductive elimination, yields the desired olefin ***2-3***. It is important to note that the addition of ***2-6*** to ***2-2*** is not stereoselective. Fortunately, the stereochemical information gained in the addition step is lost during the reductive-elimination step.



Scheme 1 – Mechanism of Julia-Lythgoe olefination.

The main attractivity of Julia-Lythgoe olefination is in its simple and versatile disconnection approaches. Targeted olefins can be always accessed olefin disconnection to two basic fragments

wherein one of the fragments is nucleophile (carbanion) and the other is electrophile (carbonyl). And any of the two possible disconnections is, in theory, the privileged one (Scheme 2).

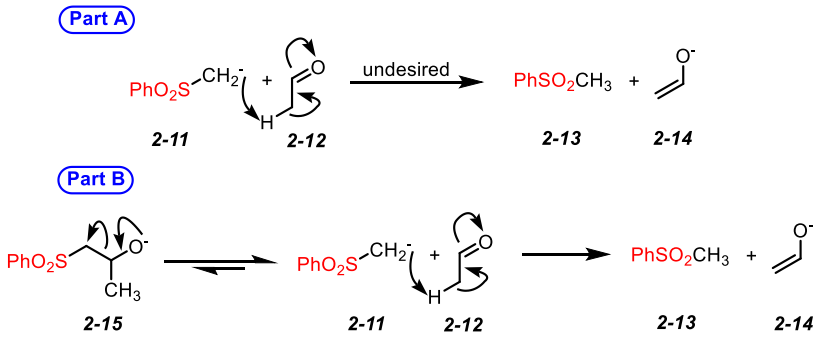


Scheme 2 – Retrosynthetic approach to olefins using Julia-Lythgoe olefination method.

In reality, one of the two disconnections are "always better", since *the other* possibility provides two fragments with one or more "possible complications" that could arise either during the fragment synthesis or during the coupling steps Concerning the coupling sequence, the care should be taken in several cases:

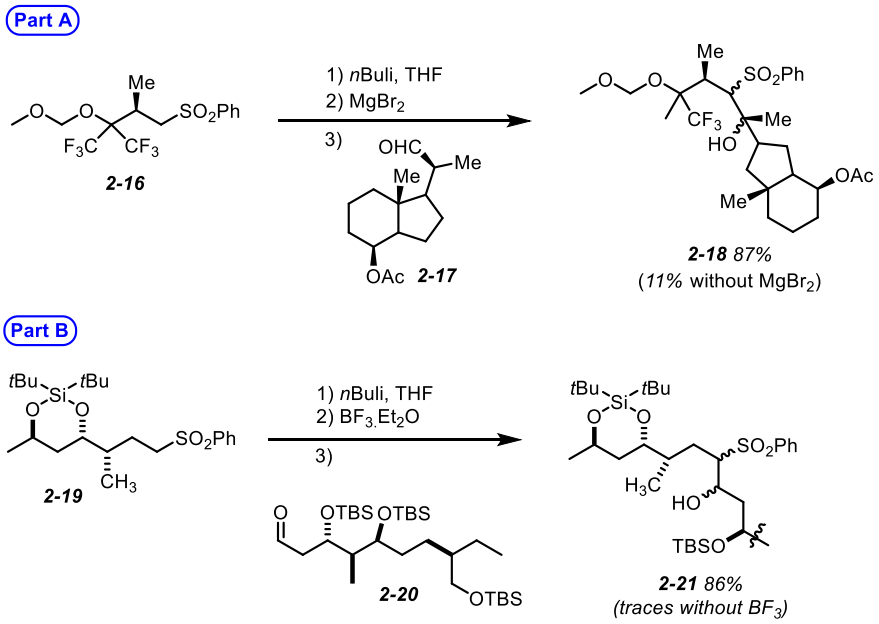
a) the number and the nature of the substituents on sulfone fragment should be considered.
b) the nature of the counter-ion formed during metalation step (base selection) should be considered.
c) the nature and reactivity of the carbonyl part (aldehyde or ketone) and possible base-promoted side reactions should be considered.

Most commonly the Julia-Lythgoe olefination is used to generate 1,2 disubstituted olefins. However, even in this case, the care should be taken when the disconnection partners are planned. One of the most commonly encountered problems during the coupling step is the side reactions linked with the carbanion ***2-11*** chemistry. If ***2-11*** lacks the reactivity towards the carbonyl partner (mostly due to the steric hindrance) or is highly basic, several base/related side reactions might be encountered (Scheme 3, Part A). Similarly, the same side reactions can be encountered if the adduct ***2-15*** readily undergoes to retro-aldol type reaction (Scheme 3, Part B). The same is true if well stabilized α-metallated sulfonyl anions are used (Scheme 3)[17].



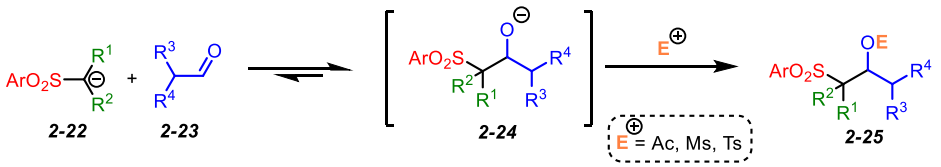
Scheme 3 – Side reactions previously observed during the Julia-Lythgoe reaction – addition step.

Obviously not always we can easily switch the disconnection fragments. Thus, several methods allowing us to overcome such type of problems was developed. It was found that the change in the nature of counter cation has a tremendous effect on the carbanion reactivity. Thus the change of lithium to magnesium[18] or boron trifluoboride[19] effectively drives the coupling step to completion (via the change in basicity – diminishes the side reactions, or by shifting the reaction equilibrium – stabilize the adduct), and improve the yields of the final adducts (Scheme 4).



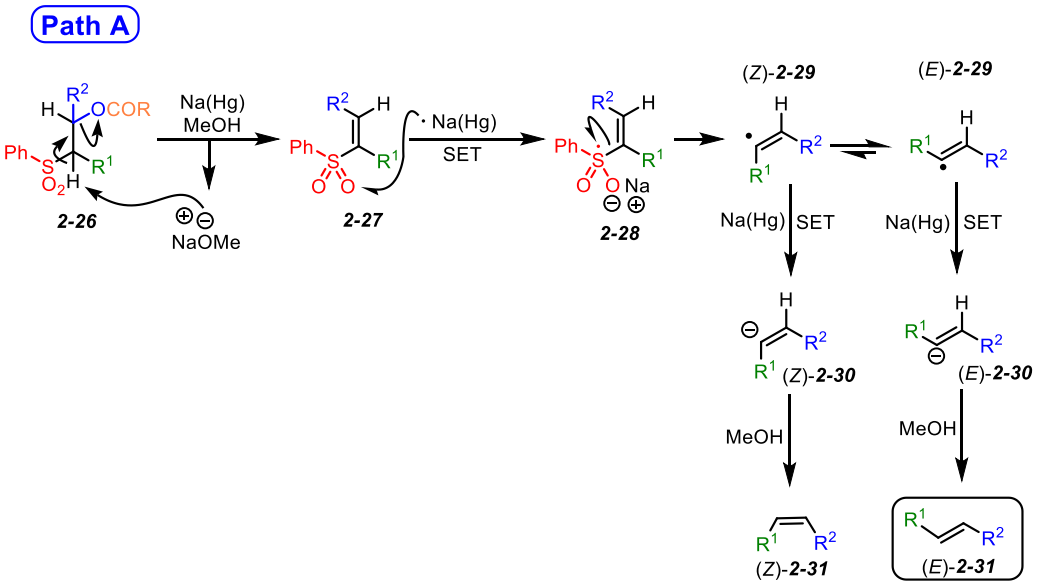
Scheme 4 – Solving the problems of the side reactions in Julia-Lythgoe reaction – coupling step.

Of course, the most common way how to shift the equilibrium from the starting materials (carbanion ***2-22*** and carbonyl ***2-23***) to adduct ***2-24*** is to trap *in situ* the generated alcoholate ***2-24*** with an external electrophile (Scheme 5). In advantage, it was further observed that the next step of the sequence - reductive-elimination – proceeds with higher yields when *O*-modified adducts ***2-25*** are used as a reductive-elimination starting material.



Scheme 5 – Solving the problems in Julia-Lythgoe reaction with the coupling step reaction yields.

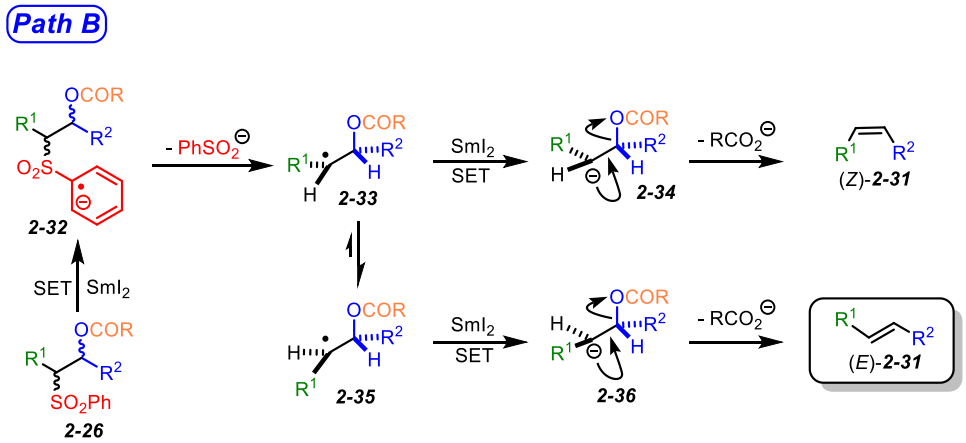
The final step of Julia-Lythogoe olefination is reductive elimination. Many different reducing agents can be employed in this last step. Most commonly used reagent is Na(Hg) amalgam – readily commercially available, air-stable, and simple to use reagent. Since 1990, the use of SmI_2 as a new reductive-elimination reagent also slowly increases.[20] Even though the mechanism of Julia-Lythgoe olefination is not completely understood, three main mechanistic explanations are believed to operate during the reductive-elimination (Scheme 6, Scheme 7, and Scheme 8). When Na(Hg) amalgam is used as a reducing agent (Scheme 6), the reaction proceeds under weakly basic conditions. And since the reaction is generally carried out in MeOH, $CH_3O^-Na^+$ is spontaneously generated *in situ*. In such case, the reductive-elimination step is proceeded by the vinyl sulfone ***2-27*** formation (via β-elimination in ***2-26*** that is triggered by the α-hydrogen deprotonation). Subsequently, a single electron transfer from Na(Hg) to ***2-27*** occurs. Generated sulfone radical ***2-28*** spontaneously fragments to yield (*Z*)-***2-29*** vinylic radical. Vinyl radical (*Z*)-***2-29*** readily equilibrates to thermodynamically more stable (*E*)-***2-29*** radical, and the second SET forms the vinyl anion ***2-30***. Vinyl anions (*Z*)-***2-30*** and (*E*)-***2-30*** are configurationally stable and they are further protonated with the proton from MeOH and yields the desired olefins (*Z*)-***2-31*** and (*E*)- ***2-31*** (Scheme 6)[21].



Scheme 6 – Julia-Lythgoe olefination and Na(Hg)-mediated reductive-elimination step – a mechanism.

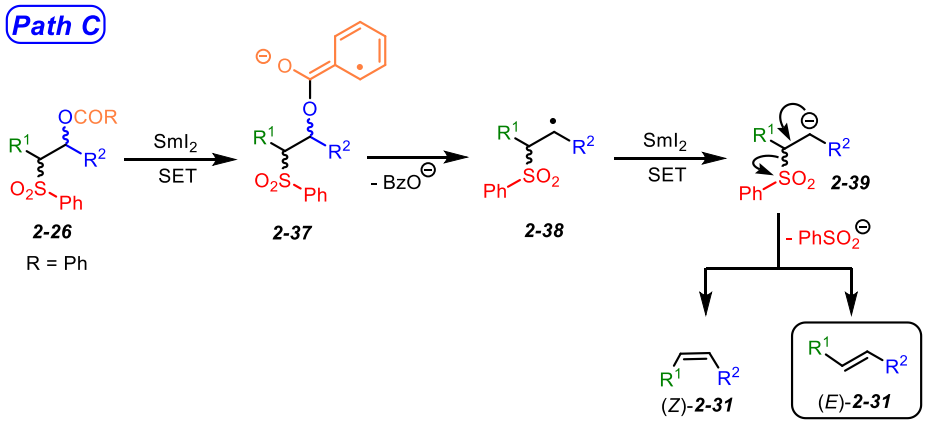
The different mechanism operates when a non-basic reducing agent such as SmI_2 is used (Scheme 7). In that case, the reaction starts with SET to a phenylsulfonyl group in ***2-26***. Generated

radical anion ***2-32*** than undergoes to spontaneous phenyl sulfinate elimination and generates configurationally unstable radical ***2-33***. The second SET generates carbanion ***2-34*** that undergoes to the β-elimination and yields desired olefin ***2-31***[22].



Scheme 7 - Julia-Lythgoe olefination and SmI_2-mediated reductive-elimination step – a mechanism.

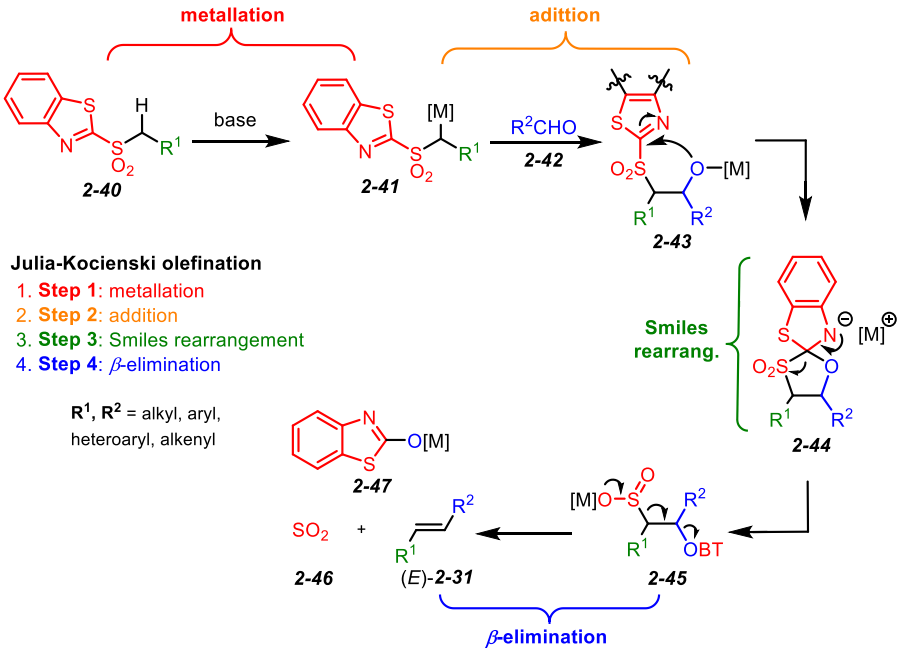
The last reductive-elimination mechanism covered in this chapter is based on the experimental data gathered by Markó et al. during their study of SmI_2-mediated reductive-elimination processes. They observed that depending on the *O*-substitution in Julia-Lythgoe adduct, the reaction rate of the reductive elimination differs. Interestingly under-tested reaction conditions, the transformation of β-benzoyloxy sulfones were faster than that of β-hydroxy or β-acetyloxy sulfones.[23] Such observation along with additional competitive experiments led Markó et al. to propose another reaction mechanism for the reductive-elimination step. They suggested that SET does not occur to the phenylsulfonyl group, but benzoyloxy group instead (Scheme 8). Radical anion ***2-37*** is generated and its fragmentation yields β-alkyl radical ***2-38***. Immediate second SET generating carbanion ***2-39*** occurs, and the subsequent β-elimination finally yields thermodynamically more stable olefin ***2-31***.



Scheme 8 - Julia-Lythgoe olefination and SmI_2-mediated reductive-elimination step – an alternative mechanism.

2.3 Modified Julia-Lythgoe olefination – Julia-Kocienski reaction

The Julia-Lythgoe olefination is a great olefination protocol with one small but important disadvantage – it consists of two separate steps. Thus, when in 1991 Silvestre Julia (brother of Mark Julia) published a protocol that allowed direct synthesis of olefins from α-lithiated heterocyclic sulfones ***2-40*** and carbonyl compounds ***2-42***, the publication met with tremendous success.[15] This one-pot modification of classical Julia olefination protocol brought the Julia olefination sequence to a whole new era of development. The key modification in the protocol was the replacement of the sulfonyl phenyl group with the heteroaryl group (benzothiazole – BT). The installation of the BT-group allowed the reaction sequence to incorporate a Smiles rearrangement step that made the reductive-elimination disposable (Scheme 9). The desired olefin is then prepared from the rearranged product only via simple β-elimination. In details, generated carbanion ***2-41*** reacts with carbonyl ***2-42*** to yield β-alkoxy sulfone ***2-43***. Spontaneous alkoxide intramolecular Smiles rearrangement[24] that proceeds via 5-membered cyclic spiro intermediate ***2-44*** generate sulfenium anion ***2-45***, and final antiperiplanar β- elimination of ***2-45*** releases along with SO_2 (driving force) and heterocycle ***2-47*** the desired olefin ***2-31***.



Scheme 9 – Mechanism of Julia-Kocienski olefination – overview of basic steps.

The reaction protocol becomes very popular due to its simple setup and mild reaction conditions. In addition, it also overcame the two main drawbacks of the Julia-Lythgoe olefination: (a) it is a one-pot protocol, and (b) no air-sensitive or toxic reducing agents are required. Soon after the reaction introduction to the synthetic community, Kocienski et al. have observed that the nature of heterocycle has a huge impact on the reaction *E*/*Z* selectivity. Thus, various heterocycles were tested

as BT-equivalent in the Julia-Kocienski olefination reaction conditions (Figure 1), and few of them as pyridine-2-yl (PYR)[25], 1-phenyl-1H-tetrazole-5-yl (PT)[26], 1-tert-butyl-1H-tetrazole-5-yl (TBT)[27] and 3,5 - bis. (trifluoromethyl) phenyl (BTFP)[28] (and some others[29]) become the standard heterocyclic groups used in Julia-Kocienski reaction.

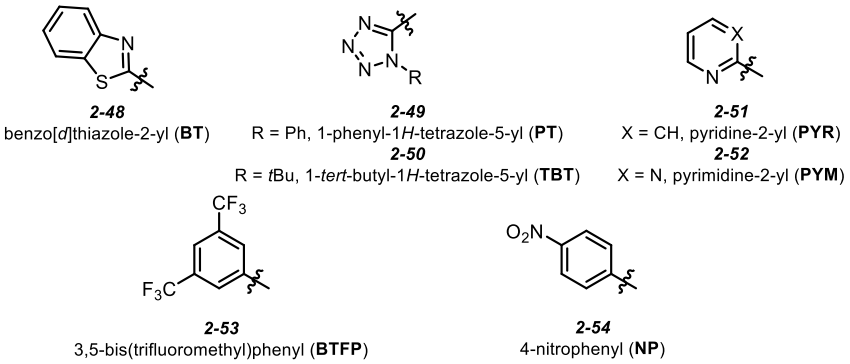
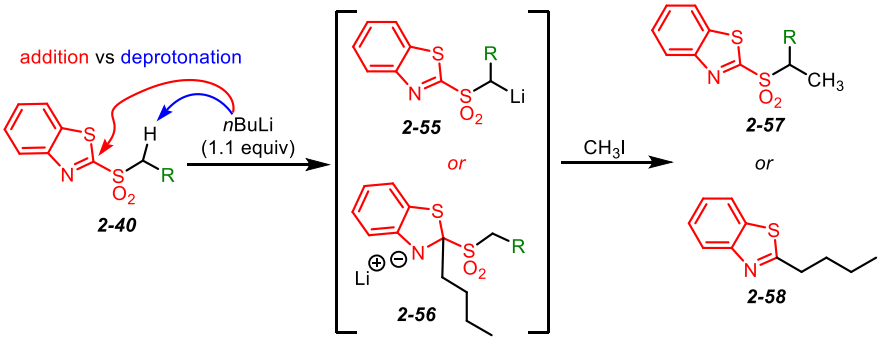


Figure 1 – Most commonly used heterocyclic sulfones in Julia-Kocienski olefination.

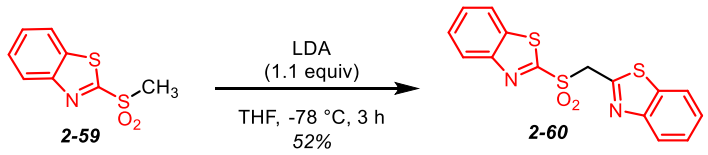
As shown in Scheme 9, to allow the olefination reaction to proceed, heteroaryl group having a strong electrophilic centre α to a sulfone group must be employed. This reactive centre will then serve as the electrophilic site for *in situ* generated alcoholate nucleophile intramolecular attack. It will trigger the Smiles rearrangement. The centre however cannot be too reactive. In that case, two undesired situations can occur. First, a base (such as *n*-Buli) can act as a strong nucleophile and instead of desired carbanion generation it could add to the sulfone ***2-40*** heterocycle and yield intermediate ***2-56***. The experimental evidence for such behaving was obtained when sulfone ***2-40*** was reacted with *n*-BuLi and generated intermediates ***2-55*** and ***2-56*** were quenched with MeI.[30] Both expected products ***2-57*** and ***2-58*** were isolated (Scheme 10).



*Scheme 10 – Side reactions of **2-40** observed when n-BuLi was used as a base.*

Such drawback can be easily overcome if non-nucleophilic bases as [M]-HMDS or lithium-tetramethyl-piperidine are used. However, one should not forget that even in such cases, generated α-lithiated heteroaryl sulfone can react as a nucleophile and add to the molecule of non-deprotonated sulfone. Hopefully, in most cases, the auto-dimerization is a rather slow process (Scheme 11).[31] In the

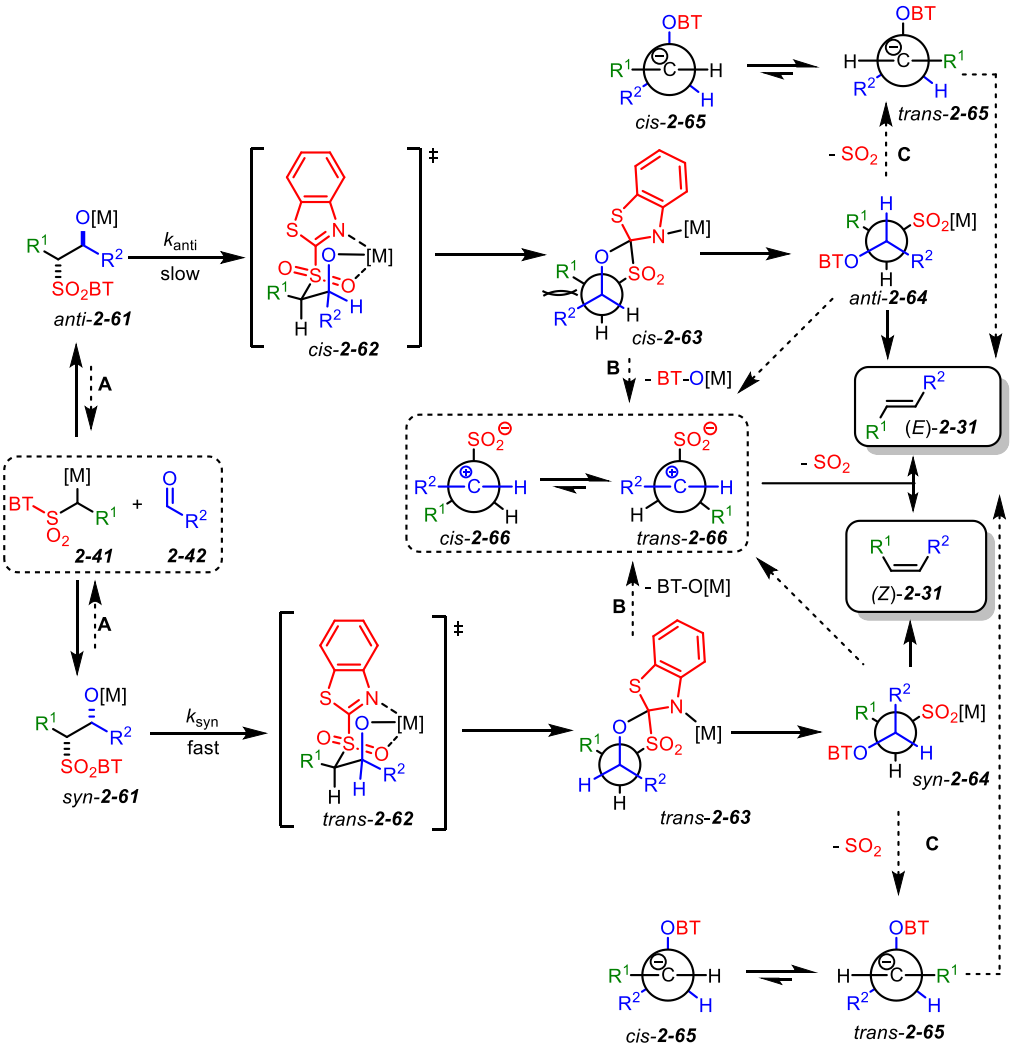
literature is widely reported that the use of PT group in the Julia-Kocienski olefination process generates carbanions that are less prone to self-condensation.[26] However if heteroaryl sulfone is attached to α,β-unsaturated alkyl group or branched alkyl chains are part of the sulfone, the BT group has proven to be less prone to self-condensation than the PT group.[32] Other heterocycles mentioned in Figure 1 do not undergo rapid self-condensation, presumably due to their lower reactivity towards external nucleophiles. Such groups are however not widely explored in the literature, mostly due to their lower *E/Z*-stereoselectivity (*E/Z* is ~50:50) and to harsher reaction conditions that these groups require to react.



Scheme 11 – Self-condensation reaction using more reactive heterocyclic sulfones.

Regardless of such drawbacks, the Julia-Kocienski olefination fast established itself as a robust olefination method with broad functional groups tolerance and mild reaction conditions. Facile synthesis of the starting materials is also responsible for its success. In terms of *E/Z* selectivity, the method is very sensitive to the reaction conditions and small changes in base, counter cation, solvent, etc., can strongly influence the stereochemical outcome. However, when optimized, excellent selectivity can be achieved. The method is particularly powerful when 1,2 substituted olefins are targeted.[33]

A current understanding of the Julia-Kocienski mechanism is depicted in Scheme 12. It should be noted that in vast majority cases the Julia-Kocienski reactions is used to prepare 1,2-disubstituted olefins. Therefore, the reaction mechanism was studied mostly on such model cases, and therefore presented reaction reflects and is based on such cases. The reaction begins with the addition of the metallated sulfone ***2-41*** to the carbonyl ***2-42*** to give two possible intermediates, *syn* and *anti*-***2-61***. The diastereoselectivity of this step strongly depends on the reaction conditions and is crucial for the observed *E/Z* selectivity of final olefin ***2-31***. If sulfone ***2-41*** with R^1= alkyl is used, the addition is irreversible. On the other hand, by introducing a carbanion-stabilizing substituent (vinyl, aryl, or carbonyl group) the addition reaction is reversible and rapid addition/retro-addition process may lead to the formation of a more thermodynamically stable diastereomer (Path A). Subsequently, intramolecular addition of generated alkoxide ***2-62*** to electrophilic centre within heterocycle leads to the formation of a spirocyclic intermediate ***2-63***. This is the first step of the Smiles rearrangement, that is finished up with the spiro-intermediate opening to sulfinate ***2-64***. The presence of the spirocyclic intermediate was confirmed by NMR analysis and in one special case spiro intermediate was even isolated.[34]



Scheme 12 – Current mechanistic understanding of Julia-Kocienski reaction.

The Smiles rearrangement and especially the first part, spirocyclization, is an important step that can influence/determine the *E*/*Z* selectivity outcome of the reaction. For steric reasons, the formation of *trans*-***2-63*** spiro intermediate is faster than the formation of *cis*-***2-63*** isomer.[30] This observation has two consequences. First, *cis*-***2-63*** intermediate that is more difficult to generate (higher activation barrier) yields overall (*E*)-olefin ***2-31***. The desired and major product of most of studied Julia-Kocienski reactions. The *trans*-***2-63*** that is easy to generate, yield generally minor *Z*-***2-31*** olefin. Thus, the reaction stereoselectivity outcome is not spiro-intermediate formation dependent. Based on these data we can conclude that the addition of metallated ***2-61*** to the carbonyl of ***2-62*** is (a) irreversible, and (b) proceeds via open transition state since the *anti*–***2-61*** adduct is the major product of the addition. If *Z*-olefin should be formed as the major olefin isomer of the reaction, the diastereoselectivity of the addition step should be inversed, and *syn*-***2-61*** adduct must become the major product of the addition. In some cases, a high *Z* selectivity is indeed observed. It is generally believed that such a situation is caused by the reversibility of the addition step. The fast equilibrium

between both ***2-61*** diastereoisomers followed up by the Smiles rearrangement of syn-***2-61*** (lower activation barrier) then yields predominantly *Z*-olefins.[33] Once Smiles rearrangement step is over, β-aryloxy sulfinates ***2-64*** undergo to β-elimination and a double bond is formed.

The detailed reaction mechanism description of the elimination step is unknown but based on the experimental data two possibilities were proposed. In the first one, orbital-driven β-elimination that proceeds via an antiperiplanar arrangement of electron donor and the leaving group is proposed. In the case of *anti*-***2-64***, *E*-olefin ***2-31*** is formed; and in the case of *syn*-***2-64*** *Z*-olefin ***2-31*** is generated (for R^1,R^2 = alkyl). Recently, this mechanistic proposal was confirmed by DFT calculations, where the reaction of $PTSO_2Et$ with acetaldehyde is perfectly matching with the above-proposed mechanism.[35] However, if substituents R^1 and/or R^2 differ from the alkyl chain, e.g. are unsaturated (olefin, aryl), a non-stereospecific transformation of the β-aryloxy sulfinate ***2-64*** to the olefin is presumed to occur. It was suggested for R^2 = aryl, vinyl, that the elimination process proceeds via two-step via the E1 mechanism (Path B). This mechanism was suggested by Silvestre et al. in his seminal work on Julia-Kocienski olefination to explain a high *E* selectivity of olefination method when aromatic aldehydes were used as a substrate. If the anion-stabilizing group is used as R^2, the mechanism may change to E1cb elimination (Path C). Such intermediates were suggested by DFT calculations and supported with experimental data[36–38]. Further studies showed that in some cases the concerted *syn* E2 elimination process may occur[39]. Some other calculations have shown that if 3,5-bis (trifluoromethyl) phenyl sulfonyl acetate is used as BT-equivalent, the elimination can proceed spontaneously from the spiro intermediate. The two leaving components (β-aryloxy and sulfinate) are then simultaneously eliminated[37].

In general, many factors affect the stereochemical outcome of the reaction and the outcome of the reaction can be dramatically influenced by proper choice of the base, solvent, complexing agents, etc. Probably the biggest influence on the reaction stereoselectivity, however, has the choice of coupling partners structure. In general, the reacting partners can be divided into four classes (for selectivity discussion, see below):

1) Sulfone anion and carbonyl are not stabilized/substituted with α, β-unsaturated substituent.
2) Sulfone anion bears α, β-unsaturated substituents, carbonyl not.
3) Sulfone is not substituted with α, β-unsaturated substituents, the carbonyl is.
4) Both partners are stabilized/substituted with α, β-unsaturated substituents.

These “rules” apply to 1,2 disubstituted alkenes but can be extended also to tri and tetrasubstituted alkenes. However, it should be noted that the stereochemical outcome is less predictable in the case of tri and tetrasubstituted olefins due to the steric demands of reacting partners.[33]

2.3.1 Type I – sulfone anion and carbonyl are not stabilized/substituted with α, β-unsaturated substituent

In such types of reaction, stereoselectivity is determined in the first step. The addition of metallated sulfone ***2-41*** to carbonyl ***2-42*** is irreversible and subsequent steps are stereospecific. Using the original reaction conditions developed by Julia and co-workers (BT or PYR sulfones, LDA, THF, -78 °C to room temperature), very low stereoselectivities (50:50) were achieved. However, it was demonstrated that *E*/*Z* selectivity can be significantly increased by proper choice of the base cation and polarity of the solvent[40–42]. Based on these findings, Kocienski et. al investigated the effects of the base, solvent and heteroaromatic sulfones (Figure 2) on olefination *E*/*Z* selectivity in the case of unbranched coupling partners (BT vs. PT)[26].

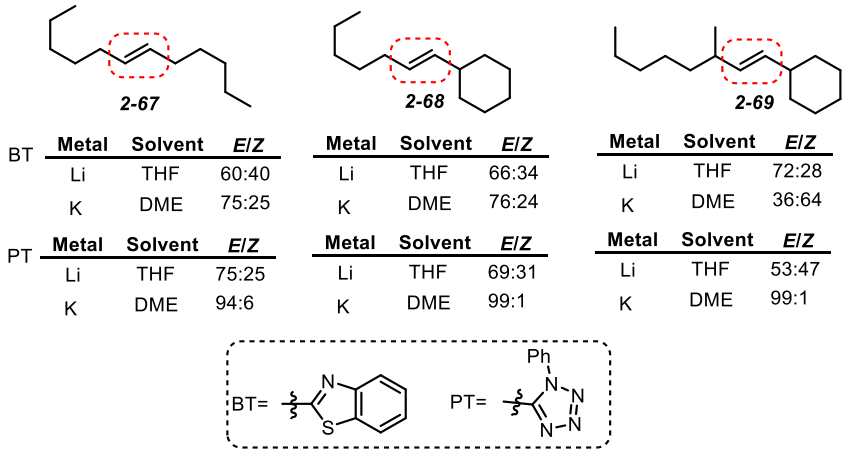


Figure 2 – Effects of base, solvent and heteroaromatic sulfone on E/Z selectivity of Julia-Kocineski olefination (Type I).

Collected experimental results suggest that the *E*/*Z* selectivity outcome of such transformations can be generalized in two types of the T.S. – opened and closed (Figure 3). Based on this model, the *E*/*Z* selectivity of the reaction can be empirically predicted.

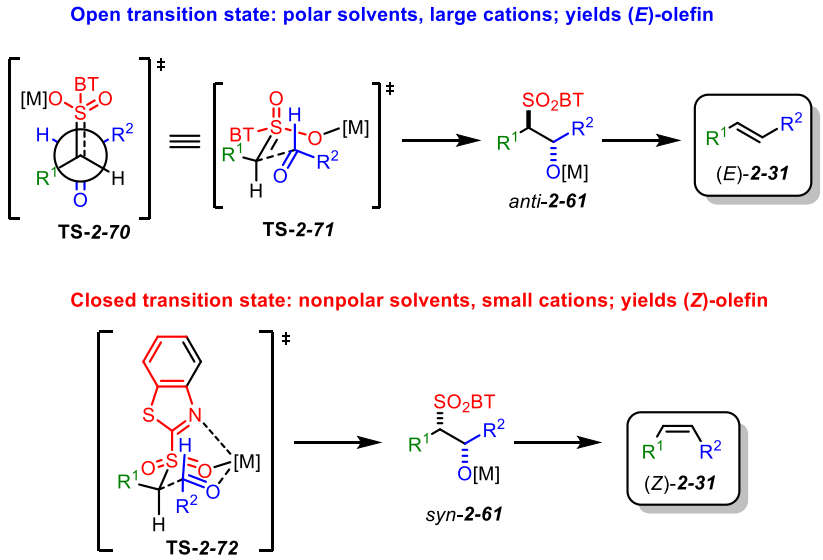
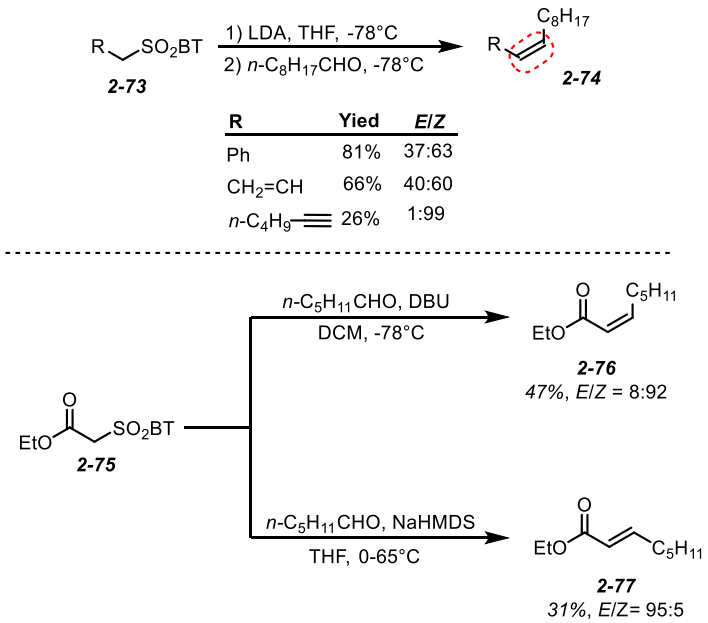


*Figure 3 – Two types of T.S. of Type 1 Julia-Kocienski olefination reaction – opened **2-70** and closed **2-72**.*

2.3.2 Type II – Sulfone anion bears α, β-unsaturated substituents, carbonyl not.

In the case of additional stabilization of α-anion in sulfone ***2-41*** (R^1 = carbonyl, vinyl, alkynyl, aryl), the equilibrium between the two adducts (*syn* and *anti*) can be established since generated *β*-alkoxy sulfone ***2-61*** undergoes rapidly to retroaddition reaction. The retroaddition process was experimentally confirmed via cross-experiments with highly reactive aldehydes.[7,39,43] Therefore, the *E*/*Z* stereochemical outcome is not determined by the addition step diastereoselectivity. Based on the theoretical studies of the reaction, it was estimated that *syn*-*β*-alkoxy sulfone ***2-61*** cyclize faster than the *anti*-***2-61***.[38] Thus, *Z*-alkenes are generated as the main product of the reaction. Overall, if there is sufficient energy gap between *syn* and *anti*-***2-61*** cyclization activation energy barriers, and at the same time the addition step is reversible, only the (*Z*)-olefins are produced. Few examples of such situation are shown in Scheme 13.[38,44]

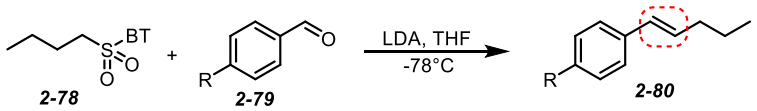


Scheme 13 – Influence of stabilizing group in α-position of sulfone on reaction outcome.

2.3.3 Type III - Sulfone is not substituted with α, β-unsaturated substituents, the carbonyl is

Type III covers the reactions of unstabilized α-sulfuryl carbanions ***2-41*** (Scheme 12) with aryl and α,β-unsaturated aldehydes and ketones. In this case, *E*-selectivity is preferably achieved, especially in the case of 1,2 disubstituted alkenes. The "rule" is very general and is not sensitive to reaction conditions. As in the previous case, final alkene configuration is not determined by the first step. However, in that case, the Smiles rearrangement/elimination process seems to proceed via more complex mechanism. S. Julia proposed the formation of a zwitterionic intermediate ***2-66*** (Scheme 12, path B). Resulting carbocation-intermediate ***2-66*** can easily adopt a thermodynamically more stable conformation that upon the SO_2 elimination generates *E*-olefin. The formation of the carbocation intermediate thus erases any stereochemistry generated in the first addition step. This proposal is based on the observation that electron-donating substituents on the aryl ring of the aldehyde are influencing the reaction stereoselectivity (majority of the mechanism thus follow the zwitterionic route B) (Scheme 14). Such hypothesis, however, faces one of the main drawbacks – expects the formation of a carbocation in the highly nucleophilic environment. In addition, DFT calculations contradict this mechanistic proposal.[39] Recently Robiette and Pospíšil revisited this theory and proposed new relevant hypothesis that is based on both DFT calculations and experimental studies. In brief, they propose two different mechanisms of elimination for *anti*-***2-64*** and *syn*-***2-64*** (Scheme 12). In the first case, *anti*-***2-64*** intermediate undergoes to antiperiplanar β-elimination (a standard mechanism). The second stereoisomer, *syn*-***2-64*** elimination process can proceed either via a standard antiperiplanar β- elimination process that yields *Z*-olefin or, at the same time, via *syn*-periplanar elimination process that yields the *E*-isomer. Both experiments and DFT calculations showed that electron-donating

substitution on the aryl group increases the *syn*-elimination process thus increases *E*-selectivity of the reaction.



R	Yield	*E*/*Z*
H	68%	94:6
MeO	95%	99:1
Cl	51%	77:23

Scheme 14 – Influence of EDG (aryl group) on stereoselectivity outcome of Julia-Kocienski olefination (Type III).

2.3.4 Type IV – Both partners are stabilized/substituted with α, β-unsaturated substituents

The stereoselectivity outcome of the Type IV case is the least predictable. The reason behind is that competitive reaction mechanisms including the elimination processes described in chapters 2.3.2 and 2.3.3 can occur. The final (observed) *E*/*Z* selectivity is then based on the relevant contribution of all involved reaction mechanisms.

2.4 Julia-Lythgoe and Julia-Kocienski olefination reaction - comparison

As was demonstrated, both variations of Julia-type olefination have advantages and disadvantages that will determine their application. Overall it is not so clear to decide which of the two methods is better. Thus, I have decided to present a short table that would highlight the advantages of any of the two methods in terms of reaction yields and selectivity (Table 2).

Table 2 – Comparison of Julia-Lythgoe and Julia-Kocienski olefination methods.

	Julia-Lythgoe	**Julia-Kocienski**
Practical difference	Two-pot protocol	One-pot protocol
Olefin selectivity generated in	Reductive-elimination step	Addition step
Scopes: olefin formation (sequence overall yield)		
- **Terminal olefins**	✓	✓
- **1,2-disubstituted olefins**	✓	✓
- **Trisubstituted olefins**	✓	≈
- **Tetrasubstituted olefins**	≈	X
Scopes: stereoselectivity of the olefin formation – *E*-selective		
- **1,2-disubstituted olefins**	✓	✓
- **Trisubstituted olefins**	≈	X
- **Tetrasubstituted olefins**	≈	X
Scopes: (*Z*)-selective	X	✓ if **TBT**-activating group used

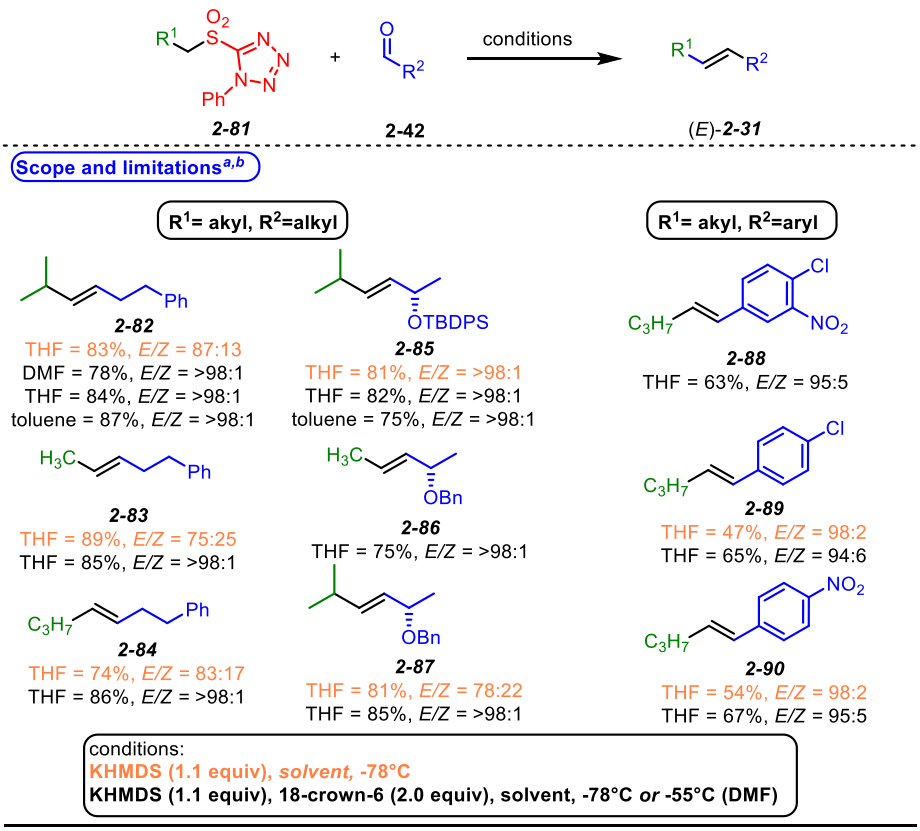
✓ – good to excellent; ≈ – acceptable; X – unsatisfactory result(s).

2.5 Previous results of our group in the field of olefination methods

The Julia-Kocienski reaction has a longstanding history in our research group. Our research interest was mainly focused on the reaction selectivity and mechanistic evaluation of the transformation.

First, the main interest was focused on the reaction selectivity. Especially on the improvement of the *E*-selectivity in case of unstabilized α-metallated PT-sulfone carbanions (Table 3). As discussed previously, the selectivity of the transformation is directly linked with the first addition step. Since the step is irreversible, more *anti*-selective addition reaction conditions had to be designed. By other words, we had to increase the amount of the kinetic product that is generated via an open transition state (Figure 3). To reach this goal, α-metallated sulfone species had to be made more reactive - "naked". To do so, the use of cation-selective ion scavengers was envisaged. After some optimization, the use of (1) KHMDS / 18-crown-6 or TDA-1 and (2) LiHMDS / 12-crown-4 couples of base/scavenger partners proved to be beneficial. In general, when alkyl aldehydes were used, the selectivity was increased. However, lower selectivity was observed when α,β-unsaturated aldehydes were used.[45]

Table 3 – Julia-Kocienski olefination – quest for better E-selectivity.

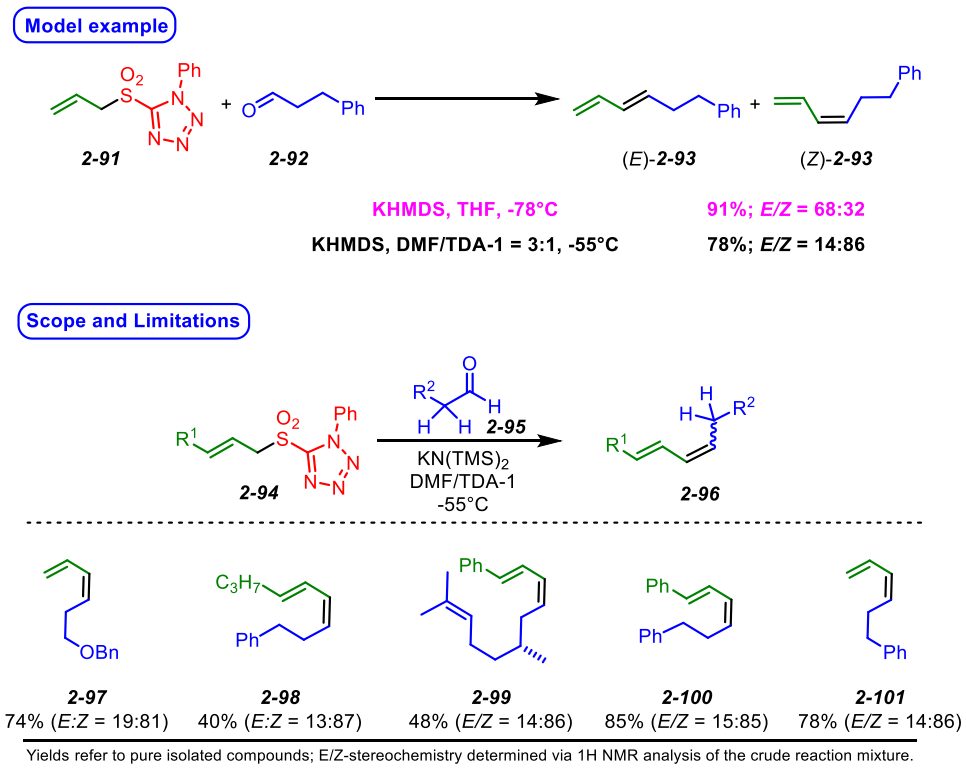


[a]Yields refer to pure isolated compounds; [b]*E*/*Z*-stereochemistry determined via ^{1}H NMR analysis of the crude reaction mixture.

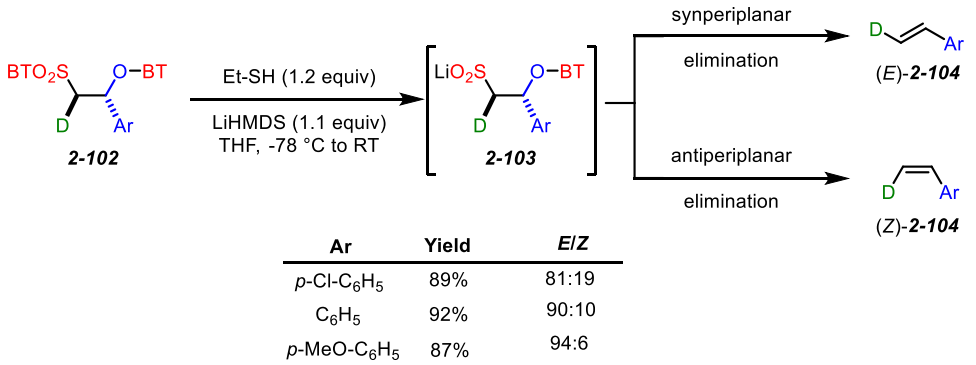
Satisfied with the obtained results, our attention was turned to the *Z*-selective protocol. It was expected that stabilized sulfonyl carbanion (stabilized with aryl or α,β-unsaturated substituents) should undergo to reversible addition to the carbonyl group. Thus, if the *syn*-***2-61*** undergoes a faster

Smiles rearrangement in comparison with its *anti*-stereoisomer, *Z*-olefins should be formed preferentially. By other words, if the equilibrium between addition/retroaddition is established rapidly, *Z*-olefins should be produced selectively. To accelerate the equilibrium establishment, we speculated that the same trick as in the previous case will work. Thus, the chelating agents were added to the reaction mixture. It was also speculated that cation chelation will not only accelerate the equilibrium adducts/starting material formation but that it will also increase the rate of the Smiles rearrangement. Indeed, the addition of naked alcoholate oxygen should be faster than that of the chelated one. Our hypothesis proved to be successful since the addition of allyl-PT-sulfone ***2-91*** to aldehyde ***2-92*** proceeded under our new reaction conditions as *Z*-selective and it was shown that the selectivity tendency was reversed when compared to the *E*-selectivity observed under normal reaction conditions (Table 4). Unfortunately, it was also showed that the method is rather limited in substrate scope and in general yields the desired olefins only moderate yields.[17]

Table 4 – Attempted Z-selective Julia-Kocienki olefination – scope and limitations.

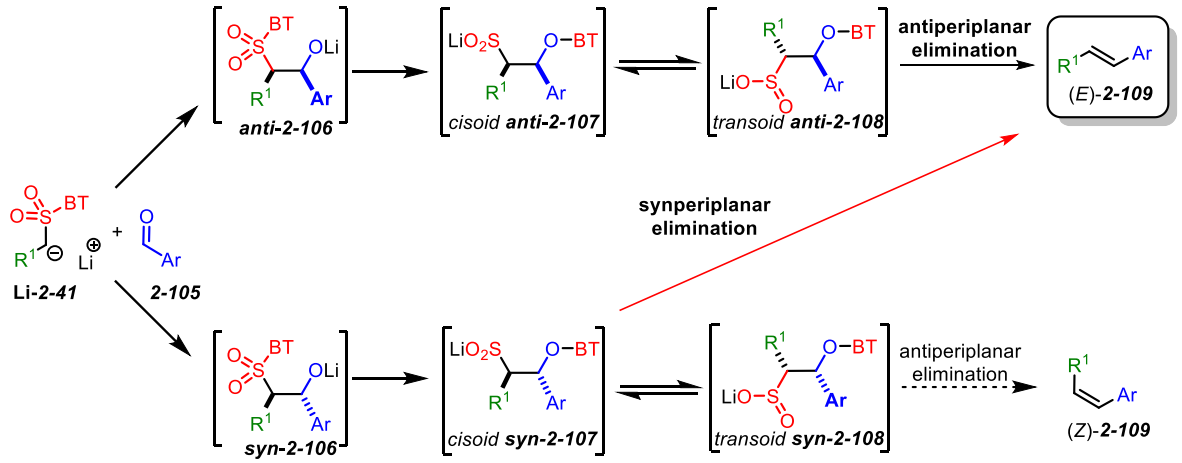


Our research group has also taken its part in the mechanistic investigation of the Julia-Kocienski olefination reaction. In collaboration with prof. R. Robiette (DFT calculations), the question of the *E*-selectivity observed in case of α, β-unsaturated and aryl aldehydes was studied. As a consequence, new hypotheses describing the *syn*-elimination process as a competing process to the β-elimination was advanced. For more details see Chapter 2.3.3, Scheme 15 and Scheme 16).[39]



Ar	Yield	E/Z
p-Cl-C_6H_5	89%	81:19
C_6H_5	92%	90:10
p-MeO-C_6H_5	87%	94:6

Scheme 15 – Influence of substituents on aryl ring to the E/Z selectivity in Julia-Kocienski reaction using isotope labelling.



Scheme 16 – Proposed rationalization for observed high E-selectivity in Julia-Kocienski olefination with aromatic aldehydes as substrates.

2.6 Diversity-Oriented synthesis (DOS)

2.6.1 Introduction

Since the discovery of the cells and microorganism, scientists were fascinated by biological processes in living organisms. The reason behind is in the hope that if we can characterize and understand these processes, we could influence them. Modern medical chemistry seeks to understand such processes and to develop procedures and methods allowing us to interact with macromolecules involved in the pathways of biological systems. One of the most straightforward possibility is to use small organic molecules that have a direct effect on biological processes. These molecular probes can serve as a valuable tool for a basic understanding of metabolic pathways. In the case of the chemical library containing these modulators, the general rule, bigger library = better library, that was so common in the 1990s and early 21st century, become gradually abandoned over past 15 years. Recently scientists figured out that the vision of "big library" is not enough since evaluated library must also possess wide structure diversity.[1–3] And such trend overcomes till today. In this subchapter, I would like to briefly discuss the methods that allow us to constitute such "modern" chemical libraries.

2.6.2 Generating diversity in chemical library

Small molecules can interact with macromolecules through charges, polarity, or other specific interactions. That gives us a hell of possible combinations. In search of inspiration for such molecules, we went to the kingdom of natural products. Indeed, especially in the domain of secondary plant metabolites, we found a great deal of complexity and a very diverse molecular scaffold. Even if for example simple phenylpropanoid dimers were considered[46] Thus, it is not surprising that if chemical libraries poor in complexity failed in the quest to find novel chemical probes. As a consequence, a novel systematic approach that would allow us to construct in a simple way structurally and functional group-complex small molecules-related libraries was needed. Such an approach become widely known as Diversity-Oriented synthesis and its key concepts will be developed in this chapter.

The basic concept was to design the synthetic strategy that would allow us to address within one chemical library-wide window in chemical space[47]. Thus, we wished to develop synthetic transformations that would start from limited basic building block pool, that would be transformed in a few steps to scaffolds and functional-diverse small organic molecules. Such diversity in our molecules should then allow us to cover wider chemical space and therefore should facilitate finding the chemical structure that would interact with biomolecules within tested biological cell/organism. Having such "hit" we could further build up a structurally focused chemical library that will allow us to identify structural features necessary for observed interactions and further describe the mode of action of such molecule within the studied biological process.

At this point we should discuss an important point – how do define if the library is sufficiently diverse. The common agreement is that the library can be considered as diverse if it fulfils three diversity criteria. It means it must have:

1) Appendage diversity (diversity of building blocks) – It is based on the connecting of different/various appendages to the common molecular skeleton/framework
2) Stereochemical diversity – possible orientation in space; important for interacting with macromolecule(s)
3) Skeleton diversity – the presence of a large variety of molecular skeletons/features; should have in the library various molecular skeletons that will assure great structural diversity

If we would consider the ways how to plan the library generation, DOS typically relay on the synthetic forward planning strategy. Such approach is based, in comparison with Target-Oriented Synthesis (TOS) that is using highly specific transformations allowing the formation of the specific bond/introduction of the specific appendage/functional group, on synthetic transformations that generates several (but one per time in a specific way) different products from the same starting material using the right reaction conditions (Figure 4).

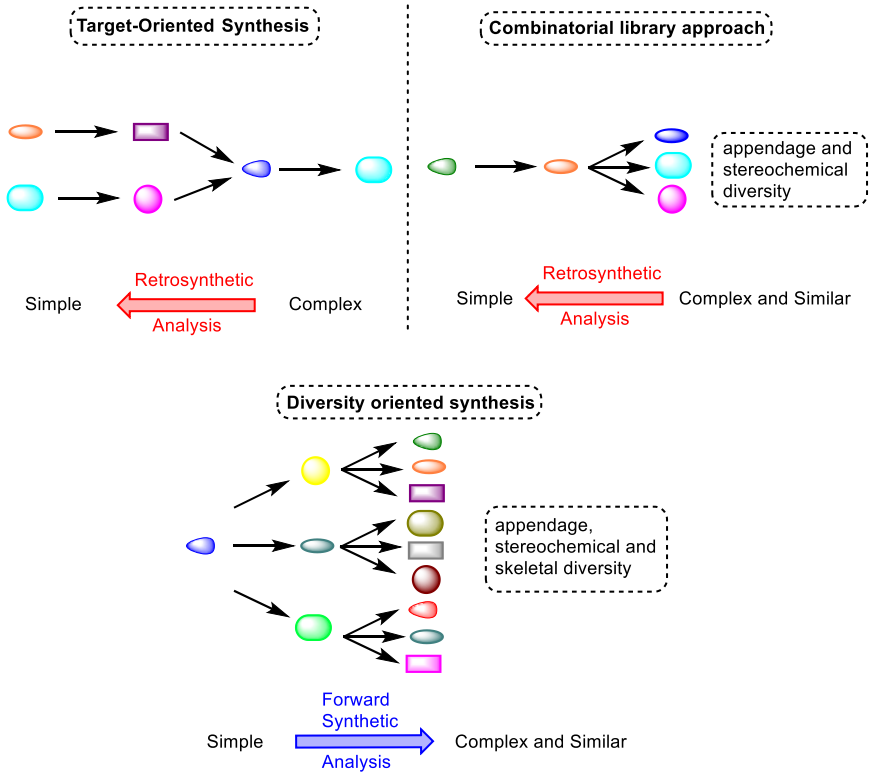


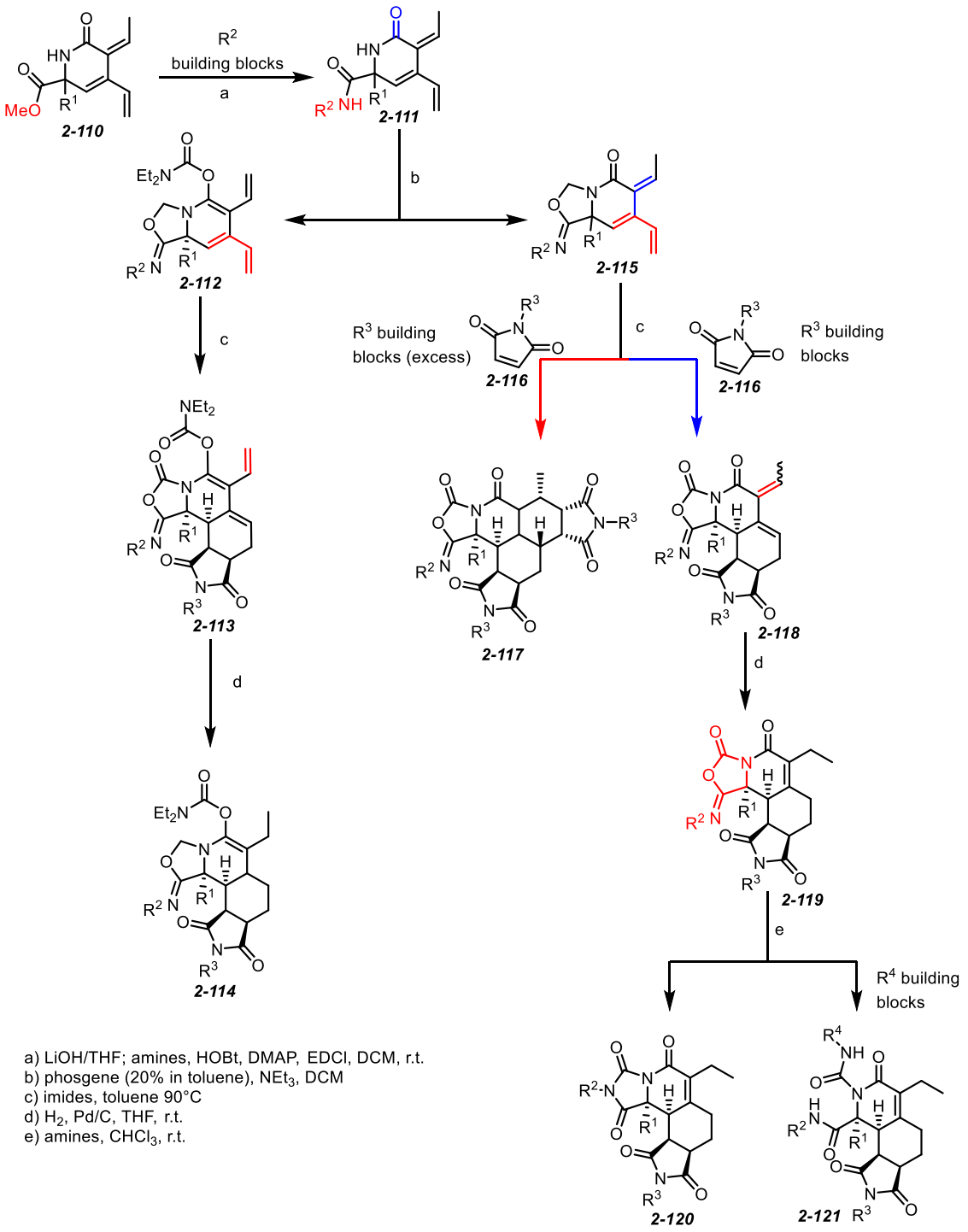
Figure 4 – Comparison of the two main approaches used to generate chemical libraries.[47]

2.6.2.1 Appendage diversity

One of the easiest ways to generate diversity in the chemical library is to use the appendage diversity approach. The aim is to introduce different appendages (chains, functional groups) on a predefined basic molecular skeleton. If a common intermediate contains several reactive centres that can be reacted orthogonally (independently), such approach has a great potential to be used to generate various diverse structures (from the combinatorics point of view). In this case, a multiplicative increase in the number of products is achieved (number of products is related to the number of different reaction conditions that can be used). Ideally, it generates all possible appendage combinations within the skeleton[5]. This approach has proved to be very effective when already known biologically active molecular scaffolds are used as a starting point, and the purpose of the generated library is used to find better/more selective/more robust/more metabolically stable derivative of the original compound. This approach was used, is used, and will be used to create chemical libraries of hundreds, thousands or even millions of structures in just a few steps.[48,49]

An interesting example of this approach is the modification of γ-lactam, which in its structure contains an electron-poor triene system and a diamide functional group (Scheme 17). Such system offers the possibility to create several structural motifs such as 5-iminooxazolidine-2-ones, hydantoins and acyl ureas. The whole sequence is based on the exploitation of a few reactive centres within the molecule in only 4 to 5 steps. In the first steps, lactam ester ***2-110*** is transformed to lactam amide ***2-111*** by the reaction with phosgene using various reaction times and temperatures to compound ***2-112***

or triene ***2-115***. Further Diels-Alder cycloaddition, hydrogenation, and amination, respectively, yields seven structurally different tetracyclic products.

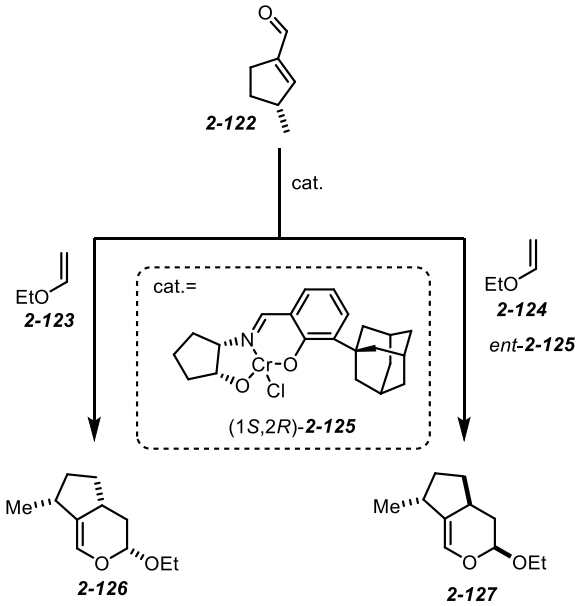


Scheme 17 – Example of appendage diversity using γ-lactams as a starting material.

Thus, under the right reaction conditions various transformation is achieved, and structurally different compounds ***2-113***, ***2-117*** and ***2-118*** are generated. The diversity is further extended with further transformations that yielded diverse acyl ureas ***2-121*** and hydantoins ***2-120***. The key success of the approach is the systematic and selective use of different reactive centres. Overall, authors were able to prepare chemical library of approximately 200 different small organic compounds.[50]

2.6.2.2 Stereochemical diversity

The rigid orientation of a molecule in space is one of the key factors influencing its interactions with biomacromolecules. Such situation must be reflected in stereochemical diversity and obviously, the stereochemical diversity is a mandatory feature of a newly constituted chemical library. Considering such fact via chemical transformation "filter", all used synthetic sequences must provide targeted molecules in a highly stereoselective manner.[5]



Scheme 18 - Stereochemical diversity via asymmetric catalysis.

To demonstrate just one example of such an approach, the transformation of ***2-122*** to the corresponding THP ring was selected. In this case, Jacobsen and co-workers used chiral catalyst (***2-125***) to generate two diastereomers of THP bicycles, compounds ***2-126*** and ***2-127***, via hetero-Diels-Alder reaction in high selectivity.[51] The whole sequence is influenced by proper choice of the starting material (Scheme 18). It should be noted that developed catalyst can be used to generate otherwise hardly achievable *exo* and *endo* adducts.[5]

2.6.2.3 Skeletal diversity

The skeletal or scaffold diversity is another extremely important feature that must be considered during the chemical library design. It can be achieved by two different but complementary strategies. First, *reagent-based approach*, exploits one (or few) common intermediate(s) that is used in several subsequent reactions. The divergence is introduced by varying chemical reagents that subsequently generates various structurally different molecules. The second strategy, *substrate-based approach*, exploits several starting molecules, that have pre-encoded skeletal information that is referred to as *σ*-elements. The diversity is introduced by the application of common reaction conditions that due to

diverse/various molecular scaffolds of starting molecules generate structurally unrelated molecular scaffolds (Figure 5).

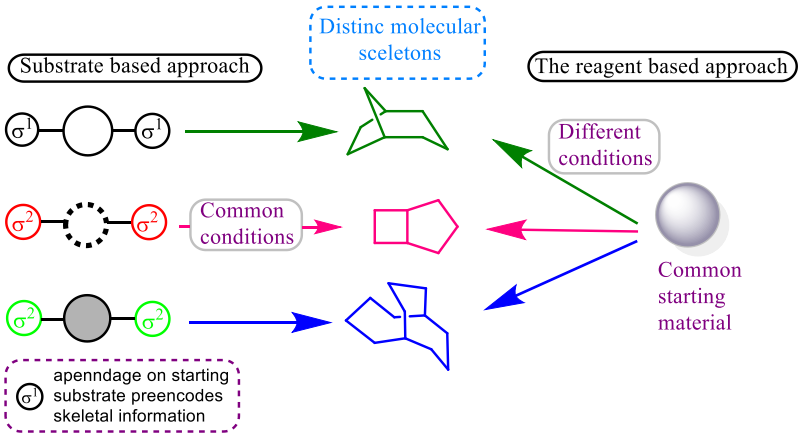
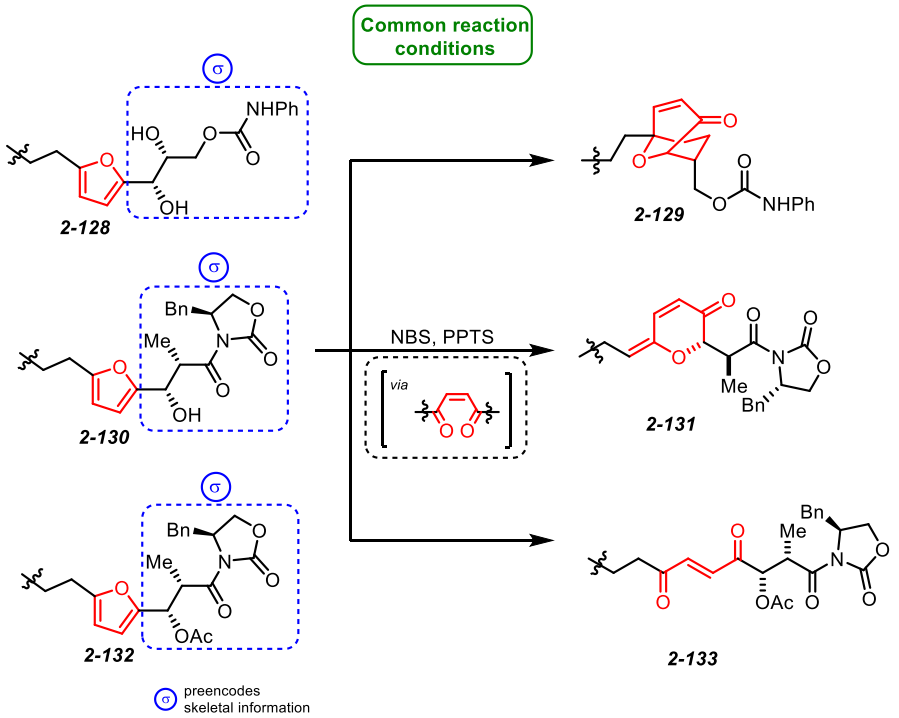


Figure 5 – Approaches leading to scaffold/skeletal diversity –substrate-based approach vs. reagent-based approach.

2.6.2.3.1 The substrate-based approach

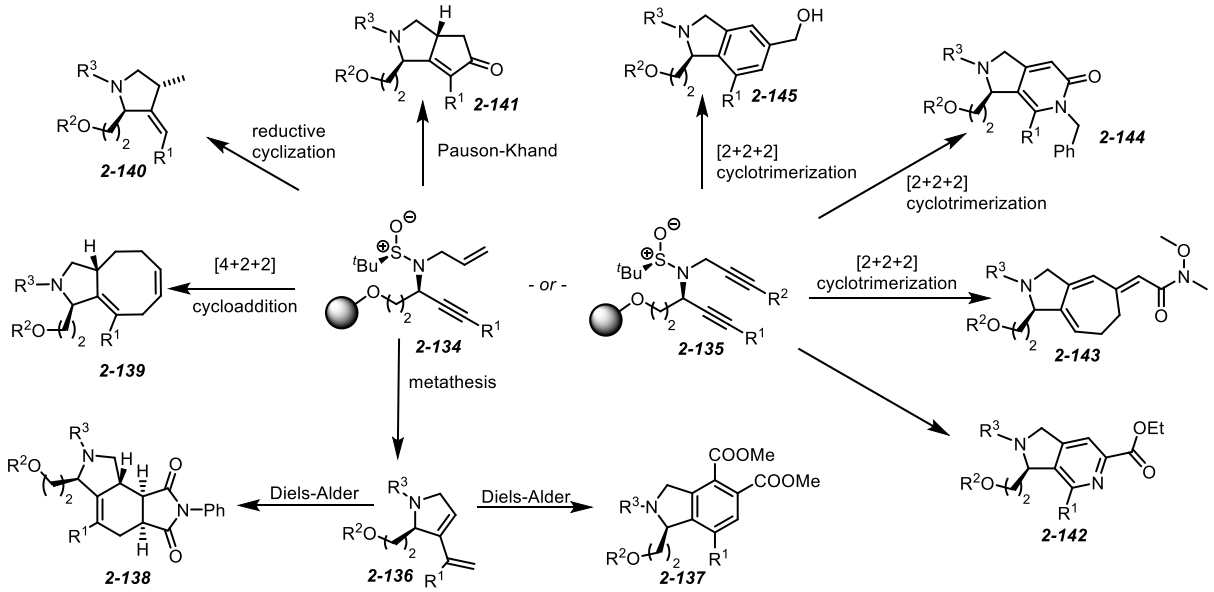
For a better understanding of this approach, one can imagine that the pre-encoded skeletal information is translated into the product in the same way as if the polypeptide chain will fold to generate protein. Nature uses an amino acid sequence as a pre-encoded sequence that is further folded into the proteins with different shape and function according to the amino acid appendages.[52] A similar process is taking place when the diversity generated with small compounds is made. The choice of appropriate *σ*-elements (responsible for the folding process) brings the skeletal complexity into the molecule. In the selected example, the authors used the furan ring, that upon treatment with NBS is transformed into the enedione intermediate (Scheme 19). At this stage previously incorporated alkyl side chains (*σ*-elements), alter the chemical reactivity of the enedione and structurally different compounds can be prepared (Scheme 19).[53] Furan ***2-128*** with two adjacent nucleophilic hydroxy groups undergoes to the ring expansion and a bicyclic product ***2-129*** can be obtained. Subsequently, if only one nucleophilic hydroxy group is present in the side chain (compound ***2-130***), alkylidyne pyran-3-one ***2-131*** is isolated. Finally, in the absence of any nucleophilic group, *E*-enedione ***2-133*** was obtained.



Scheme 19 – Example of the substrate-based approach using pre-encoded furan derivatives.

2.6.2.3.2 The reagent-based approach

This strategy is based on the use of highly functionalized molecules with pluripotent functional groups. Such intermediates have in their structure included several functional groups that differ in their reactivity. As a consequence, care must be taken during the design of such pluripotent intermediates since they can easily undergo various transformations. Indeed, if well designed, such molecules can be readily transformed into various skeletons if well-defined reaction conditions are used. Besides, obtained products serve as a starting point for further transformations and allow further diversification. Thus, the design of highly functionalized molecules is an essential part of this approach. One of the excellent examples of such an approach is shown in Scheme 20. Using solid-phase synthesis, authors were able to prepare up to a 190-membered library of alkaloid/terpenoid-like scaffolds starting from just two very similar starting molecules.[54]



Scheme 20 – Example of the reagent-based approach.

2.6.2.4 Build/Couple/Pair strategy in DOS

A prominent place among the DOS approaches has a strategy called **Build/Couple/Pair** (**B/C/P**) developed by Schreiber.[55] Such development was a logical consequence and sort of "compilation" of all previously adopted strategies used to build up the complexity in constituted chemical libraries. **Build**/**Couple**/**Pair** terms can be explained in the following way:

1) **Build** – the phase that focuses on the preparation of (chiral) building blocks with several functional groups that can be further explored in **Couple** and **Pair** phase.
2) **Couple** – Building blocks are connected together to form one advanced intermediate. The "couple" transformation should be chemo and stereoselective.
3) **Pair** – Functional groups incorporated in building blocks (**Build phase**) that were further interconnected via **Couple** phase, are now reacted together – "paired" together – via (in majority cases) intramolecular fashion.

The purpose of **build phase** is to prepare various building blocks. The preparation of chiral building blocks using enantio- and diastereoselective reactions or molecules from the chiral pool (amino acids, terpenes, etc.) is of particular interest.

Overall **B**/**C**/**P** sequence must be short and concise to minimize the number of steps. In addition, the functional groups required for **Couple** and **Pair** phase should be already incorporated in original building blocks, even though in most cases some additional functional groups are further introduced after the **Couple** step of the sequence.[55]

In subsequent **Couple** phase, intermolecular connective reactions of Building Blocks are carried out. The sequence yields one key *pluripotent building block* that combines previous building blocks, possess a dense array of functional groups and is a great starting point for further transformations.

Finally, the **Pair** phase is performed. The **Pair** phase is a series of intramolecular coupling reactions, that strategically combine the appendages together to produce compounds with high diversity (Figure 6).[56]

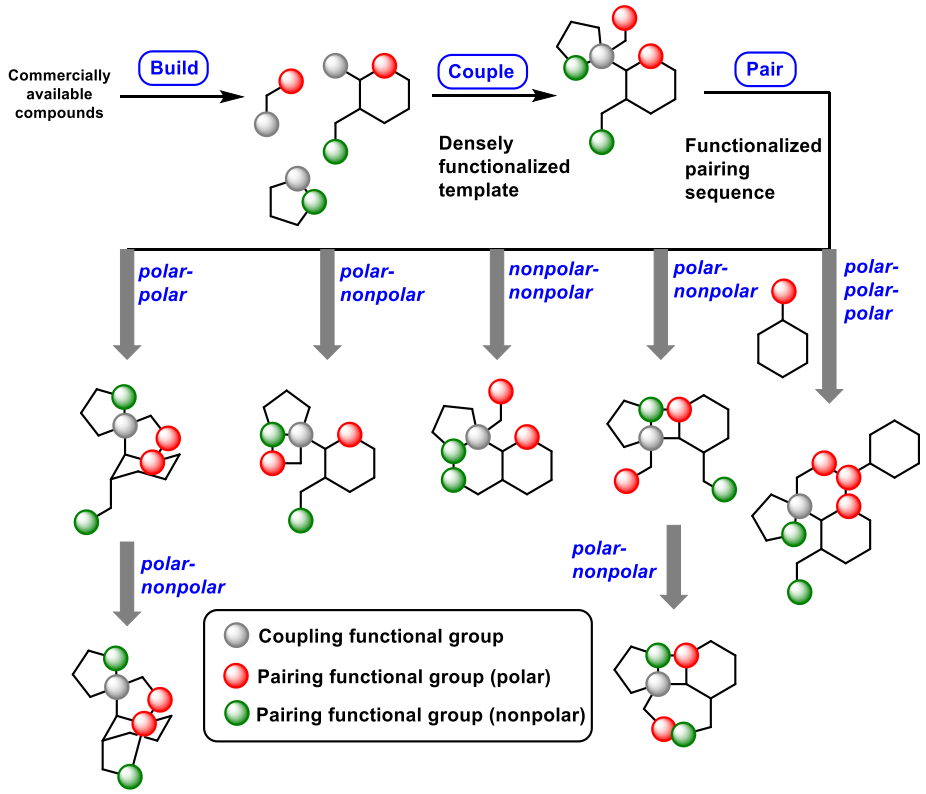
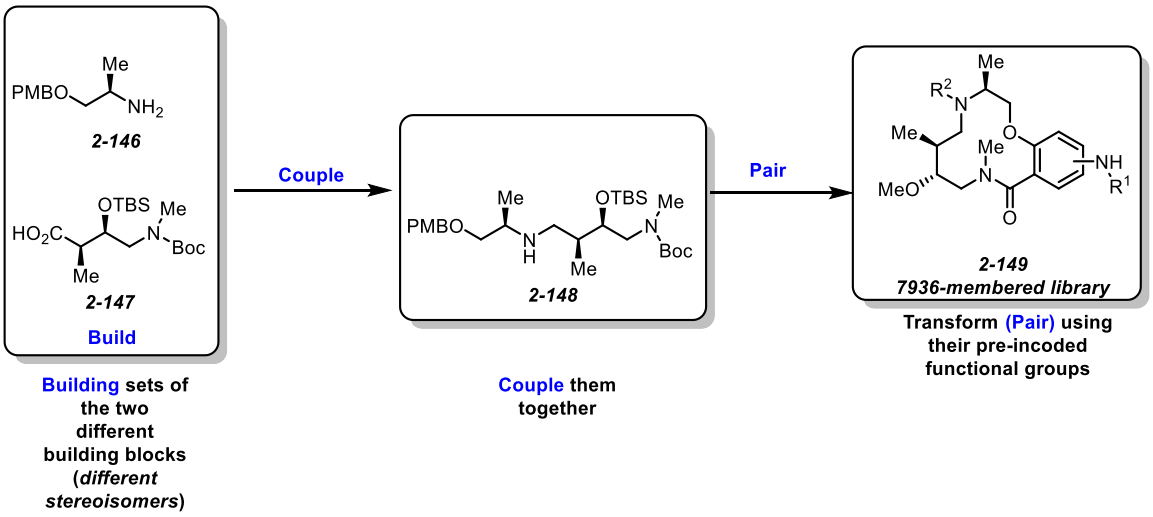


*Figure 6 – Illustrative example of **Build/Couple/Pair** strategy.*

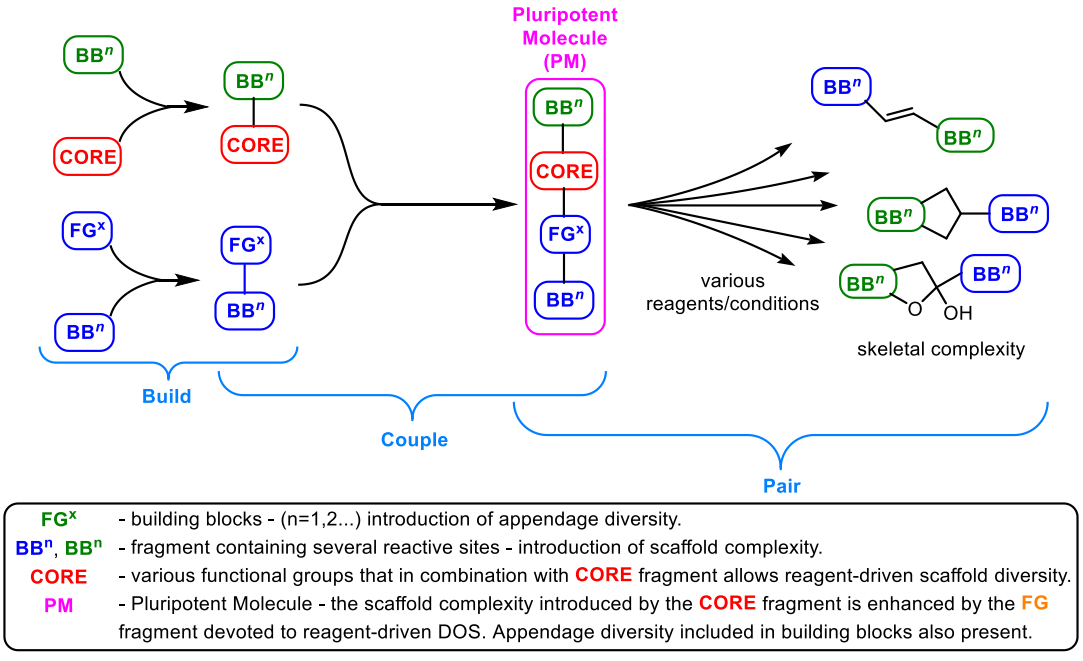
To give some example. The **B/C/P** strategy was e.g. applied to construct the library of 12-membered macrolactames.[57] The goal of authors was to evaluate the biological properties of such rings and to study SAR of the complete matrix of their stereoisomers. Starting from simple 1,2 aminoalcohol ***2-146*** and aldol derived γ-amino acid ***2-147***, unbelievable nearly 8000 molecules with core structure ***2-149*** was be prepared. The key step in **Pair** phase was the macrocyclization (Scheme 21).



*Scheme 21 – Demonstration of B/C/P strategy on the preparation of various macrolactames **2-149**.*

2.6.3 Our design of pluripotent building blocks for B/C/P strategy

One of the aims of our research group is to develop novel synthetic strategies that would allow synthesis of diverse molecular scaffolds in a short time, and by simple and efficient manner/way from readily available starting materials. The key step in our strategy is the design of readily available highly functionalized intermediates (*pluripotent molecules*) that would allow us to transform them into highly stereo and scaffold-diverse products in one to three additional steps. We call this intermediate **Pluripotent Molecule** (**PM**) (Scheme 22).[17] In Schreiber´s nomenclature of **B/P/C** the **PM** corresponds to the product of **Couple** stage.



Scheme 22 – Pluripotent Molecules as the key intermediate in the B/C/P strategy.

The key to the success of a **PM**-based strategy is the development of the **CORE** motif for our **PM** molecules. The **CORE** motif/fragment is the part of the **PM** responsible for the diversity of the sequence in **Pair** step. Thus, the **CORE** should contain different reactive sites, which would be further useful in the construction of a chemical library. Therefore, the **CORE** molecule should be readily available and further modifiable with additional building blocks. There is one key restriction applying to the **Pluripotent Molecule** design. During the **Couple** process, a connection of **CORE-BB** and **FG-BB** fragments must be fast, versatile and high yielding. Only the final **PM** molecule is the important intermediate. It is ***THE INTERMEDIATE*** that upon the application of external reagents (e.g. heat/catalyst/UV-light) yields novel molecular scaffolds – members of our targeted library. In brief, the **Pair** step of the strategy is the point where all the elusive goals and targets mix with our expectations.

Based on the previous experience of our research group, especially in the field of Julia olefination methods, the key role of **CORE** motif was given to BT-sulfones (Figure 7).[17] The advantage of heteroaryl sulfones in the **PM** is directly connected with the additional reactive sites, namely by multiple reactive sites as electrophilic and nucleophilic centres on benzothiazole ring, acidic hydrogen in α position to sulfone, and heterocyclic (BT) group exploitable in radical chemistry, that are added to the rest of the molecular scaffold. In addition, BT- group can be easily replaced within the **PM** scaffold by another heterocycle, aryl, and alkyl chain allowing us to further increase/differentiate the number of reactive sites within **PM**.

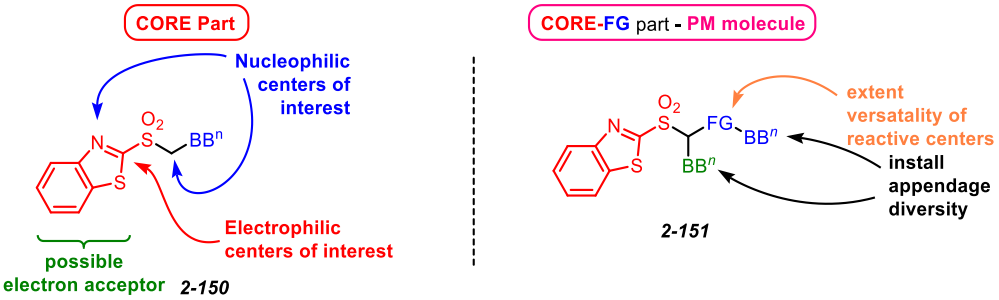
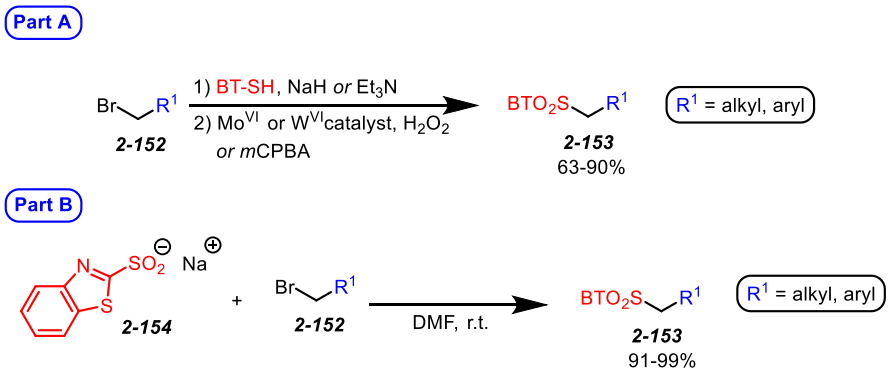


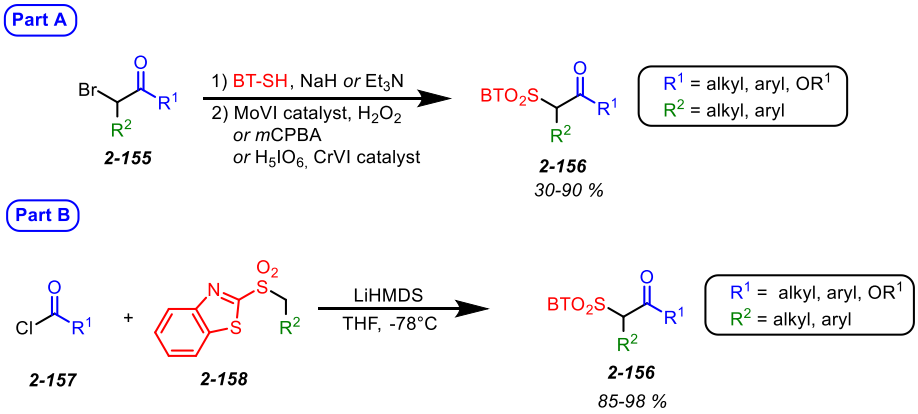
Figure 7 – Pluripotent molecules base on BT-sulfones.

Synthetic versatility and adaptability of sulfones ***2-150*** and ***2-151*** are well demonstrated in the literature. The synthesis of ***2-150*** is well documented and used over the past 60 years. In general, sulfones ***2-150*** are prepared either via BT-SH alkylation/oxidation sequence[33] (Scheme 23, Scheme 24, Part A) or starting from the corresponding sulfinic salt[58] (Scheme 23, Part B).



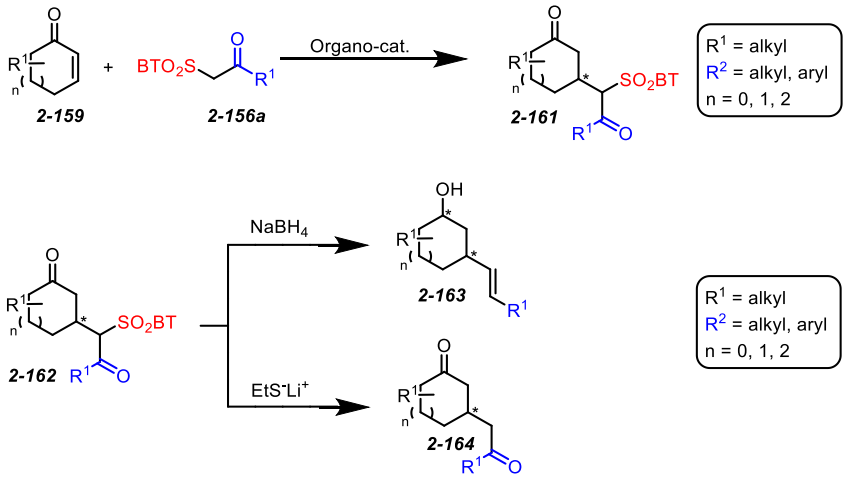
*Scheme 23 – Sulfone **2-153** synthesis.*

Targeted **PM** molecule ***2-151*** can be prepared in two ways. First is based on the substitution/oxidation sequence of α-halogen carbonyl compounds ***2-155*** (Scheme 24, Part A)[59] and the second, developed in our group in 2011, is based on the acylation of sulfones ***2-153***[60,61](Scheme 24, Part B).



*Scheme 24 – Sulfone **2-156** synthesis.*

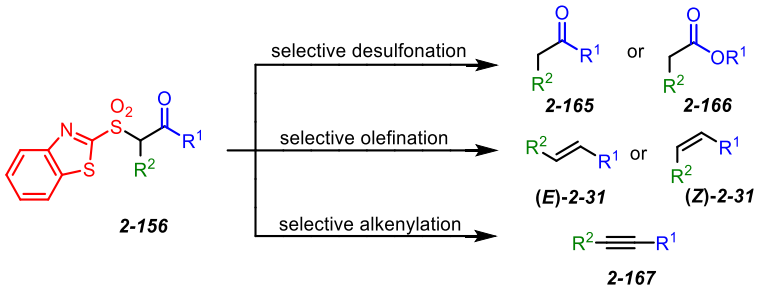
The first approach developed by Jørgensen et al. (there are some previous efforts to prepare such compounds but they suffer from low yielding oxidation step) was triggered by the necessity to develop an efficient way to the class of C-nucleophiles (***2-156a***) they used in organocatalytic reactions.[59,62,63] Compounds ***2-156a*** were successfully used as C-nucleophiles and proved to be also very useful in post-addition transformations of introduced BT-sulfones (Scheme 25).



*Scheme 25 – Sulfone **2-156a** as a valuable C-nucleophile in organocatalytic reactions and post/addition transformations.*

Our approach to ***2-151*** reflects its further use in the context of **Couple** phase in **B**/**C**/**P** strategy. Already this compound can be considered as **PM** molecule since it allows us to generate by varying the reaction conditions ketones (desulfonation), olefins or alkynes (Scheme 26).

In the case of desulfonation, we explored a wide range of various reagents[64] that we're able to accomplish selectively such transformations in a chemoselective manner. Typically, three sets of conditions might be used: 1) nucleophilic attack to the electrophilic site of the benzothiazole, 2) via, a metal-mediated reductive-elimination of the $BTSO_2$ group, and 3) via metal-free radical removal of the $BTSO_2$ group (Scheme 26). Additionally, the transformation of ***2-156*** to alkenes (***2-31***) and alkynes ***2- 167***, respectively, were achieved. Thus, our first-generation **Pluripotent molecule** (**PM-1**) could be exploited in several ways.



*Scheme 26 – Possible transformation of sulfone **2-156**.*

To move further to reach "real" diversity that could be achievable by **PM-1**, we have decided to develop the 2nd generation of **PM** molecule. The design of **PM-2** (***2-168***) is based on **PM-1** (***2-160***) and adds a novel functional feature – activated olefin (Figure 8). Such olefin should be explorable in cycloaddition reactions and Michael-type additions. The **PM-2** was designed to be obtained starting from **PM-1** molecule via Knoevenagel condensation with aldehyde/ketone.

In brief, the "hunt" for such molecule and the use of it in the context of DOS is the main focus of my theses and the description of it you can find in Chapter 3. But before that, I must mention other achievements in the field of DOS that we have achieved within our group, and that is not connected

with my theses. Indeed, I should describe the first successful application of **Pluripotent Molecule** design in our group.

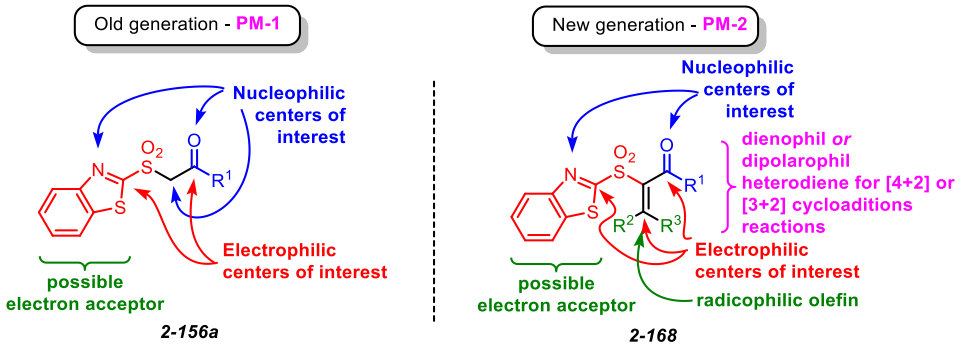
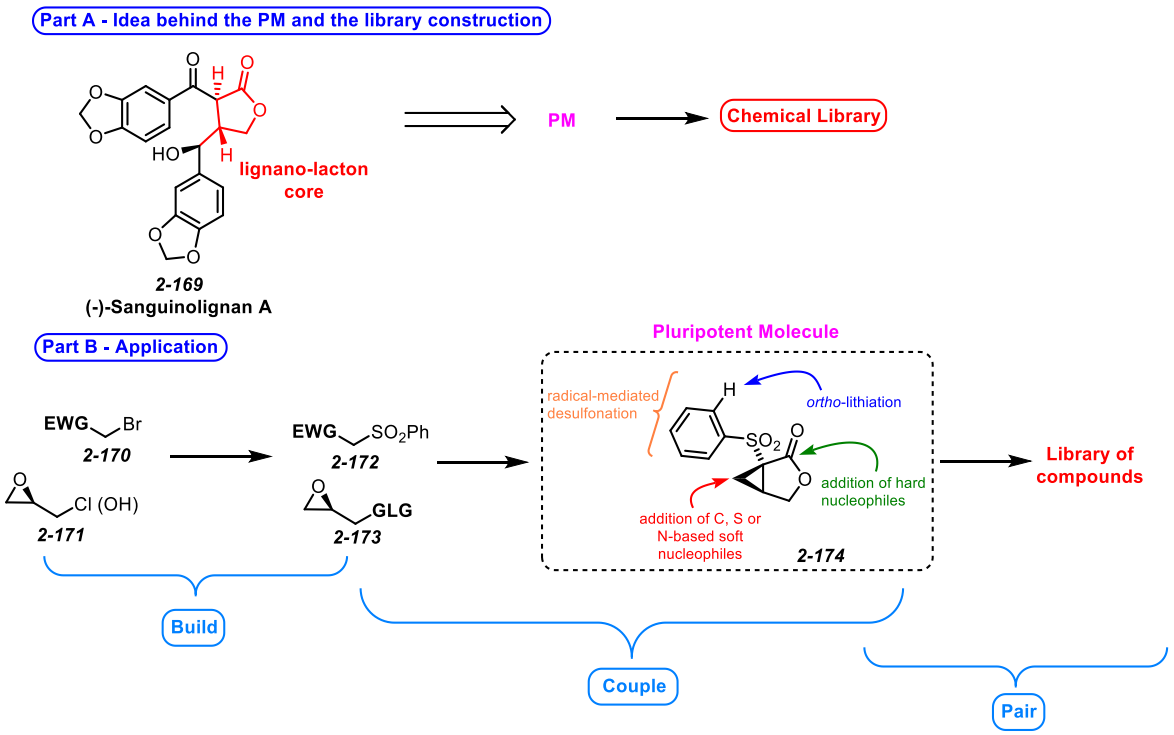


Figure 8 – First and the Second generation of Pluripotent Molecule and their properties.

