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New Carbanion Rearrangement of Sulfur Compounds and Its Application
Nový karbaniontový přesmyk sloučenin síry a jeho využití

Ph.D. Thesis

Supervisor: Dr. Ullrich Jahn

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Prohlášení:

Prohlašuji, že jsem předloženou doktorskou dizertační práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 18.6.2015

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Lucie Řehová

Abstract

This thesis reports the investigation of an unusual reversal in the metalation selectivity of alkyl aryl sulfones and sulfoxides and its application. Such compounds undergo initial directed *ortho*-metalation at −78 °C despite having an acidic α-hydrogen atom and the resulting aryllithiums rearrange subsequently completely to the initially expected α-sulfonyllithiums on warming. The scope and the limitations for this process were identified. Both carbanion types of sulfones were applied in reactions with various electrophiles. α-Lithiated sulfones generated upon the transmetalation process were used in Julia olefinations.

A mechanistic study of the course of the transmetalation reaction is presented. The kinetics of the transmetalation were determined. Investigations concerning the concentration dependence, proton transfer equilibria between the different *ortho*-sulfonyllithium intermediates and crossover experiments provided the evidence that a concerted intermolecular pathway prevails.

On this basis a new integrated synthetic approach to naturally occurring iridoids was developed. It is based on a tandem alkoxycarbonylation/oxidative radical cyclization of the olefins synthesized by the Julia reaction after the investigated transmetalation. Total syntheses of dihydronepetalactone and dolicholactone were accomplished.

Abstrakt

Předložená disertační práce je zaměřena na studium neobvyklé metalační selektivity alkyl aryl sulfonů a sulfoxidů a její využití. Tyto sloučeniny, nehledě na to, že mají kyselý α-vodíkový atom, podléhají přímé *ortho*-metalaci při −78 °C a výsledné aryllithné soli následně při zahřátí transmetalují na původně očekávané α-sulfonyllithné soli. Byl stanoven rozsah a omezení tohoto procesu. Sulfonylové karbanionty byly využity v reakcích s různými elektrofily. α-Lithné soli sulfonů generované transmetalací byly uplatněny v Juliově olefinaci.

Dále jsou zde prezentovány výsledky mechanistických studií průběhu transmetalace. Pomocí kinetických měření, zkřížených experimentů, měření závislosti této reakce na koncentraci a studia přenosu protonu mezi různými *ortho*-sulfonyllithnými intermediáty bylo dokázáno, že zde převažuje součinný intermolekulární průběh transmetalace.

Na základě získaných informací byl vyvinut nový přístup k iridoidům vyskytujícím se v přírodě. Je založen na tandemové alkoxykarbonylaci/oxidativní radikálové cyklizaci olefinů, které byly připraveny Juliovou reakcí s využitím transmetalace. Dihydronepetalakton a dolicholakton byly připraveny s využitím výše popsané metodiky.

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1. Introduction

1.1. Cyclopentanoid monoterpenes – iridoids

1.1.1. Iridoid structures and features

Cyclopentanoid monoterpenes (iridoids) have long been recognized as an important class of plant secondary metabolites displaying a wide range of biological activities.[1–7] Naturally occurring compounds of this type are often active ingredients of traditional folk medicines used as sedatives, febrifuges, hypotensives, cough medicines and remedies for skin disorders and wounds. Thanks to their anti-inflammatory, antioxidative, neuroprotective, anticancer and antibacterial activity, the iridoids have attracted considerable attention. The iridoid structures are often highly oxygenated and are characterized by a functionalized cyclopentane ring *cis*-fused to a dihydropyran, δ-lactone or δ-lactol. The iridoid carbon skeleton consists usually of nine or ten carbons (Figure i1).

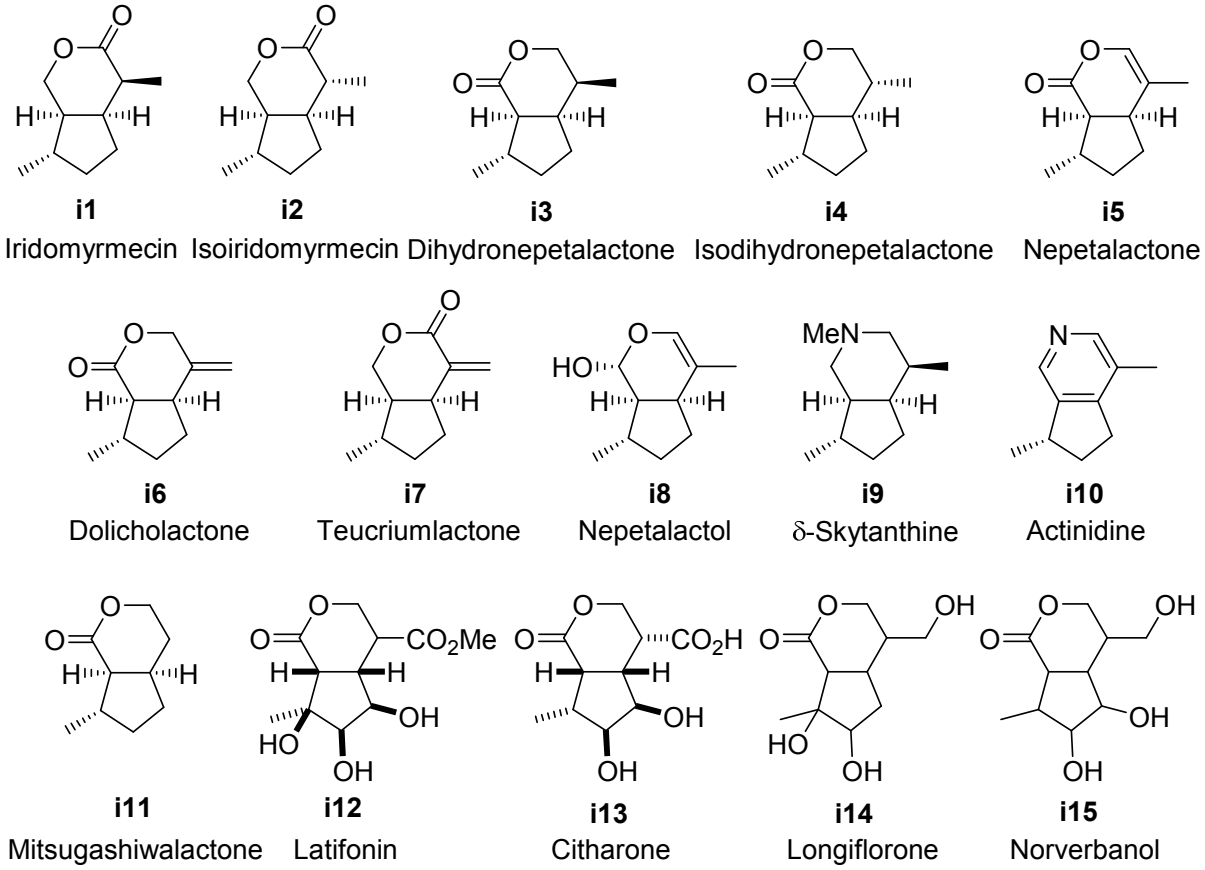


Figure i1. Examples of cyclopentanoid monoterpenes.

Iridomyrmecin **i1** and isoiridomyrmecin **i2** were discovered and isolated in 1950s as the first examples of cyclopentanoid monoterpenes. Iridoids are important insect semiochemicals[8] and can be potentially used as control agents for pest species.[9,10] The name 'iridoid' has its origin in the isolation of class members from the secretion of ants belonging to the genus *Iridomyrmex*. Apart from iridomyrmecin **i1** and isoiridomyrmecin **i2**, dihydronepetalactone **i3** and isodihydronepetalactone **i4**, representing another type of cyclopentanoid monoterpenes, were isolated from the volatile oils present in leaves and galls of the cat-attracting plant *Actinidia polygama*.[11] The iridoids **i1-4** were also isolated from the oil of *Nepeta cataria*, commonly known as catnip or catmint, accompanied with nepetalactone **i5** as a major component.[12] Catnip is famous for its irresistible action on cats and has been recently used in medical preparations as antidiaphoretic, antispasmodic, stomachic and mild sedative. Nepetalactone **i5** has been identified as an effective insect repellent compound.[13] Dolicholactone **i6** and teucriumlactone **i7** were first isolated from the wild plant *Teucrium marum* which grows in the Mediterranean area.[14]

There are many other iridoids found in nature such as nepetalactol **i8**, δ-skytanthine **i9**, actinidine **i10** and mitsugashiwalactone **i11**. In some cases an absolute (**i12-13**) or even a relative configuration (**i14-15**) of stereocenters is not known as well as their biological activities. Both of these features still remain to be explored for example for highly oxygenated latifonin **1-12**, citharone **i13**, longiflorone **i14** or norverbanol **i15**. Thus finding the approach to these compounds is highly desirable.

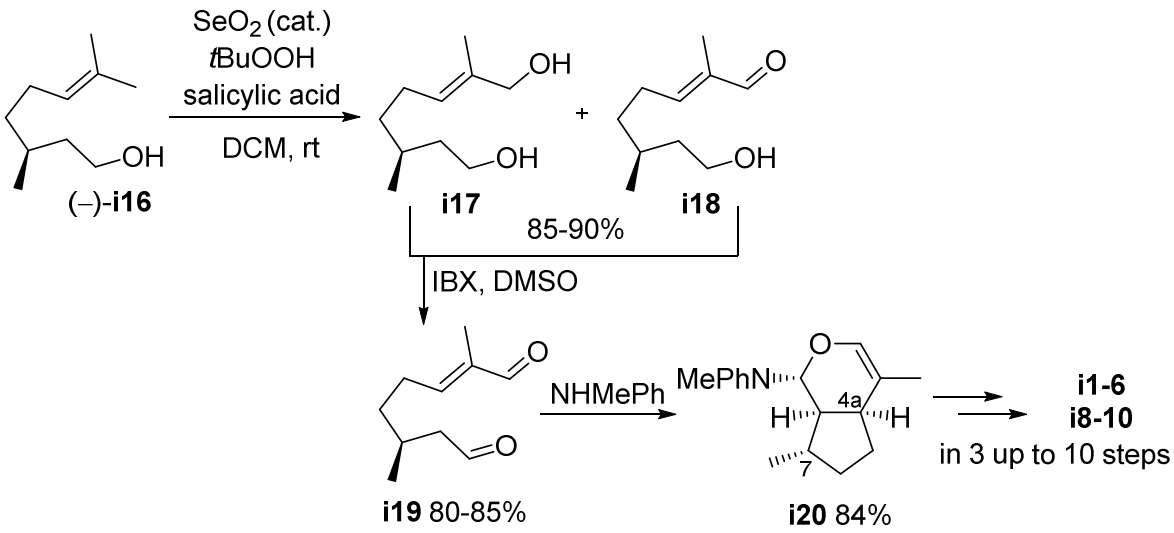
1.1.2. Synthetic approaches to iridoid natural products

The iridoid ring scaffold is biosynthesized from 8-oxocitral by the enzyme irridoid synthase.[15] However, the isolation of iridoids from plants in sufficient purity and amount is often complicated. The stereochemistry at the four neighboring asymmetric centers has drawn the attention of synthetic chemists as being a challenging target. The first synthesis of iridomyrmecins **i1-2** and related compounds was reported independently by Korte[16] and Robinson.[17] The synthesis of (±)-nepetalactone **i5** was published one year later by Sakan and colleagues,[18] followed by publication of the synthesis of four of the possible eight stereoisomers of dihydronepetalactone **i3**.[19] However, the majority of approaches for the synthesis of dihydronepetalactone **i3** provided the desired iridoid in racemic form.[20,21] Over the decades, a huge progress in synthetic strategies, including the approaches to optically pure iridoid skeletons, was made.[22–36] However still a number of these syntheses are

multistep reactions which are not suitable for preparation of these compounds in larger amounts. Therefore efficient total syntheses of these products and their analogues are desired.

Overall, cyclopentanoid monoterpenes have been synthesized applying various synthetic strategies leading mostly to one or a few iridoids. Recently a useful divergent chemical synthesis that makes use of a common intermediate to access more target iridoids was reported (Scheme i1).[35,36] The highly diastereoselective synthesis of aminal **i20** using an intramolecular enamine/enal cycloaddition, first described by Schreiber,[37] has long been used as a valuable approach to the iridoid skeleton.[9,38–40] Citronellol (−)-**i16** was used as a starting material and was treated with catalytic SeO_2 and stoichiometric reoxidant *t*BuOOH giving a 1:2 mixture of diol **i17** and aldehyde **i18**. The mixture was subsequently submitted to IBX oxidation to afford 1,8-enedial **i19**. The treatment of **i19** with *N*-methylaniline allowed a rapid approach to the iridoid carbon framework generating both stereochemically stable positions (C4a and C7). Moreover, the dihydropyrane part of aminal **i20** can well serve for chemical differentiation between the masked aldehyde functionalities.

Cyclopentanoid monoterpenes are small enough to be easily synthesized and yet structurally sufficiently complex. Thus enantio- and stereoselective total syntheses of these physiologically active and structurally appealing compounds still pose a challenge.

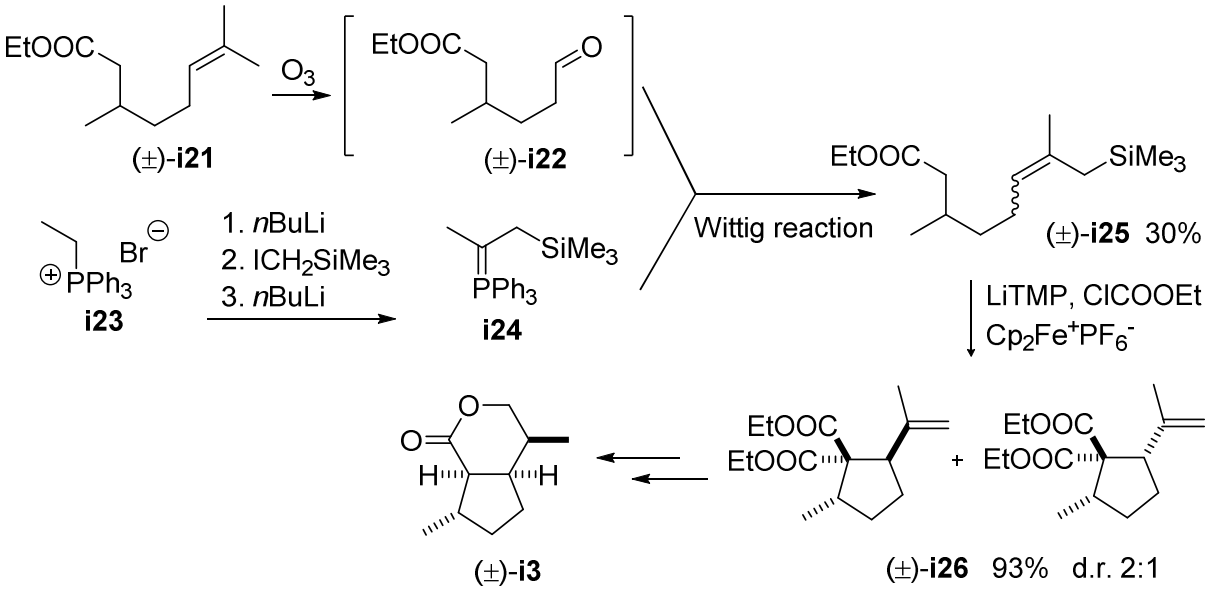


Scheme i1. Divergent diastereoselective synthesis of iridoids **i1**-**6** and **i8**-**10**.

1.1.3. Stereoselective synthetic approach to the iridoid cyclopentane skeleton

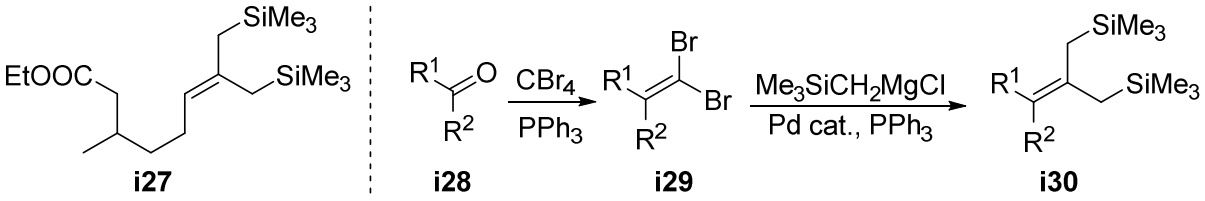
A short racemic approach to iridoid monoterpenes and its analogs based on a tandem alkoxycarbonylation/oxidative radical cyclization using ferrocenium hexafluorophosphate as a single electron transfer (SET)[41] oxidant was reported previously (Scheme i2).[42] Racemic citronellate (±)-**i21** was used as a starting material in a one-pot sequential ozonolysis/Wittig reaction. Phosphorane **i24**, generated from salt **i23** using sequential deprotonation/alkylation/deprotonation, was submitted to Wittig reaction with the crude aldehyde (±)-**i22** prepared by ozonolysis of alkene (±)-**i21**. Silyl citronellate (±)-**i25** was obtained as a 1:1 *E/Z* mixture in unoptimized 30% yield. Silyl citronellate (±)-**i25** underwent the anionic-radical-cationic tandem sequence consisting of alkoxycarbonylation, SET oxidation, radical 5-*exo* cyclization and oxidation/carbenium ion desilylation providing the desired cyclopentanes (±)-**i26** in excellent yield, however as an inseparable 2:1 *trans/cis*-diastereomeric mixture. The synthesis was completed by performing hydroboration/oxidation, lactonization and final Krapcho dealkoxycarbonylation affording (±)-dihydronepetalactone **i3**.

The main drawback of the reported synthesis[42] is the ineffective preparation of olefin **i25** by a Wittig reaction. Another limitation of the synthesis is the asymmetric nature of olefin **i25**, in which the energies of the cyclization transition state are not enough differentiated. Modified cyclization precursor – bis(allylsilane) **i27** (Scheme i3) may provide better *trans*-diastereoselectivity of the radical *5-exo* cyclization.



Scheme i2. Racemic approach to cyclopentanoid monoterpene dihydronepetalactone (±)-**i3**.

There are only a few approaches to bis(allylsilanes) **i30** reported in the literature.[43–47] One of the approaches transforms aldehydes or ketones **i28** to 1,1-dibromo-1-alkenes **i29** by reaction with carbon tetrabromide and triphenylphosphine. Subsequent palladium-catalyzed tandem Kumada-Tamao-Corriu cross-coupling reaction with the trimethysilylmethyl Grignard reagent affords the desired bis(allylsilane) **i30** (Scheme i3).[43] Because the majority of known methods to access these compounds are not applicable because of functional-group tolerance issues or the ease of preparation of precursors, the Julia reaction remains the most promising approach enabling the preparation of olefin **i27**. It is based on the reaction of α-deprotonated sulfones with aldehydes or ketones followed by reductive elimination (see Chapter 1.3).



Scheme i3. Alternative cyclization precursor **i27** and preparation of bis(allylsilanes) **i30**.

1.2. General reactivity of sulfones and sulfoxides towards bases

1.2.1. α-Deprotonation of sulfones and sulfoxides

Organolithium compounds represent one of the main reactive carbanion intermediates in organic chemistry.[48–54] As key intermediates, they are involved in a number of broadly applied transformations, such as nucleophilic addition,[48–59] alkylation,[60,61] cross-coupling reactions,[62,63] carbolithiation reactions[49,64–67] and rearrangement reactions,[68–74] as for instance the [1,2]-[75,76] or [2,3]-Wittig rearrangements.[77–81]

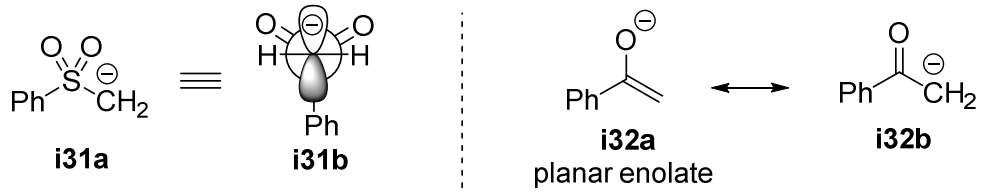
Generally, the stability and reactivity of carbanions is determined by several main factors.[48,82–85] These include the stabilization of the negative charge by neighboring electron-withdrawing activating functional groups by polar and resonance effects. Therefore the selectivity and ease of carbanion generation strongly depend on the presence of electron-accepting activating functional groups that delocalize the charge. Electron-withdrawing substituents cause very large increases in the acidity of adjacent α-hydrogen atoms. Among such functional groups that display a strong stabilizing effect on carbanions are carbonyl, nitro, cyano, sulfonyl, sulfinyl and phosphoryl groups.

An eligible basis for comparing stabilizing abilities of these functional groups is the p*K*a values of differently substituted methanes. Bordwell and co-workers identified the relative acidities of these substituted methanes with reference to aromatic hydrocarbon indicators in dimethyl sulfoxide (Table i1).[86–91] The data showed clearly the extent of contribution of the electron-accepting groups to the stabilization of carbanion, which is evident from the p*K*a values for the proton next to these groups, establishing the order: NO_2>COPh>SO_2Ph>CN>SOPh>SPh. Additional alkyl substitution increases the pK_a, for example the pK_a values in $PhSO_2$*i*Pr and $PhSO_2CH_2$*t*Bu are 32.1 and 31.2 respectively.[88]

Table i1. Equilibrium acidities of substituted methanes in dimethyl sulfoxide.

Entry	Compound	pK_a
1	CH_3NO_2	17.2
2	CH_3COPh	24.7
3	CH_3SO_2Ph	29.0
4	CH_3CN	31.3
5	CH_3SOPh	33.0
6	CH_3SPh	42.0

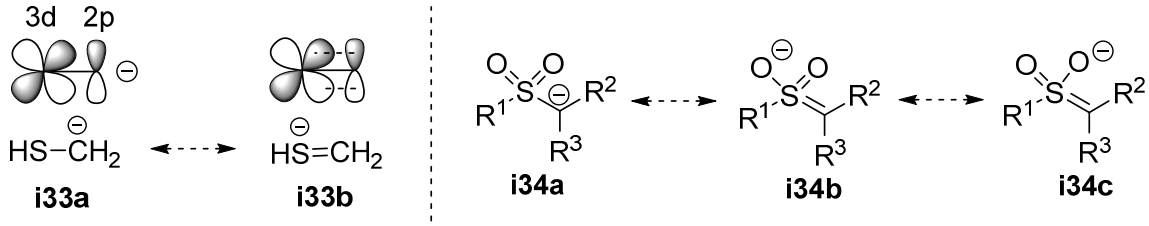
Sulfone-stabilized carbanion **i31a** has two oxygen atoms and the anionic carbon atom next to sulfur is considered to be planar having the negative charge in a p orbital aligned between the S=O bonds (**i31b**, Scheme i4). Enolate **i32a**, having the negative charge mainly on the oxygen atom, is in contrast to sulfone **i31** planar and is greatly stabilized by conjugation (**i32a,b**).



Scheme i4. Sulfone-stabilized anion **i31** and the planar structure of enolate **i32**.

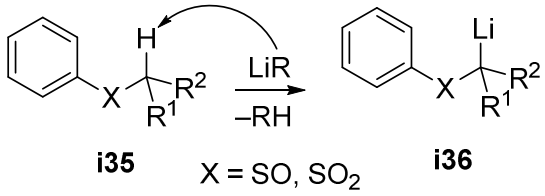
There is a controversy over the reason for the stabilization of carbanions by sulfides, sulfoxides and sulfones. Clearly, the oxygen atoms are important, as indicated by the best stabilization of carbanion by sulfones followed by sulfoxides and sulfides. However, the oxygen atoms cannot be the only reason for the stability since also the sulfide group acidifies

neighboring protons. The first theory proposes that the stability is higher thanks to the overlap of the unshared pair with an empty d orbital (*p*π-*d*π bonding),[92,93] therefore a thia carbanion **i33a** would have the structure **i33b** and similarly α-sulfonyl carbanion **i34a** would have the structure **i34b,c** (Scheme i5). Although the resonance is allowed only for the elements of 2nd row of periodic table, it was used here to depict the alternative structures. In contrast, *ab initio* calculations support polarization and hyperconjugation effects causing the stabilization.[94–96] Calculations also showed that C−S bond in **i33a** is longer than in CH_3SH, however the delocalization would shorten the bond due to partial double-bond character. Another theory states similarly that a carbanion adjacent to PhS substituent is stabilized by a combination of inductive and polarizability effects of the PhS group and *p*π-*d*π rezonance and negative hyperconjugation play a minor role, if any.[97]



Scheme i5. Possible structures of stabilized α-thia carbanion **i33** or α-sulfonyl carbanion **i34**.

Although the reasons for stabilization of sulfonyl and sulfinyl carbanions are disputable it can be assumed that the stabilization is derived from polar and polarization effects and that structures **i33a** and **i34a** are more likely. To conclude, the sulfonyl and sulfinyl groups display a strong acidifying effect on adjacent α-hydrogen atoms similarly as the carbonyl group. Therefore **i35** can be easily deprotonated giving **i36** (Scheme i6).[98–104] The Julia olefination and its related variants are based on that effect.[105–110]



Scheme i6. Generally observed metalation mode for alkyl phenyl sulfones and sulfoxides bearing α-H.

The degree of covalency or oxophilicity of counterion will influence the carbanion structure as well. Here the α-lithium sulfone is depicted as a structure containing the lithium

atom bonded to α-carbon for clear specification of the regioselectivity of metalation, despite this representation is not entirely correct. In fact, α-lithiated sulfones have the lithium atom typically bonded to oxygen[54] leaving a bare or weakly coordinated carbanion carbon in the solid state.[111,112] Dipole stabilized α-Li[$R^1(R^2)CSO_2R^3$], where R^1,R^2 = alkyl, aryl, H and R^3 = alkyl, aryl, containing usually THF[113] coligands or chelating ligands like TMEDA[114–116] or diglyme,[117,118] were found to crystallize most typically as dimers in the solid state.[119] X-ray structures showed centrosymmetric dimers with central $Li_2S_2O_4$ eight-membered structural units (Figure i2). The two SO_2 groups bridge the two lithium atoms. The crystal structures of **i37a-c** prove the presence of strong Li-O bonds exclusively and no formation of Li-C bonds. The tetrahedral donor set of lithium is completed mostly by chelating ligands. The electron lone pairs of the "free" carbanions bisect the O-S-O angle. However rare examples can be found,[120,121] such as less solvated α-lithiated ethyl phenyl sulfone **i38** showing an unusual Li-C bonding additional to Li-O bonding in its polymeric ladder structure. This crystal structure was prepared by deprotonation of ethyl phenyl sulfone by *n*BuLi in the absence of chelating ligands in hexane at −78 °C. The resulting precipitation of solvate-free organolithium was isolated and dissolved in THF and precipitated with hexane/pentane. Sulfonyl carbanion structures in solution are less well-defined; they seem to be minimally aggregated in THF forming mostly dimers and monomers.[112,122–124]

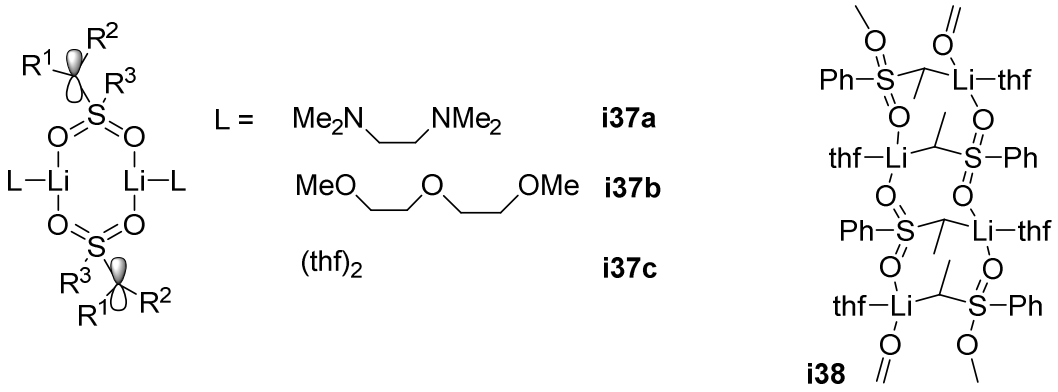
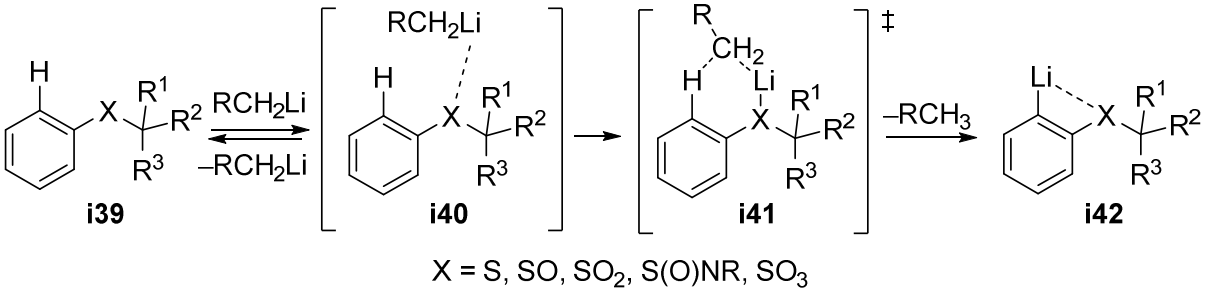


Figure i2. Usual Li-O coordination modes in **i37** vs. rare Li-C bonding in **i38**.

1.2.2. Directed *ortho*-metalation of sulfoxides and sulfones

Aryl sulfones, sulfonates, sulfonamides, sulfoximines, sulfoxides, sulfides and related compounds **i39** bearing no α-hydrogen atoms undergo directed *ortho*-metalations (DoM) at the aryl unit according to the complex-induced proximity effect (CIPE), a well-known strategy for removing protons kinetically (Scheme i7).[49,125–129] The most widely accepted

mechanism for DoM involves the formation of a prelithiation complex **i40**[130–132] of the alkyllithium coordinated to the directing group. The activating group acts as a Lewis base coordinating the counterion of the base, which is in close proximity to the *ortho*-proton in **i41**, and thus allows irreversible deprotonation in a more distant position forming *ortho*-lithiated compound **i42**.

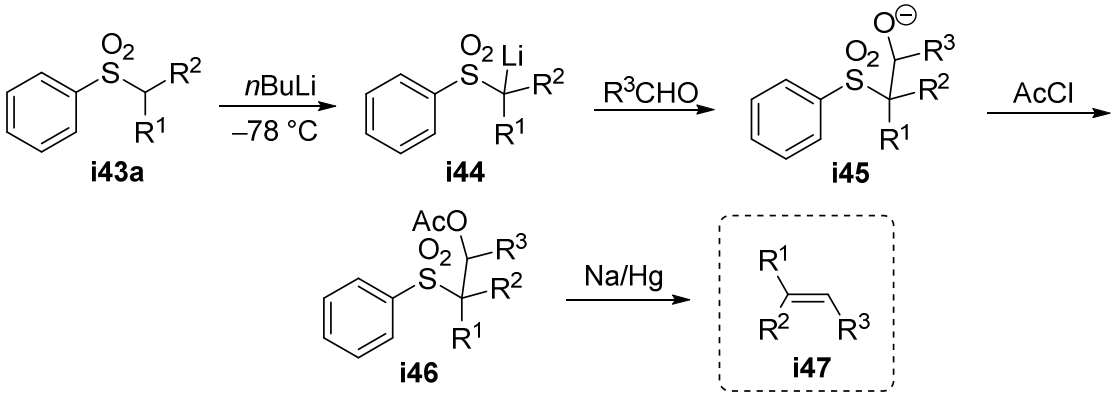


Scheme i7. Directed *ortho*-metalation for compounds bearing no α-hydrogen.

The rate and regioselectivity *of ortho*-lithiation is controlled by two factors: the strength of the coordination between organolithium and the heteroatom of activating group and the acidity of the *ortho*-proton. The sulfonamide, carboxamide and sulfone substituents are generally considered to be very strong activators in DoM.[133,134] Under kinetically controlled conditions, which are usually used for *ortho*-lithiation reaction, it is rather difficult to quantify the thermodynamic information acidity. Nevertheless, Fraser and colleagues described a quantified scale of acidifying effect for differently monosubstituted benzenes in THF.[135] However, the majority of substituents gave rise to very similar pK_a values of ca 39 and reflect no correspondence between the order of activating power of the various directing groups and the pK_a values. Therefore the correlation between the acidity of *ortho*-hydrogen atoms and the deprotonation rate is relatively loose.

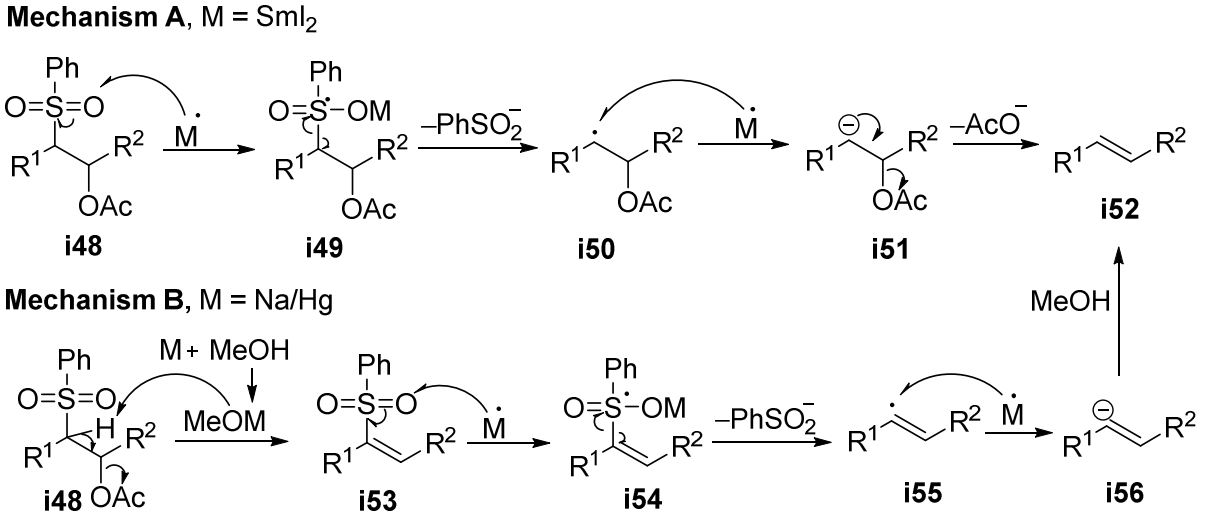
1.3. The Julia olefination: conditions and mechanism

The classical Julia reaction[136] was discovered by M. Julia in 1973 and enables the synthesis of (*E*)-alkenes (Scheme i8). This olefination reaction consists of a multi-step sequence including nucleophilic attack of α-metallated aromatic sulfones **i44**, generated from aryl sulfones **i43a**, to aldehydes giving alkoxide intermediates **i45**. Its acylation by acetyl chloride *in situ* afforded acetates **i46**. Reductive elimination gives the target olefins **i47**.[137,138]



Scheme i8. Classical two-step Julia reaction.

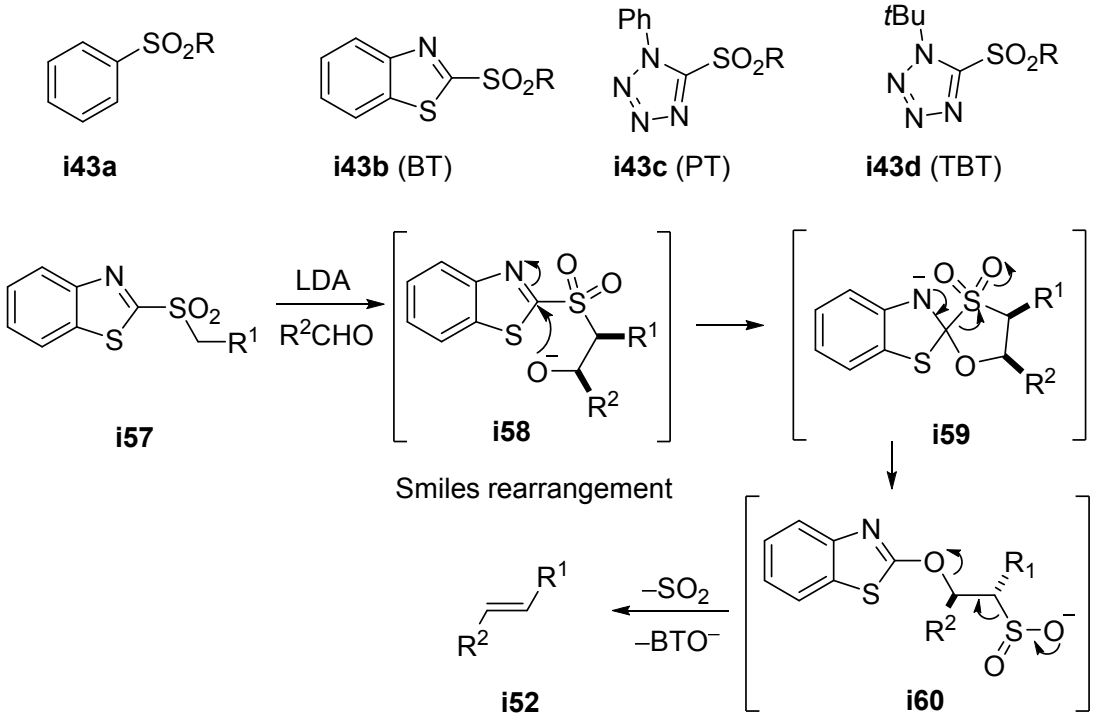
The crucial step of the Julia olefination, which is responsible for (*E*)-selectivity, is the reductive elimination of acetoxy derivative **i48** (Scheme i9). This step proceeds using sodium amalgam as a reducing agent or alternatively samarium diiodide as a single electron reductant, as Kende and co-workers demonstrated.[139] The mechanism of reductive elimination depends on the type of reductant. The originally proposed mechanism for the classical Julia reaction using sodium amalgam turned out to be plausible for the reaction using samarium iodide (Mechanism A).[138] The first step is an electron transfer from the reducing agent to the sulfonyl group in **i48** forming radical **i49**, which fragments to a radical **i50**. The radical **i50** is reduced via SET to carbanion **i51**, which affords (*E*)-olefin **i52** by elimination of acetate.



Scheme i9. Proposed mechanisms for reductive elimination.

The first step of classical reductive elimination with sodium amalgam would in contrast rather be elimination leading to vinyl sulfone **i53** (Mechanism B, Scheme i9).[138] Vinyl

sulfone **i53** would subsequently undergo a reductive single electron transfer followed by cleavage of **i54**. The resulting vinyl radical **i55** would be reduced by excess Na/Hg to carbanion **i56**, which is quenched by methanol giving alkene **i52**. Both possible mechanisms were supported by the fact, that the reaction with sodium amalgam in MeOD as a solvent led to incorporation of deuterium into the product. This was not observed in the case of using samarium diiodide as reductant. The pathway of classical reductive elimination with sodium amalgam might also proceed *via* different intermediates avoiding the formation of unstable vinyl radical **i55**, however such an alternative mechanism is not reported in the literature.



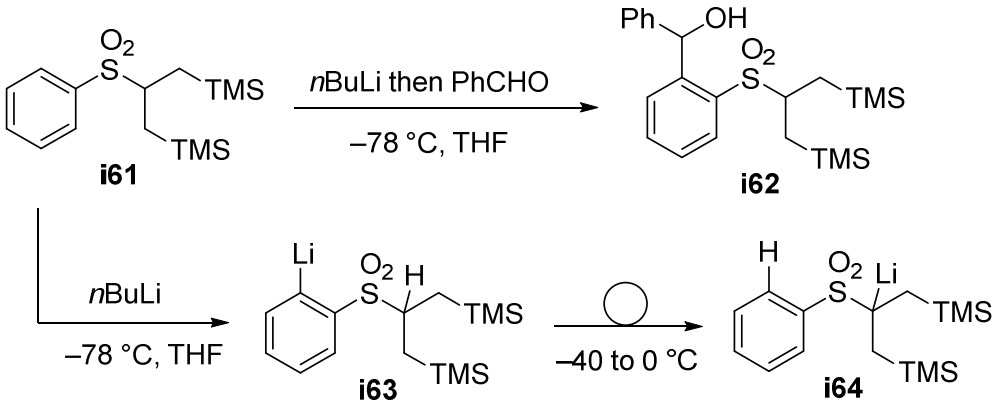
Scheme i10. Modification of Julia olefination reaction.

One of the most fundamental change in the original design of Julia reaction was made by Sylvestre Julia in 1991, who presented a direct synthesis of olefins from carbonyl compounds and benzothiazol-2-yl sulfones (BT) **i43b**[140] (Scheme i10). This reaction is commonly known as the modified Julia reaction. It proceeds via the addition of deprotonated sulfone **i57** to an aldehyde forming β-alkoxy sulfone **i58**, which subsequently undergoes a Smiles rearrangement.[141] The alkoxide ion intramolecularly attacks the neighboring C=N group affording spirocyclic anion intermediate **i59**, which undergoes an S to O benzothiazole transfer giving intermediate **i60**. The final step involves the extrusion of sulfur dioxide and formation of benzothiazolone showing the preference for forming (*E*)-olefin **i52**. The

modified Julia reaction was further investigated by Kocienski et al., who introduced 1-phenyl-1*H*-tetrazol-5-yl (PT) **i43c**[142] and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT) **i43d**[143] sulfones and reported procedures, which lead to (*E*)-olefins in one step.

