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Sulfur-based methodologies in the context of olefination and diversity-oriented synthetic methods

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Habilitační práce

Vědní obor: Organická chemie

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Prohlašuji, že předloženou práci jsem vypracoval samostatně s využitím informačních zdrojů, které jsou citovány.

V Olomouci dne 30.08.2017 RNDr. Jiří Pospíšil, Ph.D.

In memory of my Ph.D. supervisor professor István E. Markó, who passed away prematurely this summer…

Acknowledgement

At this point I would like to thanks to my wife, Corinne, for her presence, encouragement and support, because without that I would not be able to reach this particular point – writing my Habilitation Theses.

Additionally I have decided to thanks to all 'Blood', 'Scientific' and 'Friend' family members that have had a key influence to my life. To do so I have made a list of key "phrases" that had and some still has influence on my life.

"Good work praises itself, so do not expect me to ever praise you…" (Jiří Pospíšil*, my father*).

"*So Jiří you're going to work on 1.3-dipolar cycloadditions ..."* (prof. Milan Potáček, *when he accepted me as a 1st year university student in his group).*

"Soooo, what's new?" (prof. Alois Fürstner and prof. Milan Potáček, *about once per week when passing by through the lab*).

"How is doing my ambruticin?" (prof. István E. Markó, *asking about the progress in the total synthesis*)

"What a Mickey mouse molecule" (prof. Alois Fürstner, *commenting the next failed approach in aspecyclide C synthesis*).

"Some people are lucky, some less. Just keep fighting. It will turn." (prof. Samir Zard, *while discussing chemistry and other things with him*).

"Remember, your publications will never be ***perfect****. Just publish!!"* (prof. Philippe Henne, o.p., *during the discussion we had in summer 2016*).

"Can we go with you to the lab?" **and** *"Can I have also my lab when I will be older to play with molecules?"* (my kids – those who are already able to talk ☺).

Table of contents

1. Introduction

Organic synthesis. A term that according to Wikipedia encyclopedia describes organic synthesis as 'a special branch of chemical synthesis and is concerned with the construction of organic compounds *via* organic reactions'.[1] The definition so precise (just one sentence) and, at the same time, so inaccurate. The field of organic synthesis includes so many well-defined subfields that are not obviously included within the above-mentioned encyclopedia definition. One can easily imagine that the development of new synthetic methodologies is a key part of the domain. However, additional subfields such as organic reaction mechanism determination, synthesis of new materials, shedding light into biochemical transformations, or studying metabolic pathways within living organisms are most of the time out of consideration when the term is used. As a consequence, when one introduces himself/herself as an organic synthetic chemist, you never know if this person devotes his/hers life to the synthesis of awkwardly complex natural or nature-inspired compounds, or if they studied the mechanism of a specific enzymatic transformation.

As shown above, the field of interest of organic synthesis is very broad and includes many different subfields. At first glance, most of them do not have much in common linking them together. However, there is one very important constant through-out the field of organic synthesis as an imaginary tine red line – *the creativity*. Indeed, creativity is the aspect to which organic synthetic chemists devote their lives to, directly – *compounds generating activities*, or indirectly – *studying how compounds themselves are created*. One such field is focused on bioactive small molecules.

Small molecules were, are, and will be in the collimator of an organic chemist's interest. In the beginning, the interest was focused on the small molecules already present in living systems. The quest focused on the small molecules presented throughout living organisms that have virtually no reason for being there. In the end, the curiosity driven research resulted in the discovery of glucose (A. Marggraf, 1747), amino acids (1st half of the 19th century), vitamins (1st half of the 20th century), hormones (1st half of the 20th century), neurotransmitters (1st half of the 20th century), to name a few. From the 2nd half of the 20th century, small molecules slowly but progressively started to occupy the place of life processes probes. First newly discovered small molecules with unknown functions in the organism were synthetically modified. The behavior and the destiny of such small molecules within the living cells then allowed us to study and to understand various biological processes. To give a few examples, such an approach was adopted during the study of ion channels and neurotransmissions,[2] protein kinases and signal transduction,[3] or when colchicine and cytochalasins were used to illuminate the molecular components of the cytoskeleton[4] (Figure 1).

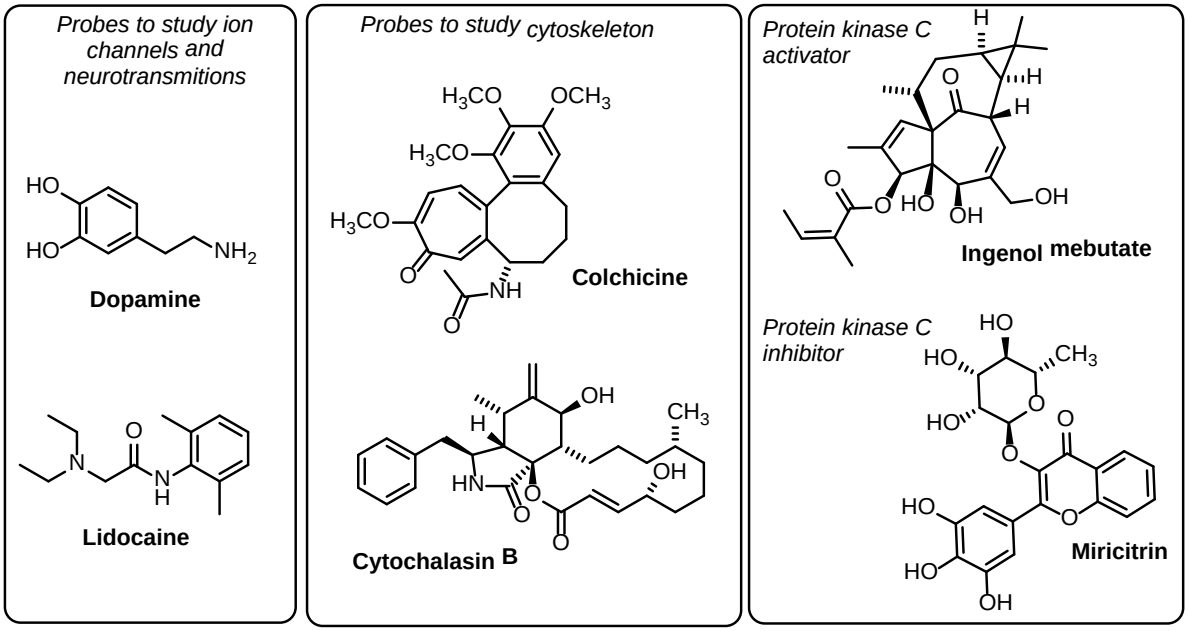


Figure 1. Selected examples of small molecules that contributed to the understanding of life processes.

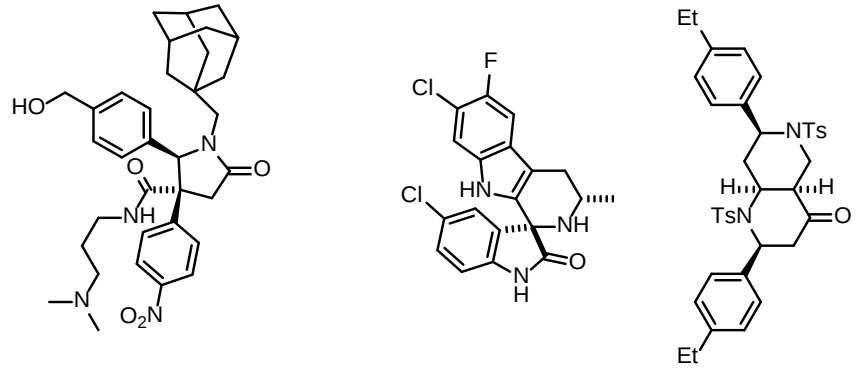
At the onset of the 21st century, small molecules 'changed the role' and became a key part of newly born discipline – chemical genetics *(biology)*. From the definition, chemical genetics/*biology* can be defined as the study of biological systems using small molecules as tools. The concept behind it is to use the ability of cell permeable and selective small molecules to modulate gene product function (*biological systems*) rapidly and reversibly. As a great advantage, the use of selected small molecules may be done in a concentration dependent manner and they can be administered conditionally in either cellular or in a whole organismal context. As a result, this approach based on small molecules has become highly popular and an extremely powerful tool to control and influence biological processes.

This situation is a consequence of the ability of small molecules to interact with macromolecules and perturb their function.[5] In general, the use of small molecules brings on a rapid, temporal, and often reversible method of how to modulate biological functions in a concentration depended manner. This observation, widely explored in medicine, makes however small molecules also useful as chemical probes to study biological systems.[5a,c,6]

On the other hand, the identification of the small molecules that would 'serve a specific purpose' proved to be a rather lengthy and arduous process. To carry out this process quickly and efficiently, throughout the 90-ties of the 20th century big pharma industry employed high-throughput screening (HTC) techniques of large libraries of compounds.[7] Other libraries of compounds were screened by chemical biologists in phenotypic assays to identify compounds which would elicit a particular biological effect.[5c,6a] First, impressive quantum of compounds were screened with the hope to find some leads against many human diseases. Unfortunately, in late 90-ties it become obvious that all screened libraries suffer from one important draw-back – they were comprised of large numbers of structurally similar compounds. As a consequence, the screening campaigns that were focused around known natural ligands or structures derived from molecular modelling have proven to be very successful at generating leads of known and already evaluated targets (e.g. G-protein coupled receptors or kinase enzymes).[7a]

Disappointingly however, many other human disease-related targets such as protein-protein and protein-DNA interactions or transcription factors were not addressed by these small molecules

included in the screened libraries. The first interpretation of this observation was that small molecules are not suitable to address such targets (diseases were marked as 'undruggable') and new ways of targeting such diseases were searched. Fortunately, very soon after the conclusions were 'reconsidered' and new 'data interpretation' suggested that the failure might have been caused by the compound library choice.[8] Structurally too similar compounds were tested against in most cases even unknown targets! As a solution to this, libraries of small molecules consisting of *functionally diverse* molecules were designed and evaluated.[9] Some of the lead compounds that arose from this modified HTS approach are summarized in Figure 2.



inhibitor of transcription factor HOXA 13-DNA interaction

$PfATP_4$ inhibitor

Activator of endothelium driven immunity

Figure 2. Selected examples of small molecule modulators of protein function discovered via structurally diverse library screening[9]

Within the first decade of the 21st century 'a hunt' for the new libraries consisting of functionally diverse compounds was started. Shortly after several new chemical probes with desired and sought-after biological function were identified confirming the success of the selected approach.[10] Virtually overnight the construction of functionally diverse compound libraries has become a venerable field of organic chemistry known as 'diversity-oriented synthesis' (DOS). The aim of DOS is to synthesize structurally complex small molecules in an efficient manner.[11] This is also one of the ultimate goals of the submitters research project.

This Presented *Habilitation Thesis* consists of two parts. The first part is focused on the development of new C-C bond forming reactions. Within this part the development of several novel modifications of 'classical' sulfur and phosphorus-based olefination methods is described. Versatility of these methods is demonstrated in the context of the total synthesis of several natural products.

The second part of the *Habilitation Theses* is then focused on the development of new synthetic methods explorable in the context of functionality-driven DOS methodologies. The aim of this part is the development of short and efficient strategies that would allow preparing highly functionalized molecular scaffolds called Parent Molecules (PM). PM, when exposed to various reaction conditions, furnishes various structurally different molecular scaffolds.

The submitter of this Habilitation Thesis has worked in the field of C-C bond forming reactions during his gradual studies, and subsequently during his independent carrier as F.S.R.-FNRS research fellow at Université catholique de Louvain (Belgium). Interest in olefination reactions, especially the Julia-Kocienski reaction was slowly transformed and gradually evolved into the new domain – development of new highly functionalized molecular scaffolds – parent molecules. This part of the project started back in Belgium in 2010 and with several breakthroughs and dead ends has become one of the three main projects of the submitter's interest. The other projects are focused on the synthesis, biosynthesis

and possible application of two very different classes of natural products – gibberellins (plant hormones) and phenylpropanoids (plant secondary metabolites, with a main interest in monomers and dimers and their oxido-redox properties).

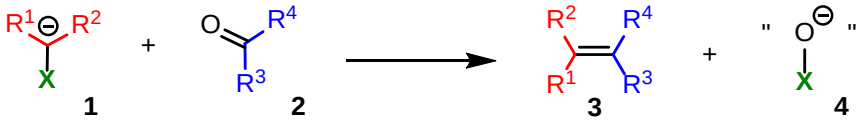
The presented *Habilitation Thesis* is written in the form of briefly commented results of the submitter's research. The majority of these presented results were published in the form of papers in reviewed impacted journals. The submitter was actively involved in all research results presented in this Habilitation as well as in publications that were used as a source of those results. Selected research papers are gathered in the appendix of this Habilitation. The reader is invited to consult them if any detailed information about the presented research data is needed.

2. Olefination reactions in organic chemistry

The formation of carbon-carbon double bond is, no doubt, one of the most important synthetic transformations in organic synthetic chemistry, since C=C bonds are omnipresent in virtually all natural products and biologically active compounds. Synthetic methodologies leading to alkenes are well documented in the literature and abundantly explored in the context of natural product and advanced material synthesis. Indeed, now-a-days a plethora of synthetic olefination methods allows us, synthetic chemists, to link two molecular fragments or to introduce olefinic side chains under very mild reaction conditions and in a highly selective manner. It is hard to believe that this was not always the case.

Until 1953 with the seminal work of Wittig,[12] olefins were accessible only via elimination processes that typically proceeded under very harsh reaction conditions. As one can imagine, using such conditions it was already difficult to prepare olefins in a regioselective manner. Stereoselectivity was thus the last think to think of. In general, Saitseff-type olefins with *E*-configuration were targeted, leaving the *Z*-olefins rather inaccessible (Hofmann elimination could provide a solution in some cases). Then came Wittig olefination process providing for the first time a connective C=C bond forming reaction that proceeded under mild conditions which was regiospecific, and often also stereoselective with either *E* or *Z*-olefins formed. The stereoselectivity of the olefination protocol was, till high extension, predictable and dependent upon the coupling partners and the reaction conditions employed. Since then many novel olefination methods were developed. However, many of them still follow the same reaction pattern set up by Wittig olefination: carbanion (or ylide) stabilized by an adjacent oxophilic group **1** reacts with carbonyl **2** (Table 1). The addition of **1** to **2** initiates a cascade of fundamental steps that results in the formation of alkene **3** and an oxidized form of the activating group **4**. The newly created olefin is located in between the carbon atoms previously incorporated in **1** and **2**.

Table 1: Selected carbonyl-based olefination methods commonly used in organic synthesis.



Activating unit X	Olefination method	Litt. reviews
$PhSO_2$	Julia-Lythgoe	Ref.[13]
$ActSO_2$	Julia-Kocienski	Ref.[13]
R_3P^+	Wittig	Ref.[14]
$R_2P(=O)$	Wittig-Horner	Ref.[14]
$(RO)_2P(=O)$	Horner-Wodsworth-Emmons (HWE)	Ref.[15]
R_3Si	Peterson	Ref.[16]
R_2B	Boron-Wittig	Ref.[17]

Additionally to these methods, various other selective and powerful strategies designed to introduce olefinic functionality into the targeted molecular structure based on transition metal catalysis (e.g. cross-coupling reactions, carbometallation of alkynes etc.) or devoted to connective olefin-forming reactions (e.g. metathesis reactions) have been developed. However, carbonyl-based olefination methods remain an indispensable method as they provide the capability to connect two fragments with simultaneous stereocontrolled generation of a carbon-carbon olefinic bond.

In this chapter, the main emphasis will be focused on the sulfur-based olefination methods. Two main olefination methodologies – Julia-Lythgoe and Julia-Kocienski olefination – are briefly introduced and the key features that are influencing the reaction stereoselectivity are discussed. Our contribution to this field followed by the application of the developed methods in the field of natural product synthesis is concluding the section devoted to the sulfur-based olefination methods. The last subchapter of chapter 2 then describes the application of microwave-assisted Wittig reactions of stabilized ylides in the field of phenylpropanoid-based plant secondary metabolite synthesis.

2.1 Sulfur-based olefination methods

Julia-Lythgoe and Julia-Kocienski are the two sulfur-based olefination methods that have attracted the most of the attention of scientific community. Both methods are based on the addition of α-metallated aryl alkyl sulfones to carbonyl compounds. Even though the first step in both methods is the same, the addition of α-metallated sulfones to carbonyl groups, the following steps are as different as the originators of their disclosers: Mark Julia introduced, what is now-a-days referred to as the "classical" (Julia-Lythgoe) olefination method back in 1973,[18] while his brother Silvestre Julia introduced the so called "modified" (Julia-Kocienski) version of the olefination 18 years later.[19] Both methods are capable of linking together fragments of great complexity, with a high degree of stereocontrol and under mild reaction conditions. The difference is that the 'classical' Julia-Lythgoe olefination proceeds in two to three 'pots'* albeit 'modified' Julia-Kocienski olefination yields the desired olefins in a one-pot protocol.

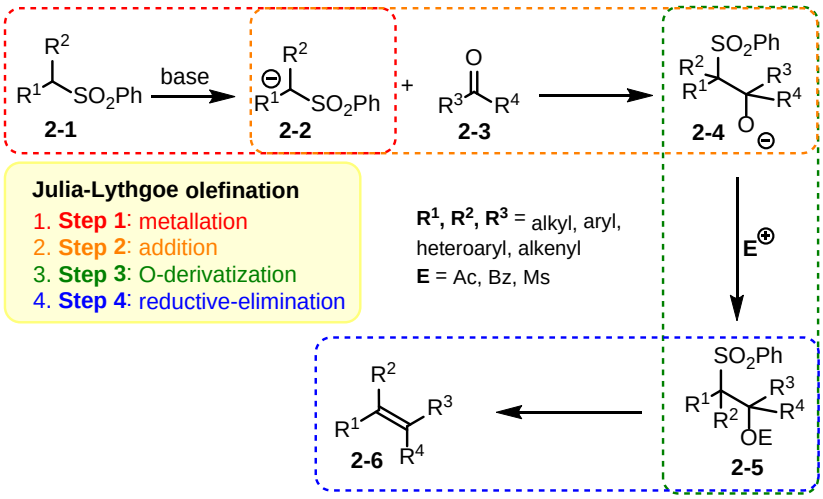
The popularity of above mentioned protocols within the synthetic community is directly linked to the effectiveness of the overall process and the simplicity under which the starting materials, aryl alkyl sulfones, might be prepared in comparison with the corresponding phosphorus and silicon alternatives required for analogous Wittig, Horner-Wadsworth-Emmons, Horner-Wittig, or Petersen olefination methods.

2.1.1 Julia-Lythgoe olefination method

- **Overview of the process**

The Julia-Lythgoe olefination is a multi-step process for the connective synthesis of alkenes based on the reductive elimination of β-acyl(sulfonyl)oxysulfones **2-5** generated by the addition of α-metallated alkylarylsulfones **2-2** to carbonyl compounds **2-3**.[13,20] The transformation was first disclosed by (Mark) Julia and Paris in 1973[18] and subsequently developed into a synthetically useful transformation by Kocienski and Lythgoe[21]. The transformation consists of four distinct stages: (1) metallation of an alkylarylsulfone **2-1**, (2) addition of the resulting carbanion species **2-2** to an aldehyde or ketone **2-3**, (3) O-acylation (sulfonylation) of the adduct **2-4**, and (4) reductive-elimination of the β-acyl (sulfonyl) oxysulfone **2-5** intermediate (Scheme 1).

* 'pots' refers to reaction vessels needed to carry out the sequence.

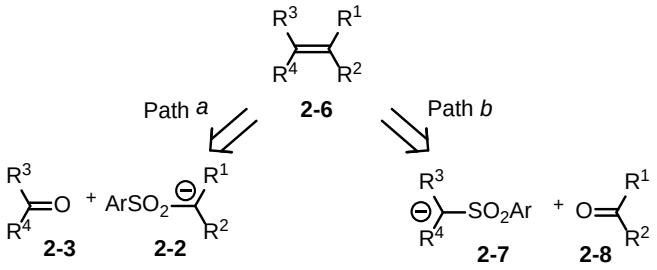


Scheme 1: Julia-Lythgoe olefination – step by step.

Although all three steps can be, in an ideal case, conducted in a single reaction vessel, in practice two-pot protocol based on the isolation and purification of O-derivatized intermediate is generally adopted. The addition **2-3** to **2-2** typically yields product **2-4** as a mixture of all possible diastereoisomers; however, this is of no consequence because the stereochemical information encoded in **2-4** is lost during the reductive-elimination step. A common feature of Julia-Lythgoe olefination is its high (*E*)-stereoselectivity – a consequence of the various radical mechanisms that operate in the final stage of reductive elimination.

- **Coupling step**

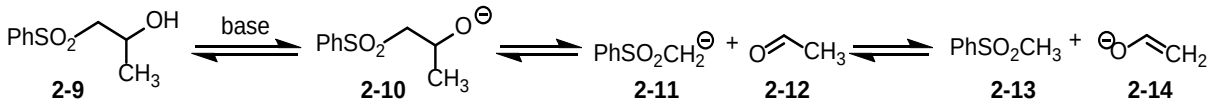
The main advantage of Julia-Lythgoe olefination can be found in its versatility when the retrosynthetic disconnection of the targeted olefin **2-6** is planned (Scheme 2). Obviously, one of the coupling fragments will always carry the arylsulfonyl group, and the second the carbonyl functionality, but *a priori* each fragment can be alternatively chosen as either one or the other. However, the proper choice of the coupling partners usually determines the success of olefin formation and also the degree of the stereoselectivity. Thus, the choice must be decided considering several aspects of the connective step in order to avoid potential problems. The most relevant aspects are: (1) the nature and number of substituents of the sulfone-bearing fragment, (2) the nature of the counter-ion, and (3) the nature and reactivity of the carbonyl compound. What this means in the real case scenarios will be demonstrated on the following several show case examples.



Scheme 2: Two possible retrosynthetic disconnections accessible in Julia-Lythgoe olefination.

When 1,2-disubstituted olefins are targeted, in general, both α-metallated sulfone and aldehyde partners are unhindered and reactive enough to minimize the possible retrograde fragmentation of starting materials.[22] However, the retro-aldol-type reaction is commonly encountered under the basic conditions required for the initial addition step (Scheme 3). Thus extra care must be taken if stabilized

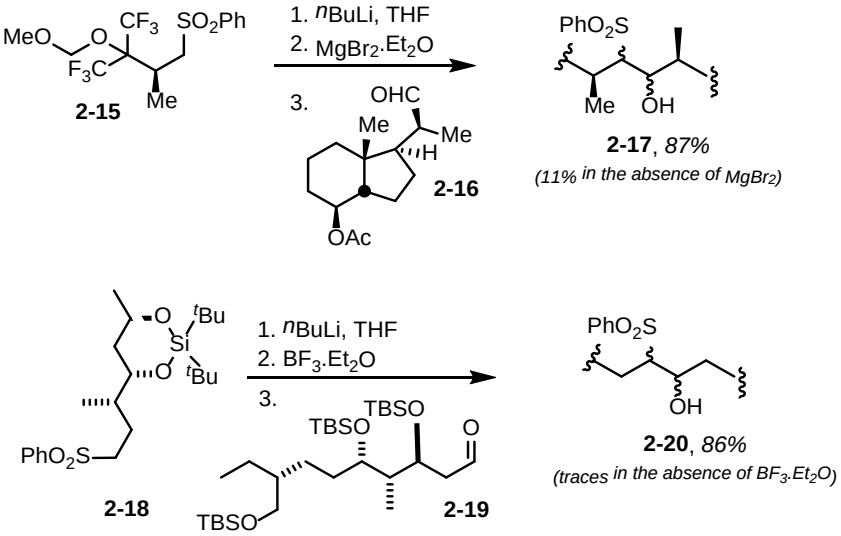
or sterically hindered α-metallated sulfonyl anions are used, since the conjugation or chelation of the anion with the proximal unsaturated system or heteroatom can favor the reverse addition.[23]



Scheme 3: Retro-aldol-type reaction encountered under basic conditions.

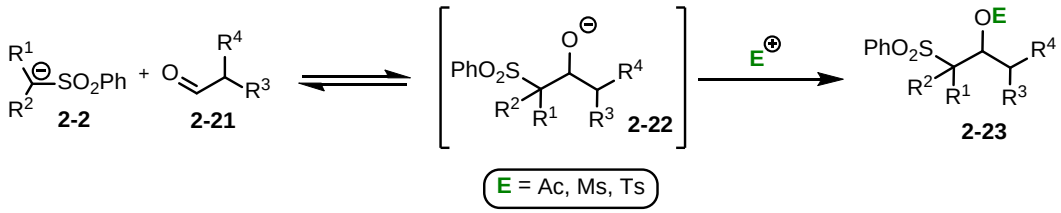
There are several solutions to this problem:

(A) For instance, varying the nature of the counter anion can efficiently shift this unfavorable equilibrium. Thus, replacing lithium by magnesium[24] or the use of a lithiated sulfone/boron trifluoride combination[25] has proven to be effective. The examples of these approaches are shown below (Scheme 4).



Scheme 4: The influence of the additives on the addition step.

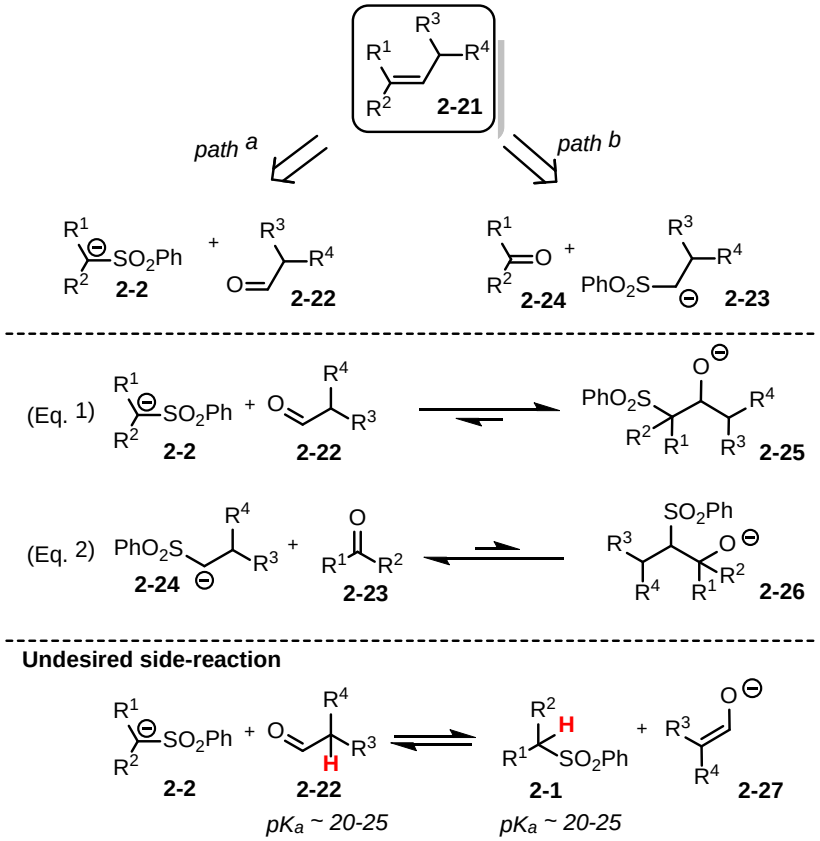
(B) An obvious solution to the problem is to capture the generated β-alkoxy **2-22** intermediate with external electrophile (Scheme 5). Such modifications moreover increases the overall yield of the olefination method since the reductive-elimination of β-hydroxy sulfones proceeds always with lower yields when compared with the captured intermediates (*vide infra*).



Scheme 5: Capturing generated adduct **2-22** with an external electrophile.

(C) The enolization of the carbonyl coupling partner caused by the basic conditions might occur. As a consequence, a large amount of recovered starting material can be re-isolated after the reaction. In general, the change of the solvent polarity towards more polar ones suppresses the undesired enolization of the starting material.[26]

When the retrosynthetic analysis of trisubstituted olefin (e.g. **2-21**) is carried out, extra care must be taken (Scheme 6). Indeed, all above described hurdles might be encountered and become impossible to be solved if the wrong retrosynthetic disconnection is made. For example, addition of secondary sulfonyl carbanion **2-2** to aldehyde **2-22** (*path a*) may lead to undesirable aldehyde enolization, whilst condensation of a more reactive and accessible primary sulfonyl carbanion **2-23** and ketone **2-24** (*path b*) may suffer from retroaldolization reaction (tertiary alcoholate **2-26** is formed).



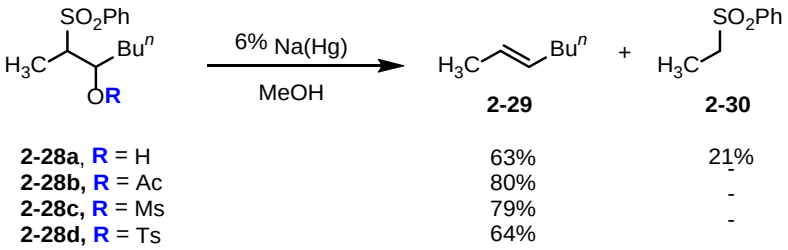
Scheme 6: The difficulties related to trisubstituted olefin retrosynthetic planning.

As a matter of fact, none of the solutions presented above to problems possibly encountered during the olefin synthesis guarantee a 100% success rate in synthetic problem-solving. One must always keep in mind that the correct retrosynthesis depends on careful evaluation of the stability of both, coupling partners and the generated intermediates.

- **Reductive-elimination step**

Since 1973 with the first publication of the Julia-Lythgoe olefination, the majority of the method improvements focused on the reductive-elimination step. Prior 1990, the reductive elimination step was mostly effected using Na(Hg) amalgam leaving other successfully tested reducing agents (RMgX/Pd, Fe or Ni catalyst;[27] Bu_3SnH;[28] Li naphtalene;[28a,29] Li or Na in liquid ammonia or in ethylamine;[30] $Na_2S_2O_4$;[31] Raney Nickel;[32] Potassium graphite;[33] electroreductive reactions;[34] $Te/NaBH_4$;[35] Al(Hg) amalgam and $LiAlH_4$, with or without $CuCl_2$[36]) largely unexplored by the majority of synthetic chemists. In 1990, Kende and Mendoza[37] introduced SmI_2 as an alternative to Na(Hg) and since then the Na(Hg) and SmI_2 have become the 'flagships' of the reducing agents used to promote the reductive elimination step in the Julia-Lythgoe olefination sequence. Thus, this chapter will focus only on these two reagents.

Similarly, the original protocol in which β-alkoxy phenyl sulfones were submitted to Na(Hg)-promoted reductive-elimination conditions was quickly abandoned due to undesired base-promoted side reactions (Scheme 7)[22], and only β-acyl or β-sulfonyl derivatives were used as a starting materials in the reductive elimination step. Currently, almost exclusively reductive elimination of β-acylated oxo sulfone derivatives is carried out. So, this chapter will focus on these.



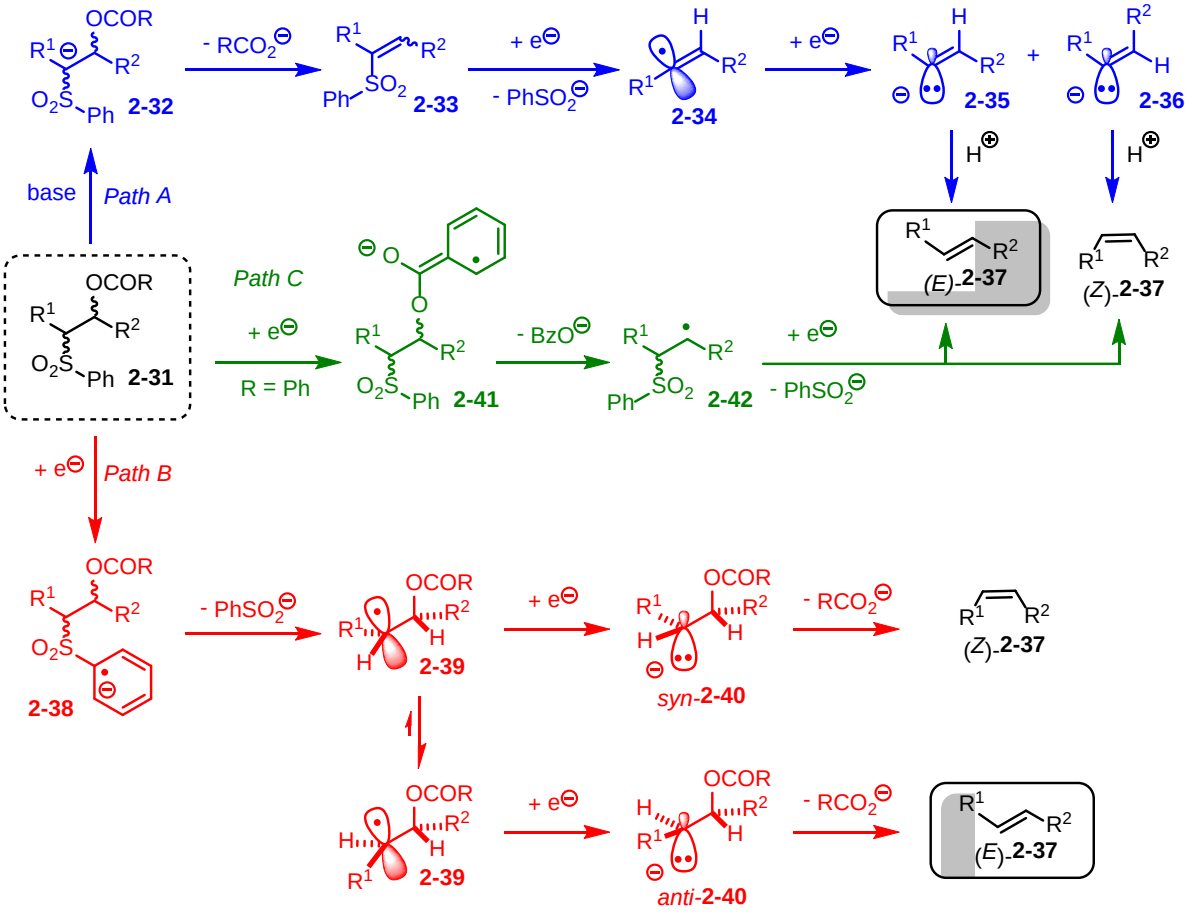
Scheme 7: Na(Hg)-promoted reductive elimination – the influence of the O-derivatization.

Even with such a limitation (focus on O-acylated β-hydroxy sulfones), three different mechanistic pathways that operate during the reductive elimination step were identified (Scheme 8).

Path A:[38] Reductive-elimination promoted by Na(Hg) proceeds in basic conditions due to the *in situ* generated of $CH_3O^-Na^+$ (caused by the presence of Na^o). Thus, first starting sulfone **2-31** undergoes an α-sulfone deprotonation generating anion **2-32** which yields upon the β-elimination process vinyl sulfone **2-33**. A pair of the electron transfer events produce predominantly (*E*)-configured vinyl anion **2-35** (vinyl anions are configurationally stable) that is quenched by proton to yield the final olefin **2-37**. Since vinyl radical **2-34** is configurationally labile, the stereochemistry of the olefin **2-37** results from the ratio of vinyl anions **2-35**/**2-36** established during their formation.

Path B:[39] When non-basic reducing agent as SmI_2 is used to promote reductive elimination step, first one electron transfer yields the radical anion **2-38**. Radical anion **2-38** then collapses upon the release of $PhSO_2$ group and yields β-acyloxy stabilized radical **2-39**. Radical **2-39** is configurationally unstable and rapidly flips between its two possible geometrical forms. The second electron transfer occurs and configurationally stable β-acyloxy anions *syn*- and *anti*-**2-40** are formed. Rapid β-elimination process then yields the desired olefin **2-37**. Again, the stereochemistry of the olefin formed is directed by the stereochemistry of the intermediate **2-40**.

Path C:[40] The third mechanistic pathway was introduced by Markó and co-workers to account for the large rate differences observed in the SmI_2-mediated reductive eliminations of β-hydroxy, and β-acetyloxy sulfones versus β-benzoyloxy sulfones in various competitive experiments. It was suggested that the first electron transfer forms radical anion **2-41**. The loss of BzO^- group yields β-phenylsulfonyl-stabilized radical **2-42**, that upon the second electron transfer yields anion intermediate that immediately releases the $PhSO_2^-$ group and yields desired olefin **2-37**. The stereochemical outcome is presumably determined by the ratio of both possible anion intermediates formed just after the radical **2-42** reduction.



Scheme 8. Three mechanistic pathways operating during the reductive elimination process. The major product of the elimination is highlighted (boxed).

2.1.2 Julia-Kocienski olefination method

The story of the Julia-Kocienski olefination reaction (also known as Silvestre-Julia, modified-Julia or 'one-pot' Julia olefination) started in 1991 when Silvestre Julia (brother of Mark Julia of the Julia-Lythgoe olefination) published with his co-workers the seminal work describing the synthesis of alkenes using a one-pot protocol.[19] In common with his brother's protocol (Julia-Lythgoe olefination), the reaction started with the addition of α-metallated aryl alkyl sulfone to a carbonyl compound.[13,41] However in this case the aryl group of the alkyl aryl sulfone functionality is an electron-acceptor (e.g. as BT group – see Figure 3) and the initially generated β-alkoxy sulfone adduct **2-46** undergoes spontaneous Smiles rearrangement (S to O migration of the heteroaryl group).[42] Subsequent β-elimination of SO_2 (**2-50**) and of an aryloxide anion (**2-49**) directly forms olefin **2-37** (Scheme 9).

The originally introduced BT-group remained as the only electron-acceptor aryl group suitable for the Julia-Kocienski olefination method only for short period of time, because other groups as pyridine-2-yl (**PYR**),[43] 1-phenyl-1H-tetrazole-5-yl (**PT**),[44] 1-tert-butyl-1H-tetrazole-5-yl (**TBT**),[45] and 3,5-bis(trifluoromethyl)phenyl (**BTFP**)[46] and others[43a,47] were soon introduced by other researches (Figure 3). Now-a-days, **PT** and **BT** heteroaryl activating groups are the most commonly used in the context of the olefination method.

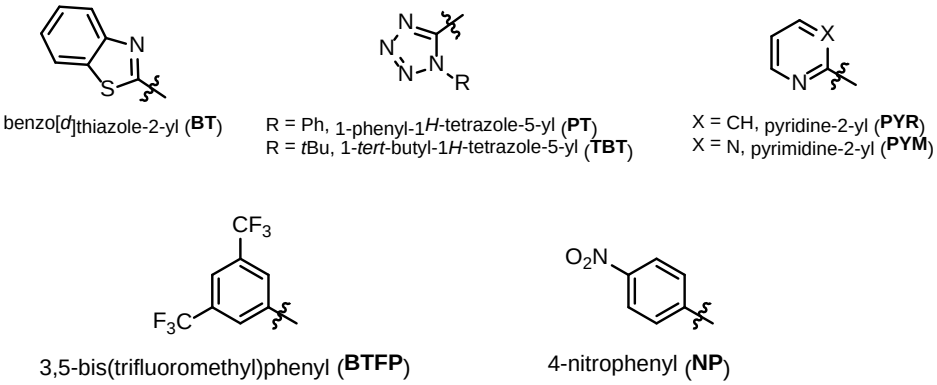
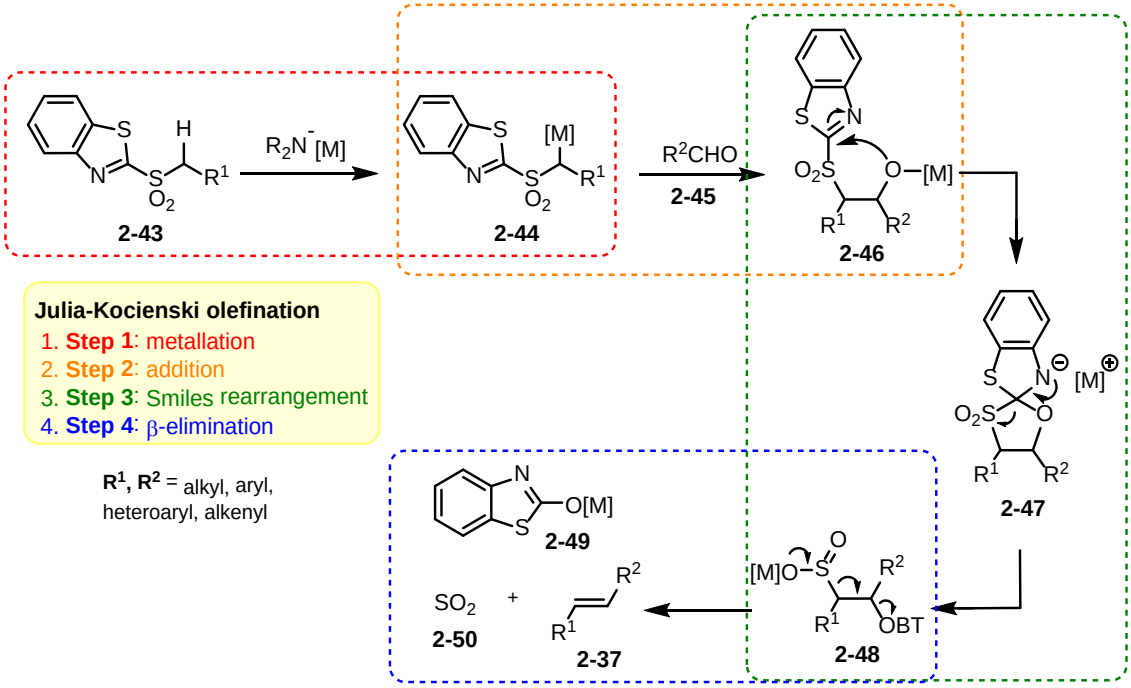


Figure 3. Most commonly used activators in the Julia-Kocienski olefination.



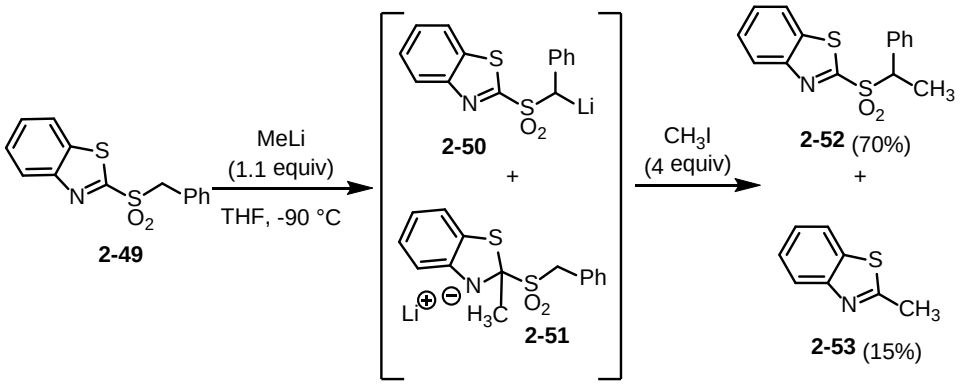
Scheme 9. Julia-Kocienski olefination employing a benzothiazole-2-yl (BT) sulfone – step by step

The operational simplicity of the Julia-Kocienski protocol coupled with the facility offers to fine-tune the stereochemical outcome of the reaction on the basis of substrate selection and reaction conditions. Along with its broad functional group tolerance, the method has contributed to a fast and widespread acceptance of this one-pot protocol as a generally applicable tool for advanced fragment linkage.

- **Factors influencing the reactivity and selectivity**

A) Choice of the base

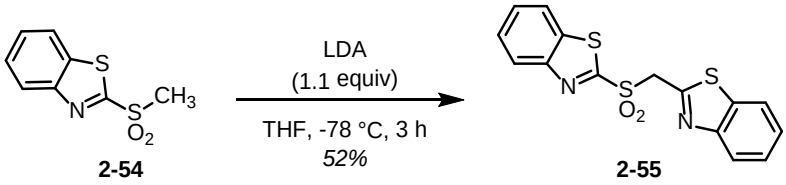
The aryl sulfones used in the Julia-Kocienski olefination reaction are by design electrophilic at the carbon-bearing the sulfonyl group. As a consequence, non-nucleophilic bases as LDA or the family of hexamethyldisilazanes (LiHMDS, NaHMDS and KHMDS) must be generally employed to perform α-metallation of sulfones.[43a] Use of nucleophilic bases as e.g. MeLi can yield side-reactions involving *ipso*-substitution of a sulfonate nucleofuge, as indicated by the formation of a significant quantity of 2-methyl benzothiazole **2-53** during the attempted alkylation of BT sulfone **2-49** (Scheme 10).



Scheme 10. Use of nucleophilic base, MeLi, to deprotonate sulfones bearing electron-acceptor activating group.

B) Amphibility of α-metallated sulfones

Even if the correct base is selected (non-nucleophilic), side reactions caused by premature *ipso*-susbstitution of sulfinate may still be encountered. The reason for this is the amphibility of the generated sulfone metallates which are capable of a pair-wise self-condensation reaction.[43a] The susceptibility of activated aryl sulfones towards the self-condensation depends on the type of aromatic activator (the list of most commonly used ones are shown in Figure 3) and on the steric factors around the α-metallated anion on the alkyl chain. Sterically encumbered α-metallated BT-sulfones are particularly susceptible to self-condensation (Scheme 11).[43a]



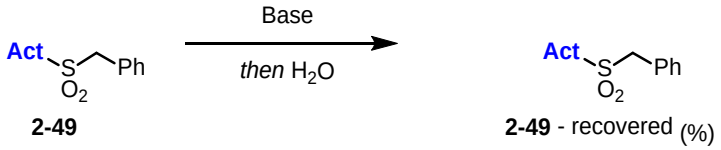
Scheme 11. Non-nucleophilic base-promoted self-condensation of BT-sulfone **2-54**.

Based on the literature results it was postulated that PT activating group are less susceptible in comparison with the BT-group to self-condensation.[44] However a recent stability study of Nájeda and co-workers revealed that the BT-activating group is actually more resistant than the PT group in the case of sulfone anions stabilized by an adjacent α,β-unsaturated group or 'shielded' by a sterically encumbered branched alkyl chain.[48]

Other less activated aryl groups such as TBT, BTFP[46] or PYR[43] are in general less prone to self-condensation when compared to commonly used BT and PT groups. On the other hand, the use of these groups is less explored due to their lower stereoselectivity during the olefination reactions.

The self-condensation reaction might be overcome by employing a Barbier-type addition protocol – the α-metallation of the sulfone is carried in the presence of the carbonyl compound. In this manner, the α-metallated sulfone reacts immediately *in situ* with the carbonyl, minimizing the opportunity for self-condensation reaction to occur. The same approach might be used if base-related destruction or enolization of aldehyde/ketone is feared. Based on the numerous literature experiments that were carried out over past 25 years, it is recommended to test the pre-metalation protocol first and then to employ the Barbier one only if self-condensation/carbonyl compound destruction/inactivation occurs.

Table 2: Evaluation of the activating group stability in basic conditions.



2-49 **2-49** - recovered (%)

Conditions: Activating group (Act)	LDA, THF, -78 °C, 24 h	KHMDS, DME, -60 °C, 24 h	P4-*t*-Bu, THF, -78 °C, 24 h	KOH, Bu_4NBr, THF, r.t., 24 h
BT	>95 %	84 %	73 %	5 %
PT	>95 %	50 %	64 %	0 %
TBT	>95 %	99 %	78 %	0 %
BTFP	>95 %	75 %	88 %	32 %

C) Influence of the structure on the reaction selectivity

The Julia-Kocienski olefination method is particularly suitable for the highly stereoselective synthesis of 1,2-disubstituted olefins. The same mechanistical principles, that are applicable in the case of 1,2-disubstituted olefins synthesis might be applied in the case of tri- and tetra-substituted olefins. However, in this case the stereoselectivity of the transformation is highly compromised.[49] To discuss the stereochemical outcome of the olefination, the discussion must be divided into two parts – first where the sulfone anion is not stabilized (part a), and the second where it is (part b).

a. Unstabilized sulfone anion

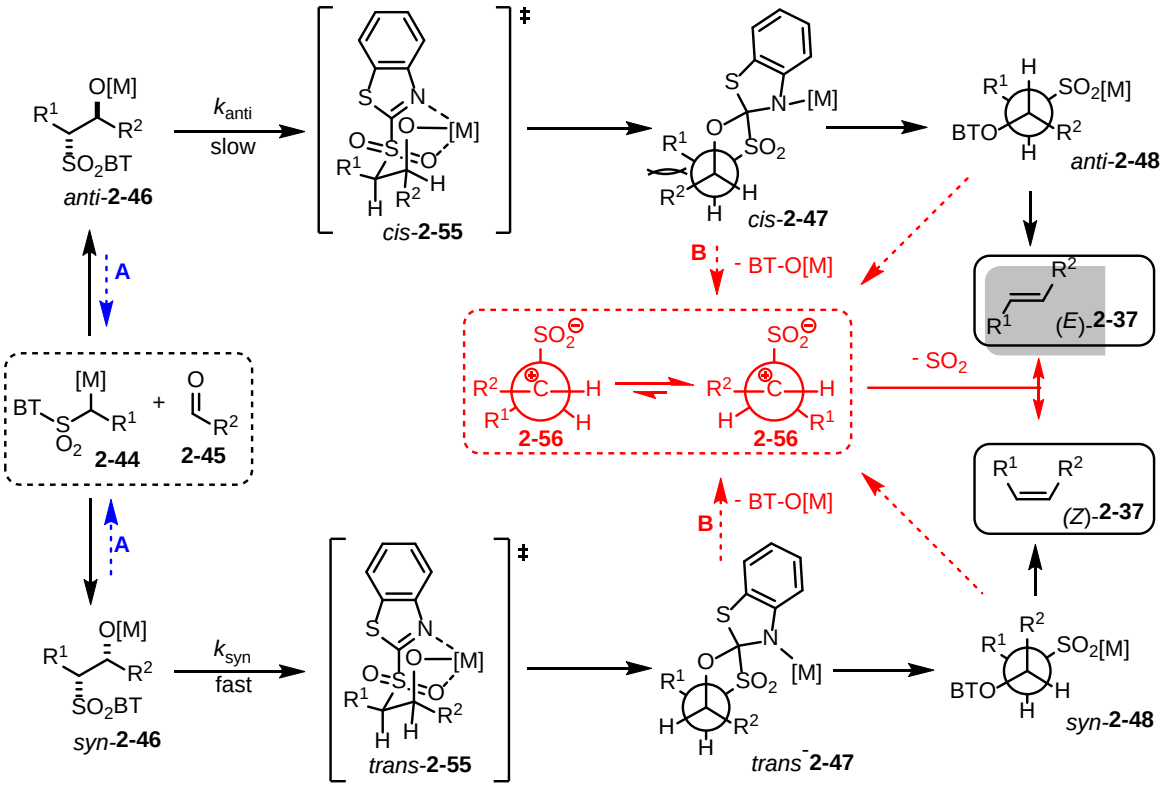
In the case of the unstabilized sulfone anions, the stereochemical outcome of the reaction is determined by kinetic diastereoselectivity of the addition step (Scheme 12). The evidence of this statement was independently confirmed for the following activating groups – BT,[50] PT,[50] and PYR.[41a] The mechanistic investigation presented in above mentioned studies suggested that the *syn* and *anti*-**2-46** adducts undergo irreversible Smiles rearrangement *via* intermediates *cis*-**2-47** and *trans*-**2-47**. β-elimination of *syn*- and *anti*-**2-48**, where electrofuge (SO_2) and nucleofuge (BT-O^-) adopts an antiperiplanar arrangement yields the desired (*E*) or (*Z*)-olefin **2-37**.

As pointed out above, the overall stereoselectivity of the olefin formation is governed by the first step – addition of the α-metallated sulfone to the carbonyl compound. The addition process can proceed *via* two different transition states – open (**TS-1**) and closed (**TS-2**) (Figure 4).

When (*E*)-olefin formation is desired (which is generally the case), the reaction conditions that favor the open transition state (**TS-1)** during the addition step should be employed. In short, polar aprotic solvents that stabilize the dipole moment generated during the addition step and large cations that diminish the possibility of the chelating closed transition state should be utilized.

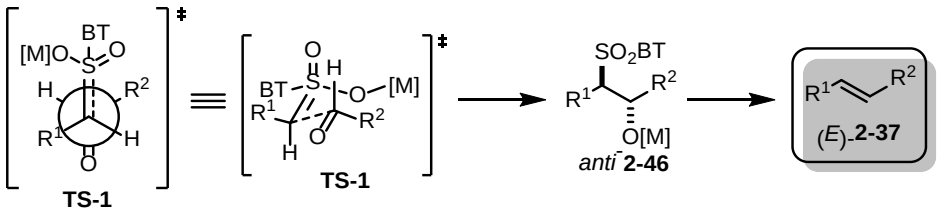
To favor (*Z*)-olefin formation, the closed transition state (**TS-2)** should be aimed for during the addition step. To do so, rather nonpolar aprotic solvents and small chelating cations should be used. In general, small cations as Li^+ and Na^+, and toluene as a solvent would yield (*Z*)-olefin preferentially when employed in a reaction.

An example that would demonstrate the influence of the cation and the solvent on the stereoselectivity of the Julia-Kocienski olefination is showed in Table 3.[51]



Scheme 12. A mechanistic proposal for the origin of stereoselectivity in the Julia-Kocienski olefination illustrated for a BT sulfone. $k_{syn}>k_{anti}$; Path **A** valid for R^1 unsaturated; Path **B** valid for R^2 unsaturated – tentative proposition.

Open transition state: polar solvents, large cations; yields (*E*)-olefin



Closed transition state: nonpolar solvents, small cations; yields (*Z*)-olefin

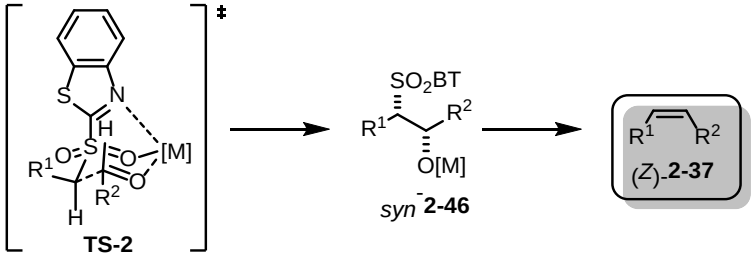
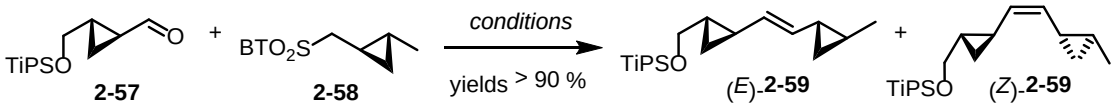


Figure 4. Transition states of the addition step in the Julia-Kocienski olefination.

Table 3: The influence of the reaction conditions on the reaction selectivity.

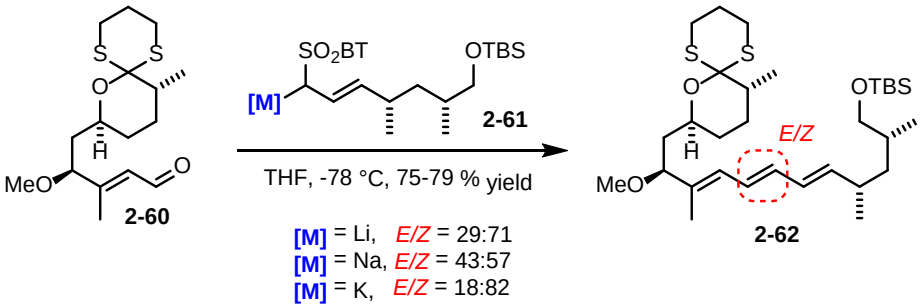


Reaction conditions	*E/Z* ratio of 2-59
NaHMDS, DMF, -60 °C	78:22
NaHMDS, DME, -60 °C	71:29
KHMDS, THF, -78 °C	55:45
KHMDS, toluene, -78 °C	21:79
NaHMDS, Et_2O, -78 °C	11:89
NaHMDS, toluene, -78 °C	9:91

b. Stabilized sulfone anion

When the sulfone anion is stabilized (R^1 = allyl, aryl,…), the initial addition step is reversible allowing to establish the equilibrium between *syn*-**2-46** and *anti*-**2-46** adducts (Scheme 12, path **A**). As a consequence, the reaction rate of the Smiles rearrangement (k_{syn} vs. k_{anti}) determines the stereochemical outcome of the olefination process. One should keep in mind that the subsequent β-elimination is irreversible. The rearrangement of the *anti*-**2-46** adduct is considerably slower than that of the *syn*-**2-46** due to the severe eclipsing interactions encountered during the formation of the spiro *cis*-**2-55** intermediate. As a consequence, the formation of the (*Z*)-olefin becomes favoured.[52]

Thus, if the rate of equilibrium between *anti*-**2-46** and *syn*-**2-46** is significantly faster than the Smiles rearrangement, a preference for the formation of (*Z*)-**2-37** olefin is anticipated on the basis of the Curtiss-Hammett principle. The possibility of the retroaddition of β-alkoxysulfones **2-46** where R^1 = Ph has been verified and proven *via* crossover experiments.[41a]



Scheme 13. The influence of the counter cation on the stereoselectivity of the reaction when using a stabilized sulfonyl anion.

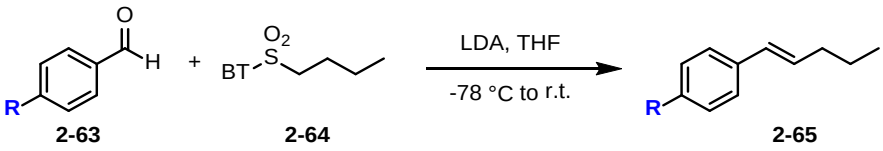
D) α,β-unsaturated carbonyl compounds

In the case of α,β-unsaturated aldehydes and non-conjugated sulfone metallates, an E_1-type elimination pathway involving a putative zwitterionic species was proposed by Julia to explain high (*E*)-selectivity of such olefination reactions (Scheme 12, path **B**).[43a] Based on this assumption, direct loss of an aryloxide anion from spirocycle **2-47**, or similar event from intermediate **2-48** that follows the Smiles rearrangement, produces zwitterion **2-56**. Zwitterion **2-56** should then experience conformational relaxation prior to release of SO_2. As a consequence, preferential formation of the (*E*)-olefin **2-37** should occur. For this suggested pathway to be completely viable, R^2 must be an unsaturated and electron donating functionality to offer conjugative stabilization to the carbocation center of **2-56**. Taking in account

comparatively low nucleofugacity of aryloxide anion, this hypothesis is rather suspicious; however, it does account for the observed increase in *E/Z* ratio for the Julia-Kocienski reaction of benzaldehyde **2-63** as the aromatic ring becomes more electron rich (Table 4).[43a]

It should be noted that we believe to have better explanation of this phenomena – see next chapter or ref [53].

Table 4: The influence of the *para*-aromatic aldehyde substitution on the olefination stereoselectivity.



2-63 **2-64** **2-65**

Substitution (R) of aldehyde 2-63	*E/Z* ratio of adduct 2-65
OMe	99:1
H	94:6
Cl	77:23

2.2 Our contribution to the field of sulfur-based olefination methods

2.2.1 Sulfoxide version of Julia-Lythgoe olefination

Our contribution to the field of the Julia-Lythgoe olefination started as a consequence of severe obstacles we have encountered during the synthesis of ambruticin VS (**2-66**) and jerangolid D (**2-67**) (Figure 5).[54] The main interest of this chapter is focused on the stereoselective preparation of the trisubstituted olefinic bond C16-C17 (in **2-66**) and C9-C10 (in **2-67**), respectively. Since both structural motives are very similar and the synthetic approach to them was quite the same, the story that led us to develop sulfoxide-Julia-Lythgoe olefination method will be told using the jerangolid D structure as a witness of our efforts.

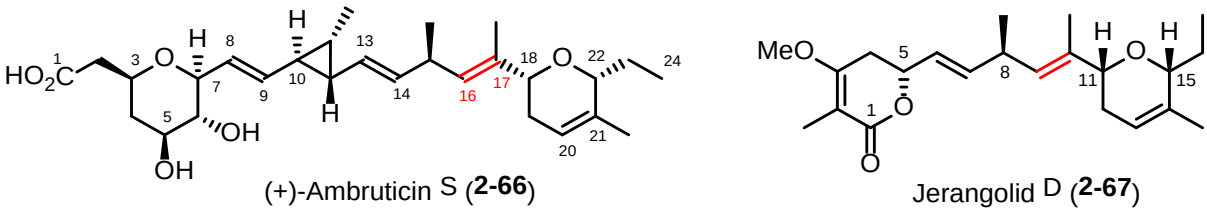
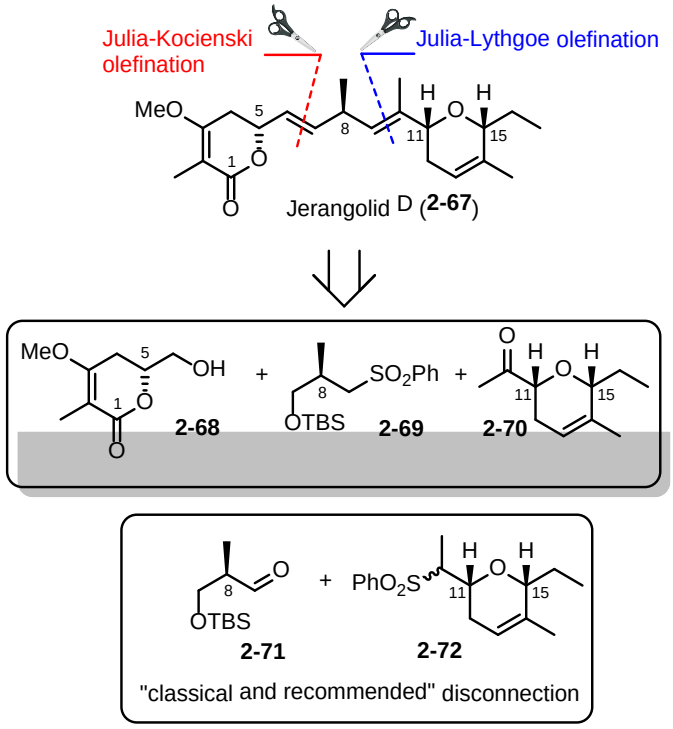


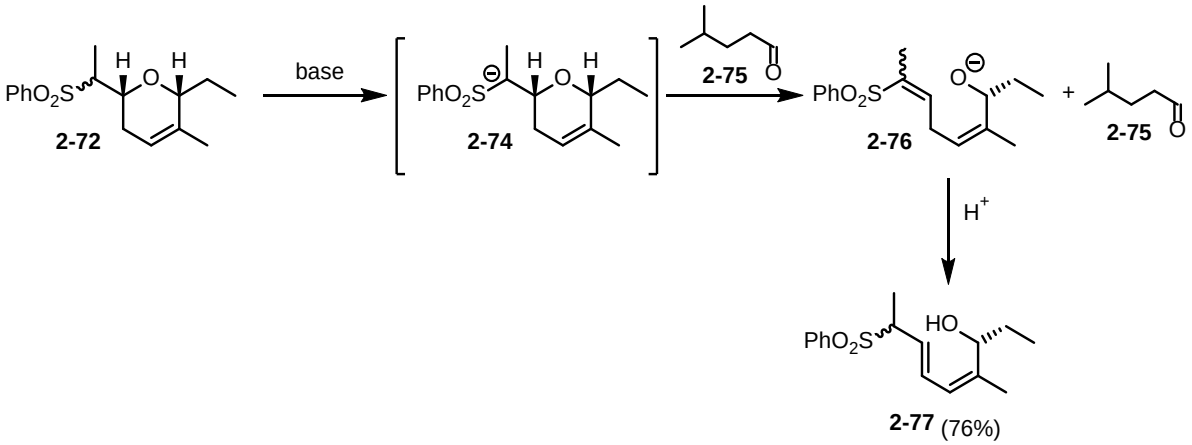
Figure 5: Structure of ambruticin S (**2-66**) and jerangolid D (**2-67**).

During the retrosynthesis, jerangolid D (**2-67**) was disconnected into three fragments along the olefinic bonds C6-C7 and C9-C10, to provide the right-hand (**2-68**), central (**2-69**) and left-hand (**2-70**) fragments (Scheme 14). Both olefinic bonds should have been reconnected with help of Julia-type olefination methods, C6-C7 using Julia-Kocienski olefination and C9-C10 via Julia-Lythgoe olefination reaction. Unfortunately, the olefin-bond in-between the central fragment **2-69** and right-hand fragment **2-70** is trisubstituted. The standard disconnection approach would in this case suggest to reunite aldehyde **2-71** with sulfone **2-72** to avoid the possible problems related to the reaction of α-metallated sulfone **2-73** generated from **2-69** with sterically encumbered ketone **2-70**.

In reality, we knew that this more obvious retrosynthetic approach would not work, because the reaction of sulfonyl anion **2-74** generated form **2-72** with model aldehyde **2-75** under various reaction conditions was evaluated (Scheme 15). Unfortunately in all cases rapid intramolecular elimination reaction yielding opened diene **2-77** occurred.



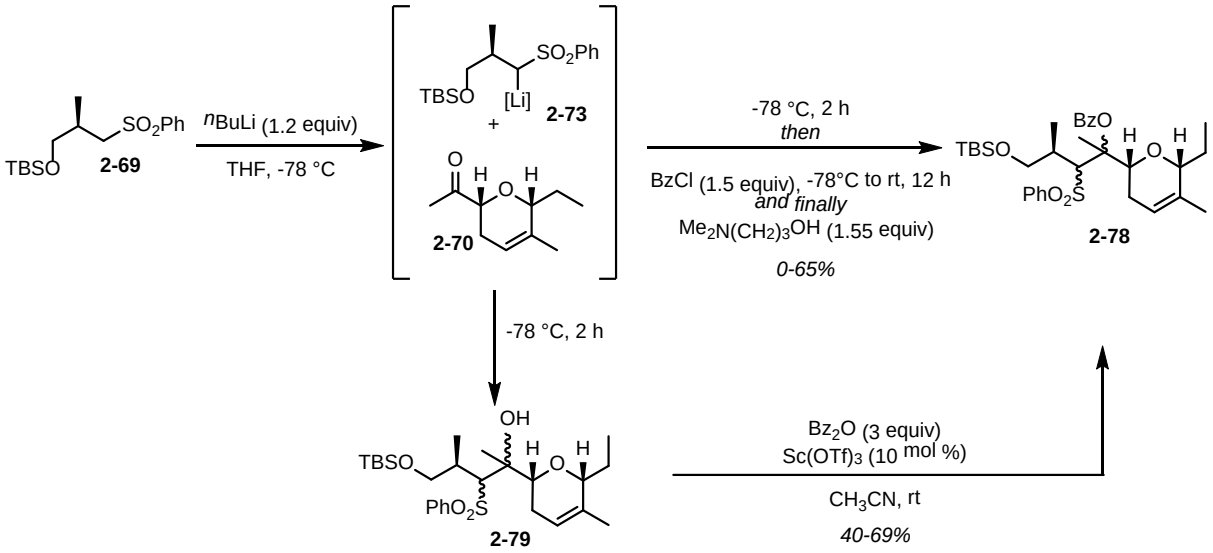
Scheme 14: Retrosynthetic disconnection of the jerangolid D.



Scheme 15: Side reaction of sulfone **2-72** when Julia-Lythgoe olefination coupling was attempted on model substrate.

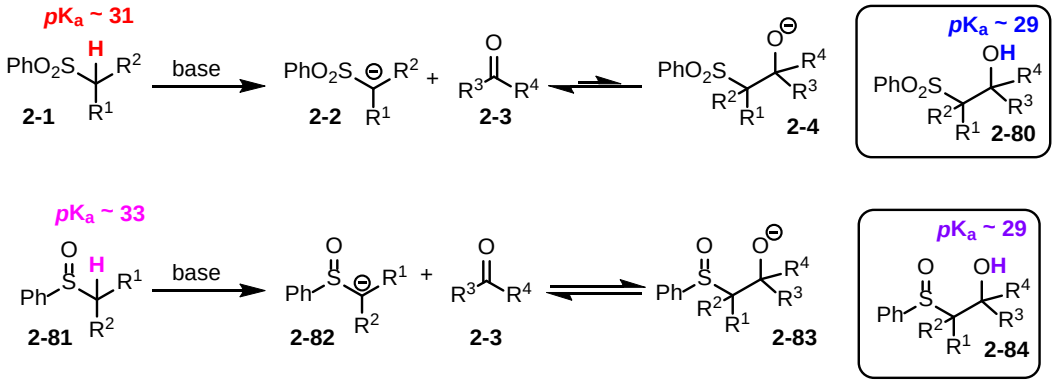
Thus the opposite approach based on the reaction of sulfonyl anion **2-73** generated from **2-69** with ketone **2-70** was evaluated. Unfortunately, the desired adduct **2-78** was formed only in moderate yield (Scheme 16). More importantly, the reaction proved to be very capricious and irreproducible. After tedious optimization, we were able to get the desired product in acceptable yields, but the procedure was laborious and not very practical.

The difficulties encountered during this synthetic approach were attributed mainly to the low tertiary alcoholate stability along with the low steric accessibility of such alcoholate towards the external electrophile. To avoid such problems in the future, we decided to develop a novel modification of the Julia-Lythgoe olefination that would be able to overcome problems linked to the adduct formation.



Scheme 16: Coupling step between sulfone **2-69** and ketone **2-70**. On route to a reproducible synthetic transformation.

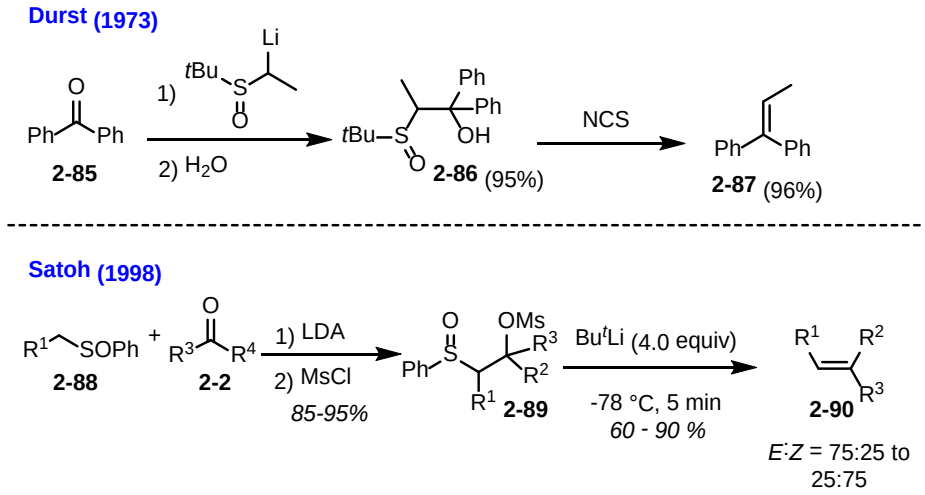
Our idea how to overcome such type of troubles was based on the shift of the reaction equilibria between starting materials **2-2** and **2-3** and tertiary alcoholate adduct **2-4**. After careful evaluation of several possible approaches, we decided to employ aryl alkyl sulfoxides instead of corresponding sulfones as reacting partners in the addition sequence (Scheme 17). We reasoned that α-hydrogen atom in sulfoxide **2-81** (**pK$_a$** value in DMSO **~33**) is less acidic when compared to the corresponding sulfone **2-1** (**pK$_a$** value in DMSO **~31**), but still sufficiently acidic to be removed quantitatively with common bases (LDA or *n*BuLi). Thus, four orders of magnitude makes a big difference when the pK$_a$ value is compared to the pK$_a$ of the newly formed alcoholate **2-4** or **2-83**, respectively to their conjugated acids **2-80** and **2-84** (**pK$_a$** value in DMSO **~29**). This comparison suggests that at least from a thermodynamic point of view (equilibrium values), the formation of the adduct **2-84** should be preferred when the sulfoxide anion **2-82** is reacted with the carbonyl **2-3**, than when the corresponding sulfonyl anion **2-2** is used. Thus we shall expect a higher reaction yield of the desired adduct.