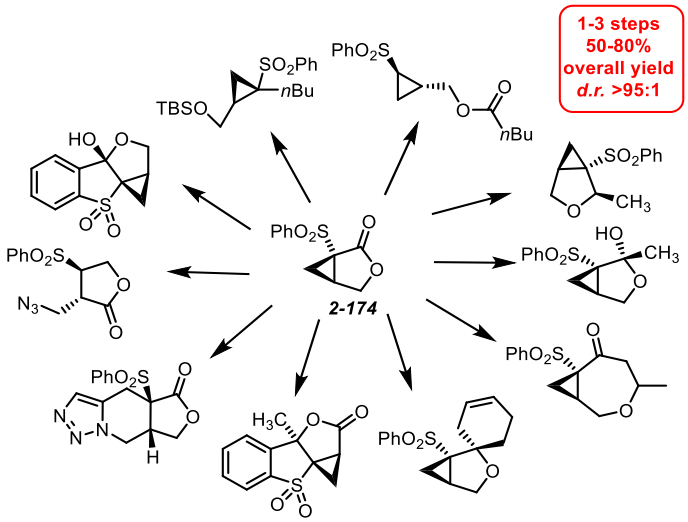
2.6.4 Previous successful application of Pluripotent Molecule design in our group

The idea and the application of the **PM** molecule concept are not, of course, limited only to BT-sulfone-based molecules. During her Doctoral Thesis, D. Konrádová applied such an approach to the synthesis of a lignan-inspired chemical library.[65] The key feature of her work was to design a new **Pluripotent Molecule** inspired by **Sanguinolignan A** natural product, that was used as starting point to generate structurally diverse chemical library (Scheme 27, Part A). As a result of this effort, readily available bicyclic lactone ***2-174*** was proposed as **PM** molecule and synthesized in two steps starting from commercially available building blocks (Scheme 27, Part B)



*Scheme 27 – Pluripotent molecule based on bicyclic lactone **2-174** and possible reactivity.*

Having PM ***2-174*** in hands, the **Pair** step of the **B/C/P** strategy was explored. From the literature, it was previously known that molecule ***2-174*** undergoes to reductive desulfonation,[66] reduction,[67] and aminolysis.[68] In addition to these transformations, further PM molecule manipulations as cyclopropane opening with various nucleophiles (C, N, S-soft nucleophiles), selective lactone opening sequence based on the use of hard nucleophiles (organolithium and magnesium reagents), *ortho*-lithiation reactions, and cycloaddition reactions were developed.[69] All reactions proceeded with high stereoselectivity and the approach generated in 1 to 3 steps highly structurally diverse molecular scaffolds such as bicycles, tricycles, and tetracyclines arranged in fused and spiro fashion (Scheme 28).



*Scheme 28 –Transformation of lactone **2-174** to structurally diverse molecules.*[69]

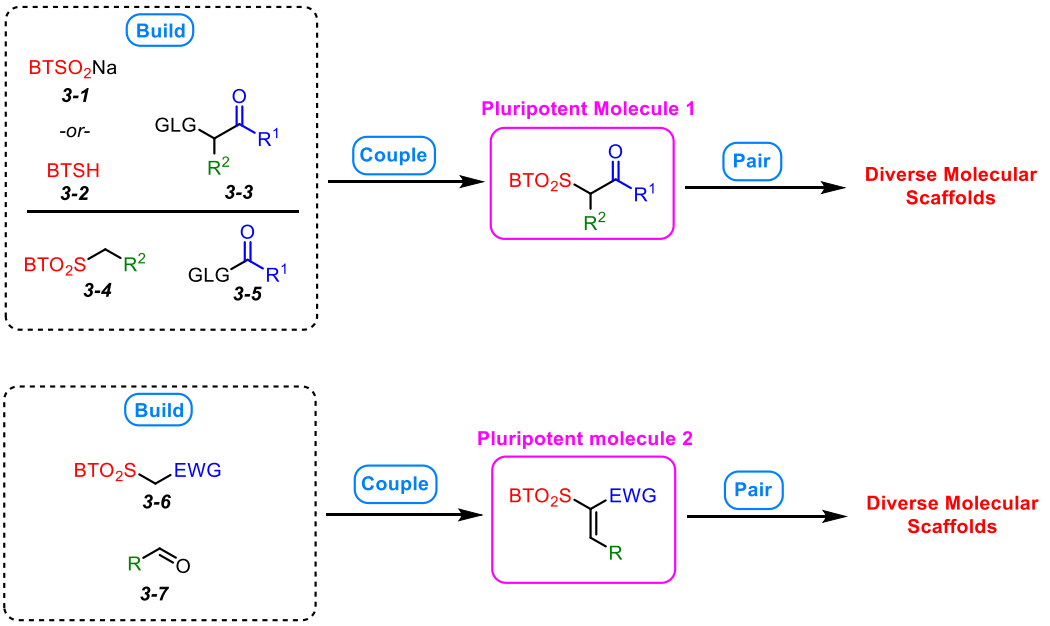
Overall the library of ~100 members was constituted and evaluated for its biological activity against *Leishmania major*. As a result, three new structural motives with high activity were identified. These motives now serve as a starting point for the focused-library constitution and hopefully will allow us to identify a biological target of action of these molecules since it seems that newly identified "hit" molecules are interacting with *L. major* via novel so far not disclosed biochemical pathway.

3 Results and discussion

3.1 Introduction – Our design of B/C/P strategy

The aim of this thesis is to develop a new type of **PM** molecules that are exploitable in **B/C/P** strategy. Our previous experience with BT-sulfone based chemistry and the interest of our research group in diversity-oriented synthesis led us to extend the use of previously developed α-activated BT-sulfones ***3-6*** [64] to the field of **B/C/P**. We speculated that sulfone ***3-6*** can be used as valuable **PM-1** type reagent. And if in **PM-1** R^2 = H, we expected that its Knoevenagel condensation with aldehydes can generate even better pluripotent molecule **PM-2**. We expected that both reagents **PM-1**, and especially **PM-2** will due to a presence of numerous reactive centres within molecules generate structurally diverse molecular scaffolds (Scheme 29).

The main emphasis in our strategy is given to skeletal diversity and therefore the rest of this theses will discuss different approaches towards skeletal diversity-driven product generation. Yet, we will start from the beginning, the **Building** phase. After describing the starting molecules synthesis (Building block preparation), **Couple** phase focused on their assembly and generation of **PM** molecules will be discussed. Finally, **Pair** phase, where all possible and attempted transformations of **PM** molecules will be disclosed (Scheme 29).

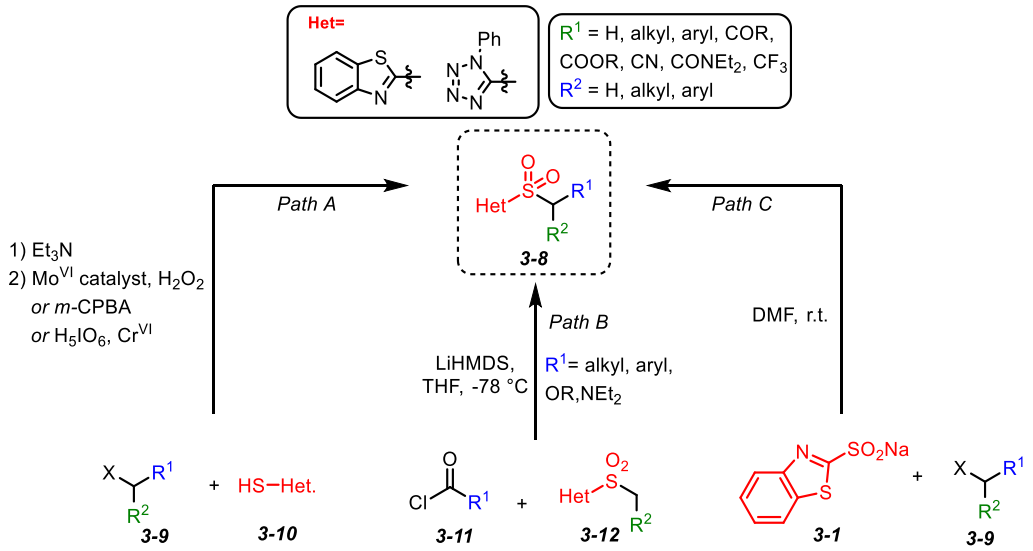


Scheme 29 – Discussed synthetic approaches presented in my Theses in context of Build/Couple/Pair strategy.

3.2 Build phase – Building block synthesis – Build and Couple phase

Building blocks should be, by the definition, readily available. The best case is if they are commercially available. Some of the starting molecules used in this thesis are commercially available, others were in general prepared in one or two straightforward and high yielding steps (Scheme 30).

In the case of **PM-1**, three different routes to Building blocks can be used. Obviously, each approach has its advantages and disadvantages related to their structure and availability of the starting materials (Scheme 30).



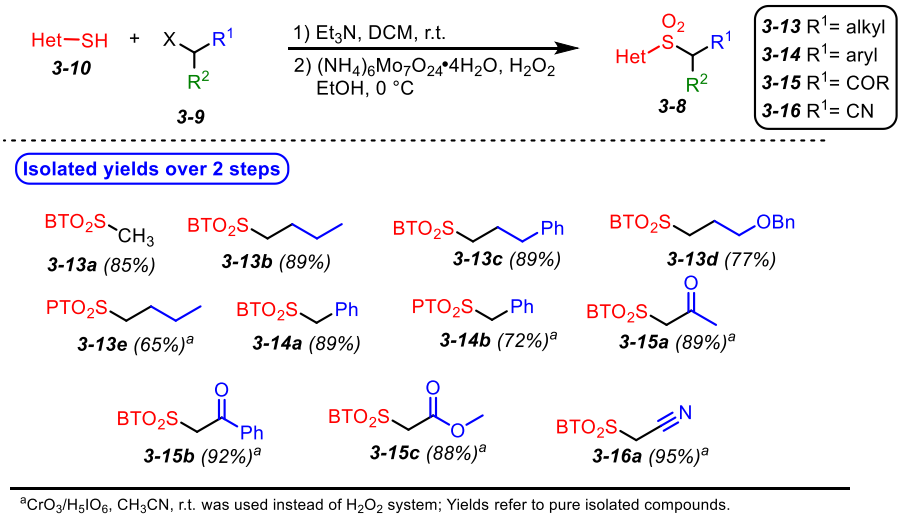
*Scheme 30 – Three different synthetic approaches to sulfone **3-8**.*

The products of the **Build** phase can be obtained via Path A and Path C showed in Scheme 30. The first approach (Scheme 30, path A) is based on the two steps protocol where alkyl halide ***3-9*** is reacted with thiol ***3-10*** in presence of Et_3N and the resulting crude product is oxidized with H_2O_2 in the presence of Mo^{VI} or W^{VI} catalyst (Table 5).[7,70] Alternatively, oxidation with *m*CBPA,[71] or with H_5IO_6/CrO_3 system[59] can be employed. The desired sulfones can be also prepared (Scheme 30, path C) starting from sulfinic salt ***3-1*** (starting from BT-S-S-BT ***3-18***)[72,73] and alkyl halide ***3-9*** (Table 6). In the first case (path A), generated sulfide intermediate must be oxidized to the corresponding sulfones ***3-13*** – ***3-16.*** However, it was found that Mo^{VI} or W^{VI} catalyst-mediated oxidation of sulfide to sulfone with H_2O_2 fail to generate the desired product and yield only the partially oxidized intermediate, corresponding sulfoxide. The reason is the ability of the sulfoxide intermediate to play the role of metal-ligand and coordinate to Mo^{VI} or W^{VI} catalyst. The resulting interaction is sufficiently strong to inhibit the catalytic cycle. Similarly, the oxidation mediated with *m*CBPA fails to produce desired sulfones and remains in the stage of sulfoxide. Fortunately, Jøergensen et al. developed recently H_5IO_6/CrO_3 system that achieves the oxidation in high yields (Table 5, sulfones ***3-15*** and ***3-16***).[59]

Finally, the "real" **Coupling** step of the sequence that yields **PM-1** (Scheme 30, Path B) was exploited. Using this approach, previously prepared sulfones ***3-13*** (Table 5) were reacted with various acyl halides and chloro-carbonyl derivatives (Table 7).[61,74] This protocol previously developed in our group and allowed us to prepare various **PM-1** in a short and efficient manner. The method can be applied to various substrates with one limitation. The drawback of this method is in possible degradation of sulfone ***3-13*** that can be encountered if addition to acylating reaction partner is not

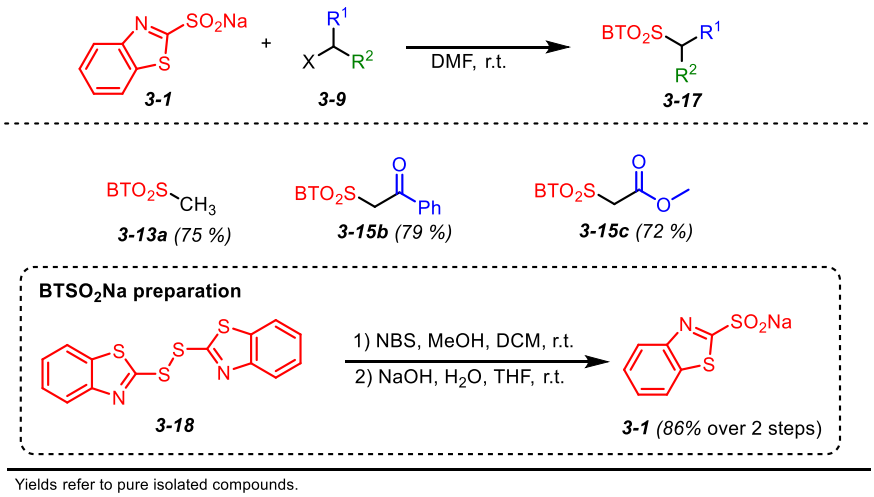
sufficiently fast (Scheme 31). By other words, if the reaction of ***3-13a*** with external electrophile is not fast enough, competitive addition of ***3-13a*** anion to unreacted ***3-13a*** occur. Generated adduct ***3-20*** then further undergoes to *in situ* desulfonation and yields an undesired product of self-condensation ***3-21*** (Scheme 31).

*Table 5 – Sulfone **3-8** synthesis based on the substitution/oxidation sequence (Scheme 30, path A).*



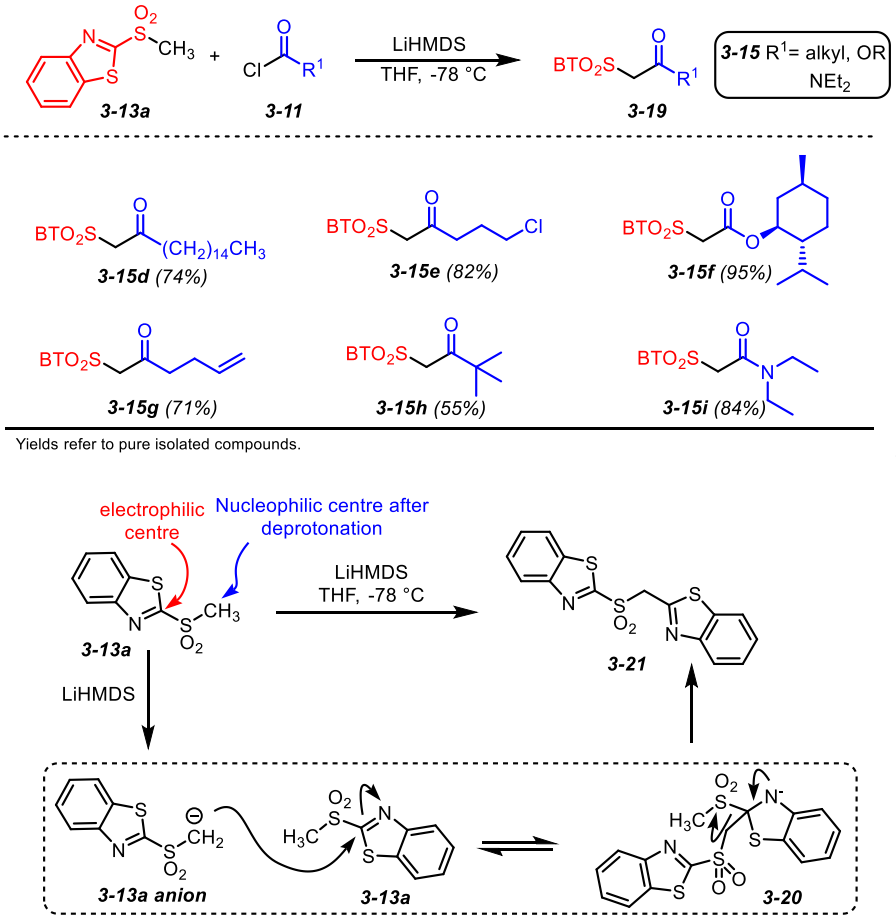
[a]CrO_3/H_5IO_6, CH_3CN, r.t. was used instead of H_2O_2 system; Yields refer to pure isolated compounds.

*Table 6 - Sulfone **3-17** synthesis based on the sulfinic salt **3-1** (Scheme 30, path C).*



Yields refer to pure isolated compounds.

*Table 7 - Sulfone **3-15** synthesis based on the condensation of 3-13a with acyl carbonyl derivatives (Scheme 30, path B).*



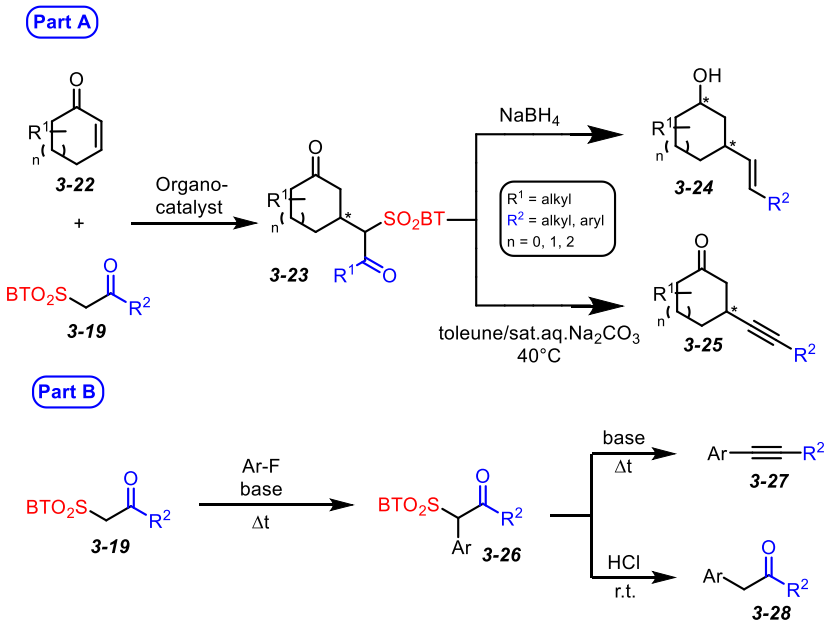
Scheme 31 – Possible side-reaction using the strong base and less reactive electrophiles (esters, bulky anhydrides).

As can be seen in Table 5, Table 6, and Table 7, we have disclosed several robust and complementary ways to prepare virtually all imaginable Building blocks (**Build** phase) or **PM-1** molecules (**Couple** phase).

3.3 Couple and Pair phase – from PM-1 to PM-2

3.3.1 Previous results achieved in the context of β-keto sulfone reactivity

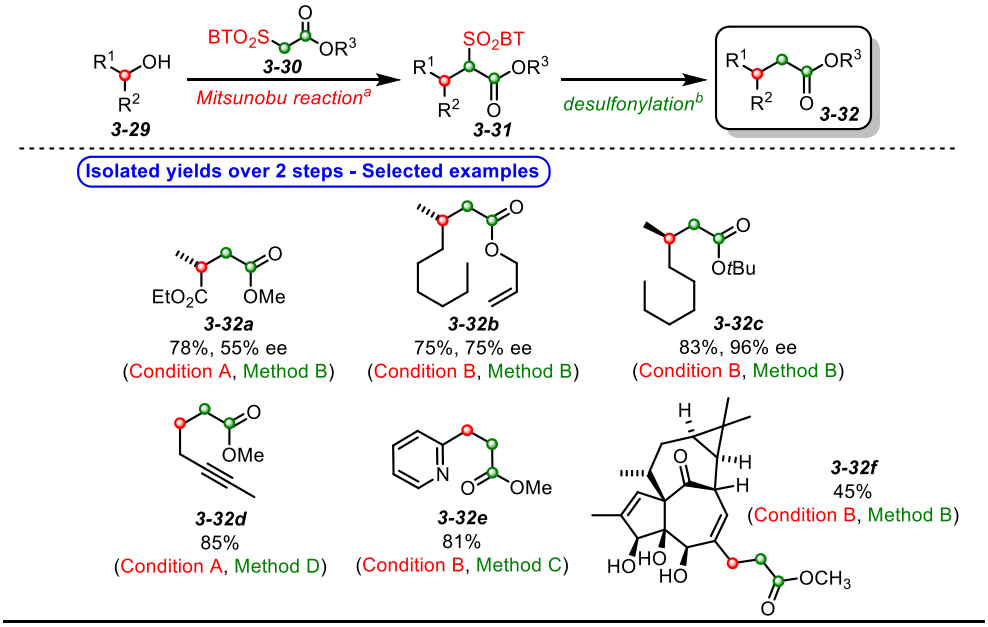
PM-1 type molecules have due to their interesting reactivity rather long history in the recent literature. In general **PM-1** like scaffolds were used as C-acids (Scheme 32). In this role, they were employed mainly by Jørgensen et al as a C-nucleophile in the organocatalyzed reactions.[62,63] Such type of reaction can be also viewed (and used) used as a "**Pair** reactions" in the context of our **PM-1** development.



Scheme 32 – Usage of PM-1 molecules in organocatalyzed reaction as C-nucleophile.

Later on, our group exploited **PM-1** like molecules as C-nucleophiles in Mitsunobu type homologation.[64] In this context, **PM-1** was used as a two-carbon homologation reagent of alcohols. Overall the reaction proceeds in acceptable yields but in case of chiral alcohols only in moderate to good inversion of their stereogenic centre. However, when applied to the homologation of the terminal alcohols, it proved to be applicable even in the case of complex natural products (Table 8).

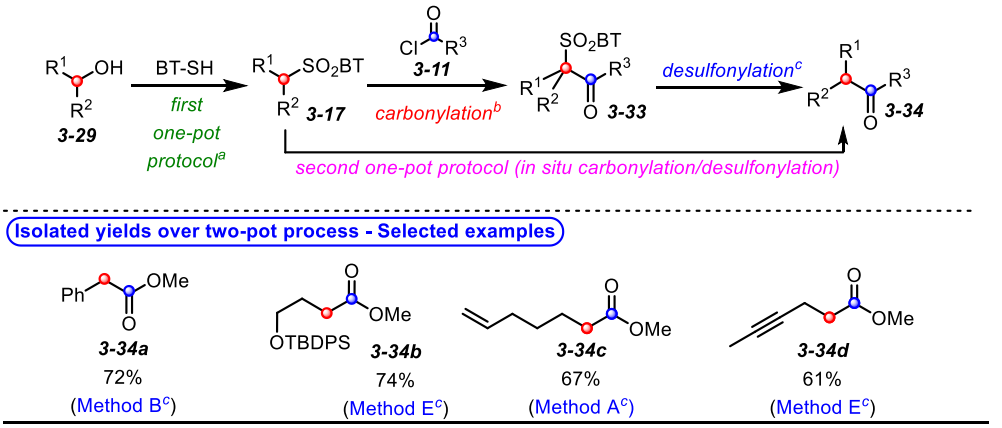
*Table 8 - Two carbon homologation of alcohols using **PM-1** type molecule.*



[a]Conditions A: alcohol ***3-29*** (1.0 equiv), ***3-30*** (1.2 equiv), ADDP (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0°C to RT, 12h; Conditions B: alcohol ***3-29*** (1.0 equiv), C-acid (1.2 equiv), DEAD (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0°C to RT, 6h
[b]Desulfonation Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0°C, 1h, then TFA (20 equiv), 2h; Method B: nBu_3SnH (1.25 equiv), AIBN (0.2 equiv), benzene, 80°C, 1h; Method C: nBu_3SnCl (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1mL to 1 mmol of KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110°C, 3h. Method D: SmI_2 (6.5 equiv), MeOH (50 equiv), THF, -78 °C, 30 min; Method E: Zn dust (5.0 equiv), THF/AcOH = 5:1 (V/V), 0°C to RT, 8h

In addition, if **PM-1** was formed using reaction using of BT-sulfones ***3-17*** with various chloro carbonyl derivatives ***3-11***, obtained **PM-1** can be further selectively desulfonylated to yield products of formal one carbon extension in comparison to alcohol **3-29** (Table 9).

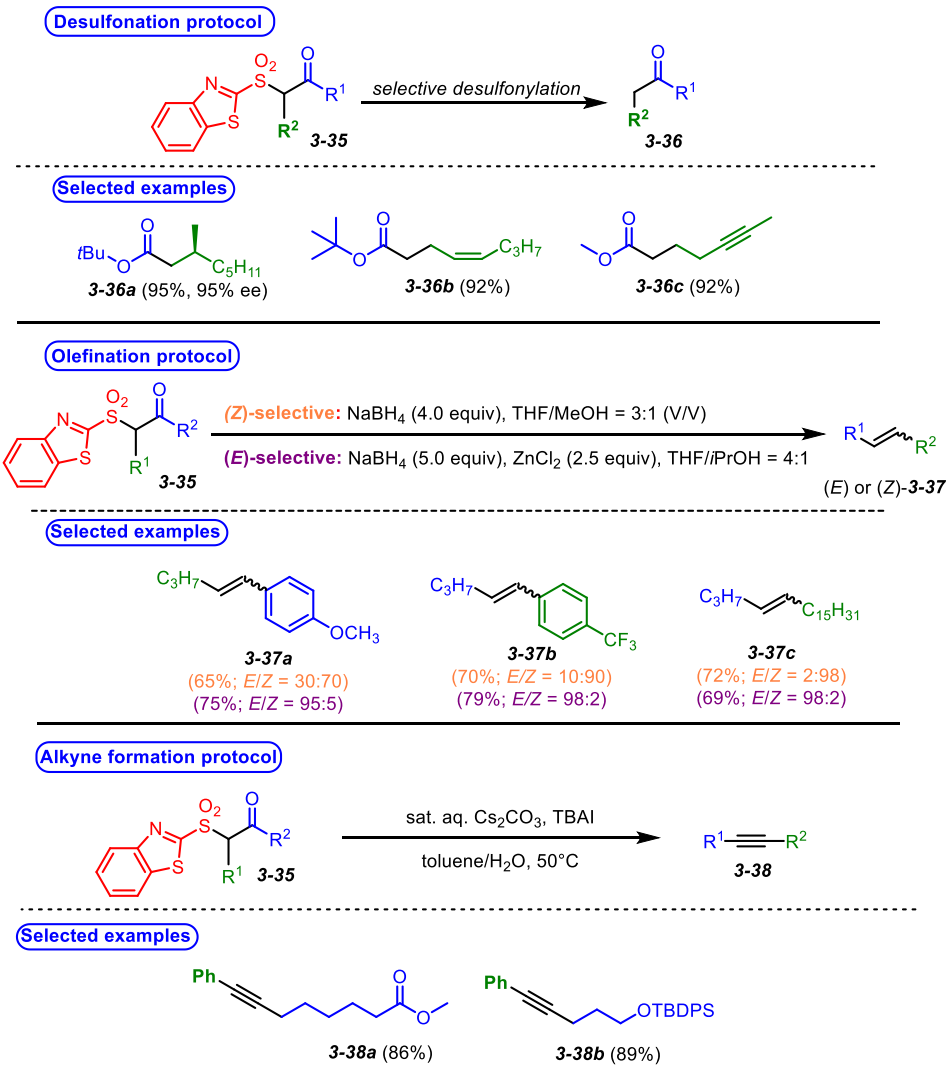
*Table 9 - PM-1-based one-carbon homologation of alcohol **3-29** using a two-pot protocol.*



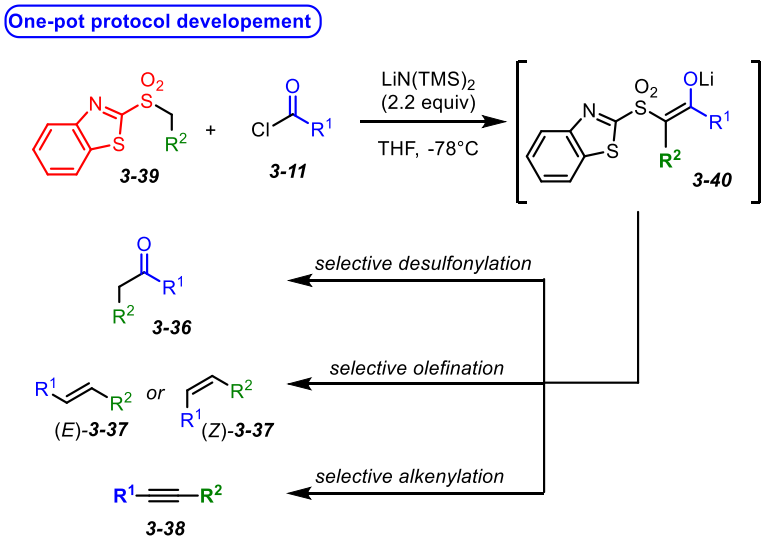
[a]Conditions: alcohol ***3-29*** (1.0 equiv), BT-SH (1.2 equiv), DEAD (1.2 equiv), PPh_3 (1.2 equiv), THF, 0°C to RT, 12h then $Na_2WO_4\,2H_2O$ (0.1 equiv), 30% aq. H_2O_2 (30 equiv), EtOH, 0°C to RT, 12h. [c]Conditions: sulfone ***3-17*** (1.0 equiv), carbonyl reagent ***3-11*** (1.05 equiv), LiHMDS (2.2 equiv), THF, -78 °C, 30 min.
[c]Desulfonation Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0°C, 1h, then TFA (20 equiv), 2h; Method B: nBu_3SnH (1.25 equiv), AIBN (0.2 equiv), benzene, 80°C, 1h; Method C: nBu_3SnCl (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1mL to 1 mmol of KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110°C, 3h. Method D: SmI_2 (6.5 equiv), MeOH (30 equiv), THF, -78 °C, 30 min; Method E: Zndust (5.0 equiv), THF/AcOH = 5:1 (V/V), 0°C to RT, 8h.

The key step of the last two transformations is selective desulfonylation reactions that were either newly developed or adapted from the literature precedents. Indeed, orthogonal in the reactivity, several sets of reaction conditions based on the Brønsted acid catalysis, nucleophiles (thiolate or methanolate), and tin radicals were developed and successfully applied.[64] Along with the desulfonylation, additional transformations of **PM-1** were investigated.[75] Especially we got inspired

by the work of Jørgensen group[62,63] that described the transformation of β-keto-BT-sulfone motives to olefins and alkynes. After some optimization, three new protocols that allow the transformation of β-keto-BT-sulfone intermediates to *E* or *Z* olefins, and alkynes were developed (Scheme 33). These methods were nice but suffered from several drawbacks since β-keto-BT-sulfones proved to be sensitive to SiO_2, and more importantly, we had some issues with the olefination step reproducibility. Especially the first reason, silica gel instability of β-keto-BT-sulfones was an important trigger to our attempts to develop a one-pot protocol that would allow us to generate targeted ketones, olefins and alkynes directly from sulfones ***3-39*** and acyl chlorides ***3-11*** (Scheme 34). Such an approach would offer much simpler reaction procedures without the necessity to isolate individual intermediates. Moreover, the development of a one-pot protocol would essentially correspond to the **Build-Couple-Pair** phases merged into one single reaction flask. But still, by applying different reagents we will obtain structural diversity after the reaction work-up. Obviously, we had all simple steps, single chemical transformations in our hands, but the question was – will all these steps work in one "kettle"?



*Scheme 33 – Jørgensen approach-inspired selective transformations of **3-35** to E-olefin, Z-olefin, and alkynes.*



Scheme 34 – The proposed one-pot strategy for alkene, alkyne, and ketone synthesis.

3.3.2 In situ generated PM-1 – transposing the "pluripotent reagents" to "pluripotent protocols"

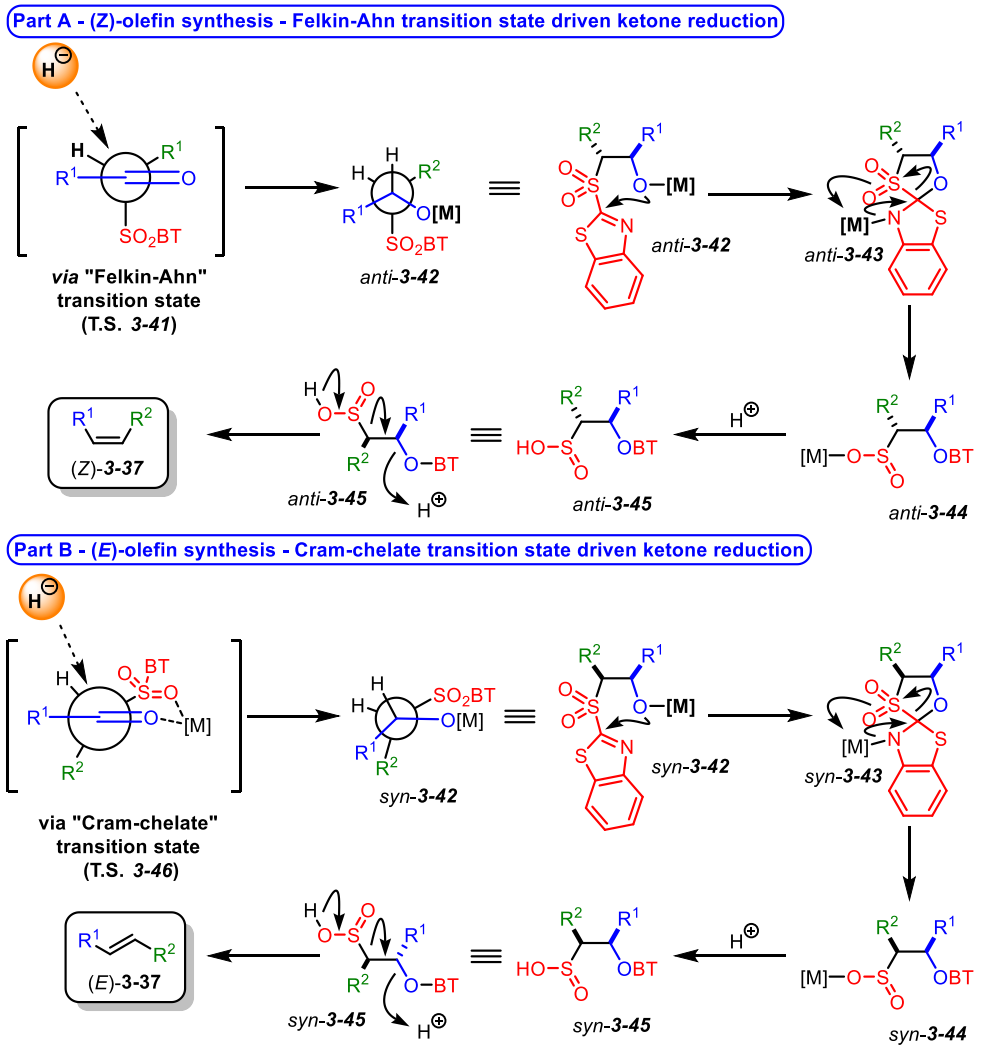
The original concept discussed in this chapter basically connects **Couple** and **Pair** phase in the one-pot protocol. The idea behind was, since our PM-1s are not always easy to handle (purification, etc), why not to transform them immediately after their formation. Thus, the reaction of sulfone ***3-39*** with ***3-11*** (**Couple** step), creates *in situ* lithium enolate ***3-40*** (enolate form of PM-1) that should be transformed immediately with properly chosen reagent (**Pair** step) to olefins, alkynes and carbonyl-containing compounds. First, we have focused on olefin formation (Table 10). To accomplish this transformation, the selective reduction of the β-carbonyl group in PM-1 must be achieved. Not only that the carbonyl group must be selectively reduced in the presence of other electrophilic reactive centres, but it must be also reduced stereoselectively (*syn* or *anti*) with respect to BT-sulfonyl group. Indeed, *syn* or *anti*-stereochemical outcome of the reduction will have an impact on the *E* or *Z*-olefin formation (see chapter 2.3). Based on this goal, we have established two different approaches: (a) in the first one the reduction of the β-carbonyl proceeds via Felkin-Ahn transition state ***3-41***, and yields via *anti*-intermediate *Z*-olefin (Scheme 35, Part A); and (b) in the second case, the reduction of carbonyl via Cram-chelate transition state ***3-46*** yields *syn*-isomer that generated *E*-olefin (Scheme 35, Part B).

Based on this hypothesis, the one-pot protocol for *Z*-selective olefination was attempted. First, the generated lithium enolate ***3-40a*** formed *in situ* from ***3-13b*** or ***3-13e*** (coupling step) was quenched with MeOH, and to the resulting mixture $LiBH_4$ was added (Table 10, entry 1). After 4 h at 0°C, saturated aqueous NH_4Cl was added to protonate expected sulfinate salt intermediate *anti*-***3-44***, and the whole mixture was stirred at rt for 2h. After this time, the *anti*-elimination process occurred and yielded the desired olefin *Z*-***3-37b*** olefin in 61% yield and 10:90 *E*/*Z* selectivity. Further evaluation

of the THF/MeOH ratio, counter anion influence, and the role of work-up on the reaction yield and selectivity determined that the use of THF/MeOH = 3:1 (V/V) mixture of solvents, 10 equivalent of $NaBH_4$ as reducing agent, and 1.0M aqueous solution of HCl for the reaction work-up are the best reaction/work-up conditions (Table 10, entry 5). In such a case, the overall transformation proceeded with a 71% yield and 1:99 *E*/*Z* selectivity.

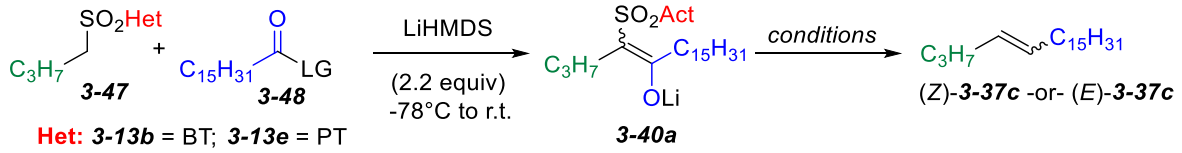
The role of acid during the work-up proved to be essential to obtain the desired olefin ***3-37c*** in good yield especially in the case of PT-heterocycles (Table 10, entry 6 vs entry 7). It is expected that in this case, strong acid helps to "destroy" (dissociate) presumably formed clusters that could disable the formation of the protonated sulfinic acid intermediate. The key intermediate that further undergoes to the *anti*-elimination.

Having an excellent condition for the *Z*-selective olefination protocol, reaction conditions that would yield *E*-olefination were searched. In this case, pre-coordination of the keto-sulfone with bidentate metal was required to achieve a high level of *E*-selectivity. Thus, several bidentate metals as Zn^{2+}, Co^{2+}, Mg^{2+} were evaluated and added to the reaction mixture before the $NaBH_4$ and a co-solvent (alcohol) (Table 10, entries 11 to 20). It was observed that $ZnCl_2$ is the best chelating metal in terms of reaction yield and selectivity. Moreover, it was observed that the anion of the alcohol, and especially its steric requirements play a crucial role in further increase of the *E*/*Z* selectivity (MeOH= 75:25, *i*PrOH= 98:2, BuOH=88:22, *t*-BuOH= 90:10). Also, in this case, the role of the workup (aqueous HCl vs. sat. sol. of NH_4Cl) in case of PT-sulfones on the reaction yield proved to be important. Similarly, the origin of the leaving group in acylating agents (coupling step) proved to be important when it comes to the reaction yields of the sequence (Table 10, entries 18, 21 and 22).



Scheme 35 – Proposed transition states that allow the selective formation of E and Z-olefins.

Table 10 - Optimization of one-pot olefination protocols.



Het: ***3-13b*** = BT; ***3-13e*** = PT

Entry	Het.	LG	Conditions[a]	Yield[b]	*E*/*Z*[c]
1	BT	Cl	$LiBH_4$ (10 equiv), THF/MeOH (10:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	61 %	10:90
2	BT	Cl	$LiBH_4$ (5 equiv), THF/MeOH (5:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	67 %	6:94
3	BT	Cl	$NaBH_4$ (5 equiv), THF/MeOH (5:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	70 %	5:95
4	BT	Cl	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	72 %	2:98
5	BT	Cl	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	71 %	1:99
6	PT	Cl	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	26 %	5:95
7	PT	Cl	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	72 %	2:98
8	BT	CN	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	69 %	2:98
9	BT	$OC(O)C(CH_3)_3$	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	73 %	2:98
10	BT	$OC(O)C(CH_3)_3$	$NaBH_4$ (10 equiv), THF/MeOH (3:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	68 %	3:97
11	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/MeOH (10:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	54 %	95:5
12	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/MeOH (5:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	56 %	75:25
13	BT	Cl	$MgBr_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/MeOH (5:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	29 %	81:19
14	BT	Cl	$CoCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/MeOH (5:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	12 %	*n.d.*
15	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	69 %	98:2
16	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*t*BuOH (4:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	47 %	90:10
17	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*s*BuOH (4:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	72 %	88:22
18	BT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	68 %	98:2
19	PT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* sat. aq. NH_4Cl, RT, 2h	16 %	95:5
20	PT	Cl	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	56 %	98:2
21	BT	CN	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	71 %	97:3
22	BT	$OC(O)C(CH_3)_3$	$ZnCl_2$ (2.5 equiv), $NaBH_4$ (5.0 equiv), THF/*i*PrOH (4:1 (V/V)), 0°C, 4h *then* 1.0M aq. HCl, RT, 2h	70 %	98:2

[a]Sulfone 1 (1.0 equiv), acylating agent 2 (1.05 equiv), LiHMDS (2.2 equiv), THF, -78 °C, 30 min, *then conditions* in table. [b] Refers to pure isolated compounds. [c] Based on the ^1H NMR spectra of the crude reaction mixture.

Having in hands optimized reaction conditions, the scope, and limitations of both olefination protocols were established. First, the reaction of alkyl sulfones ***3-39*** (R^2 = alkyl) and aryloyl and acyl chlorides ***3-11*** were evaluated. In all attempted cases high yields and *E/Z*-selectivities were obtained (Table 11, Part A, ***3-37a***-***3-37d***). Unfortunately, if long alkyl chains were used on sulfone ***3-39*** part and acyl chloride ***3-11***, only *E*-olefins were obtained as the products of the coupling reaction (***3-37i***-***3-37j***). It seems that long alkyl chains hammer the Felkin-Ahn transition state and the reduction issues only the *syn*-isomers.

Sulfones ***3-39*** (R^2= Ph) were also tested as the reaction partners. In this case, the application of the *Z*-selective protocol proved to be problematic in the case of aryl-containing acyl chlorides ***3-11***. The reaction worked perfectly, however, obtained *Z*-olefins spontaneously isomerized to its thermodynamically more stable *E*-olefin. Nevertheless, high yields of the desired olefins were obtained using both *E*- and *Z*-selective protocols (Table 11, ***3-37e***-***3-37g***). In this case, we also focused on comparing the reactivity of BT and PT sulfones, and on the evaluation of the effect of heterocycle on the reaction outcome. In general, based on experimental observation (Table 11, Part B), the PT sulfones proved to be worse reaction partners in the olefination protocol (except for ***3-37c***) in terms of both, reaction yield and selectivity. A significant difference was observed especially in the case of the *Z*-selective protocol, where low selectivity was in general achieved.

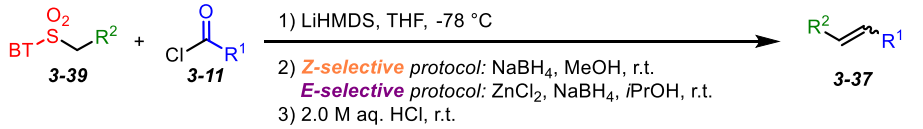
Finally, the possibility of the deuterium incorporation was also explored (Table 12). The idea behind was to evaluate if the use of $NaBD_4$ during the β-keto sulfone reduction will cause the full deuterium incorporation to newly generated olefin. Such a situation would open us a new way to the *E/Z*-olefin formation where one of the two hydrogen atoms is deuterium. It was observed that in principle the protocol works and yields the desired *E* or *Z* olefins. Unfortunately, if long aliphatic chains were used in both, sulfone and acyl part of the coupling partners, only *E*-olefins were obtained. The deuterium enrichment was in all cases >98%.

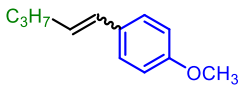
Having established a powerful one-pot olefination protocol, we focused our attention to one-pot ketone/ester formation (Table 13). In such case the *in situ* generated lithium enolate ***3-40*** was quenched with an excess of AcOH and generated β-keto-BT-sulfone was desulfonylated with help of Samarium metal[76] (literature procedure) or Zinc dust (for proposed mechanistic rationalization see Scheme 36). Previously we exploited Zn dust as a reducing agent in case of one-carbon homologation reactions (see Table 9). Therefore we decided to use similar procedure for this newly developed one-pot protocol that should give us ketones and esters. Indeed, this strategy proved to be successful and using a one-pot coupling/desulfonylation protocol various ketones and esters (Table 13) were prepared. All attempted acyl chlorides ***3-11*** (R^1= alkyl, aryl) yielded in this sequence the final products in good to very good yields. In addition, our method allowed us to prepare rather unstable symmetrical

1,4 diketones (see Table 13, ***3-36h*** and ***3-36e***). Thus, our synthetic protocol could be extended to the synthesis of heterocycles.

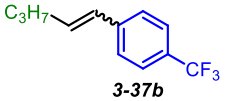
Table 11 - Scope and limitations of one-pot E/Z-selective olefination protocol.

Part A - One- pot olefin formation using BT

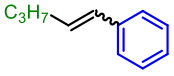




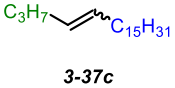
3-37a
(65%; *E/Z* = 30:70)[a]
(75%; *E/Z* = 95:5)[a]



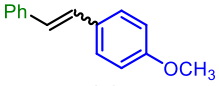
3-37b
(70%; *E/Z* = 10:90)[a]
(79%; *E/Z* = 98:2)[a]



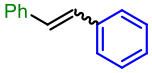
3-37d
(85%; *E/Z* = 7:93)[a]
(74%; *E/Z* = 98:2)[a]



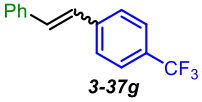
3-37c
(72%; *E/Z* = 2:98)[a]
(69%; *E/Z* = 98:2)[a]



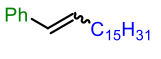
3-37e
(69%; *E/Z* = 93:7)[a]
(74%; *E/Z* = 98:2)[a]



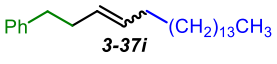
3-37f
(67%; *E/Z* = 46:54)[a]
(73%; *E/Z* = 97:3)[a]



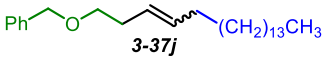
3-37g
(67%; *E/Z* = 38:62)[a]
(73%; *E/Z* = 97:3)[a]



3-37h
(63%; *E/Z* = 27:73)[a]
(62%; *E/Z* = 81:19)[a]



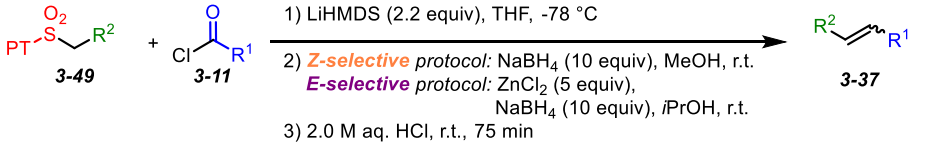
3-37i
(34%; *E/Z* = 75:25)[a]
(8%; *E/Z* = 96:4)[a]

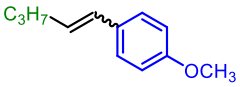


3-37j
(46%; *E/Z* = 99:1)[a]
(46%; *E/Z* = 88:12)[a]

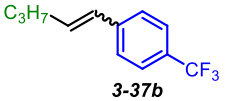
[a]refers to isolated yields; *E/Z* selectivity based on the ^{1}H NMR spectra of the crude reaction mixture

Part B - One- pot olefin formation using PT[b]

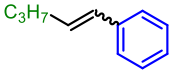




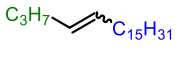
3-37a
(81%; *E/Z* = 38:62)[a]
(58%; *E/Z* = 95:5)[a]



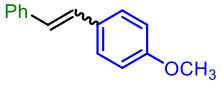
3-37b
(58%; *E/Z* = 12:88)[a]
(42%; *E/Z* = 98:2)[a]



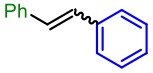
3-37d
(94%; *E/Z* = 20:80)[a]
(63%; *E/Z* = 95:5)[a]



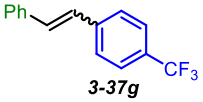
3-37c
(72%; *E/Z* = 2:98)[a]
(56%; *E/Z* = 98:2)[a]



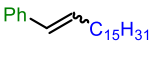
3-37e
(55%; *E/Z* = 92:8)[a]
(39%; *E/Z* = 98:2)[a]



3-37f
(39%; *E/Z* = 52:48)[a]
(17%; *E/Z* = 93:7)[a]



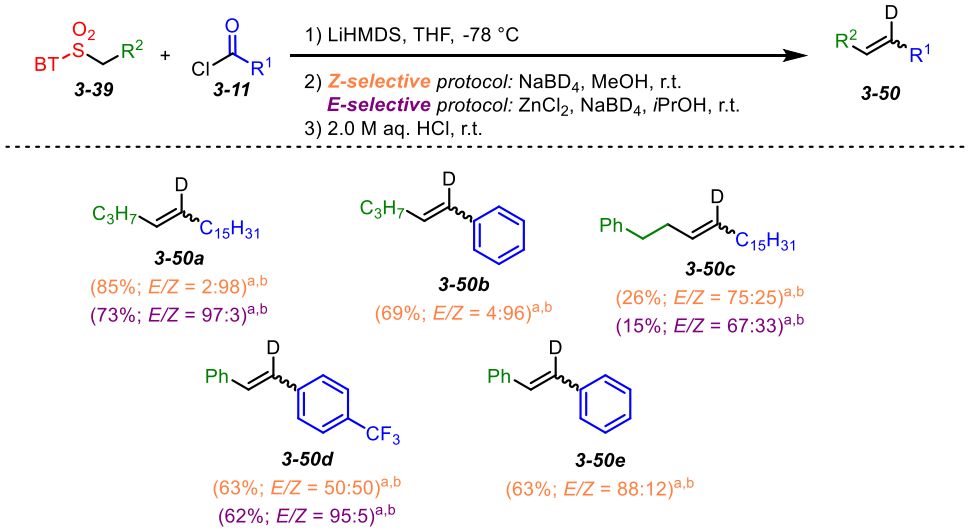
3-37g
(48%; *E/Z* = 93:7)[a]
(55%; *E/Z* = 97:3)[a]



3-37h
(63%; *E/Z* = 32:68)[a]
(78%; *E/Z* = 69:31)[a]

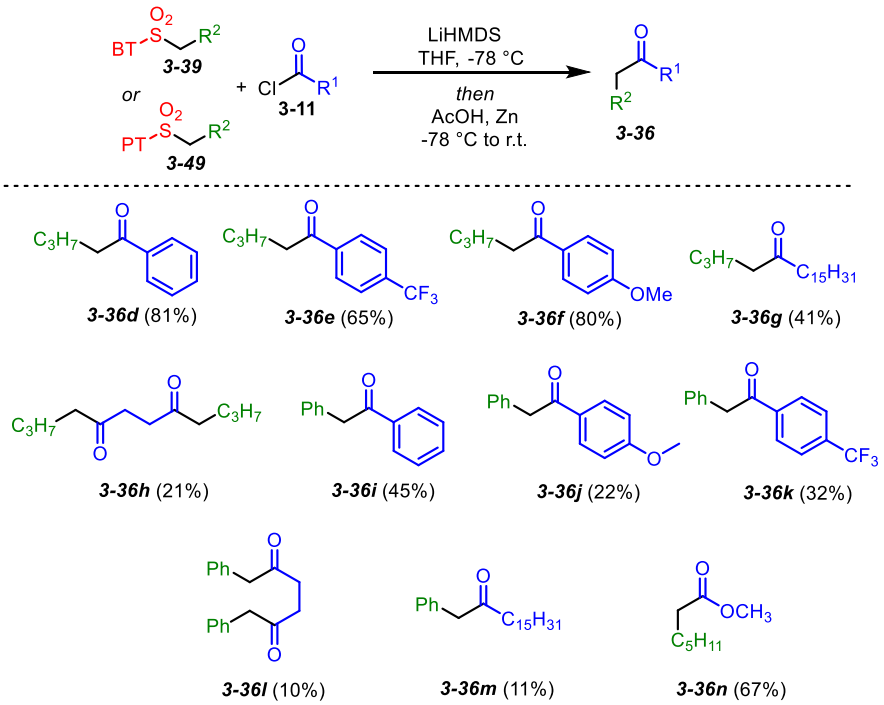
[a]refers to isolated yields; *E/Z* selectivity based on the ^{1}H NMR spectra of the crude reaction mixture
[b]results taken from bachelor thesis of Vendula Ferugová

Table 12 – Selective synthesis of E and Z-olefins using $NaBD_4$ as a deuterium source.

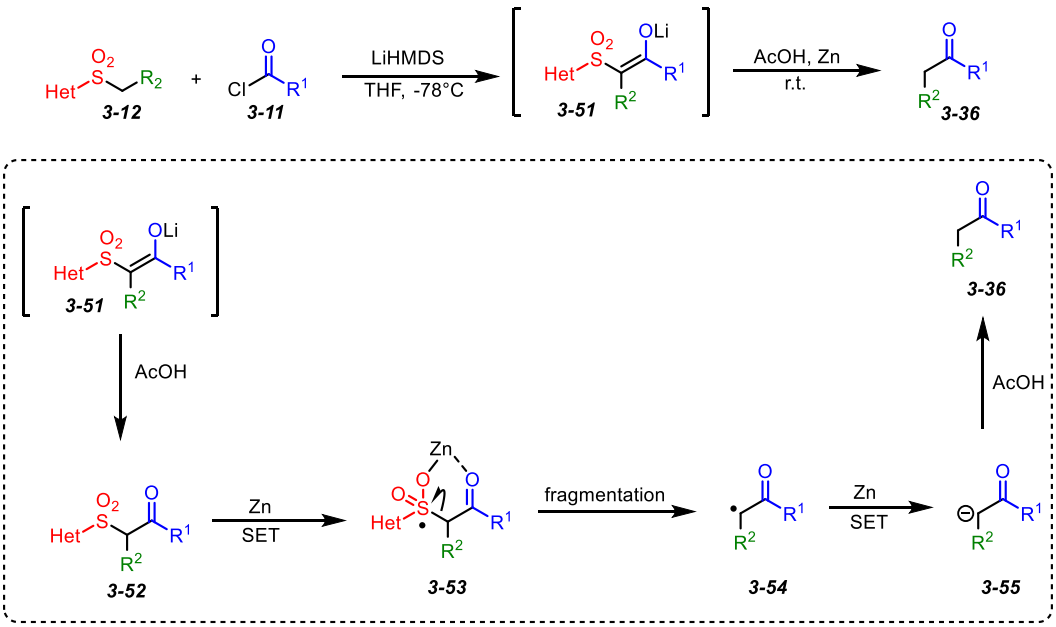


[a]refers to isolated yields; *E/Z* selectivity based on the ^{1}H NMR spectra of the crude reaction mixture
[b] >98% deuterium incorporation

Table 13 – Extension of our one-pot protocol to ketone and ester synthesis – scopes and limitations.



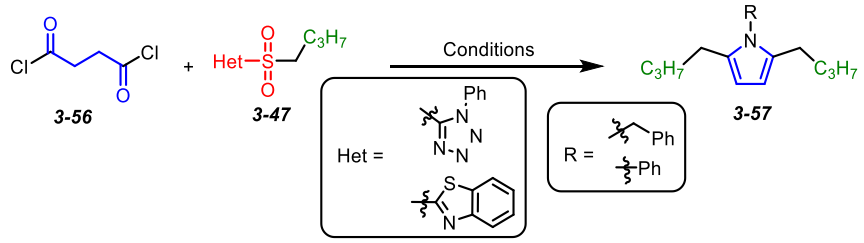
Yields refer to pure isolated compounds.

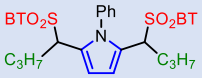
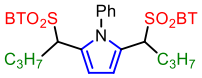
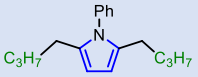
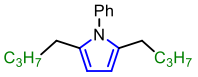
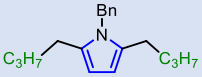
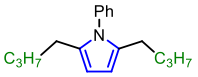
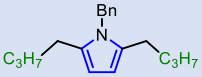
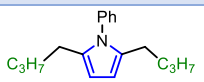


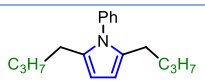
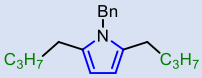
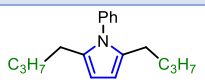
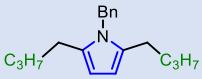
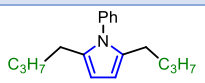
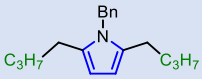
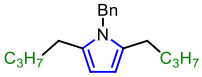
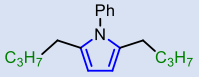
Scheme 36 – Proposed mechanism of Zn mediated reduction.

Having in hands short and efficient route to 1,4-diketone synthesis, the pyrrole synthesis becomes virtually mandatory. We speculated that if simply primary amine is added to the reaction mixture, the desired pyrrole should be formed. To evaluate our hypothesis, two equivalents of sulfone ***3-47*** were reacted in the presence of LiHMDS (4.4 equiv) with diacyl chloride ***3-56***. Generated bis-lithium dienolate was quenched with AcOH addition and aniline was added. No traces of product ***3-57a*** were however detected (Table 14, entry 1). Further changes in reaction conditions did not bring better results. We have concluded that the reason behind the failed pyrrole synthesis is the keto/enol tautomerism of the double adduct ***3-51*** that fails to generate a sufficient amount of the keto form available to react with the presented amine. To avoid enol form formation, Zn-mediated desulfonylation step was inserted to the reaction sequence before the amine addition. Gratifyingly, the desired pyrrole ***3-57b*** was isolated in 16% yield (over 4 steps) (Table 14, entry 4). When the same transformation was attempted using benzylamine, the desired pyrrole ***3-57c*** was isolated in 9% overall yield (entry 5). A further variation of the reaction times of different steps, equivalents of reagents, and temperatures lead us to disclose optimum reaction conditions (Table 14, entries 16 and 17) that yielded *N*-phenylpyrrole ***3-57b*** in 28% overall yield, and *N*-benzylpyrrole ***3-57c*** with 37% overall yield, respectively. If we re-calculate the reaction yield from overall to step related, the reaction proceeded with ~80% yield per step. The synthesis of pyrroles ***3-57b*** and ***3-57c*** served us as a proof of principle that our **PM-1** reagent can be further used in various one-pot transformations. The concept that might be further developed e.g. to other pyrroles, furans or thiophenes synthesis.

Table 14 - Optimization of one-pot protocol for pyrroles synthesis (Best optimized conditions highlighted in Table 15).

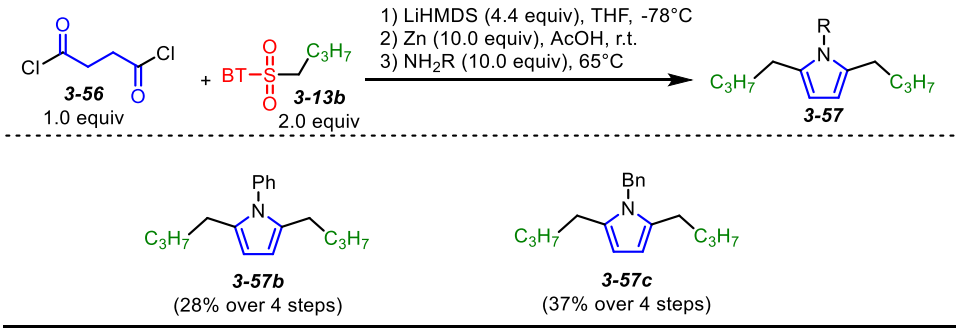


Entry	Het	R	Conditions	Expected product Yield [%]
1[a]	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (5.6 mL) at -78°C, 25 min 3. **R-NH$_2$** (2.0 equiv), 10 min at 0°C, then 12h at r.t.	 ***3-57a*** (<5%)[b]
2[a]	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min, then warmed to 0°C 2. AcOH (5.6 mL) at 0°C, 15 min 3. **R-NH$_2$** (2.0 equiv), 15 min at 0°C, 20h at r.t., 3.5h at 55°C, 1h at 70°C	 ***3-57a*** (<5%)[b]
3	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min, then warmed to -25°C 2. AcOH (5.6 mL) at -25°C, 25 min 3. Zn (10.0 equiv) at -25°C, 20 min, then 15h at r.t. 4. **R-NH$_2$** (2.0 equiv), 24h at r.t.	 ***3-57b*** (12 %)[c]
4	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 30 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 16h at r.t. 4. **R-NH$_2$** (2.0 equiv) at r.t., then 7.5h at RT, 5h at 50°C, 13h at 65°C	 ***3-57b*** (16%)[c]
5	BT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 30 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 20h at r.t. 4. **R-NH$_2$** (2.0 equiv) at r.t., then 8h at r.t., 16h at 65°C	 ***3-57c*** (9%)[c]
6	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 5 min 3. Zn (10.0 equiv) at -78°C, 5 min 4. **R-NH$_2$** (2.0 equiv) at -78°C, 5 min, then 22h at r.t., 1.5h at 65°C	 ***3-57b*** (5%)[c],[d]
7	BT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 5 min 3. Zn (10.0 equiv) at -78°C, 5 min 4. R-NH$_2$ (2.0 equiv) at -78°C, 5 min, then 22h at r.t., 1.5h at 65°C	 ***3-57c*** (<5%)[b]
8	PT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 5 min 3. Zn (10.0 equiv) at -78°C, 5 min 4. **R-NH$_2$** (2.0 equiv) at -78°C, 5 min, then 22h at r.t.	 ***3-57b*** (<5%)[b]
9	PT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 5 min 3. Zn (10.0 equiv) at -78°C, 5 min 4. **R-NH$_2$** (2.0 equiv) at -78°C, 5 min, then 26h at r.t., 1.5h at 65°C	 ***3-57c*** (<5%)[b]

10	PT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 16h at r.t. 4. **R-NH$_2$** (2.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57b*** (9%)[c]
11	PT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 16h at r.t. 4. **R-NH$_2$** (2.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57c*** (9%)[c]
12	PT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 16h at r.t. 4. **R-NH$_2$** (5.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57b*** (13%)[c]
13	PT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 22h at r.t. 4. **R-NH$_2$** (5.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57c*** (13%)[c]
14	BT	Ph	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 22h at r.t. 4. **R-NH$_2$** (10.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57b*** (8%)[c]
15	BT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 22h at r.t. 4. **R-NH$_2$** (5.0 equiv) at r.t., 5 min, then 24h at 65°C	 ***3-57c*** (17%)[c]
16	BT	Bn	1. LiHMDS (4.4 equiv), THF, -78°C, 30 min 2. AcOH (6.5 mL) at -78°C, 15 min 3. Zn (10.0 equiv) at -78°C, 5 min, then 22h at r.t. 4. **R-NH$_2$** (10.0 equiv) at r.t., 5 min, then 4h at 65°C	 ***3-57c*** (37%) [c]
17	BT	Ph	5. LiHMDS (4.4 equiv), THF, -78°C, 30 min 6. AcOH (6.5 mL) at -78°C, 15 min 7. Zn (10.0 equiv) at -78°C, 5 min, then 20h at r.t. 8. **R-NH$_2$** (10.0 equiv) at r.t., 5 min, then 4h at 65°C	 ***3-57b*** (28%) [c]

a) Attempt to form pyrrole ring without the sulfone reduction.
b) Based on ^{1}H NMR of the crude reaction mixture.
c) Isolated yield.
d) Low purity (approx. 75-85%).

Table 15 - Pyrrole synthesis using the one-pot protocol.



3.4 PM-1 as a starting point in PM-2 synthesis

Having disclosed several ways how **PM-1** can be used in the context of Diversity-Oriented synthesis, we have decided to push limits of our methodology and to add a couple of reactive sites to the original **PM-1** molecular scaffold. To do so, **PM-1** reaction with aldehyde ***3-7*** under (formal) Knoevenagel type condensation reaction conditions was envisaged (Figure 9).

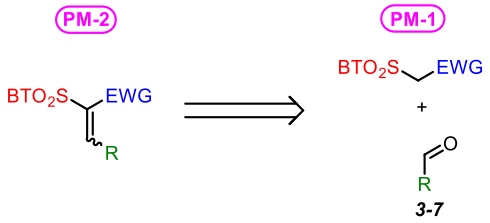


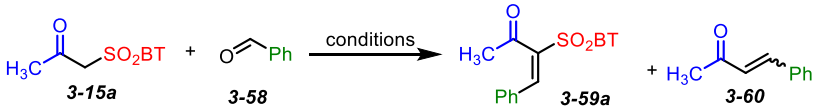
Figure 9 –PM-2 molecule retrosynthesis.

Indeed, newly designed **PM-2** molecule should possess very different reactivity in comparison with **PM-1** due to its bis activated α,β-unsaturated system. But such consideration can come only after the **PM-2** is prepared. And **PM-2** syntheses proved to be more challenging than expected. Table 16 that contains (selected relevant) optimization data should testify the journey we took on our way to the efficient **PM-2** synthesis.

Search for Knoevenagel-type condensation conditions started with the screen of classical Knoevenagel reaction conditions.[77] No hurdle on the way was expected **PM-1** has enolizable α-hydrogens (pKa~12-13) with similar pKa as diethyl malonate, standard Knoevenagel reaction partner. Unfortunately, reality proved to be very different. Attempted "classical" condensation reactions mostly led to the formation of formally Julia-Kocienski olefination product ***3-60***, or no starting material consumption was observed (Table 16, entries 1-13). In the case of EDDA catalyzed reaction, a mixture of desired Knoevenagel adduct ***3-59a*** and Julia-Kocienski olefination product ***3-60*** were obtained.

Having these data in hands, all collected experimental data could be carefully evaluated. And the evaluation revealed two important conclusions: (a) no base should be used during the condensation step; (b) we need to activate/promote the formation of the enolate in **PM-1**. To put to the context the first case. The presence of a strong base promotes direct Julia-Kocienski olefination reaction (Scheme 37, Part A). To avoid such a situation, the presence of the base had to be avoided. Next, olefin ***3-60*** could be also formed if external nucleophile would add to ***3-59a*** adduct heterocyclic electrophilic site (Scheme 37, Part B). In such case, neutral or slightly acidic protic condition should allow the *in-situ* generation of sulfinic acid ***3-65*** from the corresponding salt ***3-64*** and would trigger the spontaneous release of SO_2 and generates olefin ***3-60***. Still, even under neutral or slightly acidic conditions the olefin ***3-60*** may be formed via olefination protocol.

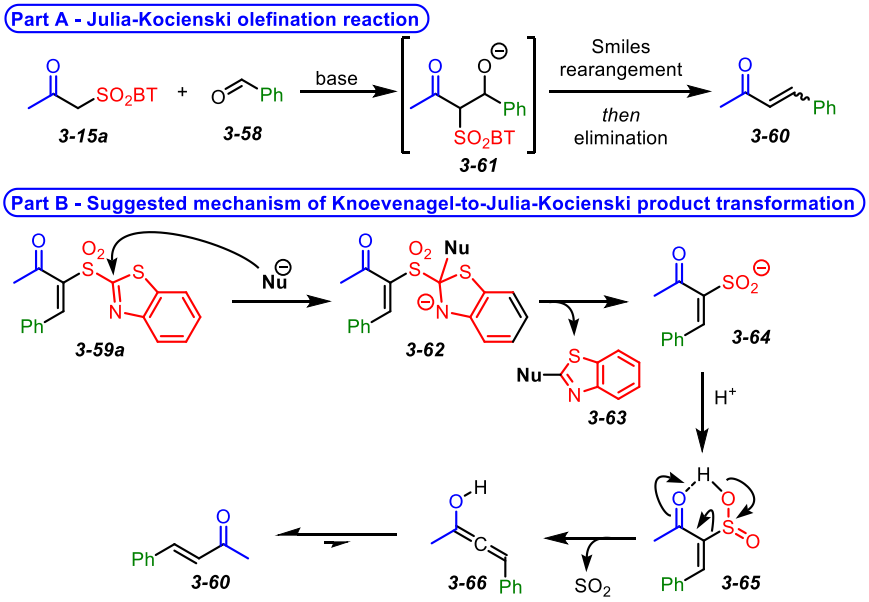
*Table 16 -Towards **PM-2**: Optimization of Knoevenagel condensation reaction.*



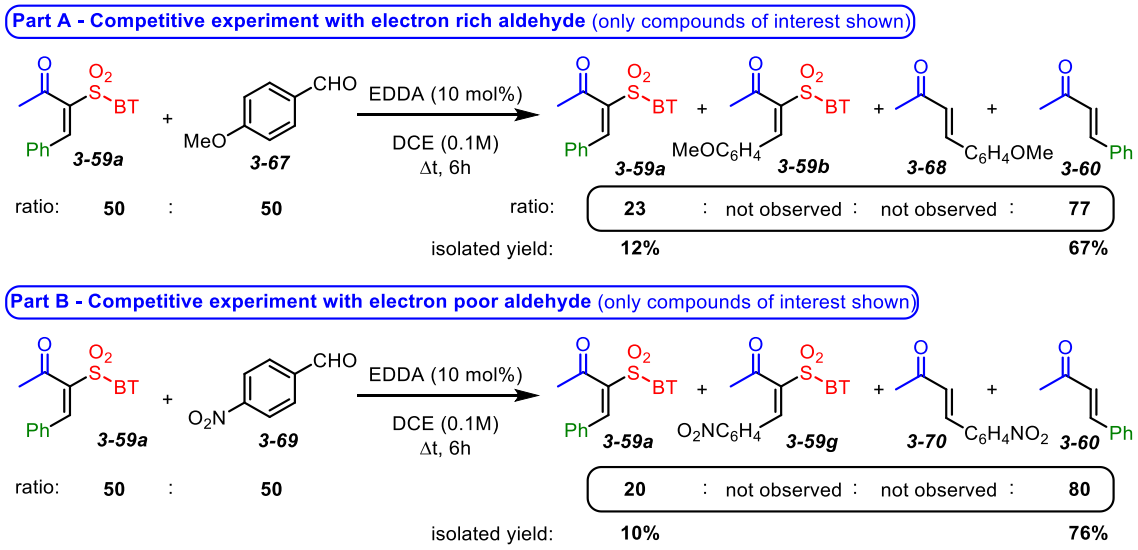
Entry	Reaction Conditions	*3-59a*/*3-60* ratio[a]	Yield (%)[b]	Note
1	CH_3COONH_4 (0.4 equiv), MeOH, r.t., 16h	**0/100**	72	>95% conversion of ***3-15a*** [a)]
2	Piperidine (0.1 equiv), EtOH, r.t., 6h	**0/100**	88	>95% conversion of ***3-15a*** [a)]
3	$(NH_4)_2HPO_4$(0.2 equiv), CH_3CN, r.t., 16h	-	-	***3-15a*** recuperated
4	Piperidine (0.15 equiv), pyridine, r.t., 16h	**0/100**	43	>95% conversion of ***3-15a*** [a)]
5	CH_3COONH_4 (0.15 equiv), AcOH (0.3 equiv), toluene, reflux, 16h	**0/100**	57	>95% conversion of ***3-15a*** [a)]
6	EDDA (10 mol%), DCE, reflux, 24h	**0/100**	63	>95% conversion of ***3-15a*** [a)]
7	EDDA (10 mol%), DCE, reflux, 3h	**81/19**	26	62% ***3-15a*** conversion [a)]
8	EDDA (10 mol%), DCE, reflux, 12h	**50/50**	36	90% **15a** conversion [a)]
9	EDDA (10 mol%), DCE, 40°C, 12h	-	-	***3-15a*** recuperated
10	$CeCl_3.7\ H_2O$ (1.35 equiv), NaI (1.35 equiv), CH_3CN, r.t., 16h	-	-	***3-15a*** recuperated
13	CsF (0.15 equiv), Et_2NH_2Cl (1.9 equiv), toluene, reflux, 16h	**0/100**	32	>95% conversion of ***3-15a*** [a)]
14	$Ti(O\text{-}iPr)_4$ (2.0 equiv), toluene, reflux, 6h	**100/0**	37	>95% conversion of ***3-15a*** [a)]
15	$Ti(O\text{-}iPr)_4$ (2.0 equiv), toluene, r.t., 5h	**100/0**	70	>95% conversion of ***3-15a*** [a)]
16	$Ti(O\text{-}iPr)_4$ (1.0 equiv), toluene, r.t., 5h	**100/0**	30	~50% conversion of ***3-15a*** [a)]
17	$Ti(O\text{-}iPr)_4$ (2.0 equiv), CH_3CN, r.t., 5h	**100/0**	71	>95% conversion of ***3-15a*** [a)]
18	$Ti(O\text{-}iPr)_4$ (1.0 equiv), CH_3CN, r.t., 5h	**100/0**	49	~60% conversion of ***3-15a*** [a)]
19	$Ti(O\text{-}iPr)_4$ (3.0 equiv), CH_3CN, r.t., 5h	**100/0**	65	>95% conversion of ***3-15a*** [a)]
20	$Sc(OTf)_3$ (10 mol%), CH_3CN, r.t., 5h	**14/86**	Not determined	~36% conversion of ***3-15a*** [a)]
21	$Sc(OTf)_3$ (0.5 equiv), CH_3CN, r.t., 5h	**5/95**	Not determined	~69% conversion of ***3-15a*** [a)]
22	$Bi(OTf)_3$ (0.5 equiv), CH_3CN, r.t., 5h	**<5/>95**	Not determined	~45% conversion of ***3-15a*** [a)]

[a]Based on crude ^1H NMR; [b]Isolated yield.

To shed some light into the reaction system based on the EDDA catalysis, few control experiments were carried out. First, the condensation reaction was carried out for 3h (Table 16, entry 7). After this time, the condensation product ***3-59a*** was the major product, but the formation of olefination product was observed. Within the 24h, however, the olefination product became the only observable product in the reaction mixture (Table 16, entry 6). At this stage, we wished to know if the olefination product arises directly from the condensation adduct ***3-59a***, or if it is formed due to the reversibility of the condensation step. Independent competitive experiments with electron-withdrawing (EWG) substituted and electron-donating (EDG) group substituted aldehydes proved the retro condensation is irreversible (Scheme 38). Indeed, no traces of any cross-coupling products were detected. Only unreacted Knoevenagel adduct ***3-59a*** (partially) and formally olefination product ***3-60*** (major) were isolated after 6h of competitive experiments. Interestingly, isolated yields of both reaction products were about the same for both attempted reactions, suggesting that external aldehydes added to the reaction mixture had no or little effect on the reaction kinetic.



Scheme 37 – Knoevenagel condensation reaction optimization – observed side reaction.

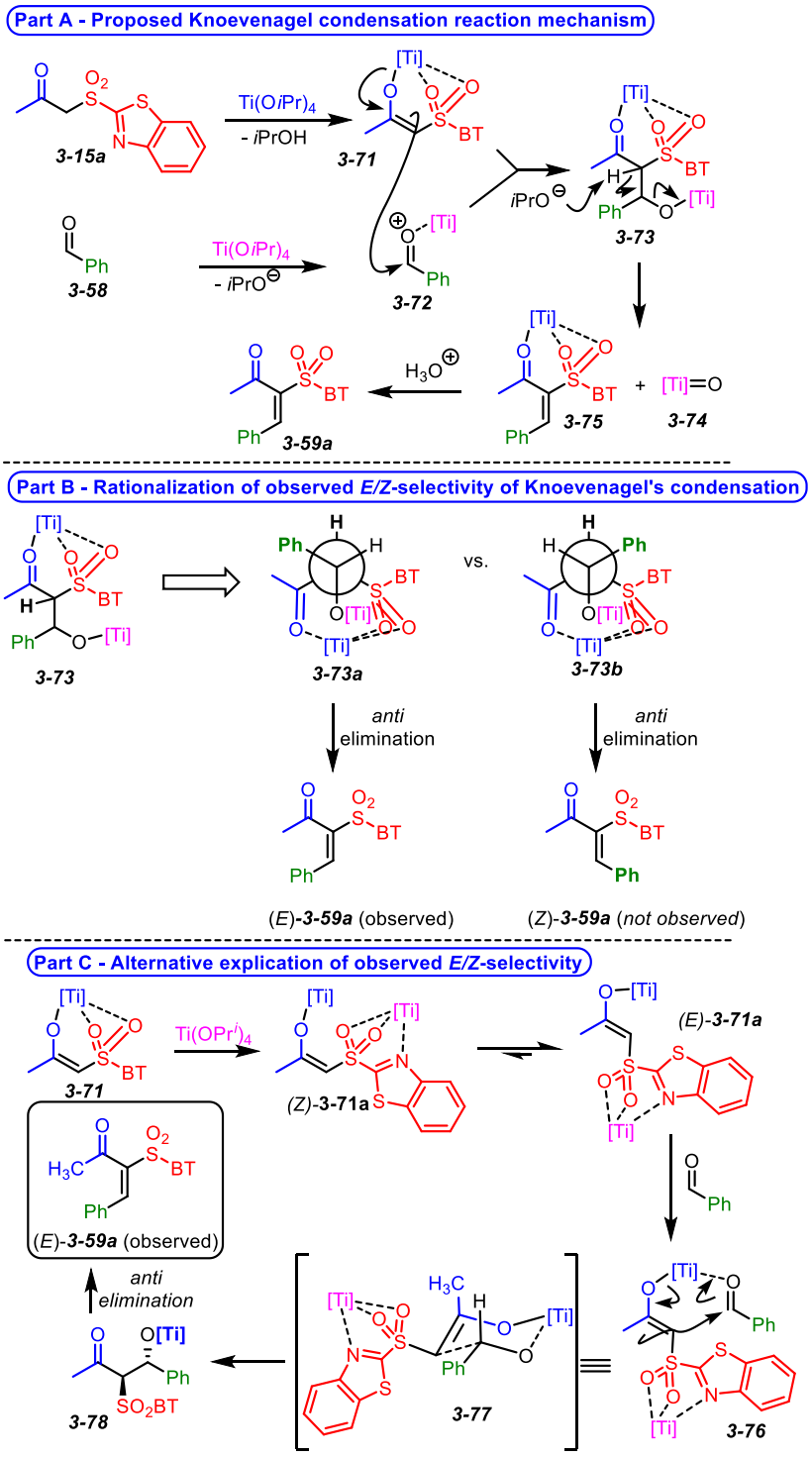


Scheme 38 – Competitive experiments with electron-poor and electron-rich aldehydes.

These findings led us to switch from classical Knoevenagel condensation reaction conditions to the Lewis acid-mediated Knoevenagel condensation reaction (Table 16, entries 10-22). Various Lewis acids and solvents were screened, however only the Ti(O-*i*Pr)$_4$ promoted the formation of desired product ***3-86*** (Table 16, entries 14-19). After reaction condition optimization it was found that the condensation proceeds the best (71% yield) if 2.0 equivalent of Ti(O*i*Pr)$_4$ is used in the presence of equimolar quantities of both starting materials (Table 16, entry 17) and the reaction is carried out at rt in CH_3CN. The use of 2.0 equiv of Ti(O-*i*Pr)$_4$ proved to be essential, since lower Ti(O-*i*Pr)$_4$ loading did not drive the reaction to completion, and higher loading had no significant influence neither on the reaction yield nor on its stereoselectivity. Our understanding of this phenomenon is based on the proposed reaction mechanism depicted in Scheme 39. In such case, ketosulfone ***3-15a*** should upon the interaction with Ti(O-*i*Pr)$_4$ generate enolate ***3-71***, that reacts with an activated aldehyde (second Ti(O-*i*Pr)$_4$ equivalent), and generates the adduct ***3-73***. Elimination of formally aldehydic oxygen in ***3-73*** further yields desired Knoevenagel adduct ***3-59a***. The reaction proceeds with observed excellent *E* selectivity. It is believed that observed *E*-stereoselectivity is generated via the *anti*-elimination process. In this context, two competitive conformational states must be considered (Scheme 35, Part B). Thermodynamically more favourable conformation required for the *anti*-elimination process yields *E*-isomer of ***3-59a***.

Alternatively, one can imagine that both equivalents of Ti(O-*i*Pr)$_4$ will interact with ketosulfone ***3-15a***. In such case generated Ti-enolate ***3-71*** will interact with the 2nd molecule of Ti(O-*i*Pr)$_4$ to generate bis-Ti-species *Z*-***3-71a***. This *Z*-enolate is less thermodynamically stable and therefore will isomerize to the *E*-enolate ***3-71a***. The reaction of such *E*-enolate with aldehyde will proceed via classical cyclic transition state and will yield *anti*-adduct ***3-78***. *Anti*-elimination then generates isolated

adduct *E*-**3-*59a***. At the present stage, we do not have any experimental/theoretical data that would allow us to distinguish between the two reaction pathways.



Scheme 39 - Proposed Knoevenagel reaction mechanism: (Part A) The role of the two Ti(O-iPr)$_4$ equivalents. (Part B) Rationalization of the observed E-selectivity. (Part C) Alternative explanation for observed E-selectivity.

Having established optimal reaction conditions for Knoevenagel-like condensation, the scope and limitations of the reaction were established (Table 17, Table 18). To do so, **PM-1**-like molecules were reacted under the optimized condensation conditions with various aldehydes ***3-7*** and two

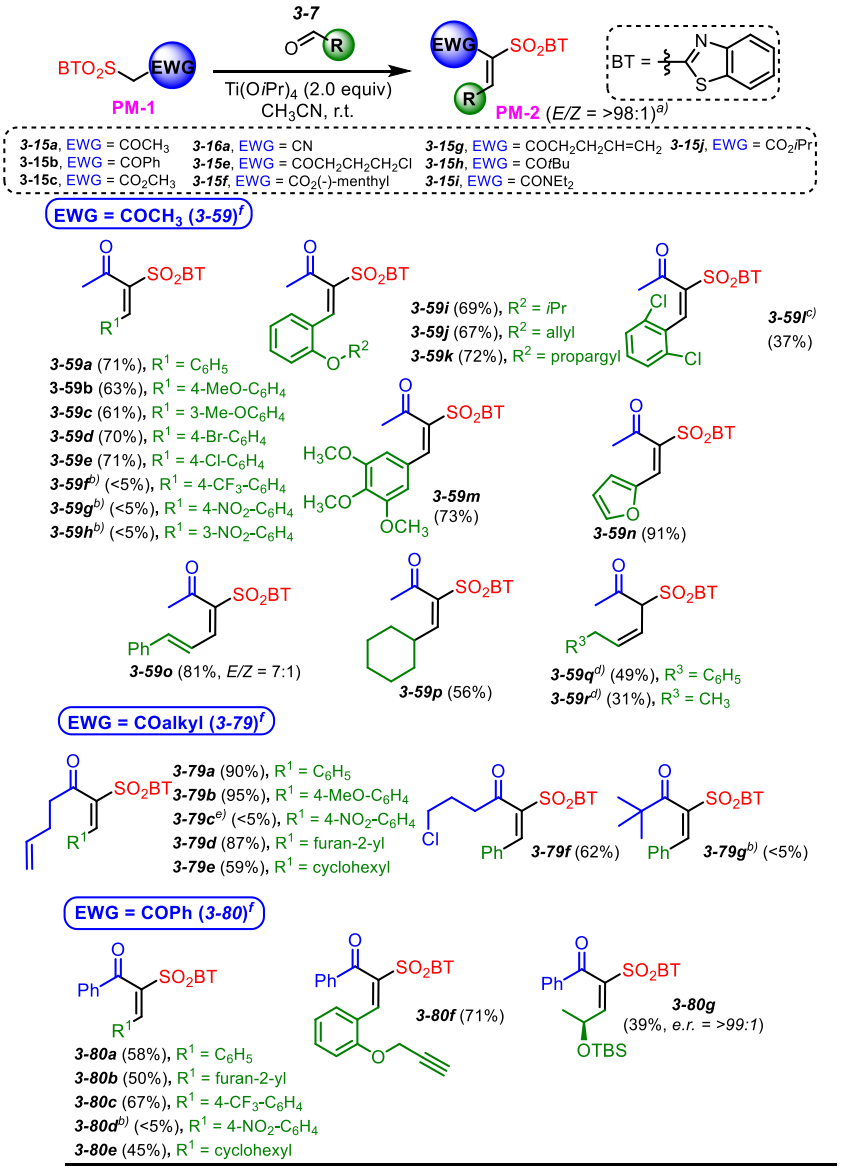
different ketones. It was observed that ketones failed to react under such conditions (Table 19). From the stereochemistry viewpoint, all generated adducts **PM-2** were prepared as *E*-olefins (*E/Z* = >98:1). The only exception was the adduct ***3-59o*** that resulted from the condensation reaction of cinnamaldehyde. It this case adduct ***3-59o*** was generated in 7:1 *E*/*Z* ratio on the newly generated olefinic bond. Next, aromatic aldehydes and the influence of the aryl group substitution on the reaction yield was evaluated It was observed that unsubstituted aromatic aldehydes and aromatic aldehydes with one or several EDGs reacted well and yielded the desired adducts in good to excellent yields and selectivity (Table 17 and Table 18). In contrary, aromatic aldehydes substituted with EWG (CF_3, NO_2, CN) proved to be troublemakers. In general, the condensation reaction proceeded but generated adducts proved to be too reactive and spontaneously reacted with *i*PrOH that originated from the $Ti(OiPr)_4$ (Table 19). Unfortunately, all our efforts directed to *i*PrOH elimination failed and the degradation of ***3-84c*** adduct was the only observed result. Interestingly, when phenyl keto-BT sulfone ***3-15b*** and nitrile-BT sulfone ***3-16a*** were used as reaction substrates, the desired 4-CF_3 substituted adduct was isolated. Even in those cases, however, the reaction failed for the corresponding 4-nitro derivatives.

The third limitation (after ketones, and EWG-substituted aryl aldehydes) of our method is the use of linear α-unsubstituted aliphatic aldehydes (Table 17). In these cases, a competitive γ-elimination process that yields products of formal keto-sulfone ***3-15a*** allylation occur (Scheme 40, Part A). In contrary, if α-branched aliphatic aldehydes are used as substrates, γ-elimination is not observed. It is believed that the difference in the reaction outcome (Scheme 40, Part B) is caused by steric reasons. The generation of the allyl group-containing products can be also rationalized by the thermodynamically driven formation of enolate ***3-98***. Acidic work-up would then yield observed allylated sulfone ***3-59q***. However, if α-branched adducts were left under the reaction condition for an extended period of time (up to 7 days) or at elevated temperatures (up to 60°C for 4 days), no product of double bond migration was observed. Thus, we believe that possibility depicted in Scheme 41 is improbable. But based on our experimental data we cannot exclude it. If enantiomerically enriched α-chiral aldehydes are used, no epimerization was observed during the reaction (Table 17, Table 18, ***3-80g*** and ***3-81j***).

Next, we focused on the role of EWG in **PM-1**. If alkyl ketones ***3-15e***, ***3-15g***, ***3-15h*** were used as substrates, the steric hindrance proved to be a challenge. Aryl ketones reacted smoothly but the reaction yields were slightly (5-10%) lower. Next, carboxylic acid derivatives as esters ***3-15c***, ***3-15f-h***, amide ***3-15i*** and nitriles were evaluated. In all cases, the reaction proceeded with good yields and high *E*-selectivity. However, in all ester bearing sulfones *in situ* transesterification (***3-15j***) to *i*Pr group occurred (Scheme 42). The only exception was *tert*-butyl ester ***3-15h***, however, this substrate failed to react completely. At this point, a question arose if the observed transesterification occurs prior

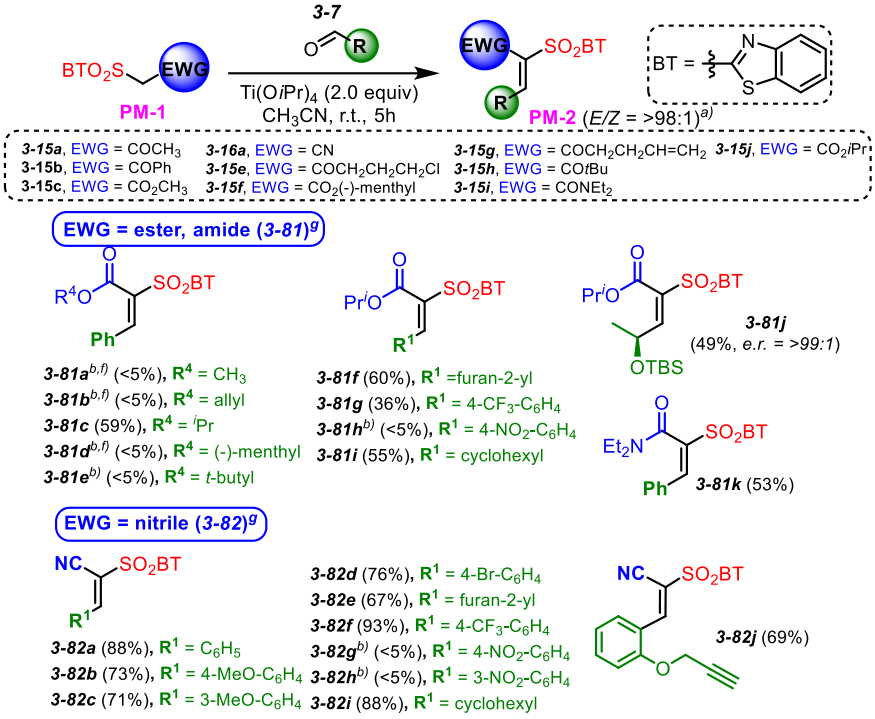
to the reaction or only once the adduct is formed. To shed some light into this question, two control experiments were carried out. First, the reaction of ***3-15c*** with benzaldehyde under the standard reaction conditions was done and its progress was carefully monitored. It was observed that within 3min *iso*propyl ester ***3-15j*** started to appear and within 15min it was the only sulfone presented in the reaction mixture. No traces of methyl ester-containing product ***3-15c*** were detected. Corresponding isopropyl ester adduct ***3-81c*** was isolated in 59% yield. When controlled reaction (Scheme 42, Part B) where methyl ester sulfone ***3-15c*** was treated with Ti(O-*i*Pr)$_4$ was performed, the similar progress was observed. The full transformation of ***3-15c*** to ***3-15j*** was accomplished within 15min. The isolated yield of ***3-15j*** was 95%.

Table 17 - Scope and limitations of Knoevenagel condensation I.



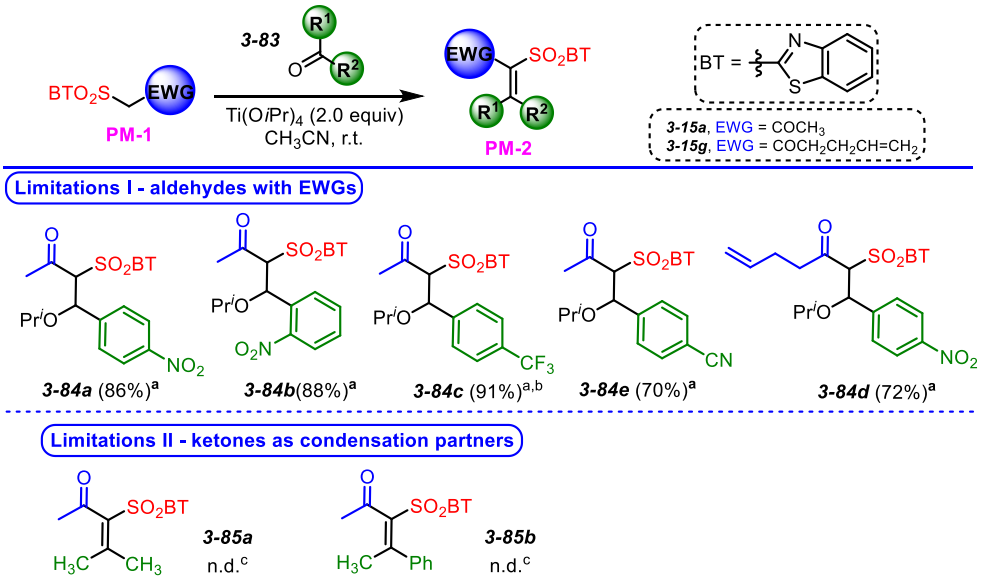
a) Based on the 1H NMR spectra of the crude reaction mixture. b) No traces of product observed. c) Reaction carried out at 80 °C for 6h. d) Only olefin migration products were isolated as the products of the reaction. e) only the product of 1,4-addition of *i*-PrOH were detected suggesting that trace amount of the desired product was formed. f) Yields refer to pure isolated compounds.

Table 18 - Scope and limitations of Knoevenagel condensation II.

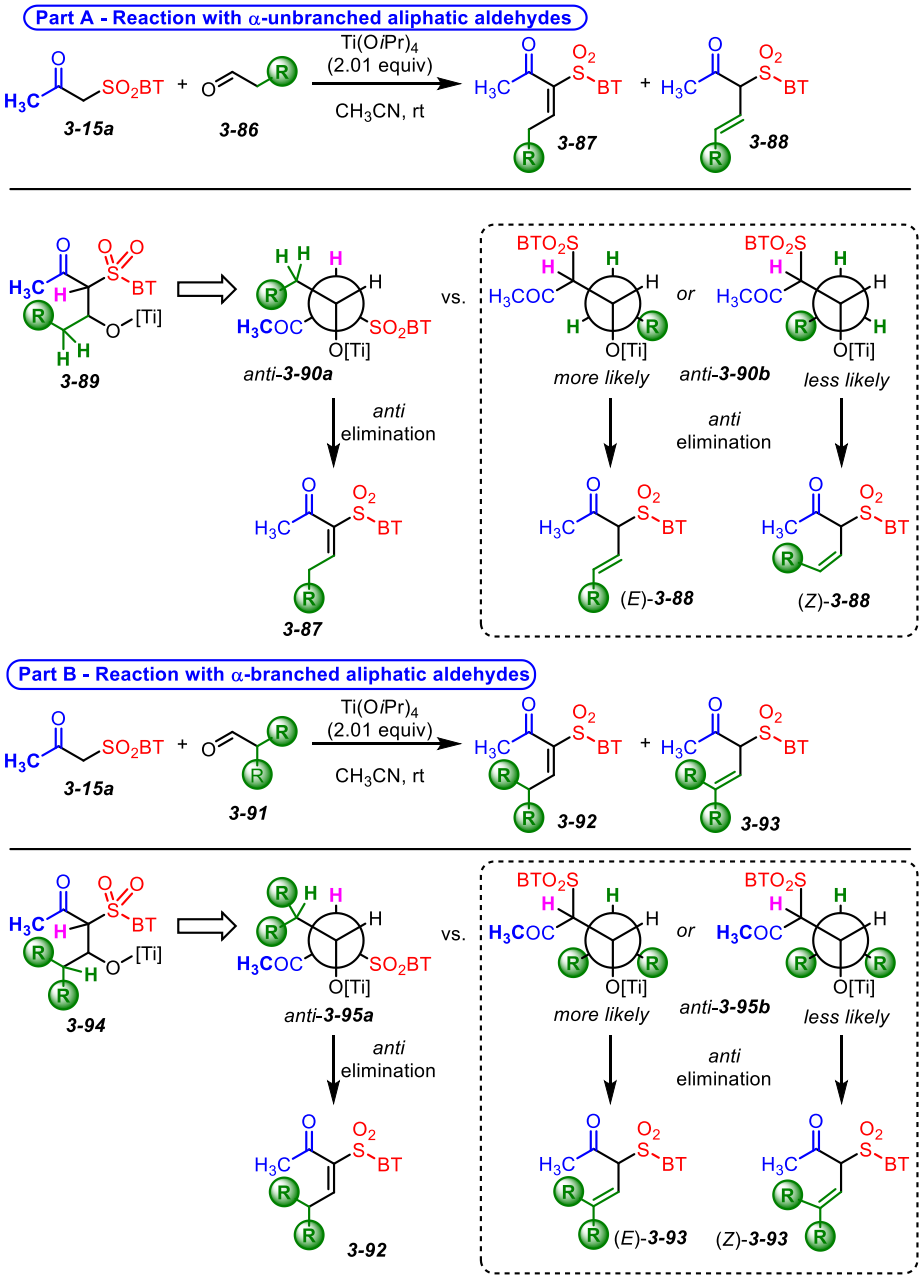


a) Based on the 1H NMR spectra of the crude reaction mixture. b) No traces of product observed. c) Reaction carried out at 80 °C for 6h. d) Only olefin migration products were isolated as the products of the reaction. e) only the product of 1,4-addition of *i*-PrOH were detected suggesting that trace amount of the desired product was formed.
f) Only product ***3-81c*** was isolated in 58-61% yields. g) Yields refer to pure isolated compounds.