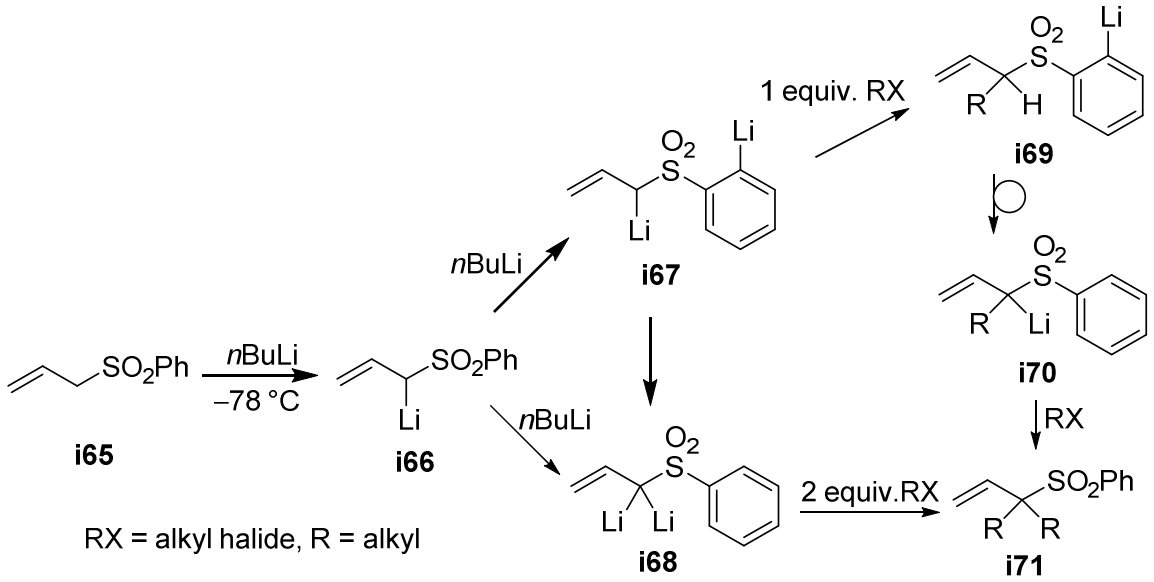
1.4. Initial observation of an unusual metalation selectivity and subsequent transmetalation

Generally, the two basic metalation modes (α-lithiation and DoM), mediated using strong bases such as *n*-, *s*-, or *t*BuLi as well as LDA, exclude each other because of the dominating acidity of α-protons, thus the regioselectivity of the deprotonation process can be easily predicted. If an alkyl group bearing hydrogen atoms in α-position to the electron-accepting group is present, deprotonation takes place at this position according to the rules outlined above (Chapter 1.2.1, Scheme i6). DoM is thus only possible if α-hydrogen atoms are absent (Chapter 1.2.2, Scheme i7). Initial experiments treating sulfone **i61** with *n*BuLi and benzaldehyde at −78 °C under standard Julia reaction conditions provided the *ortho*-substituted sulfone **i62** instead of originally expected olefination product (Scheme i11).[144] Using TMEDA as an additive led to the same result. Such a DoM was never observed before as the initial process for sulfones having α-hydrogen atoms.[145,146] The site of deprotonation was determined by deprotonation/deuteration studies. Sulfone **i61** initially undergoes DoM with essentially complete regioselectivity, despite having an acidic α-proton and the generated aryllithium **i63** rearranges subsequently completely to the sulfonylalkyllithium **i64** on warming. It was demonstrated for a single example of a branched *tert*-butyl phenyl sulfone that DoM dominates as well.



Scheme i11. Reversed metalation selectivity and transmetalation of *ortho*-metalated sulfone **i63**.

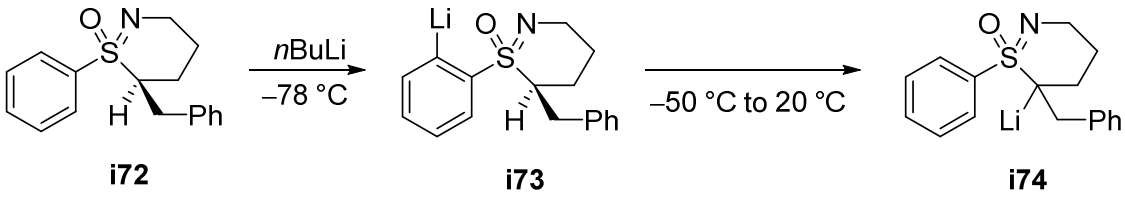
So far only one way existed to reverse the selectivity of metalation, which consists of generating a dianion by initial α-deprotonation and subsequent DoM.[147–150] Phenyl allyl sulfone **i65** was α-metalated using standard conditions giving metalated sulfone **i66** (Scheme i12).[148] The second lithiation proceeds in the position *ortho* to the sulfonyl group to provide **i67** in a kinetically controlled reaction with high selectivity. However, this procedure is compromised by the low atom economy, since one equivalent of base is wasted. Lithiation in the α-position proceeds as well forming dilithio sulfone **i68**. The selectivity decreases with increasing temperature. Complete transmetalation to thermodynamically more stable dilithio sulfone **i68** occurs on warming to 50 °C. The reaction of dilithiated sulfone **i68** with various alkyl halides regioselectively gave **i71** at –50 °C in THF. Surprisingly, nearly the same results were obtained for the reaction of *orho*,α-dilithium **i67** with alkyl halides. The initial alkylation of **i67** occurred at the α-position affording **i69** and was followed by complete transmetalation to α-lithio derivative **i70**, which gave sulfone **i71** upon a second alkylation.



Scheme i12. *ortho*→α-Transmetalation of *ortho*-lithiated **i69**.

Gais and coworkers reported later that a number of conformationally constrained sulfoximines also react by initial DoM followed by transmetalation to the corresponding α-carbanions **i74** (Scheme i13). Here an interesting temperature effect, similar to the reported transmetalation on β,β-disilylated sulfone,[144] was observed for sulfoximine **i72**. Whereas treatment of sulfoximine **i72** with *n*BuLi at −78 °C afforded the *orho*-lithiosulfoximine **i73**, similar treatment at −50°C to 20 °C provided the α-lithiosulfoximine **i74**.[151] A conceptually

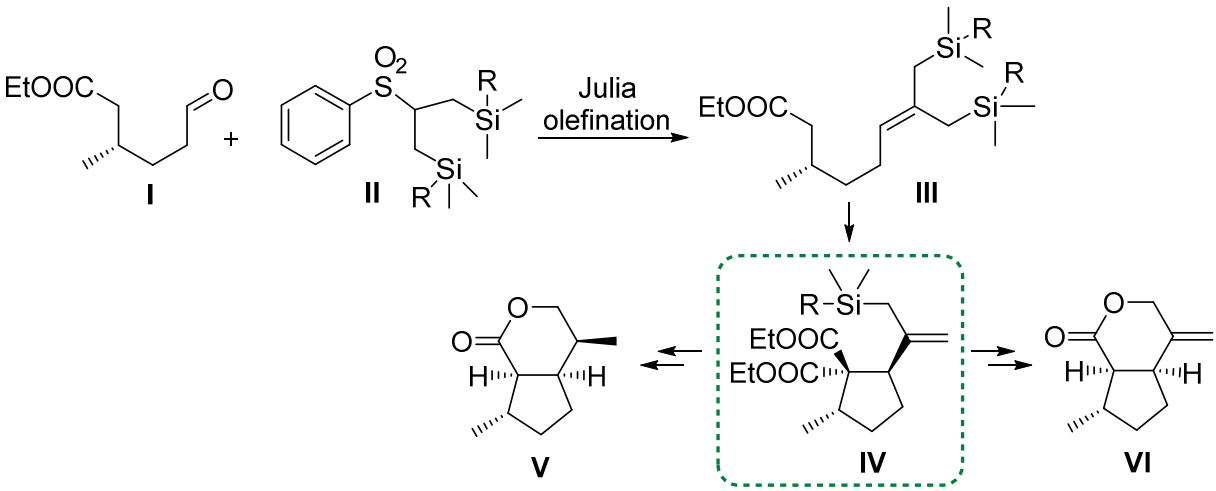
different γ→α-transmetalation of two similarly acidic positions initiated by deprotonation with LDA was very recently observed in alkynyl benzyl sulfones.[152]



Scheme i13. *ortho*→α Transmetalation of *ortho*-lithiosulfoximine **i73**.

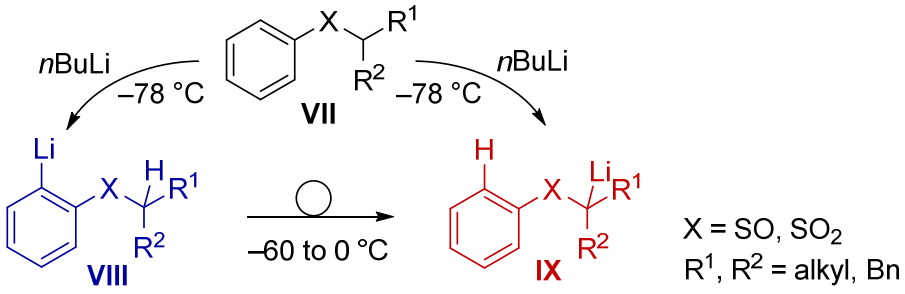
2. Aims of the Work

In order to eliminate the drawbacks of the previously reported racemic synthesis of iridoids and to develop a more efficient asymmetric approach, a modified olefin structure **III** and its alternative preparation by a Julia reaction is proposed (Scheme I). An additional bulky silicon substituent is expected to improve the *trans*-diastereoselectivity of the envisaged tandem alkoxycarbonylation/oxidative radical cyclization affording cyclopentane **IV**.



Scheme I. Second generation asymmetric total synthesis of iridoid type compounds.

However, the initial experiment using a β,β-disilylated sulfone **II** showed the surprising reversal in the metalation selectivity hampering its application in the Julia reaction in the total syntheses.



Scheme II. Metalation regioselectivity dependence of sulfones and sulfoxides on their structure.

Nothing was known about the scope and the limitation of the reverse metalation for alkyl aryl sulfones and sulfoxides **VII** as well as about the subsequent transmetalation and the mechanism of this process (Scheme II). Therefore, the following points must be addressed:

- Detailed investigation of the reactivity of differentially substituted alkyl aryl sulfones and sulfoxides **VII** towards bases.
- Determination of the factors responsible for initial metalation.
- Selective application of *ortho*- and α-carbanions (**VIII** and **IX**), generated either by initial metalation of alkyl aryl sulfones or by subsequent transmetalation, in reactions with various electrophiles, especially in the Julia olefination.
- Elucidation of the course of the transmetalation reaction.
- Development of a new asymmetric integrated synthetic approach to iridoids, effective preparation of modified olefin **III** by a Julia reaction and diastereoselective radical cyclization of olefin **III** giving cyclopentane iridoid building block **IV**.
- Elaboration of stereoselective total syntheses of dihydronepetalactone **V** and dolicholactone **VI**.

3. Results and Discussion

3.1. Divergent reactivity of alkyl aryl sulfones and sulfoxides with bases

3.1.1. Preparation of starting materials

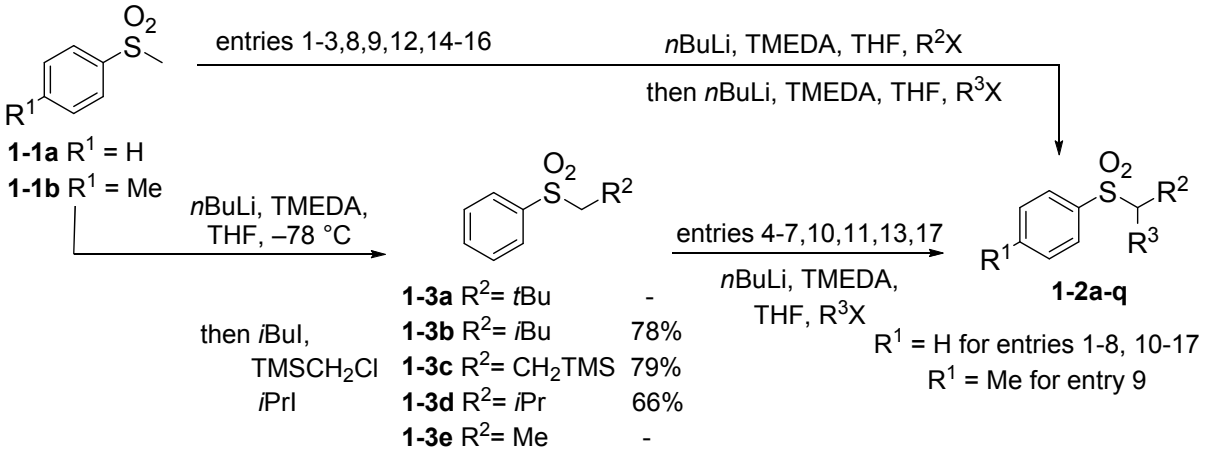
Diverse β,β-disilylated sulfones, intended to be applied in the total synthesis of iridoids using the Julia reaction, were prepared for the study of their ability of α-deprotonation and a series of differently branched alkyl aryl sulfones and sulfoxides was synthesized for the investigation of their reactivity towards bases.[153] β,β-disilylated sulfones **1-2a-c** were synthesized by sequential alkylation of **1-1a** with different (chloromethyl)silanes in the presence of TMEDA in good yield by a one-pot procedure (Table 1.1, entries 1-3). Sulfone **1-2a** can be alternatively prepared with more direct approach using 2.6 equiv. of LDA, and 2.7 equiv. of (trimethylsilyl)methyl chloride in one step at –78 °C. The reaction mixture was stirred overnight at room temperature affording sulfone **1-2a** in 88% yield, which is comparable with that of sequential alkylation preparation (entry 1).

The symmetrically branched alkyl sulfones **1-2h,l,n-p** and **1-2i** ($R^2 = R^3$) were synthesized by sequential alkylation of **1-1a** and **1-1b**, respectively, with the identical alkyl iodide in the presence of TMEDA in good to excellent yield by a one-pot procedure (entries 8,9,12,14-16). The more direct approach using 2.6 equiv. of LDA and the alkyl iodide furnished mixtures of the desired symmetrically branched products **1-2** and monoalkylated sulfones **1-3** in less satisfactory yields, because the reaction stops after some time.

The syntheses of isopentyl phenyl sulfone (**1-3b**), 1-(trimethylsilyl)eth-2-yl phenyl sulfone (**1-3c**) and isobutyl phenyl sulfone (**1-3d**) were performed starting from methyl phenyl sulfone (**1-1a**) by deprotonation with *n*BuLi followed by alkylation with isobutyl iodide, (chloromethyl)trimethylsilane or isopropyl iodide, respectively.

The monoalkylated sulfones **1-3b-d**, commercially available ethyl phenyl sulfone (**1-3e**) and sulfone **1-3a**, prepared by Zn/CuI-mediated reductive coupling procedure (Scheme 1.1), served as starting materials for the preparation of unsymmetrically branched sulfones **1-2d-g,j,k,m** (entries 4-7,10,11,13) and symmetrical **1-2q** (entry 17) by alkylations in good to excellent yields. No overalkylation was observed except for **1-2g** and **1-2q**, where 36% and 10% of trialkylated sulfone was formed (not shown).

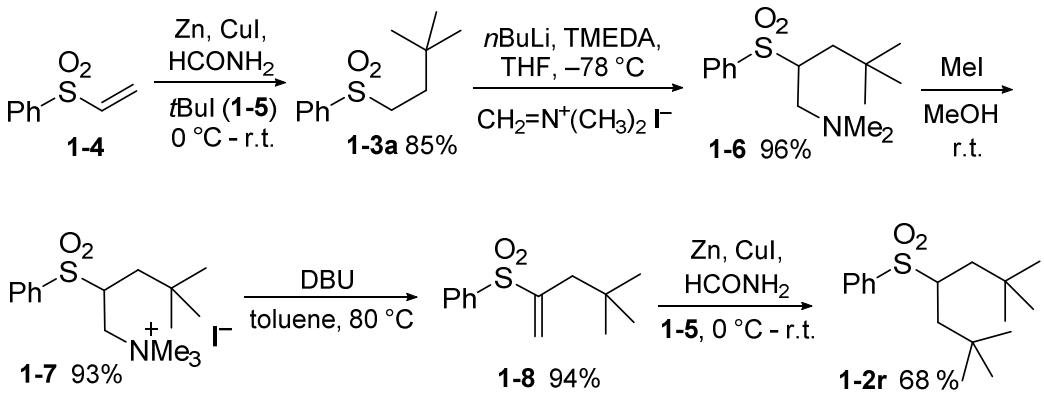
Table 1.1. Synthesis of α-substituted alkyl phenyl sulfones **1-2a-q** via alkylation reactions.[a]



Entry	**1-3** or **1-1**	R^3X	Product	R^2	R^3	Yield [%][b]
1	**1-1a**	$TMSCH_2Cl$[c]	**1-2a**	CH_2TMS	CH_2TMS	89
2	**1-1a**	$DMPSCH_2Cl$[c,d]	**1-2b**	CH_2DMPS	CH_2DMPS	58
3	**1-1a**	$DMVSCH_2Cl$[c,e]	**1-2c**	CH_2DMVS	CH_2DMVS	61
4	**1-3a**[f]	EtI	**1-2d**	CH_2tBu	Et	95
5	**1-3a**[f]	MeI	**1-2e**	CH_2tBu	Me	94
6	**1-3b**	$TMSCH_2Cl$	**1-2f**	*i*Bu	CH_2TMS	65
7	**1-3c**	EtI	**1-2g**	CH_2TMS	Et	45[g]
8	**1-1a**	*i*BuI[c]	**1-2h**	*i*Bu	*i*Bu	81
9[h]	**1-1b**	*i*BuI[c]	**1-2i**	*i*Bu	*i*Bu	79
10	**1-3b**	EtI	**1-2j**	*i*Bu	Et	89
11	**1-3b**	MeI	**1-2k**	*i*Bu	Me	85
12	**1-1a**	*i*PrI[c]	**1-2l**	*i*Pr	*i*Pr	54
13	**1-3d**	EtI	**1-2m**	*i*Pr	Et	80
14	**1-1a**	BnBr[c]	**1-2n**	Bn	Bn	70
15	**1-1a**	*i*PentI[c,i]	**1-2o**	*i*Pent	*i*Pent	61
16	**1-1a**	EtI[c]	**1-2p**	Et	Et	72
17	**1-3e**[j]	MeI	**1-2q**	Me	Me	79[k]

[a] General conditions: 10 mmol sulfone, 13 mmol *n*BuLi, 20 mmol TMEDA, –78 °C, 10 min, then 13 mmol alkyl halide, –78 °C, 10 min, then warmed to defined T (see Chapter 5.2.1) until the reaction was complete (entries 4-7,10,11,13,17). For symmetrically branched sulfones, the addition of reagents was repeated (entries 1-3,8,9,12,14-16). [b] Isolated. [c] $R^2X = R^3X$. [d] DMPS = $SiMe_2Ph$. [e] DMVS = $SiMe_2CH{=}CH_2$. [f] For preparation see Scheme 1.1. [g] 36% of 2-ethyl-1-(trimethylsilyl)but-2-yl phenyl sulfone. [h] R^1 = Me. [i] *i*Pent = isopentyl. [j] Used from commercial supplier. [k] 10% of *tert*-butyl phenyl sulfone isolated.

2,2,6,6-Tetramethylhept-4-yl phenyl sulfone (**1-2r**) was prepared recently by standard alkylation in insufficient 0.8% yield.[144] Radical addition conditions were much more efficient to afford **1-2r** (Scheme 1.1). Monoalkylated sulfone **1-3a** was synthesized by Zn/CuI-mediated reductive coupling of commercially available phenyl vinyl sulfone (**1-4**) and *tert*-butyl iodide (**1-5**) in formamide in good yield.[154] Alkylated sulfone **1-3a** was deprotonated by *n*BuLi in the presence of TMEDA. Subsequent nucleophilic addition of the resulting α-carbanion to Eschenmoser´s salt afforded amine **1-6** in excellent yield.



Scheme 1.1. Approach to 2,2,6,6-tetramethylhept-4-yl phenyl sulfone (**1-2r**).

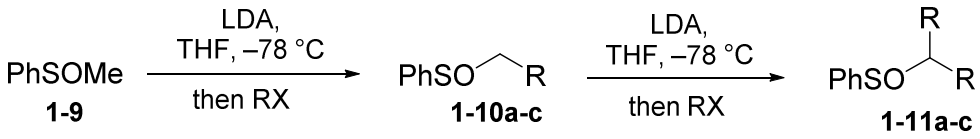
nding starting **1-6** with methyl iodide in methanol was followed by treatment of the corresponding quarternary ammonium salt **1-7** with DBU affording vinyl sulfone **1-8**. The reductive *tert*-butyl radical addition was repeated providing dialkylated sulfone **1-2r** in an overall 49% yield over five steps.

Sulfoxides **1-11a** and **1-11b** representing differently branched analogs of sulfones **1-2p** and **1-2h** were prepared by similar alkylation reactions from methyl phenyl sulfoxide (**1-9**) in two steps (Table 1.2). *n*BuLi in the presence of TMEDA was not efficient enough for the preparation of monoalkylated sulfoxides giving only low yields around 40% (not shown), therefore LDA was used as a base. Monoalkylated sulfones **1-10a-c** were isolated (entries 1-4) and the second alkylation afforded the desired sulfoxides **1-11a-b** in good yields (entries 1-2).

However, the reaction of **1-10c** did not afford β,β-disilylated sulfoxide **1-11c**, which would represent an analog of β,β-disilylated sulfone **1-2a**, giving an inseparable mixture of side products and recovered starting material (entry 3-4). Using *t*BuLi or *n*BuLi in the presence of HMPA did not lead to any improvement. Attempts to perform the alkylation of **1-10c** with isobutyl iodide did not afford the corresponding sulfoxide as well (not shown).

Similar alkylations[155] of α-lithium sulfoxide, prepared by lithiation of **1-10c** with MeLi in the absence of additives, were reported earlier as well as its reaction with various aldehydes, ketones and epoxides.[156] Even repeating the reported conditions did not lead to the desired sulfoxide **1-11c**, giving 56% of recovered starting material and an unidentified mixture of side products (not shown). The corresponding α-sulfinylalkyllithium is probably not reactive enough towards the silylated halides, thus competing reactions occur. The reason for that is not clear, however the role of steric factors is unlikely considering the facile preparation of **1-11b**.

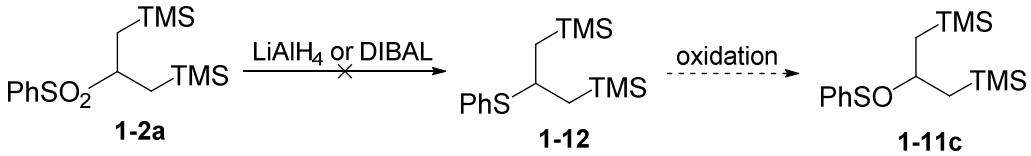
Table 1.2. Preparation of α-substituted phenyl sulfoxides **1-10a-c** and **1-11a-b** by alkylation reactions.[a]



Entry	RX	R	Product	Yield [%]	Product	Yield [%]
1	EtI	Et	**1-10a**	67	**1-11a**	55
2	*i*BuI	*i*Bu	**1-10b**	75	**1-11b**	82
3	$TMSCH_2Cl$	CH_2TMS	**1-10c**	57	**1-11c**	0[b]
4	$TMSCH_2I$	CH_2TMS	**1-10c**	79	**1-11c**	0[c]

[a] General conditions: 14 mmol diisopropylamine, 13 mmol *n*BuLi, –78 °C, 30 min, then 10 mmol sulfoxide, –78 °C, 20 min, then 14 mmol RX, –78 °C, 15 min, then warmed to –40 °C (entry 1) or 0 °C (entries 2-4) until complete. [b] 68% **1-10c** recovered. [c] 53% **1-10c** recovered.

Another approach to sulfoxide **1-11c** via reduction of sulfone **1-2a** to sulfide **1-12** and subsequent oxidation was not successful (Scheme 1.2). Sulfone **1-2a** was not reduced neither by lithium alluminium hydride nor by DIBAL under standard conditions even using large excess of reducing agents. Addition of $TiCl_4$ to $LiAlH_4$ did not lead to the reduction but to a partial decomposition of the starting material.

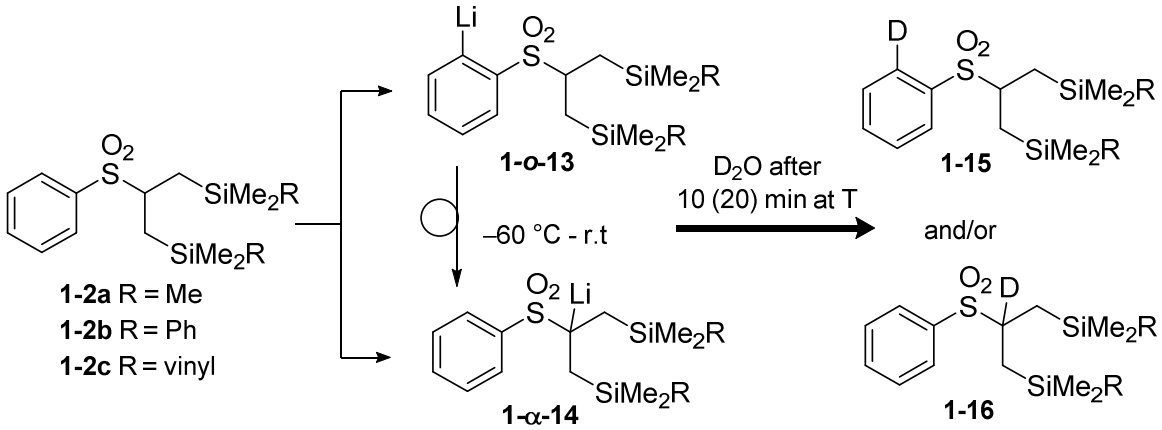


Scheme 1.2. Alternative attempts on synthesis of disilylated sulfoxide **1-11c**.

3.1.2. Investigation of transmetalation at potential precursors for the Julia reactions

The initial deprotonation of β,β-disilylated sulfone **1-2a** by *n*BuLi in the presence of TMEDA at –78 °C proceeded selectively at the *ortho*-position and a transmetalation occurred on warming to 0 °C (Table 1.3, entry 1).[144] The regioselectivity of metalation and the facility of transmetalation was investigated by deprotonation/deuteration experiments. Sulfones **1-2b,c** with different substitution pattern were treated with *n*BuLi in the presence of different additives at –78 °C for a constant time of 10 min (Table 1.3, entries 2-7).

Table 1.3. Metalation selectivity of silylated sulfones **1-2a-c** and subsequent transmetalation.[a]



Entry	**1-2**	*n*-BuLi [equiv.]	Additive[b]	Solvent	**1-15/1-16** [c]					
					–78 °C	–60 °C	–40 °C	–20 °C	0 °C	r.t.
1	**1-2a**[d]	1.3	TMEDA	THF	10:1	-	3:1	-	1:5	1:20
2	**1-2b**[e]	1.2	TMEDA	THF	100:0	100:0	99:1	85:15	74:25	73:23
3	**1-2b**[e]	1.2	TMEDA	DME	100:0	99:1	99:1	95:5	95:4	-
4	**1-2b**[e]	1.2	HMPA	THF	80:20	50:50	40:60	40:60	39:61	-
5	**1-2c**[e]	1.2	TMEDA	THF	88:4	78:1	77:1	52:23	1:57	-
6	**1-2c**[f]	1.2	TMEDA	Et_2O	73:26	-	-	-	0:81	0:66
7	**1-2c**[f]	1.5	TMEDA[g]	Et_2O	74:40[h]	-	-	-	3:85	0:84

[a] Initial conditions: 0.5 mmol sulfone, excess *n*BuLi, solvent, additive, –78 °C. [b] 1 mmol TMEDA or 3 mmol HMPA. [c] Ratio ***o*-D/α-D** determined by integration of the ^{1}H NMR spectra, expressed in percent of deuteration of *ortho*- and α-position, respectively, 1H = 100%. [d] From ref. [144], 0.65 mmol TMEDA, the investigation was performed in 30 min intervals, the ratio not expressed in percent of deuteration. [e] Change of temperature in 10 min intervals. [f] Initial deprotonation at –78 °C, then change of temperature in 20 min intervals to room temperature. [g] 0.75 mmol TMEDA. [h] The total amount of deuterium content referring to more than 100% results from the excess *n*BuLi.

A defined amount of the reaction mixture was removed quickly by a syringe and added to a flame dried vial containing a small amount of deuterium oxide under inert conditions. The products **1-15** and/or **1-16** were isolated and analyzed by ^{1}H NMR spectroscopy. The remaining reaction mixture was warmed in intervals to room temperature and aliquots were analyzed likewise. The mass balance of all investigated reactions was quantitative and the observed ratio of **1-15**/**1-16** accounts for the deprotonation and/or transmetalation intermediates **1-*o*-13**/**1-α-14**. However, taking the samples by syringe involves a minor temperature error, which is inherent to all entries. Nevertheless, the same error applies to all entries as well as the integration error of ^{1}H NMR spectroscopy, thus the results as such are self-consistent.

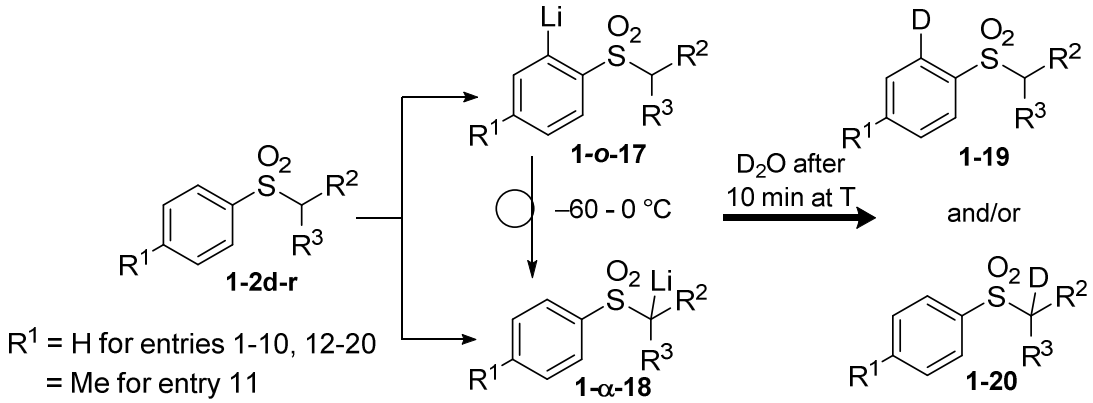
Sulfone **1-2b** was initially *ortho*-lithiated forming **1-*o*-13b**, however, the subsequent transmetalation to **1-α-14b** did not occur to a significant extent in THF or DME (entries 2,3). Using HMPA as an additive led to a change in metalation selectivity and **1-α-14b** was generated via partial transmetalation of **1-*o*-13b** on warming (entry 4).

Sulfone **1-2c** was not deprotonated efficiently by 1.2 equiv. of *n*BuLi in the presence of TMEDA in DME resulting in 60% of **1-*o*-13c**. Moreover, nearly no transmetalation leading to **1-α-14c** occurred on warming to 0 °C (not shown). Repeating the reaction under the same conditions in THF afforded 88% of *ortho*-metalated sulfone **1-*o*-13c**, which transmetalated to **1-α-14c** on warming, however the overall degree of lithiation of sulfone **1-2c** decreased from 92% at –78 °C to 58% at 0 °C (entry 5). The desired transmetalation giving **1-α-14c** occurred similarly on warming in dry diethyl ether, but the overall lithiation of sulfone **1-2c** dropped from 99% at –78 °C to 81% at 0 °C and 66% at room temperature (entry 6). Using 1.5 equiv. of *n*BuLi in the presence of TMEDA led to high overall lithiation even on warming to room temperature (entry 7).

3.1.3. Scope and the limitation of the transmetalation of alkyl aryl sulfones

The regioselectivity of lithiation of sulfones **1-2d-r** and the facility of the subsequent rearrangement was studied by treating sulfones with *n*BuLi or LDA in the presence of different additives at –78 °C (Table 1.4).[153] Aliquots of the reaction mixture were removed in 10 min intervals at defined temperature, quenched with deuterium oxide and the products **1-19** and/or **1-20** were isolated and analyzed by ^{1}H NMR spectroscopy. The observed ratio of **1-19**/**1-20** accounts for the deprotonation and/or transmetalation intermediates **1-*o*-17**/**1-α-18**.

Table 1.4. Metalation selectivity of sulfones **1-2d-r** and subsequent transmetalation.[a]



Entry	**1-7**	R^2	R^3	Additive	**1-19/1-20**[b]				
					–78 °C	–60 °C	–40 °C	–20 °C	0 °C
1	**1-2r**	CH_2tBu	CH_2tBu	TMEDA	24:1	12:1	1:1.4	1:6	1:9
2	**1-2d**	CH_2tBu	Et	TMEDA	8:1	7:1	2:1	0:100	0:100
3[c]	**1-2e**	CH_2tBu	Me	TMEDA	1.4:1	1.5:1	1:1.7	1:2.5	1:3
4	**1-2e**	CH_2tBu	Me	HMPA[d]	0:100	1:57	n.d.[e]	n.d.	n.d.
5	**1-2f**	CH_2TMS	*i*Bu	TMEDA	32:1	19:1	1.1:1	1:49	1:49
6	**1-2g**	CH_2TMS	Et	TMEDA	1:1.4	1:1.7	1:13	1:65	1:99
7	**1-2h**	*i*Bu	*i*Bu	TMEDA	31:1	23:1	3:1	1:46	1:46
8	**1-2h**	*i*Bu	*i*Bu	TMEDA/ LiCl[f]	12:1	4:1	1:1.6	0:100	0:100
9[g]	**1-2h**	*i*Bu	*i*Bu	-	17:1	2:1	1:2	1:6	1:75
10	**1-2h**	*i*Bu	*i*Bu	HMPA[d]	0:100	0:100	n.d.[e]	n.d.	n.d.
11[h]	**1-2i**	*i*Bu	*i*Bu	TMEDA	99:1	9:1	4:1	1:4	1:11
12	**1-2j**	*i*Bu	Et	TMEDA	1:1.3	1:4	1:35	1:68	0:100
13	**1-2k**	*i*Bu	Me	TMEDA	1:3	1:3	n.d.[e]	n.d.	n.d.
14[c]	**1-2l**	*i*Pr	*i*Pr	TMEDA	2:1	1:3	1:47	0:100	0:100
15	**1-2l**	*i*Pr	*i*Pr	HMPA[d]	1:99	1:99	n.d.[e]	n.d.	n.d.
16	**1-2m**	*i*Pr	Et	TMEDA	1:4	1:7	0:100	0:100	0:100
17	**1-2n**	Bn	Bn	TMEDA	1:13	1:10	1:24	1:31	1:10
18	**1-2o**	*i*Pent[i]	*i*Pent	TMEDA	1:30	1:75	n.d.[e]	n.d.	n.d.
19	**1-2p**	Et	Et	TMEDA	1:16	1:13	n.d.[e]	n.d.	n.d.
20	**1-2q**	Me	Me	TMEDA	1:24	1:24	n.d.[e]	n.d.	n.d.

[a] Initial conditions: 0.5 mmol sulfone, 0.55 mmol *n*BuLi, 1 mmol TMEDA, THF, –78 °C. [b] Ratio **1-19/1-20** determined by integration of the ^{1}H NMR spectra. [c] Reaction run multiple times with very similar result. [d] 3 mmol HMPA. [e] n.d. = not determined since immediate α-deprotonation. [f] 2 mmol LiCl. [g] 0.55 mmol LDA as a base with no additives. [h] R^1 = Me. [i] *i*Pent = isopentyl.

The **1-19**/**1-20** ratios were determined by integration of the corresponding *ortho*- and α-H signals in the ^{1}H NMR spectra (Chapter 5.4, Figure 5.1). The original 2.00 integral of the two *ortho*-H in non deuterated sulfone **1-2h** was after the deprotonation/deuteration at low temperature decreased to 1.15 showing 85% *ortho*-deuteration. The signals of the *meta*- and *para*-aromatic signals were taken as a reference. The integral of the α-proton signal was lowered from 1.00 to 0.86 indicating 14% α-deuteration. Similarly, after warming the reaction mixture, the 1.98 *ortho*-proton integral indicates 2% *ortho*-deuteration and the 0.07 α-proton integral indicates 93% α-deuteration (Chapter 5.4, Figure 5.2).

The deprotonation of symmetrically substituted sulfones **1-2h,i,r** and unsymmetrically substituted sulfone **1-2f** with γ-branched alkyl groups in the presence of TMEDA at –78 °C afforded *ortho*-carbanions with high selectivity (Table 1.4, entries 1,5,7,11). The transmetalation of the generated *ortho*-carbanions to the corresponding α-carbanions **1-α-18f,h,i,r** proceeded on warming to 0 °C. Replacing one of the branched groups by a smaller linear alkyl chain as in unsymmetrical sulfones **1-2d,e,g,j** led to a decrease of the initial metalation selectivity forming mixtures of **1-*o*-17** and **1-α-18** (entries 2,3 vs.1; entry 6 vs. Chapter 3.1.2, Table 1.3, entry 1; and entry 12 vs. 7). The bulkier the γ-branching of one alkyl chain is, the slower was the transmetalation of **1-*o*-17** to **1-α-18** (entries 2,3 vs. 12).

Additives exhibited significant effects on the direction of the metalation. HMPA caused for all studied substrates **1-2e**,**h,l** the reversal of the regioselectivity and thus forming immediately α-carbanions **1-α-18e,h,l** (entries 4,10,15). No **1-*o*-17** was observed even after very short deprotonation times. Moreover, **1-*o*-17h** formed by metalation of **1-2h** in the presence of 2 equiv. TMEDA instantly transmetalated to **1-α-18h** at –78 °C when adding 6 equiv. of HMPA (not shown). Lithium chloride, which causes the modification of aggregates of organolithium compounds and acts as a catalyst in a number of transformations,[157,158] did not influence the deprotonation regioselectivity of **1-2h** to a large extent, but accelerated the transmetalation of **1-*o*-17h** to **1-α-18h** (entry 8). LDA can also be used as a base with similar results (entry 9), whereas KHMDS was unreactive under the conditions (not shown).[159–162]

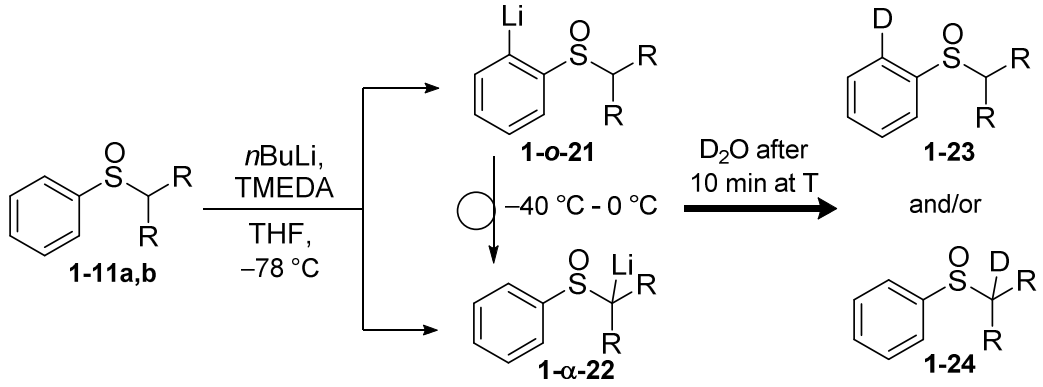
Only a low deprotonation selectivity in favor of DoM intermediate **1-*o*-17l** was observed for sulfone **1-2l** bearing β-branched alkyl chains (entry 14). An experiment performed at –100 °C led to a change of the initial metalation **1-*o*-17l/1-α-18l** ratio to 6:1 (not shown). For the less branched substrates **1-2k** and **1-2m**, the selectivity switched to preferred formation of **1-α-18k** and **1-α-18m** (entries 13, 16). A two-dimensional branching

as in the diarylated sulfone **1-2n** or a more distant δ-branching as in **1-2o** changed the regioselectivity to complete initial α-deprotonation forming **1-α-18n,o** (entries 17,18). Sulfones **1-2p** and **1-2q** having chains without additional branching were also selectively metalated at the α-position (entries 19,20). Experiments run with sulfones **1-2p** and **1-2q** at –78 °C for shorter time (30 s, 1 min and 2 min) showed that the deprotonation occurred initially at the α-position and thus **1-α-18p** and **1-α-18q**, respectively, are not a result of initial *orho*-deprotonation followed by rapid transmetalation.

3.1.4. Initial metalation and potential transmetalation of alkyl aryl sulfoxides

The deprotonation selectivity of alkyl aryl sulfoxides and the potential transmetalation was investigated by metalation followed by deuteration (Table 1.5). Sulfoxide **1-11a** bearing small substituents underwent initial α-lithiation immediately at –78 °C (entry 1). In contrast, sulfoxide **1-11b** bearing bulky γ-branched alkyl chains underwent directed *ortho*-metalation at –78 °C and generated **1-*o*-21b** transmetalated to **1-α-22b** in the range of –40 °C to –20 °C (entry 2). Deuterated sulfones **1-23b** and **1-24b** were accompanied with butyl phenyl sulfoxide, generated via competing sulfoxide-lithium exchange, in up to 10% yield on warming. Its structure was confirmed by MS analysis.