Scheme 17: Addition of sulfone anion vs. sulfoxide anion to carbonyl function – a comparison.

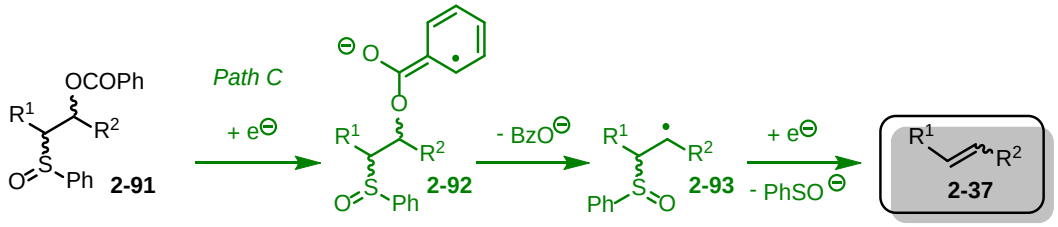
A brief literature search revealed that there are two previous contributions in the literature describing Julia-Lythgoe olefination reaction with sulfoxides. The first of which was published back in 1973 by Durst[55] and co-workers while the second was published 25 years later by Satoh[56] and co-workers. In both cases, the LDA promoted coupling step proceeded well and also the reductive-elimination of the generated adducts yielded the desired olefins (1,2-disubstituted and even trisubstituted) in good yields and (*E/Z*) selectivity (Scheme 18). Unfortunately, neither of the two sequences were applicable to our

substrates due to reductive-elimination conditions used – *N*-chlorosuccinimide and excess of *tert*-butyl lithium, respectively. Thus, an alternative procedure to the already developed reductive elimination protocols was required. At this stage we speculated that if we explore the previously proposed reductive-elimination mechanism developed in the context of β-benzoyloxysulfones (Scheme 8, **path C** – *however no direct evidence supporting this mechanistic proposal has been established so far*) and apply it to β-benzoyloxysulfoxides, we might accomplish the reductive elimination step under milder reaction conditions.



Scheme 18: Literature examples of Julia-Lythgoe olefination reaction exploring the use of sulfoxides instead of sulfones.

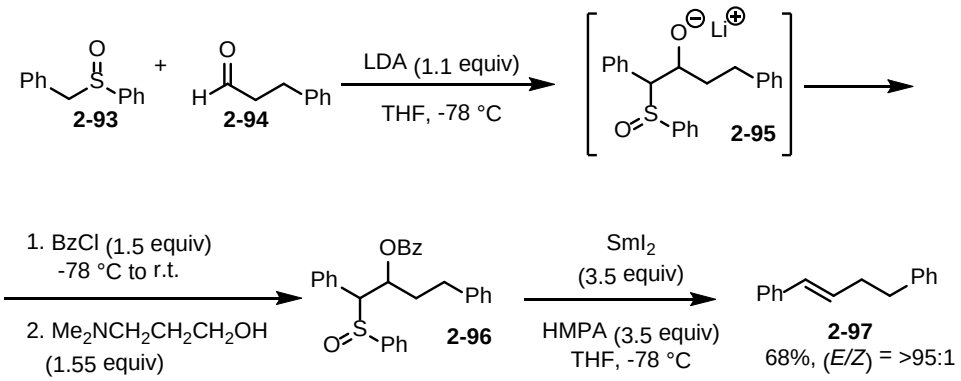
It would mean that the β-benzoylsulfoxide adduct **2-91** would undergo reductive elimination as shown in Scheme 19. It was assumed that the reducing power of SmI_2/HMPA system used in the case of the β-benzoyloxysulfones (**2-31**, R = Bz) should be sufficient for the β-benzoyloxysulfoxides (**2-91**), since in the first step electron transfer to the benzoyl functionality takes place. The only question was if the phenylsulfanolate anion would be a sufficiently good leaving group to yield the desired olefin in the final stage of the process.



Scheme 19: Mechanistical proposal of the β-benzyloxysulfoxide reductive-elimination step in Julia-Lythgoe olefination sequence.

To test our hypothesis the reaction of sulfoxide **2-93** and aldehyde **2-94** was evaluated (Scheme 20).[57] It was found that LDA (1.1 equiv) promoted addition step terminated with a BzCl quench yields the desired adduct **2-96** in high yields. Unfortunately, but not surprisingly, the adduct **2-96** is yielded as a mixture of four diastereoisomers (one center of chirality on sulfur and two on carbon atoms) which makes possible purification of the adducts difficult and impractical. Thus we decided to test the reductive elimination step directly on the crude adduct **2-96**. To our great pleasure, the reductive elimination step proceeded well with 3.5 equiv of both SmI_2 and HMPA, respectively, required to accomplish the desired transformation. In theory, only 2.0 equivalents (two electrons) of SmI_2 and

HMPA are needed, however, it was observed that 3.5 equivalent of each are necessary for reaction reproducibility. We speculated that it is due to impurities presented in the crude adduct **2-96**.

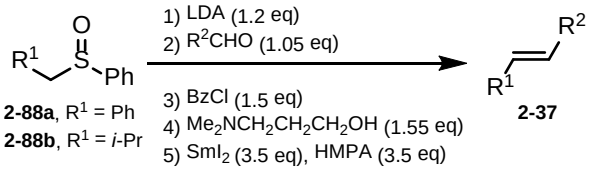


Scheme 20: Optimized reaction sequence of sulfoxide-modified Julia-Lythgoe olefination reaction.

Having optimized reaction conditions in hand, the scope and limitations of the method were established (Table 5).[57] In the case of 1,2-disubstituted olefins very good yields (60-70 % over the whole sequence) and excellent stereoselectivity (>90:<10) were generally obtained. In the case of trisubstituted olefins, the yields remained constantly high (50-60 % over the whole sequence) but the selectivity dropped to (*E/Z*) ~75:25. Interestingly, even tetrasubstituted olefins could be prepared using our sulfoxide-modified Julia-Lythgoe olefination method, although in low yields (~30 %) but high stereoselectivity (~90:10).

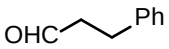
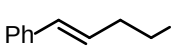
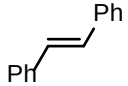
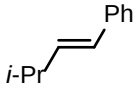
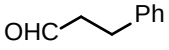
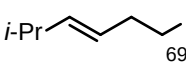
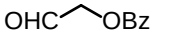
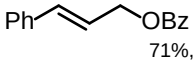
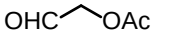
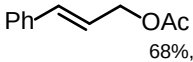
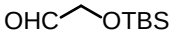
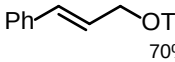
To shed some light on the reaction mechanism, a set of stereodefined isomers of β-benzyloxysulfoxides substituted either with phenyl-phenyl groups (**2-101**) or alkyl-dialkyl groups (**2-102**) were prepared and submitted to the reductive-elimination conditions. Stereochemical outcome of the experiments (in the range of experimental error) confirmed that the stereochemistry of the newly formed olefin is independent on the stereochemistry of the β-benzoyloxysulfoxide adducts **2-101** and **2-102**. This observation strongly suggest that the SmI_2/HMPA mediated reductive elimination follows mechanistically the **pathway C** as proposed in Scheme 19.

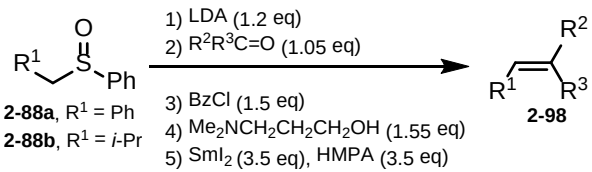
Table 5: Scope and limitations of the sulfoxide-modified Julia-Lythgoe olefination reaction



2-88a, R^1 = Ph
2-88b, R^1 = *i*-Pr

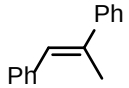
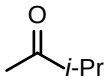
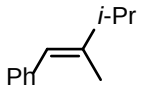
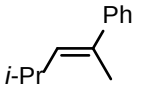
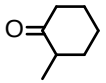
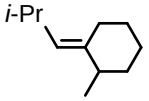
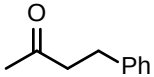
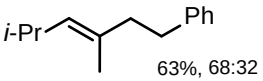
2-37

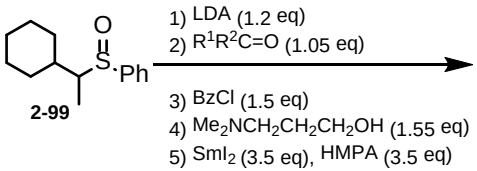
entry	**2-88**	R^2CHO	product	yield[a] (%) *E* / *Z*[b]
1	**a**			67%, >95:1
2	**a**			75% >95:1
3	**b**			70% 76:24
4	**b**			69%, 94:6
5	**a**			71%, >95:1
6	**a**			68%, >95:1
7	**a**			70%, >95:1



2-88a, R^1 = Ph
2-88b, R^1 = *i*-Pr

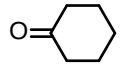
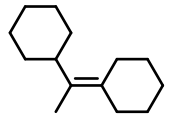
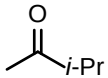
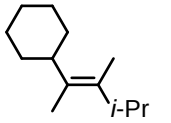
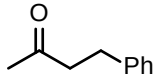
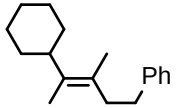
2-98

entry	**2-88**	$R^2R^3C=O$	product	yield[a] (%) *E* / *Z*[b]
8	**a**			51% 76:24
9	**a**			57% 91:9
10	**b**			64% 74:26
11	**b**			64% 88:12
12	**b**			63%, 68:32

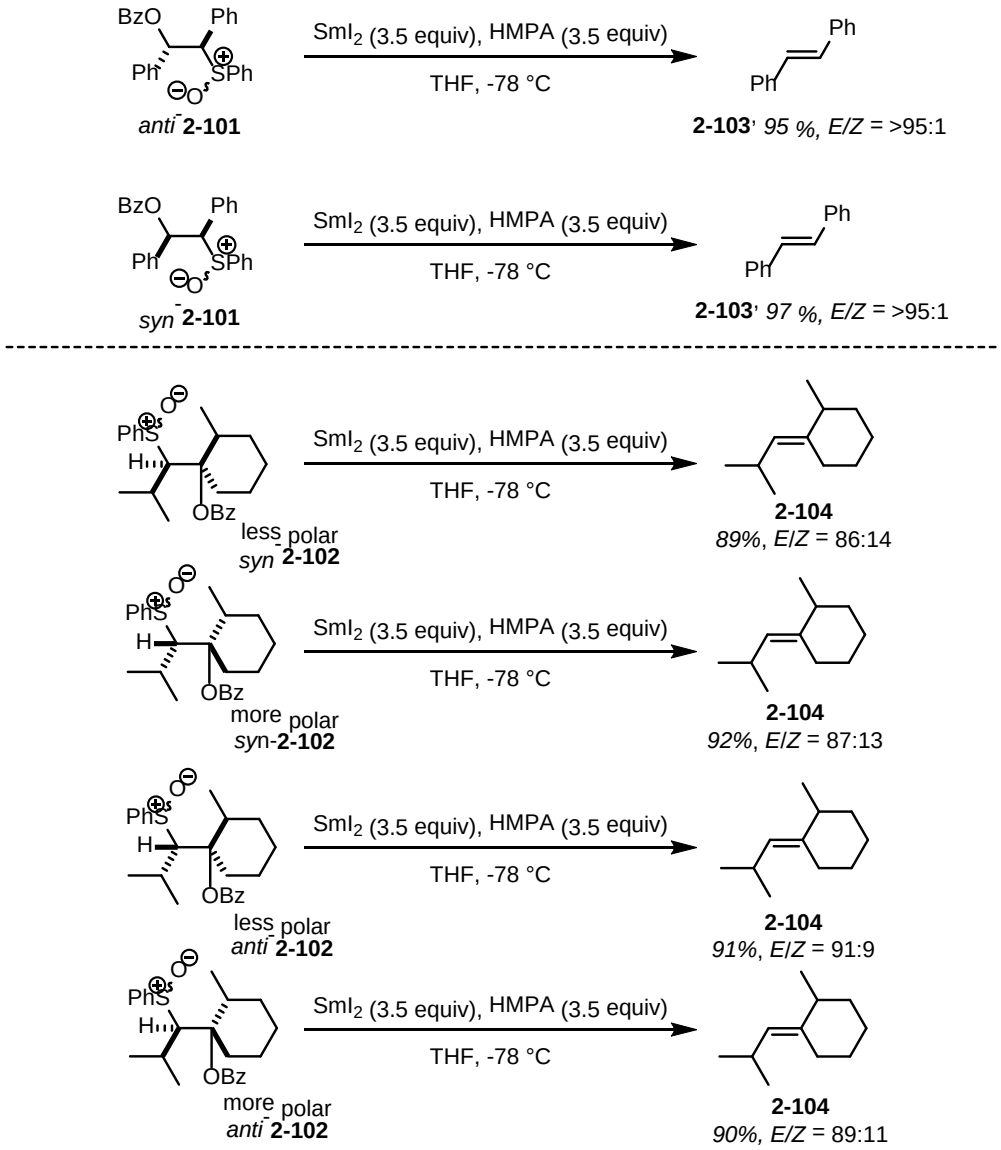


2-99

2-100

entry	$R^2R^3C=O$	product	yield[a] (%) *E* / *Z*[b]
13			33%
14			29% 97:3
15			32% 91:9

[a] Overall yields refer to pure, isolated products
[b] Determined by ^{1}H-NMR spectroscopy



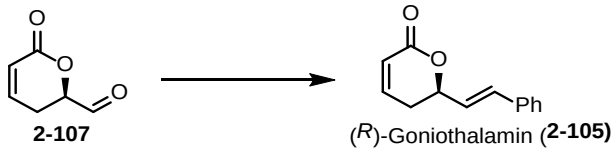
Scheme 21: Mechanistical investigation of the sulfoxide-modified Julia-Lythgoe olefination.

2.2.2 Sulfoxide-modified Julia-Lythgoe olefination reaction – applications in natural product synthesis

Having developed a new modification of the Julia-Lythgoe olefination reaction, we decided to demonstrate its utility and applicability in the field of natural product synthesis. Naturally, we have focused on the targets where the 'classical' Julia-Lythgoe olefination had failed to furnish the desired product, the yield was low, or the stereochemical outcome was lousy.

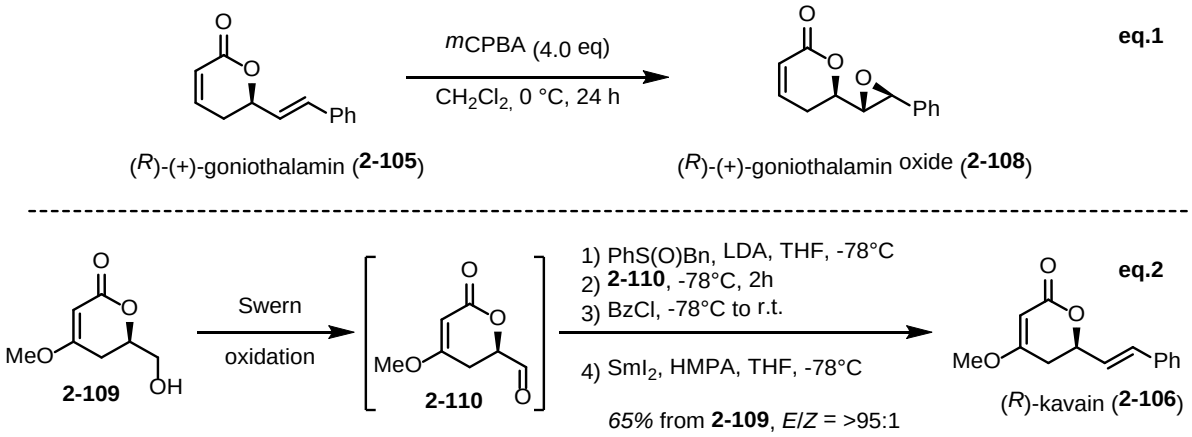
Our first targets were (*R*)-goniothalamin[58] (**2-105**), potential anticancer agent,[59] and (*R*)-kavain[60] (**2-106**), member of kava-lactone family known for their psychoactive properties[61]. In the case of goniothalamin **2-105**, various olefination methods were explored to install selectively (*E*)-olefinic functionality (Table 6). However, the employed methods either yielded undesired (*Z*)-olefin (entries 1 and 2) or yielded the desired product in very low yield (entry 3). The 'classical' Julia-Lythgoe olefination protocol itself failed to deliver the desired product (entry 4). Fortunately, the sulfoxide modification of Julia-Lythgoe olefination yielded the product **2-105** in 78% yield and excellent >98:1 (*E/Z*) selectivity.

Table 6: Various olefination methods in the context of the synthesis of goniothalamine.



Entry	Olefination method	Conditions	Yield (%)	*E/Z* ratio
1[62]	Wittig	$BnPPh_3^+Cl^-$, *n*BuLi, THF, -78 °C to RT	53	1:3
2[63]	Wittig	$BnPPh_3^+Br^-$, *n*BuLi, DME, -60 °C to RT	57	1:9
3[62]	Julia-Kocienski	$PTSO_2Bn$, KHMDS, THF, -78 °C to RT	18	>98:1
4	Julia-Lythgoe	$BnSO_2Ph$, *n*BuLi, THF, -78 °C to RT	<5	n.d.
5	Sulfoxide-modified Julia-Lythgoe	BnSOPh, LDA, THF, -78 °C to RT	78	>98:1

High yielding and stereoselective access to (*R*)-goniothalamin (**2-105**) allowed us to target the synthesis of some of its derivatives such as (*R*)-goniothalamin oxide (**2-108**) (Scheme 22, eq. 1). Similarly, the power of the sulfoxide-modified Julia-Lythgoe olefination was applied to the synthesis of (*R*)-kavain (**2-106**) (Scheme 22, eq. 2). The targeted natural product was prepared in 65% yield and >98:1 (*E/Z*)-selectivity.

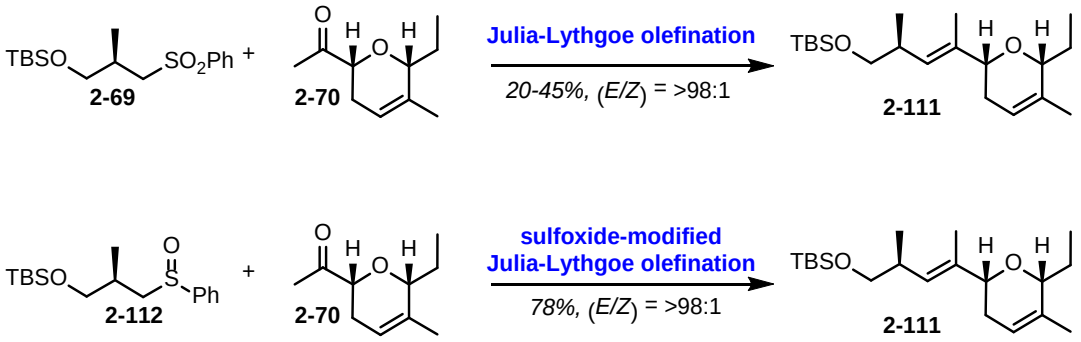


Scheme 22: Synthesis of (*R*)-goniothalamin (**2-108**) and (*R*)-kavain (**2-106**).

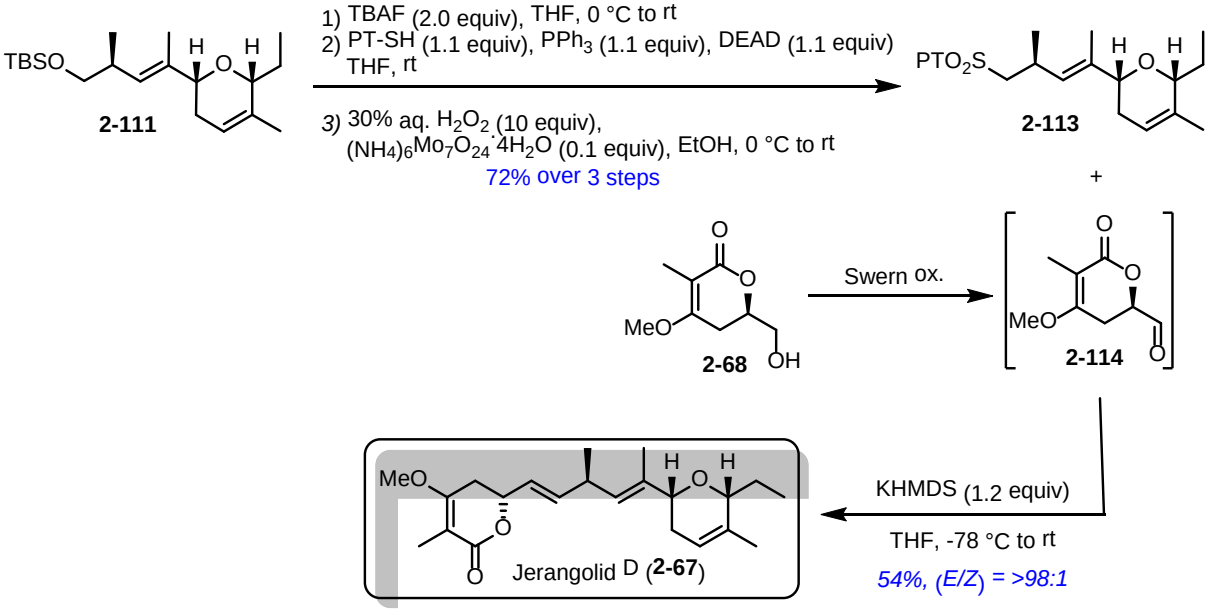
Having successfully applied our methodology to small natural products, we turned our attention back to the synthesis of jerangolid D (**2-67**). Having all three fragments in hand in a very short and elegant way (for details see[54]), the reunion *via* sulfoxide-modified Julia-Lythgoe olefination was carried out (Scheme 23). As expected, the reaction proceeded well and the desired trisubstituted olefin **2-111** was formed in 78% yield and >98:1 (*E/Z*)-selectivity. Indeed, we reached a significant progress in terms of the reaction yield when the result is compared with the originally employed Julia-Lythgoe olefination protocol.

TBS-protected alcohol in **2-111** was then transformed into the PT-sulfone **2-113** via TBS-removal/Mitsunobu substitution/oxidation sequence (3 steps, 72% overall yield). The final step of the synthesis, connecting the left-hand fragment **2-68** with sulfone **2-113** *via* Julia-Kocienski olefination protocol then yielded the jerangolid D (Scheme 24). Overall, jerangolid D was prepared in 22 steps (12

steps in longest linear sequence) and 6.1% overall yield (14.5% in longest linear sequence) starting from the commercially available starting materials.[54]



Scheme 23: Connecting the right-hand and central fragments of jerangolid D.

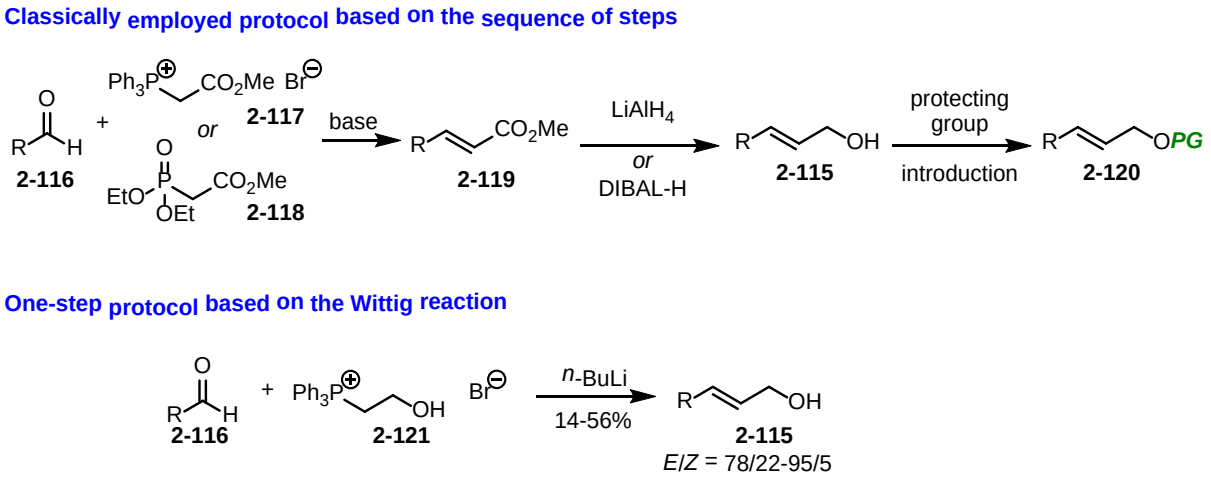


Scheme 24: Final steps of the jerangolid D (**2-67**) total synthesis.

2.2.3 Entering the world of the Julia-Kocienski olefination

Having developed the new modification of classical Julia-Lythgoe olefination reaction, we have focused our attention to the field of Julia-Kocienski olefination reaction. Our adventure started with the development of new types of reagents suitable for the selective transformation of aldehydes to compounds containing TBS-protected allylic functionality. The trigger for this project was the situation where we had several ongoing synthetic projects in Markó's group that needed to selectively install allylic function into the molecules. The classical way to accomplish such a transformation was the two step protocol consisting of Wittig or Horner-Wadsworth-Emmons olefination/DIBAL-H reduction sequence (Scheme 25). In general, the resulting allylic alcohol **2-115** also had to be additionally protected, since the protecting-group bearing allylic alcohol was required.

In my opinion, the sequence was rather long. Too long. A brief look of the literature revealed that the shortest published sequence to allylic alcohols (**2-115**) starting from the aldehyde (**2-116**) consisted of addition of a rather exotic Wittig reagent **2-121** (Scheme 25).[64] What unfortunately hampered the use of this reagent in organic synthesis was the low reaction yields (14-56%) whilst the reported (*E/Z*)-selectivity was good to excellent (78:22 to 95:5).



Scheme 25: Installation of the allylic group/O-protected allylic group – classical vs. a one step approach.

As the answer to this challenge we designed the sulfone reagent **2-122** (Figure 6). It was reasoned that TBS-O-protected β-hydroxy group would be sufficiently robust to resist (**a**) base mediated deprotection and (**b**) competitive β-elimination process. Indeed, if the TBS protecting group would be removed under the reaction conditions (**a**), a Julia-Kocienski-like reaction would occur and ethylene **2-125** would be generated *in situ*. Fortunately, it is known from the literature that TBS O-protected alcohols are stable under the basic conditions.[65] Similarly, if an antiperiplanar arrangement of α-sulfonyl anion and TBS-oxy group occurred, a β-elimination process might take place (**b**). Such a situation is known from the literature, where several PT or BT sulfones substituted with β-acyloxy or β-alkoxy groups underwent intramolecular β-elimination to yield the corresponding vinyl sulfones[66] rather than the desired addition to the carbonyl functionality.

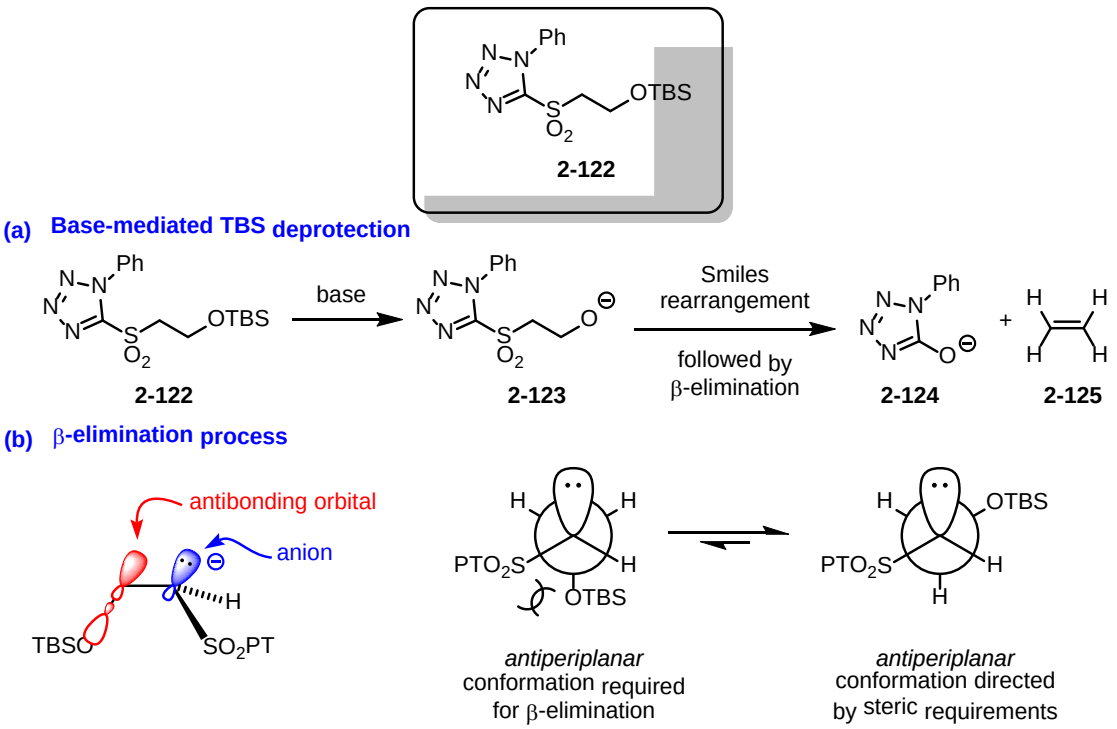
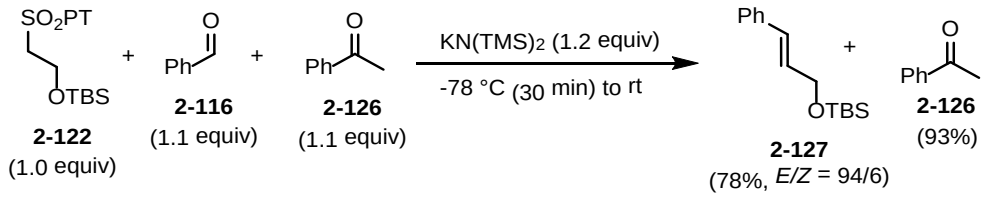


Figure 6. Possible degradation pathways of TBS-sulfone reagent **2-122** that should be avoided.

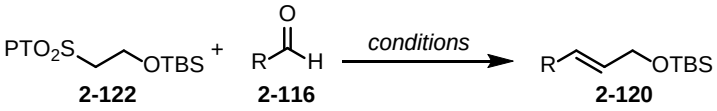
Luckily neither of these "worse-case scenarios" occurred and under the Barbier conditions our sulfone **2-122** reagent reacted with aldehydes **2-116** and furnished the desired TBS-protected allylic alcohols

2-120 in good yields and (*E*)-selectivity (Table 7).[67] The scope and limitations of the reaction are very broad and virtually all aldehydes can be transformed into the targeted molecules. Additionally to this, it was demonstrated that ketones are unreactive under the reaction conditions. Moreover, the competitive experiments showed that the aldehyde functionality might be transformed into the O-TBS-allylic alcohol in the presence of ketone functionality (Scheme 26).

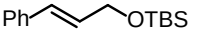
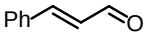
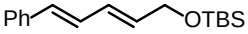
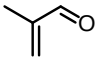
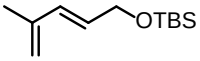
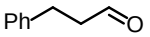
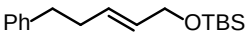
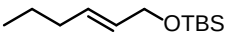
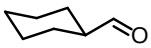
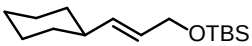
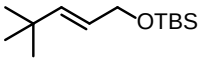
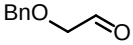
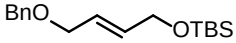
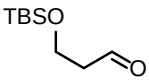
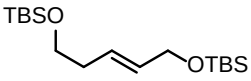
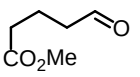
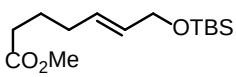


Scheme 26. Evaluation the reactivity of aldehydes and ketones towards **2-122** – Competitive experiments.

Table 7: Scope and the limitations of the O-TBS-allyl alcohol synthesis



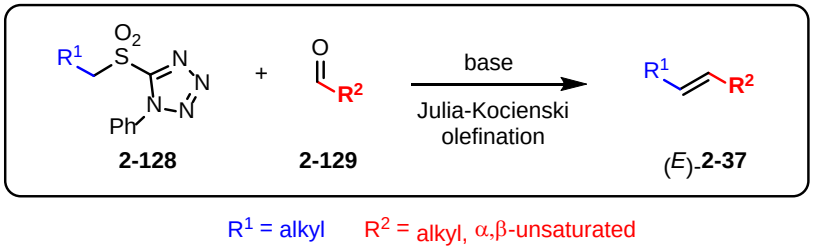
Conditions: sulfone (1.0 equiv), aldehyde (1.1 equiv), -78 °C, 5 min, *then* KN(TMS)2 (1.2 equiv), addition over 10 min via syringe pump, -78 °C (30 min) to rt

entry	aldehyde	solvent	product	yield[a] (*E*/*Z*)[b]
1		THF		83% (98/2)
2		DME		80% (>99/1)
3		THF		81% (97/3)
4		DME		69% (99/1)
5		THF		91% (96/4)
6		THF		88% (84/16)
7		DME		83% (91/9)
8		THF		89% (88/12)
9		THF		84% (93/7)
10		THF		87% (>99/1)
11		THF		91% (92/8)
12		THF		88% (98/2)
13		THF		89% (96/4)

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy. DME = dimethoxyether, TBS = *tert*-butyldimethylsilyl

2.2.4 Julia-Kocienski olefination – enhancing the (*E*)-selectivity

Our first real efforts to increase the stereoselectivity of the Julia-Kocienski reaction began with the reaction of unstabilized sulfonyl anions with carbonyl compounds (Scheme 27). As discussed previously (Scheme 12), it is known that the selectivity of such reactions depends on the addition step. In other words, the transition state (opened vs. closed, steric factors, role of solvent,…) directly influences the stereochemistry of the adduct (*syn* vs. *anti*) and thus the final stereochemistry of the olefin (*E* vs. *Z*) is due to irreversibility of this addition step. As demonstrated by Charette[51] and Jacobsen[68], the open transition state (*or closed*) can be favored if a polar solvent (*or less polar*) and large cations (*or small*) are used. However, even in such cases the selectivity is not always optimal and is hard to predict.



Scheme 27. Julia-Kocienski reaction – unstabilized sulfonyl anions.

Thus we decided to develop a new protocol that would be operationally simple and would yield the desired olefin in even better (*E*)-selectivity.[69] The solution to this challenge should bring an increase in the selectivity of the addition step. Thus, the **TS-1** should be preferred during the addition (formation of *anti*-adduct *anti*-**2-46**) over the second possible open-chain transition state **TS-3** (Figure 7).

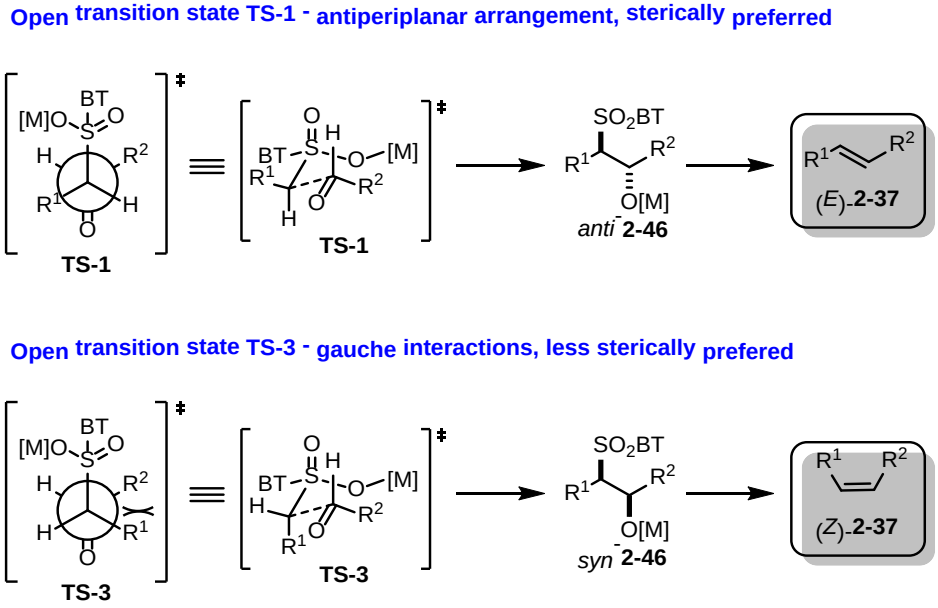
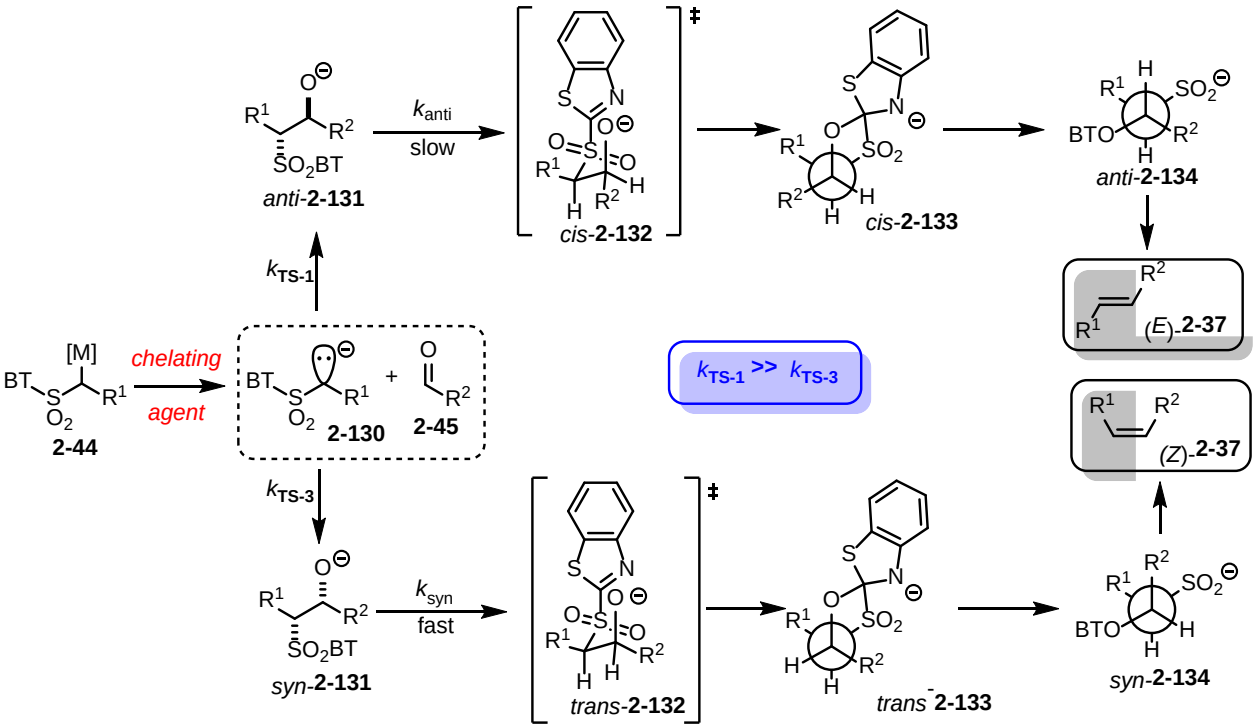


Figure 7. Two possible open transition states for the Julia-Kocienski olefination reaction.

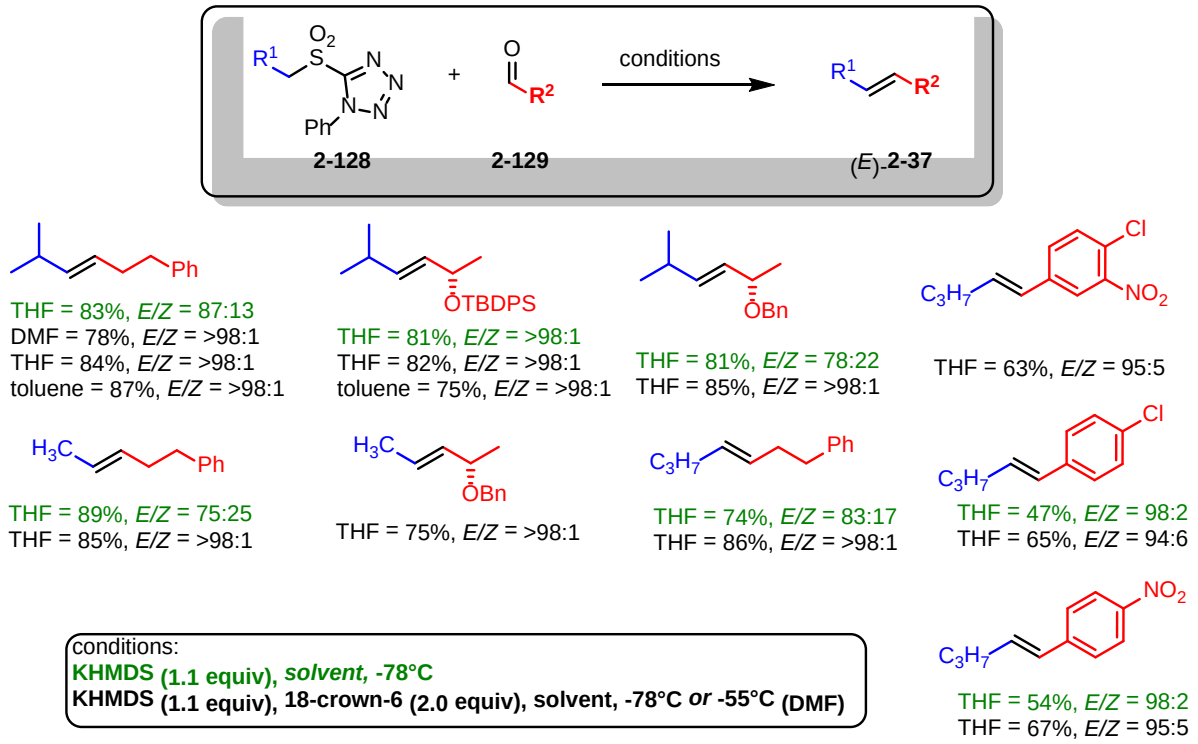
We assumed that our goal might be reached with the help of selective cation scavengers. The idea behind this was that the selective cation scavengers would, by chelating the counted cations of the *in situ* generated sulfonyl anion, increase the reactivity of "naked" sulfonyl anions **2-130**. The addition of the highly reactive intermediate **2-130** to aldehyde would be then kinetically driven and the **TS-1** would be even more preferred over the **TS-3** due to the undesired eclipsed interactions in the later one (Scheme 28). The only drawback of the sequence could be a possible increase in the rate of the self-

condensation of the "naked" anion **2-130** (Scheme 11). Though we were confident that we might be able to overcome such a 'hurdle' if our hypothesis stands.



Scheme 28. Expected influence of the chelating agent addition to the reaction mechanisms. BT-group selected to represent activated aromatic group.

Gratifyingly, after some reaction condition optimization we came up with two sets of conditions: (1) KHMDS/18-crown-6 *or* TDA-1[70], and (2) LiHMDS/12-crown-4 that fulfilled the criteria. The first conditions - KHMDS/K^+-selective chelating agent, proved to be suitable in the case of 1,2-disubstited olefin preparation; while the second conditions - LiHMDS/12-crown-4, were suitable for the synthesis of trisubstituted olefins (Scheme 29). The scope and limitations of the reaction conditions revealed, that if sulfone **2-128** is reacted with alkyl aldehydes **2-129**, dramatic increase in (*E*)-selectivity is observed. Surprisingly, this effect was absent, when under the same reaction conditions, aryl- or α,β-unsaturated aldehydes were reacted. In these cases, worse (*E*)-selectivity of the reaction was observed. The only exception was observed when electron rich aryl aldehydes were reacted. In these cases, no drop of the selectivity was observed. This observation pushed us to investigate more in detail the reaction mechanism of the Julia-Kocienski reaction (especially **pathway B** in Scheme 12) and this will be discussed in more detail in chapter 2.2.6.



Scheme 29. Scope and limitations of the KHMDS/18-crown-6 reaction conditions in Julia-Kocienski olefination reaction. **In green** yields and selectivity under 'standard' conditions; **in black** the yields and selectivity under modified conditions.

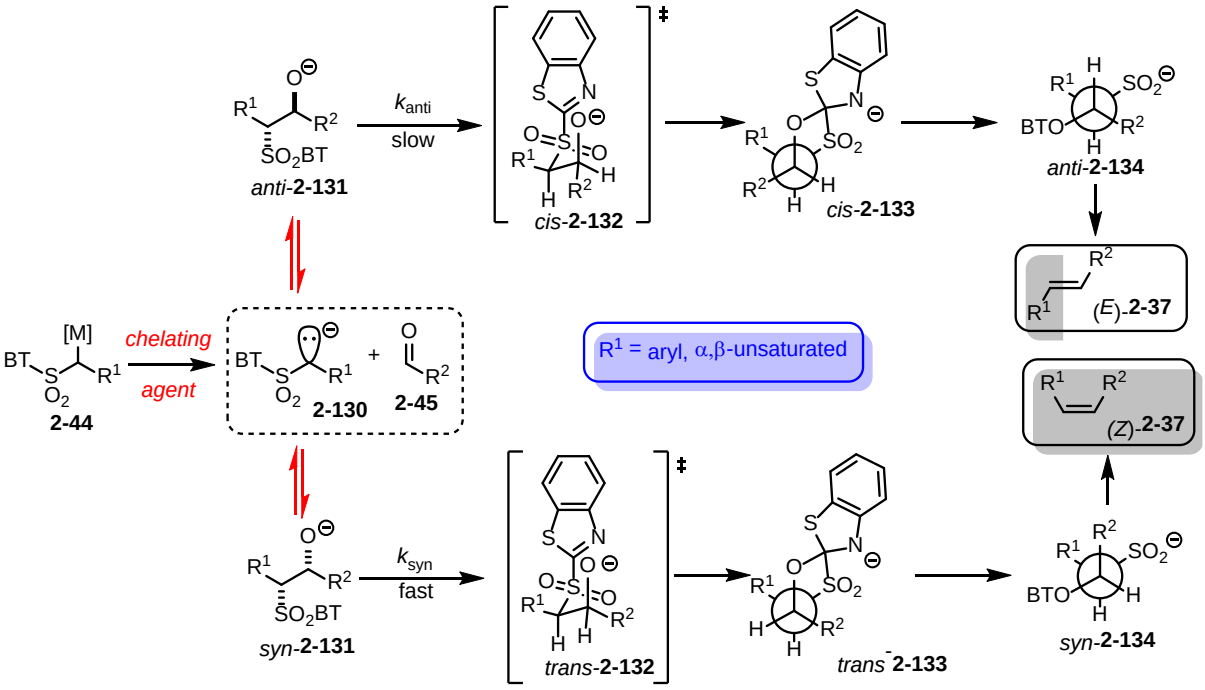
2.2.5 Julia-Kocienski olefination – enhancing the (*Z*)-selectivity

Having established (*E*)-selective modification of the Julia-Kocienski reaction, we turned our attention towards the (*Z*)-selective modifications. First we focused our attention to the reactivity of stabilized sulfonyl anions **2-128** (R^1 = aryl, α,β-unsaturated, Scheme 30). As suggested earlier (Scheme 12, pathway A), in the case of stabilized sulfonyl anions the addition to carbonyl compound is a reversible process. Since the Smiles rearrangement of *syn*-adduct *syn*-**2-131** proceeds faster than that of *anti*-**131** adduct (k_{syn} >> k_{anti}), (*Z*)-olefins are preferentially formed. Thus, even better (*Z*)-selectivity should be achieved, if the rate constants of addition/retroaddition reactions could be increased.[71]

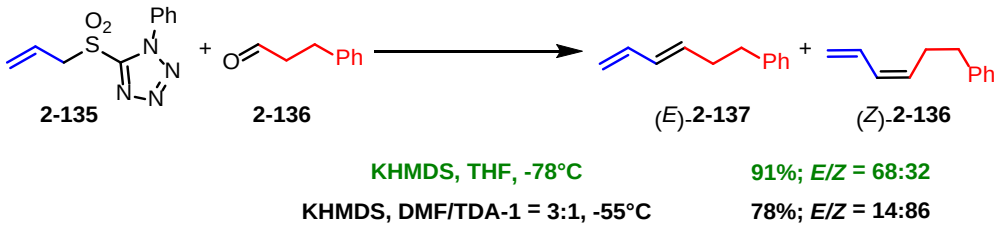
We reasoned that by introducing the cation scavenger into the reaction mixture, the stability of the 'naked' sulfonyl anion **2-130,** and that of *syn* and *anti*-adducts would be diminished. Thus, the rate constant of the addition and retroaddition reactions should be increased. Such situation should diminish the total population of the *syn* and *anti*-adducts, and as a consequence should allow faster Smiles rearrangement of the *syn*-adduct **2-131** to intermediate *syn*-**2-134** to form final olefin (*Z*)-**2-37** in better selectivity.

Having this hypothesis in mind, various reaction conditions were evaluated and finally it was observed that if KHMDS/DMF:TDA=3:1 or KHMDS/18-crown-6 system was used, then the selectivity of the reaction between allylsulfone **2-135** and aldehyde **2-136** was inverted from the original (*E*/Z) = 68:32 (KHMDS/THF system) to 14:86 (Scheme 31).

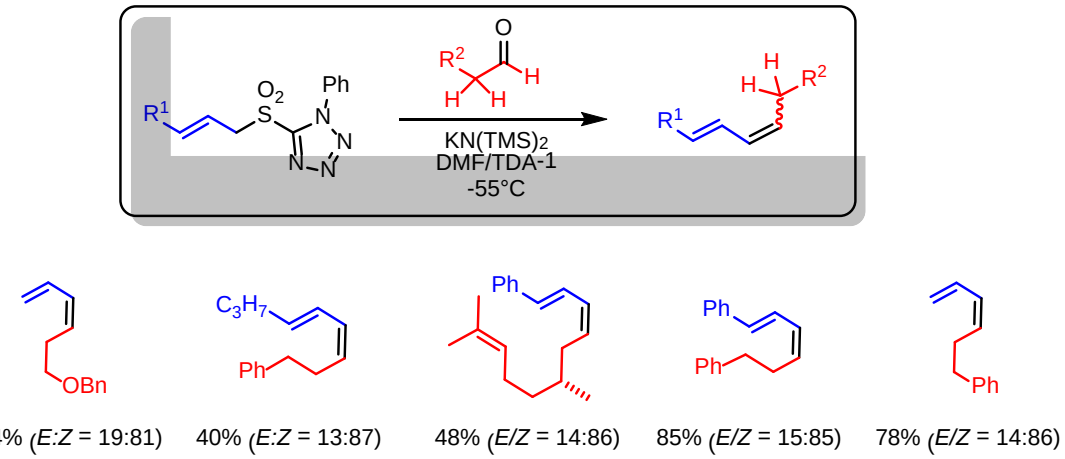
Unfortunately it was found that this modification of the Julia-Kocienski olefination was subjective and applicable only for linear alkyl aldehydes (Scheme 32).



Scheme 30. Expected influence of the chelating agent on the reaction mechanisms of stabilized sulfonyl anions **2-44**. BT-group selected to represent activated aromatic group; k_{syn} >> k_{anti}.



Scheme 31. (*E*/*Z*)-selectivity inversion in Julia-Lythgoe olefination of stabilized sulfonyl anions with aldehydes.

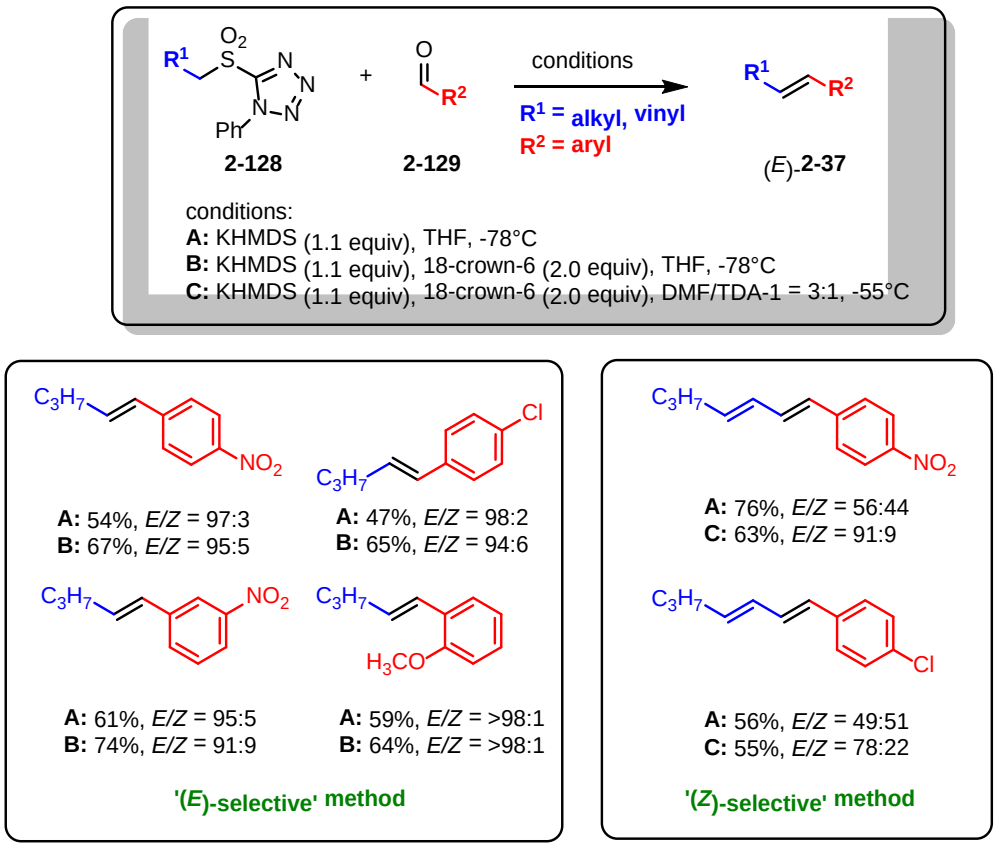


Scheme 32. Selected examples of the (*Z*)-selective Julia-Kocienski olefination protocol application.

2.2.6 New insights into the reaction mechanism of the Julia-Kocienski olefination reaction

As mentioned in the previous two chapters, 2.2.4 and 2.2.5, when aryl aldehydes were reacted under (*E*) and (*Z*)-selective Julia-Kocienski olefination conditions, the observed olefin selectivity never followed the general pattern of the method. In general, the reactions were (*E*)-selective, however with

different degrees of selectivity. Many times the observed selectivity was even lower than that obtained for olefins created under the 'standard' reaction conditions. There was also a difference if electron rich or electron poor aryl aldehydes were used as a starting material (Scheme 33).

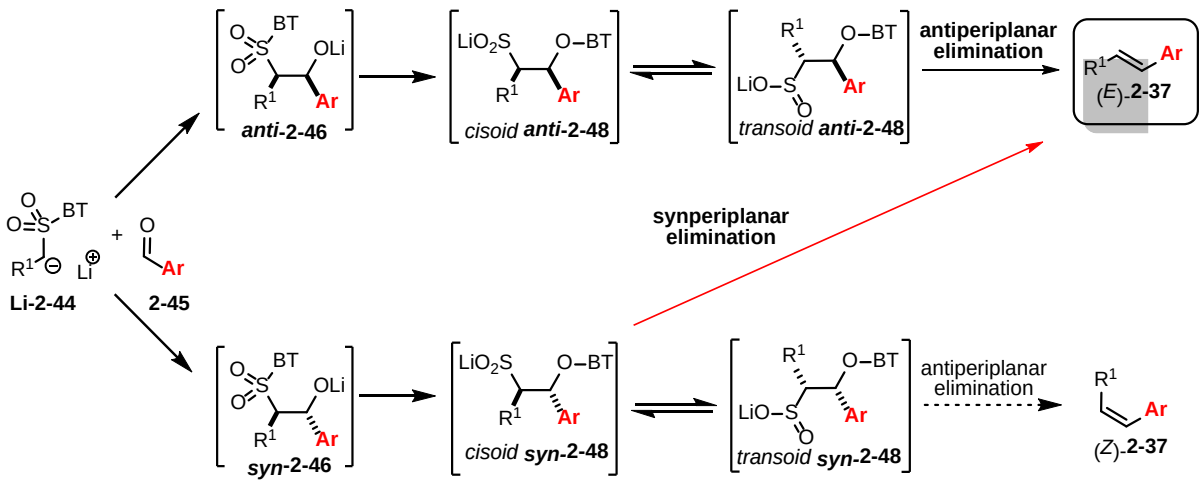


Scheme 33. Contradictory results obtained for (*E*) and (*Z*)-selective olefination methods of Julia-Kocienski reaction in our group.

Interestingly, a similar observation was already made by S. Julia[43a,50] when the basis of Julia-Kocienski reaction was revealed. At that time he proposed a reaction mechanism based on the formation of zwitterionic intermediate **2-56** (Scheme 12, path B). It was postulated that this is only a tentative explanation (see discussion in chapter 2.1.2), but since that time it was the only explanation that rationalized the influence of the electronic properties of the aryl group to the reaction selectivity.

Taking into account newly developed reaction conditions, and especially the influence of the chelating agents on the reaction intermediates stability, it was hard for us to believe that this postulated reaction mechanism was correct. Thus we joined our forces with theoretical chemist R. Robiette (UCLouvain) and we designed and carried out an extensive theoretical and experimental search to elucidate a more relevant reaction mechanism proposition.[53]

Many competitive experiments, labelled substrates, *in situ* prepared reaction intermediates *etc*. were evaluated under the Julia-Kocienski olefination reaction conditions (for more details see ref[53], especially the supporting information section). Based on the obtained data, several hypotheses were elucidated and evaluated by means of DFT-calculations. In the end, we postulated a new mechanistical hypothesis based on the possible *syn*-periplanar elimination of the *syn*-**2-48** intermediate (Scheme 34).



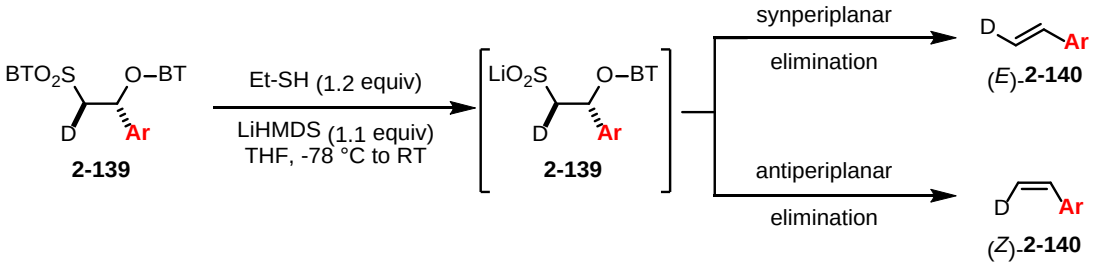
Scheme 34. Rationale for observed high (*E*)-selectivity in Julia-Kocienski olefination of aromatic aldehydes.

Theoretical calculations suggested that in the case of the *transoid* form of *syn*-**2-48** intermediate, that is required for the antiperiplanar elimination of *syn*-**2-48** to (*Z*)-**2-37** olefin, 1,2-steric interactions play an important role. Thus this conformation is less preferred leaving room for the unexpected syn-periplanar elimination that proceeds from the *cisoid* form of *syn*-**2-48** and yields (*E*)-olefin **2-37**. In the case of the *anti*-**2-48** intermediate it is the *cisoid* conformation that suffers from 1,2-steric repulsion. The preferred conformation is then the *transoid* one, and that is the conformation required for the antiperiplanar elimination process.

Such results however do not answer the question about the mechanism fully, because from the experiments it is known that the elimination process for the substrates, where the **aryl** part of the **2-48** intermediate is replaced by **alkyl**, proceeds by an antiperiplanar elimination process.[19,43a,50] Calculations on model systems reveal that the presence of the phenyl group also plays an important role in the stabilization of the syn-periplanar transition state. A natural bond orbital (NBO) analysis showed that the key interaction in the transition state responsible for this action is an electronic donation from the π system of the phenyl to the positively charged previously aldehyde carbon atom. This result also explains the influence of the electron donating groups on the reaction selectivity – more electron donating groups on the aryl functionality results in higher electron donation and thus, better syn-periplanar TS stabilization. Thus, a higher proportion of the syn-periplanar elimination occurs over the anti-periplanar elimination in *syn*-**2-48** elimination process leading to olefin **2-37** formation. Overall, higher (*E*)-olefin selectivity is observed.

To support our postulated syn-periplanar elimination process hypothesis, a set of substrates **2-138** was prepared (Table 8). *In situ* compounds **2-138** were converted into the reaction intermediates **2-139** that could undergo either a syn-periplanar or anti-periplanar elimination process. The selective installation of hydrogen and deuterium atoms on **2-138** should assure that no additional steric demands would interfere with the stereochemical outcome of the reaction. Gratifyingly, the experimental data confirmed that *syn*-periplanar elimination process is indeed a major elimination process for the tested substrates, and the experimental results also showed that the presence of electron-donating group on aromatic ring leads to an increase of the syn-periplanar elimination process.

Table 8: Various olefination methods in the context of goniothalamine synthesis.

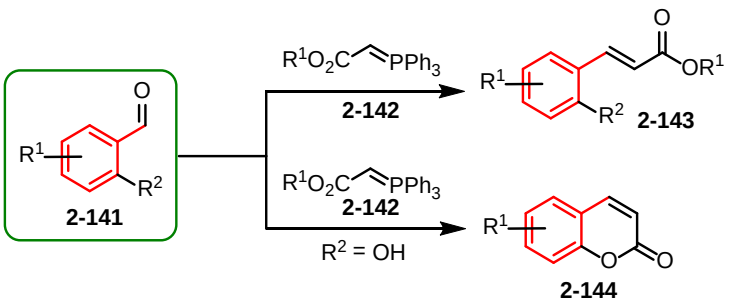


Entry	Ar	olefin	Yield (%)	*E/Z* ratio
1	*p*-Cl-C_6H_5	**2-140a**	89	81:19
2	C_6H_5	**2-140b**	92	90:10
3	*p*-MeO-C_6H_5	**2-140c**	87	94:6

2.3 Microwave promoted Wittig reaction in the plant secondary metabolite synthesis

Finally, having introduced several modifications of Julia-Lythgoe and Julia-Kocienski olefination reaction, we become interested also in Wittig reaction and it's application. Our interest in this type of olefination reaction was driven by our new research project that focused on the synthesis of plant secondary metabolites – phenylpropanoids, lignans, monolignols, neolignans and coumarins. The overall goal of the project is to find a way how to simply and efficiently identify secondary plant metabolites in the plant metabolome. Especially we are interested in the secondary metabolites produced/related to oxidation processes.[72] As a consequence we have become interested in the development of a highly efficient synthetic route that would lead to the phenylpropanoid related products (Scheme 35).

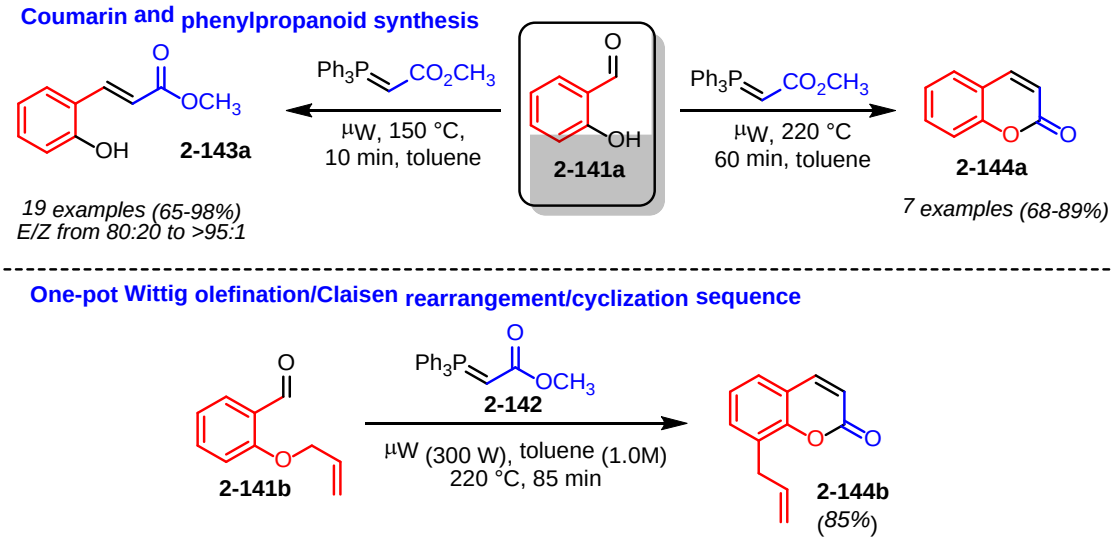
Based on this criteria we speculated that by reacting aromatic aldehydes **2-141** with stabilized Wittig regent **2-142** under thermal conditions, selectively either phenylpropanoids **2-143** (R^1 = OH, alkyl,…) or coumarins **2-144** (R^1 = OH) could be obtained.[73]



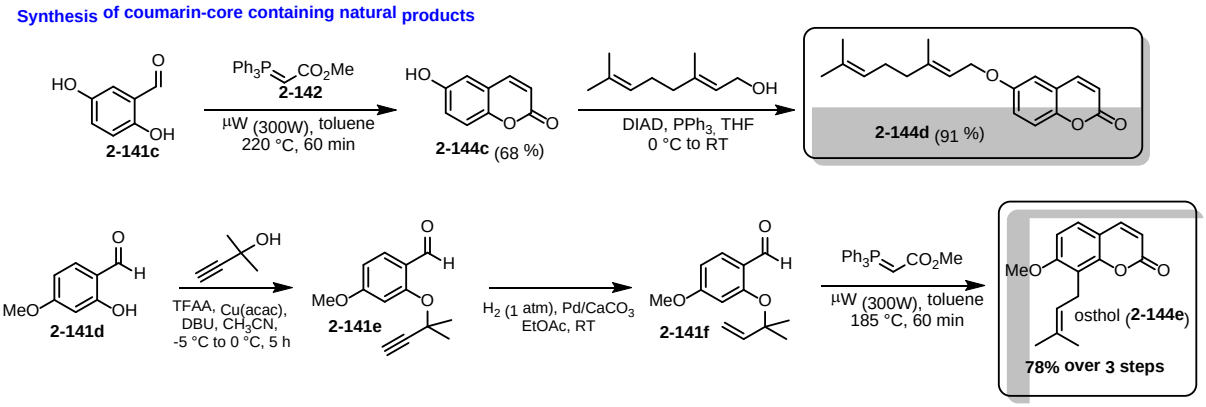
Scheme 35: Phenylpropanoid and coumarin synthesis.

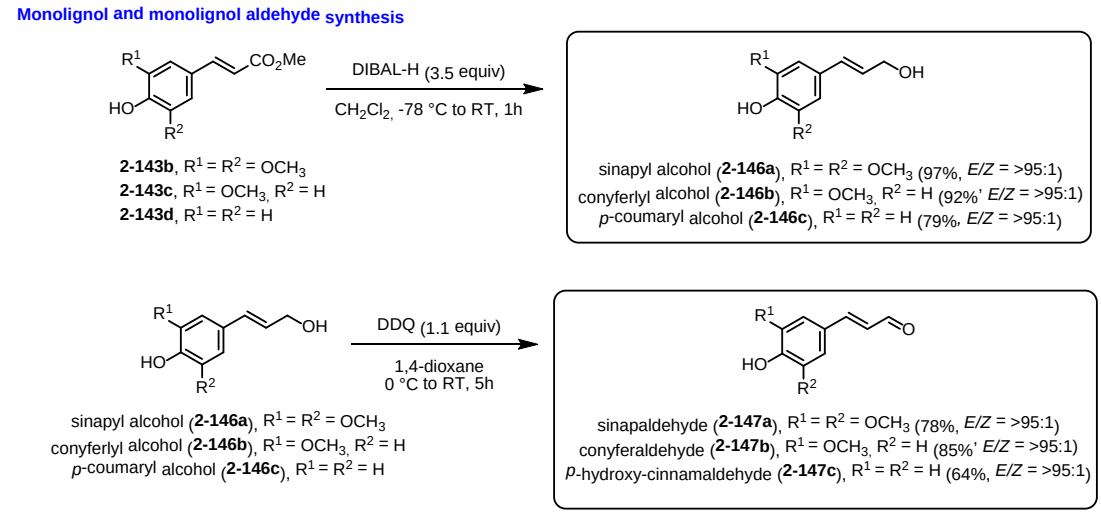
Indeed, by applying the two different sets of reaction conditions, coumarin **2-144a** and phenylpropanid **2-143a**, respectively, have been selectively prepared (Scheme 36). Additionally to this, when O-allyl substituted aldehydes were reacted under the appropriate reaction conditions, a one-pot Wittig olefination/Claisen rearrangement/cyclization sequence could be accomplished (Scheme 36).

Finally, the above mentioned approaches were applied to the synthesis of several natural products as monolignols, monolignol aldehydes and coumarin-core containing products such as osthol (Scheme 37).



Scheme 36. Selective microwave assisted one-pot synthesis of coumarins and phenyl propanoids.





Scheme 37. Natural products prepared via a microwave initiated one-pot protocol.

3. Diversity-Oriented synthesis

3.1 Introduction

Small molecule modulators of biological function, or the lead compounds for drug development, can be discovered through screening of libraries of compounds. Since the early 90-ties of the past century the main emphasis on the design of such libraries was placed on the size of the library.[5a,6a,7a,8,9b,c,11] Such "the size matters" approach in compound library construction, however, underwent over the past 15 years to a slow but important transformation.[9b,c,11b-d] Now-a-days, the previous "the size (*of the library*) matters" goal emphasized during the compound library construction was slowly replaced by a "structural and functional diversity matters" aim. Diversity-Oriented Synthesis (DOS) aims to generate such structural diversity efficiently.[11b-d]

Within the introductory chapter to the second part of my Habilitation Thesis I would like to cover key aspects and features essential to the design of new generations of compound libraries where the main focus is on the structural and functional diversity. Along with this the synthetic strategies suitable for DOS will be presented.

3.1.1 Ideal functionally diverse library

Ideal compound libraries would contain all possible modulators for all existing biological processes. In other words, chemicals within the library would cover the entire bioactive area of chemical space. Thus, the library would presumably contain all thermodynamically stable molecules. The estimations based on the theoretical calculations suggested that the number of drug-like chemicals (for compounds < 500 Da) is ~10^{63}.[ref. 74] The real size of the library is obviously substantially smaller since a large portion of the bioactive chemical space has been already restricted due to way nature assembles molecules. But still, the compound library size is rather impressive.

In recent years, advances in genomic and proteomic technologies have revealed many new biological targets suitable for therapeutic interventions. The given trend, discovery of new biological targets will likely continue still for some time. But now, at this particular moment, the time of chemical exploration of these newly identified targets with functionally diverse small molecules is arriving. It is the time to find out if the function of these targets might be modulated with the help of small molecules or not. And at this particular moment, the ***composition*** of the screened libraries is of paramount importance.

Thus, the question is *how to construct a library* where the *functional diversity* would be as large as possible?

3.1.2 Designing the library

The functional diversity of the small molecules included in the library is directly related to the three-dimensional information that the surface of the molecule presents (offer) to a macromolecule (biological target) with which it interacts. Thus the functional diversity is directly connected with the structural diversity. And the structural diversity within the library can be introduced in the following four ways:

(a) Appendage diversity – variations in structural moieties around a common skeleton.
(b) Functional group diversity – variation in the functional groups.
(c) Stereochemical diversity – variation in the orientation of possibly interacting groups in space.
(d) Skeleton (scaffold) diversity – presence of many distinct molecular skeletons.