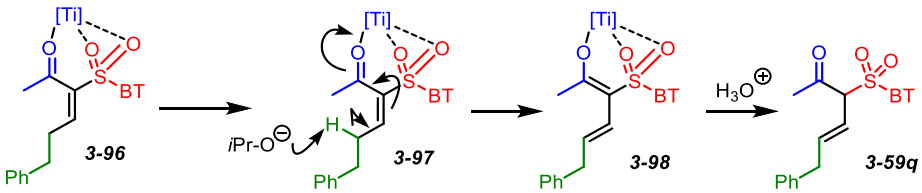
Table 19 - Limitations of Knoevenagel condensation.



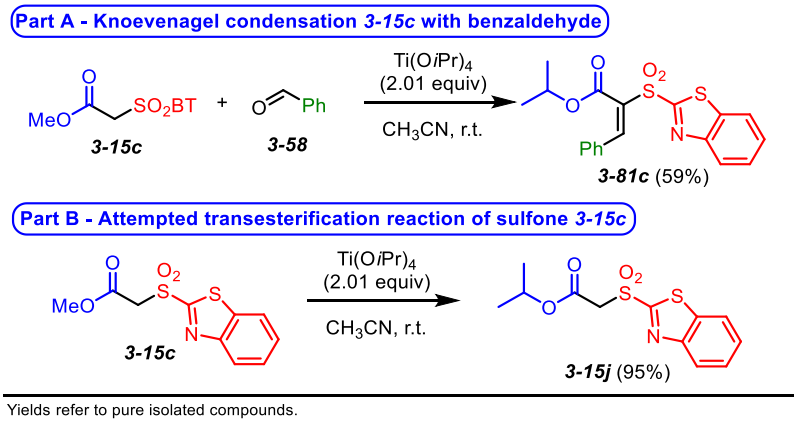
a) Based on the 1H NMR spectra of the crude reaction mixture. b) Failed attempted elimination reaction conditions: 1) K_2CO_3, CH_3CN, 50°C; 2) DBU, CH_3CN, 50°C; 3) *p*-TSA, CH_3CN, 50°C; 4) Et_3N, CH_3CN, 50°C; in every case decomposition of starting sulfone occured
c) starting sulfone recovered



Scheme 40 – Knoevenagel condensation with aliphatic aldehydes (α-unbranched vs. α-branched aldehydes).



*Scheme 41 – Proposed **3-59q** compound formation based on the olefin migration.*



*Scheme 42 – Limitations of Knoevenagel condensation if ester-sulfone **3-18** is used.*

Finally, the *E* configuration determination should be discussed. It was noted that the *E*-olefin was the only product of the condensation reaction. The stereochemistry was determined using the product ***3-81i*** as a representative example with the use of 1D NOE experiments (Figure 10).

Similar 1D NOE experiments were also carried out on several other adducts, however, the conclusions were less convincing (weaker transfer of energy). But still, the trend was the same as in the case of compound ***3-81i***, therefore we believe that the stereochemistry is the same – *E*. Unfortunately, no X-ray data are available up to date (we were unable to prepare any monocrystal suitable for the X-ray analysis).

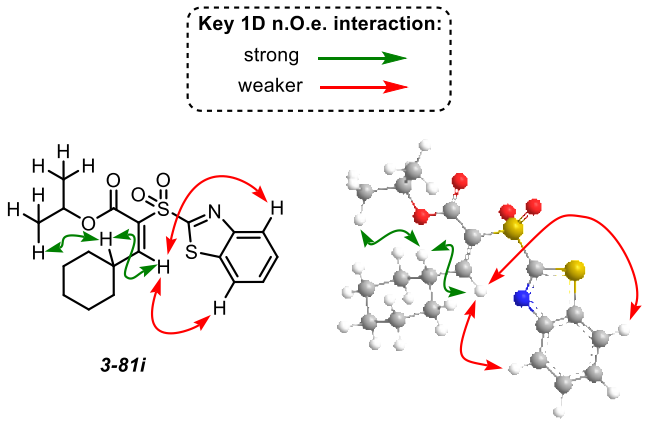


*Figure 10 – Key interactions observed by 1D n.O.e. that allowed us to determine the stereochemistry of compound **3-81i**.*

3.5 PM-2 in action: applications

As pointed out at the onset of our journey to **PM-2**, the main goal of our "quest" is to explore the reactivity of **PM-2** building block. Thus, this chapter will be devoted to the application of **PM-2** in the context of organic synthetic transformations. The summary of different reactive sites of **PM-2** that determines the **PM-2** reactivity can be found in Figure 11. As one can imagine, our wish was to explore the role of **PM-2** under various reaction conditions where **PM-2** played a role of dienophile, dipolarophile, heterodiene, Michael acceptor or of radicophilic species.

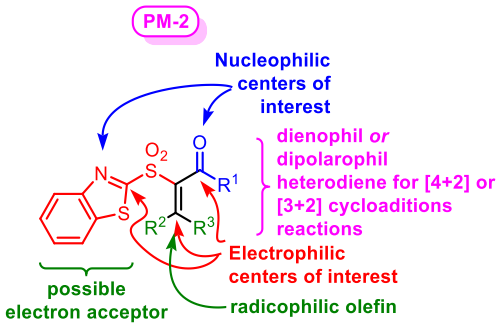
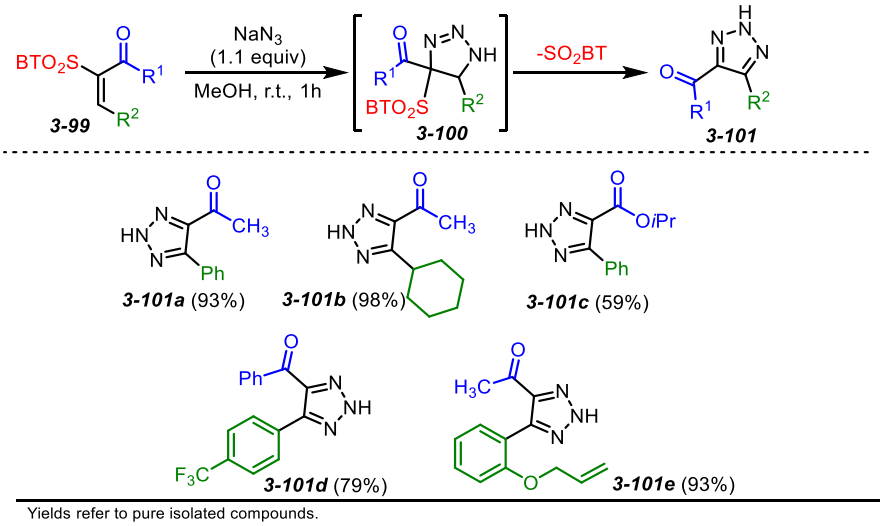


*Figure 11 – **PM-2** molecule - pluripotent building block for DOS.*

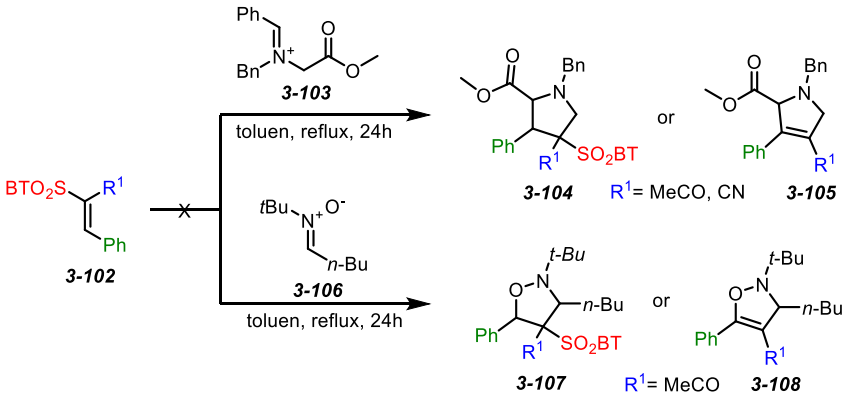
3.5.1 PM-2 as dipolarophile

For sentimental reasons, my supervisor wished the first tested reactions were 1,3-dipolar cycloadditions. First, the reaction of azides was investigated.[78] From the HOMO/LUMO viewpoint, in this reaction HOMO of azides (dipole) reacts with LUMO of dipolarophile (sulfone ***3-99***). Thus, not surprisingly the reaction of NaN_3 with various ***3-99*** in MeOH proceeded smoothly at rt and yielded the desired triazoles ***3-101*** in excellent yields (Table 20). The reaction proceeds with loss of BT-SO_2 group and no limitations of this method were observed during our scope search.

*Table 20 - (3+2) cycloaddition reaction between **PM-2** and NaN_3.*



Different situation occurred if the reaction of **PM-2** with azomethine ylides[79] and nitrones[80] was attempted (Scheme 43). In these cases, no products of cycloadditions were observed, and only the decomposition of dipolarophile (sulfone ***3-102***) occurred.

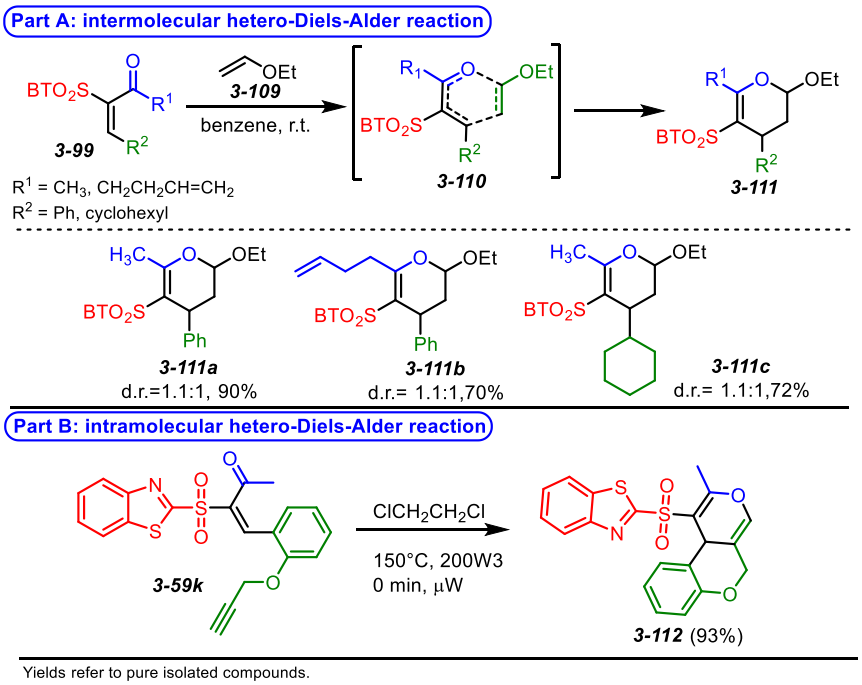


Scheme 43 – Attempted (3+2) cycloaddition with azomethine ylide and nitrone.

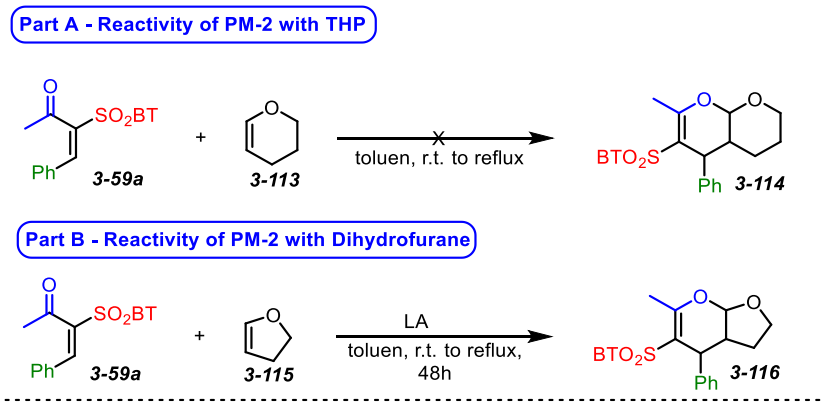
3.5.2 PM-2 in hetero-Diels-Alder reaction

Having used sulfones ***3-99*** as dipolarophiles in (3+2) cycloaddition reactions motivated us to explore other cycloaddition reactions. The structure of **PM-2** inspired us to explore its use as electron-deficient hetero-diene in hetero-Diels-Alder reaction. It was expected that our **PM**-scaffold can successfully react as a diene in hetero-Diels-Alder cycloaddition with inversed electron demand since it has a low lying LUMO orbital.[81] To evaluate such possibility, electron-rich dienophiles such as ethyl vinyl ether were reacted with ***3-99*** in benzene at rt (Table 21). The resulting dihydropyrans ***3-111*** were obtained with excellent yields. The intramolecular variant of hetero-Diels-Alder reaction proved to be also possible, however, since less electron-rich olefin was used, it had to be carried out at a higher temperature and μW irradiation

*Table 21 – Hetero- Diels-Alder reaction with inverse electron demand: Part A – Reaction of **PM-2** with ethyl vinyl ether; Part B – Intramolecular cycloadditions.*



To extend our methodology further, cyclic 1,2-disubstituted enol ethers were used as enol ether equivalents (Scheme 44). In these cases, however, only traces of the desired adducts were detected (LC-MS) when Lewis acid catalysts were employed. Moreover, the presence of Lewis acid also dramatically increased the enol ether polymerization process making the isolation of the product virtually impossible. The solution to this problem would be to carry on the reaction under high pressure,[82] however, such a possibility was not evaluated at this stage.



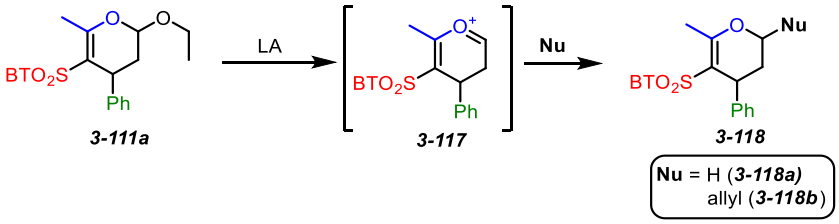
LA	Results[a]
no cat.	5% of ***3-116***
$Sc(OTf)_3$	n.d.
$Yb(OTf)_3$	n.d.
$Bi(OTf)_3$	n.d.
$In(OTf)_3$	n.d.
$ZnCl_2$	6% of ***3-116***
$ZnBr_2$	n.d.
MgI_2	6% of ***3-116***
LiCl	5% of ***3-116***
$Mn(OAc)_3$	n.d.
$Ti(O\text{-}iPr)_4$	n.d.

[a]Based on LC-MS analysis

*Scheme 44 – Hetero-Diels-Alder reaction of **PM-2** with cyclic vinyl ethers.*

Instead, the dihydropyran ***3-111*** reactivity was explored due to structural similarity with DHP and THP motives. Both above mentioned structural motives are widespread in nature and can be found in sugars but also in various THP-ring containing natural products. Thus, we have decided to explore further transformations of our structural motives to pave the way for future target/diversity-oriented synthesis. First, we focused on the acetal structural motive. We got inspired in the sugar chemistry were the acetal groups are routinely treated with Lewis acids to generate the oxonium intermediates. Oxonium intermediates are then reacted with allyl-TMS group,[83–85] or reduced with Et_3SiH.[86] Thus, in our case, the generation of oxonium intermediate ***3-117*** should, upon the reaction with external nucleophile (Et_3SiH or ally-TMS) yield desired DHP ring ***3-118***. Unfortunately, in all attempted cases, the traces of the desired product ***3-118*** were detected only in one single case (Table 22, entry 1). In all other cases the starting material was recuperated unchanged. The observation that suggests that we have failed to generate the key oxonium intermediate ***3-117***. The situation that is caused probably due to competitive interaction of Lewis acid with $BTSO_2$ group (Figure 12).

*Table 22 - Unsuccessful modifications of dihydropyran **3-111a**.*



Entry	Condition	L.A.	Nu	Result[a]
1	DCM, -78°C to r.t., 48h	$BF_3.Et_2O$	Et_3SiH	5% of ***3-118a***
2	DCM, r.t., 72h	$BF_3.Et_2O$	Ally-TMS	n.r.
3	DCM, r.t., 72h	$Sc(OTf)_3$	Ally-TMS	n.r.
4	DCM, r.t., 72h	$Yb(OTf)_3$	Ally-TMS	n.r.
5	DCM, r.t., 72h	$Bi(OTf)_3$	Ally-TMS	n.r.
6	DCM, r.t., 72h	$In(OTf)_3$	Ally-TMS	n.r.
7	DCM, r.t., 72h	$ZnCl_2$	Ally-TMS	n.r.

[a]Based on LC-MS analysis.

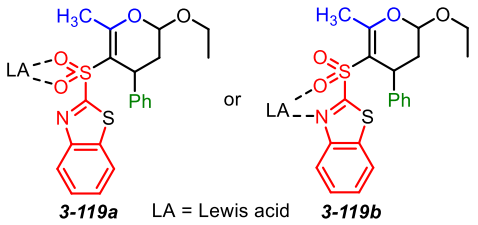
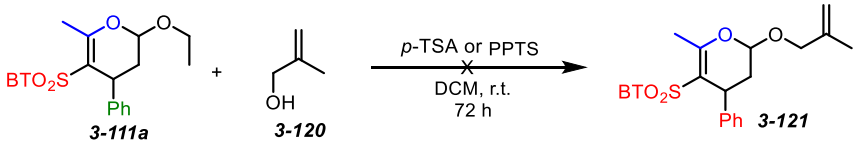


Figure 12 – Expected interactions of BT-sulfone group with Lewis acids.

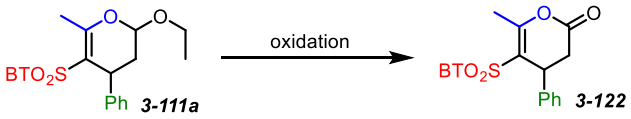
Having failed to generate oxonium intermediate with help of Lewis acids, Bronsted acid-mediated oxonium generation was attempted (Scheme 45). Thus, DHP acetal ***3-111a*** was reacted with *p*-TSA or PPTSA in the presence of an excess of methallyl alcohol ***3-120***. Unfortunately, even in this case, no product of the ethanol/methallyl alcohol exchange was observed. Again, it seems we failed to generate oxonium.



Scheme 45 – Failed generation of oxonium - no acetal group under acid condition.

Disappointed from these results we turned our attention to the acetal oxidation (Table 23) and hydrolysis (Table 24). In both cases, we attempted to carry out standard literature oxidation protocols[87,88] and hydrolysis reactions[89,90] commonly used in sugar chemistry. However, in no attempted case we observed the formation of the desired products. Thus, we turned our attention to the BT-SO_2 group modification. At this point, we could take advantage of the BT group on the sulfone function. Indeed, BT group can be readily removed with the help of EtSLi and the resulting lithium sulfinic salt can be e.g. transformed into the corresponding sulfonyl fluoride (Scheme 46). The sulfonyl fluoride could be further diversified[91] using Sharples SuFEX chemistry.[92]

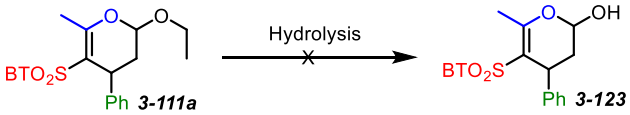
*Table 23 - Attempted oxidation of dihydropyran **3-111a**.*



Oxidation reaction condition	Results[a]
CrO_3, H_2SO_4 acetone, r.t., 48h	10% of ***3-122***
m-CBPA,BF_3 Et_2O DCM, r.t., 24h	degradation[b]
CrO_3 AcOH, r.t., 24h	n.r.[c]

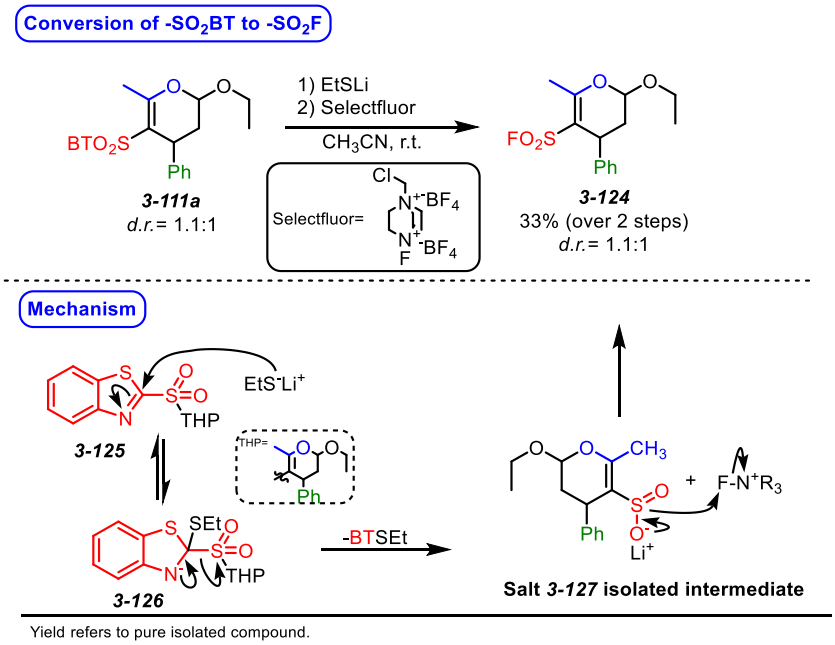
[a]Based on crude ^{1}H NMR analysis
[b]Decomposition of ***3-111a***
[c]Starting compound recovered

*Table 24 - Attempted dihydropyran **3-111a** hydrolysis.*



Hydrolysis reaction condition	Results[a]
50% AcOH 100°C, 48 h	degradation[b]
$CoCl_2$ $6H_2O$ CH_3CN, r.t.. 20 h	n.r.[c]

[a]Based on crude ^{1}H NMR analysis
[b]Decomposition of ***3-199***
[c]Starting compound recovered



*Scheme 46 – Modification of -SO_2BT group of dihydropyran **3-111a**.*

3.5.3 PM-2 as a Michael acceptor

Having explored cycloaddition reactions of **PM-2**, our interest turned to the electrophilic properties of **PM-2**. Thus the reactions with nucleophiles were explored (Figure 13). Obviously, Michael type reactions were explored in such context first since vinyl sulfones are known as an excellent Michael-type acceptor that can readily react with various O, S, N and C nucleophiles.[80] The advantage of our system over previously published work is the possibility of post-addition modifications of generated adducts that are based on the exploration of the BT-sulfone reactivity (Julia-Kocienski olefination, Mitsunobu reaction, reductive-elimination).[64]

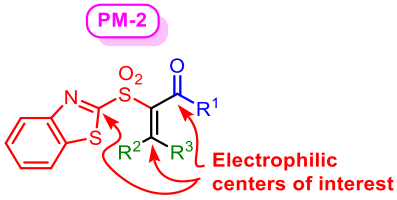


Figure 13 – PM-2 electrophilic centres of interest.

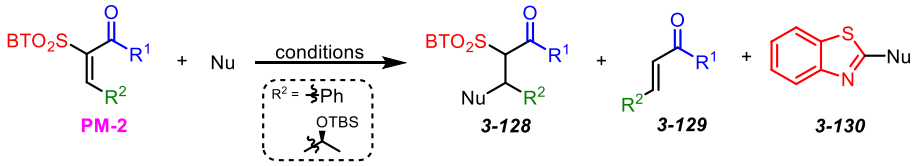
We aimed to evaluate the reactivity of **PM-2** in the presence of various nucleophiles. Since there are reactive sites in the skeleton of **PM-2** (Figure 13), the challenge was to target one centre per time to ensure none or a limited number of side reactions. The overview of attempted reactions can be found in Table 25. First, we explored the reactivity of EtSLi (Table 25, entry 1). This reagent was previously used for selective BT-group removal from the BT-sulfones.[64] Not surprisingly, the same type of reactivity was observed in this case. No product of 1,4-addition (or 1,2-addition) was therefore detected. Next, *N*-nucleophiles as morpholine, imidazole and pyrrolidine were tested. BT-group removal (morpholine, pyrrolidine) or degradation (imidazole) was observed in these cases (Table 25,

entries 2-4). The evaluation of nucleophile reactivity continued with several *O*-nucleophiles (AcONa, MeONa, MeOH and isobutenol) (Table 25, entries 5-12). The use of AcONa (Table 25, entry 5) led to the decomposition of the starting material but in the case of sodium methoxide (Table 25, entry 6), a mixture of desulfonylated product and the product of 1,4-addition was observed. To diminish the nucleophilicity of methoxy anion, MeOH was used instead of MeONa (Table 25, entry 7). In this case, the desired 1,4-addict was isolated as the only product of the reaction. Unfortunately, it was observed that the adduct ***3-128*** spontaneously slowly degrades and partially eliminates. Thus, it was decided to submit the generated adduct directly to the reductive conditions and to generate desulfonylated product ***3-132b*** (Table 26, Part A). The same protocol was used in the case of compound ***3-80g*** substituted with a chiral centre in the γ-position (Table 25, entry 8). In this case, after the desulfonylation reaction, formal 1,4-adduct ***3-132b*** was formed as *anti*-isomer with acceptable 7:1 *d.r.* The observed stereochemical outcome of this addition is rationalized in Scheme 47.

The obvious drawback of these reactions is that MeOH is used as a solvent. The situation that disqualifies the use of this method if commercially unavailable/solid alcohols would be used. Therefore, we have focused our attention on developing complementary reaction conditions where only 1 equivalent of alcohol would be used (Table 25, entries 9-12). Unfortunately, in all tested reaction conditions either a mixture of adducts (BT-group addition and 1,4 addition) were obtained or sluggish reactivity was observed. Various catalyst (bases - organic and inorganic) and Lewis acids were attempted, however, only "positive" result was obtained when $Ti(O\text{-}iBu)_4$ was generated *in situ* and reacted with **PM-2** (Table 25, entry 12). In this case, a rather unexpected product of the rearrangement was obtained (for more details, see chapter 3.5.4.

Since our plans linked with *O*-nucleophiles burned in flames and fumes, we switched our attention to *C*-nucleophiles, Meldrum´s acid (Table 25, entry 13), acetoacetate (Table 25, entry 14), and ***3-15a*** (Table 25, entry 15). In the first two cases, the addition of nucleophiles to BT-group were the only products of the reactions. However, when the reaction of ***3-15a*** with **PM-2** was carried out, dihydrofuran ***3-145*** was isolated as a major product of the reaction (for more details see chapter 3.5.5).

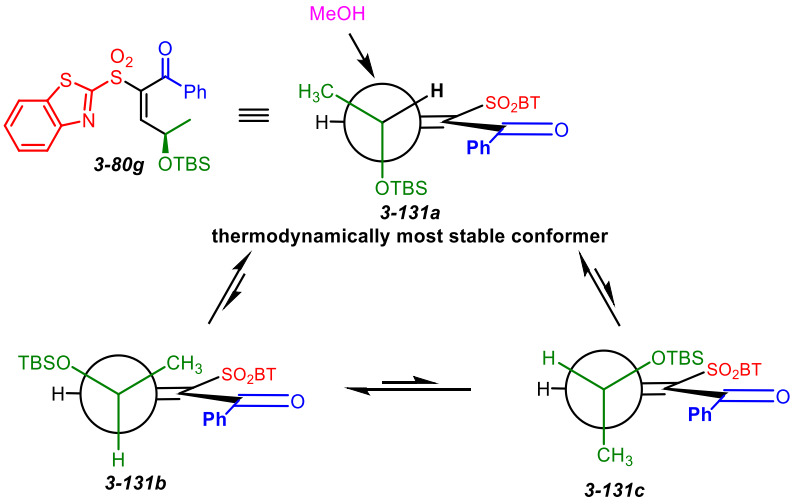
*Table 25 - Reaction of **PM-2** with various nucleophiles: an overview of tested reactions.*



Entry	R^1	R^2	Nu	Conditions	Ratio[a] (PM-2 : *3-128* : *3-129* : *3-130*)	Comment
1	CH_3,	Ph	EtSLi	PM-2 (1.0 equiv), Nu (1.5 equiv), CH_3CN, r.t.	0 : 0 : 1 : 1	-
2	CH_3	Ph	Morpholine	PM-2 (1.0 equiv), Nu (1.5 equiv), $CHCl_3$, r.t.	0 : 0 : 1: 1	-
3	CH_3	Ph	Imidazole	PM-2 (1.0 equiv), Nu (1.5 equiv), $CHCl_3$, r.t.	-	Decomposition
4	CH_3	Ph	Pyrrolidine	PM-2 (1.0 equiv), Nu (1.5 equiv), $CHCl_3$, r.t.	0 : 0 : 1: 1	-
5	CH_3	Ph	AcONa	PM-2 (1.0 equiv), Nu (1.5 equiv), AcOH, 50°C	-	Decomposition
6	CH_3	Ph	MeONa	PM-2 (1.0 equiv), Nu (1.5 equiv), AcOH, 50°C	0 : 0.6 : 1 : 1	-
7	CH_3	Ph	MeOH	PM-2 (1.0 equiv), MeOH, r.t.	0: 1 : 0 : 0	*d.r.*= 1:1 see Table 26 Part A
8	Ph	OTBS	MeOH	PM-2 (1.0 equiv), MeOH, r.t.	0 : 1 : 0 : 0	*d.r* = 9:1 see Table 26, Part A
9	CH_3	Ph	Isobutenol	PM-2 (1.0 equiv), Nu (1.5 equiv), *t*-BuOK (1.5 equiv), toluen, r.t.	0 : 0.2 : 1 : 1	-
10	CH_3	Ph	Isobutenol	PM-2 (1.0 equiv), Nu (1.5 equiv), *t*-BuOK (1.5 equiv), THF, r.t.	0 : 0.2 : 1 : 1	-
11	CH_3	Ph	Isobutenol	PM-2 (1.0 equiv), Nu (1.5 equiv), $Ti(O\text{-}iPr)_4$ (1.5 equiv), toluen, r.t.	1 : 0.2 : 0 : 0	Poor conversion, 80°C led to decomposition of PM-2
12	CH_3	Ph	Isobutenol	PM-2 (1.0 equiv), Nu (8.0 equiv), $TiCl_4$ (4.0 equiv), DCM, r.t.	Not applicable	Unexpected product – see chapter 3.5.4
13	CH_3	Ph	Meldrum´s acid	PM-2 (1.0 equiv), Nu (1.5 equiv), Et_3N (1.5 equiv), toluen, r.t.	0 : 0 : 1 : 1	-
14	CH_3	Ph	Methyl-acetoacetate	PM-2 (1.0 equiv), Nu (1.5 equiv), Et_3N (1.5 equiv), toluen, r.t.	0 : 1 : 1 : 1	-
15	CH_3	Ph	$MeCOCH_2SO_2BT$ ***3-15a***	PM-2 (1.0 equiv), Nu (1.5 equiv), Et_3N (1.5 equiv), toluen, r.t.	Not applicable	For more details see discussion

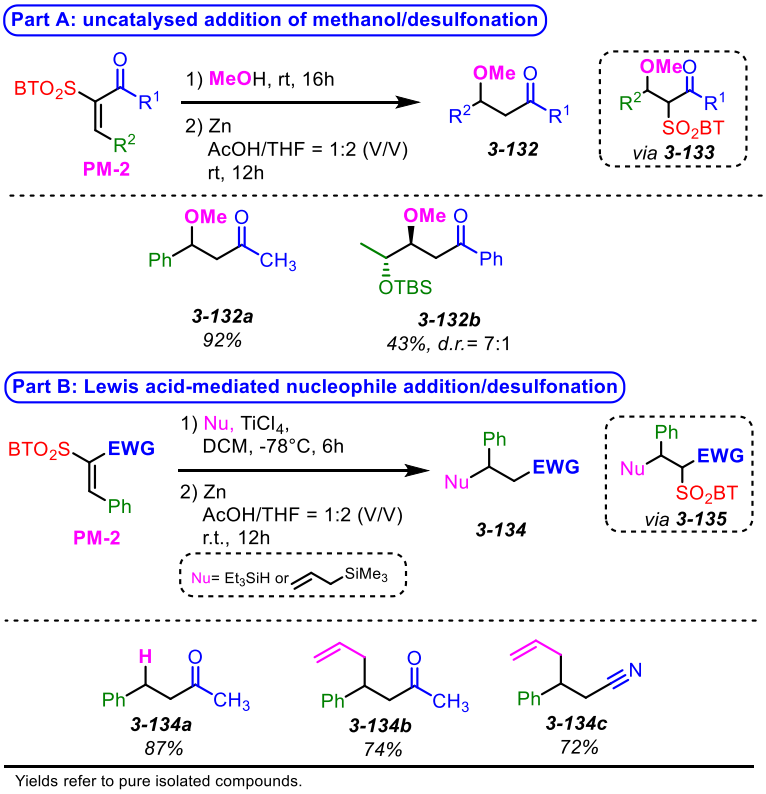
16	CH_3	Ph	Allyl-$SiMe_3$	**PM-2** (1.0 equiv), Nu (3.0 equiv), $TiCl_4$ (3.0 equiv), DCM, -78°C	0 : 1 : 0 : 0	*d.r.*= 1:1 see Table 26, Part B
17	CH_3	Ph	EtSiH	**PM-2** (1.0 equiv), Nu (3.0 equiv), $TiCl_4$ (3.0 equiv), DCM, -78°C	0 : 1 : 0 : 0	*d.r.*= 1:1 see Table 26, Part B
[a]Based on ^{1}H NMR crude mixture.						

For historical reasons (see Theses of my promoter), we have also focused on the Lewis acid-mediated additions of allyl-TMS (Table 25, entry 16) and Et_3SiH (Table 25, entry 17). In both cases, the reactions proceeded smoothly and yielded the desired adducts in excellent 1,4-selectivity. Obtained crude adducts were immediately desulfonylated (Table 26, Part B) and expected β-allylated ketones or nitriles were isolated in very good yields (over two steps). At this stage, we have decided to abandon further screening of various nucleophiles and focused on two unexpected reactions we have encountered during the first part of screening.



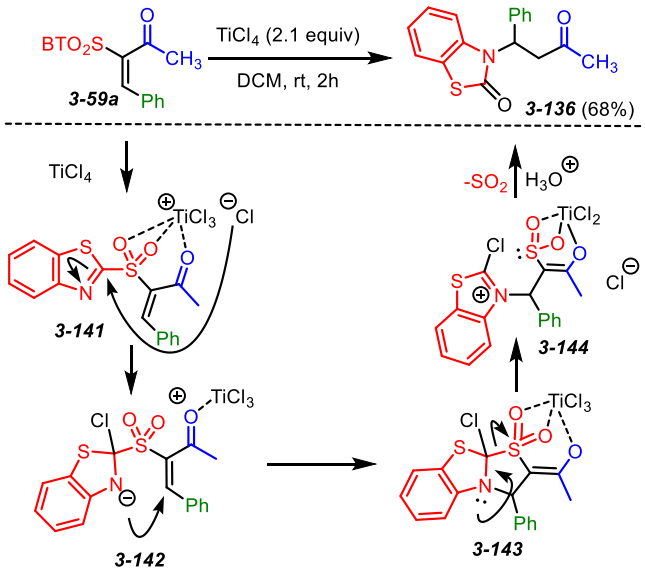
*Scheme 47 – Proposed explanation of observed diastereoselectivity during the MeOH addition to **3-131a**.*

Table 26 – Reactions of alcohols with α,β-unsaturated vinyl sulfones followed with subsequent desulfonylation process



3.5.4 PM-2 - Lewis acid mediated rearrangement

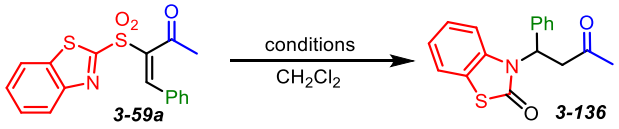
As mentioned in the previous chapter, a new unexpected transformation was observed when **PM-2** was exposed to $TiCl_4$/*i*BuOH mixture (Table 25, entry 12). Analysis of isolated product (1D and 2D NMR experiments, HRMS) revealed that the obtained product contains no sulfonyl group but has BT group in the β-position. In was also established that the BT-group is connected with the rest of the skeleton via a nitrogen atom. Structure-based mechanistic interpretation of the way how the molecule was generated led us to propose the reaction mechanism depicted in Scheme 48. It is expected that Lewis acid-activated **PM-2** molecule ***3-59a*** undergoes to Cl^- anion (generated *in situ*) addition to BT-group. Newly generated *N*-centered anion then undergoes to intramolecular 1,4-addition and Ti-enolate ***3-143***. Further reorganization yields sulfinic salt ***3-144*** that releases upon acidic work-up SO_2 molecule and generates observed adduct ***3-136***. It should be mentioned that such transformation can be formally seen as intramolecular Smiles rearrangement.[93]



Scheme 48 – Proposed mechanism of Lewis acid promoted Smiles rearrangement.

Based on our knowledge on this mechanism, we have decided to vary the reaction conditions to see the limitations connected with various Lewis acids. The aim was to develop milder reaction conditions. Our attempts are summarized in Table 27. First, it should be pointed out that in all cases the conversion of ***3-59a*** was never complete. Next, it was observed that highly oxophilic Lewis acids promote reaction better than less oxophilic ones. Yet, the most important observation came after the remarque of one of the reviewers of our JOC article that was questioning the role of the chlorine anion in our reaction mechanism. To shed more light into its role, external chloride source was added into the reaction mixture and this addition had a beneficial role in the reaction kinetics (Table 27, entries 10 and 11). These observations had an immense impact on the project since most of the previously attempted rearrangements of other **PM-2** substrates yielded only undesired α,β-unsaturated olefins as the products of the reaction (Table 28, entries 3 and 4; Table 29). In the case of cyano-derivatives of **PM-2** only the starting material was recuperated (Table 28, entries 1 and 2). At this stage, we believe that the use of external chlorine anion is the key aspect that can transform this rearrangement from synthetic curiosity to useful synthetic method.

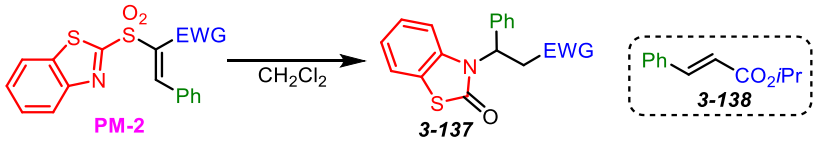
Table 27 – Intramolecular Smiles-type rearrangement optimization.



Entry	Lewis acid (equiv)	Conditions	Conversion of ***3-59a***[a]	Isolated Yield (%)
1	$TiCl_4$ (2.1)	r.t., 2h	70%	68%
2	$TiCl_4$ (2.1)	-78°C, 2h	<5%	n.d.
3	$TiCl_4$ (2.1)	0°C, 2h	10%	Traces of ***3-136***
4	$Ti(OMe)_2Cl_2$ (2.1)	r.t., 2h	69%	65%
5	$TiCl_4$. THF complex (2.1)	r.t., 2h	55%	49%
6	$BF_3.OEt_2$ (2.1)	r.t., 18h	77%	65%
7	BF_3.MeOH (2.1)	r.t., 24h	6%	n.d.
8	$AlCl_2Et$ (2.1)	r.t., 2h	41%	35%
9	$ZnBr_2$ (2.1)	r.t., 18h	32%	15%
10	$TiCl_4$ (2.1), KCl (2 equiv)	0°C, 2h	85%	78%
11	$Ti(OPr^i)_4$ (2.1), KCl (4 equiv), 18-crown-6 (4 equiv)	0°C, 2h	95%	65%

[a]Based on ^{1}H NMR of the crude reaction mixture.

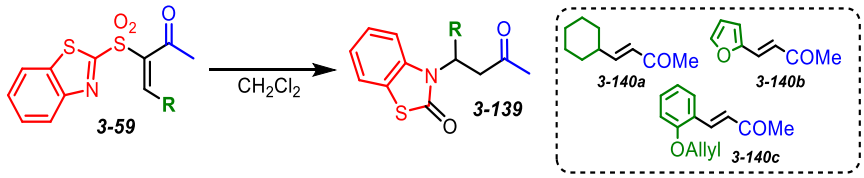
Table 28 - Scope and limitations of Smiles-type rearrangement – the influence of the EWG group.



Entry	Lewis acid (equiv)	EWG	Condition	Conversion of PM-2[a]	Isolated Yield	Comment
1	$TiCl_4$ (2.1)	CN	r.t., 2h	<5%	<5%	-
2	$BF_3.OEt_2$ (2.1)	CN	r.t., 18h	<5%	<5%	-
3	$TiCl_4$ (2.1)	CO_2iPr	r.t., 2h	~40%	<5%	***3-138*** observed
4	$BF_3.OEt_2$ (2.1)	CO_2iPr	r.t., 18h	~55%	<5%	***3-138*** observed

[a]Based on LC-MS and ^{1}H NMR analysis of crude reaction mixture.

*Table 29 - Scope and limitations of Smiles-type rearrangement – the influence of the **R** group.*



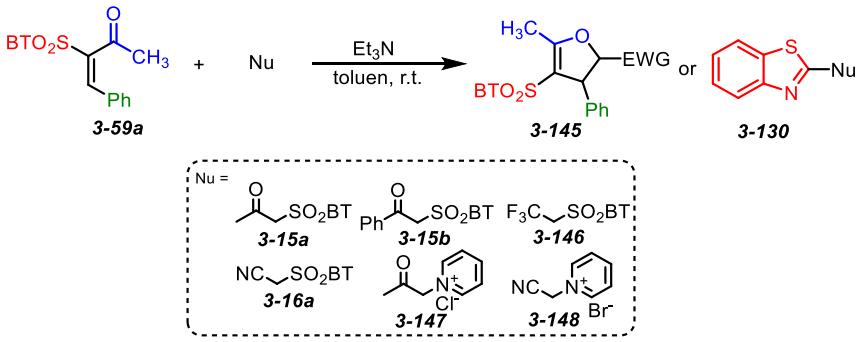
Entry	Lewis acid (equiv)	R	Condition	Conversion of *3-59*[a]	Isolated Yield	Comment
1	$TiCl_4$ (2.1)	cyclohexyl	r.t., 2h	~65%	<5%	***3-140a*** observed
2	$BF_3.OEt_2$ (2.1)	cyclohexyl	r.t., 18h	~89%	<5%	***3-140a*** observed
3	$TiCl_4$ (2.1)	furan-2-yl	r.t., 2h	~67%	<5%	***3-140b*** observed
4	$BF_3.OEt_2$ (2.1)	furan-2-yl	r.t., 18h	~77%	<5%	***3-140b*** observed
5	$TiCl_4$ (2.1)	2-(allyloxy)phenyl	r.t., 2h	~89%	<5%	***3-140c*** observed
6	$BF_3.OEt_2$ (2.1)	2-(allyloxy)phenyl	r.t., 18h	~76%	<5%	***3-140c*** observed

[a] Based on LC-MS and ^1H NMR analysis of crude reaction mixture.

3.5.5 PM-2 - Dihydrofuran synthesis via (4+1) annulation

The second unexpected transformation we have disclosed during the screening of nucleophiles (Table 30) was the reaction of PM-1 ***3-15a*** with PM-2 (Table 25, entry 15). In this particular case, the addition of ***3-15a*** to PM-2 was not very selective since a ~1:1 mixture of 1,4- and BT-adducts were obtained (Table 30, entry 1). To push the selectivity towards 1,4-addition products, other BT-sulfone-containing C-nucleophiles were evaluated. Phenyl ketone ***3-15b*** yielded selectively 1,4 adduct ***3-145*** with 87% yield., CF_3-containing sulfone ***3-146*** gave no reaction (Table 30, entry 3) and cyano sulfone ***3-16a*** yielded only the BT-adduct ***3-220*** (Table 30, entry 4).

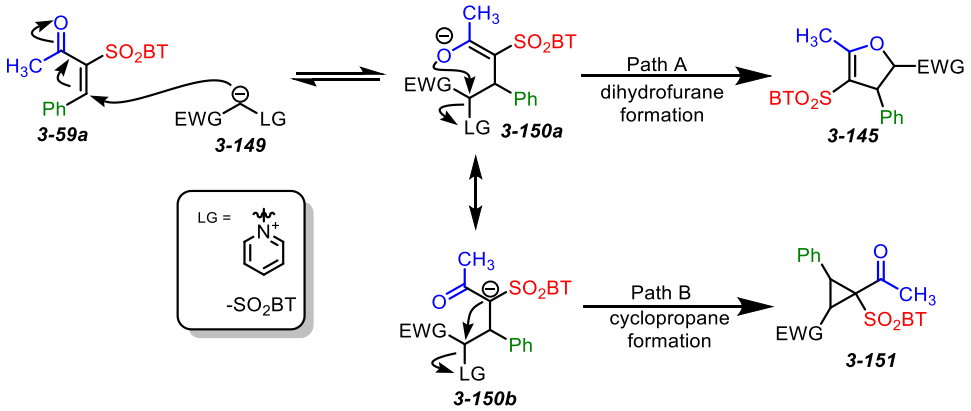
*Table 30 – Dihydrofuran **3-145** synthesis.*



Entry	Nu	Ratio[a] (*3-145* : *3-130*)	Comment	Isolated Yield of *3-145*	d.r.[a]
1	***3-15a***	1 : 1	-	46%	99:1
2	***3-15b***	1 : 0	-	87%	99:1
3	***3-146***	-	No reaction	-	
4	***3-16a***	0 : 1	-	-	-
5	***3-147***	1 : 0	-	98%	99:1
6	***3-148***	0 : 1	see below for further discussion	-	-
[a]Based on ^{1}H NMR analysis of the crude reaction mixture					

We were literarily disappointed with such results. To overcome present substrate limitations, we looked closely on the reaction mechanism (Scheme 49). A closer look makes immediately apparent that the C-nucleophiles (PM-1 type molecules) are having two roles. First, the acidity of α-hydrogen allows its easy removal and promotes the 1,4-addition reaction. Generated enolate ***3-150a*** can further undergo either cyclization to yield dihydrofuran ring ***3-145*** (observed) or C-cyclization to yield the formation of cyclopropane ***3-151*** (not observed). In both cases, BT-SO_2 group in PM-1 plays the role of leaving group. And, indeed, it is not a very good leaving group. Thus, we decided to use C-nucleophiles that would be substituted with another better leaving group. Our choice falls on the pyridine group, more precisely to the pyridinium salts.[94,95] To evaluate our choice, keto pyridinium reagent ***3-147*** and cyano equivalent of it, ***3-148***, were prepared and evaluated (Table 30, entries 5 and

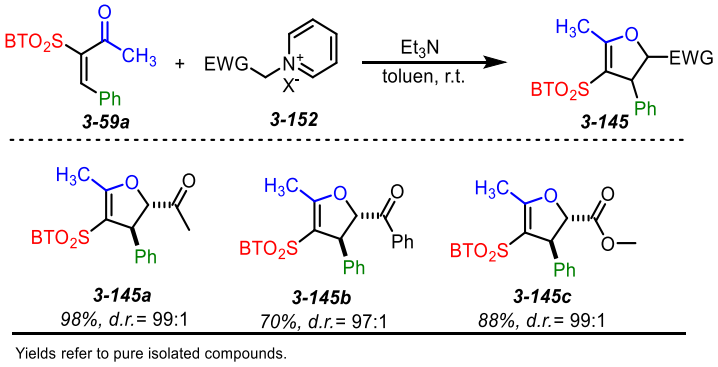
6) in our reaction conditions. The first reagent yielded the desired compound in good yield and excellent selectivity (Table 30, entry 5), but the second one yielded unexpected, and first nonidentified, product (see discussion below). Soon after it was observed that various pyridinium salts with the general structure of ***3-152*** reacted with ***3-59a*** to yield the desired dihydrofurans ***3-145a*** – ***3-145c*** in excellent yield (70-98%) and diastereoselectivity (*d.r.* = 97:1 – 99:1) (Table 31).



Scheme 49 – Proposed reaction mechanism that yields the dihydrofurans (4+1) or cyclopropane (2+1) structures.

*Table 31 - Dihydrofuran **3-145** synthesis using pyridinium salts with different EWG.*

Ammonium salt mediated (4+1) annulation



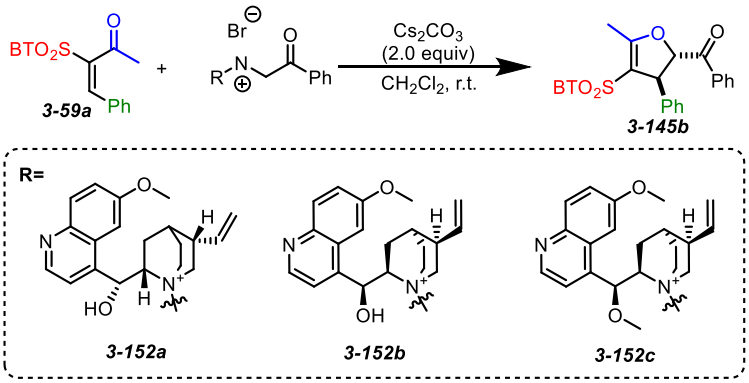
Yields refer to pure isolated compounds.

In addition, when chiral equivalents of ammonium salts[96–98] based on chiral quinine or cinchonine were used, the reaction could be carried out not only with excellent diastereoselectivity, but also with high enantioselectivity (Table 32). By proper choice of chiral ammonium salt, we could also obtain the opposite enantiomer of our products. Thus, both antipodes of the same tetrahydrofuran heterocycle could be prepared.

As mentioned previously, when cyano pyridinium salt ***3-148*** was reacted with ***3-59a***, an unexpected new product was obtained. The compound was bright red and stable on column (SiO_2). However, we failed to determine its structure. After many nights and several broken pencils, we suggested that an isolated compound is in fact salt ***3-153a*** (Scheme 50, Part A). Our structure (and mechanism) suggestion is based on the experimental data (NMR, HRMS) and was further confirmed by Dr. Maloň and Dr. Koshino from Jeol Japan and Riken institute, respectively. Unfortunately, we are

still not 100% sure about the structure since the X-Ray analysis of the compound was not performed (no single crystal was prepared).

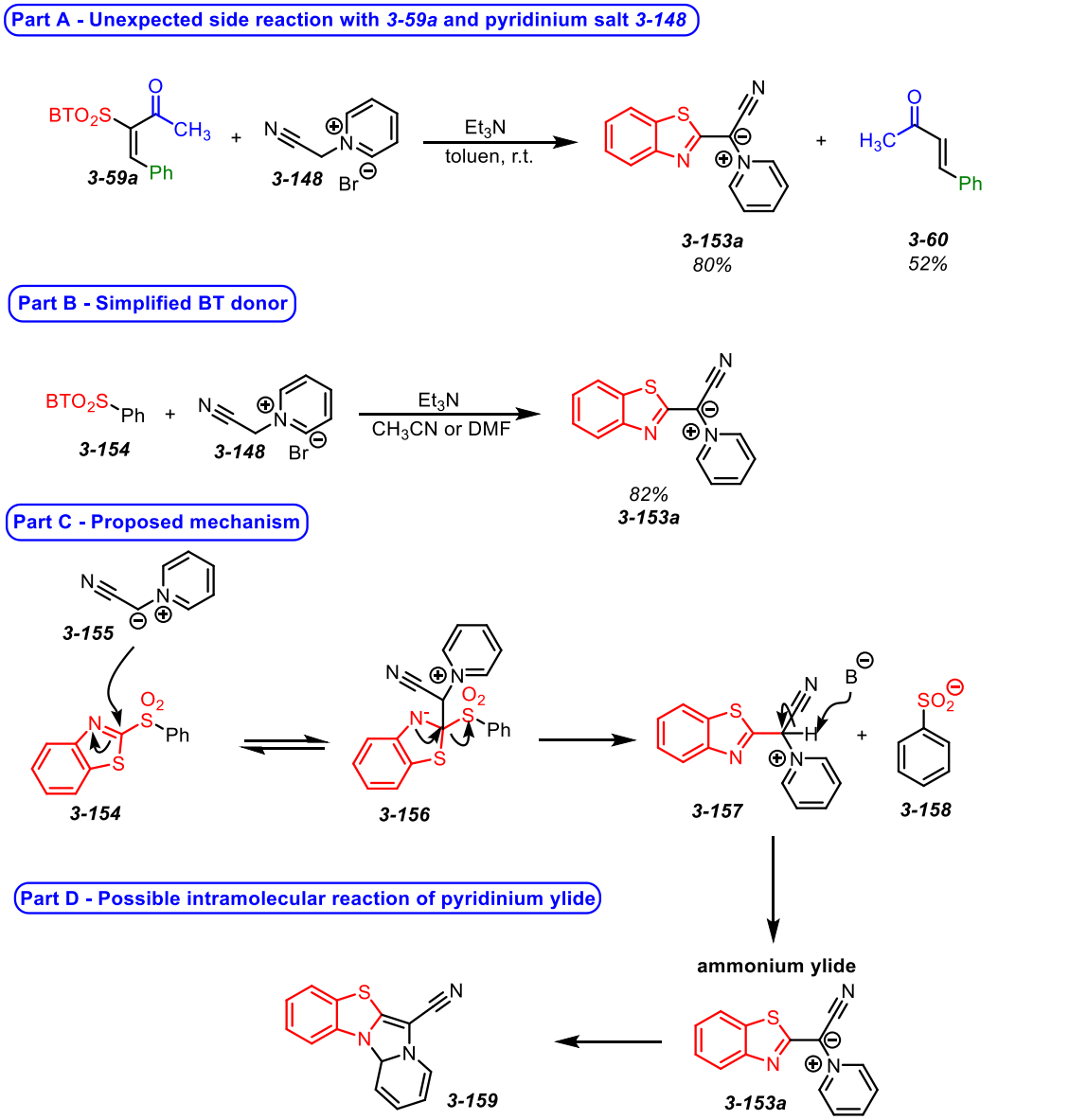
Table 32 - Optimization of dihydrofuran asymmetric protocol.



Entry	Reaction Conditions	*e.r.*[a]	Yield (%)[b]	Note
1	Sulfone (1.0 equiv), salt ***3-152a*** (1.5 equiv), Et_3N (1.5 equiv.), DCM, r.t.	-	n.d.	Decomposition of sulfone
2	Sulfone (1.0 equiv), salt ***3-152a*** (1.5 equiv), Cs_2CO_3 (2.0 equiv.), DCM, r.t.	82:18	37	-
3	Sulfone (1.0 equiv), salt ***3-152a*** (1.5 equiv), Cs_2CO_3 (2.0 equiv.), DCM, r.t.	94:6	20	Sulfone added dropwise as a solution in DCM
4	Sulfone (2.0 equiv), salt ***3-152a*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), DCM, r.t.	95:5	56	-
5	Sulfone (2.0 equiv), salt ***3-152a*** (1.0 equiv), K_2CO_3 (2.0 equiv.), DCM, r.t.	85:15	40	-
6	Sulfone (2.0 equiv), salt ***3-152a*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), THF, r.t.	97:3	70	-
7	Sulfone (2.0 equiv), salt ***3-152a*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), CH_3CN, r.t.	82:18	39	-
8	Sulfone (2.0 equiv), salt ***3-152a*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), toluen, r.t.	-	n.d.	Decomposition of sulfone
9	Sulfone (1.0 equiv), salt ***3-152a*** (1.3 equiv), Cs_2CO_3 (2.0 equiv.), DCM, r.t.	98:2	31	
10	Sulfone (2.0 equiv), salt ***3-152b*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), THF, r.t.	11:89	71	-
11	Sulfone (2.0 equiv), salt ***3-152c*** (1.0 equiv), Cs_2CO_3 (2.0 equiv.), THF, r.t.	1:99	68	-

[a] Determined by HPLC ; [b] Refers to pure isolated compound.

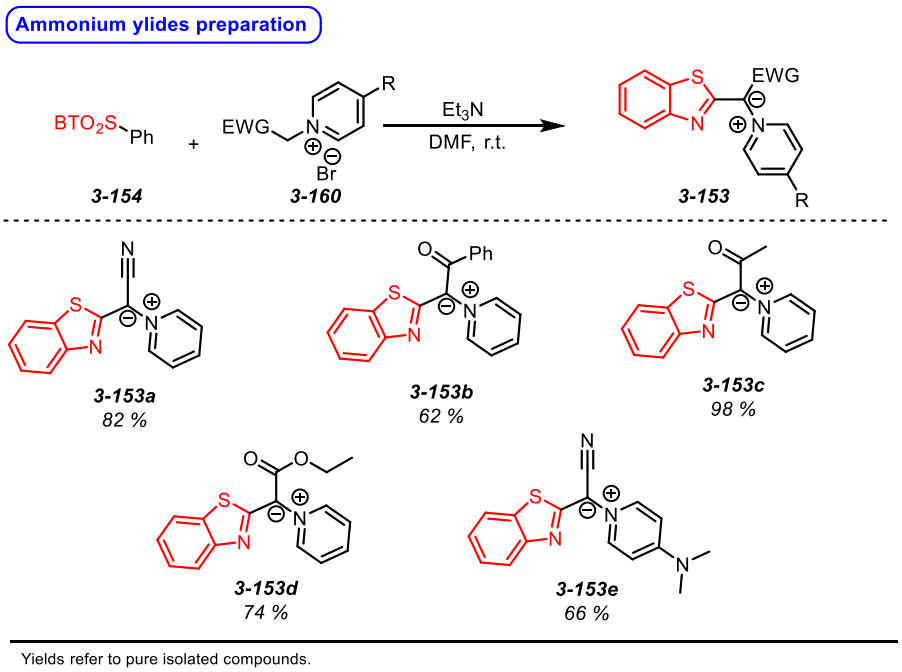
How we came up with the proposed zwitterionic salt structure. First, we knew that an isolated compound contains neither sulfone part nor the olefin part of **PM-2**. However, it contained BT group. Thus, we suggested that ylide ***3-153a*** reacted with the BT-heterocycle instead of adding in 1,4-fashion to ***3-59a***. To evaluate our hypothesis, BT-phenyl sulfone ***3-154*** was prepared and reacted with the salt ***3-148***. The same product as in the previous case was isolated in comparable yield (Scheme 50, Part B, 82% vs. previously obtained 80% isolated yield). This experiment proved that (a) we do not need all big α,β-unsaturated olefin part and (b) that the first step is the addition of a nucleophile to BT heterocycle. The addition step further released phenyl sulfinate as a side product (control experiments proved that we need the help of aryl group to stabilize the sulfinic salt. If BT-methyl-sulfones or BT-*tert*-Butyl-sulfones were used as substrates, no product was observed). At this stage, we suggested that the presence of the excess of the base will further deprotonate labile α-to pyridinium hydrogen and will generate zwitterion ***3-153a***. Moreover, we speculated that such structure can be presumably stabilized via intramolecular cyclization (Scheme 50, Part D), however, all characterization data, especially ^{15}N-correlations carried out by Dr. Maloň and Dr. Koshino, disapproved this type of structures. Upon their analysis, no nitrogen (BT)- carbon (pyridinium) bond is present in the ***3-153a***. Indirect prove for this statement was gathered when compound ***3-153e*** was prepared (Table 33). If this compound would be present in its cyclized form, all hydrogen atoms on the pyridine ring will have a different chemical shift. However, in the case of ***3-153e***, only two sets of different signals that integrate for 2 are present.



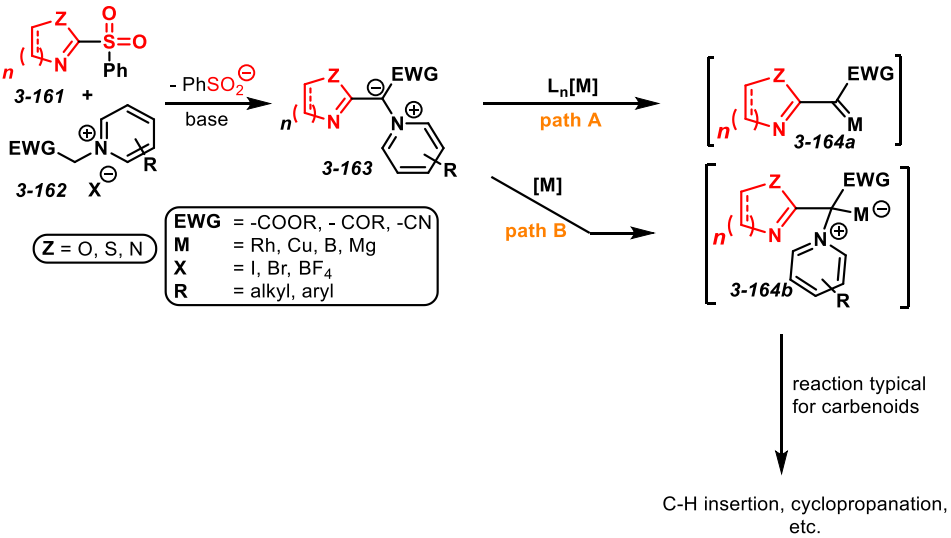
*Scheme 50 - Unexpected reaction involving the pyridinium salt **3-153a**, and sulfones **3-59a** and **3-154**, respectively.*

Next, we wished to check if compounds ***3-153*** synthesis is limited to compounds with the cyano group (Table 33). It was observed that aryl and alkyl ketone, as well as ester group, substituted pyridinium salts are tolerated under the reaction conditions and yields the desired zwitterionic salts ***3 -153*** in moderate to good yields. In addition, the electron-donating group on the pyridine is also well tolerated.

*Table 33 - Pyridinium ylides as reaction partners: Synthesis of zwitterionic salts **3-153** – Scope and limitations.*



At this point, the project stopped but is far from being finished. First, we wish to be sure about the structure of the adduct. When confirmed, we believe that it is a very promising compound that could readily replace the diazo compounds in organic synthetic chemistry. Indeed, we wish to develop this chemistry in the context of Rh and Cu catalyzed cyclopropanations.[99,100] Scheme 51 depicts the ways we expected such type of compounds could be used in organic chemistry. The ways how they can be transformed into metal carbenes and carbenoids.

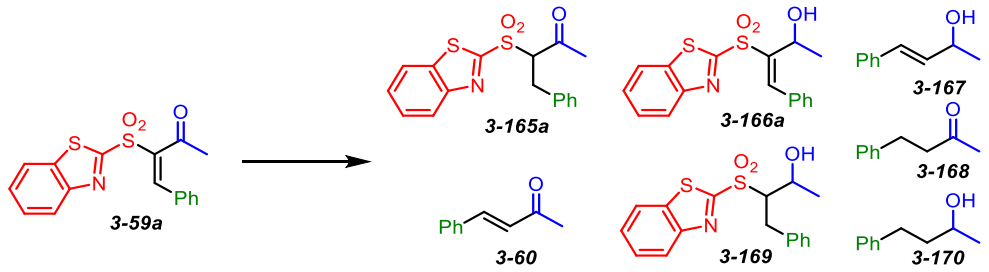


Scheme 51 – Exploring the use of zwitterionic ylides in organic synthesis.

3.5.6 PM-2 and 1,2- vs. 1,4-hydride addition/reduction

The next goal of our research was to achieve a selective 1,2 or 1,4 reduction of carbonyl/olefin in **PM-2**. Along with these two types of reduction, we feared a competitive C=N bond reduction in BT-group. In this case, the undesired desulfonylation reaction would occur, hammering further use of reduced compounds. In addition, if the excess of reducing agents would be used, both 1,2 and 1,4-reduction could occur along with other undesired side product (Table 34).

*Table 34 - Optimization of 1,2 vs 1,4 reduction of **3-59a**.*



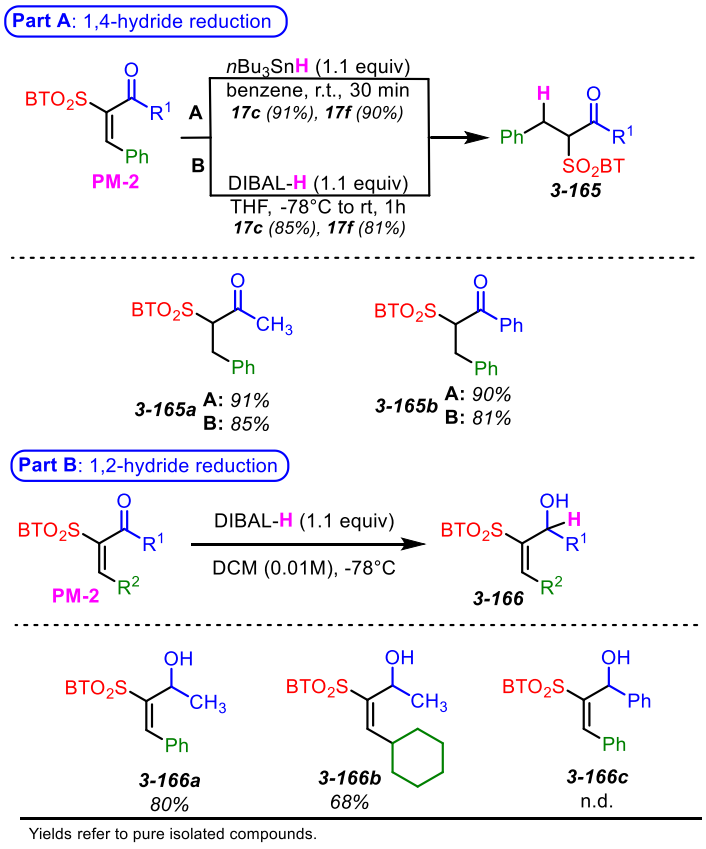
Entry	Hydride source	Conditions	Product ratio[a] ***3-165a / 3-166a / 3-60 / 3-169 / 3-170***	Isolated yields
1	DIBAL-H	1.0 equiv, CH_2Cl_2 (0.1M), -40°C	1:2:0:0:0	n.d.
2	DIBAL-H	1.0 equiv, CH_2Cl_2 (0.1M), -78°C	1:8:0:0:0	***3-166a*** (51%)
3	DIBAL-H	1.0 equiv, CH_2Cl_2 (0.01M), -78°C	0:1:0:0:0	***3-166a*** (80%)
4	DIBAL-H	1.0 equiv, THF (0.1M), -78°C	1:0:0:0:0	***3-165a*** (85%)
5	DIBAL-H	1.0 equiv, toluene, -40°C	1:5:0:0:0	***3-166a*** (78%)
6	$LiBH_4$	1.1 equiv, THF, -78°C	0:0:0:1:0	n.d.
7	$NaBH_4$	1.1 equiv, EtOH, -78°C	2:0:0:5:0	***3-165a*** (12%)
8	$NaBH_4/CeCl_3$	1.1 equiv/1.1 equiv, EtOH, -78°C	1:0:0:7[b]:0	n.d.
9	KBH_4	1.1 equiv, THF, -78°C	1:0:0:7:0	n.d.
10	KBH_4/Sc(OTf)3	1.1 equiv/1.1 equiv, THF, -78°C	1:0:0:5:0	n.d.
11	K-selectride	1.1 equiv, THF, -78°C	1:0:0:0:0	n.d.
12	$Li[AlH(OBu^t)_3]$	1.1 equiv, THF, -78°C	1:0:0:0:0	***3-165a*** (89%)
13	$LiAlH_4$ (solid)	1.1 equiv, THF, -78°C to RT	0:0:0:0:1	***3-286*** (76%)
14	$LiAlH_4$ (1.0M in Et_2O	1.1 equiv, THF, -78°C	1:0:0:0:10	n.d.
14	nBu_3SnH	1.1 equiv, benzene, rt[c]	1:0:0:0:0	***3-165a*** (91%)
15	nBu_3SnH	1.1 equiv, CH_2Cl_2, -78°C[c]	1:0:0:0:0	***3-165a*** (86%)
16	Et_3SiH	1.1 equiv, CH_2Cl_2, 0°C to RT	n.r.	***3-59a*** (97%)

[a]based on ^1H NMR of the crude reaction mixture
[b]only ~40% conversion of ***3-59a***
[c]The reaction proceeds in the presence of radical scavenger

During the optimization of the ***3-59a*** reduction using various aluminium, boron, tin and silicon-based hydrides, it was observed that DIBAL-H in DCM at -78°C, preferentially generates a product of 1,2 -addition (Table 34, entry 2). This trend was even more pronounced if the reduction was carried

out in high dilution conditions (Table 34, entry 3). On the other hand, if the reaction was carried out in more concentrated solution, at the higher temperature, or if THF was used as a solvent, 1,4-adduct was obtained as a major or even exclusive product. When boron-based hydrides were used, 1,4-reduction (or mixed 1,2 and 1,4 reduction) occurred (Table 34, entries 6-11). In the case of $LiAlH_4$ (and its derivatives) overreduction (1,2 and 1,4-reduction and desulfonation) occurred (Table 34, entries 12-14). In the case of nBu$_3$SnH (uncatalyzed), selective 1,4-reduction was observed. No reaction was observed when Et$_3$SiH reduction was attempted (uncatalyzed). The best-obtained results regarding the selective 1,2- or 1,4-hydride addition are collected in Table 35.

Table 35 – Selective 1,2 and 1,4-addition/reduction of PM-2.

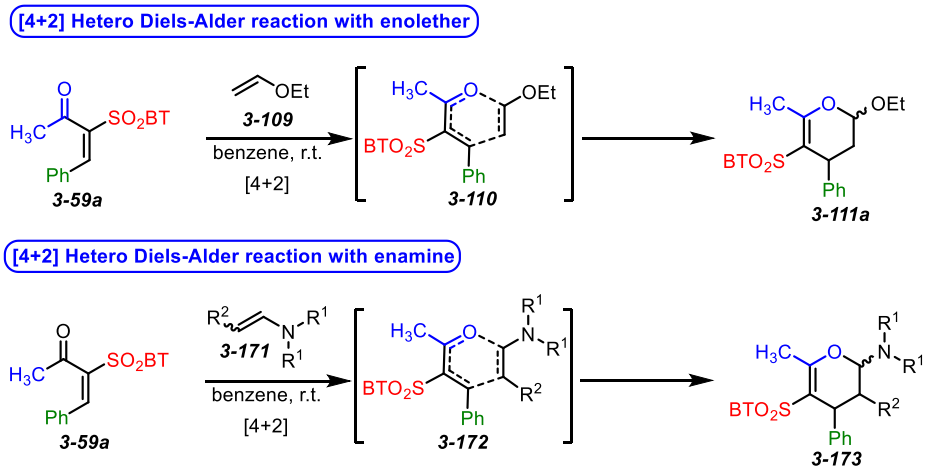


3.6 PM-2 and organocatalysis

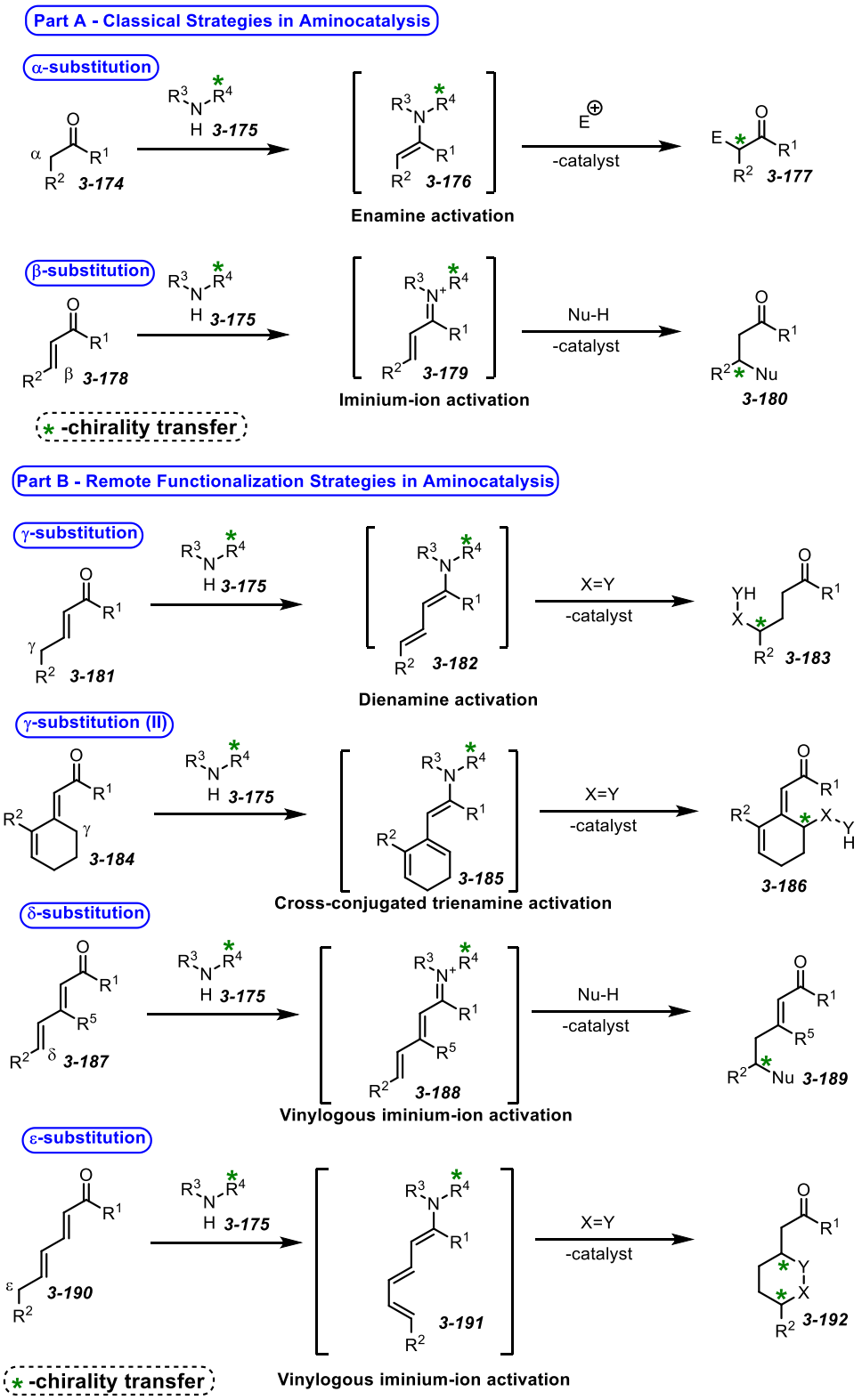
3.6.1 Introduction

The skeleton of **PM-2** molecule virtually "calls" to be used as a substrate for organocatalytic reactions. Indeed, while we were carrying out hetero-Diels-Alder reactions (chapter 3.5.2), the analogy between our reactions where enol ether serves as a dienophile, and the reaction of enamines with our activated olefin was more than obvious (Scheme 52). And if we talk about enamines, we talk about organocatalysis.[101,102]

Secondary chiral amines catalysis is widely used in organic synthesis. And the most recently developed methods that generate chiral enamines are exploited in organocatalytic hetero-Diels-Alder reactions or (4+2) cyclizations, that yield product with excellent stereocontrol. The methods are so robust, that they can be exploited even in the context of total synthesis.[103] From the historical viewpoint, (chiral) enamines were first used in the context of aldol type reactions. Later on, the method was extended to alkylation reactions (formal α-substitution of aldehydes and ketones, Scheme 53, Part A),[104] and further even to β-substitution,[105] Next, α,β-unsaturated and $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds were exploited as substrates in (chiral) amine-catalyzed reactions. Due to a larger variety of functional groups employed, richer reactivity was observed (Scheme 53, Part B). First, *in situ* enamine formation allowed γ -substitution in α,β–unsaturated substrates or $\alpha,\beta,\gamma,\delta$–unsaturated substrates if sp^3 hybridization carbon was present. In addition to those, if $\alpha,\beta,\gamma,\delta$–unsaturated substrates are used, δ–substitution is possible. In addition, *in situ* generated enamine can undergo (4+2)-cyclization to yield 6-membered ring. But what is important and amazing, amine-catalyzed reactions are the source of the stereoinduction. It is the generated enamine that directs, control and is a source of the stereoinduction.[106] Thus, you can see that a small chiral amine and α,β-unsaturated aldehyde can generate highly diverse products. And that is what we wish to achieve with our **PM** molecules. Thus, if we react α,β-unsaturated aldehydes-generated enamines with our **PM-2** (both diversity generating substrates), hopefully, interesting scaffolds can be obtained.



*Scheme 52 -Hetero-Diels-Alder reaction of **PM-2** with enol ethers or enamines.*

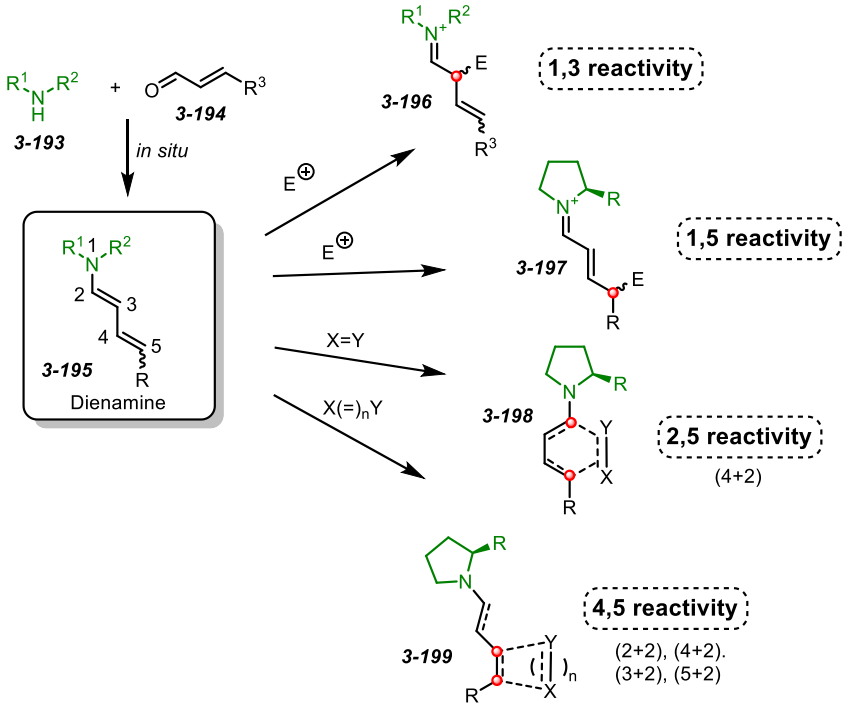


Scheme 53 – Different types of carbonyl activation with chiral amines[101].

3.6.2 Reactivity of dienamines

Versatile reactivity and interesting properties of dienamines strongly influenced the stereoselective reactions and transformations carried out with the help of asymmetric

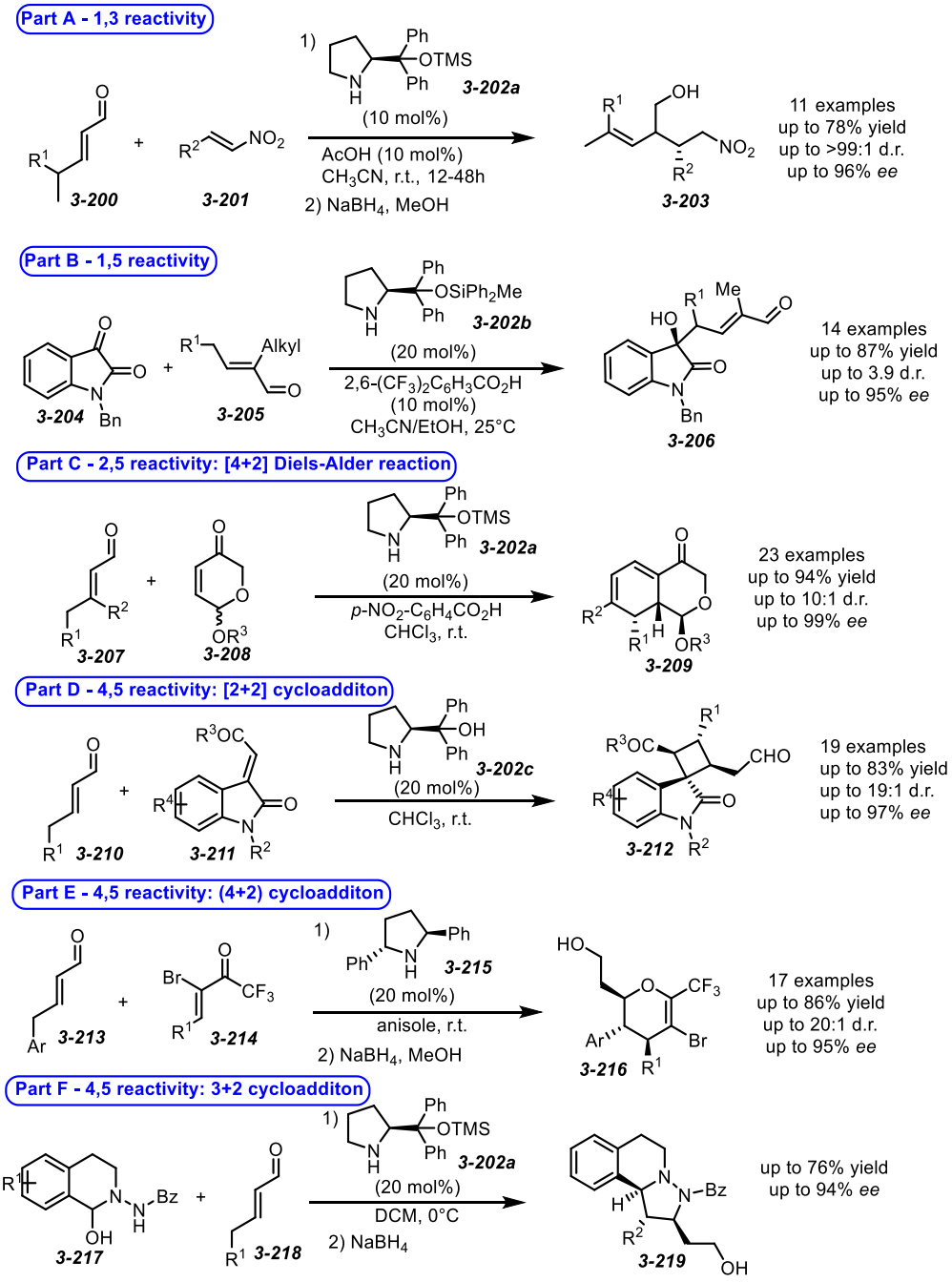
aminocatalysis.[107] The pioneering work in this area is attributed to prof. Serebryakov, who already in the early '90s successfully explored the reactions of dienamines. In his pioneering work, the main focus was paid to cyclohexadiene synthesis in both achiral and chiral manner.[108–110] Since then, a decade of "silence" became in the field. Everything change again in 2006 when Jørgensen et al. published their seminal work on aza-1,5-functionalization of α,β-unsaturated aldehydes.[111] Shortly after, the field of dienamines underwent literally to an explosion with dozens of published papers per year. The reactivity of dienamines is strongly influenced by its electrophilic and nucleophilic properties (HOMO and LUMO energies).[112] The most common reactivities are presented in Scheme 54. In general, dienamines can react at 1,3; 1,5; 2,5 and 4,5 positions and reactions can be classified as Michael-type or various cyclization reactions (2+2, 4+2, 3+2, 5+2). Interestingly, the regio and stereo (diastero and enantio) selectivity is strongly influenced by amine used as a catalyst. Examples of dienamine catalysis selected to demonstrate its utility, catalytic activity and a broad spectrum of its applicability are listed in Scheme 55.



Scheme 54 – Reactivity of dienamine intermediate.

An interesting example of 1,3 reactivity (Scheme 55, Part A) was published in 2009. In the presented case, one of the first chemo-, regio and stereoselective Michael addition of γ-disubstituted α,β-unsaturated aldehydes ***3-200*** to nitroolefins ***3-201*** was reported. The desired alcohols ***3-203*** were obtained with excellent yields, and dia- and enantioselectivities. Proper choice of γ-substitution allowed the reaction to proceed also with high regioselectivity. Obtained adducts were successfully transformed to various six-membered cycles such as cyclohexenes or piperidines (Scheme 55, Part A).[113] Interestingly if additional substituent was placed to the α-position, 1,5 reactivity (Scheme 55,

Part B)[114] was observed. Versatile reactivity of dienamines was also exploited in the dynamic kinetic resolution of 5-acyl dihydropyranones ***3-208*** (Scheme 55, Part C). In this case, racemic pyranones ***3- 208*** and α,β-unsaturated aldehydes ***3-207*** reacted in the presence of Hayashi-Jørgensen catalyst ***3- 202a*** and yielded chiral products of (4+2)-hetero-Diels-Alder reaction (2,5 reactivity) in good yields and stereoselectivity (Scheme 55, Part C)[115].



Scheme 55 – Examples of dienamine reactivity[112].

The dienamine reactivity can also be tuned to allow [2+2] cycloaddition reactions (Scheme 55, Part D). In 2014, Wang and his colleagues described the synthesis of various spirooxyindols ***3-212*** with cyclobutene ring in its core structure. This particular transformation is driven by the hydrogen bond

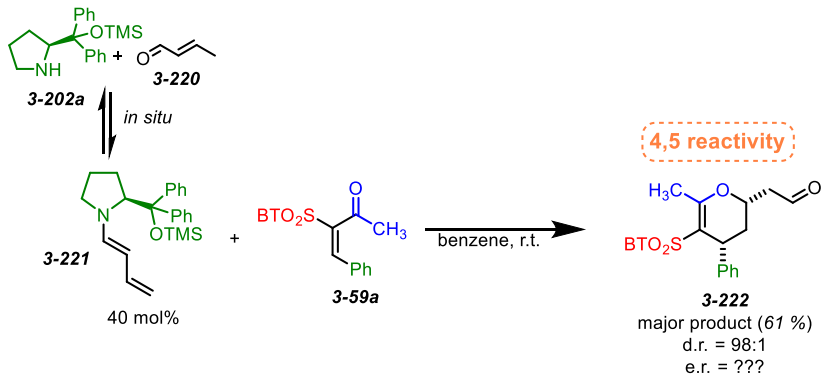
donor interaction generated by proline-based aminocatalyst (Scheme 55, Part D).[116] Next example is the reaction we wish to explore in our case - hetero-Diels-Alder reaction. Jørgensen and co-workers described the stereoselective formation of highly substituted CF_3-dihydropyrans (Scheme 55, Part E) using such a method. The methodology exploited C-2 symmetry-based 2,5-diphenyl pyrrolidine catalyst ***3-215*** in combination with α,β-unsaturated CF_3 ketones ***3-214***. The developed protocol allowed the synthesis of a wide range of 5-bromo-6-CF_3-dihydropyranes ***3-216*** in moderate yields and excellent enantioselectivities (Scheme 55, Part E).[117] The last example demonstrates the reactivity of dienamines in context of (3+2) cycloadditions (Scheme 55, Part F). *In situ* generated dienamine was in this case coupled with azomethine ylide and generated condensed 5-membered heterocycles ***3-219***. Transformations were achieved in good yields and enantioselectivities. Moreover, the developed method proved to be relatively robust and tolerates various substituents on the aromatic ring of both reaction partners (Scheme 55, Part F)[118].

As demonstrated in our short overview, the chemistry of dienamines is very interesting, versatile and rich in reactivity. On the other hand, if asymmetric transformations are considered, only very few chiral amines are eligible as efficient catalysts. In short, they are mostly limited to Hayashi-Jørgensen catalyst and its derivatives. The choice of the catalyst for our transformation was therefore easy.

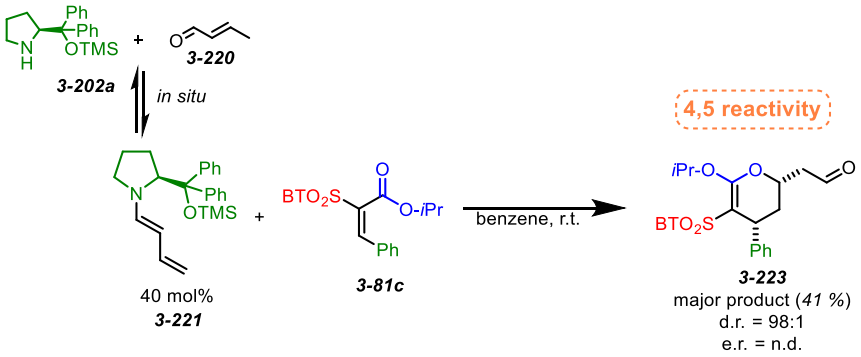
3.6.3 PM-2 and organocatalyzed (4+2) cycloadditions

Inspired by the results of [4+2] cycloaddition reaction of vinyl ethers (Chapter 3.5.2), we have decided to extend such type of transformation to the field of dienamines. Thus, dienamine ***3-221*** *in situ* generated from Hayashi-Jørgensen catalyst and crotonaldehyde were reacted with Knoevenagel product ***3-59a*** and ***3-81c,*** respectively. In the first case, the reaction proceeded smoothly and yielded the 4,5-position adduct ((4+2) cyclization adduct) in 61% isolated yield and excellent >98:1 diastereoselectivity. It should be pointed out that no other cyclization or addition product formation was observed either via LC-MS or ^{1}H NMR analysis of the reaction mixture. And, even more surprisingly, the same situation was observed in the case of ester equivalent of ***3-59a***, compound ***3-81c***. In this case (4+2) adduct ***3-223*** was isolated in a moderate yield of 41%, but still as a virtually single diastereomer (*d.r.* = >98:1). The drawback of these transformations is fact that we have failed to determine the *e.r.* of the reactions due to our inability to separate the two enantiomers with help of available separation techniques (both enantiomers were prepared using racemic catalyst). Indeed, various analytical separation methods were tested, however, soon we figured out that the instability of our products is presumable of the reasons why the separation failed. Just to demonstrate the difficulties: if MeOH was used as a solvent for SFC analysis, new adduct (LC-MS analysis, compound structure based on MS-MS analysis) was detected as the only product in the chromatogram (Scheme 58). And still, no separation of the two enantiomers was achieved. Thus, the high reactivity of obtained adducts forced us

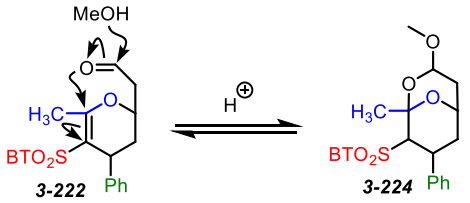
to abandon the attempts of direct (4+2) cyclization product isolation. Instead, *in situ* derivatization of generated aldehydes was performed. But before discussing this approach and *e.r.* determination I would like to draw your attention to another interesting feature of our (4+2)-cyclization reaction – virtually exclusive diastereoselectivity.



*Scheme 56 -Reaction of in situ generated dienamine **3-221** and PM-2 structure **3-59a**.*



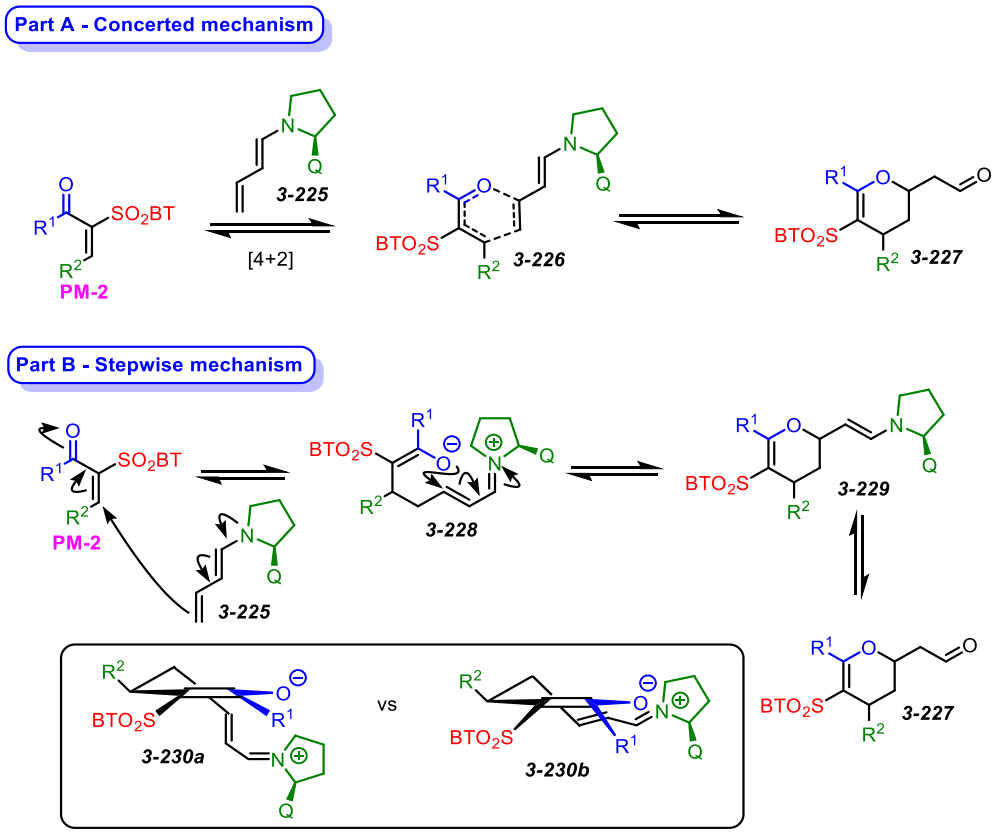
*Scheme 57 - Reaction of in situ generated dienamine **3-221** and sulfone **3-81c**.*



*Scheme 58 – Proposed structure of the product **3-224** generated during the LC-MS analysis and the rationalization of its formation.*

If we consider the mechanism of (4+2) cyclization reaction, two distinct mechanisms must be discussed – concerted ([4+2] hetero-Diels-Alder) and stepwise (Scheme 59). In both cases, the terminal olefin of dienamine ***3-225*** seems to be the preferred target of the attack due to a steric reason. In the first case, *endo/exo*-transition states should be considered. Taking into account second orbital interaction, *endo*-transition state that yields *cis* relationship between the two newly created stereogenic centres on dihydropyran ring should be preferred. Asymmetric and stereo induction should be generated in this step. In the second case, a stepwise mechanism, the first step, Michael-addition, should be responsible for the asymmetric induction while the second enolate addition (via

oxygen of generated enolate) will "just" generate the diastereoselectivity of the reaction. It is expected that chair-like conformation will lead to high selectivity in the second step of the cyclization. Now, if the first mechanism operates, we believe that the enantioselectivity of the reaction will be high since the center of the chirality is in relative proximity to interacting orbitals. On the other hand, in the stepwise mechanism, the distance between the chiral inductor and interacting dienamines is rather big and thus presumably less efficient.



*Scheme 59 – Proposed mechanistic pathways yielding the adduct **3-227**.*

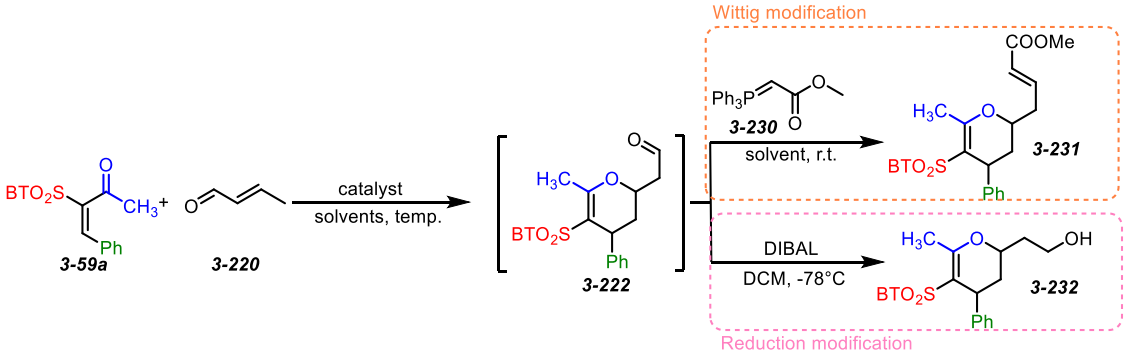
Keeping these two-reaction mechanisms in mind and having in mind the necessity to transform generated adduct ***3-222*** *in situ* to the more stable product, the optimization of (4+2) cyclization reaction begin. First, the derivatization strategy had to be chosen. We decided to evaluate two different approaches to limit the possibility that our derivatization step will anyhow modify the reaction stereoselectivity. Thus, the reaction of a generated aldehyde with stabilized Wittig reagent ***3- 230*** was the first choice, and the DIBAL-H mediated reduction of the aldehyde was the second choice. Having designed these two benchmark reactions, the optimization of the (4+2) cyclization with respect to enantioselectivity could begin.