Table 1.5. Metalation selectivity of sulfoxides **1-11a,b** and subsequent carbanion transmetalation.[a]

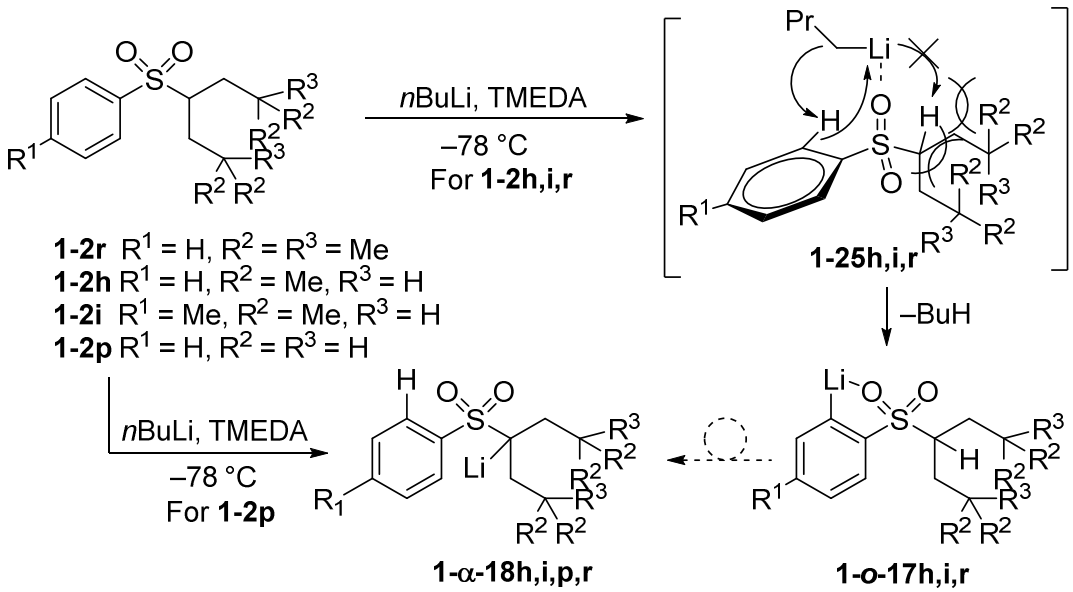


Entry	**1-11**	R	**1-23/1-24**[b]				
			–78 °C	–60 °C	–40 °C	–20 °C	0 °C
1	**1-11a**	Et	1:99	1:49	n.d.[c]	n.d.	n.d.
2	**1-11b**	*i*Bu	100:0	99:1	3:1	1:3	1:99

[a] Initial conditions: 0.5 mmol sulfoxide, 0.55 mmol *n*BuLi, 1 mmol TMEDA, THF, –78 °C. [b] Ratio **1-23/1-24** determined by integration of the ^{1}H NMR spectra. [c] n.d.= not determined since immediate α-deprotonation.

3.1.5. Factors responsible for the initial metalation selectivity

In contrast to other known alkyl aryl sulfones, γ-branched sulfones **1-2h,i,r** undergo initial DoM instead of α-deprotonation forming **1-*o*-17h,i,r**, despite having an α-hydrogen atom (Scheme 1.3). The generated metalated sulfone **1-*o*-17h,i,r** transmetalates subsequently to **1-α-18h,i,r**. Sulfone **1-2p** with no additional branching undergo in contrast the originally expected α-lithiation forming **1-α-18p**.



Scheme 1.3. Mechanistic proposal for the initial lithiation of sulfones **1-2h,i,p,r**.

Sulfones **1-2h**, **1-2l**, and **1-2p** are examples of the most and least sterically hindered investigated derivatives. Their structures were determined by X-ray crystallography to demonstrate possible correlation between their geometrical features and metalation selectivity (Figures 1.1-1.3). The α-hydrogen atom of **1-2h** is in an almost synclinal arrangement to the methyl groups C10 and C14, respectively, which leads to significant steric shielding (Figure 1.1). In contrast, the α-hydrogen atom of **1-2l** displays a close contact to only one methyl group (Figure 1.2). Sulfones **1-2h** and **1-2p** have an almost staggered confomation around the C7-S1 bond. Sulfone **1-2l** deviates more strongly from a staggered conformation having torsion angles from O1 to C8, C11 and H(C7) of –83.0, 49.9 and 162.9°, respectively, and from O2 to C8, C11 and H(C7) of 48.1, –179.5 and –66.1°, respectively. The torsion angles O1-S1-C1-C2 of **1-2h**, **1-2l** and **1-2p** vary to some extent and amount to 12.2(1), –8.3(2) and 11.1(3)°, respectively, while the O1-S1-C1-C6 torsion angle has a narrow range of –40.3(1), 40.2(2) and –38.9(3)°, respectively. The distances between O1 and H(C2) are

similar around 2.5 Å (2.53, 2.50, 2.52 Å), while the O1-H(C6) distance is around 2.77 Å (2.76, 2.79, 2.75 Å). The distance of the gauche-oriented O2 to H(C7) is with 2.80-2.83 Å (2.82, 2.83, 2.80 Å) relatively similar, but significantly longer.

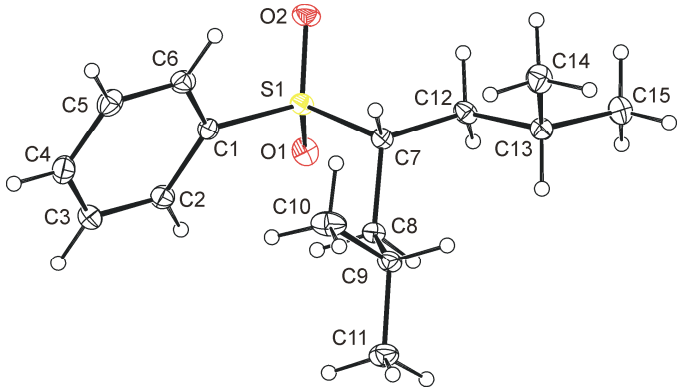


Figure 1.1. Crystal structure of 2,6-dimethylhept-4-yl phenyl sulfone (**1-2h**). Displacement ellipsoids are drawn at 30% probability level.

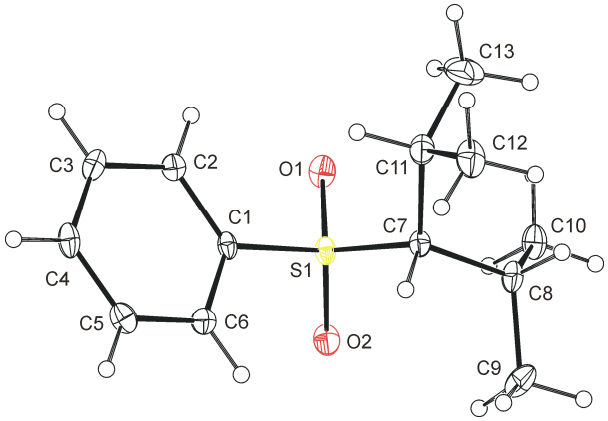


Figure 1.2. X-Ray crystallographic view of 2,4-dimethylpent-3-yl phenyl sulfone (**1-2l**). Displacement ellipsoids are drawn at 30% probability level.

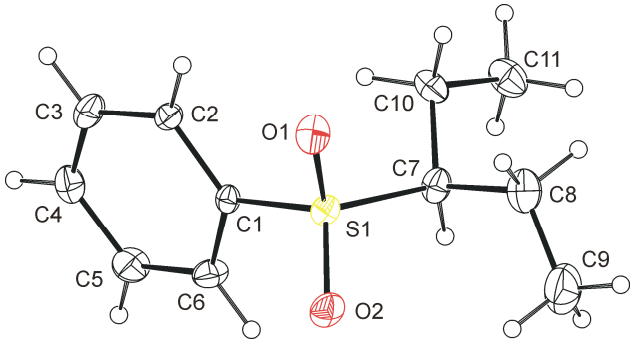


Figure 1.3. X-Ray crystal structure of pent-3-yl phenyl sulfone (**1-2p**). Displacement ellipsoids are drawn at 30% probability level. (The molecule contains two independent units in the elementary cell.)

Steric hindrance seems to be the factor responsible for the regioselectivity of the metalation. In compounds **1-2h,i,r** the α-hydrogen atom is not well accessible for the base (Figure 1.1). *n*BuLi precomplexes to a sulfonyl oxygen atom (**1-25h,i,r**) and thus the access to the at best *gauche*-oriented α-hydrogen atom is blocked by R^2 of the alkyl chain in the transition state (Scheme 1.3). This allows to deprotonate the thermodynamically less acidic *ortho*-position. Using HMPA as an additive causes the reversal of the regioselectivity and α-lithiation is favored for all investigated substrates. This feature can be explained by coordination of the stronger Lewis base HMPA to the lithium cation of *n*BuLi, therefore the base can access the more acidic α-position directly without coordination at the sulfone.

When only one alkyl chain is γ-branched as in **1-2d-g,j** the regioselectivity in favor of *ortho*-lithiation was decreased, since the α-hydrogen atom is more accessible and thus α-lithiation competes (Chapter 3.1.3, Table 1.4). The originally expected α-deprotonation in the presence of TMEDA occurs either for substrates **1-2p,q** with no additional branching or for sulfones **1-2n** and **1-2o** with flat or more remote branching, respectively, where the α-hydrogen can be easily approached by the base. Sulfone **1-2l** in spite of closer β-branching, can occupy orientations in which only one face around the α-proton is shielded by a neighboring methyl group (*cf.* Figure 1.2). Therefore α-deprotonation competes with moderately favored DoM.

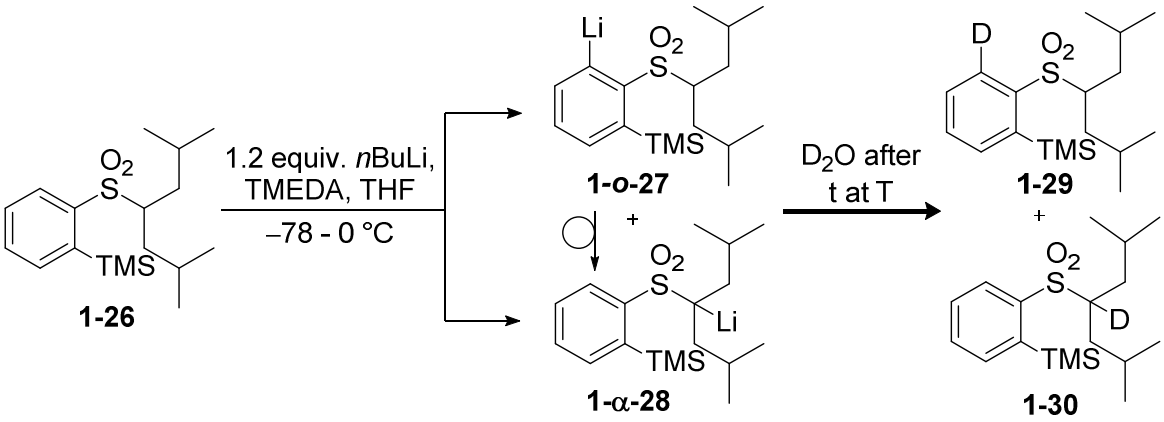
Sulfones **1-2b,c** with differentially substituted silyl groups reacted by initial DoM (Chapter 3.1.2, Table 1.3) as the earlier reported **1-2a**.[144] However, only **1-*o*-13c** rearranged completely to **1-α-14c** allowing the application in Julia reaction in the total synthesis of iridoids. Steric factors do not enable complete transmetalation of sulfone **1-*o*-13b** to **1-α-14b** and thus further application of sulfone **1-2b** in the Julia olefination is not possible. Initial *ortho*-metalation and subsequent transmetalation for sterically demanding sulfoxide **1-11b** was observed similarly as for corresponding sulfone **1-2h**, whereas **1-11a** underwent only α-lithiation (Chapter 3.1.4, Table 1.5).

Regarding all the results from monitoring the initial deprotonation and potential transmetalation, the type of branching and its distance from the sulfonyl group are the main factors determining the initial metalation regioselectivity. The studies on model sulfoxides with analogous structures to sulfones proved that DoM followed by the transmetalation represents a more general feature and revealed possible applications to sulfides or phosphine oxides.[163]

3.1.6. Initial metalation and potential transmetalation of *ortho*-substituted alkyl aryl sulfones

ortho-Substituted sulfone **1-26** was prepared from sulfone **1-2h** (Chapter 3.2.1, Table 2.2). The investigation of initial metalation of **1-26** and subsequent transmetalation showed that directed *ortho*-deprotonation occurred initially at –78 °C and thus generated metalated sulfone **1-*o*-27** showed very similar transmetalation features as sulfone **1-2h** forming **1-α-28** on warming, as was confirmed by ^{1}H NMR analysis after deuteration (Table 1.6 vs. Chapter 3.1.3, Table 1.4, entry 7).

Table 1.6. Initial metalation and subsequent transmetalation of sulfone **1-26**.



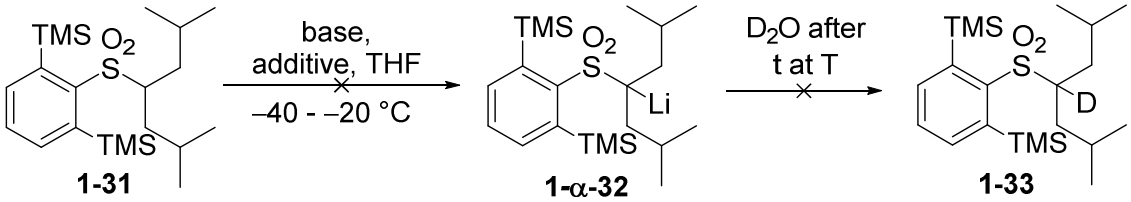
Entry	T [°C]	t [min][a]	**1-29**/**1-30**[b]
1	–78	10	99:1
2	–60	20	99:1
3	–40	30	1:1
4	–20	40	1:98
5	0	50	1:99

[a] Time refers to the start of the deprotonation. [b] Ratio **1-29**/**1-30** determined by ^{1}H NMR spectroscopy, quantitative mass balance.

ortho,ortho'-Bis(trimethylsilyl)phenyl sulfone **1-31** was prepared from sulfone **1-26** (Chapter 3.2.3, Table 2.7). Its α-deprotonation by *n*BuLi in the presence of TMEDA did not afford **1-α-32** at all even after 30 min at −40 °C, as indicated by the absence of deuterated sulfone **1-33** after quenching the reaction with D_2O (Table 1.7, entry 1). Using HMPA as an additive surprisingly also did not allow α-metalation (entry 2). Application of *t*BuLi as a stronger base (entry 3) and raising the reaction temperature to −20 °C (entry 4) were also not

successful, suggesting that sulfone **1-31** is too sterically hindered for deprotonation by lithium bases.

Table 1.7. Initial deprotonation of sulfone **1-31**.

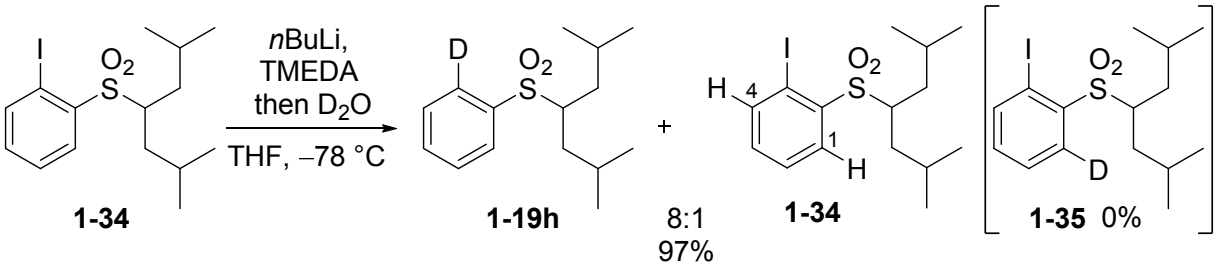


1-31 **1-α-32** **1-33**

Entry	Base [equiv.]	Base	Additive[a]	T [°C]	t [min][b]	**1-33** [%][c]
1	1.1	*n*BuLi	TMEDA	−40	30	0
2	1.1	*n*BuLi	HMPA	−40	30	0
3	2.2	*t*BuLi	TMEDA	−40	10	0
4	2.2	*t*BuLi	TMEDA	−20	20	0

[a] 2 equiv. TMEDA or 6 equiv. HMPA. [b] Time after start of the deprotonation. [c] Determined by integration of the ^{1}H NMR spectra, quantitative mass balance.

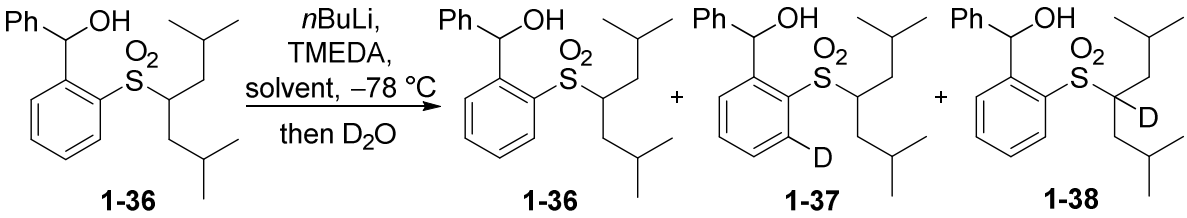
Lithium-halogen exchange is typically an extremely fast reaction and is helpful for the generation of organolithiums, which could be further functionalized by reaction with various electrophiles.[49,164–166] Therefore the investigation of the initial metalation regioselectivity of *ortho*-iodo derivative **1-34** was mandatory in order to compare the reaction rates of DoM vs. lithium-iodine exchange (Scheme 1.4). *ortho*-Iodo derivative **1-34** was prepared from sulfone **1-2h** (Chapter 3.2.1, Table 2.2) and was treated with 1.1 equiv. of *n*BuLi in the presence of TMEDA at −78 °C. Aliquots of the reaction mixture were quenched with D_2O after 5 and 30 min. The samples were analyzed by ^{1}H NMR spectroscopy and showed identical results. The reaction afforded sulfone **1-19h** and a small amount of starting material **1-34** in an 8:1 ratio. This ratio was determined from the 8:1 integration ratio of α-protons of **1-19h** and **1-34** assuming potential α-deprotonation occurring only to a negligible extent at low temperature (Chapter 3.1.3, Table 1.4). *ortho*-Deuterated sulfone **1-35** was not formed as indicated by the 1:1 integration ratio of H^1 and H^4. Including experimental and inherent integration errors of ^{1}H NMR spectroscopy, the lithium-iodide exchange proved to be at least twenty times faster than DoM when treating sulfone **1-34** with *n*BuLi.



Scheme 1.4. Investigation of lithium-halogen exchange reaction as a competition to *ortho*-deprotonation.

ortho-(Hydroxybenzyl)phenyl alkyl sulfone **1-36** was prepared from sulfone **1-2h** (Chapter 3.2.1, Table 2.1). Because of the presence of a free hydroxy group, sulfone **1-36** was deprotonated with 2.2 equiv. of *n*BuLi in the presence of TMEDA in THF at −78 °C (Table 1.8, entries 1-3). Samples of the reaction mixture were quenched with D_2O after 10, 30 and 50 min at this temperature. The samples were analyzed by ^1H NMR spectroscopy and showed consistent results. Sulfone **1-36** was deprotonated in *ortho*-position only to an extent of 23% even after longer reaction time as indicated by the formation of deuterated sulfone **1-37**. The experiment was repeated in DME giving similar results. Sulfone **1-36** was *ortho*-deprotonated to an extent of 33-35% (entries 4-5).

Table 1.8. Metalation selectivity of sulfone **1-36**.

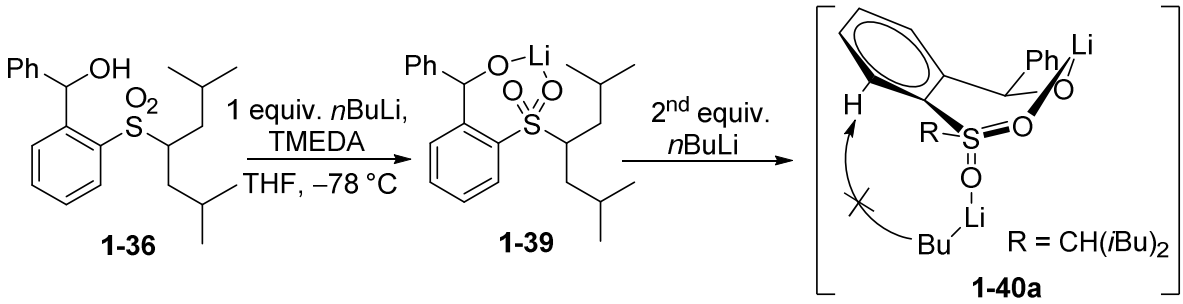


Entry	*n*BuLi [equiv.]	Solvent	t [min][a]	**1-36**[%][b]	**1-37** [%][b]	**1-38** [%][b]
1	2.2	THF	10	77	23	0
2	2.2	THF	30	77	23	0
3	2.2	THF	50	77	23	0
4	2.2	DME	5	67	33	0
5	2.2	DME	50	65	35	0
6	3	THF	5	9	65	26
7	3	THF	50	8	68	24

[a] Time after start of the deprotonation. [b] Determined by integration of the ^1H NMR spectra, quantitative mass balance.

Therefore, three equivalents of *n*BuLi were used for deprotonation of sulfone **1-36** in the presence of TMEDA in THF and samples of the reaction mixture were quenched with D_2O after 5 and 50 min (entries 6,7). This approach provided 65% of *ortho*-deuterated **1-37** after 5 min accompanied by 26% of α-deuterated **1-38** and 9% of the recovered starting material **1-36** (entry 6). The metalation ratio remained similar after 45 min giving sulfones **1-37** and **1-38** in 2.8:1 ratio (entry 7).

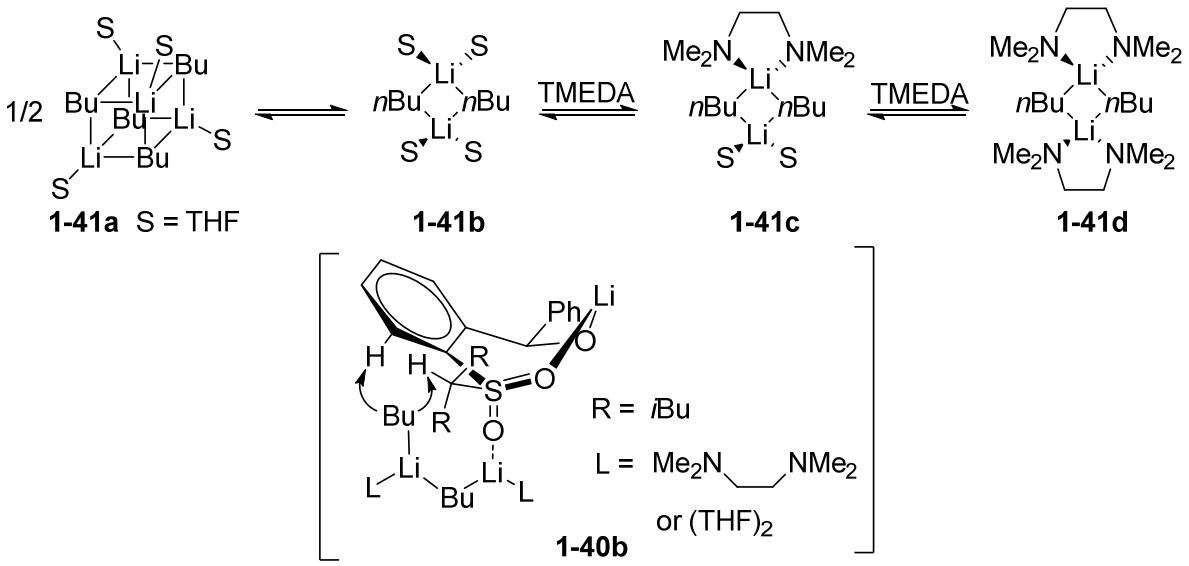
The different behavior can be rationalized as follows. The hydroxybenzyl group in **1-36** is first deprotonated giving seven-membered chelated lithium alkoxide **1-39** thus limiting the conformational flexibility of the molecule (Scheme 1.5). The phenyl ring of the o*rtho*-hydroxybenzyl group and the alkyl group will occupy pseudo-equatorial positions in the energetically favored extended chair-like conformation (**1-40a**). This leads to pseudo-axial orientation of the second oxygen atom of the sulfonyl group. Therefore, *n*BuLi can subsequently coordinate only to this oxygen atom. In this arrangement the base cannot reach the *ortho*-hydrogen efficiently.



Scheme 1.5. Deprotonation of generated lithium alkoxide **1-39**.

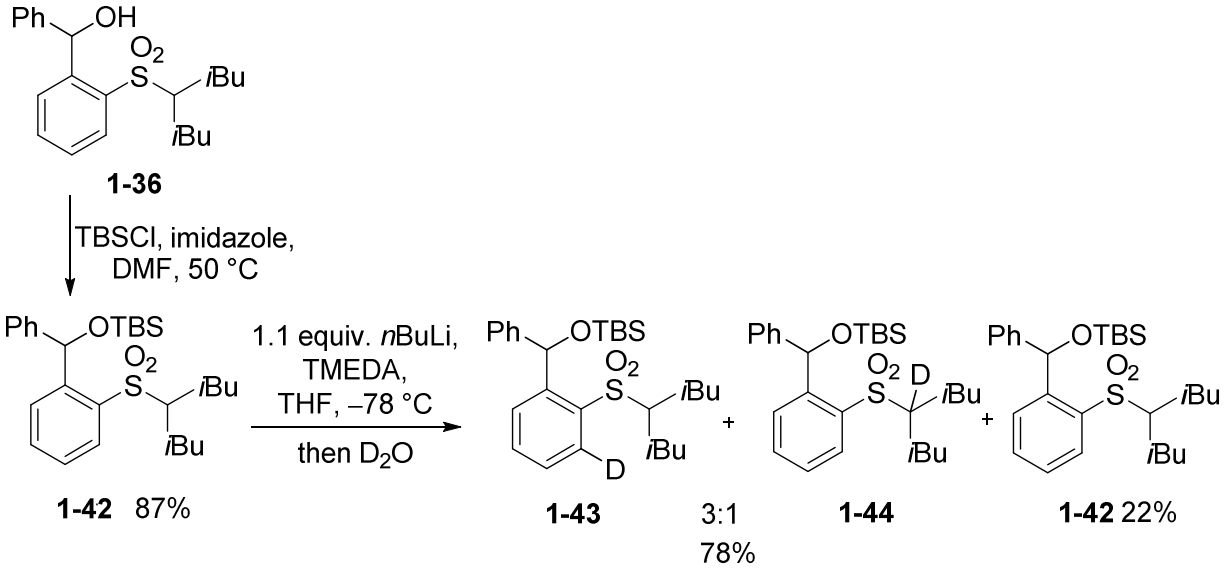
However monomeric forms of *n*BuLi are not known. It forms chelated dimers **1-41d**, when solvated by TMEDA,[167–169] or a mixture of tetramer **1-41a** and dimer **1-41b** in THF (Scheme 1.6).[170] Seebach and coworkers showed that the addition of TMEDA to *n*BuLi in THF shifts the tetramer-dimer mixture toward dimers.[171] This shift has been deduced as evidence that TMEDA and THF are both important in *n*BuLi/TMEDA/THF mixtures.[172] Further investigation of the structure of the *n*BuLi dimer in a mixture of THF and TMEDA provided evidence that TMEDA serially displaces THF in dimeric **1-41b** forming **1-41d** probably via mixed-solvated dimer **1-41c**.[173] Since open dimers have been frequently proposed as intermediates for 1,2-addition of alkyllithiums to imines,[173–175] the *ortho*-hydrogen might be thus reached by the second *n*BuLi unit in an open dimer-based transition state similar to **1-40b** (Scheme 1.6). However, the α-hydrogen is accessible to the

base in this transition state as well resulting in good metalation yield, but lower DoM selectivity.



Scheme 1.6. Structure of *n*BuLi aggregates **1-41** in THF/TMEDA and open dimer-based transition state **1-40b** for deprotonation of lithium alkoxide **1-39**.

To prevent chelation by the hydroxy group in **1-36**, it was protected as a *tert*-butyldimethylsilylether with TBSCl in the presence of imidazole in DMF (Scheme 1.7). Protected alcohol **1-42** was deprotonated under standard conditions using 1.1 equiv. of *n*BuLi and the reaction mixture was subsequently quenched with D_2O after 10 min. The deprotonation regioselectivity was lower giving deuterated sulfones **1-43** and **1-44** in a 3:1 ratio in 78% yield.



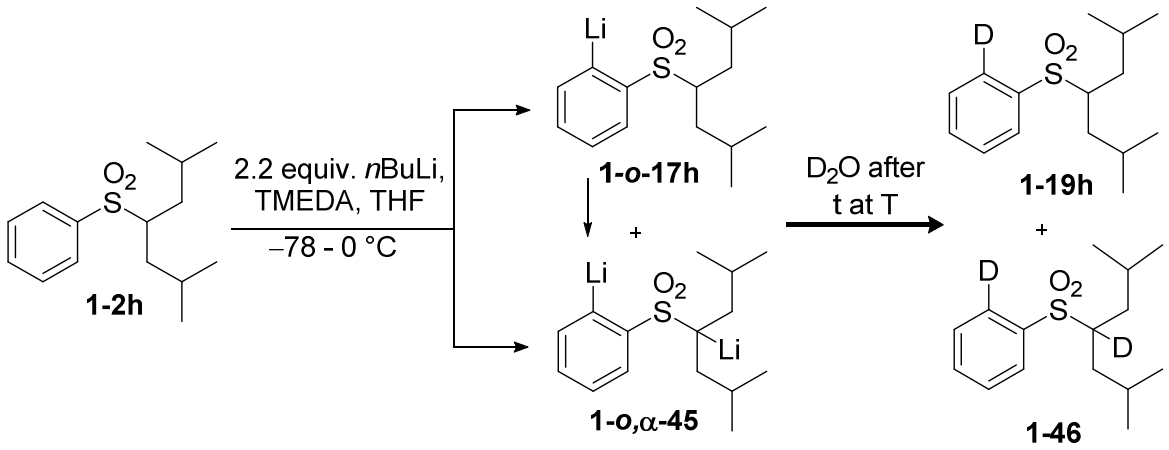
Scheme 1.7. Metalation selectivity of protected sulfone **1-42**.

This ratio approximately corresponds to the 2.5:1 ratio obtained by deprotonation/deuteration of unprotected alcohol **1-36** with three equivalents of *n*-BuLi (Table 1.8, entry 6). The lower metalation selectivity is probably caused by bulky (silyloxy)benzyl group. Even though, α-metalation competes to a significant extent (Table 1.8 and Scheme 1.7), this approach can still be suitable for the preparation of *ortho,ortho*'-disubstituted sulfones.

3.1.7. Twofold deprotonation of alkyl aryl sulfones

The sequential, twofold deprotonation of sulfone **1-2h** was investigated (Table 1.9), because dilithio sulfones could be preparatively useful in a variety of ways, as was observed for dilithioallyl phenyl sulfone (see Chapter 1.4).[148]

Table 1.9. Two-fold deprotonation of sulfone **1-2h**.[a]



Entry	T [°C]	t [min] [c]	Ratio **1-19h/1-46**[b]	Entry	T [°C]	t [min] [c]	Ratio **1-19h/1-46**[b]
1	–78	5	78:22	6	–78	5	77:23
2	–60	15	46:54	7	–78	10	67:33
3	–40	25	14:86	8	–60	15	50:50
4	–20	35	6:94	9	–60	30	31:69
5	0	45	4:96	10	–60	40	20:80

[a] Initial conditions: 1 mmol sulfone, 2.2 mmol *n*BuLi, 5 mmol TMEDA, –78 °C. [b] Ratio **1-19h/ 1-46** determined by integration of the ^{1}H NMR spectra (quantitative mass balance). Complete *ortho*-lithiation observed during the reaction period (1.00 *ortho*-H integral). [c] Time after start of the deprotonation.

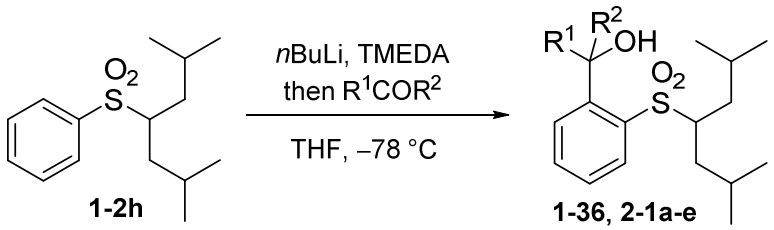
Deprotonation of sulfone **1-2h** with 2.2 equiv. of *n*BuLi in the presence of TMEDA followed by quenching with D_2O showed that the initial deprotonation at –78 °C proceeded quickly at the *ortho*-position giving **1-19h** and only somewhat slower at the α-position resulting in **1-46** (Table 1.9, entries 1,6). The second equiv. of *n*BuLi is, however, consumed much slower at the α-position generating dianion **1-*o*,α-45** on warming (entries 2,3). Dilithiated **1-*o*,α-45** was generated selectively at –20-0 °C (entry 4,5). It was also shown that the dianion **1-*o*,α-45** is formed to a significant extent even at low temperatures after longer reaction time (entry 7,8) and is generated as the predominant intermediate after 30 min at –60 °C (entry 9,10). Another experiment proved the selective generation of dianion **1-*o*,α-45** at –40 °C after 30 min (not shown). The first compounds of this type[147–150] were in contrast to **1-*o*,α-45** generated in a reverse fashion by initial α-lithiation and subsequent *ortho*-lithiation (see Chapter 1.4).

3.2. Preparative applications of selected sulfonyl carbanions

3.2.1. Reactivity of initially generated *ortho*- and α-sulfonyl carbanions

The regioselective deprotonation of sulfone **1-2h** forming carbanion **1-*o*-17h** is synthetically valuable.[153] The aryllithium derived from **1-2h**, generated under standard conditions at −78 °C after short deprotonation time, underwent addition to aldehydes providing secondary benzylic alcohols **1-36** and **2-1a-c** in good to excellent yield (Table 2.1, entries 1-4). Moreover, nucleophilic additions to enolizable and non-enolizable ketones giving tertiary benzylic alcohols proceeded in very good yield as well (entries 5 and 6).

Table 2.1. Metalation of **1-2h** and addition of **1-*o*-17h** to aldehydes and ketones.

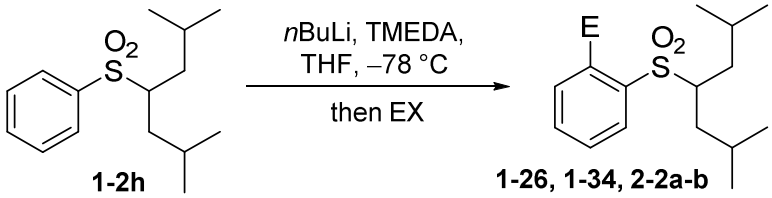


Entry	Product	R^1	R^2	Yield [%]
1	**1-36**	Ph	H	84
2	**2-1a**	*i*Pr	H	90
3	**2-1b**	EtCH=CH	H	79
4	**2-1c**	$PhCH_2CH_2$	H	93
5	**2-1d**	$-(CH_2)_5-$		85
6	**2-1e**	Ph	Ph	94

Several other electrophiles are also applicable in the DoM mode to selectively obtain functionalized products **1-26**, **1-34** and **2-2a-b** (Table 2.2). The aryllithium **1-*o*-17h**, generated under standard conditions at −78 °C after short deprotonation time, underwent the reaction with electrophiles **EX** at low temperature during two hours forming **1-26**, **1-34** and **2-2a-b** in good yields (entries 1-4). It was found that applying identical conditions for deprotonation of **1-2h**, adding TMSCl at −78°C and subsequent warming of the reaction mixture to 0 °C for 15 min led to the formation of **1-26** in 88% yield (not shown). This approach significantly shortened the reaction time without any formation of α-substituted

derivative. Sulfone derivatives **1-34** and **2-2a-b** represent interesting substrates, which can be further used in various cross-coupling reactions.

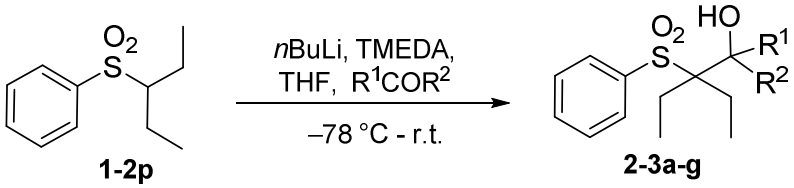
Table 2.2. Scope of the *ortho*-carbanion reaction with electrophiles.



Entry	EX	E	Product	Yield [%]
1	TMSCl	TMS	**1-26**	83
2	I_2	I	**1-34**	77
3	Br_2	Br	**2-2a**	63[a]
4	$B(OMe)_3$	$B(OH)_2$	**2-2b**	83

[a] Not separable from the starting material **1-2h** (31%).

Table 2.3. Metalation of **1-2p** and addition of **1-α-18p** to aldehydes and ketones.



Entry	Product	R^1	R^2	Yield [%]
1	**2-3a**	Ph	H	80
2	**2-3b**	4-Br-C_6H_4	H	65
3	**2-3c**	*i*Pr	H	70
4	**2-3d**	EtCH=CH	H	64
5	**2-3e**	PhCH=CH	H	71
6	**2-3f**	-$(CH_2)_5$-		13[a]
7	**2-3g**	Ph	Ph	0[b]

[a] Product **2-3f** inseparable from 80% of recovered **1-2p**, structure confirmed by MS analysis. [b] 97% **1-2p** and 95% benzophenone recovered.

The α-carbanion generated from sulfone **1-2p** added easily to aldehydes at –78 °C affording α-(hydroxyalkyl)phenyl sulfones **2-3a-e** in good yield (Table 2.3, entries 1-5).

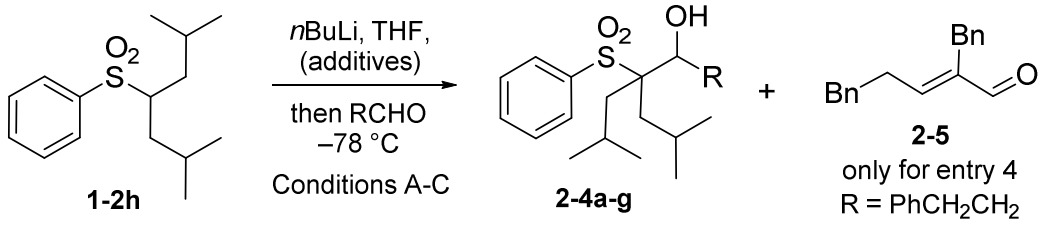
However, its reaction with ketones either afforded the tertiary alcohol **2-3f** in poor yield (entry 6) or did not furnish the desired tertiary alcohol **2-3g** at all (entry 7).

3.2.2. Reactivity of α-carbanions generated via transmetalation

The transmetalation of carbanions **1-*o*-17** to **1-α-18** is synthetically valuable as well. For sulfones, such as **1-2h**, which are initially *ortho*-metalated, conditions for a selective reaction with aldehydes at the α-position, the first step of the Julia olefination, had to be optimized by varying the deprotonation conditions (Table 2.4). Under conditions A the starting sulfone **1-2h** was deprotonated by *n*BuLi with TMEDA in THF at –78 °C and the reaction mixture was warmed to 0 °C over one hour allowing the transmetalation of **1-*o*-17h** to **1-α-18h** to proceed. Subsequently, structurally different aldehydes were added giving α-(hydroxyalkyl)phenyl sulfones **2-4a-g** (entries 1-7). Starting sulfone **1-2h** was recovered in 26-64%. The reaction with ketones did not provide the desired products (not shown) similarly to the reaction with deprotonated **1-2p** (Chapter 3.2.1, Table 2.3).

Conditions B involved deprotonation of sulfone **1-2h** by *n*BuLi in the presence of TMEDA at –20 °C for 10 min and subsequent addition of the aldehyde to the reaction mixture at –78 °C. Under conditions C, the deprotonation of **1-2h** by *n*BuLi and HMPA as an additive was performed at –78 °C for 10 min followed by addition of the aldehyde. Benzaldehyde provided the hydroxy sulfone **2-4a** in good yield under all conditions (entry 1), products **2-4b-c** resulting from reactions of **1-2h** with bromobenzaldehydes were obtained in moderate yield and were accompanied by partial recovery of starting material and unidentified byproducts (entries 2,3). Reaction with enolizable hydrocinnamic aldehyde was complicated by competing formation of the self-aldol condensation product **2-5** (entry 4). Conditions A proved to be the best, while HMPA gave a low yield of **2-4d**. Reactions with α,β-unsaturated aldehydes afforded hydroxy sulfones **2-4e** and **2-4f** in good to excellent yields (entries 5,6). Surprisingly, the reaction of **1-α-18h** with isobutyraldehyde afforded tertiary alcohol **2-4g** only in poor yield (entry 7).

Table 2.4. *ortho*-Metalation of **1-2h**, transmetalation to **1-α-18h** and addition to aldehydes.