At the end of the 20th century and in the 1st decade of the 21st century, the main emphasis during the library construction was placed on the appendage diversity, while especially stereochemical diversity was left behind. Unluckily for this approach, over past 15 years it was demonstrated that the overall

three-dimensional shape diversity of constructed library is primarily dependent on the diversity presented in the central scaffold; demonstrating that the peripheral substituents are of minor importance.[75] Later on, the pioneering work Schreiber and co-workers[76] demonstrated that the selectivity in the protein binding is achieved only for the compounds with intermediate stereocomplexity[†] ($0 < C_{stereo}/C_{total} < 0.25$); compounds with simple stereocomplexity ($C_{stereo}/C_{total} = 0$) showed the biggest promiscuity, and those of high stereocomplexity ($C_{stereo}/C_{total} > 0.25$) achieved the lowest overall "hit" rate being too specific.

3.1.3 Sources of small molecules

There are in principle two strategies used by organic chemists to discover biologically active structurally diverse small molecules that can lead to the discovery of biological probes and drugs.

The first strategy is inspired by small molecules isolated from natural sources – so called '**natural products**'. In the past, natural products have served principally as a target for organic synthetic chemists. Structures themselves were THE target of synthetic efforts and the development of new synthetic methods and methodologies was the only justification of the attempted synthesis. In the context of small-molecule library construction, however, synthetic approaches aim for the short and modular syntheses of structural variants of specific natural products. As a consequence, improved or novel properties of structurally already known molecular probes or drugs might be disclosed. Unfortunately, there are several problems associated with using natural products in biological screens and drug development (e.g. already known targets are screened, access to supply is limited, chemical modifications related to chemical structure, purification, concerns about the intellectual property rights…).[77]

The second strategy is inspired by the **complexity and diversity** of existing natural products. This means that the strategy tries to generate within the library as many different structural motives as can be found in nature or created by the imagination of synthetic chemists rather than to focus on one specific natural product scaffold. Within the approach, chemists use modular syntheses of compounds having features such as intermediate ratios of atoms with sp^2 and sp^3 hybridization, multiple stereogenic elements, and rigidifying skeletal elements. Generated molecular structures further on can lead to the discovery of various modulators of many disparate biological targets. The reason is that libraries of small molecules created using previously mentioned principles (structural and functional diversity) interrogate large areas of bioactive chemical space including those previously unmapped.

From the **synthetic approach** view point, the most challenging facet of DOS, and the key to its success, is the efficient generation of scaffold diversity within a library.[11b,75] To do so, two key approaches – the *reagent-based* DOS and the *substrate-based* DOS – are used.[11b] Additionally to these two approaches, Nielsen and Schreiber have developed a strategy called **Build/Couple/Pair**.[78] This strategy somewhat combines the two previously mentioned approaches – *reagent based* and *substrate-based* – and, in the same time, brings a different approach into the library construction. The details of the above mentioned approaches and strategy will be discussed in the following part of the chapter.

However, before this, another aspect of DOS library construction should be revealed. When a DOS library is designed, synthetic approaches used should yield the complex molecules in an efficient and modular manner, typically in no more than five synthetic steps. Such an approach allows, in the case of a 'hit', easy and straightforward synthesis of the compound of interest in large amounts.

[†] Stereocomplexity is defined as a number of stereogenic carbons divided by the total amount of carbons (C_{stereo}/C_{total}). Only carbon atoms included on the main scaffold counts.

Additionally, the focused library might be conveniently generated around the 'hit' structure (Figure 8).[78-79]

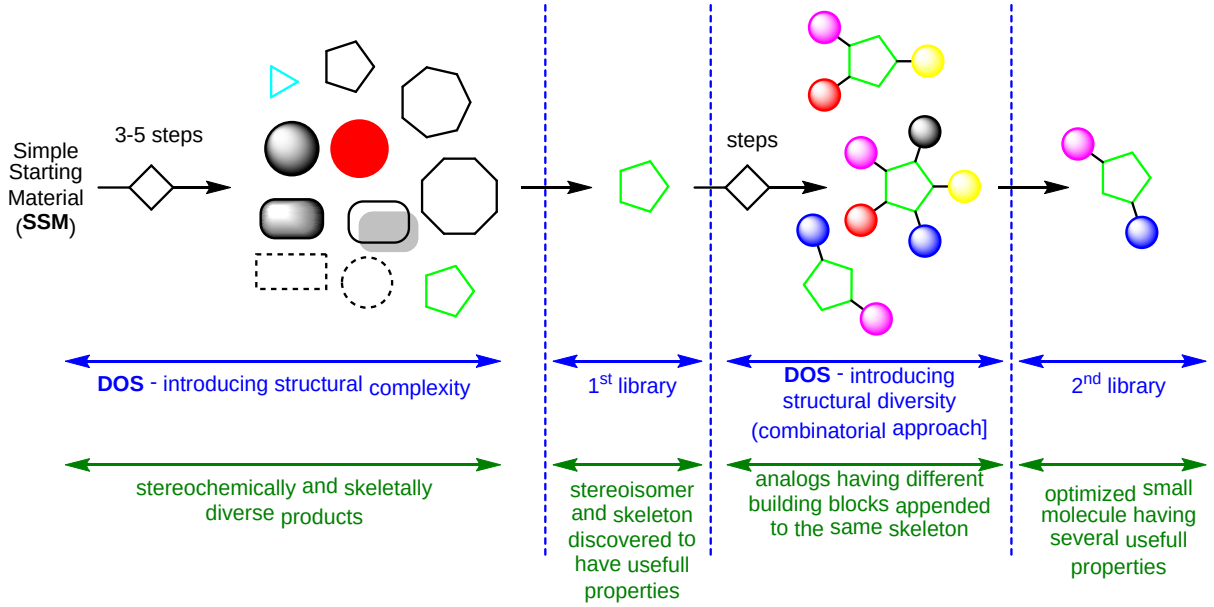
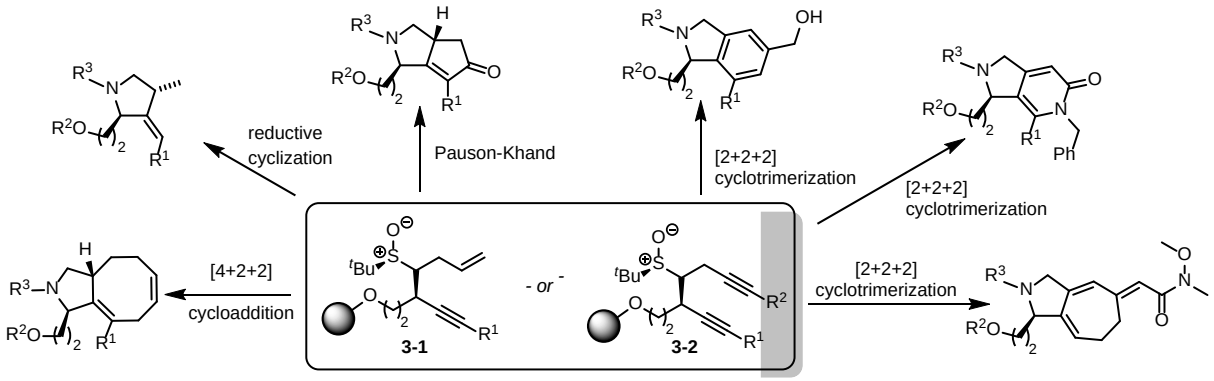


Figure 8: Overall DOS-based approach allowing to identify and develop small-molecule 'hits' into the biological probes or drugs.[79]

3.1.4 DOS approaches focused on the generation of diverse libraries

3.1.4.1 The reagent-based approach

This approach is based on the use of pluripotent functional groups and methods that use densely functionalized molecules. Such molecules are transformed by different reagents to create scaffold diversity. Crucial to the success of this approach is the choice of the original (parent) densely functionalized molecule that enables many transformations or intramolecular reactions. As an example of such approach, the transformation of *tert*-butylsulfinimide tethered enynes (**3-1**) and diynes (**3-2**) by various reagents/conditions to various molecular scaffold is shown (Scheme 38).[80]

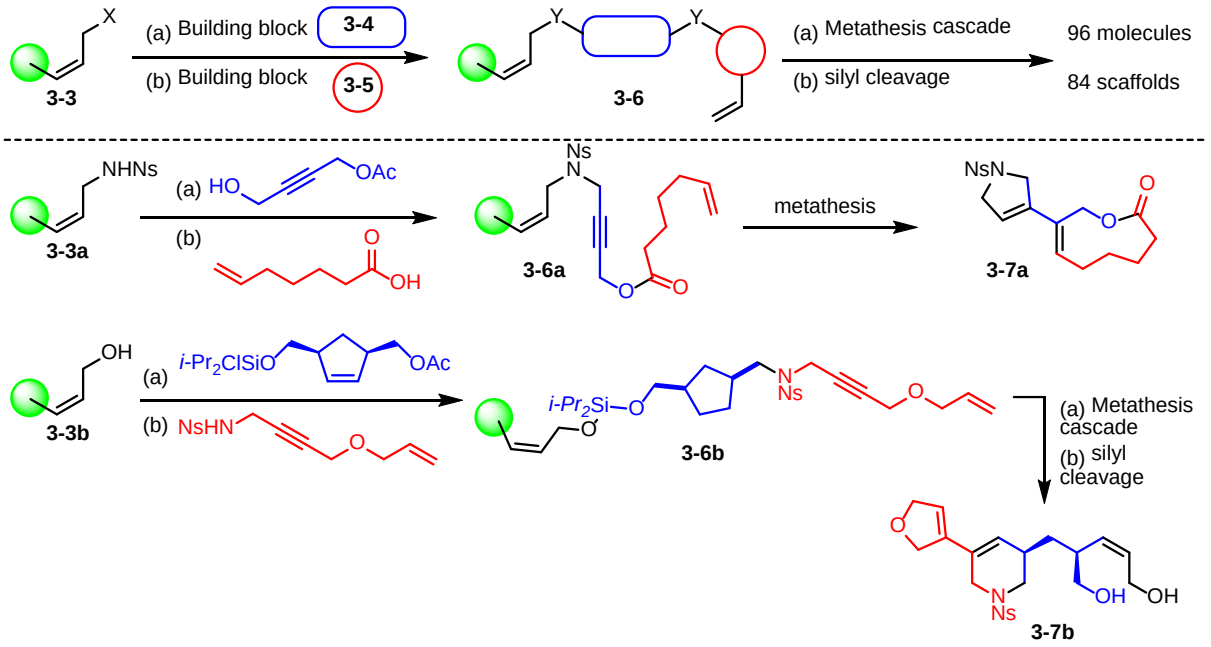


Scheme 38. The reagent-based approach (overall 190 molecules with 10 distinct scaffolds).[80]

3.1.4.2 The substrate-based approach

The substrate-based approach is based on the use of common reaction conditions to a collection of different substrates. The post transformation (or reaction condition-induced) folding process then transforms the "pre-coded" substrates into structurally different molecular skeletons.

The example of such an approach is depicted in Scheme 39.[81] In the selected example, the fluorous-supported functionalized olefin **3-3** is in a sequence of two steps modified with two sets of building blocks (**3-4** and **3-5**) containing at least one unsaturated functionality each. When such intermediate **3-6** is subjected to metathesis conditions, an intramolecular cyclization cascade occurs and, upon the release from the fluorous tag, structurally different cycles are formed.



Scheme 39. The substrate-based approach application in DOS synthesis. Library of 96 molecules with 84 different scaffolds.

3.1.4.3 The Build/Couple/Pair strategy (B/C/P)

The **B/C/P** strategy was introduced by Nielsen and Schreiber at the end of the first decade of the 21st century.[78] This strategy somewhat combines the previous two approaches mentioned above, but at the same time, proposing a different, more complex approach to build up complexity driven library construction. The strategy divides the small molecule construction into three distinct phases. In the first one ('**Build**' phase), the building blocks of diverse complexity (or commercially available) are prepared (Figure 9). The second phase ('**Couple**') involves the connective reaction of those building blocks with the aim to connect structurally different building blocks together. Finally, in the third phase ('**Pair**'), in general an intramolecular cyclization reaction(s) cascade occurs. At this stage, pre-encoded location of the key functional groups yields different molecular scaffolds. The example of such approach is shown in the context of the PfATP4 inhibitor synthesis (only the 'hit' molecule is shown).[9c]

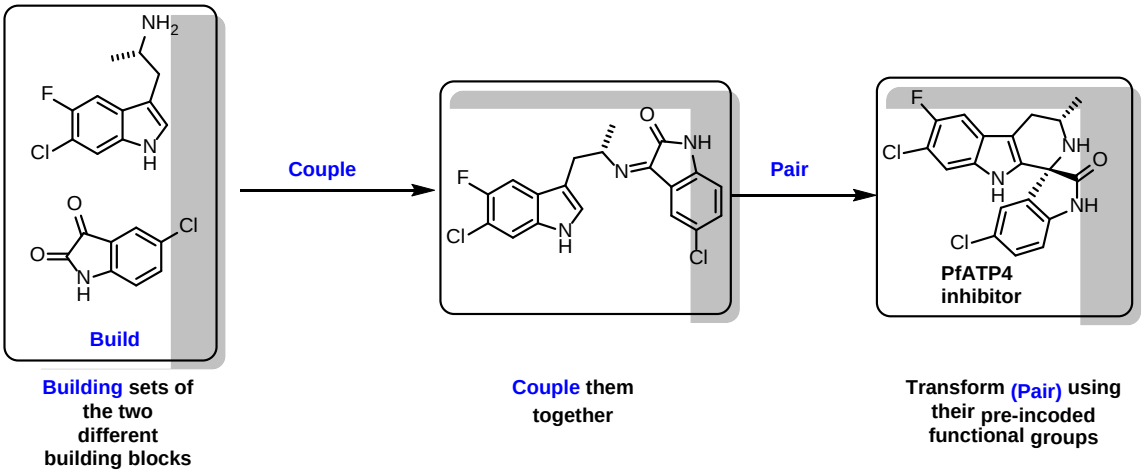


Figure 9. Build/Couple/Pair strategy exemplified on the showcase of the PfATP4 inhibitor synthesis.[9c]

3.2 Our design of synthetic strategies suitable for structural and functional complexity driven DOS

Our aim in DOS synthesis is to develop a general synthetic strategy that would allow us to access diverse molecular scaffolds from the simple highly functionalized molecular intermediates – **Parent Molecule** (Figure 10).

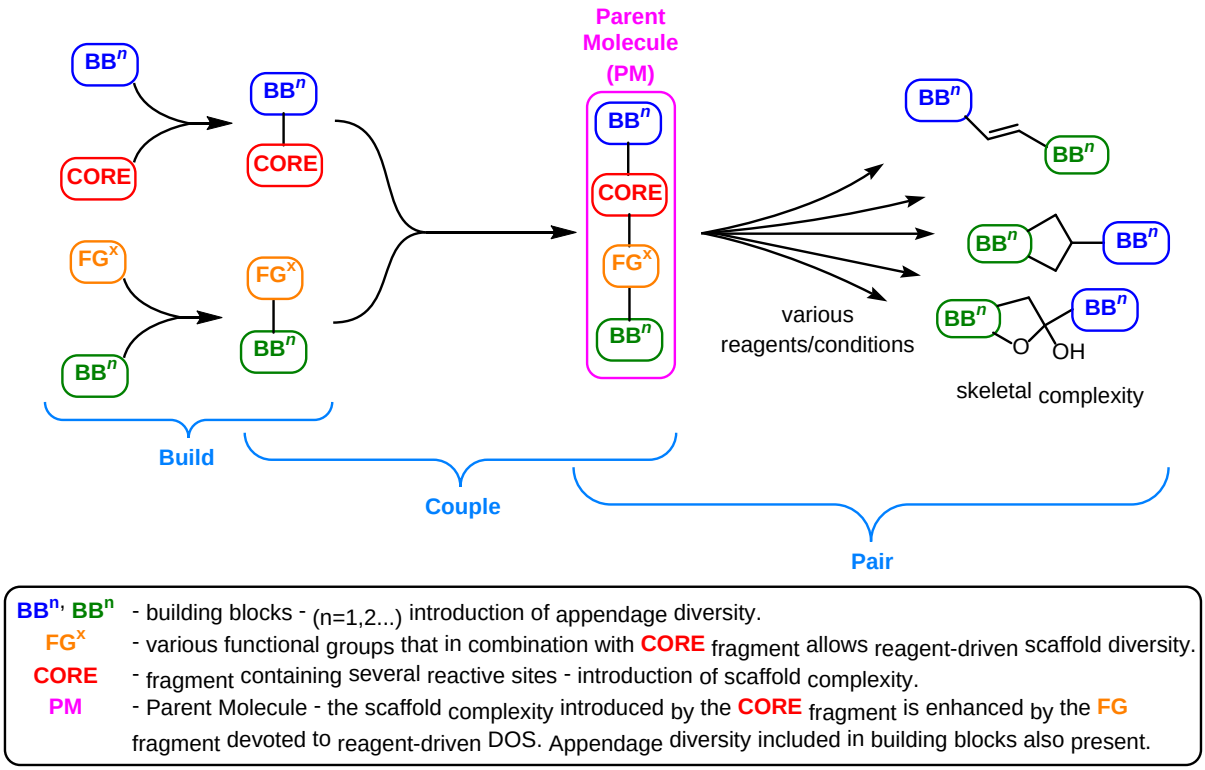


Figure 10. Synthetic strategy leading to chemical libraries with high scaffold diversity is devised into three stages (Build/Couple/Pair) as described by Schreiber.

In our design, the **CORE** structure should possess various reactive sites that might be further exploited in the scaffold diversity driven library compound construction. The **CORE** fragment should be also easily accessible and modulable with the use of standard commercially available building blocks **BB^n** (**Build** phase). The **CORE-BB^n** molecules shall be combined in the '**Couple**' phase with the **FG^x-BB^n** structures possessing at least one functional group (**FG^x**). Such functional groups should serve to

further extend the possible scaffold diversity in the library construction *via* reagent – driven DOS. The resulting coupled product, intermediate BB^n-CORE-FG^x-BB^n which we have decided to call Parent Molecule (PM), will serve as the starting point for the final Pair phase of the sequence – the external reagent-triggered scaffold complexity of compounds in the newly created compound library. It shall be noted that the appendage diversity was already introduced in the Build phase of the sequence.

Thus, if the above reasoning is analyzed in detail, the correct choice of the CORE molecular structure is key for the success in our synthetic strategy. For this reason and due to our previous experience closely related with the Julia-Kocienski olefination we have opted to use benzothiazoyl sulfones **3-8** as our CORE fragment (Figure 11).

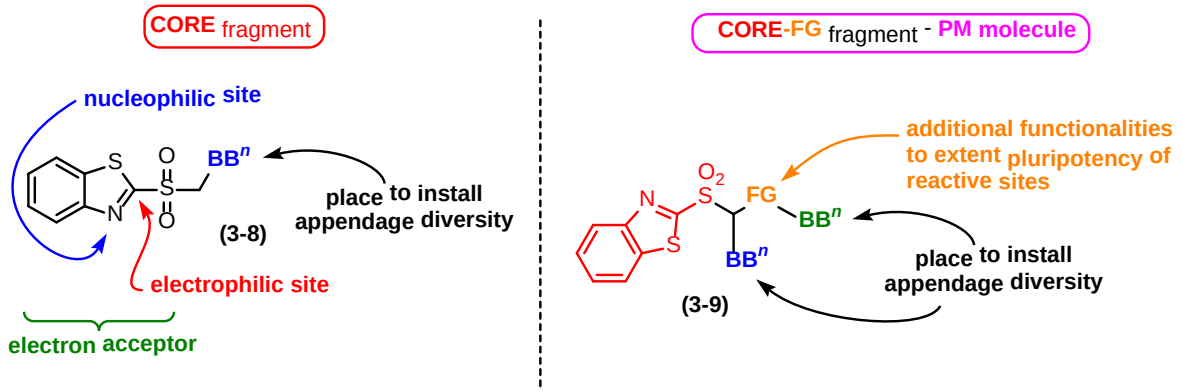


Figure 11. Design of the benzothiazoyl sulfone-based **CORE** structure and on **3-8** structure-based **Parent Molecule** **3-9**.

Sulfones **3-8** possess several reactive sites (electrophilic, nucleophilic and can be an electron acceptor in radical processes), several heteroatoms that can be further used to change the molecule reactivity *via* metal cation complexation, and also an acidic hydrogen atom in the sulfone α-position (not shown on the scheme). We reasoned that when such a CORE structure is combined with additional functional groups, a pluripotent PM molecule containing various reactive sites can be obtained. To evaluate our approach, the carbonyl group was selected as the FG group. Such choice then ultimately lead to the α-carbonyl BT sulfones **3-10** and put them into the role of our first PM structures (Figure 12). α-keto and alkoxycarbonyl sulfones **3-10a** and **3-10b**, respectively, thus become the proof-of-concept molecules for our project.

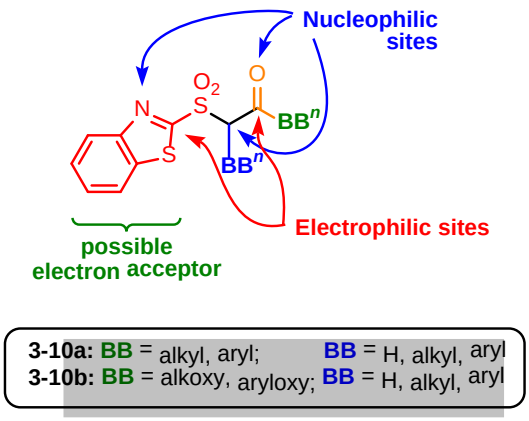
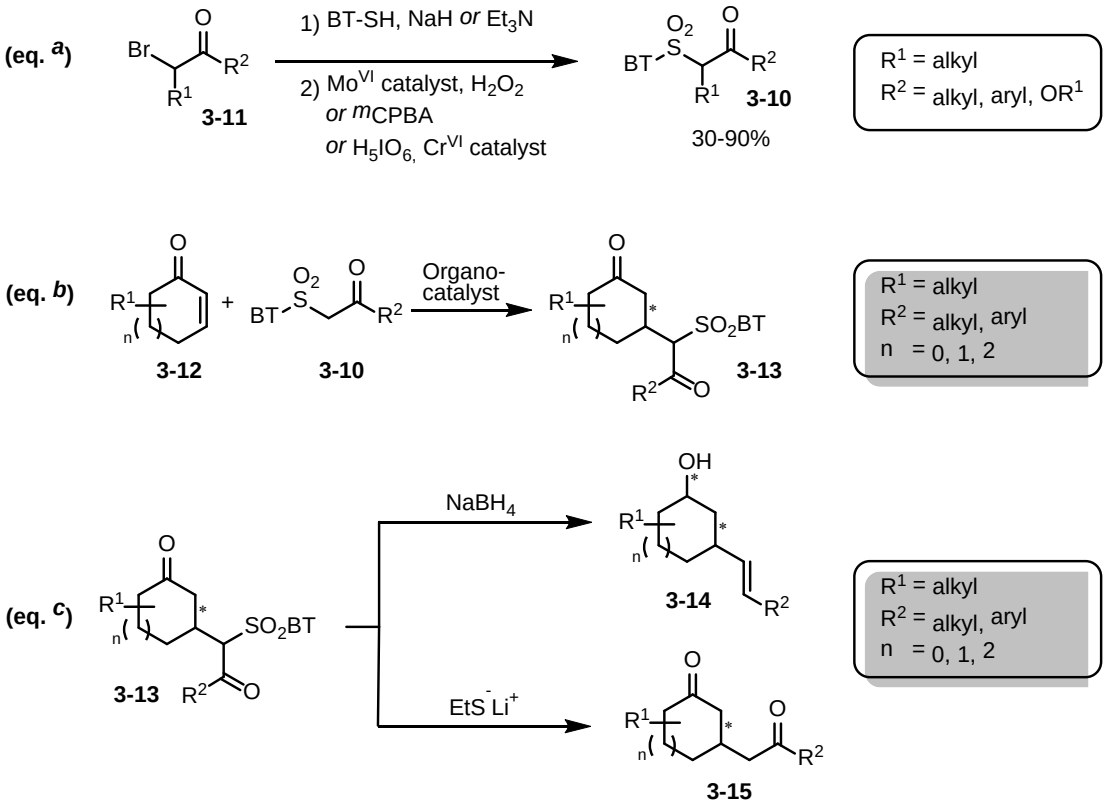


Figure 12. The first generation of the PM molecules **3-10** – proof-of-concept.

Additionally, there were other three reasons we have opted for sulfones **3-10** as the proof-of-concept PM molecules:

a) The structures **3-10a** and **3-10b** were already known in the literature and the synthesis has been previously described.[41a,82] (Scheme 40, eq. *a*)
b) Compounds **3-10a** were successfully used by Jørgensen and co-workers as a C-nucleophile in organocatalyzed 1,4-additions to α,β-unsaturated cyclic ketones.[83] (Scheme 40, eq. *b*)
c) Subsequent transformations based on the chemoselective reactivity of various reactive sites that yielded either ketones or olefins were shown.[83b,c] (Scheme 40, eq. *c*)



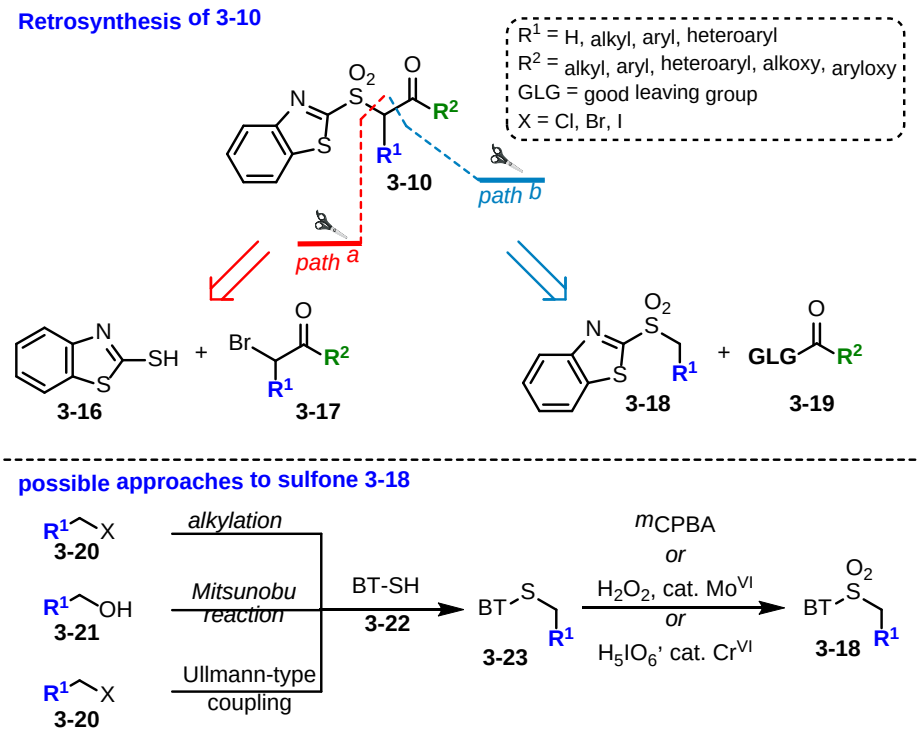
Scheme 40. Previous synthetic use and preparation of sulfone **3-10**.

In the following part of the Thesis, application of the compounds **3-10** within the context of the **B/C/P** strategy will be discussed.

3.2.1 Build and Couple phase – synthesis of Parent Molecules 3-10

As mentioned previously, the synthesis of compound **3-10** has already been described in the literature.[41a,82] Unfortunately, the approach applied during this synthesis (Scheme 41, *path a*) is not consistent with our **B/C/P** strategy. Indeed, using this approach, introduction of the building blocks required for the appendage diversity of the constructed library would not be possible. Thus another retrosynthetic approach had to be designed (Scheme 41).

In our purpose-driven retrosynthetic disconnection, we suggested that compound **3-10** should be accessed starting from BT-sulfone **3-18** and carbonylating agent **3-19** (Scheme 41, *path b*). Such approach would allow us to generated two pools of the advanced intermediates **3-18** and **3-19**. Thus, during the pool construction (**Build** phase) two different Building Block pools might be independently introduced into compounds **3-18** and **3-19**. Sulfone **3-18** might be prepared in two steps from corresponding halides **3-20** or alcohols **3-21**, respectively, and commercially available BT-sulfide **3-22**. Carbonylating reagents **3-19** are commercially available in the form of acyl chlorides, chloro formates etc., or *via* the standard synthetic protocols.

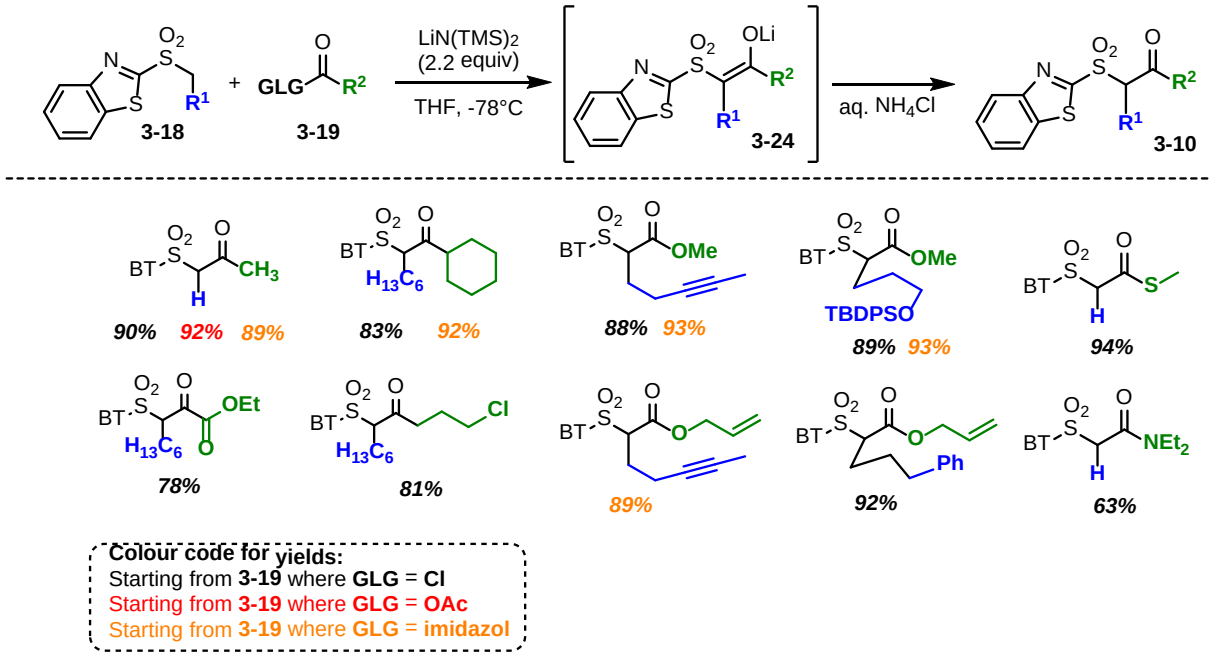


Scheme 41. Retrosynthetic approach to sulfone **3-10**: literature-based (*path a*) and ours (*path b*).

The key step was to reunite the two coupling partners **3-18** and **3-19** together – and this operation become the first hurdle of the synthesis. It was known from the literature that α-metallated sulfones **3-10** undergo spontaneous self-condensation[43a] (for more details see Scheme 11 and the accompanying text). Never-the-less, we have decided to study this transformation in details hoping to solve efficiently this problem. Indeed, soon we came with solution that solved the self-condensation side reaction and allowed us to prepare the desired compounds **3-10** in very good yields[84] (Scheme 42). Our approach took advantage of the rapid carbonylation of *in situ* generated α-lithiated sulfone **3-18**. Moreover, generated carbonylated sulfone **3-10** was *in situ* transformed into the corresponding enolate **3-24** which further diminished undesired self-condensation – type side reactions. BT-heterocycle in **3-24** is less sensitive to any nucleophilic attack when compared to **3-10**.[84a]

The second key point of this transformation is the lability of the leaving group in carbonylating agent **3-19**. In this case, chloride, oxyacetate or imidazole group proved to be a suitable nucleofuge for the reaction. On the other hand, alkoxy groups were not suitable, and when esters were used as **3-19** alternatives, only self-condensation reaction of methallated sulfones **3-18** occurred.

Based on the two above presented reasons it was evident (and experimentally later on validated) that our method could be easily extended to the syntheses of the corresponding alkoxy-, alkylthio-, and dialkylaminocarbonyl derivatives of **3-10**. However the method miserably failed when the synthesis of silylated, and tosylated or mesylated derivatives was attempted.[84a]

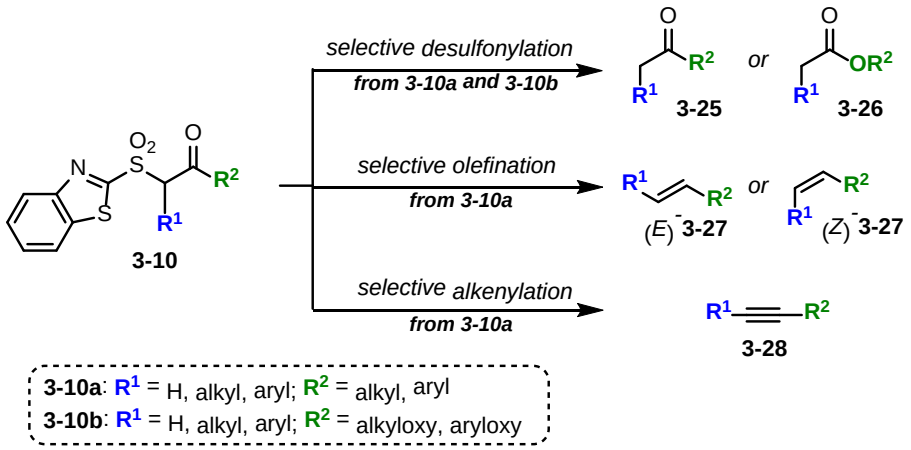


Scheme 42. Carbonyl sulfones **3-10** synthesis.

3.2.2 Pair phase - reagent-driven DOS synthesis

Having secured the 'Build' and 'Couple' steps of our project, we focused on the intermediate **3-10** reactivity in context of the reagent-driven DOS synthesis.[85] At the onset of our project our interest was based on the three following compound **3-10** transformations (Scheme 43):

1) Selective removal of the benzothiazole sulfonyl group. Such transformation would yield the ketone **3-25** or carboxylic acid derivative (ester) **3-26**.
2) Selective transformation of β-keto BT-sulfone **3-10a** to (*E*) or (*Z*)-olefins **3-27**.
3) Selective transformation of β-keto BT-sulfone **3-10a** to the corresponding alkyne **3-28**.



Scheme 43. Targeted selective compound **3-10** transformations.

3.2.2.1 Target: ketones (3-25) and esters (3-26)

Our first attempts in this field were focused on the ester **3-26** synthesis. Our goal was to prepare the esters from **3-10b** exploring three different reaction sites/mechanisms that could be applied on the targeted generalized structure **3-10b** (Figure 13). We aimed to develop multiple conditions for the same transformation to ensure that at least one of them will tolerate majority of functional groups

present in the reacted substrates. In short, the desulfonylation step was tested using three mechanistically different sets of the conditions:

(a) Using a nucleophile to attack the electrophilic site in the benzothiazole ring (*conditions a* – 'nucleophilic').
(b) *Via* reductive-elimination of the BT-SO_2 group (*conditions b* – 'reductive-elimination').
(c) Using a radical-initiated BT-SO_2 group removal (*conditions c* – 'radical').

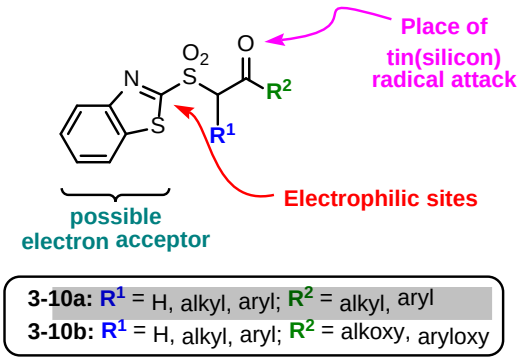
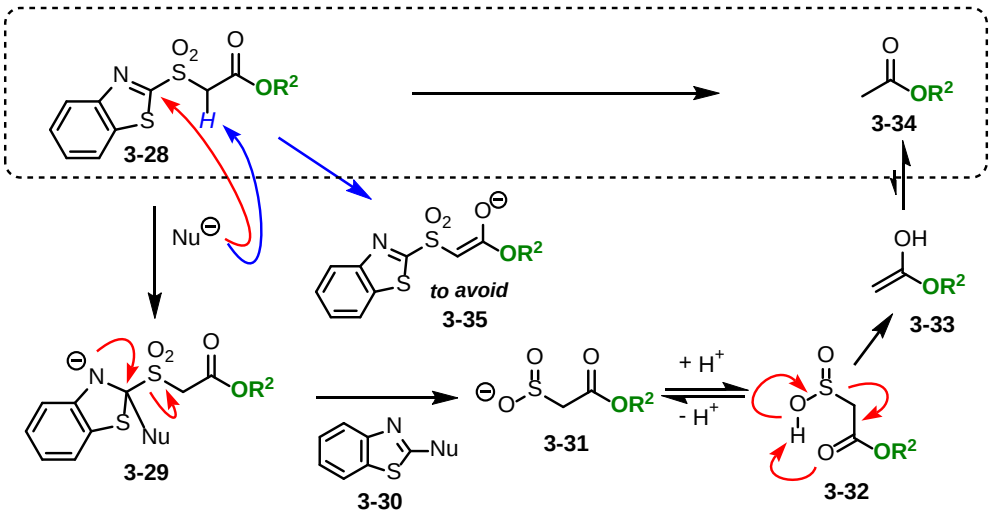


Figure 13. Targeted reactive sited in carbonyl sulfone **3-10**.

- ***Nucleophilic BT group cleavage.***

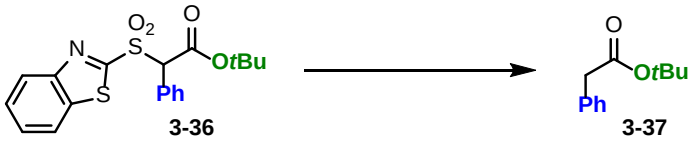
First, the nucleophile-promoted selective BT group removal was tested. Based on our assumptions, the selected nucleophile should attack the electrophilic site in the BT group and, in the same time, it should avoid the deprotonation of acidic α-sulfonyl hydrogen atom (Scheme 44). Thus, the chosen nucleophile must be sufficiently nucleophilic to react with activated heterocyclic ring (BT) but not too basic to promote the enolization of **3-28** to the corresponding enolate **3-35**. Overall, the addition of nucleophile to **3-28** will cause the release of the sulfinic salt **3-31** that, upon the protonation, shall undergo spontaneous desulfonation yielding the desired ester **3-34**.



Scheme 44. Envisaged reaction mechanism of 'nucleophile'-triggered desulfonylation of ester **3-28**.

Various reaction conditions and nucleophiles were tested, and sodium ethylthiolate proved to be the most suitable reagent for our purposes (Table 9). Under these conditions, upon the BT-group release, the ester **3-37** was generated with help of TFA (protonation of sulfinic salt followed by spontaneous SO_2 release).

Table 9: Nucleophile-based desulfonylation of BT-sulfone ester derivative **3-36**.



Entry	Conditions	Yield (%)
1	MeO^-Na^+ (20 equiv), THF/H_2O, 40 °C, 2 days	93
2	MeO^-Li^+ (20 equiv), THF/H_2O, 40 °C, 1 day	98
3	MeO^-K^+ (20 equiv), THF/H_2O, 40 °C, 5 days	76
4	1) EtS^-Na^+ (4 equiv), CH_2Cl_2, rt, 2h 2) TFA (10 equiv), rt, 5h	93

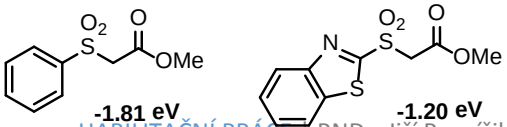
- ***Reductive-elimination based BT-SO_2 release.***

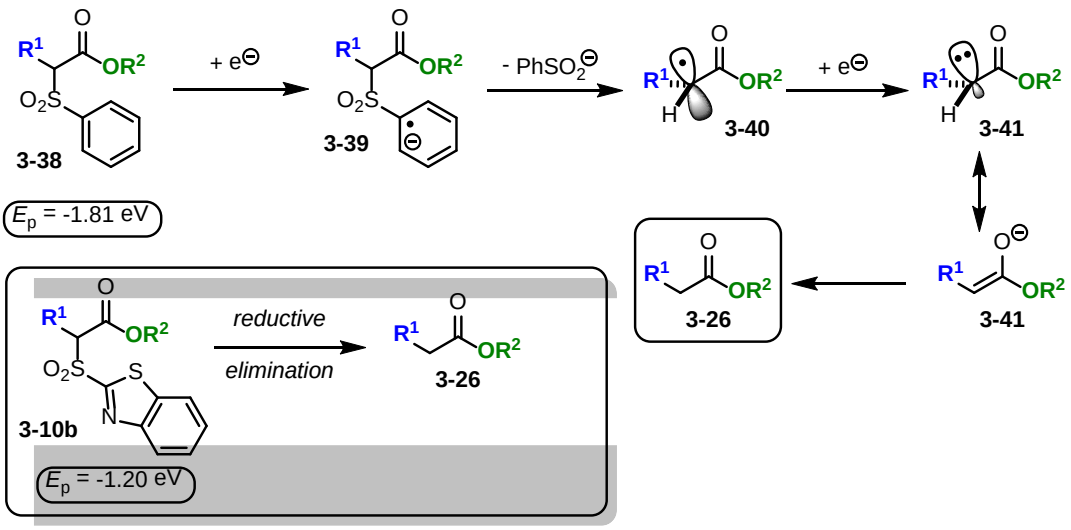
The second explored approach was based on the reductive elimination process based on the analogy between phenylsulfonyl group and BT-SO_2 group. It is known from the literature[86] that phenylsulfonyl esters undergo cleavage smoothly upon treatment with metal amalgam, magnesium (metallic), or lithium/naphthalene mediated reductive elimination.[87] From the mechanistic view point, upon electron transfer to the sulfone (reduction potential E_p = 1.81 eV), the fragmentation of the resulting radical anion **3-39** to sulfinate anion and the more stable organic radical **3-40** occurs. The second electron reduction of the generated radical **3-40** followed by the enolate **3-41** protonation yields the desired sulfur-free product **3-26** (Scheme 45).

We expected that the reductive-elimination of the BT-sulfone **3-10b** will proceed via the same reaction mechanism. Our confidence was even more enhanced when experimentally measured reduction potential of **3-10b** showed to be even lower than that of the phenylsulfone **3-38** (E_p = -1.20 eV),[‡] suggesting that the reductive-elimination should proceed rather smoothly.

[‡] J.P. is grateful to Dr. Kevin Lam (UCLouvain, Belgium) for measuring the values of the reduction potential (E_p).

The values were measured for the two following compounds:

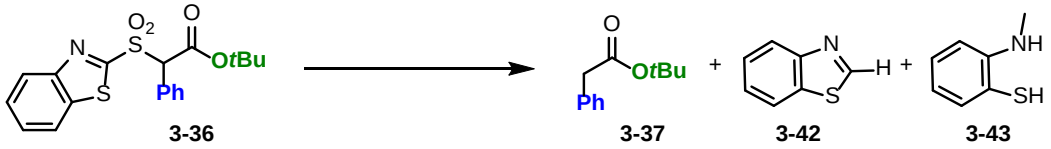




Scheme 45. Mechanism of metal-promoted reductive-elimination of carbonyl sulfonates.

Thus we were rather surprised that none of the metal amalgams or other "common" reducing reagents yielded the desired esters **3-26** in good yields (Table 10, entries 1 to 3). The only two reducing agents we found to be able to accomplish the desired transformation were SmI_2/MeOH and Zn/AcOH mixtures (Table 10, entries 4 to 7).

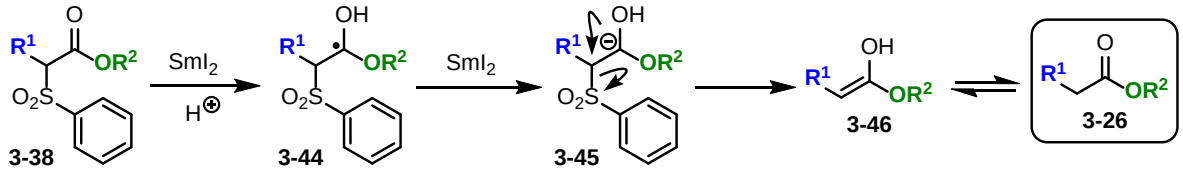
Table 10. Reductive-elimination of the sulfonyl ester **3-36** to ester **3-37**.



Entry	Conditions	3-37 (%)	3-42 (%)	3-43 (%)
1	Mg (10 equiv), THF/MeOH = 3:1 (V/V), rt, 2 days	<5	<5	<5
2	Al(Hg) (10 equiv), THF/MeOH = 10:1 (V/V), rt, 2 days	<5	<5	<5
3	Na(Hg) (10 equiv), THF/MeOH = 10:1 (V/V), rt, 2 days	<5	<5	<5
4	SmI_2 (2 equiv), THF, MeOH (30 equiv), -78°C, 5 min	32	7	28
5	SmI_2 (4 equiv), THF, MeOH (30 equiv), -78°C, 5 min	52	9	43
6	SmI_2 (6.2 equiv), THF, MeOH (50 equiv), -78°C, 5 min	93	<5	39
7	Zn (4 equiv), THF/AcOH = 5:1 (V/V), rt, 6h	91	<5	<5

One can see that the two suitable conditions we found to promote the reductive elimination step are quite different. In the case of zinc-promoted reductive-elimination, the reaction proceeds at rt and is rather slow (6h). On the other hand, SmI_2-promoted reaction is fast (5 min) and proceeds even at very low temperatures (-78°C). The second difference is in the amount of the reducing reagent required to drive the conversion of the sulfonyl ester **3-36** to completion. In the case of zinc, 4 equiv are used. Theoretically, the reaction require only 2.1 equiv of Zn^0, but in that case the reaction takes 28 hrs. In the case of SmI_2, 6.2 equiv was necessary to transform all starting material **3-36** to the desired ester **3-37**. Even in this case only 2.0 equiv of SmI_2 is theoretically required to accomplish the transformation, but when 2.1 equiv of SmI_2 is used, only partial conversion of **3-36** was observed. We believe that the main reason of this observation is the *in situ* formation of benzothiazole **3-42** during the reaction as a side product. This compound then undergoes competitive reduction with the SmI_2 to yield over-reduced aniline **3-43**.

Both of the above mentioned observations brings us to the conclusion that the two processes, Zn and SmI_2-mediated reductive eliminations do not proceed *via* the same reaction mechanism. We believe that the desulfonylation carried out in the presence of the Zn/AcOH mixture proceeds *via* the mechanism depicted in Scheme 45, while the SmI_2-promoted reductive elimination operates according the reaction mechanism suggested in Scheme 46.[88]

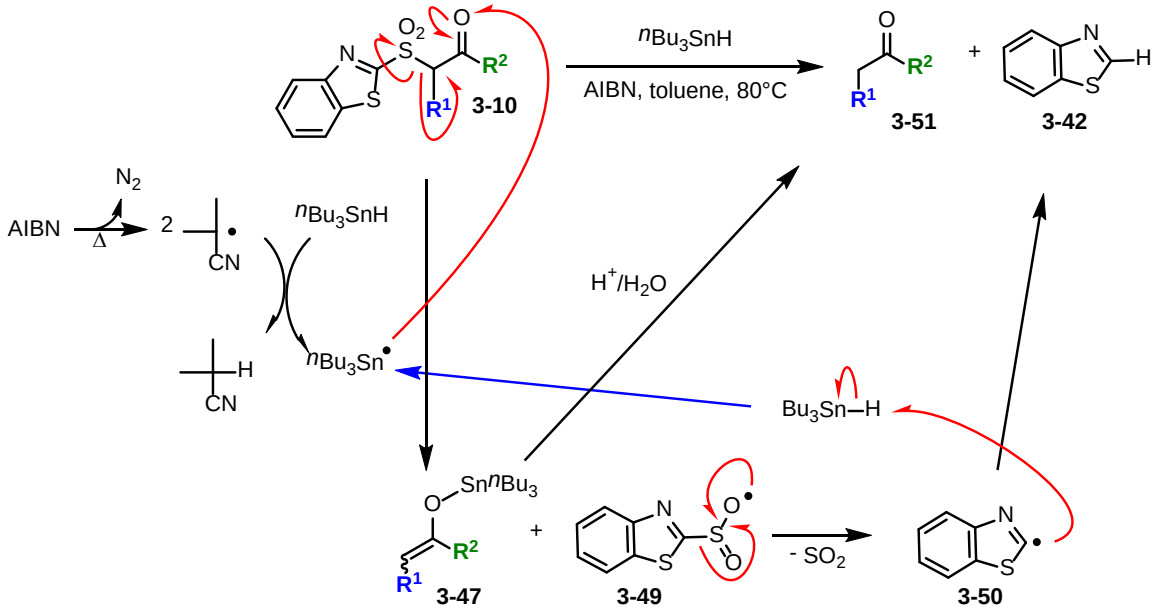


Scheme 46. Mechanisms SmI_2/H^+ promoted reductive elimination of **3-38**.

Finally, regardless of the reaction mechanism employed, both reduction-elimination protocols might be used to accomplish the desulfonylation of targeted β-carbonyl sulfones in good yields.

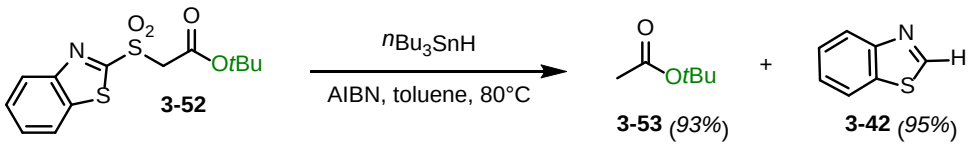
- ***Radical reaction-based BT-SO_2 release.***

Next, we decided to explore the radical-mediated desulfonylation of **3-10**. Our approach was based on the literature precedence[89] where α-carbonyl pyrimidine sulfones where desulfonylated using a *n*Bu_3SnH/AIBN procedure. The mechanistic rationalization behind this is depicted in Scheme 47.



Scheme 47. Mechanistic rationalization of the carbonyl BT-sulfone **3-10** radical desulfonyzation.

In this case we were delighted to observe that the reaction proceeds as planned and simple treatment of our testing substrate **3-52** with stoichiometric amount of *n*Bu_3SnH and 10 mol % of AIBN as radical initiator yielded the desired desulfonylated product **3-53** in excellent yield (Scheme 48). The expected side product **3-42** was also isolated during the reaction.

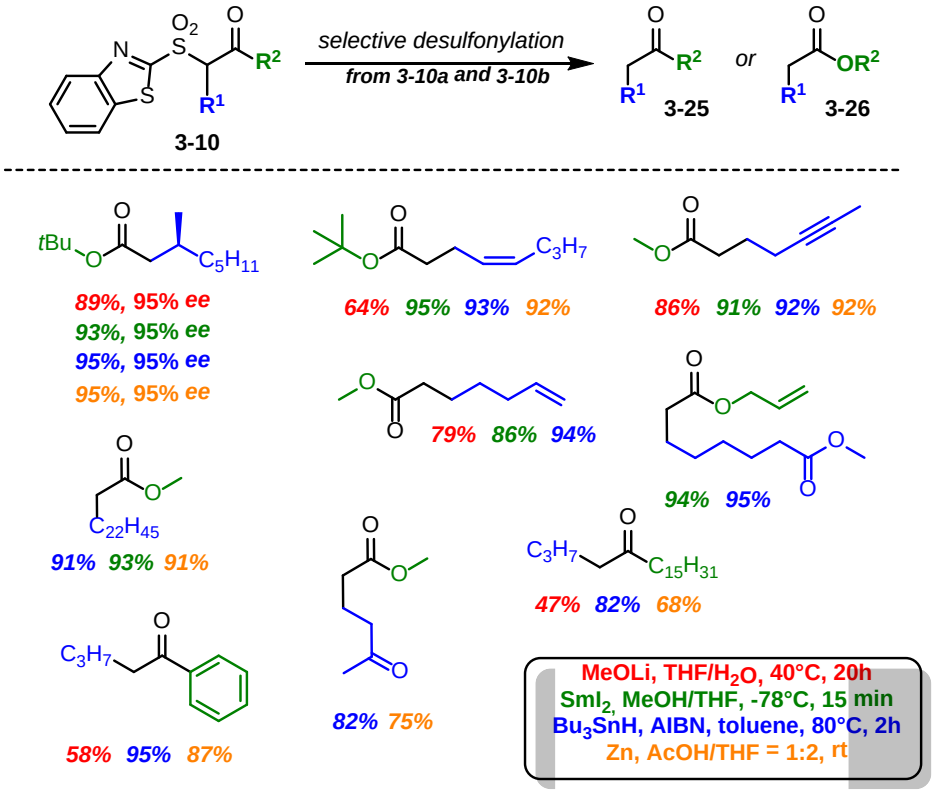


Scheme 48. Radical-based desulfonylation of the α-carbonyl BT-sulfones.

- ***Application.***

Having developed three independent and mechanistically different ways of desulfonylation of BT-sulfones **3-10**, we decided to apply them to a series of substrates and to compare the outcomes (Table 11). It is obvious that not all methods are generally applicable and the outcome of the **3-10** desulfonylation to ketones **3-25** or esters **3-26** relies on the method used. For example, when MeO^-Li^+ method is employed, the transesterification of esters present in the molecule occurs (not valid for *tert*-butyl esters). In the case of the SmI_2-mediated transformation, large waste production is accompanied with the product formation due to the excessive amounts of the reagent used, which in some cases makes purification of the products rather difficult. The same applies when the nBu$_3$SnH/AIBN procedure is used. Finally, the most convenient method seems to be based on the use of the Zn/AcOH. Obviously, the limitation of this method is restricted to substrates that do not undergo reduction in the presence of metallic zinc.

Table 11. Comparative application of developed desulfonylation methods.



3.2.2.2 *Target: selective synthesis of (E) and (Z)-olefins* ***3-27***

The next reaction sites of interest we wished to explore within our reagent-driven DOS synthesis were the electrophilic centers of **C**=O carbonyl functionality and the **C**=N in benzothiazole of **3-10a** (Figure 14). We wished to do this so in a selective manner where the carbonyl site reacts first and chemoselectively in the presence of the C=N site of the benzothiazole heterocycle. The reason behind

this was to trigger, by the chemoselective hydride reduction of the carbonyl group, the Smiles rearrangement within the skeleton that would finish up with the transformation of the sulfonyl carbonyl moiety within the **3-10a** molecule into the olefinic functionality (similarly to the Julia-Kocienski olefination reaction). The stereoselectivity of the carbonyl reduction would then define the stereochemical outcome of the newly created olefinic bond (Scheme 49).

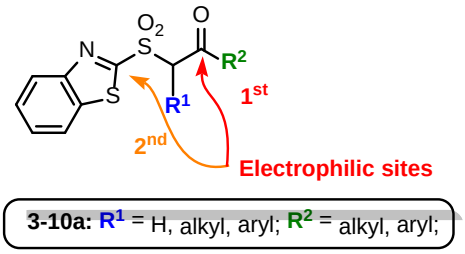
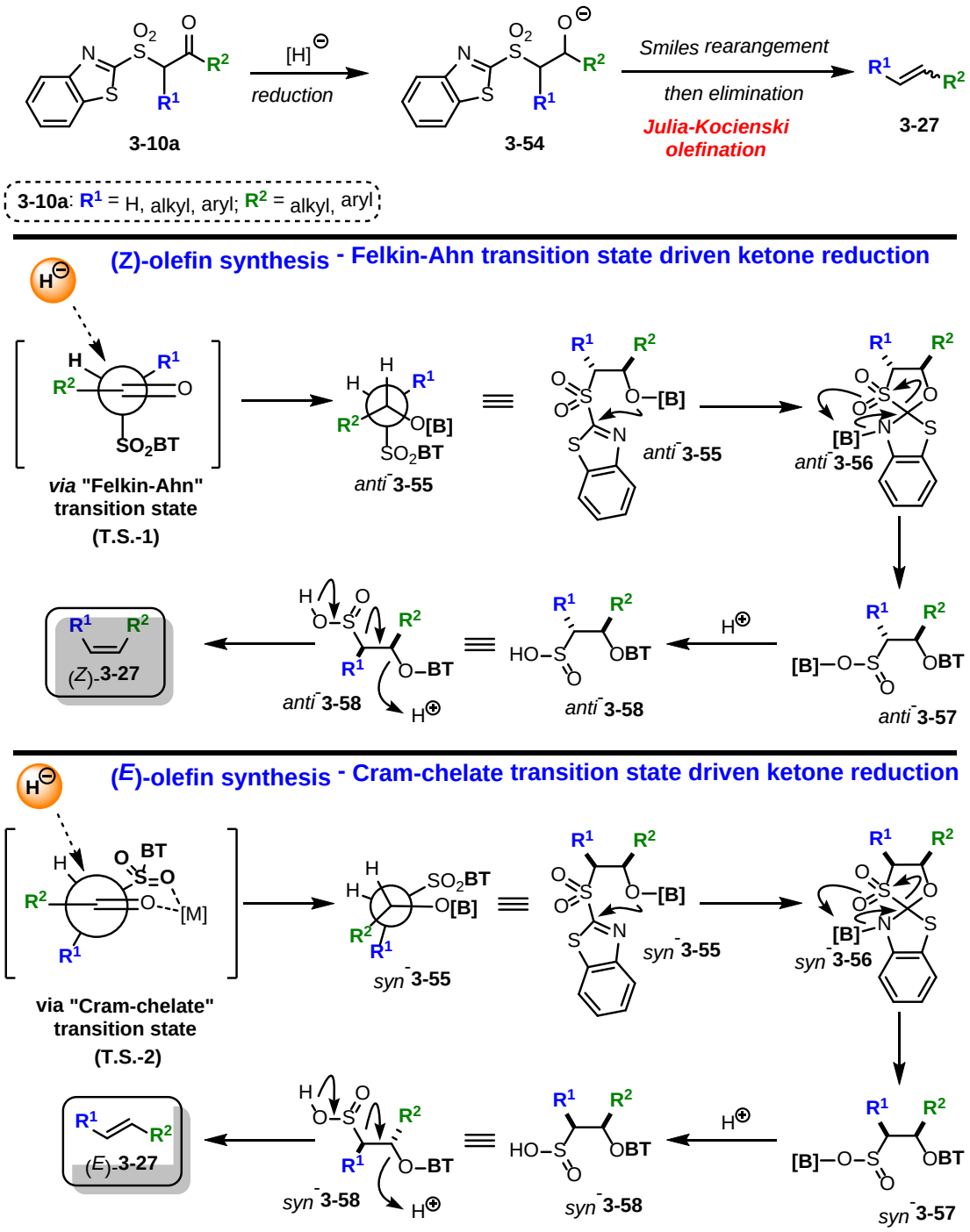


Figure 14. Electrophilic sites presented in **3-10a** of interest.

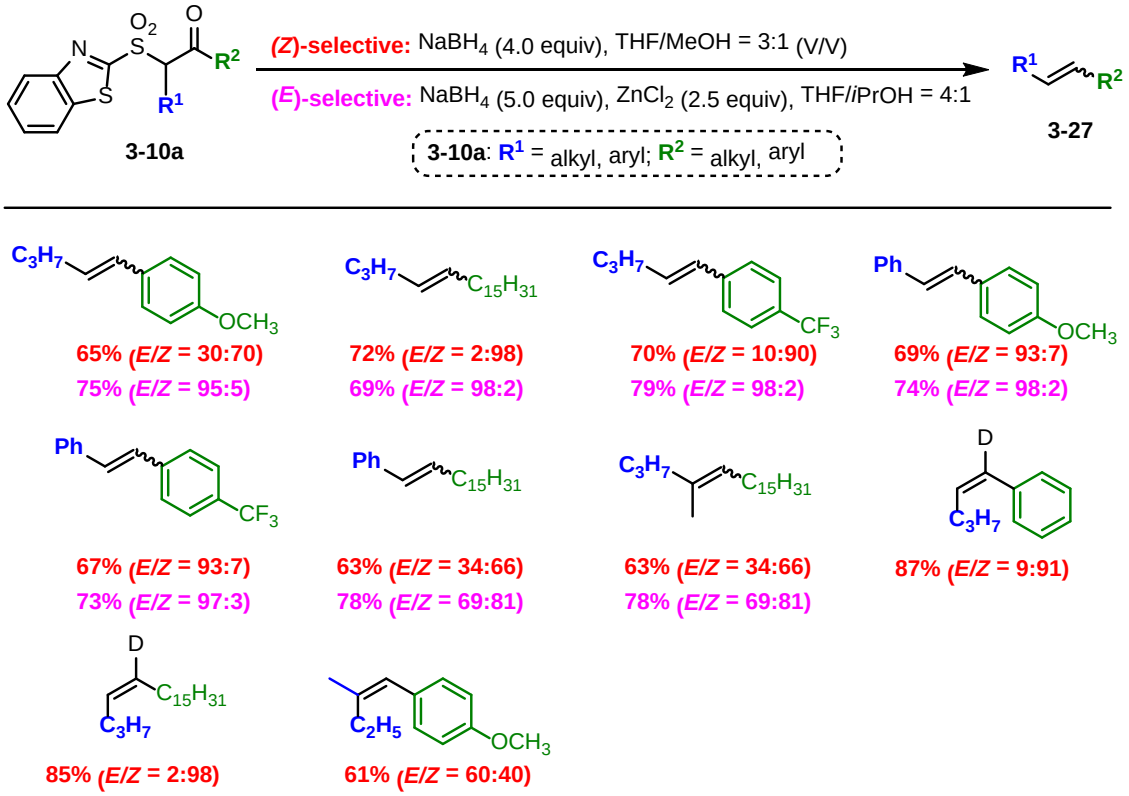
But first we had to choose an appropriate reducing agent that would be able reduce the carbonyl function, but would not be enough basic to deprotonate acidic hydrogen α to sulfone group. With little hesitation we decided to use the $NaBH_4$ reagent. The additional reason for this choice was that we can modulate the reactivity of the hydride reagent by changing the boron substituents and the counter cations. Thus, we should be able further to influence the *syn*/*anti* selectivity of the ketone reduction (in regards to the BT-sulfone group). We were expecting that the selectivity of the reduction would be dependent on the transition state *via* which the reduction proceeds (Scheme 49). Thus, if the desired product should be olefin (*Z*)-**3-27**, the reduction should proceed *via* the Felkin-Ahn transition state and yield *anti*-adduct *anti*-**3-55**. On the other hand, if the (*E*)-olefin (*E*)-**3-27** is desired as the product, the Cram-chelate transition state is required.

Having this idea in mind we designed two reaction condition setups where the ketone reduction should proceed either *via* the Felkin-Ahn transition state (TS-1; $NaBH_4$ (4 equiv), THF/MeOH=3:1 (V/V)), or *via* the Cram-chelate transition state (TS-2; $ZnCl_2$ (5 equiv), THF/*i*PrOH = 3:1 *then* $NaBH_4$ (2.5 equiv). Gratifyingly, in both cases the reaction proceeded well and yielded the desired olefins in good to very good yields. The selectivity of the overall olefination reaction yielded expected (*E*) or (*Z*)-products as long as the R^1 and R^2 were aliphatic. However, when the R^1 and R^2 groups are aromatic, the presence of the thermodynamic (*E*)-olefin becomes more significant and overall the (*Z*)-selectivity of the (*Z*)-selective protocol starts to drop. When three substituted olefins were prepared, the reaction proceeded with very low overall selectivity.



Scheme 49. Stereoselective olefin synthesis *via* $NaBH_4$-promoted Julia-Kocienski-type olefin formation

Table 12. Selected examples of the olefination protocol.



3.2.2.3 *Target: alkyne 3-28 synthesis*

Finally we focused our attention to alkyne **3-28** synthesis. From the reaction site point of view, we wished to explore the reactivity based on three aspects. Firstly, the acidity of the hydrogen α to sulfone (1st)and subsequently, at the same time, the nucleophilicity of the newly created enolate (2nd) *and* lastly the electrophilicity of the carbon atom in the **C**=N function (3rd) of the benzothiazol heterocycle (Figure 15).

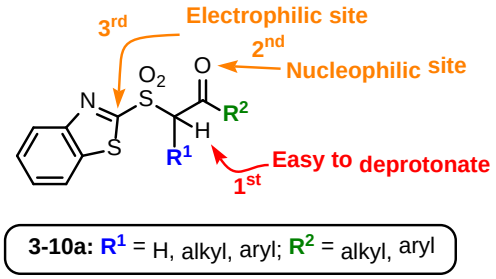
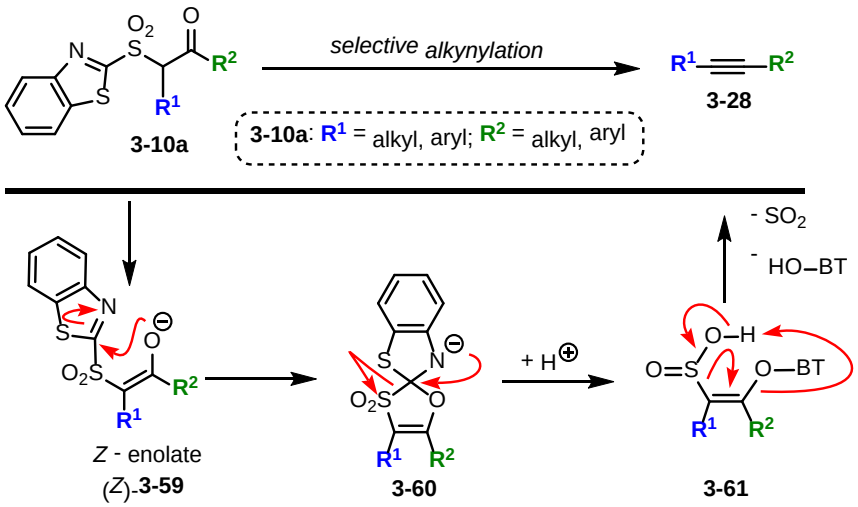


Figure 15. Reaction sites explored in the alkyne formation.

Mechanistically we had assure that during the reaction we can simultaneously (1) deprotonate acidic a to sulfone proton, (2) allow the formation of the (*Z*)-enolate (equilibrium, (*E*)-enolate generally preferred due to steric reasons), give enough energy to the system that the Smiles rearrangement can occur, (3) protonate the rearrangement product **3-61** so it can undergo *syn* elimination to yield the desired alkyne **3-28**.

During the reaction setup, we had to face to several problems. First, the BT group can be hydrolyzed under nucleophilic conditions (see Scheme 44). As a solution to this problem we proposed the use of the biphasic system, where the base would be situated out of the biphasic system, where the base

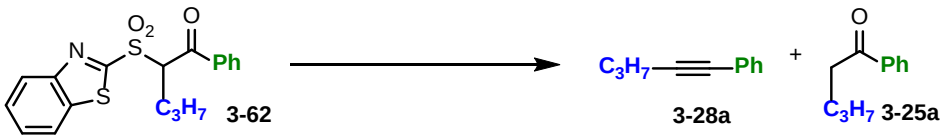
would be presented only in the aqueous phase and, when needed, transferred by phase transfer catalyst into the organic phase. To increase the basicity, toluene was used as the solvent. We hoped that this setup will also allow the equilibration to shift between (*E*) and (*Z*)-enolate required for the Smiles rearrangement.



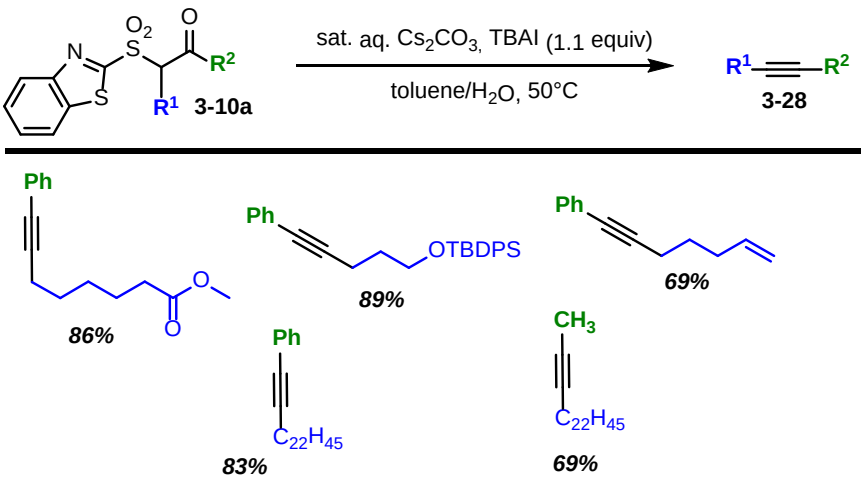
Scheme 50. Reaction mechanism rationalizing the alkyne **3-28** formation.

Finally, after some reaction optimization, we were happy to observe the alkyne formation (Table 13). However, for the time being, this method has only limited scope and we are struggling with its generalization and overall reproducibility. So, the concept is proven, but it requires more work to find better and more appropriate conditions that would allow us to form the desired alkynes in good yields.

Table 13. Optimization of the alkyne **3-28** formation – selected examples.



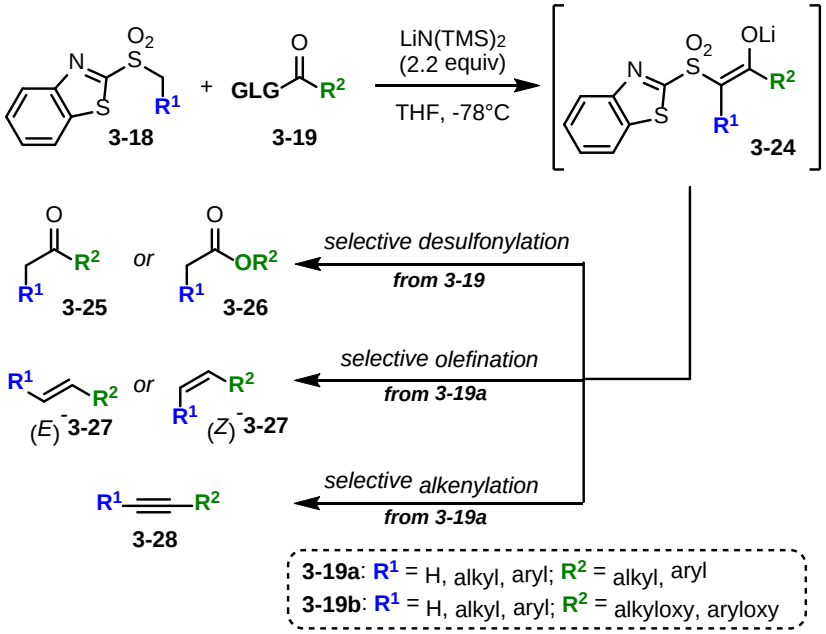
Entry	Conditions	3-28a (%)	3-25a (%)
1	sat. aq. Na_2CO_3, TBAI (1.1 equiv), THF/H_2O, 50°C	9	82
2	sat. aq. Na_2CO_3, TBAI (1.1 equiv), toluene/H_2O, 50°C	21	64
3	sat. aq. Li_2CO_3, TBAI (1.1 equiv), toluene/H_2O, 50°C	5	75
4	sat. aq. K_2CO_3, TBAI (1.1 equiv), toluene/H_2O, 50°C	45	48
5	sat. aq. Cs_2CO_3, TBAI (1.1 equiv), toluene/H_2O, 50°C	78	5



Scheme 51. Selected examples of the alkyne formation.