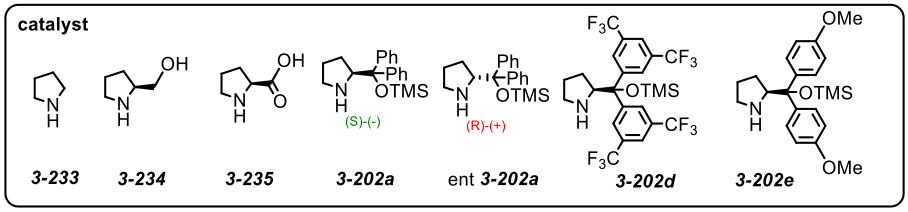
First reactions where pyrrolidine ***3-233***, prolinol ***3-234*** and proline ***3-235*** were used as catalysts were attempted. Only the degradation of the starting material was observed (Table 36, entries 1-3). Next, the reaction catalyzed with Hayashi-Jørgensen catalyst in various solvents was tested (Table 36,

entries 4-8). The full conversion of the starting compound was observed only in case of benzene. The diastereoselectivity was high, but *e.r.* could not be determined. Thus, the time of planned derivatization had come and generated aldehyde-containing products were *in situ* derivatized with help of Wittig reagent ***3-230*** (Table 36, entry 9) and DIBAL-H reagent (entry 10). In these cases, *e.r.* of generated olefin and alcohol could be determined with the help of SFC analysis, and it was determined that the reactions proceed with 77:23 *e.r.* (Wittig) and 70:30 *e.r.* (DIBAL-H), respectively. To ensure that we have really separated two enantiomers of the same compound, the same sequence was carried out again but this time the opposite enantiomer of Hayashi-Jørgensen catalyst was used (*e.r.* = 25:75, Wittig); (*e.r.* = 24:76, DIBAL-H). Having obtained these results that confirmed that (a) we achieved to separate both enantiomers, and (b) that the derivatization methods yields about the same *e.r.* for tested reactions reproducibly, it was decided that future *e.r.*'s of optimization reactions will be done on the crude material of the olefinic (Wittig reagent) derivative of the cycloadduct (Table 36, entries 13-27). Various solvents were tested, but when Hayashi-Jørgensen catalyst was used, no improvement in enantioselectivity was observed (slight increase if THF was used as a solvent, entry 16). Next, we attempted the transformation with CF_3-modified Hayashi-Jørgensen catalyst ***3-202d***. In the literature in general higher enantiomeric enrichments are achieved with this catalyst, however, in our case worse *e.r.* were obtained regardless of the solvent and temperature used. Again, the best *e.r.* were obtained when THF was used as a solvent and the reaction was performed at 0°C (Table 36, entry 25). Subsequently, the reaction was performed using MeO-modified Hayashi-Jørgensen catalyst[119] (Table 36, entry 28). In this case, slow reaction rate was observed comparing with ***3-202a*** and ***3-202d***. Unfortunately, *e.r.* has not been determined during the submitting of the manuscript.

Overall, this organocatalytic (4+2)-cyclization reaction still needs to be studied and developed to reach higher levels of enantioselectivity. On the other hand, if we consider only isolated compounds, it has already proved that our **PM-2** molecules in combination with Hayashi-Jørgensen catalyst can lead in the one-pot protocol to both antipodes of complex heterocyclic structures (Scheme 60).

*Table 36 - Optimization of enantioselective protocol for **3-222**.*



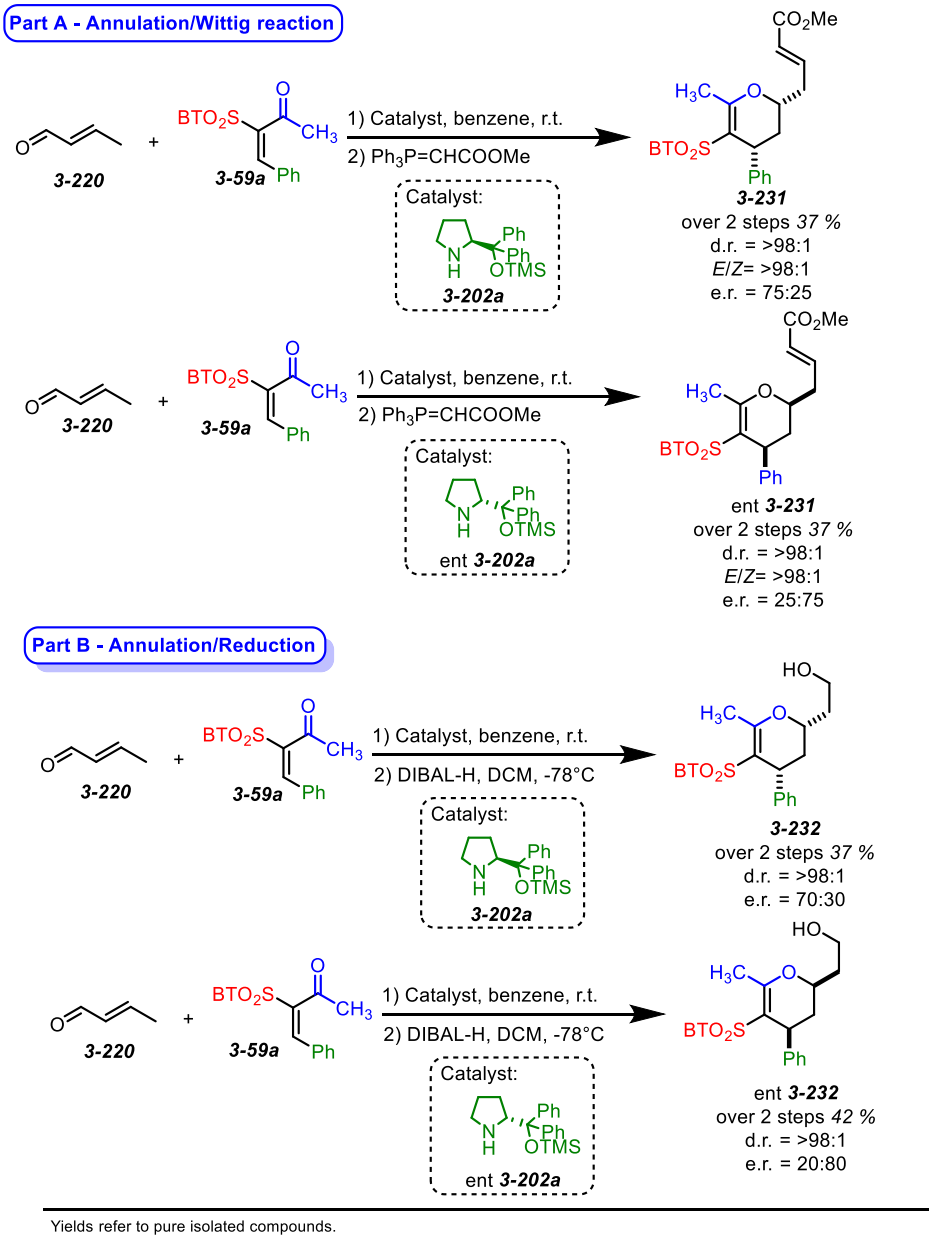


Entry	Conditions	Catalyst	Conversion	Yield[b]	e.r.[c]	d.r.[a]	Comment
1	Benzen, r.t. 24h	***3-233***	100%	Decomposition of ***3-59a***	-	-	-
2	Benzen, r.t. 24h	***3-234***	100%	Decomposition of ***3-59a***	-	-	-
3	Benzen, r.t. 24h	***3-235***	100%	Decomposition of ***3-59a***	-	-	-
4	Benzen, r.t. 24h	***3-202a***	100%	61 % (***3-222***)	-	>98:1	-
5	Toluene, r.t., 24h	***3-202a***	90%	-	-	>98:1	-
6	Toluene, 0°C, 24h	***3-202a***	25%	-	-	>98:1	-
7	$CHCl_3$, r.t. 24 h	***3-202a***	55%	-	-	>98:1	-
8	CH3CN, r.t., 24h	***3-202a***	- (starting compound re-isolated)	-	-	-	-
9	Benzene, r.t., 24h +1h (reduction)	***3-202a***	100 %	***3-232*** (37%)	70:30	>98:1	-
10	Benzene, r.t., 24h+1h Wittig r.	***3-202a***	100%	***3-231*** (37%)	77:23	>98:1	-
11	Benzene, r.t., 24h+1h reduction	ent ***3-202a***	100%	***3-232*** (40%)	24:76	>98:1	-
12	Benzene, r.t., 24h+1h Wittig r.	ent ***3-202a***	100%	***3-231*** (37%)	25:75	>98:1	-

13	Toluene, r.t., 6h+1h Wittig r.	***3-202a***	100%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
14	$CHCl_3$, r.t., 6h+1h Wittig r.	***3-202a***	100%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
15	DCM, 6h+1h Wittig r.	***3-202a***	100%	-	74:26	>98:1	Crude reaction mixture on SFC analysis
16	THF, r.t. 24h+1h Wittig r.	***3-202a***	100%	-	80:20	>98:1	Crude reaction mixture on SFC analysis
17	THF, 0°C, 24h+1h Wittig r.	***3-202a***	100%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
18	DMF, r.t., 24h	***3-202a***	20%	-	-	-	-
19	DCE, r.t., 24h+1h Wittig r.	***3-202a***	50%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
20	Hexan : DCM (1:1), r.t., 28h+1h Wittig r.	***3-202a***	100%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
21	Toluene, 0°C, 48h+1h Wittig r.	***3-202a***	75%	-	75:25	>98:1	Crude reaction mixture on SFC analysis
22	Toluene, r.t., 24h+1h Wittig r.	***3-202d***	80%	-	60:40	>98:1	Crude reaction mixture on SFC analysis
23	$CHCl_3$, 24h+1h Wittig r.	***3-202d***	75%	-	68:32	>98:1	Crude reaction mixture on SFC analysis
24	THF, r.t., 24h+1h Wittig	***3-202d***	85%	-	69:31	>98:1	Crude reaction mixture on SFC analysis
25	THF, 0°C, 48h+1h Wittig r.	***3-202d***	68%	-	73:27	>98:1	Crude reaction mixture on SFC analysis
26	Et_2O, 0°C, 72h+1h Wittig r.	***3-202d***	50%	-	50:50	-	Crude reaction mixture on SFC analysis

27	Et_2O, -16°C, 72h+1h Wittig r.	***3-202d***	25%	-	50:50	-	Crude reaction mixture on SFC analysis
28	THF, r.t., 72h,+1h Wittig	***3-202e***	75%	-	-	>98:1	-

[a]Based on ^{1}H NMR of the crude reaction mixture
[b]Refers to isolated compounds
[c]Based on SFC analysis



*Scheme 60 - **PM-2** annulation/Wittig and annulation/reduction reaction sequence that yields products **3-231** and **3-232**.*

3.6.4 PM-2 – from simple olefins to the chemistry of allenoates

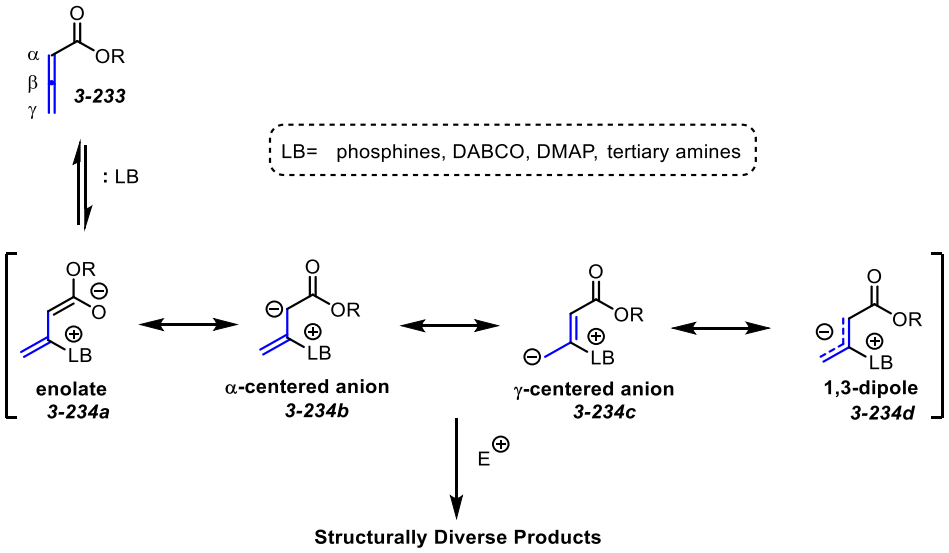
Our results with Hayashi-Jørgensen catalyst encouraged us to enter the "kingdom of organocatalysis". However, we were lacking any experience in this field and therefore we asked for

help the group of prof. M. Waser (JKU, Linz, Austria). The main focus of the Waser group is asymmetric catalysis with Phase-Transfer Catalysts (PTC) and on the field of chiral ammonium salts.[96,97,120] Thus, our groups found easily common interest when it comes up to the design of new chemical transformations that would combine the diversity approach (**PM-2** molecule) and organocatalysis (PR_3-based catalyst).[121] Our common interest focused on the reactivity of allenoates that in the presence of Lewis base (PR_3) generates enolate ***3-234a*** (Scheme 61). Enolate ***3-234a*** can be represented as 1,3-dipole ***3-234d*** that can be further represented in the two borderline resonance structures ***3-234b*** and ***3-234c***, respectively. Finally, the reaction of these dipoles with electrophile should yield structurally interesting compounds.[122]

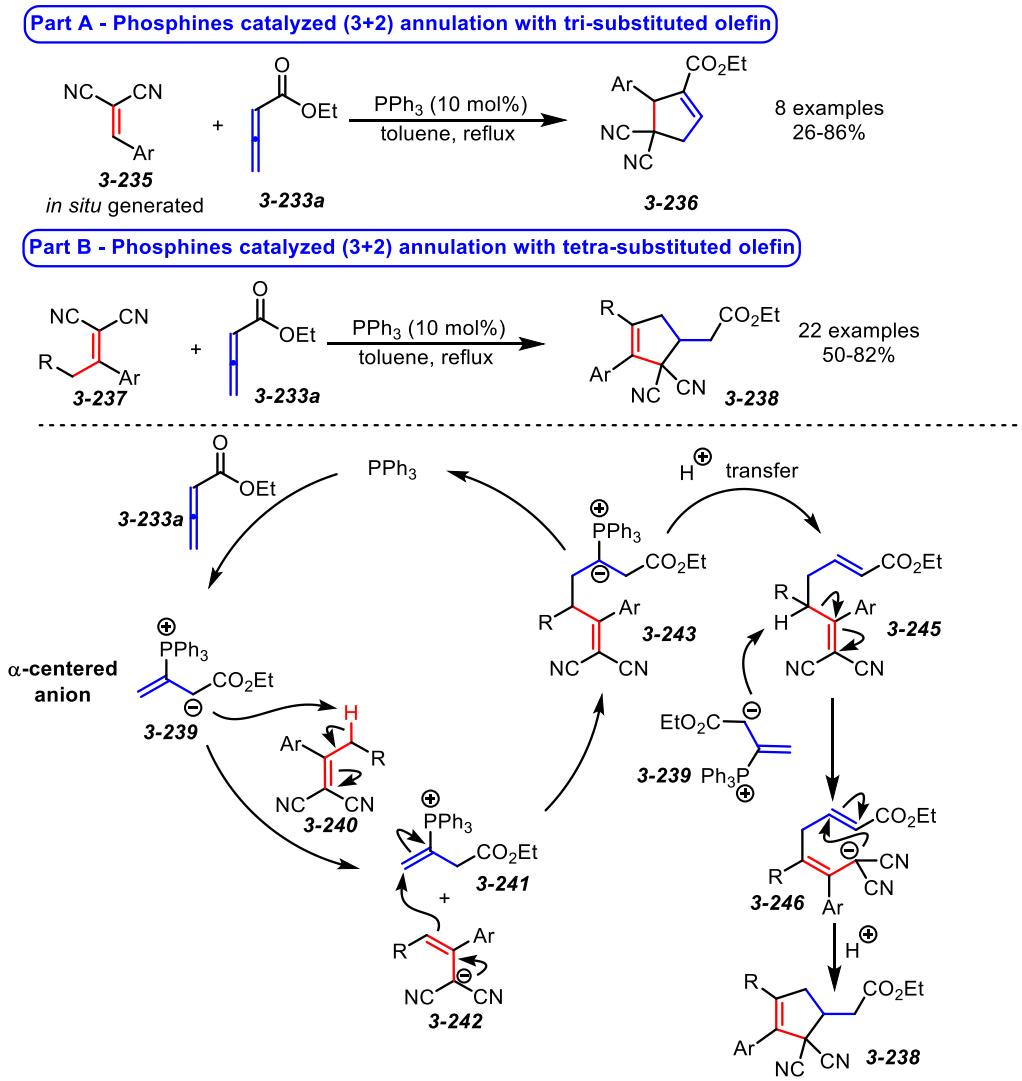
Indeed, those type of dipoles can be reacted e.g. with highly reactive electron-deficient olefins. This principle was used by Lu and Zhang to generate carbocycles ***3-236*** (Scheme 62).[123] Interestingly, when the same reaction conditions were employed to react the same allenoates ***3-233a*** with tetrasubstituted olefin ***3-237***, very different products were observed[124] (mechanistic explanation of the transformation can be found in Scheme 62).

In addition, it was also observed that the nucleophilic character of the R-groups in PR_3 can influence the catalyst reactivity. If electron-deficient (less basic) phosphines were used as a catalyst, (4+2) formal cycloaddition products were formed (Scheme 63). The opposite regioisomer could be prepared if an electron rich phosphine was instead.[125] Finally, if non-racemic phosphine catalysts were used, optically enriched carbocycles were prepared (Scheme 64).[126] In addition, the reactivity of allenoates could be further extended to aldehydes,[127] imines,[128,129] or umpolung additions.[130,131]

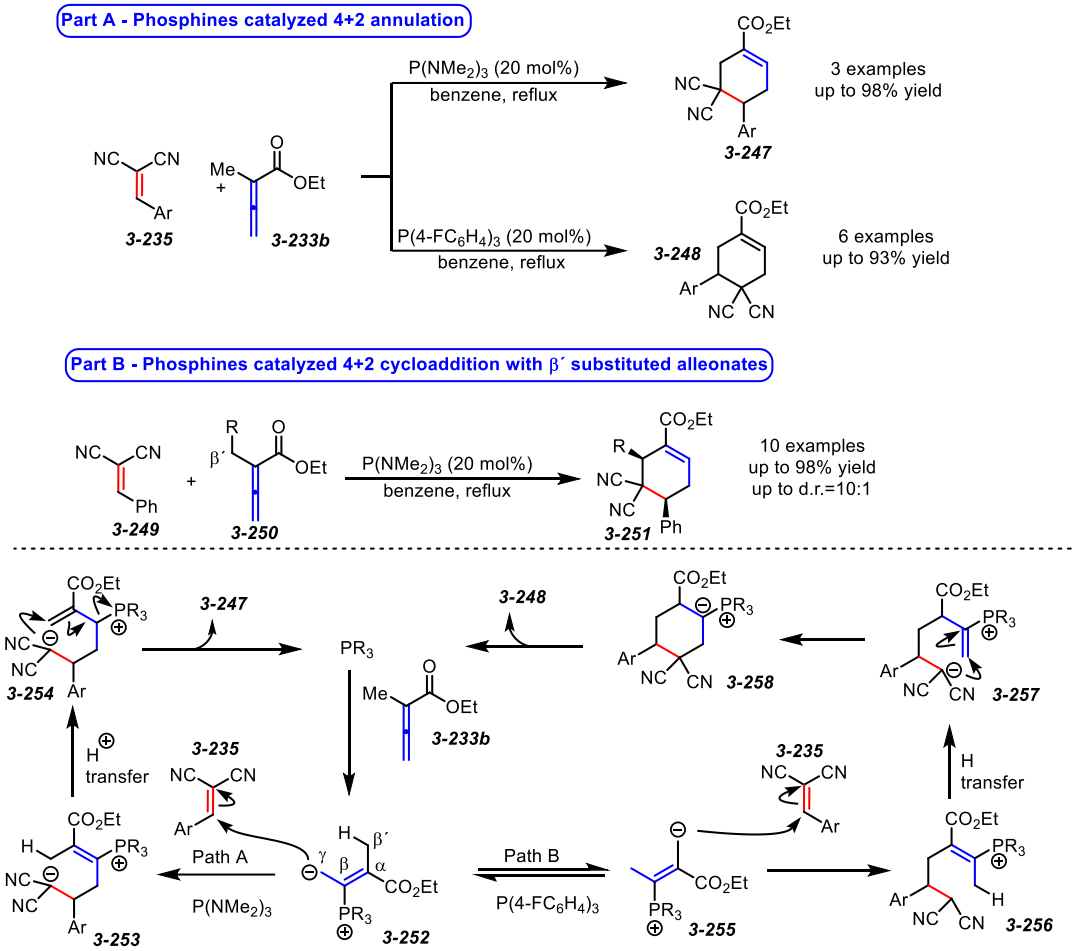
Taking into account the literature precedents, we have decided to test our **PM-2** molecules as electrophiles in NR_3 and PR_3 catalyzed reactions with allenoates ***3-233a***, ***3-250a***, and Morita-Baylis-Hillman carbonate ***3-265***. In this context, various tertiary amines and trialkyl and triaryl phosphines were evaluated (Table 37). Unfortunately, in all tested combinations, electrophile ***3-59a*** gradually decomposed. We expect that the degradation is caused by too high reactivity of ***3-59a*** in comparison with ***3-233a***, ***3-250a*** and ***3-265***. Indeed, compound ***3-59a*** contain two electrophilic sites that can serve as excellent nucleophile-attractor. Thus, we attempted to carry out reactions using the conditions where ***3-59a*** was added to the pre-mixed mixture of allenoate or MBH carbonate with DABCO or PBu_3. Unfortunately, also, in this case, the rapid degradation of ***3-59a*** was observed. Thus, we had to abandon the idea of using **PM-2** in the context of the allenoate chemistry.



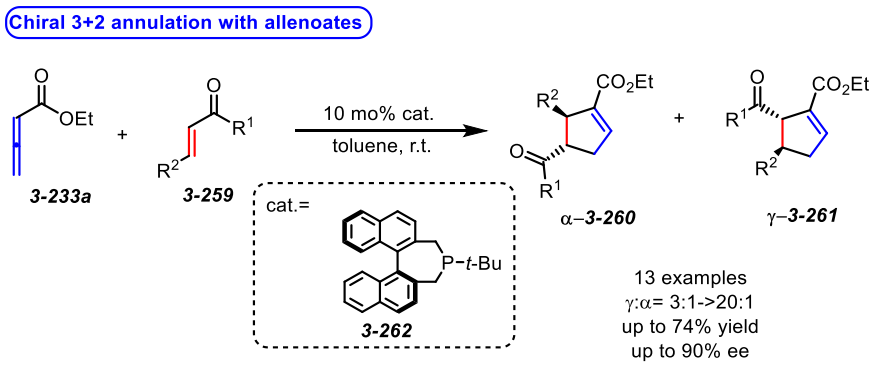
Scheme 61 – Rationalization of the reactive intermediates of allenoates[122].



*Scheme 62 – (3+2) annulation reaction of tri- and tetra-substituted olefins **3-235**, **3-237** and allenoate **3-233a**.*

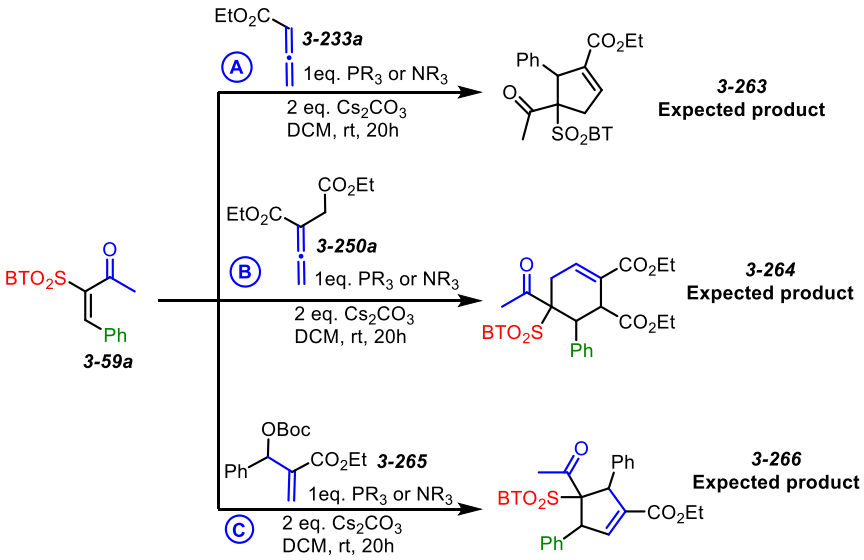


*Scheme 63 – (4+2)-annulation reaction based on the α or β´-substituted allenoate **3-233b**, **3-250** and arylydines **3-235**.*



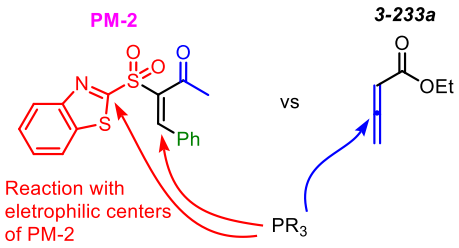
Scheme 64 – Enantioselective (3+2) annulation reaction of allenoates and chalcones.

*Table 37 - Reaction of **3-59a** with allenoates **3-233a**, **3-250a** and MBH carbonates **3-265** – attempted transformations.*



Entry	Donor (alleonate or MBH carbonate)	PR_3/NR_3	Yield of products[a] (*3-263/3-264/3-266*)	Comment
1	***3-233a***	PPh_3	n.d.	Decomposition of ***3-59a***
2	***3-233a***	PBu_3	n.d.	Decomposition of ***3-59a***
3	***3-233a***	DABCO	n.d.	Decomposition of ***3-59a***
4	***3-250a***	PPh_3	n.d.	Decomposition of ***3-59a***
5	***3-250a***	Pbu_3	n.d.	Decomposition of ***3-59a***
6	***3-250a***	DABCO	n.d.	Decomposition of ***3-59a***
7	***3-265***	PPh_3	n.d.	Decomposition of ***3-59a***
8	***3-265***	Pbu_3	n.d.	Decomposition of ***3-59a***
9	***3-265***	DABCO	n.d.	Decomposition of ***3-59a***

[a]Based on LC-MS of the crude reaction mixture.

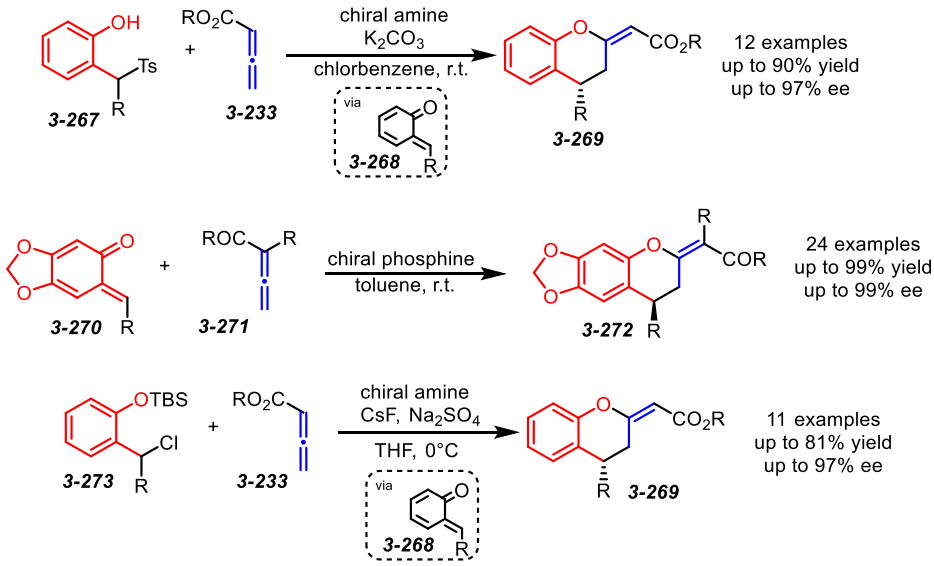


*Scheme 65 – Electrophilic centres in **3-59a** and allenoate **2-333a** prone to interact with Lewis base/nucleophile.*

3.6.5 Reactivity of Quinone-methides towards α-branched allenoates

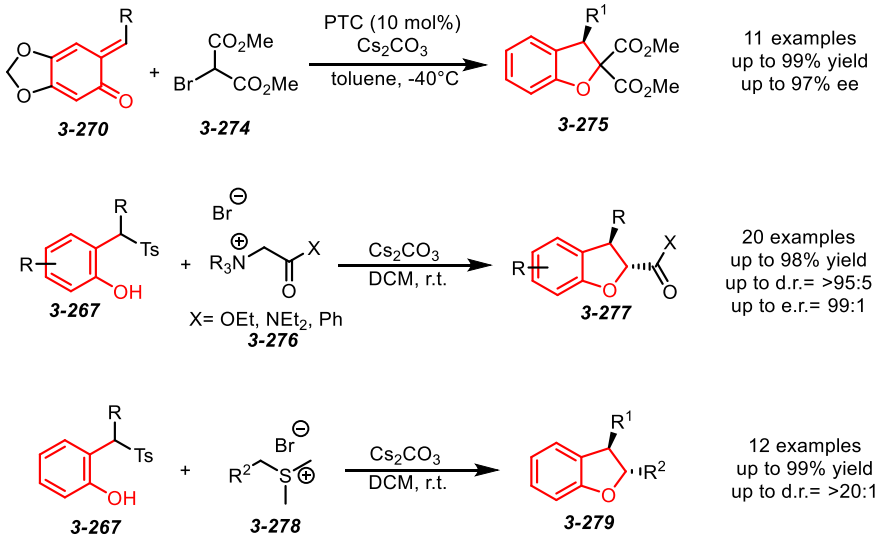
Even though our plans with the allenoates blow up, we decided to develop further the chemistry based on them. We got interested in a different type of electrophile – Quinone methides (QMs). Our interest in such compounds, and especially in the products that can be generated using them, is closely related to another project in our group – phenylpropanoid-based secondary plant metabolites and their activity against the leishmaniosis.[132,65] But before I will disclose the chemistry of QMs I was working within my Theses, I would like to mention some interesting pieces of information about Quinine-methides.

Quinone-methides are interesting building blocks for (asymmetric) diverse oriented transformations. These reactive intermediates readily undergo cyclization reactions and their growing popularity in the field of organic synthesis is closely related to their applications in the field of material chemistry, fine chemicals and pharmaceuticals.[133,134] An important class of quinone methides are *ortho*-quinone methides (*o*-QM), that can be easily exploited in a wide range of annulation reactions (4+n).[135–139] Recently, an interesting (4+2) annulations catalyzed with tertiary amines or phosphines based on *o*-QM (preformed or *in situ* generated) and allenoates (allene ketones) attracted the attention of synthetic community (Scheme 66).[136,140,141]



Scheme 66 – Recently described (4+2) annulation reactions of o-QM and allenoates.

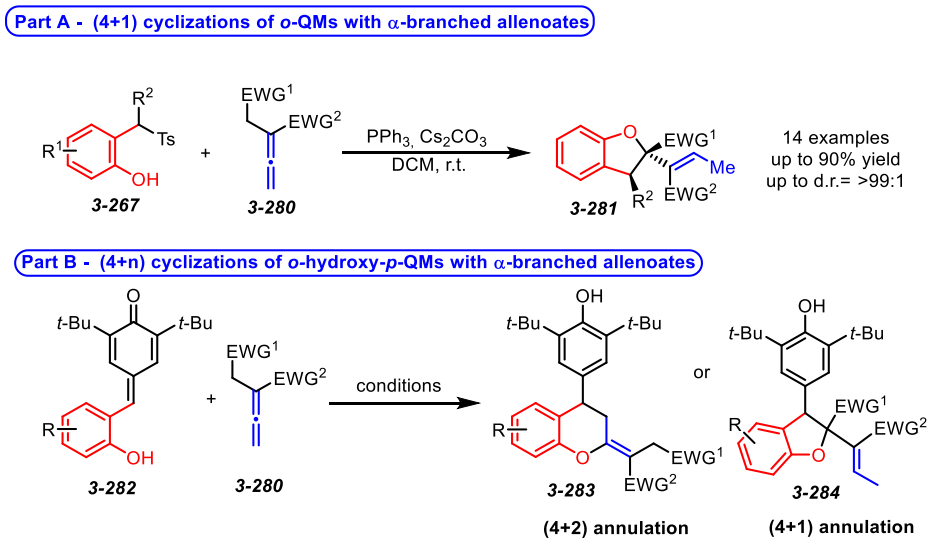
In addition, *o*-QM were also used in quite challenging (4+1) cyclization reactions with sulfonium ylides ***3-278***,[142] ammonium ylides ***3-276***,[96] and α-halocarbonyl compounds ***3-274***[143] (C1 synthon) (Scheme 67).



Scheme 67 – (4+1) annulation reactions of o-QM.

In this context, allenoates were previously used as a highly versatile C4 synthone in (4+1) cyclization reaction.[144] However, their use as C1 synthons is rather rare.[145] In such cases the reactivity of allenoates in γ or β-positions is explored. Interestingly, the β'-position, however, remains unexplored.[121] At this point, Waser group has joined the *o*-QM's rush and developed a highly enantioselective protocol for (4+1) cyclization of *in situ* generated *o*-QM with allenoates that was catalysed with chiral ammonium salts.[96] Such transformation was further studied in this group with the focus on the α-branched allenoates. And it was in this context that surprising and unexpected reactivity of such allenoates was observed. Instead of expected (4+2) cyclization reaction, (4+1) – cyclization occurred (Scheme 68, Part A).[121] At this point the research project became interesting for us since the products ***3-281*** is structurally very similar to neolignane class of secondary plant metabolites currently studied in our group[46]. To further extend the utility of this transformation, and also to prepare these interesting molecular scaffolds with the aim to test them for their biological activity, we started to collaborate with the Waser group in the field of (4+1) cyclization reactions of allenoates.

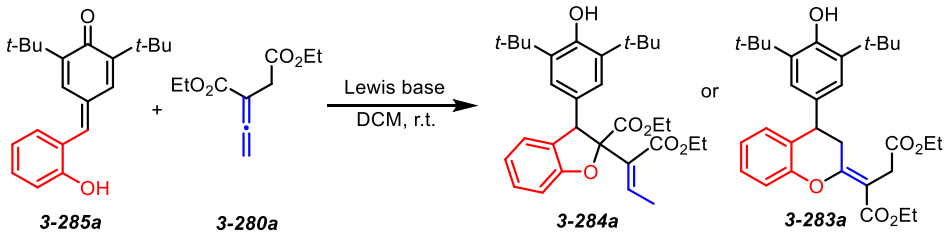
The main goal of my research was to find out which type of reactivity will be observed in case of the reaction of *ortho*-hydroxy-*para*-quinone methides (*o*-h-*p* QMs) and α-branched allenoates (Scheme 68, Part B).[146]



Scheme 68 – Part A - (4+1) annulation reactions with o-QM and α-branched allenoates; Part B - Possible cyclization reactions between o-hydroxy-p QMs.

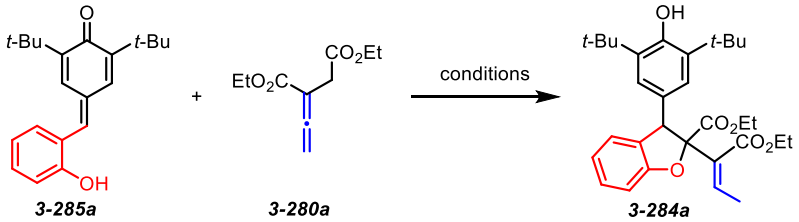
Initial screening of the reaction where *o*-h-*p* QM ***3-285a*** was reacted with allenoate ***3-280a*** in the presence of PPh_3 and DABCO catalysts, respectively, revealed mainly the formation of the (4+1) cyclization product in low yield (Table 38, entry 2). Encouraged with these results, the annulation reaction conditions were optimized with respect to the base origin, its amount, reaction temperatures, solvent and finally catalyst loading. Under the optimized conditions, the loading of PPh_3 as a catalyst could be diminished to 20mol% if K_2CO_3 (2 equiv) were used and the reaction was carried out in DCM (Table 39, entry 17).

*Table 38 - Preliminary optimization results for reaction o-h-p QM **3-285a** and α-ester allenoate **3-280a**.*



Entry	***3-285a*** (equiv)	***3-280a*** (equiv)	LB (equiv)	Base (equiv)	Temp.	Yield (***3-418*** or ***3-419***)
1	1.0	1.0	PPh_3 (1.0)	-	r.t.	n.d.
2	1.0	1.0	PPh_3 (1.0)	Cs_2CO_3 (1.0)	r.t.	***3-284a*** (25 %)
3	1.0	1.0	DABCO (1.0)	-	r.t.	n.d.
4	1.0	1.0	DABCO (1.0)	Cs_2CO_3 (1.0)	r.t.	n.d.

*Table 39 - Optimization procedure for (4+1) annulation reaction of o-h-p QM **3-285a** and allenoate **3-280a**.*



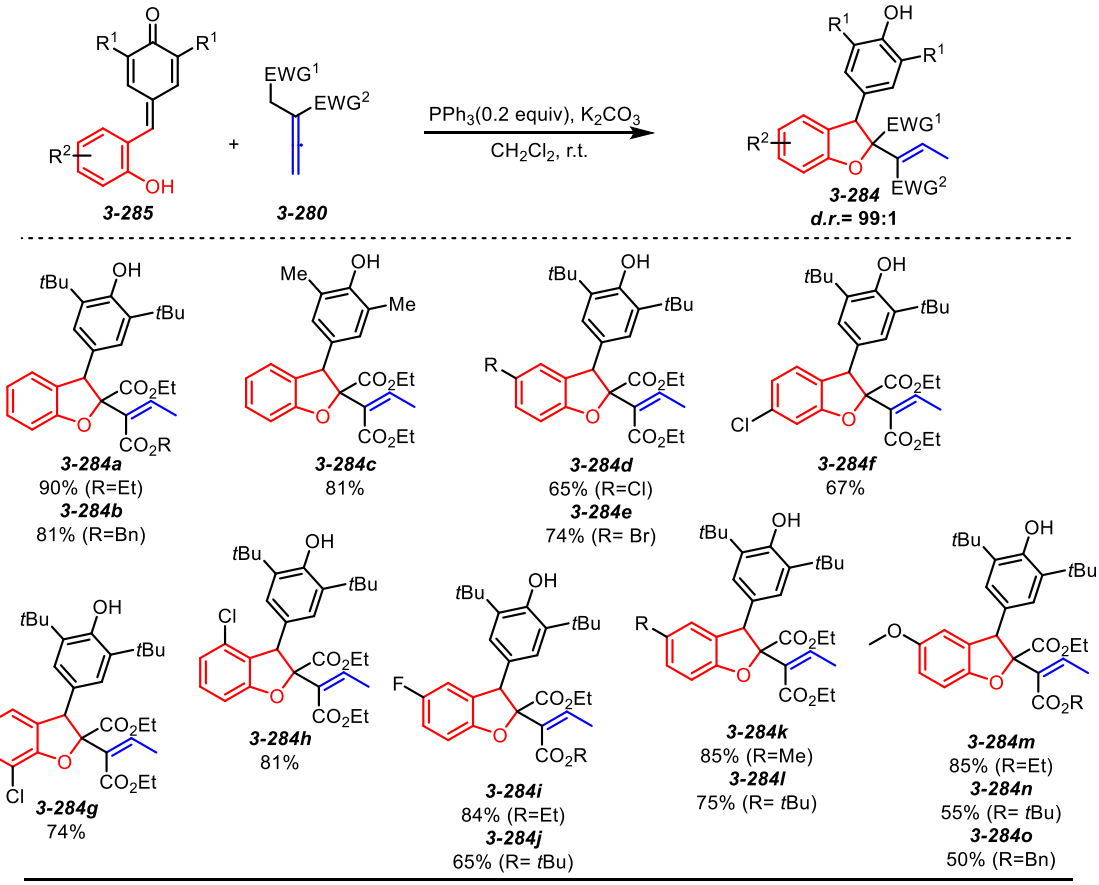
3-285a ***3-280a*** ***3-284a***

Entry	*o*-h-*p* QM (equiv)	Allene (equiv)	PPh_3 (equiv)	Base (equiv)	Solvent	Temp.	Yield[a]
1	2.0	1.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	DCM	r.t.	16 %
2	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	DCM	r.t.	30 %
3	2.0	1.0	PPh_3 (1.0)	Cs_2CO_3 (10.0)	DCM	r.t.	-
4	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	DCM	0°C	-
5	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	DCM	r.t.	33 %
6	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (0.2)	DCM	r.t.	63 %
7	1.0	2.0	PPh_3 (0.2)	Cs_2CO_3 (2.0)	DCM	r.t.	27 %
8	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	DCM	reflux	0 %
9	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	Toluene	r.t.	45 %
10	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	$CHCl_3$	r.t.	62 %
11	1.0	2.0	PPh_3 (1.0)	K_2CO_3 (2.0)	DCM	r.t.	72 %
12	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	EtOAc	r.t.	0 %
13	1.0	2.0	PPh_3 (1.0)	Cs_2CO_3 (2.0)	IPA	r.t.	0 %
14	1.0	2.0	PPh_3 (1.0)	K_2CO_3 (2.0)	DCM	r.t.	82 %
15	1.0	2.0	PPh_3 (1.0)	K_2CO_3 (1.0)	DCM	r.t.	82 %
16	1.0	2.0	-	K_2CO_3 (2.0)	DCM	r.t.	-
17	**1.0**	**2.0**	**PPh_3 (0.2)**	**K_2CO_3 (2.0)**	**DCM**	**r.t.**	**91 %**
18	1.0	2.0	PPh_3 (0.2)	-	DCM	r.t.	84 %
19	1.0	2.0	PPh_3 (0.2)	K_2CO_3 (0.5)	DCM	r.t.	89 %
20	1.0	2.0	PPh_3 (0.2)	K_2CO_3 (0.5)	DCM	r.t.	84 %
21	1.0	2.0	PPh_3 (0.2)	-	DCM	r.t.	90 %
22	1.0	1.5	PPh_3 (0.2)	-	DCM	r.t.	86 %

[a] Refers to isolated yield.

Developed method proved to be robust and tolerated various substitution on the aromatic ring (MeO, Me, *t*-Bu, halogens) of *o*-h-*p*-QM ***3-285*** and various EWG on the allenoate ***3-280***. It was observed that in the case of EWG[2], the change in substitution (from Et to *t*-Bu to Bn) had an impact on the reaction rate. More bulky substituents prolonged the reaction times and diminished the reaction yields (more unidentified side products formed) (Table 40).

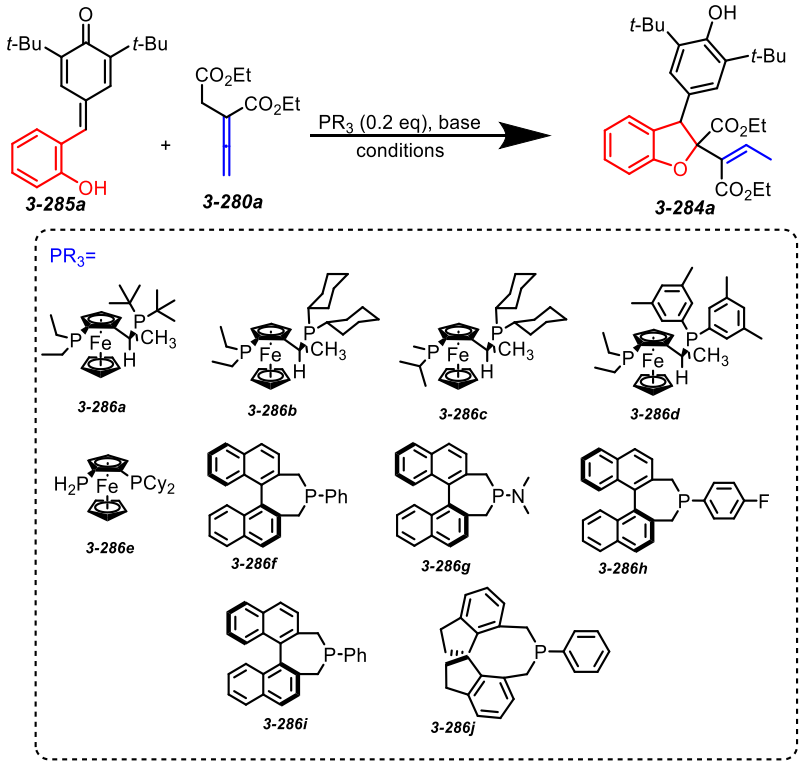
*Table 40 - Scope and limitations of the (4+1) annulation reaction of o-h-p QMs **3-285** and α-ester allenoates **3-280**.*



Yields refer to pure isolated compounds.

Having in hands a robust synthetic method, we have decided to extend the reaction to its asymmetric variation. To do so, various chiral phosphines were evaluated as the reaction promotors (Table 41). Initially, several bulky phosphines were tested (Table 41, ***3-286a – 3-286e***) but without any success. Next, our attention turned to BINAP-based chiral ligands (Table 41, ***3-286f – 3-286i***). Also, these failed to promote the reaction. Gratifyingly, when spiro phosphine (Table 41, ***3-286j***), was used as the reaction catalyst, the reaction proceeded with good yield and *e.r.* (Table 41, entry 1). Further reaction conditions screening and optimization revealed that toluene is the best solvent for the transformation, and the best *e.r.* are obtained if the reaction is carried out in the presence of K_2CO_3 (2 equiv)at 10°C (Table 41, entry 8). It should be noted, that reaction carried out under the same conditions but without base resulted in the same yield and *e.r.* (Table 41, entry 4). However, later it was observed that base-containing reactions are “more robust” towards the substrates and have better reproducibility. It proved to apply to a wide variety of substrates where base-free conditions failed (see later).

Table 41 – Towards the asymmetric version of the annulation reaction.



Entry	Phosphine	Base (equiv)	Solvent	Temperature	Yield[a]	e.r.[b]
1	***3-286j***	-	DCM	r.t.	84 %	88:12
2	***3-286j***	-	DCM	0°C	no rxn	-
3	***3-286j***	K_2CO_3 (1.0)	DCM	r.t.	70 %	87:13
4	***3-286j***	-	Toluen	r.t.	89 %	94:6
5	***3-286j***	-	THF	r.t.	85 %	86:14
6	***3-286j***	-	Toluen	10°C	no rxn	-
7	***3-286j***	K_2CO_3 (2.0)	Toluen	r.t.	80%	92:8
8	***3-286j***	**K_2CO_3 (2.0)**	**Toluen**	**10°C**	**79 %**	**94:6**
9	***3-286j***	K_2CO_3 (2.0)	Toluen	0°C	60%	93:7

[a]Isolated yields.
[b]Based on HPLC with the chiral stationary phase

Next, the scope and limitations of our method were established (Table 42). It was observed that in allenoate part (EWG^2) ethyl ester can be replaced with benzyl and even *tert*-butyl, without significant loss in reaction yields and selectivity. Replacement of the *tert* -butyl group with a methyl group in *o*-h-*p*-QM proved to be on the other hand limitation of the reaction. In this case, the product ***3-284c*** was obtained only with moderate *e.r.* = 88:12 (Table 42). In addition, substituent at C3 and C6 positions in *o*-h-*p*-QM caused a dramatic drop in observed enantioselectivity (79:21). Also, substituents at the C6 position are not tolerated under the conditions of the asymmetric protocol, and such transformation can be carried out only using the racemic version of the protocol. Gratifyingly, positions 4 and 5 were very well tolerated, and all tested reactions yielded the desired products in high yields and enantioselectivities (Table 42). It should be also pointed out that all preformed reactions

proceeded with excellent diastereoselectivity and in each case, virtually only one diastereomer was observed. The relative configuration of the final products was determined using NOE experiments (Figure 14). Unfortunately, the absolute stereochemistry was again not determined, since we were unable to grow a monocrystal suitable for X-Ray analysis.

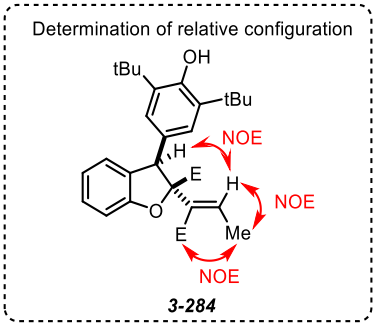
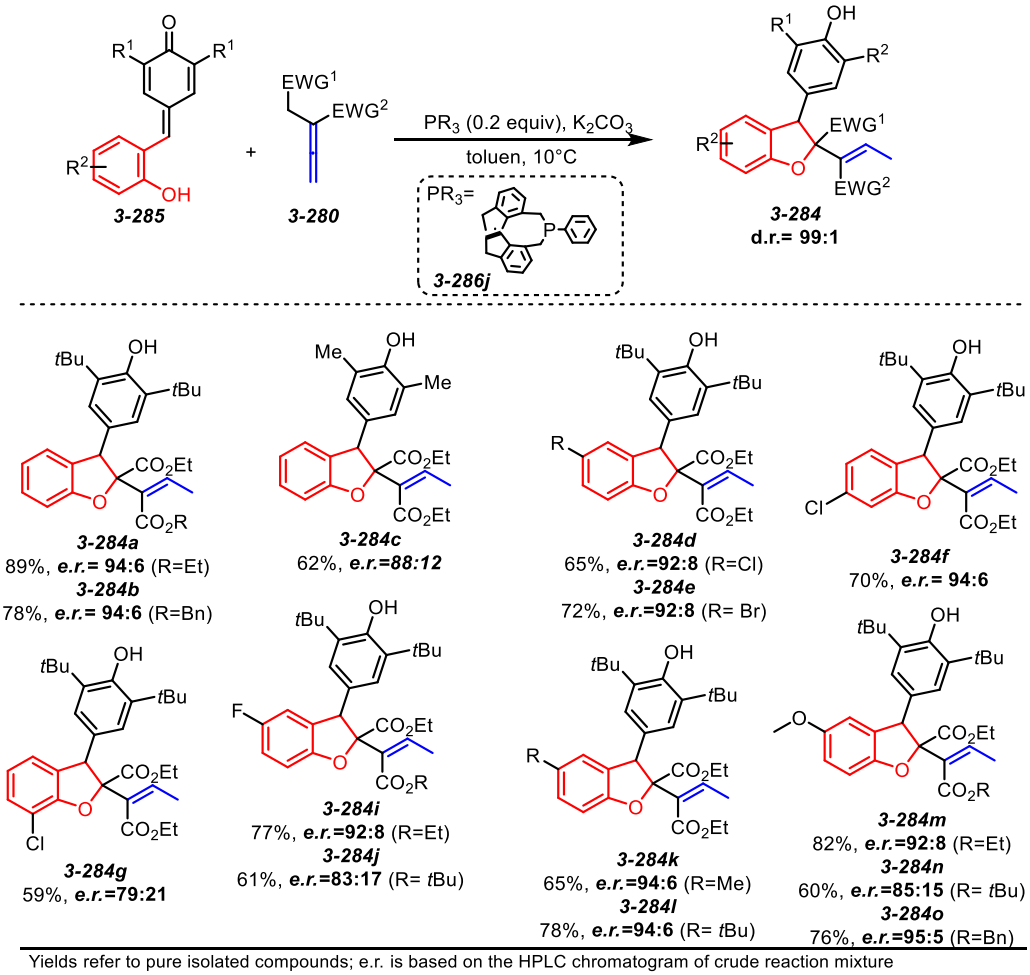


*Figure 14 – n.O.e interactions used to determine the relative stereochemistry of (4+1)-cyclization product **3-284**.*

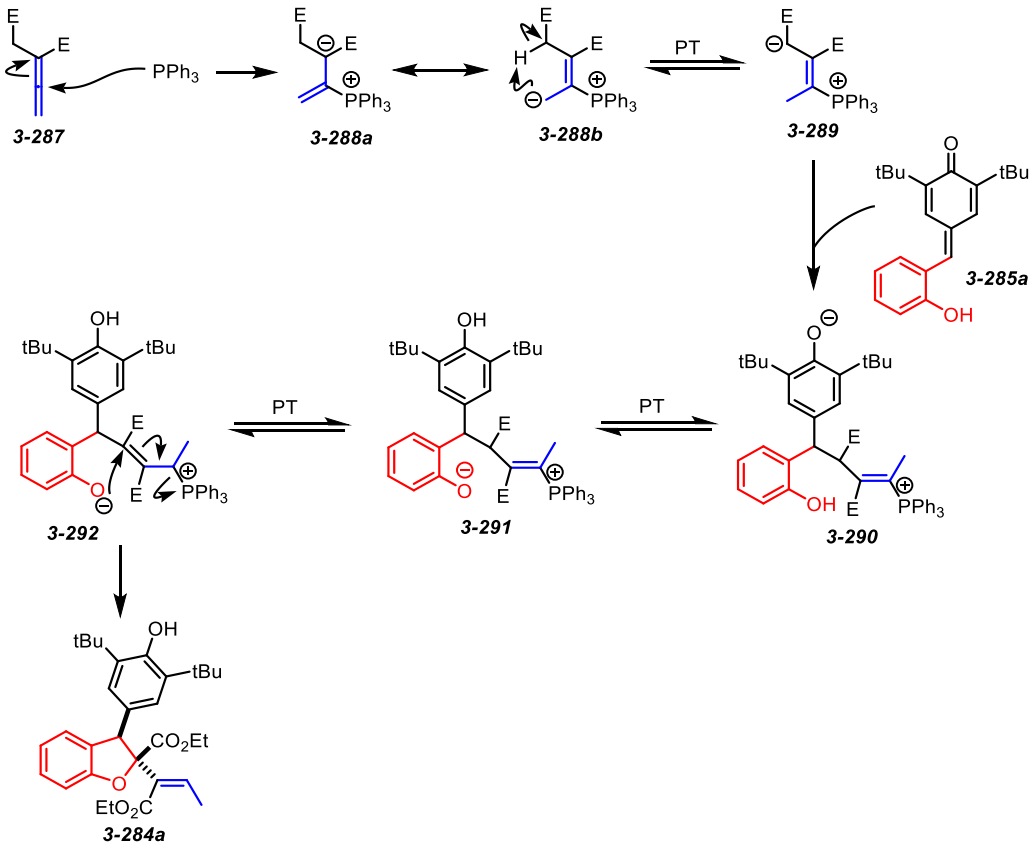
Table 42 - Scope and limitations of asymmetric (4+1) annulation reaction.



Yields refer to pure isolated compounds; e.r. is based on the HPLC chromatogram of crude reaction mixture

Finally, I would like to discuss briefly proposed reaction mechanism of this transformation (Scheme 69). The mechanism is rather speculative since there are not enough experiment- and theory-based insides into it.[121] The whole process begins presumably with the activation of the allenoate with

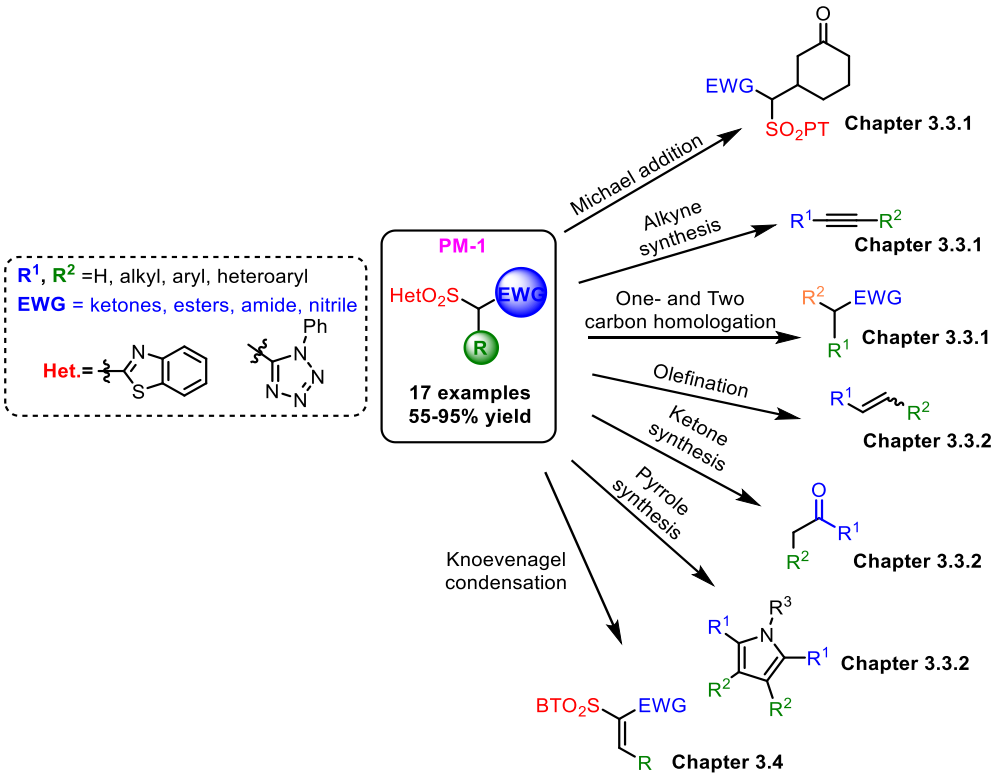
PPh_3. Zwitterion ***3-288a*** is formed and then the proton transfer occurs. Generated β-stabilized anion ***3-289***, then adds to the electrophile (QM). Subsequently, a series of proton transfers followed with 5-*exo*-dig cyclization occurs, and the catalyst is released to regenerate the cycle and yields the desired product ***3-284a***. For more information about mechanistic experiments and observations connected with the transformation, see appendices 7.2.



*Scheme 69 – Proposed mechanism leading to the formation of **3-284a**.*

4 Conclusion and Perspectives

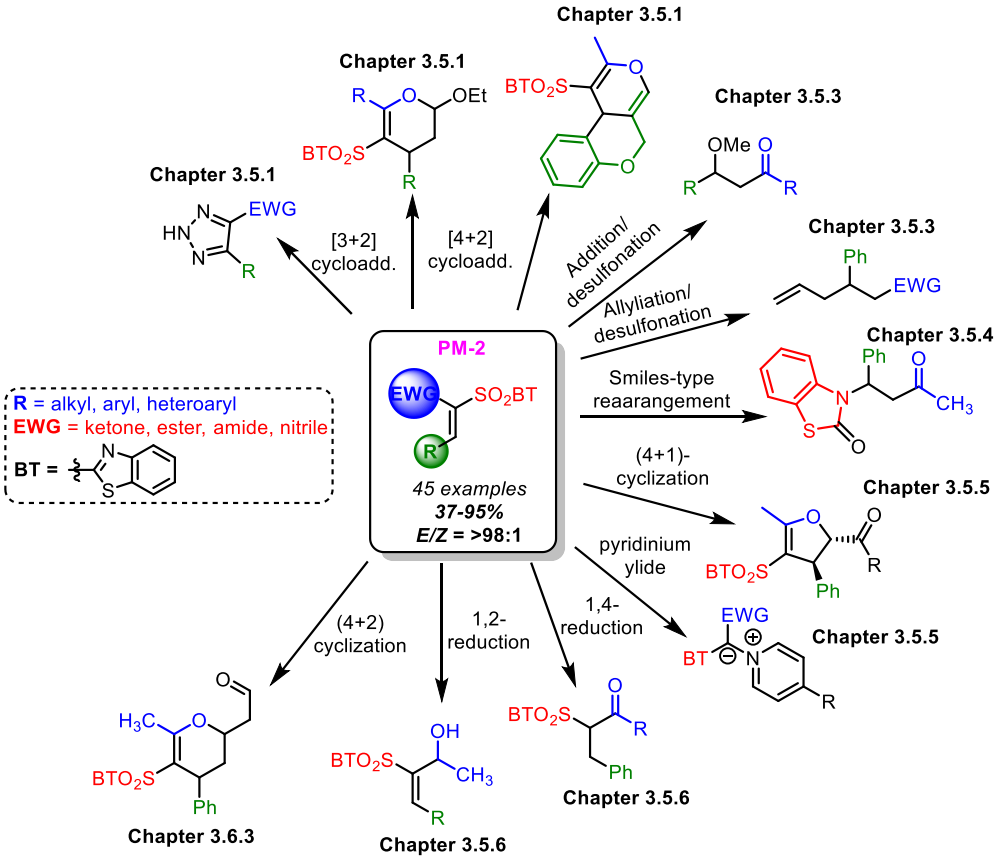
The presented Ph.D. Thesis covers mainly the area of Diversity-oriented synthesis. For this purpose, we have chosen a strategy that aims to develop and utilize Pluripotent molecules (**PM**), that is based on the benzo[d]thiazol-2-yl sulfones. First, we focused on the use of the **PM-1** molecules, which is already known from the literature, but our goal was the "push the limit" of this molecule. In our case, we used **PM-1** molecule in one or two-carbon homologation with application to the modification of natural products (Ingenol). Subsequently, we pushed the limit further and succeeded in developing a new type of one-pot protocol that allows the stereoselective formation of a C=C bond depending on the reaction conditions. In addition, we have further optimized this protocol and now we are able to prepare alkynes, ketones, esters and heterocyclic compounds (pyrroles) using the one-pot procedure (Scheme 70).



*Scheme 70 – **PM-1** the reactivity in the context of Diversity-oriented synthesis.*

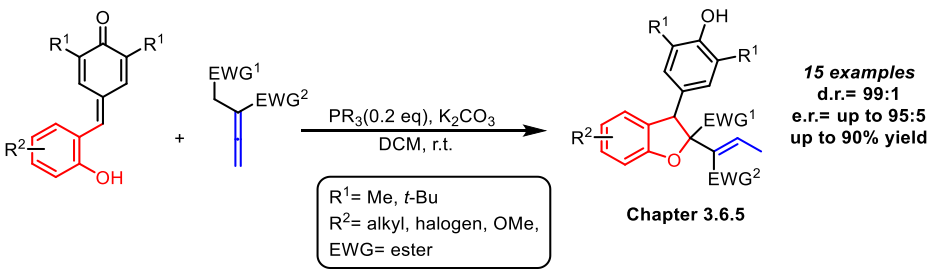
PM-1 molecule was used as a starting material in the formal Knoevenagel reaction, which allowed us to prepare a new type of pluripotent reagent with more reactive centres. The development and optimization reaction condition of the Knoevenagel reaction using Lewis acid allowed us to prepare around 50 examples of **PM-2** molecules. An easy approach leading to the preparation of the **PM-2** molecules allowed us to subsequently study its reactivity depending on the reaction conditions. The **PM-2** molecule was successfully used in cycloaddition reactions ((3+2), [4+2]). The electrophilic properties of the **PM-2** molecule were evaluated using different nucleophiles (O, S,

N, C). This screening allowed us to discover new "unplanned" transformations, which led to the formation of enantioenriched dihydrofurans ((4+1) cyclization), a new type of pyridinium ylides and intramolecular Smiles-type rearrangement. Finally, the **PM-2** molecule could be employed in (4+2) cyclization reaction catalyzed by Hayashi-Jørgensen catalyst. Moreover, the desired products of formal (4+2) cycloaddition could be further modified (one-pot) to increase product diversification (reduction, Wittig reaction) (Scheme 71)



*Scheme 71 – **PM-2** reactivity in context of the Diversity-oriented synthesis.*

Expansion to the field of organocatalysis opens us imaginable "gate" to possible collaborations, namely to Prof. Waser (JKU, Linz, Austria). The fruitful collaboration allowed us to disclose the new type of cyclization (4+1) based on the use of allenoates and *ortho*-hydroxy-*para* Quinone methides.



Scheme 72 – Unprecedented (4+1) cyclization of allenoates and o-h-p-QMs.

I would like to conclude that the chemistry and reactivity of **PM-1** molecules are rich and interesting. Yet, one of the best achievements was the development of a one-pot protocol employing such molecule., which is diverse itself. However, exploring the reactivity of the **PM-2** molecules overcome our expectations and the transformations led to the preparation of interesting structural motifs. Hopefully, we have shown that the **PM-2** molecule will be a valuable tool for creating diversity in the context of molecular structures.

Talking about the future directions for the **PM-1** and **PM-2** molecule, there are countless possibilities. Above all, we would like to further optimize the one-pot protocol for the preparation of pyrroles and apply it to prepare other heterocycles as furans, thiophenes, or focus on the development of a method for preparation of non-symmetrical heterocycles. Furthermore, we would like to study in detail intramolecular Smiles-type rearrangement, to study its mechanism, and to define the scope and limitations of the process with the aim to extend the method to β-amino acid synthesis. Probably the biggest challenge will be developing a methodology based on pyridinium ylides (source of diazo free carbenes) and their application in organic synthesis. The field of the organocatalysis is also promising area for **PM-2** molecules. In this context, we should focus on optimizing (4+2)-cyclization reaction and increased the enantioselectivity for the reaction.

From a long-term perspective, the main goal will be to move towards the next level – the application of **PM-1** and **PM-2** in the field of total synthesis of natural products and their modification.

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6 Experimental part

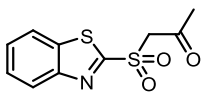
General information. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. Progress of reactions was monitored by thin-layer chromatography (TLC) - aluminium plates pre-coated with silica gel (silica gel 60 F254). Column chromatography was performed on silica gel 60 (40-63 µm) or neutralized silica gel (40-63 µm) using 5% solution of Et_3N in petroleum ether. Reactions carried out at elevated temperatures were carried out using the oil bath and indicated temperatures refer to the oil bath temperature. Determination of melting points was done on a Büchi melting point apparatus and was uncorrected. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were measured on Bruker Avance III 300 MHz spectrometer with a broad band observe probe, Jeol ECA400II (400 and 101 MHz) or Jeol 500 ECA (500 and 126 MHz) in $CDCl_3$ or DMSO. Chemical shifts are reported in ppm and their calibration was performed (a) in case of ^{1}H NMR experiments on residual peak of non-deuterated solvent δ ($CHCl_3$) = 7.26 ppm; δ (DMSO) = 2.50 ppm, (b) in case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CDCl_3$) = 77.2 ppm; δ (DMSO-d_6) = 39.5 ppm, and (c) in case of ^{19}F{^{1}H} NMR experiments on the external calibrant $CFCl_3$ (δ ($CFCl_3$) = 0 ppm). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt) and multiplet (m). HRMS data were obtained using the quadrupole/ion trap mass analyzer. HPLC was performed using a Dionex Summit HPLC system with a CHIRAL ART Cellulose-SB (250 x 4.6 mm, 5 µm) or CHIRALPAK IE-3 chiral stationary phase with mobile phase 2-propanol/hexane, 2-propanol/CO_2, MeOH/CO_2. HRMS analysis was performed using LC chromatography (Dionex UltiMate 3000, Thermo Fischer Scientific, MA, USA) + mass spectrometer Exactive Plus Orbitrap high-resolution (Thermo Fischer Scientific, MA, USA) with electrospray ionization; Chromatographic separation: column Phenomenex Gemini (C18, 50 x 2 mm, 3 µm particle), isocratic elution, MP: 80 % ACN and 20 % buffer (0,01M ammonium acetate) or 95% MeOH + 5% water + 0.1% HCOOH. Microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 mL glass vials sealed with a Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

Chiral aldehyde ***3-7***[147], pyridium salts ***3-160***[148], chiral ammonium salts ***3-152***[96,97], BT-sulfones ***3-13a***[60,61]**,** ***3-154***[149] (α)-2-menthyl 2-bromoacetate[150], catalyst ***3-202d***[119],*o*-h-*p* QM ***3-285*** [151], allenoates ***3-280***[152,153] and were prepared using reported procedures.

Synthesis of α-electron-withdrawing BT-sulfones (PM-1)

Method A. *Synthesis of sulfide intermediate.* A mercaptobenzthiazole (10.0 g, 1.0 equiv) and α-halo compound (1.0 equiv) were dissolved in CH_2Cl_2 (0.2 M) and the mixture was cooled to 0°C. Triethylamine (8.6 mL, 2.0 equiv) was added dropwise and resulting mixture was allowed warm to r.t. and stirred for 4 hours. 2 M aq. HCl (20 mL) was added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x20 mL) and the resulting organic extracts were combined, washed with water (30 mL), brine (20 mL), dried over $MgSO_4$ and solvents were evaporated under reduced pressure. Crude product was used in the next step without further purification. *Synthesis of targeted sulfone.* Sulfide (1.1 g, 1.0 equiv) and periodic acid (2.8 g, 3.0 equiv) were dissolved in acetonitrile (0.2 M) and mixture was cooled to 0°C. CrO_3 (0.123 g, 0.3 equiv) was added portion wise and the resulting mixture stirred for 30 minutes, before it was warmed to r.t. The reaction was stirred for another 4 hours before it was cooled to 0°C and quenched by adding sat. aq. Na_2SO_3. Filtration over the Celite®, washed (5x25 mL EtOAc). Layers were separated, and organic phase was washed with sat. Na_2SO_3 (2x20 mL), water (2x20mL), brine (2x20mL) and dried over $MgSO_4$. Solvents were removed under the reduced pressure. **Method B.** A solution of -(methylsulfonyl)benzo[d]thiazole[25,26] (0.300 g, 1.41 mmol, 1.0 equiv) in dry THF (7.0 mL, 0.2 M) was cooled to -78°C and LiHMDS (1.0 M sol. in THF) (3.7 mL, 2.2 equiv) was added dropwise. A color of the reaction mixture turned from colorless or slightly yellow to orange/red. Immediately after, a solution of acyl halide (1.69 mmol, 1.2 equiv) in THF (3 mL) was added. The color of the reaction mixture faded within few minutes. The resulting mixture was stirred at -78°C for 60 min, allowed to warm to r.t. within 1h, and stirred at r.t. for additional 60 min before sat. aq. NH_4Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3x75 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Resulting crude product was used further without any purification, if not stated otherwise.

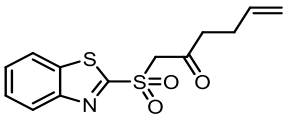
*1-(benzo[d]thiazol-2-ylsulfonyl)propan-2-one (**3-15a**)*.



3-15c

Crude product was prepared using the method A and obtained with enough purity as yellow solid (4.2 g, 89%). M.p. = 125-127°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.03 – 7.99 (m, 1H), 7.67 – 7.57 (m, 2H), 4.57 (s, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 194.7, 164.9, 152.5, 137.0, 128.4, 127.9, 125.7, 122.5, 65.5, 31.6; MS (ESI), m/z (%) 256 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M - H]^-$ Calcd for $C_{10}H_8NO_3S_2$ 253.9951; Found 253.9950.

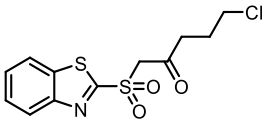
*1-(benzo[d]thiazol-2-ylsulfonyl)hex-5-en-2-one (**3-15g**)*.



3-15g

Crude product was prepared using the method B and purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 6), isolated as a yellow oil (1.4 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.19 (m, 1H), 8.05 – 8.00 (m, 1H), 7.67 – 7.58 (m, 2H), 5.81 – 5.70 (m, 1H), 5.08 – 4.95 (m, 2H), 4.59 (s, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.41 – 2.29 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.4, 165.0, 152.5, 137.0, 136.0, 128.4, 127.9, 125.7, 122.5, 116.1, 64.7, 43.6, 27.1; MS (ESI), m/z (%) 294 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_3S_2$ 296.0410; Found 296.0407.

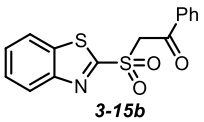
*1-(benzo[d]thiazol-2-ylsulfonyl)-5-chloropentan-2-one (**3-15e**)*.



3-15e

Crude product was prepared using method B and purified using flash column chromatography (SiO_2; Et_2O: P.E. = 3: 1), isolated as an orange oil (0.485 g, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.20 (m, 1H), 8.04 – 8.01 (m, 1H), 7.68 – 7.59 (m, 2H), 4.61 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.12 – 2.02 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.2, 164.9, 152.5, 137.0, 128.5, 128.0, 125.7, 122.6, 64.9, 43.8, 41.3, 26.0; MS (ESI), m/z (%) 282 $[M-Cl]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{13}ClNO_3S_2$ 318.0020; Found 318.0021.

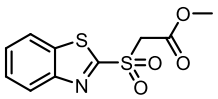
*2-(benzo[d]thiazol-2-ylsulfonyl)-1-phenylethan-1-one (**3-15b**)*.



3-15b

Crude product was prepared using the method A and obtained with enough purity as a light brown solid (3.9 g, 92%). M.p. = 118-120°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.18 (m, 1H), 8.02 – 7.99 (m, 1H), 7.95 – 7.90 (m, 2H), 7.66 – 7.57 (m, 3H), 7.50 – 7.44 (m, 2H), 5.20 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 187.3, 165.4, 152.6, 137.2, 135.6, 134.8, 129.1, 129.1, 128.3, 127.8, 125.7, 122.5, 61.3; MS (ESI), m/z (%) 318 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{12}NO_3S_2$ 318.0253; Found 318.0251.

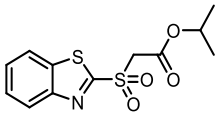
*methyl 2-(benzo[d]thiazol-2-ylsulfonyl)acetate (**3-15c**)*.



3-15c

Crude product was prepared using the method A and obtained as a yellow solid (2.8 g, 88%). M.p. = 68-70°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.21 (m, 1H), 8.04 – 8.01 (m, 1H), 7.68 – 7.59 (m, 2H), 4.58 (s, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.0, 162.3, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 58.7, 53.5; MS (ESI), m/z (%) 272 $[M+H]^+$ (27); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_4S_2$ 272.0046; Found 272.0043.

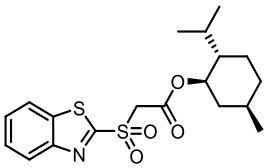
*isopropyl 2-(benzo[d]thiazol-2-ylsulfonyl)acetate (**3-15j**)*.



3-15j

Crude product was prepared using the method B and obtained as a light yellow solid (0.199 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.21 (m, 1H), 8.08 – 7.99 (m, 1H), 7.68 – 7.58 (m, 2H), 5.00 (hept, *J* = 6.4 Hz, 1H), 4.54 (s, 2H), 1.15 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.2, 161.2, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 71.1, 59.1, 21.6; MS (ESI), m/z (%) 298 $[M-H]^-$ (100); HR-MS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{13}NO_4S_2$ 299.0286; Found 299.0284.

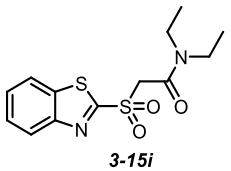
*(2S,5R)-2-isopropyl-5-methylcyclohexyl 2-(benzo[d]thiazol-2-ylsulfonyl)acetate (**3-15f**)*.



3-15f

Crude product was prepared using the method A from (–)-2-menthyl 2-bromoacetate and obtained with enough purity as a green viscose syrup (2.24 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.17 (m, 1H), 8.07 – 7.97 (m, 1H), 7.69 – 7.54 (m, 2H), 4.65 (td, *J* = 10.8, 4.4 Hz, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 15.2 Hz, 1H) 1.97 – 1.85 (m, 1H), 1.69 – 1.52 (m, 3H), 1.47 – 1.31 (m, 1H), 1.24 – 1.10 (m, 1H), 1.03 – 0.84 (m, 2H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.84 – 0.67 (m, 1H), 0.68 (d, *J* = 7.2 Hz, 3H), 0.61 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.3, 161.3, 152.6, 137.0, 128.3, 127.9, 125.6, 122.5, 58.9, 46.7, 40.4, 34.1, 31.4, 26.0, 23.1, 22.0, 20.6, 16.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd. for $C_{19}H_{26}NO_4S_2$ 396.1298; Found 396.1300; α_D^{22}= - 32.5 (c 0.2, $CHCl_3$).

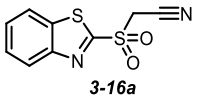
*2-(benzo[d]thiazol-2-ylsulfonyl)-N,N-diethylacetamide (**3-15i**)*.



3-15i

Crude product was prepared using the method B and purified using flash column chromatography (SiO_2; EtOAc: P.E. = 3:1), isolated as a yellow solid (0.366 g, 84%). M.p. = 125-126°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.20 (m, 1H), 8.01 – 7.98 (m, 1H), 7.64 – 7.55 (m, 2H), 4.63 (s, 2H), 3.46 (q, *J* = 7.2 Hz, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.5, 160.0, 152.6, 137.4, 128.1, 127.7, 125.7, 122.6, 58.0, 43.3, 41.1, 14.6, 12.9; MS (ESI), m/z (%) 313 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{16}N_2NaO_3S_2$ 335.0495; Found 335.0494.

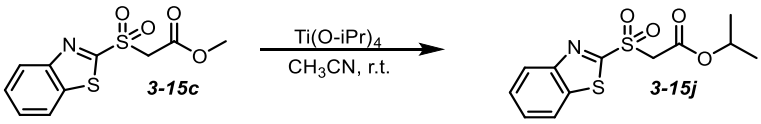
*2-(benzo[d]thiazol-2-ylsulfonyl)acetonitrile (**3-16a**)*.



3-16a

Crude product was prepared using the method A and obtained with enough purity as a brown solid (3.4 g, 95%). M.p. = 172-174°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 – 8.25 (m, 1H), 8.09 – 8.05 (m, 1H), 7.74 – 7.65 (m, 2H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.5, 152.4, 137.3, 129.1, 128.4, 126.0, 122.7, 109.2, 44.1; MS (ESI), *m/z* (%) 237 $[M-H]^-$ (25); HRMS (ESI) *m/z*: $[M - H]^-$ calcd for $C_9H_5N_2O_2S_2$: 236.9798, found 236.9798.

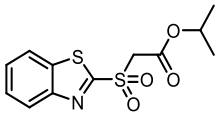
Ti(O-*i*Pr)$_4$-mediated transesterification



3-15c ***3-15j***

To solution of sulfone ***3-15c*** (0.200 g, 0.73 mmol, 1.0 equiv) in CH_3CN (4.0 mL, 0.2 M), Ti(O-*i*Pr)$_4$ (0.435 mL, 1.46 mmol, 2.0 equiv) was added dropwise at r.t. and the resulting mixture was stirred for 2h. CH_2Cl_2 (15 mL) and sat. aq. NH_4Cl (5 mL) were added and the resulting mixture was filtered through Celite®. Filtrate cake was washed with CH_2Cl_2 (5x20mL) and combined filtrates were washed with sat. aq. NH_4Cl (2x15 mL), brine (2x15 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude product was isolated as a light yellow solid (0.219 g, 95%).

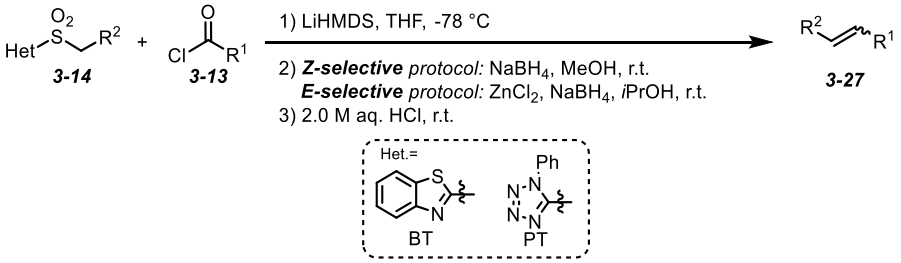
*isopropyl 2-(benzo[d]thiazol-2-ylsulfonyl)acetate (**3-15j**)*



3-15j

Crude product was isolated as a light yellow solid (0.199 g, 90%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 8.24 – 8.21 (m, 1H), 8.08 – 7.99 (m, 1H), 7.68 – 7.58 (m, 2H), 5.00 (hept, *J* = 6.4 Hz, 1H), 4.54 (s, 2H), 1.15 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ(ppm): 165.2, 161.2, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 71.1, 59.1, 21.6; MS (ESI): m/z (%) 298 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{13}NO_4S_2$ 299.0286; Found 299.0284.

One-pot olefination protocol



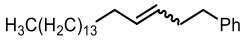
(*Z*)-selective one-pot olefination protocol

The sulfone ***3-14*** (1 mmol; 1.0 equiv) was dissolved in dry THF (0.1M) and cooled to −78 °C (acetone/dry ice). After 5 minutes, LiHMDS (2.2 mmol; 2.2 equiv; 1.0 M solution in THF) was added dropwise and the reaction mixture immediately turned to light orange. Subsequently, acyl chloride ***3-13*** (1.1 mmol; 1.1 equiv) was added over 5 minutes. The resulting reaction mixture was allowed to stir at −78 ° C for 30 minutes. The cooling bath was then removed, and the reaction mixture was stirred for an additional 20 minutes at r.t. MeOH (10 mL; 0.1M) was added and the reactive mixture was stirred for 5 minutes at r.t., before $NaBH_4$ or $NaBD_4$ (10 mmol; 10 equiv) was added. The resulted reaction mixture was stirred for another 15 h at r.t. Afterwards, the reaction was cooled to 0 °C and quenched by addition of 2M HCl (20 mL). The resulting reaction mixture was stirred at r.t. for 1 h. The resulting phases were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (10 mL), brine (15 mL), dried over Na_2SO_4 and volatiles were evaporated under reduced pressure to provide the crude product.

(*E*)-selective one-pot olefination protocol

The sulfone ***3-14*** (1 mmol; 1.0 equiv) was dissolved in dry THF (0.1M) and cooled to −78 °C (acetone / dry ice). After 5 minutes, LiHMDS (2.2 mmol; 2.2 equiv; 1.0 M solution in THF) was added dropwise and the reaction mixture immediately turned light orange. Subsequently, acyl chloride ***3-13*** (1.1 mmol; 1.1 equiv) was added over 5 minutes. The resulting reaction mixture was allowed to stir at −78 ° C for 30 minutes. The cooling bath was then removed, and the reaction mixture was stirred for an additional 20 minutes at r.t. 2-Propanol (1.0M) was added and the reaction mixture was stirred at r.t. for 5 minutes. Subsequently, anhydrous $ZnCl_2$ (5 mmol; 5.0 equiv) was added and the resulting suspension was stirred for an additional 5 minutes and $NaBH_4$ or $NaBD_4$ (10 mmol; 10 equiv) was added and the reaction mixture was stirred at r.t. for another 15 hours. Afterwards, the reaction was cooled to 0 °C and quenched by addition of 2M HCl (20 mL). The resulting reaction mixture was stirred at r.t. for 1 h. The resulting phases were separated, and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (10 mL), brine (15 mL), dried over Na_2SO_4 and volatiles were evaporated under reduced pressure to provide the crude product.

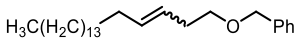
*nonadec-3-en-1-ylbenzene (**3-37i**)*



3-37i

Starting from sulfone ***3-13c*** (0.317 g, 1.0 equiv). *Z* and *E*-selective protocols were used to yield crude product, that was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 4) and isolated as a colorless oil (*Z*-selective protocol: 0.117 g, 34%, *E*/*Z*= 75:25; *E*-selective protocol: 0.029 g, 8%, *E*/*Z*= 96:4); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 5.46 – 5.34 (m, 2H), 2.72 – 2.61 (m, 2H), 2.42 – 2.25 (m, 2H), 2.02 – 1.92 (m, 2H), 1.26 (s, 26H), 0.88 (d, *J* = 5.7 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ(ppm): 142.3, 142.3 (*Z*-isomer), 131.3 (*Z*-isomer), 130.9, 129.3 (*Z*-isomer) 128.7, 128.3 (*Z*-isomer), 128.6, 128.4, 125.9, 125.7 (*Z*-isomer), 36.3 (*Z*-isomer), 36.2, 34.5 (*Z*-isomer), 32.7 (*Z*-isomer), 32.1, 29.9, 29.7, 29.5, 29.5, 29.4 (*Z*-isomer), 29.3, 29.2 (*Z*-isomer), 27.4, 22.9, 14.3; HR-MS (ESI) *m*/*z*: $[M]^+$ *calcd.* for $C_{25}H_{42}$ 269.2143; Found 269.2142

*((nonadec-3-en-1-yloxy)methyl)) benzene (**3-37j**)*

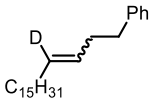


3-37j

Starting from sulfone ***3-13d*** (0.200 g, 1.0 equiv). *Z* and *E*-selective protocols were used to yield crude product, that was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 3) and isolated as a colorless oil (*Z*-selective protocol: 0.103 g, 46%, *E*/*Z*= 99:1; *E*-selective protocol: 0.103 g, 46%, *E*/*Z*= 88:12); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 7.36 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 5.51 – 5.44

(m, 1H), 5.43 – 5.35 (m, 1H), 4.53 (s, 2H), 3.48 (t, *J* = 7.1 Hz, 2H), 2.45 – 2.32 (m, 2H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.26 (s, 26H), 0.88 (d, *J* = 13.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ(ppm): 138.7, 132.3, 128.5, 127.8, 127.6, 125.5, 73.0, 70.2, 32.1, 29.9, 29.8, 29.7, 29.5, 29.5, 28.1, 27.5, 22.9, 14.3; HR-MS (ESI) *calcd.* for $C_{26}H_{44}O$ $[M+H]^+$: 372.3392; Found 372.3392

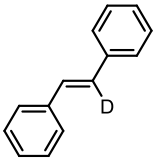
*nonadec-3-en-1-yl-4-d benzene (**3-50c**)*



3-50c

Starting from sulfone ***3-13c*** (0.200 g, 1.0 equiv). *Z* and *E*-selective protocols were used to yield crude product, that was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 6) and isolated as a colorless oil (*Z*-selective protocol: 0.054 g, 26%, *E*/*Z*= 75:25; *E*-selective protocol: 0.016 g, 8%, *E*/*Z*= 67:33); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 5.47 – 5.36 (m, 1H), 2.66 (td, *J* = 7.9, 3.4 Hz, 2H), 2.39 – 2.27 (m, 2H), 2.03 – 1.92 (m, 2H), 1.26 (s, 26H), 0.91 – 0.85 (m, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-d) δ(ppm): 142.3, 130.5 (t, *J* = 23.0 Hz), 129.3, 128.7 (*Z*-isomer), 128.6, 128.4, 125.9, 125.8 (*Z*-isomer), 36.3 (*Z*-isomer), 36.2, 34.6 (*Z*-isomer), 32.6 (*Z*-isomer), 32.1, 29.9, 29.7, 29.5, 29.5, 29.3, 27.4 (*Z*-isomer), 27.3, 22.9.; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{25}H_{42}D$ 344.3422; Found 344.3423.

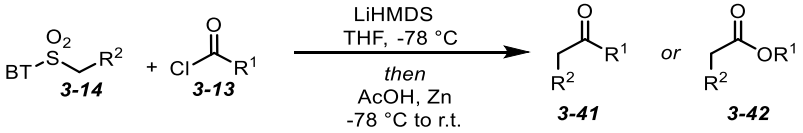
*(E)-(ethene-1,2-diyl-1-d)dibenzene (**3-50e**)*



3-50e

Starting from sulfone ***3-14a*** (0.200 g, 1.0 equiv). *Z*-selective protocols were used to yield crude product, that was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 5) and isolated as a colorless oil (*Z*-selective protocol: 0.090 g, 72%, *E*/*Z*= 88:12; ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 7.58 – 7.44 (m, 4H), 7.41 – 7.32 (m, 4H), 7.30 – 7.22 (m, 1H), 7.13 – 7.07 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ(ppm): 137.4, 137.3, 128.8, 128.7, 127.7, 126.6; HRMS (ESI) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{12}D$ 182.1075; Found 182.1074

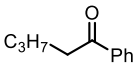
One-pot protocol for ketones and esters preparation



3-14 ***3-13*** ***3-41*** ***3-42***

The sulfone ***3-14*** (1 mmol; 1.0 equiv) was dissolved in dry THF (0.1M) and cooled to −78 °C (acetone/dry ice). After 5 minutes, LiHMDS (2.2 mmol; 2.2 equiv; 1.0 M solution in THF) was added dropwise and the reaction mixture immediately turned light orange. Subsequently, acyl chloride ***3-13*** (1.1 mmol; 1.1 equiv) was added over 5 minutes. The resulting reaction mixture was allowed to stir at −78 ° C for 30 minutes. Glacial AcOH (5 mL; 0.2M) was added and the reaction mixture stirred at −78 ° C for an additional 5 minutes. To this mixture Zn powder (5 mmol; 5.0 equiv) was added and the cooling bath was removed. The resulting reaction mixture was allowed to warm spontaneously to r.t., then stirred for 9 hours. The reaction was quenched upon addition of EtOAc (20 mL) and the whole solution was filtered through Celite®. The filter cake was washed with EtOAc (3 x 15 mL) and the combined filtrates were washed with saturated aqueous Na_2CO_3 (20 mL), brine (25 mL), dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to yield the crude product.

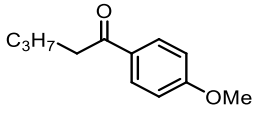
*1-phenylpentan-1-one (**3-36d**)*



3-36d

Starting from sulfone ***3-13c*** (0.200 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; Et_2O: P.E. = 1: 20) and isolated as a colorless liquid (0.093 g, 74%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 7.99 – 7.93 (m, 2H), 7.59 – 7.52 (m, 1H), 7.49 – 7.42 (m, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 1.72 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.41 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ(ppm): 200.8, 137.3, 133.1, 128.7, 128.3, 38.5, 26.7, 22.7, 14.2; HR-MS (ESI) *m/z*: $[M+H]^+$ *calcd.* for $C_{11}H_{15}O$ 163.1117; Found 163.1118

*1-(4-methoxyphenyl)pentan-1-one (**3-36f**)*

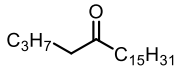


3-36f

Starting from sulfone ***3-13c*** (0.200 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; Et_2O: P.E. = 1: 20) and isolated as a colorless oil (0.120 g, 80%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 7.96 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.92 (dd, *J* = 11.3, 3.7 Hz, 2H), 1.72 (dt, *J* = 20.8, 7.5 Hz, 2H), 1.41 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ(ppm): 199.5, 163.5, 130.6, 130.3, 113.9, 55.7, 38.3, 26.9, 22.8, 14.2; HR-MS (ESI) *m/z*: $[M+H]^+$ *calcd.* for $C_{12}H_{17}O_2$ 193.1223; Found 193.1223

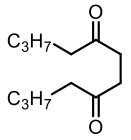
*icosan-5-one (**3-36g**)*



3-36g

Starting from sulfone ***3-13c*** (0.200 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; Et_2O: P.E. = 1: 20) and isolated as a white solid (0.095 g, 41%); m.p. = 49-50°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 2.38 (td, *J* = 7.5, 2.4 Hz, 4H), 1.54 (p, *J* = 7.5 Hz, 4H), 1.30 (dd, *J* = 15.1, 7.5 Hz, 4H), 1.25 (s, 22H), 0.94 – 0.83 (m, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ(ppm): 211.9, 43.0, 42.7, 32.1, 29.8, 29.8, 29.6, 29.6, 29.5, 29.4, 26.1, 24.1, 22.9, 22.5, 14.3, 14.0; HR-MS (ESI) *m/z*: $[M+H]^+$ *calcd.* for $C_{20}H_{41}O$ 297.3152; Found 297.3151

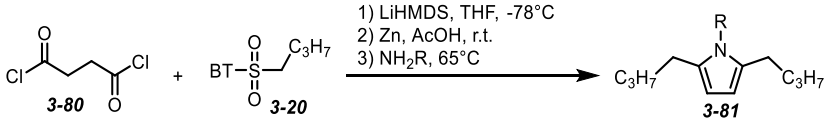
*dodecane-5,8-dione (**3-36h**)*



3-36h

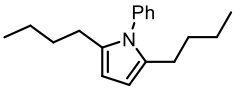
Starting from sulfone ***3-13c*** (0.200 g, 2.0 equiv) and bis acyl chloride ***3-80*** (0.060 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; Et_2O: P.E. = 1: 20) and isolated as a white crystaline solid (0.014 g, 18%); m.p. = 46-50°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.77 (s, 4H), 2.53 – 2.44 (m, 4H), 1.61 – 1.49 (m, 4H), 1.34 (dd, *J* = 14.3, 7.3 Hz, 4H), 0.97 (t, *J* = 6.6 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 210.11, 42.83, 36.26, 26.19, 22.56, 14.10; HR-MS (ESI) *m/z*: $[M+H]^+$ *calcd.* for $C_{12}H_{23}O_2$ 199.1693; Found 199.1692

One-pot protocol for pyrrole synthesis



The sulfone ***3-20*** (2 mmol; 2.0 equiv) was dissolved in dry THF (0.1M) and cooled to −78 °C (acetone / dry ice). After 5 minutes, LiHMDS (4.4 mmol; 4.4 equiv; 1.0 M solution in THF) was added dropwise and the reaction mixture immediately turned light orange. Subsequently, acyl chloride ***3-80*** (1.0 mmol; 1.0 equiv) was added over 5 minutes. The resulting reaction mixture was allowed to stir at −78°C for 30 minutes. Glacial AcOH (5 mL; 0.2M) was added and the reaction mixture stirred at −78°C for an additional 5 minutes. To this mixture Zn powder (5 mmol; 5.0 equiv) was added and the cooling bath was removed. The resulting reaction mixture was allowed to warm spontaneously to r.t., then stirred for 9 hours. Subsequently, NH_2R (10 mmol, 10.0 equiv) was added and reaction warmed to 65°C and stirred for 10 hours. The reaction was quenched up the addition of EtOAc (20 mL) and the whole solution was filtered through Celite®. The filter cake was washed with EtOAc (3 x 15 mL) and the combined filtrates were washed with saturated aqueous Na_2CO_3 (20 mL), brine (25 mL), dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure to yield the crude product.

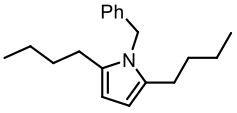
*2,5-dibutyl-1-phenyl-1H-pyrrole (**3-57b**)*



3-57b

Starting from sulfone ***3-13c*** (0.660 g, 2.0 equiv) and bis acyl chloride ***3-80*** (0.200 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 10) and isolated as a colorless oil (0.093 g, 28%) ; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.37 (m, 3H), 7.23 – 7.19 (m, 2H), 5.94 (s, 2H), 2.31 (t, *J* = 7.7 Hz, 4H), 1.43 (dt, *J* = 15.3, 7.5 Hz, 4H), 1.24 (dq, *J* = 14.5, 7.3 Hz, 4H), 0.80 (t, *J* = 7.3 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 139.1, 134.0, 129.1, 128.8, 127.9, 104.5, 31.3, 26.8, 22.5, 14.0; HR-MS (ESI) *m*/*z*: $[M+H]^+$ *calcd.* for $C_{18}H_{25}N$ 256.2060; Found 256.2059

*1-benzyl-2,5-dibutyl-1H-pyrrole (**3-57c**)*

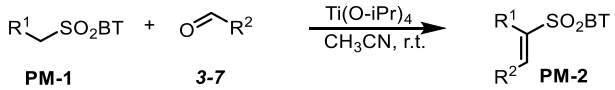


3-57c

Starting from sulfone ***3-13c*** (0.660 g, 2.0 equiv) and bis acyl chloride ***3-80*** (0.200 g, 1.0 equiv). Crude product was purified using flash column chromatography (SiO_2; EtOAc: P.E. = 1: 8) and isolated as a colorless oil (0.126 g, 37%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 2H), 7.25 – 7.19 (m,

1H), 6.86 (d, *J* = 7.4 Hz, 2H), 5.91 (s, 2H), 5.03 (s, 2H), 2.42 (t, *J* = 7.8 Hz, 4H), 1.55 (p, *J* = 7.5 Hz, 4H), 1.33 (dq, *J* = 14.6, 7.3 Hz, 4H), 0.86 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 139.1, 133.0, 128.8, 127.0, 125.7, 104.3, 46.5, 31.0, 26.4, 22.7, 14.1; HR-MS (ESI) *m/z*: $[M+H]^+$ *calcd.* for $C_{19}H_{27}N$ 270.2216; Found 270.2217

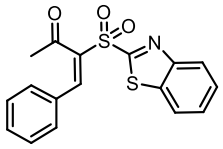
General procedure for Knoevenagel condensation reaction (PM-2)



PM-1 ***3-7*** **PM-2**

To a sulfone **PM-1** (1.0 mmol, 1.0 equiv) in CH_3CN (5.0 mL, 0.2 M) at r.t. was added Ti(O-*i*Pr)$_4$ (0.925 mL, 3.0 equiv) and the resulting mixture was stirred for 30 minutes. An aldehyde ***3-7*** (2.0 mmol, 2.0 equiv) was added dropwise and the mixture was stirred for the indicated time. The reaction was quenched upon addition of CH_2Cl_2 (15 mL) and sat. NH_4Cl (5 mL) and the resulting suspension was filtered through Celite®. The filtrate cake was rinsed with CH_2Cl_2 (5x20 mL), and the combined filtrates were washed with sat. NH_4Cl (2x15 mL), brine (2x15 mL), dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to provide the crude product.

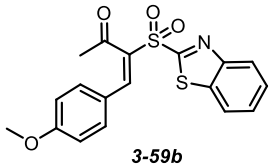
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-phenylbut-3-en-2-one (**3-59a**)*.



3-59a

Reaction was carried out using the described procedure with 1.5g (4.37 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-59a*** as a light yellow solid (1.43 g, 71%). M.p. = 104-107°C; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.18 (m, 1H), 8.14 (s, 1H), 8.01 – 7.98 (m, 1H), 7.59 (ddd, *J* = 7.2, 6.4, 1.6 Hz, 2H), 7.41 (s, 5H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 198.3, 166.0, 152.9, 145.1, 139.3, 137.6, 132.2, 131.3, 130.3, 129.4, 128.1, 127.6, 125.7, 122.40, 31.92; MS (ESI), *m/z* (%) 344 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}NO_3S_2$ 344.0410; Found 344.0413.