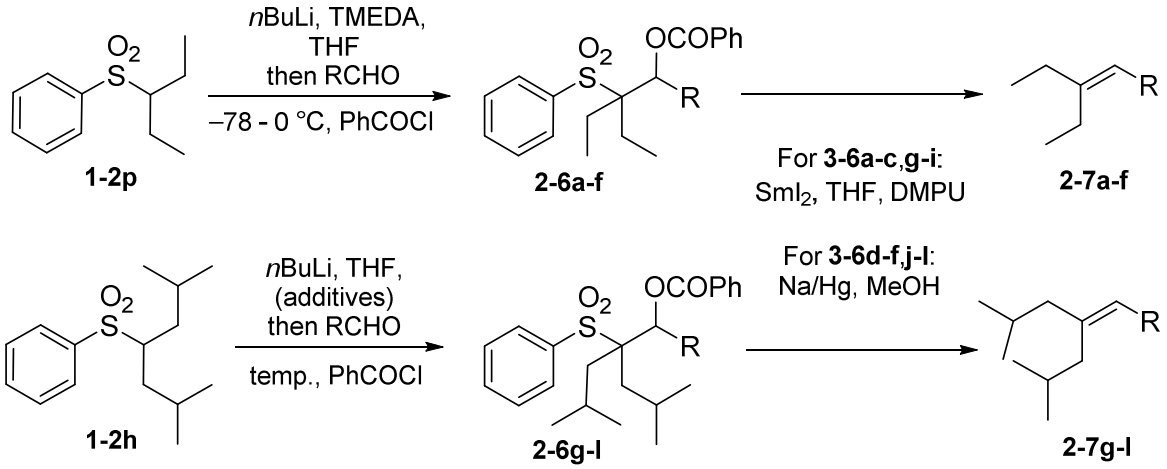


Entry	R	Product	Yield [%] conditions A[a]	Yield [%] conditions B[b]	Yield [%] conditions C[c]
1	Ph	**2-4a**	78	82	75
2	4-BrC_6H_4	**2-4b**	42[d]	-[e]	48[f]
3	3-BrC_6H_4	**2-4c**	44[g]	-[e]	63[h]
4	$PhCH_2CH_2$	**2-4d**	61[i]	53[j]	25[k]
5	EtCH=CH	**2-4e**	50	-[e]	61
6	PhCH=CH	**2-4f**	70	96	98
7	*i*Pr	**2-4g**	17[l]	16[m]	44[n]

[a] Conditions A: Deprotonation at –78 °C in the presence of 2 equiv. TMEDA, then warmed to 0 °C during 1 h, addition of the aldehyde at –78 °C. [b] Conditions B: Deprotonation at –20 °C in the presence of 2 equiv. TMEDA for 10 min, addition of the aldehyde at –78 °C. [c] Conditions C: Deprotonation in the presence of 6 equiv. HMPA at –78 °C for 10 min, addition of the aldehyde at –78 °C. [d] 45% **1-2h** recovered. [e] Not performed. [f] 31% **1-2h** recovered. [g] 33% **1-2h** recovered. [h] 18% **1-2h** recovered. [i] Additionally, 29% **2-5** formed and 26% **1-2h** recovered. [j] Additionally, 31% **2-5** formed and 41% **1-2h** recovered. [k] Additionally, 63% **2-5** formed and 69% **1-2h** recovered. [l] 64% **1-2h** recovered. [m] 57% **1-2h** recovered. [n] 36% **1-2h** recovered.

The Julia olefination is one of the crucial applications of α-sulfonyl carbanions, therefore it was applied to substrates **1-2p** (Table 2.5, entries 1-6) and **1-2h** (entries 7-12). For **1-2p** standard deprotonation conditions (*cf.* Chapter 3.2.1, Table 2.3) worked well for the reaction with diverse aldehydes (entries 1-6). For the reaction of aromatic and α,β-unsaturated aldehydes with **1-2h**, the deprotonation in the presence of HMPA as an additive according to conditions C (Table 2.4) proved to be optimal (entries 7-9). However, the deprotonation of **1-2h** with *n*BuLi in the presence of TMEDA followed by transmetalation of **1-*o*-17h** to **1-α-18h**, similar to conditions A (*cf.* Table 2.4), were the most efficient conditions for aliphatic aldehydes to avoid competitive deprotonation of the aldehyde (entries 10-12).

Table 2.5. Scope of the Julia reaction with **1-2p** and **1-2h**.



Entry	R	Product	Yield [%]	Product	Yield [%]
1	Ph	**2-6a**	88[a]	**2-7a**	82[d]
2	4-BrC_6H_4	**2-6b**	87[a]	**2-7b**	78[d]
3	PhCH=CH	**2-6c**	88[a]	**2-7c**	68[d]
4	$PhCH_2CH_2$	**2-6d**	91[a]	**2-7d**	76[e]
5	C_5H_{11}	**2-6e**	66[a]	**2-7e**	64[e]
6	$C_{11}H_{23}$	**2-6f**	83[a]	**2-7f**	92[e]
7	Ph	**2-6g**	55[b]	**2-7g**	68[d]
8	4-BrC_6H_4	**2-6h**	61[b]	**2-7h**	71[d]
9	PhCH=CH	**2-6i**	80[b]	**2-7i**	82[d]
10	$PhCH_2CH_2$	**2-6j**	67[c]	**2-7j**	79[e]
11	C_5H_{11}	**2-6k**	78[c]	**2-7k**	89[e]
12	$C_{11}H_{23}$	**2-6l**	58[c]	**2-7l**	64[e]

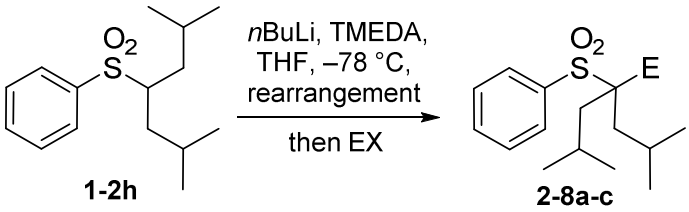
[a] General conditions: 0.5 mmol sulfone, 0.6 mmol *n*BuLi, 1 mmol TMEDA, –78 °C, 10 min, then 0.6 mmol aldehyde, warmed to 0 °C until complete conversion, then 0.65 mmol benzoyl chloride, –78 °C, 20 min, then 0.75 mmol 3-(dimethylamino)propan-1-ol. [b] General conditions: 0.37 mmol sulfone, 0.43 mmol *n*BuLi, 2.22 mmol HMPA, –78 °C, 10 min, then 0.47 mmol aldehyde, –78 °C until complete conversion, then 0.49 mmol benzoyl chloride, 20 min, warmed to r.t., then 0.56 mmol 3-(dimethylamino)propan-1-ol. [c] General conditions: 0.74 mmol sulfone, 0.86 mmol *n*BuLi, 2 mmol TMEDA, –78 °C to –20 °C, 1 h, then 0.93 mmol aldehyde at –78 °C, then –20 °C until complete conversion, then 0.96 mmol benzoyl chloride, 20 min, warmed to r.t., then 1.11 mmol 3-(dimethylamino)propan-1-ol. [d] 0.16 mmol **2-6**, 6 mmol DMPU, 0.96 mmol SmI_2, 0 °C, 2 h. [e] 0.13 mmol **2-6**, 0.31 mmol Na/Hg, –20 °C, 3 h.

All generated alkoxides were *in situ* acylated with benzoyl chloride providing β-benzoyloxy sulfones **2-6a-l** in good yields (Table 2.5, entries 1-12). For the reductive elimination of **2-6a-c** and **2-6g-i** SmI_2 in THF/DMPU was used at –78 °C[176] giving the corresponding olefins **2-7a-c** and **2-7g-i** in good yields (entries 1-3 and 7-9).

Saturated β-benzoyloxy sulfones **2-6d-f** and **2-6j-l** resulting from aliphatic aldehydes were inert to treatment with SmI_2 and even after longer reaction time the starting material was entirely recovered. Nevertheless, the classical deoxygenation by sodium amalgam in methanol at –20 °C provided the desired olefins **2-7d-f** and **2-7j-l** in good to excellent yields (entries 4-6 and 10-12). These results are in accordance with recent results observed with different substrates.[177,178]

Other electrophiles were also used in the α-deprotonation mode to obtain functionalized α-substituted sulfones **2-8a-c** (Table 2.6). Deprotonation of **1-2h** at –78 °C followed by transmetalation to **1-α-18h** on warming to –20 °C during one hour and subsequent reaction with electrophile **EX** at –78 °C afforded sulfone **2-8a** in poor yield (entry 1). Derivatives **2-8b,c**, which allow potential further modification of α-substituted alkyl phenyl sulfones, were obtained in good yield (entries 2-3).

Table 2.6. Range of the α-carbanion reaction with electrophiles.[a]



Entry	EX	E	Product	Yield [%]
1	TMSCl	TMS	**2-8a**	10[b]
2	I_2	I	**2-8b**	69
3	Br_2	Br	**2-8c**	86

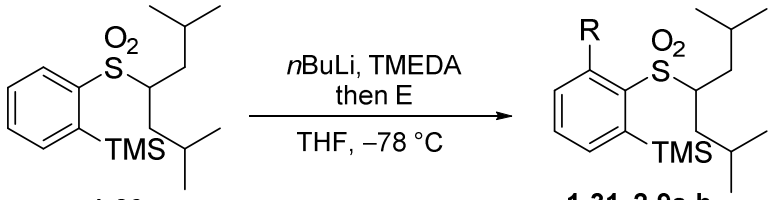
[a] General conditions: 0.5 mmol sulfone, 0.6 mmol *n*BuLi, 1 mmol TMEDA, –78 °C, 10 min, warmed to –20 °C during 1 h, –78 °C, then 0.6 mmol EX. [b] Approximate yield of **1-2h** in a mixture.

3.2.3. Preparation of *ortho,ortho'*-disubstituted alkyl phenyl sulfones

Sulfone **1-26** was regioselectively deprotonated under standard conditions at –78 °C generating **1-*o*-27** (Table 2.7). After short deprotonation time carbanion **1-*o*-27** underwent reaction with various electrophiles **E** at –78 °C. The reaction with aldehydes provided

secondary benzylic alcohols **2-9a-e** in good to excellent yield (entries 1-5). However, in contrast to unsubstituted **1-*o*-17h** (Chapter 3.2.1, Table 2.1, entries 5,6), nucleophilic additions of **1-*o*-27** to ketones giving tertiary benzylic alcohols **2-9f,g** did not proceed in good yields (entries 6,7). Reaction of **1-*o*-27** with TMSCl or iodine afforded sulfones **1-31** and **2-9h**, respectively (entries 8-9).

Table 2.7. Metalation of **1-26** and reaction of **1-*o*-27** with electrophiles.[a]



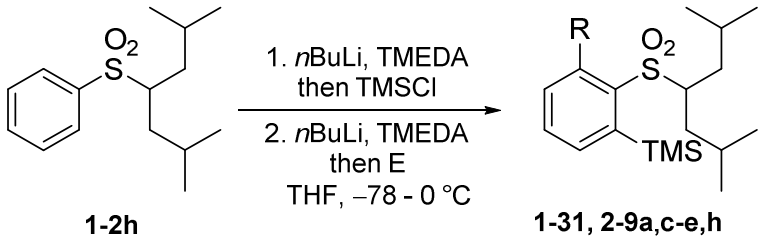
1-26 **1-31, 2-9a-h**

Entry	Product	E	R	Yield [%]
1	**2-9a**	PhCHO	CH(OH)Ph	82
2	**2-9b**	4-BrC_6H_4CHO	CH(OH)C_6H_4-4-Br	88
3	**2-9c**	*i*PrCHO	CH(OH)*i*Pr	81
4	**2-9d**	EtCH=CHCHO	CH(OH)CH=CHEt	80
5	**2-9e**	$PhCH_2CH_2CHO$	$CH(OH)CH_2CH_2Ph$	74
6	**2-9f**	Ph_2CO	$C(OH)Ph_2$	32
7	**2-9g**	$C_6H_{10}O$[b]	$C(OH)C_6H_{10}$	20
8	**1-31**	TMSCl	TMS	87
9	**2-9h**	I_2	I	68

[a] General conditions: 1 mmol sulfone, 1.2 mmol *n*BuLi, 2 mmol TMEDA, –78 °C, 10 min, then 1.3 mmol E, –78 °C, 2 h. [b] $C_6H_{10}O$ = cyclohexanone.

Di-*ortho*-substituted sulfones were also prepared by a one-pot procedure as an alternative and more facile approach (Table 2.8). Sulfone **1-2h** was deprotonated by *n*BuLi in the presence of TMEDA in THF at –78 °C, TMSCl was added and the reaction mixture was warmed to 0 °C for 15 min forming *ortho*-silylated sulfone **1-26**. The deprotonation by *n*BuLi at –78 °C was repeated and structurally different electrophiles **E** were added and the reaction mixture was kept at this temperature for 2 h. This approach afforded sulfones **1-31** and **2-9a,c-e,h** in better yields compared to the stepwise approach where sulfone **1-26** was isolated (*cf.* Table 2.7).

Table 2.8. Generation of **1-*o*-27** *in situ* from **1-2h** and subsequent reaction with electrophiles.



1-2h **1-31, 2-9a,c-e,h**

Entry	Product	E	R	Yield [%][a]	Yield [%][b]
1	**2-9a**	PhCHO	CH(OH)Ph	89	72
2	**2-9c**	*i*PrCHO	CH(OH)*i*Pr	74	71
3	**2-9d**	EtCH=CHCHO	CH(OH)CH=CHEt	72	70
4	**2-9e**	$PhCH_2CH_2CHO$	$CH(OH)CH_2CH_2Ph$	73	65
5	**1-31**	TMSCl	TMS	86	76
6	**2-9h**	I_2	I	81	60

[a] Conditions: 1 mmol sulfone, 1.2 mmol *n*BuLi, 2 mmol TMEDA, –78 °C, 10 min, then 1.3 mmol TMSCl, –78 °C, 10 min, then warmed to 0 °C, 15 min, then cooled to –78 °C, 1.2 mmol *n*BuLi, 2 mmol TMEDA, 10 min, 1.3 mmol E, –78 °C, 2 h. [b] Calculated yield for the two-step procedure, sulfone **1-26** prepared in 88% yield, then reaction of **1-26** with electrophiles (Table 2.7).

Such *ortho,ortho'*-disubstituted alkyl aryl sulfones can be potentially further transformed to their *ortho,ortho'*-disubstituted phenyl sulfinic acid analogs by reductive cleavage. This approach would afford differently trisubstituted benzene derivatives. Reductive desulfonylation is typically accomplished with active metals or salts (Na/Hg, Mg, SmI_2).[179–181]

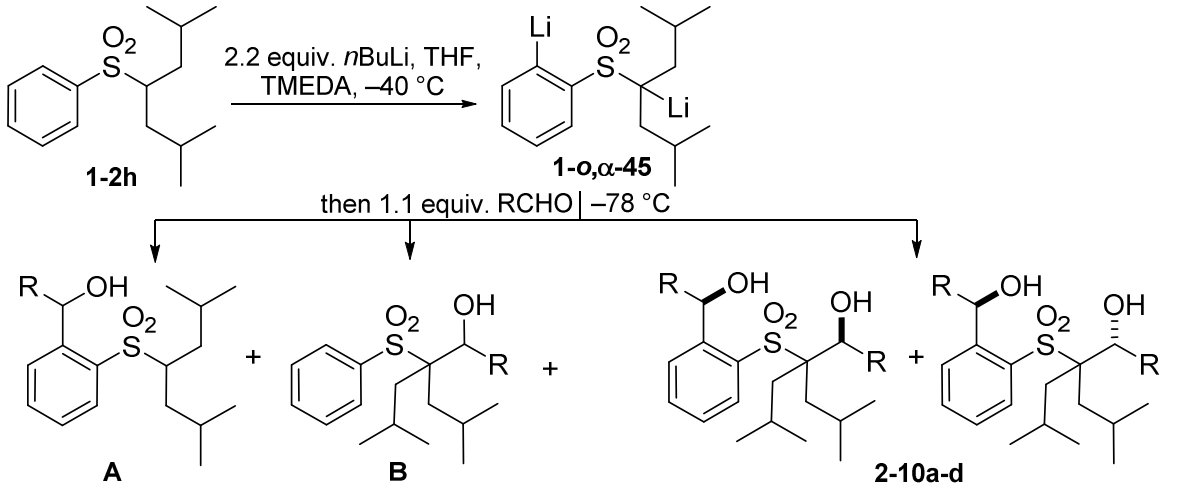
3.2.4 *ortho*- vs. α-Carbanions in reaction with structurally different aldehydes

In order to compare the reactivity of *ortho*- vs. α-carbanions, the dilithiated intermediate **1-*o*,α-45** was generated using 2.2 equiv. of *n*BuLi in the presence of TMEDA at –40 °C (see Chapter 3.1.7) and submitted to the reaction with 1.1 equiv. of structurally different aldehydes at –78 °C (Table 2.9). The reaction afforded alcohols **A** and **B** as an inseparable mixture and diols **2-10** in different ratios depending on the structure of the aldehyde (entries 1-4). The **A/B** product ratio was determined by ^{1}H NMR analysis.

Reaction of dianion **1-*o*,α-45** with benzaldehyde gave alcohols **1-36**, **2-4a** and diol **2-10a** in a 3:1:1.3 ratio (entry 1). Alcohols **2-1a** and **2-4g** and diol **2-10b** were obtained from

the reaction of **1-*o*,α-45** with isobutyraldehyde in a 4:1.7:1 ratio (entry 2). Alcohols **2-1b**, **2-4e**, **2-10c** and **2-1c**, **2-4d**, **2-10d** were formed by reaction with sterically less demanding aldehydes in a 1.7:1.3:1 and 2.3:2.5:1 ratio, respectively (entries 3-4).

Table 2.9. Generation of **1-*o*,α-45** and reaction with 1.1 equiv. of aldehydes.[a]



Entry	R	Product **A**	Product **B**	**A+B** Yield [%]	Product **2-10**	**2-10** Yield [%]	**A/B/2-10**
1	Ph	**1-36**	**2-4a**	46[b]	**2-10a**	14	3:1:1.3
2	*i*Pr	**2-1a**	**2-4g**	54[c]	**2-10b**	9	4:1.7:1
3	EtCH=CH	**2-1b**	**2-4e**	42[d]	**2-10c**	14	1.7:1.3:1
4	$PhCH_2CH_2$	**2-1c**	**2-4d**	43[e]	**2-10d**	~9[f]	2.3:2.5:1

[a] Initial conditions: 1 mmol sulfone, 2.2 mmol *n*BuLi, 5 mmol TMEDA, THF, –40 °C, 30 min, then –78 °C, 1.1 mmol aldehyde, –78 °C, 3 h. [b] 24% **1-2h** recovered. [c] 24% **1-2h** recovered. [d] 27% **1-2h** recovered. [e] 28% **1-2h** recovered. [f] max. approximate yield of **2-10d** in an inseparable mixture of unidentified side products, structure of **2-10d** determined by HRMS analysis.

The resulting 3:1 ratio of alcohols **1-36** and **2-4a** suggests that steric factors play role in the *ortho*- vs. α-regioselectivity of the reaction with bulky benzaldehyde (entry 1). Therefore, the substitution in the *ortho*-position is favored. Reaction with sterically less demanding aldehydes afforded alcohols **A** and **B** in an approximate 1:1 ratio (entries 3,4). The 2.3:1 ratio of alcohols **2-1a** and **2-4g** reflects the previously observed difficult formation of α-substituted sulfone **2-4g** (Chapter 3.2.2, Table 2.4) compared to *ortho*-substituted **2-1a** (Chapter 3.2.1, Table 2.1).

Surprisingly, one diastereomer of **2-10a** was isolated predominantly (d.r. 10:1, entry 1) in the reaction of **1-*o*,α-45** with benzaldehyde. However, the exact stereochemistry

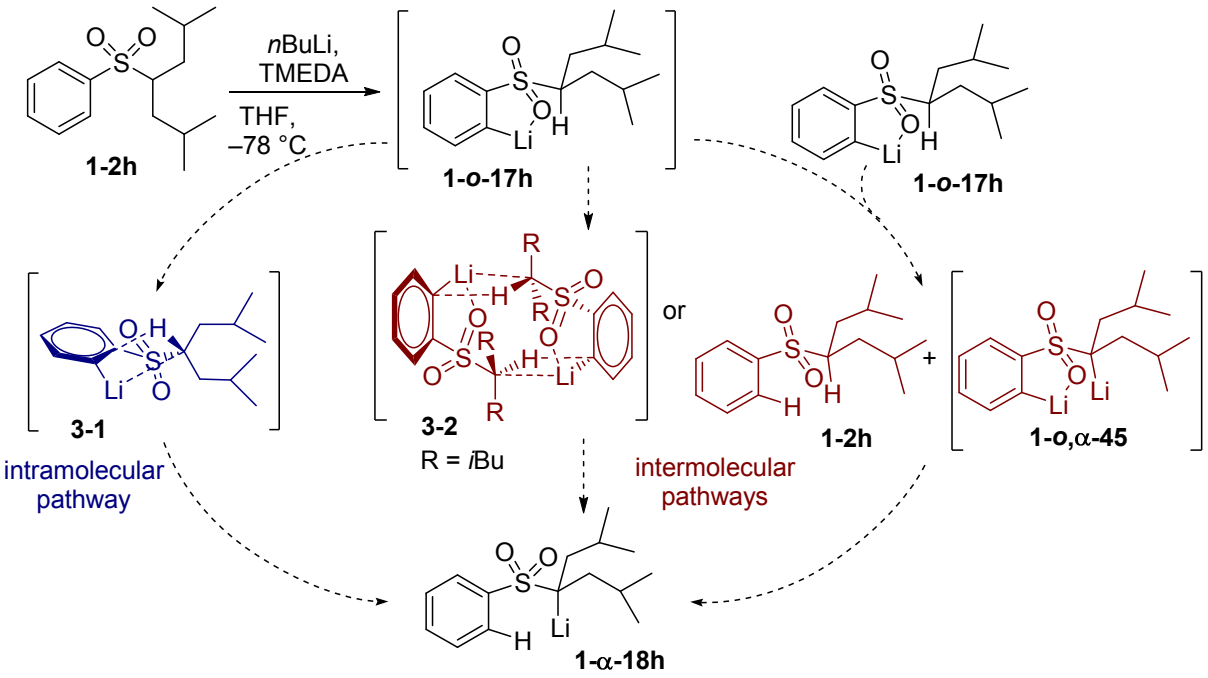
of diol **2-10a** could not be determined by NMR analysis. In the addition of **1-*o*,α-45** to other aldehydes the stereoselectivity was not controlled, diols **2-10b-d** were isolated as a 1:1 diastereomeric mixture (entries 2-4).

A first example of such dilithiated species - *ortho*,α-dilithioallyl phenyl sulfone, which was generated by successive metalation of the α- and *ortho*-positions, was initially alkylated at the α-position, when subjected to the reaction with one equivalent of alkyl halide (Chapter 1.4, Scheme i12).[148] Compared to the previously reported reactivity of dilithiated species with alkyl halides, the reaction of dilithiated species **1-*o*,α-45** with the aldehydes does not lead to the regioselective formation of *ortho*- or α-substituted alkyl phenyl sulfones. However, this can be caused by the fact, that the addition of carbanions to aldehydes is generally faster than the alkylation and thus less selective.

3.3. Elucidation of the mechanism of the *ortho*→α transmetalation

3.3.1. Potential pathways of the transmetalation reaction

Nothing was known about the mechanism of *ortho*→α transmetalation of alkyl aryl sulfones, but three possible pathways of the transmetalation of branched aryllithium to α-sulfonylalkyllithium intermediates can be proposed.[182] The transmetalation of aryllithium **1-*o*-17h**, generated by deprotonation of **1-2h**, to α-sulfonylalkyllithium **1-α-18h** may on one hand occur intramolecularly in a concerted process via a four-membered transition state **3-1** (Scheme 3.1).



Scheme 3.1. Potential pathways of the transmetalation of *ortho*-sulfonylphenyllithium **1-*o*-17h** to α-sulfonylalkyllithium **1-α-18h**.

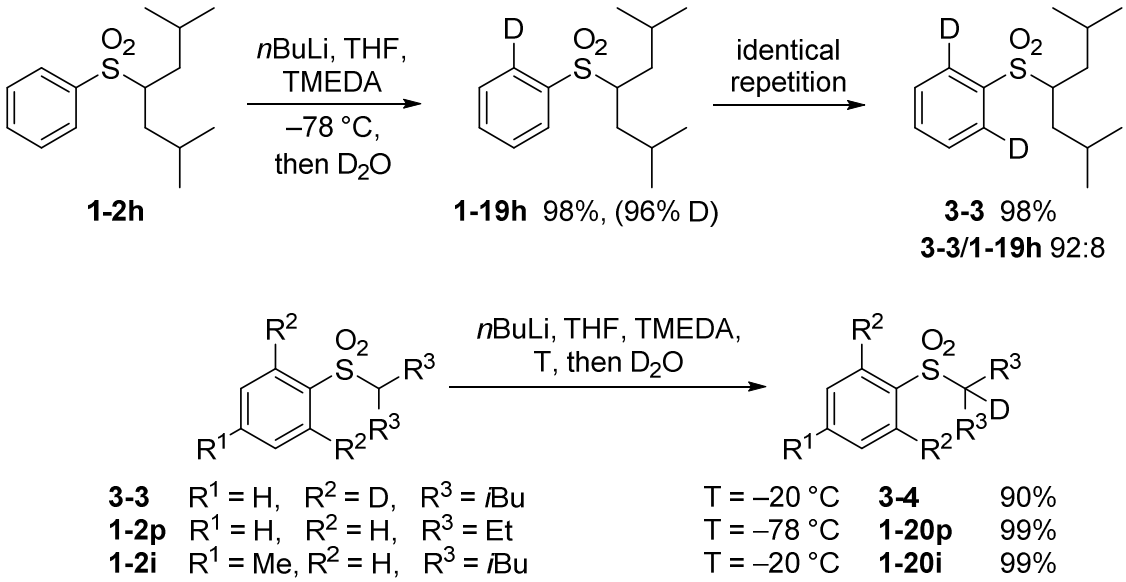
On the other hand, two intermolecular pathways have to be considered as well. The first potential intermolecular pathway is based on a concerted proton transfer from an aggregate[183] or two monomeric *ortho*-sulfonylphenyllithium units **1-*o*-17h** via a symmetrical transition state **3-2**. Alternatively, *ortho*,α-dilithium intermediate **1-*o*,α-45** and sulfone **1-2h** can be formed by an initial intermolecular proton transfer, which can be successively followed by a second proton transfer, forming two units of α-sulfonylalkyllithium **1-α-18h**. Dilithiated intermediates, similar to **1-*o*,α-45** were

previously individually generated by Gais and colleagues by an inverse strategy of initial α- and subsequent *ortho*-metalation (see Chapter 1.4).[147–151,184,185]

To get more information about the reaction mechanism, kinetic studies are often used. Such studies can generally distinguish between mono- vs. bimolecular pathways, which correspond to **3-1** vs. **3-2** and **1-2h/1-*o*,α-45** intermediates in this particular case. However, this method cannot specifically determine the type of intermolecular pathway, since the same rate law can apply to both. Another convenient way to determine, whether the transmetalation occurs intra- or intermolecularly, are crossover experiments. It can be assumed that variously deuterated sulfones would be appropriate reaction components, because it can be expected that the reaction rates differ, but the general course should not change. The advantage of using such deuterated sulfones is that the products can be directly detected and identified by ^{1}H NMR spectroscopy and mass spectrometry techniques. However, this requires the determination of deuterium kinetic isotope effects (KIE)[186–197] before the crossover experiments are designed, because particularly during metalation, large deuterium KIEs, which influence the reaction rate and selectivity, may be observed.[157,198–203]

3.3.2. Preparation of starting materials

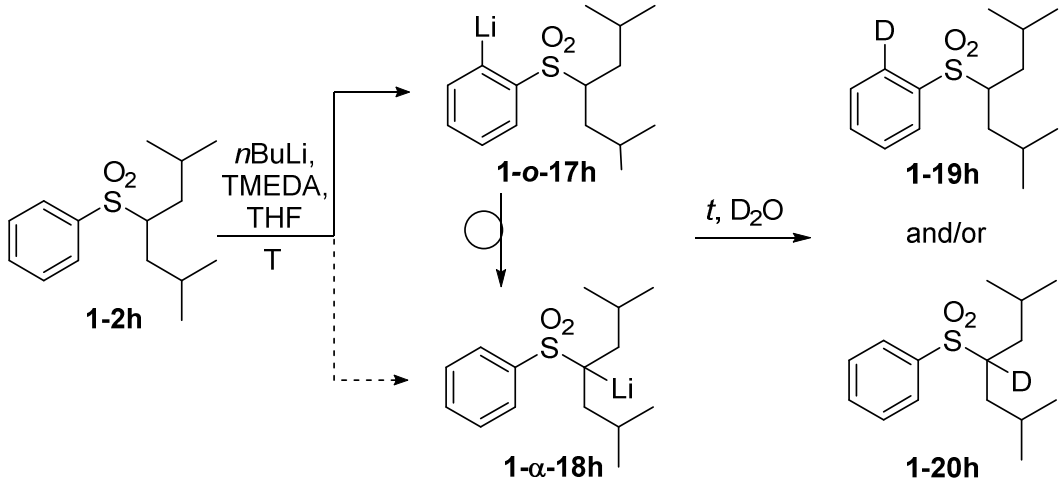
The deuterated sulfones intended for the determination of KIEs and crossover experiments were synthesized by deprotonation of **1-2h** with *n*BuLi in the presence of TMEDA and subsequent deuteration (Scheme 3.2). *ortho,ortho'*-Dideuterated sulfone **3-3** was prepared from sulfone **1-2h** via *ortho*-deuterated **1-19h** by two successive deprotonations followed by addition of deuterium oxide in 98% yield as a 92:8 mixture of dideuterated **3-3** and monodeuterated derivative **1-19h**. However, it was not possible to completely deuterate both *ortho*-positions without further undesired α-deuteration. Deprotonation of sulfone **3-3** under similar conditions with a small excess of *n*BuLi at –20 °C and subsequent addition of D_2O afforded trideuterated sulfone **3-4** in very good yield and with complete α-deuteration. α-Deuterated sulfones **1-20p** and **1-20i** were obtained by deprotonation/deuteration of **1-2p** and **1-2i**, respectively, with complete α-deuteration.



Scheme 3.2. Preparation of deuterated alkyl aryl sulfones.

3.3.3. Kinetic investigation of the course of the transmetalation

Sulfone **1-2h** served as the substrate for the kinetic investigation of the transmetalation (Scheme 3.3). It was deprotonated with *n*BuLi in THF in the presence of TMEDA at –50 °C, –45 °C, –40 °C, –35 °C and –30 °C (Figure 3.1, Chapter 5.2.3, Tables 5.3-5.7). Using TMEDA proved to be beneficial for obtaining optimal *ortho*/α-selectivity.[144]



Scheme 3.3. Kinetic investigation of transmetalation of **1-*o*-17h** to **1-α-18h**.

After given times, aliquots of the reaction mixture were taken, quenched by D_2O and analyzed by ^1H NMR spectroscopy. Their mass balance was determined and proved to be

quantitative. The ratio of deuterated compounds **1-19h** and **1-20h** reflects the ratio of organolithium intermediates **1-*o*-17h** and **1-α-18h**.

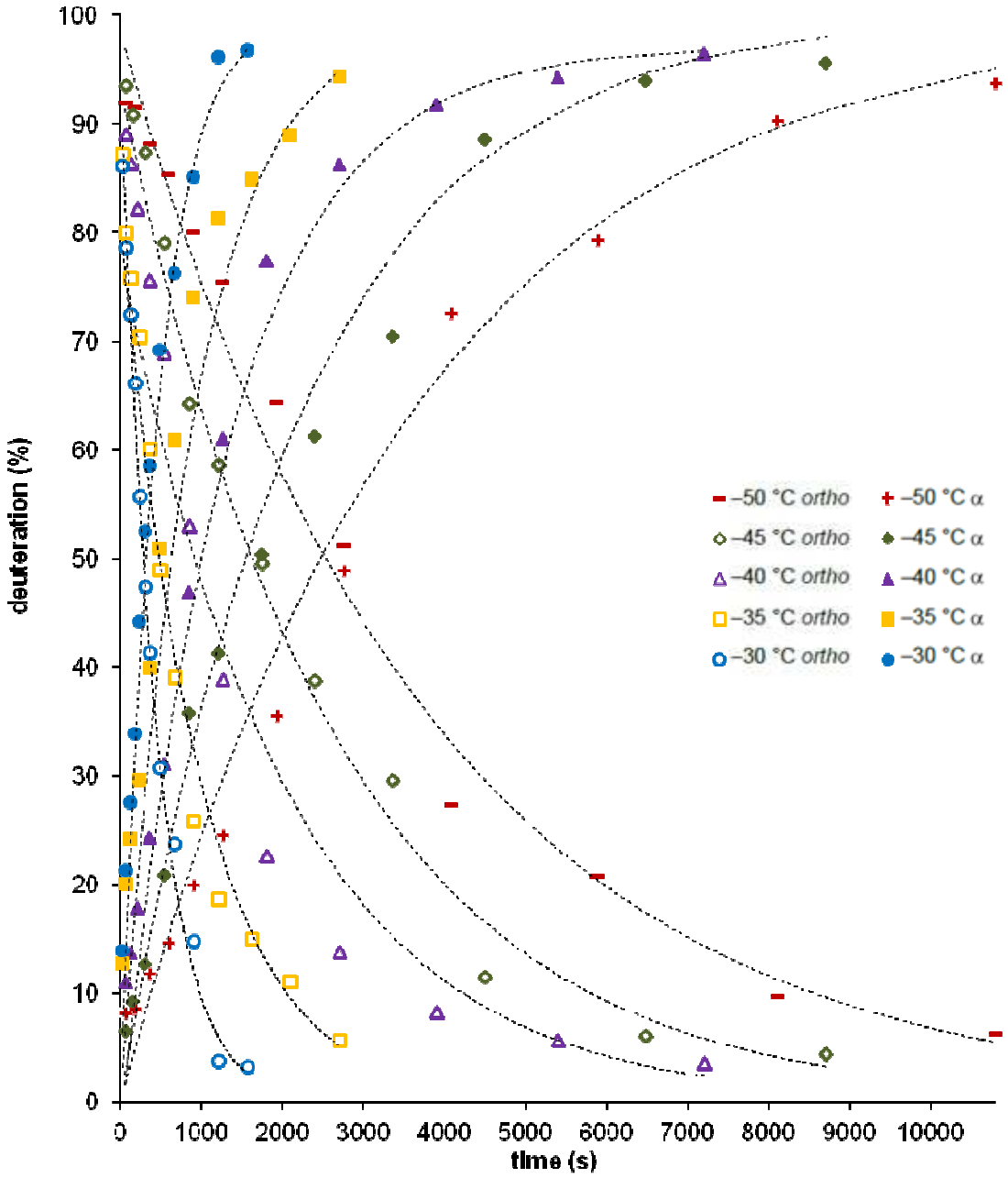


Figure 3.1. Kinetic trace of the transmetalation of **1-*o*-17h** to **1-α-18h** (For the raw data see Chapter 5.2.3, Tables 5.3-5.7).

The experimentally found values fit better to first-order kinetics (Figure 3.2) than to second-order kinetics (Figure 3.3). The first-order rate constants of the transmetalation were calculated to $k = 2.67\times10^{-4}$ s^{-1} at –50 °C, $k = 3.85\times10^{-4}$ s^{-1} at –45 °C, $k = 4.85\times10^{-4}$ s^{-1} at –40 °C, $k = 1.02\times10^{-3}$ s^{-1} at –35 °C and $k = 2.28\times10^{-3}$ s^{-1} at –30 °C. An application of

2nd-order kinetics led to a more considerable deviation from linearity (Figure 3.3). The integral method for determining the reaction order was also used,[204] however, the calculated values of the rate constants differ significantly.

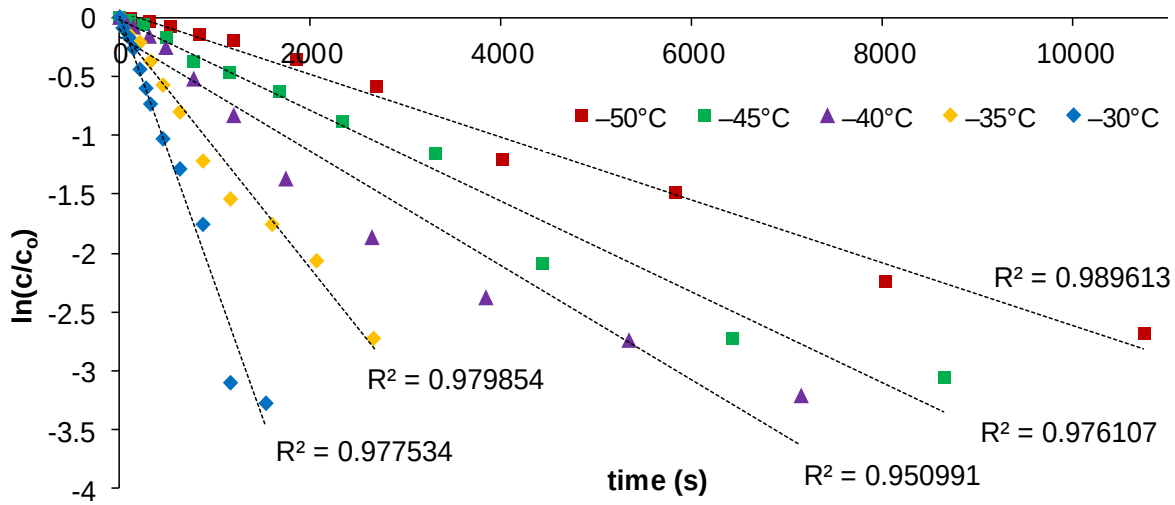


Figure 3.2. First-order plot for the transmetalation of monomeric *ortho*-sulfonylphenyl lithium **1-*o*-17h** to **1-α-18h**.

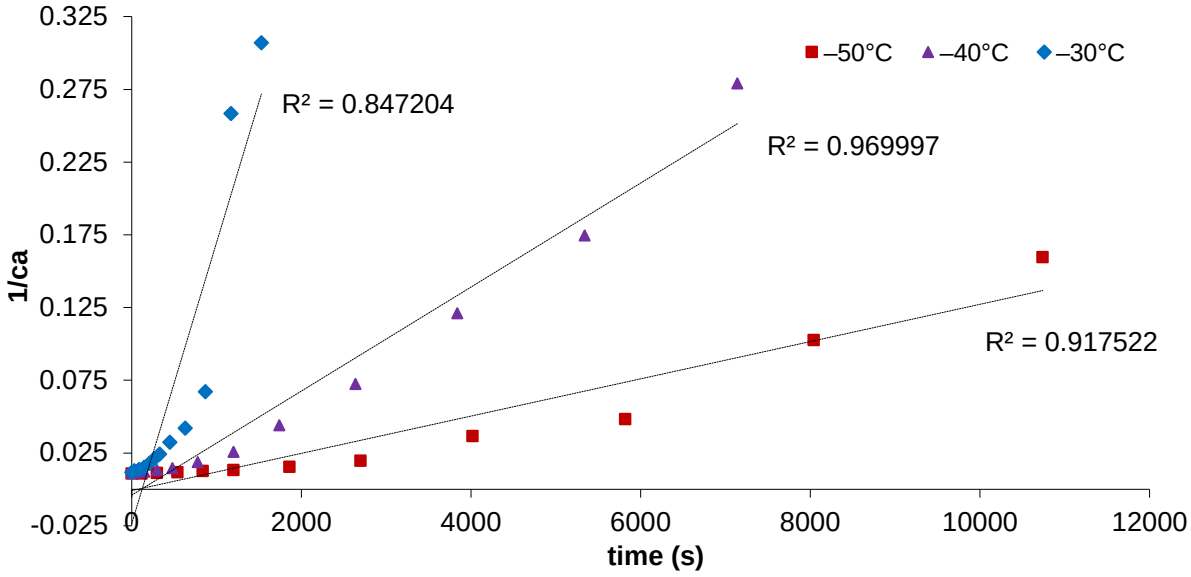


Figure 3.3. Second-order rate profile of the transmetalation of *ortho*-sulfonylphenyllithium **1-*o*-17h**.

Sulfonyl lithium intermediates **1-*o*-17h** or **1-α-18h** can form aggregates in solution,[54,111–115,119–124,183,205–207] therefore the kinetics were also calculated for dimers or tetramers of these intermediates, however, unsatisfactory results were obtained as well.

Regarding these results, the transmetalation can occur either intramolecularly via **3-1** or as an aggregate through a transition state similar to **3-2** (*cf.* Scheme 3.1).

In order to get more information about the mechanism the kinetics of the transmetalation of **1-*o*-17h** to **1-α-18h** were determined at –40 °C at three different concentrations (Figure 3.4, Chapter 5.2.3, Table 5.8). Figure 3.4 shows the decreasing amount of *ortho*-deuterium incorporation which reflects the decrease of *ortho*-metalation with time. The results clearly showed that the higher the concentration of the reaction mixture is, the higher becomes the rate of the transmetalation. This contradicts first-order kinetics and rather corresponds with second-order kinetics.