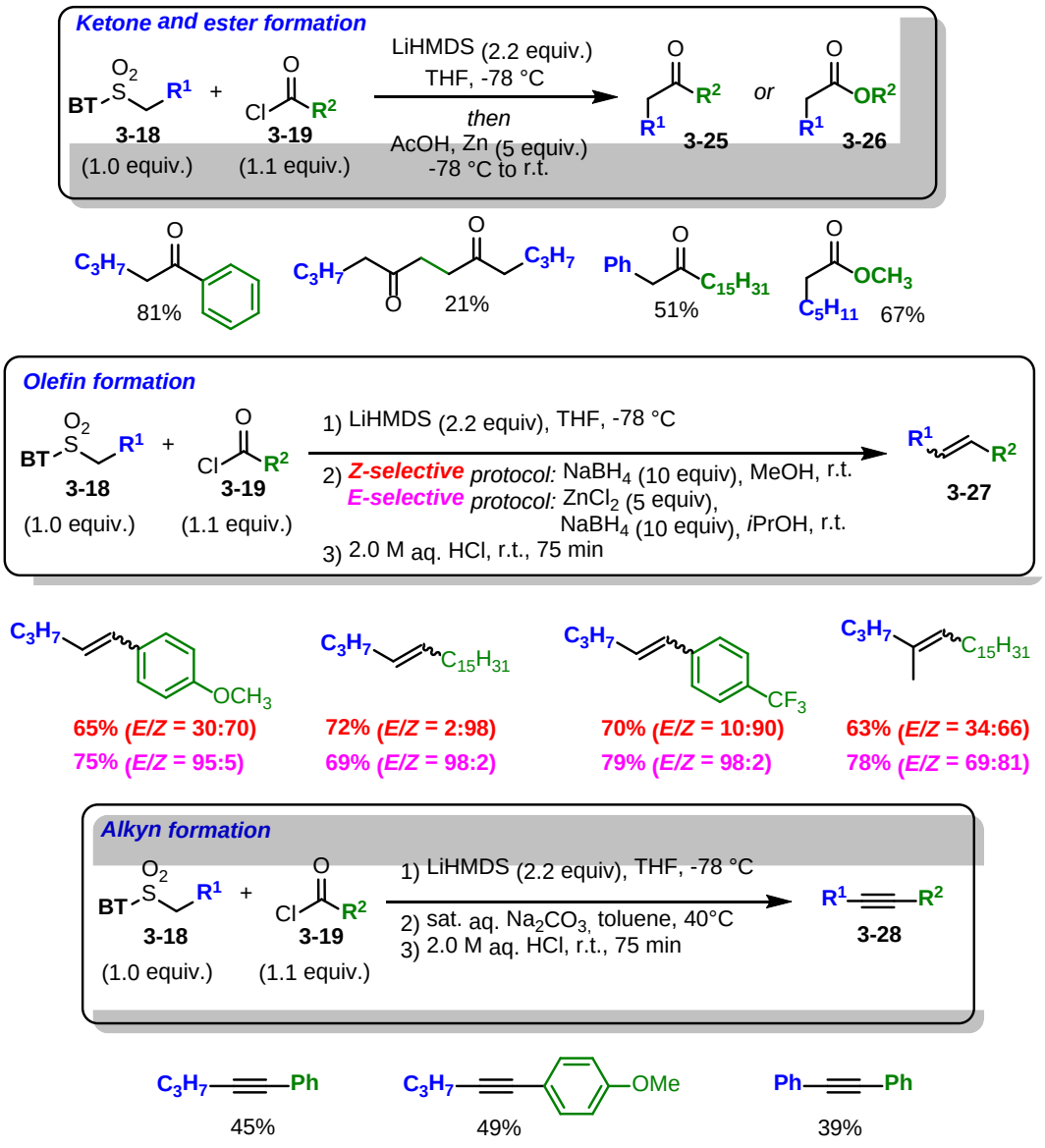
3.2.3 One-pot Couple/Pair phase – towards the new C-C coupling reaction

In the previous chapter we have demonstrated that when carbonyl sulfones **3-10** are reacted under appropriate conditions, ketones (**3-25**), esters (**3-26**), alkenes (**3-27**) and alkynes (**3-28**) can be prepared. Our next question was, can we make this type of transformation even more useful and straightforward? By other means, could we combine the Couple (chapter 3.2.1) and Pair (chapter 3.2.2) steps to operate in one-pot protocol? Or, can we develop a new C-C bond forming reaction that would react BT-sulfones **3-18** with carbonylating agent **3-19** and would *upon the reaction work up* yield the corresponding products **3-25**, **3-26**, **3-27** or **3-28** (Scheme 52).



Scheme 52. One-pot C-C connective reaction yielding upon the reaction work-up ketones, esters, olefins or alkynes.

And we were happy to see that by slight work up modifications we could have reunite the coupling conditions leading originally to carbonylated BT-sulfones **3-10** with the reagent-driven DOS conditions yielding any of the three types of the products mentioned in the Scheme 52. And more interestingly, the overall transformations have not lost the original selectivity. Chosen representative examples are showed in Scheme 53.



Scheme 53. One-pot connective C-C bond forming reaction – applications.

3.2.4 Divergence in B/C/P strategy - use of 3-10 as C-nucleophiles in Mitsunobu reaction

The second issue, along with the one-pot coupling reaction, we have decided to tackle, was a subsequent modification of the carbonylated BT-sulfones **3-10**. Our idea was to extend the use of such building blocks as the C-nucleophiles. As was showed in the introduction of the chapter 3.2, Jørgensen's group very nicely developed the use of β-carbonyl BT-sulfones **3-10a** in organocatalytic reactions. Our idea was to focus on the BT-sulfone ester derivatives **3-10b** and to explore their reactivity in the context of the Mitsunobu reaction.

We have chosen deliberately the Mitsunobu reaction, because it is known from the literature that the Mitsunobu reaction of phenylsulfonyl esters **3-63** do not proceed well (generally at all).[90] The main reason is the low acidity of the α to sulfone hydrogen atom (pKa ~ 13.5). Generated C-nucleophilic center then competes as nucleophile with alcohols (pka ~ 15) and the overall reaction do not proceeds. We were expecting that the presence of the BT electron acceptor group on the sulfone function will increase the pKa of the hydrogen atom α to sulfone and will allow us to use BT-sulfones **3-10b** as C-nucleophiles in the Mitsunobu reaction (Figure 16).

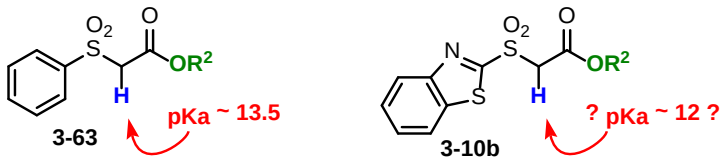
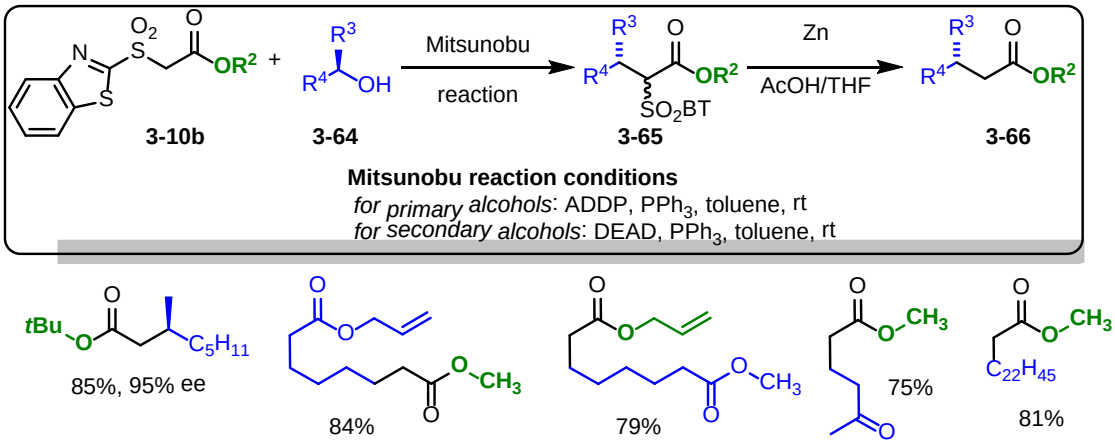


Figure 16. The pKa values of **3-63** (measured) and **3-10b** (estimated).

After some tedious reaction optimization we come up with two sets of the reaction conditions that allowed us to prepare the desired alkylated products **3-66** in good yields (Scheme 54).



Scheme 54. Some examples of the Mitsunobu reaction/desulfonylation synthesis of the esters **3-66**.

4. Conclusions and perspectives

In the previous two chapters of this Habilitation Theses I have tried to give you a flavor of the chemistry I have with my colleagues pursued over past few years. I am still interested in, and I wish to pursue in in the near future. To be fully honest, this Thesis contains the overview of only one of the three main topics on which we are working on. But, the research gathered within this Theses is sort of Origin, Beginning and a Consequence of the remaining two topics focused on the natural product synthesis (not covered here). Indeed, it is the chemistry of sulfur, and mainly of the Julia-Lythgoe and Julia-Kocienski olefination reactions, that strongly influenced my projects in the field of methodology development. That chemistry allowed my research evolve from the *desire* to increase the versatility and selectivity of Julia-type transformations to the *design* of new systems of pluripotent compounds suitable for reagent-driven DOS. For the time being, this is the ultimate Goal of my research – the design of pluripotent functional molecules. Those parent molecules, upon treatment with various reagents, yields structurally very different molecular scaffolds. This complexity driven synthesis should allow us to prepare and identify new molecular probes suitable to study targeted biological processes. It should be also mentioned, that from the synthetic point-of-view, PM should be easily available *via* short (1-3 steps) synthesis from commercially available building blocks. Quite obviously, in the future we would like to transfer our methodology to solid-support. This move should allow us to enhance the versatility and operational simplicity of the transformations.

Clearly, the development of methodologies allowing short and efficient synthesis of complexity-driven compound libraries is not the only goal we are heading to. Indeed, we wish also to apply those methods. Currently, we are investigating the mode of action of lignan-based plant secondary metabolites, that are used in traditional medicine against the parasites of *Leishmania*-type. In this particular case, it is known that several naturally occurring lignans (for more details see [91]) are used as a part of traditional herb-based remedy by South American Shamans, but the mode of action remains unknown. We hope that in collaboration with our colleagues from the biology department we will be able to shed some light on the mode of action of those molecules.

Along with this ‘complexity-driven small molecule synthesis’, we are also interested in the determination of reaction mechanisms. We have already, in collaboration with our colleagues from the theoretical department, helped understand better several important key steps of some chemical transformations as e.g. Julia-Kocienski reaction. Indeed, the mechanistical studies and the evaluation of various functional group reactivity is a key to our design of pluripotent PM molecules.

Finally, the two research topics not presented in this Thesis, that are currently pursued in collaboration with several colleagues in the department of Chemical Biology and Genetic, are focused on the natural product synthesis. Particularly we are interested in two classes of natural products of plant origin – derivatives of phenylpropanoids (lignans and neolignans in particular) and compounds related to plant hormones (derivatives of gibberellic acid). Our main interest in this field is to apply our synthetic methods to accomplish selected chemo-, regio- and stereoselective modifications of targeted compounds.

Finally, we are also interested in the synthesis of isotopically labelled natural products. Such compounds find their application as probes and internal standards when metabolomic analysis is carried out.

5. Literature

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Appendix

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Sulfoxides in Julia–Lythgoe Olefination: Efficient and Stereoselective Preparation of Di-, Tri-, and Tetrasubstituted Olefins

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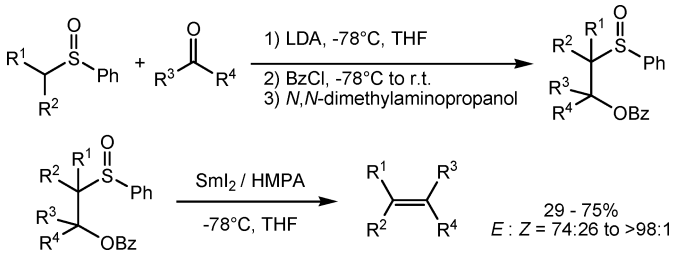
ABSTRACT

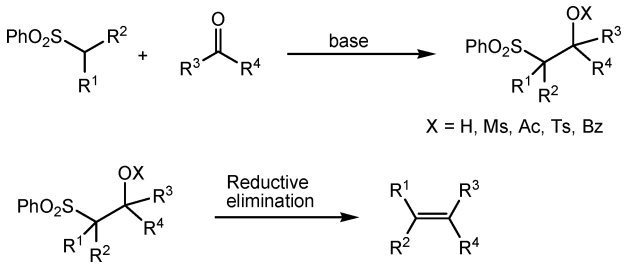


A novel modification of the classical Julia–Lythgoe olefination, using sulfoxides instead of sulfones, affords, after in situ benzoylation and SmI_2/HMPA- or DMPU-mediated reductive elimination, 1,2-di-, tri-, and tetrasubstituted olefins in moderate to excellent yields and *E*/*Z* selectivity. The conditions are mild, and the procedure is broadly applicable.

The formation of olefins from sulfones and carbonyl compounds, known as the Julia−Lythgoe olefination, is one of the most powerful tools of modern organic chemistry.[1] The initial reductive elimination of the intermediate β-hydroxysulfones using Na−Hg has been gradually superseded by mild, more selective, and less toxic reducing agents such as SmI_2[2] or Mg[3] (Scheme 1).

Disappointingly, this widely used method still suffers from several drawbacks. One of them is the relatively high stability of the sulfonyl anion which limits its reactivity. For example, if an additional electron-withdrawing substituent is present on the anion-bearing carbon, this organometallic species becomes so stable that it does not add even to activated

Scheme 1. Julia−Lythgoe Olefination



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(6) The pK_a of the hydrogen on the carbon bearing sulfinyl group is four orders higher than the pK_a of the equivalent hydrogen on the carbon bearing sulfonyl group.

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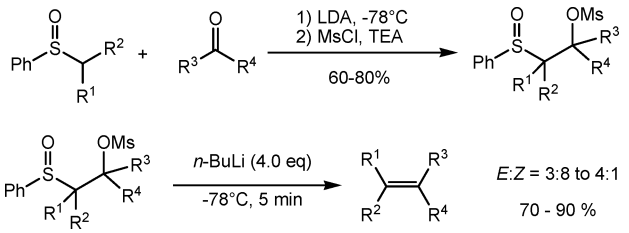
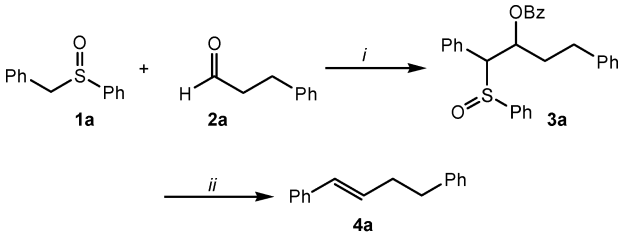
Scheme 2. Sulfoxide Version of the Julia−Lythgoe Olefination



aldehydes.[2c] Moreover, in the case of the reaction of nonstabilized sulfones with some aldehydes and with ketones, the position of the equilibrium between the starting carbonyl compound and the sulfone anion is shifted toward the starting materials. The desired adduct (tertiary alkoxide) is therefore present in the reaction mixture as a minor component. Trapping this intermediate in situ with several electrophiles, such as benzoyl chloride, mesyl chloride, or acyl chloride, is a common trick employed to shift the equilibrium toward the products. It is interesting to note that these β-acyloxy, benzoyloxy, and mesyloxy sulfone derivatives undergo smoother reductive elimination than the parent β-hydroxy sulfones.

Table 1. Optimization of Reductive Elimination Step Using SmI_2



i) (a) LDA (1.1 eq), THF, -78°C; (b) BzCl (1.5 eq), -78°C to r.t. (c) $Me_2NCH_2CH_2CH_2OH$ (1.55 eq)
ii) SmI_2 (3.5 eq), THF, -78°C, additive

entry	additive	equiv to SmI_2	yield[a] (%)	*E*/*Z*[b]
1	–	–	–	na
2	HMPA	0.25	25	>95:1
3	HMPA	0.5	34	>95:1
4	HMPA	0.75	43	>95:1
5	HMPA	1.0	67	>95:1
6	HMPA	2.0	64	>95:1
7[c]	DMPU	15.0	12	na
8[d]	DMPU	15.0	32	>95:1
9[e]	DMPU	15.0	48	>95:1
10[f]	DMPU	15.0	10	na

[a] Overall yields refer to pure, isolated products. [b] Determined by capillary GC. [c] Reaction carried out at −50 °C. [d] Reaction carried out at −25 °C. [e] Reaction carried out at 0 °C. [f] Reaction carried out at rt.

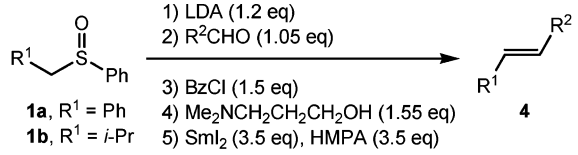
Nevertheless, such modifications are useless when the generated sulfonyl anion is so stable that it does not add to the carbonyl compound. Recently, Satoh et al. reintroduced[4] sulfoxides as a sulfone equivalent in the Julia−Lythgoe olefination.[5] As an advantage, the carbanion generated α to the sulfoxide group is far less stabilized[6] than in the case of the corresponding sulfone and the addition reaction, leading to the formation of the C−C bond, is favored even in the case of ketones. The reductive elimination was carried out via sulfoxide/lithium exchange, followed by elimination of the β-mesyloxy or acyloxy group (Scheme 2).

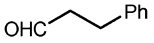
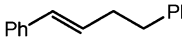
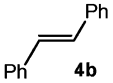
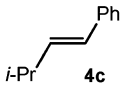
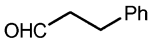
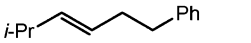
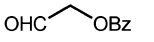
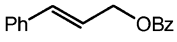
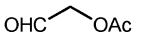
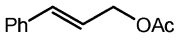
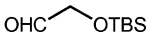
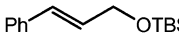
Using this method, stilbene derivatives could be prepared via this Julia−Lythgoe modification for the first time, though with rather modest *E*/*Z* selectivity. On the other hand, the use of an excess (4 equiv) of a strong base (*n*-BuLi) can be rather inconvenient in the case of functionalized substrates.

For some time, we have been interested in various modifications of the Julia−Lythgoe reaction[2c,7] and have recently introduced the SmI_2/HMPA-mediated reductive elimination of β-benzoyloxysulfones, formed by the addition of α-sulfone anions to ketones, as an efficient and stereoselective route toward trisubstituted olefins.

Based upon our previous results, we envisaged that the SmI_2-mediated reductive-elimination of β-benzoyloxy sul-

Table 2. Synthesis of 1,2-Disubstituted Olefins

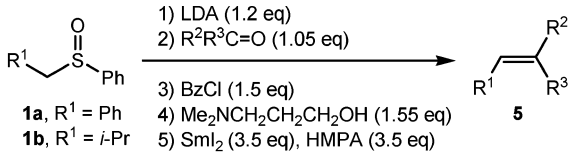


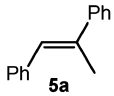
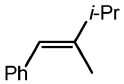
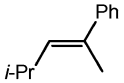
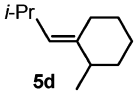
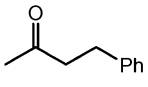
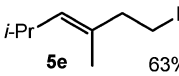
entry	1	R^2CHO	product	yield[a](%) *E* / *Z*[b]
1	1a		 4a	67%, >95:1
2	1a		 4b	75% >95:1
3	1b		 4c	70% 76:24
4	1b		 4d	69%, 94:6
5	1a		 4e	71%, >95:1
6	1a		 4f	68%, >95:1
7	1a		 4g	70%, >95:1

[a] Overall yields refer to pure, isolated products. [b] Determined by ^1H NMR spectroscopy.

(7) Marko, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballaresb, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609.

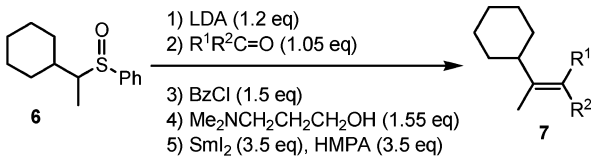
Table 3. Preparation of Trisubstitted Olefins

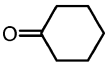
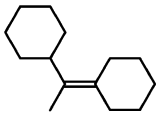
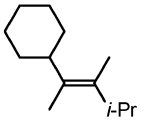
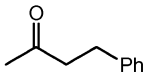
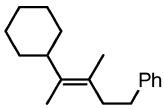


entry	1	R^2R^3C=O	product	yield[a](%) *E* / *Z*[b]
1	**1a**		 **5a**	51% 76:24
2	**1a**		 **5b**	57% 91:9
3	**1b**		 **5c**	64% 74:26
4	**1b**		 **5d**	64% 88:12
5	**1b**		 **5e**	63%, 68:32

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy.

Table 4. Preparation of Tetrasubstituted Olefins



entry	R^2R^3C=O	product	yield[a](%) *E* / *Z*[b]
1		 **7a**	33%
2		 **7b**	29% 97:3
3		 **7c**	32% 91:9

[a] Overall yields refer to pure, isolated products. [b] Determined by ^{1}H NMR spectroscopy.

foxides might produce the desired olefins in high yield and with good *E*/*Z* selectivity.

To test our hypothesis, the coupling of sulfoxide **1a** with aldehyde **2a** was carried out (Table 1).[8] In the first step of this reaction, a new C−C bond is formed. As a consequence, two new stereogenic centers are created which, added to the one present in the sulfoxide moiety, leads to four different diastereoisomers of **3a**. To avoid their tedious separation, it was decided to use the mixture of adduct **3a** in the subsequent reductive elimination step.[9] Some pertinent results are collected in Table 1.

As can be seen in Table 1, SmI_2 itself does not promote the reaction (Table 1, entry 1). HMPA and DMPU were then tested as additives in order to increase the reduction power of SmI_2.[10] Gratifyingly, the presence of small amounts of HMPA already resulted in olefin formation, though the rate of the reaction was rather slow (Table 1, entry 2). The use of one equivalent of HMPA was found to be optimal, and adding more of this cosolvent did not increase the yield of the reaction (Table 1, entries 5 and 6).

DMPU was explored as an alternative, nontoxic HMPA equivalent. However, under all reaction conditions tested, the yields remained lower than with HMPA (Table 1, entries 7−10). Moreover, a large excess of DMPU and higher temperature (0 °C to rt) had to be employed (Table 1, entries 9 and 10).

Having devised suitable reaction conditions to effect this sulfoxide variant of the Julia−Lythgoe olefination, we explored its scope and limitations. A selection of pertinent results are collected in Tables 2 and 3.

The phenyl bearing sulfoxide **1a** gave, upon reaction with aryl and alkyl aldehydes, the corresponding disubstituted olefins **4a** and **4b** in good yields. Only the thermodynamically more stable (*E*)-double bond isomer was observed (Table 2, entries 1 and 2). The *iso*-propyl substituted sulfoxide **1b** afforded, upon reaction with dihydrocinnamaldehyde, the desired disubstituted olefin **4d** in good yield and a respectable 94:6 *E*/*Z* ratio (Table 2, entry 4). To our surprise, when **1b** was reacted with benzaldehyde, the resulting product **4c** was obtained with a modest *E*/*Z* ratio of 76:24 (Table 2, entry 3). When **1a** was reacted with methyl isopropyl ketone, the *E*-isomer **5b** was formed as the major product in a 91:9 ratio (Table 3, entry 2). Moreover, we were delighted to observe that even acetophenone did react under these conditions and afforded the desired olefin **5a** in 51% yield and with an *E*/*Z* ratio of 76:24. Essentially the same ratio of isomers was observed when **1b** was condensed with acetophenone. Olefin **5c** was formed in 64% yield and a 74:26 E/Z ratio (Table 3, entry 3). The reaction of **1b** with other

(8) All the reactions presented in Table 1 are carried out on the mixture of adduct **3a**.

(9) The excess of benzoyl chloride was reacted with *N*,*N*-dimethyl-3-aminopropanol and the amines was removed upon acidic workup.

(10) (a) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A., II. *Tetrahedron Lett.* **1998**, *39*, 4429. (b) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137. (c) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. (d) Dahlen, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393.

(11) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

dialkyl substituted ketones (Table 3, entries 4 and 5) gave olefins **5d** and **5e** in a respectable 88:12 and a reasonable 68:32 *E*/*Z* ratio, respectively.

Finally, to test the robustness of our method, the preparation of tetrasubstituted alkenes was attempted, using the sterically hindered sulfoxide **6**.[11] We were delighted to observe that the expected olefins **7** were formed in an excellent *E*/*Z* ratio and still acceptable yields (Table 4).

In summary, we have developed a novel, highly stereoselective method for the synthesis of 1,2-di-, tri-, and tetrasubstituted olefins.[12] Under our conditions, sterically hindered sulfoxide anion (such as the one derived from sulfoxide **6**) and unreactive ketones (e.g., acetophenone) could be coupled in good to acceptable yields. A variety of functions and protecting groups are also tolerated (Table 2, entries 5−7).

Further studies are now directed toward optimizing these conditions, broadening the scope of this method and applying it to relevant natural product synthesis.

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Supporting Information Available: Experimental procedures, characterization of new compounds, and references to known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050649E

(12) **Typical Experimental Procedure. Coupling Step.** A solution of sulfoxide (1.0 mmol) in dry THF (10 mL, 0.1 M solution) was cooled to −78 °C and LDA (550 μL, 1.1 mmol) was added dropwise. The color of the mixture changed from slightly yellow to orange/red. After the mixture was stirred at −78 °C for 30 min, the aldehyde/ketone (1.05 mmol), dissolved in dry THF (0.5 mL), was added dropwise, and the mixture was stirred for an additional 2 h at −78 °C. Benzoyl chloride (1.5 mmol) in dry THF (0.5 mL) was then added, the resulting mixture was stirred for 30 min at −78 °C and then allowed to warm to rt over 1 h. After an additional 30 min at rt, $Me_2N(CH_2)_3OH$ (1.55 mmol) was added and the resulting suspension was stirred for 10 min at rt. The suspension was then diluted with $Et_2O/H_2O = 1{:}1$ (10 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with 1.0 M aq HCl (10 mL), H_2O (10 mL), and brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product, which was used without additional purification in the subsequent step. **Reductive Elimination.** To a solution of SmI_2 (35 mL, 0.1 M in THF, 3.5 equiv) was added HMPA (613 μL, 3.5 equiv), and the mixture was cooled to −78 °C. The crude coupled product (1.0 mmol) in dry THF (0.5 mL) was added dropwise, and the resulting mixture was stirred at −78 °C for an additional 30 min. Then, aqueous satd NH_4Cl (20 mL) was added, and the whole was allowed to warm to rt. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The pooled organic layers were washed with 10% aq $Na_2S_2O_3$ (20 mL), H_2O (20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was then purified by chromatography on silicagel.

SULFOXIDE-MODIFIED JULIA–LYTHGOE OLEFINATION: HIGHLY STEREOSELECTIVE DI-, TRI-, AND TETRASUBSTITUTED DOUBLE BOND FORMATION

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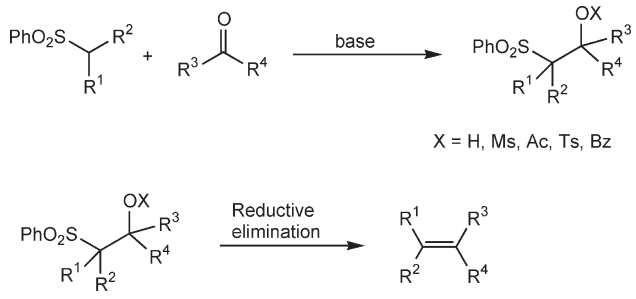
A novel modification of the classical Julia–Lythgoe olefination, using sulfoxides instead of sulfones, affords, after in situ benzoylation and SmI_2/HMPA or SmI_2/DMPU-mediated reductive elimination, 1,2-di-, tri- and tetrasubstituted olefins in moderate to good yields and *E*/*Z* selectivity. The conditions are mild and the procedure is widely applicable. The reaction mechanism was studied and a general model, describing the reaction selectivity, is proposed.
Keywords: Olefinations; Samarium; Reaction mechanisms; Additions; Synthetic methods; Julia–Lythgoe olefination; Sulfoxides; Alkenes; Reductive elimination.

The Julia olefination ranks among most powerful methods for the formation of C–C double bonds in modern organic chemistry. Originally, this procedure was based on the reaction of sulfones with carbonyl compounds. In the first step, an anion in α-position to sulfone group was added to a carbonyl compound, furnishing the corresponding β-hydroxysulfone[1] (Scheme 1). In the second step, this β-hydroxysulfone was treated with Na–Hg and underwent reductive elimination to give the desired olefin. Later on, it was observed that the transformation of the alcohol function of the β-hydroxysulfone into a better leaving group led to increased yields in the reductive-elimination step. Therefore, β-mesyloxy- or (acyloxy)sulfones are preferentially used nowadays as the intermediates subjected to the reductive elimination. As an additional advantage, acylating or mesylating reagents can be employed as trapping agents during the addition of the sulfonyl anion to the carbonyl function. The in situ capture of the β-alkoxysulfone anion intermediate further increases the yields of the addition step. Gradually, the original reductive-elimination method using Na–Hg amalgam has been superseded by mild, more selective and less toxic reducing agents such as SmI_2 (ref.[2]) or Mg (ref.[3]).

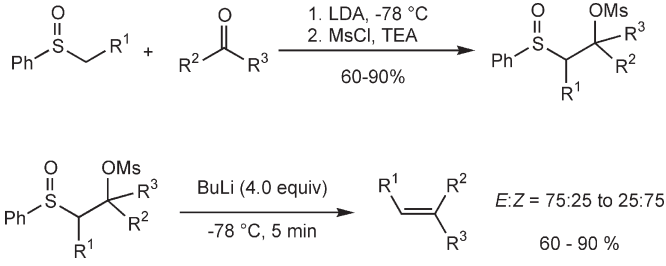


SCHEME 1

Disappointingly, this widely used method still suffers from several drawbacks. One of them is the relatively high stability of the sulfonyl anion which limits its reactivity. For example, if an additional electron-withdrawing substituent is present on the anion-bearing carbon, this negatively charged organometallic species becomes so stable that it does not add even to activated aldehydes[2c]. Moreover, in the case of the reaction of unstabilized sulfones with hindered aldehydes and with ketones, the position of the equilibrium between the starting carbonyl compounds and the sulfone anion is shifted towards the reactants. The desired adduct (tertiary alkoxide) is therefore present in the reaction mixture as a minor component. Trapping this intermediate in situ with some electrophiles, such as benzoyl chloride, mesyl chloride or acyl chloride, is a common trick employed to shift the equilibrium towards the products. However, in the case of highly crowded sulfones and/or ketones, even if the electrophile-trapping protocol is employed, the addition reaction does not proceed at all or only in a very low yield.

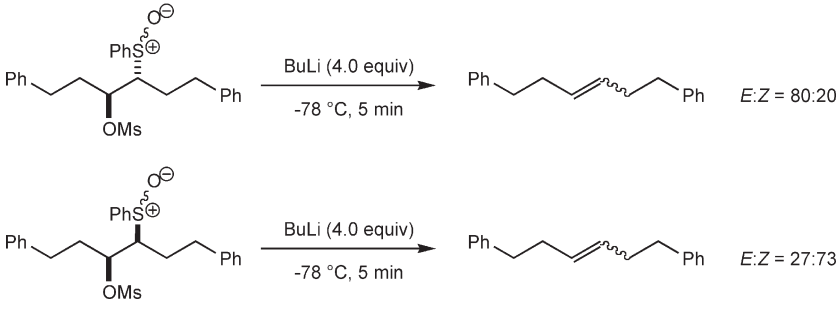
Moreover, this in situ capture method is not useful if the anion α to the sulfone is so stable that it does not add even to highly activated aldehydes. This problem occurs when the anion is present on the sulfonyl carbon bearing also phenyl or an electron-withdrawing group. To overcome this disadvantage, Satoh et al. reintroduced[4] recently sulfoxides as sulfone equivalents in the Julia–Lythgoe olefination[5]. To advantage, the carbanion generated (to the sulfoxide group is far less stabilized[6] than in the case of the corresponding sulfone and the addition reaction, leading to the formation of the C–C bond, is favored even in the case of ketones. The β-hydroxysulfoxides were then mesylated and subjected to BuLi (4 equivalents) mediated reductive elimination to give the desired olefins (Scheme 2). Using this modification, styrene and stilbene derivatives were prepared by the Julia olefination method for the first time. Disappointingly, the *E*/*Z* stereoselectivity was rather low. For example, 1,2-disubstituted olefins were gen-

erally prepared in 60–90% yields, with *E*/*Z* ratios varying, in the best cases, between 75:25 and 25:75. Trisubstituted alkenes were obtained from various α-branched sulfoxides and cyclohexanone in 60–90% yields. Unsymmetrical ketones were not studied. It was reported, though, that tetrasubstituted olefins could not be generated using this method.



SCHEME 2

Mechanistic studies of this reaction by Satoh showed that this elimination was highly stereospecific and that the geometry of the newly formed olefin depended on the relative configuration of the β-hydroxysulfoxide. Thus, if the *anti*-diastereoisomer was subjected to BuLi-mediated reductive elimination, the *E* isomer was preferentially formed. In contrast, if the *syn*-diastereoisomer was used, the *Z* isomer was generated as the major product. The influence of additional stereogenic centres present on sulfur atoms, on the stereoselectivity of the reaction was not studied (Scheme 3).



SCHEME 3

For some time now, we have been interested in the modification and development of various Julia–Lythgoe olefination methods[2c,7]. Recently, we have introduced the SmI_2/HMPA-mediated reductive elimination of β-(benzoyloxy)sulfones, formed by the addition of α-sulfone anions to ketones, as an efficient and stereoselective route to trisubstituted olefins. Based upon our previous results, we envisaged that the SmI_2-mediated

reductive elimination of β-(benzoyloxy)sulfoxides might produce the desired olefins in high yields and with good *E*/*Z* selectivity. Moreover, we envisioned that the trapping of the β-oxysulfoxide anion intermediate by the benzoyl group would increase the yield of the addition product. The resulting β-(benzoyloxy)sulfoxides, if properly substituted, might lead, for the first time, to tetrasubstituted olefins.

In this article, we wish to report in detail the results of our investigation in the development of a sulfoxide version of the Julia–Lythgoe olefination based on the concepts described above[8].

RESULTS AND DISCUSSION

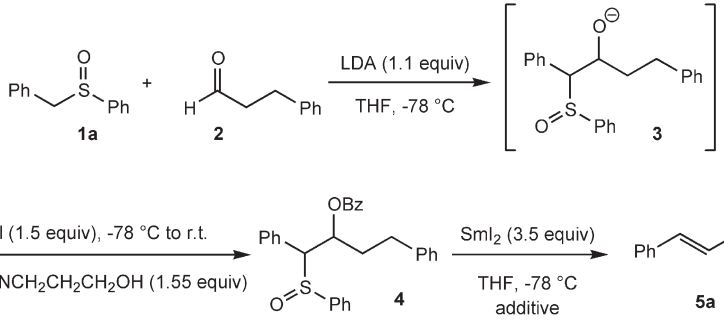
At the onset of our work, it was crucial to assess the feasibility of the SmI_2-mediated reductive elimination. Therefore, sulfoxide **1a**[9] was reacted with aldehyde **2** and the in situ generated β-hydroxysulfoxide **3** was trapped with benzoyl chloride to give the β-(benzoyloxy)sulfoxide **4**. During the addition of the sulfoxide anion to aldehyde **2**, two new stereogenic centres are formed and intermediate **4** is thus obtained as a mixture of all four possible diastereoisomers. To avoid their tedious separation, it was decided to use the mixture of adducts **4** in the subsequent reductive-elimination step[10]. Some pertinent results are collected in Table I[11].

As can be seen from Table I, SmI_2 itself does not promote the reductive elimination, not even at room temperature (Table I, entries 1 and 2). Therefore, HMPA and DMPU were added as additives[12] to increase the reduction potential of SmI_2 (–1.33 V)[13]. It was found that the presence of only small quantities of HMPA (0.25 equivalent) promoted the reductive elimination and furnished the desired olefin **5a** in 25% yield (Table I, entry 3). Further optimization of the reaction conditions showed that addition of one equivalent of HMPA was optimal (Table I, entry 6). Further increase in the HMPA loading did not give better results (Table I, entry 7). This observation suggests that a reduction potential of –1.43 V (HMPA/SmI_2 = 1:1) is the optimum potential required for the reductive-elimination. If the potential is increased (Table I, entry 7) to –1.46 V (HMPA/SmI_2 = 2:1), the reaction does not proceed faster or with better yields.

DMPU was next employed as an alternative, non-toxic HMPA equivalent. However, under all the reaction conditions tested, the yields remained lower than with HMPA (Table I, entries 8–15). Moreover, a large excess of DMPU and higher temperatures (0 °C to room temperature) had to be employed (Table I, entries 11–15). Using this additive, as for HMPA, the best results were obtained when a reduction potential of –1.42 V was reached[14].

TABLE I

Optimization of the reductive elimination step



Entry	Additive	Equiv. to SmI_2	Temp. (°C)	Yield[a] (%)	*E* /*Z* [b]
1	-	-	-78	-	n/a
2	-	-	25	-	n/a
3	HMPA[c]	0.25	-78	25	>95:1
4	HMPA	0.5	-78	34	>95:1
5	HMPA	0.75	-78	43	>95:1
6	HMPA	1.0	-78	67	>95:1
7	HMPA	2.0	-78	64	>95:1
8	DMPU[d]	15.0	-78	2	n/a
9	DMPU	15.0	-50	12	n/a
10	DMPU	15.0	-25	32	>95:1
11	DMPU	15.0	0	48	>95:1
12	DMPU	15.0	25	10	n/a
13	DMPU	5.0	0	-	n/a
14	DMPU	10.0	0	11	>95:1
15	DMPU	20.0	0	41	>95:1

[a] Overall yields refer to pure, isolated products

[b] Determined by capillary GC

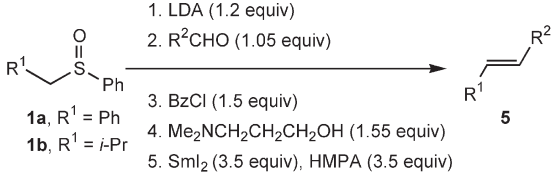
[c] HMPA - hexamethylphosphoramide

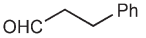
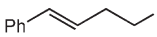
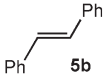
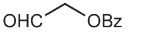
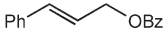
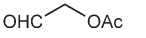
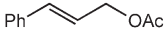
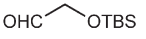
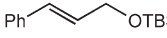
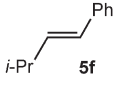
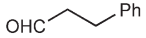
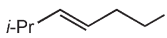
[d] DMPU - 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone

Having designed suitable reaction conditions to successfully effect this sulfoxide variant of the Julia–Lythgoe olefination, the scope and limitations of this protocol were next investigated.

Initially, our attention focused on the formation of 1,2-disubstituted olefins. Thus, sulfoxide **1a** was reacted with aliphatic and aromatic aldehydes, affording the corresponding 1,2-disubstituted olefins **5a**–**5e** in good yields and with excellent stereoselectivities (Table II, entries 1–5). It is noteworthy that some of the most commonly used OH-protecting groups are perfectly tolerated in this transformation (Table II, entries 3–5).

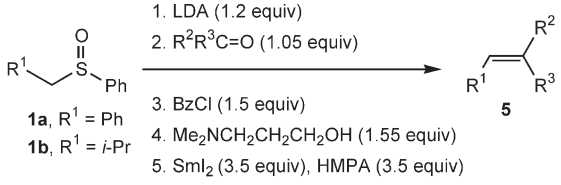
TABLE II
Preparation of 1,2-disubstituted olefins

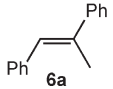
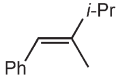
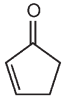
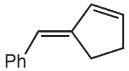
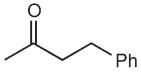
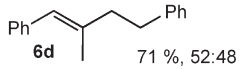
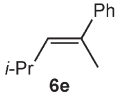
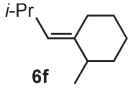
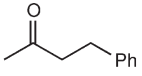
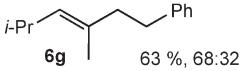
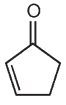
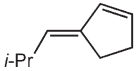
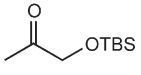
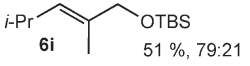


Entry	1	R^2CHO	Product	Yield[a] *E* / *Z*[b]
1	**1a**		 **5a**	67 %, >95:1
2	**1a**		 **5b**	75 % >95:1
3	**1a**		 **5c**	71 %, >95:1
4	**1a**		 **5d**	68 %, >95:1
5	**1a**		 **5e**	70 %, >95:1
6	**1b**		 **5f**	70 % 76:24
7	**1b**		 **5g**	69 %, 94:6

[a] Overall yields refer to pure, isolated products
[b] Determined by ^{1}H NMR spectroscopy

TABLE III
Preparation of trisubstituted olefins



Entry	1	$R^2R^3C=O$	Product	Yield[a] *E* / *Z*[b]
1	**1a**		 **6a**	51 % 76:24
2	**1a**		 **6b**	57 % 91:9
3	**1a**		 **6c**	68 % 65:35
4	**1a**		 **6d**	71 %, 52:48
5	**1b**		 **6e**	64 % 74:26
6	**1b**		 **6f**	64 % 88:12
7	**1b**		 **6g**	63 %, 68:32
8	**1b**		 **6h**	63 % 75:25
9	**1b**		 **6i**	51 %, 79:21

[a] Overall yields refer to pure, isolated products
[b] Determined by ^{1}H NMR spectroscopy

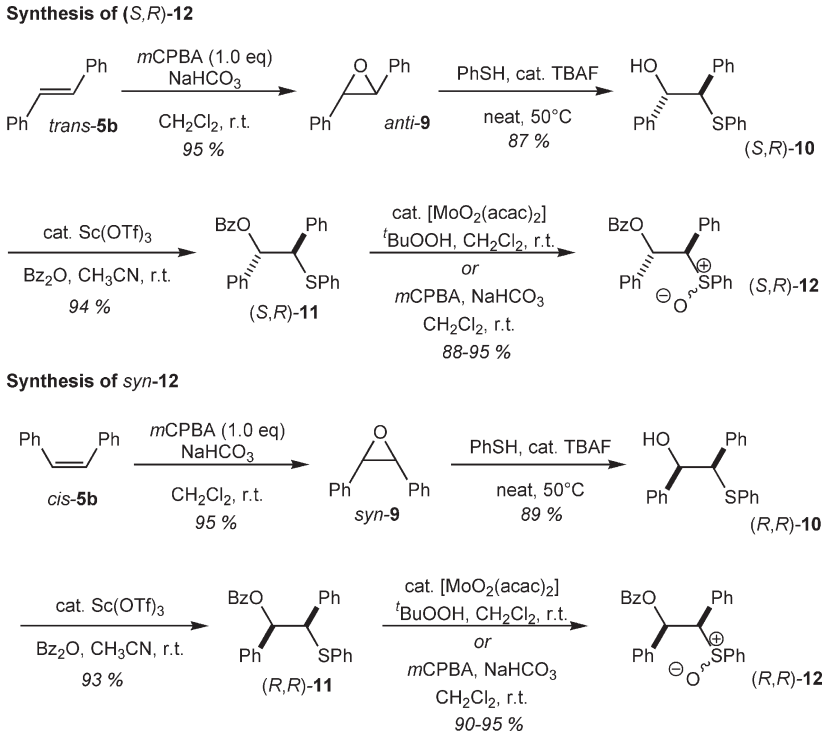
Next, the coupling of the more hindered sulfoxide **1b** was examined under these reaction conditions. It was found that if **1b** was reacted with aliphatic aldehydes (Table II, entry 7), the desired olefin **5g** was formed in good yield and with very high selectivity (*E*/*Z* = 94:6). Surprisingly, when **1b** was reacted with benzaldehyde, the desired alkene **5f** was formed with only moderate selectivity *E*/*Z* = 76:24, though in a similar yield (Table II, entry 6).

The formation of trisubstituted olefins also proceeded smoothly (Table III). Sulfoxides **1a** and **1b** were reacted with various ketones furnishing the desired adducts **6a**–**6i** in unoptimized yields ranging from 51 to 71%. The stereoselectivity of the C–C bond linkage was lower with trisubstituted olefins than in the case of 1,2-disubstituted ones. Generally, aryl-substituted alkenes formed by the reaction of **1a** with ketones, gave slightly higher *E*/*Z* ratios than those bearing an isopropyl side chain. Additionally, it was observed that the *E*/*Z* selectivity depended upon the steric discrimination between the groups present in the ketone molecule. When the carbonyl function was bonded to a methyl group on one side and a linear alkyl on the other side, the newly formed double bond was generated with low selectivity (Table III, entries 4 and 7). In the case of bulkier alkyl, the *E* isomer was formed preferentially (Table III, entries 2, 6 and 9). Remarkably, this modified Julia–Lythgoe olefination proceeds smoothly when enones are employed as substrates though the highly conjugated, thermodynamically more favored olefin was formed only in a moderate *E*/*Z* ratio (Table III, entries 3 and 8).

Based on these results, it can be concluded that, during the reductive elimination step, the steric requirements of the substrate are overruling the conjugative effect present in the final adduct.

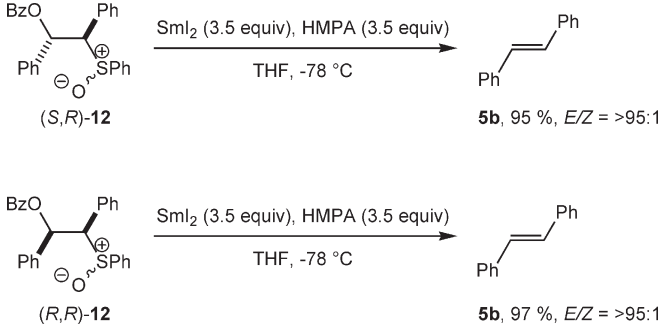
Finally, the formation of tetrasubstituted olefins was examined under our standard conditions. Accordingly, sulfoxide **7** [15] was reacted with various ketones to give tetrasubstituted olefins **8** in low yield but excellent *E*/*Z* selectivity (Table IV). To the best of our knowledge, this is the first report describing the successful preparation of tetrasubstituted alkenes, using this sulfoxide variant of the Julia–Lythgoe olefination, with such high selectivity levels.

At this stage, it was deemed important to find out whether the reductive elimination, mediated by the SmI_2/HMPA system, was a stereoselective or a stereospecific process. Therefore, the *syn*- and *anti*-β-(benzoyloxy)sulfoxides **12** were prepared[16] (Scheme 4) and independently subjected to the reductive elimination conditions.



SCHEME 4

In both cases, olefin **5b** was obtained in an excellent *E*/*Z* ratio of >95:1, indicating that the reductive-elimination step proceeded via a stereoselective process (Scheme 5).

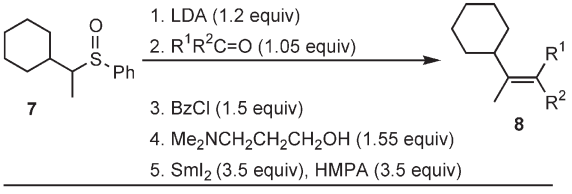


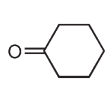
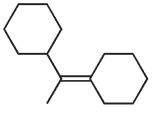
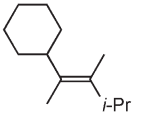
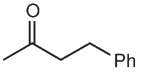
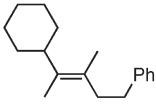
SCHEME 5

To generalize our observation, the *syn*- and *anti*-sulfoxides **13** were prepared and their reductive elimination was examined (Scheme 6). Since direct access to each individual diastereoisomers of **13** would have been prohibitive, **13** was synthesized according to our standard Julia olefination procedure, as a mixture of isomers. The desired four diastereoisomers (a pair of *syn*-**13** and a pair of *anti*-**13**) were then separated via tedious column chromatography (7 columns required). The relative stereochemistry of more and less polar (*R*,*R*)-**13** and more and less polar (*S*,*R*)-**13** was established by their conversion to the corresponding sulfone derivatives, (*R*,*R*)-**14** and (*S*,*R*)-**14**, respectively, and by comparison with their reported literature data.

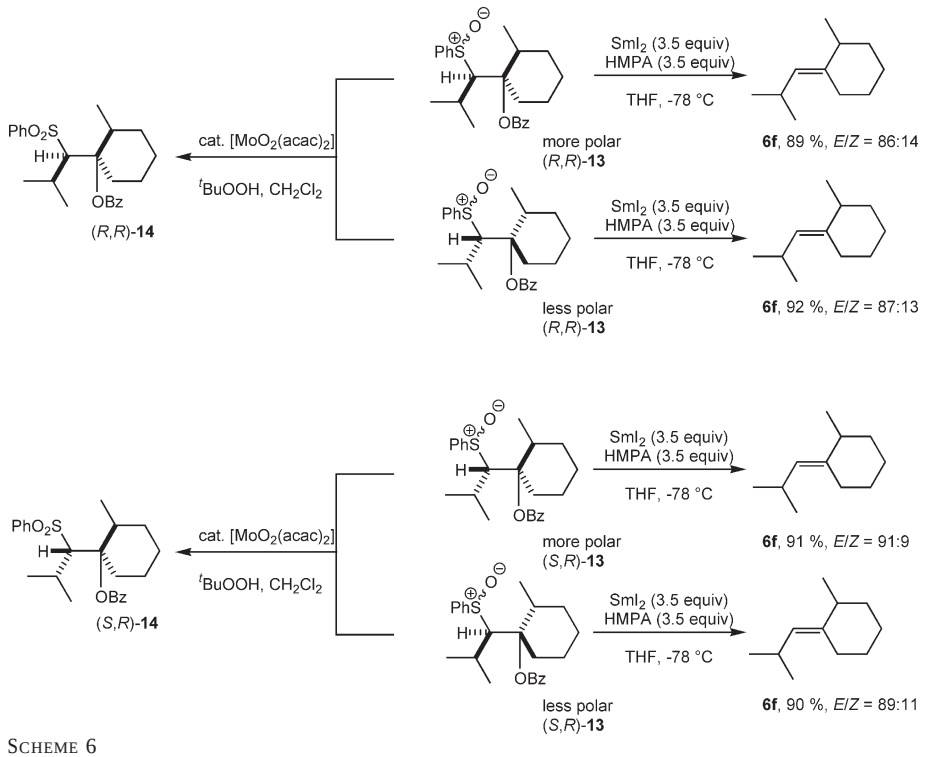
Interestingly, the reductive elimination of pure more and less polar (*R*,*R*)- and (*S*,*R*)-sulfoxides **13** gave essentially the same *E*/*Z* ratio, ranging from 86:14 to 91:9. When the reaction was performed with a mixture of all four diastereoisomers, the 88:12 *E*/*Z* ratio was obtained, which is a good average of the individually measured stereoselectivities. This observation clearly

TABLE IV
Preparation of tetrasubstituted olefins



Entry	$R^2R^3C=O$	Product	Yield[a] *E* / *Z*[b]
1		 **8a**	33 %
2		 **8b**	29 % 97:3
3		 **8c**	32 % 91:9

[a] Overall yields refer to pure, isolated products
[b] Determined by ^{1}H NMR spectroscopy

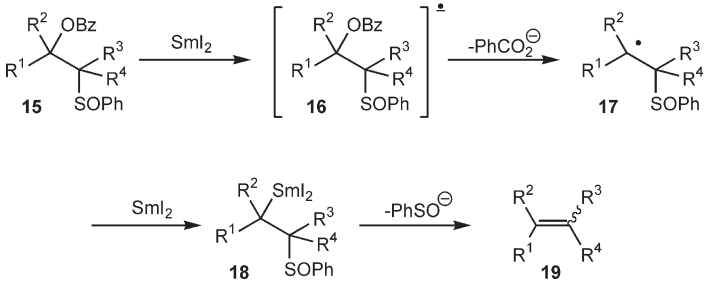


SCHEME 6

suggests that the double bond geometry of the final alkene **6f** is independent of the relative stereochemistry of the sulfoxide adduct **13**.

Based on these results, a plausible mechanism for the reductive elimination, and a mnemonic model generalizing the observed *E*/*Z* selectivities, can be proposed. We believe that the reductive elimination of β-(benzoyloxy)-sulfoxides proceeds in the same way as in the case of the β-(benzoyloxy)-sulfones[17] (Scheme 7). Thus, transfer of a single electron to the benzoate moiety, which appears to be the lowest energy pathway, leads to the radical anion **16**. Subsequent collapse of this intermediate liberates the benzoate anion and produces radical **17**[18]. Further transformation of **17** to the organosamarium intermediate **18**, followed by elimination of the phenylsulfinyl group, eventually affords the olefin **19**.

It is plausible that the formation of the organosamarium species **18** is a slower process than epimerization of the radical-bearing centre. Moreover, the samarium derivative **18** might not be configurationally stable and inversion might occur faster than elimination to **19**. The elimination of the phenylsulfinyl group is believed to proceed through an E_2 type process,



SCHEME 7

leading to the general model for the stereoselectivity of the double bond formation depicted in Fig. 1. Based on this model, steric hindrance of the substituents present on the sulfoxide and on the carbonyl substrate play a crucial role in final *E*/*Z* stereoselectivity.

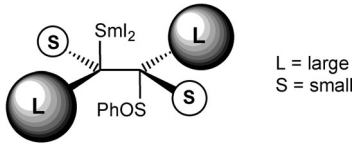


FIG. 1
General model for the stereoselectivity of the double bond formation

CONCLUSIONS

In summary, we have developed a novel, highly stereoselective version of the Julia–Lythgoe olefination. This method embraces a wider scope than the classical Julia olefination protocol. For the first time, tetrasubstituted olefins were prepared in a highly stereoselective manner. We have also shed some light on the reaction mechanism and proposed a mnemonic model that predicts the stereochemical outcome of the olefination process. The use of this method in natural product synthesis and in the assembly of products previously impossible to prepare via the classical Julia procedure, is currently in progress in our laboratory.

EXPERIMENTAL

General

IR spectra (ν, cm^{-1}) were recorded on a FTIR ATI Mattson spectrophotometer in NaCl cell or KBr tablets. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-2000 (300 and 75 MHz, respectively) or on a Bruker AC-250 (250 and 62.5 MHz, respectively) at ambient

temperature in $CDCl_3$ (Aldrich or Rocc). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Mass spectra were recorded on a Finigan TSQ 7000. All compounds (Acros, Aldrich and Fluka) were used as received. THF was distilled under argon from sodium benzophenone ketyl. Flash chromatography was performed on silica gel 60 (40–63 μm) (Rocc).

The identity of every product was confirmed by comparison with literature data. The structure determination of new compounds was made using 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments. The following compounds have been previously described: **5a** [19], **5b** [20], **5c** [21], **5d** [22], **5e** [23], **5f** [24], **5g** [25], **6a** [26], **6b** [27], **6e** [28], **6d**, **6e** [8] and **8a**–**8c** [8]. The corresponding sulfoxides **7** [29], (*R*,*R*)-**12** and (*S*,*R*)-**12** [16] were prepared according to the literature.

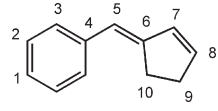
Coupling Step

A solution of a sulfoxide (1.0 mmol) in dry THF (10 ml, 0.1 mol/l) was cooled to –78 °C and LDA (550 μl, 1.1 mmol) was added dropwise. The colour of the mixture changed from slightly yellow to orange-red. After stirring at –78 °C for 30 min, an aldehyde/ketone (1.05 mmol), dissolved in dry THF (0.5 ml), was added dropwise and the mixture was stirred at –78 °C for an additional 2 h. Benzoyl chloride (1.5 mmol) in dry THF (0.5 ml) was then added. The resulting mixture was stirred for 30 min at –78 °C and then allowed to warm to room temperature over 1 h. After an additional 30 min at room temperature, $Me_2N(CH_2)_3OH$ (1.55 mmol) was added and the resulting suspension was stirred at room temperature for 10 min. The suspension was then diluted with Et_2O–H_2O, 1:1 (10 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 ml) and the combined organic layers were washed with aqueous 1.0 M HCl (10 ml), H_2O (10 ml) and brine (10 ml), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give the crude product, which was used without additional purification in the subsequent step.

Reductive Elimination

To a solution of SmI_2 (35 ml, 0.1 mol/l in THF, 3.5 equivalents), HMPA (613 μl, 3.5 equivalents) was added and the mixture was cooled to –78 °C. The crude coupled product (1.0 mmol) in dry THF (0.5 ml) was added dropwise and the resulting mixture was stirred at –78 °C for an additional 30 min. Then, aqueous NH_4Cl (20 ml) was added and the whole was allowed to warm to room temperature The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 ml). The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ (20 ml), H_2O (20 ml), brine (20 ml), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude product was then purified by chromatography on silica gel.

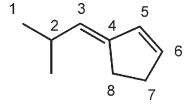
Compound **6c** (Table III, entry 3): purified by column chromatography (2.5 cm × 11 cm, SiO_2, 5 ml fractions; *n*-pentane) to give 106 mg (68%, *E*/*Z* = 65:35) of **6c** as a colourless oil.



IR (NaCl, neat): 3084 (w), 3072 (w), 3021 (w), 2954 (m), 2923 (m), 2868 (w), 1602 (w), 1495 (w), 1454 (w), 742 (m), 699 (m). ^{1}H NMR (250 MHz, $CDCl_3$): 1.71–1.83 (m, 2 H, H-9); 2.20–2.31 (m, 2 H, H-10); 6.19 (broad s, 1 H, H-5^{cis}); 6.22 (m, 1 H, H-7^{trans}); 6.49–6.52 (m,

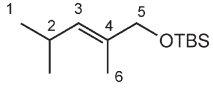
1 H, H-8); 6.52 (broad s, 1 H, H-5^{trans}); 7.25 (broad s, H-7^{cis}); 7.02–7.68 (m, 5 H, arom. CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 28.3 (C-10^{trans}); 30.4 and 30.5 (C-9); 37.2 (C-10^{cis}); 117.2 (C-5^{cis}); 132.4 (C-5^{trans}); 27.3 (C-2^{trans}); 29.9 (C-2^{cis}); 34.4 (C-5^{cis}); 35.0 (C-6); 41.8 (C-5^{trans}); 123.5–137.2 (arom. CH and C_q); 132.7 (C-7^{trans}); 134.5 (C-7^{cis}); 143.2 (C-8). MS (CI, CH_4/N_2O), *m/z* (%): 156.11 (100) [M^+], 157.25 [M^+ + 1] (23), 79.2 (26), 77.5 (16). For $C_{12}H_{12}$ (156.2) calculated: 92.26% C, 7.74% H; found: 92.34% C, 7.66% H.

Compound **6h** (Table III, entry 7): purified by column chromatography (2.5 cm × 11 cm, SiO_2, 5 ml fractions; *n*-pentane) to give 77 mg (63%, *E*/*Z* = 68:32) of **6h** as a colourless oil.



IR (NaCl, neat): 3058 (w), 2957 (m), 2862 (w), 1604 (w), 1494 (w), 1453 (w). ^{1}H NMR (250 MHz, $CDCl_3$): 0.92 (dd, 6 H, $^3J_{1,2}$ = 6.7, $^3J_{1,1'}$ = 1.4, H-1^{cis}); 0.95 (dd, 6 H, $^3J_{1,2}$ = 6.7, $^3J_{1,1'}$ = 1.4, H-1^{trans}); 1.52–1.74 (m, 2 H, H-7); 1.98–2.09 (m, 2 H, H-8); 2.36 (m, 1 H, H-2^{cis}); 2.61 (m, 1 H, H-2^{trans}); 5.17 (d, 1 H, $^3J_{3,2}$ = 9.1, H-3^{trans}); 5.44 (d, 1 H, $^3J_{3,2}$ = 10.1, H-3^{cis}); 6.28 (broad s, 1 H, H-5^{trans}); 6.78 (m, 1 H, H-6); 7.35 (m, 1 H, H-5^{cis}). ^{13}C NMR (62.5 MHz, $CDCl_3$): 21.4 (C-1^{cis}); 23.2 (C-1^{trans}); 28.3 (C-2^{trans}); 29.2 (C-8^{trans}); 30.3 (C-2^{cis}); 31.9 (C-7); 36.2 (C-8^{cis}); 134.2 (C-5^{trans}); 134.3 (C-4^{cis}); 134.5 (C-5^{cis}); 135.9 (C-4^{trans}); 137.2 (C-3^{cis}); 138.2 (C-3^{trans}); 140.6 (C-6). MS (CI, CH_4/N_2O), *m/z* (%): 122.19 (100) [M^+], 95.7 (15), 79.7 (39), 51.3 (8). For C_9H_{14} (122.2) calculated: 88.45% C, 11.55% H; found: 88.51% C, 11.49% H.

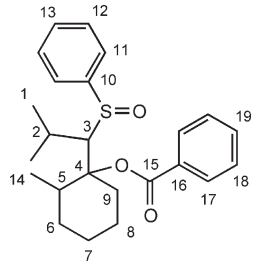
Compound **6i** (Table III, entry 9): purified by column chromatography (2.5 cm × 11 cm, SiO_2, 5 ml fractions; 100% *n*-pentane) to give 117 mg (51%, *E*/*Z* = 79:21) of **6i** as a colourless oil.



^{1}H NMR (250 MHz, $CDCl_3$): 0.03 (s, 6 H, Si**Me**$_2$Bu^t); 0.91 (s, 9 H, SiMe$_2$**Bu**^{t}); 0.92 (dd, 6 H, $^3J_{1,2}$ = 6.7, $^3J_{1,1'}$ = 1.5, H-1^{cis}); 0.96 (dd, 6 H, $^3J_{1,2}$ = 6.7, $^3J_{1,1'}$ = 1.4, H-1^{trans}); 1.67 (m, 1 H, H-6^{trans}); 1.89 (m, 1 H, H-6^{cis}); 2.49 (m, 1 H, H-2^{trans}); 2.75 (m, 1 H, H-2^{cis}); 4.01–4.12 (m, 2 H, H-5); 4.76 (d, 1 H, $^3J_{3,2}$ = 9.5, H-3^{trans}); 5.11 (d, 1 H, $^3J_{3,2}$ = 9.3, H-3^{cis}). ^{13}C NMR (62.5 MHz, $CDCl_3$): –3.2 (Si**Me**$_2$Bu^t); 14.0 (C-6^{trans}); 18.7, 21.4 (C-6^{cis}); 22.9 (C-1^{cis}); 23.2 (C-1^{trans}); 24.1 (C-2^{trans}); 26.2 (SiMe$_2$**Bu**^{t}); 28.1 (C-2^{cis}); 64.2 (C-5^{trans}); 70.2 (C-5^{cis}); 132.1 (C-4^{cis}); 132.3 (C-4^{trans}); 138.9 (C-3^{trans}); 148.8 (C-3^{cis}). MS (CI, CH_4/N_2O), *m/z* (%): 128.45 (67) [M^+], 114.6 (100), 97.9 (65), 77.2 (15), 55.2 (12). For $C_{13}H_{28}OSi$ (228.5) calculated: 68.35% C, 12.35% H, 12.29% Si; found: 68.51% C, 12.23% H, 12.24% Si.

Sulfoxides **13**

Compounds **13** were prepared according to the standard coupling procedure. The crude mixture was purified by repeated (7×) column chromatography (2.5 cm × 11 cm, SiO_2, 5 ml fractions; petroleum ether–Et_2O, 20:1) to give four diastereoisomers more polar (*R*,*R*)-**13** (11 mg), less polar (*R*,*R*)-**13** (15 mg), more polar (*S*,*R*)-**13** (25 mg) and less polar (*S*,*R*)-**13** (28 mg).



More polar (*R*,*R*)-**13**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.86 (dd, 3 H, $^3J_{1,2}$ = 6.5, $^2J_{1,1'}$ = 1.4, one of H-1); 1.06 (d, 3 H, $^3J_{14,5}$ = 7.2, H-14); 1.21 (dd, 3 H, $^3J_{1,2}$ = 6.8, $^2J_{1,1'}$ = 1.3, the other H-1); 1.17–2.27 (m, 10 H, H-2, 5–9); 3.89 (d, 1 H, $^3J_{3,2}$ = 7.0, H-3); 7.11–8.24 (m, 10 H, arom. CH). ^{13}C NMR (75 MHz, $CDCl_3$): 13.5, 20.3, 21.8, 22.9, 24.3, 29.2, 31.8, 32.8, 36.2, 71.9 (C-3); 76.8 (C-4); 124.3–147.9 (arom. CH and C_q); 166.2 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 586.46 (67) [M^+], 587.67 [M^+ + 1] (34), 121 (100), 181.3 (43), 96.9 (15), 77.3 (20). HR CI MS calculated: 398.1916; found: 398.1924.

Less polar (*R*,*R*)-**13**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.86 (dd, 3 H, $^3J_{1,2}$ = 6.5, $^2J_{1,1'}$ = 1.4, one of H-1); 1.07 (d, 3 H, $^3J_{14,5}$ = 7.2, H-14); 1.20 (dd, 3 H, $^3J_{1,2}$ = 6.8, $^2J_{1,1'}$ = 1.2, the other H-1); 1.17–2.28 (m, 10 H, H-2, 5–9); 4.12 (d, 1 H, $^3J_{3,2}$ = 7.1, H-3); 7.10–8.25 (m, 10 H, arom. CH). ^{13}C NMR (75 MHz, $CDCl_3$): 13.6, 20.3, 21.8, 22.9, 24.4, 29.3, 31.8, 32.8, 36.2, 71.4 (C-3); 76.5 (C-4); 124.1–147.9 (arom. CH and C_q); 166.1 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 586.4 (63) [M^+], 587.6 [M^+ + 1] (33), 121.4 (100), 181.3 (38), 96.9 (19), 77.3 (21). HR CI MS calculated: 398.1916; found: 398.1918.

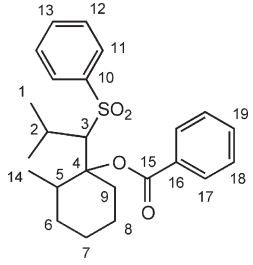
More polar (*S*,*R*)-**13**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (dd, 3 H, $^3J_{1,2}$ = 6.5, $^2J_{1,1'}$ = 1.3, one of H-1); 1.07 (d, 3 H, $^3J_{14,5}$ = 7.2, H-14); 1.21 (dd, 3 H, $^3J_{1,2}$ = 6.8, $^2J_{1,1'}$ = 1.3, the other H-1); 1.17–2.25 (m, 10 H, H-2, 5–9); 4.26 (d, 1 H, $^3J_{3,2}$ = 6.9, H-3); 7.11–8.24 (m, 10 H, arom. CH). ^{13}C NMR (75 MHz, $CDCl_3$): 13.4, 20.5, 21.8, 22.8, 24.8, 29.3, 31.8, 32.8, 36.3, 72.3 (C-3); 77.1 (C-4); 124.5-147.9 (arom. CH and C_q); 165.1 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 586.6 (78) [M^+], 587.9 [M^+ + 1] (40), 122.4 (100), 181.9 (43), 97.0 (17), 77.4 (21). HR CI MS calculated: 398.1916; found: 398.1910.

Less polar (*S*,*R*)-**13**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (dd, 3 H, $^3J_{1,2}$ = 6.5, $^2J_{1,1'}$ = 1.3, one of H-1); 1.07 (d, 3 H, $^3J_{14,5}$ = 7.1, H-14); 1.21 (dd, 3 H, $^3J_{1,2}$ = 6.9, $^2J_{1,1'}$ = 1.3, the other H-1); 1.17–2.25 (m, 10 H, H-2, H5–H9); 4.36 (d, 1 H, $^3J_{3,2}$ = 7.1, H-3); 7.14–8.25 (m, 10 H, arom. CH). ^{13}C NMR (75 MHz, $CDCl_3$): 13.4, 20.4, 21.8, 22.9, 24.8, 29.3, 31.7, 32.8, 36.8, 72.1 (C-3); 76.7 (C-4); 124.7–147.7 (arom. CH and C_q); 164.9 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 586.4 (45) [M^+], 587.6 [M^+ + 1] (23), 121.7 (100), 182.1 (43), 96.7 (24), 77.0 (16). HR CI MS calculated: 398.1916; found: 398.1907.

Preparation of Sulfones (*R*,*R*) and (*S*,*R*)-**14**

A solution of sulfoxide **13** (5 mg, 12.5 μmol, 1.0 equivalent) in CH_2Cl_2 (1 ml) was degassed by the freeze-pump-thaw method (3×) and [$MoO_2(acac)_2$] (0.82 mg, 2.5 μmol, 0.2 equivalent) was added. The resulting mixture was cooled to 0 °C and TBHP (15 drops, 5.5 M solution in dodecane) was added dropwise. An exothermic reaction occurred and the resulting orange solution was stirred at room temperature for 4 h. A saturated solution of $Na_2S_2O_3$ (1 ml) was added and the layers were separated. The aqueous layer was extracted with EtOAc

(2 × 2 ml) and the pooled organic layers were washed with H_2O (1 ml), brine (1 ml), dried over anhydrous $MgSO_4$ and evaporated in vacuo to give 7–8 mg of a pale yellow oil (the product contains dodecane). Purification by column chromatography (1.0 cm × 10 cm, SiO_2, 2.5 ml fractions; petroleum ether–EtOAc, 1:1) gave 5.1–5.2 mg (99%) of colourless oil.



(*R*,*R*)-**14**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (dd, 3 H, $^3J_{1,2}$ = 6.8, $^2J_{1,1'}$ = 1.3, one of H-1); 0.99 (d, 3 H, $^3J_{14,5}$ = 7.0, H-14); 1.20 (dd, 3 H, $^3J_{1,2}$ = 6.7, $^2J_{1,1'}$ = 1.4, the other H-1); 1.27–2.09 (m, 10 H, H-5–H9); 3.65 (m, 1 H, H-2); 3.87 (d, 1 H, $^3J_{3,2}$ = 7.1, H-3); 7.14–8.25 (m, 10 H, arom. CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 16.4, 20.5, 23.3, 24.1, 24.9, 30.9, 34.2, 35.1, 39.2, 71.8 (C-3); 85.9 (C-4); 126.6–140.3 (arom. CH and C_q); 167.1 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 414.7 (100) [M^+], 415.6 [M^+ + 1] (22), 141.9 (34), 121.5 (56), 181.3 (28), 77.0 (15).

(*S*,*R*)-**14**. ^{1}H NMR (300 MHz, $CDCl_3$): 0.88 (dd, 3 H, $^3J_{1,2}$ = 6.8, $^2J_{1,1'}$ = 1.4, one of H-1); 1.01 (d, 3 H, $^3J_{14,5}$ = 7.0, H-14); 1.20 (dd, 3 H, $^3J_{1,2}$ = 6.7, $^2J_{1,1'}$ = 1.5, the other H-1); 1.26–2.10 (m, 10 H, H-5–H9); 3.67 (m, 1 H, H-2); 3.89 (d, 1 H, $^3J_{3,2}$ = 7.1, H-3); 7.14–8.25 (m, 10 H, arom. CH). ^{13}C NMR (62.5 MHz, $CDCl_3$): 16.3, 20.5, 23.8, 24.5, 24.9, 31.1, 34.2, 35.3, 39.2, 71.6 (C-3); 86.1 (C-4); 126.7–140.1 (arom. CH and C_q); 167.2 (C-15). MS (CI, CH_4/N_2O), *m/z* (%): 414.7 (100) [M^+], 415.6 [M^+ + 1] (21), 141.9 (34), 121.5 (48), 181.3 (23), 77.0 (16).