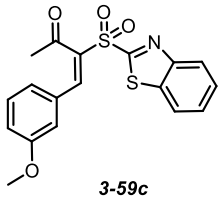
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(4-methoxyphenyl)but-3-en-2-one (**3-59b**).*



3-59b

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59b*** as a yellow solid (0.143 g, 63%). M.p. = 119-121°C; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.20 – 8.18 (m, 1H), 8.07 (s, 1H), 8.00 – 7.98 (m, 1H), 7.62 – 7.55 (m, 2H), 7.39 – 7.36 (m, 2H), 6.94 – 6.91 (m, 2H), 3.85 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 198.7, 166.5, 163.0, 152.8, 145.1, 137.5, 136.2, 132.8, 128.0, 127.6, 125.7, 123.7, 122.4, 114.9, 55.7, 31.9; MS (ESI), *m/z* (%) 374 $[M+H]^+$ (50); HRMS (ESI) *m/z*: $[M]^+$ calcd. for $C_{18}H_{16}NO_4S_2$ 374.0515; Found 374.0519.

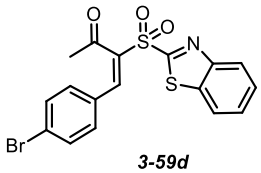
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(3-methoxyphenyl)but-3-en-2-one (**3-59c**).*



3-59c

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the **3-59c** as a yellow oil (0.138 g, 61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.17 (m, 1H), 8.10 (s, 1H), 8.00 – 7.97 (m, 1H), 7.62 – 7.54 (m, 2H), 7.37 – 7.28 (m, 1H), 7.06 – 6.94 (m, 3H), 3.78 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 198.3, 165.9, 160.1, 152.8, 145.0, 139.5, 137.6, 132.5, 130.4, 128.1, 127.6, 125.7, 122.6, 122.4, 118.1, 115.0, 55.5, 32.0; MS (ESI), *m/z* (%) 374 $[M+H]^+$; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_4S_2$: 374.0515; Found 374.0518.

*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(4-bromophenyl)but-3-en-2-one (**3-59d**)*.

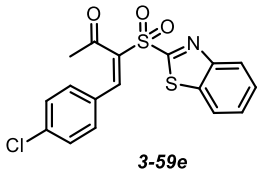


3-59d

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-59d*** as a yellow oil (0.231 g, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.19 (m, 1H), 8.05 (s, 1H), 8.03 – 8.00 (m, 1H), 7.65 – 7.59 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.28

(d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 198.0, 165.7, 152.9, 143.5, 140.1, 137.6, 132.8, 131.6, 130.2, 128.3, 127.8, 127.1, 125.8, 122.5, 32.0; MS (ESI), *m/z* (%) 422 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}BrNO_3S_2$ 421.9515; Found 421.9514.

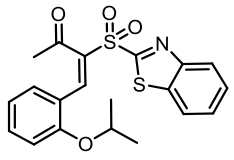
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(4-chlorophenyl)but-3-en-2-one (**3-59e**)*.



3-59e

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59e*** as a colorless oil (0.212 g, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.24 – 8.17 (m, 1H), 8.06 (s, 1H), 8.03 – 7.99 (m, 1H), 7.64 – 7.56 (m, 2H), 7.44 – 7.39 (m, 2H), 7.37 – 7.33 (m, 2H), 2.41 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, Chloroform-*d*) δ 198.0, 165.8, 152.9, 143.5, 140.0, 138.6, 137.6, 131.5, 129.8, 128.3, 127.8, 125.8, 122.4, 32.0; MS (ESI), *m/z* (%) 378 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{12}ClNaNO_3S_2$ 399.0939; Found 399.0940.

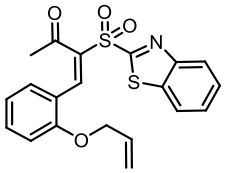
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(2-isopropoxyphenyl)but-3-en-2-one (**3-59i**)*.



3-59i

Reaction was carried out using the described procedure with 0.233 g (0.92 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59i*** as a yellow oil (0.274 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.01 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.58 (tt, *J* = 7.2, 5.6 Hz, 2H), 7.43 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.02 – 6.85 (m, 2H), 4.63 (hept, *J* = 6.0 Hz, 1H), 2.30 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 197.8, 167.0, 157.0, 142.9, 138.2, 137.5, 133.8, 131.1, 127.9, 127.4, 125.5, 122.3, 121.5, 120.7, 114.0, 71.9, 53.6, 31.3, 21.9; MS (ESI), *m/z* (%) 402 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{19}NNaO_4S_2$ 424.0653; Found 424.0648.

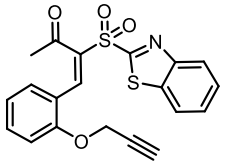
*(E)-4-(2-(allyloxy)phenyl)-3-(benzo[d]thiazol-2-ylsulfonyl)but-3-en-2-one (**3-59j**)*.



3-59j

Reaction was carried out using the described procedure with 0.255 g (1.0 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59j*** as a yellow oil (0.267 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 8.23 – 8.16 (m, 1H), 8.05 – 7.95 (m, 1H), 7.66 – 7.52 (m, 2H), 7.49 – 7.40 (m, 1H), 7.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.01 – 6.90 (m, 2H), 6.02 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.30 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.70 – 4.59 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 197.8, 166.8, 157.4, 152.8, 142.2, 138.5, 137.5, 133.9, 132.2, 131.1, 128.0, 127.5, 125.6, 122.4, 121.1, 120.8, 118.3, 112.8, 69.4, 31.5; MS (ESI), *m/z* (%) 400 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{17}NNaO_4S_2$ 422.0497; Found 422.0490.

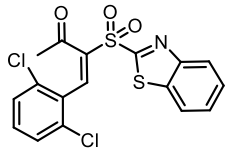
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(2-(prop-2-yn-1-yloxy)phenyl)but-3-en-2-one (**3-59k**)*.



3-59k

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided the ***3-59k*** as a brown solid (0.224 g, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.19 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.00 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.51 – 7.45 (m, 1H), 7.24 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 197.8, 166.7, 156.2, 152.9, 141.7, 139.0, 137.6, 133.8, 131.4, 128.0, 127.6, 125.7, 122.4, 121.9, 121.3, 113.1, 56.2, 31.6; MS (ESI), *m/z* (%) 397 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{15}NNaO_4S_2$ 420.0340, Found 420.0335.

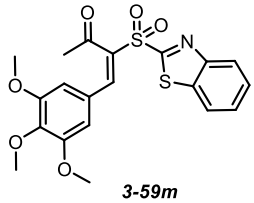
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(2,6-dichlorophenyl)but-3-en-2-one (**3-59l**)*.



3-59l

Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59l*** as a yellow oil (0.06 g, 37%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 8.21 – 8.18 (m, 1H), 8.04 – 8.01 (m, 1H), 7.65 – 7.58 (m, 2H), 7.41 – 7.38 (m, 2H), 7.35 – 7.30 (m, 1H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 193.6, 166.2, 152.7, 143.8, 137.5, 133.9, 131.6, 130.7, 128.6, 128.3, 127.7, 126.6, 125.8, 122.5, 30.2; MS (ESI), *m/z* (%) 412 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{11}Cl_2NNaO_3S_2$ 433.9455; Found 433.9449.

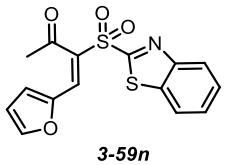
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(3,4,5-trimethoxyphenyl)but-3-en-2-one (**3-59m**)*.



3-59m

Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-59m*** as a yellow oil (0.131 g, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 – 8.19 (m, 1H), 8.04 (s, 1H), 8.03 – 7.99 (m, 1H), 7.66 – 7.55 (m, 2H), 6.64 (s, 2H), 3.90 (s, 3H), 3.82 (s, 6H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 198.7, 166.0, 153.6, 152.9, 145.1, 141.6, 138.1, 137.6, 128.2, 127.7, 126.4, 125.8, 122.4, 107.7, 61.2, 56.3, 32.2; MS (ESI), *m/z* (%) 434 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_6S_2$: 423.0727, found 423.0728.

*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-(furan-2-yl)but-3-en-2-one (**3-59n**)*.

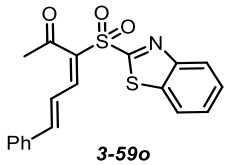


3-59n

Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-59n*** as a yellow oil (0.237 g, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.17 (m, 1H), 7.99 – 7.96 (m, 1H), 7.74 (s, 1H), 7.62 – 7.58 (m, 3H), 7.04 (d, *J* = 3.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 2.61 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.8, 166.1, 152.9, 148.1,

147.6, 137.5, 134.3, 129.7, 128.1, 127.6, 125.7, 122.3, 122.0, 113.6, 32.3; MS (ESI), *m/z* (%) 334 $[M+H]^+$ (49); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{12}NO_4S_2$ 334.0202; Found 334.0203.

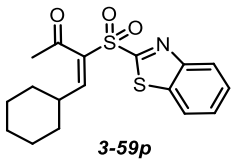
*(3E,5E)-3-(benzo[d]thiazol-2-ylsulfonyl)-6-phenylhexa-3,5-dien-2-one (**3-59o**)*.



3-59o

Reaction was carried out using the described procedure with 0.740 g (2.9 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the ***3-59o*** as a yellow solid (0.866 g, 81%, *E*/*Z*=7:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.14 (m, 1H), 8.02 – 7.97 (m, 2H), 7.69 (dd, *J* = 15.2, 11.6 Hz, 1H), 7.62 – 7.56 (m, 4H), 7.41 (m, 3H), 7.37 (d, *J* = 15.2 Hz, 1H), 2.65 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 194.1, 167.5, 152.7, 152.4, 152.3, 137.0, 135.7, 135.1, 131.4, 129.3, 128.9, 128.2, 127.7, 125.7, 123.0, 122.4, 31.9; MS (ESI), *m/z* (%) 370 $[M+1]^+$ (60); HRMS (ESI) *m/z*: Calcd for $C_{19}H_{16}NO_3S_2$ $[M + H]^+$ 370.0566; Found 370.0568.

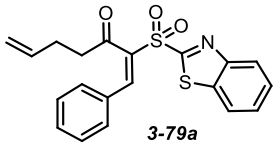
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-cyclohexylbut-3-en-2-one (**3-59p**)*.



3-59p

Reaction was carried out using the described procedure with 1.0 g (3.9 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-59p*** as a colorless oil (0.764 g, 56%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.16 (m, 1H), 8.00 – 7.97 (m, 1H), 7.64 – 7.54 (m, 2H), 7.25 (d, *J* = 10.8 Hz, 1H), 2.57 (s, 3H), 1.76 (bs, 5H), 1.28 (bs, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 195.1, 166.5, 159.0, 152.6, 139.8, 137.1, 128.1, 127.7, 125.7, 122.4, 39.5, 32.2, 31.6, 25.5, 25.0; MS (ESI), *m/z* (%) 350 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_3S_2$ 350.0879; Found 350.0877.

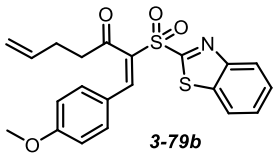
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-phenylhepta-1,6-dien-3-one (**3-79a**)*.



3-79a

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15g***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the ***3-79a*** as a yellow oil (0.234 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.19 (m, 1H), 8.16 (s, 1H), 8.02 – 7.99 (m, 1H), 7.64 – 7.56 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.40 (m, 2H), 7.39 – 7.35 (m, 2H), 5.69 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.01 – 4.92 (m, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.39 – 2.32 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 200.1, 166.0, 153.0, 145.2, 139.2, 137.7, 136.1, 132.2, 131.4, 130.4, 129.4, 128.2, 127.7, 125.8, 122.4, 116.2, 43.5, 27.4; MS (ESI), *m/z* (%) 384 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{18}NO_3S_2$ 384.0723; Found 384.0720.

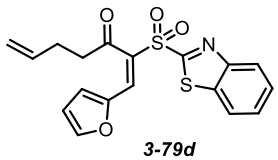
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-(4-methoxyphenyl)hepta-1,6-dien-3-one (**3-79b**)*.



3-79b

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15g***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the **3t** as a yellow oil (0.266 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.17 (m, 1H), 8.07 (s, 1H), 8.01 – 7.97 (m, 1H), 7.62 – 7.54 (m, 2H), 7.35 – 7.31 (m, 2H), 6.93 – 6.89 (m, 2H), 5.73 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.04 – 4.94 (m, 2H), 3.85 (s, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.42 – 2.35 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 200.5, 166.5, 163.0, 152.9, 145.2, 137.6, 136.3, 136.0, 132.9, 128.0, 127.6, 125.8, 123.8, 122.4, 116.1, 114.9, 55.7, 43.5, 27.5; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_4S_2$ 414.0828; Found 414.0827.

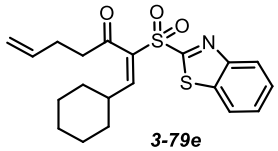
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-(furan-2-yl)hepta-1,6-dien-3-one (**3-79d**)*.



3-79d

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15g***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided the ***3-79d*** as a yellow oil (0.220 g, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.18 (m, 1H), 8.00 – 7.97 (m, 1H), 7.74 (s, 1H), 7.63 – 7.53 (m, 3H), 7.00 – 6.98 (m, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.85 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.06 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.99 (ddt, *J* = 10.0, 1.6, 1.2 Hz, 1H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.50 – 2.43 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 198.6, 166.1, 152.9, 148.0, 147.7, 137.6, 136.8, 134.5, 129.7, 128.1, 127.7, 125.8, 122.4, 121.7, 115.7, 113.6, 43.9, 27.5; MS (ESI), *m/z* (%) 374 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_4S_2$ 374.0515; Found 374.0513.

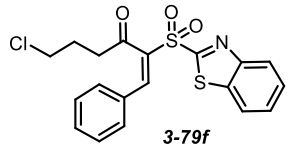
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-cyclohexylhepta-1,6-dien-3-one (**3-79e**)*.



3-79e

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15g***. Product ***3-79e*** was obtained with enough purity as a yellow oil (0.155 g, 59%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.16 (m, 1H), 8.01 – 7.97 (m, 1H), 7.64 – 7.55 (m, 2H), 7.21 (d, *J* = 10.8 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 5.07 – 4.94 (m, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.54 – 2.43 (m, 1H), 2.39 (dtd, *J* = 7.2, 6.0, 1.6 Hz, 2H), 1.82 – 1.68 (m, 5H), 1.33 – 1.22 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 197.4, 166.5, 158.1, 152.8, 139.9, 137.3, 136.5, 128.2, 127.7, 125.8, 122.4, 115.8, 43.7, 39.5, 31.7, 27.5, 25.6, 25.0; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{23}NNaO_3S_2$ 412.1012; Found 412.1013.

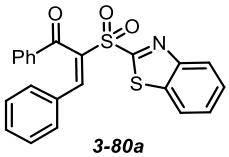
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-6-chloro-1-phenylhex-1-en-3-one (**3-79f**)*.



3-79f

Reaction was carried out using the described procedure with 0.100 g (0.68 mmol) of sulfone ***3-15e***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-79f*** as a yellow oil (0.079 g, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.18 (m, 1H), 8.17 (s, 1H), 8.03 – 7.98 (m, 1H), 7.64 – 7.55 (m, 2H), 7.52 – 7.47 (m, 1H), 7.46 – 7.41 (m, 2H), 7.39 – 7.35 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.13 – 2.03 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 199.9, 165.9, 152.9, 145.5, 139.0, 137.6, 132.3, 131.3, 130.2, 129.5, 128.2, 127.7, 125.8, 122.4, 43.7, 41.2, 26.4; MS (ESI), *m/z* (%) 406 $[M]^+$ (100), 407 $[M+1]^+$ (23); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{17}ClNO_3S_2$ 406.0333; Found 406.0333.

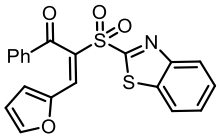
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1,3-diphenylprop-2-en-1-one (**3-80a**)*.



3-80a

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15b***. Purification using flash chromatography (passive SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-80a*** as a yellow solid (0.367 g, 58%). M.p. = 150-153°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (s, 1H), 8.24 – 8.16 (m, 1H), 8.00 – 7.93 (m, 1H), 7.91 – 7.82 (m, 2H), 7.65 – 7.51 (m, 2H), 7.47 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.24 – 7.13 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 191.2, 166.0, 152.9, 145.9, 137.7, 136.7, 135.3, 134.7, 131.9, 131.2, 130.9, 129.9, 129.1, 128.9, 128.1, 127.6, 125.8, 122.4; MS (ESI), *m/z* (%) 406 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{16}NO_3S_2$ 406.0566; Found 406.0563.

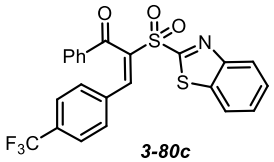
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**3-80b**)*.



3-80b

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15b***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-80b*** as a yellow solid (0.120 g, 50%). M.p. = 168-170°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (m, 1H), 8.00 (s, 1H), 7.96 – 7.93 (m, 1H), 7.92 – 7.89 (m, 2H), 7.61 – 7.54 (m, 2H), 7.53 – 7.49 (m, 1H), 7.39 – 7.33 (m, 2H), 7.24 (dq, *J* = 1.6, 0.8 Hz, 2H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 190.1, 166.2, 152.9, 147.9, 147.5, 137.7, 136.4, 134.3, 132.3, 130.9, 129.7, 128.8, 128.0, 127.5, 125.7, 122.3, 121.4, 113.2; MS (ESI), *m/z* (%) 396 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{14}NO_4S_2$ 396.0359; Found 396.0359.

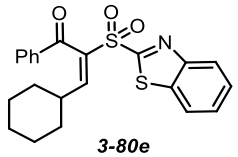
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**3-80c**)*.



3-80c

Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone ***3-15b***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-80c*** as a white solid (0.200 g, 67%). M.p. = 57-59°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 8.23 – 8.20 (m, 1H), 8.00 – 7.97 (m, 1H), 7.88 – 7.85 (m, 1H), 7.65 – 7.56 (m, 2H), 7.54 – 7.44 (m, 5H), 7.36 – 7.31 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 190.6, 165.3, 153.0, 143.5, 139.5, 137.8, 135.1, 135.0, 134.5, 133.1 (q, *J* = 32.9 Hz), 130.8, 129.9, 129.1, 128.3, 128.2, 126.7 (d, *J* = 272.1 Hz), 126.0 (q, *J* = 3.7 Hz), 125.8, 122.4; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -63.17(s, 3F); MS (ESI), *m/z* (%) 474 $[M]+1^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{15}F_3NO_3S_2$ 474.0440; Found 474.0438.

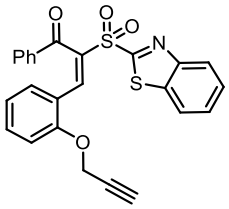
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-cyclohexyl-1-phenylprop-2-en-1-one (**3-80e**)*.



3-80e

Reaction was carried out using the described procedure with 0.050 g (0.16 mmol) of sulfone ***3-15b***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-80e*** as a colorless oil (0.029 g, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.15 (m, 1H), 7.97 – 7.93 (m, 1H), 7.91 – 7.87 (m, 2H), 7.63 – 7.58 (m, 2H), 7.57 – 7.53 (m, 1H), 7.43 (td, *J* = 8.4, 7.6, 0.8 Hz, 2H), 7.37 (d, *J* = 10.8 Hz, 1H), 2.12 – 1.99 (m, 1H), 1.75 – 1.57 (m, 4H), 1.39 – 1.14 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 190.0, 166.2, 155.5, 152.8, 137.7, 137.6, 136.5, 134.7, 129.9, 128.9, 128.0, 127.5, 125.7, 122.3, 39.8, 31.3, 25.3, 24.8; MS (ESI), *m/z* (%) 413 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{22}NO_3S_2$ 412.1036; Found 412.1038.

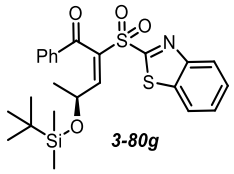
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-1-phenyl-3-(2-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one (**3-80f**)*.



3-80f

Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone ***3-15b***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided the ***3-80f*** as a light brown solid (0.103 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.22 – 8.17 (m, 1H), 7.97 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.87 – 7.82 (m, 2H), 7.57 (pd, *J* = 7.2, 1.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.27 (td, *J* = 8.4, 3.2 Hz, 3H), 7.12 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H).; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 191.1, 166.6, 156.3, 152.9, 142.0, 137.7, 136.2, 135.6, 134.3, 133.4, 131.4, 129.7, 128.7, 127.9, 127.5, 125.7, 122.3, 121.5, 121.1, 112.7, 77.7, 76.5, 56.0; MS (ESI) *m/z* (%) 460 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{17}NNaO_4S_2$ 482.0497; Found 482.0490.

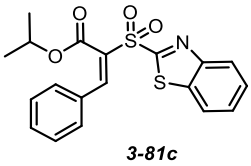
*(S,E)-2-(benzo[d]thiazol-2-ylsulfonyl)-4-((tert-butyldimethylsilyl)oxy)-1-phenylpent-2-en-1-one (**3-80g**)*.



3-80g

Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone ***3-15b***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the ***3-80g*** as a colorless oil (0.059 g, 39%, e.r.= >99:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.19 (m, 1H), 7.97 – 7.94 (m, 1H), 7.90 – 7.85 (m, 2H), 7.64 – 7.57 (m, 2H), 7.57 – 7.54 (m, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.44 – 7.39 (m, 2H), 4.49 (p, *J* = 6.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.70 (s, 9H), -0.15 (s, 3H), -0.19 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 189.3, 165.6, 153.0, 137.8, 137.6, 136.6, 134.5, 130.2, 128.8, 128.1, 127.6, 125.8, 122.4, 67.0, 25.8, 23.3, 18.2, -4.8, -5.1; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{30}NO_4S_2Si$ 488.1380; Found 488.1383; α_D^{27}= + 31.4 (c 0.7,$CHCl_3$); HPLC (CHIRALPAK IE-3, eluent: CO_2: MeOH = 95:5, 2.2 mL/min, 38°C, retention time: t = 13.22 min).

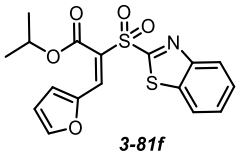
*isopropyl (E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-phenylacrylate (**3-81c**)*.



3-81c

Reaction was carried out using the described procedure with 2.4 g (8.86 mmol) of sulfone ***3-15c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-81c*** as a yellow solid (2.0 g, 59%). M.p. = 76-78°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (s, 1H), 8.21 – 8.18 (m, 1H), 8.03 – 7.99 (m, 1H), 7.64 – 7.55 (m, 4H), 7.51 – 7.39 (m, 3H), 5.15 (hept, *J* = 6.0 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 166.6, 161.8, 152.8, 148.2, 137.4, 132.3, 132.2, 131.4, 130.8, 129.0, 128.1, 127.6, 125.7, 122.3, 71.2, 21.4; MS (ESI), *m/z* (%) 328 [M-OiPr]$^+$ (100); HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{18}NO_4S_2$ 388.0672; Found 388.0672.

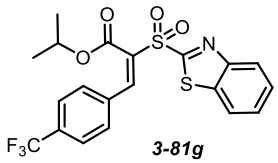
*isopropyl (E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(furan-2-yl)acrylate (**3-81f**)*.



3-81f

Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone ***3-15c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-81f*** as a yellow oil (0.164 g, 60%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.14 (m, 1H), 8.06 (s, 1H), 8.01 – 7.97 (m, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.61 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.15 (hept, *J* = 6.4 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 167.3, 161.1, 152.7, 148.4, 148.0, 137.3, 134.6, 127.9, 127.6, 126.3, 125.6, 123.6, 122.3, 114.0, 70.8, 21.6; MS (ESI): *m/z* (%) 318 $[M]^+$ (100), 378 $[M+1]^+$(21); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_5S_2$ 378.0464; Found 378.0461.

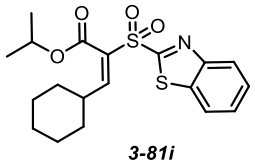
*isopropyl (E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(4-(trifluoromethyl)phenyl)acrylate (**3-81g**)*.



3-81g

Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone ***3-15c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the ***3-81g*** as a white solid (0.120 g, 36%). M.p. = 135-137°C; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.27 (s, 1H), 8.22 – 8.19 (m, 1H), 8.05 – 8.01 (m, 1H), 7.68 (s, 4H), 7.65 – 7.57 (m, 2H), 5.12 (hept, *J* = 6.4 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 166.0, 161.1, 152.7, 146.4, 137.4, 135.0, 134.8, 133.2 (q, *J* = 33.0 Hz), 130.6, 128.2, 127.7, 125.8 (q, *J* = 3.7 Hz), 125.7, 123.6 (q, *J* = 273.2 Hz), 122.3, 71.5, 21.3; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) δ -63.04 (s, 3F); MS (ESI), *m/z* (%) 414 $[M]^+$ (100), 456 $[M+1]^+$(32); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}F_3NO_4S_2$ 456.0546; found 456.0548.

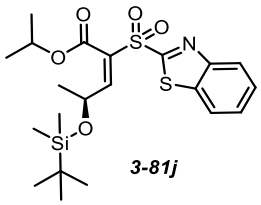
*isopropyl (E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-cyclohexylacrylate (**3-81i**)*.



3-81i

Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone ***3-15c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-81i*** as a yellow oil (0.160 g, 55%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.12 (m, 1H), 8.03 – 7.94 (m, 1H), 7.63 (d, *J* = 10.4 Hz, 1H), 7.60 – 7.53 (m, 2H), 5.05 (hept, *J* = 6.0, 1H), 3.17 – 3.04 (m, 1H), 1.90 – 1.68 (m, 5H), 1.37 – 1.24 (m, 5H), 1.13 (d, *J* = 6.0 Hz, 6H; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 167.7, 164.5, 160.8, 152.9, 137.4, 132.3, 128.2, 127.8, 125.8, 122.6, 70.8, 39.9, 31.9, 26.0, 25.5, 21.9; MS (ESI), *m/z* (%) 352 $[M]^+$ (100), 394 $[M+1]^+$ (53); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_4S_2$ 394.1141; Found 394.1141.

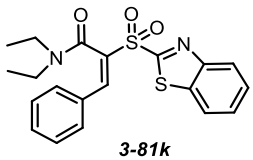
*isopropyl (S,E)-2-(benzo[d]thiazol-2-ylsulfonyl)-4-((tert-butyldimethylsilyl)oxy)pent-2-enoate (**3-81j**)*.



3-81j

Reaction was carried out using the described procedure with 0.100 g (0.37 mmol) of sulfone ***3-15c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-81j*** as a yellow oil (0.084 g, 49%, e.r.= >99:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.12 (m, 1H), 8.02 – 7.99 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.54 (m, 2H), 5.22 (dq, *J* = 7.6, 6.4 Hz, 1H), 5.04 (hept, *J* = 6.4 Hz, 1H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 166.9, 162.9, 160.0, 152.6, 137.1, 131.2, 128.0, 127.6, 125.5, 122.3, 70.8, 66.6, 25.9, 23.0, 21.6, 21.5, 18.3, -4.5, -4.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{32}NO_5S_2Si$ 470.1486; Found 470.1489; α_D^{27} = + 41.2 (c 1.0,$CHCl_3$) ; HPLC (CHIRALPAK IE-3, eluent: CO_2: *i*-PrOH = 95:5, 2.2 mL/min, 38°C, retention time: t = 5.14 min).

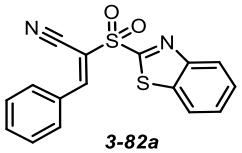
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-N,N-diethyl-3-phenylacrylamide (**3-81k**)*.



3-81k

Reaction was carried out using the described procedure with 0.070 g (0.22 mmol) of sulfone ***3-15i***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-81k*** as a white solid (0.048 g, 53%). M.p.= 158-161°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.19 (m, 1H), 8.01 (s, 1H), 7.98 – 7.95 (m, 1H), 7.60 – 7.51 (m, 4H), 7.48 – 7.41 (m, 1H), 7.41 – 7.33 (m, 2H), 3.62 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.38 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 166.3, 162.1, 152.9, 143.0, 138.0, 134.5, 132.0, 131.7, 130.3, 129.2, 128.0, 127.5, 125.9, 122.4, 43.5, 39.7, 13.7, 12.0; MS (ESI), *m/z* (%) 401 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{20}N_2NaO_3S_2$ 423.0808; Found 423.0809.

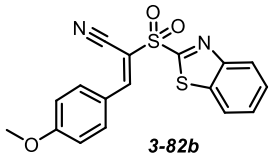
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-phenylacrylonitrile (**3-82a**)*.



3-82a

Reaction was carried out using the described procedure with 2.0 g (8.4 mmol) of sulfone **2l**. Crude product **6a** was isolated with enough purity as a light yellow solid (2.4 g, 88%). M.p. = 158-160°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.26 – 8.23 (m, 1H), 8.06 – 8.03 (m,1H), 8.03 – 7.99 (m, 2H), 7.69 – 7.60 (m, 3H), 7.58 – 7.52 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.0, 156.0, 153.3, 138.0, 135.5, 132.2, 130.5, 130.1, 129.0, 128.5, 126.4, 122.8, 112.8, 112.2; MS (ESI), *m/z* (%) 327 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{11}N_2O_2S_2$ 327.0256; Found 327.0254.

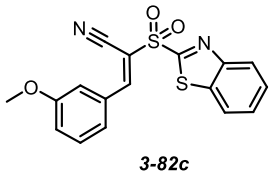
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(4-methoxyphenyl)acrylonitrile (**3-82b**)*.



3-82b

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-82b*** as a yellow oil (0.109 g, 73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (s, 1H), 8.24 – 8.21 (m, 1H), 8.04 – 7.99 (m, 3H), 7.66 – 7.58 (m, 2H), 7.03 – 7.00 (m, 2H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.5, 164.4, 155.0, 152.9, 137.6, 134.7, 128.5, 128.0, 125.9, 123.0, 122.5, 115.3, 113.2, 107.7, 56.0; MS (ESI), *m/z* (%) 374 $[M+H_2O]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_3S_2$ 357.0362; Found 357.0359.

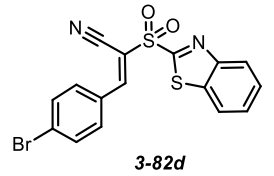
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(3-methoxyphenyl)acrylonitrile (**3-82c**)*.



3-82c

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-82c*** as a yellow solid (0.106 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H), 8.28 – 8.19 (m, 1H), 8.08 – 7.99 (m, 1H), 7.70 – 7.57 (m, 2H), 7.61 – 7.50 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 3.85 (s, 3H).; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 55.7, 112.0, 112.5, 114.9, 122.1, 122.5, 125.1, 126.0, 128.1, 128.7, 130.7, 131.2, 137.7, 152.9, 155.8, 160.3, 163.7; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_3S_2$ 357.0362; Found 357.0360.

*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(4-bromophenyl)acrylonitrile (**3-82d**)*.

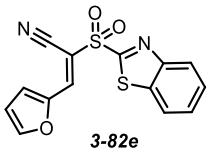


3-82d

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-82d*** as a light-yellow syrup (0.129 g, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (s, 1H), 8.27 – 8.22 (m, 1H), 8.06 – 8.03 (m, 1H), 7.89 – 7.85 (m, 2H), 7.71 – 7.67 (m, 2H), 7.67 – 7.61 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ(ppm): 163.5, 154.1, 153.0, 137.7,

133.3, 132.8, 130.5, 128.9, 128.8, 128.2, 126.1, 122.5, 112.6, 112.3; MS (ESI), *m/z* (%) 406 $[M+H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{10}BrN_2O_2S_2$ 404.9362; Found 404.9360.

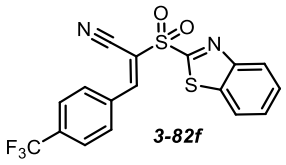
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(furan-2-yl)acrylonitrile (**3-82e**)*.



3-82e

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-82e*** as a yellow oil (0.089 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.22 (m, 1H), 8.18 (s, 1H), 8.05 – 8.02 (m, 1H), 7.83 (dt, *J* = 1.6, 0.4 Hz, 1H), 7.67 – 7.59 (m,2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.72 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.0, 152.9, 150.3, 147.3, 139.5, 137.6, 128.6, 128.0, 125.9, 125.3, 122.5, 114.7, 112.2, 107.2; MS (ESI), *m/z* (%) 334 $[M+H_2O]^+$ (100), 317 $[M+1]^+$ (34); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_9N_2O_3S_2$ 317.0049; Found 317.0047.

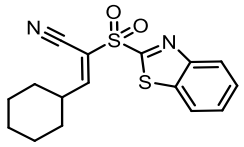
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(4-(trifluoromethyl)phenyl)acrylonitrile (**3-82f**)*.



3-82f

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Crude product ***3-82f*** was isolated with enough purity as a colorless oil (0.157 g, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (s, 1H), 8.26 – 8.22 (m, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.07 – 8.04 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.70 – 7.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 163.0, 153.5, 152.9, 137.7, 135.7 (q, *J* = 33.4 Hz), 133.0, 131.7, 128.9, 128.2, 126.7 (q, *J* = 3.7 Hz), 126.5, 126.0, 123.4 (d, *J* = 272.7 Hz), 114.9, 111.9; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-d) δ -63.34 (s, 3F); MS (ESI), *m/z* (%) 177 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{10}F_3N_2O_2S_2$ 395.0130; Found 395.0128.

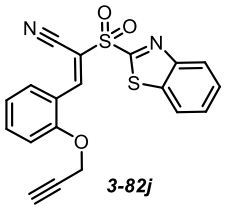
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-cyclohexylacrylonitrile (**3-82i**)*.



3-82i

Reaction was carried out using the described procedure with 0.050 g (0.21 mmol) of sulfone ***3-16a***. Crude product ***3-82i*** was isolated with enough purity as a yellow solid (0.060 g, 88%). M.p.= 112-114°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 – 8.23 (m, 1H), 8.05 – 8.02 (m, 1H), 7.76 (d, *J* = 10.4 Hz, 1H), 7.69 – 7.60 (m, 2H), 2.77 – 2.67 (m, 1H), 1.89 – 1.70 (m, 5H), 1.41 – 1.22 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 169.0, 163.5, 152.9, 137.6, 128.7, 128.1, 126.1, 122.5, 116.5, 110.6, 42.0, 31.1, 25.3, 24.8; MS (ESI), *m/z* (%) 333 $[M+1]^+$ (100); HR-MS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_2S_2$ 333.0726; Found 333.0725.

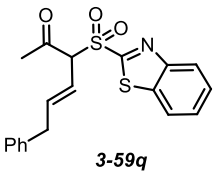
*(E)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-(2-(prop-2-yn-1-yloxy)phenyl)acrylonitrile (**3-82j**)*.



3-82j

Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone ***3-16a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-82j*** as a brown solid (0.110 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.96 (s, 1H), 8.35 – 8.20 (m, 2H), 8.05 – 8.00 (m, 1H), 7.63 (ddd, *J* = 9.2, 5.6, 2.0 Hz, 3H), 7.19 – 7.07 (m, 2H), 4.88 (d, *J* = 2.4 Hz, 2H), 2.58 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.0, 157.9, 152.9, 149.9, 137.6, 136.9, 129.7, 128.6, 128.0, 126.0, 122.5, 122.2, 119.8, 113.3, 112.9, 111.1, 77.3, 56.6; MS (ESI), *m/z* (%) 381 $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{12}N_2NaO_3S_2$ 403.0187; Found 403.0181.

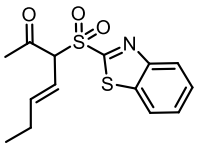
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-6-phenylhex-4-en-2-one (**3-59q**)*.



3-59q

Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone ***3-15a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the **3-59q** as a white solid (0.036 g, 49%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 – 8.16 (m, 1H), 8.01 – 7.95 (m, 1H), 7.69 – 7.56 (m, 2H), 7.13 – 7.06 (m, 3H), 6.94 – 6.86 (m, 2H), 5.92 – 5.77 (m, 2H), 5.22 (d, *J* = 9.2 Hz, 1H), 3.35 (d, *J* = 6.0 Hz, 2H), 2.51 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 196.6, 164.2, 152.6, 142.5, 138.1, 137.1, 128.6, 128.4, 128.3, 127.8, 126.5, 125.7, 122.5, 117.5, 78.0, 39.1, 31.2; MS (ESI), *m/z* (%) 372 $[M+1]^+$ (37); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_3S_2$ 372.0723; Found 372.0725.

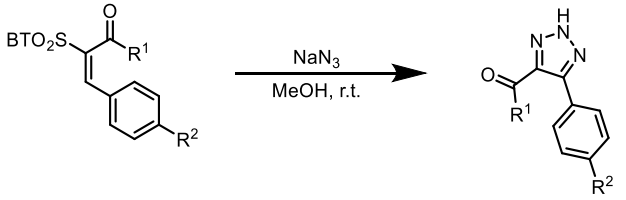
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)hept-4-en-2-one (**3-59r**)*.



3-59r

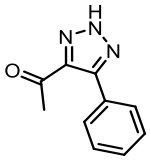
Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone ***3-15a***. Crude product proved to be unstable on SiO_2. The yield of the crude material was 0.019 g, 31%, (keto/enol = 1.7:1). *Peaks attributed to enol form marked with **; ^{1}H NMR (400 MHz, Chloroform-*d*) δ(ppm): 0.84 (t, *J* = 7.6 Hz, 3H*), 1.00 (t, *J* = 7.6 Hz, 3H), 2.04 (qd, *J* = 7.6, 6.8, 5.2 Hz, 2H), 2.48 (dd, *J* = 7.6, 3.6 Hz, 1H*), 2.50 (s, 3H*), 2.52 (dd, *J* = 7.6, 0.4 Hz, 1H*), 2.57 (s, 3H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.65 – 5.85 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H*), 7.55 – 7.69 (m, 2H & 2H*), 7.98 – 8.04 (m, 1H & 1H*), 8.17 – 8.20 (m, 1H), 8.24 (ddd, *J* = 8.4, 1.6, 0.8 Hz, 1H*); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{15}NNaO_3S_2$ 332.0391, found 332.0393.

3,4 substituted-2*H*- triazole synthesis



To a **PM-2** (0.291 mmol, 1.0 equiv) in MeOH (1.5 mL, 0.2 M) at r.t. was added sodium azide (0.021 g, 0.32 mmol, 1.1 equiv) in one portion and the mixture was stirred for 20 hours. H_2O (10 mL) and EtOAc (10 mL) were added and aqueous phase was extracted with EtOAc (4x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide the crude product.

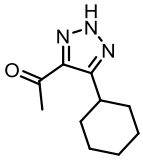
*1-(5-phenyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**3-101a**)*.



3-101a

Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-101a*** as a pale yellow solid (0.032 g, 93%). M.p. = 108-110°C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.77 (m, 2H), 7.51 – 7.34 (m, 3H), 2.73 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 193.6, 141.9, 130.2, 129.2, 128.7, 127.5, 28.8; MS (ESI), *m/z* (%) 186 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}O$ 188.0818; Found 188.0819.

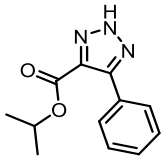
*1-(5-cyclohexyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**3-101b**)*.



3-101b

Reaction was carried out using the described procedure with 0.050 g (0.14 mmol) of vinyl-sulfone ***3-59p***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-101b*** as a white solid (0.027 g, 98%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.42 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.71 (s, 3H), 2.04 – 1.95 (m, 2H), 1.84 (dq, *J* = 13.5, 3.5 Hz, 2H), 1.78 (dqd, *J* = 12.5, 3.0, 1.5 Hz, 1H), 1.57 – 1.39 (m, 4H), 1.29 (qt, *J* = 13.0, 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) δ 25.9, 26.3, 28.3, 31.9, 34.2, 141.9, 149.7, 194.4; MS (ESI), *m/z* (%) 192 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{16}N_3O$ 194.1288; Found 194.1289.

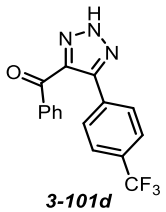
*isopropyl 5-phenyl-2H-1,2,3-triazole-4-carboxylate (**3-101c**)*.



3-101c

Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone ***3-81c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the **15c** as a yellow oil (0.034 g, 59%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.75 (m, 2H), 7.42 – 7.38 (m, 3H), 5.23 (h, *J* = 6.4 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 134.4, 129.7, 129.4, 128.3, 114.0, 69.8, 21.8; MS (ESI), *m/z* (%) 230 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{14}N_3O_2$ 232.1081; Found 232.1082.

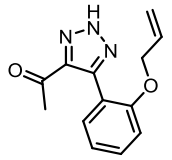
*phenyl(5-(4-(trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)methanone (**3-101d**)*.



3-101d

Reaction was carried out using the described procedure with 0.100 g (0.21 mmol) of vinyl-sulfone ***3-80c***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided the ***3-101d*** as a yellow oil (0.051 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 6.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 187.7, 156.0, 141.6, 136.9, 133.5, 130.1, 129.3, 128.4, 128.1, 125.4, 125.3 (q, *J* = 3.6 Hz), 122.7; ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6) δ -61.15 (s, 3F); MS (ESI): *m/z* (%) 316 $[M-H]^-$ (100); HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{11}F_3N_3O$ 318.0849; Found 318.0850.

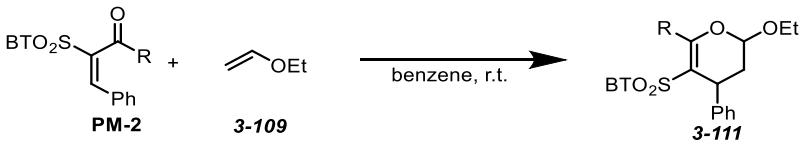
*1-(5-(2-(allyloxy)phenyl)-2H-1,2,3-triazol-4-yl)ethan-1-one (**3-101e**)*.



3-101e

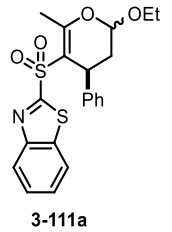
Reaction was carried out using the described procedure with 0.050 g (0.125 mmol) of vinyl-sulfone ***3-59j***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-101e*** as a colorless oil (0.028 g, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.00 (bs, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04 – 6.95 (m, 1H), 6.01 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.42 – 5.27 (m, 2H), 4.62 (dt, *J* = 5.4, 1.4 Hz, 2H), 2.76 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 29.0, 29.8, 69.9, 112.6, 115.0, 119.1, 121.5, 132.0, 132.1, 132.3, 142.5, 155.6, 193.6; MS (ESI): *m/z* (%) 200 [M-allyl]$^-$ (100), 242 [M-H]$^-$ (45); HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{13}H_{14}N_3O_2$ 244.1081; Found 244.1079.

General procedure for dihydropyran *3-111* synthesis



A **PM-2** (0.100 g, 0.29 mmol) was dissolved in benzene (1.5 mL, 0.2 M) and vinyl-ether (0.278 mL, 2.9 mmol) was added in one portion. The mixture was stirred for 24 hours. Volatilities were evaporated under reduced pressure to yield the crude product.

*2-(((4S)-2-ethoxy-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**3-111a**)*.

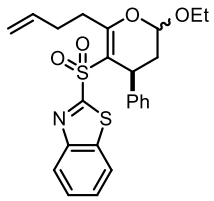


3-111a

Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-111a*** as a yellow oil (0.129 g, 90%, *d.r.* = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.08 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.53 – 7.44 (m, 2H), 7.08 (bs, 5H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 2H), 5.11 (dd, *J* = 6.8, 2.4 Hz, 1H), 4.95 (t, *J* = 6.0 Hz, 1H), 4.31 (t, *J* = 4.4 Hz, 1H), 4.19 (t, *J* = 7.6 Hz, 1H), 3.99 – 3.88 (m, 2H), 3.62 – 3.52 (m, 2H), 2.68 (bs, 3H), 2.64 (bs, 3H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4

Hz, 1H), 2.12 – 2.04 (m, 3H), 1.19 (t, *J* = 6.0 Hz, 3H), 1.16 (t, *J* = 6.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.2, 169.6, 168.1, 167.8, 152.7, 152.5, 142.7, 141.6, 137.2, 136.9, 128.9, 128.6, 128.1, 127.8, 127.4, 127.2, 127.2, 127.0, 126.8, 126.4, 125.3, 125.2, 122.1, 121.9, 113.9, 110.6, 100.2, 98.7, 65.6, 65.2, 39.1, 38.5, 37.7, 35.9, 21.2, 20.7, 15.2, 15.1; MS (ESI), *m/z* (%) 416 $[M+H]^+$ (62); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{22}NO_4S_2$ 416.0985; Found 416.0987.

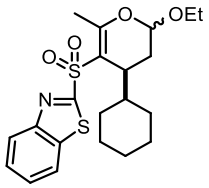
*2-(((4S)-6-(but-3-en-1-yl)-2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**3-111b**)*.



3-111b

Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone ***3-79a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-111b*** as a yellow oil (0.109 g, 70%, *d.r.* = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (t, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.53 – 7.45 (m, 2H), 7.09 (bs, 5H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 2H), 5.97 (dddt, *J* = 20.8, 16.8, 10.4, 6.8 Hz, 2H), 5.19 – 5.07 (m, 3H), 5.06 – 4.98 (m, 2H), 4.96 – 4.89 (m, 1H), 4.33 (t, *J* = 4.8 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.94 (dqd, *J* = 9.6, 7.2, 2.4 Hz, 2H), 3.56 (ddq, *J* = 18.8, 9.6, 7.2 Hz, 2H), 3.33 – 3.15 (m, 3H), 3.09 – 3.01 (m, 1H), 2.60 – 2.48 (m, 4H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4 Hz, 1H), 2.11 – 2.02 (m, 3H), 1.18 (dt, *J* = 14.0, 7.2 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.4, 170.1, 170.0, 169.7, 152.6, 152.5, 142.7, 141.6, 137.6, 137.4, 137.3, 137.0, 128.9, 128.5, 128.1, 127.8, 127.5, 127.3, 127.0, 126.8, 126.4, 125.2, 125.1, 122.1, 121.9, 115.6, 115.5, 114.4, 111.1, 100.1, 98.6, 65.5, 65.2, 39.3, 38.6, 37.8, 35.8, 33.3, 32.7, 32.1, 32.1, 29.8, 15.2, 15.1; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_4S_2$ 456.1298; Found 456.1300.

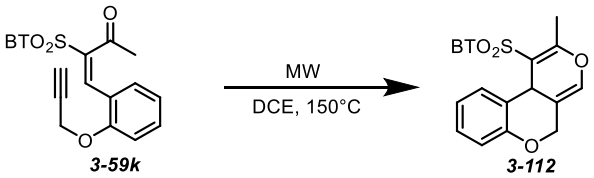
*2-((4-cyclohexyl-2-ethoxy-6-methyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**3-111c**).*



3-111c

Reaction was carried out using the described procedure with 0.070 g (0.2 mmol) of vinyl-sulfone ***3-59p***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided the ***3-111c*** as a colorless oil (0.069 g, 72%, *d.r.* = 1.1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (dddd, *J* = 8.0, 2.4, 1.6, 0.8 Hz, 2H), 7.96 (dddd, *J* = 8.0, 6.0, 1.6, 0.8 Hz, 2H), 7.61 – 7.49 (m, 4H), 5.16 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.91 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.95 (ddq, *J* = 14.0, 9.6, 7.2 Hz, 2H), 3.61 (dq, *J* = 9.6, 7.2 Hz, 2H), 2.05-2.97 (m,1H), 2.95-2.88 (m,1H), 2.45 (d, *J* = 1.2 Hz, 3H), 2.39 (d, *J* = 0.8 Hz, 3H), 2.18 (dt, *J* = 14.0, 3.6 Hz, 1H), 2.10 – 1.88 (m, 2H), 1.88 – 1.75 (m, 3H), 1.73 – 1.57 (m, 9H), 1.55 – 1.46 (m, 1H), 1.41 – 1.31 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.20 – 0.81 (m, 8H), 0.77 – 0.59 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 170.0, 169.8, 168.5, 166.8, 152.7, 152.6, 136.5, 136.5, 127.6, 127.6, 127.4, 125.3, 122.2, 114.9, 112.5, 101.5, 99.7, 65.5, 65.3, 41.1, 39.6, 38.5, 37.5, 31.8, 31.6, 30.2, 30.1, 29.4, 27.1, 27.0, 26.9, 26.8, 26.6, 26.5, 26.0, 21.3, 20.9, 15.2.; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{28}NO_4S_2$ 422.1454; Found 422.1456.

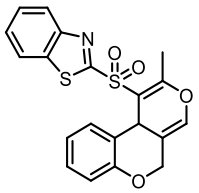
Intramolecular Diels-Alder reaction



3-59k ***3-112***

General procedure for intramolecular Het. Diels-Alder reaction. A vinyl-sulfone ***3-59k*** (0.017 g, 0.04 mmol, 1.0 equiv) was dissolved in DCE (4.0 mL, 0.01 M) and the reaction mixture was stirred under microwave conditions (200W, 150°C, 5 min ramp, 30 min hold). The solvent was evaporated under reduced pressure to yield the crude product.

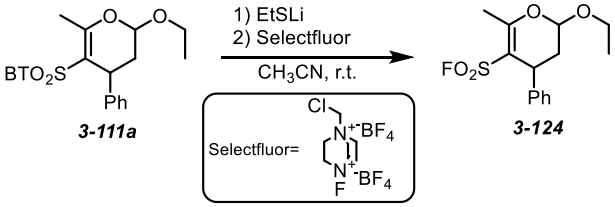
*2-((2-methyl-5H,10bH-pyrano[3,4-c]chromen-1-yl)sulfonyl)benzo[d]thiazole (**3-112**)*.



3-112

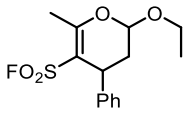
Reaction was carried out using the described procedure with 0.017 g (0.04 mmol) of vinyl-sulfone ***3-59k***. Desired product ***3-112*** was isolated as a yellow oil (0.016 g, 93%) in sufficient purity. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 – 8.18 (m, 1H), 8.06 – 7.97 (m, 1H), 7.61 (dtd, *J* = 20.0, 7.6, 1.2 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.20 – 7.10 (m, 1H), 6.98 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.44 – 6.32 (m, 1H), 4.88 – 4.81 (m, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ(ppm): 19.5, 33.7, 67.8, 110.9, 113.7, 117.3, 121.3, 122.4, 125.7, 126.3, 127.7, 128.0, 128.2, 129.6, 134.4, 136.8, 152.8, 153.8, 165.2, 168.4; MS (ESI), *m/z* (%) 398 $[M+H]^+$ (30); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{15}NNaO_4S_2$ 420.0340; Found 420.0336.

Preparation of dihydropyran *3-124* sulfuryl-fluoride



Dihydropyran ***3-111a*** (0.050g, 0.12 mmol, 1.0 equiv) was dissolved in CH_3CN (2.0 mL, 0.1M). Subsequently, EtSLi (0.36 mmol, 3.0 equiv) was added in one portion and the resulting reaction mixture stirred for 24h at r.t. Selectfluor (0.36 mmol, 3.0 equiv) was added and solution stirred for additional 2 hours at r.t. The reaction was quenched upon addition of H_2O (2 mL) and EtOAc (3 mL). The organic phase was washed H_2O (2x5 mL), brine (2x5 mL) and dried over $MgSO_4$. Solvents were evaporated under reduced pressure to yield the crude product.

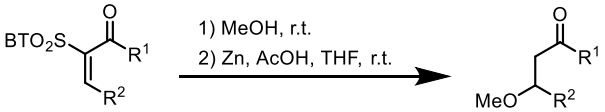
*2-ethoxy-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-5-sulfonyl fluoride (**3-124**)*



3-124

Reaction was carried out using the described procedure with 0.050 g (0.12 mmol) of dihydropyran ***3-111a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:8) and concentration of the relevant fractions provided the ***3-124*** as a colorless oil (0.012 g, 33% over 2 steps, *d.r.* = 1.1:1); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 2H), 7.24 – 7.19 (m, 3H), 4.96 (dd, *J* = 7.4, 4.1 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.95 (dq, *J* = 9.4, 7.1 Hz, 1H), 3.55 (ddq, *J* = 9.4, 8.3, 7.1 Hz, 2H), 2.46 (t, *J* = 1.0 Hz, 3H), 2.14 (dd, *J* = 4.4, 3.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, Chloroform-*d*)* δ 7.36 (ddd, *J* = 7.6, 6.4, 1.2 Hz, 5H), 5.16 (dd, *J* = 5.6, 2.6 Hz, 1H), 4.06 – 4.00 (m, 1H), 3.86 (dq, *J* = 9.4, 7.1 Hz, 1H), 3.58 – 3.51 (m, 2H), 2.43 (t, *J* = 1.2 Hz, 3H), 2.35 (ddd, *J* = 14.1, 7.5, 2.6 Hz, 1H), 2.19 (ddd, *J* = 8.3, 6.2, 5.1 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 167.6, 142.1, 128.9, 128.3, 127.5, 127.4,106.87 (d, *J* = 21.1 Hz), 106.8, 98.9, 65.7, 38.6, 35.8, 20.4, 15.1.; ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*)* δ 167.6, 141.9, 128.7, 128.2, 127.8, 127.4, 109.88 (d, *J* = 20.3 Hz), 100.3, 65.6, 37.0, 30.2, 21.0, 15.3; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}FO_4S$ 301.0904; Found 301.0905.

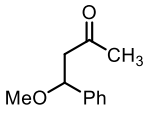
Michael type addition and desulfonation



PM-2 ***3-132***

A **PM-2** (0.69 mmol, 1.0 equiv) was dissolved in MeOH (4.0 mL, 0.2 M) and solution was stirred for 16 hours. After consumption of the starting material the solvent was evaporated under reduced pressure to yield the crude product, that was used in the next step without further purification. The resulting methoxy sulfone adduct was dissolved in THF (7.0 mL, 0.1 M) and AcOH (4.0 mL, 0.2 M). Zn (0.226 g, 5.0 equiv) was added in one portion and the resulting mixture was stirred overnight. The reaction was quenched upon addition of EtOAc (20 mL) and the resulting suspension filtered through Celite®, and filtrate cake was washed with EtOAc (5x20mL). The combined filtrates were washed with sat. $NaHCO_3$ (2x20 mL), brine (2x20 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide the crude product.

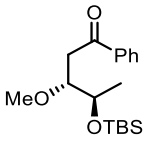
*4-methoxy-4-phenylbutan-2-one (**3-132a**)*.



3-132a

Reaction was carried out using the described procedure with 0.238 g (0.69 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:9) and concentration of the relevant fractions provided the ***3-132a*** as a colorless liquid (0.051 g, 92% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36–7.26 (m, 5H), 4.62 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.18 (s, 3H), 2.95 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.57 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.14 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 206.4, 140.9, 128.5, 127.9, 126.4, 79.5, 56.6, 51.9, 31.0; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{14}NaO_2$ 201.0886; Found 201.0887.

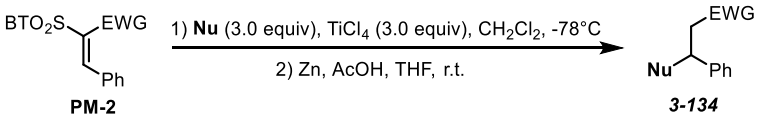
*(3S,4S)-4-((tert-butyldimethylsilyl)oxy)-3-methoxy-1-phenylpentan-1-one (**3-132b**)*.



3-132b

Reaction was carried out using the described procedure with 0.336 g (0.69 mmol) of vinyl-sulfone ***3-80g***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:20) and concentration of the relevant fractions provided the ***3-132b*** as a colorless liquid (0.102 g, 43% over 2 steps, *d.r.*=7:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.95 (m, 2H), 7.60 – 7.53 (m, 1H), 7.49 – 7.43 (m, 2H), 4.08 (qd, *J* = 6.4, 4.4 Hz, 1H), 3.88 (ddd, *J* = 8.0, 4.4, 3.6 Hz, 1H), 3.37 (s, 3H), 3.19 – 3.06 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 199.4, 137.6, 133.1, 128.7, 128.4, 80.8, 68.1, 58.6, 38.5, 26.0, 18.2, 17.9, -4.5, -4.7; HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{30}NaO_3Si$ 345.1862; Found 345.1855; α_D^{22} $\alpha_D^{22}\alpha_D^{22}$=-7.1 (c 0.65,$CHCl_3$).

Michael type allylation and desulfonation

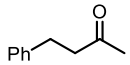


PM-2 ***3-134***

A **PM-2** (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL, 0.1 M) and the solution was cooled down to -78°C (acetone/dry ice). After 30 minutes, **Nu** (0.290 mmol, 3.0 equiv) was added and the mixture stirred for another 30 minutes, followed by addition of $TiCl_4$ (0.870 mL, 3.0 equiv, 1.0M solution in CH_2Cl_2). The mixture was stirred for 6 hours. $NaHCO_3$ (10 mL) was added and the suspension warmed to r.t.. The aqueous phase was extracted with CH_2Cl_2 (4x10 mL) and the combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvents were removed

under reduced pressure. The crude product was used in the next step without further purification. Crude sulfone was dissolved in THF (3.0 mL, 0.1 M). AcOH (1.5 mL, 0.2 M) and Zn (0.019 g, 5.0 equiv) were added in one portion. The resulting heterogenic mixture was stirred overnight before it was quenched with the addition of EtOAc (20 mL). The resulting slurry was filtered through Celite® and the filtrate cake was washed with EtOAc (5x15mL). The filtrates were washed with sat. $NaHCO_3$ (2x15 mL), brine (2x15 mL), dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to yield the crude product.

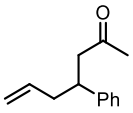
*4-phenylbutan-2-one (**3-134a**)*.



3-134a

Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:10) and concentration of the relevant fractions provided the ***3-134*** as a colorless liquid (0.037 g, 87% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28-7.26 (m, 2H), 7.22–7.16 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.76-2.72 (m, 2H), (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 207.8, 140.9, 128.4, 128.2, 126.0, 45.1, 30.1, 29.6; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{13}O$ 149.0961; Found 149.0961.

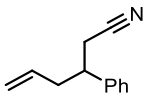
*4-phenylhept-6-en-2-one (**3-134b**)*.



3-134b

Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:8) and concentration of the relevant fractions provided the ***3-134b*** as a colorless oil (0.040 g, 74% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 5.72 – 5.58 (m, 1H), 5.03 – 4.94 (m, 2H), 3.26 (p, *J* = 7.2 Hz, 1H), 2.82 – 2.68 (m, 2H), 2.39 – 2.33 (m, 2H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 207.8, 144.2, 136.3, 128.6, 127.6, 126.6, 116.9, 49.7, 41.0, 40.9, 30.8; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{17}O$: 189.1274, found 189.1274.

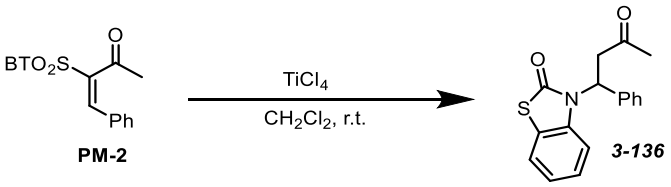
*3-phenylhex-5-enenitrile (**3-134c**)*.



3-134c

Reaction was carried out using the described procedure with 0.050 g (0.153 mmol) of vinyl-sulfone ***3-82a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided the ***3-134c*** as a colorless oil (0.019 g, 72% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.32 (m, 2H), 7.30 – 7.27 (m, 1H), 7.25 – 7.21 (m, 2H), 5.66 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.12 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 1H), 3.04 (p, *J* = 7.2 Hz, 1H), 2.70 – 2.57 (m, 2H), 2.55 (tt, *J* = 7.2, 1.2 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 141.4, 134.7, 128.9, 127.6, 127.3, 118.5, 118.2, 41.8, 39.2, 24.0; HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{13}N$ 171.1048; Found 171.1049.

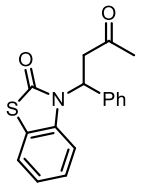
Lewis acid-mediated rearrangement



PM-2 ***3-136***

A **PM-2** (0.050 g, 0.145 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL, 0.1 M) at r.t., and $TiCl_4$ (0.580 mL, 4.0 equiv, 1.0M solution in CH_2Cl_2) was added. The mixture was stirred for 1 hour at r.t. prior to addition of CH_2Cl_2 (10 mL) and sat. NH_4Cl (5 mL). The resulting suspension was filtered through Celite® and the filter cake was washed with CH_2Cl_2 (5x10mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to yield the crude product.

*3-(3-oxo-1-phenylbutyl)benzo[d]thiazol-2(3H)-one (**3-136**)*.

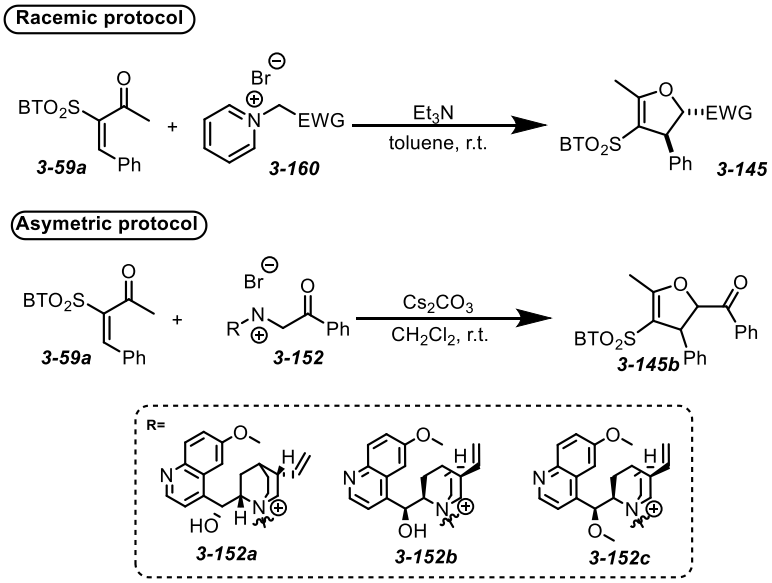


3-136

Reaction was carried out using the described procedure with 0.050 g (0.145 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided the ***3-136*** as a pale-yellow oil (0.043 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.35 (m, 3H), 7.35 – 7.27 (m, 1H), 7.16 – 7.10 (m, 2H), 6.01 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.96 (dd, *J* = 18.0, 8.0 Hz, 1H), 3.44 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz,

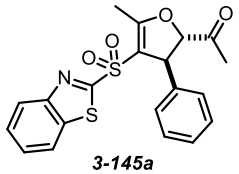
Chloroform-*d*) δ 205.4, 138.2, 137.2, 129.1, 128.3, 127.0, 126.4, 122.9, 122.7, 111.9, 54.5, 45.8, 30.3.; MS (ESI), *m/z* (%) 297 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{15}NO_2S$ 297.0823; Found 297.0825.

Ammonium salt mediated (4+1) annulation



Racemic protocol: A vinyl-sulfone ***3-59a*** (0.050 g, 0.15 mmol, 1.0 equiv) and pyridinium salt ***3-152*** (0.217 mmol, 1.5 equiv) were dissolved in toluene (1.5 mL, 0.1 M). After 5 minutes, Et_3N (0.030 mL, 1.5 equiv) was added and the mixture was stirred for an additional 4 hours at r.t. H_2O (10 mL) followed by EtOAc (10 mL) were added and the resulting layers were separated. The aqueous phase was extracted with EtOAc (4x10 mL) and the combined organic layers were washed brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide the crude product. Asymmetric protocol: A vinyl-sulfone ***3-59a*** (0.030 g, 0.086 mmol, 2.0 equiv) and chiral ammonium salt ***3-152*** (0.043 mmol, 1.0 equiv.) were dissolved in dry CH_2Cl_2 (1.0 mL, 0.043 M). After 5 minutes, Cs_2CO_3 (0.028 mg, 2.0 equiv.) was added in one portion and the mixture was stirred for an additional 20 hours. H_2O (10 mL) and EtOAc (10 mL) were added and the aqueous phase was extracted with EtOAc (4x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide the crude product.

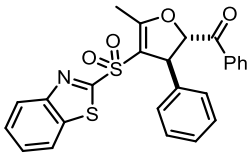
*1-((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl)ethan-1-one (**3-145a**)*.



3-145a

Reaction was carried out using the described racemic procedure with 0.050 g (0.15 mmol) of vinyl-sulfone ***3-59a***. Product ***3-145a*** was isolated in good crude purity as a yellow oil (0.062 g, 98%, d.r.= 99:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.05 (m, 1H), 7.80 – 7.77 (m, 1H), 7.58 – 7.54 (m, 1H), 7.51 – 7.47 (m, 1H), 7.04 – 7.01 (m, 2H), 6.97 – 6.91 (m, 3H), 4.83 (d, *J* = 5.2 Hz, 1H), 4.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 2.63 (d, *J* = 1.2 Hz, 3H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 203.7, 171.2, 168.9, 152.6, 139.5, 137.3, 128.7, 127.9, 127.7, 127.5, 127.2, 125.4, 122.0, 112.1, 93.2, 52.0, 26.1, 14.5; MS (ESI), *m/z* (%) 400 [M+1]$^{+}$ (62); HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{20}H_{18}NO_4S_2$ 400.0672; Found 400.0669.

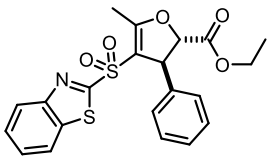
*((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl)(phenyl)methanone (**3-145b**)*.



3-145b

Reaction was carried out using the described asymmetric or racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided the ***3-145b*** as a colorless oil (0.068 g, 98%, *d.r.* = 97:1). Product ***3-145b*** was also prepared in enantioenriched form purified using flash column chromatography (SiO_2; CH_2Cl_2:heptane=6:1) and isolated as a light red oil in following manner: starting from salt ***3-152a***: 0.013 g, 70%, *e.r.* = 97:3, *d.r.*=99:1; starting from salt ***3-152c***: 0.012 g, 68%, e.r. = 1:99, *d.r.*=99:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 8.03 (m, 1H), 7.79 – 7.74 (m, 3H), 7.63 – 7.53 (m, 2H), 7.50 – 7.41 (m, 3H), 7.07 – 7.04 (m, 2H), 7.01 – 6.95 (m, 3H), 5.77 (d, *J* = 4.8 Hz, 1H), 4.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.66 (d, *J* = 1.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 191.9, 172.0, 169.0, 152.6, 139.2, 137.3, 134.4, 133.0, 129.1, 129.0, 128.8, 128.2, 127.9, 127.4, 127.1, 125.4, 122.0, 111.9, 90.3, 52.2, 14.4; MS (ESI), *m/z* (%) 462 [M+1]$^{+}$ (54); HRMS (ESI) *m/z*: [M + H]$^{+}$ Calcd for $C_{25}H_{20}NO_4S_2$ 462.0828; Found 462.0827; α_D^{25}=+161.4 (c 0.5,$CHCl_3$) – first enantiomer (ret. Time – 29.35 min); α_D^{25}=-148.2 (c 0.5,$CHCl_3$) – second enantiomer (ret. Time – 32.7 min); HPLC (CHIRAL ART Cellulose-SB, eluent: *n*-hexane: *i*-PrOH = 4:1, 0.5 mL/min, 10°C, retention times: t = 29.3 and t = 32.7 min).

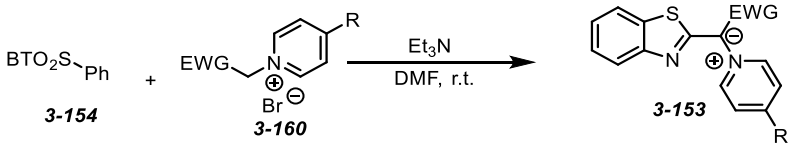
*ethyl (2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylate (**3-145c**)*.



3-145c

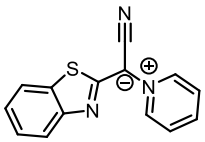
Reaction was carried out using the described racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided the ***3-145c*** as a colorless oil (0.054 g, 88%, *d.r.* = 99:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 8.05 (m, 1H), 7.80 – 7.77 (m, 1H), 7.58 – 7.53 (m, 1H), 7.51 – 7.46 (m, 1H), 7.04 – 7.01 (m, 2H), 6.97 – 6.91 (m, 3H), 4.90 (d, *J* = 4.8 Hz, 1H), 4.62 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.30 – 4.20 (m, 2H), 2.62 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 171.8, 168.9, 168.7, 152.6, 139.4, 137.3, 128.6, 127.8, 127.8, 127.5, 127.2, 125.4, 122.0, 111.9, 86.7, 62.3, 53.3, 14.4, 14.2; MS (ESI), *m/z* (%) 430 $[M+1]^+$ (48); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_5S_2$ 430.0777; Found 430.0777.

Pyridinium ylide preparation



Sulfone ***3-154*** (0.200g, 0.726 mmol, 1.0 equiv), pyridinium salt ***3-160*** (0.268g, 1.5 equiv) were dissolved in DMF (7.0 mL, 0.1 M) and Et_3N (0.405 mL, 2.9 mmol, 4.0 equiv) was added. White suspension immediately turned to the dark red colour solution. The reaction mixture was stirred for 20h at r.t. before EtOAc (10 mL) and H_2O (10 mL) was added. The aqueous phase was extracted EtOAc (5x15 mL). Combined organic layers were washed using brine (2x15 mL) and dried over $MgSO_4$. Solvents were evaporated under reduced pressure to yield the crude product.

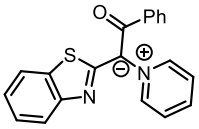
*benzo[d]thiazol-2-yl(cyano)(pyridin-1-ium-1-yl)methanide (**3-153a**)*



3-153a

Reaction was carried out using the general procedure with 0.200 g (0.726 mmol) of sulfone ***3-154***. Purification using flash chromatography (SiO_2; DCM/MeOH = 10:1) and concentration of the relevant fractions provided the ***3-153c*** as a orange solid (0.150 g, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.31 – 9.23 (m, 2H), 7.90 (ddd, *J* = 8.1, 1.1, 0.6 Hz, 1H), 7.52 (ddd, *J* = 7.8, 1.2, 0.5 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.09 – 7.00 (m, 1H), 6.29 (t, *J* = 6.9 Hz, 2H), 6.24 – 6.18 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.4, 154.6, 133.7, 132.1, 130.3, 126.5, 125.8, 122.7, 121.4, 120.8, 119.5, 80.5.; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{10}N_3S$ 252.0590; Found 252.0590.

*1-(benzo[d]thiazol-2-yl)-2-oxo-2-phenyl-1-(pyridin-1-ium-1-yl)ethan-1-ide (**3-153b**)*

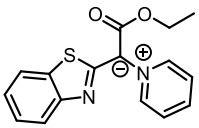


3-153b

Reaction was carried out using the general procedure with 0.200 g (0.726 mmol) of sulfone ***3-154***. Purification using flash chromatography (SiO_2; DCM/MeOH = 10:1) and concentration of the relevant fractions provided the ***3-153c*** as a light red solid (0.149 g, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (dd, *J* = 6.7, 1.3 Hz, 2H), 8.44 (t, *J* = 7.8 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.13 (m, 6H), 7.07 (t, *J* = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 152.1, 149.9, 144.4, 140.7, 133.1, 128.2, 127.9, 127.2, 126.9, 124.9, 121.0, 121.0, 120.9, 118.5*; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{15}N_2OS$ 331.0900; Found 331.0901.

*low quality spectrum due to fast equilibrium between resonance structures and slow decomposition during longer NMR experiments

*1-(benzo[d]thiazol-2-yl)-2-ethoxy-2-oxo-1-(pyridin-1-ium-1-yl)ethan-1-ide (**3-153d**)*

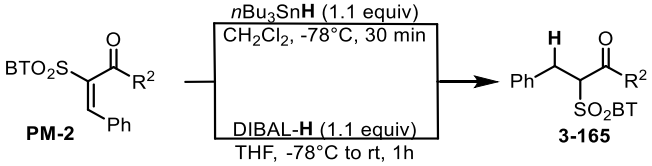


3-153d

Reaction was carried out using the general procedure with 0.200 g (0.726 mmol) of sulfone ***3-154***. Purification using flash chromatography (SiO_2; DCM/MeOH = 10:1) and concentration of the relevant fractions provided the ***3-153d*** as a violet solid (0.160 g, 74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.85 (bs, 2H), 8.10 (t, *J* = 7.1 Hz, 1H), 7.77 (t, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.21 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.08 – 6.99 (m, 1H), 4.28 (bs, 2H), 1.52 – 1.12 (m, 3H).; ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 153.1, 148.8, 140.6, 134.1, 126.1, 125.1, 120.8, 120.6, 118.3, 59.3, 15.1*; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}N_2O_2S$ 299.0849; Found 299.0848.

*lower quality spectrum due to fast equilibrium between resonance structures and slow decomposition during longer NMR experiments

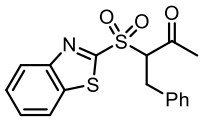
1,4 reduction of vinyl-sulfones



Procedure A: A **PM-2** (0.582 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6.0mL, 0.1 M) and solution was cooled down to -78°C (acetone/dry ice). After 15 minutes, *n*Bu_3SnH (0.138 mL, 1.1 equiv) was added and the mixture was stirred for an additional 30 minutes. After consumption of the starting material, CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the volatiles were removed under reduced pressure. The crude material was dissolved in CH_3CN (25mL) and washed with hexane (2x20mL) to remove any remaining organotin compounds. The resulting acetonitrile solution was concentrated under reduced pressure to provide the crude product. Procedure B: A **PM-2** (0.582 mmol, 1.0 equiv) was dissolved in THF (0.1 M) and the solution was cooled down to -78°C (acetone/dry ice). After 15 minutes, DIBAL (0.640 mL, 1.1 equiv, 1M solution in hexane) was added dropwise and the mixture was stirred at -78°C for 10 min and at r.t. for another 1 h (consumption of the SM monitored by TLC). After consumption of starting material, the reaction mixture was cooled down to -78°C and saturated aq. solution of Rochelle salt (5 mL) was added. The resulting mixture was allowed to warm to r.t. and stirred until the solution became clear (~ 6 hours). The whole mixture was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were

washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and solvents were removed under reduced pressure to provide the crude product.

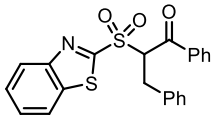
*3-(benzo[d]thiazol-2-ylsulfonyl)-4-phenylbutan-2-one (**3-165a**)*.



3-165a

Reaction was carried out using the described procedure with 0.200 g (0.583 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-165a*** as a yellow solid **Procedure A** (0.181 g, 91%); **Procedure B** (0.170 g, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 – 8.23 (m, 1H), 8.09 – 7.95 (m, 1H), 7.76 – 7.55 (m, 2H), 7.25 – 7.16 (m, 3H), 7.14 – 7.08 (m, 2H), 4.91 (dd, *J* = 9.2, 5.6 Hz, 1H), 3.55 – 3.36 (m, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 32.8, 32.9, 75.6, 122.5, 125.9, 127.5, 128.0, 128.5, 129.0, 129.1, 135.4, 137.3, 152.7, 164.1, 198.2; MS (ESI), *m/z* (%) 346 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3S_2$ 346.0566; Found 346.0563.

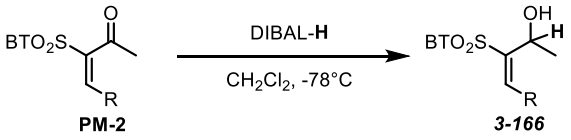
*2-(benzo[d]thiazol-2-ylsulfonyl)-1,3-diphenylpropan-1-one (**3-165b**)*.



3-165b

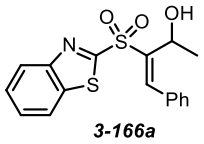
Reaction was carried out using the described procedure with 0.100 g (0.246 mmol) of vinyl-sulfone ***3-80a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided the ***3-165b*** as a colorless oil: **Procedure A:** (0.090 g, 90%); **Procedure B:** (0.081 g, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.18 (m, 1H), 8.01 – 7.92 (m, 1H), 7.79 – 7.69 (m, 2H), 7.68 – 7.53 (m, 2H), 7.49 – 7.38 (m, 1H), 7.35 – 7.24 (m, 2H), 7.20 – 7.04 (m, 5H), 5.82 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.82 – 3.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 33.7, 70.6, 122.4, 125.8, 127.3, 127.8, 128.4, 128.7, 128.9, 129.2, 134.1, 135.6, 137.0, 137.4, 152.6, 164.3, 191.0; MS (ESI), *m/z* (%) 408 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M+ H]^+$ Calcd for $C_{22}H_{18}NO_3S_2$ 408.0723; found 408.0725.

1,2-reduction of vinyl sulfones



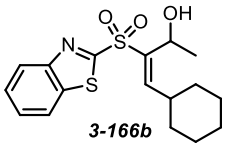
A **PM-2** (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL, 0.01 M) and resulting solution was cooled to -78°C (acetone/dry ice). After 15 minutes, DIBAL-H (0.320 mL, 1.1 equiv, 1M solution in hexane) was added dropwise and the mixture was stirred at -78°C for an additional 4 hours. After consumption of the starting material (checked via TLC), a saturated aqueous solution of Rochelle salt (5 mL) was added and the reaction mixture was allowed to warm to r.t. The resulting mixture was stirred until the solution became clear (cca 6 hours). The whole mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to provide the crude product.

*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-phenylbut-3-en-2-ol (**3-166a**)*.



Reaction was carried out using the described procedure with 0.100 g (0.291 mmol) of vinyl-sulfone ***3-59a***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided the ***3-166a*** as a pale-yellow oil (0.080 g, 80%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.14 (m, 1H), 8.07 (s, 1H), 8.02 – 7.97 (m, 1H), 7.67 – 7.52 (m, 4H), 7.45 (dd, *J* = 5.2, 2.0 Hz, 3H), 5.23 (q, *J* = 6.8 Hz, 1H), 1.63 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 22.2, 64.8, 122.5, 125.4, 127.7, 128.1, 129.0, 130.6, 130.6, 132.7, 136.7, 142.1, 145.3, 152.3, 169.2; MS (ESI), *m/z* (%) 346 $[M+1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_3S_2$ 346.0566; Found 346.0565.

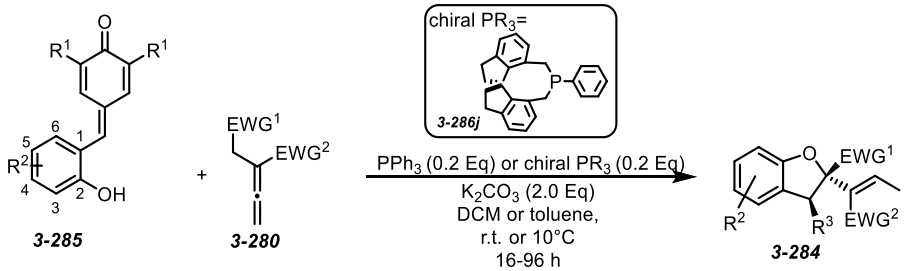
*(E)-3-(benzo[d]thiazol-2-ylsulfonyl)-4-cyclohexylbut-3-en-2-ol (**3-166b**)*.



Reaction was carried out using the described procedure with 0.050 g (0.143 mmol) of vinyl-sulfone ***3-59p***. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided the ***3-166b*** as a colorless oil (0.034 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.12 (m, 1H), 8.02 – 7.93 (m, 1H), 7.65 – 7.51 (m, 2H), 6.98 (d, *J* = 10.8 Hz, 1H), 5.04 (dt, *J* = 13.2, 6.8 Hz, 1H), 2.94 (d, *J* = 6.0 Hz, 1H), 2.76 (tdt, *J* = 10.8, 6.8, 3.6 Hz, 1H), 1.84 – 1.64 (m,

5H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.34 – 1.17 (m, 5H); $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 23.6, 25.2, 25.2, 25.7, 31.8, 31.9, 38.3, 65.1, 122.4, 125.4, 127.6, 128.0, 136.7, 140.7, 152.3, 154.2, 169.0; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3S_2$ 352.1036; Found 352.1034.

Formal (4+1)-Addition of Allenoates to para-Quinone Methides using PPh_3 or chiral PR_3



3-285a: R^1 = *t*-Bu, R^2 = H
3-285b: R^1 = *t*-Bu, R^2 = 5-Me
3-285c: R^1 = *t*-Bu, R^2 = 5-Br
3-285d: R^1 = *t*-Bu, R^2 = 5-Cl
3-285e: R^1 = *t*-Bu, R^2 = 5-OMe
3-285f: R^1 = *t*-Bu, R^2 = 5-F
3-285g: R^1 = *t*-Bu, R^2 = 5-*t*-Bu
3-285h: R^1 = *t*-Bu, R^2 = 4-Cl
3-285i: R^1 = *t*-Bu, R^2 = 3-Cl
3-285j: R^1 = *t*-Bu, R^2 = 6-Cl
3-285k: R^1 = Me, R^2 = H

3-280a: EWG^1 = CO_2Et, EWG^2 = CO_2Et
3-280b: EWG^1 = CO_2Et, EWG^2 = CO_2*t*-Bu
3-280c: EWG^1 = CO_2Et, EWG^2 = CO_2Bn

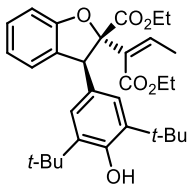
General Racemic Procedure:

The solution of the allenoate ***3-280*** (0.1 mmol, 2.0 eq.) in dry CH_2Cl_2 (2 mL) was added to the mixture of the *ortho*-hydroxy-*para*-quinone methide ***3-285*** (0.05 mmol, 1.0 eq.), K_2CO_3 (0.1 mmol, 2.0 eq.) and PPh_3 (0,01 mmol, 0.2 eq.). The resulting mixture was stirred under Argon atmosphere at r.t. for the indicated time. The reaction was diluted with DCM (5 mL), filtered over a pad of Na_2SO_4 and the filtration cake was washed with DCM (5x 5 mL). The solvent was removed under reduced pressure and the crude products were purified using column chromatography to give the products ***3-284*** in the given yields.

General Chiral Procedure:

The mixture of the *ortho*-hydroxy-*para*-quinone methide ***3-285*** (0.05 mmol, 1.0 eq.), K_2CO_3 (0.1 mmol, 2.0 eq.) and chiral PR_3 (0.01 mmol, 0.2 eq.) was cooled to 10°C and a solution of allenoate ***3-280*** (0.1 mmol, 2.0 eq.) in toluene (2 mL) was added. The resulting mixture was stirred under Ar-atmosphere at 10°C for the indicated time. The reaction was diluted by the addition of 5 mL DCM at 10°C, filtrated over the pad of Na_2SO_4 and washed with DCM (5x5mL). The solvent was removed under reduced pressure and the crude products were purified using column chromatography to give the chiral products ***3-284*** in the given yields.

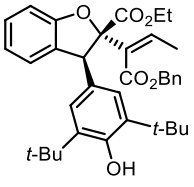
*ethyl (2S,3S)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284a**)*



3-284a

Starting from *p*-QM ***3-285a*** (15.5 mg, 0.05 mmol), allenoate ***3-280a*** (19.8 mg, 0.1 mmol) following the chiral procedure the reaction mixture was stirred for 20h and crude product purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 10:1) giving the enantioenriched product **3-284a** as yellow oil (22.6 mg, 89%, *e.r.*= 94:6). This reaction was also carried out on racemic 1.0 mmol scale giving the product in 86% yield after 20h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.82 (t,*J* = 7.2 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.36 (s, 18H), 1.89 (d, *J* = 7.2 Hz, 3H), 3.52-3.77 (m, 2H), 4.26-4.36 (m, 2H), 5.11 (s, 1H), 5.24 (s, 1H), 6.40 (q, *J* = 7.1 Hz, 1H), 6.83 (s, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 7.01-7.09 (m, 2H), 7.19-7.26 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.4, 14.2, 15.5, 30.2, 34.2, 55.8, 60.8, 61.1, 94.0, 110.2, 121.8, 125.7, 126.1, 128.9, 129.4, 130.0, 132.7, 133.2, 135.1, 153.0, 158.1, 167.2, 168.44 ppm. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{40}O_6$: 509.2898; Found: 509.2897. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{major} = 9.4 min, t_{minor} = 11.0 min); α_D^{23}= +64.6 (c = 0.15, $CHCl_3$)

*ethyl (2S,3S)-2-((Z)-1-(benzyloxy)-1-oxobut-2-en-2-yl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284b**)*

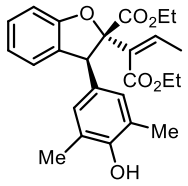


3-284b

Starting from *p*-QM ***3-285a*** (0.05 mmol, 15.5 mg) and allenoate ***3-280c*** (0.1 mmol, 27.3 mg) following the chiral procedure the reaction mixture was stirred for 24h and crude product was purified using column chromatography (silica gel, heptanes:aceton = 10:1 to 3:1) giving the enantioenriched product ***3-284b*** as a pale yellow oil (22.2 mg, 78%, *e.r.*= 94:6). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 81% yield after 16h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.71 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 18H), 1.84 (d, *J* = 7.1 Hz, 3H), 3.39 – 3.62 (m, 2H), 5.09 (s, 1H), 5.18 – 5.28 (m, 2H), 5.31 (d, *J* = 12.4 Hz, 1H), 6.41 (q, *J* = 7.1 Hz, 1H), 6.81 (s, 2H), 6.90 (td, *J* = 7.4, 1.0 Hz, 1H), 6.96 – 7.12 (m, 2H), 7.15 – 7.26 (m, 1H), 7.29 – 7.45 (m, 5H) ppm. ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ

13.6, 15.7, 30.4, 34.3, 56.0, 61.3, 66.8, 94.1, 110.3, 121.9, 125.8, 126.2, 128.3, 128.6, 128.9, 129.5, 130.0, 133.1, 133.4, 135.3, 135.9, 153.2, 158.2, 167.2, 168.5. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{42}O_6$ 571.3054; Found 571.3053. HPLC (CHIRAL ART Amylose-SA, eluent: Hexane:*i*-PrOH = 90:10, 0.5 mL/min, 10 °C, retention times: t_{minor} = 9.5 min, t_{major} = 11.6 min); α_D^{23} = +68 (c 0.5, $CHCl_3$).

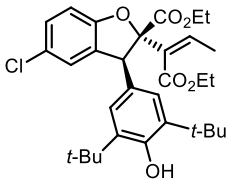
*ethyl (2S,3S)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-3-(4-hydroxy-3,5-dimethylphenyl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284c**)*



3-284c

Starting from *p*-QM ***3-285k*** (0.05 mmol, 11.3 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 24h and crude product was purified using column chromatography (silica gel, heptanes:aceton = 10:1 to 1:1) giving the enantioenriched product ***3-284c*** as a colourless solid (13 mg, 62%, *e.r.*=88:12). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 81% yield after 24h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.86 (d, *J* = 7.1 Hz, 3H), 2.14 (s, 6H), 3.60 – 3.81 (m, 2H), 4.20 – 4.39 (m, 2H), 4.50 (s, 1H), 5.20 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.66 (s, 2H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.95 – 7.07 (m, 2H), 7.16 – 7.25 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.6, 14.3, 15.6, 15.9, 55.4, 61.0, 61.5, 94.0, 110.5, 122.1, 122.5, 125.6, 128.9, 129.6, 129.7, 131.0, 132.8, 133.3, 151.7, 158.2, 167.3, 168.5 ppm. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{28}O_6$ 425.1959; Found 425.1960. HPLC (CHIRAL ART Amylose-SA, eluent: Hexane:*i*-PrOH = 90:10, 0.5 mL/min, 10 °C, retention times: t_{minor} = 13.6 min, t_{major} = 20.9 min); α_D^{24} = +62.8 (c 0.25, $CHCl_3$).

*ethyl (2S,3S)-5-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284d**)*

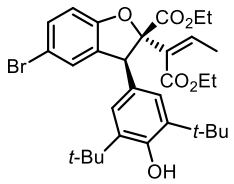


3-284d

Starting from *p*-QM ***3-285d*** (0.05 mmol, 17.2 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 21h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 7:1) giving the enantioenriched product

3-284d as a yellow oil (17 mg, 65%, 92:8). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 65% after 21h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.35 (m, 21H), 1.88 (d, *J* = 7.1 Hz, 3H), 3.47 – 3.84 (m, 2H), 4.28 (qd, *J* = 7.1, 1.4 Hz, 2H), 5.13 (s, 1H), 5.18 (s, 1H), 6.35 (q, *J* = 7.1 Hz, 1H), 6.81 (s, 2H), 6.95 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 7.16 (dd, *J* = 8.5, 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.5, 14.2, 15.5, 30.2, 34.2, 55.7, 60.9, 61.2, 94.6, 111.3, 125.7, 125.9, 126.5, 128.8, 129.3, 131.6, 132.9, 133.0, 135.4, 153.3, 156.6, 166.9, 168.0; HRMS (ESI) *m/z*: [M+H]$^{+}$ Calcd for $C_{31}H_{39}ClO_6$ 543.2508; Found 543.2007. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 98:2, 0.5 mL/min, 10 °C, retention times: t_{major} = 11.9 min, t_{minor} = 14.3 min); α_D^{22} = +65 (*c* 0.3, *$CHCl_3$*).

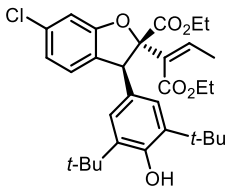
*ethyl (2S,3S)-5-bromo-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284e**)*



3-284e

Starting from *p*-QM ***3-284c*** (0.05 mmol, 19.5 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 48h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 7:1) giving the enantioenriched product ***3-284e*** as a yellow oil (21 mg, 72%, *e.r.*= 92:8). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 76% after 19h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.36 (m, 21H), 1.88 (d, *J* = 7.1 Hz, 3H), 3.48 – 3.85 (m, 2H), 4.28 (qd, *J* = 7.1, 1.3 Hz, 2H), 5.14 (s, 1H), 5.18 (s, 1H), 6.35 (q, *J* = 7.1 Hz, 1H), 6.81 (s, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 2.2, 0.9 Hz, 1H), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.3, 34.4, 55.7, 61.0, 61.4, 94.7, 112.0, 113.8, 126.0, 128.7, 129.4, 131.8, 132.2, 133.0, 133.2, 135.5, 153.4, 157.3, 167.0, 168.1; HRMS (ESI) *m/z*: [M+H]$^{+}$ Calcd for $C_{31}H_{39}BrO_6$ 587.2003; Found 587.2001. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{major} = 10.1 min, t_{minor} = 11.8 min); α_D^{23} = +36.3 (*c* 0.4, *$CHCl_3$*)

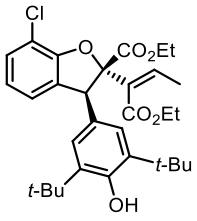
*ethyl (2S,3S)-6-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284f**)*



3-284f

Starting from *p*-QM ***3-285h*** (0.05 mmol, 17.2 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 68h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 7:1) giving the enantioenriched product ***3-284f*** as a colourless oil (19 mg, 70%, *e.r.*= 94:6). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 67% after 48h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 21H), 1.89 (d, *J* = 7.1 Hz, 3H), 3.47 – 3.76 (m, 2H), 4.28 (qd, *J* = 7.2, 2.1 Hz, 2H), 5.13 (s, 1H), 5.18 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.81 (s, 2H), 6.89 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.96 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.4, 34.4, 55.4, 61.0, 61.4, 95.0, 111.1, 122.1, 126.1, 126.4, 128.4, 129.5, 133.1, 133.1, 134.1, 135.4, 153.3, 159.0, 167.1, 168.1; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{39}ClO_6$ 543.2508; Found 543.2508. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 100:1, 0.5 mL/min, 10 °C, retention times: t_{major} = 12.4 min, t_{minor} = 15.4 min); α_D^{22} = +97.1 (c 0.35, *$CHCl_3$*).

*ethyl (2S,3S)-7-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284g**)*

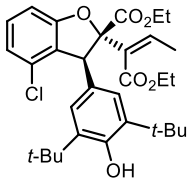


3-284g

Starting from *p*-QM ***3-285i*** (0.05 mmol, 17.2 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 42h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 15:1 to 4:1) giving the enantioenriched product ***3-284g*** as a colourless oil (16 mg, 59%, *e.r.*= 79:21). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 74% after 18h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.2 Hz, 3H), 1.35 (m, 21H), 1.88 (d, *J* = 7.1 Hz, 3H), 3.51 – 3.72 (m, 2H), 4.20 – 4.41 (m, 2H), 5.13 (s, 1H), 5.37 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.79 – 6.90 (m, 3H), 6.89 – 6.99 (m, 1H), 7.19 – 7.23 (m, 1H); ^{13}C{^{1}H}

NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.4, 34.4, 56.8, 61.0, 61.3, 94.7, 115.6, 122.7, 124.2, 126.2, 129.2, 129.4, 131.2, 132.4, 132.9, 135.4, 153.3, 154.5, 167.2, 167.8; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{39}ClO_6$ 543.2508; Found 543.2507. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 100:1, 0.5 mL/min, 10 °C, retention times: t_{major} = 11.9 min, t_{minor} = 18.5 min); α_D^{24} = +36 (c 0.25, $CHCl_3$).

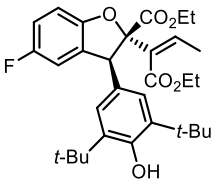
*ethyl (2S,3S)-4-chloro-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284h**)*



3-284h

Starting from *p*-QM ***3-285j*** (0.05 mmol, 17.2 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg). Following the racemic procedure the reaction mixture was stirred for 30h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 4:1) giving the racemic product ***3-284h*** as a yellow oil (22 mg, 81%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.80 (t, *J* = 7.1 Hz, 3H), 1.34 (m, 21H), 1.88 (d, *J* = 7.1 Hz, 3H), 3.55 – 3.78 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.09 (s, 1H), 5.20 (s, 1H), 6.35 (q, *J* = 7.1 Hz, 1H), 6.80 (bs, 2H), 6.88 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.7, 30.4, 34.3, 55.2, 61.1, 61.4, 94.3, 109.0, 122.4, 125.9, 127.7, 128.4, 130.1, 131.2, 132.9, 133.3, 135.2, 153.2, 158.7, 167.0, 168.0; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{39}ClO_6$ 543.2508; Found: 543.2507.

*ethyl (2S,3S)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-5-fluoro-2,3-dihydrobenzofuran-2-carboxylate (**3-284i**)*

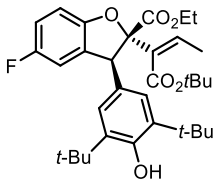


3-284i

Starting from *p*-QM ***3-285f*** (0.05 mmol, 16.4 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 17h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 4:1) giving the enantioenriched product ***3-284i*** as a yellow oil (20 mg, 77%, *e.r.*= 92:8). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 84% after 12h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.1 Hz, 3H),

1.35 (m, 21H), 1.88 (d, *J* = 7.1 Hz, 3H), 3.49 – 3.77 (m, 2H), 4.29 (qd, *J* = 7.1, 1.3 Hz, 2H), 5.13 (s, 1H), 5.19 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.76 (dd, *J* = 7.9, 2.6 Hz, 1H), 6.81 (s, 2H), 6.82 – 6.99 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.3, 34.4, 56.0, 61.0, 61.3, 94.8, 110.7 (d, *J* = 8.5 Hz), 112.7 (d, *J* = 25.0 Hz), 115.3 (d, *J* = 24.3 Hz), 126.1, 129.4, 131.1 (d, *J* = 8.7 Hz), 133.0, 133.2, 135.5, 153.4, 154.1, 158.4 (d, *J* = 238.3 Hz), 167.2, 168.3; $^{19}F\{^1H\}$ NMR (282 MHz, Chloroform-*d*) δ -122.7 (s, 1F); HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{39}FO_6$ 527.2803; Found 527.2802. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 99:1, 0.5 mL/min, 10 °C, retention times: t_{major} = 14.9 min, t_{minor} = 18.6 min); α_D^{22} = +101.7 (c 0.35, *CHCl₃*).

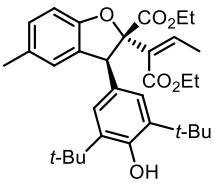
*ethyl (2S,3S)-2-((Z)-1-(tert-butoxy)-1-oxobut-2-en-2-yl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-fluoro-2,3-dihydrobenzofuran-2-carboxylate (**3-284j**)*



3-284j

Starting from *p*-QM ***3-285f*** (0.05 mmol, 16.4 mg) and allenoate ***3-280b*** (0.1 mmol, 22.6 mg). following the chiral procedure the reaction mixture was stirred for 96h and crude product was purified using column chromatography (silica gel, heptanes:aceton = 30:1 to 10:1) giving the enantioenriched product ***3-284j*** as a pale yellow oil (17 mg, 61%, *e.r.*= 83:17). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 65% after 96h. ^1H NMR (300 MHz, Chloroform-*d*) δ 0.75 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 18H), 1.54 (s, 9H), 1.87 (d, *J* = 7.1 Hz, 3H), 3.65 (q, *J* = 7.2 Hz, 2H), 5.12 (s, 1H), 5.19 (s, 1H), 6.27 (q, *J* = 7.0 Hz, 1H), 6.70 – 6.80 (m, 1H), 6.82 (bs, 2H), 6.84 – 6.97 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, Chloroform-*d*) δ 13.7, 15.4, 28.3, 30.4, 34.4, 55.9, 61.3, 82.0, 94.9, 110.6 (d, *J* = 8.5 Hz), 112.7 (d, *J* = 24.8 Hz), 115.2 (d, *J* = 24.2 Hz), 126.0, 129.6, 131.2 (d, *J* = 8.4 Hz), 131.3, 134.5, 135.5, 153.3, 154.2, 158.3 (d, *J* = 238.0 Hz), 166.3, 168.3 ppm. $^{19}F\{^1H\}$ NMR (282 MHz, Chloroform-*d*) δ -123.0 (s, 1F); HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{43}FO_6$ 555.3116; Found 555.3115. HPLC (CHIRAL ART Amylose-SA, eluent: Hexane:*i*-PrOH = 98:2, 0.5 mL/min, 10 °C, retention times: t_{minor} = 9.2 min, t_{major} = 13.3 min); α_D^{24} = +55.6 (c 0.5, *CHCl₃*).