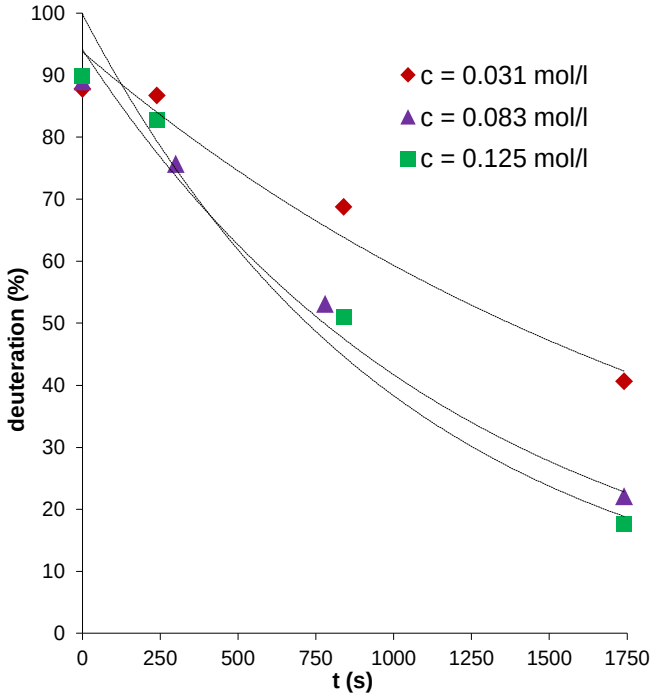


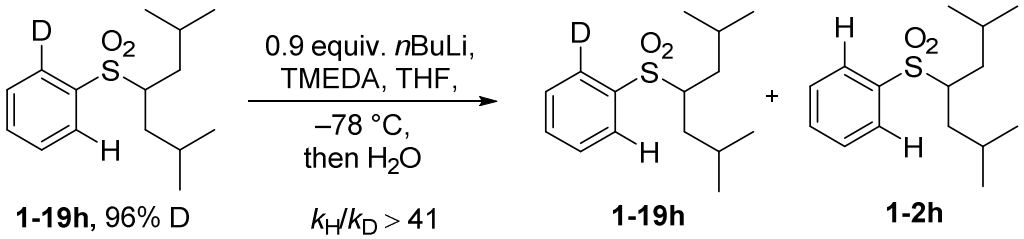
Figure 3.4. Dependence of the transmetalation rate on the concentration at –40 °C. The values of trace at c = 0.083 mol/l were taken from the kinetic trace in Figure 3.1.

3.3.4. Kinetic isotope effects

Variously deuterated sulfones were planned to be used in a crossover investigation (see Chapter 3.3.7). Therefore, it had to be confirmed that deuterium kinetic isotope effect (KIE) values are high enough to avoid undesired *ortho*→α deuterium transfer and competitive dedeuteration by *n*BuLi. Whereas KIEs for DoM exhibit typical values exceeding 19,[157,202,203] KIEs for sulfones have not been determined so far. Metalation and

transmetalation investigation with differentially deuterated sulfones had to be performed first.

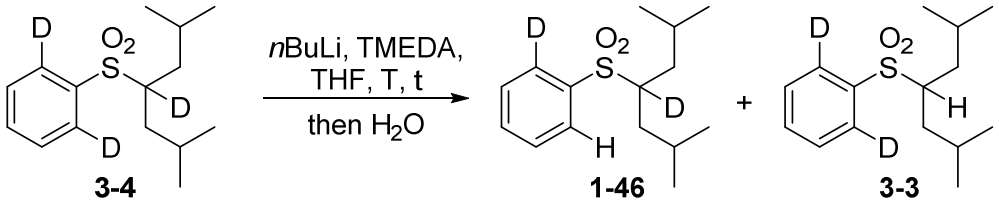
The intramolecular kinetic isotope effect for the *ortho*-lithiation of sulfone **1-19h** with 96% *ortho*-D was determined by deprotonation with 0.9 equiv. of *n*BuLi in the presence of TMEDA at –78 °C for 5 min (Scheme 3.4). Two aliquots of the reaction mixture were taken at the same time, separately quenched with water and D_2O, respectively, and analyzed by ^{1}H NMR spectroscopy. The intramolecular KIE was derived from the ratio of products **1-19h** and **1-2h** after quenching with water. The integral increase of the *ortho*-H resonance amounted to a maximum of 2%. The sample of the reaction mixture quenched by D_2O showed that lithiation proceeded to an extent of 84% (not shown). This leads to an *ortho*-D/H ratio of 82:2, from which an intramolecular KIE of k_H/k_D = 41 for the *ortho*-lithiation of **1-19h** can be calculated. However, the error of the KIE determination is considered relatively large because of the small extent of *ortho*-H incorporation[202] and the inherent integration error of ^{1}H NMR spectroscopy.



Scheme 3.4. Determination of the intramolecular KIE for *ortho*-metalation of **1-19h**.

Treating trideuterated sulfone **3-4** with *n*BuLi should in principle lead to a similar *ortho*→α metalation selectivity as that of **1-2h**, therefore the ease of the subsequent *ortho*→α transmetalation can be derived. Sulfone **3-4** was deprotonated under standard conditions and quenched by water at –78 °C affording a 90:9 mixture of sulfones **1-46** and **3-3** (Table 3.1, entry 1). The *ortho*-metalation selectivity of **3-4** was thus slightly lower than that of **1-2h**, which amounted to 31:1 under identical conditions (Chapter 3.1.3, Table 1.4, entry 7). The *ortho*→α transmetalation did not occur below –40 °C as indicated by the almost constant hydrogen content in *ortho*- and α-positions of **1-46** and **3-3**, respectively (entries 2,3). The transmetalation started to take place at –40 to 0 °C (entries 4,5), which means at significantly higher temperature compared to **1-2h** (–50 °C, Chapter 3.3.3, Figure 3.1). Because the temperature of *ortho*→α transmetalation of metalated sulfone **3-4** is not similar to that of **1-2h**, an exact value of kinetic isotope effect for the *ortho*→α transmetalation could not be determined, but it is considered to be large.

Table 3.1. DoM and transmetalation of trideuterated sulfone **3-4**.



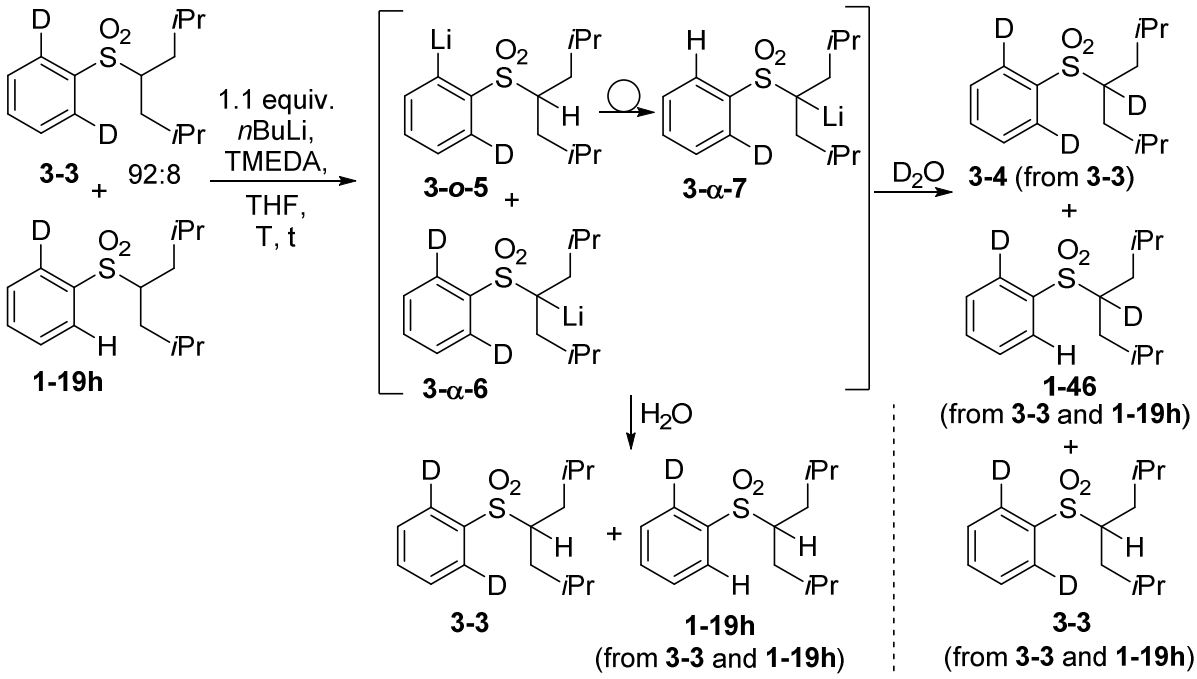
3-4 96% *ortho*-D, 100% α-D **1-46** **3-3**

Entry	T [°C]	t [min][a]	**1-46**/**3-3** [%][b]
1	–78	10	90:9[c]
2	–60	20	92:8[c]
3	–40	30	93:7
4	–20	40	87:12
5	0	50	30:63

[a] Time refers to the start of the deprotonation. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction run in duplicate with similar results.

ortho,ortho'-Dideuterated sulfone **3-3** (**3-3**/**1-19h**, 92:8 mixture based on 184% *ortho*-D, 16% residual *ortho*-H signal by integration of the ^{1}H NMR spectrum) was used to study the metalation regioselectivity (Table 3.2). The metalation experiment was performed with the **3-3**/**1-19h** mixture under standard conditions at –78 °C. Aliquots were subsequently quenched with D_2O at given temperatures and times to determine the metalation regioselectivity forming **3-*o*-5** and/or **3-α-6** and the other aliquots were quenched with water at the same time to confirm that DoM to **3-*o*-5** proceeded. Quenching the generated organolithium intermediates at –78 °C after 1 or 5 min reaction time by D_2O and analyzing the mixture by ^{1}H NMR spectroscopy showed an essentially unchanged *ortho*-H integral of 15% corresponding to 185% D compared to the starting mixture. Simultaneously, the initial 100% α-H integral decreased to 54% and 50% as a result of 46% and 50% α-deuteration, respectively (entries 1,2). This indicates the formation of an approximately 1:1 mixture, containing recovered **3-3** on one hand and trideuterated product **3-4** on the other hand. Trideuterated sulfone **3-4** is therefore a result of competitive initial α-deprotonation of dideuterated sulfone **3-3** to **3-α-6** at –78 °C, because the transmetalation of **3-*o*-5** to **3-α-7** does not proceed at this temperature as it is obvious from the transmetalation studies of **1-*o*-17h** to **1-α-18h** (Chapter 3.1.3, Table 1.4).

Table 3.2. Metalation selectivity and transmetalation of dideuterated sulfone **3-4**.[a]



Quench by:			D_2O		H_2O	
Entry	T [°C]	t [min][b]	% *ortho*-D[c] (**3-4**+ **1-46**+ **3-3**)	% α-D (**3-4**+ **1-46**)	% *ortho*-H[d] (**1-19h**)	% α-H (**3-3**+ **1-19h**)
1	–78	1	185	46	63	97
2	–78	5	188	50	69	96
3	–20	15	141	90	64	93

[a] Reaction run in duplicate with very similar results. [b] Time refers to the start of the deprotonation. [c] Deuterium content in *ortho*-position determined by integration of the residual *ortho*-H resonance in the ^{1}H NMR spectrum. Theoretically, **3-3** has two *ortho*-D = 200%. [d] *ortho*-H Content determined by integration of the ^{1}H NMR spectrum; 100% = one *ortho*-H.

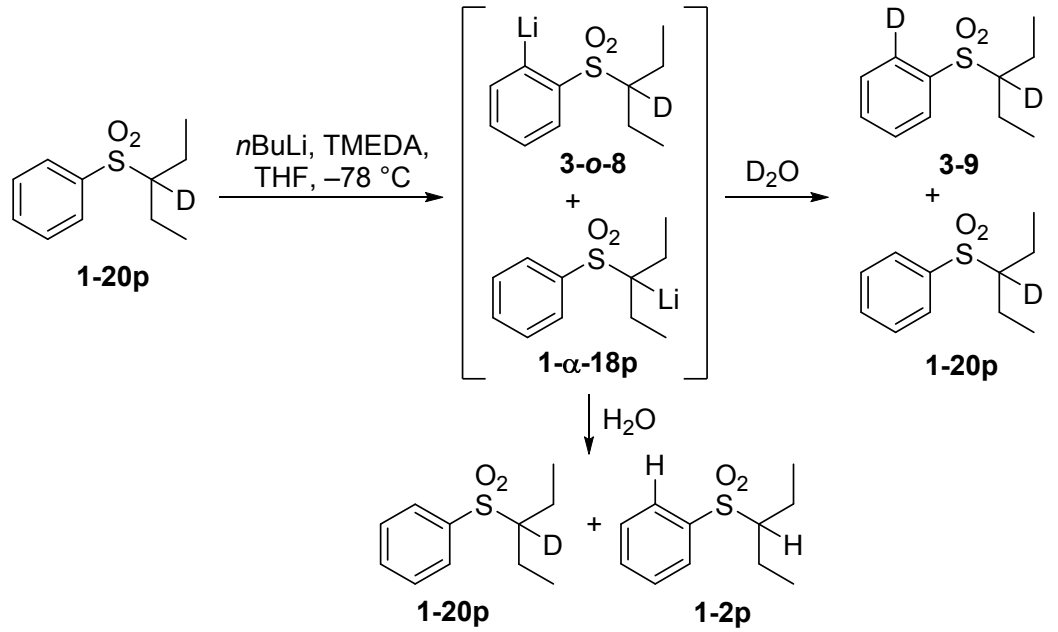
The reaction mixture was warmed to –20 °C during 15 min and quenched by D_2O. ^{1}H NMR analysis revealed an increase of the *ortho*-H integral to 59%, corresponding to a decreased *ortho*-deuterium content of 141% at the *ortho*-position and an almost equal decrease of the 1H integral at the α-position to 10% (90% deuteration) (entry 3). Therefore, the transmetalation of **3-*o*-5** to **3-α-7** proceeded on warming similarly as that of **1-*o*-17h** to **1-α-18h** in the non-deuterated series (Chapter 3.1.3, Table 1.4).

The samples of the reaction mixture quenched by water at –78 °C after 1 or 5 min confirmed that metalation of the **3-3**/**1-19h** mixture was complete and it complements the results of D_2O quenching. The *ortho*-H content is expected to be 100% if only DoM of **3-3** followed by protonation by water took place. Since the experimentally obtained *ortho*-H

content amounted to 63% and 69%, respectively, it indicated that a little more than 50% of *ortho*-metalation to **3-*o*-5** occurred (entries 1,2). The observed higher values results predominantly from the presence of monodeuterated sulfone **1-19h** in the starting material. No change of *ortho*-H content was observed on warming, because the transmetalation of **3-*o*-5** to **3-α-7** involves exchange of the α-hydrogen atom forming **1-19h** after quenching by water (entry 3). The proton content in the α-position remained, as expected, close to 100%, indicating that no transmetalation involving exchange of a deuterium atom took place.

These results indicated that dedeuteration at the *ortho*-position of **3-3** leading to **3-*o*-5** was significantly retarded compared to deprotonation of **1-2h** leading to **1-*o*-17h** (Chapter 3.1.3, Table 1.4). Therefore, the initial deprotonation at the α-position giving **3-α-6** competed with approximately similar reaction rate.

Table 3.3. Metalation selectivity of α-deuterated sulfone **1-20p**.



Quench by:		D_2O		H_2O	
Entry	t [min][a]	**3-9** [%][b]	**1-20p** [%][b]	**1-20p** [%][b]	**1-2p** [%][b]
1	1	29	71	31	69
2	5	29	71	31	69
3	10	31	69	30	70

[a] Time refers to the start of the deprotonation. [b] Determined by ^{1}H NMR spectroscopy.

Another potential substrate for crossover experiments was α-deuterated sulfone **1-20p**. This substrate should be in principle recovered unchanged after the normally observed

α-lithiation to **1-α-18p** and subsequent quenching with deuterium oxide, but should afford **1-2p** by quenching with water, under the condition that no significant kinetic isotope effect is involved. However, lithiation of **1-20p** at –78 °C followed by quenching with D_2O afforded *ortho*,α-dideuterated derivative **3-9** together with **1-20p** in 3:7 ratio, which did not change significantly over 10 min at –78 °C (Table 3.3, entries 1-3). Protonation gave sulfones **1-20p** and **1-2p** in a 3:7 ratio. This clearly shows that dedeuteration of **1-20p** at the α-position generating **1-α-18p** was retarded compared to the α-deprotonation of **1-2p** (Chapter 3.1.3, Table 1.4). Therefore, DoM resulting in the formation of **3-*o*-8** competed to a significant extent. The 3:7 ratio of **3-*o*-8**/**1-α-18p** did not change during 10 min at –78 °C, indicating that the *ortho*→α transmetalation of **3-*o*-8** does not proceed at this temperature.

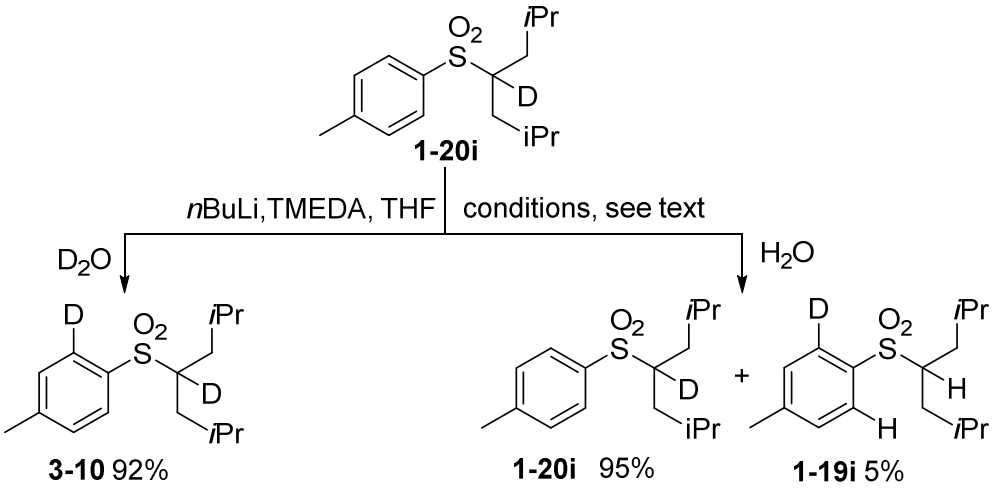
Overall, deuterated sulfones **3-3**, **3-4**, and **1-20p** provided valuable information about the metalation selectivity. When hydrogen atoms in *ortho*- as well as in α-position are substituted by deuterium, the selectivity changes to a significant extent. Although some kinetic isotope effects could not be exactly determined because of the change of metalation selectivity, they can be considered large. These features did not allow the application of **3-3**, **3-4** and **1-20p** in the crossover experiments, because their rates of metalation and/or subsequent transmetalation are not compatible with those of **1-2h**.

3.3.5. Investigation of potential precursors for crossover experiments

The *ortho*→α transmetalation of sulfone **3-4** displays a large kinetic isotope effect and thus make the transmetalation remarkably slower (Chapter 3.3.4, Table 3.1). This suggests that an α-deuterated substrate, similar to **1-2h**, but bearing a remote substituent at the aromatic ring, can be suitable for the application in the crossover investigation. Therefore, the metalation and transmetalation behavior of *p*-tolyl sulfone **1-2i** was investigated under identical conditions as those for sulfone **1-2h** (Chapter 3.1.3, Table 1.4). The initially generated *ortho*-sulfonylphenyllithium **1-*o*-17i** transmetalated to **1-α-18i**, as indicated by isolation of the deuterated compounds **1-19i** and/or **1-20i**, but slightly slower than observed for **1-2h** (Table 1.4, entry 7).

Regarding these results, α-deuterated *p*-tolyl sulfone **1-20i** can serve as one of the components in the crossover reaction, because its *ortho*-hydrogen atoms are distinguishable from those of **1-2h** (Scheme 3.5). However, its metalation and transmetalation behavior had to be studied first. Initial *ortho*-metalation of sulfone **1-20i** at –78 °C, warming to 0 °C over 50 min and quenching with D_2O furnished *ortho*,α-dideuterated sulfone **3-10** as the exclusive

product in 92% yield. This result confirmed the facility of DoM. However, it did not prove that undesirable transmetalation did not occur to some extent.



Scheme 3.5. Time- and temperature-dependent metalation of **1-20i** followed by deuteration or protonation.

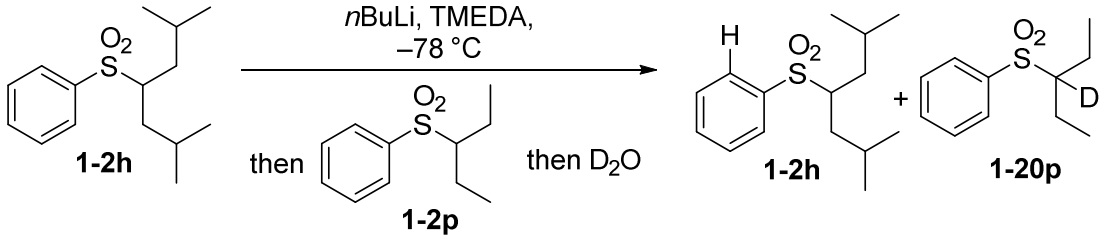
Therefore, a sample of the reaction mixture was quenched by water at –20 °C after 30 min, which afforded 95% of **1-20i** and maximally 5% of *ortho*-deuterated product **1-19i** as was determined by integration of the ^{1}H NMR spectra. These results clearly show that deprotonation of **1-20i** followed by deuteration or protonation occurred at *ortho*-position and that the *ortho*→α transmetalation proceeded only to a very small extent. This can be explained by the significant kinetic isotope effect of the transmetalation (*cf.* Table 3.1). These facts allow the application of **1-20i** in the crossover investigation.

3.3.6. Proton transfer equilibria between *ortho*-lithiated sulfones and their neutral precursors

Neutral non-deprotonated sulfones, for which α-proton pK_a values of 29-31 in DMSO were determined, should be acidic enough to serve as proton donors towards the *ortho*-sulfonylphenyllithium intermediate **1-*o*-17h**.[86] Such behavior can thus contribute to the transmetalation process. Therefore, **1-2h** was *ortho*-lithiated by *n*BuLi under standard conditions at –78 °C generating **1-*o*-17h**, which was confirmed by deuteration forming **1-19h** (Table 3.4, entry 1). Subsequently, the free, relatively unhindered sulfone **1-2p** was added and samples of reaction mixture were taken at defined temperatures after defined times and quenched by D_2O (entries 2-4). A basically complete, fast proton transfer proceeded giving **1-**

2h and deuterated sulfone **1-20p** after deuterium oxide quench (entry 2). The **1-2h**/**1-20p** ratio did not change even after longer reaction times (entries 3,4). This result demonstrates the thermodynamic basicity difference between *ortho*- and α-lithiated sulfones and indicates that intermolecular proton transfer from free unhindered sulfones to **1-*o*-17h** is possible at low temperature.

Table 3.4. Intermolecular proton transfer between **1-*o*-17h** and free **1-2p**.

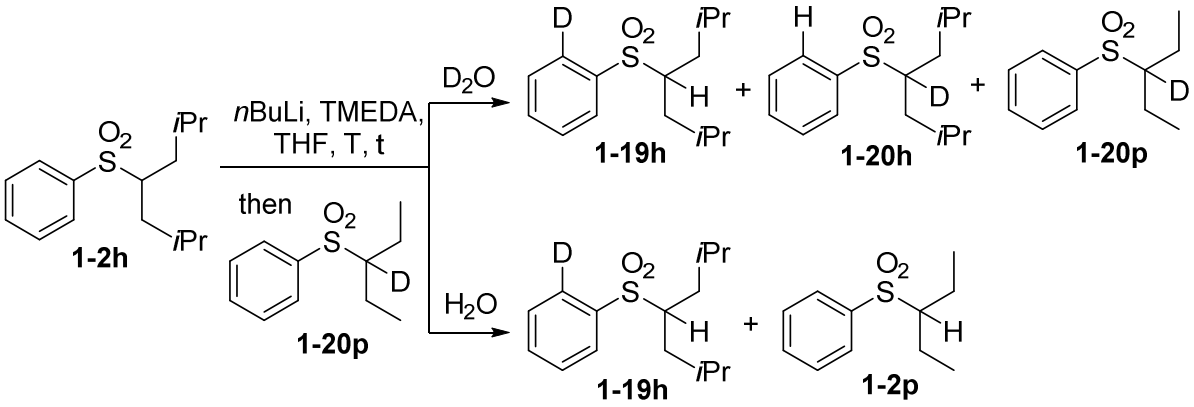


Entry	t [min][a]	T [°C]	**1-19h** [%][b]	**1-2h** [%][c]	**1-20p** [%][c]
1	5	–78	85[d]	11	-
2	15[e]	–78	N.d.[f]	100	80
3	25	–60	N.d.	100	80
4	35	–40	N.d.	100	81

[a] Time refers to the start of the deprotonation. [b] Quenched by D_2O before addition of **1-2p**. [c] Determined by ^1H NMR spectroscopy. [d] Additionally, 4% of α-deuterated compound was detected. The remainder of the mass balance was undeprotonated **1-2h**. [e] Compound **1-2p** was added after 5 min, the sample was taken after 10 min (15 min total). [f] Not detected.

Deuterium transfer from neutral α-deuterated sulfone **1-20p** to **1-*o*-17h** generated by standard deprotonation of **1-2h** also proceeded easily (Table 3.5). The D_2O quench of individually deprotonated sulfone **1-2h** afforded almost exclusively *ortho*-deuterated **1-19h** (entry 1). Subsequent addition of deuterated sulfone **1-20p** to the reaction mixture followed by deuterium oxide quench after 10 min gave **1-19h** and **1-20p** with good deuterium incorporation (entry 2). Their ratio did not change significantly on warming to –60 °C (entry 3). More importantly, hydrolysis under identical conditions and analysis of products by ^1H NMR spectroscopy indicated the formation of **1-19h** and **1-2p** to a good extent (75%) and thus confirmed the deuterium transfer from **1-20p** to intermediate **1-*o*-17h**. The extent of α-dedeuteration corresponds with the results of metalation of sulfone **1-20p** (Chapter 3.3.4, Table 3.3).

Table 3.5. Intermolecular deuterium transfer from deuterated **1-20p** to *ortho*-lithiated **1-2h**.



Quench by:			D_2O			H_2O	
Entry	t [min][a]	T [°C]	% *ortho*-D (**1-19h**)	% α-D (**1-20h**)	% α-D (**1-20p**)	% *ortho*-D (**1-19h**)	% α-H (**1-2p**)
1	5	–78	84	1	-	-	-
2	15[b]	–78	87	2	97	74[c]	74[d]
3	25	–60	91	4	98	75[c]	76[d]

[a] Time refers to the start of the deprotonation. [b] Compound **1-20p** was added after 5 min, the sample was taken after 10 min (15 min total). [c] The remainder of the mass balance was ca 25% of **1-2h**. [d] The remainder of the mass balance was ca 25% of **1-20p**.

Overall, these results document that proton as well as deuterium can easily transfer from the α-position of neutral unhindered sulfones **1-2p** or **1-20p** to *ortho*-sulfonylphenyllithium **1-*o*-17h** even at low temperature. Therefore, the deprotonation should be complete when using unhindered sulfones to obtain mechanistically meaningful results. This is however not true when neutral branched sulfones are used as a proton source. When sulfone **1-2h** was deprotonated using only 0.5 equiv. of *n*BuLi in the presence of TMEDA (*cf*. Figure 1), the level of deprotonation forming **1-*o*-17h** was naturally only 50%. The remaining sulfone **1-2h** can in principle serve as an α-proton donor and thus mediate the transmetalation reaction.

However, this hypothesis was not confirmed (Table 3.6). The *ortho*-sulfonylphenyllithium **1-*o*-17h** remains stable at –78 - –60 °C (entries 1,2) and transmetalates basically identically as under the previously reported stoichiometric lithiation conditions (entries 3-5 vs. Chapter 3.1.3, Table 1.4, entry 7). Despite the metalation of **1-2h** was not complete, remaining **1-2h** neither initiate the transmetalation at low temperature (entry 1 vs.

1-2p, Table 3.4) nor influence the rate of the transmetalation on warming. Thus **1-2h** and, presumably, related sulfone **1-2i** as well do not serve as proton donors toward **1-*o*-17h**.

Table 3.6. Deprotonation of sulfone **1-2h** by 0.5 equiv. of *n*BuLi and its transmetalation.

Entry	T [°C]	t [min]	**1-19h/1-20h**[a]	**1-19h/1-20h**[b]
1	–78	10[c]	42:1	31:1
2	–60	20	19:1	22:1
3	–40	30	2.3:1	2.7:1
4	–20	40	1:34	1:46
5	0	50	1:37	1:46

[a] Determined by ^{1}H NMR spectroscopy. [b] Values from Chapter 3.1.3, Table 1.4, entry 7. [c] Time after start of the deprotonation.

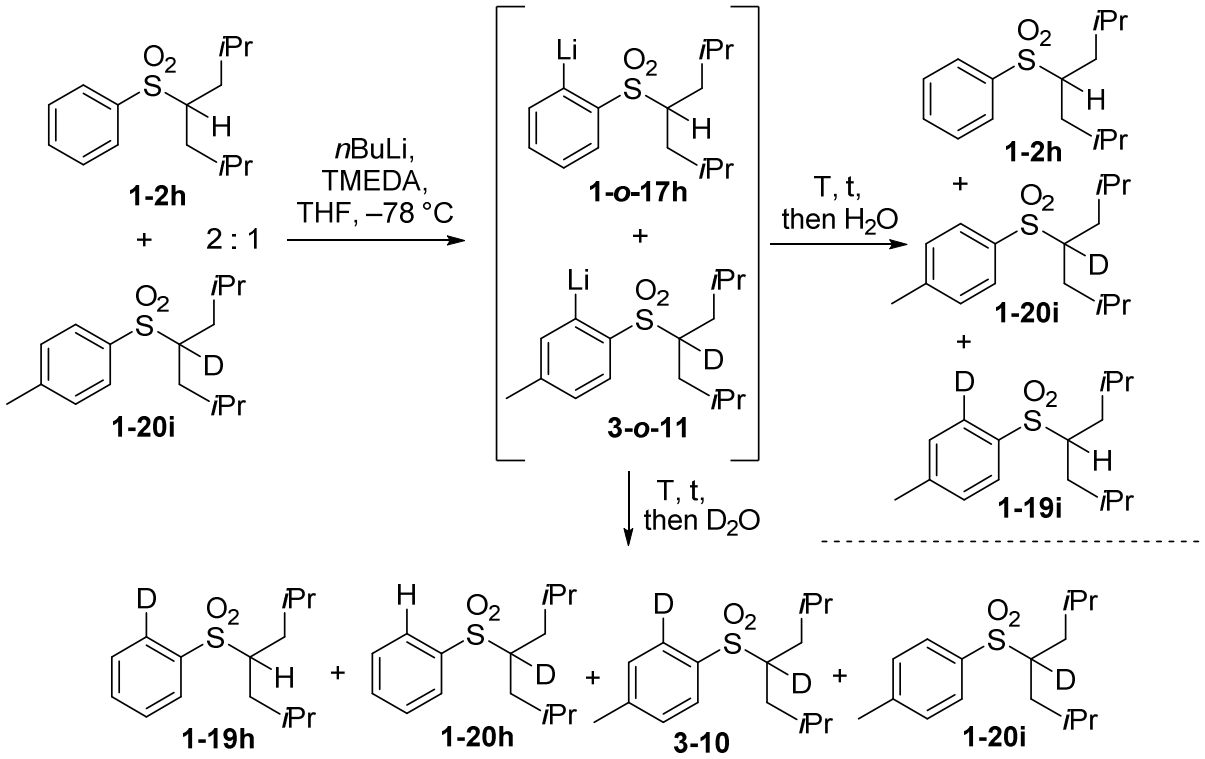
3.3.7. Crossover experiments

Based on the results of the investigation above, crossover experiments were performed by subjecting a 2:1 mixture of sulfones **1-2h** and **1-20i** to DoM under standard deprotonation conditions (Table 3.7). Samples of the reaction mixture were taken at defined temperatures and times and quenched by D_2O or water separately at the same time. The ratio of compounds **1-19h**, **1-20h**, **3-10**, and **1-20i** generated by deuteration revealed that the initial deprotonation occurred at the *ortho*-positions of both **1-2h** and **1-20i** forming both **1-*o*-17h** and **3-*o*-11** (entry 1). The determination of metalation regioselectivity was based on the formation of **1-19h** and **3-10** as the dominating products in a 2:1 ratio. The reaction mixture was warmed to –30 °C and another aliquot quenched by D_2O after 10 min showed that **1-*o*-17h** transmetalated to **1-α-18h** resulting in 50% of **1-19h** and 37% of **1-20h** (entry 2). Moreover 5% of **1-20i** was detected, whereas the amount of **3-10** was reduced to 45%. After further 30 min at –30 °C and deuterium quench, the content of **1-19h** dropped, whereas the amount of **1-20h** with the deuterium atom at the α-position was almost 100%, thus indicating almost complete *ortho*→α transmetalation (entry 3). Simultaneously, the amount of α-deuterated, but *ortho*-protonated **1-20i** increased to 18% going along with a parallel decrease of amount of **3-10** from 45% to 32%. This results can be only explained by a partial intermolecular proton transfer from the α-position of **1-*o*-17h** to **3-*o*-11**.

The product ratio of **1-2h/1-20i/1-19i** after quenching aliquots with water was basically identical and not dependent on the reaction time. The deuterium atom remained in

the α-position in **1-20i**. This revealed that a potential lithium-deuterium transmetalation, which would be proved by an increase of the α-H content in **1-20i**, did not occur to a significant extent. An identical experiment using equimolar amounts of **1-2h** and **1-20i** gave very similar results.

Table 3.7. Product distribution of the crossover experiment between **1-2h** and **1-20i**.



Quench by:			D_2O	H_2O
Entry	t [min][a]	T [°C]	**1-19h/1-20h/3-10/1-20i**[b]	**1-2h/1-20i/1-19i**[b]
1	10	–78	>95:<5:>45:<5	>95:>45:<5
2	20	–30	50:37:45:5	>95:>45:<5
3	50	–30	<5:95:32:18	>95:>45:<5

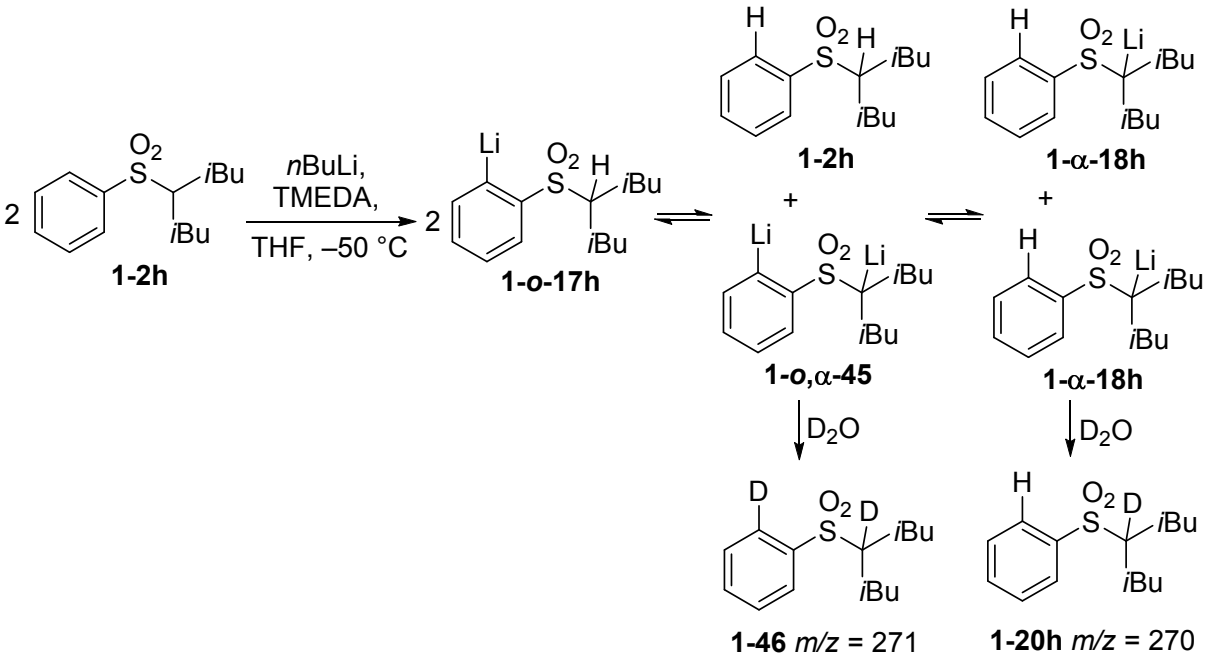
[a] Time refers to the start of the deprotonation. [b] Starting ratio **1-2h**/**1-20i** 2:1; compound ratio determined by integration of the ^{1}H NMR spectra.

All samples from the crossover experiment quenched by D_2O were analyzed by the GC/+CI-MS and showed a strongly predominant peak of **1-19h** and **1-20h** at *m/z* = 270. The 32:18 ratio of **3-10**/**1-20i** was also confirmed by a 2:1 ratio of peaks at *m/z* 285 and 284 in the spectra. In the GC/+CI-MS spectra of the sample quenched by water after 50 min, a peak at *m/z* 283 indicating the presence of non-deuterated *p*-tolyl sulfone **1-2i** was detected

with only 4% intensity confirming that metalation at the deuterated α-position of **1-20i** or transmetalation of **3-*o*-11** to the deuterated α-position took place only to a negligible extent.

3.3.8. Proton transfer equilibria among lithiated sulfones

The intermolecular pathway of the transmetalation would proceed either concerted or stepwise involving *ortho*,α-dilithio sulfone **1-*o*,α-45** (*cf.* Scheme 3.1). In the successive process the aryllithium **1-*o*-17h** acts as the base to the α-proton of another molecule **1-*o*-17h** leading to neutral sulfone **1-2h** and dilithium intermediate **1-*o*,α-45** in equilibrium (Scheme 3.6), which undergo subsequently a second thermodynamically favored proton transfer to form two molecules of **1-α-18h**.

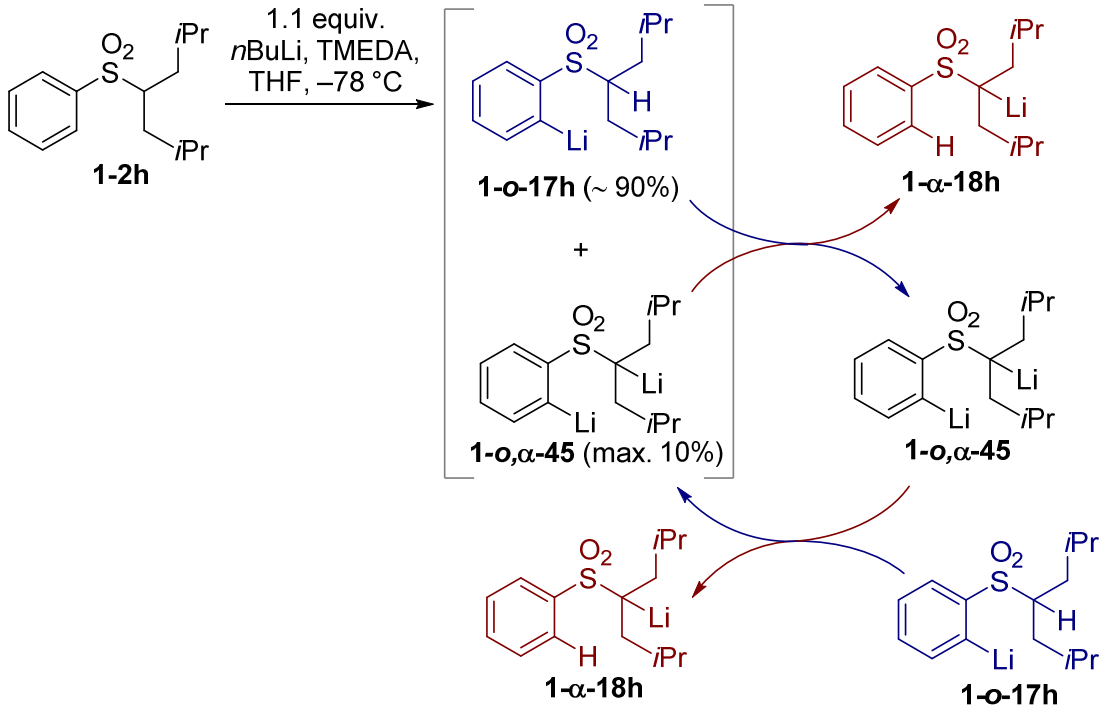


Scheme 3.6. The potential involvement of dilithiated species **1-*o*,α-45** during transmetalation.