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9. Sulfoxides **1a** and **7** were selected because the corresponding sulfones react very poorly (or not at all) under the standard Julia–Lythgoe conditions for electronic (**1a**) or steric (**7**) reasons.
10. The excess of benzoyl chloride was reacted with 3-(dimethylamino)propan-1-ol (neat) and the amine was removed upon aqueous acid work-up.
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Efficient and Stereoselective Synthesis of Allylic Ethers and Alcohols

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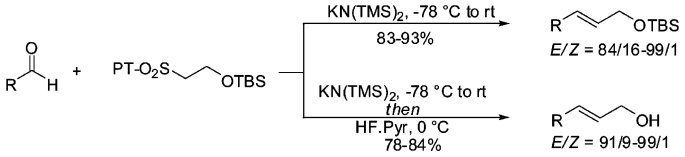
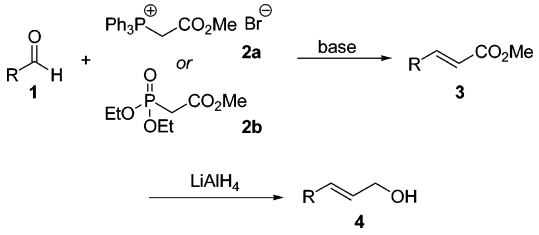
ABSTRACT



A short and efficient synthesis of allylic TBS ethers and allylic alcohols has been developed, based upon a unique Kocienski–Julia olefination reaction. Allylic alcohols and allylic ethers are obtained in good to excellent yields and with high (*E*)-selectivity. The conditions are mild and the procedure is broadly applicable.

Allylic alcohols are important building blocks in synthetic organic chemistry, being easily transformed into useful epoxides,[1] α,β-unsaturated aldehydes,[2] carboxylic acid derivatives,[3] and polyenes.[4] Their synthesis usually entails the reaction of an aldehyde **1** with a stabilized Wittig (**2a**) or Horner−Wadsworth−Emmons (**2b**) reagent[5] followed by the subsequent reduction of the resulting α,β-unsaturated ester **3** (Scheme 1). Surprisingly, even though the transformation

Scheme 1. Synthesis of Allylic Alcohols



of aldehydes into the corresponding allylic alcohols is often encountered in total synthesis, this two-step sequence is still classically employed. To reach the corresponding allylic ethers, a third step is required.

Recently, the synthesis of allylic alcohols, ethers, and halides was also accomplished via olefination/cross-metathesis protocol.[6]

To the best of our knowledge, the only way to transform aldehydes into allylic alcohols in a single step involves the use of the β-hydroxy phosphonium salt **5**. When reacted with aldehyde **1**, in the presence of an excess of base, salt **5** affords the desired allylic alcohol **4** (Scheme 2).[7] Disappointingly, this olefination reaction proceeds with poor to moderate yields, presumably due to the low stability of the generated phosphonium ylide.[6b,c]

(1) (a) Johnson, A. A.; Sharpless, K. B. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, UK, 1990; Vol. 7. (b) Finn, M. G.; Sharpless, K. B. *Asymmetric synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5. (c) Burns, C. J.; Martin, C. A.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2826.

(2) (a) Lee, D. G. *Oxidation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1969; Vol 1. (b) Ball, S.; Goodwin, T. W.; Morton, R. A. *Biochem. J.* **1948**, *42*, 516.

(3) Corey, E. J.; Gilman, N, W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(4) Catalan, J.; Hopf, H.; Mlynek, C.; Klein, D.; Kilickiran, P. *Chem. Eur. J.* **2005**, *11*, 3915.

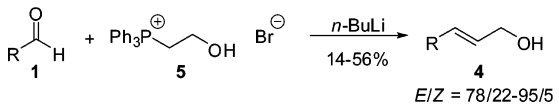
(5) For an extensive review on phosphorus-based olefination methods, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. For recent examples see: (a) Christoph, G.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2189.(b) Ding, P.; Miller, M. J.; Chen, Y.; Helquist, P.; Oliver, A. J.; Wiest, O. *Org. Lett.* **2004**, *6*, 1805.

(6) (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(7) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **1968**, *7*, 650. (b) Schlosser, M.; Christmann, F. K.; Piskala, A.; Coffinet, D. *Synlett* **1971**, 29. (c) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc.* **1971**, *93*, 1490. (d) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am Chem. Soc.* **1985**, *107*, 217.

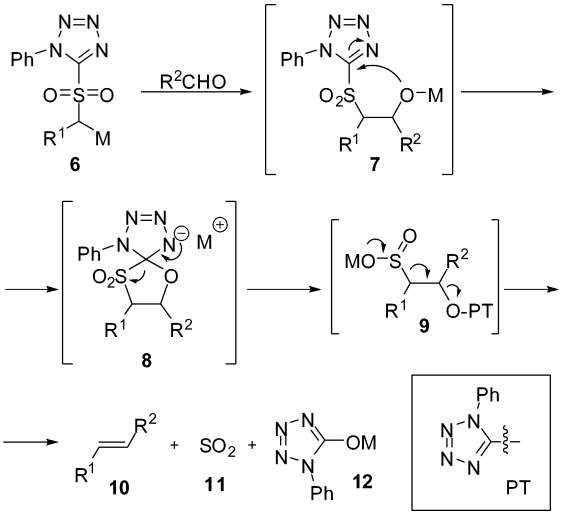
10.1021/ol062433y CCC: $33.50
Published on Web 11/29/2006

Scheme 2. One-Step Transformation of Aldehydes to Allylic Alcohols



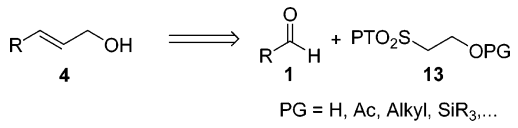
As a part of our ongoing research program aimed at the development of novel modifications of the Julia olefination reaction,[8,9] a short and efficient synthesis of allylic ethers and alcohols was targeted. To fulfill this goal, the Kocienski−Julia variant[10] was selected as the desired sequence (Scheme 3).

Scheme 3. The Kocienski−Julia Reaction



From a retrosynthetic point of view, allylic alcohol **4** can be divided into sulfone **13** and aldehyde **1** (Scheme 4).

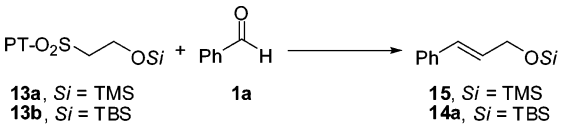
Scheme 4. Retrosynthetic Approach to Allyl Alcohols



Unfortunately, β-hydroxy sulfones **7** cannot be directly employed. Indeed, when treated with a base, they undergo a rapid rearrangement, affording olefin **10**. Similarly, β-alkyloxy and β-acyloxy sulfones[11] suffer a rapid β-elimination, yielding the corresponding vinyl sulfones. Therefore, we envisioned that β-trialkylsilyloxy sulfones **13**, bearing a poor silyloxy leaving group, might be good reagents for the desired transformation. The β-elimination process might be sufficiently slowed down to enable the desired olefination reaction to proceed competitively.

To test our hypothesis, the coupling of sulfones **13a** (PG = TMS) and **13b** (PG = TBS) with benzaldehyde was attempted (Table 1).

Table 1. Optimization of the Olefination Reaction



13a, *Si* = TMS
13b, *Si* = TBS

1a

15, *Si* = TMS
14a, *Si* = TBS

Method A: *i*) base (1.2 equiv), **13** (1.0 equiv), THF, -78 °C, 10 min; *ii*) **1a** (1.1 equiv), -78 °C (30 min) to rt
Method B: *i*) **13** (1.0 equiv), **1a** (1.1 equiv), THF, -78 °C, 5 min; *ii*) base (1.2 equiv), -78 °C (30 min) to rt
Method C: *i*) **13** (1.0 equiv), **1a** (1.1 equiv), THF, -78 °C, 5 min; *ii*) base (1.2 equiv), addition over 10 min via syringe pump, -78 °C (30 min) to rt

entry	sulfone	method	base	yield[a]	*E*/*Z*[b]
1	**13a**	A	$LiN(TMS)_2$	deg	n/a
2	**13a**	B	$LiN(TMS)_2$	40%	52/48
3	**13a**	C	$LiN(TMS)_2$	45%	62/38
4	**13a**	C	$NaN(TMS)_2$	35%	72/28
5	**13a**	C	$KN(TMS)_2$	28%	81/19
6	**13b**	C	$LiN(TMS)_2$	81%	67/23
7	**13b**	C	$NaN(TMS)_2$	79%	89/11
8	**13b**	C	$KN(TMS)_2$	83%	98/2

[a] Overall yields refer to pure, isolated products. [b] Determined by capillary GC. TMS = trimethylsilyl.

Initially, the Li anion of **13a** was generated at low temperature and the aldehyde was added after 10 min (Table 1, entry 1). In this case, only degradation of the sulfone **13a** was observed. It was thought that this decomposition was due to the low stability of the sulfonyl anion. Hence, Barbier-type conditions, in which the anion α to the sulfone is generated in the presence of an aldehyde, were employed. Gratifyingly, the desired product **15** could be isolated in 40% yield. However, the *E*/*Z*-selectivity was extremely poor (Table 1, entry 2). It was also observed that the slow addition of the base to the reaction mixture led to a slight increase in both the yield and the selectivity of this process (Table 1, entry 3).

Next, it was decided to evaluate the influence of the nature of the cation associated with the base. As can be seen in Table 1 (entries 4 and 5), the use of $NaNTMS_2$ and $KNTMS_2$

(8) For a recent review on the Julia reaction, see: Dumeunier, R.; Markó, I. E. *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 104−150.

(9) (a) Pospíšil, J.; Pospíšil, T.; Markó, I. E. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1953. (b) Pospíšil, J.; Pospíšil, T.; Markó, I. E. *Org. Lett.* **2005**, *7*, 2373. (c) Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609. (d) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089.

(10) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

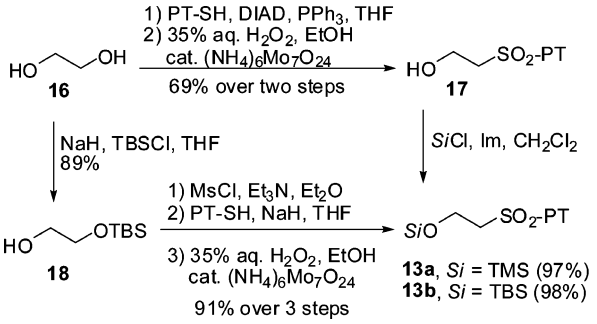
(11) (a) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* **1999**, 188. (b) Keck, G. E.; Savin, A. K.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett.* **1996**, *37*, 3291. (c) Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395.

further improved the control of the double bond geometry, affording the olefin **15** with an *E*/*Z* ratio of up to 81:19, though at the expense of the yield that plummeted down to 28% (Table 1, entry 5).

At this stage, it was realized that the low stability of the TMS ether function under the reaction conditions was responsible for the formation of only modest amounts of the desired allylsilyl ether **15**. Therefore, sulfone **13b** bearing a more robust TBS group was employed (Table 1, entries 6−8). Much to our delight, a dramatic enhancement in the yield of **14a** was observed. Furthermore, the influence of the counter cation on the geometry of the double bond present in **14a** was also improved, leading ultimately to **14a** in 83% yield and with an *E*/*Z* ratio of 98:2.

The synthesis of sulfones **13a** and **13b** is depicted in Scheme 5. Having devised suitable reaction conditions to

Scheme 5. Synthesis of the Sulfones **13a** and **13b**



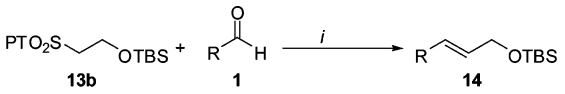
effect this allylic TBS ether preparation, its scope and limitations were explored. A selection of pertinent results are depicted in Table 2.

It was observed that aryl (Table 2, entry 1), α,β-unsaturated (Table 2, entries 3 and 5), and alkyl aldehydes (Table 2, entries 6−13) react smoothly with sulfone **13b**, yielding the desired TBS protected allylic alcohols **14a**−**j** in good to excellent yields. It is noteworthy that, in essentially all cases, a remarkably high control of the *E*/*Z* alkene gemetry could be exercised, favoring largely the (*E*)-isomer. For aliphatic aldehydes, the selectivity for the *trans*-olefin increased as the steric bulk of the alkyl substituent became larger (Table 2, entries 8−10). To further improve the *E*/*Z* ratio, THF was replaced by DME.[8b] In full accord with previous results described by Kocienski et al., it was observed that the use of DME led to the corresponding allylic ethers in higher stereoisomeric purity, though in somewhat lower yields (Table 2, entries 1−4, 6, and 7).

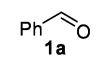
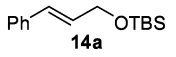
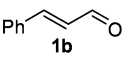
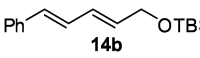
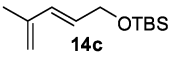
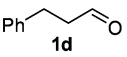
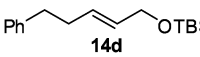
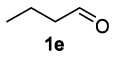
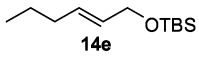
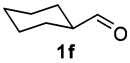
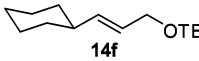
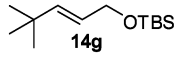
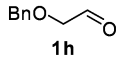
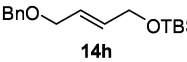
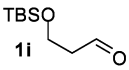
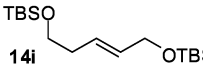
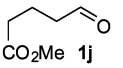
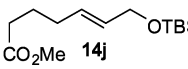
Importantly, various functionalities, including esters, TBS ethers, and benzyl ethers (Table 2, entries 11−13), are tolerated under the reaction conditions.

Several synthetic ventures currently ongoing in our laboratory require the chemoselective Julia olefination of an aldehyde function in the presence of a ketone. Therefore, we wondered if a ketone group would also be tolerated under these reaction conditions. Hence, a set of competitive experiments was designed involving a combination of aromatic and

Table 2. Preparation of TBS Allyl Ethers **14**



Conditions: sulfone (1.0 equiv), aldehyde (1.1 equiv), -78 °C, 5 min, *then* $KN(TMS)_2$ (1.2 equiv), addition over 10 min via syringe pump, -78 °C (30 min) to rt

entry	aldehyde	solvent	product	yield[a] (*E*/*Z*)[b]
1	 **1a**	THF	 **14a**	83% (98/2)
2		DME		80% (>99/1)
3	 **1b**	THF	 **14b**	81% (97/3)
4		DME		69% (99/1)
5	 **1c**	THF	 **14c**	91% (96/4)
6	 **1d**	THF	 **14d**	88% (84/16)
7		DME		83% (91/9)
8	 **1e**	THF	 **14e**	89% (88/12)
9	 **1f**	THF	 **14f**	84% (93/7)
10	 **1g**	THF	 **14g**	87% (>99/1)
11	 **1h**	THF	 **14h**	91% (92/8)
12	 **1i**	THF	 **14i**	88% (98/2)
13	 **1j**	THF	 **14j**	89% (96/4)

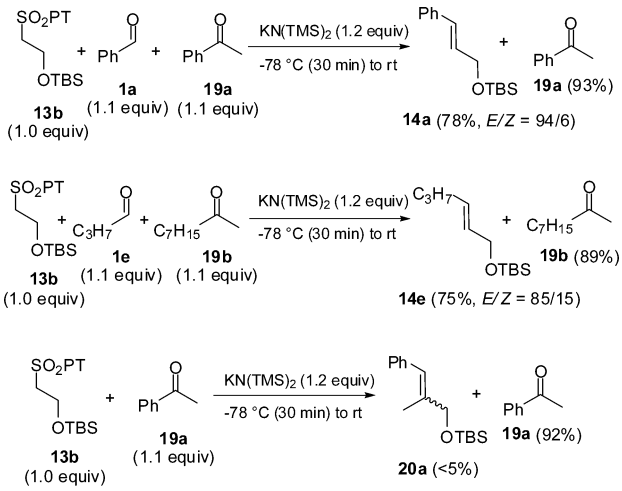
[a] Overall yields refer to pure, isolated products. [b] Determined by ^1H NMR spectroscopy. DME = dimethoxy ether; TBS = *tert*-butyldimethylsilyl.

aliphatic substrates (Scheme 6). Thus, the anion generated from sulfone **13b** was allowed to react with a 1:1 mixture of aldehyde **1a** and ketone **19a** and with an equimolar amount of **1e** and **19b**. In both cases, the expected ethers **14a** and **14e** were isolated as the only products of the reaction along with the recovered starting ketones **19a** and **19b**. To understand the origin of this excellent chemoselectivity, a control reaction between sulfone **13b** and ketone **19a**, under the same reaction conditions, was attempted. Surprisingly, no olefination product was observed and the ketone **19a** was recovered in 92% yield. On the other hand, sulfone **13b** was completely decomposed under these conditions. We speculate that this degradation was due to the low stability of the generated organo potassium species at the higher temperatures required for addition on the ketone function.[12]

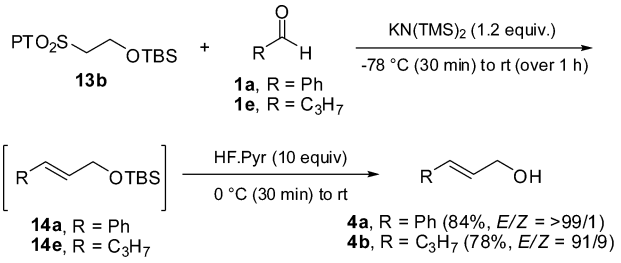
Finally, we have developed a simple and efficient one-pot synthesis of allylic alcohols **4** starting from aldehydes and employing the sulfone **13b** (Scheme 7). Hence, addition of an excess of the HF Pyr complex to the crude reaction

(12) For the stability of PT-SO_2-CH_2-Li species, see ref 10a.

Scheme 6. Competition Experiments between Aldehydes and Ketones



Scheme 7. One-Pot Olefination/Deprotection Preparation of Allyl Alcohols



mixture obtained by condensing **13b** with **1a** and **1e** results in the smooth deprotection of the TBS group, affording the desired allylic alcohols **4a** and **4b** in high yields and excellent stereochemical purity.

In summary, we have uncovered a novel, highly stereoselective method for the synthesis of allyl TBS ethers and allylic alcohols. Under our conditions, aryl, α,β-unsaturated, and alkyl aldehydes can be easily transformed, via a one-step procedure, into the corresponding TBS allyl ethers. Additionally, this reaction can be further extended into the one-pot synthesis of allylic alcohols. A variety of functions and protecting groups are also tolerated.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as experimental procedures. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Total synthesis of (*R*)-(+)-goniothalamin and (*R*)-(+)-goniothalamin oxide: first application of the sulfoxide-modified Julia olefination in total synthesis

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Abstract—A short and efficient synthesis of (*R*)-(+)-goniothalamin **1** and (*R*)-(+)-goniothalamin oxide **2** is described. During this approach, the sulfoxide-modified Julia olefination was used as a key step to connect aldehyde **5** to sulfoxide **6**. The desired styryl-containing adduct is obtained in good yield and with excellent *E*/*Z* selectivity.

Chiral lactones are commonly present in a number of natural and synthetic products, including various pheromones and medicinal compounds. Interestingly, these small exogenous molecules exert powerful effects on the cell functions, making them useful tools for understanding life processes and for treating life-threatening diseases.

Styryl lactones are a group of secondary metabolites commonly isolated from the genus Goniothalamus.[1] Recent studies have demonstrated that these compounds display cytotoxic and antitumour properties. (*R*)-(+)-Goniothalamin **1** is a typical representative of this class of compounds (Fig. 1).

(*R*)-(+)-Goniothalamin **1** was isolated in 1967 from the dried bark of *Cryptocarya caloneura*[2] and given the (*S*)-configuration. A decade later, the configuration of the stereocentre was revised and established as being (*R*).[3] Later on, (*R*)-(+)-**1** was isolated from *Cryptocarya moschata*,[4] *Bryonopsis laciniosa*[5] and various other species of *Goniothalamus*[6] (115 species[7] distributed throughout the tropics and subtropics). Some of the isolated goniothalamin-based derivatives are shown in Figure 1.

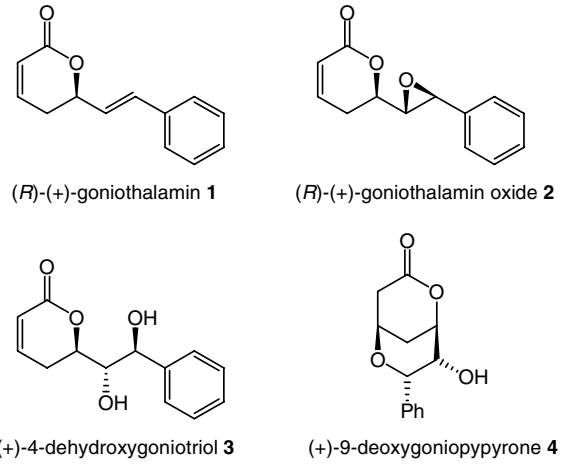

Figure 1. Some of the isolated goniothalamin-based derivatives.

(*R*)-(+)-Goniothalamin **1** displays in vitro cytotoxic effects on different cell lines, including MCF-7, T47D and MDA-MB-231 (breast carcinoma), HeLa cells (human cervical carcinoma), gastric carcinoma (HGC-27), leukemia carcinoma (HL-60) and ovarian carcinoma (Caov-3).[1a,8,9b] This cytotoxic activity, which results from the selective induction of apoptosis[9] on the cancer cell lines, was shown to be surprisingly low on nonmalignant cells.

In vivo studies revealed that (*R*)-(+)-**1** possessed tumouricidal and tumouristatic properties on Sprague–Dawley

Keywords: Goniothalamin; Julia olefination; Sulfoxide; Goniothalamin oxide; Metathesis.
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rats with 7,12-dimethylbenzanthracene (DMBA)-induced mammary tumours.[10]

Due to the interesting biological activity of (*R*)-**1**, several successful approaches to this natural product have been reported.[11] Even though the most commonly used antithetic approach to **1** is based on the C2–C3 and/or C6–C7 double bond disconnections (Fig. 2), other methods, such as asymmetric hetero-Diels–Alder cycloadditions and intramolecular nucleophilic additions to ketenes, have been employed.

Our interest in the total synthesis of (*R*)-(+)-**1** arose from the observation that all previous syntheses, that relied upon various olefination methods to establish the C6–C7 double bond, provided the styryl lactone either in poor yields and/or with mediocre selectivity.[11a,1] It was surmised that our recently developed sulfoxide-modified Julia olefination might serve as an ideal method to accomplish the desired olefination in high yield and selectivity.[12] The successful implementation of this approach will also enable us to prepare rapidly a varied library of goniothalamin **1** analogues from a common precursor, aldehyde **5**.

Our retrosynthesis of (*R*)-(+)-**1** is presented in Scheme 1. (*R*)-(+)-Goniothalamin **1** was disconnected at the C6–C7 bond, leading to aldehyde **5** and sulfoxide **6**. It was envisioned that aldehyde **5** might be easily assembled from the optically pure glycidol ether **8** via a ring opening/acylation/metathesis sequence. The benzylic sulfoxide **6** would be readily prepared by oxidation of the corresponding, commercially available, sulfide.

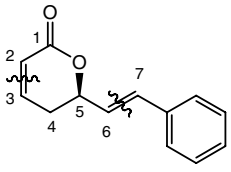
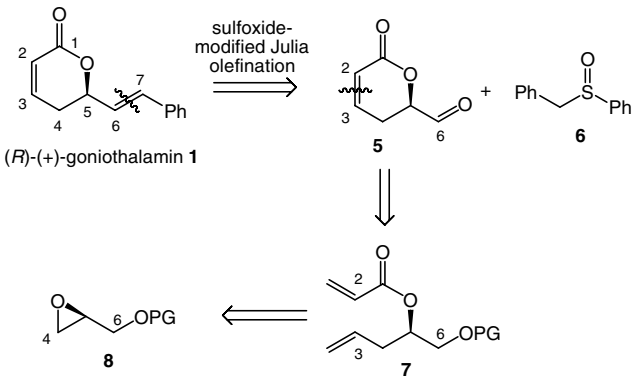


Figure 2. Most common (*R*)-(+)-goniothalamin **1** retrosynthetic disconnections.



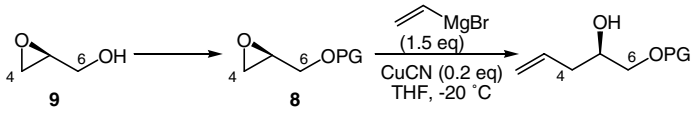
Scheme 1. Retrosynthesis of (*R*)-(+)-goniothalamin **1**.

To test the generality of our approach, it was decided to also evaluate the influence of four commonly used protecting groups (Bn, PMB, TBS and TBDPS) on the yields and selectivity of this sequence.

Our synthesis began with commercially available (*R*)-glycidol **9**, which was protected with PMB, TBS and TBDPS-groups, yielding the corresponding epoxy ethers **8b–d** (Scheme 2).[13] Copper-catalyzed opening of epoxides **8** with vinyl magnesium bromide furnished the optically enriched homoallylic alcohols **10a–d** in excellent yields and purities.

Acylation of alcohols **10a–d**, using either acryloyl chloride or acrylic acid, afforded smoothly the metathesis precursors **7a–d** (Scheme 3).

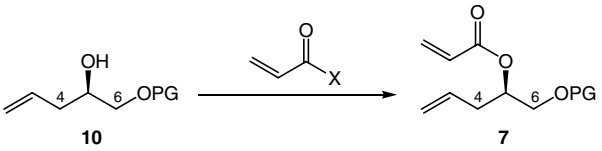
Finally, the metathesis step was evaluated. It was observed that the nature of the protecting group in substrate **7** had a significant influence on the reaction rate (Table 1). Indeed, when the benzyl protected ester **7a** was treated with the 1st generation Grubbs' catalyst (**GC-1**), only poor conversion of **7a** into **11a** was observed (Table 1, entry 1). It was thought that the lone pairs of the oxygen present in the benzyl ether function[14] could compete with the olefins for the vacant coordination sites present in **GC-1**. Even though this process is reversible, it decreases the reaction rate by sequestering



Entry	Product	PG	Conditions	Yield[a] [%]
1	**8a**	Bn	-	-[b]
2	**8b**	PMB	NaH, PMBCl TBAI, DMF	86
3	**8c**	TBS	TBSCl, Im, CH_2Cl_2	99
4	**8d**	TBDPS	TBDPSCl, Im, CH_2Cl_2	99

[a] Refers to pure isolated compounds
[b] Commercially available compound

Scheme 2. Synthesis of homoallylic alcohols **10**.

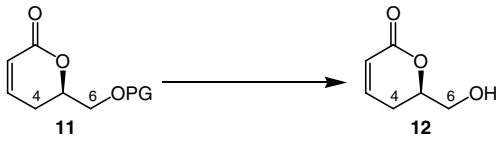


Entry	PG	X	Conditions	Product	Yield[a] [%]
1	Bn	OH	DCC, CH_2Cl_2, r.t.,12 h	**7a**	94
2	PMB	OH	DCC, CH_2Cl_2, r.t.,12 h	**7b**	91
3	TBS	Cl	TEA, CH_2Cl_2, 0 °C, 30 min	**7c**	89
4	TBDPS	Cl	TEA, CH_2Cl_2, 0 °C, 30 min	**7d**	91

[a] Refers to pure isolated compounds

Scheme 3. Synthesis of metathesis precursors **7**.

Table 2. Deprotection of alcohol **11**



Entry	PG	Conditions	Yield[a] (%)
1	Bn	$FeCl_3$, CH_2Cl_2, rt, 5 min	80
2	Bn	BCl_3, CH_2Cl_2, −78 °C, 2 h	83
3	PMB	DDQ, CH_2Cl_2, rt, 2.5 h	92
4	TBS	TBAF, THF, 0 °C, 3 h	43
5	TBS	TBAF, DMF, 0 °C, 12 h	87
6	TBDPS	TBAF, DMF, 0 °C, 12 h	88

[a] Refers to pure, isolated compounds.

the catalyst, resulting in a competitive thermal decomposition of the ruthenium species and therefore requiring a higher catalyst loading.

To overcome this problem, and as originally proposed by Fürstner, $Ti(OPr^i)_4$ was added as an additive[15] with the aim of preferentially blocking the ether oxygen lone pairs. In the event, treatment of substrate **7a** with **GC-1**/$Ti(OPr^i)_4$ resulted in the smooth formation of the desired lactone **11a** in 92% yield (Table 1, entry 2).

A similar situation was encountered with the PMB-protected derivative **11b** (Table 1, entries 3–5), though in this case, even the use of **GC-1**/$Ti(OPr^i)_4$ did not lead to complete conversion of **7b** to **11b**. Therefore, the more reactive 2nd generation Grubbs' catalyst (**GC-2**)/$Ti(OPr^i)_4$ had to be employed (Table 1, entry 5).

As for the TBS and TBPDS-containing substrates **7c** and **d**, the addition of $Ti(OPr^i)_4$ was unnecessary since the steric bulk of these protecting groups effectively inhibits any undesired interaction between the ether and Grubbs' catalyst (Table 1, entries 6 and 7).

Having obtained lactones **11a–d**, we next investigated their selective deprotection (Table 2). Initially, removal of the benzyl group was efficiently accomplished, in the presence of the activated olefins, by treatment of **11a** with $FeCl_3$ (Table 2, entry 1).[16] Unfortunately, this reaction proved to be temperamental[17] and an alternative method, using BCl_3, was employed (Table 2, entry 2).

Pleasingly, DDQ-mediated deprotection of the PMB group proceeded smoothly, yielding alcohol **12** in 92% yield (Table 2, entry 3).

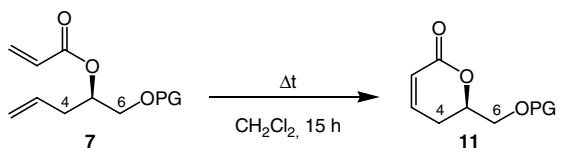
The unravelling of both silicon-containing substrates was achieved using TBAF. Interestingly, it was observed that the polarity of the solvent strongly influenced the product distribution (Table 2, entries 4–6). Indeed, when THF was used as a solvent, a large amount of nonidentified side products were generated, accompanied by the desired alcohol **12**, which was isolated in only 43% yield (Table 2, entry 5). On the other hand, if DMF was employed as the solvent,[18] TBAF-mediated deprotection of **11c** and **d** cleanly furnished alcohols **12** in 87% and 88% yields, respectively.

Swern oxidation of alcohol **12** yielded the unstable aldehyde **5**, which was immediately reacted with sulfoxide **6** under our standard sulfoxide-modified Julia olefination sequence, producing (*R*)-(+)-goniothalamin **1**[19] in 78% yield (starting from alcohol **12**) and with excellent *E*/*Z*-selectivity (Scheme 4).

It is important to note that our sulfoxide-modified Julia olefination afforded the natural product (*R*)-(+)-**1** with both an excellent yield and nearly perfect control of the C6–C7 double bond geometry. Such an observation stands in sharp contrast to the results obtained using alternative olefination methods, such as Wittig, classical Julia and Kociensky–Julia protocols, which accomplished this transformation either in low yields and/or modest selectivity (Table 3).

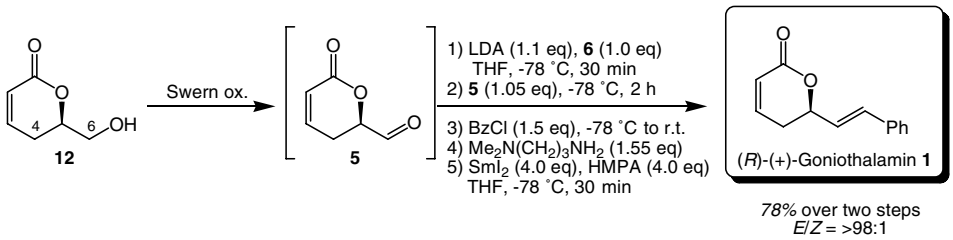
Since it is known that (*R*)-(+)-goniothalamin **1** is a precursor to other related natural products,[20] its stereoselective conversion to (*R*)-(+)-goniothalamin oxide **2** was attempted. After brief optimization of the reaction conditions, (*R*)-(+)-goniothalamin oxide **2** was isolated in 98% yield in a satisfactory 19:1 diastereomeric ratio (Table 4).

Table 1. Optimization of the metathesis reaction



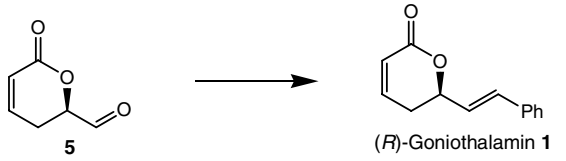
Entry	PG	Grubb's cat. (equiv)	Additive	Product	Yield[a] (%)
1	Bn	**GC-1** (0.1)	—	**11a**	45
2	Bn	**GC-1** (0.1)	$Ti(OPr^i)_4$	**11a**	92
3	PMB	**GC-1** (0.1)	—	**11b**	<10
4	PMB	**GC-1** (0.1)	$Ti(OPr^i)_4$	**11b**	78
5	PMB	**GC-2** (0.05)	$Ti(OPr^i)_4$	**11b**	99
6	TBS	**GC-1** (0.1)	—	**11c**	96
7	TBDPS	**GC-1** (0.1)	—	**11d**	89

[a] Refers to pure, isolated compounds.



Scheme 4. Sulfoxide-modified Julia olefination.

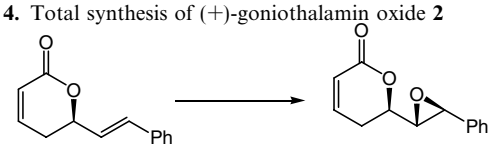
Table 3. Comparison of the various olefination methods in the context of the synthesis of (*R*)-(+)-goniothalamin



Entry	Olefination	Conditions	Yield (%)	*E*/*Z*
1[a]	Wittig	$BnPPh_3^+Cl^-$, *n*-BuLi	53	1:3
2[b]	Wittig	$BnPPh_3^+Br^-$, *n*-BuLi	57	1:9
3[a]	Kociensky–Julia	$PTSO_2Bn$, KHMDS	18	>98:1
4	Julia	$BnSO_2Ph$	<5	n.d.
5	Sulfoxide–Julia	BnS(O)Ph	78	>98:1

[a] Ref. 11l.
[b] Ref. 11a.

Table 4. Total synthesis of (+)-goniothalamin oxide **2**



Entry	Conditions	Yield (%)	dr
1	*m*-CPBA[a] (4.0 equiv), CH_2Cl_2, Δ, 4 h	69	3:2
2	*m*-CPBA[b] (4.0 equiv), CH_2Cl_2, rt, 24 h	97	10:1
3	*m*-CPBA[b] (4.0 equiv), CH_2Cl_2, 0 °C, 24 h	98	19:1

[a] Commercially available 70% *m*-CPBA was used.
[b] Purified acid and H_2O-free *m*-CPBA was used.

In summary, we have demonstrated that the sulfoxide-modified Julia olefination is a powerful method for the selective and connective formation of alkenes previously difficult to access by standard olefination protocols (Table 3). Moreover, we have shown that this reaction could be successfully employed in the context of natural product synthesis and have prepared (*R*)-(+)-goniothalamin **1** in six steps (51–55% overall yield) or five steps (55% overall yield) starting from commercially available (*R*)-glycidol **9** or (*R*)-benzyl glycidol **8a**, respectively.

In contrast to the previous total syntheses of **1**, the styryl subunit was efficiently introduced during the final step. Since it is known that changes in electronic and steric properties of the phenyl group strongly influence the biological activity of this family of natural products, our approach enables the efficient assembly of a variety of goniothalamin **1** analogues by uniting the common intermediate **5** with a range of different sulfoxides **6**.

Finally, (*R*)-(+)-goniothalamin oxide **2** has been obtained in excellent yield by diastereoselective epoxidation of (*R*)-(+)-**1**.

Acknowledgements

Financial support of this work by the Université catholique de Louvain, Rhodia Ltd. (studentship to J.P.) and SHIMADZU Benelux (financial support for the acquisition of a FTIR-8400S spectrometer) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.054.

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18. For similar observations, see: Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929–8936.
19. Experimental data for (*R*)-(+)-goniothalamin **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.56 (m, 2H), 5.12 (1H, dq, $J = 6.5$ Hz, $J = 1.2$ Hz), 6.10 (dt, 1H, $J = 9.7$ Hz, $J = 1.7$ Hz), 6.29 (dd, 1H, $J = 16.1$ Hz, $J = 6.5$ Hz), 6.74 (d, 1H, $J = 15.8$ Hz), 6.94 (dt, 1H, $J = 9.7$ Hz, $J = 4.4$ Hz), 7.30–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 30.1, 78.1, 121.9, 125.8, 133.3, 144.8, 126.9–136.0 (arom. CH and Cq), 164.1. Mp = 82–83 °C; lit.[111] 81–82 °C. MS (APCI), *m*/*z* (%): 201.0 (39) [M^++H], 183.1 (100), 155.2 (66), 130.1 (41). $[\alpha]_D^{20}$ +169.8 (*c* 1.45, $CHCl_3$); lit.[6c] $[\alpha]_D^{25}$ +170.3 (*c* 1.38, $CHCl_3$).
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Total Synthesis of Jerangolid D

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Jerangolids A, B, D, E, and H (Figure 1) are secondary metabolites produced by the myxobacterium *Sorangium cellulosum* (strain So ce 307), a myxobacterium isolated in 1987 in the soil of Jerusalem.[1] In vitro tests suggested that jerangolid A (**1**) and D (**2**) might be potential antifungal agents (other jerangolid derivatives were not tested), since they exhibit interesting activities against the developing cells of *Hansenula anomala* and *Mucor hiemalis* (~70 ng/mL), *Pichia membranaefaciens*, *Debaryomyces hansenii*, and *Trichosporon terrestre* (0.1−0.4 μg/mL), and *Trichoderma hamata*, *Botritis cinerea*, and *Candida albicans* (4−7 μg/mL). The mechanism of their action is believed to be similar to that of ambruticin,[2] another well-known myxobacterium isolate. However, even in the case of ambruticin, its mode of the action is not clear. Despite their promising antifungal properties, no total synthesis of any member of this class of natural products has been disclosed so far.[3]

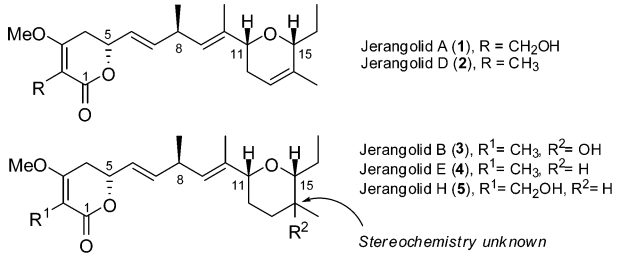


Figure 1. Members of the jerangolid natural products family.

Herein we report a short and convergent total synthesis of jerangolid D. At the onset of this project, it was decided that our approach to **2** should be easily adaptable to the synthesis of various structural analogues of **2**. Hence, it was envisioned that jerangolid D would derive from three fragments: lactone **6**, sulfone **7,** and dihydropyran **8** (Figure 2). These fragments would then be ultimately connected via a modified Julia and a Kocienski−Julia olefination.[4]

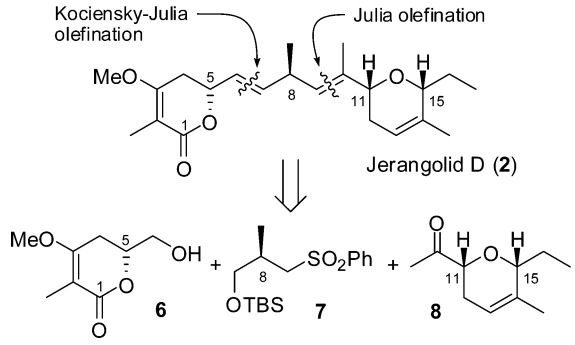
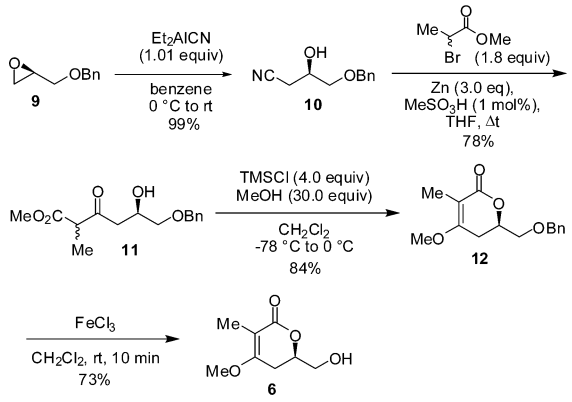


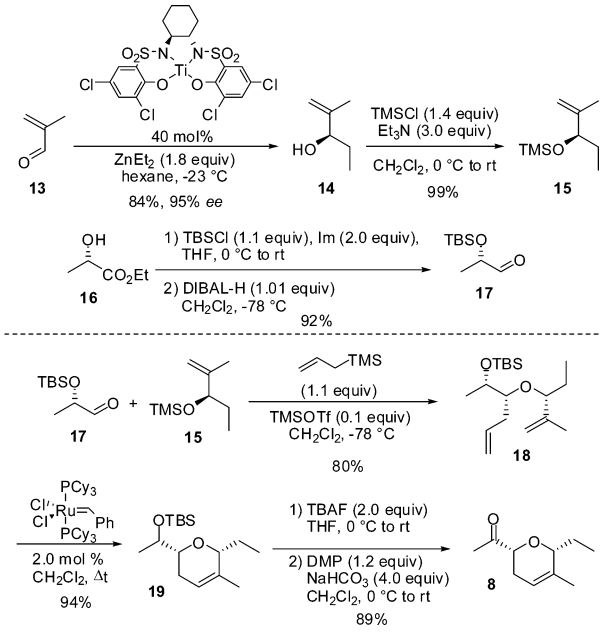
Figure 2. Retrosynthesis of jerangolid D.

The synthesis of lactone **6** is described in Scheme 1. Thus, Et_2AlCN mediated epoxide **9** opening[5] gave an easy access to the

Scheme 1. Synthesis of Lactone **6**



Scheme 2. Synthesis of Pyran **8**

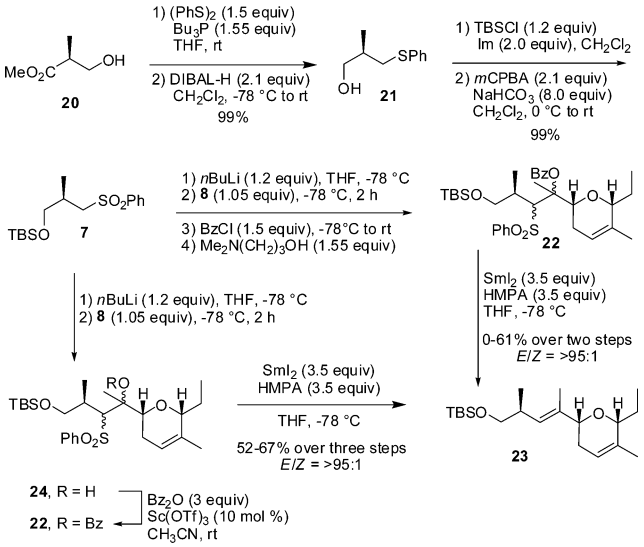


β-hydroxynitrile **10**, which was reacted with methyl bromoacetate in the presence of activated zinc dust.[6] To our delight, the Blaise reaction proceeded smoothly and furnished the desired β-ketoester **11** in 78% yield. Interestingly, the free hydroxyl group was tolerated under the reaction's conditions.[7] The Lewis acid mediated one-pot cyclization/enol ether formation[8] furnished lactone **12** in 84% yield. Finally, $FeCl_3$-promoted deprotection of the benzyl group[9] completed the synthesis of the left-hand fragment **6**.

The construction of the right-hand portion **8** was based upon the diastereoselective three-component Sakurai condensation protocol[10] recently developed in our laboratory (Scheme 2). Accordingly, the readily available ether **15**[11] and aldehyde **17** were mixed with allyltrimethylsilane at −78 °C and a catalytic amount of

10.1021/ja0691728 CCC: $37.00

Scheme 3. Synthesis of Sulfone **7** and First Julia Coupling

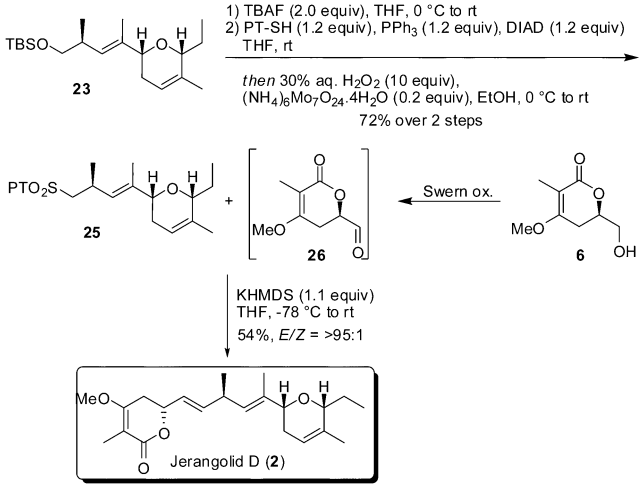


TMSOTf was added. The syn−syn adduct **18** was obtained as a single stereoisomer in 80% yield. Ring closing metathesis followed by TBS removal and oxidation of the resulting alcohol then accomplished the synthesis of the right-hand subunit **8**. The C7−C9 remnant **7** was prepared from the Roche ester **20** in four steps and 97% overall yield (Scheme 3).

Having established an easy access to all three fragments, we then focused our efforts on their union, and a Julia olefination reaction between sulfone **7** and ketone **8** was selected (Scheme 3). It was envisioned that the stereoselective formation of the trisubstituted C9−C10 olefin could be accomplished via the SmI_2-mediated reductive elimination[12] of the β-benzoyloxysulfones **22**. Initially, a one-pot condensation between **7** and **8** followed by the in situ benzoylation of the generated adducts was attempted. Surprisingly, this sequence proved to be irreproducible and therefore a two-steps procedure had to be used.[13] The SmI_2-mediated reductive elimination of the sulfones **22** then furnished the desired olefin **23** in good yield and excellent *E*/*Z* selectivity.

At this stage, only the coupling between fragment **23** and subunit **6** remained to complete the first total synthesis of jerangolid D (Scheme 4). Silylether **23** was thus transformed into the corresponding sulfone **25**. In parallel, alcohol **6** was oxidized into aldehyde **26**. Finally, fragments **25** and **26** were reacted under the standard Kociensky−Julia olefination conditions[14] yielding jerangolid D **2** in 54% yield and >95:1 *E*/*Z* selectivity.

Scheme 4. Completion of the Total Synthesis of Jerangolid D



In summary, we have accomplished the first total synthesis of jerangolid D in 22 steps (12 steps in the longest linear sequence) and 6.1% overall yield (14.5% in the longest linear sequence) starting from the commercially available epoxide **9**, Roche ester **20**, methacrylate **13**, and ethyl lactate **16**. While the synthesis of the left-hand fragment **6** was based upon a Blaise reaction (four steps, 46.7% overall yield), the Eastern ketone **8** was assembled using a diastereoselective multicomponent Sakurai condensation (eight steps, 51.2% overall yield). The synthesis of jerangolid D analogues as well as other members of the jerangolid family is currently in progress in our laboratory.

Acknowledgment. We are grateful to Dr. P. Washausen (Helmholtz Zentrum für Infektionsforschung) for kindly supplying us with spectral data of jerangolid D and with a sample of the natural product itself. Financial support of this work by the Université catholique de Louvain, Rhodia Ltd. (studentship to J.P.) and SHIMADZU Benelux (financial support for the acquisition of a FTIR-8400S spectrometer) is gratefully acknowledged.

Note Added after ASAP Publication: After this paper was published ASAP on February 23, 2007, the Supporting Information was updated with additional (and corrected) experimental details for **21A** and **23A** and NMR spectra for **19A** and **23**. Typographical errors and proton misassignments were also corrected. The revised Supporting Information was published March 7, 2007.

Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Metathesis-based synthesis of 3-methoxy α,β-unsaturated lactones: total synthesis of (*R*)-kavain and of the C1–C6 fragment of jerangolid D

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Abstract

The total synthesis of (*R*)-kavain and of the C1–C6 fragment of jerangolid D has been achieved in nine and seven steps, respectively, from commercially available dimethyl D-malate. A metathesis reaction of vinyl ethers and a sulfoxide-modified Julia olefination have been employed as the key steps.

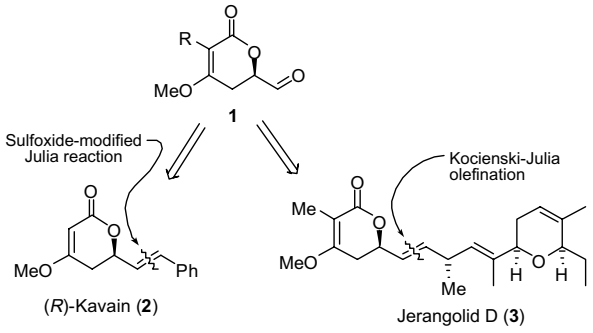
Keywords: Kavain; Jerangolid D; Metathesis; Julia olefination; Sulfoxide-modified Julia olefination

A wide variety of natural products contain a lactone core in their structures. In many cases, these compounds display antitumor activities and the presence of an *endo*- or *exo*-cyclic α,β-unsaturated lactone[1] typically confers to the molecule some antineoplastic activities (among others).[2]

As a part of our ongoing research program toward the efficient synthesis of natural products possessing anticancer and antifungal properties, we became interested in the development of novel approaches for the assembly of various lactone-bearing subunits. Our initial efforts in this field culminated recently in the establishment of two novel strategies leading to *exo*-methylenelactones. More recently, the synthesis of 3-methoxy α,β-unsaturated lactones of the general structure **1** was targeted.[3]

We became attracted by this particular class of lactones because of their presence in various natural products, such as kavain **2** and jerangolid D **3** (Scheme 1).

Kavain **2** belongs to the group of styryl lactone-derivatives and it can be found in the Kava plant (*Piper methysticum*). The Kava plant has a long and colorful history spanning several thousand years.[4] Kava has been used by Pacific Island societies to prepare an intoxicating ceremonial beverage renowned for its relaxing effects and ability to promote sociability. Modern use of Kava root, commonly available in dietary supplements labeled 'Kava Kava', is mostly reported for its purported anxiolytic[5] and soporific qualities. Analgesic,[6] anesthetic, antifungal, antithrombotic,[7] anticonvulsive,[8] and muscle-relaxing[9] properties have also been reported.[4]



Scheme 1. Retrosynthesis of kavain (**2**) and jerangolid D (**3**).

Jerangolid D[10] is a secondary metabolite produced by the myxobacterium *Sorangium cellulosum* (strain So ce 307), a myxobacterium isolated in 1987 in the soil of Jerusalem. In vitro tests suggested that jerangolid D might be a

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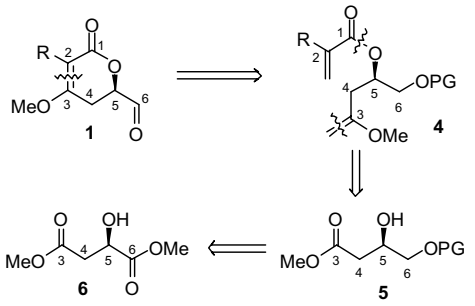
potentially useful antifungal agent, since it exhibits interesting activities against the developing cells of *Hansenula anomala* and *Mucor hiemalis* (~70 ng/mL); *Pichia membranaefaciens*, *Debaryomyces hansenii*, and *Trichosporon terrestre* (0.1–0.4 μg/mL); and *Trichoderma hamata*, *Botritis cinerea*, and *Candida albicans* (4–7 μg/mL). The mechanism of its action is believed to be similar to that of ambruticin,[11] another well-known myxobacterium isolate, for which the mode of action is still unclear.

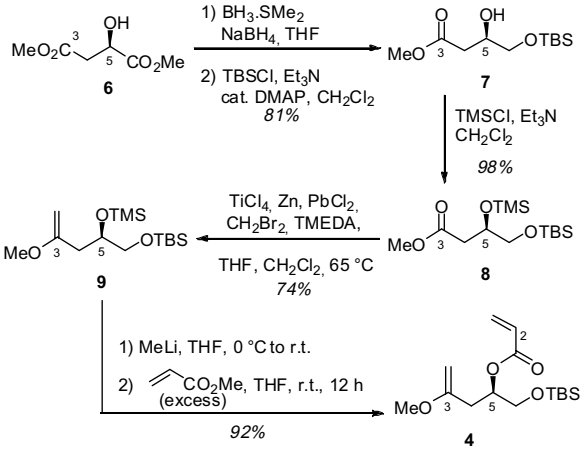
Our retrosynthesis of lactone **1** was designed to use the metathesis reaction as a key step (Scheme 2). As a consequence, lactone **1** was disconnected at the C2–C3 positions, leading to acrylate **4**. The required vinyl ether function present in **4** could then be prepared from ester **5** via titanium alkylidenation of the C3 carbonyl group.

The synthesis began with the selective reduction of the C6 ester of (*R*)-dimethyl malate **6** to the corresponding primary alcohol,[12] followed by the transformation of the resulting C6 alcohol[13] into a TBS ether (Scheme 3). The remaining C5 alcohol was masked as a TMS ether and the resulting compound **8** was reacted with titanium alkylidene reagents. In our hands, Rainer's modification of the Takai–Utimoto reaction[14] gave the best results,[15] affording the desired enol ether **9** in 74% yield.

Finally, a selective one pot TMS group removal/base mediated esterification of the resulting C5 alkoxide accomplished the synthesis of the metathesis precursor **4**.



Scheme 2. Retrosynthesis of lactone **1**.



Scheme 3. Synthesis of metathesis precursor **4**.

Having established an easy access to the desired intermediate **4**, our first key step, the Grubbs' metathesis, could be challenged. From the literature precedents, it is known that the metathesis reaction of electron-rich olefins,[16] in particular enol ethers, is rather difficult and requires harsh conditions, for example, prolonged reaction times, high temperatures and high catalyst loading. For this reason, the use of Schrock's more reactive, though more sensitive, catalyst[17] is generally preferred.

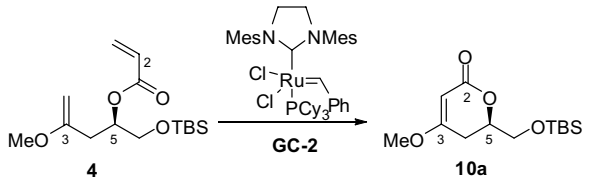
The sensitivity of the Schrock carbene prompted us to perform our reactions using the 2nd generation Grubbs' catalyst (**GC-2**) in a non-polar solvent.[16a] Thus, ester **4** was treated with **GC-2** in deuterated toluene and the influence of the reaction conditions on the conversion was monitored (Table 1).

It was observed that the metathesis reaction proceeded somewhat better at 50 °C (Table 1, entry 1) than at higher temperatures. In all cases, the catalyst was fully decomposed under the reaction conditions within 4–7 h. Therefore, constant addition of the catalyst over a period of 66 h (5 mol % of **GC-2** every 6 h) was performed. The starting material **4** gradually disappeared, yielding the desired lactone **10** in 88% yield (Table 1, entry 5). Unfortunately, up to 55 mol % of **GC-2** was consumed in this single experiment.

These results, though rather encouraging, could not be reconciled with our idea of a useful synthetic transformation. It was suggested that the low reactivity of **4** could be due, among other potential problems, to its difficulty in adopting an (*S*)-*cis* conformation and hence, enabling the two alkene termini to reach a proper distance for the reaction to occur.[18] To overcome this problem and to reduce the catalyst loading, it was decided to use the modified metathesis precursor **11** (Fig. 1).[19]

The synthesis of **11** began with the monoprotected diol **7**, which was transformed into acetals **12a** and **12b** via

Table 1
Metathesis reaction of the precursor **4**



Entry	Conditions	Conversion[a] (%)	Yield[a] (%)
1	5 mol %, toluene-d_8, 12 h, 50 °C	20	20
2[b]	5 mol %, toluene-d_8, 12 h, 60 °C	18	18
3[b]	5 mol %, toluene-d_8, 12 h, 70 °C	10	10
4[c]	5 mol %, toluene-d_8, 12 h, 80 °C	5	5
5[d]	55 mol %, toluene-d_8, 66 h, 50 °C	91	88[e]
6	10 mol %, toluene-d_8, 72 h, rt	8	<5

[a] Based on ^{1}H NMR spectra.
[b] Conversion stopped after 5–7 h.
[c] Conversion stopped after 4 h.
[d] 5 mol % of **GC-2** was added every 6 h.
[e] Isolated yield.

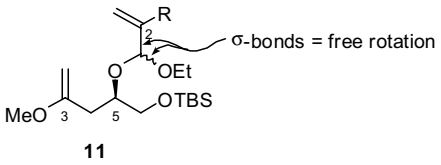
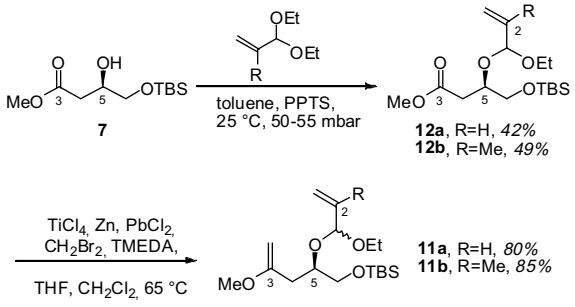


Fig. 1. Alternative metathesis precursor **11**.

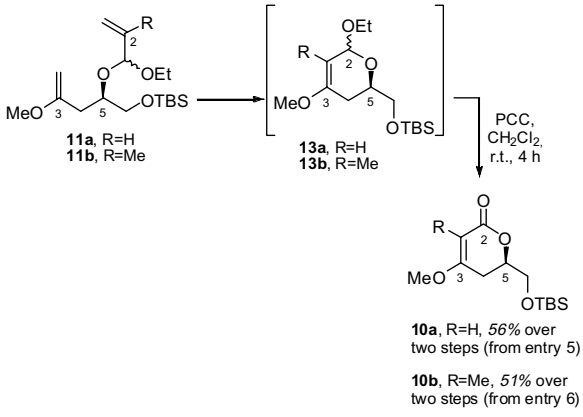
PPTS-catalyzed *trans*-acylation of acrolein diethyl acetal and methacrolein diethyl acetal,[20] respectively (Scheme 4). Acetals **12a** and **12b** were then submitted to the Takai–Utimoto olefination yielding the desired precursors **11a** and **11b** in 80% and 85% yields.

With the desired substrates in hand, the crucial ring closing metathesis could be tested again (Table 2). To our surprise, no important changes in the reactivity of **11a**, as compared to substrate **4**, were observed (Table 2, entries 1–3).



Scheme 4. Synthesis of precursor **11**.

Table 2
RCM reaction of **11**



Entry	R	**GC-2** loading (mol %)	Conditions	Yield[a] (%)
1	H	20[b]	Benzene, 50 °C, 4 h	21
2	H	30[b]	Benzene, 70 °C, 6 h	26
3	H	30[b]	Toluene, 50 °C, 6 h	21
4	H	50	Benzene, rt, 24 h	39
5	H	10	Benzene, rt, 72 h	93
6	Me	10	Benzene rt, 84 h	95

[a] Based on the ^{1}H NMR spectra.
[b] 10 mol % of **GC-2** was added every 2 h.

The reaction proceeded with a slightly higher conversion, but the decomposition of the catalyst under the reaction conditions was still significant.

To avoid this decomposition, the reaction was attempted at rt. in the presence of 50 mol % of **GC-2** (Table 2, entry 4). After 24 h, a 39% conversion of **11a** to cyclic acetal **13a** was reached. Allowing the cyclization to proceed longer led to improved conversions.

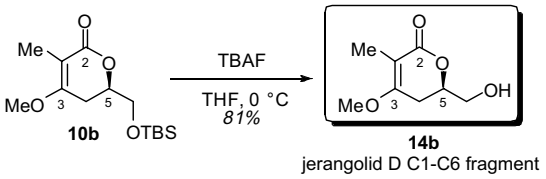
Under the optimized conditions, only 10 mol % of **GC-2** was required to fully transform **11** to **13** (Table 2, entries 5 and 6).[21] The oxidation of acetals **13** with PCC then afforded the desired lactones **10a** and **10b** in 56% and 51% yields, respectively, over two steps.

Removal of the TBS group of **10b** furnished alcohol **14b**, the left-hand fragment of jerangolid D (**3**), in 81% yield (Scheme 5).[22]

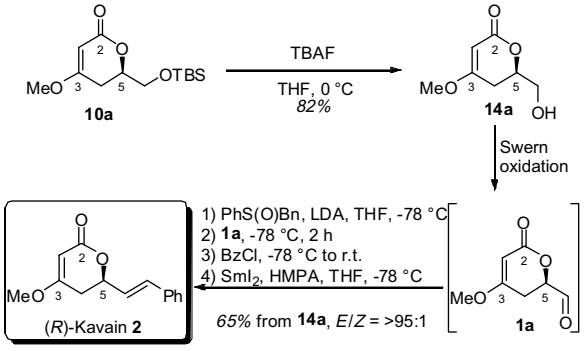
The C2 desmethyl lactone **10a** was also deprotected (82% yield) and the resulting alcohol **14a** was then used in the synthesis of (*R*)-kavain[23] **2** (Scheme 6). Thus, alcohol **14a** was transformed into aldehyde **1a** via Swern oxidation. Lactone **1a** was immediately reacted with benzyl phenyl sulfoxide under our sulfoxide-Julia olefination conditions[24] (Scheme 6), affording (*R*)-kavain **2** in 65% yield and with an excellent *E*/*Z* selectivity.

The necessity to employ the sulfoxide version of the Julia olefination reaction in this ultimate transformation had been discussed previously.[24c]

In summary, the penultimate precursor of the left-hand fragment of jerangolid D, alcohol **14b**, was prepared in seven steps and 16% overall yield from commercially available dimethyl D-malate **6**. Similarly, (*R*)-kavain[25] **2** was



Scheme 5. Synthesis of the C1–C6 fragment of jerangolid D.



Scheme 6. Total synthesis of (*R*)-kavain **2**.

synthesized in nine steps and in 7.7% overall yield. To achieve these goals, a simple approach toward 3-methoxy α,β-unsaturated lactones of the general structure **1**, based upon the metathesis reaction of electron-rich alkenes, coupled with our sulfoxide Julia olefination procedure was employed.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.113.

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25. *Experimental data for* (*R*)-(+)-*kavain* **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.55 (dd, 1H, $J = 17.1$ Hz, $J = 4.6$ Hz), 2.68 (dd, 1H, $J = 17.1$ Hz, $J = 10.7$ Hz), 3.77 (s, 3H), 5.06–5.09 (m, 1H), 5.20 (s, 1H), 6.27 (dd, 1H, $J = 16.1$ Hz, $J = 6.3$ Hz), 6.73 (d, 1H, $J = 16.0$ Hz), 7.29–7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 33.8, 56.5, 76.5, 91.1, 125.8, 133.2, 167.2, 127.0, 128.8, 129.2, 136.3, 172.6. Mp = 113–114 °C; lit. 112–113 °C.[23a] IR (KBr) ν (cm^{-1}): 3063, 2967, 1703, 1626, 1394, 1248, 1233, 1063, 1024, 971, 747, 693. $[\alpha]_D^{20}$ +120.3 (*c* 1.02, EtOH); lit. $[\alpha]_D^{25}$ +124.3 (*c* 1.00, EtOH).[23a]

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Simple protocol for enhanced (*E*)-selectivity in Julia–Kocienski reaction

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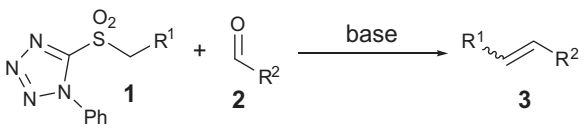
ABSTRACT

A short and efficient Julia–Kocienski olefination protocol, based upon the use of chelating agents (18-crown-6 or TDA-1 for K^+; 12-crown-4 or HMPA for Li^+), was developed. This protocol enhances the (*E*)-selectivity of the reaction and the desired olefins are obtained generally with >10:1 (*E*/*Z*)-selectivity.

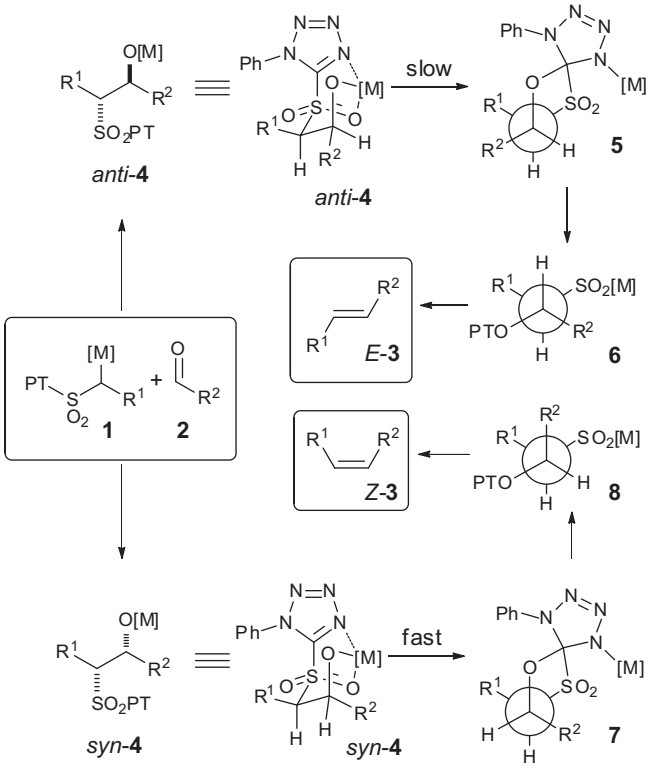
The formation of C=C double bonds is of paramount importance in the field of organic chemistry.[1] The reason for this lies not only in the fact that this structural motif (olefin) is present in various natural and nonnatural bioactive compounds, but also in the fact that olefins can be easily transformed into a wide variety of different functional groups.

Recently, Julia–Kocienski reaction has become a very popular method to achieve the double bond formation thanks to its wide functional group tolerance and possibility to perform the transformation under very mild reaction conditions. As a consequence, this reaction has become one of the most favorite late stage coupling methods used in total synthesis (Scheme 1).[2]

In general, the Julia–Kocienski reaction yields olefins predominantly in (*E*)-configuration on newly formed double bond. However, low, missing, or even inversed selectivity ((*Z*)-isomer formed as the major one) was also observed when the standard reaction conditions were used.



Scheme 1. Julia–Kocienski olefination.



Scheme 2. Proposed mechanism of Julia–Kocienski olefination.

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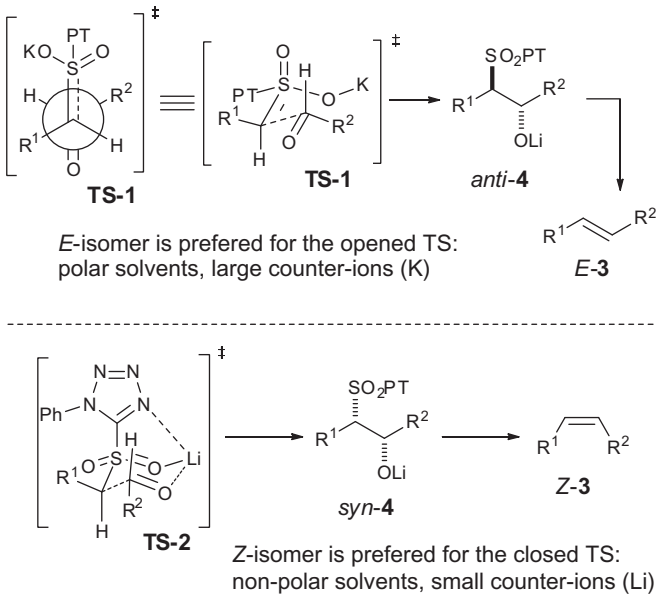


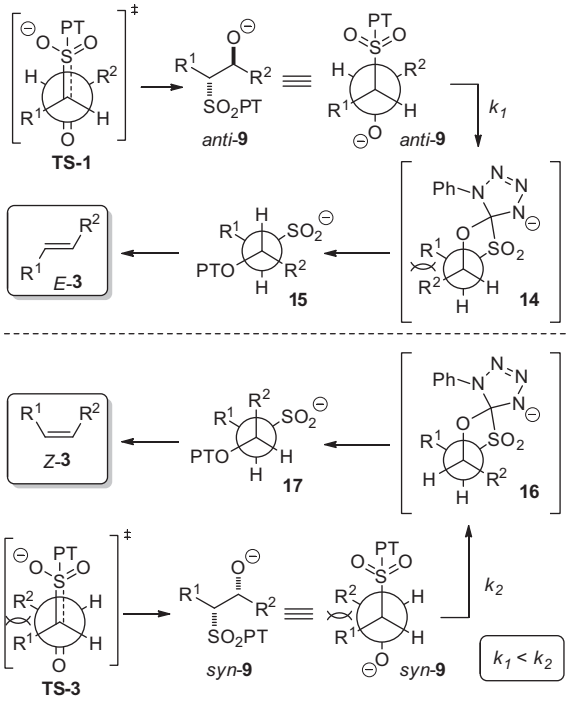
Scheme 3. Proposed guidelines for the reaction selectivity.

For this reason, it became important to postulate some guidelines that would allow us to predict the reaction selectivity. Such guidelines, based on the generally accepted Julia–Kocienski reaction mechanisms[2,3] (Scheme 2), and some additional experimental observations,[4] were proposed (Scheme 3). It was stated that if the addition of aliphatic α-metalated sulfones to aldehydes is a nonreversible process, then the stereochemical outcome of the reaction directly depends upon the *syn*/*anti* selectivity of the addition step.[2,5] By other means, if the addition of α-sulfonyl anion proceeds via an open **TS-1** (K^+-bases/polar solvent), formation of (*E*)-olefin should be observed. Contrary, if a closed **TS-2** (Li^+-bases/nonpolar solvents) is preferred, *Z*-olefins should be obtained.

These statements are based on observations that the rest of the sequence, namely the transformation of the *anti*- and *syn*-**4** adducts to the corresponding olefins **3**, via a Smiles rearrangement/elimination sequence, is stereospecific (Scheme 2).[2,5]

However, there are exceptions to these guidelines. In some cases, the best (*E*)-selectivity (addition via open **TS-1**) was achieved when a Li^+-containing base (LiHMDS) was used in combination with polar solvents (DMF/HMPA).[6,7] Thus, in general, it is difficult to predict with high level of confidence the selectivity outcome of the reaction; this situation being rather inconvenient when the coupling of two complex fragments is desired. Therefore, we decided to develop a new protocol that would allow the Julia–Kocienski reaction to proceed with high (*E*)-selectivity.

We assumed that the addition of selective metal–cation chelating species into the reaction mixture might increase the selectivity

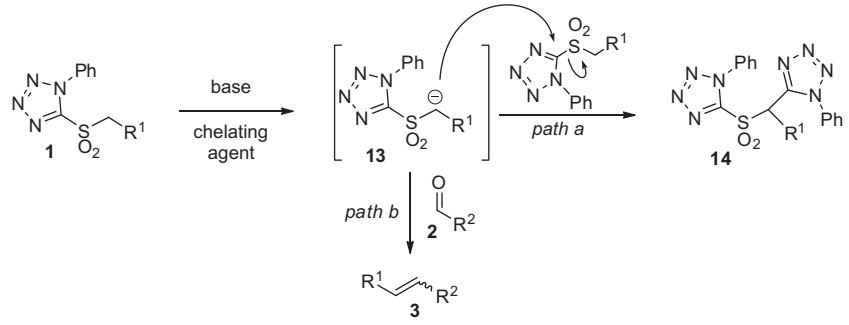


Scheme 5. Addition of anion generated from α-monosubstituted sulfone to aldehyde.

of the transformation. This assumption was based upon the expectation that selective cation chelation will create 'naked' sulfonyl anion **13**. As a consequence, the highly reactive intermediate **13** can either undergo a rapid self-condensation (Scheme 4, path a) or it can react with aldehyde **2** (Scheme 4, path b). To favor the addition (path b) over the self-condensation (path a), the aldehyde has to be added to the reaction mixture rapidly after the base. On the other hand, we have to let some time to the chelating agents to chelate the specific alkali metal cation to generate the more reactive 'naked' carbon-based anion **13**.