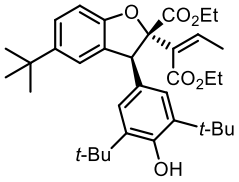
*ethyl (2S,3S)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-5-methyl-2,3-dihydrobenzofuran-2-carboxylate (**3-284k**)*



3-284k

Starting from *p*-QM ***3-285b*** (0.05 mmol, 16.2 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 16h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 7:1) giving the enantioenriched product ***3-284k*** as a yellow oil (17 mg, 65%, *e.r.*= 94:6). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 85% after 16h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.79 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 21H), 1.86 (d, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 3.48 – 3.76 (m, 2H), 4.28 (q, *J* = 7.4 Hz, 2H), 5.10 (s, 1H), 5.16 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.82 (s, 2H), 6.86 – 7.03 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 21.0, 30.4, 34.4, 56.0, 60.9, 61.2, 94.2, 109.9, 126.1, 126.2, 129.3, 129.5, 130.3, 131.2, 132.7, 133.5, 135.2, 153.2, 156.1, 167.3, 168.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{42}O_6$ 523.3054; Found 523.3054. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{major} = 9.6 min, t_{minor} = 11.1 min); α_D^{21}= +50.6 (*c* 0.15, $CHCl_3$).

*ethyl (2S,3S)-5-(tert-butyl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-2,3-dihydrobenzofuran-2-carboxylate (**3-284l**)*

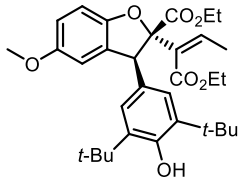


3-284l

Starting from *p*-QM ***3-285g*** (0.05 mmol, 18.3 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 19h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 4:1) giving the enantioenriched product ***3-284l*** as a colourless oil (22 mg, 78%, *e.r.*= 94:6). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 75% after 19h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.78 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 9H), 1.34 (m, 21H), 1.89 (d, *J* = 7.1 Hz, 3H), 3.60 (ddq, *J* = 38.0, 10.7, 7.2 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 5.10 (s, 1H), 5.26 (s, 1H), 6.39 (q, *J* = 7.1 Hz, 1H), 6.80 (s, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 2.1 Hz, 1H), 7.23 (dd, *J* = 8.5, 2.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.4, 31.8, 34.4, 34.6, 56.1, 60.9, 61.2, 94.4, 109.3, 122.9, 125.7, 126.4, 128.5, 130.1, 132.9, 133.4,

135.1, 144.9, 153.1, 156.3, 167.5, 168.8; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{35}H_{48}O_6$ 565.3524; Found 565.3522. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 98:2, 0.5 mL/min, 10 °C, retention times: t_{major} = 10.5 min, t_{minor} = 12.5 min); α_D^{22} = +21 (c 0.3, *CHCl₃*).

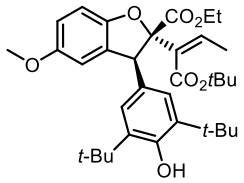
*ethyl (2S,3S)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-((Z)-1-ethoxy-1-oxobut-2-en-2-yl)-5-methoxy-2,3-dihydrobenzofuran-2-carboxylate (**3-284m**)*



5m

Starting from *p*-QM ***3-285e*** (0.05 mmol, 17 mg) and allenoate ***3-280a*** (0.1 mmol, 19.8 mg) following the chiral procedure the reaction mixture was stirred for 17h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 4:1) giving the enantioenriched product ***3-285m*** as a yellow oil (22 mg, 82%, *e.r.*= 92:8). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 85% after 22h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.80 (t, *J* = 7.2 Hz, 3H), 1.35 (m, 21H), 1.86 (d, *J* = 7.1 Hz, 3H), 3.49 – 3.72 (m, 2H), 3.71 (s, 3H), 4.17 – 4.49 (m, 2H), 5.10 (s, 1H), 5.17 (s, 1H), 6.36 (q, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.83 (s, 2H), 6.93 (d, *J* = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.7, 14.3, 15.6, 30.4, 34.4, 56.1, 56.3, 60.9, 61.2, 94.4, 110.6, 111.1, 114.6, 126.1, 129.9, 130.4, 132.8, 133.4, 135.3, 152.3, 153.2, 155.2, 167.3, 168.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{42}O_7$ 539.3003; Found 539.3004. HPLC (CHIRAL ART Cellulose-SB, eluent: Hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{major} = 12.0 min, t_{minor} = 14.1 min); α_D^{22} = +62 (*c* 0.45, *CHCl₃*).

*ethyl (2S,3S)-2-((Z)-1-(tert-butoxy)-1-oxobut-2-en-2-yl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-methoxy-2,3-dihydrobenzofuran-2-carboxylate (**3-284n**)*

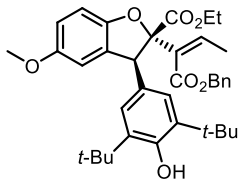


3-284n

Starting from *p*-QM ***3-285e*** (0.05 mmol, 17.0 mg) and allenoate ***3-280b*** (0.1 mmol, 22.6 mg) following the chiral procedure the reaction mixture was stirred for 96h and crude product was purified using column chromatography (silica gel, heptanes:EtOAc = 20:1 to 4:1) giving the enantioenriched product ***3-284n*** as a colourless oil (17 mg, 60%, *e.r.*= 85:15). This reaction was also carried out on racemic

0.05 mmol scale giving the product in 55% after 96h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.75 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 18H), 1.54 (s, 9H), 1.85 (d, *J* = 7.1 Hz, 3H), 3.65 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 5.10 (s, 1H), 5.18 (s, 1H), 6.27 (q, *J* = 7.0 Hz, 1H), 6.61 (d, *J* = 2.7 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.83 (bs, 2H), 6.91 (d, *J* = 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.8, 15.4, 28.3, 30.4, 34.4, 56.1, 56.2, 61.2, 81.8, 94.6, 110.5, 111.1, 114.5, 126.1, 130.1, 130.5, 131.0, 134.6, 135.3, 152.4, 153.2, 155.1, 166.5, 168.6; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{46}O_7$ 567.3316; Found 567.3315. HPLC (CHIRAL ART Amylose-SA, eluent: Hexane:*i*-PrOH = 95:5, 0.5 mL/min, 10 °C, retention times: t_{minor} = 9.1 min, t_{major} = 11.6 min); α_D^{24} = +35.7 (c 0.45, $CHCl_3$).

*ethyl (2S,3S)-2-((Z)-1-(benzyloxy)-1-oxobut-2-en-2-yl)-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-methoxy-2,3-dihydrobenzofuran-2-carboxylate (**3-284o**)*



3-284o

Starting from *p*-QM ***3-285e*** (0.05 mmol, 17 mg) and allenoate ***3-280c*** (0.1 mmol, 27.3 mg) following the chiral procedure the reaction mixture was stirred for 24h and crude product was purified using column chromatography (silica gel, heptanes:aceton = 10:1 to 3:1) giving the enantioenriched product ***3-284o*** as a pale yellow oil (20.1 mg, 76%, *e.r.*= 95:5). This reaction was also carried out on racemic 0.05 mmol scale giving the product in 50% after 24h. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 0.71 (t, *J* = 7.1 Hz, 3H), 1.34 (s, 18H), 1.83 (d, *J* = 7.1 Hz, 3H), 3.42 – 3.60 (m, 2H), 3.71 (s, 3H), 5.10 (s, 1H), 5.18 (s, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.31 (d, *J* = 12.4 Hz, 1H), 6.39 (q, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 2.7 Hz, 1H), 6.74 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.82 (bs, 2H), 6.91 (d, *J* = 8.7 Hz, 1H), 7.36 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, Chloroform-*d*) δ 13.6, 15.7, 30.4, 34.3, 56.1, 56.3, 61.2, 66.8, 94.4, 110.6, 111.1, 114.6, 126.2, 128.3, 128.6, 129.8, 130.3, 133.1, 133.2, 135.3, 135.9, 152.3, 153.2, 155.2, 167.2, 168.5; HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{37}H_{44}O_7$ 601.3160; Found 601.3162. HPLC (CHIRAL ART Amylose-SA, eluent: Hexane:*i*-PrOH = 90:10, 0.5 mL/min, 10 °C, retention times: t_{minor} = 11.3 min, t_{major} = 15.1 min); α_D^{23} = +66 (c 0.5, $CHCl_3$).

7 Appendices

7.1 One and Two-Carbon Homologation of Primary and Secondary Alcohols to Corresponding Carboxylic Esters Using β-Carbonyl BT Sulfones as a Common Intermediate

- Bon, D. J. Y. D.; Kováč, O.; Ferugová, V.; Zálešák, F.; Pospíšil, J. *J. Org. Chem.* **2018**, *83*, 4990–5001; IF^{2018}=4.745; https://doi.org/10.1021/acs.joc.8b00112

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One and Two-Carbon Homologation of Primary and Secondary Alcohols to Corresponding Carboxylic Esters Using β-Carbonyl BT Sulfones as a Common Intermediate

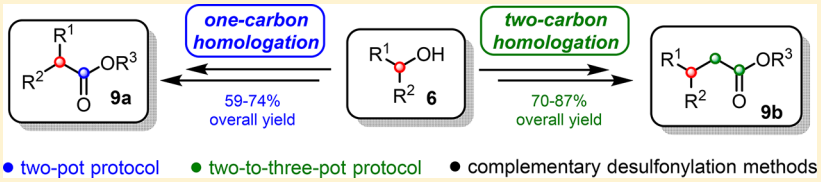
David J.-Y. D. Bon,[†] Ondřej Kováč,[†] Vendula Ferugová,[†] František Zálešák,[‡] and Jiří Pospíšil*[,†,§]

[†]Department of Organic Chemistry, Faculty of Science, Palacky University, tř. 17. listopadu 1192/12, CZ-771 46 Olomouc, Czech Republic

[‡]Institute of Molecular and Translation Medicine, Faculty of Medicine and Dentistry, Palacký University, Hněvotínská 5, 779 00 Olomouc, Czech Republic

[§]Laboratory of Growth Regulators, Palacký University and Institute of Experimental Botany AS CR, Šlechtitelů 27, 783 71 Olomouc, Czech Republic

Supporting Information



ABSTRACT: Herein we report the efficient one- and two-carbon homologation of 1° and 2° alcohols to their corresponding homologated esters via the Mitsunobu reaction using β-carbonyl benzothiazole (BT) sulfone intermediates. The one-carbon homologation approach uses standard Mitsunobu C−S bond formation, oxidation and subsequent alkylation, while the two-carbon homologation uses a less common C−C bond forming Mitsunobu reaction. In this latter case, the use of β-BT sulfone bearing esters lowers the pK_a sufficiently enough for the substrate to be used as a carbon-based nucleophile and deliver the homologated β-BT sulfone ester, and this superfluous sulfone group can then be cleaved. In this paper we describe several methods for the effective desulfonylation of BT sulfones and have developed methodology for one-pot alkylation-desulfonylation sequences. As such, overall, a one-carbon homologation sequence can be achieved in a two-pot (four step) procedure and the two-carbon homologation in a two-pot (three step) procedure (three-pot; four step when C-acid synthesis is included). This methodology has been applied to a wide variety of functionality (esters, silyl ethers, benzyls, heteroaryls, ketones, olefins and alkynes) and are all tolerated well providing good to very good overall yields. The power of our method was demonstrated in site-selective ingenol C20 allylic alcohol two-carbon homologation.

INTRODUCTION

Elongation of the existing molecular framework by one or two functionalized carbon atoms is one of the most commonly encountered operations in organic synthesis. Such transformation is in general achieved in two to four (or more) synthetic transformations with regard of the oxidation state of the starting substrate and the desired product. Most commonly, carbonyl compounds are employed as starting materials within such transformations.[1] Among these, Arndt−Eistert homologation,[2] Wittig reaction,[3] or Julia olefination methods[4] are most commonly employed to successfully achieve such transformations.

However, when it comes to primary and secondary alcohols, in comparison only few options are available when the above-mentioned extensions are attempted.[5,6] The standard protocols used to extend an alcohol by one or two carbons requires in principle 3 distinct synthetic operations: (1) activation of the alcohol (transformation to a good-leaving group: GLG); (2) displacement of activated alcohol by C-nucleophile (e.g., cyanide for one carbon extension[7] or carbonyl enolate for two carbon extension[8]); and (3) transformation of the introduced functional group into the desired functionality (e.g., hydrolysis of nitrile to carboxylic acid; hydrolysis and monodecarboxylation of dimethylmalonate, etc.).

One can immediately recognize that in situ direct activation of alcohols would be beneficial for the overall transformation. In this context the Mitsunobu reaction is the first transformation that comes to mind.[9] Indeed, mild reaction conditions, wide substrate scope and high stereospecificity make the Mitsunobu reaction the reaction of the choice when it comes to the transformation of the C−O bond in primary and secondary alcohols to C−O, C−S, and C−N bond. Unfortunately when it comes to a C−C bond formation, the method is rather limited. The reason is that the Mitsunobu reaction requires rather acidic nucleophiles to proceed[10] (upper pK_a limit is ≤15;[11] but in general pK_a of 11 to 12 is required to achieve satisfactory results[12]). From the literature it is known

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that although bis(phenylsulfonyl)methane **1** (pK_a = 12.2)[13] is a suitable C-nucleophile for the Mitsunobu reaction,[14] sulfoesters **2** (pK_a ~ 13 to 13.5) or diesters 3 (pK_a ~ 16)[15] are rather poor ones. At this stage we speculated that the electrophilic properties of benzothiazole in BT-sulfonyl ester **4**[16,17] might diminish the pK_a value of β-alkoxycarbonyl BT-sulfones **4** to the suitable level allowing their use in the Mitsunobu reaction (Figure 1).

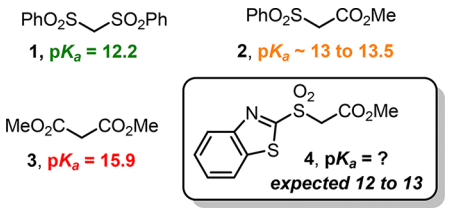
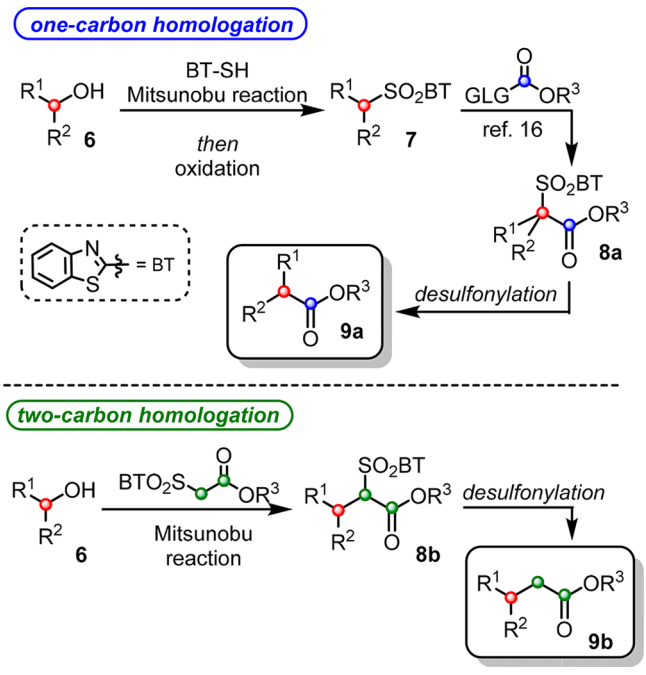


Figure 1. pK_a values of relevant C-acids used in the Mitsunobu reaction[13,15]

RESULTS AND DISCUSSION

Sometime ago we developed a short and efficient approach to β-carbonyl BT-sulfones,[18] and recently we have decided to extend their use as one and two carbon homologation-functionalization reagents (Scheme 1). In our design, common

Scheme 1. Planned One- and Two-Carbon Homologation Reaction Sequences



intermediate **8** of both homologation approaches plays a key role in our strategy, since we were expecting to develop the selective desulfonylation reaction of **8** to **9** under nucleophilic, radical or reductive-elimination conditions (Figure 2). Such approach should ensure wide functional group tolerance of the overall homologation transformations.

Since the first two steps of the one-carbon homologation approach have been already described,[18] our initial study was aimed to validate our homologation approaches focused on the Mitsunobu reaction required for the two-carbon homologation.

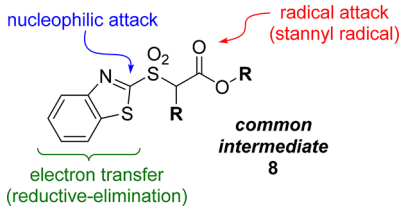


Figure 2. Three main approaches chosen to desulfonylate intermediate **8**.

Thus, the reaction of *tert*-butyl BT-sulfonyl acetate with primary alcohols was evaluated (Table 1, entry 1).[19] It was found that the use of ADDP (1.5 equiv) and PPh_3 (1.5 equiv) delivered the desired adduct in 87% yield (conditions A). Interestingly, when these conditions were applied to secondary or allylic alcohols (Table 1, entries 6 to 10), the desired product was obtained in very low yields. In these cases further reaction optimization revealed that the Mitsunobu reaction had to be carried out in the presence of DEAD instead of the ADDP-activating reagent (conditions B).[19]

Having secured the first step of the two carbon homologation process, we turned our attention to the desulfonylation step. First we decided to explore the reactivity of the nucleophilic attack to the C=N carbon atom in the BT group. Various nucleophilic reagents and conditions were screened[20] to accomplish the desired transformation and the combination of EtS^-Na^+/TFA were identified as the reagents of choice (Table 1, Method A).[21] In this one-pot two-step process the thiolate anion acts as the nucleophile that cleaves the BT-group. The resulting sodium sulfinate then, upon protonation with TFA, releases SO_2 and yields the desired ester **9** (Scheme 2).

Next we turned our attention to stannyl radical-mediated desulfonylation reaction. This approach is based on the work of Wnuk and Robbins[22] that previously reported selective and high yielding desulfonylation reaction of π-deficient heterocyclic sulfones. The desired transformation proceeded smoothly under "classical" nBu_3SnH (1.25 equiv)/AIBN (0.2 equiv)/benzene/80 °C conditions (Table 1, Method B) as well as catalytic Bu_3SnCl (0.10 equiv)/AIBN/PMHS/KF/H_2O/toluene/110 °C conditions[23] (Table 1, Method C) in very good to excellent yields.

Finally, the desulfonylation of the intermediate **8** was attempted using metal-mediated reductive conditions. Since many metals are known to promote desulfonylation of β-carbonyl phenyl sulfones,[24] we expected that the identification of the suitable conditions would be rather easy. Surprisingly this was not the case, and only SmI_2/MeOH and Zn_{dust}/AcOH systems were able to yield the desired desulfonylated products in good to excellent yields (Table 1, Methods D and E).[18] The disadvantage of the SmI_2/MeOH reduction conditions (Method D) is the use of large excess of SmI_2 (min 6.0 equiv) caused by the follow up reduction of the eliminated BT group to *N*-methyl-2-thioaniline **13** (Scheme 3). On the other hand, the transformation proceeds at low temperature and is rather fast. In the case of Zn_{dust}/AcOH, the reaction proceeds at RT in a mixture of THF/AcOH (5:1, V/V), and does not require anoxic or anhydrous conditions, making it more suitable for practical large-scale synthesis.

Having found suitable desulfonylation conditions our attention turned to a one-carbon homologation sequence. Since the synthesis of β-carbonyl BT-sulfones **8** has already

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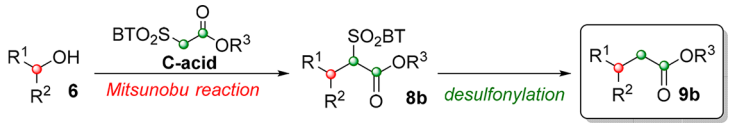
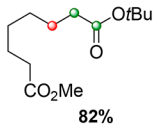
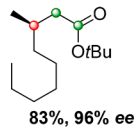
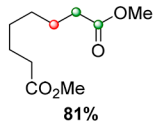
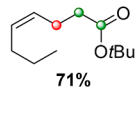
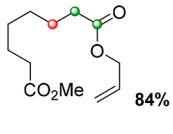
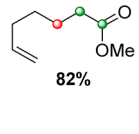
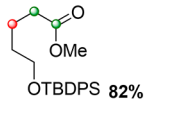
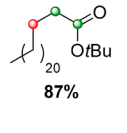
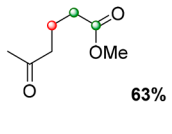
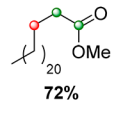
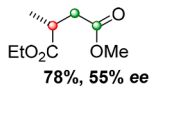
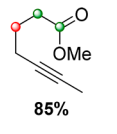
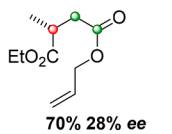
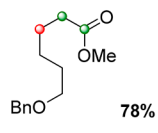
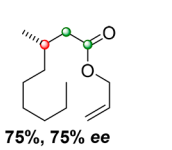
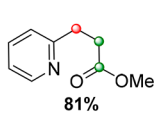
Table 1. Two-Carbon Homologation Two-Pot Process: Mitsunobu Reaction Followed by Desulfonylation



Entry	Mitsunobu reaction[a,b]	Desulfonylation method[b,c]	Product Overall yield[b,d]	Entry	Mitsunobu reaction[a,b]	Desulfonylation method[b,c]	Product Overall yield[b,d]
1	Cond. A (87%) Cond. B (53%)	**A** (44%) **B** (88%) **C** (81%) **D** (94%) **E** (78%)	 **82%**	9	Cond. A (18%) Cond. B (88%)	**A** (77%, 90% *ee*) **B** (94%, 95% *ee*) **C** (91%, 96% *ee*) **D** (81%, 96% *ee*) **E** (85%, 96% *ee*)	 **83%, 96% *ee***
2	Cond. A (89%) Cond. B (46%)	**A** (49%) **B** (87%) **C** (91%) **D** (85%) **E** (76%)	 **81%**	10	Cond. A (26%) Cond. B (86%)	**A** (35%) **B** (82%) **C** (83%) **D** (76%) **E** (74%)	 **71%**
3	Cond. A (91%) Cond. B (42%)	**A** (58%) **B** (87%) **C** (85%) **D** (92%) **E** (82%)	 **84%**	11	Cond. A (89%) Cond. B (46%)	**A** (83%) **B** (92%) **C** (90%) **D** (89%) **E** (89%)	 **82%**
4	Cond. A (88%) Cond. B (49%)	**A** (76%) **B** (93%) **C** (90%) **D** (86%) **E** (89%)	 **82%**	12	Cond. A (91%) Cond. B (62%)	**A** (45%) **B** (89%) **C** (93%) **D** (95%) **E** (69%)	 **87%**
5	Cond. A (78%) Cond. B (32%)	**A** (54%) **B** (81%) **C** (80%) **D** (71%) **E** (72%)	 **63%**	13	Cond. A (88%) Cond. B (56%)	**A** (34%) **B** (82%) **C** (84%) **D** (77%) **E** (71%)	 **72%**
6	Cond. A (11%) Cond. B (87%)	**A** (65%, 24% *ee*) **B** (90%, 55% *ee*) **C** (88%, 56% *ee*) **D** (90%, 55% *ee*) **E** (78%, 56% *ee*)	 **78%, 55% *ee***	14	Cond. A (91%) Cond. B (62%)	**A** (72%) **B** (88%) **C** (89%) **D** (93%) **E** (78%)	 **85%**
7	Cond. A (12%) Cond. B (79%)	**A** (42%, 12% *ee*) **B** (88%, 28% *ee*) **C** (81%, 27% *ee*) **D** (76%, 29% *ee*) **E** (73%, 28% *ee*)	 **70% 28% *ee***	15	Cond. A (78%) Cond. B (31%)	**A** (63%) **B** (89%) **C** (81%) **D** (82%) **E** (67%)	 **78%**
8	Cond. A (15%) Cond. B (83%)	**A** (73%, 71% *ee*) **B** (90%, 75% *ee*) **C** (89%, 75% *ee*) **D** (72%, 75% *ee*) **E** (76%, 75% *ee*)	 **75%, 75% *ee***	16	Cond. A (12%) Cond. B (92%)	**A** (72%) **B** (81%) **C** (84%) **D** (83%) **E** (71%)	 **81%**

[a]Conditions A: alcohol **6** (1.0 equiv), **C-acid** (1.2 equiv), ADDP (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0 °C to RT, 12 h; Conditions B: alcohol **6** (1.0 equiv), **C-acid** (1.2 equiv), DEAD (1.5 equiv), PPh_3 (1.5 equiv), toluene, 0 °C to RT, 6 h. [b]Refers to pure isolated compounds. [c]Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0 °C, 1 h, *then* TFA (20 equiv), 2 h; Method B: nBu_3SnH (1.25 equiv), AIBN (0.2 equiv), benzene, 80 °C, 1 h; Method C: nBu_3SnCl (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1 mL/mmol KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110 °C, 3 h. Method D: SmI_2 (6.5 equiv), MeOH (50 equiv), THF, −78 °C, 30 min; Method E: Zn_{dust} (5.0 equiv), THF/AcOH = 5:1 (V/V), 0 °C to RT, 8 h. [d]Yield over two steps related to the highest yielding Mitsunobu step and desulfonylation method.

been reported,[25] we have focused on the desulfonylation conditions (Table 2). At this stage we wished to develop a two-pot (four steps) protocol suitable for the direct transformation of alcohol **6** to ester **9a** (Table 2). The first "one-pot" transformation of alcohol **6** to BT-sulfone **7** via Mitsunobu reaction/oxidation sequence is well documented in the literature and commonly used in the context of total syntheses.[26] On the other hand the second part, one-pot two step procedure combining already known base-promoted coupling of sulfone **7** with carbonylating agent[18] with desulfonylation had to be developed. As a desulfonylating agent we decided to employ the Zn/AcOH system. Gratifyingly, the coupling adduct intermediate, upon the AcOH quench and subsequent Zn_{dust} addition, smoothly desulfonylated to yield the desired ester in good to very good overall yields (Table 2). Overall, the one-carbon homologation

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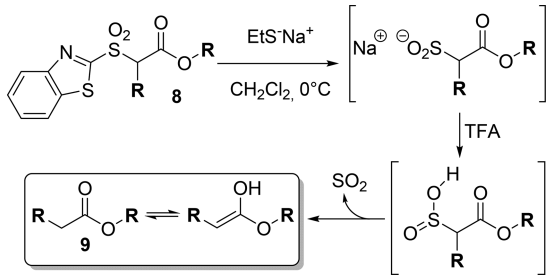
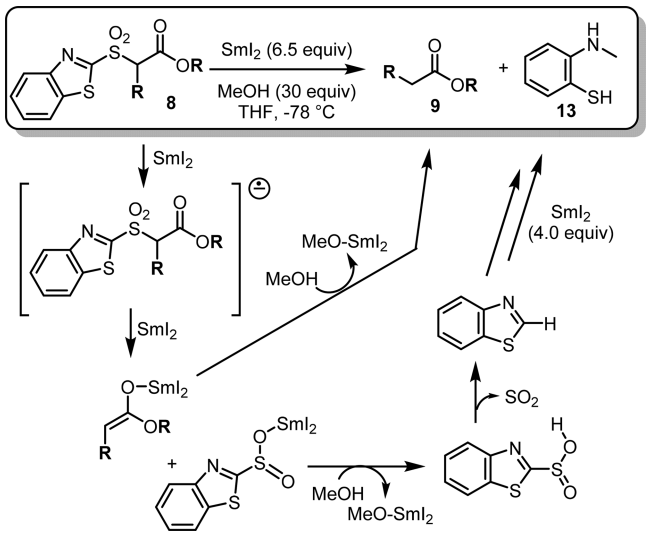
Scheme 2. EtS$^-$Na$^+$/TFA Promoted Desulfonylation Reaction[a]



[a]EtS$^-$Na$^+$, sodium ethanthiolate; TFA, trifluoracetic acid.

Scheme 3. SmI_2/MeOH Promoted Reductive Desulfonylation: Proposed Reaction Mechanism



reaction sequence can be easily achieved in a two-pot operationally simple protocol and yields the desired homologated products in good to excellent overall yields.

Finally the two important aspects of the two homologation sequences should be discussed, functional group tolerance and stereoselectivity. First, it was observed that radical-based (Methods B and C) and metal-mediated (Methods D and E) reductive desulfonylation conditions yields, in general, the desired esters in higher overall yields when compared to EtS$^-$Na$^+$/TFA (Method A) system (Table 1, Table 2). From the functional group point-of-view, esters (Table 1, entries 1, 2, 3, 6 and 7), TBDPS ether (Table 1, entry 4; Table 2, entry 5), benzyl ether (Table 1, entry 15), ketone (Table 1, entry 5), olefins (Table 1, entries 10 and 11; Table 2, entries 6 and 7), (hetero)aryls (Table 1, entry 16; Table 2, entries 1 and 2), and alkynes (Table 1, entry 14; Table 2, entry 8) are tolerated. From the stereoselectivity viewpoint, it was observed that the Mitsunobu reactions do not proceed with full inversion of the secondary alcohol and partial erosion of the inverted stereogenic center is observed (Table 1, entries 8 and 9). If ethyl lactate was used as the starting secondary alcohol, stereodegradation was even more significant (Table 1, entries 6 and 7). It seems that the degree of the stereo integrity strongly depends on the steric requirements of the C-acid. Additional epimerization of the alcohol-originated stereogenic center was also observed during the EtS$^-$Na$^+$/TFA promoted desulfonylation reaction (Table 1, entries 6 to 9).[27]

Finally, we were interested in evaluating the robustness and site-selectivity of our method. To evaluate the robustness, 2.52 g of *tert*-butyl tetracosonoate was prepared in 3 steps and 67% overall yield from the corresponding alcohol (Scheme 4).

To address the second challenge, two-carbon homologation of natural product ingenol (**14**) was attempted (Scheme 5). Recently, we have disclosed that C20 hydroxy group in **14** can be selectively (only one out of four hydroxy groups) transformed into its acetate.[36] Thus, we were interested if our C-acids could also be used in this reaction as nucleophiles. Gratifyingly, using our method the C20 hydroxy group was selectively in two steps and 45% overall yield transformed into the corresponding ingenol derivative **16**.

CONCLUSIONS

In conclusion, we have developed a new synthetic strategy allowing one and two-carbon homologation of primary and secondary alcohols in good to very good overall yields. The strong point of the overall processes is the desulfonylation reaction that could be carried out using several chemically different reaction conditions. In both cases, ester (one-carbon homologation) or alkyl acetate (two-carbon homologation) groups could be successfully introduced. Thus, developed methods are an alternative to already existing one- and two-carbon homologation/functionalization methods, and we believe that due to their versatile character they will soon find use in total synthesis of complex natural products.

EXPERIMENTAL SECTION

General Information. All reactions were performed in round-bottom flasks fitted with rubber septa using the standard laboratory techniques. Reactions sensitive to air and/or moisture were performed under a positive pressure of argon. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with silica gel (silica gel 60 F254). TLC plates were visualized by exposure to ultraviolet light and then were stained by submersion in basic potassium permanganate solution or in ethanolic phosphomolybdic acid solution followed by brief heating. Flash-column chromatography was carried out on silica gel (60 Å, 230−400 mesh) using Petroleum ether/EtOAc solvent mixtures (for appropriate ratios see experimental part). All reagents were obtained from commercial suppliers and were used without further purification. Diethyl azodicarboxylate (DEAD, 97%) was purchased from Alpha Aesar. Dry solvents were obtained using standard drying protocols: THF was distilled under argon from sodium benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; and CH_3CN from P_2O_5. Sulfones **7** and **8a** (Table 2), and **C-acids** used in two-carbon homologation protocol (Table 1) were prepared using the previously published protocols.[18] ^1H and ^{13}C spectra were recorded at 500, 400, or 300 MHz (for ^1H NMR), and 125, 100, or 75 MHz (for ^{13}C NMR), respectively, at 25 °C in $CDCl_3$. Chemical shifts (δ ppm) ^1H NMR are reported in a standard fashion with relative to the remaining $CHCl_3$ present in $CDCl_3$ (δH = 7.27 ppm). ^{13}C NMR chemical shifts (δ ppm) are reported relative to $CHCl_3$ (δC = 77.23 ppm, central line of triplet). Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quintet (quint), quintet of doublet (quintd), and multiplet (m), and coupling constants (J) are reported in Hz. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments. HRMS data were obtained using quadrupole/ion trap mass analyzer. Melting points (mp) were tested on a capillary melting point apparatus. The *ee* of products was determined by chiral GC using Chiraldex γ-TA capillary column, and Chiraldex β-PM column, respectively. The major enantiomer was determined with help of optical rotation measurement.

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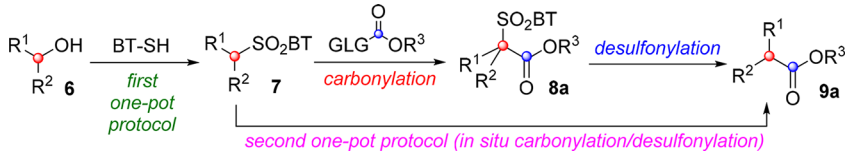
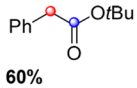
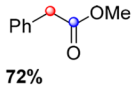
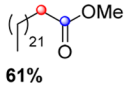
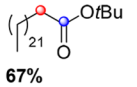
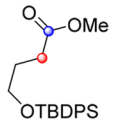
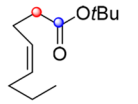
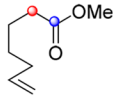
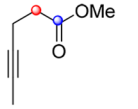
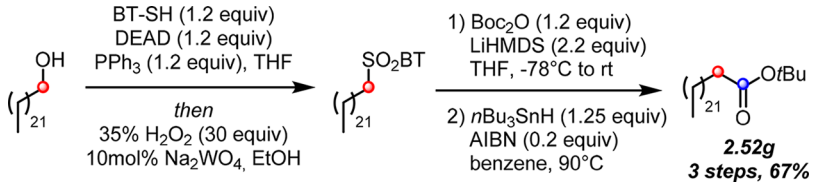
Table 2. One-Carbon Homologation via a Two-Pot Process: Mitsunobu Reaction Followed by Desulfonylation



Entry	1st one-pot protocol[a,b] / 2nd one-pot protocol[b,d]	Carbonylation step[b,c] (GLG group)	Desulfonylation method[b,d]	Product Overall yield[b,e]
1	96% / 62%	91% (OBoc)	**A** (65%) **B** (85%) **C** (75%) **D** (94%) **E** (67%)	 **60%**
2	96% / 75%	93% (CN)	**A** (45%) **B** (81%) **C** (80%) **D** (86%) **E** (67%)	 **72%**
3	89% / 69%	93% (CN)	**A** (34%) **B** (82%) **C** (84%) **D** (77%) **E** (71%)	 **61%**
4	89% / 75%	90% (OBoc)	**A** (45%) **B** (89%) **C** (93%) **D** (95%) **E** (69%)	 **67%**
5	90% / 82%	93% (CN)	**A** (76%) **B** (93%) **C** (90%) **D** (86%) **E** (89%)	 **74%**
6	78% / 75%	87% (OBoc)	**A** (35%) **B** (82%) **C** (83%) **D** (76%) **E** (74%)	 **59%**
7	89% / 75%	94% (CN)	**A** (83%) **B** (92%) **C** (90%) **D** (89%) **E** (89%)	 **67%**
8	86% / 71%	94% (CN)	**A** (72%) **B** (88%) **C** (89%) **D** (93%) **E** (78%)	 **61%**

[a]Conditions: alcohol **6** (1.0 equiv), **BT-SH** (1.2 equiv), DEAD (1.2 equiv), PPh_3 (1.2 equiv), THF, 0 °C to RT, 12 h *then* $Na_2WO_4{\cdot}2H_2O$ (0.1 equiv), 30% aq. H_2O_2 (30 equiv), EtOH, 0 °C to RT, 12 h. [b]Refers to pure isolated compounds. [c]Conditions: sulfone (1.0 equiv), carbonyl reagent (1.05 equiv), LiHMDS (2.2 equiv), THF, −78 °C, 30 min. [d]Method A: EtS^-Na^+ (2.0 equiv, CH_2Cl_2, 0 °C, 1 h, *then* TFA (20 equiv), 2 h; Method B: $n$$Bu_3SnH$ (1.25 equiv), AIBN (0.2 equiv), benzene, 80 °C, 1 h; Method C: $n$$Bu_3SnCl$ (0.10 equiv), AIBN (0.03 equiv), PMHS (0.1 mL/mmol KF), KF (2.0 equiv), toluene/H_2O = 4/1 (V/V), 110 °C, 3 h. Method D: SmI_2 (6.5 equiv), MeOH (30 equiv), THF, −78 °C, 30 min; Method E: Zn_{dust} (5.0 equiv), THF/AcOH = 5:1 (V/V), 0 °C to RT, 8 h. [e]Yields obtained over two one-pot protocols.

Scheme 4. Multigram Scale Synthesis of *tert*-Butyl Tetracosonoate



One-Carbon Homologation Protocol. General Procedure for Alcohol 6 to Sulfone 7 Transformation. A solution of benzo[*d*]-thiazol (BT-SH) (1.2 mmol, 1.2 equiv), PPh_3 (1.2 mmol, 1.2 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in THF (10 mL, 0.1 M) was cooled to 0 °C and DEAD (1.2 mmol, 1.2 equiv) was added. The resulting solution was allowed to warm to rt and stirred for 5−8 h. The resulting solution was diluted with EtOH (25 mL), cooled to 0 °C and $Na_2WO_4{\cdot}2H_2O$ (0.1 mmol, 0.1 equiv) in one portion. After 5 min at 0 °C, an aqueous 35% solution of H_2O_2 (30.0 mmol, 30 equiv) was added dropwise with a use of pipet Pasteur. The resulting yellowish solution was allowed to warm to rt and stirred at rt for 10 h. Water (50 mL) was added and the whole mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on SiO_2 using the appropriate eluting system.

*2-(Benzylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entries 1 and 2).*[19] The residue was purified by flash column chromatography (petroleum ether:EtOAc = 10:1 → 2:1) yielding the desired sulfone (0.278 g, 96%). mp = 112−113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1H, H-2), 7.23−7.38 (m, 5H), 7.56−7.75 (m, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.2, 122.5, 125.7, 126.5, 127.9, 128.2, 129.1, 129.4, 131.3, 137.3, 152.8, 165.4; MS (CI), m/z (%) 290 (43) $[M]^+$. Anal. Calcd for $C_{14}H_{11}NO_2S_2$: C, 58.11; H, 3.83; N, 4.84. Found: C, 58.14; H, 3.80; N 4.86.

*2-(Tricosanylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entries 3 and 4).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 50:1 → 10:1) yielding the desired sulfone (0.459 g, 89%). mp = 35−36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.8 Hz, 3H, H-3), 1.05−1.79 (m, 40H), 1.88 (dt, J = 12.1, 7.6 Hz, 2H, H-2), 3.51 (dd, J = 9.1, 7.0 Hz, 2H, H-1), 7.62 (quintd, J = 7.2, 1.4 Hz, 2H), 8.03 (dd, J =

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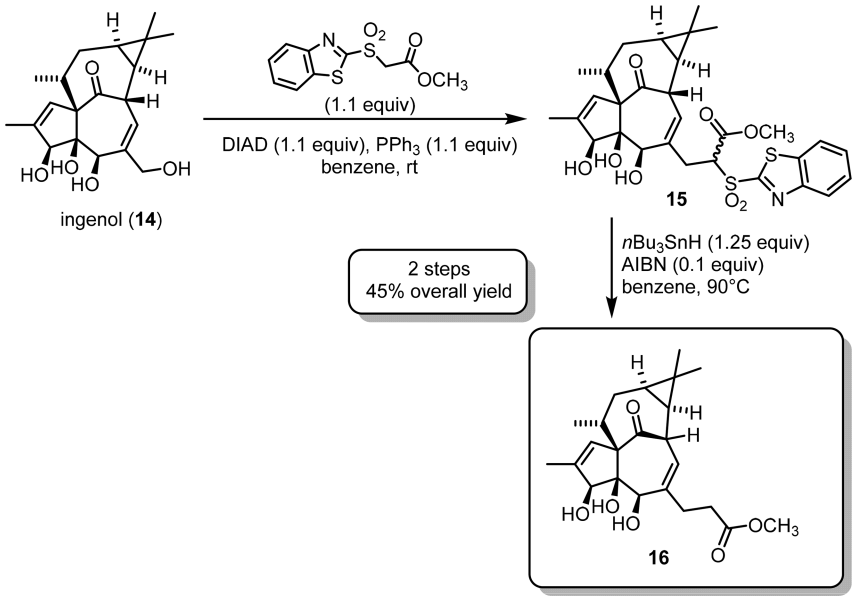
Scheme 5. Selective C20 Hydroxy Group Two-Carbon Homologation of Ingenol (14)



7.2, 1.7 Hz, 1H), 8.23 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (C-6), 22.9, 26.4, 27.1, 29.2, 29.3, 29.6, 29.8, 29.9, 31.5, 54.8 (C-1), 122.4, 125.6, 127.8, 128.2, 136.9, 152.9, 166.1 (C-4); MS (APCI), m/z (%) 522 (100) $[M]^+$. Anal. Calcd for $C_{30}H_{51}NO_2S_2$: C, 69.05; H, 9.85; N, 2.68. Found: C, 69.07; H, 9.84; N, 2.69.

*2-(Hex-5-en-1-ylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entry 7).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1) yielded the desired sulfone (0.250 g, 89%). mp = 42−43 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.36 (m, 2H), 1.67 (dt, J = 14.6, 6.7 Hz, 2H), 2.34 (dt, J = 12.1, 7.6 Hz, 2H, H-5), 3.48 (dd, J = 9.3, 7.0 Hz, 2H, H-2), 4.92−5.08 (m, 2H, H-7), 5.65 (ddt, J = 16.1, 11.2, 6.4 Hz, 1H, H-6), 7.63 (quintd, J = 7.2, 1.3 Hz, 2H), 8.01 (dd, J = 7.2, 1.7 Hz, 1H), 8.22 (dd, J = 7.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 28.7, 31.5, 55.6, 115.8, 122.54, 125.63, 127.83, 128.18, 133.8, 136.95, 152.93, 166.1; MS (APCI), m/z (%) 282 (100) $[M]^+$. Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.51; H, 5.38; N, 4.97.

*2-(Hex-3-yn-1-ylsulfonyl)benzo[d]thiazole (**7**, Table 2, Entry 8).*[19] Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1) yielded the desired sulfone (0.216 g, 86%). mp = 40−41 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (t, J = 2.3 Hz, 3H, H-6), 2.03−2.23 (m, 2H, H-2), 2.38−2.52 (m, 2H, H-3), 3.25 (t, J = 8.2 Hz, 2H, H-2), 7.64 (quintd, J = 7.2, 1.5 Hz, 2H), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.26 (dd, J = 7.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.2, 25.8, 60.6, 75.9, 78.2, 122.5, 125.9, 128.0, 128.5, 137.4, 152.8, 164.2 (C-1); MS (APCI), m/z (%) 280 (100) $[M]^+$. Anal. Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.89; H, 4.69; N, 5.01. Found: C, 55.90; H, 4.69; N, 5.00.

General Procedure for Sulfone 7 to Ester 9a Transformation. To a solution of sulfone 7 (1.0 mmol, 1.0 equiv) in THF (10 mL, 0.1 M) cooled to −78 °C was added LiHMDS (2.2 mL, 2.2 mmol, 2.2 equiv; 1.0 M sol. in THF). After 30 s acylating reagent (1.1 mmol, 1.1 equiv) in THF (1.1 mL, 1.0 M to acylating reagent) was added. The resulting mixture was stirred at −78 °C for an additional 30 min before it was allowed to warm to 0 °C (exchange of cooling baths). After 10 min at 0 °C, AcOH (5 mL, 0.2 M to BT-sulfone) was added and the resulting mixture was allowed to stir at RT for an additional hour. Zinc dust (0.327 g, 5.0 mmol, 5.0 equiv) was added and the resulting mixture was stirred at RT for 8 h. The mixture was diluted with EtOAc (50 mL), filtered through a pad of Celite and the filter cake was washed with an additional EtOAc (3× 25 mL). The combined organic filtrates were washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure to provide the crude product.

General Procedure for Two Step Sulfone 7 to ester 9a Transformation. *Reaction of the BT-Sulfone 7 with Carbonylating Reagent.* A solution of BT-sulfone 7 (1.0 mmol, 1.0 equiv) in THF (5 mL, 0.20 M) was cooled to −78 °C and LiHMDS (1.0 M sol. in THF) (2.2 mL, 2.2 mmol, 2.2 equiv) was added dropwise. Immediately after the addition, a solution of alkoxy carbonylating agent (Boc_2O or methyl cyanoformate (Mander's reagent) or allyl cyanoformate) (1.1 mmol, 1.1 equiv) in THF (0.5 mL) was added. The resulting mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C within 1 h and stirred at 0 °C for a further 30 min before sat. aq. sol. of NH_4Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3 × 75 mL) and the combined organic layers were washed with brine (50 mL), dried over $NaSO_4$, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system to yield desired β-carbonyl sulfone **8a**.

General Protocols for Desulfonylation Reaction. *Method A.*[21] A solution of BT-sulfone ester **8** (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL, 0.1 M) was cooled to 0 °C and EtS^-Na^+ (0.084 g, 1.0 mmol, 2.0 equiv) was added. The resulting mixture was stirred at 0 °C for 1 h and trifluoroacetic acid (0.766 mL, 10.0 mmol, 20 equiv) was added. Stirring was continued for the next 2 h prior to toluene (10 mL) addition. The resulting mixture was evaporated under reduced pressure to provide the crude product.

Method B.[22] To a solution of BT-sulfone ester **8** (0.1 mmol, 1.0 equiv) in benzene (0.5 mL, 0.2 M) was added nBu$_3$SnH (0.336 mL, 0.125 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.003 g, 0.02 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to RT (heating bath removed). CH_3CN (10 mL) was added and the reaction mixture was extracted with n-pentane (3× 15 mL). The acetonitrile layer was dried over $MgSO_4$, filtered and evaporated to dryness to provide the crude product.

Method C.[23] Argon was bubbled (5 min) through a solution of BT-sulfone ester **8** (0.25 mmol, 1.0 equiv), Bu_3SnCl (0.007 mL, 0.025 mmol, 0.1 equiv), and AIBN (0.002 g, 0.008 mmol, 0.03 equiv) in toluene (2 mL) for 15 min. The solution was heated at reflux and PMHS (0.05 mL) and KF (0.03 g, 0.5 mmol, 2.0 equiv; in H_2O (0.5 mL)) were sequentially added in three portions (t = 0 min, 1 h and 2 h). After 3 h, the reaction mixture was cooled to RT and volatiles were removed under reduced pressure. The residue was partitioned between EtOAc (10 mL) and sat. aq. $NaHCO_3$ (10 mL). Resulting layers were separated and the aqueous layer was extracted with EtOAc (2 × 10

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mL). The organic layers were washed with brine (10 mL), dried over Na_2SO_4, and evaporated to dryness to provide the crude product.

Method D. A solution of SmI_2 (6.25 mL, 0.625 mmol, 6.25 equiv; 0.1 M solution in THF) was placed under inert atmosphere and MeOH (0.202 mL, 5.0 mmol, 50 equiv) was added. The resulting mixture was cooled to −78 °C (dry ice/acetone) and BT-sulfone ester **8** (0.1 mmol, 1.0 equiv) in dry THF (1 mL) was added. If the typical deep blue color of SmI_2 faded upon the sulfone solution addition, additional SmI_2 was added until the deep blue color persisted. The resulting mixture was stirred at −78 °C for an additional 15 min before the sat. aq. NH_4Cl (10 mL) was added. The resulting phases were separated and the water layer was extracted with EtOAc (3× 15 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (10 mL), brine (10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to provide the crude product.

Method E. To a solution of BT-sulfone ester **8** (0.5 mmol, 1.0 equiv) in THF (5 mL, 1.0 M) was added zinc dust (0.163 g, 2.5 mmol, 5.0 equiv), the mixture was cooled to 0 °C and AcOH (1.0 mL) was added. The reaction was allowed to warm and stirred at RT for 8 h. The mixture was diluted with EtOAc (25 mL), filtered through a pad of Celite and the filter cake was washed with EtOAc (3× 20 mL). The combined filtrates were washed with brine (10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to provide the crude product.

*tert-Butyl 2-phenylacetate (**9**, Table 2, Entry 1).*[28] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as colorless oil (R_f = 0.94, petroleum ether:EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.56 (s, 2H), 7.11−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 42.8, 80.9, 122.0, 123.7, 125.7, 126.3, 126.9, 128.6, 129.3, 134.8, 154.0, 171.0; MS (CI$^+$), *m*/*z* (%) 193 (38) [M + H]$^+$; HRMS (ESI) calcd for $C_{12}H_{16}NaO_2$ [M + Na]$^+$: 215.1043, found 215.1044.

*Methyl 2-phenylacetate (**9**, Table 2, Entry 2).*[29] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as colorless oil (R_f = 0.88, petroleum ether:EtOAc = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 2H), 3.69 (s, 3H), 7.14−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.2, 52.1, 127.1, 128.6, 129.3, 134.0, 172.1; HRMS (ESI) calcd for $C_9H_{10}NaO_2$ [M + Na]$^+$: 173.0568, found 173.0573. Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 72.01; H, 6.70.

*tert-Butyl tetracosanoate (**9**, Table 2, Entry 4; Table 1, Entry 12).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1) and yielded the targeted compound as white solid (R_f = 0.91, petroleum ether:EtOAc = 20:1). mp = 67−69 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 1.26 (s, 40H), 1.45 (s, 9H), 1.51−1.67 (m, 2H), 2.20 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.4, 28.3, 29.3, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 35.9, 80.1, 173.5; IR (film) ν^{-1} 3008 (w), 2982 (w), 2925 (m), 2853 (m), 1724 (m), 1467 (m), 1369 (m), 1155 (s), 908 (s), 729 (s); MS (APCI$^+$), *m*/*z* (%) 426 (12) [M + H]$^+$. Anal. Calcd for $C_{28}H_{56}O_2$: C, 79.28; H, 13.38. Found: C, 78.86; H, 13.38.

*Methyl tetracosanoate (**9**, Table 2, Entry 3; Table 1, Entry 13).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as white solid (R_f = 0.91, petroleum ether:EtOAc = 4:1). mp = 58−59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.26 (s, 40H), 1.62 (q, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 34.3, 51.6, 174.5; IR (film) ν^{-1} 2921 (s), 2946 (s), 1749 (m), 1477 (m), 1467 (w), 1169 (m), 904 (s); MS (APCI$^+$), *m*/*z* (%) = 383 (100) [M]$^+$. Anal. Calcd for $C_{25}H_{50}O_2$: C, 78.47; H, 13.17. Found: C, 78.53; H, 13.24.

*1-(tert-Butyl) 8-methyl octanedioate (**9**, Table 1, Entry 1).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as colorless viscous oil (R_f = 0.71, petroleum ether:EtOAc = 10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (dq, *J* = 7.3, 3.4 Hz, 4H), 1.44 (s, 9H), 1.51−1.70 (m, 4H), 2.20 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.1, 28.3, 28.9, 29.0, 34.2, 35.7, 51.7, 80.2, 173.4, 174.4; IR (film) ν^{-1} 2977 (w), 2948 (w), 2932 (m), 1733 (s), 1458 (m), 1434 (w), 1369 (m), 848 (w); MS (APCI$^+$), *m*/*z* (%) = 245 (27) [M + H]$^+$. Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.22; H, 9.95.

*Dimethyl octanedioate (**9**, Table 1, Entry 2).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1) and yielded the targeted compound as colorless viscous oil (R_f = 0.73, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (quint, *J* = 3.7 Hz, 4H), 1.62 (t, *J* = 7.3 Hz, 4H), 2.30 (td, *J* = 7.3, 2.2 Hz, 4H), 3.66 (d, *J* = 2.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.9, 34.1, 51.7, 174.3; IR (film) ν^{-1} 2948 (w), 2929 (w), 1739 (s), 1436 (m); MS (APCI$^+$), *m*/*z* (%) 203 (55) [M + H]$^+$. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.67; H, 9.21.

*1-Allyl 8-methyl octanedioate (**9**, Table 1, Entry 3).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1) and yielded the targeted compound as colorless oil (R_f = 0.68, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (quint, *J* = 3.6 Hz, 4H), 1.53−1.76 (m, 4H), 2.31 (q, *J* = 7.8 Hz, 4H), 3.65 (d, *J* = 2.2 Hz, 3H), 4.53−4.62 (m, 2H), 5.22 (dt, *J* = 10.4, 1.5 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.80−6.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.9, 34.2, 34.3, 51.6, 65.1, 118.3, 132.5, 173.5, 174.3; IR (film) ν^{-1} 2949 (w), 2926 (w), 1732 (s), 1435 (m); MS (APCI$^+$), *m*/*z* (%) 229 (100) [M + H]$^+$. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.96; H, 9.04.

*Methyl 5-((tert-butyldiphenylsilyl)oxy)pentanoate (**9**, Table 1, Entry 4; Table 2, Entry 5).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as a slightly yellow oil (R_f = 0.83, petroleum ether:EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.53−1.70 (m, 2H), 1.70−1.83 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 3.68 (s, 3H), 7.32−7.48 (m, 7H), 7.60−7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.6, 27.1, 32.1, 34.0, 51.7, 63.6, 127.8, 129.8, 134.1, 135.8, 174.3; IR (film) ν^{-1} 2949 (w), 2950 (w), 2940 (w), 2895 (w), 1739 (s), 1429 (m), 1111 (s); MS (APCI$^+$), *m*/*z* (%) = 371 (48) [M + H]$^+$. Anal. Calcd for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.49; H, 8.25.

*Methyl 5-oxohexanoate (**9**, Table 1, Entry 5).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1) and yielded the targeted compound as a colorless oil (R_f = 0.65, petroleum ether:EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (quint, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 30.1, 33.2, 42.6, 51.8, 173.8, 208.2; IR (film) ν^{-1} 2961 (w), 2952 (w), 1729 (s), 1712 (s), 1438 (m), 1253 (m); MS (APCI$^+$), *m*/*z* (%) 145 (73) [M + H]$^+$. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.57; H, 8.19.

*1-Ethyl 4-methyl (R)-2-methylsuccinate (**9**, Table 1, Entry 6).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1 → 4:1) and yielded the targeted compound as a colorless oil (R_f = 0.70, petroleum ether:EtOAc = 4:1). α_D^{23} = +3.02 (*c* 1.2, *CHCl*$_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.1 Hz, 3H), 2.38 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.72 (dd, *J* = 16.4, 8.2 Hz, 1H), 2.89 (dq, *J* = 13.9, 7.1 Hz, 1H), 3.66 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 17.1, 36.0, 37.5, 51.8, 60.8, 172.4, 175.3; IR (film) ν^{-1} 2963 (w), 2949 (w), 1730 (s), 1716 (s), 1434 (m), 1251 (m); MS (CI$^+$), *m*/*z* (%) 175 (41) [M + H]$^+$; HRMS (EI$^+$), *m*/*z* calcd. for $C_8H_{14}O_4$ [M]$^+$: 174.0892, found 174.0886; *ee* = 56%. The *ee* of the product was determined by chiral GC using γ-TA column (80 °C, $\tau_{(S)\text{-minor}}$ = 30.6 min, $\tau_{(R)\text{-major}}$ = 34.3 min). The major enantiomer was determined to be (*R*) with help of optical rotation measurement (the sign of the measured value was compared with known values).[30]

*4-Allyl 1-ethyl (R)-2-methylsuccinate (**9**, Table 1, Entry 7).* The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 10:1) and yielded the targeted compound as a colorless oil (R_f = 0.55, petroleum ether:EtOAc = 10:1). α_D^{23} = +0.62 (*c* 1.11, *CHCl*$_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ

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1.21 (d, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 2.42 (dd, J = 16.4, 6.0 Hz, 1H), 2.76 (dd, J = 16.4, 8.2 Hz, 1H), 2.89 (dt, J = 14.0, 7.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 4.57 (dt, J = 5.7, 1.3 Hz, 2H), 5.21 (dq, J = 10.5, 1.2 Hz, 1H), 5.30 (dq, J = 17.1, 1.5 Hz, 1H), 5.89 (ddt, J = 17.3, 10.4, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 17.2, 36.0, 37.7, 60.8, 65.4, 118.4, 132.2, 171.7, 175.3; IR (film) ν^{-1} 2990 (w), 2979 (w), 2921 (w), 2875 (w), 1729 (s), 1381 (m); MS (CI^+), m/z (%) 201 (100) $[M + H]^+$; HRMS(EI^+), m/z calcd for $C_{10}H_{17}O_4$ $[M + H]^+$: 201.1127, found 201.1125; *ee* = 28%. The *ee* of the product was determined by chiral GC using γ-TA column (110 °C (25 min) → 10 °C/min until 170 °C → 170 °C (15 min), $\tau_{(S)\text{-minor}}$ = 32.50 min, $\tau_{(R)\text{-major}}$ = 32.81 min). The major enantiomer was determined to be (R) with help of optical rotation measurement (the sign of the measured value was compared with known values).[31]

Allyl (S)-3-methylnonanoate (**9**, Table 1, Entry 8). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.75, petroleum ether:EtOAc = 10:1). α_D^{23} = −0.14 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.2 Hz, 7H), 0.93 (d, J = 6.6 Hz, 3H), 1.13−1.38 (m, 10H), 1.96 (quint, J = 6.5 Hz, 1H), 2.13 (dd, J = 14.7, 8.2 Hz, 1H), 2.33 (dd, J = 14.6, 6.1 Hz, 1H), 4.57 (dd, J = 5.7, 1.5 Hz, 2H), 5.22 (dt, J = 10.4, 1.2 Hz, 1H), 5.31 (dt, J = 17.2, 1.4 Hz, 1H), 5.91 (dddd, J = 17.4, 11.5, 5.7, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.9, 22.8, 27.1, 29.6, 30.6, 32.0, 36.9, 42.0, 65.0, 118.2, 132.6, 173.1; IR (film) ν^{-1} 2959 (w), 2927 (w), 2855 (w), 1739 (s), 1381 (w); MS (CI^+), m/z (%) = 213 (100) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{13}H_{24}O_2Na$ $[M + Na]^+$: 235.1669, found 235.1669. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39; Found: C, 73.55; H 11.41; *ee* = 75%. The *ee* of the product was determined by chiral GC using CHIRALDEX β-PM column (100 °C (25 min) → 10 °C/min until 160 °C → 160 °C (4 min), $\tau_{(R)\text{-minor}}$ = 27.80 min, $\tau_{(S)\text{-major}}$ = 29.05 min). The major enantiomer was determined to be (S) with help of optical rotation measurement (the sign of the measured value was compared with known values).[32]

tert-Butyl (R)-3-methylnonanoate (**9**, Table 1, Entry 9). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 50:1) and yielded the targeted compound as a colorless oil (R_f = 0.81, petroleum ether:EtOAc = 50:1). α_D^{23} = +1.07 (*c* 1.1, *hexane*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 7.6 Hz, 2H), 1.17−1.40 (m, 6H), 1.44 (s, 9H), 1.46−1.64 (m, 4H), 1.89 (q, J = 5.2 Hz, 1H), 2.00 (dd, J = 14.2, 8.0 Hz, 1H), 2.20 (dd, J = 14.1, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.9, 22.9, 26.8, 28.3, 30.7, 32.2, 36.9, 43.4, 80.1, 173.0; IR (film) ν^{-1} = 2956 (w), 2930 (w), 2853 (w), 1702 (s), 1465 (w); MS (CI^+), m/z (%) 229 (100) $[M + H]^+$; HRMS(CI^+), m/z calcd. for $C_{14}H_{29}O_2H$ $[M + H]^+$: 229.2162, found 229.2161; *ee* = 95%. The *ee* of the product was determined by chiral GC using CHIRALDEX β-PM column (100 °C (25 min) → 10 °C/min until 160 °C → 160 °C (4 min), $\tau_{(R)\text{-major}}$ = 27.49 min, $\tau_{(S)\text{-minor}}$ = 28.38 min). The major enantiomer was determined to be (R) with help of optical rotation measurement (the sign of the measured value was compared with known values).[32]

tert-Butyl (Z)-oct-4-enoate (**9**, Table 1, Entry 10; Table 2, Entry 6). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.98, petroleum ether:EtOAc = 4:1). (E/Z) = 2:>95. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.38 (dt, J = 14.9, 7.5 Hz, 2H), 1.45 (s, 9H), 2.03 (dd, J = 13.9, 6.7 Hz, 2H), 2.20−2.39 (m, 4H), 5.37 (quintd, J = 10.8, 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.0, 23.2, 28.3, 29.5, 35.8, 80.3, 128.0, 131.2, 172.0; IR (film) ν^{-1} 2959 (w), 2934 (w), 2921 (w), 1733 (s), 1460 (w); MS ($APCI^+$), m/z (%) 199 (24) $[M + H]^+$; HRMS (EI^+), m/z calcd. for $C_{12}H_{22}O_2H$ $[M + H]^+$: 199.1693, found 199.1695. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.73; H, 11.10.

Methyl hept-6-enoate (**9**, Table 1, Entry 11; Table 2, Entry 7). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 100:1 → 20:1) and yielded the targeted compound as a colorless oil (R_f = 0.88, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (quint, J = 7.5, 7.1 Hz, 2H), 1.58−1.72 (m, 2H), 2.07 (q, J = 7.2 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 4.95 (dq, J = 10.1, 1.2 Hz, 1H), 5.01 (q, J = 17.4, 2.0 Hz, 1H), 5.79 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 28.5, 33.5, 34.1, 51.7, 114.9, 138.6, 174.3; HRMS (ESI^+), m/z calcd. for $C_8H_{14}O_2Na$ $[M + Na]^+$: 165.0886, found 165.0892.

tert-Butyl tetracosanoate (**9**, Table 1, Entry 12; Table 2, Entry 4). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as a colorless solid (R_f = 0.92, petroleum ether:EtOAc = 4:1). mp = 62−63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 3H), 1.28 (s, 40H), 1.48 (s, 9H), 1.63 (quint, J = 7.1 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 22.8, 25.2, 28.0, 29.3, 29.5, 29.6, 29.7, 29.83, 29.89, 29.93, 32.2, 34.3, 80.1, 174.8; MS (CI), m/z (%) 426 (72) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{28}H_{56}O_2Na$ $[M + Na]^+$: 447.41725, found 447.41733.

Methyl tetracosanoate (**9**, Table 1, Entry 13; Table 2, Entry 3). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1) and yielded the targeted compound as a colorless solid (R_f = 0.88, petroleum ether:EtOAc = 4:1). mp = 53−54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1.26 (s, 40H), 1.62 (quint, J = 7.1 Hz, 2H), 2.31 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 32.2, 34.3, 51.6, 174.5; MS (APCI), m/z (%) 383 (23) $[M + H]^+$; HRMS (ESI^+), m/z calcd. for $C_{25}H_{50}O_2Na$ $[M + Na]^+$: 405.3703, found 405.3705.

Methyl hept-5-ynoate (**9**, Table 1, Entry 14; Table 2, Entry 8). The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as a colorless oil (R_f = 0.82, petroleum ether:EtOAc = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (t, J = 2.5 Hz, 3H), 1.83 (quint, J = 7.1 Hz, 2H), 2.20 (ddq, J = 7.1, 5.1, 2.5 Hz, 2H), 2.44 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.6, 22.6, 26.1, 34.4, 51.7, 76.6, 78.1, 174.0; MS (APCI), m/z (%) 141 (15) $[M + H]^+$; HRMS (EI^+), m/z calcd. for $C_8H_{12}O_2H$ $[M + H]^+$: 141.0910, found 141.0919.

Methyl 6-(benzyloxy)hexanoate (**9**, Table 1, Entry 15).[33] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 4:1 → 2:1 → 1:1) and yielded the targeted compound as colorless oil (R_f = 0.16, petroleum ether:EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.52 (m, 2H), 1.62−1.70 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 3.49 (t, J = 6.5 Hz, 2H), 3.69 (s, 3H), 4.52 (s, 2H), 7.33−7.43 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 25.6, 29.5, 33.7, 51.5, 70.5, 73.0, 127.8, 128.0, 128.3, 138.1, 174.2; HRMS (ESI) calcd. for $C_{14}H_{20}NaO_3$ $[M + Na]^+$: 259.1305, found 259.1301. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.50.

Methyl 3-(pyridin-2-yl)propanoate (**9**, Table 1, Entry 16).[34] The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 10:1 → 4:1→ 2:1) and yielded the targeted compound as colorless oil (R_f = 0.26, petroleum ether:EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (t, J = 7.5 Hz, 2H), 3.12 (t, J = 7.5 Hz, 2H), 3.66 (s, 3H), 7.07−7.14 (m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.58 (td, J = 7.7, 1.8 Hz, 1H), 8.52 (d, J = 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 33.2, 51.6,121.4,122.9, 136.4,149.3,160.0, 173.5; HRMS (ESI) calcd. for $C_9H_{11}NNaO_2$ $[M + Na]^+$: 188.0682, found 188.0686. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; N, 8.48; H, 6.71. Found: C, 65.45; N, 8.52; H, 6.70.

General Protocol for Mitsunobu Reaction Reactions. *Conditions A.* A solution of BT-sulfone (**C-acid**) (1.2 mmol, 1.2 equiv), PPh_3 (0.393 g, 1.5 mmol, 1.5 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in toluene (10 mL, 0.1 M) was cooled to 0 °C and ADDP (1,1′-(azodicarbonyl)dipiperidine) (0.378 g, 1.5 mmol, 1.5 equiv) was added. The resulting solution was allowed to warm to rt and stirred at this temperature for additional 12 h. Silica gel (2 g per 1 mmol of alcohol **6**) was added and the whole mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system.

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Conditions B. A solution of BT-sulfone (**C-acid**) (1.2 mmol, 1.2 equiv), PPh_3 (0.393 g, 1.5 mmol, 1.5 equiv) and alcohol **6** (1.0 mmol, 1.0 equiv) in toluene (10 mL, 0.1 M) was cooled to 0 °C and DEAD (Diethyl azodicarboxylate) (0.238 mL, 1.5 mmol, 1.5 equiv) was added. The resulting solution was allowed to warm to rt and stirred at this temperature for additional 6 h. Silica gel (2 g per 1 mmol of alcohol **6**) was added and the whole mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on SiO_2 with appropriate solvent system.

Products 8b Prepared via Mitsunobu Reaction. *1-(tert-Butyl) 8-methyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 1).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); R_f = 0.34 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.45−1.59 (m, 4H), 1.58−1.75 (m, 2H), 2.05−2.29 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H), 4.36 (dd, J = 8.9, 6.2 Hz, 1H), 7.61−7.66 (m, 2H), 8.03 (dd, J = 7.9, 0.3 Hz, 1H), 8.25 (dd, J = 7.8, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 25.8, 26.6, 27.6, 28.5, 33.8, 51.5, 70.3, 84.0, 122.3, 125.6, 127.7, 128.2, 137.0, 152.6, 163.6, 164.7, 173.9; MS (CI^+), m/z (%) 442 (11) $[M + H]^+$; HRMS (ESI) calcd. for $C_{20}H_{27}NNaO_6S_2$ $[M + Na]^+$: 464.1172, found 464.1170.

*Dimethyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 2).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); R_f = 0.71 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−1.51 (m, 4H), 1.62 (quint, J = 7.3 Hz, 2H), 2.14−2.35 (m, 4H), 3.65 (s, 3H), 3.73 (s, 3H), 4.44 (dd, J = 8.6, 6.2 Hz, 1H), 7.55−7.72 (m, 2H), 8.02 (ddd, J = 7.4, 1.4, 0.7 Hz, 1H), 8.19−8.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.2, 26.8, 28.6, 33.9, 51.7, 53.5, 69.8, 122.5, 125.9, 127.9, 128.5, 137.3, 152.8, 164.4, 165.5, 174.0; MS (CI^+), m/z (%) 401 $[M + H]^+$; HRMS (ESI) calcd. for $C_{17}H_{21}NNaO_6S_2$ $[M + Na]^+$: 422.0702, found 422.0702.

*1-Allyl 8-methyl 2-(benzo[d]thiazol-2-ylsulfonyl)octanedioate (**8b**, Table 1, Entry 3).* Starting from methyl 5-hydroxypentanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); R_f = 0.22 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03−1.57 (m, 4H), 1.54−1.81 (m, 2H), 2.15−2.37 (m, 4H), 3.65 (s, 3H), 4.46 (dd, J = 8.6, 6.2 Hz, 1H), 4.58 (ddd, J = 6.0, 2.7, 1.2 Hz, 2H), 5.12 (dd, J = 10.4, 1.2 Hz, 1H), 5.19 (dt, J = 17.2, 1.4 Hz, 1H), 5.70 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 7.52−7.79 (m, 2H), 7.92−8.09 (m, 1H), 8.17−8.29 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 26.1, 26.7, 28.6, 33.9, 51.7, 67.2, 69.8, 119.7, 119.8, 122.4, 125.8, 127.9, 128.4, 130.7, 137.3, 152.8, 164.4, 164.7, 174.0; MS (CI^+), m/z (%) 427 $[M + H]^+$; HRMS (ESI) calcd. for $C_{19}H_{23}NO_6S_2H$ $[M + H]^+$: 426.1040, found 426.1042.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-5-((tert-butyldiphenylsilyl)oxy)pentanoate (**8b**, Table 1, Entry 4).* Starting from 4-hydroxybutan-2-one. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); Keto/enol = ∼6:1; Peaks belonging to enol form are marked with *; R_f = 0.46 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H, H-9), 1.58−1.77 (m, 2H), 2.33−2.48 (m, 2H), 3.68 (t, J = 5.9 Hz, 2H), 3.73 (s, 3H), 4.62 (dd, J = 9.6, 5.4 Hz, 1H), 5.30 (s, 1H*), 7.30−7.47 (m, 6H), 7.57−7.69 (m, 6H), 7.85−7.94 (m, 2H*), 8.02 (dd, J = 6.7, 2.1 Hz, 1H), 8.24 (dd, J = 7.2, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 23.6, 26.9, 29.7, 53.5 (C-4), 63.0, 69.7, 122.5, 126.0, 127.9, 128.4, 129.9, 133.6, 135.7, 137.4, 152.9, 164.5, 165.5; MS (APCI), m/z (%) 568 (100) $[M^+]$. Anal. Calcd for $C_{29}H_{33}NO_5S_2Si$: C, 61.35; H, 5.86; N, 2.47. Found: C, 61.34; H, 5.89; N, 2.48.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-5-oxohexanoate (**8b**, Table 1, Entry 5).*[18b] Starting from 4-hydroxybutan-2-one. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1 → 1:1); R_f = 0.36 (petroleum ether:EtOAc = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.37−2.89 (m, 4H), 3.70 (s, 3H), 4.60 (dd, J = 8.3, 5.8 Hz, 1H), 7.51−7.73 (m, 2H), 8.02 (d, J = 7.9 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 30.0, 39.8, 53.5, 68.4, 122.5, 125.8, 127.9, 128.5, 137.3, 152.7, 164.3, 165.3, 206.4; IR (film) ν^{-1} 2957 (w), 2938 (w), 2929 (w), 2855 (w), 1747 (s), 1471 (m), 1429 (m), 1340 (s), 1317 (m), 1151 (s), 1111 (s), 910 (s), 764 (s), 704 (s), 600 (w); MS (CI^+), m/z (%) 342 $[M + H]^+$; HRMS (ESI) calcd. for $C_{14}H_{15}NNaO_5S_2$ $[M + Na]^+$: 364.0284, found 364.0284.

*4-Ethyl 1-methyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylsuccinate (**8b**, Table 1, Entry 6).* Starting from ethyl (*R*)-2-hydroxypropanoate. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixture of stereoisomers; R_f = 0.73 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17−1.35 (m, 3H), 1.41 (d, J = 6.9 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.61 (d, J = 7.2 Hz, 3H), 2.87 (d, J = 5.0 Hz, 1H), 3.53−3.63 (m, 1H), 3.63 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 4.06−4.33 (m, 2H), 4.59 (s, 1H), 4.90 (d, J = 8.6 Hz, 1H), 5.25 (d, J = 6.7 Hz, 1H), 7.53−7.72 (m, 2H), 8.02 (dt, J = 6.6, 1.5 Hz, 1H), 8.16−8.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.3, 15.8, 20.6, 37.6, 38.9, 53.4, 53.5, 58.7, 61.8, 61.9, 66.9, 70.0, 71.5, 122.5, 122.6, 125.7, 125.8, 127.9, 127.9, 128.5, 137.3, 152.6, 162.3, 164.1, 165.1, 172.2, 172.7, 175.9; MS (CI^+), m/z (%) 372 $[M + H]^+$; HRMS (ESI) calcd. for $C_{15}H_{17}NNaO_6S_2$ $[M + Na]^+$: 394.0389, found 394.0390.

*1-Allyl 4-ethyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylsuccinate (**8b**, Table 1, Entry 7).* Starting from ethyl (*R*)-2-hydroxypropanoate. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); as a mixure of stereoisomers; R_f = 0.54 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13−1.30 (m, 3H), 1.51 (dd, J = 7.2, 1.2 Hz, 3H), 1.63 (dd, J = 7.2, 1.2 Hz, 3H), 1.69 (d, J = 7.3 Hz, 3H), 3.54−3.68 (m, 1H), 3.94−4.26 (m, 3H), 4.40−4.52 (m, 1H), 4.56 (dt, J = 5.9, 1.3 Hz, 2H), 4.93 (dd, J = 8.6, 1.2 Hz, 1H), 5.01−5.22 (m, 2H), 5.28 (d, J = 6.6 Hz, 1H), 5.48−5.82 (m, 1H), 7.47−7.75 (m, 2H), 7.94−8.09 (m, 1H), 8.16−8.28 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 14.1, 14.2, 14.2, 15.9, 17.0, 37.6, 38.8, 42.0, 61.4, 61.8, 61.9, 67.1, 67.3, 69.8, 71.0, 71.4, 119.5, 119.7, 122.4, 125.8, 125.8, 127.7, 127.9, 127.9, 128.4, 128.5, 130.5, 132.5, 137.2, 137.3, 152.6, 163.3, 164.3, 164.8, 165.3, 172.1, 172.7; MS (CI^+), m/z (%) 399 $[M + H]^+$; HRMS (ESI) calcd. for $C_{17}H_{19}NNaO_6S_2$ $[M + Na]^+$: 420.0546, found 420.0545.

*Allyl (3S)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylnonanoate (**8b**, Table 1, Entry 8).* Starting from ethyl (*R*)-octan-2-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixure of stereoisomers; R_f = 0.45 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72−0.96 (m, 3H), 1.08−1.46 (m, 13H), 1.55−1.75 (m, 1H), 2.54−2.78 (m, 1H), 2.89−3.17 (m, 1H), 4.41−4.69 (m, 2H), 4.90 (q, J = 6.3 Hz, 1H), 5.04−5.29 (m, 2H), 5.60−5.90 (m, 1H), 7.56−7.71 (m, 2H), 8.02 (dt, J = 7.3, 2.4 Hz, 1H), 8.23 (ddd, J = 8.5, 7.4, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 16.8, 18.0, 19.8, 22.7, 25.3, 26.6, 29.2, 29.3, 30.4, 30.7, 31.8, 32.6, 33.1, 33.8, 35.2, 35.7, 66.8, 66.9, 69.2, 72.8, 74.4, 74.9, 119.7, 119.8, 122.5, 125.7, 125.9, 127.8, 127.9, 128.3, 128.4, 130.9, 131.6, 137.2, 152.7, 164.0, 164.5, 165.9; MS (CI^+), m/z (%) 411 $[M + H]^+$; HRMS (ESI) calcd. for $C_{20}H_{27}NNaO_4S_2$ $[M + Na]^+$: 432.1274, found 432.1273.

*tert-Butyl (3R)-2-(benzo[d]thiazol-2-ylsulfonyl)-3-methylnonanoate (**8b**, Table 1, Entry 9).* Starting from ethyl (*S*)-octan-2-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); As a mixure of stereoisomers; R_f = 0.87 (petroleum ether:EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (dt, J = 13.5, 6.9 Hz, 3H), 1.16−1.37 (m, 20H), 1.37−1.56 (m, 1H), 1.56−1.77 (m, 1H), 2.59 (dt, J = 12.7, 6.4 Hz, 1H), 4.41 (d, J = 7.3 Hz, 1H), 4.51 (d, J = 4.9 Hz, 1H), 7.62 (quintd, J = 7.2, 1.5 Hz, 2H), 7.98−8.05 (m, 1H), 8.17−8.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 16.8, 18.0, 22.7, 26.4, 27.8, 27.9, 31.7, 31.9, 32.5, 33.1, 33.6, 35.2, 73.3, 75.6, 84.0, 122.5, 125.6, 127.8, 128.2, 137.1, 152.7, 163.6, 164.1, 166.4; MS (CI^+), m/z (%) 427 $[M + H]^+$; HRMS (ESI) calcd. for $C_{21}H_{31}NNaO_4S_2$ $[M + Na]^+$: 448.1587, found 448.1586.

*tert-Butyl (Z)-2-(benzo[d]thiazol-2-ylsulfonyl)oct-4-enoate (**8b**, Table 1, Entry 10).* (*Z*)-Hex-2-en-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 4:1 → 2:1); As a mixure of stereoisomers; R_f = 0.73 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.4 Hz, 3H), 1.34 (s, 9H), 1.32−1.45 (m, 2H), 2.05 (tdd, J = 9.2, 6.4, 1.9 Hz, 2H), 2.87−3.19 (m, 2H), 4.38 (dd, J = 10.5, 4.5 Hz, 1H), 5.24−5.39 (m, 1H), 5.50−5.64 (m, 1H), 7.54−7.85 (m, 2H), 7.98−8.11 (m, 1H), 8.18−8.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.7, 24.5, 27.8, 29.5, 70.2, 84.1,

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122.3, 122.5, 125.8, 127.9, 128.4, 134.9, 137.2, 152.9, 160.5, 164.9; MS (CI^+), m/z (%) 397 $[M + H]^+$; HRMS (ESI) calcd. for $C_{19}H_{25}NNaO_4S_2$ $[M + Na]^+$: 418.1117, found 418.1112.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)hept-6-enoate (**8b**, Table 1, Entry 11).*[18b] Starting from pent-4-en-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1); Keto/enol forms = ∼11:1; R_f = 0.51 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.58 (m, 2H), 2.11 (dt, J = 14.2, 4.7 Hz, 2H), 2.20−2.32 (m, 2H), 3.73 (s, 3H), 4.47 (td, J = 7.9, 5.4 Hz, 1H), 4.95 (dd, J = 10.5, 1.3 Hz, 1H), 5.05 (dt, J = 3.0, 1.5 Hz, 1H), 5.73 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 7.64 (quintd, J = 7.2, 1.5 Hz, 2H), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.25 (dd, J = 7.4, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 26.3, 33.1, 53.5, 69.8, 115.9, 122.5, 125.9, 127.9, 128.5, 137.2, 137.3, 152.8, 164.4, 165.5; IR (film) ν^{-1} = 2940 (w), 2932 (w), 2923 (w), 2911 (w), 2903 (w), 1739 (s), 1641 (w), 1554 (w), 1471 (m), 1338 (s), 1149 (s), 1024 (m), 854 (m), 764 (s), 731 (s), 619 (m); MS (APCI), m/z (%) 340 (100) $[M^+]$. Anal. Calcd for $C_{15}H_{17}NO_4S_2$: C, 53.08; H, 5.05; N, 4.13. Found: C, 52.95; H, 5.17; N 4.16.

*tert-Butyl 2-(benzo[d]thiazol-2-ylsulfonyl)tetracosanoate (**8b**, Table 1, Entry 12).*[18b] Starting from docosan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 50:1 → 20:1). mp = 101−103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.05−1.46 (m, 40H), 1.51 (s, 9H), 2.14−2.34 (m, 2H), 4.42 (dd, J = 8.8, 6.1 Hz, 1H), 7.59−7.72 (m, 2H), 8.02 (dd, J = 7.1, 1.9 Hz, 1H), 8.25 (dd, J = 7.2, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 26.4, 27.1, 28.9, 29.2, 29.3, 29.6, 29.6, 29.8, 29.8, 29.9, 29.9, 32.1, 70.0, 81.0, 122.5, 125.9, 127.9, 128.4, 137.4, 152.8, 164.5, 165.6.; IR (film) ν^{-1} = 3062 (w), 2997 (s), 2929 (s), 1802 (w), 1748 (s), 1471 (m), 1331 (s), 1142 (s), 1122 (s); MS (APCI), m/z (%) 622 (100) $[M^+]$. Anal. Calcd for $C_{35}H_{59}NO_4S_2$: C, 67.59; H, 9.56; N, 2.25. Found: C, 67.62; H, 9.52; N, 2.29.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)tetracosanoate (**8b**, Table 1, Entry 13).*[18b] Starting from docosan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 20:1 → 10:1). Keto/enol forms = ∼8:1. Peaks belonging to enol form are marked with *. mp = 111−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.05−1.71 (m, 40H), 2.14−2.34 (m, 2H), 3.64 (t, J = 6.7 Hz, 2H*), 3.74 (s, 3H, H-4), 4.44 (dd, J = 8.8, 6.0 Hz, 1H, H-2), 5.30 (s, 1H*), 7.58−7.71 (m, 2H), 8.03 (dd, J = 7.1, 1.9 Hz, 1H), 8.26 (dd, J = 7.2, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 26.4, 27.1, 29.2, 29.3, 29.6, 29.8, 29.9, 32.1, 53.5, 70.0, 122.5, 125.9, 127.9, 128.4, 137.4, 152.8, 164.5, 165.6; IR (film) ν^{-1} = 3061 (w), 2996 (s), 2929 (s), 1801 (w), 1744 (s), 1472 (m), 1331 (s), 1143 (s), 1122 (s), 761 (s), 727 (s); MS (APCI), m/z (%) 580 (100) $[M^+]$. Anal. Calcd for $C_{32}H_{53}NO_4S_2$: C, 66.28; H, 9.21; N, 2.42. Found: C, 66.49; H, 9.17; N, 2.57.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)hept-5-ynoate (**8b**, Table 1, Entry 14).*[18b] Starting from pent-3-yn-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1 → 1:1). Keto/enol forms = ∼8:1. Peaks belonging to enol form are marked with *. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (t, J = 2.3 Hz, 3H), 2.13−2.33 (m, 1H), 2.34−2.49 (m, 3H), 2.67−2.87 (m, 2H*), 3.74 (s, 3H), 4.70 (dd, J = 7.8, 6.1 Hz, 1H), 5.31 (s, 1H*), 5.39−5.55 (m, 1H), 7.49−7.37 (m, 1H*), 7.63 (quint, J = 7.2 Hz, 1H), 7.65 (quint, J = 7.2 Hz, 1H), 7.94−7.80 (m, 2H*), 8.03 (dd, J = 7.2, 2.1 Hz, 1H), 8.26 (dd, J = 7.4, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 3.6, 14.4, 16.7, 21.2, 25.8, 53.6, 60.6, 68.9, 75.8, 78.6, 122.5, 125.9, 128.0, 128.5, 137.4, 152.8, 164.2, 165.2; IR (film) ν^{-1} = 2954 (w), 2917 (w), 1739 (s), 1471 (m), 1436 (m), 1336 (s), 1149 (s), 1024 (m), 854 (m), 764 (s), 731 (s), 694 (m), 640 (m); MS (APCI), m/z (%) 338 (100) [M+]. Anal. Calcd for $C_{15}H_{15}NO_4S_2$: C, 53.40; H, 4.48; N, 4.15. Found: C, 53.71; H, 4.63; N, 4.25.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-6-(benzyloxy)hexanoate (**8b**, Table 1, Entry 15).* Starting from 4-(benzyloxy)butan-1-ol. Purification by flash chromatography (petroleum ether:EtOAc = 10:1 → 4:1 → 2:1); R_f = 0.34 (petroleum ether:EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38−1.52 (m, 1H), 1.53−1.77 (m, 3H), 2.21 (dtd, J = 11.3, 6.5, 5.6 Hz, 1H), 2.29−2.41 (m, 1H), 3.32−3.48 (m, 2H), 3.73 (s, 3H), 4.36 (d, J = 11.9 Hz, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.49 (t, J = 5.9 Hz, 1H), 7.23−7.32 (m, 5H), 7.37−7.45 (m, 2H), 7.91 (dd, J = 7.5, 1.6 Hz, 1H), 7.95 (dd, J = 7.1, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 24.7, 29.5, 52.9, 68.9, 70.5, 73.0, 122.5, 124.4, 127.7, 127.9, 127.9, 128.0, 128.4, 135.2, 138.2, 153.1, 164.5, 165.5; MS (CI^+), m/z (%) 435 $[M + H]^+$; HRMS (ESI) calcd. for $C_{21}H_{23}NNaO_5S_2$ $[M + Na]^+$: 456.0910, found 456.0908. Anal. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.18; H, 5.35. Found: C, 58.21; H, 5.33.

*Methyl 2-(benzo[d]thiazol-2-ylsulfonyl)-3-(pyridin-2-yl)-propanoate (**8b**, Table 1, Entry 16).* Starting from pyridin-2-ylmethanol. Purification by flash chromatography (petroleum ether:-EtOAc = 10:1 → 4:1); R_f = 0.46 (petroleum ether:EtOAc = 4:1); mp = 143−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (d, J = 7.6 Hz, 2H), 3.73 (s, 2H), 4.44 (t, J = 7.6 Hz, 1H), 7.09−7.15 (m, 2H), 7.40−7.48 (m, 2H), 7.86 (td, J = 7.6, 1.5 Hz, 1H), 7.92−7.98 (m, 2H), 8.54 (dd, J = 3.8, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.8, 52.7, 69.0, 122.1, 122.7, 124.2, 127.7, 128.8, 136.5, 137.0, 149.5, 153.1, 155.2, 166.0, 172.7; MS (ESI^+), m/z (%) 363 $[M + H]^+$; HRMS (ESI) calcd. for $C_{16}H_{14}N_2NaO_4S_2$ $[M + Na]^+$: 385.0287, found 385.0291. Anal. Calcd for $C_{16}H_{14}N_2O_4S_2$: C, 53.03; H, 3.89. Found: C, 53.05; H, 3.88.

Side Products of the SmI_2-Mediated Reductive Elimination. *Benzo[d]thiazole.* Purification by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1 → 4:1) and yielded the targeted compound as colorless oil (R_f = 0.56, petroleum ether:EtOAc = 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.59−7.50 (m, 1H), 7.50−7.42 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 122.1, 123.7, 125.8, 126.4, 133.7, 153.0, 154.2.

*2-(Methylamino)benzenethiol (**13**).*[35] Purification by column chromatography on silica gel (petroleum ether:EtOAc = 50:1 → 20:1 → 10:1 → 4:1) and yielded the targeted compound as colorless oil (R_f = 0.42, petroleum ether:EtOAc = 4:1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (s, 3H), 4.90 (t, J = 1.3 1H), 6.49−6.63 (m, 2H), 7.12−7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9, 122.1, 123.9, 125.8, 126.4, 154.1; MS (ESI^+), m/z (%) 140 $[M + H]^+$; HRMS (ESI) calcd. for C_7H_9NNaS $[M + Na]^+$: 162.03479, found 162.03480. Anal. Calcd for C_7H_9NS: C, 60.39; H, 6.52; N, 10.06. Found: C, 60.43; H, 6.57; N, 9.97.

Multigram Scale Synthesis of *tert*-Butyl Tetracosanoate (Scheme 4). *Sulfone (**7**, Table 2, Entry 4).* A solution of benzo[*d*]thiazol (BT-SH) (1.77 g, 10.6 mmol, 1.2 equiv), PPh_3 (2.77 g, 10.6 mmol, 1.2 equiv) and docosan-1-ol (3.0 g, 8.8 mmol, 1.0 equiv) in THF (88 mL, 0.1 M) was cooled to 0 °C and DEAD (1.67 mL, 10.6 mmol, 1.2 equiv) was added. The resulting solution was allowed to warm to rt and stirred for 12 h. The resulting solution was diluted with EtOH (250 mL), cooled to 0 °C and $Na_2WO_4.2H_2O$ (413 mg, 1.1 mmol, 0.1 equiv) was added in one portion. After 15 min at 0 °C, an aqueous 35% solution of H_2O_2 (25.6 mL, 264 mmol, 30 equiv) was added dropwise with the use of a dropping funnel over a period of 45 min. The resulting yellowish solution was allowed to warm to rt and stirred at rt for 18 h. Deionized water (500 mL) was added and the mixture was extracted with EtOAc (6× 250 mL). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on SiO_2 (petroleum ether:EtOAc = 50:1 → 10:1) yielding the desired sulfone (4.22 g, 91%).

*β-Carbonyl Sulfone (**8a**, Table 2, Entry 4).* A solution of BT-sulfone 7 (4.22 g, 8.1 mmol, 1.0 equiv) and Boc_2O (2.12 g, 9.7 mmol, 1.2 equiv) in THF (41 mL, 0.20 M) was cooled to −78 °C and precooled (−20 °C) LiHMDS (1.0 M sol. in THF) (17.8 mL, 17.8 mmol, 2.2 equiv) was added within 2 min. The resulting mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C within 3 h and stirred at 0 °C for a further 60 min before sat. aq. sol. of NH_4Cl (150 mL) was added. The mixture was extracted with EtOAc (3× 250 mL) and the combined organic layers were washed with brine (250 mL), dried over $NaSO_4$, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether:EtOAc = 50:1 → 20:1) yielding the desired product (3.98 g, 79%).

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*tert-Butyl Tetracosanoate (**9**, Table 2, Entry 4).* To a solution of BT-sulfone ester (3.98 g, 6.4 mmol, 1.0 equiv) in benzene (35 mL, 0.2 M) was added nBu$_3$SnH (2.16 mL, 8.0 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.21 g, 1.28 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to rt (heating bath removed). CH_3CN (250 mL) was added and the reaction mixture was extracted with n-pentane (3× 100 mL). The acetonitrile layer was dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc = 20:1 → 10:1) and yielded the targeted compound as colorless viscous oil (2.52 g, 93%).

Two-Carbon Homologation of Ingenol (16, Scheme 5). *Ingenol Derivative **15**.* A solution of ingenol **14** (0.032 g, 0.09 mmol, 1.0 equiv), methyl ester C-acid (0.028 g, 0.1 mmol, 1.1 equiv) and PPh_3 (0.027 g, 0.1 mmol, 1.1 equiv) in dry benzene (1.0 mL, 0.1 M) was cooled to 0 °C and the resulting mixture was stirred for 5 min prior to DIAD (19.8 μL, 0.1 mmol, 1.1 equiv) addition. The resulting mixture was stirred at 0 °C for an additional 30 min and then at rt for 12 h. The resulting mixture was evaporated under reduced pressure to dryness and the residue was purified by column chromatography on silica gel ($CHCl_3$/EtOAc = 4:1 → 2:1 → 1:1 → 0:100) to give 0.028g (51%) of desired adduct **15** (two diastereoisomers in ∼1:1 ratio). R_f = 0.11 ($CHCl_3$/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (td, J = 8.6, 6.3 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.11 (s, 3H), 1.27 (dt, J = 9.9, 7.2 Hz, 1H), 1.76 (ddd, J = 15.7, 6.3, 5.2 Hz, 1H), 1.85 (d, J = 1.4 Hz, 3H), 2.27 (ddd, J = 15.6, 8.9, 3.1 Hz, 1H), 2.30−2.38 (m, 1H), 3.35−3.48 (m, 2H), 3.68 (s, 1H), 3.78 (s, 3H), 4.08 (dd, J = 11.3, 3.6 Hz, 1H), 4.43 (s, 1H), 4.63−4.79 (m, 1H), 5.94 (d, J = 1.5 Hz, 1H), 6.10 (dd, J = 4.7, 1.3 Hz, 1H), 7.56−7.71 (m, 2H), 8.01 (dd, J = 7.1, 1.7 Hz, 1H), 8.27 (dd, J = 7.0, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 15.6, 17.1, 17.4, 21.2, 22.9, 23.0, 23.1, 23.2, 23.8, 23.9, 30.6, 30.9, 33.1, 33.2, 39.2, 39.8, 44.1, 44.2, 53.0, 53.4, 68.8, 70.9, 72.5, 72.6, 73.7, 79.8, 79.9, 84.3, 84.4, 122.4, 125.8, 125.9, 127.7, 128.5, 132.3, 136.0, 136.3, 137.3, 137.4, 139.5, 139.6, 152.7, 164.1, 164.2, 165.3, 165.5, 207.1, 207.2; HRMS (ESI) m/z calcd. for $C_{30}H_{35}NNaO_8S_2$ $[M + Na]^+$ 624.1696, found 624.1697.

*Product of Ingenol Homologation (**16**).* To a solution of BT-sulfone ester **15** (0.027 g, 0.045 mmol, 1.0 equiv) in benzene (0.5 mL) was added nBu$_3$SnH (0.056 mL, 0.056 mmol, 1.25 equiv) and the resulting mixture was stirred at rt for 5 min. AIBN (0.002 g, 0.009 mmol, 0.2 equiv) was added and the mixture was placed on a preheated oil bath (90 °C). The mixture was kept at 90 °C (external) for 60 min before it was allowed to cool to rt (heating bath removed). CH_3CN (10 mL) was added and the reaction mixture was extracted with n-pentane (3× 10 mL). The acetonitrile layer was dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica gel ($CHCl_3$/EtOAc = 4:1 → 2:1 → 1:1 → 0:100) and yielded the targeted compound **16** (0.016 g, 89%). R_f = 0.15 ($CHCl_3$/EtOAc = 1:1); α_D^{23} = +39 (c 1.01, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (td, J = 8.5, 6.3 Hz, 1H), 0.93 (dd, J = 11.5, 8.5 Hz, 1H), 0.96 (d, J = 7.0 Hz, 3H), 1.05 (s, 3H), 1.11 (s, 3H), 1.20 (t, J = 7.0 Hz, 1H), 1.39−1.71 (broad s, 3H), 1.71−1.79 (m, 2H), 1.85 (d, J = 1.2 Hz, 3H), 2.09−2.21 (m, 2H), 2.27−2.39 (m, 2H), 2.62−2.75 (m, 2H), 3.72 (s, 3H), 3.81 (s, 1H), 4.11 (ddd, J = 10.4, 6.4, 2.1 Hz, 1H), 4.40 (s, 1H), 5.94 (quint, J = 1.5 Hz, 1H), 6.04 (d, J = 5.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.3, 15.5, 15.6, 17.6, 21.2, 23.0, 23.4, 23.9, 28.6, 31.0, 31.1, 32.4, 39.4, 44.1, 51.8, 72.7, 74.9, 79.9, 84.3, 127.3, 128.9, 139.3, 140.7, 171.4, 208.4; HRMS (ESI) m/z calcd. for $C_{23}H_{32}NaO_6$ $[M + Na]^+$ 427.2091, found 427.2090.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00112.

Additional optimization data for Mitsunobu reaction (Table S1 and S2) and desulfonylation reactions (Table S3 and Table S4), Scheme S1 and accompanying text, copies of ^{1}H, and ^{13}C NMR spectra, and relevant chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: j.pospisil@upol.cz.

ORCID

Jiří Pospíšil: 0000-0002-0198-8116

Author Contributions

D.J.-Y.D.B., O.K., V.F. and F.Z. performed most of the experiments. D.J.-Y.D.B. and J.P. led the team for synthesis and analyzed chemistry and structure-related results. D.J.-Y.D.B. partially designed the experimental plans. J.P. initiated the project, led the project team, designed experiments, analyzed results and wrote the paper with input from all authors.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated with deep respect to Professor Miroslav Strnad on the occasion of his 60th birthday.