To determine, whether a dilithium intermediate **1-*o*,α-45** can mediate the transmetalation, six of the twelve samples quenched by deuterium oxide during the kinetic study at –50 °C (Chapter 3.3.3, Figure 3.1) were analyzed by the GC/+CI-MS technique. If such an intermediate would be present in the reaction mixture, a significant concentration of dideuterated sulfone **1-46** resulting from deuteration of **1-*o*,α-45** should lead to a significant increase of the peak at *m/z* = 271 [M(**1-46**)+H^+] and at *m/z* = 269 [M(**1-2h**)+H^+]. However, the peak at *m/z* = 270, which represents the sum of singly deuterated **1-19h** and **1-20h**

[M(**1-19h/1-20h**)+H^+], was strongly predominant in all samples. The intensity of the peak at *m/z* = 271, representing the sum of the ^{13}C isotope peak of **1-19h/1-20h** and a potential dideuterated sulfone **1-46**, corresponded only to the intensity of the ^{13}C isotope peak and no further increase of its intensity was observed. This indicates, that if an intermediate **1-*o*,α-45** was present under the transmetalation conditions, it was present only to a very small extent. The intensity of the peak of neutral **1-2h** at *m/z* = 269 was also very small, confirming the results above. Similarly, no evidence for the presence of a dideuterated sulfone **1-46** was found analyzing the products obtained in the crossover experiment (Chapter 3.3.7, Table 3.7).

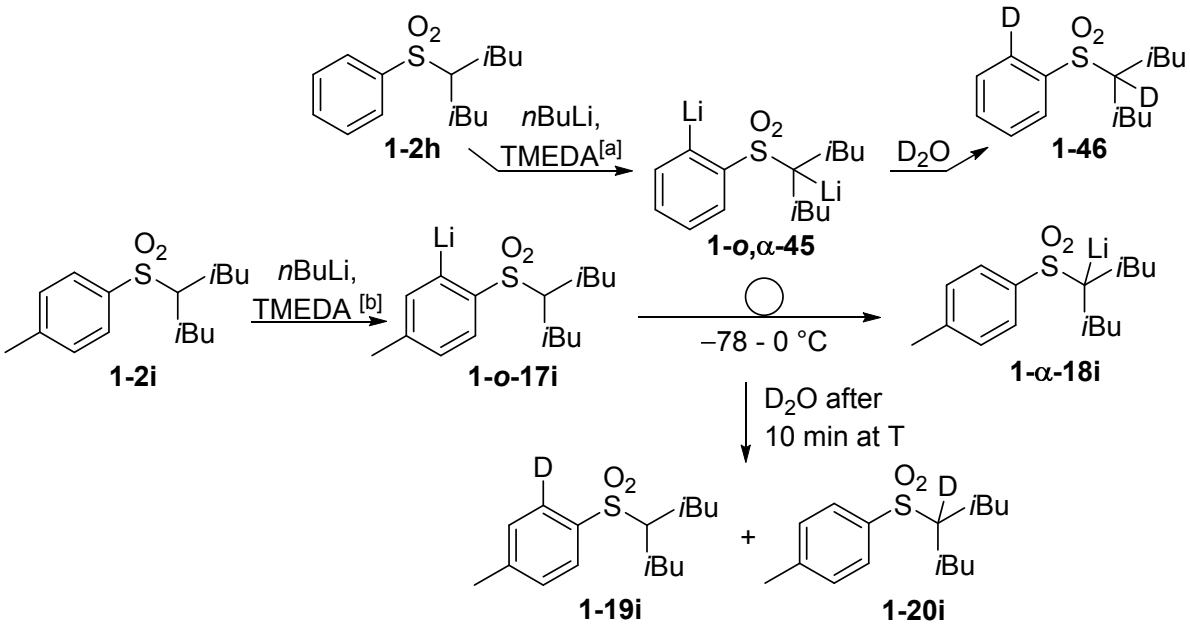
For the deprotonation of sulfones, *n*BuLi was used in a slight excess (1.05-1.15 equiv.) in order to deprotonate them to the highest possible extent. Assuming that up to 10% of **1-*o*,α-45** can be also generated during deprotonation using 1.1 equiv. of *n*BuLi, it can, in principle, act as a catalyst for the transmetalation reaction (Scheme 3.7).



Scheme 3.7. Potential action of **1-*o*,α-45** as a catalyst during transmetalation.

Intermediate **1-*o*,α-45** can initiate a proton transfer from the α-position of **1-*o*-17h**, thus regenerating the catalyst **1-*o*,α-45** and generating unreactive **1-α-18h**. This cycle could be repeated until all **1-*o*-17h** transmetalated to **1-α-18h**. In order to obtain information about the feasibility of such a proposed mechanism (Scheme 3.7), the dilithium intermediate **1-*o*,α-45** was individually generated (Table 3.8, entry 1) and subsequently added to a threefold excess of **1-*o*-17i** generated from tolylsulfone **1-2i** (entry 2).

Table 3.8. Transmetalation of **1-*o*-17i** to **1-α-18i** in the presence of dilithium intermediate **1-*o*,α-45**.



Entry	T [°C]	t [min]	% *ortho*-D (**1-19i**)	% α-D (**1-20i**)	**1-19i**/**1-20i**	% *ortho*-D (**1-46**)	% α-D (**1-46**)
1	–40	30[a]	-	-	-	91	96
2	–78	5[b]	91	1	91:1	-	-
3	–78	10[c]	89	1	89:1	93	96[d]
4	–60	20	87	5	17:1	91	96[d]
5	–40	30	77	17	4.5:1	89	96[d]
6	–20	40	12	85	1:7	93	96[d]
7	0	50	9	89	1:10	87	96[d]

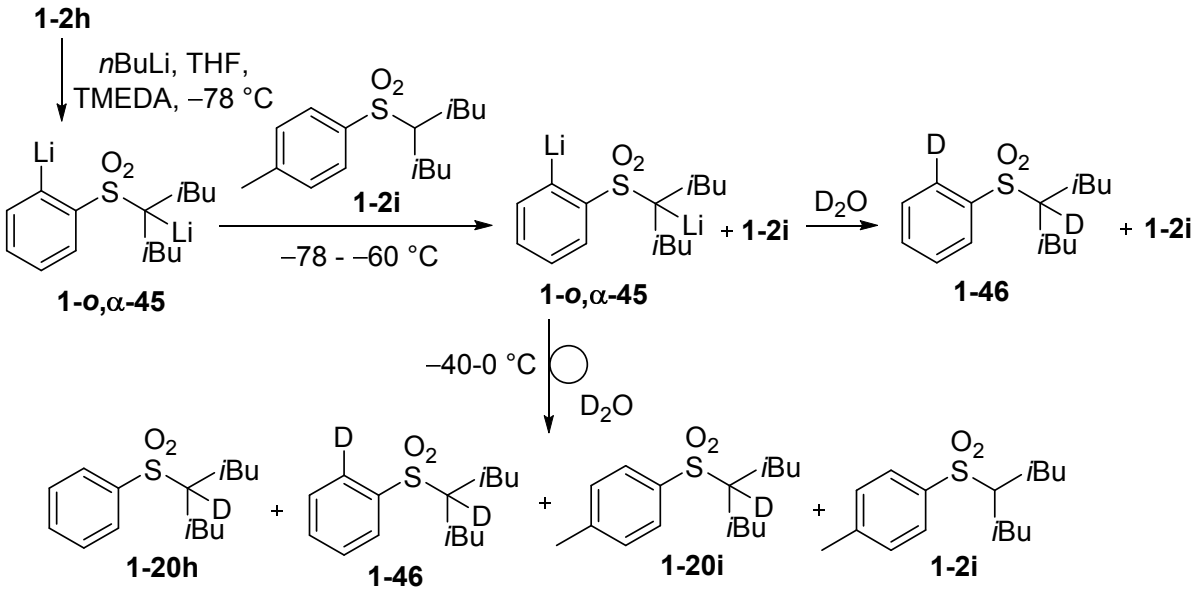
[a] Separate deprotonation of **1-2h** with 2 equiv. *n*BuLi. [b] Separate deprotonation of **1-2i** with 1 equiv. *n*BuLi. [c] Time 0 refers to mixing of **1-*o*,α-45** with **1-*o*-17i** at –78 °C. [d] α-H signals of **1-19i** and **1-46** are not distinguishable by ^{1}H NMR spectroscopy. It is assumed that the residual H-content of **1-46** is negligible and the decrease of the proton content is due to the transmetalation.

The mixture of **1-*o*,α-45** and **1-*o*-17i** remained stable at –78 °C for 10 minutes as proven by quenching samples of the reaction mixture by D_2O and isolation of **1-19i** and **1-46**, resulting from deuteration of **1-*o*-17i** and **1-*o*,α-45**, respectively (entry 3). The reaction mixture was warmed subsequently using the same times and temperatures (Table 3.8, entries 4-7) as the individual transmetalation of **1-*o*-17i** to **1-α-18i** (Chapter 3.1.3, Table 1.4, entry 11). The transmetalation was not accelerated by added **1-*o*,α-45**, even though it was present in a very high concentration. The dianion **1-*o*,α-45** remained unchanged during the

whole transmetalation process, because the deuterium content of **1-46** decreased only to a small extent over the reaction time. The reverse experiment, in which the dianion generated from **1-2i** was added to a solution of **1-*o*-17h** generated from **1-2h**, gave very similar results (not shown). The small excess of *n*BuLi with respect to the starting sulfone can be therefore considered to have no influence on the course of the transmetalation.

An experiment, concerning the ease of intermolecular proton transfer between dilithiated intermediate **1-*o*,α-45** and neutral sulfones was performed (Table 3.9). Neutral sulfone **1-2i** was added to a solution of **1-*o*,α-45**, generated by dilithiation at –78 °C, and the reaction was monitored by ^{1}H NMR spectroscopy after quenching with D_2O.

Table 3.9. Transmetalation reaction of the dilithium intermediate derived from **1-2h** with neutral **1-2i**.



Entry	T [°C]	t [min]	% *ortho*-D[a] (**1-46**)	% α-D[a,b] (**1-20i**)
1	–40	30[c]	90	-
2	–78	10[d]	87	1
3	–60	20	85	1
4	–40	30	75	9
5	–20	40	53	26
6	0	50	20	69

[a] Determined by integration of the ^{1}H NMR spectra. [b] The α-D signals of **1-46**, **1-20h** and **1-20i** cannot be distinguished. Because the α-D contents of **1-20h** and **1-46** do not change, the decrease of the intensity of the α-H resonance of **1-2i** corresponds to the increase of the α-D content of **1-20i**. [c] Separate deprotonation of sulfone **1-2h** with 2.2 equiv. of *n*BuLi. [d] Time 0 refers to mixing of **1-*o*,α-45** with **1-2i** at –78 °C.

Dilithium intermediate **1-*o*,α-45** was stable up to –60 °C and no proton transfer with **1-2i**, which would lead to the formation of **1-20h** and **1-20i,** was observed. Sulfones **1-46** and **1-2i** were the observed products (entries 1-3). On warming to 0 °C, **1-*o*,α-45** deprotonated neutral **1-2i** in α-position giving **1-20h** and **1-20i** via **1-α-18h** and **1-α-18i**, respectively. The *ortho*-position of **1-2i** was not deprotonated during the reaction time. These results demonstrate that the rate of proton transfer from **1-2i** to the dilithium intermediate **1-*o*,α-45** was somewhat slower than the transmetalation of **1-*o*-17i** to **1-α-18i** at a similar concentration (Chapter 3.1.3, Table 1.4, entry 11).

3.3.9. Determination of the mechanism of *ortho*→α transmetalation

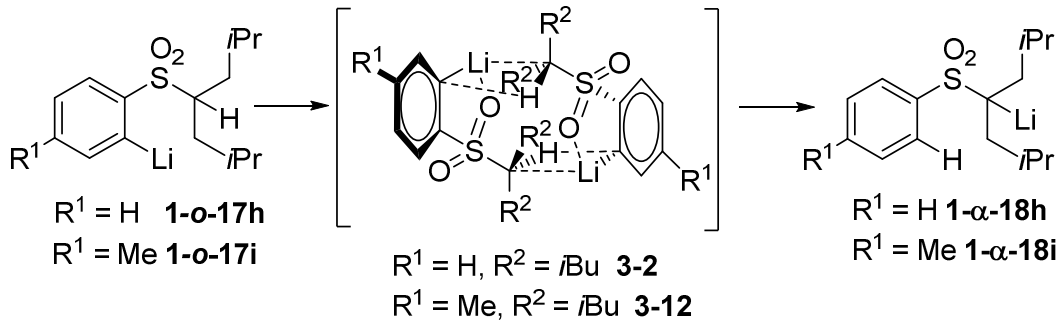
The mechanism of the *ortho*→α transmetalation of *ortho*-sulfonylphenyllithium to the thermodynamically more stable α-sulfonyl carbanion was deeply investigated performing differently aimed experiments. Significant kinetic isotope effects were observed for the initial deprotonation and the *ortho*→α transmetalation as well. The intramolecular KIE value of monodeuterated sulfone **1-19h** was determined to be 41 (Chapter 3.3.4, Scheme 3.4), however, the exact determination was not possible for the corresponding metalation of deuterated sulfones, because reaction rate of deprotonation and dedeuteration differs significantly causing undesired competitive α-deprotonation or DoM, respectively (**3-3** and **1-20p**, recpectively).

A kinetic study of the transmetalation process was performed. It was found that the rates of the *ortho*→α transmetalation better fit to first order kinetics, but in contrast display a clear concentration dependence. These results indicate that the transmetalation does not proceed intramolecularly via **3-1**, but that rather an intermolecular pathway via aggregates or by two-step proton transfer is followed (Chapter 3.3.1, Scheme 3.1).

Suitable substrates for crossover experiments were selected. Crossover experiments provided evidence that the *ortho*→α transmetalation follows the intermolecular pathway. The two remaining possibilities of such an intermolecular process were studied. The first option for an intermolecular process is a pathway based on a concerted proton transfer of two monomeric aryllithium units via an organized transition state similar to **3-2**, or from a dimeric aggregate (Scheme 3.8). Both pathways show a concentration dependence.

A two-step process mediated through dilithiated intermediate **1-*o*,α-45** (Chapter 3.3.8, Scheme 3.6) represent the second option for an intermolecular process. However, the transmetalation proceeds even if an excess of free sulfone, which does not allow the

formation of **1-*o*,α-45,** is present in the reaction mixture. Moreover, dideuterated compounds were not detected by GC/+CI-MS monitoring. Another potential action of **1-*o*,α-45** as a catalyst was, however, not supported by the results (Chapter 3.3.8, Scheme 3.7, Table 3.8). The participation of dilithium intermediates in the transmetalation can be thus excluded.



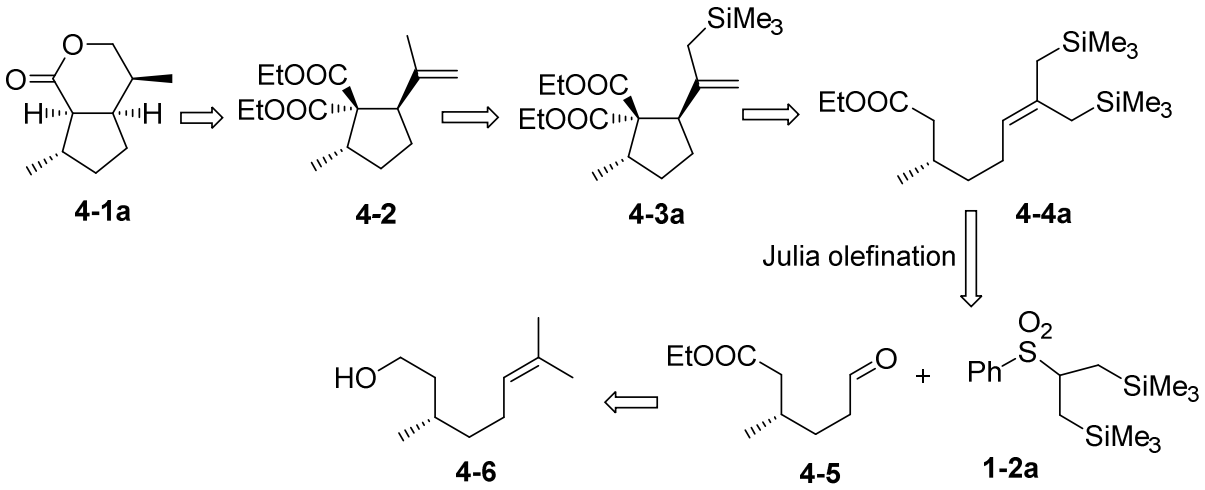
Scheme 3.8. Mechanistic proposal for the *ortho*→α-transmetalation of lithiated **1-2h,i**.

Regarding all the evidence, it is most likely that the *ortho*→α transmetalation of α,γ-branched sulfones such as **1-2h,i** occurs via an intermolecular concerted process via transition state **3-2** or **3-12** or from a similar dimeric aggregate (Scheme 3.8).

3.4. Application of the transmetalation in total syntheses

3.4.1. Retrosynthetic analysis of approach to cyclopentanoid monoterpenes

On the basis of the previously reported total synthesis of racemic dihydronepetalactone **4-1a** (see Chapter 1.1.3)[42] a similar retrosynthetic disconnection was proposed (Scheme 4.1). It is based on a three-step transformation of dicarboxylate **4-2** to dihydronepetalactone **4-1a** via hydroboration/oxidation followed by lactonization and dealkoxycarbonylation.

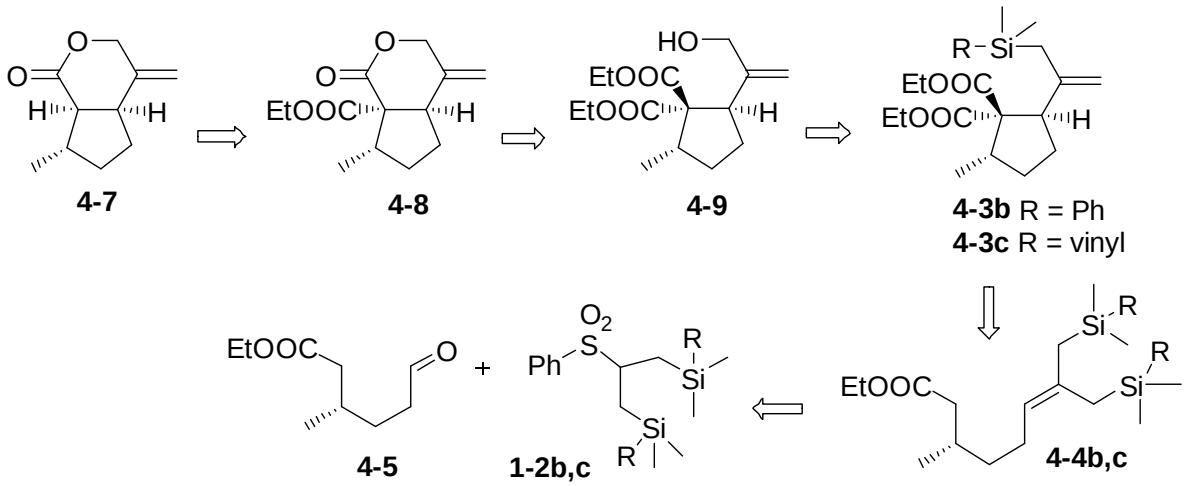


Scheme 4.1. Retrosynthesis of dihydronepetalactone **4-1a**.

In the new approach, dicarboxylate **4-2** should be provided by protodesilylation of allylsilane **4-3a**. Olefin **4-4a** should serve as the precursor for the construction of the cyclopentane skeleton **4-3a** in a tandem alkoxycarbonylation/oxidative radical cyclization reaction. In comparison with the recent approach the additional bulky silicon substituent in the key olefin should strenghten the *trans*-diastereoselectivity of the radical *5-exo* cyclization by favoring a chair-like transtition state, leading to the desired *trans*-2-alkenylcyclopentanecarboxylate **4-3a**. The Julia reaction is expected to result in a significant improvement of the efficiency of the synthesis. Moreover, the symmetric nature of sulfone **1-2a** will prevent the formation of *E*/*Z* diastereomeric mixtures. For that purpose, it was necessary to prepare β,β-disilylated sulfone **1-2a** and aldehyde **4-5** starting from optically pure (*S*)-citronellol (**4-6**).

The approach to other naturally occurring iridoid derivatives, such as dolicholactone **4-7** involves the dealkoxycarbonylation of intermediate **4-8** (Scheme 4.2). Lactone **4-8** should be provided by lactonization of allylic alcohol **4-9**. Modified silyl groups should allow the

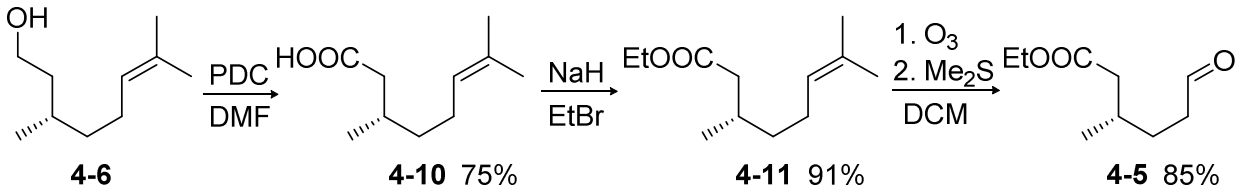
direct transformation of silanes **4-3b,c** to alcohol **4-9** by using Tamao-Fleming oxidation.[208] Precursors **4-3b,c** should be prepared similarly as **4-3a** (*cf.* Scheme 4.1) from olefins **4-4b,c**, which should be synthesized by Julia reaction from the corresponding starting sulfones **1-2b,c** and aldehyde **4-5** (Scheme 4.2).



Scheme 4.2. Retrosynthetic analysis of approach to dolicholactone **4-7**.

3.4.2. Preparation of starting materials

Aldehyde **4-5** was synthesized from commercially available optically pure (*S*)-citronellol (**4-6**) in 3 steps (Scheme 4.3). Citronellol was oxidized by pyridinium dichromate (PDC) in dry DMF. The reaction of resulting citronellic acid (**4-10**) with sodium hydride and ethyl bromide afforded ethyl ester **4-11** in very good yield. Subsequent ozonolysis of **4-11** provided the desired aldehyde **4-5**.



Scheme 4.3. Three-step reaction sequence of the synthesis of aldehyde **4-5**.

Symmetric β,β-disilylated sulfones **1-2a-c** were prepared by sequential alkylation of methyl phenyl sulfone (**1-1a**) with diverse (chloromethyl)silanes in the presence of TMEDA in good yield by a one-pot procedure (Chapter 3.1.1, Table 1.1).

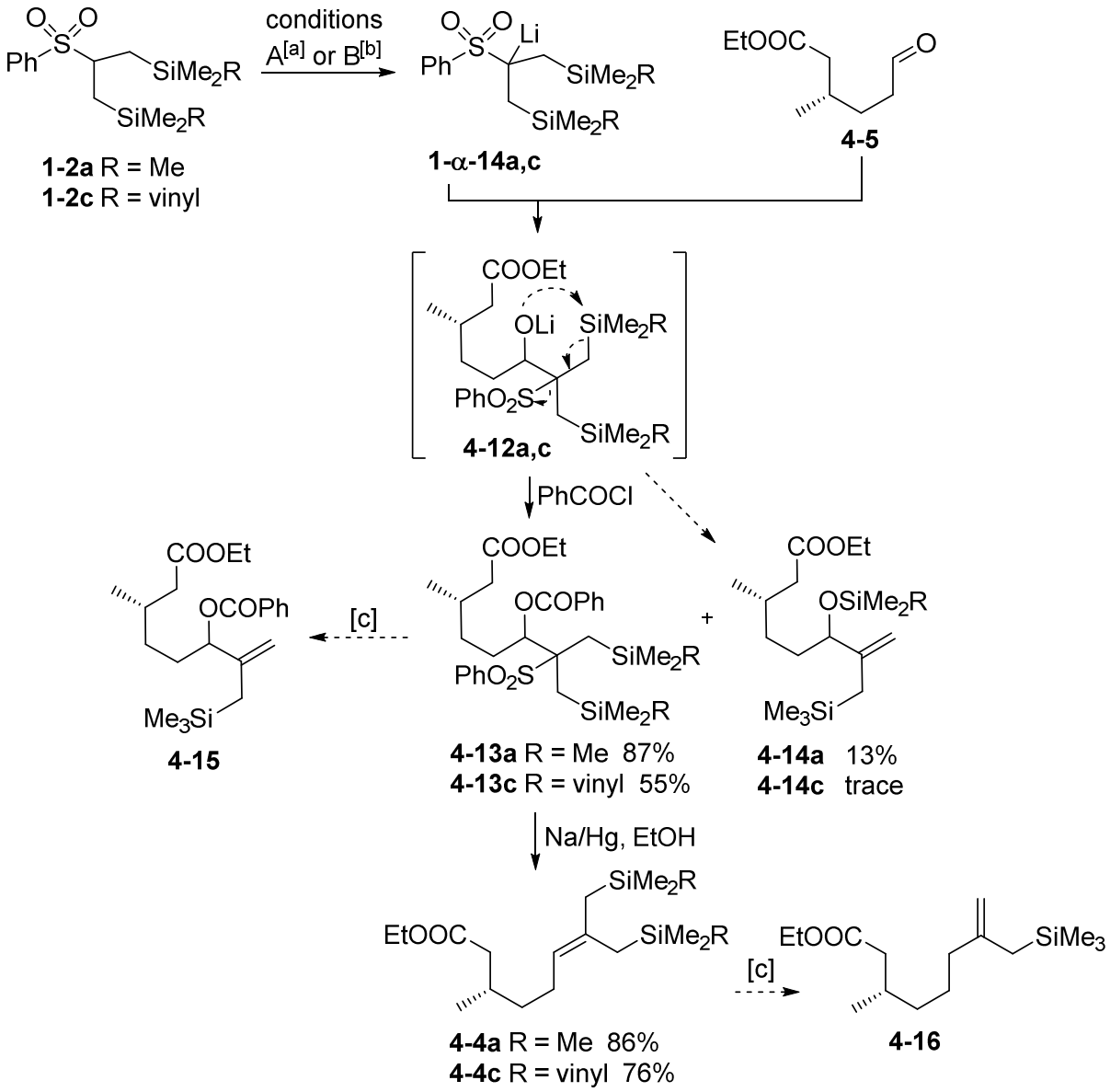
3.4.3. Optimization of the Julia reaction

Investigation of *ortho*→α transmetalation of differentially silylated potential precursors for Julia reactions showed that only *ortho*-metalated sulfones **1-2a** and **1-2c** transmetalate completely to required **1-α-14a,c**, which allow their application in the Julia reaction in the total synthesis (Chapter 3.1.2, Table 1.3). The *ortho*→α transmetalation of *ortho*-metalated sulfone **1-2b** generated by *n*BuLi in the presence of TMEDA occurred only to a small extent. HMPA supported the transmetalation to α-position. However, as was reported,[144] this additive also supports the Brook rearrangement of an alkoxide formed by a reaction of α-carbanion with an aldehyde. Sulfone **1-2b** is thus not suitable for further application in the Julia reaction.

The optimal conditions A and B, leading to the α-metalation of sulfones **1-2a** and **1-2c**, respectively, forming **1-α-14a,c** were applied (Scheme 4.4). The aldehyde **4-5** was added to the reaction mixture and resulting alkoxides **4-12a,c** were acylated *in situ* with benzoyl chloride affording β-benzoyloxy sulfones **4-13a,c** in good yields. The desired products **4-13a,c** were accompanied by small amounts of compounds **4-14a,c** resulting from a Brook rearrangement. Silyl ether **4-14a** was isolated and characterized, **4-14c** was present in trace amount. β-Benzoyloxy sulfones **4-13a,c** are unstable on silica gel and undergo carbon-silicon and carbon-sulfur bond cleavage, thus 2% of triethylamine was added to the eluents used for chromatographic purification. The product of decomposition of sulfone **4-13a**, alkene **4-15**, was isolated and characterized.

In contrast to the reported Julia reaction with similar substrates,[144] the Julia olefination of **4-13a** using SmI_2 did not afford the desired olefin **4-4a**. However, classical deoxygenation by sodium amalgam in dry ethanol provided the corresponding olefins **4-4a,c** in good yield. Dry ethanol was used instead of methanol to prevent the formation of the corresponding methyl esters by transesterification.

Allylsilanes **4-4a,c** are not stable on silica gel as well, thus 2% of triethylamine was added to the eluents used for chromatographic purification. Compound **4-16**, formed by undesired protodesilylation[209] of **4-4a**, was not fully characterized, because it could not be separated from the desired product. It was identified by ^{1}H NMR spectroscopy showing significant signals of two hydrogen atoms of a 1,1-disubstituted double bond. The structure was moreover confirmed by HRMS analysis.



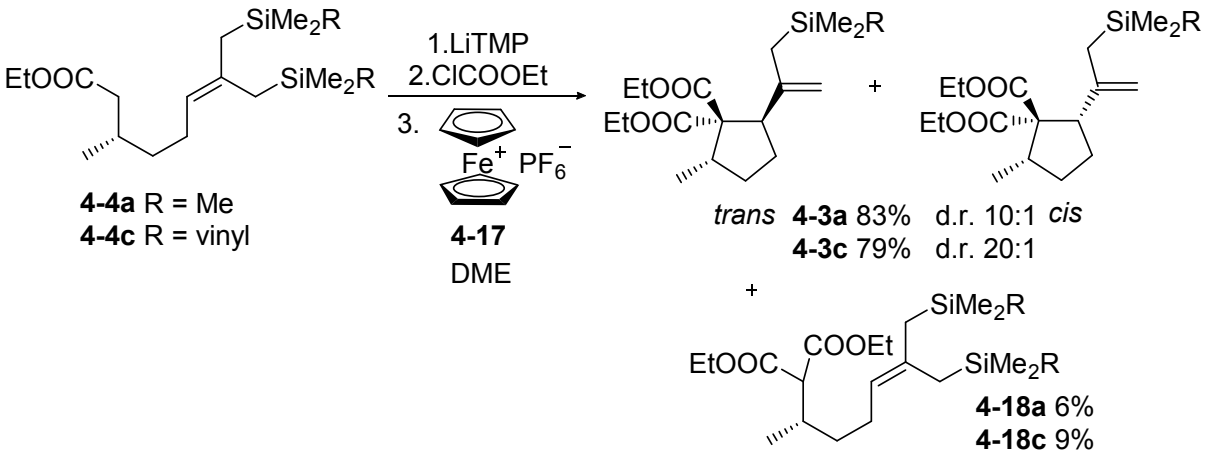
Scheme 4.4. Preparation of **4-4a,c** via β-benzoyloxy sulfones **4-13a,c**.

[a] Deprotonation conditions A (for **1-2a**): ref. [144] 1 mmol sulfone, 1.2 mmol *n*BuLi, 1.2 mmol TMEDA, DME, –78 °C, 10 min, then warmed to r.t. during 2 h, addition of 1.1 mmol aldehyde at –78 °C. [b] Deprotonation conditions B (for **1-2c**): 1 mmol sulfone, 1.5 mmol *n*BuLi, 1.5 mmol TMEDA, diethyl ether, –78 °C, 10 min, then warmed to 0 °C for 30 min, addition of 1.1 mmol aldehyde at –78 °C. [c] Undesired product formation during purification on silica gel without triethylamine in eluent.

3.4.4. Tandem alkoxycarbonylation/SET/radical cyclization

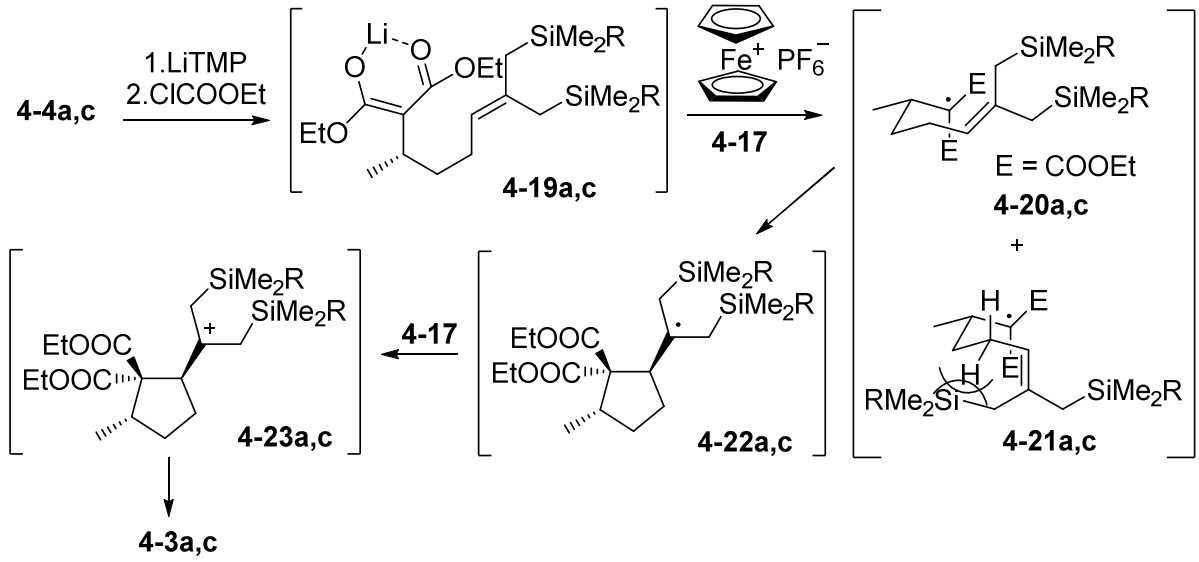
Cyclization precursors **4-4a,c** were subjected to the tandem alkoxycarbonylation/oxidative radical cyclization reaction by deprotonating with 2.6 equiv. of LiTMP, adding 1.2 equiv. of ethyl chloroformate followed by 2.3 equiv. of SET oxidant

ferrocenium hexafluorophosphate (**4-17**) according to the optimized reported procedure (Scheme 4.5).[42]



Scheme 4.5. Tandem alkoxycarbonylation/oxidative radical cyclization of **4-4a,c**.

The desired *trans*-diastereomers of cyclopentanes **4-3a,c** were obtained in very good yield and significantly improved 10:1 and 20:1 *trans/cis* selectivity, respectively, compared to the 2:1 selectivity in the cyclization of monosilylated olefin (±)-**i24** (Chapter 1.1.3, Scheme i2).[42] The diastereomeric mixtures of *trans*- and *cis*-cyclopentanes **4-3a,c** could not be separated at that stage. Side products **4-18a,c** generated from the uncyclized reaction intermediates **4-19a,c** (Scheme 4.6) were isolated in small amounts. Dicarboxylate **4-18a** was fully characterized to confirm its structure.

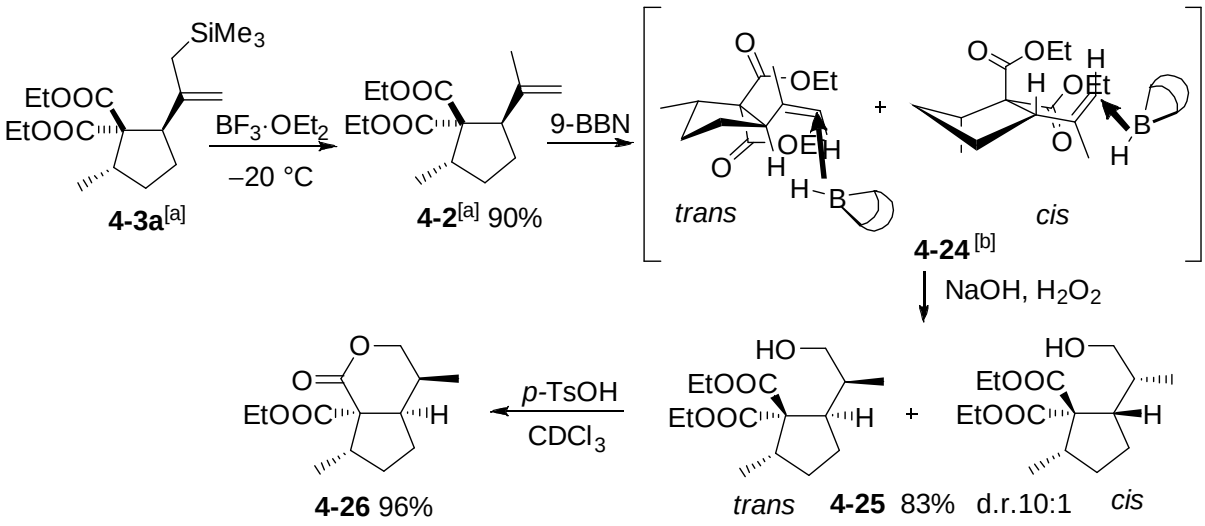


Scheme 4.6. Mechanism and diastereoselectivity of tandem alkoxycarbonylation/oxidative radical cyclization of **4-4a,c**.

The cyclization of **4-4a,c** proceeds via enolates **4-19a,c**, which undergo selective electron transfer mediated by ferrocenium hexafluorophosphate **4-17** (Scheme 4.6). Thus generated radicals **4-20a,c** cyclize to radicals **4-22a,c**. A high *trans*-diastereoselectivity of the radical 5-*exo* cyclization is secured by favoring energetically more stable chair-like transition state **4-20a,c**. In contrast, boat-like transition state **4-21a,c** is disfavored because of the bulky silyl group, which causes allylic strain.[210] Subsequently, carbocations **4-23a,c** are generated by a second SET oxidation. Their desilylation affords predominantly *trans*-cyclopentanes **4-3a,c**.

3.4.5. Synthesis of dihydronepetalactone

Protodesilylation of the diastereomeric mixture **4-3a** by $BF_3{\cdot}OEt_2$ at –20 °C afforded a diastereomeric mixture of *trans*- and *cis*-cyclopentanedicarboxylates **4-2** in very good yield (Scheme 4.7). The reaction with TBAF gave in contrast an inseparable mixture of undesired products and 50% of recovered starting material. The inseparable diastereomeric mixture **4-2** was carried through the hydroboration/oxidation reaction sequence performed by 9-BBN and $NaOH/H_2O_2$ providing the separable alcohols **4-25**.



Scheme 4.7. Protodesilylation of **4-3a**, hydroboration/oxidation and lactonization to **4-26**.

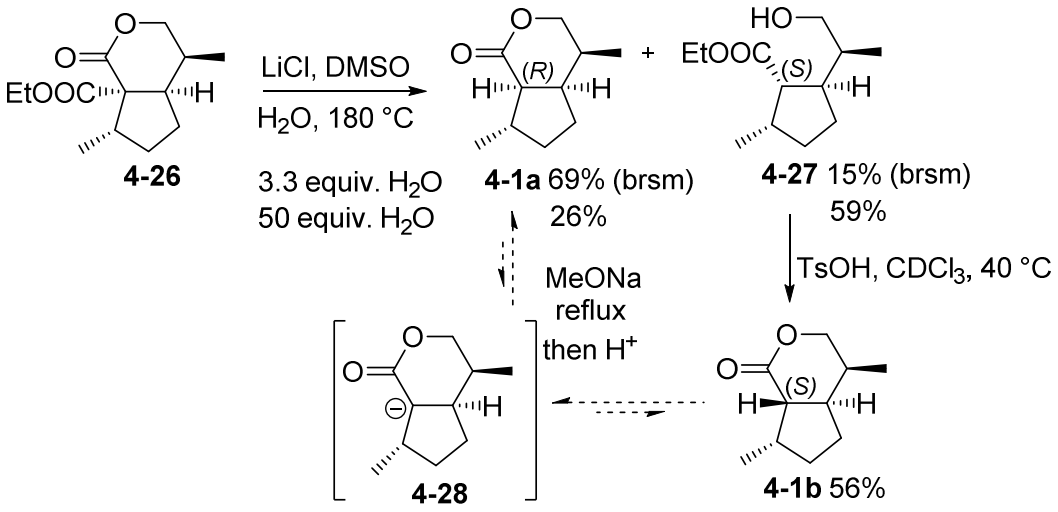
[a] *trans*/*cis* Diastereomers in 10:1 ratio. [b] Favored conformation avoiding allylic 1,3-strain.

The rationale for the observed high diastereoselectivity of the hydroboration reaction is the strongly preferred low energy conformation of the isopropenyl group in **4-24** dictated by allylic 1,3-strain.[210] In this conformation the two esters groups effectively shield one face, thus the borane exclusively attacks the double bond from the opposite face. The separation of

the *cis*-diastereomer of alcohol **4-25** was not necessary, because only the *trans*-diastereomer underwent selective and quantitative lactonization to **4-26** induced by a catalytic amount of *p*-toluenesulfonic acid in chloroform at room temperature.

However, the last step of the synthesis, Krapcho dealkoxycarbonylation in DMF/water in the presence of LiCl, did not provide dihydronepetalactone **4-1a** as selectively as was reported performing the reaction with racemic lactone **4-26**.[42] A significant amount of alcohol **4-27** was formed (Scheme 4.8). Using the previously reported conditions (1.7 equiv. of LiCl, 3.3 equiv. of water in dry DMSO, 160 °C for 3 h) afforded 49% of desired **4-1a** (69% based on recovered starting material (brsm)), 29% of starting material **4-26** and 11% (15% brsm) of alcohol **4-27**. The other problematic aspect of the reaction is that the desired product **4-1a** could not be separated from the starting lactone **4-26**, thus the lactone had to be fully converted into products before chromatographic separation. Moreover, as the impossibility of chromatographic separation indicated, the reaction could not be monitored by TLC, therefore the GC analysis of the reaction mixture was necessary. Such monitored reaction was not completed even after heating in DMSO for 36 h.

Various conditions were examined to reproduce the reported experiment. Repetition of reaction in the presence of 50 equiv. of water gave an increased 59% yield of alcohol **4-27** and only 26% of desired **4-1a** in a significantly shorter time of 5h.