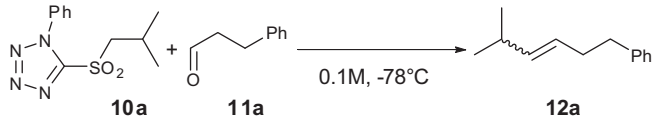
We believe that if we would find good reaction conditions where the chelating agent would have enough time to chelate the corresponding cation but the self-condensation of **13** would be sufficiently slow, then the addition of **13** to aldehyde **2** should proceed via an open **TS-1** to yield adduct *anti*-**9** (Scheme 5). We expect that **TS-1** will be preferred over the other possible open transition state **TS-3**. In **TS-3** the groups R^1 and R^2 suffer from severe steric repulsions. Additionally, we expect that the addition of **13** to aldehyde **2** is an irreversible process, since the retro-addition would form highly unstable 'free' carbon-based anion species.

The presence of a chelating agent should play an important role even after the addition step, since under standard reaction condi-



Scheme 4. Julia–Kocienski reaction in the presence of chelating agents: two plausible competitive pathways.

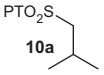
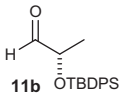
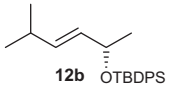
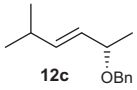
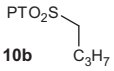
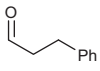
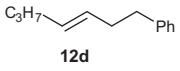
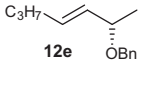
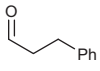
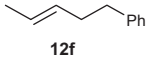
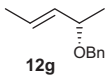
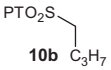
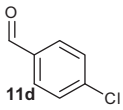
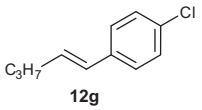
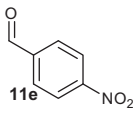
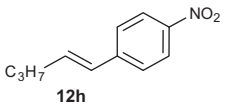
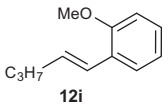
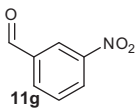
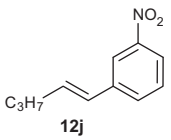
Table 1
Reaction conditions optimization



Entry	Conditions	Solvent	Yield[a]	(*E*/*Z*)[b]
1	KHMDS (1.1 equiv)	THF	88%	4.3:1
2	KHMDS (1.1 equiv), 18-crown-6 (1.1 equiv)	THF	86%	15:1
3	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	THF	84%	>50:1
4	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	Toluene	87%	>50:1
5	KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	DMF	78%	>50:1
6	KHMDS (1.1 equiv)	DMF/TDA-1 3:1[c]	83%	>50:1
7	NaHMDS (1.1 equiv), 18-crown-6 (2.0 equiv)	THF	78%	4:1
8	NaHMDS (1.1 equiv)	DMF/TDA-1 3:1[c]	81%	4:1
9	LiHMDS (1.1 equiv)	THF	90%	2.1:1
10	LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv)	THF	79%	3:1
11[c]	LiHMDS (1.1 equiv)	DMF/HMPA 3:1	92%	5:1
12[c]	LiHMDS (1.1 equiv)	DMF/DMPU 3:1	88%	4.4:1

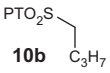
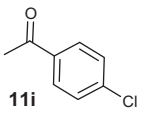
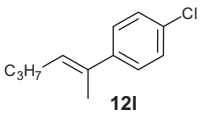
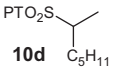
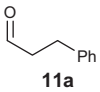
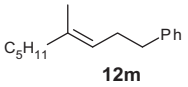
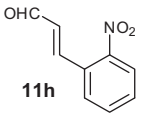
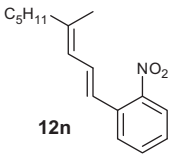
[a] Average of three runs; refers to pure isolated compounds.
[b] Average of three runs; based on crude ^{1}H NMR spectra.
[c] Reaction performed at −60 °C.

Table 2
Preliminary scope and limitations—1,2-disubstituted olefins

Entry	Sulfone	Carbonyl compound	Product	Condition[a]	Yield (*E*/*Z*)
1				A	81% (21:1)
2	**10a**	**11b**	**12b**	B	82% (>50:1)
3				A	78% (19:1)
4		**11c**	**12c**	B	75% (>50:1)
5				A	74% (5:1)
6	**10b**	**11a**	**12d**	B	86% (>50:1)
7				A	68% (9:1)
8		**11c**	**12e**	B	63% (>50:1)
9				A	72% (8:1)
10	**10c**	**11a**	**12f**	B	62% (>50:1)
11				A	76% (4:1)
12		**11c**	**12g**	B	75% (19:1)
13				A	47% (50:1)
14	**10b**	**11d**	**12g**	B	65% (25:1)
15				A	54% (30:1)
16		**11e**	**12h**	B	67% (20:1)
17				A	59% (>50:1)
18		**11f**	**12i**	B	64% (>50:1)
19				A	61% (19:1)
20		**11g**	**12j**	B	74% (10:1)

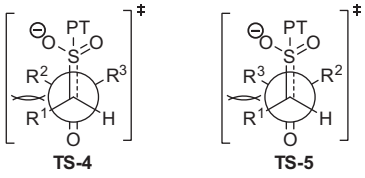
[a] Conditions: (A) KHMDS (1.1 equiv), THF; (B) KHMDS (1.1 equiv), 18-crown-6 (2.0 equiv), THF.

Table 3
Preliminary scope and limitations—trisubstituted olefins

Entry	Sulfone	Carbonyl compound	Product	Condition[a]	Yield (*E*/*Z*)
1	 **10b**	 **11i**	 **12l**	C	Nr
2				D	76% (1.6:1)
3				E	87% (2.6:1)
4				F	73% (2.6:1)
5	 **10d**	 **11a**	 **12m**	C	Nr
6				E	97% (1.2:1)
7		 **11h**	 **12n**	C	Nr
8				E	75% (1.2:1)

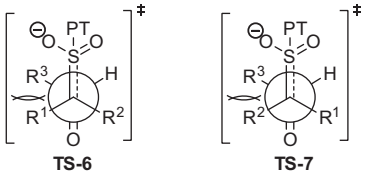
[a] Conditions: (C) KHMDS, various conditions; (D) LiHMDS (1.1 equiv), THF; (E) LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv), THF; (F) LiHMDS (1.1 equiv), 12-crown-4 (2.0 equiv), toluene.

Addition of anion generated from α monosubstituted sulfone to ketone



Two possible open transition states

Addition of anion generated from α disubstituted sulfone to aldehyde



Two possible open transition states

Scheme 6. Proposed TS for α-monosubstituted sulfones addition to ketones and α-disubstituted sulfones to aldehydes.

tions (reaction performed without the presence of any chelating agent), the adduct *anti*-**9** should undergo the Smiles rearrangement only very slowly (due to the steric repulsion between R^1 and R^2 as showed in adduct *anti*-**4**, see Scheme 2). In our case, the rearrangement of adduct *anti*-**9** should proceed with faster reaction rate due to enhanced nucleophilic character of alkoxide anion. Similarly, the fragmentation of intermediate **15** should proceed faster than when chelating agents are not used.

To test our hypothesis, the olefination reaction of sulfone **10a** with aldehyde **11a** was investigated (Table 1).[8] Under the standard reaction conditions (KHMDS used as a base); the desired olefin **12a** was obtained in 88% yield with a 4.3:1 (*E*/*Z*)-selectivity (Table 1, entry 1). However, when the reaction was performed in the presence of 1.0 equiv of 18-crown-6, olefin **12a** was isolated in 86% yield and with a greater than 15:1 (*E*/*Z*)-selectivity (Table 1, entry 2). Further increase in 18-crown-6 loading yielded alkene **12a** in comparable yield and with an excellent >50:1 (*E*/*Z*)-selectivity (Table 1, entry 2). Interestingly, no solvent effect was observed on the reaction selectivity (Table 1, entries 3–5). Additionally, TDA-1[9] was used as 18-crown-6 surrogate, yielding olefin **12a** in excellent yield and exquisite (*E*/*Z*)-selectivity (Table 1, entry 6). In all these experiments, aldehyde **11a** was added 0.5 min after the base (to avoid the undesired self-condensation reaction).

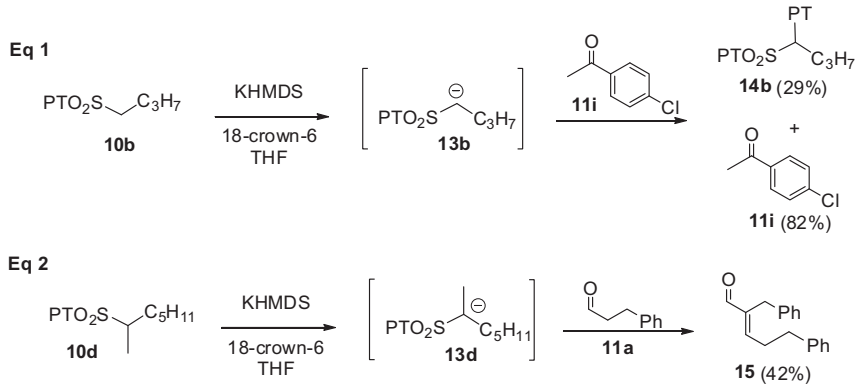
Control experiments to clarify if the 18-crown-6 and the TDA-1 behave as K^+ scavengers were also performed. First, we replaced KHMDS in the standard reaction conditions set (KHMDS/18-crown-6/THF or KHMDS/DMF:TDA-1 = 3:1) with NaHMDS (Table 1, entries 7 and 8). As expected, the (*E*/*Z*)-selectivity of both reactions dropped and the original 4:1 (*E*/*Z*)-ratio was recuperated (Table 1, entry 1).

Additionally, the olefination reaction between sulfone **10a** and aldehyde **11a**, promoted by LiHMDS, was investigated (Table 1, entries 9–11). As expected, the addition of 12-crown-4 (Table 1, entry 10) or HMPA as a co-solvent (Table 1, entry 11) increased the (*E*)-selectivity of the coupling, but the influence of these additives was less pronounced when compared with the KHMDS/18-crown-6 system. We believe that this is due to a slower chelation of the Li^+ cation by 12-crown-4 or HMPA when compared to the K^+/18-crown-6 system.[10]

Having optimized the reaction conditions, the preliminary scope and limitations of our protocol were established (Tables 2 and 3). First, the (*E*/Z)-selectivity of 1,2-disubstituted olefins prepared from linear or β-branched sulfones **10a–c** reacting with linear and/or α-substituted aldehydes **11a–c** under our reaction conditions were examined (Table 2, entries 1–12). In all studied cases, the olefins **12b–g**, that were prepared using KHMDS/18-crown-6 conditions, were furnished with very good to excellent (*E*)-selectivity. It is important to note that the observed (*E*/*Z*)-selectivities were always superior to those obtained under the classical reaction conditions (KHMDS/THF).

Next, the reaction of sulfone **10b** with aromatic aldehydes **11d–g** was examined (Table 2, entries 13–20). Surprisingly, in these cases, the (*E*/*Z*)-selectivity of the olefin formation was worse if the chelating agents were used. On the other hand, the reaction yields were in general 10% higher.

Finally, the stereoselective synthesis of trisubstituted olefins was attempted (Table 3). First, the reaction between α-monosubstituted sulfone **10b** and ketone **11i** was attempted (Table 3, entries 1–4). Interestingly, if KHMDS was used as a base, the formation of olefin **12l** was not observed. In contrast to this result, the use of LiHMDS provided the desired olefin **12l** in very good yield (Table 3, entries 2–4). The same situation occurred if α-disub-



Scheme 7. Side products obtained during the KHMDS-mediated attempts of trisubstituted olefin synthesis.

stituted sulfone **10d** reacted with aromatic or aliphatic aldehyde **11h** or **11a** (Table 3, entry 5). Also in this case, the use of LiHMDS as a base furnished the desired olefins **12m** and **12n** in good to excellent yields (Table 3, entries 6 and 7). In all these cases, very low or virtually missing (*E*)-selectivity was observed. We believe that the missing selectivity can be attributed to the fact that both possible open transition states, by which the reaction can proceed, suffer from rather severe steric restrictions (Scheme 6).

As shown in Table 3, if the synthesis of trisubstituted olefins via Julia–Kocienski olefination reaction was attempted under our KHMDS/18-crown-6 or KHMDS/TDA-1 conditions, no olefin formation was observed (Scheme 7). In all cases, only the products of sulfone self-condensation (product **14**) or aldol condensation reaction (compound **15** if aldehyde was used as the coupling partner), were obtained. It was suggested that the formation of these undesired products might be caused either by the low reactivity of the electrophilic partner (ketone vs aldehyde) or by the steric hindrance presented around the generated anion. In both cases, the addition of anion **13b** to ketone **11i** (Scheme 7, Eq. 1) or of anion **13d** to aldehyde **11a** is kinetically less favored than the addition of anion **13b** to aldehyde **11a** (Scheme 7, Eq. 2) due to steric reasons. As a consequence, a competitive deprotonation of α-carbonyl hydrogens might occur. The protonated sulfonyl species then might easily undergo the self-condensation reaction with another molecule of metalated sulfone **10**.

The same is true, of course, if LiHMDS is used as a base. However, in this case, the Li^+ cation presumably serves as a Lewis acid that activates carbonyl group and, therefore, facilitates the addition of generated lithium sulfonyl anion.

In conclusions, new conditions for the Julia–Kocienski olefination, that use specific metal cation chelating agents to enhance the reaction's (*E*)-selectivity, were developed.[11] Even though the exact role of chelating reagents is not clear at the moment and requires further investigation, we believe that this new modification of the standard olefination reaction will find a wide application in the synthesis of complex natural products.

Acknowledgments

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Supplementary data

Supplementary data (full experimental details and characterization data of synthetic compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.086.

References and notes

1. (a) Dumeunier, R.; Markó, I. E. In *Modern Carbonyl Olefination*; Takeda, T., Ed.; Wiley-VCH: Weinheim, Germany, 2004; pp 104–161; (b) Kocienski, P. J. In *Comp. Org. Synth.*; Trost, B. M., Fleming, I., Eds., 1991; 6, pp 987–1000.
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5. Markó, I. E.; Pospíšil, J. In *Science of Synthesis*; de Meijere, A., Ed.; Georg Thieme Verlag KG: Stuttgart, 2010; pp 105–160.
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7. It was also reported that the addition of 18-crown-6 (for KHMDS promoted coupling) might increase the reaction selectivity if an α *O*-alkyl substituted aldehyde was used as a reaction substrate. It was suggested that the presence of 18-crown-6 disabled possible stabilization of the adduct and so, prevented the retro addition reaction. Ishigami, K.; Watanabe, H.; Kitahara, T. *Tetrahedron* **2005**, *61*, 7546–7553.
8. For complete reaction optimization table see Table S-1.
9. TDA-1 = tris[2-(2-methoxyethoxy)ethyl]amine; selective K^+ chelating agent, see e.g. Tamao, K.; Nakagawa, Y.; Ito, Y. *Org. Synth.* **1996**, *73*, 94–109.
10. (a) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res.* **1997**, *30*, 338–345; (b) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035–1042.
11. *Typical procedure:* A solution of sulfone **10a** (50 mg, 0.188 mmol, 1.0 equiv) and 18-crown-6 (99.4 mg, 0.376 mmol, 2.0 equiv) in THF (2 mL, 0.1 M) was cooled down to −78 °C and KHMDS (451 μL, 0.5 M solution in toluene, 1.2 mmol, 1.2 equiv) was added dropwise within 10 s. After additional 30 s, aldehyde (73 mg, 0.21 mmol, 1.1 equiv) in THF (500 μL) was added. The resulting mixture was stirred at −78 °C for 30 min before saturated aqueous NH_4Cl (10 mL) was added. The resulting phases were separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (P.E./EtOAc = 100:0→20:1) yielding 54.4 mg (82%) of colorless oil ((*E*/*Z*) = >50:1).

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Practical Synthesis of β-Acyl and β-Alkoxycarbonyl Heterocyclic Sulfones

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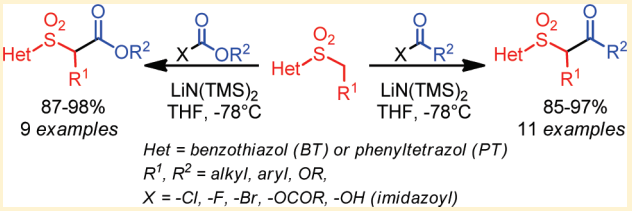
Supporting Information

ABSTRACT: A short and efficient synthesis for β-acyl and β-alkoxycarbonyl heterocyclic sulfones containing benzothiazol (BT) and phenyltetrazol (PT) heterocyclic core is presented here. The method seems to be general and provides the desired C-nucleophiles in very good to excellent yields from readily available starting materials.



Over the past two decades, asymmetric organocatalysis has developed into a field permitting the elegant introduction of chiral information into a plethora of various substrates.[1] During this period, several efficient organocatalytic protocols that create a novel C−C bond have been developed. The asymmetric organocatalytic conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl substrates is one typical example.[2] It is therefore surprising that efficient protocols allowing the addition of alkynylic[3] and alkenylic[3,4] functionalities have only been recently developed by MacMillan[4] and Jørgensen.[3] Even though both of these protocols provide the desired alkenylic derivatives in excellent yields and enantioselectivities, they are conceptually different. MacMillan's approach is based on the use of vinyl-type borate complexes[5] that acts as nucleophiles during the organocatalytic asymmetric conjugate addition process. The Jørgensen approach, on the other hand, is based on a two-step tandem process (see Scheme 1). First, an organocatalyst-promoted conjugate addition of β-keto heterocyclic sulfone **2** nucleophile to α,β-unsaturated carbonyl compound generates adduct **3**, which is then transformed to olefin **4** (via reduction/Smile rearrangement[6] protocol) or alkyne **5** (via enolization/Smile rearrangement protocol[6]).

Later on, Jørgensen et al. used the same β-keto heterocyclic sulfones **2** to perform a formal transition-metal-free Sonogashira coupling and α-carbonyl arylation reaction[7] (Scheme 1).

Finally, if β-acyl-heterocyclic sulfones **9** are used as reagents in the Julia−Kocienski olefination reaction, α,β-unsaturated esters **10** can be prepared (Scheme 2).[8]

In our laboratory we recently started several synthetic ventures that use and/or are based on the compounds that contains β-keto and/or β-alkoxycarbonyl motifs, and to our great surprise, we found out that in the literature there is only one synthetic approach that yields sulfones **2** or **9**. In this method, sulfones **2** and **9** are prepared in two steps starting from α-bromo (halo) ketones or esters as the key intermediates toward **2** or **9** (Scheme 3). Unfortunately, in our case the synthesis of the desired α-halo carbonyl compounds proved to be long and tedious, and therefore we decided to evaluate a new synthetic approach to β-carbonyl heterocyclic sulfones that would better fit our purposes.

To achieve the most versatile approach to sulfones of general structure **11**, we decided to base the synthesis on the pairing of sulfone **13** with electrophile **14** (Scheme 4). Even though this type of disconnection seems to be obvious and is easily applicable to β-keto phenyl sulfone synthesis,[9] this approach is not easily applicable if β-keto BT- and PT-sulfones are wanted. The reason is that both BT- and PT-sulfones contain one electrophilic center within their heterocyclic core. As a consequence, if BT- or PT-sulfones **13** are treated with a non-nucleophilic base,[10] self-condensation occurs (Scheme 5).[11]

Thus if we want to prepare the desired β-carbonyl sulfones **11** starting from sulfone **13** and carbonyl electrophile **14**, conditions under which nucleophiles present in the reaction mixture are unreactive toward the nucleophilic center have to be found.

To find suitable coupling conditions, we decided to study a pairing between sulfone **13a** and benzoyl chloride **14a** (Table 1). Initially, the Li anion generated from **13a** was prepared with the use of the non-nucleophilic base ($LiN(TMS)_2$) at low temperature, and BzCl, an electrophile, was added after 30 min (Table 1, entry 1). In this case, the desired product **11a** was obtained only in very low yield. Since the control experiment showed that the low yield is not caused by instability or self-condensation of the intermediate[16,12] it remains that the low yield is caused by self-condensation of **13a**. To avoid this side reaction, the mixing time of **13a** with the base was progressively diminished (Table 1, entries 2 and 3). Gratifyingly, it was observed that the desired product **11a** was isolated in excellent yield (96%) if generated sulfone anion **13a** was quenched rapidly (BzCl was added immediately after the base).[13]

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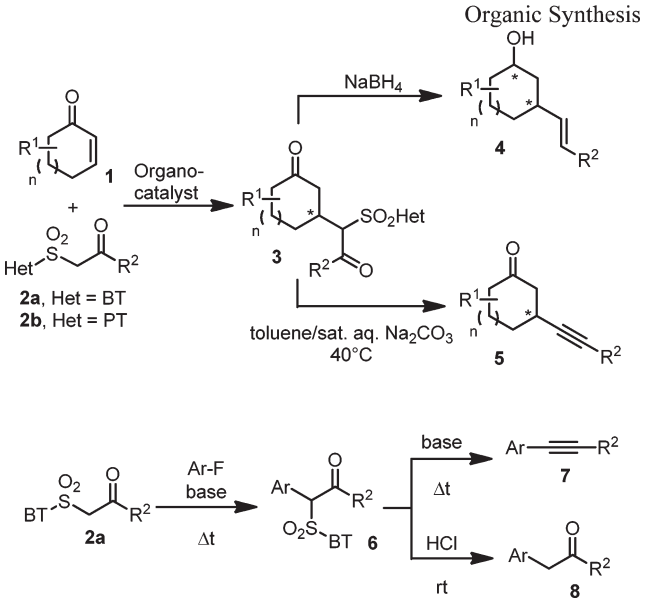
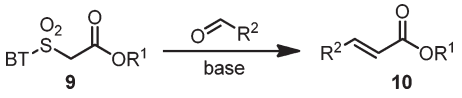
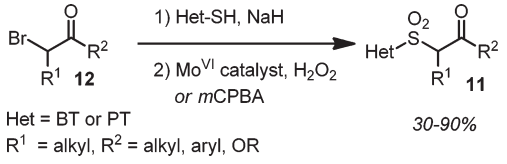
Scheme 1. Application of β-Keto-heterocyclic Sulfone 2 in Organic Synthesis



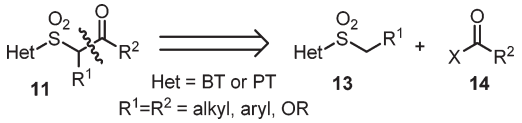
Scheme 2. β-Acyl-heterocyclic Sulfone 9 in the Context of a Julia−Kocienski Reaction



Scheme 3. Standard Approach to β-Carbonyl Heterocyclic Sulfones 11



Scheme 4. Retrosynthetic Approach to β-Carbonyl Heterocyclic Sulfones 11



At this stage we decided to test the coupling reaction with other types of benzoyl electrophiles to evaluate its scope and limitations. Unsurprisingly benzoylating agents with reactivity similar to that of benzoyl chloride, such as BzF, BzBr, Bz_2O, or benzoyl imidazole[14] (Table 1, entries 7, 9−11), yielded the desired β-keto sulfone **11a** in essentially the same yield. On the other hand, methyl benzoyl ester proved to be unreactive under our reaction

Scheme 5. Alkyl BT-Sulfone Base-Mediated Self-Condensation

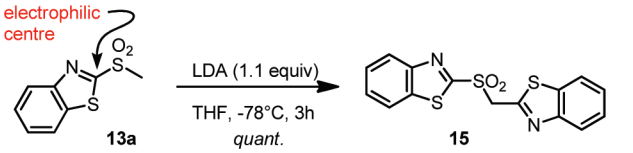
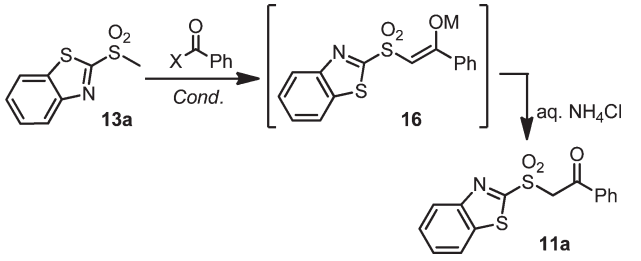


Table 1. Optimization of the Reaction Conditions



entry	X	Conditions	yield[a] (%)
1	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 30 min *then* BzCl (1.2 equiv)	7
2	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 15 min *then* BzCl (1.2 equiv)	15
3	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF, 1 min *then* BzCl (1.2 equiv)	65
4	Cl	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	96
5	Cl	$NaN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	67
6	Cl	$KN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzCl (1.2 equiv)	42
7	OCOPh	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* Bz_2O (1.2 equiv)	92
8	OMe	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzOMe (1.2 equiv)	traces
9	F	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzF (1.2 equiv)	93
10	Br	$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* BzBr (1.2 equiv)	97
11		$LiN(TMS)_2$ (2.2 equiv), -78°C, THF *then* Bz-Im (1.2 equiv)	92

[a] Overall yields refer to pure, isolated products.

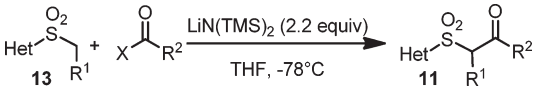
conditions (Table 1, entry 8). In this case, only the self-condensation product of **13a** (compound **15**) was observed.[15]

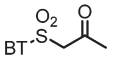
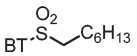
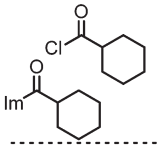
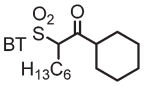
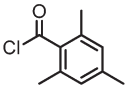
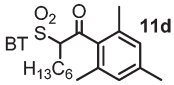
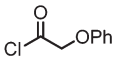
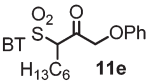
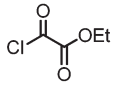
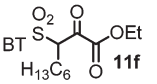
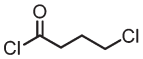
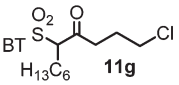
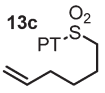
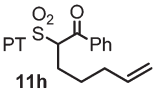
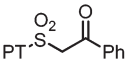
Having devised suitable reaction conditions to prepare this β-acyl sulfone, its scope and limitations were explored. A selection of pertinent results is shown in Table 2.

Both alkyl and aryl acyl derivatives react smoothly with lithiated sulfones **13** (Table 2). In all cases the reaction yields were more than 80% except when sulfone **13b** was reacted with monoethyl oxalyl chloride (Table 2, entry 8). In this case the desired product **11f** was obtained in 78% yield. Even acyl chlorides, bearing enolizable hydrogen atoms in the α position, reacted under the given reaction conditions to yield the desired α-acyl sulfones in very good yields.

dx.doi.org/10.1021/jo102326p |J. Org. Chem. 2011, 76, 2269–2272

Table 2. Preparation of Acyl Heterocyclic Sulfones 11 Starting from Sulfones 13 and Acyl-Containing Electrophiles



entry	sulfone	electrophile	product	yield[a] (%)
1	 **13a**	AcCl	 **11b**	90
2		Ac_2O		92
3		Im-Ac		89
4	 **13b**		 **11c**	83
5				92
6			 **11d**	89
7			 **11e**	86
8			 **11f**	78
9			 **11g**	81
10	 **13c**	PhCOCl	 **11h**	88
11		Bz_2O		89
12		PhCO-Im		93
13	 **13d**	PhCOCl	 **11i**	97
14		$(PhCO)_2O$		85
15		PhCO-Im		92

[a] Overall yields refer to pure, isolated products.

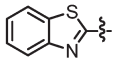
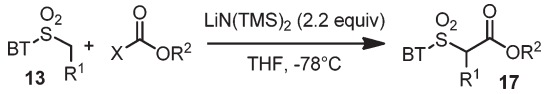
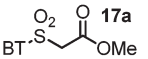
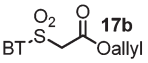
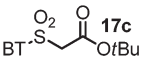
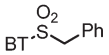
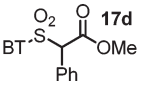
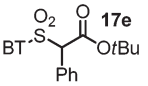
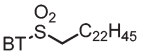
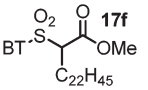
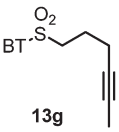
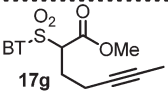
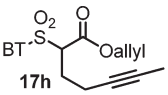
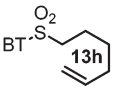
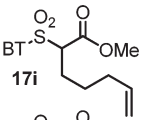
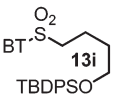
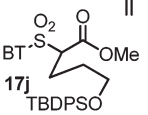
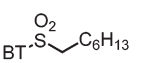
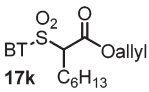
Het = BT 
Het = PT 
Im = 

Table 3. Preparation of Alkoxycarbonyl Heterocyclic Sulfones 11 Starting from Sulfones 13 and Alkoxy Carbonyl-Containing Electrophiles



entry	sulfone	electrophile	product	yield[a] (%)
1	 **13a**	Cl-COOMe	 **17a**	94
2		Im-COOMe		89
3		ClCOOallyl	 **17b**	95
4		Boc_2O	 **17c**	94
5		ImCOO*t*Bu		98
6	 **13e**	Cl-COOMe	 **17d**	88
7		Im-COOMe		94
8		Boc_2O	 **17e**	91
9		ImCOO*t*Bu		98
10	 **13f**	Cl-COOMe	 **17f**	88
11		Im-COOMe		94
12	 **13g**	Cl-COOMe	 **17g**	88
13		Im-COOMe		93
14		ClCOOallyl	 **17h**	89
15	 **13h**	Cl-COOMe	 **17i**	87
16		Im-COOMe		95
17	 **13i** TBDPSO	Cl-COOMe	 **17j** TBDPSO	89
18		Im-COOMe		93
19	 **13j**	ClCOOallyl	 **17k** C_6H_{13}	92

[a] Overall yields refer to pure, isolated products.

BT =
Im =

At this stage this protocol was extended to the synthesis of *β*-alkoxy carbonyl sulfones **17** (Table 3). For this purpose, three different types of alkoxy carbonylating reagents (bearing Cl, imidazole,[16] or OCOR as a leaving group) were tested. The nature of the leaving group was shown to have little effect on the reaction yields, and all three electrophiles might be used as coupling partners.

Additionally, the reaction conditions tolerate various functionalities, e.g., TBDPS ethers, phenyl ethers, and halogenated or unsaturated alkanes (Table 2, entries 7−10 and Table 3, entries 12−18).

In summary, we have uncovered a short and efficient approach to α-acyl and α-alkoxy carbonyl heterocyclic sulfones **11** and **17**, respectively, starting from heterocyclic sulfones and acyl or alkoxy carbonyl derivatives. We believe that this general approach to making this class of C-nucleophiles, which can be easily transformed into olefins or alkynes, will extend their use beyond the field of asymmetric organocatalysis. Further development and use of *β*-carbonyl heterocyclic sulfones of general structure **11** and **17** is now in progress in our laboratory.

EXPERIMENTAL SECTION

Representative Procedure for the Preparation of 2-(Benzo[*d*]thiazol-2-ylsulfonyl)-1-phenylethanone (11a). A solution of

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sulfone **13a** (100 mg, 0.47 mmol, 1.0 equiv) in THF (2.4 mL, 0.20M) was cooled to −78 °C, and $LiN(TMS)_2$ (1.0 M solution in THF) (1.03 mL, 1.03 mmol, 2.2 equiv) was added dropwise. The color of the reaction mixture turned from colorless or slightly yellow to orange within approximately 10−20 s. Immediately after, a solution of benzoyl chloride (60 μL, 0.52 mmol, 1.1 equiv) in THF (0.25 mL) was added. The color of the reaction mixture faded within 1 to 5 min after the benzoyl chloride addition. 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 a saturated aqueous solution of NH_4Cl (7.5 mL) was added. The whole mixture was extracted with EtOAc (3 × 40 mL); the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and filtered; and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc = 4:1 → 2:1 → 1:1), and the reaction yielded 143 mg (96%) of **11a** as slightly yellow solid: mp 123−124 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 2H), 7.43−7.53 (m, 2H), 7.55−7.69 (m, 3H), 7.94 (dd, J = 8.4 Hz, J = 1.2 Hz, 2H), 8.01 (dd, J = 7.0 Hz, J = 2.2 Hz, 1H), 8.20 (dd, J = 7.2 Hz, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.4, 122.6, 125.7, 127.9, 128.4, 129.17, 129.19, 134.9, 135.6, 137.3, 152.6, 165.5, 187.3; IR (neat) ν^{-1} 1683 (s); MS (APCI) (relative intensity) m/z 318 ($M^+ + 1$, 100), 319 (20), 236 (9), 105 (11). Anal. Calcd for $C_{15}H_{11}NO_3S_2$: C, 56.76; H, 3.49; N, 4.41. Found: C, 56.78; H, 3.11; N, 4.67.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic and analytical data for all new compounds, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Julia–Kocienski Reaction-Based 1,3-Diene Synthesis: Aldehyde-Dependent (*E*,*E*/*E*,*Z*)-Selectivity

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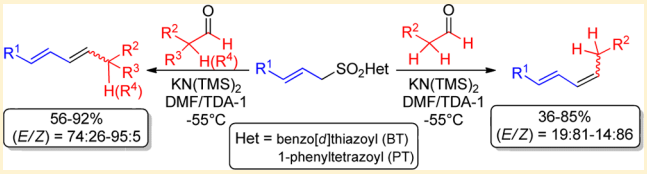
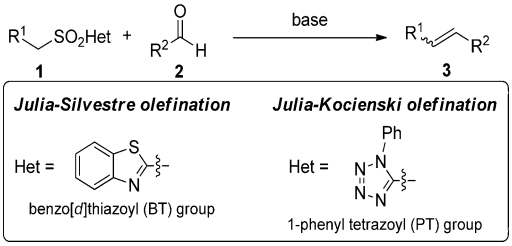
Supporting Information

ABSTRACT: A new modification of Julia–Kocienski olefination reaction based on the use of cation-specific chelating agents that yields 1,3-dienes with predictable (*E*/*Z*)-selectivity on newly created double bond was developed. The influence of the aldehyde structure on reaction (*E*/*Z*) selectivity is discussed and rationalized.



Over the past few decades, our synthetic tools were enriched by various novel and fundamentally different approaches to alkene synthesis. Unfortunately, none of the developed methods yet provided a universal solution in terms of yield, selectivity, and functional group tolerance. Since the mid-1990s, the second-generation Julia olefination reaction has become a privileged synthetic method when two complex molecular fragments should be connected (Scheme 1).[1] The

Scheme 1. Second-Generation Julia Olefination Reaction

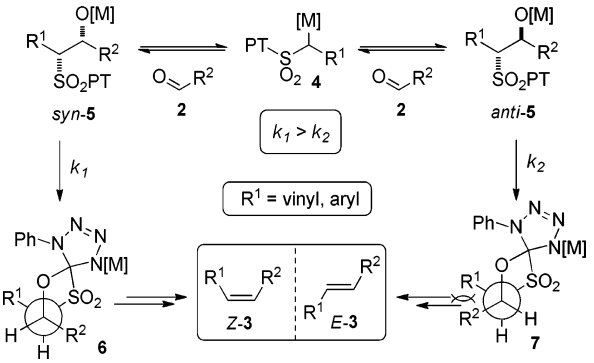


popularity of this synthetic method is based not only on its versatility, wide functional group tolerance and mild reaction conditions under which the reaction proceeds, but also on its generally high (*E*)-selectivity.

In our group, we are focused on the development of new more selective modifications of Julia–Kocienski olefination reaction.[2] After our recent success where we were able to increase the (*E*)-selectivity of this reaction,[2] we decided to focus our attention on the development of (*Z*)-selective modification of this reaction (Scheme 2). Taking into account the mechanism of the Julia–Kocienski reaction,[1] we reasoned that if the addition of sulfonyl anion **4** to aldehyde **2** was reversible,[3] reaction selectivity would be determined by the relative rate of Smiles rearrangement of *syn* and *anti* alkoxides **5**. It is known that for steric reasons the Smiles rearrangement of *syn*-**5** adduct that yields (*Z*)-olefins proceeds faster as compared to the rearrangement of *anti*-**5** adduct that yields (*E*)-olefins.[4]

In the literature, the addition of sulfonyl anion **4** to aldehyde **2** (R^1, R^2 = alkyl) is reported to be nonreversible.[1b,4] However,

Scheme 2. Proposed Equilibrium-Based Approach to (*Z*)-Olefins



we assumed that if allylic or benzylic anions **4** (R^1 = alkyl or benzyl) would be reacted with aldehyde **2**, the addition reaction might be reversible.[5] To investigate this hypothesis, the reactivity and reaction selectivity of α-sulfonyl anions generated from allylic and benzylic sulfones[6] were studied in the context of 1,3-diene synthesis.[7]

Our study started with the investigation of the key step of our hypothesis, the reversibility of the addition of allylic and benzylic sulfonyl anions to aldehydes. Thus, hydroxy sulfones **8a** and **8b** were prepared[8] and reacted with $LiN(TMS)_2$ or $KN(TMS)_2$ in the presence of *p*-nitrobenzaldehyde **12b** (Table 1).[9] The goal of these experiments was to find suitable reaction conditions under which alcoholate **9** would not undergo Smiles rearrangement (transformation of alcoholate **9** to olefin **13a**) but rather retroaddition reaction (transformation of alcoholate **9** to benzylic anion **11** and aldehyde **12a**) (Scheme 3). The formation of the benzylic anion **11** would then be proved by its trapping with reactive aldehyde **12b** and the consecutive olefin **13b** formation.

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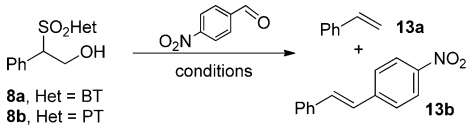
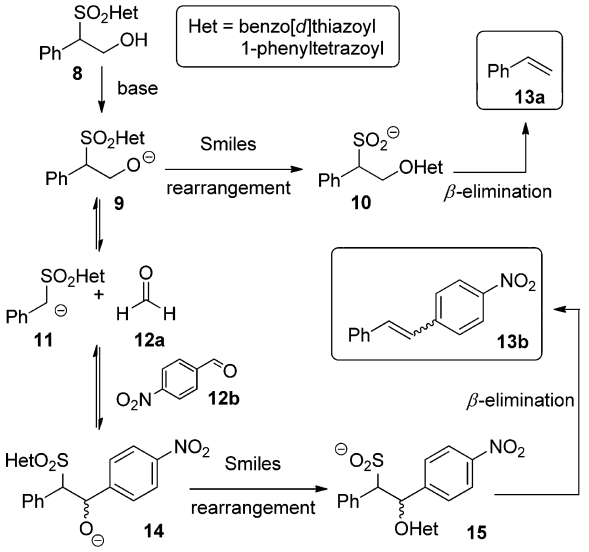
Table 1. Hydroxy Sulfone 8 Retroaddition Reaction Evaluation



entry	sulfone	conditions	13a:13b ratio[a]
1	8a	$LiN(TMS)_2$ (2.2 equiv),−60 °C, DMF/HMPA = 3:1	>98:<2
2	8a	$KN(TMS)_2$ (1.2 equiv), DMF, −55 °C	>98:<2
3	8a	$KN(TMS\}_2$ (1.2 equiv), 18-crown-6 (2.5 equiv), DMF, −55 °C	34:66
4	8a	$KN(TMS)_2$ (1.2 equiv), DMF/TDA-1 = 3:1,−60 °C	22:78 (72)[b]
5	8b	$KN(TMS)_2$ (1.2 equiv), −55 °C, 18-crown-6 (2.5 equiv), DMF	15:85 (65)[b]
6	8b	$KN(TMS)_2$ (1.2 equiv), DMF/TDA-1 = 3:1, −60 °C	<2:>98 (93)[b]

[a]Based on HPLC analysis. [b]Isolated yield of **13b** (in %).

Scheme 3. Competitive Experiment Designed To Determine if Hydroxy Sulfone 8 Can Undergo Retroaddition Reaction



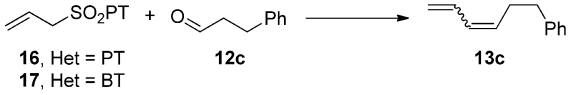
Our competitive experiments showed that the hydroxy sulfones **8** undergo retroaddition only when polar solvents and efficient cation-chelating agents (18-crown-6, TDA-1 for K^+) are used. Moreover, it was shown that BT-containing sulfone **8a** underwent retroaddition less readily as compared to sulfone **8b** (Table 1, entries 3 vs 5 and 4 vs 6). This observation could be explained by the difference in reactivity of the imine-like electrophilic centers present in BT- and PT-sulfones.[1,9,10]

Having established the conditions under which the addition of benzylic sulfones to aldehydes is reversible, we focused our attention on the (*E*/*Z*)-selectivity of the newly created olefin bond evaluation (Table 2).[9] Our goal was to find reaction conditions under which the transformation of *syn*-**5** adduct to spiro **6** (k_1, yields olefin (*Z*)-**3**) proceeds faster than the adduct *anti*-**5** to spiro **7** (k_2, yields olefin (*E*)-**3**) (Scheme 2).

First, the reaction of allyl PT-sulfone **16** and aldehyde **12c** was carried out using the standard Barbier-type[11] Julia olefination protocol (Table 1, entries 1 and 2). As expected, if THF was used as solvent, (*E*)-**13c** olefin was formed predominantly (entry 1). The use of "equilibrating" reaction conditions, DMF as a solvent and 18-crown-6 as cation scavenger, flipped the selectivity and yielded (*Z*)-**13c** olefin as the major product (entry 2). To increase further the (*Z*)-selectivity, we decided to premetalate sulfone **16** with $KN(TMS)_2$ and add aldehyde **12c** 30 min later (entry 3). Gratifyingly, olefin **13c** was formed in an increased 25:75 (*E*/*Z*) ratio. Addition of K^+-specific chelating agent, 18-crown-6, increased further the (*Z*)-selectivity of the olefin **3c** formation ((*E*/*Z*) = 16:84) but substantially diminished the reaction yield (entry 4).

It was found that prolonged premetalation reaction time carried out in the presence of cation scavenger led to rapid sulfone **16** degradation. Gratifyingly, the stirring of sulfone **16** with $KN(TMS)_2$ and 18-crown-6 for only 2 min prior to aldehyde **12c** addition yielded the targeted olefin **13c** with a 15:85 (*E*/*Z*) ratio and 74% yield (entry 6). If a shorter

Table 2. Reaction between Allyl Sulfones 16 and 17 and Dihydrocinnamaldehyde 12c



entry	conditions[a]	yield[b] (%)	*E*/*Z*[c]
1	$KN(TMS)_2$ added to a solution of **16** and **12c** in THF at −78 °C	nd	68:32
2	$KN(TMS)_2$ added to a solution of **16**, **12c** and 18-crown-6 in DMF at −55 °C	73	35:65
3	$KN(TMS)_2$ added to a solution of **16** in DMF at −55 °C, stirred for 30 min, aldehyde **12c** added at −55 °C	64	25:75
4	$KN(TMS)_2$ added to a solution of **16** and 18-crown-6 in DMF at −55 °C, stirred for 30 min, aldehyde **12c** added at −55 °C	17	16:84
5	$KN(TMS)_2$ added to a solution of **16** and 18-crown-6 in DMF at −55 °C, stirred for 1 min, aldehyde **12c** added at −55 °C	79	23:77
6	$KN(TMS)_2$ added to a solution of **16** in DMF/TDA-1 = 3:1 (v/v) at −60 °C, stirred for 2 min, aldehyde **12c** added at −60 °C	78	14:86
7	$KN(TMS)_2$ added to a solution of **17** in DMF/TDA-1 = 3:1 (v/v) at −60 °C, stirred for 2 min, aldehyde **12c** added at −60 °C	52	16:84

[a]The following quantities of given reagents were used: sulfone **16** or **17** (1.0 equiv), $KN(TMS)_2$ (1.1 equiv), aldehyde **12c** (1.1 equiv), and 18-crown-6 (2.3 equiv). [b]Average of two runs. Isolated yield. [c]Average of two runs. Based on GC analysis.

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Table 3. Synthesis of Dienes 13 via Julia–Kocienski and Julia–Silvestre Reactions

entry	sulfone	aldehyde	product[a]	conditions[b]: yield[c] (*E*/*Z*)[d]
1	SO_2PT			**A:** 72% (63:37)
2				**B:** 65% (58:42)
3	**16**	**12c**	**13c**	**C:** 74% (15:85)
4		Ph	Ph	**D:** 78% (14:86)
5				**A:** 68% (79:21)
6				**B:** 47% (62:38)
7		**12d**	**13d**	**C:** 36% (15:85)
8		OBn	OBn	**D:** 48% (14:86)
9				**A:** 82% (66:34)
10				**B:** 67% (55:45)
11		**12e**		**C:** 63% (69:31)
12		OBn	BnO **13e**	**D:** 72% (72:28)
13				**A:** 65% (71:29)
14	SO_2PT			**B:** 58% (40:60)
15		**12c**		**C:** 50% (16:84)
16	C_3H_7 **18**	Ph	Ph **13f**	**D:** 40% (13:87)
17				**A:** 69% (55:45)
18				**B:** 59% (66:34)
19		**12e**		**C:** 55% (75:25)
20		OBn	BnO **13g**	**D:** 56% (74:26)
21				**A:** 82% (62:38)
22				**B:** 69% (54:46)
23				**C:** 50% (83:17)
24		TBDPSO **12g**	TBDPSO OBn **13h**	**D:** 62% (82:18)
25				**A:** 73% (65:35)
26				**B:** 63% (51:49)
27		**12h**	**13i**	**C:** 59% (77:23)
28				**D:** 68% (82:18)
29				**A:** 59% (61:39)
30				**B:** 65% (70:30)
31		TBSO **12i**	**13j**	**C:** 58% (94:6)
32			OTBS	**D:** 63% (96:4)
33				**A:** 64% (55:45)
34				**B:** 55% (51:49)
35		**12j**	**13k**	**C:** 51% (76:24)
36		Cl	Cl	**D:** 58% (74:26)
37				**A:** 70% (56:44)
38				**B:** 60% (48:52)
39		**12b**	**13l**	**C:** 65% (86:14)
40		O_2N	O_2N	**D:** 63% (89:11)
41				**A:** 68% (56:44)
42	SO_2PT			**B:** 69% (52:48)
43		**12c**		**C:** 59% (16:84)
44	Ph **19**	Ph	Ph **13m**	**D:** 60% (14:86)
45				**A:** 57% (65:35)
46				**B:** 53% (60:40)
47		**12n**	**13n**	**C:** 36% (15:85)
48		O		**D:** 48% (14:86)
49				**A:** 81% (42:58)
50				**B:** 63% (55:45)
51		**12e**		**C:** 55% (60:40)
52		OBn	BnO **13o**	**D:** 69% (56:44)
53				**A:** 81% (55:45)
54	SO_2PT			**B:** 75% (63:47)
55		BnO TBDPSO **12g**	TBDPSO OBn **13p**	**C:** 72% (88:12)
56	Ph **19**			**D:** 80% (82:18)
57				**A:** 66% (58:42)
58				**B:** 52% (69:21)
59		**12j**	**13q**	**C:** 45% (92:8)
60				**D:** 49% (95:5)
61				**A:** 68% (59:41)
62	SO_2BT			**B:** 53% (57:43)
63		**12c**	**13c**	**C:** 39% (30:70)
64	**17**	Ph	Ph	**D:** 42% (20:80)
65				**A:** 69% (65:35)
66				**B:** 65% (52:48)
67		**12d**	**13d**	**C:** 73% (20:80)
68		OBn	OBn	**D:** 74% (19:81)
69				**A:** 72% (56:44)
70				**B:** 66% (52:48)
71		**12e**		**C:** 70% (68:32)
72		OBn	BnO **13e**	**D:** 71% (70:30)
73				**A:** 75% (58:42)
74	SO_2BT			**B:** 72% (55:45)
75		**12c**		**C:** 69% (20:80)
76	C_3H_7 **20**	Ph	Ph **13f**	**D:** 73% (17:83)
77				**A:** 68% (55:45)
78				**B:** 69% (60:40)
79		TBSO **12i**	**13j**	**C:** 65% (90:10)
80			OTBS	**D:** 70% (91:9)
81				**A:** 56% (49:51)
82				**B:** 49% (45:55)
83		**12j**	**13k**	**C:** 53% (72:28)
84		Cl	Cl	**D:** 55% (78:22)
85	SO_2BT			**A:** 86% (57:43)
86				**B:** 79% (55:45)
87		**12c**		**C:** 82% (18:82)
88	**21** Ph	Ph	Ph **13m**	**D:** 85% (15:85)
89				**A:** 95% (48:52)
90	SO_2BT			**B:** 92% (42:58)
91		**12c**		**C:** 74% (15:85)
92	Ph **22**	Ph	Ph **13r**	**D:** 73% (14:86)
93				**A:** 85% (42:58)
94				**B:** 70% (32:68)
95		**12e**		**C:** 91% (81:19)
96		OBn	BnO **13s**	**D:** 92% (83:17)

[a] Overall yields refer to pure, isolated products. [b] **Method A**: Sulfone (1.0 equiv), aldehyde (1.1 equiv), THF (-78°C) then $KN(TMS)_2$ (1.1 equiv). **Method B**: Sulfone (1.0 equiv), aldehyde (1.1 equiv), DMF (-55°C) then $KN(TMS)_2$ (1.1 equiv). **Method C**: Sulfone (1.0 equiv), 18-crown-6 (2.5 equiv), $KN(TMS)_2$ (1.1 equiv), DMF (-55°C), 2 min at -55°C then aldehyde (1.1 equiv). **Method D**: Sulfone (1.0 equiv), $KN(TMS)_2$ (1.1 equiv), DMF/TDA-1 = 3:1 (V/V) (-60°C), 2 min at -60°C then aldehyde (1.1 equiv). [c] (*E*/*Z*)-Ratio refers to newly created olefin bond. Based on crude ^{1}H-NMR analysis. [d] Color code indicates a substantial increase in (*E*) or (*Z*) selectivity in olefin **13** formation observed under our newly developed cation-free conditions.

premetalation period (1 min) was employed, erosion of the (*Z*)-selectivity was observed (entry 5). To further increase the (*Z*)-**13c** formation, TDA-1[12] was used as cosolvent (entries 6 and 7). The use of DMF/TDA-1 = 3:1 (V/V) solvent mixture afforded olefin **13c** in the same (*E*/*Z*) ratio but slightly better yield (entry 6).

The selectivity of BT-containing sulfone **17** under the developed reaction conditions was also evaluated. Because of the results of our preliminary addition/retroaddition study (Table 1), we expected that the reaction of BT-sulfone **17** with aldehyde **12c** might proceed with lower (*Z*)-selectivity. However, under all tested reaction conditions, olefins **13c** were obtained with similar (*E*/Z)-selectivity, although in lower yield (see Table 2, entry 6 vs entry 7).[9]

Having established the optimal reaction conditions, the scope and limitations of this method (Table 3) were examined and the results were compared with reactions performed without the presence of chelating agents.[13]

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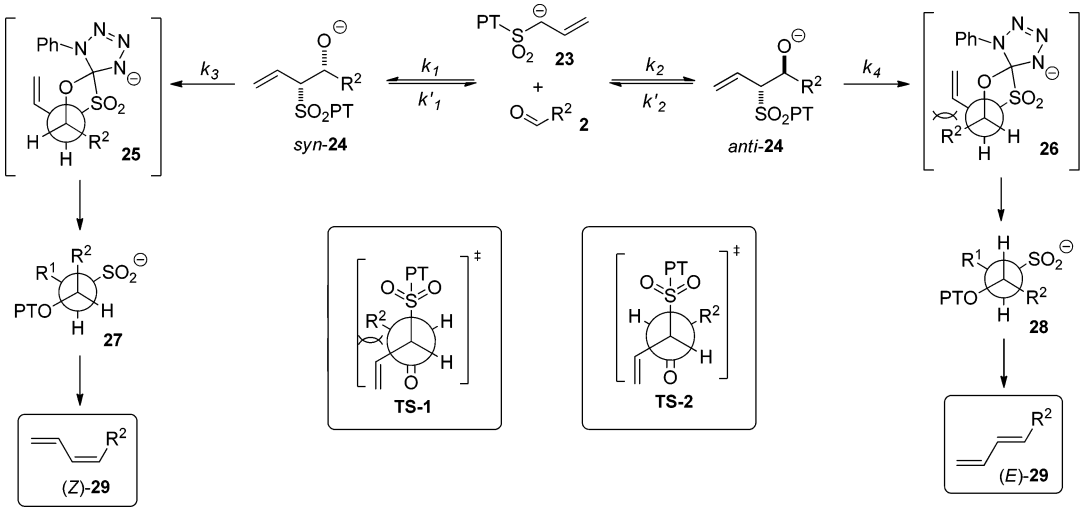
Scheme 4. Proposed Mechanism of "Cation-Free" Julia–Kocienski Reaction of Allyl PT-sulfones



In general, reactions of PT-sulfones **16**, **18**, and **19** (Table 3, entries 1–60) were more stereoselective than those performed with BT-sulfones **17** and **20–22** (Table 3, entries 61–96). In both cases, the (*E*/*Z*)-selectivity of newly formed olefins **13** proved to be aldehyde dependent. When primary α-nonbranched aldehydes **12c,d** were used, the newly created olefins formed under "cation-free" conditions (methods C and D) were obtained with higher (*Z*)-selectivity as compared to standard conditions (methods A and B). The only exception was found when nonbranched α-alkoxy aldehyde **12e** was used (entries 9–12, 17–20, 49–52, 69–72, and 93–96). In these cases, the reactions yielded the corresponding olefins **13h–l,n,p,q** with moderate to good (*E*)-selectivity. The same trend was observed when α di- and trisubstituted or aromatic aldehydes **12g–j** and **n** were used (entries 21–40, 45–48, 53–60, and 77–80). In these cases, the (*E*)-olefins **13h–l,n,p,q** were formed as main products of the reaction. Interestingly, in these cases the obtained (*E*/*Z*) ratio was also superior to that obtained under the standard reaction conditions.

We believe that the stereochemical outcome of the 1,3-dienes **13** prepared by Julia–Kocienski and Julia–Silvestre reactions and presented in Table 3 can be easily rationalized (Scheme 4). If the olefination reactions were carried out under standard reaction conditions (methods A or B, addition step is not reversible ($k'_1,k'_2 \ll k_3,k_4$)), the (*E*/*Z*) ratio of **13** corresponds to the *syn*/*anti*-**24** adduct ratio.[1,2a] Thus, the Smiles rearrangement becomes the rate-determining step, but the addition step is the selectivity-determining step.

However, if chelating agents are employed (methods C and D), the addition step is reversible ($k'_1,k'_2 \ll k_3,k_4$) and the Smiles rearrangement becomes the rate and selectivity determination step. However, the final stereochemical outcome of the reaction ((*E*/*Z*) ratio) strongly depends on the aldehyde structure. If α-nonbranched aldehydes are employed, we expect that, for steric reasons, the Smiles rearrangement of adduct *syn*-**24** to intermediate **27** proceeds faster than the rearrangement of adduct *anti*-**24** to intermediate **28** ($k_3 > k_4$). (*Z*)-Olefins are thus preferentially formed.

However, the reaction becomes (*E*)-selective if the steric repulsion between R^2 and the vinyl group in TS-1 becomes important (α-branched and aromatic aldehydes). In this case, the relative rate of *syn* and *anti* addition starts to play a role in determining selectivity; *anti* addition is predicted to be preferred ($k_2 > k_1$).

In summary, we have developed a new modification of the Julia reaction that allows us to prepare 1,3-dienes, starting from PT- and BT-allyl sulfones, with high (*Z*) or (*E*) selectivity. It was shown that the olefin stereoselectivity is substrate (aldehyde) dependent. A rational explanation for observed (*E*,*Z*) selectivity is also proposed.

EXPERIMENTAL SECTION

General Procedures for Olefination Reactions. *Method A.* A solution of aldehyde **12c** (131 μL, 1.1 mmol) and allyl sulfone **16** (250 mg, 1.0 mmol) in THF (10 mL, 0.1 M) was cooled to −78 °C, and $KN(TMS)_2$ (0.6 M solution in toluene) (1.83 mL, 1.1 mmol) was added over 2 min. The resulting mixture was stirred at −78 °C for 1 h before it was allowed to warm to rt. After being stirred at rt for 6 h, a saturated aqueous solution of NH_4Cl (10 mL) was added. The whole mixture was extracted with EtOAc (3 × 10 mL); the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered; the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc = 50:1), and the reaction yielded 114 mg (72%, *E*/*Z* = 63:37) of **13c** as a yellowish oil.

Method B. A solution of aldehyde **12c** (131 μL, 1.1 mmol) and allyl sulfone **16** (250 mg, 1.0 mmol) in DMF (10 mL, 0.1 M) was cooled to −55 °C, and $KN(TMS)_2$ (0.6 M solution in toluene) (1.83 mL, 1.1 mmol) was added over 2 min. The resulting mixture was stirred at −55 °C for 1 h before it was allowed to warm to rt. After 6 h at rt, the reaction was terminated and purified using the same protocol as mentioned in method A. The reaction yielded 103 mg (65%, *E*:*Z* = 58:42) of **13c** as a yellowish oil.

Method C. A solution of allyl sulfone **16** (250 mg, 1.0 mmol) and 18-crown-6 (661 mg, 2.5 mmol) in DMF (10 mL, 0.1 M) was cooled to −55 °C, and $KN(TMS)_2$ (0.6 M solution in toluene) (1.83 mL, 1.1 mmol) was added dropwise within 10 s. The resulting mixture was stirred at −55 °C for 2 min, and aldehyde **12c** (131 μL, 1.1 mmol) in DMF (0.2 mL) was added dropwise. The resulting mixture was stirred at −55 °C for 1 h before it was allowed to warm to rt. After 6 h at rt, the reaction was terminated and purified using the same protocol as mentioned in method A. The reaction yielded 117 mg (74%, *E*/*Z* = 15:85) of **13c** as a yellowish oil.

Method D. A solution of allyl sulfone **16** (250 mg, 1.0 mmol) in DMF/TDA-1 = 3:1 (v/v) (10 mL, 0.1 M) was cooled to −60 °C, and $KN(TMS)_2$ (0.6 M solution in toluene) (1.83 mL, 1.1 mmol) was added dropwise within 10 s. The resulting mixture was stirred at −60 °C for 2 min, and aldehyde **12c** (131 μL, 1.1 mmol) in DMF (0.2 mL)

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was added dropwise. The resulting mixture was stirred at −60 °C for 1 h before it was allowed to warm to rt. After 6 h at rt, the reaction was terminated and purified using the same protocol as mentioned in method A. The reaction yielded 123 mg (78%, *E*/*Z* = 14:86) of **13c**[14] as a yellowish oil: ^{1}H NMR[15] (300 MHz, $CDCl_3$) δ 2.45 (dd, *J* = 15.1, 7.2 Hz, 2H*), 2.55 (dd, *J* = 15.3, 7.6 Hz, 2H), 2.67−2.80 (m, 2H), 5.01 (d, *J* = 9.7 Hz, 1H*), 5.12 (d, *J* = 10.0 Hz, 1H), 5.22 (dd, *J* = 16.9, 1.7 Hz, 1H), 5.53 (dt, *J* = 10.5, 7.7 Hz, 1H), 5.79 (dt, *J* = 15.1, 7.1 Hz, 1H*), 6.06 (t, *J* = 10.9 Hz, 1H), 6.15 (dd, *J* = 15.1, 10.4 Hz, 1H*), 6.35 (dt, *J* = 16.9, 10.2 Hz, 1H*), 6.65 (dtd, *J* = 16.9, 10.6, 1.0 Hz, 1H), 7.15−7.26 (m, 3H), 7.28−7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 34.6*, 35.8*, 36.0, 115.4*, 117.5, 126.1, 128.5, 128.6, 129.9, 131.6 (*E*), 131.8, 132.3, 134.5, 137.4, 141.9, 142.0*; IR (film) ν^{-1} 3031, 2956, 2887, 1524, 1487, 1334, 1001, 906, 800, 746, 702; MS (EI) *m*/*z* 158 (14) [M$^+$], 143 (6), 117 (32), 91 (100), 65 (12); HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}$ 158.1090, found 158.1094.

Olefin 13d:.[15,16] yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (q, *J* = 6.7 Hz, 2H*), 2.54 (dd, *J* = 14.2, 7.2 Hz, 2H), 3.54 (td, *J* = 6.8, 4.6 Hz, 2H), 4.53 (s, 2H*), 4.55 (s, 2H), 5.01 (d, *J* = 9.8 Hz, 1H*), 5.12 (d, *J* = 9.8 Hz, 1H), 5.15 (s, 1H*), 5.23 (d, *J* = 15.6 Hz, 1H), 5.51 (dt, *J* = 10.4, 7.7 Hz, 1H), 5.74 (dt, *J* = 15.3, 7.0 Hz), 6.06−6.19 (m, 1H), 6.33 (dt, *J* = 16.9, 10.3 Hz, 1H), 6.66 (dt, *J* = 17.2, 10.9 Hz, 1H), 7.47−7.16 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.7*, 33.2, 69.85, 69.88*, 73.1, 115.7, 117.8, 127.8, 127.86, 127.89*, 128.6, 131.1, 131.4*, 132.3, 132.9*, 137.3, 138.6*; IR (film) ν^{-1} 3031, 3024, 2986, 1604, 1582, 1463, 1132, 1041, 952, 863, 704; MS (CI) *m*/*z* 188 (100) [M]$^+$, 189 (35) [M + H]$^+$; HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O$ 188.1201, found 188.1203.

Olefin 13e:.[15,16] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (d, *J* = 6.3 Hz, 2H), 4.22 (dd, *J* = 6.7, 1.3 Hz, 2H*), 4.54 (s, 2H and 2H*), 5.08−5.44 (m, 2H and 2H*), 5.66 (dt, *J* = 11.8, 6.8 Hz, 1H*), 5.84 (dt, *J* = 14.4, 6.0 Hz, 1H), 6.19 (t, *J* = 11.1 Hz, 1H*), 6.26−6.45 (m, 2H), 6.60 (dt, *J* = 16.8, 10.6 Hz, 1H*), 7.27−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.0, 70.4, 72.3, 117.8, 119.4, 121.4, 122.5, 124.8, 125.1, 126.6, 128.0, 128.6, 130.3, 131.9, 132.3, 133.5, 136.5, 138.4; IR (film) ν^{-1} 3086, 3028, 2930, 2851, 1456, 1427, 1238, 1095, 1074, 1003, 910, 756, 727; MS (CI) *m*/*z* 174 (84) [M$^+$], 175 (20) [M$^+$+1], 149 (100), 145 (54), 133 (49), 118 (56), 117 (81), 115 (62), 105 (94); HRMS (EI) *m*/*z* calcd for $C_{12}H_{14}O$ 174.1039, found 174.1038.

Olefin 13f:[15] yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H*), 1.39−1.47 (m, 2H), 2.02−2.19 (m, 2H), 2.37−2.57 (m, 2H), 2.72 (dd, *J* = 8.9, 6.7 Hz, 2H,), 5.37 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.50 (td, *J* = 15.8, 7.6 Hz, 1H), 5.59−5.78 (m, 2H), 5.98−6.14 (m, 2H), 6.30 (dd, *J* = 15.2, 10.9, 1H), 6.39 (dd, *J* = 15.1, 11.1 Hz, 1H), 7.19−7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.95, 13.99*, 22.72, 22.76*, 29.8, 34.7*, 34.9*, 35.2, 36.11*, 36.16; 123.8, 124.4, 125.8, 126.0, 126.5, 128.5, 129.4, 130.5, 131.1, 132.6, 133.5, 135.2, 142.2; IR (film) ν^{-1} 3086, 3028, 2930, 2851, 1456, 1427, 1238, 1095, 1074, 1003, 910, 756, 727; MS (EI) *m*/*z* 200 (13) [M$^+$], 201 (2) [M$^+$+1], 143 (12), 129 (13), 117 (15), 109 (68), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}$ 200.1560, found 200.1560.

Olefin 13g:[15] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 6.1 Hz, 3H), 0.96 (t, *J* = 5.2 Hz, 3H*), 1.39−1.51 (m, 2H), 2.10 (q, *J* = 7.1 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H*), 4.08 (d, *J* = 6.3 Hz, 2H), 4.12 (d, *J* = 6.2 Hz, 1H*), 4.21 (d, *J* = 6.8 Hz, 1H*), 4.54 (s, 2H), 4.56 (s, 2H*), 5.50 (dt, *J* = 15.1, 7.6 Hz, 1H), 5.64−5.78 (m, 2H and 1H*), 6.09 (dd, *J* = 14.7, 10.5 Hz, 1H), 6.27 (dd, *J* = 15.2, 10.3 Hz, 1H), 6.59 (ddd, *J* = 15.2, 11.0, 1.1 Hz, 1H*), 7.27−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.88, 22.6, 23.0*, 30.0*, 34.9, 35.0*, 66.0*, 70.8, 72.1, 72.3*, 125.0, 125.5, 127.5, 127.7, 127.8, 128.3, 130.2, 130.4, 132.3, 133.1, 135.4, 138.4; IR (film) ν^{-1} 3063, 3026, 2957, 2927, 2858, 1659, 1497, 1454, 1362, 1099, 1070, 989, 734, 696; MS (CI) *m*/*z* 216 (64) [M]$^+$, 217 (12) [M + H]$^+$, 159 (100), 134 (78), 125 (52), 91 (82); HRMS (CI) *m*/*z* calcd for $C_{15}H_{20}O$ 216.1514, found 216.1521.

Olefin 13h:[15] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H, H-1), 1.06 (s, *J* = 9.8 Hz, 9H), 1.44 (dq, *J* = 14.6, 7.3 Hz, 2H), 2.02−2.17 (m, 2H), 2.13−2.24 (m, 2H*), 3.65 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.81 (dd, *J* = 10.5, 6.6 Hz, 1H), 4.01 (dt, *J* = 12.1, 6.9 Hz, 2H*), 4.45 (d, *J* = 10.0 Hz, 1H*), 4.46 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 9.9 Hz, 1H*), 4.65 (d, *J* = 12.1 Hz, 1H), 5.18 (dd, *J* = 10.0, 9.6 Hz, 1H*), 5.46 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.54 (dd, *J* = 15.4, 7.4 Hz, 1H*), 5.71 (dt, *J* = 15.0, 7.2 Hz, 1H), 6.05 (dd, *J* = 14.9, 10.5 Hz, 1H), 6.21 (dd, *J* = 15.3, 10.4 Hz, 1H), 6.52 (dd, *J* = 11.1, 9.3 Hz, 1H*), 7.28−7.48 (m, 11H), 7.61−7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 15.0*, 19.3, 22.4, 22.8*, 24.4*, 26.8, 34.7, 34.9, 66.7*, 67.0, 70.4, 70.5*, 80.6*, 80.7, 127.3, 127.58, 127.64, 127.9*, 128.3, 128.4*, 129.6, 129.7*, 133,4*, 133.9, 135.5*, 135.7, 137.2, 138.8*, 138.9; IR (film) ν^{-1} 3069, 3031, 2986, 2928, 2852, 1470, 1431, 1103, 1089, 989, 702; MS (FAB) *m*/*z* 507 (65) [M + Na]$^+$, 271 (56), 249 (42), 198 (100); HRMS (FAB) *m*/*z* calcd for $C_{32}H_{40}O_2SiNa$ 507.2695, found 507.2698.

Olefin 13i:.[15,17] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 5.9 Hz, 3H), 0.99−1.50 (m, 10H), 1.50−1.88 (m, 3H), 1.90−2.11 (m, 2H), 2.15 (dd, *J* = 13.9, 6.4 Hz, 2H*), 5.16 (t, *J* = 10.1 Hz, 1H*), 5.32 (dt, *J* = 15.5, 6.2 Hz, 1H*), 5.49−5.73 (m, 2H), 5.91−6.09 (m, 2H), 6.23−6.37 (m, 2H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.8, 23.1*, 26.1*, 26.3, 26.4, 30.0*, 33.2, 33.5*, 35.0, 35.2*, 37.0*, 40.9, 41.2*, 127.0*, 128.0, 131.0, 132.6, 134.7*, 136.3*, 138.5, 140.7*; IR (film) ν^{-1} 3016, 2957, 2921, 2851, 1448, 1377, 986; MS (EI) *m*/*z* 178 (56) [M]$^+$, 170 (11), 135 (28), 121 (28), 112 (33), 96 (54), 93 (42), 86 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{22}$ 178.1716, found 178.1715.

Olefin 13j:.[15,18] colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.062 (s, 3H), 0.067 (s, 3H), 0.88−0.95 (s, 12H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.31−1.58 (m, 2H), 2.06 (dd, *J* = 14.4, 7.1 Hz, 2H), 4.33 (p, *J* = 6.2 Hz, 1H), 5.57 (dd, *J* = 14.6, 5.7 Hz, 1H), 5.66 (dd, *J* = 14.5, 7.0 Hz, 1H), 5.94−6.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.61, −4.42, 14.0, 18.51, 22.7, 25.9*, 26.1, 35.0, 65.5*, 69.3, 128.7, 130.1, 134.4, 135.6; IR (film) ν^{-1} 2957, 2927, 2891, 2858, 1550, 1504, 1462, 1252, 1089, 987, 832; MS (CI) *m*/*z* 254 (100) [M]$^+$, 255 (35) [M + H]$^+$, 139 (43), 115 (65); HRMS (CI) *m*/*z* calcd for $C_{15}H_{30}OSi$ 254.2066, found 254.2068.

Olefin 13k:[15] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.3 Hz, 3H*), 0.96 (t, *J* = 7.4 Hz, 3H), 1.32−1.61 (m, 2H), 2.14 (p, *J* = 6.9 Hz, 2H), 2.28 (dt, *J* = 14.9, 7.4 Hz, 2H*), 5.47−5.73 (m. 1H*), 5.76−60.2 (m, 2H), 6.40 (d, *J* = 15.7 Hz, 1H), 6.51 (d, *J* = 10.1 Hz, 1H*), 6.75 (dd, *J* = 15.6, 10.4 Hz, 1H), 7.06 (dt, *J* = 11.1, 9.2 Hz, 1H*), 7.22−7.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.94, 14.01*, 22.6, 23.1*, 30.3*, 35.2, 124.6*, 125.3*, 126.4, 127.5, 127.7*, 128.6, 128.8*, 128.9, 130.6, 130.8*, 131.4, 132.7*, 136.4*, 136.5*, 136.7, 138.9; IR (film) ν^{-1} 3012, 2959, 2928, 2872, 1641, 1489, 1456, 1091, 1012, 986, 845, 820, 798, 735; MS (EI) *m*/*z* 206 (68) [M]$^+$, 207 (18) [M + 1]$^+$, 208 (33) [M + 2]$^+$, 209 (6) [M + 3]$^+$, 205 (11), 179 (37), 177 (100), 167 (37), 165 (87), 163 (46), 141 (49); HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}Cl$ 206.0857, found 206.0857.