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7.2 Enantioselective Catalytic [4+1]-Cyclization of *ortho* -Hydroxy- *para* -Quinone Methides with Allenoates

- Zielke, K.; Kováč, O.; Winter, M.; Pospíšil, J.; Waser, M. *Chem. – A Eur. J.* **2019**, *25*, 8163–8168; IF^{2018}= 5.16; https://doi.org/10.1002/chem.201901784

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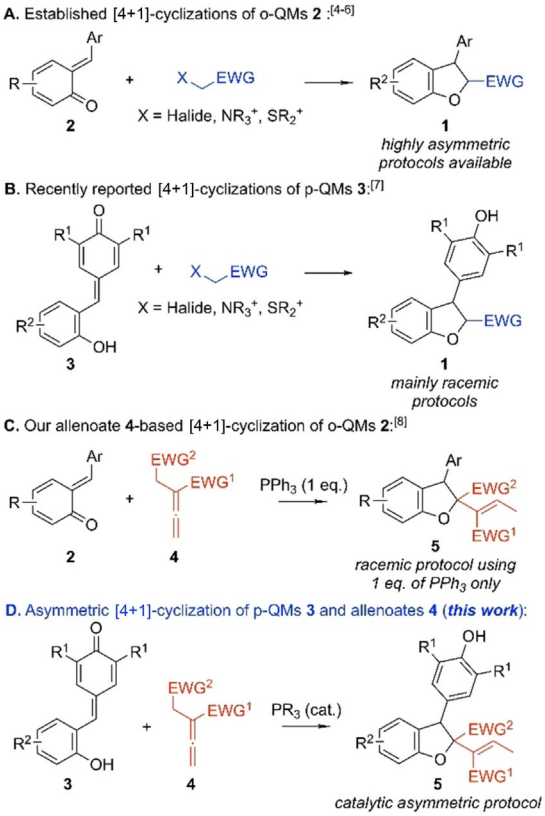
Enantioselective Catalytic [4+1]-Cyclization of *ortho*-Hydroxy-*para*-Quinone Methides with Allenoates

Katharina Zielke[+],[a] Ondřej Kováč[+],[b] Michael Winter,[a] Jiří Pospíšil,[b, c] and Mario Waser*[a]

Abstract: The first highly asymmetric catalytic synthesis of densely functionalized dihydrobenzofurans is reported, which starts from *ortho*-hydroxy-containing *para*-quinone methides. The reaction relies on an unprecedented formal [4+1]-annulation of these quinone methides with allenoates in the presence of a commercially available chiral phosphine catalyst. The chiral dihydrobenzofurans were obtained as single diastereomers in yields up to 90% and with enantiomeric ratios up to 95:5.

Introduction

The 2,3-dihydrobenzofuran scaffold is a prominent structural motif found in numerous biologically active (natural) compounds[1] and the development of novel synthesis strategies to access these targets has been a heavily investigated topic over the last years.[2–8] One especially appealing approach to access chiral 2,3-dihydrobenzofurans is the formal [4+1]-cyclization[9] between a suitable C1 building block and a carefully chosen (maybe in situ generated) acceptor–donor containing C4 building block. The most versatile class of C4 building blocks used to obtain the dihydrobenzofuran skeleton **1** via a formal [4+1]-cyclization are *ortho*-quinone methides (*o*-QMs) **2**.[10] These, usually in situ generated, reactive compounds have recently been very successfully used for racemic as well as highly stereoselective [4+1]-annulations with either sulfonium or ammonium ylides,[4] α-halocarbonyl compounds,[5] or with diazocompounds as C1 synthons (Scheme 1 A).[6] Alternatively, the hydroxy-containing *para*-quinone methides **3** have very recently emerged as powerful building blocks for formal (4 + n)-annulations as well.[7,11–13] Interestingly however, their applicability for asymmetric [4+1]-cyclizations to access dihydrobenzofurans **1** has so far been rather limited, with highly asymmetric protocols still being rare (Scheme 1 B).[7] Two years ago we reported the first highly enantioselective synthesis of compounds **1** by reacting preformed chiral ammonium ylides with in situ formed *o*-QMs **2**.[4c] More recently we found that the highly functionalized allenoates **4** can undergo a very unique (and up to then unprecedented) formal [4+1]-cyclization with accept-



Scheme 1. Previous [4+1]-approaches for the syntheses of dihydrobenzofurans (A–C) and the herein reported novel catalytic asymmetric strategy (D).

[a] K. Zielke,[+] M. Winter, Prof. M. Waser
Institute of Organic Chemistry, Johannes Kepler University Linz
Altenbergerstraße 69, 4040 Linz (Austria)
E-mail: mario.waser@jku.at

[b] O. Kováč,[+] Dr. J. Pospíšil
Department of Organic Chemistry, Faculty of Science, Palacky University
tř. 17. listopadu 1192/12, 771 46 Olomouc (Czech Republic)

[c] Dr. J. Pospíšil
Laboratory of Growth Regulators, The Czech Academy of Sciences
Institute of Experimental Botany & Palacký University
Šlechtitelů 27, 78371 Olomouc (Czech Republic)

[+] These authors contributed equally to this work.

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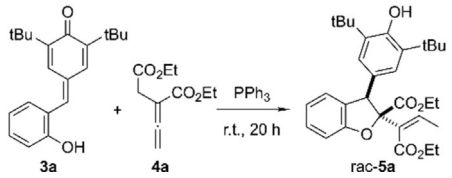
ors **2** in the presence of a stoichiometric amount of PPh_3 (Scheme 1 C).[8] The (unexpected) outcome of this reaction was in sharp contrast to other previously described reactions between *o*-QMs **2** and (differently substituted) allenoates, which all resulted in formal [4+2]-annulations.[14] Unfortunately however, we were only able to carry out this reaction in racemic manner, as even the use of a stoichiometric amount of different commonly used chiral phosphine catalysts gave low yields and poor enantioselectivities only.[8] In especially we found that the in situ formed *o*-QMs **2** decomposed rather rapidly under the previously developed reaction conditions, thus making a catalytic approach difficult. Given these limitations in catalyst turnover and asymmetric induction, we thought that maybe an alternative and slightly more stable acceptor would be beneficial to address these challenges. Thus, we decided to investigate if this methodology may also be extended to the formal [4+1]-cyclization of the *o*-hydroxy-containing *p*-QMs **3** with allenoates **4**.[12] We reasoned that this preformed and, compared to **2**, more stable acceptor molecule may be better suited to establish a truly catalytic as well as asymmetric protocol, which would then allow for the first enantioselective [4+1]-annulation of *p*-QMs **3** to access the highly functionalized chiral dihydrobenzofurans **5** (Scheme 1 D).

Table 1. Initial screening with PPh_3.



3a 4a rac-5a

Entry[a]	3a:4a	PPh_3 [equiv.]	Base ([eq.])	Solvent	Yield [%][b]
1	2:1	1	Cs_2CO_3 (2)	CH_2Cl_2	16[c]
2	2:1	1	Cs_2CO_3 (10)	CH_2Cl_2	–
3	1:2	1	Cs_2CO_3 (2)	CH_2Cl_2	33[c]
4	1:2	1	Cs_2CO_3 (2)	toluene	45[d]
5	1:2	1	Cs_2CO_3 (2)	EtOAc	–
6	1:2	1	Cs_2CO_3 (0.2)	CH_2Cl_2	63
7	1:2	1	K_2CO_3 (2)	CH_2Cl_2	82
8	1:2	0.2	K_2CO_3 (2)	CH_2Cl_2	81
9	1:2	0.1	K_2CO_3 (2)	CH_2Cl_2	49
10	1:2	0.2	K_2CO_3 (0.5)	CH_2Cl_2	89
11	1:2	0.2.	–	CH_2Cl_2	90 (86)[e]

[a] All reactions were carried out on 0.1 mmol scale (based on the *p*-QM **3a**), [b] Isolated yield; [c] Incomplete conversion of **3a** and noticeable amounts of side products; [d] complete conversion of **3a** and large amounts of unidentified side products; [e] 1 mmol scale reaction.

Results and Discussion

Initial optimization of the racemic reaction

We started our investigations by carrying out the racemic reaction between *p*-QM **3a** and diethyl allenoate **4a** in the presence of PPh_3 (Table 1 gives an overview of the most significant screening results). Our first reactions were carried out in analogy to the conditions developed for the annulation of *o*-QMs **2**[8] (please note that we previously used a twofold excess of the quinone methide **2** to compensate for its competing decomposition under the reaction conditions). Gratifyingly the targeted dihydrobenzofuran **5a** could be obtained as a single diastereomer in this initial attempt already (entry 1). The relative configuration of the product **5a** was confirmed by NOESY experiments (as shown in Scheme 4) and we also observed the same correlations for other products **5** later (Scheme 2). As the reaction was found to be rather slow, with significant amounts of unreacted **3a** being recovered (indicating its increased stability compared to *o*-QMs **2**), we next increased the amount of base (entry 2), which however had a detrimental effect (complete decomposition of starting materials).

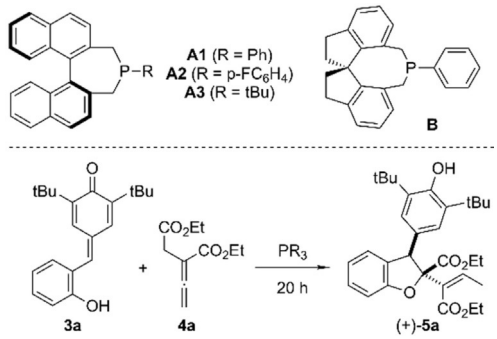
As decomposition of the acceptor **3a** was not very fast in the first attempts with 2 equivalents of base, we next used an excess of allenoate **4a**, which led to a measurable increase in yield (entry 3). The screening of different solvents revealed that toluene allows for a slightly higher yield (entry 4), but also accompanied with a more pronounced formation of various not identified side- or decomposition products. Other solvents did not give satisfactory results (see entry 5 for one example) and so further optimizations with CH_2Cl_2 were carried out. Very interestingly, lowering the amount of base (entry 6) significantly improved the yield and suppressed side product formation. By testing other bases, K_2CO_3 turned out to be the most promising (entry 7). It should be noted that other simple trialkylphosphines were tested as well,[15] but in analogy to our previous observation[8] these did not allow for this [4+1]-annulation.

With these first high yielding conditions set, we next lowered the amount of PPh_3. Gratifyingly, and in sharp contrast to the reaction with *o*-QMs **2**,[8] the use of 20 mol% PPh_3 allowed for the same yield as when using a stoichiometric amount (compare entries 7 and 8). Further lowering of the catalyst amount unfortunately slowed down the reaction measurably (entry 9). Considering the beneficial effect of using less base when using Cs_2CO_3 (entry 6), we finally also lowered the amount of K_2CO_3 (entries 10, 11), and much to our surprise the reaction proceeded well even without any base (entry 11; the reaction was reproduced several times on different scales and also on 1 mmol scale).

Development of an asymmetric catalytic protocol

Having established high yielding and robust catalytic procedures for the racemic synthesis of **5a** we next focused on the use of chiral phosphine catalysts. As already mentioned before, we were not able to identify a suited asymmetric catalyst for our previous [4+1]-annulation of *o*-QMs **2**. However, given the fact that *p*-QM **3a** performed very well in the racemic reaction and also allowed for a catalytic approach, we were confident that the well-described bulky chiral phosphines **A**[16] or **B**[17] may allow for a truly catalytic enantioselective protocol (Table 2). We first used the binaphthyl-based phosphines **A1**–**3**, but unfortunately neither of them allowed for any product formation (entries 1–3). Gratifyingly however, by switching to the commercially available chiral spiro phosphine **B** ((*R*)-SITCP)[17] we observed a very clean and reasonably enantioselective

Table 2. Development of an enantioselective catalytic protocol.



Entry[a]	PR_3 ([mol%])	Solvent	Base ([eq.])	Temp. [°C]	Yield [%][b]	e.r.[c]
1	A1 (20)	CH_2Cl_2	–	25	–	–
2	A2 (20)	CH_2Cl_2	–	25	–	–
3	A3 (20)	CH_2Cl_2	–	25	–	–
4	B (20)	CH_2Cl_2	–	25	84	88:12
5	B (20)	CH_2Cl_2	–	0	–	–
6	B (20)	CH_2Cl_2	K_2CO_3 (2)	25	70	87:13
7	B (20)	toluene	–	25	87	94:6
8	B (20)	toluene	K_2CO_3 (2)	25	90	92:8
9	B (20)	toluene	K_2CO_3 (2)	10	89	94:6
10	B (20)	toluene	K_2CO_3 (2)	0	–	–
11	B (10)	toluene	K_2CO_3 (2)	10	–	–

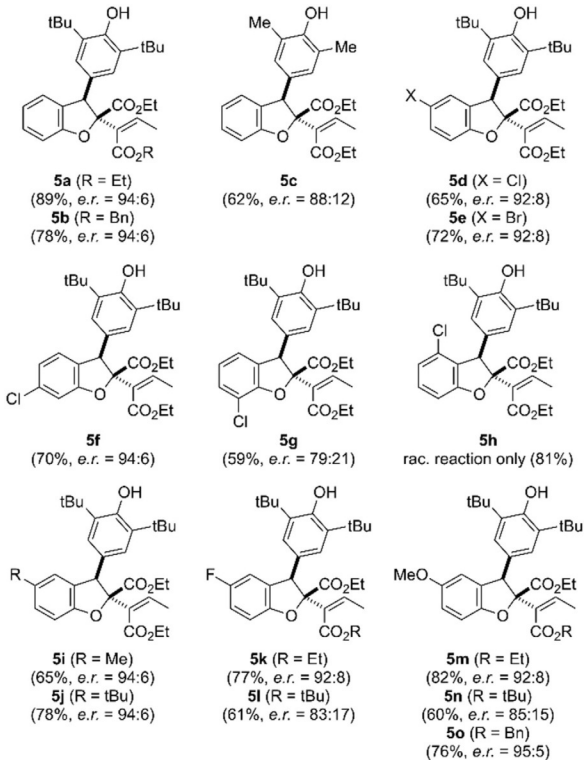
[a] All reactions were carried out on 0.1 mmol scale (based on **3a**). [b] Isolated yield. [c] Determined by HPLC using a chiral stationary phase with the (+)-enantiomer as the major product. The relative configuration was assigned by NOESY experiments (see Scheme 4) but the absolute configuration could not be determined yet.

product formation when using 20 mol% of this catalyst under base-free conditions in CH_2Cl_2 (entry 4). Lowering the reaction temperature to 0 °C unfortunately did not allow for product formation anymore (entry 5). When carrying out the reaction in the presence of two equivalents of K_2CO_3, the outcome was only slightly affected in this solvent (entry 6).

Interestingly, when changing to toluene (other solvents like THF were found to be not suited), we were able to improve the enantioselectivity significantly (entries 7–9). At room temperature reactions in the presence of K_2CO_3 as well as under base-free conditions performed very similarly, with a slightly higher e.r. in the absence of base (compare entries 7 and 8). However, when we further investigated the application scope, we realized that the base-mediated conditions were more robust when using differently substituted starting materials **3**, while not all of those allowed for good conversions under base-free conditions. Other bases were found to be less satisfactory (with for example, Cs_2CO_3 giving lower yields and K_3PO_4 giving no product at all). We thus tested if any further improvement in the presence of 2 equivalents of K_2CO_3 may be possible (entries 8–11). However, lowering of the reaction temperature was possible to some extent only (entries 9, 10), but reducing the catalyst loading to 10 mol% was unfortunately not possible anymore (entry 11). Accordingly, the best-suited and most robust catalytic enantioselective approach to access **5a** as a single diastereomer was to carry out the reaction in toluene at 10 °C in the presence of 2 equivalents of K_2CO_3 by using 20 mol% of the commercially available phosphine catalyst **B** (entry 9, the reaction was reproduced by different persons on 0.05–0.1 mmol **3a** scale giving identical results).

Application scope

Having established a high yielding and robust catalytic procedure for the synthesis of dihydrobenzofuran **5a**, we next tested the use of differently substituted quinone methides **3** and allenoates **4** (Scheme 2).



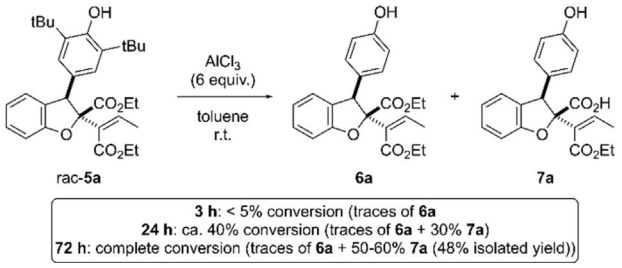
Scheme 2. Application scope (Conditions: 0.05–0.2 mmol **3**, 2 equiv **4**, 2 equiv K_2CO_3, 20 mol% **B**, toluene (0.025 M), 10 °C, min. 20 h; All yields are isolated yields and enantiomeric ratios were determined by HPLC using a chiral stationary phase with the (+)-enantiomer being the major product in each case).

First, we could show that replacement of one of the allenoate ethyl ester groups for a benzyl ester was tolerated very well (see product **5b**). Then it turned out that a dimethyl-based *p*-QM **3** can be used as well to obtain the enantioenriched product **5c** (albeit with a slightly lower selectivity than for the parent *t*Bu-based **5a**). Interestingly, substituents in the 5 and 6-position of the benzofuran backbone were very well tolerated (see compounds **5d–f**, **5i–k**, **5m**). In contrast, substituents in positions 4 and 8 turned out to be more limiting and product **5g** was only accessible with a rather low enantiomeric ratio of 79:21. Surprisingly, compound **5h** was not formed at all under the asymmetric conditions (even with longer reaction times). We were however able to obtain racemic **5h** in high yield when using PPh_3 as an achiral catalyst. Very interestingly, while we found initially that benzyl ester

containing allenoates were tolerated similarly well as ethyl ester-based ones (see targets **5a** and **5b**), we found that *tert*-butyl esters resulted in somewhat lower enantiomeric ratios compared to ethyl and benzyl esters (compare **5k** and **5l** as well as **5m**, **5n**, and **5o**). All asymmetric reactions were initially carried out on 0.05 mmol scale of the limiting agent **3** and we also reproduced selected reactions on up to 0.2 mmol scale without affecting the outcome, thus indicating that the asymmetric procedure is of similar robustness as the racemic one (Table 1, entry 11).

All substrate combinations gave the (+)-enantiomer as the major product, but unfortunately, it has not been possible to obtain suitable crystals of any of the products **5** to determine the absolute configuration by single-crystal X-ray analysis.

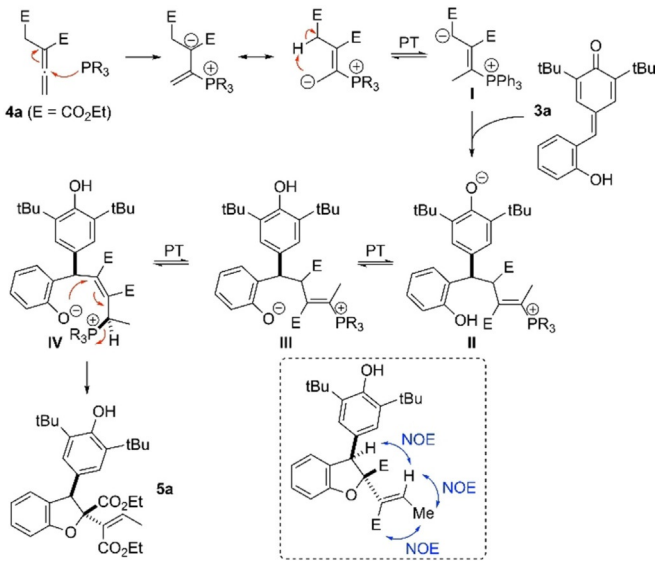
It has been described by others that the *tert*-butyl groups of the phenol derivatives obtained by addition of nucleophiles to QMs can be cleaved off under (Lewis) acidic conditions.[7a,11c] We thus carried out a few (unoptimized) test reactions to see if a similar debutylation is also possible on the highly functionalized diester-containing dihydrobenzofuranes **5** (Scheme 3). Carrying out the reaction at elevated temperature only led to decomposition. In contrast, at room temperature, the slow formation of the debutylated diester **6a** was observed by MS. Interestingly however, the major product was found to be the debutylated monoester **7a** that was formed in around 30% after one day and around 50–60% after 3 days (accompanied with some decomposition products) and which could also be isolated after column chromatography (NMR clearly confirmed that the ester group on the stereogenic center was hydrolyzed). It should be noted that no further attempts to optimize this reaction were undertaken, but this result clearly shows that the highly functionalized compounds **5a** can be used for further transformations and that the two ester groups have different reactivities.



Scheme 3. $AlCl_3$-mediated transformations of *rac*-**5a**.

Mechanistic considerations

Mechanistically this is a rather complex reaction and it should be admitted that so far, we only have some hints that may allow us to postulate the mechanistic scenario depicted in Scheme 4. This proposal is also based on our recent observations made for the racemic [4+1]-annulation of *o*-QMs **2** where we found that intramolecular rapid proton transfers are crucial to explain the outcome of this [4+1]-cyclization.[8]



Scheme 4. Postulated mechanism and NOESY results to determine the relative configuration.

Addition of the phosphine to the allenoate is supposed to give the required zwitterion **I** after proton transfer on the primary addition product. Following the reaction between PPh_3 and **4a** by ^{31}P NMR shows the appearance of two new signals around 27 ppm (the parent PPh_3 peak is at −5 ppm) substantiating the formation of alkylated phosphine species (these addition products decomposed very quickly in the absence of any electrophile). Upon addition of the quinone methide **3a** immediately a strong red color evolves, which can be rationalized by the 1,6-addition of **I** to **3a** to give the phenolate **II**. Similar color changes can also be observed when adding different nucleophiles to other *p*-QMs, substantiating the assumed initial 1,6-addition. With respect to the nature of the electrophile **3a** one could however also postulate that a prototropic shift from the phenol to the *para*-QM moiety gives an *ortho*-QM in situ, which then reacts with **I** to give **III** directly.[18] However, we found compound **3a** being rather stable under basic conditions and we never observed any other species or got any experimental hint that supports this pathway, but it should not be ruled out completely with the current state of knowledge. The phenolate **II** then needs to undergo two proton transfer reactions towards the betaine **IV**, which can then finally react to the product **5a** via an S_N2'-type cyclization. We have recently shown for the cyclizations of *o*-QMs **2** that these proton transfers are rather likely processes and we reason that the presence of a base is beneficial for these reactions, which would be an explanation why the herein presented [4+1]-cyclization is more robust under basic conditions. This beneficial effect of base became especially pronounced in those cases where no electron-donating ring substituent *para* to the OH group is present (these reactions usually proceeded a bit slower as well). This observation supports a scenario where the final ring closure may be the rate-determining step, which also rationalizes why slightly larger amounts of catalyst were necessary to obtain satisfying catalyst turnover.

With respect to the observed stereoselectivity it is likely that the catalyst controls the absolute configuration in the 1,6-addition step. An alternative may be a less selective 1,6-addition followed by base-mediated isomerization of the benzylic position on one of the chiral catalyst-bound intermediates **II** or **III**. However, as the observed enantioselectivity was more or less the same under basic and base-free conditions (compare with Table 2), this option seems less likely. The diastereoselectivity is then controlled in the final proton transfer–cyclization sequence. Given the fact that S_N2' reactions usually proceed with a *cis*-orientation of nucleophile and leaving group[19] the proton transfer towards **IV** is supposed to be highly selective, and may be steered by electrostatic attraction between the phenolate anion and the phosphonium cation in the nonpolar reaction solvent. However, it should clearly be pointed out that this is just a mechanistic hypothesis and although we were able to observe the presence of some alkylated phosphonium species by ^{31}P NMR during the reaction, none of these intermediates could be isolated or more carefully analyzed.

Conclusions

The first highly asymmetric catalytic formal [4+1]-annulation of *o*-hydroxy-*p*-quinone methides **3** with allenoates **4** has been developed. The outcome of this reaction is in sharp contrast to other recently reported reactions between quinone methides **3** and allenoates.[12] Key to success was the use of the commercially available chiral phosphine **B** as a catalyst under carefully optimized reaction conditions. This methodology allowed for the so far unprecedented synthesis of the chiral dihydrobenzofurans **5** as single diastereomers in yields up to 90% and with enantiomeric ratios up to 95:5.

Experimental Section

General details can be found in the online Supporting Information. This document also contains detailed synthesis procedures and analytical data of novel compounds and reaction products as well as copies of NMR spectra and HPLC traces.

General asymmetric [4+1]-cyclization procedure

A mixture of the *para*-quinone methide **3** (0.05–0.2 mmol), K_2CO_3 (2 equiv), and chiral phosphine **B** (20 mol%) was cooled to 10 °C and a solution of the allenoate **4** (2 equiv) in dry toluene (20 mL per mmol **4**) was added. The resulting mixture was stirred at 10 °C under an Ar atmosphere for approximately 20 h. The mixture was diluted by adding CH_2Cl_2 (5 mL), filtrated over a pad of Na_2SO_4 and the residue was rinsed with CH_2Cl_2 (5×5 mL). The combined organic layers were evaporated to dryness (under reduce pressure) and the products were purified by silica gel column chromatography (gradient of heptanes and EtOAc) giving the corresponding dihydrobenzofurans **5** in the reported yields and enantiopurities (Syntheses of racemic samples were carried out in analogy using PPh_3 instead).

Dihydrobenzofuran 5 a

Obtained as a yellow residue in 89% and e.r. = 94:6. $[\alpha]_D^{23} = 64.6$ ($c = 0.15$, $CHCl_3$, *e.r.* = 94:6); 1H NMR (300 MHz, δ, $CDCl_3$, 298 K): $\delta =$ 0.82 (t, $J = 7.2$ Hz, 3H), 1.36 (t, $J = 7.1$ Hz, 3H), 1.36 (s, 18H), 1.89 (d, $J = 7.2$ Hz, 3H), 3.52–3.77 (m, 2H), 4.26–4.36 (m, 2H), 5.11 (s, 1H), 5.24 (s, 1H), 6.40 (q, $J = 7.1$ Hz, 1H), 6.83 (s, 2H), 6.94 (t, $J = 7.3$ Hz, 1H), 7.01–7.09 (m, 2H), 7.19–7.26 ppm (m, 1H). ^{13}C NMR (75 MHz, δ, $CDCl_3$, 298 K): $\delta =$ 13.4, 14.2, 15.5, 30.2, 34.2, 55.8, 60.8, 61.1, 94.0, 110.2, 121.8, 125.7, 126.1, 128.9, 129.4, 130.0, 132.7, 133.2, 135.1, 153.0, 158.1, 167.2, 168.4 ppm; HRMS (ESI): *m/z* calcd for $C_{31}H_{40}O_6$: 509.2898 [*M*+H]+; found: 509.2897. The enantioselectivity was determined by HPLC (YMC Chiral Art Cellulose-SB, eluent: hexane/*i*PrOH = 95:5, 0.5 mL min^{-1}, 10 °C, retention times: $t_{major} = 9.4$ min, $t_{minor} = 11.0$ min).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allenoates · annulation · diastereoselectivity · enantioselectivity · organocatalysis

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7.3 Trisubstituted highly activated benzo[d]thiazol-2-yl-sulfone-containing olefins as building blocks in organic synthesis

- Kováč, O.; Zálešák, F.; Bon, D. J.-Y. D.; Roiser, L.; Baar, L. V.; Waser, M.; Pospisil, J. *J. Org. Chem.* **2020**, just accepted; IF^{2018}=4.745; https://doi.org/10.1021/acs.joc.0c00571

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Trisubstituted Highly Activated Benzo[*d*]thiazol-2-yl-sulfone-Containing Olefins as Building Blocks in Organic Synthesis

Ondřej Kováč, František Zálešák, David J.-Y. D. Bon, Lukas Roiser, Lubomír V. Baar, Mario Waser, and Jiří Pospíšil*

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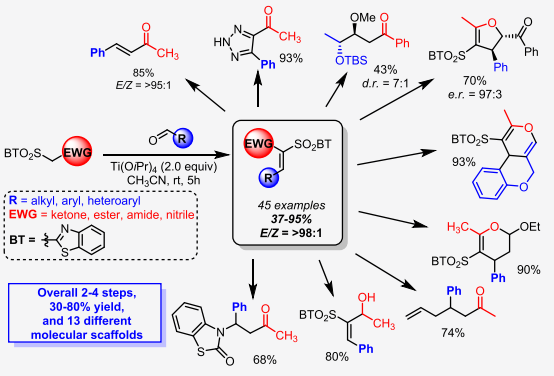
ABSTRACT: In this paper, we report the formation of highly electrophilic 1,1-deactivated olefins, their use as novel synthetic building blocks, and their transformation to structurally diverse molecular scaffolds. Synthesis of 1,1-deactivated olefins substituted with a BT-sulfonyl group and a carbonyl or nitrile, respectively, consists of unusual Ti(OPr^i)$_4$-mediated Knoevenagel-type condensation and proceed in good to excellent yields. Generated olefins can be further transformed in a highly stereoselective manner and in good yields to various polyfunctionalized heterocycles and acyclic molecular scaffolds. Overall, the obtained structures are accessed in two to four steps starting from the (mostly) commercially available aldehydes. In addition, the presence of the BT-sulfonyl group in prepared structures allows for further chemoselective functionalization/post-synthetic transformations to provide structurally diverse final compounds.



INTRODUCTION

Diversity-oriented synthesis is a synthetic strategy of choice when a chemical library of small organic molecules with a high degree of structural and functional variety have to be prepared.[1−4] In this strategy, rapid (3−5 steps) and efficient (high scaffold diversity) synthesis of structurally distinct molecules is achieved using specially designed readily available building blocks. Such building blocks are further transformed to structurally diverse frameworks.

For some time, our group has been interested in the development of such building blocks.[5,6] More recently, Michael-type acceptors, namely, aryl vinyl sulfones, have attracted our attention. Indeed, Michael-type additions to the vinylic group of aryl vinyl sulfones have attracted, over the past two decades, much attention of both the synthetic[7−11] and medicinal[12−14] community. At the same time, the use of heteroaryl vinyl sulfones as powerful electrophilic substrates was somewhat limited. Only roughly a dozen of seminal works (for selected examples see Scheme 1) focusing on the use of vinyl and/or 1,2-disubstituted olefin-bearing heteroaryl sulfones were reported.[15−22] Such olefins proved to be highly superior in their reactivity in comparison to aryl vinyl sulfones and even to 1,1-diphenylvinylsulfones.[16] We speculated that additional substitution with the electron-withdrawing (EWG) group on heteroaryl vinyl sulfone should broaden the synthetic utility of the vinyl sulfones (Figure 1). Newly generated Michael-type adducts should not only be more reactive toward external nucleophiles and radicals but should also react as substrates in cycloaddition reactions. In addition, the presence of the heteroaryl sulfonyl group in final adducts should allow further chemo selective transformations of obtained products.

In our group, we have a long-standing experience with benzo[*d*]thiazol-2-yl-sulfone chemistry, and thus we have designed the synthesis of sulfone **1** as a two-step protocol based on the Knoevenagel condensation[23] of aldehydes with readily available EWG α-substituted BT-sulfones **2**[24−26] (Figure 2). Herewith, we would like to present scope and limitations of such an approach and selected synthetic applications of prepared olefins **1**.

RESULTS AND DISCUSSIONS

Reaction Condition Optimization. Our approach to BT-sulfone **1** synthesis started with the condensation of BT-sulfone **2a** and benzaldehyde (for selected examples, see Table 1). Surprisingly, the reaction proved to be more challenging than expected, and all our efforts to obtain the desired product **3a** under the "classical" Knoevenagel reaction conditions failed (Table 1, entry 1).[27] In all cases, only the formation of olefin **4**, the product of Julia−Kocienski olefination,[28] was observed.[27] Interestingly when ethylenediamine diacetate (EDDA) was used to promote the condensation, product **3a** was isolated in

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Scheme 1. Selected Examples of Previous Use of Heteroaryl Vinyl Sulfones as Substrates in Intramolecular, Intermolecular, and Radical Reactions

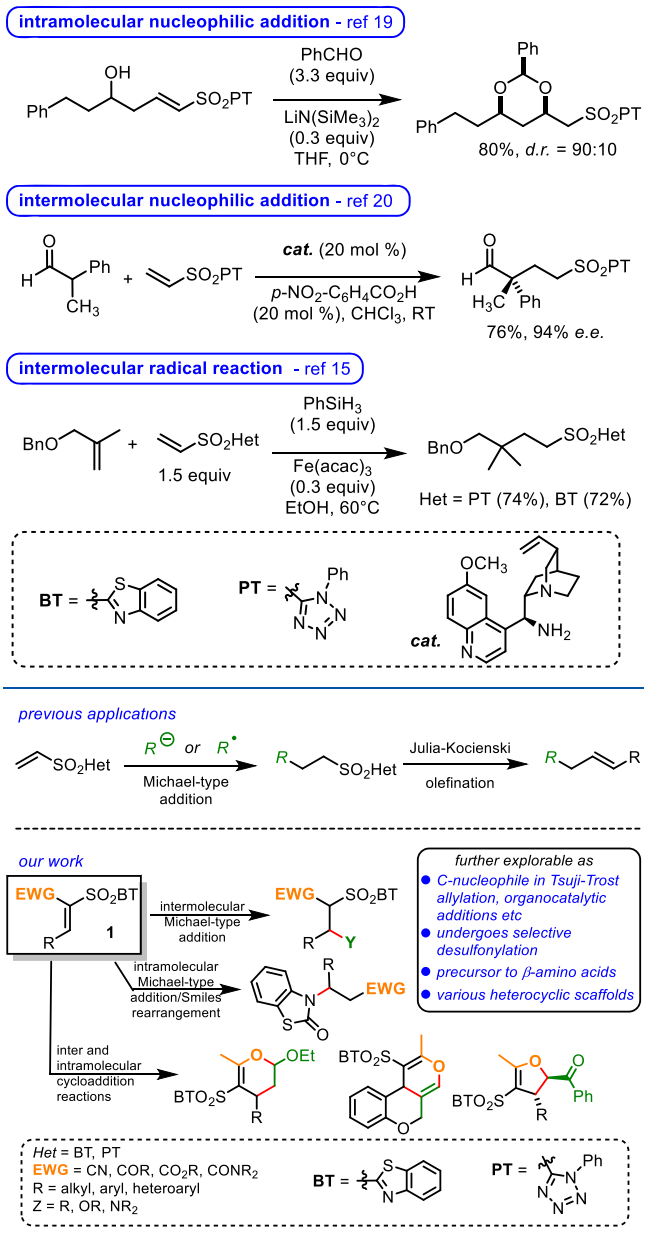


Figure 1. Comparison of previously exploited vinyl sulfones and our newly developed trisubstituted vinyl sulfones **1**.

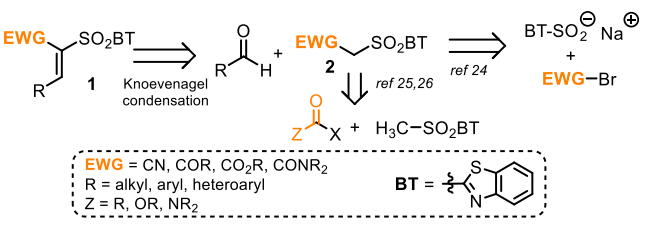
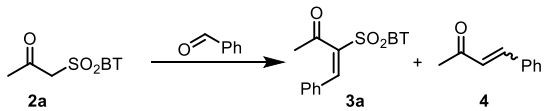


Figure 2. Retrosynthesis of trisubstituted vinyl sulfone **1**.

26% yield (Table 1, entry 2). However, further optimization and studies demonstrated that olefin **3a** is not stable under the reaction conditions and undergoes under prolonged reaction times to retro Knoevenagel reaction.[27] Observed olefin **3a**

Table 1. Knoevenagel Condensation of 1 with Benzaldehyde: Reaction Optimization



entry	conditions	3a/4 ratio[a]	yield[b] of 3a (%)
1	various "standard" Knoevenagel reaction conditions[c]	<5:>95	n.d.
2	EDDA (10 mol %), DCE, reflux, 3 h	>95:<5	26%
3	$Ti(O\text{-}iPr)_4$ (2.0 equiv), toluene, r.t., 5 h	>95:<5	70%
4	$Ti(O\text{-}iPr)_4$ (1.0 equiv), CH_3CN, r.t., 5 h	>95:<5	35%
5	$Ti(O\text{-}iPr)_4$ (3.0 equiv), CH_3CN, r.t., 5 h	>95:<5	52%
6	$Ti(O\text{-}iPr)_4$ (2.0 equiv), CH_3CN, r.t., 5 h	>95:<5	71%
7	$Ti(O\text{-}iPr)_4$ (2.0 equiv), CH_3CN, reflux, 5 h	>95:<5	52%

[a]Based on the H NMR spectra of the crude reaction mixture. [b]Isolated yields. [c]For further details, see Supporting Information

instability under basic conditions prompted us to attempt the Knoevenagel condensation under Lewis acid catalysis (Table 1, entries 3–7). Gratifyingly, it was observed that the use of $Ti(OiPr)_4$ promotes the reaction yielding the desired BT-sulfone **3a** not only as the only product of the reaction but also as the single *E*-isomer (Table 1, entry 3). Further reaction optimization revealed that the condensation proceeds best when carried out in CH_3CN at r.t. in the presence of 2.0 equiv. of $Ti(OiPr)_4$ (Table 1, entry 6). The presence of two $Ti(OiPr)_4$ equivalents proved to be crucial for the reaction to drive it to completion. To shed some light on this intriguing observation, we carried out some additional experiments[27] that led us to propose the dual role of $Ti(OiPr)_4$ during the reaction: (a) it promotes enolate formation and (b) it works as a water molecule scavenger. The exclusive E-olefin formation can be also attributed to the presence of bulky Lewis acid during the condensation step.[27]

Scope and Limitations of Knoevenagel Condensation. Having determined the optimal reaction conditions, the reaction partners' scope and limitations were evaluated (Table 2). From the *E*/*Z* olefin stereochemistry viewpoint, the condensations proceed with virtually exclusive *E* selectivity. The only exception was observed in case of the olefin **3s** (prepared from sulfone **2a** and cinnamaldehyde) that was formed as a 7:1 *E*/*Z* mixture. From the substrate viewpoint, the influence of the aldehyde-coupling partner to reaction yield was first evaluated. It was observed that aryl and heteroaryl aldehydes substituted with alkoxy and halogen substituents including sterically crowded *ortho*-monosubstituted- or *o*,*o*′-disubstituted-ones are well-tolerated. In contrary, strong EWG substituents on the aryl ring (NO_2 and CF_3) led to the (partial in case of CF_3) product degradation under the reaction conditions or during the reaction work up. Indeed, it seems that the products of olefination **3f–h**, **3v**, **3ad**, **5h**, and **6f–h** are formed under the reaction conditions but immediately undergo reaction with *i*PrOH (or another nucleophile) present in the media.[29] Only in the case of nitrile bearing condensation product **6f**, no degradation occurred and the product was isolated in 93% yield.

α-Unbranched aldehydes represent the second limitation of the condensation reaction. In those cases, the products **7a** and **7b** and the products of the olefin migration were isolated instead of the expected condensation products **3q** and **3r**.[27]

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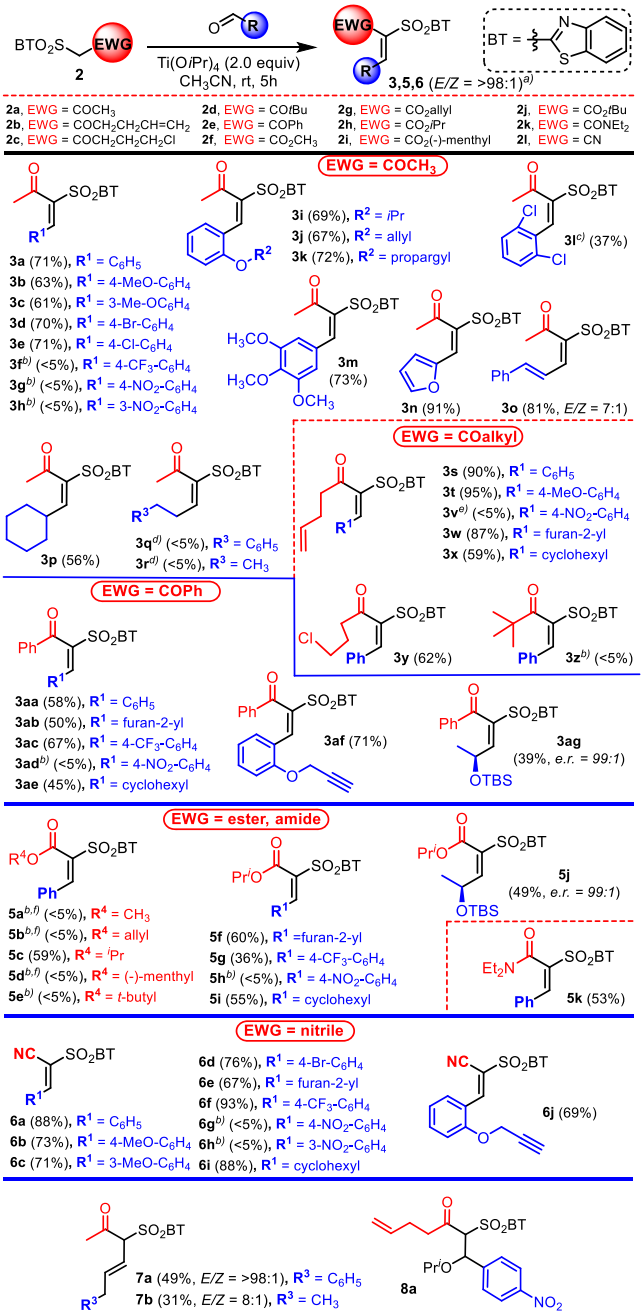
Table 2. Scope and Limitations of the Condensation Reaction



[a]Based on the ^{1}H NMR spectra of the crude reaction mixture. [b]No traces of the product observed. [c]Reaction carried out at 80 °C for 6 h. [d]Only olefin migration products **7a** and **7b** were isolated as the products of the reaction. [e]only the product of 1,4-addition of *i*-PrOH to **3v** (compound **8a**) were detected, suggesting that the trace amount of the desired product was formed. Similar observations were made when 4-cyanobenzaldehyde and 3-cyanobenzaldehyde were used as reaction substrates (not shown). [f]Only product **5c** was isolated in 58−61% yields.

Gratifyingly, when α-branched aldehydes were used, the desired products **3p**, **3x**, **3ae**, **3ag**, **5i**, **5j**, and **6i** were obtained in good to excellent yields. More importantly, when α-chiral aldehydes were used as the starting material, no stereo erosion was observed. When ketones were used as the condensation partners (not showed), no product of condensation was observed.

Next, the influence of the EWG group in **2** on the condensation was evaluated. It was observed that the condensation of alkyl ketone bearing sulfone **2d** is sensitive to the steric hindrance in carbonyl proximity (sulfone **2d** failed to yield adduct **3z**); methyl and α-unbranched functionalized BT-sulfoketones **2a−c** yielded the corresponding adducts **3a−y** in good to excellent yields; and arylketosulfone **2e** yielded the products **3aa−ag** in yields slightly lower to the corresponding alkyl sulfones **2a-c**. Ester, amide, and nitrile-bearing sulfones **2h**, **2k**, and **2l** reacted under the condensation conditions smoothly and yielded the corresponding adducts **5** and **6** in good to excellent yields and exclusive *E*-selectivity. In case of esters, however, only *i*-propyl-bearing ester adducts might be isolated after the reaction because the rapid *in situ* transesterification process of ester sulfones **2f**, **2g**, and **2i** to the sulfone **2h** occurs during the condensation.[27] In the case of *t*-butyl-bearing ester sulfone **2j**, no traces of transesterification was observed, however, no product of condensation either.

Applications of Activated Olefins in Organic Synthesis. Having desired activated olefins **3**, **5**, and **6** in hand, their reactivity in cycloadditions (Scheme 2), Michael-type (Lewis acid-mediated) nucleophilic additions (Schemes 3 and 4), hydride reductions, and radical reactions (Scheme 5) were evaluated. First, the hetero-Diels−Alder cycloaddition reaction of ketosulfones **3** with ethyl vinyl ether was investigated (Scheme 2, part A). It was observed that the reaction proceeds well and yields the desired dihydropyran **9** in excellent yields. Similarly, the intramolecular hetero-Diels−Alder reaction of ketosulfone function to alkynes can be performed albeit under harsher reaction conditions (μW, 150 °C, 200 W) (Scheme 2, part B). Ketosulfones **3** can also react with ammonium ylides to generate products of formal [4 + 1]-cycloaddition reaction in both racemic (Scheme 2, part C) and enantioselective manner (Scheme 2, part D). In both cases, the desired dihydrofurans **12** are formed in very good to excellent yields and, in the case of nonracemic ammonium ylides,[30] enantioselectivity. Lastly, activated olefins **3a**, **3p**, **3ac**, and **5c** were used as dipolarophiles in 1,3-cycloaddition reaction of sodium azide (Scheme 2, part E). In this case, products of [3 + 2]-cycloaddition **14** undergoes to spontaneous *in situ* $BTSO_2$-group elimination to provide solely corresponding triazoles **15** in good to excellent yields. In the case of compound **15e**, the reaction was chemoselective toward the activated olefin.

The reactivity of activated olefins toward nucleophiles under uncatalyzed (Scheme 3, part A) and Lewis acid-mediated (Scheme 3, part B, and Scheme 4) reaction conditions was also evaluated. It was observed that simple treatment of olefins **3a** and **3ag** with methanol at r.t. under prolonged reaction times results in the formation of 1,4-adducts **17** that can be further selectively desulfonylated[31] to yield β-methoxy ketones **16a** and **16b** (Scheme 3, part A). Interestingly, even under unoptimized reaction conditions, the addition of methanol to homochiral olefin **3ag** proceeds with high diastereoselectivity.[27] Similarly, olefins **3a** and **6a** were reacted with Et_3SiH and allylsilane in the presence of $TiCl_4$ (Scheme 3, part B). Rapid 1,4-addition followed by *in situ* desulfonylation[31] then yielded β-adducts **19a-c** in very good yields.

Another interesting reaction was observed when olefin **3a** was treated with $TiCl_4$ at r.t. without any additional additives (Scheme 4). In this case, an intramolecular smiles-like

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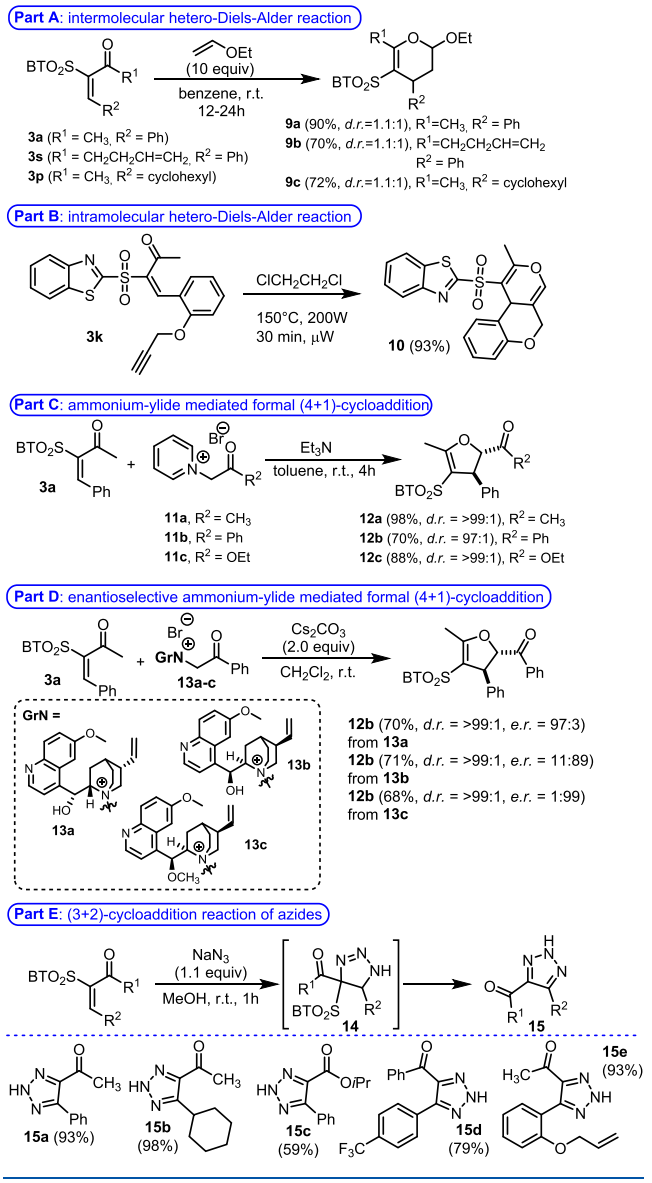
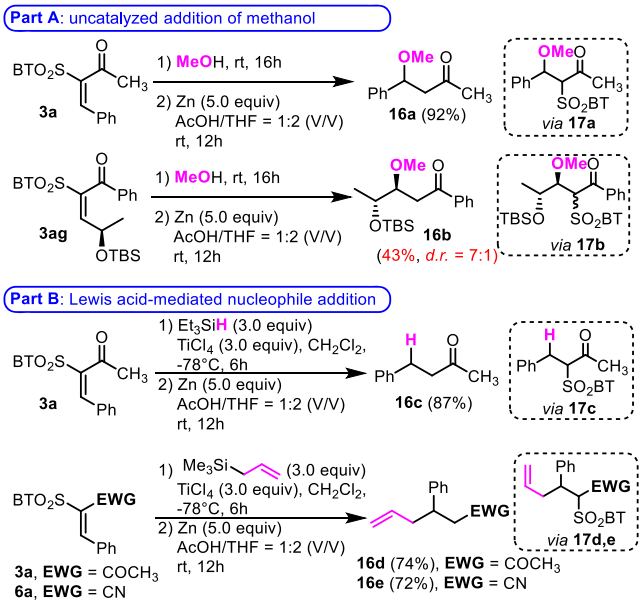
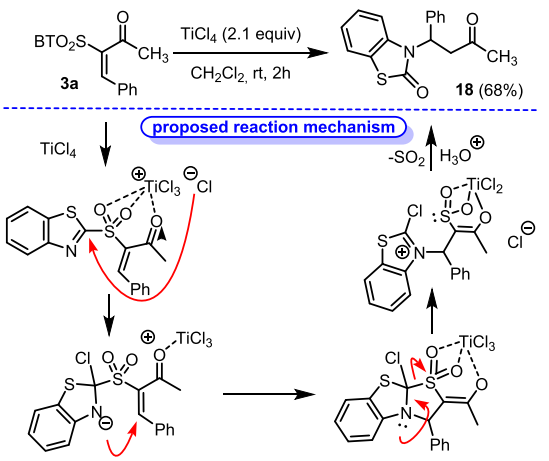
Scheme 2. Cycloaddition Reactions—Attempted Examples



Scheme 3. Uncatalyzed and Lewis Acid-Mediated Reactions of Activated Olefins 3a, 3ag, and 6a



Scheme 4. $TiCl_4$-Mediated Rearrangement of 3a to Ketone 18



rearrangement followed with desulfonylation yielded *β*-functionalized ketone **18**.[32]

Because the Lewis acid-mediated Et_3SiH addition proceeded with exclusive 1,4-addition, selectivity of 1,2- versus 1,4-hydride reduction was investigated (Scheme 5).[27] It was observed that a vast majority of standard reducing agents, to mention just a few [$n$$Bu_3SnH$[33] or DIBAL-H in tetrahydrofuran (THF)], favors 1,4-reduction products **17c,f** (Scheme 5, part A). In contrary, the selective 1,2-hydride reduction could be performed if DIBAL-H reduction was carried out in CH_2Cl_2 at −78 °C under high (0.01 M) dilution (Scheme 5, part B). Using such conditions, the desired allylic alcohols **19a,c** could be obtained in very good yields.[27] Interestingly, phenyl-substituted ketone **3aa** do not undergo to 1,2-reduction under such conditions and only 1,4-adduct **17f** is isolated.

Finally, we have decided to evaluate the radicophilic behavior of activated olefins **3**, **5**, and **6**. The original hypothesis was that these newly generated olefins will behave similarly as vinyl BT sulfone explored in the pioneering work of Baran et al. ($Fe(acac)_3$ promoted radical addition).[15] However, quick 1,4-addition of EtOH to **3** excluded such possibility.[34]

Thus, we have focused on classical Giese addition, in which an electron-deficient alkene (our olefins) is attacked by a nucleophilic alkyl radical.[35−38] Unfortunately, such conditions in general require a tin reagent. Because in our case $n$$Bu_3SnH$ spontaneously adds in a 1,4-manner to olefin **3a** even at low temperature, tris(trimethylsilyl)silane (TTMS) was used instead (Scheme 5, part C). Thus, olefins **3a**, **5c**, and **6a** were reacted with the ethyl radical generated in a TTMS/EtI/AIBN system. Surprisingly, only nitrile bearing olefin **6a** yielded the desired adduct **20**, while carbonyl bearing olefins **3a** and **5c** gave unsaturated carbonyl compounds **4** and **21**, respectively. Such an observation suggests that in the case of carbonyl-substituted olefins, the generated radical preferentially attacks the BT-sulfonyl group and, as suggested by the (*E*)-olefin **4** and **21** formation,[39] generates a vinylic radical as a reaction intermediate.

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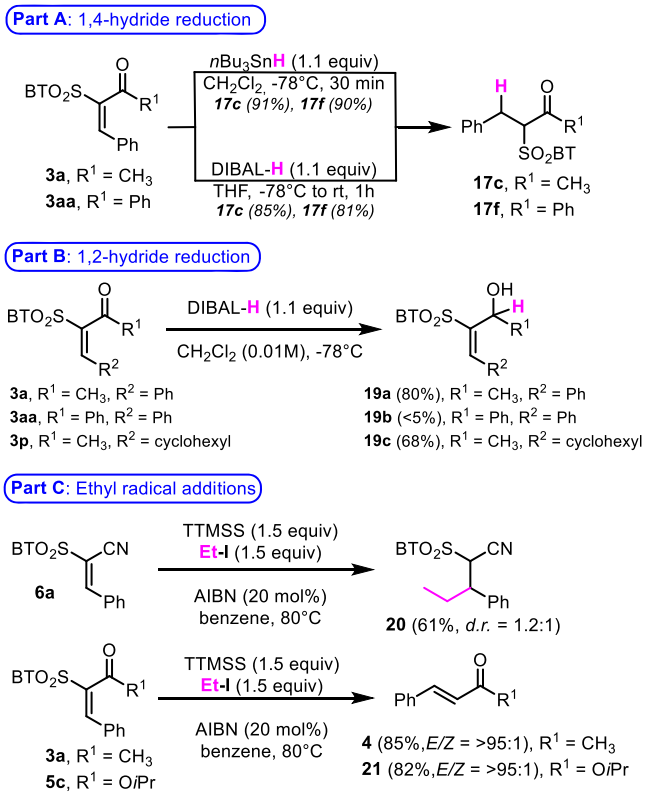
Scheme 5. Selective Hydride Reductions and Radical Addition



CONCLUSIONS

In conclusion, the synthesis of highly electrophilic olefins that can be in one or two steps transformed into valuable (enantio-enriched) heterocyclic and acyclic scaffolds has been developed. Prepared olefins can be used as hetero-dienes, dienophiles, and Michael-acceptors and can be reacted in various hetero-Diels–Alder, 1,3-dipolar, or formal [4 + 1]-cycloaddition reactions. Selective 1,2 and 1,4-hydride addition, respectively, are possible in the case of carbonyl-bearing olefins **3**. Such olefins also undergo Lewis acid-mediated 1,4-addition of allylsilanes or to unprecedented Smiles-like rearrangement products. Finally, classical Giese 1,4-radical addition of the nucleophilic ethyl radical was observed in case of nitrile-bearing olefin **6a** but not in case of the two carbonyl-group bearing analogues **3a** and **5c**. The last two transformations (smiles-like rearrangement and nucleophilic radical additions) are currently being further investigated in our group.

EXPERIMENTAL SECTION

General Information. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. Chiral aldehydes,[40] pyridium salts **11a–c**,[41] chiral ammonium salts **13a–c**,[30,42] BT-sulfones **2d**,[43] **2g**,[25,26] (−)-2-menthyl 2-bromoacetate,[44] and 2-(methylsulfonyl)benzo[*d*]thiazole[25,26] were prepared using reported procedures. Progress of reactions was monitored by thin-layer chromatography (TLC)—aluminum plates pre-coated with silica gel (silica gel 60 F254). Column chromatography was performed on silica gel 60 (40–63 μm) or neutralized silica gel (40–63 μm) using 5% solution of Et_3N in petroleum ether. Reactions run at elevated temperatures were carried out using an oil bath, and indicated temperatures refers to the oil bath temperature. Determination of melting points were done on a Büchi melting point apparatus and were uncorrected. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were measured on Jeol ECA400II (400 and 101 MHz) or Jeol 500 ECA (500 and 126 MHz) in $CDCl_3$ or dimethyl sulfoxide (DMSO). Chemical shifts are reported in ppm, and their calibration was performed (a) in case of ^1H NMR experiments on the residual peak of non-deuterated solvent δ ($CHCl_3$) = 7.26 ppm; δ (DMSO) = 2.50 ppm, (b) in case of ^{13}C NMR experiments on the middle peak of the ^{13}C signal in deuterated solvent δ ($CDCl_3$) = 77.2 ppm; δ (DMSO-d_6) = 39.5 ppm, and (c) in case of $^{19}F\{^1H\}$ NMR experiments on the external calibrant $CFCl_3$ [δ ($CFCl_3$) = 0 ppm]. Proton coupling patterns are represented as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), triplet of triplet (tt), and multiplet (m). High-resolution mass spectrometry (HRMS) data were obtained using a quadrupole/ion trap mass analyzer. High-performance liquid chromatography (HPLC) was performed using a Dionex Summit HPLC system with a CHIRAL ART Cellulose-SB (250 × 4.6 mm, 5 μm) or CHIRALPAK IE-3 chiral stationary phase with mobile phase 2-propanol/hexane, 2-propanol/CO_2, and MeOH/CO_2. HRMS analysis was performed using a LC chromatograph (Dionex UltiMate 3000, Thermo Fischer Scientific, MA, USA) + mass spectrometer Exactive Plus Orbitrap high-resolution (Thermo Fischer Scientific, MA, USA) with electrospray ionization; chromatographic separation: column Phenomenex Gemini (C18, 50 × 2 mm, 3 μm particle), isocratic elution, MP: 80% ACN and 20% buffer (0.01 M ammonium acetate) or 95% MeOH + 5% water + 0.1% HCOOH. Microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus. The reactor was used in the standard configuration as delivered, including proprietary software. The reactions were carried out in 30 mL glass vials sealed with an Silicone/PTFE Vial caps top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled to ambient temperature by gas jet cooling.

Synthesis of α-Electron-Withdrawing BT-Sulfones (2). *Method A.*[45] *Synthesis of a Sulfide Intermediate.* A mercaptobenzothiazole (10.0 g, 1.0 equiv) and α-halo compound (1.0 equiv) were dissolved in CH_2Cl_2 (0.2 M), and the mixture was cooled to 0 °C. Triethylamine (8.6 mL, 2.0 equiv) was added dropwise, and the resulting mixture was allowed to warm to r.t. and stirred for 4 h 2 M aq. HCl (20 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the resulting organic extracts were combined, washed with water (30 mL), brine (20 mL), and dried over $MgSO_4$, and solvents were evaporated under reduced pressure. The crude product was used in the next step without further purification.

Synthesis of targeted sulfone. Sulfide (1.1 g, 1.0 equiv) and periodic acid (2.8 g, 3.0 equiv) were dissolved in acetonitrile (0.2 M), and the mixture was cooled to 0 °C. CrO_3 (0.123 g, 0.3 equiv) was added portion wise, and the resulting mixture stirred for 30 min, before it was warmed to r.t. The reaction was stirred for another 4 h before it was cooled to 0 °C and quenched by adding sat. aq. Na_2SO_3. The mixture was filtered through Celite and washed (5 × 25 mL EtOAc). Layers were separated, and the organic phase was washed with sat. Na_2SO_3 (2 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over $MgSO_4$. Solvents were removed under the reduced pressure.

Method B.[25] A solution of 2-(methylsulfonyl)benzo[*d*]thiazole[25,26] (0.300 g, 1.41 mmol, 1.0 equiv) in dry THF (7.0 mL, 0.2 M) was cooled to −78 °C, and LiHMDS (1.0 M sol. in THF) (3.7 mL, 2.2 equiv) was added dropwise. The color of the reaction mixture turned from colorless or slightly yellow to orange/red. Immediately after, a solution of acyl halide (1.69 mmol, 1.2 equiv) in THF (3 mL) was added. The color of the reaction mixture faded within few minutes. The resulting mixture was stirred at −78 °C for 60 min, allowed to warm to r.t. within 1 h and stirred at r.t. for additional 60 min before sat. aq. NH_4Cl (15 mL) was added. The whole mixture was extracted with EtOAc (3 × 75 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure. The resulting crude

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product was used further without any purification, if not stated otherwise.

*1-(Benzo[d]thiazol-2-ylsulfonyl)propan-2-one (**2a**).* The crude product was prepared using method A and obtained with enough purity as a yellow solid (4.2 g, 89%). mp = 125−127 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21 (dd, *J* = 7.6, 2.0 Hz, 1H), 8.03−7.99 (m, 1H), 7.67−7.57 (m, 2H), 4.57 (s, 2H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 194.7, 164.9, 152.5, 137.0, 128.4, 127.9, 125.7, 122.5, 65.5, 31.6; MS (ESI) *m*/*z* (%) 256: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M - H]^-$ calcd for $C_{10}H_8NO_3S_2$, 253.9951; found, 253.9950.

*1-(Benzo[d]thiazol-2-ylsulfonyl)hex-5-en-2-one (**2b**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; EtOAc:P.E. = 1:6), and isolated as a yellow oil (1.4 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.19 (m, 1H), 8.05−8.00 (m, 1H), 7.67−7.58 (m, 2H), 5.81−5.70 (m, 1H), 5.08−4.95 (m, 2H), 4.59 (s, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.41−2.29 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.4, 165.0, 152.5, 137.0, 136.0, 128.4, 127.9, 125.7, 122.5, 116.1, 64.7, 43.6, 27.1; MS (ESI) *m*/*z* (%) 294: $[M - H]^-$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{14}NO_3S_2$, 296.0410; found, 296.0407.

*1-(Benzo[d]thiazol-2-ylsulfonyl)-5-chloropentan-2-one (**2c**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; diethylether:P.E. = 3:1), and isolated as an orange oil (0.485 g, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.20 (m, 1H), 8.04−8.01 (m, 1H), 7.68−7.59 (m, 2H), 4.61 (s, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 6.8 Hz, 2H), 2.12−2.02 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.2, 164.9, 152.5, 137.0, 128.5, 128.0, 125.7, 122.6, 64.9, 43.8, 41.3, 26.0; MS (ESI) *m*/*z* (%) 282: $[M - Cl]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{13}ClNO_3S_2$, 318.0020; found, 318.0021.

*2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethan-1-one (**2e**).* The crude product was prepared using method A and obtained with enough purity as a light brown solid (3.9 g, 92%). mp = 118−120 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.18 (m, 1H), 8.02−7.99 (m, 1H), 7.95−7.90 (m, 2H), 7.66−7.57 (m, 3H), 7.50−7.44 (m, 2H), 5.20 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 187.3, 165.4, 152.6, 137.2, 135.6, 134.8, 129.1, 129.1, 128.3, 127.8, 125.7, 122.5, 61.3; MS (ESI) *m*/*z* (%) 318: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO_3S_2$, 318.0253; found, 318.0251.

*Methyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2f**).* The crude product was prepared using method A and obtained as a yellow solid (2.8 g, 88%). mp = 68−70 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.21 (m, 1H), 8.04−8.01 (m, 1H), 7.68−7.59 (m, 2H), 4.58 (s, 2H), 3.74 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.0, 162.3, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 58.7, 53.5; MS (ESI) *m*/*z* (%): 272 $[M + H]^+$ (27); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_{10}NO_4S_2$, 272.0046; found, 272.0043.

*Isopropyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2h**).* The crude product was prepared using method B and obtained as a light yellow solid (0.199 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.21 (m, 1H), 8.08−7.99 (m, 1H), 7.68−7.58 (m, 2H), 5.00 (hept, *J* = 6.4 Hz, 1H), 4.54 (s, 2H), 1.15 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.2, 161.2, 152.6, 137.1, 128.4, 127.9, 125.7, 122.5, 71.1, 59.1, 21.6; MS (ESI) *m*/*z* (%) 298: $[M - H]^-$ (100); HR-MS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{12}H_{13}NO_4S_2$, 299.0286; found, 299.0284.

*(2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(Benzo[d]thiazol-2-yl-sulfonyl)acetate (**2i**).* The crude product was prepared using method A from (−)-2-menthyl 2-bromoacetate[44] and obtained with enough purity as a green viscose syrup (2.24 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.17 (m, 1H), 8.07−7.97 (m, 1H), 7.69−7.54 (m, 2H), 4.65 (td, *J* = 10.8, 4.4 Hz, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.52 (d, *J* = 15.2 Hz, 1H) 1.97−1.85 (m, 1H), 1.69−1.52 (m, 3H), 1.47−1.31 (m, 1H), 1.24−1.10 (m, 1H), 1.03−0.84 (m, 2H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.84−0.67 (m, 1H), 0.68 (d, *J* = 7.2 Hz, 3H), 0.61 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.3, 161.3, 152.6, 137.0, 128.3, 127.9, 125.6, 122.5, 58.9, 46.7, 40.4, 34.1, 31.4, 26.0, 23.1, 22.0, 20.6, 16.0; HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{26}NO_4S_2$, 396.1298; found, 396.1300; α_D^{22} = −32.5 (c 0.2, $CHCl_3$).

*2-(Benzo[d]thiazol-2-yl-sulfonyl)-N,N-diethylacetamide (**2k**).* The crude product was prepared using method B, purified using flash column chromatography (SiO_2; EtOAc:P.E. = 3:1), and isolated as a yellow solid (0.366 g, 84%). mp = 125−126 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.20 (m, 1H), 8.01−7.98 (m, 1H), 7.64−7.55 (m, 2H), 4.63 (s, 2H), 3.46 (q, *J* = 7.2 Hz, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 165.5, 160.0, 152.6, 137.4, 128.1, 127.7, 125.7, 122.6, 58.0, 43.3, 41.1, 14.6, 12.9; MS (ESI) *m*/*z* (%) 313: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{13}H_{16}N_2NaO_3S_2$, 335.0495; found, 335.0494.

*2-(Benzo[d]thiazol-2-yl-sulfonyl)acetonitrile (**2l**).* The crude product was prepared using the method A and obtained with enough purity as a brown solid (3.4 g, 95%). mp = 172−174 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.29−8.25 (m, 1H), 8.09−8.05 (m, 1H), 7.74−7.65 (m, 2H), 4.56 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 162.5, 152.4, 137.3, 129.1, 128.4, 126.0, 122.7, 109.2, 44.1; MS (ESI) *m*/*z* (%) 237: $[M - H]^-$ (25); HRMS (ESI) *m*/*z*: $[M - H]^-$ calcd for $C_9H_5N_2O_2S_2$, 236.9798; found, 236.9798.

Ti(O-*i*Pr)$_4$-Mediated Transesterification of 2f to 2h. To solution of sulfone **2f** (0.200 g, 0.73 mmol, 1.0 equiv) in CH_3CN (4.0 mL, 0.2 M), Ti(O-*i*Pr)$_4$ (0.435 mL, 1.46 mmol, 2.0 equiv) was added dropwise at r.t., and the resulting mixture was stirred for 2 h. CH_2Cl_2 (15 mL) and sat. aq. NH_4Cl (5 mL) were added, and the resulting mixture was filtered through Celite. The filtrate cake was washed with CH_2Cl_2 (5 × 20 mL), and the combined filtrates were washed with sat. aq. NH_4Cl (2 × 15 mL), brine (2 × 15 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure, and the crude product was isolated as a light yellow solid (0.219 g, 95%)

General Procedure for Knoevenagel Condensation Reaction. To a sulfone (1.0 mmol, 1.0 equiv) in CH_3CN (5.0 mL, 0.2 M) at r.t. was added Ti(O-*i*Pr)$_4$ (0.925 mL, 3.0 equiv), and the resulting mixture was stirred for 30 min. An aldehyde (2.0 mmol, 2.0 equiv) was added dropwise, and the mixture was stirred for the indicated time. The reaction was quenched upon the addition of CH_2Cl_2 (15 mL) and sat. NH_4Cl (5 mL), and the resulting suspension was filtered through Celite. The filtrate cake was rinsed with CH_2Cl_2 (5 × 20 mL), and the combined filtrates were washed with sat. NH_4Cl (2 × 15 mL), brine (2 × 15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-phenylbut-3-en-2-one (**3a**).* Reaction was carried out using the described procedure with 1.5 g (4.37 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3a** as a light yellow solid (1.43 g, 71%). mp = 104−107 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.18 (m, 1H), 8.14 (s, 1H), 8.01−7.98 (m, 1H), 7.59 (ddd, *J* = 7.2, 6.4, 1.6 Hz, 2H), 7.41 (s, 5H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.3, 166.0, 152.9, 145.1, 139.3, 137.6, 132.2, 131.3, 130.3, 129.4, 128.1, 127.6, 125.7, 122.40, 31.92; MS (ESI) *m*/*z* (%) 344: $[M + H]^+$ (100); HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{14}NO_3S_2$, 344.0410; found, 344.0413.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-methoxyphenyl)but-3-en-2-one (**3b**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3b** as a yellow solid (0.143 g, 63%). mp = 119−121 °C; ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.20−8.18 (m, 1H), 8.07 (s, 1H), 8.00−7.98 (m, 1H), 7.62−7.55 (m, 2H), 7.39−7.36 (m, 2H), 6.94−6.91 (m, 2H), 3.85 (s, 3H), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.7, 166.5, 163.0, 152.8, 145.1, 137.5, 136.2, 132.8, 128.0, 127.6, 125.7, 123.7, 122.4, 114.9, 55.7, 31.9; MS (ESI) *m*/*z* (%) 374: $[M + H]^+$ (50); HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0519.

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*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(3-methoxyphenyl)but-3-en-2-one (**3c**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3c** as a yellow oil (0.138 g, 61%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.17 (m, 1H), 8.10 (s, 1H), 8.00−7.97 (m, 1H), 7.62−7.54 (m, 2H), 7.37−7.28 (m, 1H), 7.06−6.94 (m, 3H), 3.78 (s, 3H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.3, 165.9, 160.1, 152.8, 145.0, 139.5, 137.6, 132.5, 130.4, 128.1, 127.6, 125.7, 122.6, 122.4, 118.1, 115.0, 55.5, 32.0; MS (ESI) *m/z* (%) 374: $[M + H]^+$; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0518.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-bromophenyl)but-3-en-2-one (**3d**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3d** as a yellow oil (0.231 g, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.05 (s, 1H), 8.03−8.00 (m, 1H), 7.65−7.59 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 198.0, 165.7, 152.9, 143.5, 140.1, 137.6, 132.8, 131.6, 130.2, 128.3, 127.8, 127.1, 125.8, 122.5, 32.0; MS (ESI) *m/z* (%) 422: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}BrNO_3S_2$, 421.9515; found, 421.9514.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(4-chlorophenyl)but-3-en-2-one (**3e**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3e** as a colorless oil (0.212 g, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.24−8.17 (m, 1H), 8.06 (s, 1H), 8.03−7.99 (m, 1H), 7.64−7.56 (m, 2H), 7.44−7.39 (m, 2H), 7.37−7.33 (m, 2H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.0, 165.8, 152.9, 143.5, 140.0, 138.6, 137.6, 131.5, 129.8, 128.3, 127.8, 125.8, 122.4, 32.0; MS (ESI) *m/z* (%) 378: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{12}ClNaNO_3S_2$, 399.0939; found, 399.0940.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2-isopropoxyphenyl)but-3-en-2-one (**3i**).* Reaction was carried out using the described procedure with 0.233 g (0.92 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3i** as a yellow oil (0.274 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.51 (s, 1H), 8.18 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.01 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.58 (tt, *J* = 7.2, 5.6 Hz, 2H), 7.43 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.02−6.85 (m, 2H), 4.63 (hept, *J* = 6.0 Hz, 1H), 2.30 (s, 3H), 1.35 (d, *J* = 6.0 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 167.0, 157.0, 142.9, 138.2, 137.5, 133.8, 131.1, 127.9, 127.4, 125.5, 122.3, 121.5, 120.7, 114.0, 71.9, 53.6, 31.3, 21.9; MS (ESI) *m/z* (%) 402: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_4S_2$, 424.0653; found, 424.0648.

*(E)-4-(2-(Allyloxy)phenyl)-3-(benzo[d]thiazol-2-yl-sulfonyl)but-3-en-2-one (**3j**).* Reaction was carried out using the described procedure with 0.255 g (1.0 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3j** as a yellow oil (0.267 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.53 (s, 1H), 8.23−8.16 (m, 1H), 8.05−7.95 (m, 1H), 7.66−7.52 (m, 2H), 7.49−7.40 (m, 1H), 7.21 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.01−6.90 (m, 2H), 6.02 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.30 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.70−4.59 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 166.8, 157.4, 152.8, 142.2, 138.5, 137.5, 133.9, 132.2, 131.1, 128.0, 127.5, 125.6, 122.4, 121.1, 120.8, 118.3, 112.8, 69.4, 31.5; MS (ESI) *m/z* (%) 400: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{17}NNaO_4S_2$, 422.0497; found, 422.0490.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2-(prop-2-yn-1-yloxy)-phenyl)but-3-en-2-one (**3k**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **3k** as a brown solid (0.224 g, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.45 (s, 1H), 8.19 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.00 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.63−7.53 (m, 2H), 7.51−7.45 (m, 1H), 7.24 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 197.8, 166.7, 156.2, 152.9, 141.7, 139.0, 137.6, 133.8, 131.4, 128.0, 127.6, 125.7, 122.4, 121.9, 121.3, 113.1, 56.2, 31.6; MS (ESI) *m/z* (%) 397: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{15}NNaO_4S_2$, 420.0340; found, 420.0335.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(2,6-dichlorophenyl)but-3-en-2-one (**3l**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3l** as a yellow oil (0.06 g, 37%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.31 (s, 1H), 8.21−8.18 (m, 1H), 8.04−8.01 (m, 1H), 7.65−7.58 (m, 2H), 7.41−7.38 (m, 2H), 7.35−7.30 (m, 1H), 2.26 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 193.6, 166.2, 152.7, 143.8, 137.5, 133.9, 131.6, 130.7, 128.6, 128.3, 127.7, 126.6, 125.8, 122.5, 30.2; MS (ESI) *m/z* (%) 412: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{11}Cl_2NNaO_3S_2$, 433.9455; found, 433.9449.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(3,4,5-trimethoxyphenyl)-but-3-en-2-one (**3m**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3m** as a yellow oil (0.131 g, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 8.23−8.19 (m, 1H), 8.04 (s, 1H), 8.03−7.99 (m, 1H), 7.66−7.55 (m, 2H), 6.64 (s, 2H), 3.90 (s, 3H), 3.82 (s, 6H), 2.44 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*): δ 198.7, 166.0, 153.6, 152.9, 145.1, 141.6, 138.1, 137.6, 128.2, 127.7, 126.4, 125.8, 122.4, 107.7, 61.2, 56.3, 32.2; MS (ESI) *m/z* (%) 434: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{20}NO_6S_2$, 423.0727; found, 423.0728.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-(furan-2-yl)but-3-en-2-one (**3n**).* Reaction was carried out using the described procedure with 0.200 g (0.79 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3n** as a yellow oil (0.237 g, 91%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.17 (m, 1H), 7.99−7.96 (m, 1H), 7.74 (s, 1H), 7.62−7.58 (m, 3H), 7.04 (d, *J* = 3.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 2.61 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.8, 166.1, 152.9, 148.1, 147.6, 137.5, 134.3, 129.7, 128.1, 127.6, 125.7, 122.3, 122.0, 113.6, 32.3; MS (ESI) *m/z* (%) 334: $[M + H]^+$ (49); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO_4S_2$, 334.0202; found, 334.0203.

*(3E,5E)-3-(benzo[d]thiazol-2-ylsulfonyl)-6-phenylhexa-3,5-dien-2-one (**3o**).* Reaction was carried out using the described procedure with 0.740 g (2.9 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3o** as a yellow solid (0.866 g, 81%, *E*/*Z* = 7:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.14 (m, 1H), 8.02−7.97 (m, 2H), 7.69 (dd, *J* = 15.2, 11.6 Hz, 1H), 7.62−7.56 (m, 4H), 7.41 (m, 3H), 7.37 (d, *J* = 15.2 Hz, 1H), 2.65 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 194.1, 167.5, 152.7, 152.4, 152.3, 137.0, 135.7, 135.1, 131.4, 129.3, 128.9, 128.2, 127.7, 125.7, 123.0, 122.4, 31.9; MS (ESI) *m/z* (%) 370: $[M + 1]^+$ (60); HRMS (ESI) *m/z*: calcd for $C_{19}H_{16}NO_3S_2$ $[M + H]^+$, 370.0566; found, 370.0568.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-cyclohexylbut-3-en-2-one (**3p**).* Reaction was carried out using the described procedure with 1.0 g (3.9 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3p** as a colorless oil (0.764 g, 56%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.16 (m, 1H), 8.00−7.97 (m, 1H), 7.64−7.54 (m, 2H), 7.25 (d, *J* = 10.8 Hz, 1H), 2.57 (s, 3H), 1.76 (bs, 5H), 1.28 (bs, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 195.1, 166.5, 159.0, 152.6, 139.8, 137.1, 128.1, 127.7, 125.7, 122.4, 39.5, 32.2, 31.6, 25.5, 25.0; MS (ESI) *m/z* (%) 350: $[M + 1]^+$

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(100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{20}NO_3S_2$, 350.0879; found, 350.0877.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenylhepta-1,6-dien-3-one (**3s**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3s** as a yellow oil (0.234 g, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.16 (s, 1H), 8.02−7.99 (m, 1H), 7.64−7.56 (m, 2H), 7.52−7.46 (m, 1H), 7.45−7.40 (m, 2H), 7.39−7.35 (m, 2H), 5.69 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.01−4.92 (m, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.39−2.32 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 200.1, 166.0, 153.0, 145.2, 139.2, 137.7, 136.1, 132.2, 131.4, 130.4, 129.4, 128.2, 127.7, 125.8, 122.4, 116.2, 43.5, 27.4; MS (ESI) *m/z* (%) 384: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3S_2$, 384.0723; found, 384.0720.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-(4-methoxyphenyl)hepta-1,6-dien-3-one (**3t**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3t** as a yellow oil (0.266 g, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.17 (m, 1H), 8.07 (s, 1H), 8.01−7.97 (m, 1H), 7.62−7.54 (m, 2H), 7.35−7.31 (m, 2H), 6.93−6.89 (m, 2H), 5.73 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.04−4.94 (m, 2H), 3.85 (s, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.42−2.35 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 200.5, 166.5, 163.0, 152.9, 145.2, 137.6, 136.3, 136.0, 132.9, 128.0, 127.6, 125.8, 123.8, 122.4, 116.1, 114.9, 55.7, 43.5, 27.5; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4S_2$, 414.0828; found, 414.0827.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-(furan-2-yl)hepta-1,6-dien-3-one (**3w**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **3w** as a yellow oil (0.220 g, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.21−8.18 (m, 1H), 8.00−7.97 (m, 1H), 7.74 (s, 1H), 7.63−7.53 (m, 3H), 7.00−6.98 (m, 1H), 6.57 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.85 (ddt, *J* = 16.8, 10.0, 6.4 Hz, 1H), 5.06 (dq, *J* = 17.2, 1.6 Hz, 1H), 4.99 (ddt, *J* = 10.0, 1.6, 1.2 Hz, 1H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.50−2.43 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 198.6, 166.1, 152.9, 148.0, 147.7, 137.6, 136.8, 134.5, 129.7, 128.1, 127.7, 125.8, 122.4, 121.7, 115.7, 113.6, 43.9, 27.5; MS (ESI) *m/z* (%) 374: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{16}NO_4S_2$, 374.0515; found, 374.0513.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-cyclohexylhepta-1,6-dien-3-one (**3x**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2b**. Product **3x** was obtained with enough purity as a yellow oil (0.155 g, 59%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.16 (m, 1H), 8.01−7.97 (m, 1H), 7.64−7.55 (m, 2H), 7.21 (d, *J* = 10.8 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 5.07−4.94 (m, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.54−2.43 (m, 1H), 2.39 (dtd, *J* = 7.2, 6.0, 1.6 Hz, 2H), 1.82−1.68 (m, 5H), 1.33−1.22 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 197.4, 166.5, 158.1, 152.8, 139.9, 137.3, 136.5, 128.2, 127.7, 125.8, 122.4, 115.8, 43.7, 39.5, 31.7, 27.5, 25.6, 25.0; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_3S_2$, 412.1012; found, 412.1013.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-6-chloro-1-phenylhex-1-en-3-one (**3y**).* Reaction was carried out using the described procedure with 0.100 g (0.68 mmol) of sulfone **2c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3y** as a yellow oil (0.079 g, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.18 (m, 1H), 8.17 (s, 1H), 8.03−7.98 (m, 1H), 7.64−7.55 (m, 2H), 7.52−7.47 (m, 1H), 7.46−7.41 (m, 2H), 7.39−7.35 (m, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.13−2.03 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 199.9, 165.9, 152.9, 145.5, 139.0, 137.6, 132.3, 131.3, 130.2, 129.5, 128.2, 127.7, 125.8, 122.4, 43.7, 41.2, 26.4; MS (ESI) *m/z* (%) 406: $[M]^+$ (100), 407 $[M + 1]^+$ (23); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}ClNO_3S_2$, 406.0333; found, 406.0333.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1,3-diphenylprop-2-en-1-one (**3aa**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (passive SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **3aa** as a yellow solid (0.367 g, 58%). mp = 150−153 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.33 (s, 1H), 8.24−8.16 (m, 1H), 8.00−7.93 (m, 1H), 7.91−7.82 (m, 2H), 7.65−7.51 (m, 2H), 7.47 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.38−7.27 (m, 5H), 7.24−7.13 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 191.2, 166.0, 152.9, 145.9, 137.7, 136.7, 135.3, 134.7, 131.9, 131.2, 130.9, 129.9, 129.1, 128.9, 128.1, 127.6, 125.8, 122.4; MS (ESI) *m/z* (%) 406: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_3S_2$, 406.0566; found, 406.0563.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (**3ab**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **3ab** as a yellow solid (0.120 g, 50%). mp = 168−170 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.19 (m, 1H), 8.00 (s, 1H), 7.96−7.93 (m, 1H), 7.92−7.89 (m, 2H), 7.61−7.54 (m, 2H), 7.53−7.49 (m, 1H), 7.39−7.33 (m, 2H), 7.24 (dq, *J* = 1.6, 0.8 Hz, 2H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.6, 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 190.1, 166.2, 152.9, 147.9, 147.5, 137.7, 136.4, 134.3, 132.3, 130.9, 129.7, 128.8, 128.0, 127.5, 125.7, 122.3, 121.4, 113.2; MS (ESI) *m/z* (%) 396: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{14}NO_4S_2$, 396.0359; found, 396.0359.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**3ac**).* Reaction was carried out using the described procedure with 0.200 g (0.68 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **3ac** as a white solid (0.200 g, 67%). mp = 57−59 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 8.23−8.20 (m, 1H), 8.00−7.97 (m, 1H), 7.88−7.85 (m, 1H), 7.65−7.56 (m, 2H), 7.54−7.44 (m, 5H), 7.36−7.31 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 190.6, 165.3, 153.0, 143.5, 139.5, 137.8, 135.1, 135.0, 134.5, 133.1 (q, *J* = 32.9 Hz), 130.8, 129.9, 129.1, 128.3, 128.2, 126.7 (d, *J* = 272.1 Hz), 126.0 (q, *J* = 3.7 Hz), 125.8, 122.4; $^{19}F\{^1H\}$ NMR (376 MHz, Chloroform-*d*): δ −63.17(s, 3F); MS (ESI) *m/z* (%) 474: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{15}F_3NO_3S_2$, 474.0440; found, 474.0438.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexyl-1-phenylprop-2-en-1-one (**3ae**).* Reaction was carried out using the described procedure with 0.050 g (0.16 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **3ae** as a colorless oil (0.029 g, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.15 (m, 1H), 7.97−7.93 (m, 1H), 7.91−7.87 (m, 2H), 7.63−7.58 (m, 2H), 7.57−7.53 (m, 1H), 7.43 (td, *J* = 8.4, 7.6, 0.8 Hz, 2H), 7.37 (d, *J* = 10.8 Hz, 1H), 2.12−1.99 (m, 1H), 1.75−1.57 (m, 4H), 1.39−1.14 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 190.0, 166.2, 155.5, 152.8, 137.7, 137.6, 136.5, 134.7, 129.9, 128.9, 128.0, 127.5, 125.7, 122.3, 39.8, 31.3, 25.3, 24.8; MS (ESI) *m/z* (%) 413: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{22}NO_3S_2$, 412.1036; found, 412.1038.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-1-phenyl-3-(2-(prop-2-yn-1-yl-oxy)phenyl)prop-2-en-1-one (**3af**).* Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **3af** as a light brown solid (0.103 g, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.72 (s, 1H), 8.22−8.17 (m, 1H), 7.97 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.87−7.82 (m, 2H), 7.57 (pd, *J* = 7.2, 1.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.27 (td, *J* = 8.4, 3.2 Hz, 3H), 7.12 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H).; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 191.1, 166.6, 156.3, 152.9, 142.0, 137.7,

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136.2, 135.6, 134.3, 133.4, 131.4, 129.7, 128.7, 127.9, 127.5, 125.7, 122.3, 121.5, 121.1, 112.7, 77.7, 76.5, 56.0; MS (ESI) *m/z* (%) 460 $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{17}NNaO_4S_2$, 482.0497; found, 482.0490.

*(S,E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-4-((tert-butyldimethylsilyl)oxy)-1-phenylpent-2-en-1-one (**3ag**).* Reaction was carried out using the described procedure with 0.100 g (0.31 mmol) of sulfone **2e**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **3ag** as a colorless oil (0.059 g, 39%, e.r.= >99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 7.97−7.94 (m, 1H), 7.90−7.85 (m, 2H), 7.64−7.57 (m, 2H), 7.57−7.54 (m, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.44−7.39 (m, 2H), 4.49 (p, *J* = 6.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 0.70 (s, 9H), −0.15 (s, 3H), −0.19 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 189.3, 165.6, 153.0, 137.8, 137.6, 136.6, 134.5, 130.2, 128.8, 128.1, 127.6, 125.8, 122.4, 67.0, 25.8, 23.3, 18.2, −4.8, −5.1; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{30}NO_4S_2Si$, 488.1380; found, 88.1383; α_D^{27} = +31.4 (c 0.7,$CHCl_3$); HPLC (CHIRALPAK IE-3, eluent: CO_2: MeOH = 95:5, 2.2 mL/min, 38 °C, retention time: *t* = 13.22 min).

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylacrylate (**5c**).* Reaction was carried out using the described procedure with 2.4 g (8.86 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **5c** as a yellow solid (2.0 g, 59%). mp = 76−78 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22 (s, 1H), 8.21−8.18 (m, 1H), 8.03−7.99 (m, 1H), 7.64−7.55 (m, 4H), 7.51−7.39 (m, 3H), 5.15 (hept, *J* = 6.0 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.6, 161.8, 152.8, 148.2, 137.4, 132.3, 132.2, 131.4, 130.8, 129.0, 128.1, 127.6, 125.7, 122.3, 71.2, 21.4; MS (ESI) *m/z* (%) 328: $[M - OiPr]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_4S_2$, 388.0672; found, 388.0672.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)-acrylate (**5f**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5f** as a yellow oil (0.164 g, 60%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.18−8.14 (m, 1H), 8.06 (s, 1H), 8.01−7.97 (m, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.61−7.52 (m, 2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.61 (dd, *J* = 3.6, 1.6 Hz, 1H), 5.15 (hept, *J* = 6.4 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 167.3, 161.1, 152.7, 148.4, 148.0, 137.3, 134.6, 127.9, 127.6, 126.3, 125.6, 123.6, 122.3, 114.0, 70.8, 21.6; MS (ESI) *m/z* (%) 318: $[M]^+$ (100), 378 $[M + 1]^+$(21); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{16}NO_5S_2$, 378.0464; found, 378.0461.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-ylsulfonyl)-3-(4-(trifluoromethyl)phenyl)acrylate (**5g**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **5g** as a white solid (0.120 g, 36%). mp = 135−137 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.27 (s, 1H), 8.22−8.19 (m, 1H), 8.05−8.01 (m, 1H), 7.68 (s, 4H), 7.65−7.57 (m, 2H), 5.12 (hept, *J* = 6.4 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.0, 161.1, 152.7, 146.4, 137.4, 135.0, 134.8, 133.2 (q, *J* = 33.0 Hz), 130.6, 128.2, 127.7, 125.8 (q, *J* = 3.7 Hz), 125.7, 123.6 (q, *J* = 273.2 Hz), 122.3, 71.5, 21.3; $^{19}F\{^1H\}$ NMR (376 MHz, Chloroform-*d*): δ −63.04 (s, 3F); MS (ESI) *m/z* (%) 414: $[M]^+$ (100), 456 $[M+1]^+$(32); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}F_3NO_4S_2$, 456.0546; found, 456.0548.

*Isopropyl (E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexylacrylate (**5i**).* Reaction was carried out using the described procedure with 0.200 g (0.74 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5i** as a yellow oil (0.160 g, 55%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.12 (m, 1H), 8.03−7.94 (m, 1H), 7.63 (d, *J* = 10.4 Hz, 1H), 7.60−7.53 (m, 2H), 5.05 (hept, *J* = 6.0, 1H), 3.17−3.04 (m, 1H), 1.90−1.68 (m, 5H), 1.37−1.24 (m, 5H), 1.13 (d, *J* = 6.0 Hz, 6H; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*)): δ 167.7, 164.5, 160.8, 152.9, 137.4, 132.3, 128.2, 127.8, 125.8, 122.6, 70.8, 39.9, 31.9, 26.0, 25.5, 21.9; MS (ESI) *m/z* (%) 352: $[M]^+$ (100), 394 $[M+1]^+$ (53); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{24}NO_4S_2$, 394.1141; found, 394.1141.

*Isopropyl (S,E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-4-((tert-butyldimethylsilyl)oxy)pent-2-enoate (**5j**).* Reaction was carried out using the described procedure with 0.100 g (0.37 mmol) of sulfone **2f**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **5j** as a yellow oil (0.084 g, 49%, e.r. = >99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.15−8.12 (m, 1H), 8.02−7.99 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.63−7.54 (m, 2H), 5.22 (dq, *J* = 7.6, 6.4 Hz, 1H), 5.04 (hept, *J* = 6.4 Hz, 1H), 1.40 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.9, 162.9, 160.0, 152.6, 137.1, 131.2, 128.0, 127.6, 125.5, 122.3, 70.8, 66.6, 25.9, 23.0, 21.6, 21.5, 18.3, −4.5, −4.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{32}NO_5S_2Si$, 470.1486; found, 470.1489; α_D^{27}= + 41.2 (c 1.0, $CHCl_3$); HPLC (CHIRALPAK IE-3, eluent: CO_2: *i*-PrOH = 95:5, 2.2 mL/min, 38 °C, retention time: *t* = 5.14 min).

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-N,N-diethyl-3-phenylacrylamide (**5k**).* Reaction was carried out using the described procedure with 0.070 g (0.22 mmol) of sulfone **2k**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **5k** as a white solid (0.048 g, 53%). mp= 158−161 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.22−8.19 (m, 1H), 8.01 (s, 1H), 7.98−7.95 (m, 1H), 7.60−7.51 (m, 4H), 7.48−7.41 (m, 1H), 7.41−7.33 (m, 2H), 3.62 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.38 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.27 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 166.3, 162.1, 152.9, 143.0, 138.0, 134.5, 132.0, 131.7, 130.3, 129.2, 128.0, 127.5, 125.9, 122.4, 43.5, 39.7, 13.7, 12.0; MS (ESI) *m/z* (%) 401: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{20}N_2NaO_3S_2$, 423.0808; found, 423.0809.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylacrylonitrile (**6a**).* Reaction was carried out using the described procedure with 2.0 g (8.4 mmol) of sulfone **2l**. Crude product **6a** was isolated with enough purity as a light yellow solid (2.4 g, 88%). mp = 158−160 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 8.45 (s, 1H), 8.26−8.23 (m, 1H), 8.06−8.03 (m,1H), 8.03−7.99 (m, 2H), 7.69−7.60 (m, 3H), 7.58−7.52 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 164.0, 156.0, 153.3, 138.0, 135.5, 132.2, 130.5, 130.1, 129.0, 128.5, 126.4, 122.8, 112.8, 112.2; MS (ESI) *m/z* (%) 327: $[M + 1]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}N_2O_2S_2$, 327.0256; found, 327.0254.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-methoxyphenyl)-acrylonitrile (**6b**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6b** as a yellow oil (0.109 g, 73%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.34 (s, 1H), 8.24−8.21 (m, 1H), 8.04−7.99 (m, 3H), 7.66−7.58 (m, 2H), 7.03−7.00 (m, 2H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 165.5, 164.4, 155.0, 152.9, 137.6, 134.7, 128.5, 128.0, 125.9, 123.0, 122.5, 115.3, 113.2, 107.7, 56.0; MS (ESI) *m/z* (%) 374: $[M + H_2O]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_3S_2$, 357.0362; found, 357.0359.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(3-methoxyphenyl)-acrylonitrile (**6c**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided **6c** as a yellow solid (0.106 g, 71%). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.40 (s, 1H), 8.28−8.19 (m, 1H), 8.08−7.99 (m, 1H), 7.70−7.57 (m, 2H), 7.61−7.50 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 8.4, 2.4, 1.2 Hz, 1H), 3.85 (s, 3H).; $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 55.7, 112.0, 112.5, 114.9, 122.1, 122.5, 125.1, 126.0, 128.1, 128.7, 130.7, 131.2, 137.7, 152.9, 155.8, 160.3, 163.7; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_3S_2$, 357.0362; found, 357.0360.

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*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-bromophenyl)-acrylonitrile (**6d**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; acetone/petroleum ether = 1:3) and concentration of the relevant fractions provided **6d** as a light-yellow syrup (0.129 g, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.38 (s, 1H), 8.27−8.22 (m, 1H), 8.06−8.03 (m, 1H), 7.89−7.85 (m, 2H), 7.71−7.67 (m, 2H), 7.67−7.61 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ(ppm): 163.5, 154.1, 153.0, 137.7, 133.3, 132.8, 130.5, 128.9, 128.8, 128.2, 126.1, 122.5, 112.6, 112.3; MS (ESI) *m/z* (%) 406: $[M + H]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{10}BrN_2O_2S_2$, 404.9362; found, 404.9360.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(furan-2-yl)acrylonitrile (**6e**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6e** as a yellow oil (0.089 g, 67%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.22 (m, 1H), 8.18 (s, 1H), 8.05−8.02 (m, 1H), 7.83 (dt, *J* = 1.6, 0.4 Hz, 1H), 7.67−7.59 (m,2H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.72 (dd, *J* = 3.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.0, 152.9, 150.3, 147.3, 139.5, 137.6, 128.6, 128.0, 125.9, 125.3, 122.5, 114.7, 112.2, 107.2; MS (ESI) *m/z* (%) 334: $[M + H_2O]^+$ (100), 317 $[M + 1]^+$ (34); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{14}H_9N_2O_3S_2$, 317.0049; found, 317.0047.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(4-(trifluoromethyl)-phenyl)acrylonitrile (**6f**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Crude product **6f** was isolated with enough purity as a colorless oil (0.157 g, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.48 (s, 1H), 8.26−8.22 (m, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 8.07−8.04 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.70−7.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.0, 153.5, 152.9, 137.7, 135.7 (q, *J* = 33.4 Hz), 133.0, 131.7, 128.9, 128.2, 126.7 (q, *J* = 3.7 Hz), 126.5, 126.0, 123.4 (d, *J* = 272.7 Hz), 114.9, 111.9; ^{19}F{^{1}H} NMR (376 MHz, Chloroform-d): δ −63.34 (s, 3F); MS (ESI) *m/z* (%) 177: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{10}F_3N_2O_2S_2$, 395.0130; found, 395.0128.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-cyclohexylacrylonitrile (**6i**).* Reaction was carried out using the described procedure with 0.050 g (0.21 mmol) of sulfone **2l**. Crude product **6i** was isolated with enough purity as a yellow solid (0.060 g, 88%). mp= 112−114 °C; ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.26−8.23 (m, 1H), 8.05−8.02 (m, 1H), 7.76 (d, *J* = 10.4 Hz, 1H), 7.69−7.60 (m, 2H), 2.77−2.67 (m, 1H), 1.89−1.70 (m, 5H), 1.41−1.22 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 169.0, 163.5, 152.9, 137.6, 128.7, 128.1, 126.1, 122.5, 116.5, 110.6, 42.0, 31.1, 25.3, 24.8; MS (ESI) *m/z* (%) 333: $[M + 1]^+$ (100); HR-MS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2S_2$, 333.0726; found, 333.0725.