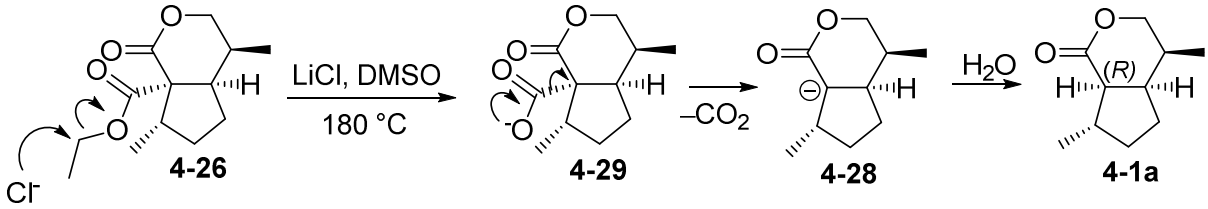


Scheme 4.8. Krapcho dealkoxycarbonylation of lactone **4-26**.

To confirm the structure of alcohol **4-27** and the stereochemistry at the α-carbon of the ester function, it was submitted to lactonization in the presence of catalytic *p*-TsOH. Alcohol **4-27** lactonized in 56% yield affording dihydroepinepetalactone **4-1b** after

warming to 40 °C for five days (Scheme 4.8). The difficulty of lactonization of **4-27** compared to that of *trans*-diastereomer **4-25** (Scheme 4.7) suggests stereochemistry of ester **4-27** to have (*S*) configuration at the ring carbon. Comparison of the ^{1}H NMR spectrum of lactone **4-1b** with the data reported in the literature[211] confirmed the assumed stereochemistry. The conversion of dihydroepinepetalactone **4-1b** into desired dihydronepetalactone **4-1a** is possible according to the literature.[212] Refluxing with sodium methoxide in methanol or potassium carbonate in xylene and subsequent acidifying with diluted hydrochloric acid would afford **4-1a**. Under these conditions enolate **4-28** would be generated and thermodynamic product **4-1a** would be formed selectively.

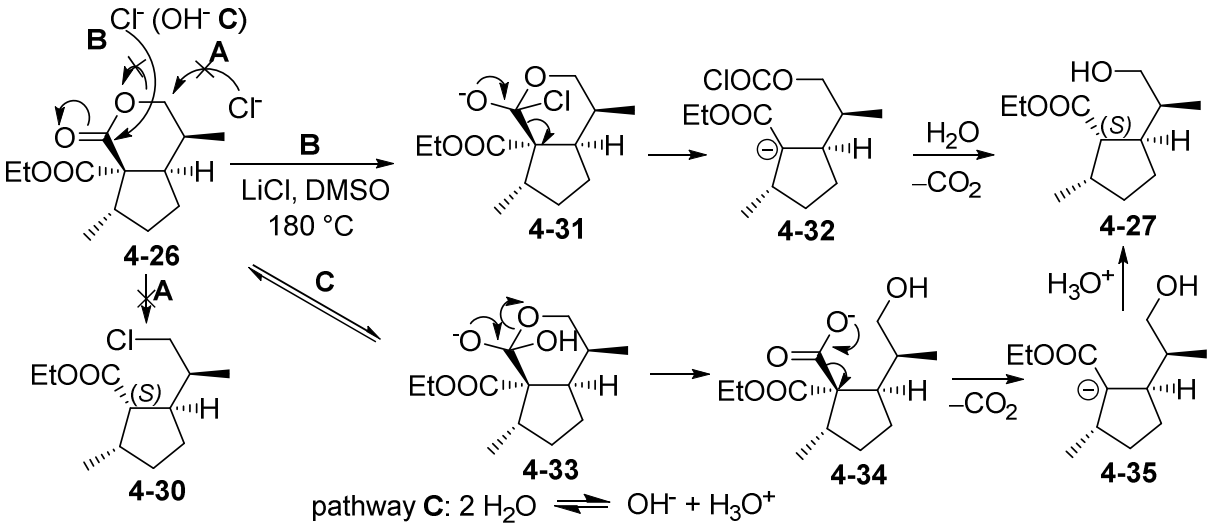
To explain the formation of **4-1a** and alcohol **4-27** in the Krapcho dealkoxycarbonylation, the possible mechanism of the reaction was proposed (Scheme 4.9).[213] The routes of Krapcho reaction depend on the substrate structure and type of nucleophile. Normally, in the case of α,α-disubstituted malonates, $B_{AL}2$ cleavage dominates and the anion of LiCl attacks the alkyl group of the ester unit in a S_N2 fashion affording intermediate **4-29**, which undergoes decarboxylation forming enolate **4-28**. Although the chirality of α-carbon is thus lost, the protonation of the enolate by water leads to selective formation of the thermodynamic product **4-1a**. This is explained by an equilibration of the protonated product with the anionic intermediate at high temperatures and long reaction times, thus the major product is the most stable diastereomer. This fact is in agreement with the conversion of **4-1b** to **4-1a** reported in the literature (*cf.* Scheme 4.8).[212]



Scheme 4.9. Presumable mechanism of dihydronepetalactone formation by the Krapcho reaction.

Alternatively, chloride anion can also attack the alkyl group of the lactone (pathway A, Scheme 4.10). However, the product of such reaction would be chloride derivative **4-30** in contrast to the isolated alcohol **4-27**. However, if the dicarboxylate is not sterically hindered a $B_{AC}2$ reaction may compete, thus chloride attacks the lactone carbonyl group to form tetrahedral intermediate **4-31** (pathway B), which would collapse to carbanion

intermediate **4-32**. Carbanion **4-32** would be protonated by water and hydrolysed providing alcohol **4-27** and carbon dioxide.



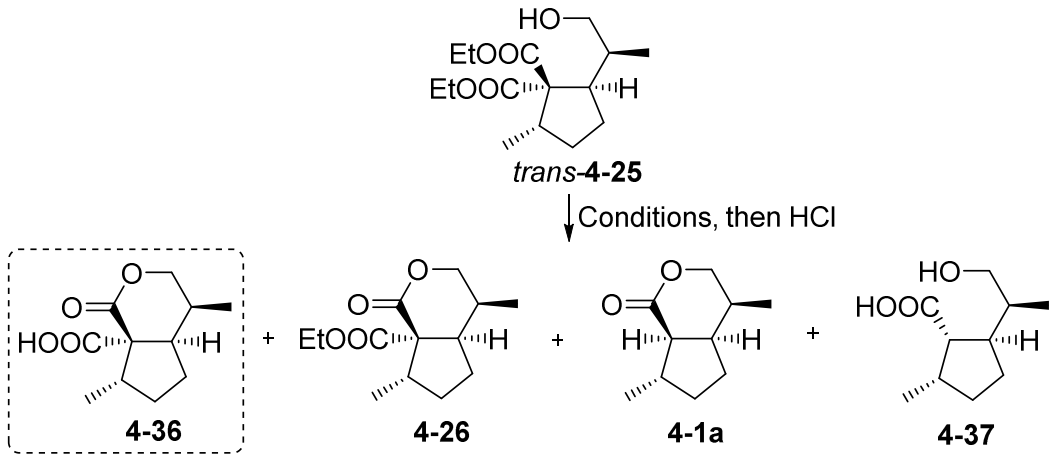
Scheme 4.10. Proposed mechanism for the formation of undesired alcohol **4-27** by the Krapcho reaction.

In the absence of LiCl, or with a large excess of water, the Krapcho reaction can proceed via nucleophilic attack of hydroxide anion or water at the unhindered ester carbonyl in a $B_{AC}2$ fashion, similarly to the neutral water-mediated hydrolysis of other acyl activated esters.[214] Thus, tetrahedral intermediate **4-33** and anionic intermediates **4-34** and **4-35** can be formed successively (pathway C). Eventhough LiCl was present in the performed Krapcho reaction, the predominant formation of alcohol **4-27** when using 50 equiv. of water supports pathway C occuring competitively (see Scheme 4.8).

Based on these results, alternatives for the last step of the total synthesis to dihydronepetalactone **4-1a** were explored. Hydrolysis of **4-25** to carboxylic acid **4-36** followed by thermal decarboxylation should be a good alternative to the Krapcho reaction (Table 4.1). Mild reaction conditions using four equivalents of lithium or potassium hydroxide in a mixture of methanol and water afforded only the lactonization product **4-26**. It was formed from starting **4-25** under the acidic work-up, because the lactone was not detected by TLC during the reaction (entries 1,2). Therefore, an excess of potassium hydroxide was used and the reaction mixture was heated to reflux for 72 h giving a 1:1 mixture of carboxylic acid **4-36** and lactone **4-26** (entry 3). Prolongation of the reaction time to 7 days under the same conditions provided the desired carboxylic acid **4-36** in 93% yield without any side products (entry 4). In order to reduce the reaction time, alcohol **4-25** was

subjected to 10 equiv. of potassium hydroxide in a microwave reactor. The reaction afforded lactone **4-26** at 105 °C after two hours (entry 5). However, warming the reaction to 120 °C afforded a mixture of significant amount of **4-26** and the desired carboxylic acid **4-36** accompanied with dihydronepetalactone **4-1a** and undesired carboxylic acid **4-37** (entry 6). The presence of the acid **4-37** was confirmed by observation of the $[M^{-}–H]$ peak at m/z 185 in the ESI^{-} spectrum.

Table 4.1. Alternative approach to dihydronepetalactone **4-1a**.



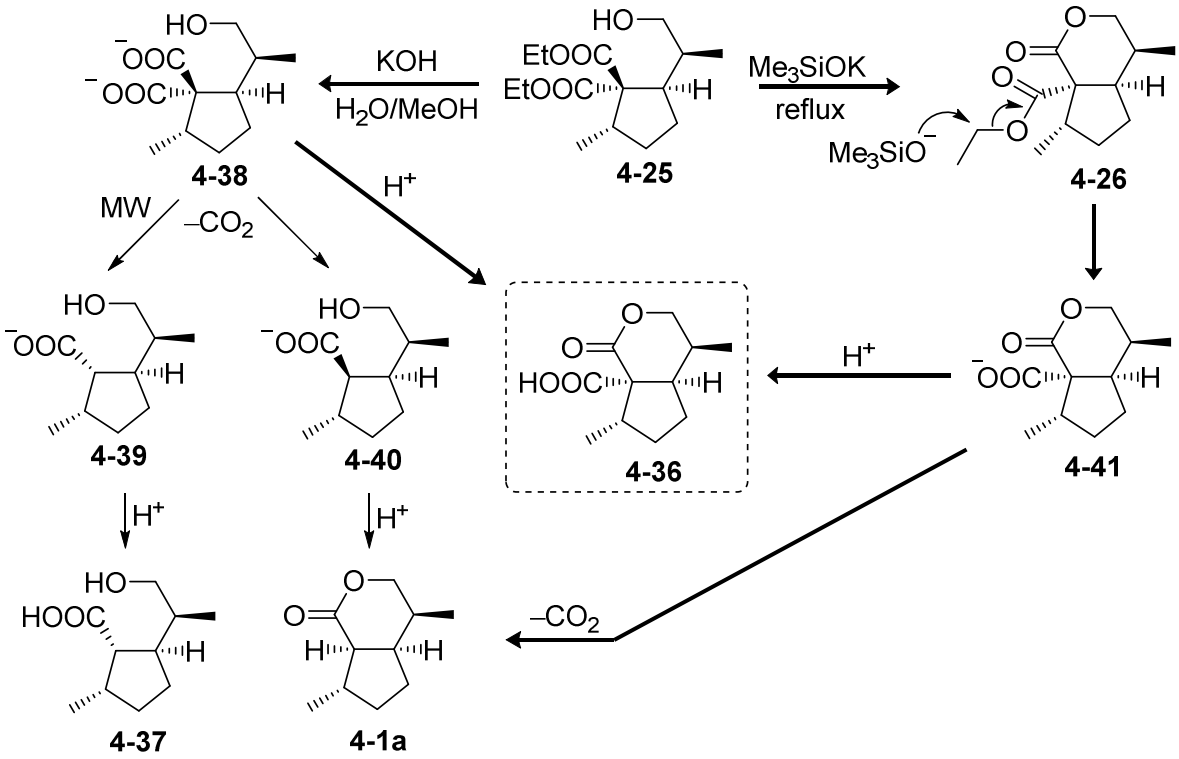
Entry	Conditions	Solvent	T [°C]	Time [h]	Product ratio[a]			
					4-36	**4-26**	**4-1a**	**4-37**
1	LiOH[b]	MeOH/H_2O	r.t.	16	-[c]	quant.[d]	-	-
2	KOH[b]	MeOH/H_2O	60	4	-	quant.	-	-
3	KOH[e]	MeOH/H_2O	reflux	72	1	1	-	-
4	KOH[e]	MeOH/H_2O	reflux	168	quant.[f]	-	-	-
5	KOH[g]	MeOH/H_2O	105	2	-	quant.	-	-
6	KOH[g]	MeOH/H_2O	120	2	1	6	1.4	1
7	Me_3SiOK	THF	r.t.	6	-	quant.	-	-
8	Me_3SiOK	THF	reflux	48	1[h]	-	1[h]	-

[a] Determined from the ^1H NMR spectra of the crude reaction mixtures. [b] 4 equiv. [c] Product not observed. [d] quant. = no other product observed. [e] 100 equiv. KOH. [f] 93% isolated yield. [g] 10 equiv. KOH in microwave reactor. [h] 96% total isolated yield (**4-36** + **4-1a**).

Hydrolysis performed by 10 equiv. of potassium trimethylsilanolate[215,216] in THF under inert conditions at room temperature afforded lactone **4-26** (entry 7). An approximately 1:1 mixture of carboxylic acid **4-36** and dihydronepetalactone **4-1a** (96%, **4-36**+**4-1a**) was formed by heating the reaction mixture to reflux for 2 days (entry 8). This approach affords

4-36 in shorter reaction time compared to hydrolysis with potassium hydroxide (entry 4). Crude carboxylic acid **4-36** was carried through the following decarboxylation without any purification. Hydrolysis of **4-25** can be performed as well with diastereomeric mixture of *trans*/*cis* alcohols affording desired carboxylic acid **4-36** in a crude mixture. The corresponding *cis*-diastereomers, which do not undergo lactonization (*cf.* Scheme 4.7), were separated by column chromatography from the final product **4-1a** after performing following final decarboxylation.

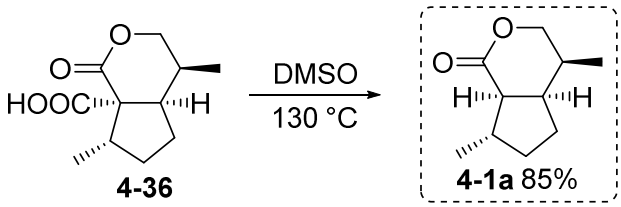
In order to explain the formation of all products obtained by hydrolysis of **4-25** plausible mechanism is proposed (Scheme 4.11). Under the conditions using potassium hydroxide both ester groups are slowly hydrolyzed via a standard $B_{AC}2$ tetrahedral reaction pathway giving dicarboxylate **4-38**, which forms the desired carboxylic acid **4-36** after lactonization on acidification (Table 4.1, entry 4). However, if the reaction temperature was higher, the thermal decarboxylation took place as well and two different monocarboxylate intermediates **4-39** and **4-40**, respectively, were formed. They afford carboxylic acid **4-37** and dihydronepetalactone **4-1a**, respectively, during acidic work-up. Compound **4-37** does not lactonize at room temperature similarly to **4-27** (Scheme 4.8).



Scheme 4.11. Proposed mechanism for hydrolysis of **4-25**.

The facts, that the reaction using potassium trimethylsilanolate in THF proceeds faster than the hydrolysis by potassium hydroxide and that the product of further decarboxylation is only dihydronepetalactone **4-1a**, suggests that the reaction proceeds by a different mechanism. The selective formation of **4-1a** by decarboxylation indicates that the decarboxylation cannot occur from symmetrical intermediate **4-38.** Most likely, lactone **4-26** was formed spontaneously under the reaction conditions. Subsequently, saponification of the ester unit of lactone **4-26** would proceed via a $B_{AL}2$ reaction mechanism by nucleophilic attack of trimethylsilanolate anion at the alkyl group with the carboxylate anion as the leaving group.[215] The resulting carboxylate **4-41** gives the desired carboxylic acid **4-36** after acidic work-up or dihydronepetalactone **4-1a** via subsequent decarboxylation.

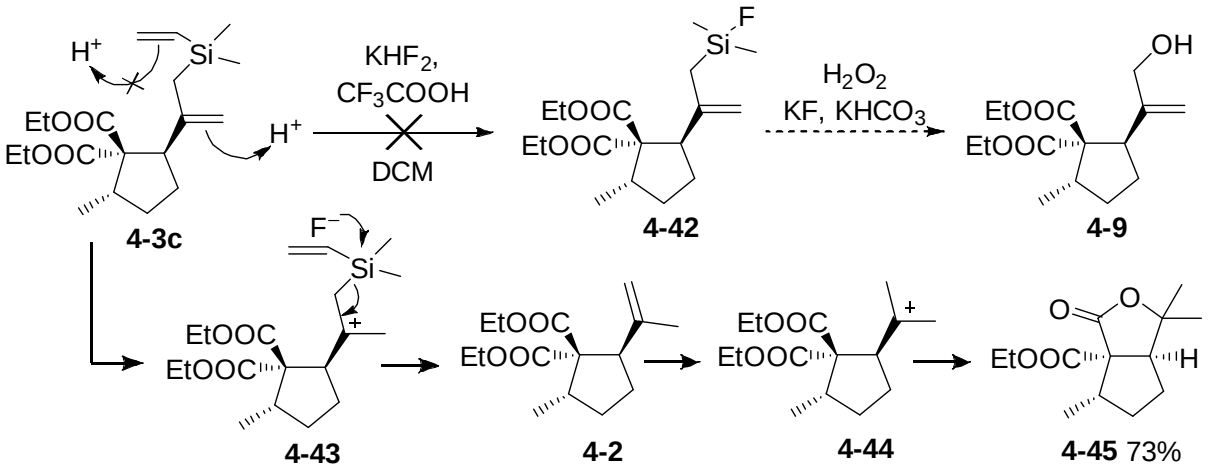
The final step of the total synthesis, the thermal decarboxylation of carboxylic acid **4-36**, was performed in DMSO at 130 °C for 5 h (Scheme 4.12), starting either from crude carboxylic acid **4-36**, generated by the saponification with KOH (Table 4.1, entry 4), or the 1:1 mixture of **4-36** and **4-1a**, generated by the reaction with potassium trimethylsilanolate in THF (Table 4.1, entry 8). The reaction proceeded quantitatively as revealed by the crude ^{1}H NMR spectrum and dihydronepetalactone **4-1a** was isolated in 85% yield. To summarize, dihydronepetalactone **4-1a** was synthesized in 10 steps in 18% overall yield under optimized conditions.



Scheme 4.12. Final decarboxylation of carboxylic acid **4-36**.

3.4.6. Completion of the synthesis of dolicholactone

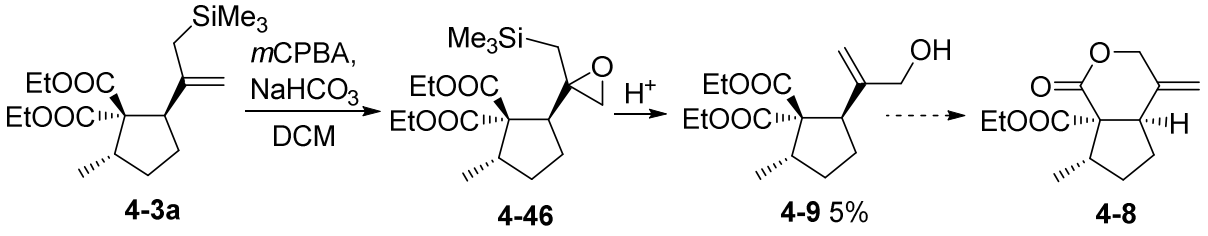
Cyclopentane **4-3c**, bearing the dimethyl(vinyl)silyl group as a masked hydroxy group, was designed as a suitable substrate for Tamao-Fleming oxidative desilylation to form allyl alcohol **4-9** (Scheme 4.13). Compound **4-3c** was submitted to the reaction with potassium hydrogen fluoride in excess of trifluoroacetic acid according to the known procedure.[217] However, the annulated butyrolactone **4-45** was formed instead of the desired silyl fluoride **4-42**, which could be directly oxidized to alcohol **4-9**.



Scheme 4.13. Attempt on Tamao-Fleming oxidative desilylation of **4-3c**.

The incompatibility of the allylsilane functionality with the reaction conditions is a consequence of the strong acidic conditions needed to remove the vinyl group.[208] The allylsilane double bond is more reactive towards electrophiles then the corresponding vinyl group because of the stabilization of carbocation intermediate **4-43** via the β-silicon effect.[218] Isopropenylcyclopentane **4-2,** which is formed via protodesilylation, is subsequently again protonated and the resulting tertiary carbenium ion **4-44** transforms into butyrolactone **4-45**.

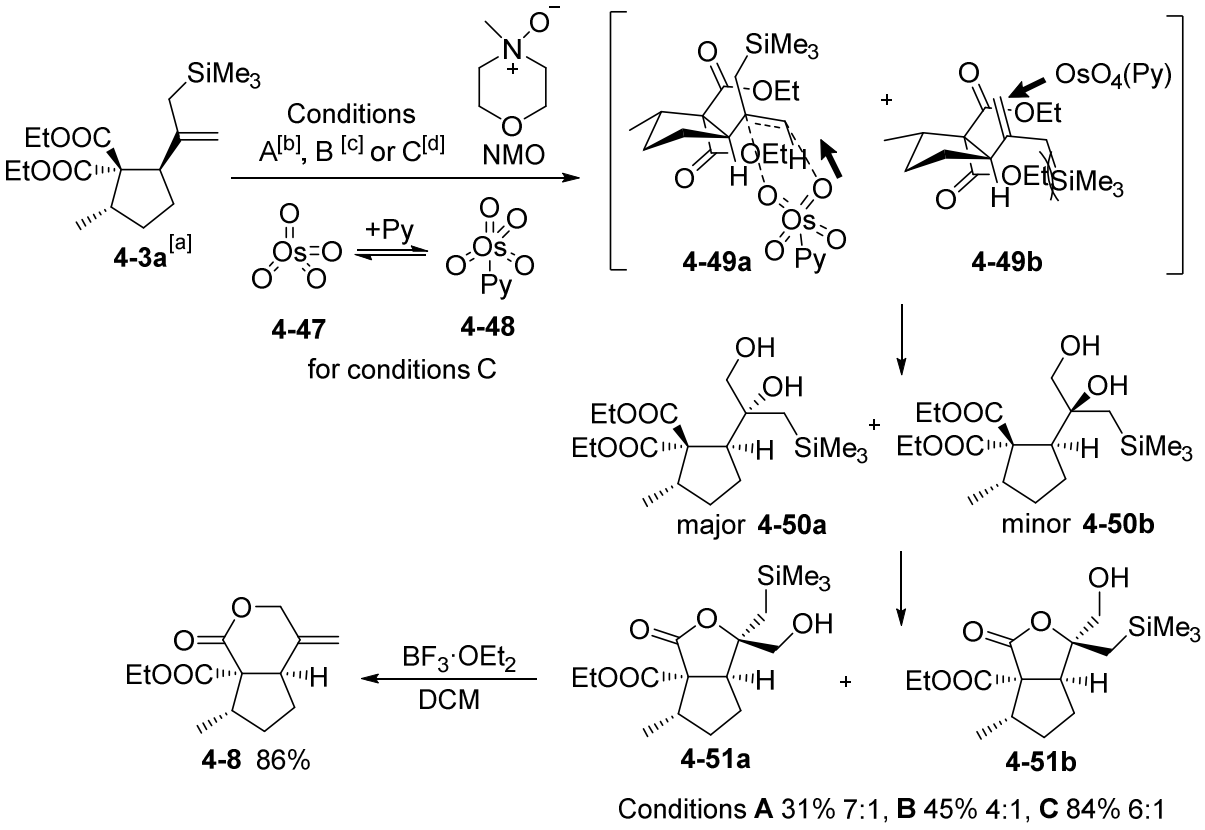
An alternative way for the preparation of alcohol **4-9** or its lactone **4-8** consist of epoxidation of the allylic double bond in **4-3a** with *m*CPBA in the presence of $NaHCO_3$, followed by desilylation and opening of the epoxide **4-46** under acidic conditions (Scheme 4.14).[219] However, allylic alcohol **4-9** was isolated from the complex reaction mixture only in 5% yield and lactonized product **4-8** was not observed at all.



Scheme 4.14. Alternative attempt for oxidative desilylation of **4-3a**.

Allylsilane **4-3a** was more successfully subjected to dihydroxylation[220] and subsequent Peterson olefination to overcome the obstacle of oxidative desilylation and to obtain the lactone **4-8** (Scheme 4.15). Osmylation of *trans*-olefin **4-3a** gave a diastereomeric mixture of lactones **4-51a,b** in different ratios in poor to good yield depending on the reaction

conditions. The reaction products of *cis*-diastereomer **4-3a** were not isolated. Conditions A and B using 2 mol.% of OsO_4 or K_2OsO_4 in the presence of citric acid and *N*-methylmorpholine-*N*-oxide (NMO) as a cooxidant in different solvent systems afforded lactones **4-51** in low yield. Conditions C, using 4 mol.% of osmium tetroxide (**4-47**), NMO and catalytic amount of pyridine as an accelerating ligand to OsO_4[221] in a 1:1:1 *t*BuOH/acetone/water solvent system, proved to be optimal for the synthesis of 6:1 diastereomeric mixture of diols **4-50**, which lactonized to lactones **4-51**. Pyridine acts as a ligand to OsO_4 (**4-47**) forming **4-48** and thus accelerates the reaction.



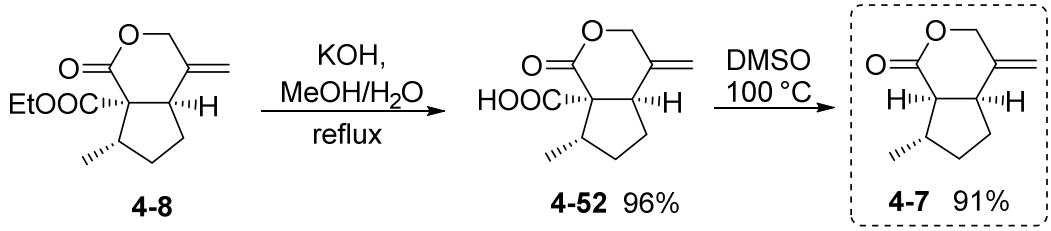
Scheme 4.15. Successful approach to lactone **4-8**.

[a] *trans*/*cis* Diastereomers in 10:1 ratio. [b] 0.02 equiv. OsO_4, 1.5 equiv. NMO, acetone/H_2O 9:1, r.t., 20 h. [c] 0.02 equiv. K_2OsO_4, 1.1 equiv. NMO, 0.75 equiv. citric acid, *t*BuOH/acetone/H_2O 1:1:1, r.t., 20 h. [d] 0.04 equiv. OsO_4, 3 equiv. NMO, cat. pyridine, *t*BuOH/acetone/H_2O 1:1:1, r.t., 16 h.

The preferred low energy conformation **4-49a** is, similarly as in the hydroboration of **4-2**, dictated by allylic 1,3-strain. The osmylation proceeds via concerted [3+2] mechanism and osmium tetroxide approaches the olefin unit preferably from the less hindered front face, similarly as in the transition state **4-24**, forming predominantly diol **4-50a**, which spontaneously lactonizes to **4-51a**. However, with the additional silyl group conformer **4-49b**

is also populated giving diastereomer **4-51b** after dihydroxylation and lactonization. Nevertheless, both diastereomers **4-51** were converted into optically pure compound **4-8** under the Peterson olefination conditions using $BF_3 \cdot OEt_2$ as a reagent.[222]

Ethyl ester **4-8** was saponified by potassium hydroxide in a mixture of methanol and water (Scheme 4.16). The alternative hydrolysis with potassium trimethylsilanolate did not provide the desired carboxylic acid but an inseparable mixture of other products. The crude carboxylic acid **4-52** was submitted to final thermal decarboxylation in dimethyl sulfoxide at 100 °C affording dolicholactone **4-7** in 91% yield. It was thus prepared in 10 steps in 20% overall yield.



4-8 **4-52** 96% **4-7** 91%

Scheme 4.16. Final steps to dolicholactone **4-7.**

4. Summary

A reversal from the typical α-metalation selectivity of alkyl aryl sulfones and sulfoxides has been discovered. Scope and limitations for initial *ortho*-metalation were investigated for differently branched alkyl aryl sulfones and sulfoxides. Steric hindrance is considered to be the major factor responsible for the metalation regioselectivity. If the alkyl units are γ-branched, the initial deprotonation occurs at the thermodynamically less acidic *ortho*-position. The originally expected α-deprotonation proceeds if the substrate has no additional or more remote branching.

The *ortho*-carbanions transmetalate to the thermodynamically favored α-carbanions on warming. The degree of branching determines the beginning of the transmetalation. The same initial metalation and transmetalation was observed for both sulfones and sulfoxides indicating that DoM followed by transmetalation is more general and reveals possible application to sulfides or phosphine oxides.

Both *ortho*- and α-carbanion types were applied as nucleophiles. The former afforded *ortho*-substituted aryl sulfones, whereas the latter was used in Julia olefination after completion of the transmetalation process. The initial deprotonation of *ortho*-substituted aryl sulfones was studied. *ortho'*-Deprotonated *ortho*-trimethylsilyl aryl sulfone was applied in the preparation of *ortho,ortho*'-disubstituted alkyl aryl sulfones.

ortho,α-Dilithiated sulfonyl species were generated by successive *ortho*- and α-lithiation by two equivalents of *n*BuLi. However the reaction of dianionic intermediate with one equivalent of aldehyde showed no selectivity affording mixtures of differentially substituted sulfones.

The mechanism of the *ortho*→α transmetalation of *ortho*-sulfonylphenyllithium to the thermodynamically more stable α-sulfonyl carbanion was investigated. Significant kinetic isotope effects were observed for the initial deprotonation as well as for the *ortho*→α transmetalation. Although not studied in detail here, deuterated sulfones may be applied to steer the metalation selectivity.

The kinetic study of the transmetalation showed that the rates of the *ortho*→α transmetalation fit better to first order kinetics, but in contrast display a clear concentration dependence. Moreover, crossover experiments provided the evidence that the *ortho*→α transmetalation follows an intermolecular pathway. A two-step process mediated by dilithiated intermediates was discarded based on experimental results in the presence of

individually generated dilithiated species. Based on the evidence, it is most likely that the *ortho*→α transmetalation of α,γ-branched sulfones occurs via an intermolecular concerted or aggregate-based process.

A significantly improved second generation total synthesis of iridoid type compounds was developed. The modified key olefin bearing an additional bulky silicon substituent was effectively prepared from the corresponding sulfone by a Julia reaction after the transmetalation. The desired silylated *trans*-cyclopentyl dicarboxylate was obtained by a tandem alkoxycarbonylation/oxidative radical cyclization with much better 10:1 diastereoselectivity compared to the reported cyclization of monosilylated olefin (d.r. 2:1). The main drawbacks of the recently published total synthesis of dihydronepetalactone were thus eliminated. Silylated *trans*-cyclopentyl dicarboxylate serves as a unique starting point for general syntheses of iridoids.

The final steps of the synthesis of dihydronepetalactone, which enabled selective dealkoxycarbonylation, were optimized. An efficient approach to dolicholactone, based on the dihydroxylation of *trans*-cyclopentyl dicarboxylate followed by Peterson olefination was elaborated. The dihydronepetalactone total synthesis was accomplished in 10 steps and 18% overall yield, whereas dolicholactone was prepared in 10 steps and 20% overall yield.

Potential modification of the approach may enable the preparation of other iridoid natural products. A similar strategy thus may be applied to accomplish the total syntheses of δ-skytanthine or related monoterpene alkaloids as well as other cyclopentanoid monoterpenes including these, whose configuration and biological activities are not yet known. Because synthetic analogs of natural products play a growing role in the field of chemistry, biology and medicine, synthetic approaches to these compounds are highly valuable.

5. Experimental Part

5.1. General experimental conditions

Solvents and additives were dried prior to use according to standard procedures. TLC analyses were conducted on TLC-PET foils SIL G/UV_{254} plates (Fluka Analytical). Chromatographic separations were performed on silica gel 60 (Fluka, 230-400 mesh). IR spectra were taken on a Bruker ALPHA FT-IR spectrometer using an ATR device. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 and 400 spectrometers working at 500.0 and 400.1 MHz for ^{1}H NMR or 125.7 and 100.6 MHz for ^{13}C NMR. Spectra are referenced to TMS or to solvent residual peak ($CDCl_3$). The connectivity was determined by ^{1}H-^{1}H COSY experiments and ^{13}C NMR assignments were obtained from HSQC and HMBC measurements. The numbering of atoms for NMR assignment is not the officially used systematic numbering. The *ortho*-carbons bearing hydrogens are numbered as C_{1} or $C_{1'}$ and the numbering of other atoms is derived from that basis. Mass spectra were recorded on LCQ Fleet (Thermo Fisher Scientific) and on QTof Micro (Waters) spectrometers. Compounds containing sulfur and silicon showed their inherent isotopic distribution in MS spectra (S [M+2] (4%); Si [M+1] (5%), [M+2] (5%)). These peaks are not stated in the MS assignments. HRMS spectra were measured on a Waters S2 Q-Tof micro spectrometer, resolution: 100000. Combustion analyses were performed at the microanalytical department of IOCB AS CR Prague. Melting points are uncorrected.

5.2. Procedures and analytical data

5.2.1 Divergent reactivity of alkyl aryl sulfones and sulfoxides with bases

Sequential dialkylation of sulfones 1-1a,b (General procedure):

*n*BuLi (8.13 mL, 13 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-1** (10 mmol) and TMEDA (3 mL, 19.5 mmol) in dry THF (50 mL) at –78 °C under a nitrogen atmosphere. After stirring for 15 min, the corresponding alkyl halide (13 mmol) was added dropwise at –78 °C. After stirring for 10 min, the reaction mixture was warmed to temperature $\mathbf{T_1}$ and stirred for time **t** (Table 5.1). The reaction mixture was cooled to –78 °C, TMEDA (3 mL, 19.5 mmol) and *n*BuLi (8.13 mL, 13 mmol, 1.6*M* in hexane) were added dropwise. After 10 min, the corresponding alkyl halide (13 mmol) was added, the solution

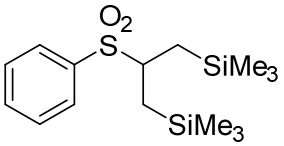
was stirred at –78 °C for 5 min, warmed to temperature **T₂** and stirred until complete as indicated by TLC. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous was extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:40, gradient to 1:10) gave differentially alkylated sulfones **1-2a-c,h,i,l,n-p**.

Table 5.1. Reaction temperatures and times for the preparation of **1-2a-c,h,i,l,n-p**.

Entry	Starting **1-1**	Halide	Product	T_1 [°C]	t [h]	T_2 [°C]
1	**1-1a**	$TMSCH_2Cl$	**1-2a**	r.t.	2	r.t.
2	**1-1a**	$DMPSCH_2Cl$[a]	**1-2b**	r.t.	2	r.t.
3	**1-1a**	$DMVSCH_2Cl$[b]	**1-2c**	r.t.	0.5	r.t.
4	**1-1a**	*i*BuI	**1-2h**	r.t.	1	r.t.
5	**1-1b**	*i*BuI	**1-2i**	0	1	0
6	**1-1a**	*i*PrI	**1-2l**	–60	4	r.t.
7	**1-1a**	BnBr	**1-2n**	r.t.	1	–78
8	**1-1a**	*i*PentI[c]	**1-2o**	–78	2	–78
9	**1-1a**	EtI	**1-2p**	0	1	r.t.

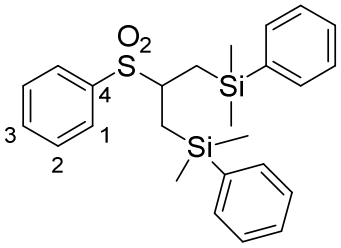
[a] DMPS = dimethylphenylsilyl. [b] DMVS = dimethylvinylsilyl. [c] *i*Pent = isopentyl.

1,3-Bis(trimethylsilyl)prop-2-yl phenyl sulfone (1-2a):[144]



Yield 2.92 g (89%) as colorless crystals, m.p. 36 °C. The spectral data are in agreement with those in the cited literature.[144]

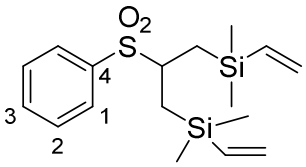
1,3-Bis[dimethyl(phenyl)silyl]prop-2-yl phenyl sulfone (1-2b):



Yield 2.63 g (58%) as colorless crystals, m.p. 67-68 °C. R_f (EtOAc/hexane 1:5) = 0.52; IR ν_{max} 3069, 2954, 1427, 1304, 1251, 1143, 1113, 840, 732, 700, 647 cm^{-1}; MS (ESI+) *m/z*

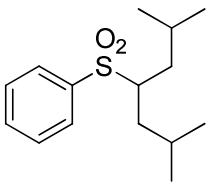
(%) 475 (100) [M+Na$^+$]; Anal. calcd for $C_{25}H_{32}O_2SSi_2$ (452.76): C 66.32, H 7.12, S 7.08; found: C 66.12, H 7.15, S 7.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 12H, Si(C*H*$_3$)$_2$), 0.92 (A part of ABM system, *J* = 7.1, 15.3 Hz, 2H, C*H*HSi), 1.19 (B part of ABM system, *J* = 6.3, 15.3 Hz, 2H, CH*H*Si), 3.10 (m, 1H, SO_2C*H*), 7.31 (m, 10H, *H$_{ar}$*), 7.45 (m, 2H, *H$_2$*), 7.62 (m, 3H, *H$_1$*, *H$_3$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ –2.4 (q, Si(*C*H$_3$)$_2$), –1.8 (q, Si(*C*H$_3$)$_2$), 18.7 (t, *C*H$_2$Si), 59.3 (d, SO_2*C*H), 128.0 (d, *C$_{ortho}$*), 129.0 (d, *C$_1$*), 129.28 (d, *C$_2$* or *C$_{meta}$*), 129.30 (d, *C$_2$* or *C$_{meta}$*), 133.4 (d, *C$_3$* or *C$_{para}$*), 133.9 (d, *C$_3$* or *C$_{para}$*), 137.1 (s, *C$_4$*), 138.1 (s, *C$_{ipso}$*).

1,3-Bis[dimethyl(vinyl)silyl]prop-2-yl phenyl sulfone (1-2c):



2.15 g (61%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.61; IR ν_{max} 3051, 3090, 2957, 2928, 2899, 2855, 2801, 1592, 1465, 1406, 1305, 1253, 1143, 1008, 958, 846, 830, 709 cm^{-1}; MS (ESI+) *m/z* (%) 727 (15) [2M+Na$^+$], 375 (100) [M+Na$^+$]; HRMS (EI) *m/z* [M+Na$^+$] calcd for $C_{17}H_{28}O_2SSi_2Na^+$: 375.1241; found: 375.1243; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 12H, Si(C*H*$_3$)$_2$), 0.83 (dd, *J* = 7.3, 15.1 Hz, 2H, C*H*HSi), 1.10 (dd, *J* = 6.3, 15.1 Hz, 2H, CH*H*Si), 3.23 (tt, *J* = 6.3, 7.3 Hz, 1H, C*H*SO_2), 5.66 (dd, *J* = 3.8, 20.1 Hz, 2H, SiCH=C*H*H), 5.98 (dd, *J* = 3.8, 14.7 Hz, 2H, SiCH=CH*H*), 6.14 (dd, *J* = 14.7, 20.1 Hz, 2H, SiC*H*=CH_2), 7.56 (m, 2H, *H$_2$*), 7.63 (m, 1H, *H$_3$*), 7.85 (m, 2H, *H$_1$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ –2.8 (q, Si(*C*H$_3$)$_2$), –2.4 (q, Si(*C*H$_3$)$_2$), 18.1 (t, *C*H$_2$Si), 59.4 (d, *C*HSO_2), 128.9 (d, *C$_1$*), 129.4 (d, *C$_2$*), 132.4 (t, SiCH=*C*H$_2$), 133.3 (d, *C$_3$*), 136.9 (s, *C$_4$*), 138.5 (d, Si*C*H=CH_2).