Olefin 13l:[15] yellowish solid; mp = 32−33 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.8 Hz, 3H), 1.42−1.53 (m, 2H), 2.16 (dt, *J* = 14.2, 6.8 Hz, 2H), 2.31 (dt, *J* = 13.1, 6.6 Hz, 2H*), 5.68 (dt, *J* = 15.6, 8.6 Hz, 1H*), 5.76−6.02 (m, 2H), 6.19 (dt, *J* = 15.4, 9.4 Hz, 1H*), 6.47 (d, *J* = 15.5 Hz, 1H), 6.53 (d, *J* = 10.6 Hz, 1H*), 6.88 (dd, *J* = 15.7, 10.4 Hz, 1H), 7.19 (dt, *J* = 11.2, 9.3 Hz, 1H*), 7.46 (t, *J* = 8.1 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 2H*), 8.03 (d, *J* = 8.7 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 2H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.5, 35.2, 124.9, 125.6, 127.4, 129.3, 129.6, 130.1, 132.0, 132.7, 133.3, 135.0, 138.7, 139.8, 140.7, 141.6, 148.9; IR (film) ν^{-1} 3062, 2983, 2945, 2875, 1523, 1346, 995, 825, 864, 723; MS (EI) *m*/*z* 217 (75) [M]$^+$, 218 (11) [M + 1]$^+$, 188 (67), 158 (34), 142 (81), 141 (100), 128 (58), 115 (46); HRMS (EI) *m*/*z* calcd for $C_{13}H_{15}O_2N$ 217.1097, found 217.1093.

Olefin 13m:[15] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (dd, *J* = 14.9, 7.1 Hz, 2H*), 2.64 (dd, *J* = 14.6, 7.3 Hz, 2H), 2.75−2.86 (m, 2H), 5.59 (dt, *J* = 10.7, 7.6 Hz, 1H), 5.88 (dt, *J* = 15.2, 7.1 Hz, 1H*), 6.20 (t, *J* = 10.9 Hz, 1H), 6.27 (dd, *J* = 15.0, 10.0 Hz, 1H*), 6.47 (d, *J* = 15.8 Hz, 1H*), 6.54 (d, *J* = 15.5 Hz, 1H), 6.77 (dd, *J* = 15.6, 10.4 Hz, 1H*), 7.03 (ddd, *J* = 15.4, 11.3 Hz, 1H), 7.19−7.42 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 34.9*, 36.0*, 36.1, 124.5, 126.2, 126.4*, 126.6, 127.4*, 127.6, 128.6, 128.7, 128.8, 129.5, 130.7*, 131.3*, 132.0, 132.6, 134.8*, 137.8, 141.9; IR (film) ν^{-1} 3071, 3024, 2924, 2870, 1495, 1452, 1074, 986, 945, 748, 729; MS (EI) *m*/*z* 234 (18) [M], 235 (3) [M + H]$^+$, 143 (100), 128 (47), 91 (54), 84 (41); HRMS (EI) *m*/*z* calcd for $C_{18}H_{18}$ 234.1403, found 234.1400.

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Olefin **13n**:[15] slightly yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J = 6.6 Hz, 3H), 1.11−1.34 (m, 1H), 1.34−1.52 (m, 1H), 1.52−1.62 (m, 1H), 1.64 (s, 3H), 1.72 (s, 3H), 2.04 (dq, J = 14.3, 7.3 Hz, 2H), 2.11−2.26 (m, 1H), 2.32 (dt, J = 13.5, 6.7 Hz, 1H), 5.14 (t, J = 7.0 Hz, 1H), 5.57 (dt, J = 10.5, 8.0 Hz, 1H), 5.84 (dt, J = 15.0, 7.4 Hz, 1H*), 6.24 (t, J = 10.9, 1H), 6.47 (d, J = 15.7 Hz, 1H*), 6.55 (d, J = 15.6 Hz, 1H), 6.80 (dd, J = 15.6, 10.3 Hz, 1H*), 7.09 (dd, J = 15.5, 11.1 Hz, 1H), 7.18−7.48 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9, 19.8, 25.9, 26.0, 29.9, 33.1*, 33.4, 35.4, 37.0, 40.6*, 124.8, 125.0, 126.3*, 126.5, 127.3*, 127.5, 128.8, 129.7, 130.1*, 131.4, 131.9*, 132.2, 132.2, 134.7*, 137.9; IR (film) ν^{-1} 3078, 3058, 2926, 2908, 2870, 1595, 1493, 1448, 1377, 984, 945, 908; MS (CI) m/z 254 (100) $[M]^+$, 255 (31) $[M + 1]^+$, 211 (23), 163 (11), 143 (16); HRMS (CI) m/z calcd for $C_{19}H_{26}$ 254.2035, found 254.2027.

Olefin **13o**:[15] yellow viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, J = 6.1 Hz, 2H), 4.36 (d, J = 6.8 Hz, 2H*), 4.63 (d, J = 6.0 Hz, 2H), 5.77 (dt, J = 11.1, 6.8 Hz, 1H*), 6.00 (dt, J = 15.1, 6.1 Hz, 1H), 6.41 (t, J = 11.0 Hz, 1H*), 6.51 (dd, J = 15.2, 10.5 Hz, 1H), 6.62 (d, J = 15.7 Hz, 1H), 6.65 (d, J = 15.5 Hz, 1H*), 6.87 (dd, J = 15.6, 10.5 Hz, 1H), 7.07 (dd, J = 15.5, 11.2 Hz, 1H*), 7.24−7.54 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.9*, 70.5, 72.1*, 72.2, 123.8, 126.5, 126.6*, 127.66, 127.70, 127.74, 127.8, 128.0, 128.3*, 128.48, 128.50, 128.7, 130.2, 132.0, 132.8, 133.0, 134.3, 137.1*, 137.2, 138.3*, 138.4; IR (film) ν^{-1} 3080, 3059, 3026, 2920, 2850, 1597, 1494, 1450, 1360, 1097, 1070, 989, 732, 692; MS (EI) m/z 250 (8) $[M]^+$, 159 (22), 131 (53), 117 (56), 115 (75); HRMS (CI) m/z calcd for $C_{18}H_{18}O$ 250.1352, found 250.1346.

Olefin **13p**:[15] yellowish syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H*), 1.07 (s, 9H), 3.70 (dd, J = 10.6, 5.0 Hz, 1H and 1H*), 3.86 (dd, J = 10.7, 6.4 Hz, 1H and 1H*), 3.89 (dd, J = 11.4, 6.8 Hz, 1H*), 4.06 (dd, J = 11.9, 6.7 Hz, 1H), 4.49 (dd, J = 12.1, 6.3 Hz, 1H and 1H*), 4.68 (dd, J = 12.2, 3.8 Hz, 1H and 1H*), 5.41 (dd, J = 10.1, 9.8 Hz, 1H*), 5.71 (dd, J = 15.4, 7.5 Hz, 1H), 6.39 (dd, J = 15.5, 10.5 Hz, 1H, H-1), 6.45 (dd, J = 10.8, 6.2 Hz, 1H*), 6.56 (d, J = 15.7 Hz, 1H, H-1), 6.57 (d, J = 15.4 Hz, 1H*), 6.78 (dd, J = 15.5, 10.2 Hz, 1H), 6.87 (dd, J = 14.9, 10.5 Hz, 1H*), 7.28−7.52 (m, 15), 7.58−7.80 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 26.9*, 27.1, 66.9*, 67.1, 70.4*, 70.9, 75.4, 80.6, 124.3, 126.6, 126.8, 127.7, 128.1, 128.5, 128.76, 128.85, 129.5, 129.8, 132.0, 132.8, 135.1, 135.9, 137.4, 138.8, 138.9; IR (film) ν^{-1} 3068, 3028, 2957, 2929, 2856, 1471, 1427, 1110, 1083, 991, 700; MS (FAB) m/z 541 (85) $[M + Na]^+$, 411 (24), 271 (68), 249 (32), 197 (100); HRMS (FAB) m/z calcd for $C_{35}H_{38}O_2SiNa$ 541.2539, found 541.2543.

Olefin **13q**:.[15,18] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H*), 1.27 (s, 9H), 5.51 (d, J = 11.9 Hz, 1H*), 5.88 (d, J = 15.5 Hz, 1H), 6.02 (t, J = 11.8 Hz, 1H*), 6.17 (dd, J = 15.5, 10.2 Hz, 1H), 6.46 (d, J = 15.4 Hz, 1H*), 6.49 (d, J = 15.7 Hz, 1H), 6.77 (dd, J = 15.6, 10.2 Hz, 1H), 7.18−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 29.6*, 29.8, 124.1*, 125.6, 126.3, 126.6*, 127.2, 127.6*, 128.8, 130.1, 130.4, 131.9*, 137.9, 147.0; IR (film) ν^{-1} 3024, 2958, 2916, 2849, 1595, 1488, 1462, 1361, 1232, 987, 910, 744; MS (EI) m/z 186 (27) $[M]^+$, 187 (2) $[M + H]^+$, 171 (26), 86 (66), 84 (100), 57 (14); HRMS (EI) m/z calcd for $C_{14}H_{18}$ 186.1403, found 186.1399.

Olefin **13r**:.[15,19] yellowish oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.62 (dd, J = 15.0, 7.0 Hz, 2H*), 2.69−2.80 (m, 2H), 2.80−3.01 (m, 2H and 2H*), 5.79 (dt, J = 11.6, 6.9 Hz, 1H), 6.35 (dt, J = 15.8, 6.7 Hz, 1H*), 6.51 (d, J = 15.9 Hz, 1H*), 6.54 (d, J = 11.6 Hz, 1H), 7.21−7.49 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.6, 35.1*, 36.1*, 36.3, 126.1*, 126.2, 126.8, 127.1*, 128.3, 128.5, 128.7, 128.9, 129.6, 130.1*, 130.5*, 132.0, 137.7, 137.9*, 141.8, 141.9*; IR (film) ν^{-1} 3061, 3024, 2922, 2854, 1601, 1495, 1452, 1074, 1030, 964, 908, 735, 696; MS (EI) m/z 208 (7) $[M]^+$, 209 (2) $[M + 1]^+$, 129 (12), 117 (100), 115 (66), 91 (86); HRMS (EI) m/z calcd for $C_{16}H_{16}$ 208.1247, found 208.1248.

Olefin **13s**:.[15,20] yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (d, J = 6.0 Hz, 2H), 4.36 (dd, J = 6.4, 1.1 Hz, 2H*), 4.58 (s, 2H*), 4.63 (s, 2H), 5.97 (dt, J = 12.4, 6.3 Hz, 1H*), 6.39 (dt, J = 15.9, 6.0 Hz, 1H), 6.67 (d, J = 11.2 Hz, 1H*), 6.69 (d, J = 16.0 Hz, 1H), 7.21−7.53 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.1*, 70.9, 72.3, 72.6*, 126.2, 126.7, 127.3*, 127.8, 127.98, 128.04*, 128.4*, 128.6, 128.7, 129.0, 129.1*, 132.0*, 132.7, 136.7*, 136.9, 138.3*, 138.4; IR (film) ν^{-1} 3061, 3026, 2922, 2848, 1494, 1452, 1360, 1112, 1072, 966, 732, 692; MS (FAB) m/z 295 (15) $[M + Na]^+$, 281 (61), 263 (20), 247 (100), 237 (35), 221 (56), 199 (42), 180 (65); HRMS (FAB) m/z calcd for $C_{16}H_{16}ONa$ 247.1099, found 247.1097.

Hydroxysulfone 8 Synthesis. *Epoxide Opening.*[8] A solution of styrene oxide (690 μL, 6.07 mmol) and BT-SH (1.12 g, 6.68 mmol) in CH_2Cl_2 (66.8 mL, 0.1 M) was cooled to 0 °C, and $Sm(OTf)_3$ (36 mg, 0.06 mmol) was added in one portion. The resulting mixture was allowed to warm to rt and stirred for 8 h. After the mixture was stirred at rt for 8 h, a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The resulting layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL); 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 residue was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc = 4:1 → 2:1), and the reaction yielded 1.70 g (98%) of **hydroxy BT-sulfide** as a colorless viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (broad s, 1H), 4.17−4.35 (m, 2H), 5.16 (dd, J = 7.2, 5.6 Hz, 1H), 7.29−7.48 (m, 7H), 7.75 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 67.5, 121.3, 121.8, 124.9, 126.5, 128.1, 128.6, 129.3, 135.7, 137.7, 152.8, 166.7; MS (CI) m/z 288 (100) $[M + 1]^+$, 289 (19) $[M + 2]^+$, 290 (11) $[M + 2]^+$, 151 (8), 149 (25); HRMS (CI) m/z calcd for $C_{15}H_{14}ONS_2$ 288.0517, found 288.0515. **Hydroxy PT-sulfide:** colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (broad s, 1H), 4.24 (d, J = 6.1 Hz, 2H), 5.19 (t, J = 6.3 Hz, 1H), 7.28−7.44 (m, 5H), 7.53 (broad s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 67.5, 121.3, 121.8, 124.9, 126.5, 128.1, 128.6, 129.3, 135.7, 137.7, 152.8, 166.7; MS (ESI) m/z 299 (100) $[M + 1]^+$, 300 (21) $[M + 2]^+$, 301 (8) $[M + 3]^+$, 239 (30), 151 (20); HRMS (ESI) m/z calcd for $C_{15}H_{15}ON_4S$ 299.0961, found 299.0964.

Sulfide Oxidation. A solution of hydroxy BT-sulfide (500 mg, 1.74 mmol) in EtOH (17.4 mL, 0.2 M) was cooled to 0 °C, and a cold (0 °C) yellow solution of molybdate (108 mg, 87 μmol) in 35% aqueous H_2O_2 (2 mL, 17.5 mmol) was added dropwise. The resulting mixture was allowed to warm to rt and stirred for an additional 18 h. The resulting slightly yellow milky solution was cooled to 0 °C, and aqueous saturated $Na_2S_2O_3$ (10 mL) was added dropwise. Water (10 mL) was added, and the whole mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 (petroleum ether/EtOAc = 2:1 → 1:1 → 0:100), and the reaction yielded 410 mg (74%) of **8a** as a colorless solid: mp = 161−162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (broad s, 2H), 4.30 (dd, J = 12.4, 4.9 Hz, 1H), 4.78 (dd, J = 12.4, 7.5 Hz, 1H), 4.93 (dd, J = 7.4, 4.9 Hz, 1H), 7.21−7.35 (m, 5H), 7.58 (dd, J = 11.2, 4.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 4.64 (dt, J = 7.7, 1.0 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.5, 72.6, 111.6, 122.4, 125.7, 127.9, 128.3, 129.2, 129.8, 130.1, 137.3, 152.7, 165.3; MS (ESI) m/z 342 (100) $[M + Na]^+$, 301 (64), 214 (17), 121 (8); HRMS (ESI) m/z calcd for $C_{15}H_{14}O_3NS_2$ 320.0410, found 320.0412.

Sulfone **8b**: colorless viscous syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (broad s, 1H), 4.20 (dd, J = 12.3, 4.8 Hz, 1H), 4.64 (dd, J = 12.3, 8.5 Hz, 1H), 5.02 (dd, J = 8.4, 4.8 Hz, 1H), 7.21−7.43 (m, 7H), 7.45−7.63 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.4, 73.8, 126.2, 127.6, 129.4, 130.3, 130.5, 131.6, 132.9, 153.7; MS (ESI) m/z 353 (100) $[M + Na]^+$, 331 (15) $[M + 1]^+$, 267 (8), 119 (10); HRMS (ESI) m/z calcd for $C_{15}H_{15}O_3N_4S$ 331.0859, found 331.0863.

■ ASSOCIATED CONTENT

Supporting Information

Optimization tables, additional information, and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) For more details, see the Supporting Information.

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(11) Barbier-like reaction conditions: the base is added to the reaction mixture containing sulfone **16** and aldehyde **12c** in appropriate solvent.

(12) TDA-1 = tris[2-(2-methoxy)ethyl]amine; selective K^+-specific chelating agent, see, e.g., ref 2 or Tamao, K.; Nakagawa, Y.; Ito, Y. *Org. Synth.* **1996**, *73*, 1035−1042.

(13) The same substrates (sulfone and aldehyde) were reacted with KHMDS using THF (method A) and DMF (method B) as solvents. Selectivity of the reaction was then compared with the reactions carried out under our optimized reaction conditions using 18-crown-6/DMF (method C) or DMF/TDA-1 = 3:1 (v/v) (method D) systems.

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PAPER

Practical synthesis of β-oxo benzo[*d*]thiazolyl sulfones: Scope and limitations†

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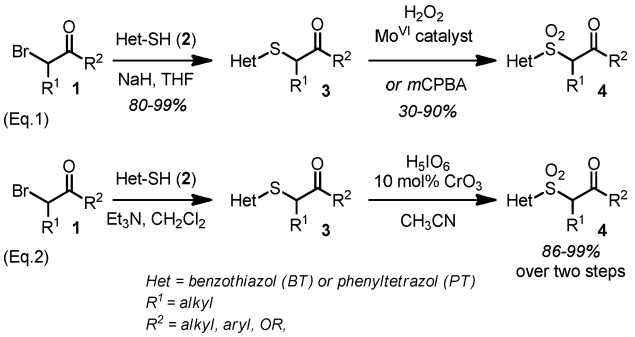
In this paper, we discuss our new synthetic approach towards functionalized benzo[*d*]thiazolyl (BT) sulfones, based on the reunion of alkyl BT sulfones and various electrophiles (*e.g.* R–CO–X, RO–CO–X, RS–CO–X, Ts–X . . .). All important aspects of this coupling reaction, including relevant and undesirable side reactions, are evaluated by means of calculations and competitive experiments. The scope and limitations of this method are established.

Introduction

Over the past 5 years, the use of β-carbonyl heteroaryl sulfones in organic synthesis, particularly in the domain of organocatalysis, has dramatically increased.[1] Especially, the use of these type of compounds as nucleophiles in the context of organocatalysis led to the synthesis of new classes of previously inaccessible compounds and structural motives. For example, the use of β-oxo benzo[*d*]thiazolyl sulfones or β-oxo phenyltetrazolyl sulfones in combination with α,β-unsaturated aldehydes and ketones has led, in the presence of a prolinol-based catalyst, to the stereoselective formation of both β-alkynylated and β-alkenylated carbonyl derivatives.[1i] The drawback of this method was the long and expensive synthesis of the starting material, β-oxo heteroaryl sulfones.[2] Additionally, only a small library, from a structural diversity point of view, of β-oxo heteroaryl sulfones could be prepared using the standard synthetic protocols.

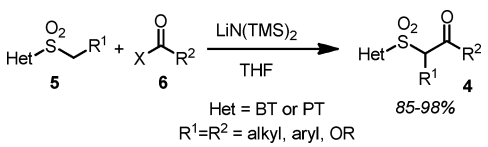
In general, this class of compounds is prepared in two steps, starting from α-bromo carbonyl compounds and corresponding heteroaryl sulfides (Scheme 1, eq. 1). To achieve a reasonable conversion of starting material to product **4**, prolonged reaction times are required (days). Unfortunately, sulfones **4** often slowly degrade under the given reaction conditions. This drawback was recently solved by Jørgensen *et al.*,[3] by introducing a new oxidation protocol of β-oxo hetoroaryl sulfides **3** to sulfones **4**. This procedure allows the isolation of the desired products, not only in excellent yields but also in very short reaction times (10–45 min) (Scheme 1, eq. 2).

Recently, we started several synthetic ventures based on the use of β-oxo benzo[*d*]thiazolyl sulfones **4** and we were searching for a more versatile access to this class of compounds. The standard approach to sulfones **4** was not only inefficient but also not general enough for our purposes.



Scheme 1 Previous approaches to β-oxo heteroaryl sulfones.

In this context, we have recently reported a practical synthesis of β-acyl and β-alkoxycarbonyl heterocyclic sulfones **4** based on the pairing of sulfone **5** with electrophile **6** (Scheme 2).[4]



Scheme 2 An alternative approach to β-oxo heteroaryl sulfones **4**.

Herein, we wish to present a full report of our experimental and computational studies, which focused on the evaluation of the reaction between benzo[*d*]thiazolyl (BT) sulfone α-anions and various electrophiles. Firstly, the behaviour of BT sulfones and targeted β-oxo BT sulfones under non-nucleophilic basic conditions is discussed. Based on these results, the reactivity of α BT sulfonyl anions with various electrophiles is evaluated, with a special mention to carbonyl electrophiles.[5] The scope and limitations of these coupling reactions are also discussed.

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† Electronic supplementary information (ESI) available: detailed experimental and computational procedures and data. See DOI: 10.1039/c1ob06510f

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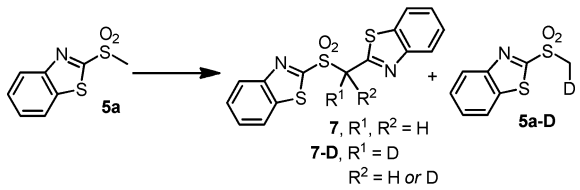
Table 1 Dimerization of sulfone **5a** under basic conditions[a]



Entry	Base (equiv)	Time at −78 °C (min)	Conv. of **5a**[b] (%)	Yield (%)[c]		
				5a–**D**	**7**	**7**–**D**
1[d]	LDA (1.1)	120	>99	n.a.	52	n.a.
2[g]	LDA (1.1)	120	>99	n.a.	61	n.a.
3	$LiN(TMS)_2$ (1.1)	120	>99	<5[e]	53[f]	
4	$LiN(TMS)_2$ (4.0)	120	>99	<5[e]	<5[e]	49
5	$KN(TMS)_2$ (1.1)	120	>99	<5[e]	82[f]	
6	$KN(TMS)_2$ (4.0)	120	>99	<5[e]	<5[e]	91
7	$LiN(TMS)_2$ (5.0)	0.5	>99	97	<5[e]	<5[e]
8	$LiN(TMS)_2$ (5.0)	2	>99	91	<5[e]	<5[e]
9	$LiN(TMS)_2$ (5.0)	5	>99	85	<5[e]	7
10	$LiN(TMS)_2$ (5.0)	15	>99	61	<5[e]	16
11	$LiN(TMS)_2$ (5.0)	30	>99	48	<5[e]	24
12	$LiN(TMS)_2$ (5.0)	60	>99	21	<5[e]	31
13	$KN(TMS)_2$ (5.0)	0.5	>99	90	<5[e]	2
14	$KN(TMS)_2$ (5.0)	2	>99	76	<5[e]	20
15	$KN(TMS)_2$ (5.0)	5	>99	53	<5[e]	31
16	$KN(TMS)_2$ (5.0)	15	>99	26	<5[e]	63
17	$KN(TMS)_2$ (5.0)	30	>99	<5[e]	<5[e]	81
18	$KN(TMS)_2$ (5.0)	60	>99	<5[e]	<5[e]	80

[a] Conditions: (i) base, THF, −78 °C, (ii) stirred at −78 °C for given time, (iii) DCl in MeOD added. [b] Based on ^{1}H NMR spectra of crude reaction mixure. [c] Isolated yield. [d] Taken from lit[9] [e] No traces of product observed (^{1}H NMR) in crude reaction mixture. [f] Mixture of mono- and di-deuterated and non-deuterated products **7-D** and **7**, respectively. [g] The reaction was quenched using HCl in MeOH.

Results and discussion

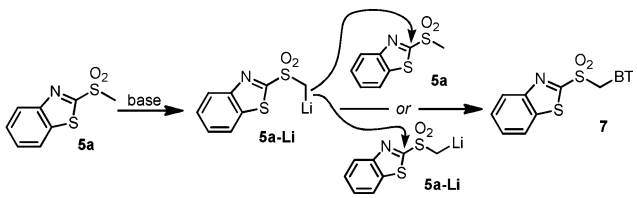
Preliminary studies

First, we evaluated the reliability of our synthetic approach to β-oxo BT sulfones, **4**, based on the addition of the sulfone **5** α anion onto the electrophile, **6**. From the literature it is known that sulfone **5** undergoes rapid self-condensation under basic conditions (Table 1, entry 1).[6] Of course, if this self-condensation reaction was too fast it would compete with the addition to electrophile **6** and our newly designed approach to the synthesis of **4** would be compromised.

To evaluate this risk, we first reproduced the literature results and reacted sulfone **5a** with a slight excess of LDA (Table 1, entry 2). Similar to the literature, we obtained the product of self-condensation **7** in 61% yield.[7] Next, we decided to use the less nucleophilic $[M]N(TMS)_2$ bases that are successfully used in the Sylvestre Julia olefination reaction to deprotonate BT sulfone **5a**,[7] even though the pK_a values of **5a** and $HN(TMS)_2$ (conjugate acid) are presumably very close.[8] These pK_a values, of course, raised the question whether the deprotonation of sulfone **5a** by $[M]N(TMS)_2$ base is quantitative. To answer the question, we decided to perform series of experiments in which sulfone **5a** would react with either a slight (1.1 equiv) or a large excess (4.0 equiv) of $LiN(TMS)_2$ and $KN(TMS)_2$ (Table 1, entries 3–6).

In all cases, complete conversion of sulfone **5a** was observed after 2 h. Interestingly, neither unreacted sulfone **5a** nor, after the reaction work-up with DCl/MeOD, its deuterated equivalent **5a-D** could be detected by ^{1}H NMR in the crude mixture. Only the dimers of **5a**, compounds **7** and/or **7-D** were observed.

To our great surprise, the self-condensation of **5a** to **7** occurred even if a large excess of base was used (Table 1, entries 4 and 6). This observation suggested that either (a) deprotonation of **5a** is not quantitative and the dimerization proceeds *via* the addition of anion **5a-Li** to non-deprotonated sulfone **5a**, or (b) the anion **5a-Li** reacts with itself (Scheme 3).

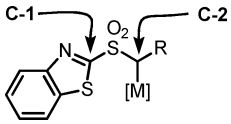


Scheme 3 Self-condensation reaction of sulfone **5a**.

To determine which of these hypotheses is correct, sulfone **5a** was reacted with a large excess (5.0 equiv) of $LiN(TMS)_2$ and the conversion of **5a** and the formation of its dimer **7** was monitored (Table 1, entries 4 and 7 – 12).

These experiments showed that, in the presence of an excess of the base, the deprotonation of the acidic hydrogen α to a sulfone group is very fast (less than 30 s, Table 1, entry 7)[9] and the concentration of anion **5a-Li** is slowly decreasing with time. Correspondingly, the formation of dimer **7-D** is increasing.

Table 2 Computed charges (NBO) at C-1 and C-2 carbons in sulfone **5a** and its derivatives[a]



Entry	R	[M]	C-1	C-2
1	H	H	–0.211	n.d.
2	H	Li	–0.191	–1.061
3		Li	–0.184	–0.802
4		Li	–0.185	–0.844
5		Li	–0.180	–0.856
6		Li	–0.194	–1.140

[a] For details, see ESI.†

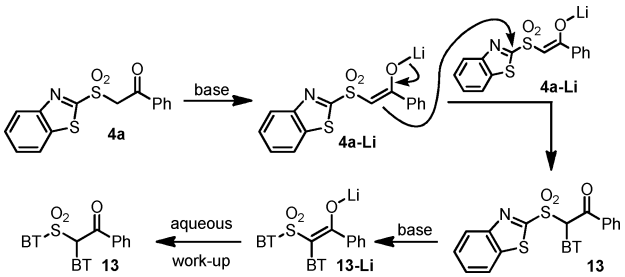
These results indicate that deprotonation of sulfone **5a** is rapid (presumably due to high kinetic acidity of the hydrogens α to sulfone group) and that dimerization of sulfone **5a** proceeds, even if this latter is fully transformed into its anion **5a-Li**. This suggests thus that anion **5a-Li** reacts with itself.

Similar behaviour was observed if an excess of $KN(TMS)_2$ was used (Table 1, entries 6 and 13–18). However, in this case we observed that newly generated anion **5a-K** is dimerizing even faster than **5a-Li**, substantially diminishing the concentration of anion **5a-K** in the reaction mixture. We believe that faster dimerization process of anion **5a-K**, as compared to anion **5a-Li**, is caused by the higher nucleophilicity of the potassium anion **5a-K**.

To shed more light into the reactivity of anion **5a-Li** and to evaluate the possibility that anion **5a-Li** might also behave as an electrophile under the reaction conditions, we decided to evaluate and compare the electrophilicity of the BT group in **5a** and **5a-Li** by computational means.[10] Relative electrophilicity of the BT group has been estimated by computing the charge on the C-1 carbon atom (Table 2).[11] The obtained partial charges on C-1 for **5a** (–0.211) and **5a-Li** (–0.191) were very similar suggesting that both species should have essentially the same electrophilic properties.[12] These results thus support our hypothesis that dimer **7** is formed by the self-reaction of **5a-Li**.

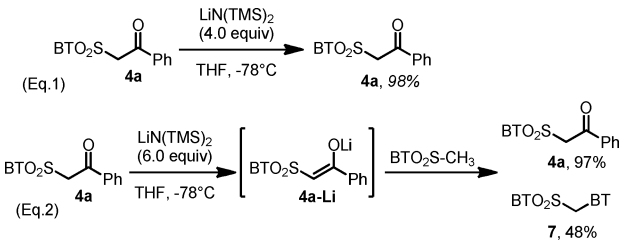
Having described the behaviour of sulfone **5a** in the presence of the base, we focused on the evaluation of the stability of the β-oxo BT sulfone **4**. As a model substrate, we used keto sulfone **4a**.[13] We feared that compound **4a** might undergo a self-condensation reaction similarly to sulfone **5a** (Scheme 4). Indeed, according to the corresponding computed charges, the C-1 carbon atom of the enolate of **4b** should be (at least) as electrophilic as the one in **5a** and **5a-Li** (Table 2, entry 3).

On the other hand, lithiated keto sulfone **4a-Li** should be less nucleophilic than sulfone anion **5a-Li** due to additional negative charge stabilization by the carbonyl group (enolate). This expectation is supported by our computational results (see charges on C-2, Table 2).



Scheme 4 Possible self-condensation of keto sulfone **4a**.

To experimentally evaluate this information, keto sulfone **4a** was first stirred with an excess of $LiN(TMS)_2$ (Scheme 5, eq. 1). No degradation of **4a** was observed. Once the stability of **4a** under basic conditions was determined, the resistance of enolate **4a-Li** against the attack of anion **5a-Li** was tested (Scheme 5, eq. 2). Again, no reaction of **4a-Li** was observed.



Scheme 5 Determination of keto sulfone **4a** stability in the presence of base and α sulfonyl anion.

These experiments did show us that self-condensation of sulfone **5a** is rather rapid (full conversion within 2 h), whereas keto sulfones **4** (the desired class of compounds) are stable under basic conditions and do not react with external nucleophiles, such as anion **5a-Li**.

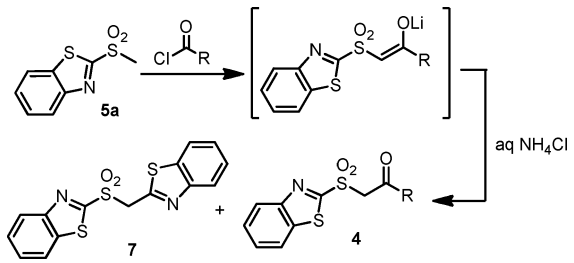
Synthesis of β-keto sulfones 4

Having collected these results, we were able to investigate the coupling between sulfone **5a** and benzoyl chloride **6a** (Table 3).

Our primary goal was to find suitable reaction conditions for this coupling (Scheme 6). We thus had to design a system in which the addition of α sulfonyl anion of **5a-Li**[14] to electrophile (**6a**) would be faster than its self-condensation to adduct **7** ($k_1 \gg k_2$). Additionally, the transformation of the adduct, **4a**, into its enolate, **4a-Li**, should be more rapid than the eventual Sylvestre Julia reaction that could occur between the ketone presented in **4a** and sulfone anion **5a-Li** ($k_5 \gg k_6$). Once all of adduct **4a** is transformed into its enolate, **4a-Li**, it should be safe, since we demonstrated that enolate **4a-Li** is stable in the presence of a base or nucleophile (Scheme 5).

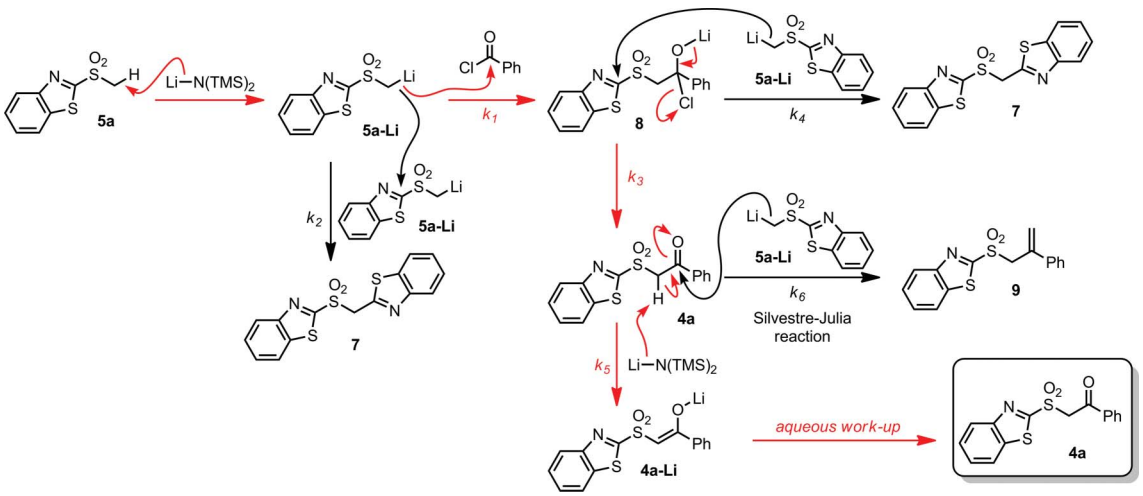
Taking into account these considerations, we started to investigate the coupling between sulfone **5a** and benzoyl chloride **6a**. Initially, generated anion **5a-Li** was stirred at –78 °C for 15 min prior to the benzoyl chloride **6a** addition (Table 3, entry 1). The desired product **4a** was isolated in 15% yield along with 32% of the dimerization product **7**. As expected, if the pre-metallation period was longer (Table 3, entry 2), the self-condensation was the predominant reaction and only trace amounts of products were formed. On the other hand, the progressive decrease of

Table 3 Optimization of reaction conditions



Entry	X	Conditions	Yield (%)[a,b] 4a	7[c]
1	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, 15 min then BzCl (1.2 equiv)	15	32
2	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, 30 min then BzCl (1.2 equiv)	7	48
3	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, 1 min then BzCl (1.2 equiv)	65	7
4	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	96	<5
5	Cl	BzCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	97	<5
6	Cl	$NaN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	82	11
7	Cl	$KN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzCl (1.2 equiv)	72	17
8	Cl	$LiN(TMS)_2$ (2.2 equiv), 12-crown-4 (4.5 equiv), −78 °C, THF, then BzCl (1.2 equiv)	74	11
9	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF/HMPA = 6 : 1 (v/v), then BzCl (1.2 equiv)	78	9
10	Cl	$KN(TMS)_2$ (2.2 equiv), 18-crown-6 (4.5 equiv), −78 °C, THF, then BzCl (1.2 equiv)	64	12
11	Cl	$KN(TMS)_2$ (2.2 equiv), −78 °C, THF/TDA-1 = 6 : 1 (v/v), then BzCl (1.2 equiv)	52	13
12	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, Et_2O, then BzCl (1.2 equiv)	95	<5
13	Cl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, DME, then BzCl (1.2 equiv)	88	5
14	F	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzF (1.2 equiv)	93	<5
15	Br	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzBr (1.2 equiv)	97	<5
16	OCOPh	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then Bz_2O (1.2 equiv)	92	<5
17		$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then Bz-Im (1.2 equiv)	92	<5
18	CN	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzCN (1.2 equiv)	91	<5
19	OMe	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then BzOMe (1.2 equiv)	<5	63
20	OMe	BzOMe (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	<5	71

[a] Overall yields refer to pure, isolated products. [b] Average of two runs. [c] Yield recalculated to 100%.

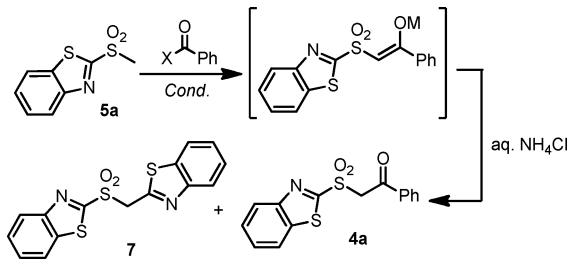


Scheme 6 Considered undesired side reactions that could compete with the β-keto sulfone **4** synthetic pathway (red).

the metallation period led to an increased yield of adduct **4a**. Finally, the highest yield of **4a** was obtained when electrophile **6a** was added immediately after the base (Table 3, entry 4).[15] We thus tested also the coupling step under the Barbier-type reaction conditions.[16] Not surprisingly, the desired product **4a** was isolated in excellent 95% yield (Table 3, entry 5).

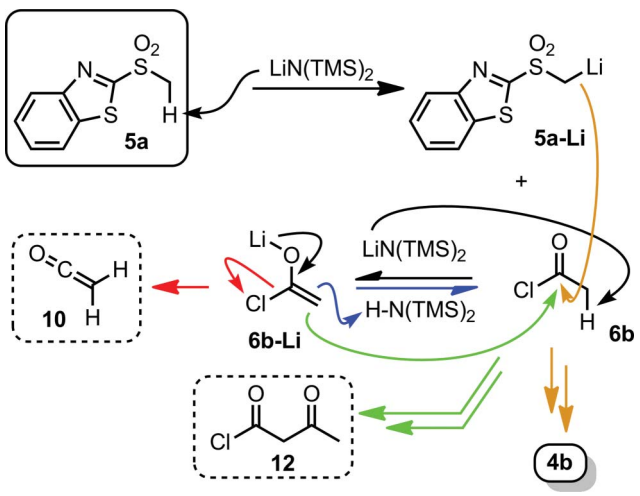
At this stage, we decided not to use the Barbier-type reaction conditions as our standard reaction protocol since we thought that they might be applicable only in the case of acylating agents that possess no α hydrogen atoms. Indeed, we expected that if, for example, acetyl chloride **6b** was used as electrophile, several side reactions might occur. Some of them are depicted in Scheme 7.

Table 4 Barbier-type reaction conditions evaluation

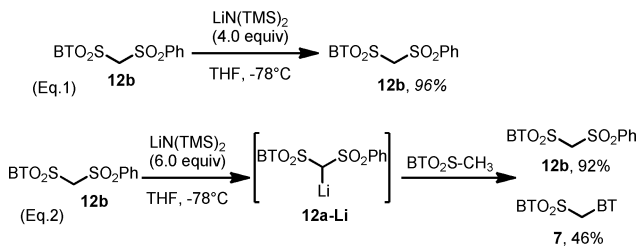


Entry	R	Conditions	Yield (%)[a] 4	7[b]
1	CH_3	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then RCOCl (1.2 equiv)	**4b**, 90	<5
2	CH_3	RCOCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**4b**, 67	14
3		$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then RCOCl (1.2 equiv)	**4h**, 83	<5
4		RCOCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**4h**, 54	21

[a] Overall yields refers to pure, isolated products. [b] Yield recalculated to 100%.



Scheme 7 Possible side reactions that could be observed if Barbier-type reaction conditions are used for the β-keto sulfone **4** synthesis.



Scheme 8 Determination of bis-sulfone **12b** stability in the presence of base and α sulfonyl anion.

As a consequence, a lower yield of the desired adducts would be isolated. To verify this hypothesis, the mixing of sulfone **5a** with acetyl chloride (**6b**) and cyclohexyl acyl chloride (**6c**) was investigated (Table 4). As suspected, the desired products **4b** and **4c** were formed in lower yield than if Barbier-type conditions were used (Table 4, entries 1 vs. 2, and 3 vs. 4).

Next, $NaN(TMS)_2$ and $KN(TMS)_2$ were tested as bases but, in both cases, lower reaction yields of **4a** were observed (Table 3, entries 6 and 7). This observation is in agreement with anion **5a-K** stability experiments we made previously (Table 1).

To gain indirect evidence that would provide a link between the anion **5a**-[**M**] reactivity and the rate of dimerization, we decided to evaluate the coupling reaction of anions **5a-Li** and **5a-K** in the presence of selective Li^+ and K^+ chelating agents (12-crown-6, 18-crown-6, TDA-1 and HMPA). By this method, we expected to generate, *in situ*, a more reactive "naked" anion of **5a** (Table 3, entries 8–11). As a consequence, the introduction of chelating agents increased the speed of sulfone **5a** self-condensation.

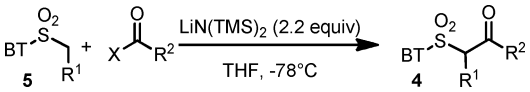
We reasoned that the nature of the solvents could have a similarly large influence. We therefore attempted the coupling reaction in THF, Et_2O and DME (Table 3, entries 4, 12 and 13, respectively).[17] As expected, reactions carried out in Et_2O and THF gave comparable yields, whereas the use of DME increased the yield of the self-condensation product **7**.

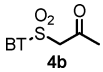
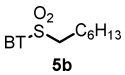
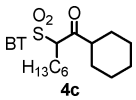
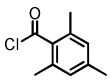
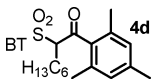
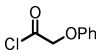
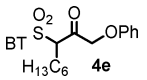
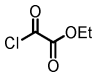
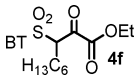
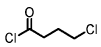
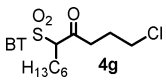
Next, we focused our attention on the nature of the leaving group in the electrophile (Table 3, entries 14–20). Benzoylating agents with reactivity similar to that of benzoyl chloride, such as BzF, BzBr, Bz_2O, benzoyl imidazole[18] or BzCN, produced the adduct **4a** in essentially same yields. On the other hand, methyl benzoyl ester was found to be unreactive under our reaction conditions as well as under Barbier-type reaction conditions (Table 3, entry 19 and 20). In both cases, only the product of dimerization **7** was isolated.

Having devised suitable reaction conditions for β-acyl sulfone synthesis, the scopes and limitations of this method were explored. A selection of pertinent results is shown in Table 5.

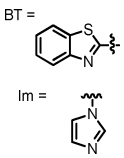
It was demonstrated that both alkyl and aryl acyl electrophiles react smoothly with lithiated sulfones **5**. In all cases the reaction yields were greater than 80%, except for when sulfone **5b** was

Table 5 Preparation of acyl benzo[*d*]thiazol sulfones **4**, starting from sulfones **5** and acyl-containing electrophiles



Entry	Sulfone	Acylating agent	Product	Yield (%)[a]
1	 **5a**	AcCl	 **4b**	90
2		Ac_2O		92
3		Ac–Im		89
4	 **5b**		 **4c**	83
5				92
6			 **4d**	89
7			 **4e**	86
8			 **4f**	78
9			 **4g**	81

[a] Overall yields refer to pure, isolated products.



reacted with monoethyl oxalyl chloride (Table 5, entry 8). In this case the desired product **4f** was obtained in 78% yield. Additionally, even acyl chlorides with enolizable hydrogen atoms reacted under the given reaction conditions to yield the desired α-acyl sulfones **4** in very good yields.

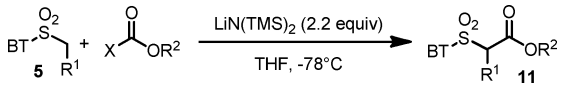
Synthesis of α-sulfonyl carboxylic acid derivatives

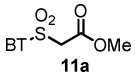
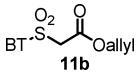
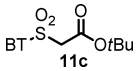
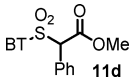
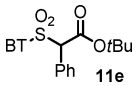
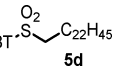
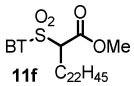
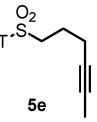
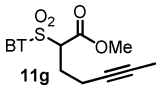
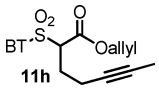
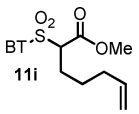
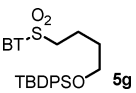
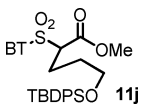
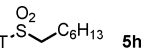
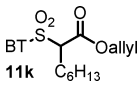
Our new protocol was also applied to the synthesis of α-sulfonyl carboxylic acid derivatives **11** (Table 6). For this purpose, four different types of alkoxy carbonylating reagents (bearing Cl, imidazole,[19] OCOR or CN as a leaving group) were tested. The nature of the leaving group was shown to have little effect on the reaction yield and all four electrophiles could be used as coupling partners. Additionally, standard functional groups are tolerated under the reaction conditions. In all cases, the desired products, **11**, were prepared in good to excellent yields.

After establishing the access to sulfonyl esters, we decided to extend this methodology to other carboxylic acid derivatives (Table 7). Interestingly, at this moment the abilities the of activating/leaving groups presented on electrophile were fully revealed.

As shown in Table 7, when a Cl^- group was used as an activating/leaving group, ester, thioester and amide BT sulfonyl derivatives **11** could be easily prepared (Table 7, entries 1–3). However, in the case of amides, the product of sulfone **5a** self-condensation, compound **7**, was also formed, along with the desired adduct, **11m**, in 11% yield (Table 7, entry 3). This observation suggests that in the case of *N*,*N*-dialkylamino chlorocarbamates, the addition of anion **5a-Li** to the carbonyl is much slower than in the case of alkyl chloroformates and thioformates. The difference in the reactivity between chloroformates and chlorocarbamates became even more evident when CN^- group was used as Cl^- equivalent (Table 7, entries 4–6). In this case, the ester and thioester derivatives were formed in very good yields (Table 7, entries 4

Table 6 Preparation of alkoxycarbonyl benzo[*d*]thiazol sulfones, **11**, starting from sulfone **5** and alkoxy carbonyl-containing electrophiles



Entry	Sulfone	Electrophile	Product	Yield (%)[a]
1	 **5a**	Cl–COOMe	 **11a**	94
2		Im–COOMe		89
3		NC–COOMe		91
4		Cl–COOallyl	 **11b**	95
5		Boc_2O		94
6		Im–COO*t*Bu	 **11c**	98
7	 **5c**	Cl–COOMe	 **11d**	88
8		Im–COOMe		94
9		NC–COOMe		92
10		Boc_2O	 **11e**	91
11		Im–COO*t*Bu		98
12	 **5d**	Cl–COOMe	 **11f**	88
13		Im–COOMe		94
14		NC–COOMe		93
15	 **5e**	Cl–COOMe	 **11g**	88
16		Im–COOMe		93
17		NC–COOMe		94
18		Cl–COOallyl	 **11h**	89
19	 **5f**	Cl–COOMe	 **11i**	87
20		Im–COOMe		95
21		NC–COOMe		94
22	 **5g**	Cl–COOMe	 **11j**	89
23		Im–COOMe		93
24		NC–COOMe		91
25	 **5h**	Cl–COOallyl	 **11k**	92

[a] Overall yields refer to pure, isolated products.

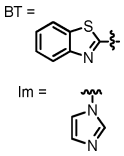
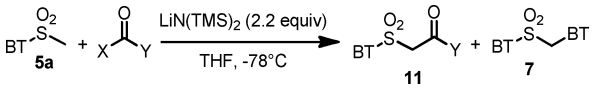
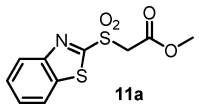
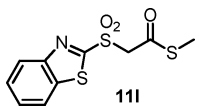
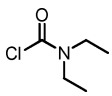
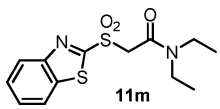
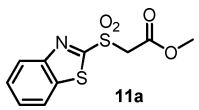
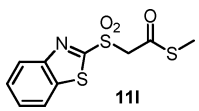
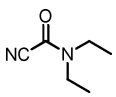
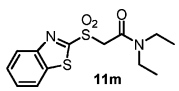
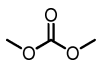
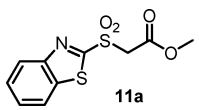


Table 7 Extending of the methodology to other carboxylic acid derivatives



Entry	Electrophile	Product	Yield (%)[a] 11	7
1		 **11a**	94	<5
2		 **11l**	94	<5
3		 **11m**	63	11
4		 **11a**	91	<5
5		 **11l**	95	<5
6		 **11m**	<5	77
7		 **11a**	<5	49

[a] Overall yields refers to pure, isolated products.

and 5), but no amide derivative was formed (Table 7, entry 6). If dimethyl carbonate was used as electrophile, no adduct **11a** of the addition was observed (Table 7, entry 7).

These results suggest that only sufficiently reactive electrophiles are capable to react with BT sulfone anions under the coupling conditions. If the electrophile is not reactive enough (Table 7, entries 3, 6 and 7), the competitive dimerization reaction starts to play an important role.

Non-carbonyl-containing electrophiles

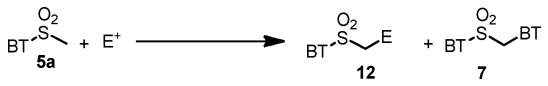
At this stage, we decided to extend our methodology to other non-carbonyl-containing electrophiles such as TMSCl, TsCl and MsCl (Table 8). Unfortunately, in all cases only the product of sulfone **5a** self-condensation, compound **7**, was isolated. Interestingly, no traces of any self-condensation or degradation products that could arise from potentially formed adducts **12a–c** were identified.

This observation suggests that the self-condensation is the fastest step under our reaction conditions. To verify this hypothesis, we decided to evaluate the bis-sulfone **12b**[20] stability under the basic conditions (Scheme 8). No degradation of bis-sulfone **12b** was observed when it was placed under the reaction conditions. This observation suggests that, at any time, desired bis-sulfone **12b** was not formed under the given reaction conditions. At this stage we believe that our unsuccessful synthesis of BT sulfonyl derivatives **12a–c** is caused by the lack of reactivity of the corresponding electrophiles (TMSCl, TsCl and MsCl) towards nucleophile **5a-Li**.

Conclusions

In summary, we have disclosed a short and efficient approach to α-acyl and α-carboxylic acid-derivative sulfones, **11**, starting from heterocyclic sulfones and appropriate electrophile. Reaction conditions tolerate various functionalities, such as TBDPS ethers, phenyl ethers and halogenated or unsaturated alkanes. We believe that this is a general approach towards this class of C-nucleophiles, which can be easily used in the context of the formation of olefins

Table 8 Coupling reaction using other non-carbonyl-containing electrophiles



Entry	E^+	Conditions	Yield (%)[a] 12	7
1	TMSCl	$LiN(TMS)_2$ (1.2 equiv), −78 °C, THF, then TMSCl (1.2 equiv)	**12a**, <5	62
2	TMSCl	TMSCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (1.2 equiv)	**12a**, <5	54
3	TsCl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then TsCl (1.2 equiv)	**12b**, <5	55
4	TsCl	MsCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**12b**, <5	57
5	MsCl	$LiN(TMS)_2$ (2.2 equiv), −78 °C, THF, then TsCl (1.2 equiv)	**12c**, <5	48
6	MsCl	MsCl (1.2 equiv), −78 °C, THF, then $LiN(TMS)_2$ (2.2 equiv)	**12c**, <5	60

[a] Overall yields refer to pure, isolated products.

or alkynes. Unfortunately, the extension of this methodology to other, non-carbonyl containing electrophiles proved to be unsuccessful. We believe that it is due to a low reactivity of these electrophiles. Additionally, the dimerization of BT sulfone **5a** under the basic conditions was evaluated using both, experimental approach and theoretical calculations.

Finally, we believe that our simple newly developed approach to β-carbonyl BT sulfones will extend their use beyond the field of asymmetric organocatalysis. Further development and use of β-carbonyl heterocyclic sulfones of general structure **4** and **11** is now under progress in our laboratory and will be reported shortly.

Experimental section

General experimental

^1H and ^{13}C NMR spectra were recorded on a Brucker AC-300 Avance II (working frequency 300 MHz and 75 MHz, respectively) at ambient temperature in $CDCl_3$ (Aldrich). Coupling constants (*J* value) are reported in hertz. The chemical shifts are shown in ppm downfield from tetramethylsilane, using residual chloroform (δ = 7.27 in ^1H NMR) or the middle peak of $CDCl_3$ carbon triplet (δ = 77.23 in ^{13}C NMR) as an internal standard. Low resolution mass spectroscopic data were recorded on a Finigan TSQ 7000. High resolution mass spectra were acquired at the University College London Mass spectroscopy facility using the Thermo Finnigan MAT900xp spectrometer.

Melting points were determined using a Büchi Flawil apparatus and are uncorrected.

Chemicals were purchased from Acros, Sigma-Aldrich and Fluka and were used as received. THF was distilled under argon from sodium benzophenone ketyl. Flash chromatography was performed on silica gel 60 (40–63 μm) (ROCC). All reactions were carried out under an atmosphere of argon in flame-dried apparatus with magnetic stirring, unless otherwise indicated. Brine refers to a saturated aqueous solution of sodium chloride.

The identity of known products was confirmed by comparison with literature spectroscopic data. The structure determination of new compounds was made with a help of 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments.

Preparation of imizadole-containing acylating and alkoxycarbonylating reagents: Ac–Im and Bz–Im,[18] and Im–CO_2Me and Im–CO_2tBu.[19]

The sulfones **5a–g**[4] and bis-sulfone **12b**[20] were prepared according to published procedures.

General procedure for the synthesis of β-oxo sulfonyl derivatives

A solution of sulfone (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. The colour of the reaction mixture turned from colourless or slightly yellow to orange/red within approx. 20 to 30 s. Immediately afterwards, a solution of acylating agent (acyl halide, carboxylic acid anhydride, acyl nitrile or acyl imidazole) or alkoxy carbonylating agent (alkoxy chloroformate, alkoxy imidazoylformate, alkoxy cyanoformate or Boc_2O) (1.1 mmol, 1.1 equiv) in THF (0.5 mL) was added. The colour of the reaction mixture faded within few minutes. 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 $MgSO_4$, filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2. See ESI file for characterization data.†

Acknowledgements

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Notes and references

1 For reviews see: (*a*) A.-N. R. Alba, X. Companyó and R. Rios, *Chem. Soc. Rev.*, 2010, **39**, 2018; (*b*) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Pixao and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2010, **49**, 2668For recent leading articles see: (*c*) C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2011, **133**, 7398; (*d*) A. Landa, A. Puente, J. I. Santis, S. Vera Oiarbide and C. Palomo, *Chem.–Eur. J.*, 2009, **15**, 11954; (*e*) J. L. García Ruano, V. Marcos and J. Alemán, *Chem. Commun.*, 2009, (29), 4435; (*f*) G. K.

S. Prakash, F. Wang, T. Steward, T. Mathew and G. A. Olah, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4090; (*g*) A. Alba, X. Companyó, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 11095; (*h*) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; (*i*) C. Cassani, L. Bernardi, F. Fini and A. Ricci, *Angew. Chem., Int. Ed.*, 2009, **48**, 5694; (*j*) A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide and C. Palomo, *Chem.–Eur. J.*, 2009, **15**, 1562; (*k*) M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2009, **131**, 10581.

2 (*a*) B. M. Trost, J. D. Chisholm, S. T. Wrobleski and M. Jung, *J. Am. Chem. Soc.*, 2002, **124**, 12420; (*b*) B. Zajc and S. Kate, *Org. Lett.*, 2006, **8**, 4457; (*c*) P. R. Blakemore, D. H. K. Ho and W. M. Nap, *Org. Biomol. Chem.*, 2005, **3**, 1365; (*d*) D. R. Williams and L. Fu, *Org. Lett.*, 2010, **12**, 808; (*e*) L. Xu, J. Cheng and L. Trudell, *J. Org. Chem.*, 2003, **68**, 5388.

3 T. Zweifel, M. Nielsen, J. Overgaard, C. B. Jacobsen and K. A. Jørgensen, *Eur. J. Org. Chem.*, 2011, **2011**, 47.

4 J. Pospíšil and H. Sato, *J. Org. Chem.*, 2011, **76**, 2269.

5 Sylvestre Julia reaction (reaction of BT sulfones **5** with aldehydes or ketones) was not the object of this research and therefore simple carbonyl-containing electrophiles (aldehydes and ketones) were not used. For more details about Sylvestre Julia reaction see: (*a*) P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2563; (*b*) C. Aïssa, *Eur. J. Org. Chem.*, 2009, **2009**, 1831; (*c*) J. Pospíšil, *Tetrahedron Lett.*, 2011, **52**, 2348.

6 J. B. Baudin, G. Hareau, S. A. Julia, R. Lorne and O. Ruel, *Bull. Soc. Chim. Fr.*, 1993, **130**, 856–878.

7 Of course, the maximal yield of sulfone **5a** self-condensation reaction is 50% but for comparison purposes the yield was recalculated to 100% value. Valid for all the yields of self-condensation reaction presented in this paper.

8 (*a*) The pK_a values known in the litterature (http://www.chem.wisc.edu/areas/reich/pkatable/): for $(TMS)_2N$–H, pK_a = 30 (in DMSO); (*b*) for BT SO_2–CH_2–H, pK_a value is not known, but pK_a for $PhSO_2CH_2$–H is 29 (in DMSO). The value for **5a** is expected to be approximately the same or lower.

9 Originally we thought that the self-condensation of **5a** in basic media is a consequence of the reaction between already deprotonated sulfone **5a** with its parent molecule.

10 Geometry optimisation has been carried out using the Jaguar 7.5 program package (Jaguar 7.5, Schrödinger, LLC, New York, NY, 2008) at the B3LYP/6-31+G*(THF) level. NBO analysis has been performed at the B3LYP/cc-pVTZ level of theory. See Electronic Supplementary Information† for full details.

11 Interestingly, optimization of **5a-Li** reveals that in the most stable isomer lithium cation is not linked to the carbon atom but instead complexed to both the nitrogen atom and one oxygen of the sulfone function. Since the charge on C-1 carbon atom was found not to depend highly on the nature of the isomer, results given in Table 2 refer only to the lowest energy isomer (see ESI† for full results).

12 In fact calculations suggest that the deprotonated sulfone **5a-Li** is even a slightly better electrophile than its protonated form **5a**.

13 Prepared for this purpose *via* standard literature protocol: C. B. Jacobsen, L. Lykke, D. Monge, M. Nielsen, L. K. Ransborg and K. A. Jørgensen, *Chem. Commun.*, 2009, (43), 6554.

14 The competitive reaction that might occur with sulfone **5** are not considered, because we showed that the transformation of sulfone **5a** to its anion **5a-Li**, in the presence of the excess of the base, is very fast (Table 1, entry 7).

15 The solution of BzCl in THF was precooled (−78 °C) before addition.

16 A precooled (−78 °C) solution of $LiN(TMS)_2$ in THF was added to a cold (−78 °C) solution of sulfone **5a** and BzCl in THF.

17 Other solvents such as toluene or DMF (reaction performed at −50 °C) were also tested, but the desired adduct **4a** was isolated in significantly lower yields.

18 Prepared *in situ* from the corresponding carboxylic acid: (*a*) C. A. Ibarra, R. C. Rodriguez, M. C. Fernandez Monreal, F. J. Garcia Navarro and J. J. Martin Tesorero, *J. Org. Chem.*, 1989, **54**, 5620.

19 Prepared according to the literature procedure: (*a*) S. P. Rannard and N. J. Davis, *Org. Lett.*, 1999, **1**, 933; (*b*) S. P. Rannard and N. J. Davis, *Org. Lett.*, 2000, **2**, 2117.

20 Prepared for this purpose *via* standard literature protocol: M. He, A. K. Ghosh and B. Zajc, *Synlett*, 2008, **2008**, 999.

SHORT COMMUNICATION

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On the Origin of *E*/*Z* Selectivity in the Modified Julia Olefination – Importance of the Elimination Step

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Dedicated to Professor Alois Fürstner on the occasion of his 50th birthday

Keywords: Density functional calculations / Elimination / Stereoselectivity / Reaction mechanisms / Olefination

The mechanism and origin of high *E* selectivity in the modified Julia olefination of aromatic aldehydes have been explored by computational and experimental means. Reversibility of addition and hence selectivity of the formation of sulfinate **5** is very variable and depends on the nature of the sulfone substrate. However, in all cases, elimination occurs through a concerted antiperiplanar and synperiplanar mechanism for sulfinates *anti*-**5** and *syn*-**5**, respectively. Both *syn* and *anti* diastereomeric pathways thus lead preferentially to the (*E*)-alkene.

Introduction

The modified Julia olefination allows the synthesis of alkenes in a single step from metallated benzothiazol-2-yl (BT) sulfones and aldehydes (Figure 1).[1,2] Over the past two decades, this olefination reaction has emerged as a powerful tool for carbon–carbon double bond formation, in particular when two complex molecular fragments should be connected.[3] The attractiveness of this connective olefination reaction arises from its versatility, its wide functional group tolerance, and the mild reaction conditions under which the reaction proceeds. The only shortcoming of the reaction is the difficulty of predicting and controlling the stereoselectivity of the newly formed double bond, which is a limitation to an even broader use of this reaction.

The experimental results showed that the stereochemical outcome of this process depends highly on the nature of the reactants: reaction of BT-sulfones **2** with aromatic aldehydes (compound **1**, R^2 = aryl) generally gives high *E* selectivity, whereas their reaction with aliphatic aldehydes (compound **1**, R^2 = alkyl) furnishes alkenes with little or no stereochemical bias.[1,4]

Although the global mechanistic sequence depicted in Figure 1 is known and widely accepted since the pioneering work of S. Julia, a detailed atomistic account of the mechanism and selectivity of this reaction is still lacking.[5]

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In the reaction of lithiated alkyl-BT-sulfones with alkyl aldehydes (R^1, R^2 = alkyl), S. Julia et al. showed that the initial addition is nonreversible and that subsequent steps are stereospecific, elimination occurring exclusively by a concerted antiperiplanar elimination (i.e. from *transoid* **5**).[5] The low selectivity observed in these cases is thus a direct consequence of the poor diastereocontrol in the initial addition step of sulfone anion **2** onto aldehyde **1**.

For aromatic aldehydes (R^2 = Ar), the situation is different: elimination from **3** is not stereospecific.[5,6] In order to account for this nonstereospecificity of the elimination and the observed high *E* selectivity, Julia et al. suggested that in these cases elimination occurs by a direct loss of benzothiazolonate from intermediates **5** to yield a zwitterion such as **6**.[5c] Stabilization of **6** by the aryl group should allow conformational equilibration and favor formation of the (*E*)-olefin upon loss of SO_2 from the more stable *anti* zwitterion **6**.

Results and Discussion

In our calculations[7–9] on the reaction of benzaldehyde with lithiated ethyl- and benzyl-BT-sulfones (**2a** and **2b**), we find a slightly exothermic addition step to form alkoxides **3** (Figure 2). For the *syn* alkoxide (*syn*-**3**), the free energy barrier to Smiles rearrangement[10,11] is computed to be lower than that for addition, thus predicting a nonreversible addition in both cases (R^1 = Me or Ph).[12] In the case of the *anti* isomer, unfavorable 1,2 steric interactions in **TS-Smiles** (Smiles transition state) lead to an increase of the barrier to Smiles rearrangement.[13] This has the result that addition of benzyl-BT-sulfone **2b** (R^1 = Ph) becomes reversible. These predictions could be confirmed by crossover ex-

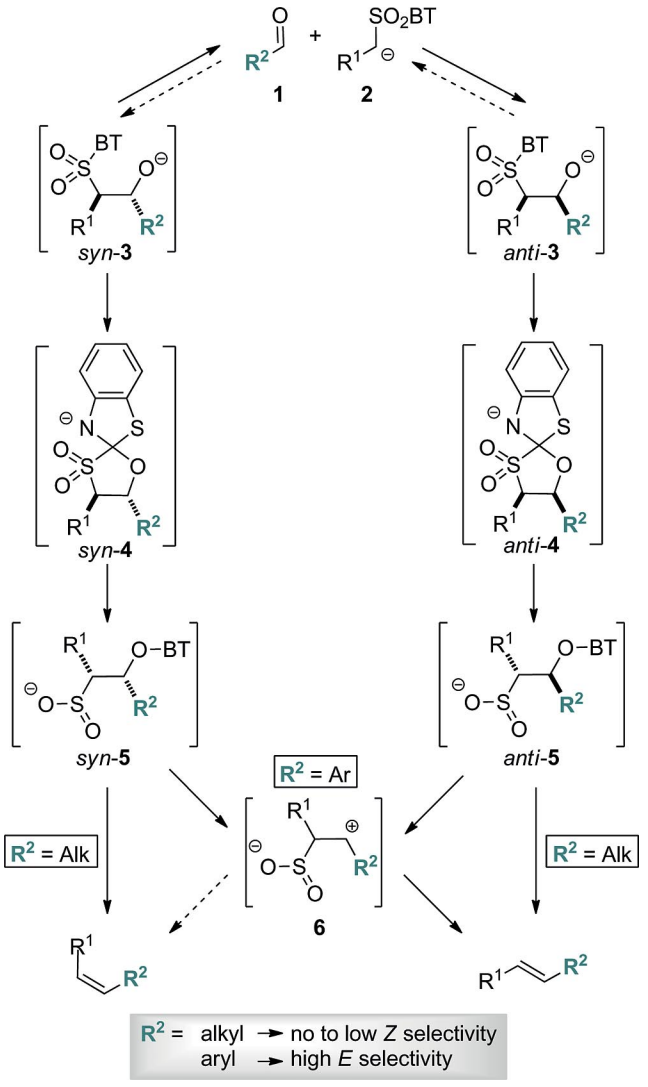


Figure 1. Generally accepted mechanism and selectivity in the modified Julia reaction.

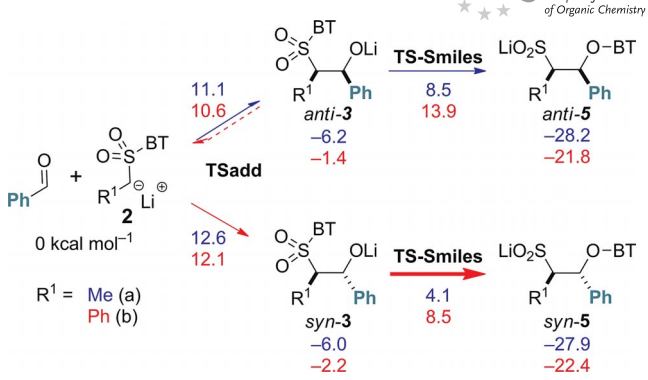
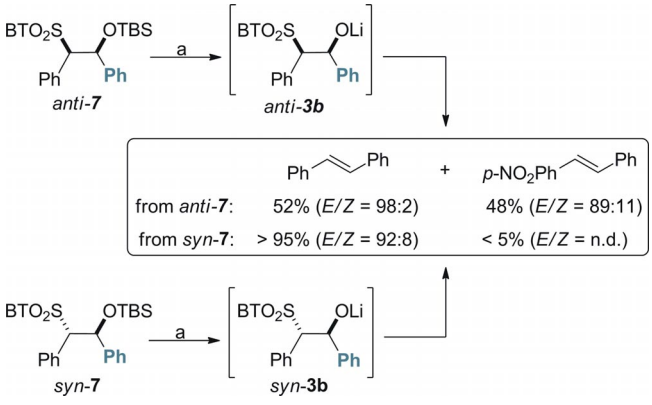


Figure 2. Computed pathways for the formation of sulfinate **5** (free energies in kcal mol^{-1} relative to reactants).



Scheme 1. Crossover experiments. Reagents and conditions: (a) TBAF (2 equiv.), LiCl (5 equiv.), *p*-$NO_2C_6H_4CHO$ (1.1 equiv.), THF, –78 °C.

periments in which the two diastereomeric β-alkoxy-BT-sulfones **3b** (R^1 = R^2 = Ph) were independently generated by another route in the presence of a more reactive aldehyde (Scheme 1).[6] Indeed, deprotection of *anti*-**7** and *syn*-**7** in the presence of *p*-$NO_2C_6H_4CHO$ gave 48% and <5% of the olefin, respectively, in which the more reactive aldehyde had been incorporated, proving the (at least partial) reversibility of the alkoxide formation in the former case and the nonreversible character of the *syn* addition.

As a consequence, sulfinate adducts **5** should be formed with a low *anti* selectivity in the case of ethyl-BT-sulfone (**2a**), addition being nonreversible and poorly selective.[6] On the other hand, for benzyl-BT-sulfone (**2b**) the observed reversibility of *anti* addition should yield predominantly *syn* sulfinate **5**.[14]

Accordingly, if the elimination step were stereospecific via an antiperiplanar arrangement as in the reaction of aliphatic aldehydes,[1,5] our calculations would predict an *E* selectivity for the reaction of ethyl-BT-sulfone (**2a**) and a preference for (*Z*)-alkene formation for the reaction of benzyl-BT-sulfone (**2b**). Experimentally, a high *E* selectivity (> 96:4) is observed in both cases.[1] Indeed, as postulated by Julia and shown by our crossover experiments (see *E*/*Z* selectivity for stylbene formation in Scheme 1),[6] both diastereomeric pathways lead, in fact, to (*E*)-alkene.

In order to identify the mechanism of formation of (*E*)-alkene from sulfinate **5**, we thus investigated the formation of zwitterion **6** as proposed by Julia et al.[5c] Every attempt to optimize such an intermediate, or a carbanion resulting from the loss of SO_2, failed, our results favoring a concerted elimination instead.[15]

However, while our calculations indicate that *anti* isomers should undergo antiperiplanar elimination to give (*E*)-olefins, *syn* isomers are actually predicted to preferentially eliminate from *cisoid syn*-**5** by a concerted synperiplanar elimination, thus leading also to (*E*)-alkenes (Figures 3 and 4).[12]

In order to provide experimental evidence for this concerted elimination from *cisoid syn*-**5** (synperiplanar elimination) in the reaction of aromatic aldehydes, we performed deuterium-labeled experiments. We reasoned that if we could form stereoselectively monodeuterated **5**-***d***, in which 1,2 steric strain is absent, we would get information on the

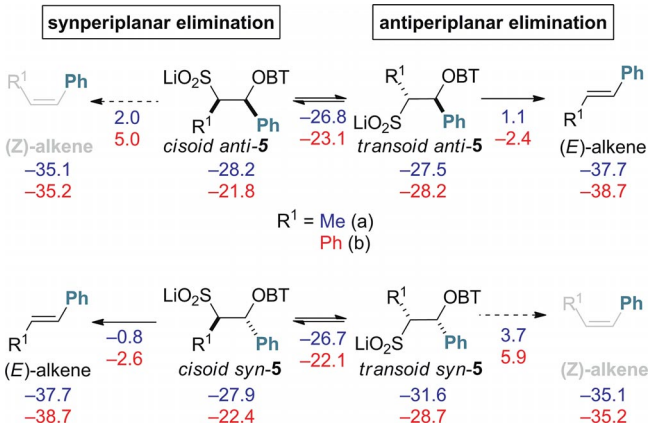


Figure 3. Computed pathways for alkene formation from **5** (free energies in kcal mol^{-1} relative to reactants).