*(E)-2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-(2-(prop-2-yn-1-yl-oxy)-phenyl)acrylonitrile (**6j**).* Reaction was carried out using the described procedure with 0.100 g (0.42 mmol) of sulfone **2l**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **6j** as a brown solid (0.110 g, 69%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.96 (s, 1H), 8.35−8.20 (m, 2H), 8.05−8.00 (m, 1H), 7.63 (ddd, *J* = 9.2, 5.6, 2.0 Hz, 3H), 7.19−7.07 (m, 2H), 4.88 (d, *J* = 2.4 Hz, 2H), 2.58 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 164.0, 157.9, 152.9, 149.9, 137.6, 136.9, 129.7, 128.6, 128.0, 126.0, 122.5, 122.2, 119.8, 113.3, 112.9, 111.1, 77.3, 56.6; MS (ESI) *m/z* (%) 381: $[M]^+$ (100); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{12}N_2NaO_3S_2$, 403.0187; found, 403.0181.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-6-phenylhex-4-en-2-one (**7a**).* Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone **2a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **7a** as a white solid (0.036 g, 49%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.24−8.16 (m, 1H), 8.01−7.95 (m, 1H), 7.69−7.56 (m, 2H), 7.13−7.06 (m, 3H), 6.94−−6.86 (m, 2H), 5.92−5.77 (m, 2H), 5.22 (d, *J* = 9.2 Hz, 1H), 3.35 (d, *J* = 6.0 Hz, 2H), 2.51 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 196.6, 164.2, 152.6, 142.5, 138.1, 137.1, 128.6, 128.4, 128.3, 127.8, 126.5, 125.7, 122.5, 117.5, 78.0, 39.1, 31.2; MS (ESI) *m/z* (%) 372: $[M + 1]^+$ (37); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_3S_2$, 372.0723; found, 372.0725.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)hept-4-en-2-one (**7b**).* Reaction was carried out using the described procedure with 0.050 g (0.2 mmol) of sulfone **2a**. The crude product proved to be unstable on SiO_2. The yield of the crude material was 0.019 g, 31% (keto/enol = 1.7:1). Peaks attributed to the enol form is marked with *; ^{1}H NMR (400 MHz, Chloroform-*d*): δ(ppm): 0.84 (t, *J* = 7.6 Hz, 3H*), 1.00 (t, *J* = 7.6 Hz, 3H), 2.04 (qd, *J* = 7.6, 6.8, 5.2 Hz, 2H), 2.48 (dd, *J* = 7.6, 3.6 Hz, 1H*), 2.50 (s, 3H*), 2.52 (dd, *J* = 7.6, 0.4 Hz, 1H*), 2.57 (s, 3H), 5.16 (d, *J* = 9.2 Hz, 1H), 5.65−5.85 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H*), 7.55−7.69 (m, 2H & 2H*), 7.98−8.04 (m, 1H & 1H*), 8.17−8.20 (m, 1H), 8.24 (ddd, *J* = 8.4, 1.6, 0.8 Hz, 1H*); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{15}NNaO_3S_2$, 332.0391; found, 332.0393.

General Procedure for Dihydropyran 9 Synthesis. A vinyl-sulfone **3** (0.100 g, 0.29 mmol) was dissolved in benzene (1.5 mL, 0.2 M) and vinyl-ether (0.278 mL, 2.9 mmol) was added in one portion. The mixture was stirred for 24 h. Volatilities were evaporated under reduced pressure to yield the crude product.

*2-(((4S)-2-ethoxy-6-methyl-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**9a**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **9a** as a yellow oil (0.129 g, 90%, d.r. = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.15−8.08 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.60−7.54 (m, 2H), 7.53−7.44 (m, 2H), 7.08 (bs, 5H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 2H), 5.11 (dd, *J* = 6.8, 2.4 Hz, 1H), 4.95 (t, *J* = 6.0 Hz, 1H), 4.31 (t, *J* = 4.4 Hz, 1H), 4.19 (t, *J* = 7.6 Hz, 1H), 3.99−3.88 (m, 2H), 3.62−3.52 (m, 2H), 2.68 (bs, 3H), 2.64 (bs, 3H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4 Hz, 1H), 2.12−2.04 (m, 3H), 1.19 (t, *J* = 6.0 Hz, 3H), 1.16 (t, *J* = 6.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 170.2, 169.6, 168.1, 167.8, 152.7, 152.5, 142.7, 141.6, 137.2, 136.9, 128.9, 128.6, 128.1, 127.8, 127.4, 127.2, 127.2, 127.0, 126.8, 126.4, 125.3, 125.2, 122.1, 121.9, 113.9, 110.6, 100.2, 98.7, 65.6, 65.2, 39.1, 38.5, 37.7, 35.9, 21.2, 20.7, 15.2, 15.1; MS (ESI) *m/z* (%) 416: $[M + H]^+$ (62); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{22}NO_4S_2$, 416.0985; found, 416.0987.

*2-(((4S)-6-(but-3-en-1-yl)-2-ethoxy-4-phenyl-3,4-dihydro-2H-pyran-5-yl)sulfonyl)benzo[d]thiazole (**9b**).* Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone **3s**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **9b** as a yellow oil (0.109 g, 70%, d.r. = 1 : 1.1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (t, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60−7.53 (m, 2H), 7.53−7.45 (m, 2H), 7.09 (bs, 5H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 2H), 5.97 (dddt, *J* = 20.8, 16.8, 10.4, 6.8 Hz, 2H), 5.19−5.07 (m, 3H), 5.06−4.98 (m, 2H), 4.96−4.89 (m, 1H), 4.33 (t, *J* = 4.8 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.94 (dqd, *J* = 9.6, 7.2, 2.4 Hz, 2H), 3.56 (ddq, *J* = 18.8, 9.6, 7.2 Hz, 2H), 3.33−3.15 (m, 3H), 3.09−3.01 (m, 1H), 2.60−2.48 (m, 4H), 2.35 (ddd, *J* = 14.0, 7.6, 2.4 Hz, 1H), 2.11−2.02 (m, 3H), 1.18 (dt, *J* = 14.0, 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 170.4, 170.1, 170.0, 169.7, 152.6, 152.5, 142.7, 141.6, 137.6, 137.4, 137.3, 137.0, 128.9, 128.5, 128.1, 127.8, 127.5, 127.3, 127.0, 126.8, 126.4, 125.2, 125.1, 122.1, 121.9, 115.6, 115.5, 114.4, 111.1, 100.1, 98.6, 65.5, 65.2, 39.3, 38.6, 37.8, 35.8, 33.3, 32.7, 32.1, 32.1, 29.8, 15.2, 15.1; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}NO_4S_2$, 456.1298; found, 456.1300.

*2-((4-Cyclohexyl-2-ethoxy-6-methyl-3,4-dihydro-2H-pyran-5-yl)-sulfonyl)benzo[d]thiazole (**9c**).* Reaction was carried out using the described procedure with 0.070 g (0.2 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **9c** as a colorless oil (0.069 g, 72%, d.r. = 1.1:1). ^{1}H NMR (400 MHz,

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Chloroform-*d*): δ 8.13 (dddd, *J* = 8.0, 2.4, 1.6, 0.8 Hz, 2H), 7.96 (dddd, *J* = 8.0, 6.0, 1.6, 0.8 Hz, 2H), 7.61−7.49 (m, 4H), 5.16 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.91 (dd, *J* = 7.6, 3.2 Hz, 1H), 3.95 (ddq, *J* = 14.0, 9.6, 7.2 Hz, 2H), 3.61 (dq, *J* = 9.6, 7.2 Hz, 2H), 2.05−2.97 (m,1H), 2.95−2.88 (m,1H), 2.45 (d, *J* = 1.2 Hz, 3H), 2.39 (d, *J* = 0.8 Hz, 3H), 2.18 (dt, *J* = 14.0, 3.6 Hz, 1H), 2.10−1.88 (m, 2H), 1.88−1.75 (m, 3H), 1.73−1.57 (m, 9H), 1.55−1.46 (m, 1H), 1.41−1.31 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.20−0.81 (m, 8H), 0.77−0.59 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 170.0, 169.8, 168.5, 166.8, 152.7, 152.6, 136.5, 136.5, 127.6, 127.6, 127.4, 125.3, 122.2, 114.9, 112.5, 101.5, 99.7, 65.5, 65.3, 41.1, 39.6, 38.5, 37.5, 31.8, 31.6, 30.2, 30.1, 29.4, 27.1, 27.0, 26.9, 26.8, 26.6, 26.5, 26.0, 21.3, 20.9, 15.2.; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{28}NO_4S_2$, 422.1454; found, 422.1456.

General Procedure for Intramolecular Het. Diels−Alder Reaction. A vinyl-sulfone (0.017 g, 0.04 mmol, 1.0 equiv) was dissolved in DCE (4.0 mL, 0.01 M), and the reaction mixture was stirred under microwave conditions (200 W, 150 °C, 5 min ramp, 30 min hold). The solvent was evaporated under reduced pressure to yield the crude product.

*2-((2-Methyl-5H,10bH-pyrano[3,4-c]chromen-1-yl)sulfonyl)-benzo[d]thiazole (**10**).* Reaction was carried out using the described procedure with 0.017 g (0.04 mmol) of vinyl-sulfone **3k**. Desired product **10** was isolated as a yellow oil (0.016 g, 93%) in sufficient purity. ^1H NMR (400 MHz, Chloroform-*d*): δ 8.28−8.18 (m, 1H), 8.06−7.97 (m, 1H), 7.61 (dtd, *J* = 20.0, 7.6, 1.2 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.20−7.10 (m, 1H), 6.98 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.44−6.32 (m, 1H), 4.88−4.81 (m, 1H), 4.69 (s, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ(ppm): 19.5, 33.7, 67.8, 110.9, 113.7, 117.3, 121.3, 122.4, 125.7, 126.3, 127.7, 128.0, 128.2, 129.6, 134.4, 136.8, 152.8, 153.8, 165.2, 168.4; MS (ESI) *m/z* (%) 398: $[M + H]^+$ (30); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{15}NNaO_4S_2$, 420.0340; found, 420.0336.

General Procedure for Dihydrofurane 12 Synthesis. *Racemic protocol.* A vinyl-sulfone **3a** (0.050 g, 0.15 mmol, 1.0 equiv) and pyridinium salt **11a−c** (0.217 mmol, 1.5 equiv) were dissolved in toluene (1.5 mL, 0.1 M). After 5 min, Et_3N (0.030 mL, 1.5 equiv) was added, and the mixture was stirred for an additional 4 h at r.t. H_2O (10 mL), followed by the addition of EtOAc (10 mL), and the resulting layers were separated. The aqueous phase was extracted with EtOAc (4 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

Asymmetric Protocol. A vinyl-sulfone **3a** (0.030 g, 0.086 mmol, 2.0 equiv) and chiral ammonium salt **13a−c** (0.043 mmol, 1.0 equiv) were dissolved in dry CH_2Cl_2 (1.0 mL, 0.043 M). After 5 min, Cs_2CO_3 (0.028 mg, 2.0 equiv.) was added in one portion, and the mixture was stirred for an additional 20 h. H_2O (10 mL) and EtOAc (10 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*1-((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl)ethan-1-one (**12a**).* Reaction was carried out using the described racemic procedure with 0.050 g (0.15 mmol) of vinyl-sulfone **3a**. Product **12a** was isolated in good crude purity as a yellow oil (0.062 g, 98%, d.r. = 99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.08−8.05 (m, 1H), 7.80−7.77 (m, 1H), 7.58−7.54 (m, 1H), 7.51−7.47 (m, 1H), 7.04−7.01 (m, 2H), 6.97−6.91 (m, 3H), 4.83 (d, *J* = 5.2 Hz, 1H), 4.58 (dd, *J* = 5.2, 1.2 Hz, 1H), 2.63 (d, *J* = 1.2 Hz, 3H), 2.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 203.7, 171.2, 168.9, 152.6, 139.5, 137.3, 128.7, 127.9, 127.7, 127.5, 127.2, 125.4, 122.0, 112.1, 93.2, 52.0, 26.1, 14.5; MS (ESI) *m/z* (%) 400: $[M + 1]^+$ (62); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_4S_2$, 400.0672; found, 400.0669.

*((2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-yl) (phenyl)methanone (**12b**).* Reaction was carried out using the described asymmetric or racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **12b** as a colorless oil (0.068 g, 98%, d.r. = 97:1). Product **12b** was also prepared in an enantioenriched form purified using flash column chromatography (SiO_2; CH_2Cl_2:heptane = 6:1) and isolated as a light red oil in the following manner: starting from salt **13a**: 0.013 g, 70%, e.r. = 97:3, d.r. = 99:1; starting from salt **13c**: 0.012 g, 68%, e.r. = 1:99, d.r. = 99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.06−8.03 (m, 1H), 7.79−7.74 (m, 3H), 7.63−7.53 (m, 2H), 7.50−7.41 (m, 3H), 7.07−7.04 (m, 2H), 7.01−6.95 (m, 3H), 5.77 (d, *J* = 4.8 Hz, 1H), 4.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 2.66 (d, *J* = 1.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 191.9, 172.0, 169.0, 152.6, 139.2, 137.3, 134.4, 133.0, 129.1, 129.0, 128.8, 128.2, 127.9, 127.4, 127.1, 125.4, 122.0, 111.9, 90.3, 52.2, 14.4; MS (ESI) *m/z* (%) 462: $[M + 1]^+$ (54); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}NO_4S_2$, 462.0828; found, 462.0827; α_D^{25} = +161.4 (c 0.5, $CHCl_3$)−first enantiomer (ret. time−29.35 min); α_D^{25} = −148.2 (c 0.5, $CHCl_3$)−second enantiomer (ret. time−32.7 min); HPLC (CHIRAL ART Cellulose-SB, eluent: *n*-hexane: *i*-PrOH = 4:1, 0.5 mL/min, 10 °C, retention times: *t* = 29.3 and *t* = 32.7 min).

*Ethyl (2S,3R)-4-(benzo[d]thiazol-2-ylsulfonyl)-5-methyl-3-phenyl-2,3-dihydrofuran-2-carboxylate (**12c**).* Reaction was carried out using the described racemic procedure with 0.050 g (0.2 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:2) and concentration of the relevant fractions provided **12c** as a colorless oil (0.054 g, 88%, d.r. = 99:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.08−8.05 (m, 1H), 7.80−7.77 (m, 1H), 7.58−7.53 (m, 1H), 7.51−7.46 (m, 1H), 7.04−7.01 (m, 2H), 6.97−6.91 (m, 3H), 4.90 (d, *J* = 4.8 Hz, 1H), 4.62 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.30−4.20 (m, 2H), 2.62 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 171.8, 168.9, 168.7, 152.6, 139.4, 137.3, 128.6, 127.8, 127.8, 127.5, 127.2, 125.4, 122.0, 111.9, 86.7, 62.3, 53.3, 14.4, 14.2; MS (ESI) *m/z* (%) 430: $[M + 1]^+$ (48); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_5S_2$, 430.0777; found, 430.0777.

General Procedure for Triazole 15 Synthesis. To a vinyl-sulfone (0.291 mmol, 1.0 equiv) in MeOH (1.5 mL, 0.2 M) at r.t. was added sodium azide (0.021 g, 0.32 mmol, 1.1 equiv) in one portion, and the mixture was stirred for 20 h. H_2O (10 mL) and EtOAc (10 mL) were added, and the aqueous phase was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*1-(5-Phenyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**15a**).* Reaction was carried out using the described procedure with 0.100 g (0.4 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15a** as a pale yellow solid (0.032 g, 93%). mp = 108−110 °C; ^1H NMR (400 MHz, Chloroform-*d*): δ 7.82−7.77 (m, 2H), 7.51−7.34 (m, 3H), 2.73 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 193.6, 141.9, 130.2, 129.2, 128.7, 127.5, 28.8; MS (ESI) *m/z* (%) 186: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{10}O$, 188.0818; found, 188.0819.

*1-(5-Cyclohexyl-2H-1,2,3-triazol-4-yl)ethan-1-one (**15b**).* Reaction was carried out using the described procedure with 0.050 g (0.14 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **15b** as a white solid (0.027 g, 98%). ^1H NMR (500 MHz, Chloroform-*d*): δ 3.42 (tt, *J* = 11.5, 3.5 Hz, 1H), 2.71 (s, 3H), 2.04−1.95 (m, 2H), 1.84 (dq, *J* = 13.5, 3.5 Hz, 2H), 1.78 (dqd, *J* = 12.5, 3.0, 1.5 Hz, 1H), 1.57−1.39 (m, 4H), 1.29 (qt, *J* = 13.0, 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, Chloroform-*d*): δ 25.9, 26.3, 28.3, 31.9, 34.2, 141.9, 149.7, 194.4; MS (ESI) *m/z* (%) 192: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{16}N_3O$, 194.1288; found, 194.1289.

*Isopropyl 5-Phenyl-2H-1,2,3-triazole-4-carboxylate (**15c**).* Reaction was carried out using the described procedure with 0.100 g (0.26 mmol) of vinyl-sulfone **5c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15c** as a yellow oil (0.034 g, 59%). ^1H

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NMR (400 MHz, Chloroform-*d*): δ 7.81−7.75 (m, 2H), 7.42−7.38 (m, 3H), 5.23 (h, *J* = 6.4 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 160.8, 134.4, 129.7, 129.4, 128.3, 114.0, 69.8, 21.8; MS (ESI) *m/z* (%) 230: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}N_3O_2$, 232.1081; found, 232.1082.

*phenyl(5-(4-(trifluoromethyl)phenyl)-2H-1,2,3-triazol-4-yl)-methanone (**15d**).* Reaction was carried out using the described procedure with 0.100 g (0.21 mmol) of vinyl-sulfone **3ac**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:1) and concentration of the relevant fractions provided **15d** as a yellow oil (0.051 g, 79%). ^1H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, *J* = 6.4 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 187.7, 156.0, 141.6, 136.9, 133.5, 130.1, 129.3, 128.4, 128.1, 125.4, 125.3 (q, *J* = 3.6 Hz), 122.7; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6): δ −61.15 (s, 3F); MS (ESI) *m/z* (%) 316: $[M - H]^-$ (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{11}F_3N_3O$, 318.0849; found, 318.0850.

*1-(5-(2-(Allyloxy)phenyl)-2H-1,2,3-triazol-4-yl)ethan-1-one (**15e**).* Reaction was carried out using the described procedure with 0.050 g (0.125 mmol) of vinyl-sulfone **3j**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **15e** as a colorless oil (0.028 g, 93%). ^1H NMR (400 MHz, Chloroform-*d*): δ 13.00 (bs, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.6, 1.6 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04−6.95 (m, 1H), 6.01 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.42−5.27 (m, 2H), 4.62 (dt, *J* = 5.4, 1.4 Hz, 2H), 2.76 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 29.0, 29.8, 69.9, 112.6, 115.0, 119.1, 121.5, 132.0, 132.1, 132.3, 142.5, 155.6, 193.6; MS (ESI) *m/z* (%) 200: $[M - allyl]^-$ (100), 242 $[M\text{-}H]^-$ (45); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_2$ 244.1081; found, 244.1079.

General Procedure for Michael Type Addition and Desulfonation. A vinyl-sulfone (0.69 mmol, 1.0 equiv) was dissolved in MeOH (4.0 mL, 0.2 M), and the solution was stirred for 16 h. After consumption of the starting material, the solvent was evaporated under reduced pressure to yield the crude product, which was used in the next step without further purification. The resulting methoxy sulfone adduct was dissolved in THF (7.0 mL, 0.1 M), and AcOH (4.0 mL, 0.2 M). Zn (0.226 g, 5.0 equiv) was added in one portion, and the resulting mixture was stirred overnight. The reaction was quenched upon addition of EtOAc (20 mL), and the resulting suspension was filtered through Celite, and filtrate cake was washed with EtOAc (5 × 20 mL). The combined filtrates were washed with sat. $NaHCO_3$ (2 × 20 mL), brine (2 × 20 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*4-Methoxy-4-phenylbutan-2-one (**16a**).* Reaction was carried out using the described procedure with 0.238 g (0.69 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:9) and concentration of the relevant fractions provided **16a** as a colorless liquid (0.051 g, 92% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.36−7.26 (m, 5H), 4.62 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.18 (s, 3H), 2.95 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.57 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 206.4, 140.9, 128.5, 127.9, 126.4, 79.5, 56.6, 51.9, 31.0; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$, 201.0886; found, 201.0887.

*(3S,4S)-4-((tert-Butyldimethylsilyl)oxy)-3-methoxy-1-phenylpentan-1-one (**16b**).* Reaction was carried out using the described procedure with 0.336 g (0.69 mmol) of vinyl-sulfone **3ag**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:20) and concentration of the relevant fractions provided **16b** as a colorless liquid (0.102 g, 43% over 2 steps, d.r. = 7:1). ^1H NMR (400 MHz, Chloroform-*d*): δ 8.01−7.95 (m, 2H), 7.60−7.53 (m, 1H), 7.49−7.43 (m, 2H), 4.08 (qd, *J* = 6.4, 4.4 Hz, 1H), 3.88 (ddd, *J* = 8.0, 4.4, 3.6 Hz, 1H), 3.37 (s, 3H), 3.19−3.06 (m, 2H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 199.4, 137.6, 133.1, 128.7, 128.4, 80.8, 68.1, 58.6, 38.5, 26.0, 18.2, 17.9, −4.5, −4.7; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{30}NaO_3Si$, 345.1862; found, 345.1855; α_D^{22} = −7.1 (c 0.65, $CHCl_3$).

General Procedure for Michael Type Allylation or Reduction and Desulfonation. A vinyl-sulfone (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (3.0 mL, 0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 30 min, **Nu** (0.290 mmol, 3.0 equiv) was added, and the mixture was stirred for another 30 min, followed by the addition of $TiCl_4$ (0.870 mL, 3.0 equiv, 1.0 M solution in CH_2Cl_2). The mixture was stirred for 6 h. $NaHCO_3$ (10 mL) was added, and the suspension warmed to r.t. The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure. The crude product was used in the next step without further purification. Crude sulfone was dissolved in THF (3.0 mL, 0.1 M) and AcOH (1.5 mL, 0.2 M), and Zn (0.019 g, 5.0 equiv) was added in one portion. The resulting heterogenic mixture was stirred overnight before it was quenched with the addition of EtOAc (20 mL). The resulting slurry was filtered through Celite, and the filtrate cake was washed with EtOAc (5 × 15 mL). The filtrates were washed with sat. $NaHCO_3$ (2 × 15 mL), brine (2 × 15 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to yield the crude product.

*4-Phenylbutan-2-one (**16c**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:10) and concentration of the relevant fractions provided **16c** as a colorless liquid (0.037 g, 87% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.28−7.26 (m, 2H), 7.22−7.16 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.76−2.72 (m, 2H), (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 207.8, 140.9, 128.4, 128.2, 126.0, 45.1, 30.1, 29.6; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{13}O$, 149.0961; found, 149.0961.

*4-Phenylhept-6-en-2-one (**16d**).* Reaction was carried out using the described procedure with 0.100 g (0.29 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:8) and concentration of the relevant fractions provided **16d** as a colorless oil (0.040 g, 74% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.32−7.26 (m, 2H), 7.22−7.16 (m, 3H), 5.72−5.58 (m, 1H), 5.03−4.94 (m, 2H), 3.26 (p, *J* = 7.2 Hz, 1H), 2.82−2.68 (m, 2H), 2.39−2.33 (m, 2H), 2.02 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 207.8, 144.2, 136.3, 128.6, 127.6, 126.6, 116.9, 49.7, 41.0, 40.9, 30.8; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{17}O$, 189.1274; found, 189.1274.

*3-Phenylhex-5-enenitrile (**16e**).* Reaction was carried out using the described procedure with 0.050 g (0.153 mmol) of vinyl-sulfone **6a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **16e** as a colorless oil (0.019 g, 72% over 2 steps). ^1H NMR (400 MHz, Chloroform-*d*): δ 7.39−7.32 (m, 2H), 7.30−7.27 (m, 1H), 7.25−7.21 (m, 2H), 5.66 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.12 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.0, 2.0, 1.2 Hz, 1H), 3.04 (p, *J* = 7.2 Hz, 1H), 2.70−2.57 (m, 2H), 2.55 (tt, *J* = 7.2, 1.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*): δ 141.4, 134.7, 128.9, 127.6, 127.3, 118.5, 118.2, 41.8, 39.2, 24.0; HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{12}H_{13}N$, 171.1048; found, 171.1049.

General Procedure for Lewis Acid-Mediated Rearrangement. A vinyl-sulfone (0.050 g, 0.145 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL, 0.1 M) at r.t., and $TiCl_4$ (0.580 mL, 4.0 equiv, 1.0 M solution in CH_2Cl_2) was added. The mixture was stirred for 1 h at r.t. prior to addition of CH_2Cl_2 (10 mL) and sat. NH_4Cl (5 mL). The resulting suspension was filtered through Celite, and the filter cake was washed with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to yield the crude product.

*3-(3-Oxo-1-phenylbutyl)benzo[d]thiazol-2(3H)-one (**18**).* Reaction was carried out using the described procedure with 0.050 g (0.145 mmol) of vinyl-sulfone **3a**. Purification using flash chromatog-

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raphy (SiO_2; EtOAc/petroleum ether = 1:6) and concentration of the relevant fractions provided **18** as a pale-yellow oil (0.043 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.41−7.35 (m, 3H), 7.35−7.27 (m, 1H), 7.16−7.10 (m, 2H), 6.01 (dd, J = 8.0, 6.0 Hz, 1H), 3.96 (dd, J = 18.0, 8.0 Hz, 1H), 3.44 (dd, J = 18.0, 6.0 Hz, 1H), 2.22 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 205.4, 138.2, 137.2, 129.1, 128.3, 127.0, 126.4, 122.9, 122.7, 111.9, 54.5, 45.8, 30.3.; MS (ESI) m/z (%) 297: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M]^+$ calcd for $C_{17}H_{15}NO_2S$, 297.0823; found, 297.0825.

General Procedure for 1,4 Reduction of Vinyl-Sulfones. *Procedure A.* A vinyl-sulfone (0.582 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (6.0 mL, 0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 15 min, nBu$_3$SnH (0.138 mL, 1.1 equiv) was added, and the mixture was stirred for additional 30 min. After consumption of the starting material, CH_2Cl_2 (10 mL) was added, and the reaction mixture was washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed under reduced pressure. The crude material was dissolved in CH_3CN (25 mL) and washed with hexane (2 × 20 mL) to remove any remaining organotin compounds. The resulting acetonitrile solution was concentrated under reduced pressure to provide the crude product.

Procedure B. A vinyl-sulfone (0.582 mmol, 1.0 equiv) was dissolved in THF (0.1 M), and the solution was cooled down to −78 °C (acetone/dry ice). After 15 min, DIBAL (0.640 mL, 1.1 equiv, 1 M solution in hexane) was added dropwise, and the mixture was stirred at −78 °C for 10 min and at r.t. for another 1 h (consumption of the SM monitored by TLC). After consumption of the starting material, the reaction mixture was cooled down to −78 °C, and saturated aq. solution of Rochelle salt (5 mL) was added. The resulting mixture was allowed to warm to r.t. and stirred until the solution became clear (cca 6 h). The whole mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and solvents were removed under reduced pressure to provide the crude product.

*3-(Benzo[d]thiazol-2-ylsulfonyl)-4-phenylbutan-2-one (**17c**).* Reaction was carried out using the described procedure with 0.200 g (0.583 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **17c** as a yellow solid: Procedure A (0.181 g, 91%); Procedure B (0.170 g, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.32−8.23 (m, 1H), 8.09−7.95 (m, 1H), 7.76−7.55 (m, 2H), 7.25−7.16 (m, 3H), 7.14−7.08 (m, 2H), 4.91 (dd, J = 9.2, 5.6 Hz, 1H), 3.55−3.36 (m, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 32.8, 32.9, 75.6, 122.5, 125.9, 127.5, 128.0, 128.5, 129.0, 129.1, 135.4, 137.3, 152.7, 164.1, 198.2; MS (ESI) m/z (%) 346: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3S_2$, 346.0566; found, 346.0563.

*2-(Benzo[d]thiazol-2-ylsulfonyl)-1,3-diphenylpropan-1-one (**17f**).* Reaction was carried out using the described procedure with 0.100 g (0.246 mmol) of vinyl-sulfone **3aa**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:3) and concentration of the relevant fractions provided **17f** as a colorless oil: Procedure A: (0.090 g, 90%); Procedure B: (0.081 g, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.23−8.18 (m, 1H), 8.01−7.92 (m, 1H), 7.79−7.69 (m, 2H), 7.68−7.53 (m, 2H), 7.49−7.38 (m, 1H), 7.35−7.24 (m, 2H), 7.20−7.04 (m, 5H), 5.82 (dd, J = 10.8, 3.6 Hz, 1H), 3.82−3.62 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 33.7, 70.6, 122.4, 125.8, 127.3, 127.8, 128.4, 128.7, 128.9, 129.2, 134.1, 135.6, 137.0, 137.4, 152.6, 164.3, 191.0; MS (ESI) m/z (%) 408: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}NO_3S_2$, 408.0723; found, 408.0725.

General Procedure for 1,2 Reduction of Vinyl Sulfones. A vinyl-sulfone (0.290 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL, 0.01 M), and the resulting solution was cooled to −78 °C (acetone/dry ice). After 15 min, DIBAL-H (0.320 mL, 1.1 equiv, 1 M solution in hexane) was added dropwise, and the mixture was stirred at −78 °C for an additional 4 h. After consumption of the starting material (checked via TLC), a saturated aqueous solution of Rochelle salt (5 mL) was added, and the reaction mixture was allowed to warm to r.t. The resulting mixture was stirred until the solution became clear (cca 6 h). The whole mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure to provide the crude product.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-phenylbut-3-en-2-ol (**19a**).* Reaction was carried out using the described procedure with 0.100 g (0.291 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **19a** as a pale-yellow oil (0.080 g, 80%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.20−8.14 (m, 1H), 8.07 (s, 1H), 8.02−7.97 (m, 1H), 7.67−7.52 (m, 4H), 7.45 (dd, J = 5.2, 2.0 Hz, 3H), 5.23 (q, J = 6.8 Hz, 1H), 1.63 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 22.2, 64.8, 122.5, 125.4, 127.7, 128.1, 129.0, 130.6, 130.6, 132.7, 136.7, 142.1, 145.3, 152.3, 169.2; MS (ESI) m/z (%) 346: $[M + 1]^+$ (100); HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO_3S_2$, 346.0566; found, 346.0565.

*(E)-3-(Benzo[d]thiazol-2-yl-sulfonyl)-4-cyclohexylbut-3-en-2-ol (**19c**).* Reaction was carried out using the described procedure with 0.050 g (0.143 mmol) of vinyl-sulfone **3p**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **19c** as a colorless oil (0.034 g, 68%). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18−8.12 (m, 1H), 8.02−7.93 (m, 1H), 7.65−7.51 (m, 2H), 6.98 (d, J = 10.8 Hz, 1H), 5.04 (dt, J = 13.2, 6.8 Hz, 1H), 2.94 (d, J = 6.0 Hz, 1H), 2.76 (tdt, J = 10.8, 6.8, 3.6 Hz, 1H), 1.84−1.64 (m, 5H), 1.54 (d, J = 6.8 Hz, 3H), 1.34−1.17 (m, 5H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 23.6, 25.2, 25.2, 25.7, 31.8, 31.9, 38.3, 65.1, 122.4, 125.4, 127.6, 128.0, 136.7, 140.7, 152.3, 154.2, 169.0; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{22}NO_3S_2$, 352.1036; found, 352.1034.

General Procedure for Radical Addition. To a vinyl-sulfone (0.050 g, 0.153 mmol, 1.0 equiv) in benzene (1.5 mL, 0.1 M) was added ethyl iodide (0.019 mL, 1.5 equiv), (Me$_3$Si)$_3$SiH (0.071 μL, 1.5 equiv), and AIBN (0.005 g, 0.2 equiv), and the reaction mixture was heated (oil bath) to reflux. After consumption of starting vinyl-sulfone (8 h), the volatilities were evaporated under reduced pressure to yield the crude product.

*2-(Benzo[d]thiazol-2-yl-sulfonyl)-3-phenylpentanenitrile (**20**).* Reaction was carried out using the described procedure with 0.050 g (0.153 mmol) of vinyl-sulfone **6a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **20** as a colorless oil (0.033 g, 61%, d.r. = 1.2:1). ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.25−8.18 (m,2H), 8.01 (ddd, J = 9.6, 7.6, 2.0 Hz, 2H), 7.72−7.57 (m, 4H), 7.45−7.35 (m, 2H), 7.39−7.23 (m, 8H), 4.96 (d, J = 5.6 Hz, 1H), 4.88 (d, J = 3.6 Hz, 1H), 3.75−3.62 (m, 2H), 2.36 (dqd, J = 13.6, 7.2, 3.6 Hz, 1H), 2.21−1.95 (m, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*): δ 163.4, 163.2, 152.4, 138.2, 137.5, 136.7, 129.3, 129.3, 128.9, 128.8, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 128.0, 125.9, 125.8, 122.5, 122.5, 112.3, 112.1, 62.1, 61.2, 44.6, 44.1, 27.8, 25.1, 11.8, 11.7; MS (ESI) m/z (%) 357: $[M + H]^+$ (100); HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{16}N_2NaO_2S_2$, 379.0551; found, 379.0546.

*(E)-4-Phenylbut-3-en-2-one (**4**).* Reaction was carried out using the described procedure with 0.100 g (0.291 mmol) of vinyl-sulfone **3a**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:4) and concentration of the relevant fractions provided **4** as a yellowish solid (0.036 g, 85%, >E/Z= 95:1). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.56−7.54 (m, 2H), 7.52 (d, J = 16.5 Hz, 1H), 7.42−7.38 (m, 3H), 6.72 (d, J = 16.5 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, Chloroform-*d*) 198.5, 143.5, 134.6, 130.7, 129.1, 128.4, 127.3, 27.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{10}H_{11}O$, 147.0804; found, 147.0806.

*(E)-Isopropyl Cinnamate (**21**).* Reaction was carried out using the described procedure with 0.100 g (0.258 mmol) of vinyl-sulfone **5c**. Purification using flash chromatography (SiO_2; EtOAc/petroleum ether = 1:5) and concentration of the relevant fractions provided **21** as a viscose oil (0.046 g, 82%, >E/Z= 95 : 1). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.67 (d, J = 16.0 Hz, 1H), 7.52 (dd, J = 7.0, 3.0 Hz, 2H), 7.41−7.35 (m, 3H), 6.42 (d, J = 16.0 Hz, 1H), 5.14 (hept, J = 6.0 Hz, 1H), 1.32 (d, J = 6.5 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz,

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Chloroform-*d*): δ 166.7, 144.4, 134.6, 130.3, 129.0, 128.1, 118.9, 67.9, 22.1; MS (ESI) *m/z* (%) 191: $[M + 1]^+$ (10), 149 (100); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{15}O_2$, 191.1067; found, 191.1068.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00571.

Relevant optimization tables, discussion of the relevant stereochemical outcomes of reactions, discussion of the stereochemistry of obtained compounds, and a copy of ^1H and $^{13}C\{^1H\}$ NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jiří Pospíšil − *Department of Organic Chemistry, Faculty of Science, Palacky University, CZ-771 46 Olomouc, Czech Republic; Laboratory of Growth Regulators, Palacky University & Institute of Experimental Botany AS CR, CZ-783 71 Olomouc, Czech Republic;* orcid.org/0000-0002-0198-8116; Email: j.pospisil@upol.cz

Authors

Ondřej Kováč − *Department of Organic Chemistry, Faculty of Science, Palacky University, CZ-771 46 Olomouc, Czech Republic;* orcid.org/0000-0001-5721-5537

František Zálešák − *Department of Organic Chemistry, Faculty of Science, Palacky University, CZ-771 46 Olomouc, Czech Republic*

David J.-Y. D. Bon − *Department of Organic Chemistry, Faculty of Science, Palacky University, CZ-771 46 Olomouc, Czech Republic*

Lukas Roiser − *Institute of Organic Chemistry, Johannes Kepler University Linz, 4040 Linz, Austria*

Lubomír V. Baar − *Department of Organic Chemistry, Faculty of Science, Palacky University, CZ-771 46 Olomouc, Czech Republic*

Mario Waser − *Institute of Organic Chemistry, Johannes Kepler University Linz, 4040 Linz, Austria;* orcid.org/0000-0002-8421-8642

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c00571

Author Contributions

O.K., F.Z., and D.J.-Y.D.B. performed most of the experiments and analyzed the experimental data. L.V.B. and O.K. carried out the Smiles-like rearrangement. L.R., O.K., and M.W. performed and optimized [4 + 1]-cycloaddition reaction. O.K. and D.J.-Y.D.B. partially designed the experimental plans. J.P. initiated the project, led the project team, designed experiments, analyzed results, and wrote the paper with input from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Palacký University Olomouc

Faculty of Science

Department of Organic Chemistry

Benzo[d]thiazol-2-ylsulfonyl-based pluripotent molecules in organic synthesis

Summary of the Ph.D. Thesis

Mgr. Ondřej Kováč

Supervisor: doc. RNDr. Jiří Pospíšil, Ph.D.

Academic Year: 2019/2020

This Ph.D. thesis was carried out at Department of Organic Chemistry, Faculty of Science, Palacký University Olomouc within the framework of the Ph.D. program P1417 Chemistry, in the field of study Organic Chemistry, within the years 2016-2020.

Ph.D. candidate:	Mgr. Ondřej Kováč
Supervisor:	doc. RNDr. Jiří Pospíšil, Ph.D.
Opponents:	doc. RNDr. Jan Veselý, Ph.D. Charles University in Prague Faculty of Science, Deparment of Organic chemistry Hlavova 2030/8, Prague, CZ-128 43
	Prof. Raphaël Robiette, Ph.D. Université catholique de Louvain Institute of Condensed Matter and Nanosciences Place Louis Pasteur 1 Box L4.01.02 B-1348 Louvain-la-Neuve Belgium

The oral defense will take place on …….. in front of the Commission for the Ph.D. Thesis of the study program Chemistry, Organic Chemistry at Department of Organic Chemistry, Faculty of Science, Palacký University Olomouc, 17. listopadu 12, Olomouc

After the defense, the PhD. Thesis is available at the Department of Organic chemistry, Faculty of Science, Palacký University Olomouc, 17. Listopadu 12, Olomouc or online at http://portal.upol.cz.

1 Introduction

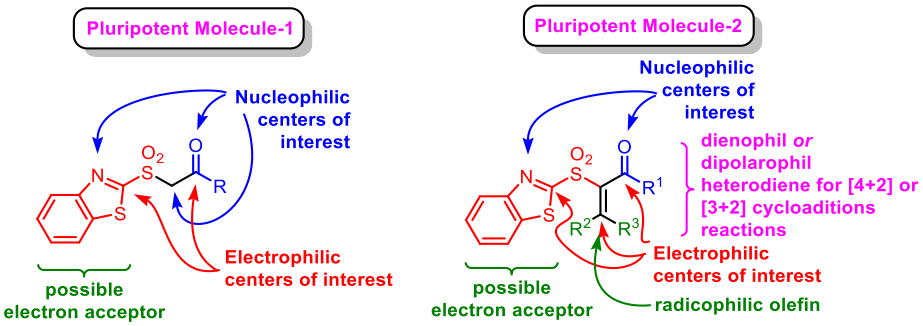
Modern medicinal chemistry focusses on the use of small molecules, which upon interaction with bio-macromolecules may lead to the modification of biological outcome of cells or organisms. Small chemical entities (molecular probes) are extremely important in the task to understand the basic interactions of biological systems (chemical biology) and processes. The easiest way to obtain active small molecules with interesting biological properties is a screening of chemical libraries. The "rule of thumb" applied in the library constitution, bigger = better, in the 90-ties and early 21st century, proved to be inefficient in such task and therefore is practically abandoned nowadays. A more interesting approach is to generate diversity-oriented chemical libraries.[1,2]

One of the goals of our research group is to develop novel synthetic strategies that would allow the synthesis of diverse molecular scaffolds in a short, simple, and efficient manner from readily available starting materials. The key step in our approach towards this challenge is the design of readily available highly functionalized intermediates that would allow us to reach readily highly stereo and scaffold-diverse products. Such intermediates, that we decided to call **Pluripotent Molecule**s (**PM**s), are the key feature of our approach towards the targeted goal, *Scaffolds Diversity*.

2 Aims of the Thesis

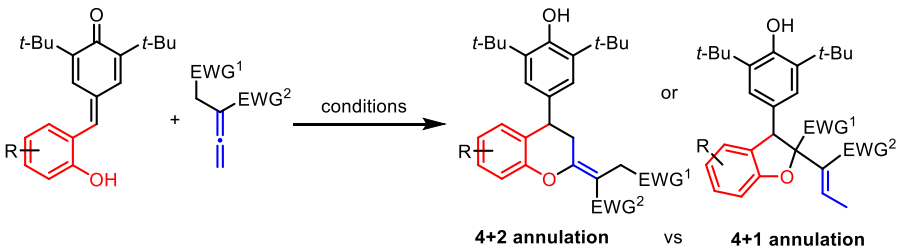
1) Preparation and application of Pluripotent Molecules 1 and 2 in the context of Divergent-Oriented synthesis.

The goal of our approach is to explore several reactive centres within one-pot protocol approach that would allow us to generate selectively C-C bonds (olefination, alkynylation, ketone/ester formation) and various 5-membered heterocycles (pyrroles, furans, thiophenes) in one single reaction vessel. Next, the goal is to develop methods for **Pluripotent molecule-2** (**PM-2**) synthesis and to explore **PM-2** reactivity under various reaction conditions (polar, radical, pericyclic, rearrangements). Finally, **PM-2** is also explored in the context of organocatalytic reactions catalyzed with chiral amines and phosphines.



2) Exploration of the reactivity between *ortho*-hydroxy-*para*-Quinone methide and allenoate

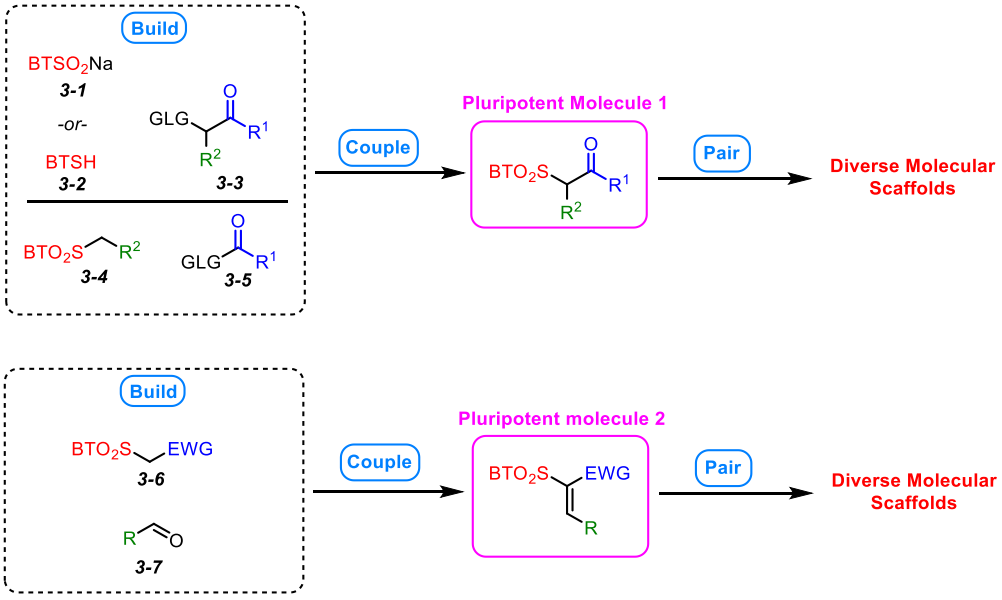
The goal is to develop reaction conditions allowing (4+2) or (4+1)-annulation reactions of allenoates and Quinone-Methides.



3 Overview of achieved results

3.1 Introduction – Our design of Build/Couple/Pair strategy

The aim of this thesis is to develop a new type of **PM** molecules that are exploitable in the **B/C/P** strategy. Our previous experience with BT-sulfone based chemistry and our group's interest in Divergent-Oriented Synthesis led us to extend the use of previously developed α-activated BT-sulfones[3] to the field of **B/C/P** strategy. We speculated that this type of sulfones can be used as valuable **PM-1** type reagent. And if **PM-1** is not α-substituted, we suggest that its Knoevenagel condensation with aldehydes can generate even more versatile reagent **PM-2**. We expected that both reagents, **PM-1** and especially **PM-2**, will due to a presence of several reactive centres orthogonal in reactivity generate structurally diverse molecular scaffolds (Scheme 1).

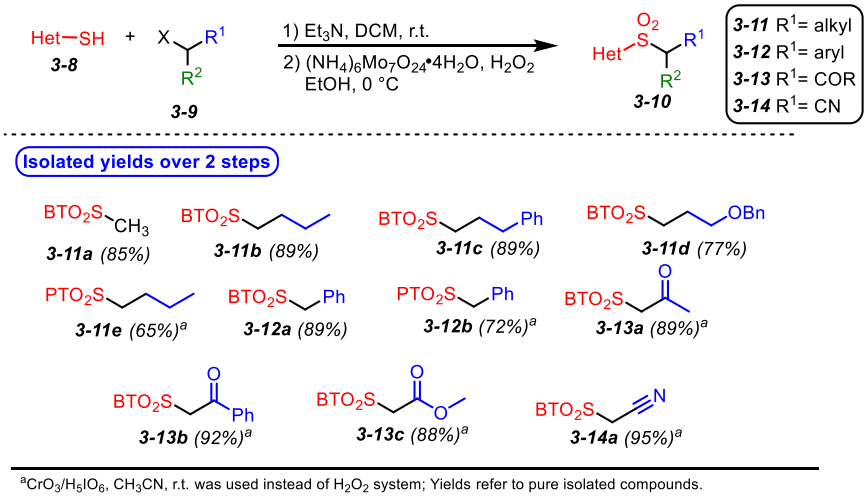


Scheme 1 – Use of PM-1 and PM-2 in context of Build/Couple/Pair strategy.

3.2 Build phase – Building block synthesis, and Build & Couple phase

In the case of **PM-1**, we can use several different routes for designed purposes and each approach has its advantages and disadvantages related to their structure and availability of starting materials. One of the approaches is based on the two steps protocol where alkyl halide ***3-9*** is reacted with thiol ***3-8*** in presence of Et_3N and the resulting crude product is then oxidized with H_2O_2 in the presence of Mo^{VI} or W^{VI} catalyst[4,5]. However, it was found that H_2O_2 oxidation of sulfide catalyzed with Mo^{VI} or W^{VI} catalyst tends to fail to generate desired sulfones. The reason is the high stability of sulfoxide intermediate that complexes with Mo^{VI} or W^{VI} catalyst and blocks the catalytic cycle. Fortunately, Jørgensen et al developed an alternative approach based on the H_5IO_6/cat. CrO_3 (Table 1).[6]

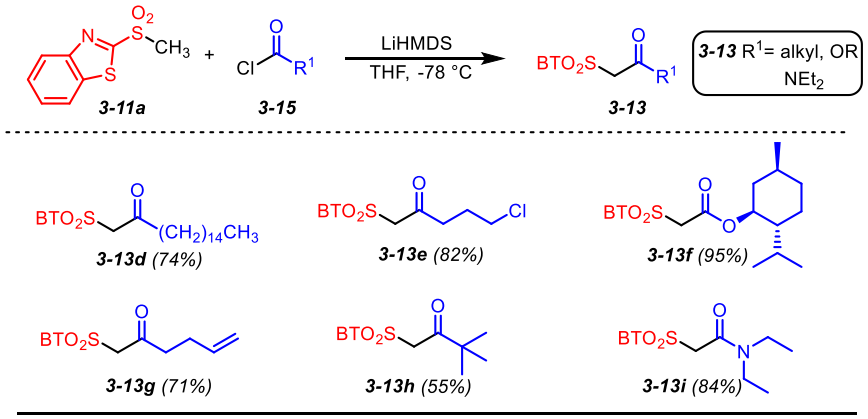
*Table 1 – Preparation of sulfones **3-10** using substitution/oxidation sequence.*



[a]CrO_3/H_5IO_6, CH_3CN, r.t. was used instead of H_2O_2 system; Yields refer to pure isolated compounds.

The second approach formally incorporates the Build and Coupling step of the sequence and yields **PM-1** in high yields. Using this approach, previously prepared sulfones ***3-11a*** (Table 1) were reacted with various acyl halides and chloro-carbonyl derivatives (Table 2).[7,8] This protocol was previously developed in our group and allows to prepare **PM-1** in a short and efficient manner.

*Table 2 – Preparation of sulfones **3-13** using acyl chlorides **3-15** and methyl-BT-sulfone **3-11a**.*



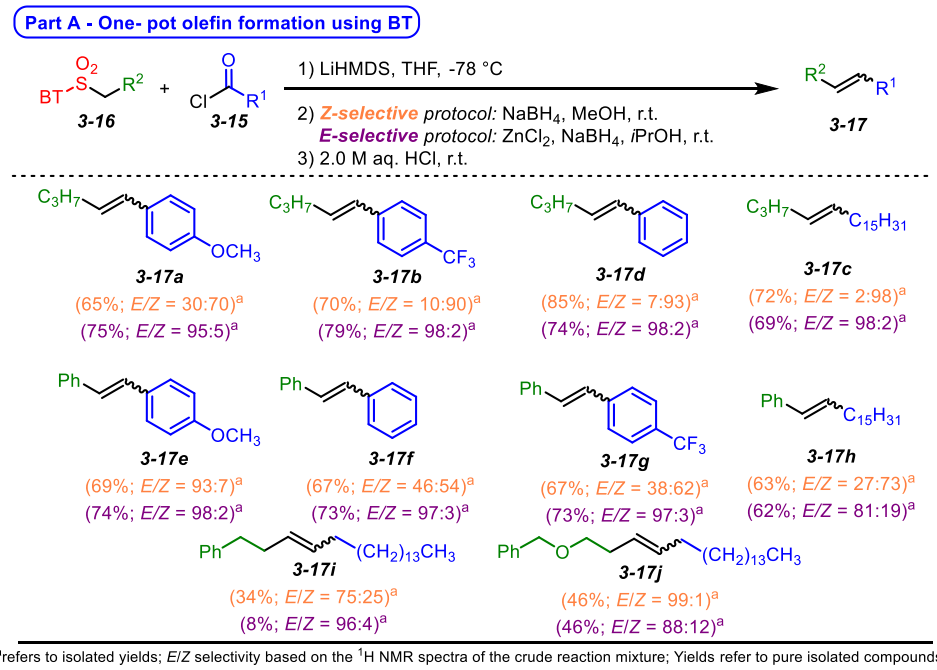
Yields refer to pure isolated compounds.

3.3 In situ generation of PM-1 – transposing the "pluripotent reagents" to "pluripotent protocol"

The original concept discussed in this chapter merges Couple and Pair phase in the one-pot protocol. The reaction of sulfone ***3-16*** with ***3-15*** (*Couple step*), creates *in situ* lithium enolate (enolate form of **PM-1**), and if the properly chosen reagent is added, transforms the **PM-1** (*Pair step*) to diverse olefins, alkynes and carbonyl-containing compounds. How the transformations are done? Let's first focus on the olefin formation. To accomplish this transformation, the selective reduction of the β-carbonyl group in **PM-1** must be achieved. And it must be done stereoselectively (Felkin Ahn transition state vs Cram-chelate transition state) since we wish to obtain selectively *E* or *Z* olefin. If

sulfones ***3-16*** (R^2 = alkyl) were reacted with aromatic acyl chlorides ***3-15***, high yields of olefins as *E* or *Z* isomers (high E/Z ratios, predictable transition state, design-driven geometry formation,Table 3,***3-17a***-***3-17c***). Unfortunately, when using alkyl acyl chlorides ***3-15***, *E* isomers are formed as the major products regardless of the protocol (Felkin-Ahn/Cram-chelate) used (***3-17i***-***3-17j***). Sulfones ***3-16*** (R^2= Ph) were also evaluated, but such reactions are problematic from the stereochemical outcome point-of-view due to the *E/Z*-isomerization process that takes place *after* the reaction (Table 3, ***3-17e***-***3-17g***).

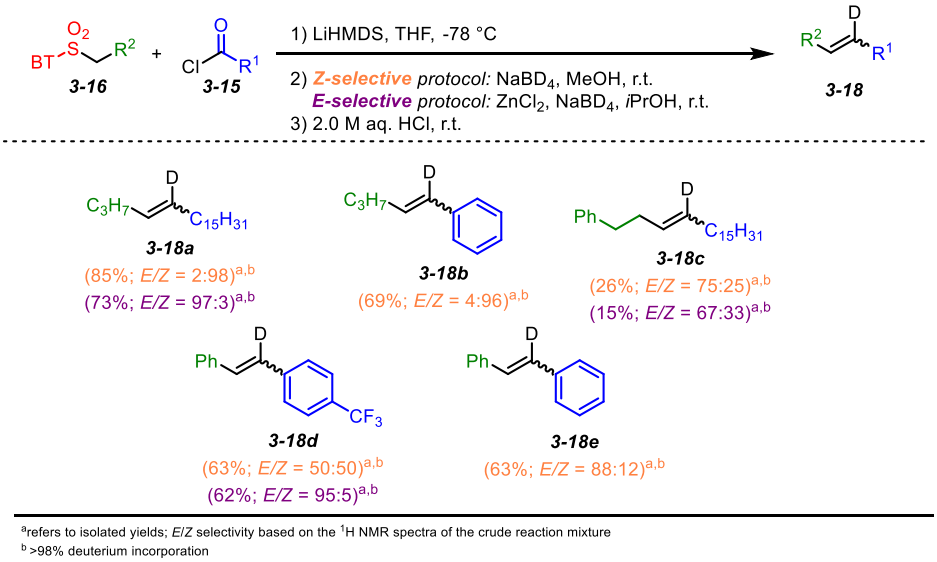
Table 3 – Scope and limitations for one-pot olefination protocol.



[a]refers to isolated yields; *E*/*Z* selectivity based on the ^{1}H NMR spectra of the crude reaction mixture; Yields refer to pure isolated compounds.

Subsequently, the possibility of deuterium incorporation during the *in-situ* reduction of the generated β-keto sulfone using $NaBD_4$ was also successfully exploited. In the case of product ***3-18a***, it was possible to selectively prepare both isomers with high *E*/*Z* selectivity and deuterium incorporation (Table 4). In other tested cases, it was possible to obtain predominantly *E*-isomers of targeted products except for ***3-18b***, which was isolated as *E*/*Z* = 4:96 mixture and in 69% yield. It is important to note that the deuterium incorporation proceeded with >98% selectivity in all cases.

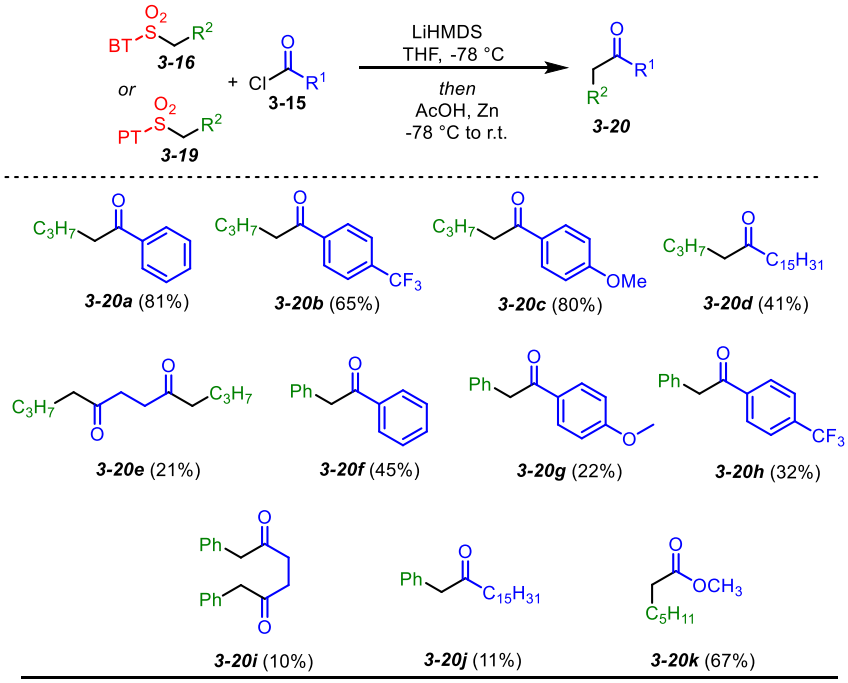
Table 4 – Stereoselective synthesis of deuterated olefins – One-pot olefination protocol using $NaBD_4$.



[a]refers to isolated yields; *E*/*Z* selectivity based on the ^{1}H NMR spectra of the crude reaction mixture
[b] >98% deuterium incorporation

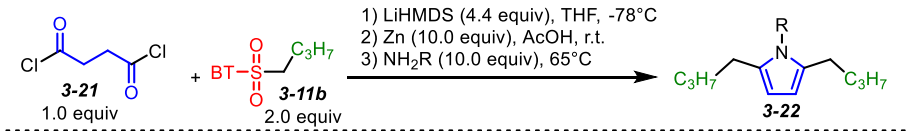
Having established a powerful one-pot olefination protocol, we focused our attention to one-pot ketone/ester formation. Indeed, this strategy proved to be successful and using this one-pot protocol, it was possible to generate various ketones. The method could be extended also for esters (Table 5). Various acyl chlorides ***3-15*** (R^1= alkyl, aryl) were used and final products were isolated with good to moderate yields. Moreover, this method allowed the synthesis of 1,4 diketones (Table 5,***3-20e*** and ***3-20i***) that allowed us to extend our one-pot protocol to the synthesis of heterocycles. Thus, nearly the same protocol was successfully employed in one-pot pyrrole synthesis. Desired pyrroles ***3-22a*** and ***3-22b*** were prepared with yields of 28% and 37%, respectively (Table 6). It means that the efficiency of every single synthetic transformation was ~80%.

Table 5 – One-pot protocol for ketones and ester synthesis.



Yields refer to pure isolated compounds.

Table 6 – Pyrrole synthesis using the one-pot protocol.

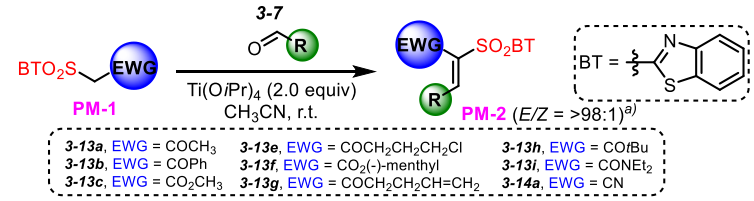


Yields refer to pure isolated compounds.

3.4 Extending the utility of PM-1 – PM-2 molecule

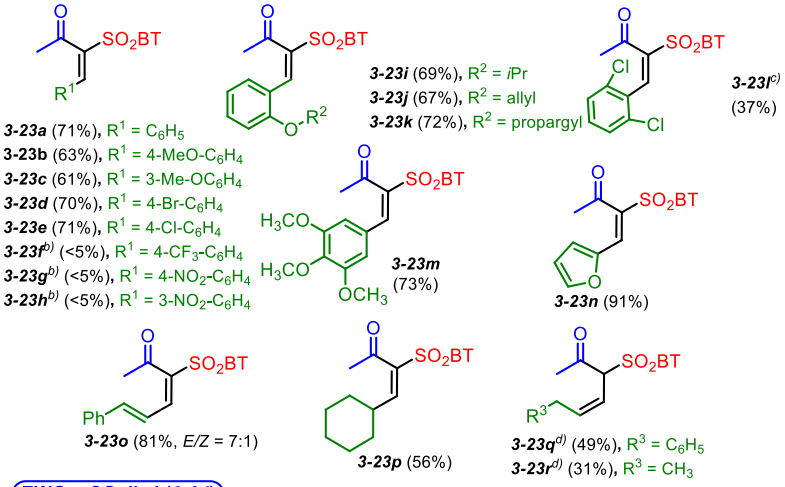
Newly designed **PM-2** molecules should possess very different reactivity in comparison with **PM-1** since it is extended with α,β-unsaturated system. But before the reactivity of **PM-2** could be explored, it had to be prepared. And it proved to be more challenging than expected. Typical reaction conditions[9] failed to generate the desired product. Fortunately, use of $Ti(O\text{-}iPr)_4$ as a reaction promoter proved to be beneficial and this method allowed us to prepare 45 examples of **PM-2** with exclusive selectivity (*E*/*Z*= >98:1) and good to very good yields (Table 7, Table 8).

Table 7 – Scope and limitations of Knoevenagel condensation I.



3-13a, EWG = $COCH_3$ ***3-13e***, EWG = $COCH_2CH_2CH_2Cl$ ***3-13h***, EWG = CO*t*Bu
3-13b, EWG = COPh ***3-13f***, EWG = CO_2(-)-menthyl ***3-13i***, EWG = $CONEt_2$
3-13c, EWG = CO_2CH_3 ***3-13g***, EWG = $COCH_2CH_2CH{=}CH_2$ ***3-14a***, EWG = CN

EWG = $COCH_3$ (*3-23*)



3-23a (71%), $R^1 = C_6H_5$
3-23b (63%), R^1 = 4-MeO-C_6H_4
3-23c (61%), R^1 = 3-Me-OC_6H_4
3-23d (70%), R^1 = 4-Br-C_6H_4
3-23e (71%), R^1 = 4-Cl-C_6H_4
3-23f[b] (<5%), R^1 = 4-CF_3-C_6H_4
3-23g[b] (<5%), R^1 = 4-NO_2-C_6H_4
3-23h[b] (<5%), R^1 = 3-NO_2-C_6H_4

3-23i (69%), R^2 = *i*Pr
3-23j (67%), R^2 = allyl
3-23k (72%), R^2 = propargyl

3-23l[c] (37%)

3-23m (73%)

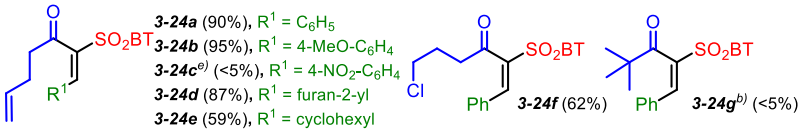
3-23n (91%)

3-23o (81%, *E/Z* = 7:1)

3-23p (56%)

3-23q[d] (49%), $R^3 = C_6H_5$
3-23r[d] (31%), $R^3 = CH_3$

EWG = COalkyl (*3-24*)

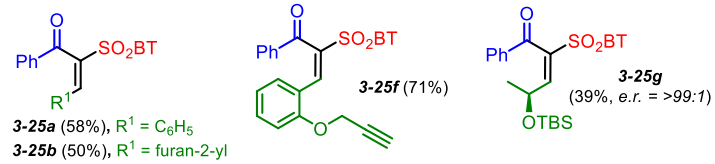


3-24a (90%), $R^1 = C_6H_5$
3-24b (95%), R^1 = 4-MeO-C_6H_4
3-24c[e] (<5%), R^1 = 4-NO_2-C_6H_4
3-24d (87%), R^1 = furan-2-yl
3-24e (59%), R^1 = cyclohexyl

3-24f (62%)

3-24g[b] (<5%)

EWG = COPh (*3-25*)



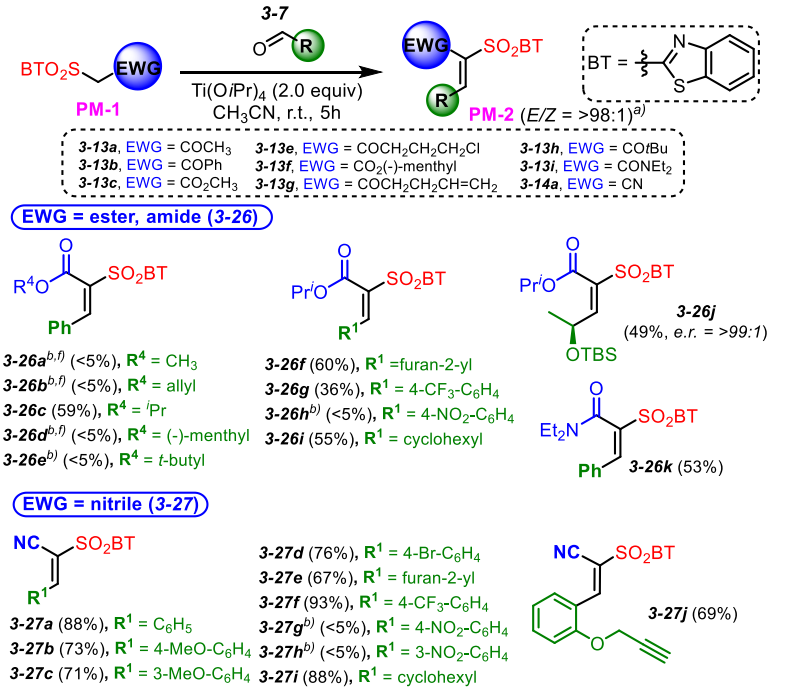
3-25a (58%), $R^1 = C_6H_5$
3-25b (50%), R^1 = furan-2-yl
3-25c (67%), R^1 = 4-CF_3-C_6H_4
3-25d[b] (<5%), R^1 = 4-NO_2-C_6H_4
3-25e (45%), R^1 = cyclohexyl

3-25f (71%)

3-25g (39%, *e.r.* = >99:1)

[a] Based on the 1H NMR spectra of the crude reaction mixture. [b] No traces of product observed. [c] Reaction carried out at 80 °C for 6h. [d] Only olefin migration products were isolated as the products of the reaction. [e] only the product of 1,4-addition of *i*-PrOH were detected suggesting that trace amount of the desired product was formed; Yields refer to pure isolated compounds.

Table 8 – Scope and limitations of Knoevenagel condensation II.



a) Based on the 1H NMR spectra of the crude reaction mixture. b) No traces of product observed. c) Reaction carried out at 80 °C for 6h. d) Only olefin migration products were isolated as the products of the reaction. e) only the product of 1,4-addition of *i*-PrOH were detected suggesting that trace amount of the desired product was formed.
f) Only product ***3-26c*** was isolated in 58-61% yields; Yields refer to pure isolated compounds.

3.5 PM-2 in action: applications

As pointed out at the onset of our journey to **PM-2**, the main goal of our "quest" is to explore the reactivity of **PM-2** building block. Having the molecule in hands, we could focus on its applications. The overview of different reactive sites incorporated in the **PM-2** molecule is showed in Figure 1. One can see that we wished to explore the reactivity of **PM-2** under various reaction conditions, where **PM-2** played the role of dienophile, dipolarophile, heterodiene, Michael acceptor or radicophilic species.

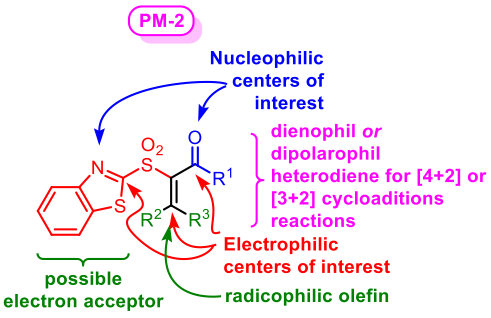


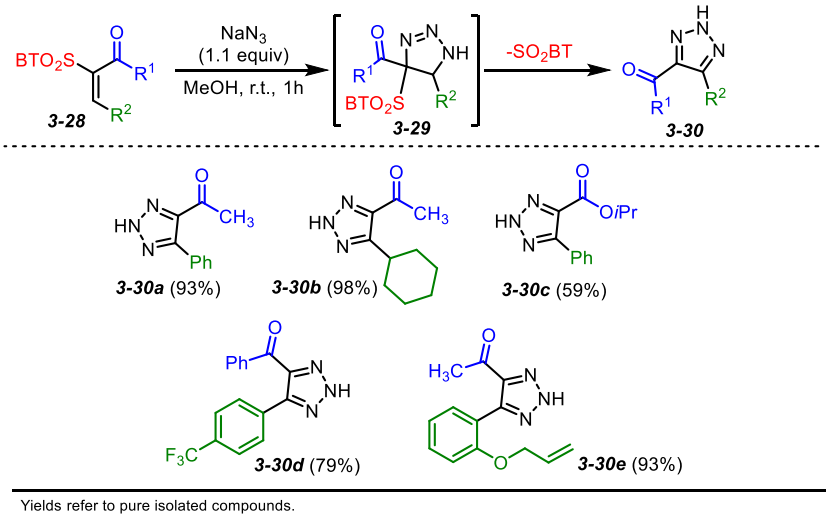
Figure 1 – PM-2 molecule as a building block for Diversity-oriented synthesis.

3.5.1 PM-2 as dipolarophile

First, we have focused on the reaction of azides.[10] From the HOMO/LUMO viewpoint, in this reaction HOMO of azides (dipole) reacts with LUMO of dipolarophile (sulfone ***3-28***). Thus, not

surprisingly the reaction of NaN_3 with various ***3-28*** in MeOH proceeded smoothly at rt and yielded the desired triazoles ***3-330*** in excellent yields (Table 9).

Table 9 – (3+2) cycloaddition reaction between PM-2 and NaN_3.

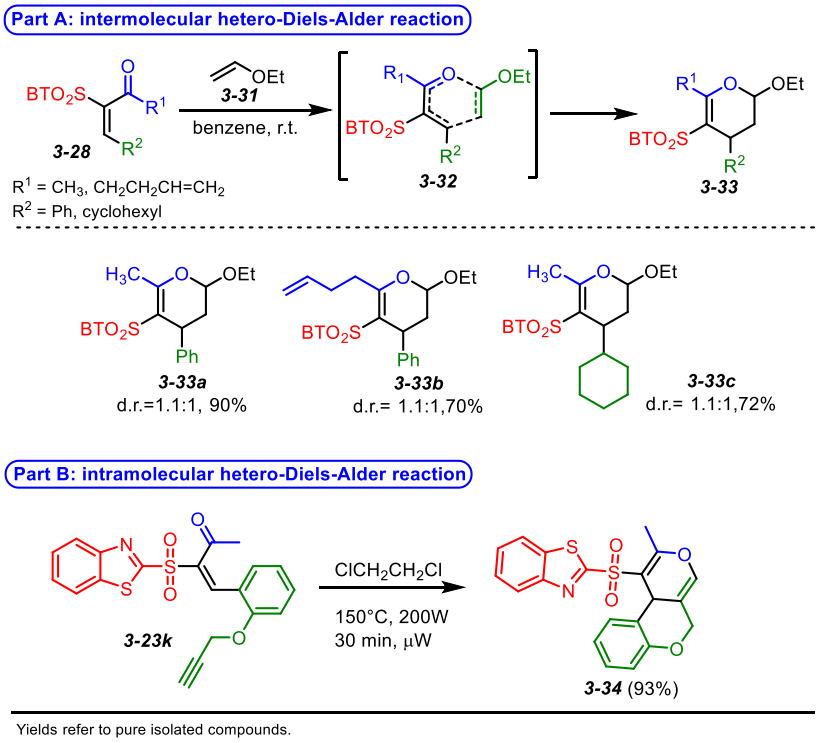


Yields refer to pure isolated compounds.

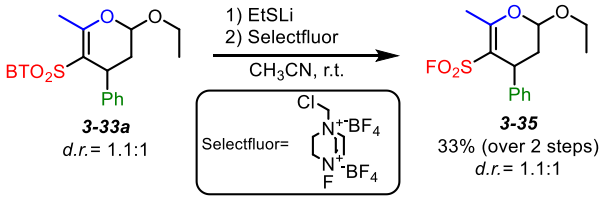
3.5.2 PM-2 in hetero Diels-Alder reaction

Having used sulfones ***3-28*** as dipolarophiles in [3+2] cycloaddition reaction motivated us to explore other cycloaddition reactions. The structure of **PM-2** inspired us to explore its use as electron-deficient heterodiene in hetero-Diels-Alder reaction. It was expected that our **PM**-scaffold can successfully react as a diene in inverse electron demand hDA due to its low lying LUMO orbital.[11] To evaluate such situation, electron-rich dienophiles such as ethyl vinyl ether were reacted with ***3-28*** in benzene at rt (Table 10, Part A). [4+2]-cycloadditions proceeded smoothly and desired dihydropyrans ***3-33*** were isolated in excellent yields (Table 10, Part A). The intramolecular variant of hetero-Diels-Alder reaction is also possible, however, since less electron-rich olefin is used, it must be carried out at higher temperature (Table 10, Part B).

Table 10 – Hetero-Diels-Alder reaction with inverse electron demand: Part A – Reaction of PM-2 with ethyl-vinyl ether; Part B – Intramolecular cycloaddition.



At this point, we could take the advantage of having the BT-group in the skeleton of the dihydropyran-ring. Indeed, BT-group can be readily removed with the help of EtSLi and the resulting sulfinic salt can be e.g. transformed into the corresponding sulfonyl fluoride (Scheme 2). The sulfonyl fluoride group can be further modified with help of Sharpless SuFEX chemistry,[12] and thus allowing further product diversification.[13]

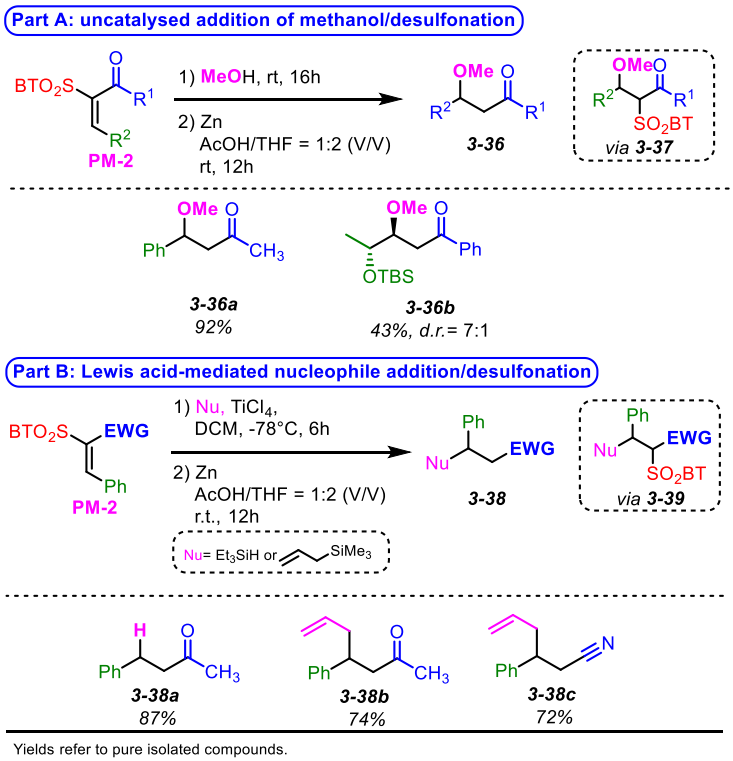


*Scheme 2 – Modification of SO_2BT group in dihydropyran **3-33a**.*

3.5.3 PM-2 as Michael acceptor

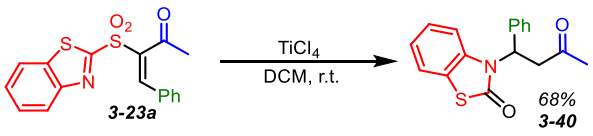
Despite the presence of several highly reactive centres in **PM-2**, a selective transformation employing Michael addition as a key reaction was accomplished. Different type of nucleophiles was tested, but the only reaction with methanol or $TiCl_4$ catalyzed allylation/reduction worked smoothly. Moreover, we extended the additional step to a one-pot procedure that consists of addition/desulfonation sequence (Table 11).

Table 11 – Part A – The addition of MeOH/desulfonylation process; Part B – Lewis acid-mediated Nu addition/desulfonylation.



3.5.4 PM-2 - Lewis acid-mediated rearrangement

While studying the reactivity of **PM-2**, interesting intramolecular Smiles-type rearrangement was disclosed. The rearrangement yielded the product ***3-40*** (Scheme 3). Unfortunately, the reaction proved to be less general than expected, and so far only a product ***3-40*** was isolated. Further optimization will hopefully handle such a problem.

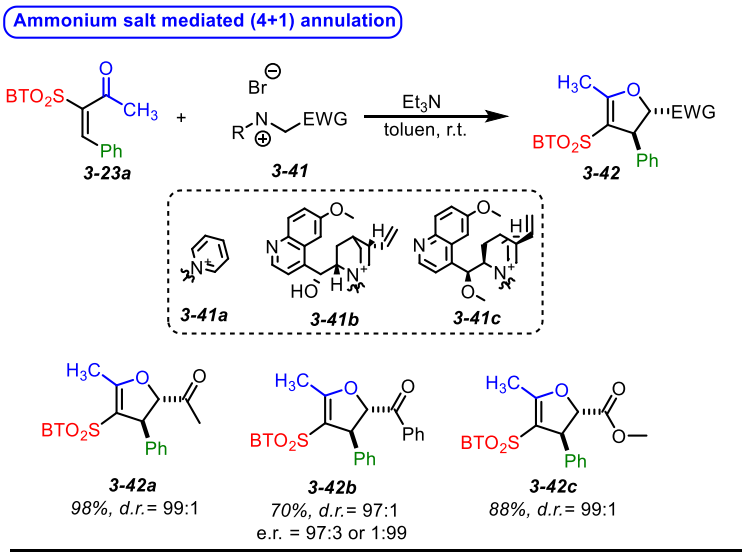


*Scheme 3 – Smiles-type rearrangement using **PM-2** molecule.*

3.5.5 PM-2 - (4+1) annulation based dihydrofuran synthesis

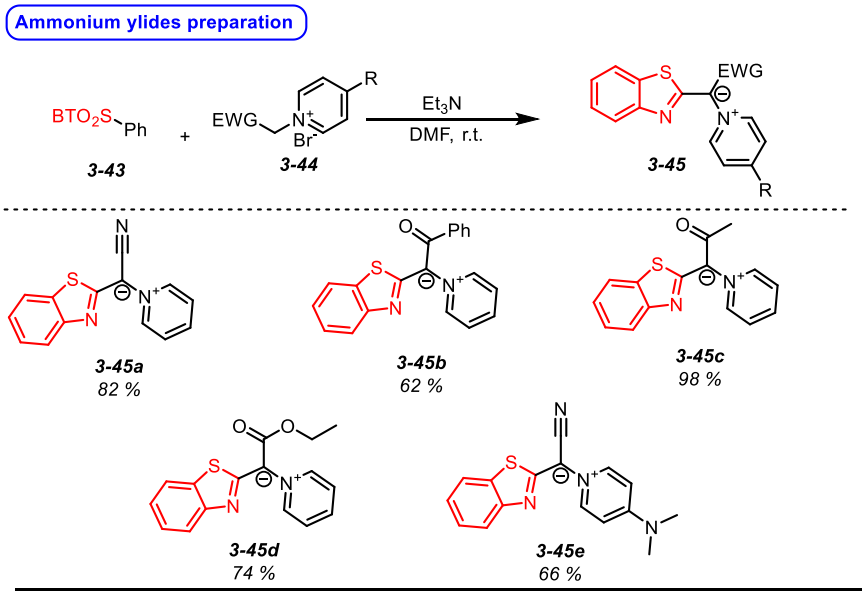
PM-2 molecule can be reacted with nucleophiles containing GLG in α-position. Employing ammonium salts as nucleophiles, we generated dihydrofuran ***3-42*** with a high degree of diastereoselectivity and at high yields (Table 12). In addition, if chiral ammonium salts[14] based on chiral quinine or cinchonine were used, the reaction was carried out not only with excellent diastereoselectivity, but also with high enantioselectivity (Table 12). By proper choice of chiral ammonium salt, we could also invert the facial selectivity and to prepare opposite antipode of previously targeted DHF heterocycle.

Table 12 – Dihydrofuran synthesis.



In addition, when cyano pyridinium salt ***3-41*** was reacted with ***3-23a,*** the unexpected new product was obtained. Surprisingly, we prepared zwitterionic pyridinium ylides, that are shelf-stable. Soon was obvious that our system was too complicated, and we decided to simplify it. Indeed, if the sulfone ***3-43*** is used, the same type of transformation is achieved. The procedure allowed us to prepare ammonium ylides ***3-45*** in good yields. The prepared product will be further tested as diazo-free carbene equivalents in cyclopropanation reaction.[15]

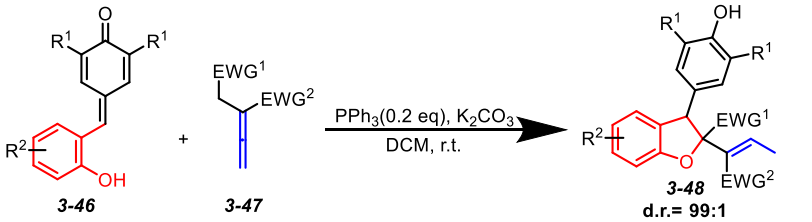
Table 13 – Pyridinium ylides – Scope and limitations.

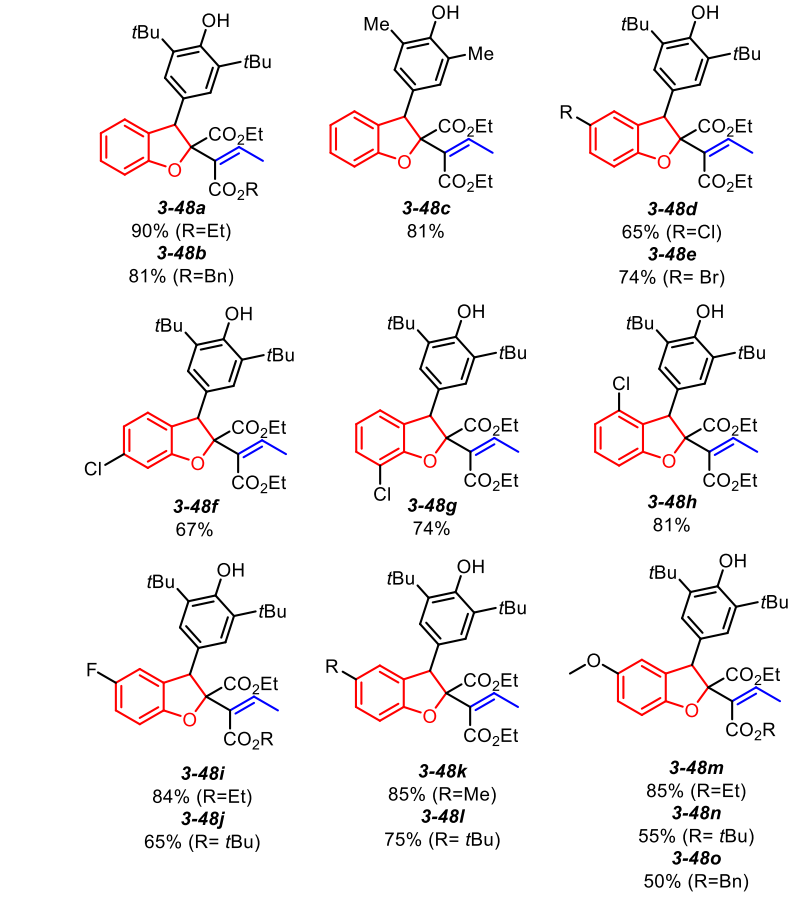


3.6 Reactivity of Quinone-methides with α-branched allenoates

Due to our growing collaboration between our group and the group of prof. Waser (JKU, Linz) we got interested in different electrophiles – Quinone methides (QMs) and chemistry of allenoates. Our interest in such compounds, and especially in the products that can be generated with help of these, is closely connected with a different project in the group – phenylpropanoid-based secondary plant metabolites and their activity in the context of leishmaniosis.[16,17] The main goal of my research was to explore the reactivity of *ortho*-hydroxy-*para*-quinone methides (*o*-h-*p* QMs) will α-branched allenoates ((4+1) vs. (4+2)). We found out, that *ortho*-hydroxy-*para*-quinone methides and allenoates reacts under PPh_3catalysis (20mol%) together and generate various benzofurans. Developed method proved to be robust and tolerated various substitution patterns on the aromatic ring (MeO, Me, *t*Bu, halogens) of *o*-h-*p*-QM ***3-46*** and various EWG on the allenoates ***3-47***. It was observed that in the case of EWG^2, the change in the substitution (from Et to *t*-Bu to Bn) had an impact and the reaction rate. More bulky substituents prolonged reaction times and diminished the reaction yields (more unidentified side products formed) (Table 14).

Table 14 – Scope and limitations of the (4+1) annulation reaction of o-h-p QMs



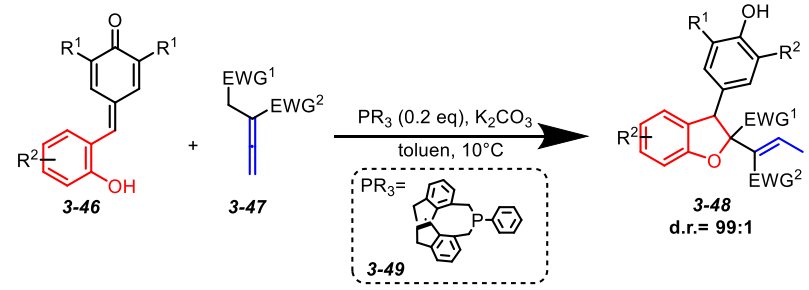


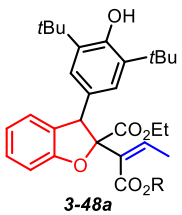
Yields refer to pure isolated compounds.

Having in hands a robust synthetic method, we have decided to extend the reaction to its asymmetric variation. Various phosphine-based catalysts were screened but only spiro-based ***3-49*** proved to be efficient and yielded the desired products in excellent *e.r.* By evaluating the scope and limitations it was observed that in allenoate part (EWG^2), ethyl ester can be replaced with benzyl and even *t*-Butyl, without significant loss in reaction yields and selectivity. Replacement of the *t*-butyl group with Me group in *o*-h-*p*-QM proved to be on the other hand limitation of the reaction. In this case, the product ***3-48c*** was obtained only with moderate *e.r.* = 88:12 (Table 15). In addition, substituent in C3 and C6 position of *o*-h-*p*-QM caused a dramatic decrease in observed enantioselectivity (79:21). Interestingly, the substituents at C6 proved to not be tolerated under asymmetric protocol. However, under the racemic protocol, the reactions work. Gratifyingly, positions 4 and 5 were very well tolerated, and all tested reactions yielded the desired products in high yields and enantioselectivities

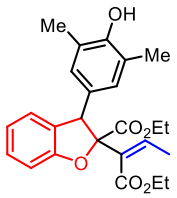
(Table 15). It should be also pointed out that all performed reactions proceeded with excellent diastereoselectivity and in each case, virtually only one diastereomer was observed.

Table 15 – Scope and limitations of asymmetric (4+1) annulation reaction.

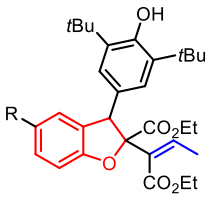




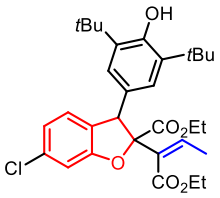
3-48a
89%, ***e.r.*= 94:6** (R=Et)
3-48b
78%, ***e.r.*= 94:6** (R=Bn)



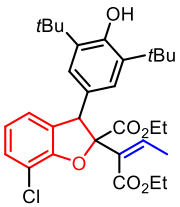
3-48c
62%, ***e.r.*=88:12**



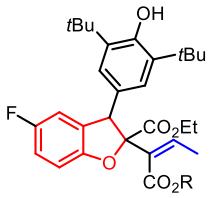
3-48d
65%, ***e.r.*=92:8** (R=Cl)
3-48e
72%, ***e.r.*=92:8** (R= Br)



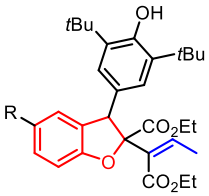
3-48f
70%, ***e.r.*= 94:6**



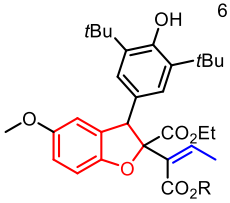
3-48g
59%, ***e.r.*=79:21**



3-48i
77%, ***e.r.*=92:8** (R=Et)
3-48j
61%, ***e.r.*=83:17** (R= *t*Bu)



3-48k
65%, ***e.r.*=94:6** (R=Me)
3-48l
78%, ***e.r.*=94:6** (R= *t*Bu)



3-48m
82%, ***e.r.*=92:8** (R=Et)
3-48n
60%, ***e.r.*=85:15** (R= *t*Bu)
3-48o
76%, ***e.r.*=95:5** (R=Bn)

Yields refer to pure isolated compounds.

4 Conclusion and perspectives

Presented Ph.D. Thesis covers mainly the area of Diversity-Oriented synthesis. For this purpose, we have chosen a strategy that aims to develop and utilize Pluripotent molecules (**PM**), that are based on Benzo[d]thiazol-2-ylsulfones. In our case, we used **PM-1** molecule in one or two-carbon homologation protocol applicable in natural product synthesis (Ingenol). Subsequently, we pushed the limits further and succeeded in developing a new type of one-pot protocol that allowed the stereoselective formation of various C=C bonds. The protocol was further extended to other substrates, and now we can prepare alkynes, ketones, esters and heterocyclic compounds (pyrroles) using just one one-pot procedure.

PM-1 molecule was used as a starting material in the formal Knoevenagel condensation, that allowed us to prepare a new type of pluripotent reagent with higher density of reactive centers. The optimized condensation protocol based on the use of [Ti]-based Lewis acid allowed us to prepare 45 examples of **PM-2** derivatives. The reactivity was studied in context of cycloaddition reactions ([3+2], [4+2]), (4+1)-asymmetric annulation, Smiles-type rearrangement, pyridinium ylides formation, and Michael-type addition reactions. We also successfully developed a method allowing preparation of enantioenriched benzodihydrofurans (15 examples) using (4+1)-annulation reaction between *ortho*-hydroxy-*para*-Quinone methides and allenoates.

And the future of the **PM-1** and **PM-2** molecules? There are countless possibilities. First, we would like to further optimize the one-pot protocol for the preparation of pyrroles and apply it for the preparation of other heterocycles as furans, thiophenes; or focus on the development of a method for preparation of non-symmetrical heterocycles. Furthermore, we would like to focus our attention to a better understanding of the Smiles-type rearrangement, study the mechanism, define the scope and limitations. The products of this rearrangement can lead to the β-amino acids. Probably the biggest challenge will be to develop a methodology based on pyridinium ylides (source of diazo free carbenes) and their application in organic synthesis. From a long-term perspective, the main goal will be move our **PM-1** and **PM-2** reagents to the next level, apply then in the context of the library generation.

5 References

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6 Summary (Souhrn)

Předložená Disertační práce se zaměřuje na chemii benzothiazol-2-yl-sulfonů (BT-sulfony) a zejména pak rozebírá jejich reaktivitu v rámci pluripotentních molekul PM-1 a PM-2. Vytvořené molekuly jsou pak studovány v kontextu mnohých reakčních podmínek (polární, radikálové, pericyklické, katalyzované tranzitními kovy) s cílem umožnit jejich budoucí využití při výstavbě nových chemických knihoven.

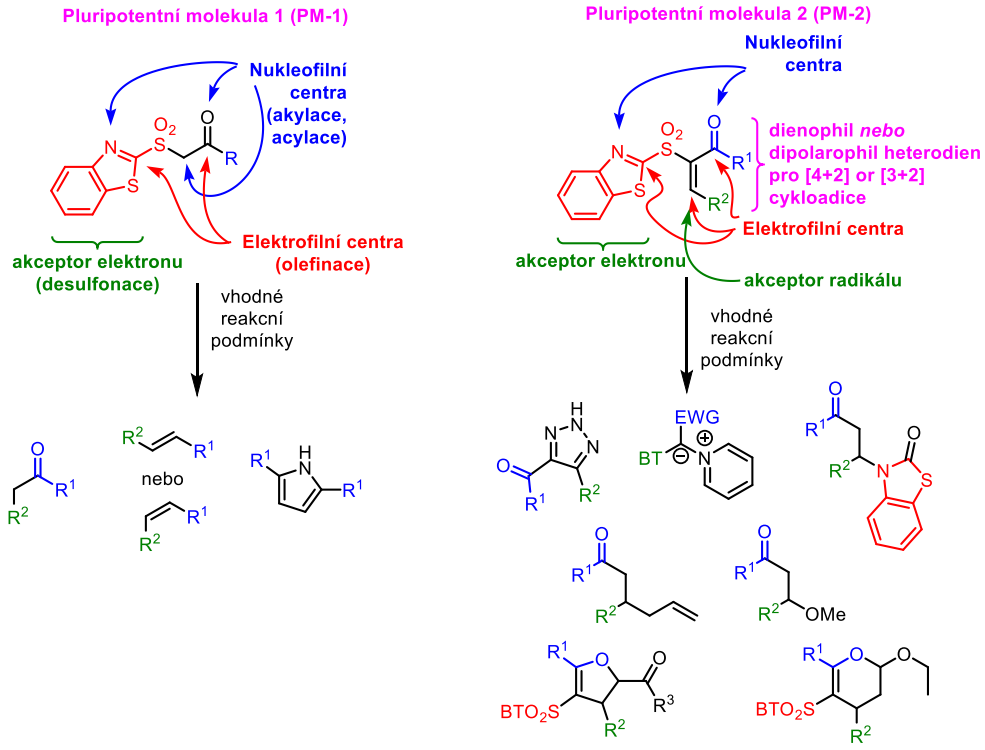

Schéma 1 – Reaktivita PM-1 a PM-2 molekul.

V rámci tohoto projektu se nám podařilo vyvinout metodologii, která využívá reakci alkyl BT-sulfonů a derivátů karboxylových kyselin (komerčně dostupné acyl chloridy a anhydridy) jako základních kamenů pro výstavbu β-keto BT-sulfonů. Tyto jsou následně *in situ* redukovány pomocí $NaBH_4$ anebo $NaBH_4/ZnCl_2$ za tvorby násobné vazby (Schéma 1). Výhodou této metody je její vysoká stereokontrola při tvorbě násobné vazby a vysoká chemoselektivita. Vhodným zvolením výchozího zdroje karbonylové funkční skupiny lze navíc dosáhnout one-pot přípravy heterocyklických sloučenin (pyrroly, furany a atd.; 30-40% výtěžek přes 4 kroky).

V další části svého doktorského studia jsem se zaměřil na vývoj metody přípravy tzv. druhé generace BT-sulfonů obsahujících ještě větší množství reaktivních center. Tento cíl (více reaktivních funkčních skupin) nám měl zajistit mnohem větší reaktivitu a vyšší variabilitu při aplikaci tohoto typu reagentu (Schéma 1).

Příprava vinyl sulfonů tohoto typu je založena na Knoevenagelově kondenzaci mezi **PM-1** a vhodným aldehydem. Daná transformace, probíhá za přítomnosti Ti(O-*i*Pr)$_4$. Touto metodou se nám povedlo připravit 45 dosud neznámých BT-vinyl sulfonů (**PM-2**) s vysokou stereoselektivitou (*E*:*Z* = 98:1). Studium jejich reaktivity nám potvrdilo očekávanou vysokou reaktivitu tohoto systému vůči elektrofilům a nukleofilům (Schéma 1). Obdobně se ukázalo, že tyto reagenty jsou vhodné substráty při pericyklických reakcích. Náš typ aktivovaných olefinů reagoval při cykloadičních reakcí s azidy ((3+2)) a vinyl ethery ([4+2]) za vzniku 5-ti a 6-ti členných heterocyklů. Při katalýze Lewisovou kyselinou se tyto reagenty přesmykovali pomocí nové modifikace Smilesova přesmyku. Elektrofilní vlastnosti byly zkoumány zejména v kontextu cyklizačních reakcí s α-karbonyl amoniovými solemi za vzniku dihydrofuranů ((4+1) anulační reakce) a cyklopropanů ((2+1) anulační reakce). Velkou výhodou tohoto přístupu je vyvinutá enantioselektivní příprava dihydrofuranů za využití chirálních amoniových solí odvozených od chininu. Byl objeven také nový tip transformace vedoucí k tvorbě nového typu pyridinových ylidů. Dále byla testována i 1,2 vs 1,4 adiční selektivita PM-2 molekul, obsahující ve své struktuře ketonovou funkční skupinu. Ukázalo se, že pouhou změnou reakčních podmínek (koncentrace reakční směsi) lze dosáhnout selektivní 1,2 nebo 1,4-redukce pomocí DIBAL-H.

Posledním projektem v rámci disertační práce byl projekt uskutečněný ve spolupráci s výzkumnou skupinou prof. Wasera (JKU, Linec, Rakousko). Jednalo se zde o vývoj (4+1)-anulační reakce katalyzované fosfiny (chirální i racemické) a vedoucí k tvorbě benzo-furanových skeletů. Finální produkty byly připraveny s vysokým výtěžky a vynikající dia-, enantioselektivitou.

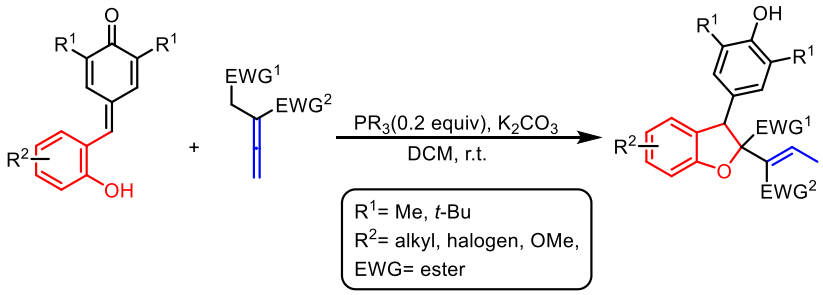

Schéma 2 – (4+1)-cyklizační reakce mezi chinon-methiony a allenoáty.