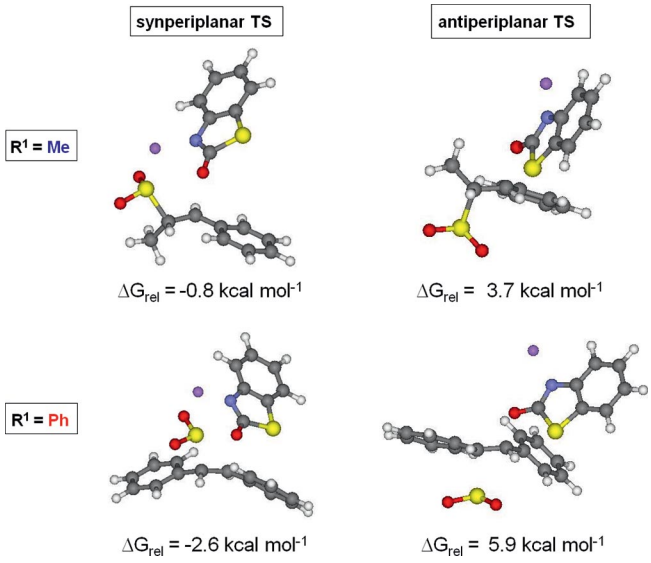


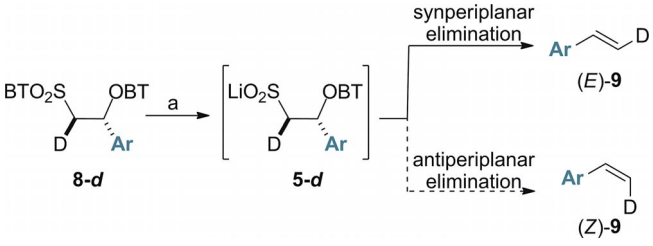
Figure 4. Transition state structures for the elimination step from *syn*-**5a** (top) and *syn*-**5b** (bottom) (free energies in kcal mol^{-1} relative to reactants).

mechanism of the elimination (Table 1). Indeed, if elimination from **5-*d*** involves formation of a carbocation such as **6**, an approximately 50:50 mixture of (*E*)- and (*Z*)-styrene-(β)-*d* would be obtained, whereas if elimination occurs selectively by a concerted mechanism, only one isomer would be formed: the (*E*)-alkene if elimination is synperiplanar and the (*Z*)-alkene if it is antiperiplanar. Addition of EtSLi onto **8-*d*** [6,16] at –78 °C allowed clean formation of sulfinates **5-*d***, which immediately undergo elimination to provide the corresponding deuterated styrenes.[17] In each case, selective (*E*)-alkene formation was observed. These results thus give support to the concerted synperiplanar elimination mechanism.

Analysis of elimination TSs for the reaction of **2a** and **2b** shows that an important factor contributing to this unexpected preference for synperiplanar elimination from *syn*-**5** is the destabilizing 1,2 steric strain present in the antiperiplanar TS (but absent in the synperiplanar one). This interaction also explains the fact that, in the case of *anti*-**5** isomer, it is the antiperiplanar elimination which is favored (see Figure 3). Indeed, in this case it is the synperiplanar TS which involves this unfavorable 1,2 steric interaction. Another difference between the two transition state structures is the degree of coordination to the lithium cation: the synperiplanar TS involves coordination of lithium by both the sulfinate and the BT groups, whereas the antiperiplanar arrangement allows coordination only by the BT group (see Figure 4).[18]

This leaves, however, the question of why *syn*-**5** undergoes synperiplanar elimination in the reaction of aromatic aldehydes while exclusive antiperiplanar elimination is observed in the reaction of alkyl aldehydes.[5] Calculations on model systems reveal that the presence of the phenyl group also plays an important role in the electronic stabilization of the synperiplanar TS: Substitution by a phenyl group leads to a higher stabilization (by 2.8 kcal mol^{-1}) of the synperiplanar TS than the antiperiplanar one (Table 2). A natural bond orbital (NBO) analysis shows that the key interaction responsible for this activation is an electronic donation from the π system of the phenyl to the positively charged aldehyde carbon atom of the TS. Corresponding *E*(2) values are 58.4 and 52.8 kcal mol^{-1} for syn- and antiperiplanar TSs, respectively,

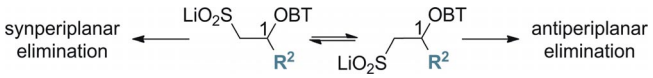
Table 1. Deuteration experiments.[a]



Entry	Ar	Olefin	Yield [%][b]	*E*/*Z*[c,d]
1	*p*-ClC$_6$H$_4$	**9a**	89	81:19
2	C$_6$H$_5$	**9b**	92	90:10
3	*p*-MeOC$_4$H$_6$	**9c**	87	94:6

[a] Reaction conditions: EtSH (1.2 equiv.), LiHMDS (1.1 equiv.) THF, –78 °C (2 h) to room temp. (6 h). [b] Refers to the pure isolated compound. [c] Based on the crude ^{1}H NMR spectra. [d] Mean of three independent experiments.

Table 2. Influence of the nature of the aldehyde (R^2) on the stereoselectivity of the elimination (free activation energies in kcal mol^{-1} from *transoid* sulfinates).



	TS synperiplanar			TS antiperiplanar		
R^2	ΔG_{rel}	d_{C-O}[a]	Charge on C(1)[b]	ΔG_{rel}	s_{C-O}[a]	Charge on C(1)[b]
H	30.5	2.07	0.329	30.9	2.00	0.241
Me	32.1	2.16	0.347	33.8	2.00	0.302
Ph	25.9	1.98	0.354	29.1	1.96	0.323

[a] C(1)–O distances (in Å) in the TS. [b] NPA (natural population analysis) charges (in a. u.) in TS.

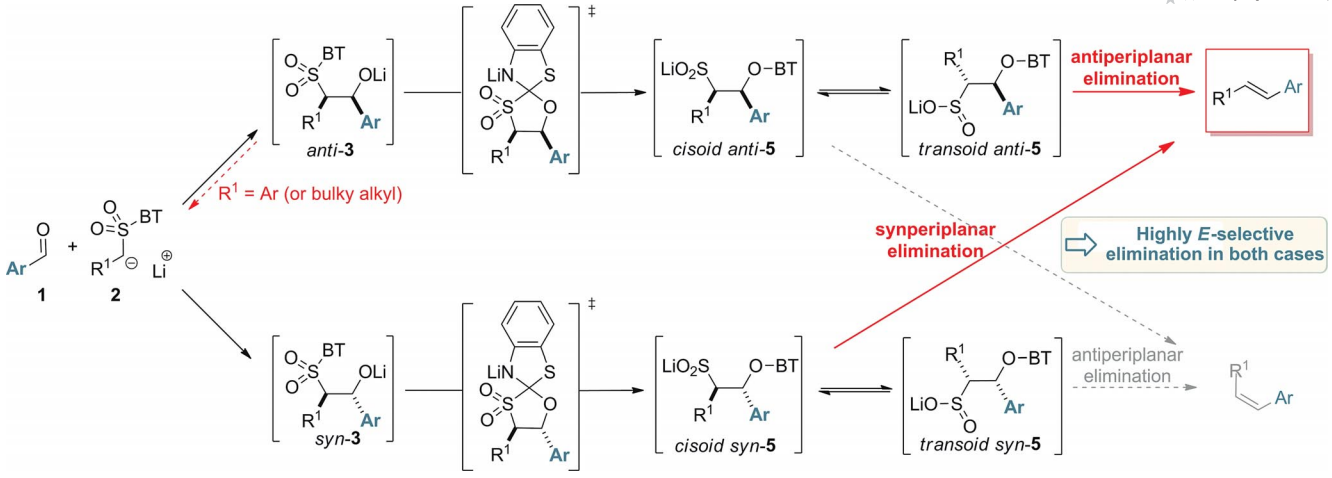


Figure 5. Rationale for observed high *E* selectivity in modified Julia olefination of aromatic aldehydes.

consistent with a higher stabilization in the former case, probably because of the slightly more positively charged C(1) carbon atom in the synperiplanar TSs (see Table 2).

Interestingly, the higher stabilization of the synperiplanar TS by electronic donation from the aryl group suggests an explanation for the fact that electron-poor aldehydes give lower *E* selectivities than electron-rich ones:[5c] Electron-poor aryl groups stabilize elimination TSs to a lesser extent, thus decreasing the preference for synperiplanar elimination, and hence they lower the *E*/*Z* selectivity. This is supported by the decrease of the *E*/*Z* ratio upon going from *p*-methoxy- to *p*-chloro-substituted aryl derivatives in our crossover experiments (see Table 1).

Conclusions

In summary, we have clarified the mechanism of elimination in modified Julia reactions of aromatic aldehydes and showed that elimination occurs through a concerted antiperiplanar and synperiplanar mechanism in the case of *anti*- and *syn*-sulfinate, respectively. The high experimental *E* selectivity is thus explained by *E*-selective elimination, from both the *syn* and the *anti* diastereomer (Figure 5). Identification of synperiplanar elimination as the main pathway for elimination from *syn*-sulfinate and understanding of factors controlling the stereoselectivity of elimination now allow us to rationalize some key experimental observations relating to modified Julia olefination of aromatic aldehydes and lithiated BT-sulfones. This analysis should assist in the design of new reagents and reaction conditions and allow further development of the modified Julia reaction process for highly *E*/*Z*-selective synthesis of alkenes.

Supporting Information (see footnote on the first page of this article): Full computational and experimental details including procedures and characterization data for all compounds and optimized Cartesian coordinates of all optimized structures.

Acknowledgments

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[1] For reviews, see: a) I. E. Markó, J. Pospíšil in *Science of Synthesis*, vol. 47b (Ed.: A. de Meijere), Thieme, Stuttgart, New York, **2010**, pp. 105–160; b) C. Aïssa, *Eur. J. Org. Chem.* **2009**, 1831–1844; c) K. Plesniak, A. Zarecki, J. Wicha, *Top. Curr. Chem.* **2007**, *275*, 163–250; d) R. Dumeunier, I. E. Markó in *Modern Carbonyl Olefination* (Ed.: T. Takeda), Wiley-VCH, Weinheim, **2004**, pp. 104–150; e) P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.

[2] Several heteroaryl substrates have been developed for this process and the nature of the heteroaryl group has shown to have, in some cases, an influence on the *E*/*Z* selectivity (see ref.[1]). BT-sulfones being the original, and still most popular, substrates in modified Julia reaction, the present study will focus on such systems.

[3] The modified Julia olefination is commonly used in total syntheses of natural and unnatural biologically active molecules. For selected examples, see ref.[1d] and a) R. Cribiú, C. Jäger, C. Nevado, *Angew. Chem.* **2009**, *121*, 8938–8941; *Angew. Chem. Int. Ed.* **2009**, *48*, 8780–8783; b) K. Sastraruji, T. Sastraruji, S. G. Pyne, A. T. Ung, A. Jatisatienr, W. Lie, *J. Nat. Prod.* **2010**, *73*, 935–941; c) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064–14066; d) J. Santos, B. M. Illescas, N. Martín, J. Adrio, J. C. Carretero, R. Viruela, E. Ortí, F. Spänig, D. M. Guldi, *Chem. Eur. J.* **2011**, *17*, 2957–2964; e) C. Rink, F. Sasse, A. Zubriene, D. Matulis, M. E. Maier, *Chem. Eur. J.* **2010**, *16*, 14469–14478; f) P. Gowrisankar, S. A. Pujari, K. P. Kaliappan, *Chem. Eur. J.* **2010**, *16*, 5858–5862.

[4] Despite numerous experimental studies, no general solution to the control of this *E*/*Z* selectivity could be found thus far. See: a) F. Billard, R. Robiette, J. Pospíšil, *J. Org. Chem.* **2012**, *77*, 6358–6364; b) J. Pospíšil, *Tetrahedron Lett.* **2011**, *52*, 2348–2352; c) S. Surprenant, W. Y. Chan, C. Berthelette, *Org. Lett.* **2003**, *5*, 4851–4854; d) P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26–28; e) A. B. Charette, H. Lebel, *J. Am. Chem. Soc.* **1996**, *118*, 10327–10328.

[5] a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175–1178; b) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 336–357; c) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* **1993**, *130*, 856–878.

[6] See Supporting Information for full details and complementary experiments.

[7] Calculations were carried out at the SCS-MP2/aug-cc-pVTZ(THF)//B3LYP/6–31+G*(THF) level of theory with the Jaguar 6.5[8] and ORCA 2.7[9] programs. Unless mentioned otherwise, reported energies are free energies relative to reactants. Since the nature of the counterion has a small influence on the *E*/*Z* selectivity (see ref.[4]), a lithium cation was included in all our calculations, LDA being the most common base used in these reactions. See Supporting Information for full computational details.

[8] *Jaguar*, version 6.5, Schrödinger, LLC, New York, NY, **2005**.

[9] F. Neese, ORCA, *An Ab Initio, DFT, and Semiempirical Electronic Structure Package*, version, 2.7.0, University of Bonn, Germany, **2010**.

[10] Interestingly, our results indicate that, conversely to what is commonly admitted, transfer of the heterocycle occurs by a concerted pathway, i.e., in a single elementary step (see the Supporting Information for full details). For a study on single-step and multistep mechanisms of aromatic nucleophilic substitution, see: M. N. Glukhovstev, R. D. Bach, S. Laiter, *J. Org. Chem.* **1997**, *62*, 4036–4046.

[11] For a review on Smiles rearrangement, see W. E. Truce, E. M. Kreiber, W. W. Brand in *Organic Reactions*, vol. 18, John Wiley & Sons, New York, **1970**, p. 99.

[12] The barrier to rotation (between *cisoid* and *transoid* conformers) in alkoxides and sulfinates indicates, in both cases, a rapid equilibrium that has no important role in determining reactivity or selectivity. See the Supporting Information for full data.

[13] This is in good agreement with experiments, which showed a higher stability of *anti*-β-alkoxy-BT-sulfones over their *syn* isomers (see ref.[5b]).

[14] One may expect sterically hindered alkyl-BT-sulfones to involve increased barriers to Smiles rearrangement for *anti* isomers, which in turn could lead to a reversal of addition. In these cases, a *syn* selectivity for sulfinate formation may thus well be observed.

[15] Additionally, during our experimental study of this reaction, no direct or indirect evidence for cation formation was observed.

[16] See the Supporting Information for the synthesis of **8-*d***.

[17] Control experiments showed that compound **5-*d*** does not reverse back to benzaldehyde and lithiated sulfone. We have also checked that no isotopic scrambling was occurring. See the Supporting Information for details.

[18] See Supporting Information for a detailed discussion of lithium cation positioning.

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Authors: Jiri Pospisil, Daniela Konrádová, Karel Doležal, and Hana Kozubíková

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FULL PAPER

Microwave-assisted synthesis of phenylpropanoids and coumarins: total synthesis of Osthol

Daniela Konrádová[a],†, Hana Kozubíková[b],†, Karel Doležal[a,b], and Jiří Pospíšil*[a,b]

Dedicated to professor Milan Potáček on the occasion of his upcoming 75th birthday anniversary.

Abstract: Herein we describe a one-pot microwave-assisted synthesis of cinnamic acid derivatives and coumarins. The synthesis starts from an aldehyde synthon and the choice of the product, coumarin or cinnamic acid derivative, is determined by the reaction conditions. A regioselective Claisen rearrangement can be also efficiently incorporated into the synthetic sequence to further increase the rapid product complexity. Of note, (1) no phenol protecting group is required. (2) high yields and selectivity are achieved.

Introduction

Phenylpropanoids are plant secondary metabolites biosynthesized within the Shikimate biosynthetic pathway.[1] The phenylpropanoid skeletal core is then further modified within the plant cells to furnish many structurally diverse secondary plant metabolites – natural products – with interesting biological properties. As a consequence, phenylpropanoid subunits are presented within the plants in the form of polyhydroxy monomers (e.g. cinnamic acid derivatives, monolignols, coumarins), dimers[2] (e.g. lignans, neolignans, flavonoids), and polymers[1d] (lignin) (Figure 1). Such secondary metabolites serve the plant in many ways as e.g. protection from UV light, defense against herbivores and pathogens, or mediators of plant-pollinator interactions (floral pigments and scent compounds).

Our interest is to understand the oxidation processes[3] related to phenolic plant secondary metabolites on a molecular level, and to describe the effect of these oxidized compounds on human health, leading us to immerge into the world of plant produced phenolic compounds.[4] However, the plant metabolome contains thousands of structurally diverse secondary metabolites, thus the identification of phenols of interest is far from being simple. The identification of phenolic derivatives possibly active in the oxidation processes in plants on molecular level has become our primary goal. To address the challenge, we have decided to develop a short and versatile protecting group-free synthetic approach that would allow us to prepare phenylpropanoids (mainly cinnamic acid derivatives) and polyfunctionalized coumarins in a short and efficient manner. [13-16]

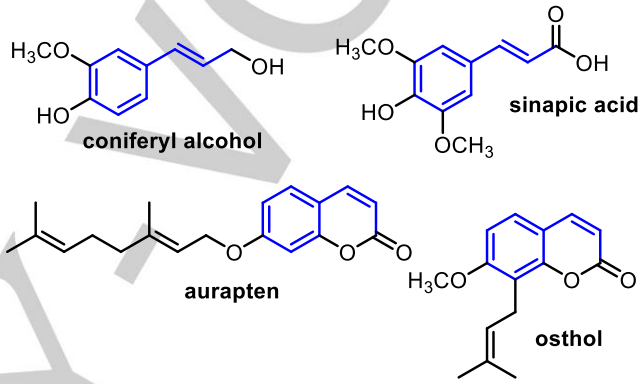

Figure 1. Examples of phenylpropanoids and coumarins.

The synthesis of cinnamic acid derivatives and coumarins was previously intensively studied.[1c,3e,6] Unfortunately, to the best of our knowledge, there is no general approach that would allow us to efficiently prepare either cinnamic acid derivatives or coumarins starting from the same building block (Scheme 1). In this article we report our synthetic approach to both classes of the targeted structures, cinnamic acid derivatives and coumarins, starting from commercially available aromatic aldehydes with use of the microwave promoted Wittig reaction of stabilized ylides. This efficient and protecting group-free method is then applied to the synthesis of several natural products and their derivatives.

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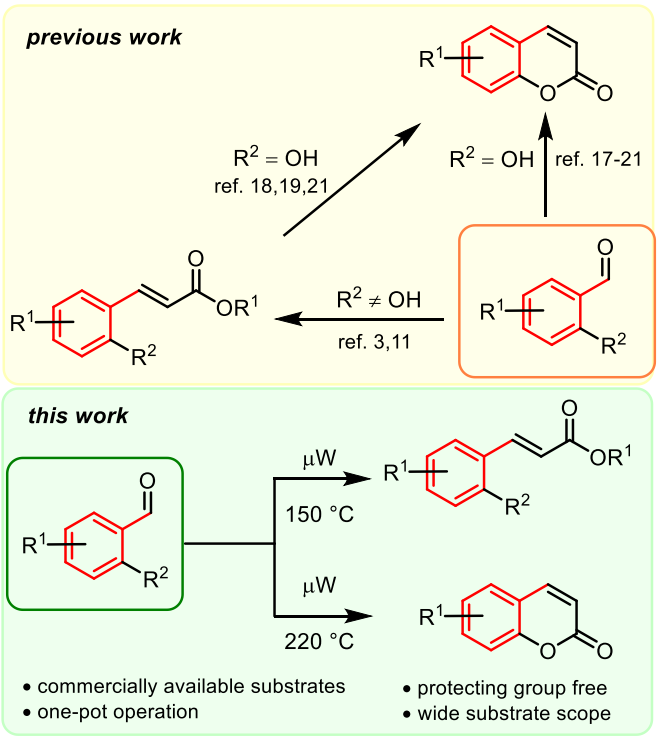


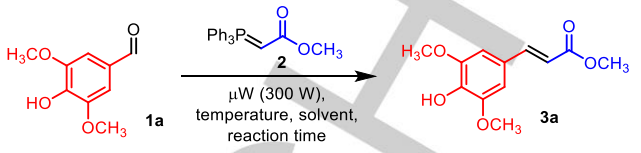
Scheme 1. Synthetic routes to phenylpropanoids and coumarins.

Results and Discussion

Our first goal was to find out if our approach was feasible. Thus the reaction of the aldehyde **1a**[7] with stabilized Wittig ylide **2**[8] was attempted (Table 1). Based on our previous experience with the cycloaddition reactions initiated by microwave irradiation[9] and by literature[10], the reaction between aldehyde **1a** and ylide **2** were performed under solvent-free conditions (Table 1, entries 1 and 2) or in THF and EtOAc, respectively (entries 3 and 4). Unfortunately, the desired product **3a** was obtained in low yields. At this stage it was expected that the employed reaction conditions could cause the degradation of starting materials or formed product, and that the degradation might have been caused by the presence of the phenolic hydroxy group.[11] To avoid additional protecting/deprotecting steps, we decided to perform the reaction of unprotected aldehyde **1a** and ylide **2** in toluene (entries 5-13). The argument behind this was that a small solubility of starting materials **1a** and **2** in toluene might avoid most of the undesired side reactions, and still allow us to perform the olefination reaction in good yield and *E/Z* selectivity. And indeed, after some reaction condition optimization (entries 5 to 13), the desired product **3a** was obtained in 95 % yield and >95:5 *E/Z* selectivity (entry 9).

Optimized reaction conditions were then extended to other aromatic aldehydes **1a-o** (Table 2, entries 1-15) and ketones **1p-s** (entries 16-19). In all cases, and regardless of the steric or electronic properties of the aldehyde or ketone, the desired cinnamoyl ester derivatives **3** were formed in good to excellent yields and *E/Z* selectivity.

Table 1. Optimization of the reaction conditions[a].



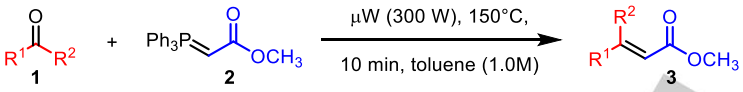
Entry	Conditions	Yield[b] (%)	E/Z[c]
1[d]	Solvent-free, 150 °C, 30 min	degradation	-
2[d]	Solvent-free, 100 °C, 30 min	degradation	-
3[e]	THF (0.1 M), 100 °C, 60 min	20	91:9
4[e]	EtOAc (0.1 M), 100 °C, 60 min	6	85:15
5	toluene (0.1 M), 100 °C, 60 min	35	>95:1
6	toluene (0.1 M), 150 °C, 60 min	42	>95:1
7[f]	toluene (0.1 M), 150 °C, 60 min	85	>95:1
8[f]	toluene (0.1 M), 150 °C, 10 min	40	>95:1
9	toluene (1.0 M), 150 °C, 10 min	95	>95:1
10	toluene (1.0 M), 110 °C, 10 min	85	>95:1
11	toluene (1.0 M), 150 °C, 6 min	94	>95:1
12	toluene (1.0 M), 170 °C, 10 min	78	>95:1
13	toluene (2.0 M), 150 °C, 10 min	73	>95:1

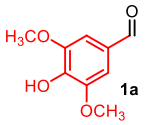
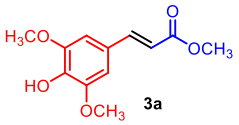
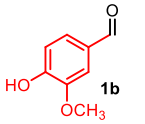
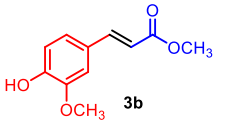
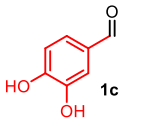
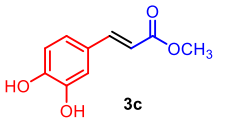
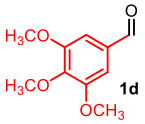
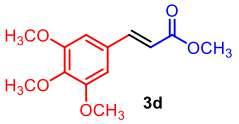
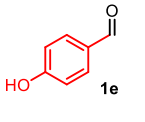
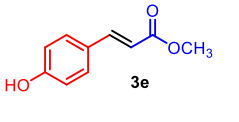
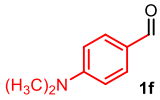
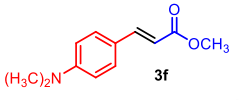
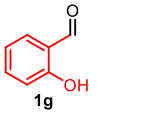
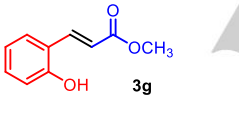
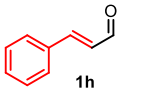
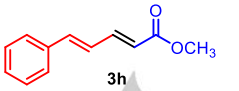
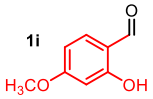
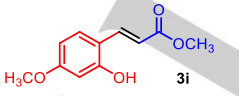
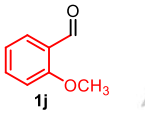
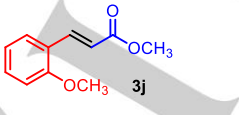
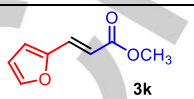
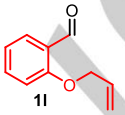
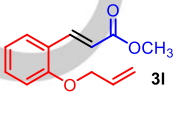
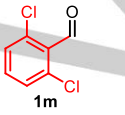
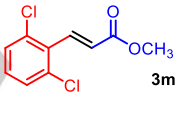
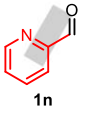
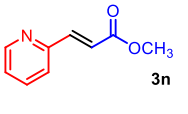
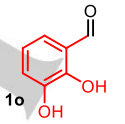
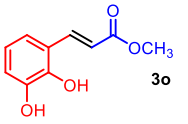
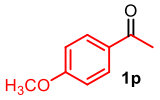
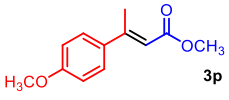
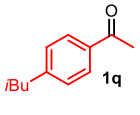
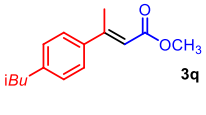
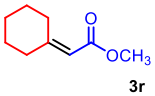
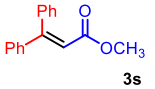
[a] Reaction conditions: **1a** (2.75 mmol) and **2** (3.0 mmol) were dissolved/suspended in appropriate solvent and placed in a microwave vessel for the indicated reaction time. [b] Isolated reaction yields. [c] Based on ^{1}H NMR spectra of the crude reaction mixture. [d] Inspired by ref. 26. [e] Inspired by ref. 25. [f] **2** (6.0 mmol) was used.

Interestingly, when 2-hydroxy aldehydes **1g,i,o** were used, no product of the thermally driven intramolecular lactonization, coumarins (see later), were detected (entries 7, 9 and 15).[12] Similarly, no product of Claisen rearrangement[13] was observed under the studied reaction conditions when aldehyde **1l** was used as a starting material (entry 12).

Having an easy access to cinnamic acid derivatives **3** we have turned our attention to the synthesis of monolignols **5a-c** and monolignol aldehydes **6a-c** (Scheme 2). The desired allylic alcohols **5a-c** were prepared via DIBAL-H mediated reduction of the corresponding esters **3**. DDQ mediated[14] oxidation of allylic alcohols **5a-c** then yielded the desired aldehydes **6a-c** in very good yields. Again, no phenol protecting group was used within the reaction sequence.

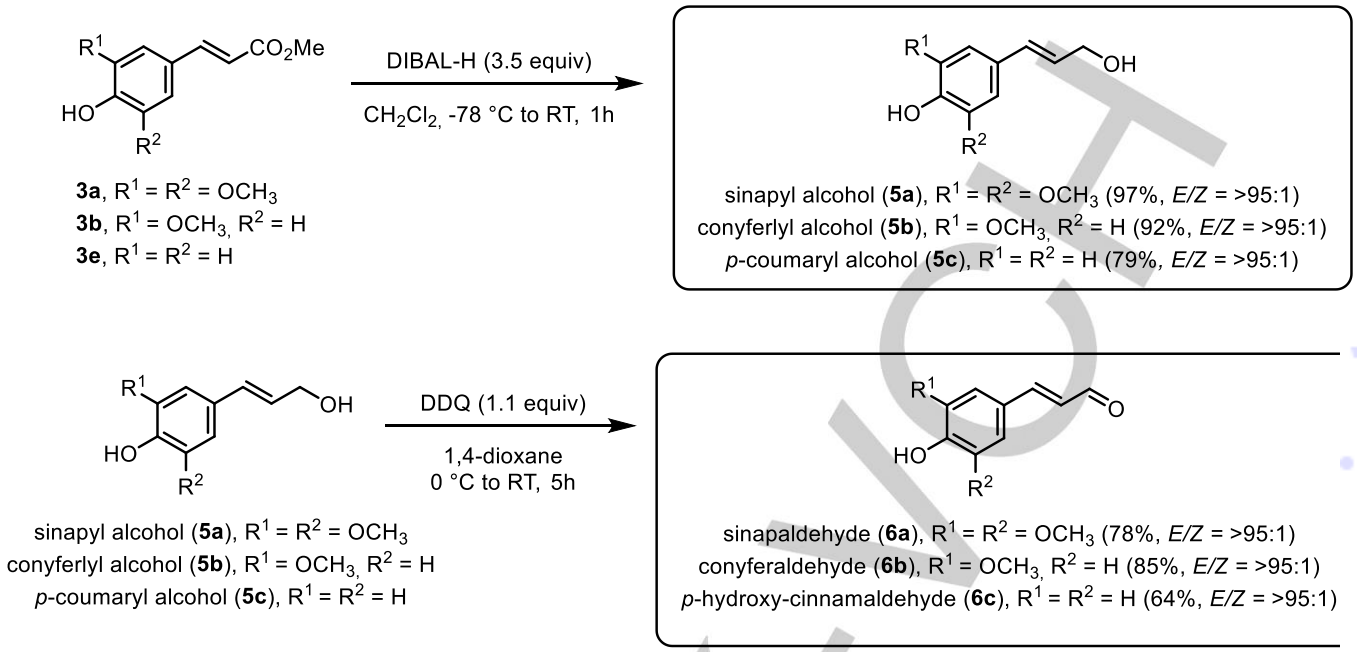
Table 2. Scope of microwave irradiation promoted cinnamic acid derivatives synthesis[a]



Entry	Aldehyde or ketone (**1**)	Product (**3**)	Yield[b] (%)	E/Z[c]
1			95	>95:1
2			98	>95:1
3			92	>95:1
4			98	>95:1
5			97	>95:1
6			94	92:8
7			82	92:8
8			95	90:10
9			89	>95:1
10			91	81:19
11			84	92:8
12			95	92:8
13			98	>95
14			92	>95
15			94	>95
16			76	80:2
17			78	82:1
18			75	-
19			62	-

[a] Reaction conditions: **1** (5.0 mmol) and **2** (5.5 mmol) were placed in a microwave reaction vessel and toluene (1.0M, 5.0 mL) was added. The reactic vessel was sealed with an aluminum/Teflon®crimp top and placed into the microwave reactor. The reaction was carried out at 150 °C (fixed reactic temperature) for 10 min. [b] Isolated reaction yields. [c] Based on ^{1}H NMR spectra of crude reaction mixture.

Having secured the synthesis of phenylpropanoid derivatives **3**, **5** and **6**, our attention turned to coumarins **4**. It is known from the literature[6a] that the thermally initiated *E/Z*-isomerization of ester **3g** can lead to the formation of the corresponding coumarin **4a**. Based on these observations, a one-pot synthesis of coumarin **4a** starting from aldehyde **1g** was attempted (Table 3).



Scheme 1. Monolignol and monolignal synthesis.

As a starting point of the transformation, prolonged reaction conditions used in the case of cinnamic acid ester **3g** synthesis were employed (Table 3, entry 1). Only traces of the desired product **4a** were obtained. However, gradual increase of the reaction temperatures (entries 2 to 6) and variation in the reaction time (entries 7 to 11) helped to identify suitable reaction conditions (entry 9). These conditions were then applied to some other 2-hydroxy benzaldehyde derivatives (**1i**,**o**,**s** and **t**) and even in these cases the desired coumarins **4b-e** were formed in good yields (Table 4).

Additionally, we have explored the incorporation of Claisen rearrangement into the coumarin synthetic sequence (Scheme 3). The idea behind this was, with help of 2-hydroxy group, to incorporate regioselectively an allylic sidechain into the newly created coumarin skeleton. It was expected that under the reaction conditions suitable for the coumarin formation, *O*-allyl salicyl aldehyde **1l** would undergo a Claisen rearrangement. The rearrangement step would selectively incorporate the allylic chain α to the hydroxy group (Scheme **3**). Rearranged intermediate **7** would yield *in situ* 2-hydroxy cinnamic acid derivative **8** that could further undergo isomerization/cyclization transformations and yield the desired coumarin ring subunit **9**. (A study with similar idea behind was recently independently published by Schmidt and Riemer[15]) In this sequence, three new C-C bonds along with one C-O bond should be formed stereoselectively in a *one-pot* protocol. Gratifyingly, the reaction proceeded as planned and the desired product **9** was formed in 85 % yield.[16]

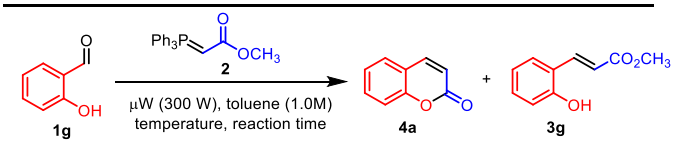
To demonstrate the synthetic utility and versatility of the above developed synthetic methods, *O*-prenylated coumarin **10**, a potent 15-lipoxygenase inhibitor,[17] was prepared in two steps and 51 % overall yield from aldehyde **1t** (Scheme 4a). Similarly, osthol **13**, calcium channel blocker,[18] was prepared starting from 2-hydroxy aldehyde **1i** in a two-pot protocol (3 steps, one purification step) and in 78 % overall yield.

Conclusions

In conclusion we have described short and efficient protecting group free microwave-assisted synthesis of cinnamic acid derivatives and coumarins. The targeted compounds are prepared in good yields and, in the case of cinnamic acid derivatives, excellent *E/Z* selectivity. These prepared compounds are, or can be transformed in 1 to 2 steps into the key members of cinnamate/monolignol biosynthetic pathway[19] and various coumarin core-containing natural products. In the case of coumarin derivatives, the method was further extended by incorporation of Claisen rearrangement step. This extension allowed us additional selective incorporation of allylic side chains to the coumarin core structure during the coumarin synthesis. Efficacy of the protocol was demonstrated by two-pot synthesis of osthol natural product.

The application of these developed methods on an understanding of the oxidation processes of plant phenolics on a molecular level, and on the development of new drug candidates with antileishmanial activity, is now in progress and will be reported in the near future.

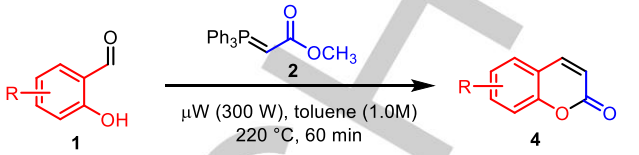
Table 3 Optimization of coumarin **4a** reaction conditions[a]

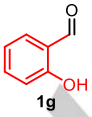
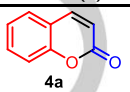
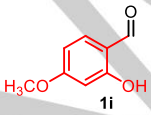
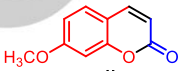
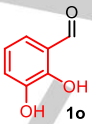
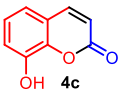
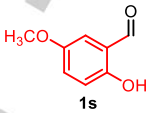
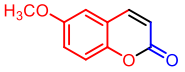
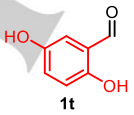
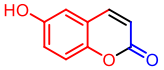
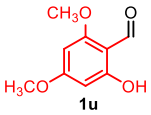
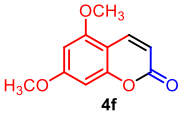


Entry	Conditions	**4a**[b] (%)	**3g**[b] (%)
1	150 °C, 30 min	-[c]	94
2	175 °C, 30 min	21	67
3	185 °C, 30 min	36	52
4	210 °C, 30 min	68	12
5	220 °C, 30 min	72	5
6	230 °C, 30 min	54	-[c]
7	210 °C, 60 min	78	-[c]
8	220 °C, 45 min	83	-[c]
9	220 °C, 60 min	88	-[c]
10	220 °C, 75 min	83	-[c]
11[d]	220 °C, 60 min	89	-[c]

[a] Reaction conditions: **1a** (2.75 mmol) and **2** (3.0 mmol) were suspended in toluene (1.0M, 2.75 mL) and placed into a microwave vessel for the indicated reaction time. [b] Isolated reaction yields. [c] Traces (<5%) in ^{1}H NMR spectra of the crude reaction mixture. [d] Reaction carried out with 2 g of aldehyde **1g**.

Table 4 Coumarin **4** synthesis[a]



Entry	Aldehyde (**1**)	Product (**4**)	Yield[b] (%)
1	 **1g**	 **4a**	89
2	 **1i**	 **4b**	86
3	 **1o**	 **4c**	72
4	 **1s**	 **4d**	78
5	 **1t**	 **4e**	68
6	 **1u**	 **4f**	74

[a] Reaction conditions: **1** (5.0 mmol) and **2** (5.5 mmol) were placed into a microwave reaction vessel and toluene (1.0M, 5.0 mL) was added. The reaction vessel was sealed with an Silicone/PTFE Vial caps top and placed into a microwave reactor. The reaction was carried out at 150 °C (fixed reaction temperature) for 10 min. [b] Isolated reaction yields.

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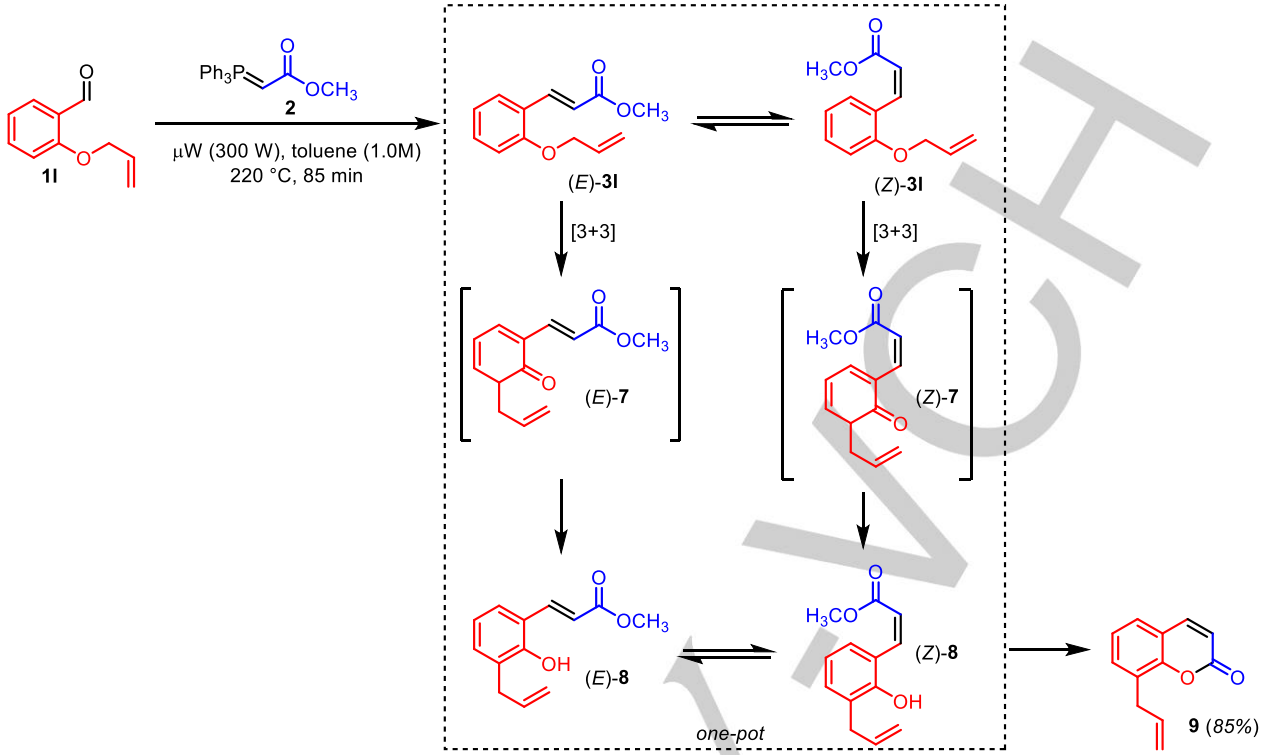
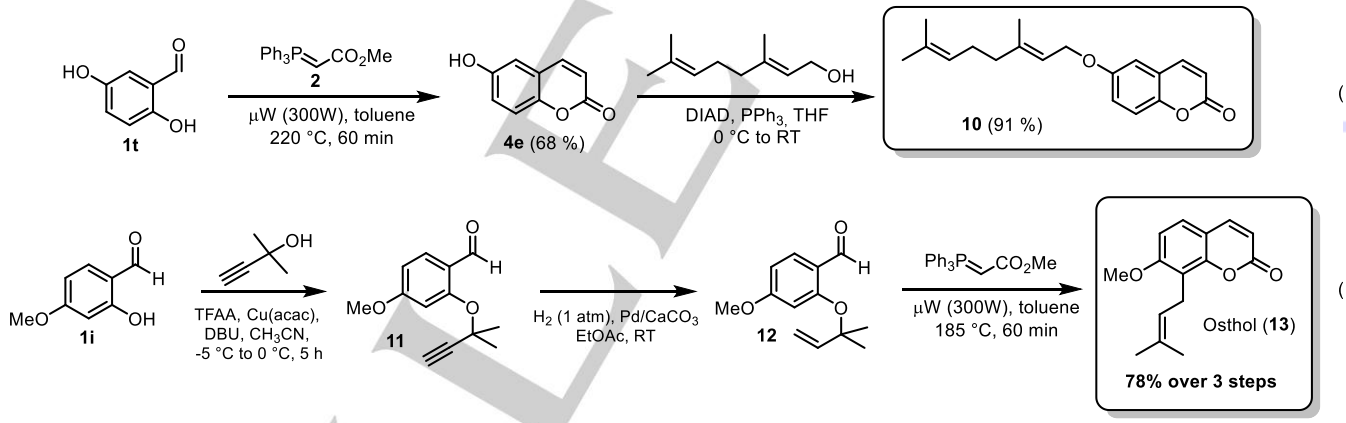


Scheme 2. Reaction sequence of Wittig olefination/Claisen rearrangement/olefin isomerization/cyclization steps yielding coumarin **9**.



Scheme 3. Application of developed methodology to selected natural product synthesis.

Experimental Section

All starting materials were used as received from commercial sources without further purification. The Wittig reagent **2** was prepared from the corresponding methyl 2-bromoacetate according to the published procedure. All reactions were carried out using the standard laboratory techniques. Column chromatography was performed on silica gel 60 (40-63 μm). Melting points were determined on a Büchi melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 and 125 MHz, respectively in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) of ^{1}H 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), and multiplet (m). HRMS data were obtained using quadrupole/ion trap mass analyser. Analysis and assignments were made by comparison with literature spectroscopic data or using 2D-COSY, HSQC, HMBC, 2D-NOESY and NOEdiff experiments.

All 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 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.

General protocol for cinnamic acid derivatives (3) synthesis

A suspension of aldehyde **1** (5.00 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (5.5 mmol, 1.1 equiv) in toluene (5.0 mL, 1.0 M to **1**) was placed in a microwave vial (35 mL) equipped with a magnetic stirring bar. The vial was sealed an Silicone/PTFE Vial cap and placed in a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 10 minutes (fixed time) at 150°C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum.

Methyl (E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylate (3a). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1) yielded resulting ester **3a** (1.13 g, 95%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 15.9 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.29 (d, *J* = 15.9 Hz, 1H), 6.10 (broad s, 1H), 3.91 (s, *J* = 4.6 Hz, 3H), 3.79 (s, 3H);); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.69, 145.28, 145.25, 137.19, 125.93, 115.60, 105.09, 56.40, 51.74; MS (ESI, *m/z*): 239 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{15}O_5^+$) 239.0919, found 239.0920.

Methyl (E)-3-(4-hydroxy-3-methoxyphenyl)acrylate (3b). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1) yielded resulting ester **3b** (1.02 g, 98%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 16.0 Hz, 1H), 7.03 (ddd, *J* = 16.2, 7.9, 1.9 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.27 (d, *J* = 15.9 Hz, 1H), 6.15 – 5.98 (m, 1H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.92, 148.10, 146.89, 145.11, 126.98, 123.13, 115.15, 114.87, 109.48, 56.00, 51.74; MS (ESI, *m/z*): 209 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{13}O_4^+$) 209.0814, found 209.0815.

Methyl (E)-3-(3,4-dihydroxyphenyl)acrylate (3c). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 2:1->1:1->0:100) yielded resulting ester **3c** (893 mg, 92%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J* = 15.9 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.99 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.25 (d, *J* = 15.9 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.05, 147.61, 145.40, 145.09, 121.86, 115.58, 114.37, 51.52; MS (ESI, *m/z*): 195 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_4^+$) 195.0657, found 195.0658.

Methyl (E)-3-(3,4,5-trimethoxyphenyl)acrylate (3d). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3d** (893 mg, 92%) in >95:1 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.60 (d, *J* = 15.9 Hz, 1H), 6.74 (s, 2H), 6.34 (d, *J* = 15.9 Hz, 1H), 3.87 (d, *J* = 4.5 Hz, 9H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.50, 153.51 , 144.99, 140.15, 129.95, 117.03, 105.29, 60.99, 56.14, 51.75; MS (ESI, *m/z*): 253 $[M+H]^+$; HRMS (ESI): calculated (for $C_{13}H_{17}O_5^+$) 253.1076, found 253.1076.

Methyl (E)-3-(4-hydroxyphenyl)acrylate (3e). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3e** (864 mg, 97%) in >95:1 *E/Z* ratio. M.p. = 133-135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.65 (broad s, 1H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.32, 158.01, 144.96, 130.12, 127.14, 116.00, 115.10, 51.85; MS (ESI, *m/z*): 179 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_3^+$) 179.0708, found 179.0702.

Methyl (E)-3-(4-(dimethylamino)phenyl)acrylate (3f). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3f** (1.06 g, 94%) in >95:1 *E/Z* ratio. M.p. = 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.62 (d, *J* = 15.9 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.9 Hz, 1H), 3.77 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.44, 156.23, 145.47, 129.87, 125.42, 121.13, 111.93, 51.45, 40.24; MS (ESI, *m/z*): 206 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{16}NO_2^+$) 206.1181, found 206.1185.

Methyl (E)-3-(2-hydroxyphenyl)acrylate (3g). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3g** (804 mg, 82%) in 92:8 *E/Z* ratio. M.p. = 136-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.26 (s, 1H), 7.83 (d, *J* = 16.2 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.72, 157.31, 140.67, 132.38, 129.43, 121.16, 120.00, 117.35, 116.74, 51.80; MS (ESI, *m/z*): 179 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_3^+$) 179.0708, found 179.0706.

Methyl (2E,4E)-5-phenylpenta-2,4-dienoate (3h). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1->1:1) yielded ester **3h** (883 mg, 95%) in 90:10 *E/Z* ratio. M.p. = 68-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.51 – 7.43 (m, 3H), 7.40 – 7.35 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.95 – 6.84 (m, 2H), 6.01 (d, *J* = 15.4 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.60, 144.97, 140.67, 136.06, 129.20, 128.92, 127.31, 126.28, 120.95, 51.74; MS (ESI, *m/z*): 189 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{13}O_2^+$) 189.0916, found 189.0917.

Methyl (E)-3-(2-hydroxy-4-methoxyphenyl)acrylate (3i). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3i** (1.01 g, 89%) in >95:1 *E/Z* ratio. M.p. = 143-145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.63 (broad s, 1H), 7.92 (d, *J* = 15.9 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 6.55-6.47 (m, 3H), 6.45 (d, *J* = 16.2 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.96, 161.81, 159.62, 137.50, 129.85, 115.93, 114.91, 106.85, 102.35, 55.83, 51.96; MS (ESI, *m/z*): 209 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{12}O_4Na^+$) 231.0633, found 231.0630.

Methyl (E)-3-(2-methoxyphenyl)acrylate (3j). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3j** (962 mg, 91%) in 89:19 *E/Z* ratio. M.p. = 290-294 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 16.2 Hz, 1H), 7.50 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 6.96 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.91 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.06, 158.43, 140.38, 131.62, 129.04, 123.42, 120.80, 118.40, 111.18, 55.50, 51.66; MS (ESI, *m/z*): 193 $[M+H]^+$; HRMS (ESI): calculated (for $C_{11}H_{13}O_3^+$) 193.0865, found 193.0862. ^{1}H NMR characteristic peaks of minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.17 (dd, *J* = 12.4, 0.5 Hz, 1H), 5.97 (d, *J* = 12.5 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H).

Methyl (E)-3-(furan-2-yl)acrylate (3k). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3k** (703 mg, 84%) in 92:8 *E/Z* ratio. M.p. = 27-30 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48 (d, *J* = 1.3 Hz, 1H), 7.44 (d, *J* = 15.7 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.47 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.32 (d, *J* = 15.7

Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.69, 151.03, 144.90, 131.42, 115.62, 115.03, 112.48, 51.90; MS (ESI, *m/z*): 153 $[M+H]^+$; HRMS (ESI): calculated (for $C_8H_9O_3^+$) 153.0552, found 153.0551.

Methyl (E)-3-(2-(allyloxy)phenyl)acrylate (3l). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3l** (1.04 g, 95%) in 92:8 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.06 (d, *J* = 16.2 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 6.98 (td, *J* = 7.4, 0.6 Hz, 1H), 6.92 (dd, *J* = 8.3, 0.6 Hz, 1H), 6.56 (d, *J* = 16.2 Hz, 1H), 6.10 (ddt, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.45 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.33 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.64 (dt, *J* = 5.2, 1.5 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 168.06, 157.39, 156.30, 140.39, 131.55, 131.55, 129.03, 128.98, 118.44, 112. 60, 112.49, 69.26, 51.64; MS (ESI, *m/z*): 219 $[M+H]^+$; HRMS (ESI): calculated (for $C_{13}H_{15}O_3^+$) 219.1021, found 219.1019. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.24 (d, *J* = 12.4 Hz, 1H), 6.00 (d, *J* = 12.5 Hz, 1H), 5.30 (dq, *J* = 10.6, 1.5 Hz, 1H *one of the* =C*H*$_2$), 4.58 (dt, *J* = 5.1, 1.6 Hz, 2H), 3.69 (s, 3H).

Methyl (E)-3-(2,6-dichlorophenyl)acrylate (3m). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1) yielded ester **3m** (1.13 g, 98%) in >95:1 *E/Z* ratio. M.p. = 50-53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 16.4 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 1H), 6.60 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (126 MHz,) δ 166.87, 138.52, 135.17, 132.14, 130.00, 128.93, 126.67, 52.23; MS (ESI, *m/z*): 231 and 233 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_9Cl_2O_2^+$) 230.9980, found 230.9981.

Methyl (E)-3-(pyridin-2-yl)acrylate (3n). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 4:1->2:1->1:1) yielded ester **3n** (750 mg, 92%) in >95:1 *E/Z* ratio. M.p. = 30-32 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.66–8.58 (m, 1H), 7.73 – 7.64 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.30-7.23 (m, 1H), 6.94 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.32, 152.89, 150.12, 143.52, 136.96, 124.44, 124.29, 121.97, 51.89; MS (ESI, *m/z*): 164 $[M+H]^+$; HRMS (ESI): calculated (for $C_9H_{10}NO_2^+$) 164.0712, found 164.0715.

Methyl (E)-3-(2,3-dihydroxyphenyl)acrylate (3o). Residue was purified by column chromatography (SiO_2; CH_2Cl_2:MeOH = 100:1->50:1) yielded ester **3o** (913 mg, 94%) in >95:1 *E/Z* ratio.

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.98 (d, *J* = 16.1 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.89 (s, 1H), 6.74 (t, *J* = 7.9 Hz, 1H), 6.57 (d, *J* = 16.1 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 167.73, 146.43, 146.19, 146.05, 140.90, 121.75, 119.70, 117.43, 117.21, 51.76; MS (ESI, *m/z*): 195 $[M+H]^+$; HRMS (ESI): calculated (for $C_{10}H_{11}O_4^+$) 195.0657, found 195.0660.

Methyl (E)-3-(4-methoxyphenyl)but-2-enoate (3p). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1->2:1) yielded ester **3p** (783 mg, 76%) in 80:20 *E/Z* ratio. M.p. = 50-53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.45 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.11 (d, *J* = 1.0 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 2.56 (d, *J* = 1.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.59, 160.55, 155.37, 134.32, 127.71, 114.81, 113.86, 55.51, 51.21, 17.84; MS (ESI, *m/z*): 207 $[M+H]^+$; HRMS (ESI): calculated (for $C_{12}H_{15}O_3^+$) 207.1021, found 207.1025. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.87 (d, *J* = 1.1 Hz, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 2.16 (d, *J* = 1.2 Hz, 3H).

Methyl (E)-3-(4-isobutylphenyl)but-2-enoate (3q). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3q** (905 mg, 78%) in 82:12 *E/Z* ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.40 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.14 (s, 1H), 3.74 (s, 3H), 2.57 (d, *J* = 1.1 Hz, 3H), 2.55 – 2.46 (m, 2H), 1.88 (dq, *J* = 13.3, 6.7 Hz, 1H), 0.90 (dd, *J* = 6.6, 2.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.54, 155.94, 143.16, 139.43, 129.37, 128.41, 115.81, 51.14, 45.17, 30.27, 27.29, 22.46; MS (ESI, *m/z*): 233 $[M+H]^+$; HRMS (ESI): calculated (for $C_{15}H_{21}O_2^+$) 233.1542, found 233.1545. Observed characteristic peaks for (*Z*)-isomer in ^{1}H NMR spectrum: ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 5.88 (d, *J* = 1.3 Hz, 1H), 3.55 (s, 3H), 2.17 (d, *J* = 1.3 Hz, 3H).

Methyl 2-cyclohexylideneacetate (3r). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3r** (578 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm:) 5.63 (d, *J* = 0.8 Hz, 1H), 3.70 (s, 3H), 2.92 – 2.82 (m, 2H), 2.27 – 2.16 (m, 2H), 1.72 – 1.56 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 167.46, 164.14, 112.77, 51.03 50.93, 30.04, 28.82, 28.02, 26.44, 21.67, 21.62; MS (ESI, *m/z*): 155 $[M+H]^+$; HRMS (ESI): calculated (for $C_9H_{15}O_2^+$) 155.1072, found 155.1074.

Methyl 3,3-diphenylacrylate (3s). Residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 10:1->4:1) yielded ester **3s** (740 mg, 62%). M.p. = 197-200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 (qd, *J* = 3.5, 2.0 Hz, 3H), 7.38 – 7.32 (m, 2H), 7.31 – 7.28 (m, 3H), 7.23 – 7.20 (m, 2H), 6.37 (s, 1H), 3.62 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 166.45, 157.11, 140.79, 138.80, 129.48, 129.11, 128.39, 128.33, 128.22, 127.91, 116.79, 51.29; MS (ESI, *m/z*): 239 $[M+H]^+$; HRMS (ESI): calculated (for $C_{16}H_{15}O_2^+$) 239.1072, found 239.1071.

General protocol for coumarin derivative (4) synthesis

A suspension of aldehyde **1** (3.6 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (4.0 mmol, 1.1 equiv) in toluene (3.6 mL, 1.0 M to **1**) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 60 minutes (fixed time) at 220 °C (see representative reaction protocol KAH-02-045 (for compound **4c**)). The reaction mixture was allowed to cool down transferred to a round-bottom flask and the toluene was removed under vacuum.

Coumarin (4a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4a** as a slightly yellow solid (468 mg, 89 %). M.p. = 69-70°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.71 (d, *J* = 9.5 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.48 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 6.41 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm:) 160.92, 154.14, 143.64, 131.97, 128.03, 124.58, 118.95, 116.98, 116.78; HRMS (ESI): calculated (for $C_9H_7O_2^+$) 147.0446 $[M+H]^+$, found 147.0445.

7-methoxy-2H-chromen-2-one (4b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4b** as a slightly yellow solid (545 mg, 86 %). M.p. = 114-115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 9.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.24 (d, *J* = 9.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 162.93, 161.34), 156.01, 143.50, 128.93, 113.27, 113.11, 112.65, 100.98, 55.80; HRMS (ESI): calculated (for $C_{10}H_9O_3^+$) 177.0552 $[M+H]^+$, found 177.0551.

8-hydroxy-2H-chromen-2-one (4c). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding

the desired product **4c** as slightly yellow solid (420 mg, 72 %). M.p. = 159-161 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 10.17 (s, 1H), 7.97 (d, *J* = 9.5 Hz, 1H), 7.16 – 7.03 (m, 3H), 6.43 (d, *J* = 9.5 Hz, 1H).; ^{13}C NMR (126 MHz, CMSO-*d*$_6$) δ (ppm): 160.44, 145.23, 145.14, 142.71, 125.04, 120.23, 118.89, 116.66, 116.58; HRMS (ESI): calculated (for $C_9H_8O_3^+$) 163.0395 $[M+H]^+$, found 163.0394.

6-methoxy-2H-chromen-2-one (4d). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4d** as a slightly yellow solid (495 mg, 78 %). M.p. = 102-103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.65 (d, *J* = 9.5 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 2H), 7.11 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.24, 156.27, 148.67, 143.40, 119.62, 119.37, 118.08, 117.29, 110.13, 56.00; HRMS (ESI): calculated (for $C_{10}H_9O_3^+$) 177.0552 $[M+H]^+$, found 177.0551.

6-hydroxy-2H-chromen-2-one (4e). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4e** as slightly yellow solid (397 mg, 68 %). M.p. = 221-222 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 8.98 (s, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 1H), 6.30 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 161.26, 156.17, 143.43, 140.00, 124.08, 118.52, 114.91, 112.63, 110.00; HRMS (ESI): calculated (for $C_9H_7O_3^+$) 163.0395 $[M+H]^+$, found 163.0395.

5,7-dimethoxy-2H-chromen-2-one (4f). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **4f** as a slightly yellow solid (549 mg, 74 %). M.p. = 145-146 °C; ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm): 7.99 (d, *J* = 9.6 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.17 (d, *J* = 9.7 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 168.88, 165.60, 162.01, 161.52, 115.94, 108.37, 100.29, 98.39, 61.61, 61.31; HRMS (ESI): calculated (for $C_{11}H_{11}O_4^+$) 207.0657 $[M+H]^+$, found 207.0656.

General protocol for monolignol (5) synthesis

Methyl ester of cinnamic acid (**3**, 8.5 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (55 mL, 0.15M to **3**) and the whole mixture was cooled to -78 °C (dry ice/acetone). DIBAL-H (29.5 mL, 29.5 mmol, 3.5 equiv; 1.0 M solution in CH_2Cl_2) was subsequently added dropwise and the whole mixture slowly turned yellowish. After additional 10 min, the cooling bath was removed and the whole mixture was allowed to stir at RT for 1 h. The whole mixture was then cooled to -78 °C and stirred for additional 10 min. Saturated aqueous solution of Rochel's salt (30 mL) was added and the whole mixture was allowed to worm to RT and stir for additional 12h. The resulting layers were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with sat. aq. NaCl (35 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was then purified by column chromatography (silica gel).

Sinapyl alcohol (5a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product **5a** as a slightly yellow solid (1.73 g, 97 %, *E/Z* = >95:1). M.p. = 62-63°C (from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.64 (s, 2H), 6.53 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.1 Hz, 1H), 5.59 (broad s, 1H), 4.32 (dd, *J* = 6.0, 1.4 Hz, 2H), 3.90 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 147.29, 134.90, 131.69, 128.39, 126.75, 103.45, 63.97, 56.47, 56.43; HRMS (ESI): calculated (for $C_{11}H_{14}O_4Na^+$) 233.0790, found 233.0789.

Conyferlyl alcohol (5b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a slightly yellow solid (1.40g, 92%, *E/Z* = >95:1). M.p. = 74-75°C (from MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.02 – 6.76 (m, 3H), 6.54 (d, *J* = 15.3 Hz, 1H), 6.23 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.72 (broad s, 1H), 4.31 (dd, *J* = 6.1, 1.5 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 146.81, 145.76, 131.58, 129.40, 126.30, 120.50, 114.64, 108.49, 64.07, 56.09; HRMS (ESI): calculated (for $C_{10}H_{12}O_3Na^+$) 203.0684, found 203.0686.

***p*-coumaryl alcohol (5c)**. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (1.01 g 79 %, *E/Z* = >95:1). M.p. = 117-120°C (from P.E.); ^{1}H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 9.09 (broad s, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.5 Hz, 2H), 6.66 (dd, *J* = 8.5, 1.7 Hz, 2H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.05 (dtd, *J* = 15.9, 5.5, 1.8 Hz, 1H), 4.07 (dd, *J* = 5.5, 1.6 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm): 157.64, 133.82, 129.20, 128.81, 128.13, 116.33, 62.39; HRMS (ESI): calculated (for $C_9H_{10}O_2Na^+$) 173.0579, found 173.0578.

General protocol for propnionaldehyde (6) synthesis

Monolignol **5** (5.5 mmol, 1.0 equiv) in dry 1,4-dioxane (55 mL, 0.1M) was cooled to 0 °C and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.89 g, 0.83 mmol, 1.5 equiv) was added in 5 portions over a period of 5 minutes. The resulting mixture (yellow-red) was stirred at 0 °C for 30 min and then at RT for 5 h. The whole mixture was then filtered and the filtrate was evaporated under reduced pressure to yield the crude product.

Sinapaldehyde (6a). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (4.58 g, 85 %, *E/Z* = >95:1). M.p. = 107-109 °C; ^{1}H NMR (500 MHz, acetone-*d*$_6$) δ (ppm): 9.65 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.09 (s, 2H), 6.70 (dd, *J* = 16.0, 7.5 Hz, 1H), 3.92 (s, 6H); ^{13}C NMR (126 MHz, acetone-*d*$_6$) δ (ppm): 192.92, 153.51, 148.18, 139.32, 126.41, 125.32, 106.49, 55.92; HRMS (ESI): calculated (for $C_{11}H_{12}O_4Na^+$) 231.0633, found 231.0632.

Conyferaldehyde (6b). The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (4.58 g, 85 %, *E/Z* = >95:1). M.p. = 78-80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.62 (d, *J* = 6.8 Hz, 1H), 7.76 (broad s, 1H), 7.38 (dd, *J* = 15.1, 0.8 Hz, 1H), 7.11 (dd, *J* = 7.8, 5.6 Hz, 1H), 7.06 (dd, *J* = 5.6, 1.3 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.59 (dd, *J* = 15.2, 6.2 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 193.61, 153.10, 148.96, 146.96, 126.62, 126.37, 124.03, 114.94, 109.50, 55.97; HRMS (ESI): calculated (for $C_{10}H_{10}O_3Na^+$) 178.0477, found 178.0479.

***p*-hydroxy cinnamaledehyde (6c)**. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 4:1->2:1->1:1) yielding the desired product as a white solid (3.52 g, 64 %, *E/Z* = >95:1). M.p. = 136-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.52 (d, *J* = 7.2 Hz, 1H), 8.98 (broad s, 1H), 7.41 (dd, *J* = 15.1, 0.8 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 7.5 Hz, 2H), 6.52 (dd, *J* = 15.1, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 194.50, 160.25, 154.15, 130.71, 125.69, 125.43, 116.08; HRMS (ESI): calculated (for $C_9H_8O_2Na^+$) 171.0422, found 171.0420.

Coumarin 10 synthesis via Claisen rearrangement/cyclization sequence and subsequent Mitsunobu substitution

A suspension of aldehyde **1l** (500 mg, 3.1 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (1.14 g, 3.4 mmol, 1.1 equiv) in toluene (3.1 mL, 1.0 M) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 85 minutes (fixed time) at 220 °C. The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->20:1->10:1->4:1) and yielded coumarin **9** (491 mg, 85%) as colorless low-melting point crystals. M.p. = 40-42 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.72 (d, *J* = 9.5 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 6.03 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 5.15 (ddd, *J* = 12.0, 3.1, 1.6 Hz, 1H), 5.12 (dt, *J* = 4.5, 1.5 Hz, 1H), 3.63 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.06, 151.86, 144.07, 135.58, 132.52, 128.58, 126.36, 124.33, 118.94, 117.05, 116.59, 33.41; HRMS (ESI): calculated (for $C_{12}H_{11}O_2^+$) 187.0759 $[M+H]^+$, found 187.0758. **Coumarin derivative 10**. A solution of coumarin **4e** (80 mg, 0.49 mmol, 1.0 equiv) in THF (5 mL, 0.1 M) was cooled to 0 °C (water/ice) and PPh_3 (155 mg, 0.59 mmol, 1.2 equiv) followed by geraniol (128 □L, 0.74 mmol, 1.5 equiv) were added. The resulting mixture was stirred at 0 °C for 5 min before diisopropyl (*E*)-diazene-1,2-dicarboxylate (DIAD) (153 □L, 0.78 mmol, 1.6 equiv) was added dropwise. The resulting mixture was allowed to warm to RT and stirred at RT for 11 h. The whole reaction mixture was evaporated to dryness and purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 20:1->10:1->4:1) to yield the desired product **10** (133 mg, 91%) as colorless crystals. M.p. = 96-97 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): ^{1}H NMR (500 MHz,) δ 7.66 (d, *J* = 9.5 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.13 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 5.49 (ddd, *J* = 7.8, 5.4, 1.2 Hz, 1H), 5.09 (ddd, *J* = 6.8, 4.1, 1.3 Hz, 1H), 4.57 (d, *J* = 6.5 Hz, 2H), 2.20 – 2.01 (m, 4H), 1.76 (s, 3H), 1.68 (d, *J* = 0.9 Hz, 3H), 1.61 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.29, 155.53, 148.54, 143.50, 142.20, 132.17, 123.85, 120.35, 119.34, 119.07, 118.05, 117.22, 111.25, 65.76, 39.74, 26.45, 25.91, 17.94, 16.95; MS (ESI^+, *m/z*): 299 $[M+H^+]$ (100%), 300 (60%), 301 (28%); HRMS (ESI): calculated (for $C_{19}H_{23}O_3^+$) 299.1647 $[M+H]^+$, found 299.1646.

Osthol (13) synthesis

Preparation of the aldehyde 11. A solution of 2-methylbut-3-yn-2-ol (1.12 mL, 10.95 mmol, 1.0 equiv) in CH_3CN (11.0 mL, 1.0M) was cooled to -5 °C (water/ice/NaCl) and DBU (2.13 mL, 14.2 mmol, 1.3 equiv) was added. The resulting mixture was stirred at -5 °C for 5 min and trifluoracetic acid anhydride – TFAA (1.52 mL, 10.95 mmol, 1.0 equiv) was added dropwise over a 20 min period. The mixture was warmed up to 0 °C (exchange of cooling baths) and stirred at 0 °C for an additional 30 min. In a separate flask, aldehyde **1i** (1.5 g, 9.9 mmol, 0.9 equiv) in CH_3CN (11 mL, 1.0M) was cooled to 0 °C and DBU (2.13 mL, 14.2 mmol, 1.3 equiv) was slowly added. The reaction mixture was stirred at 0 °C for an additional 5 min. $Cu(acac)_2$ (573 mg, 2.2 mmol, 0.2 equiv) was added and the mixture was stirred for the next 10 min at 0 °C. The resulting cold mixture was then slowly, over a period of 40 min, added into a mixture of activated propargylic alcohol and the mixture was allowed to stir at 0 °C for 5 h. The mixture was then poured into a separating funnel containing EtOAc:H_2O = 5:1 (V/V) (120 mL) and the resulting layers were separated. The organic layer was washed with water (3x25 mL), 1.0M aq. HCl (50 mL), sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->25:1) yielding the desired substituted aldehyde **11** (1.84 g, 85% - calculated to aldehyde **1i**) in the form of a yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.27 (d, *J* = 0.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 6.67 (ddd, *J* = 8.8, 2.4, 0.6 Hz, 1H), 3.87 (s, 3H), 1.74 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 189.08, 165.30, 160.43, 130.00, 122.53, 108.88, 105.74, 85.33, 75.47, 73.84, 55.81, 29.72; MS (ESI^+, *m/z*): 219 $[M+H^+]$; HRMS (ESI): calculated (for $C_{13}H_{15}O_3^+$) 219.1021 $[M+H]^+$, found 219.1020.

From aldehyde 11 to osthol 13. A solution of aldehyde **11** (900 mg, 4.13 mmol, 1.0 equiv) in EtOAc (21 mL, 0.2M) was stirred at RT and Rosenmund catalyst (5% Pd on $BaSO_4$) (41 mg, 10 mg/mmol loading) was added. The mixture was placed under hydrogen atmosphere (1 atm) and vigorously stirred for 12h. The mixture was filtered through a pad of Celite®. The filter cake was washed with EtOAc (2x25 mL) and the collected organic layers were evaporated to dryness to yield crude olefin **12** in sufficient purity to be used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.32 (d, *J* = 0.7 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 8.4, 4.3 Hz, 1H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.19 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.28 (d, *J* = 17.7 Hz, 1H), 5.24 (dd, *J* = 10.9, 0.6 Hz, 1H), 3.80 (s, 3H), 1.56 (s, 6H); ^{13}C NMR (126 MHz,) δ 189.45, 165.24, 161.34, 144.08, 130.00, 121.29, 114.41, 107.74, 105.27, 81.42, 55.70, 27.25; MS (ESI^+, *m/z*) = 221 $[M+H]^+$. A suspension of aldehyde **12** (crude from the previous reaction, 4.13 mmol, 1.0 equiv) and stabilized Wittig ylide **2** (1.52 g, 4.54 mmol, 1.1 equiv) in toluene (4.1 mL, 1.0 M) was placed into a microwave vial (10 mL) equipped with a magnetic stirring bar. The vial was sealed with a Silicone/PTFE Vial cap and placed into a CEM Discover reactor. The resulting mixture was then irradiated (300 W) for 60 minutes (fixed time) at 220 °C (see PLJ-06-073 microwave reaction monitoring record). The reaction mixture was allowed to cool down, transferred to a round-bottom flask and the toluene was removed under vacuum. The residue was purified by column chromatography (SiO_2; Petroleum ether:EtOAc = 50:1->20:1->10:1->4:1) and yielded osthol **13** (928 mg, 92%) as colorless crystals. M.p. = 77-79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.61 (d, *J* = 9.5 Hz, 1H), 7.28 (dd, *J* = 10.0, 4.7 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.23 (d, *J* = 9.4 Hz, 1H), 5.26 – 5.17 (m, 1H), 3.92 (s, 3H), 3.53 (d, *J* = 7.3 Hz, 2H), 1.84 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 161.66 160.39, 152.97, 144.00, 132.85, 126.40, 121.28, 118.12, 113.14, 107.53, 56.23, 25.98, 22.10, 18.12; MS (ESI^+, *m/z*): 245 $[M+H^+]$; HRMS (ESI): calculated (for $C_{15}H_{17}O_3^+$) 245.1178 $[M+H]^+$, found 245.1178; elemental analysis (for $C_{15}H_{16}O_3$): calc. C 73.75%, H 6.60%; found C 73.72%, H 6.59%.

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[7] The electronic properties of the substitution on aldehyde **1a** (strong electron donor) led us to identify the aldehyde **1a** as the model substrate. Most of targeted phenylpropanoids and coumarins have at least one hydroxy or methoxy group within its skeleton.

[8] Stabilized Wittig reagent **2** was chosen due to its non-basicity. It is known that cinnamic acid derivatives and monolignols are relatively unstable under basic conditions,[1c,3e,11] thus non-basic olefination reagent **2** was chosen to avoid possible side reactions.

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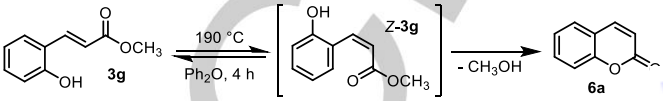

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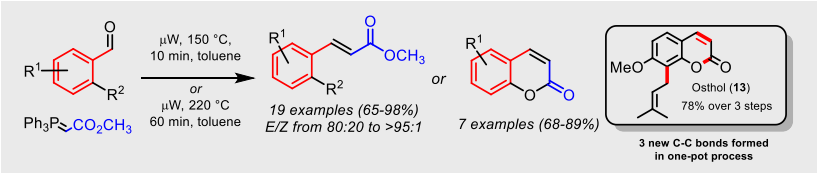

Synthetic method*

Daniela Konrádová, Hana Kozubíková, Karel Doležal, and Jiří Pospíši*

Page No. – Page No.

Microwave-assisted synthesis of phenylpropanoids and coumarins: total synthesis of Osthol

Microwave-assisted one-pot synthesis of phenylpropanoids, monolignols and coumarins. The choice of the reaction conditions and substrate determines the product of the reaction. Developed reaction conditions were applied to the synthesis of osthol (**13**) and several other natural products.

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