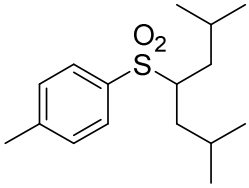
2,6-Dimethylhept-4-yl phenyl sulfone (1-2h):



Yield 2.17 g (81%) as colorless crystals, m.p. 47-48 °C. R_f (EtOAc/hexane 1:5) = 0.45; IR ν_{max} 3067, 2960, 2871, 1586, 1468, 1447, 1385, 1370, 1302, 1213, 1144, 1086, 998, 765, 735 cm^{-1}; MS (ESI+) *m/z* (%) 291 (100) [M+Na$^+$]; Anal. calcd for $C_{15}H_{24}O_2S$ (268.41): C 67.12, H 9.01, S 11.95; found: C 67.36, H 9.00, S 11.99; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.28 (m, 2H, C*H*H*i*Pr), 1.68 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 3.00 (tt, *J* = 7.2, 4.7 Hz, 1H, SO_2C*H*), 7.54 (m,

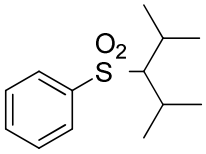
2H, H_{meta}), 7.63 (m, 1H, H_{para}), 7.86 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (q, CH(CH_3)$_2$), 23.1 (q, CH(CH_3)$_2$), 25.8 (d, $CH(CH_3)_2$), 38.8 (t, CH_2*i*Pr), 61.1 (d, SO_2CH), 129.1 (d, C_{ortho}), 129.2 (d, C_{meta}), 133.7 (d, C_{para}), 138.1 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[223]

2,6-Dimethylhept-4-yl 4-methylphenyl sulfone (1-2i):



Yield 2.23 g (79%) as colorless solid, m.p. 78-79 °C. R_f (EtOAc/hexane 1:5) = 0.78; IR ν_{max} 2958, 2919, 2867, 1594, 1493, 1466, 1386, 1370, 1300, 1287, 1187, 1140, 1120, 818, 704 cm^{-1}; MS (ESI+) *m/z* (%) 587 (10) [2M+Na$^+$], 305 (100) [M+Na$^+$]; Anal. calcd for $C_{16}H_{26}O_2S$ (282.44): C 68.04, H 9.28, S 11.35; found: C 68.04, 9.35, S 11.33; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (d, *J* = 6.2 Hz, 6H, CH(CH_3)$_2$), 0.86 (d, *J* = 6.3 Hz, 6H, CH(CH_3)$_2$), 1.25 (m, 2H, C*H*H*i*Pr), 1.68 (m, 4H, $CH(CH_3)_2$, CH*H*i*Pr), 2.43 (s, 3H, $CH_3C_6H_4$), 2.98 (m, 1H, SO_2CH), 7.32 (d, *J* = 8.0 Hz, 2H, H_{meta}), 7.72 (d, *J* = 8.0 Hz, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8 (q, $CH_3C_4H_6$), 22.1 (q, CH(CH_3)$_2$), 23.0 (q, CH(CH_3)$_2$), 25.7 (d, $CH(CH_3)_2$), 38.8 (t, CH_2*i*Pr), 61.1 (d, SO_2CH), 129.1 (d, C_{ortho}), 129.8 (d, C_{meta}), 135.1 (s, C_{ipso}), 144.5 (s, C_{para}). The spectral data are in agreement with those in the cited literature.[223]

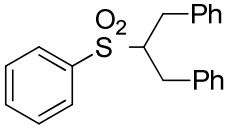
2,4-Dimethylpent-3-yl phenyl sulfone (1-2l):



Yield 1.23 g (54%) as colorless crystals, m.p. 87-88 °C. R_f (EtOAc/hexane 1:5) = 0.52; IR ν_{max} 3073, 3004, 2971, 2934, 2910, 2882, 1583, 1467, 1448, 1393, 1375, 1336, 1298, 1287, 1259, 1243, 1140, 1082, 1070, 1025, 815, 769, 740, 694, 624 cm^{-1}; MS (ESI+) *m/z* (%) 263 (100) [M+Na$^+$]; Anal. calcd for $C_{13}H_{20}O_2S$ (240.36): C 64.96, H 8.39, S 13.34; found: C 64.82, H 8.37, S 13.37; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 7.0 Hz, 6H, CH(CH_3)$_2$), 1.19 (d, *J* = 7.0 Hz, 6H, CH(CH_3)$_2$), 2.19 (dsept, *J* = 1.9, 7.0 Hz, 2H, $CH(CH_3)_2$), 2.84 (t, *J* = 1.9 Hz, 1H, SO_2CH), 7.53 (m, 2H, H_{meta}), 7.60 (m, 1H, H_{para}), 7.88 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (q, CH(CH_3)$_2$), 21.5 (q, CH(CH_3)$_2$), 27.3 (d, $CH(CH_3)_2$), 74.2 (d,

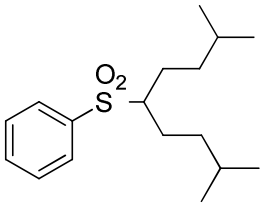
SO_2CH), 128.5 (d, C_{ortho}), 129.2 (d, C_{meta}), 133.3 (d, C_{para}), 141.0 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[223]

1,3-Diphenylprop-2-yl phenyl sulfone (1-2n):



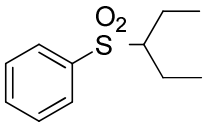
Yield 2.36 g (70%) as colorless crystals, m.p. 103-104 °C. R_f (EtOAc/hexane 1:5) = 0.40; MS (ESI+) *m/z* (%) 359 (100) [M+Na^+]; Anal. calcd for $C_{21}H_{20}O_2S$ (336.45): C 74.97, H 5.99, S 9.53; found: C 74.95, 6.02, S 9.36; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 7.8, 14.5 Hz, 2H, C*H*HPh), 3.27 (dd, *J* = 5.2, 14.5 Hz, 2H, CH*H*Ph), 3.59 (tt, *J* = 7.8, 5.2 Hz, 1H, SO_2CH), 6.87 (m, 4H, H_{ar}), 7.09 (m, 6H, H_{ar}), 7.44 (m, 2H, H_{meta}), 7.55 (m, 1H, H_{para}), 7.82 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.[224]

2,8-Dimethylnon-5-yl phenyl sulfone (1-2o):



Yield 1.81 g (61%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.45; IR ν_{max} 2955, 2870, 1467, 1447, 1302, 1141, 1084, 757, 726, 691 cm^{-1}; MS (ESI+) *m/z* (%) 615 (10) [2M+Na^+], 319 (100) [M+Na^+]; Anal. calcd for $C_{17}H_{28}O_2S$ (296.47): C 68.87, H 9.52, S 10.82; found: C 68.81, H 9.55, S 10.71; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (2×d, *J* = 6.7 Hz, 12H, $CH(CH_3)_2$), 1.13 (m, 2H, C*H*H*i*Pr), 1.24 (m, 2H, CH*H**i*Pr), 1.47 (m, 2H, $CH(CH_3)_2$), 1.52 (m, 2H, $SO_2CH(CHH)_2$), 1.79 (m, 2H, $SO_2CH(CHH)_2$), 2.86 (m, 1H, SO_2CH), 7.49 (m, 2H, H_{meta}), 7.59 (m, 1H, H_{para}), 7.82 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (q, $CH(CH_3)_2$), 22.6 (q, $CH(CH_3)_2$), 25.6 (t, $CH_2CH(CH_3)_2$), 28.0 (d, $CH(CH_3)_2$), 35.9 (t, $SO_2CH(CH_2)_2$), 65.1 (d, SO_2CH), 128.9 (d, C_{ortho}), 129.2 (d, C_{meta}), 133.6 (d, C_{para}), 138.5 (s, C_{ipso}).

Pent-3-yl phenyl sulfone (1-2p):

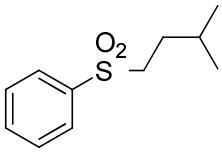


Yield 1.53 g (72%) as colorless crystals, m.p. 48-49 °C. R_f (EtOAc/hexane 1:5) = 0.59; IR ν_{max} 2972, 2939, 1590, 1302, 1289, 1143, 1085, 1074, 760, 726, 613 cm^{-1}; MS (ESI+) *m/z* (%) 235 (100) [M+Na^+]; Anal. calcd for $C_{11}H_{16}O_2S$ (212.31): C 62.23, H 7.60, S 15.10; found: C 62.42, H 7.75, S 15.01; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.5 Hz, 6H, C*H*$_3$), 1.66 (m, 2H, C*H*$_2$CH$_3$), 1.85 (m, 2H, C*H*$_2$CH$_3$), 2.78 (m, 1H, SO_2C*H*), 7.54 (m, 2H, *H*$_{meta}$), 7.62 (m, 1H, *H*$_{para}$), 7.87 (m, 2H, *H*$_{ortho}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3 (q, *C*H$_3$), 20.4 (t, *C*H$_2$CH$_3$), 67.2 (d, SO_2*C*H), 128.9 (d, *C*$_{ortho}$), 129.2 (d, *C*$_{meta}$), 133.6 (d, *C*$_{para}$), 138.9 (s, *C*$_{ipso}$). The spectral data are in agreement with those in the cited literature.[223]

Monoalkylation of methyl phenyl sulfone 1-1a (General procedure):

*n*BuLi (8.13 mL, 13 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of **1-1a** (1.56 g, 10 mmol) and TMEDA (3 mL, 19.5 mmol) in dry THF (50 mL) under a nitrogen atmosphere at –78 °C. After stirring for 15 min, the corresponding alkyl halide (13 mmol) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature for 10 min and at –60 °C until complete as indicated by TLC. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous was extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20, gradient to 1:10) gave sulfones **1-3b-d**.

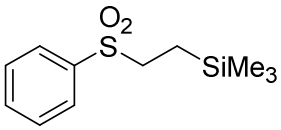
Isopentyl phenyl sulfone (1-3b):



Yield 1.65 g (78%) as colorless crystals, m.p. 46-47 °C. R_f (EtOAc/hexane 1:5) = 0.27; IR ν_{max} 3066, 2959, 1586, 1468, 1450, 1385, 1371, 1302, 1213, 1144, 1083, 998, 766, 735 cm^{-1}; MS (ESI+) *m/z* (%) 447 (20) [2M+Na^+], 235 (100) [M+Na^+]; Anal. calcd for $C_{11}H_{16}O_2S$ (212.31): C 62.23, H 7.60, S 15.10; found: C 62.28, H 7.61, S 14.99; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 1.59 (m, 3H, C*H*$_2$*i*Pr, C*H*(CH$_3$)$_2$),

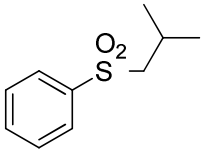
3.06 (m, 2H, SO_2CH_2), 7.55 (m, 2H, H_{meta}), 7.64 (m, 1H, H_{para}), 7.89 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (q, $CH(CH_3)_2$), 27.4 (d, $CH(CH_3)_2$), 31.2 (t, CH_2*i*Pr), 54.9 (t, SO_2CH_2), 128.2 (d, C_{ortho}), 129.4 (d, C_{meta}), 133.8 (d, C_{para}), 139.5 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[225]

1-(Trimethylsilyl)eth-2-yl phenyl sulfone (1-3c):



Yield 1.91 g (79%) as colorless crystals, m.p. 52-53 °C. R_f (EtOAc/hexane 1:5) = 0.53; MS (ESI+) *m/z* (%) 265 (100) [M+Na$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.02 (s, 9H, $Si(CH_3)_3$), 0.91 (m, 2H, CH_2Si), 2.98 (m, 2H, SO_2CH_2), 7.55 (m, 2H, H_{meta}), 7.64 (m, 1H, H_{para}), 7.88 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ –1.2 (q, $Si(CH_3)_3$), 9.4 (t, CH_2Si), 52.9 (t, SO_2CH_2), 128.5 (d, C_{ortho}), 129.4 (d, C_{meta}), 133.6 (d, C_{para}), 139.1 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[226]

Isobutyl phenyl sulfone (1-3d):



1.31 g (66%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.36; IR ν_{max} 3072, 3002, 2973, 2935, 2882, 1583, 1467, 1448, 1393, 1298, 1287, 1265, 1240, 1140, 1083, 1070, 1025, 769, 740, 694 cm^{-1}; MS (ESI+) *m/z* (%) 221 (100) [M+Na$^+$]; Anal. calcd for $C_{10}H_{14}O_2S$ (198.28): C 60.57, H 7.12, S 16.17; found: C 60.47, H 7.14, S 16.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.7 Hz, 6H, $CH(CH_3)_2$), 2.18 (m, 1H, $CH(CH_3)_2$), 2.95 (d, *J* = 6.6 Hz, 2H, SO_2CH_2), 7.52 (m, 2H, H_{meta}), 7.60 (m, 1H, H_{para}), 7.86 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (q, $CH(CH_3)_2$), 24.2 (d, $CH(CH_3)_2$), 64.1 (t, SO_2CH_2), 127.9 (d, C_{ortho}), 129.4 (d, C_{meta}), 133.7 (d, C_{para}), 140.3 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[227]

Alkylation of sulfones 1-3a-e (General procedure):

*n*BuLi (1.31 mL, 2.1 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfones **1-3a-e** (2 mmol) and TMEDA (0.6 mL, 4 mmol) in dry THF (10 mL) at –78 °C under a nitrogen atmosphere. After stirring for 15 min, the corresponding alkyl halide

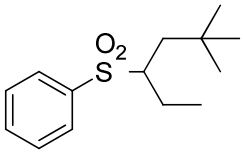
(2.2 mmol) was added dropwise at –78 °C. After 10 min, the reaction mixture was stirred at temperature T until complete as indicated by TLC (Table 5.2). The reaction mixture was quenched with saturated NH_4Cl solution, the layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **1-2d-g,j,k,m,q**.

Table 5.2. Alkylation of sulfones **1-3a-e**.

Entry	Starting sulfone **1-3**	Halide	Product	T [°C]
1	**1-3a**	EtI	**1-2d**	–60
2	**1-3a**	MeI	**1-2e**	–60
3	**1-3b**	$TMSCH_2Cl$	**1-2f**	0
4	**1-3c**	EtI	**1-2g**	–20
5	**1-3b**	EtI	**1-2j**	–40
6	**1-3b**	MeI	**1-2k**	–40
7	**1-3d**	EtI	**1-2m**	–78
8	**1-3e**	MeI	**1-2q**	-[a]

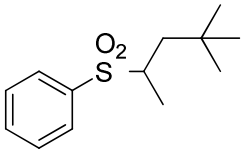
[a] Quenched directly after 10 min of deprotonation.

2,2-Dimethylhex-4-yl phenyl sulfone (1-2d):



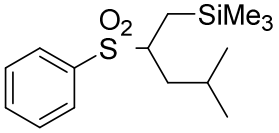
Yield 483 mg (95%) as colorless crystals, m.p. 41-42 °C. R_f (EtOAc/hexane 1:5) = 0.46; IR ν_{max} 2957, 2868, 1474, 1447, 1303, 1086, 727, 692 cm^{-1}; MS (ESI+) *m/z* (%) 277 (100) [M+Na^+], 239 (20), 185 (20); Anal. calcd for $C_{14}H_{22}O_2S$ (254.39): C 66.10, H 8.72, S 12.60; found: C 66.25, H 8.75, S 12.49; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 9H, C(C*H*$_3$)$_3$), 1.04 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.39 (dd, *J* = 7.0, 14.8 Hz, 1H, C*H*HC(CH_3)$_3$), 1.72 (m, 1H, C*H*HCH_3), 1.92 (m, 2H, CH*H*CH_3, CH*H*C(CH_3)$_3$), 2.89 (m, 1H, C*H*SO_2), 7.56 (m, 2H, H_{meta}), 7.64 (m, 1H, H_{para}), 7.90 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (q, CH_2CH_3), 24.2 (t, CH_2CH_3), 29.3 (q, C(CH_3)$_3$), 30.8 (s, C(CH_3)$_3$), 40.6 (t, CH_2C(CH_3)$_3$), 62.9 (d, CHSO_2), 129.0 (d, C_{ortho} or C_{meta}), 129.1 (d, C_{ortho} or C_{meta}), 133.6 (d, C_{para}), 138.4 (s, C_{ipso}).

2,2-Dimethylpent-4-yl phenyl sulfone (1-2e):



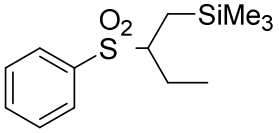
Yield 452 mg (94%) as colorless crystals, m.p. 56-57 °C. R_f (EtOAc/hexane 1:5) = 0.32; IR ν_{max} 2956, 2868, 1477, 1447, 1303, 1146, 1087, 754, 693 cm^{-1}; MS (ESI+) *m/z* (%) 263 (100) [$M+Na^+$], 239 (20), 185 (20); Anal. calcd for $C_{13}H_{20}O_2S$ (240.36): C 64.96, H 8.39, S 13.34; found: C 65.10, H 8.43, S 13.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 9H, C(C*H*$_3$)$_3$), 1.23 (dd, *J* = 8.1, 14.3 Hz, 1H, C*H*HC(CH$_3$)$_3$), 1.36 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 2.06 (broad d, *J* = 14.3 Hz, 1H, CH*H*C(CH$_3$)$_3$), 3.04 (m, 1H, C*H*SO$_2$), 7.55 (m, 2H, H_{meta}), 7.65 (m, 1H, H_{para}), 7.89 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (q, CH*C*H$_3$), 29.3 (q, C(*C*H$_3$)$_3$), 30.8 (s, *C*(CH$_3$)$_3$), 42.3 (t, *C*H$_2$C(CH$_3$)$_3$), 57.2 (d, *C*HSO$_2$), 129.0 (d, C_{ortho} or C_{meta}), 129.1 (d, C_{ortho} or C_{meta}), 133.4 (d, C_{para}), 137.4 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[154]

4-Methyl-1-(trimethylsilyl)pent-2-yl phenyl sulfone (1-2f):



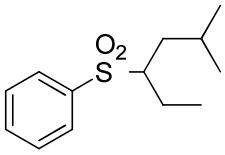
Yield 275 mg (65%) as a colorless oil. R_f (EtOAc/hexane 1:2.5) = 0.49; IR ν_{max} 2963, 1446, 1305, 1145, 734, 691 cm^{-1}; MS (ESI+) *m/z* (%) 321 (100) [$M+Na^+$], 165 (20) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{15}H_{26}O_2SSi$ (298.52): C 60.35, H 8.78, S 10.74, Si 9.41; found: C 60.26, H 8.92, S 10.55, Si 9.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 9H, Si(C*H*$_3$)$_3$), 0.63 (m, 1H, C*H*HSi), 0.75 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.23 (m, 2H, CH*H*Si, C*H*H*i*Pr), 1.64 (m, 1H, CH*Hi*Pr), 1.78 (m, 1H, C*H*(CH$_3$)$_2$), 3.08 (m, 1H, SO$_2$C*H*), 7.54 (m, 2H, H_{meta}), 7.62 (m, 1H, H_{para}), 7.84 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.6 (q, Si(*C*H$_3$)$_3$), 17.5 (t, *C*H$_2$Si), 22.5 (q, CH(*C*H$_3$)$_2$), 22.8 (q, CH(*C*H$_3$)$_2$), 25.9 (d, *C*H(CH$_3$)$_2$), 40.6 (t, *C*H$_2$*i*Pr), 60.6 (d, SO$_2$*C*H), 129.1 (d, C_{ortho}), 129.4 (d, C_{meta}), 133.6 (d, C_{para}), 137.9 (s, C_{ipso}).

1-(Trimethylsilyl)but-2-yl phenyl sulfone (1-2g):



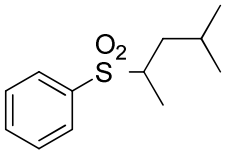
Yield 243 mg (45%) as a colorless oil. R_f (EtOAc/hexane 1:2.5) = 0.48; MS (ESI+) *m/z* (%) 293 (100) [M+Na$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H, Si(C*H*$_3$)$_3$), 0.84 (A part of ABM system, *J* = 11.2, 14.7 Hz, 1H, C*H*HSi), 0.97 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$), 1.17 (B part of ABM system, *J* = 3.0, 14.7 Hz, 1H, CH*H*Si), 1.63 (m, 1H, C*H*HCH$_3$), 1.75 (m, 1H, CH*H*CH$_3$), 2.96 (m, 1H, SO$_2$C*H*), 7.54 (m, 2H, H_{meta}), 7.62 (m, 1H, H_{para}), 7.86 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.[228]

2-Methylhex-4-yl phenyl sulfone (1-2j):



Yield 428 mg (89%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.33; IR ν_{max} 2958, 2871, 1465, 1447, 1301, 1140, 1084, 762, 728, 692 cm^{-1}; MS (ESI+) *m/z* (%) 263 (100) [M+Na$^+$]; Anal. calcd for $C_{13}H_{20}O_2S$ (240.36): C 64.96, H 8.39, S 13.34; found: C 65.13, H 8.45, S 13.47; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.88 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 0.98 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.43 (m, 1H, C*H*HCH$_3$), 1.50-1.72 (m, 3H, CH*H*CH$_3$, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.85 (m, 1H, CH*H**i*Pr), 2.89 (m, 1H, SO$_2$C*H*), 7.54 (m, 2H, H_{meta}), 7.63 (m, 1H, H_{para}), 7.86 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (q, CH$_2$*C*H$_3$), 21.95 (q, CH(*C*H$_3$)$_2$), 22.02 (t, *C*H$_2$CH$_3$), 23.1 (q, CH(*C*H$_3$)$_2$), 26.0 (d, *C*H(CH$_3$)$_2$), 36.7 (t, *C*H$_2$*i*Pr), 64.0 (d, SO$_2$*C*H), 129.1 (d, C_{ortho}), 129.3 (d, C_{meta}), 133.7 (d, C_{para}), 138.5 (s, C_{ipso}).

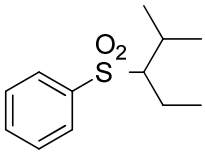
4-Methylpent-2-yl phenyl sulfone (1-2k):



Yield 385 mg (85%) as a colorless solid, m.p. 39-40 °C. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 2958, 2874, 1468, 1447, 1303, 1290, 1141, 1085, 766, 732, 692 cm^{-1}; MS (ESI+) *m/z* (%) 249 (100) [M+Na$^+$]; Anal. calcd for $C_{12}H_{18}O_2S$ (226.34): C 63.68, H 8.02, S 14.17; found: C 63.91, H 8.00, S 14.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.4 Hz, 3H,

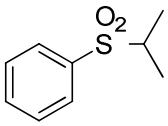
$CH(CH_3)_2$), 0.86 (d, J = 6.4 Hz, 3H, $CH(CH_3)_2$), 1.22 (d, J = 6.9 Hz, 3H, SO_2CHCH_3), 1.35 (m, 1H, $CH(CH_3)_2$), 1.68 (m, 2H, CH_2iPr), 3.02 (m, 1H, SO_2CH), 7.51 (m, 2H, H_{meta}), 7.59 (m, 1H, H_{para}), 7.82 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (q, SO_2CHCH_3), 21.1 (q, $CH(CH_3)_2$), 23.8 (q, $CH(CH_3)_2$), 25.3 (d, $CH(CH_3)_2$), 38.0 (t, CH_2iPr), 58.7 (d, SO_2CH), 129.24 (d, C_{ortho} or C_{meta}), 129.27 (d, C_{ortho} or C_{meta}), 133.7 (d, C_{para}), 137.6 (s, C_{ipso}).

2-Methylpent-3-yl phenyl sulfone (1-2m):



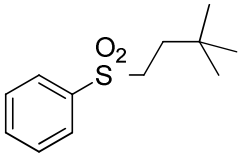
Yield 362 mg (80%) as colorless crystals, m.p. 54-55 °C. R_f (EtOAc/hexane 1:5) = 0.27; IR ν_{max} 3065, 2966, 2938, 2879, 1585, 1467, 1447, 1392, 1303, 1288, 1178, 1142, 1080, 999 cm^{-1}; MS (ESI+) *m/z* (%) 249 (100) [M+Na^+]; Anal. calcd for $C_{12}H_{18}O_2S$ (226.34): C 63.68, H 8.02, S 14.17; found: C 63.46, H 8.25, S 14.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H, CH_2CH_3), 1.00 (d, J = 6.5 Hz, 3H, $CH(CH_3)_2$), 1.01 (d, J = 7.0 Hz, 3H, $CH(CH_3)_2$), 1.69 (m, 1H, $CHHCH_3$), 1.88 (m, 1H, $CHHCH_3$), 2.36 (m, 1H, $CH(CH_3)_2$), 2.78 (td, J = 2.4, 5.8 Hz, 1H, $CHSO_2$), 7.54 (m, 2H, H_{meta}), 7.62 (m, 1H, H_{para}), 7.87 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (q, CH_2CH_3), 17.2 (q, $CH(CH_3)_2$), 17.4 (t, CH_2CH_3), 21.8 (q, $CH(CH_3)_2$), 27.0 (d, $CH(CH_3)_2$), 71.4 (d, $CHSO_2$), 128.4 (d, C_{ortho}), 129.1 (d, C_{meta}), 133.4 (d, C_{para}), 139.5 (s, C_{ipso}).

Isopropyl phenyl sulfone (1-2q):



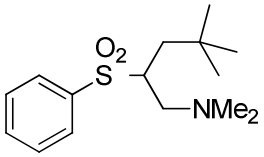
Yield 291 mg (79%) as a colorless oil. R_f (EtOAc/hexane 1:2) = 0.38; IR ν_{max} 3066, 2938, 1447, 1305, 1144, 867 cm^{-1}; MS (ESI+) *m/z* (%) 207 (100) [M+Na^+]; Anal. calcd for $C_9H_{12}O_2S$ (184.26): C 58.67, H 6.56, S 17.40; found: C 58.42, H 6.79, S 17.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 6H, CH_3), 3.17 (sept, J = 6.8 Hz, 1H, CH), 7.55 (m, 2H, H_{meta}), 7.65 (m, 1H, H_{para}), 7.87 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9 (q, CH_3), 55.4 (d, $CHSO_2$), 129.30 (d, C_{ortho} or C_{meta}), 129.31 (d, C_{ortho} or C_{meta}), 133.7 (d, C_{para}), 137.3 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[229]

3,3-Dimethylbutyl phenyl sulfone (1-3a):[154]



A mixture of zinc dust (131 mg, 2 mmol) and CuI (95 mg, 0.5 mmol) in formamide (3 mL) was stirred at 0-10 °C for 15 min. Phenyl vinyl sulfone **1-4** (202 mg, 1.2 mmol) was added followed by *tert*-butyl iodide (120 µL, 1 mmol). The mixture was aged at 0 °C for 1 h, warmed to room temperature and kept at this temperature for 4 h. Ethyl acetate (10 mL) was added and the precipitate was filtered off and rinsed with ethyl acetate. Heptane (10 mL) and HCl (1*M*, 10 mL) were added to the filtrate. The layers were separated and the organic was dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:10) gave 192 mg (85%) of sulfone **1-3a** as a colorless solid, m.p. 58-59 °C. CAUTION: The Zn/CuI residue should not be dried completely as it may self-ignite in air, particularly on larger scale. It should be covered by water after filtration and rinsing with ethyl acetate. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 2956, 2868, 1447, 1319, 1299, 1147, 1124, 1087, 738, 689 cm^{-1}; MS (ESI+) *m/z* (%) 249 (100) $[M+Na^+]$; Anal. calcd for $C_{12}H_{18}O_2S$ (226.34): C 63.68, H 8.02; found: C 63.83, H 7.87; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H, $C(CH_3)_3$), 1.58 (m, 2H, CH_2tBu), 3.04 (m, 2H, SO_2CH_2), 7.56 (m, 2H, H_{meta}), 7.65 (m, 1H, H_{para}), 7.89 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.2 (q, $C(CH_3)_3$), 30.3 (s, $C(CH_3)_3$), 36.0 (t, CH_2tBu), 53.2 (t, SO_2CH_2), 128.4 (d, C_{ortho}), 129.6 (d, C_{meta}), 133.8 (d, C_{para}), 139.4 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.

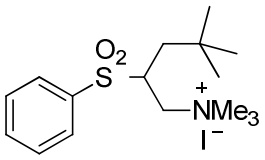
***N*,*N*,4,4-Tetramethyl-2-(phenylsulfonyl)pentylamine (1-6):**



*n*BuLi (0.316 mL, 0.51 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-3a** (100 mg, 0.44 mmol) and TMEDA (0.15 mL, 0.98 mmol) in dry THF (3 mL) under a nitrogen atmosphere at –78 °C. After stirring for 15 min, Eschenmoser´s salt (244 mg, 1.32 mmol) was added as a solid at –78 °C. The reaction mixture was warmed to room temperature and stirred for 30 min until complete as indicated by TLC. The mixture was quenched with water, acidified with HCl (1*M*) and the ammonium salt was extracted with water (2×20ml). The aqueous layer was treated with sodium hydroxide until the solution had

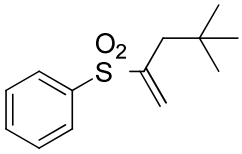
pH 8-9. The desired product was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave 120 mg (96%) of amine **1-6** as colorless crystals, m.p. 89-91 °C. R_f (EtOAc/hexane 1:5) = 0.28; IR ν_{max} 2952, 2867, 2770, 1467, 1449, 1368, 1287, 1262, 1139, 1084, 731, 690 cm^{-1}; MS (ESI+) *m/z* (%) 284 (100) $[M+H^+]$; Anal. calcd for $C_{15}H_{25}NO_2S$ (283.43): C 63.56, H 8.89, N 4.94, S 11.31; found: C 63.53, H 8.87, N 4.84, S 11.03; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 9H, C(C*H*$_3$)$_3$), 1.16 (dd, *J* = 6.3, 14.7 Hz, 1H, C*H*H*t*Bu), 1.90 (s, 6H, N(C*H*$_3$)$_2$), 2.12 (dd, *J* = 2.6, 14.7 Hz, 1H, CH*Ht*Bu), 2.28 (dd, *J* = 4.6, 13.6 Hz, 1H, C*H*HN(CH$_3$)$_2$), 2.72 (dd, *J* = 8.9, 13.6 Hz, 1H, CH*H*N(CH$_3$)$_2$), 3.07 (m, 1H, SO_2C*H*), 7.44 (m, 2H, H_{meta}), 7.53 (m, 1H, H_{para}), 7.84 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.5 (q, C(*C*H$_3$)$_3$), 31.0 (s, *C*(CH$_3$)$_3$), 39.8 (t, *C*H$_2$*t*Bu), 44.9 (q, N(*C*H$_3$)$_2$), 60.1 (d, SO_2*C*H), 61.5 (t, *C*H$_2$N(CH$_3$)$_2$), 128.6 (d, C_{ortho}), 128.9 (d, C_{meta}), 133.1 (d, C_{para}), 140.5 (s, C_{ipso}).

***N,N,N*,4,4-Pentamethyl-2-(phenylsulfonyl)pent-1-ylammonium iodide (1-7):**



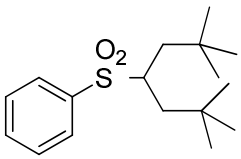
Iodomethane (185 µl, 3 mmol) was added to a solution of amine **1-6** (100 mg, 0.35 mmol) in methanol (3 mL) at room temperature. After standing in the dark for 48 h, the mixture was concentrated and the residue was diluted with diethyl ether, filtered and washed with diethyl ether, giving 138 mg (93%) of ammonium salt **1-7** as a pale yellow solid, m.p. 147-149 °C. IR ν_{max} 3001, 2954, 1477, 1447, 1303, 1237, 1147, 1085, 968, 748, 727, 693, 599 cm^{-1}; MS (ESI+) *m/z* (%) 298 (100) $[M–I^–]$, 156 (20) $[M–PhSO_2H–I^–]$; HRMS (ESI+) *m/z* $[M–I^–]$ calcd for $C_{16}H_{28}NO_2S^+$: 298.1835; found: 298.1833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 9H, C(C*H*$_3$)$_3$), 1.51 (dd, *J* = 6.7, 15.7 Hz, 1H, C*H*H*t*Bu), 1.66 (dd, *J* = 2.1, 15.7 Hz, 1H, CH*Ht*Bu), 3.74 (s, 9H, N(C*H*$_3$)$_3$), 3.90 (m, 1H, SO_2C*H*), 3.97 (dd, *J* = 2.5, 15.4 Hz, 1H, CH*H*N(CH$_3$)$_3$), 4.20 (dd, *J* = 8.1, 15.4 Hz, 1H, CH*H*N(CH$_3$)$_3$), 7.62 (m, 2H, H_{meta}), 7.70 (m, 1H, H_{para}), 7.82 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6 (q, C(*C*H$_3$)$_3$), 31.6 (s, *C*(CH$_3$)$_3$), 43.7 (t, *C*H$_2$*t*Bu), 56.6 (q, N(*C*H$_3$)$_3$), 57.8 (d, SO_2*C*H), 68.1 (t, *C*H$_2$N(CH$_3$)$_3$), 129.8 (d, C_{ortho}), 130.4 (d, C_{meta}), 135.1 (d, C_{para}), 135.8 (s, C_{ipso}).

4,4-Dimethyl-2-(phenylsulfonyl)-1-pentene (1-8):



Ammonium salt **1-7** (688 mg, 1.62 mmol) and DBU (0.48 ml, 3.23 mmol) were stirred in dry toluene (50 mL) at 80 °C for 5 h. The reaction mixture was washed with HCl (1*M*, 50 mL), water (50 mL), brine (50 mL) and dried over $MgSO_4$. After filtration and evaporation, the product was purified by column chromatography (EtOAc/hexane 1:20) giving 360 mg (94%) of **1-8** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.47; IR ν_{max} 2957, 2908, 2869, 1447, 1305, 1150, 1083, 956, 749, 690 cm^{-1}; MS (ESI+) *m/z* (%) 261 (100) $[M+Na^+]$; HRMS (ESI+) *m/z* $[M+H^+]$ calcd for $C_{13}H_{19}O_2S^+$: 239.1100; found: 239.1100; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H, $C(CH_3)_3$), 2.18 (s, 2H, CH_2tBu), 5.86 (s, 1H, =C*H*H), 6.45 (s, 1H, =CH*H*), 7.50 (m, 2H, H_{meta}), 7.58 (m, 1H, H_{para}), 7.82 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.9 (q, $C(CH_3)_3$), 32.0 (s, $C(CH_3)_3$), 41.8 (t, CH_2tBu), 126.8 (t, $=CH_2$), 128.7 (d, C_{ortho}), 129.5 (d, C_{meta}), 133.7 (d, C_{para}), 139.7 (s, C_{ipso}), 149.1 (s, $SO_2C=CH_2$). The spectral data are in agreement with those in the cited literature.[230]

Phenyl 2,2,6,6-tetramethylhept-4-yl sulfone (1-2r):



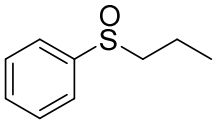
A mixture of zinc dust (153 mg, 2.52 mmol) and CuI (111 mg, 0.56 mmol) in formamide (10 mL) was stirred at 0-10 °C for 15 min. Vinyl sulfone **1-8** (340 mg, 1.4 mmol) was added followed by *tert*-butyl iodide (140 µl, 1.15 mmol). The mixture was aged at 0 °C for 1 h, warmed to room temperature and kept at this temperature for 5 h. Ethyl acetate (50 mL) was added, the precipitate was filtered off and rinsed with ethyl acetate. Heptane (50 mL) and HCl (1*M*, 30 mL) were added to the filtrate. The layers were separated, the organic was dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:10) gave 224 mg (68%) of sulfone **1-2r** as colorless crystals, m.p. 98-99 °C. CAUTION: The Zn/CuI residue should not be dried completely as it may self-ignite in air, particularly on larger scale. It should be covered by water after filtration and rinsing with ethyl acetate. R_f (EtOAc/hexane 1:5) = 0.68; IR ν_{max} 2956, 2927, 2868, 1458, 1365, 1147, 744, 723, 693 cm^{-1}; MS (ESI+) *m/z* (%) 319 (100) $[M+Na^+]$; Anal. calcd for $C_{17}H_{28}O_2S$

(296.47): C 68.87, H 9.52, S 10.82; found: C 68.61, H 9.44, S 10.63; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 18H, C(C*H*$_3$)$_3$), 1.42 (dd, *J* = 5.0, 15.5 Hz, 2H, C*H*H*t*Bu), 1.99 (dd, *J* = 5.1, 15.5 Hz, 2H, CH*Ht*Bu), 3.15 (m, 1H, C*H*SO_2), 7.54 (m, 2H, H_{meta}), 7.60 (m, 1H, H_{para}), 7.87 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (q, C(*C*H_3)$_3$), 30.6 (s, *C*(CH_3)$_3$), 45.0 (t, *C*H_2*t*Bu), 59.4 (d, *C*HSO_2), 129.1 (d, C_{ortho}), 129.4 (d, C_{meta}), 133.6 (d, C_{para}), 139.0 (s, C_{ipso}). The spectral data are in agreement with those in the cited literature.[144]

Monoalkylation of methyl phenyl sulfoxide 1-9 (General procedure):

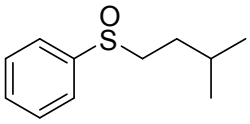
*n*BuLi (2.4 mL, 3.9 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of diisopropylamine (0.5 mL, 4.2 mmol) in dry THF (10 mL) under a nitrogen atmosphere at –78 °C. After stirring for 30 min, methyl phenyl sulfoxide **1-9** (420 mg, 3 mmol) was added. Subsequently, the corresponding alkyl halide (4.2 mmol) was added dropwise at –78 °C after 20 min. The reaction mixture was stirred at this temperature for 10 min and warmed to –40 °C or 0 °C, respectively (entry 1 or 2-4, respectively) for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous was extracted with diethyl ether (3×30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:10, gradient to 1:5) gave sulfoxides **1-10a-c**.

Propyl phenyl sulfoxide (1-10a):



Yield 336 mg (67%) as colorless oil. R_f (EtOAc/hexane 1:1) = 0.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.68 (m, 1H, C*H*HCH$_3$), 1.80 (m, 1H, CH*H*CH$_3$), 2.72-2.83 (m, 2H, SO_2C*H*$_2$), 7.51 (m, 3H, H_{meta}, H_{para}), 7.62 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.[231]

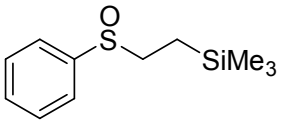
Isopentyl phenyl sulfoxide (1-10b):



Yield 441 mg (75%) as colorless oil. R_f (EtOAc/hexane 1:2.5) = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 1.39-1.66 (m, 3H, C*H*$_2$*i*Pr, C*H*(CH$_3$)$_2$), 2.76

(m, 2H, SOCH_2), 7.48 (m, 3H, H_{meta}, H_{para}), 7.59 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.[232]

2-(Trimethylsilyl)ethyl phenyl sulfoxide (1-10c):[156]

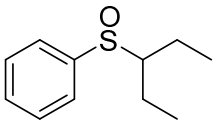


Yield 537 mg (79%) as colorless oil. R_f (EtOAc/hexane 1:2.5) = 0.56; MS (ESI+) *m/z* (%) 249 (100) [M+Na^+]; ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 9H, Si(CH_3)$_3$), 0.81 (m, 2H, CH_2Si), 2.69 (m, 1H, SOC*H*H), 2.82 (m, 1H, SOCH*H*), 7.51 (m, 3H, H_{meta}, H_{para}), 7.60 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.

Alkylation of sulfoxides 1-10a-c (General procedure):

*n*BuLi (1.2 mL, 1.95 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of diisopropylamine (0.25 mL, 2.1 mmol) in dry THF (5 mL) under a nitrogen atmosphere at −78 °C. After stirring for 30 min, sulfoxide **1-10a-c** (1.5 mmol) was added. Subsequently, the corresponding alkyl halide (2.1 mmol) was added dropwise at –78 °C after 20 min. The reaction mixture was stirred at this temperature for 10 min and warmed to –40 °C or 0 °C (entry 1 or 2-4, respectively), for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:10, gradient to 1:5) gave sulfoxides **1-11a,b**.

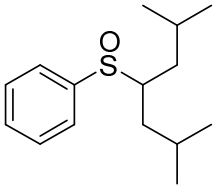
Pent-3-yl phenyl sulfoxide (1-11a):



Yield 162 mg (55%) as colorless oil. R_f (EtOAc/hexane 1:1) = 0.42; IR ν_{max} 2954, 2924, 1459, 1087, 1035, 748, 569 cm^{-1}; MS (ESI+) *m/z* (%) 415 (30) [2M+Na^+], 219 (100) [M+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{11}H_{16}OSNa^+$: 219.0814; found: 219.0814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.5 Hz, 3H, CH_3), 1.02 (t, *J* = 7.5 Hz, 3H, CH_3), 1.46 (m, 1H, C*H*HCH$_3$), 1.62 (m, 2H, CH_2CH$_3$), 1.73 (m, 1H, CH*H*CH$_3$), 2.40 (m, 1H, SOC*H*), 7.48 (m, 3H, H_{meta}, H_{para}), 7.58 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1

(q, *C*CH_3), 11.5 (q, *C*CH_3), 18.7 (t, *C*H_2CH_3), 20.3 (t, *C*H_2CH_3), 67.9 (d, SO*C*H), 125.0 (d, C_{ortho}), 128.9 (d, C_{meta}), 130.8 (d, C_{para}), 135.7 (s, C_{ipso}).

2,6-Dimethylhept-4-yl phenyl sulfoxide (1-11b):



Yield 310 mg (82%) as colorless crystals, m.p. 56-58 °C. R_f (EtOAc/hexane 1:2.5) = 0.80; IR ν_{max} 2952, 2924, 1468, 1443, 1086, 1043, 748 cm^{-1}; MS (ESI+) *m/z* (%) 527 (20) [2M+Na^+], 275 (100) [M+Na^+]; Anal. calcd for $C_{15}H_{24}O_2S$ (252.42): C 71.37, H 9.58, S 12.70; found: C 71.06, H 9.57, S 12.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.77 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.88 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.90 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.20 (m, 3H, C*H*$_2$*i*Pr), 1.43 (m, 1H, C*H*(CH$_3$)$_2$), 1.76 (m, 1H, CH*Hi*Pr), 1.88 (m, 1H, C*H*(CH$_3$)$_2$), 2.55 (tt, *J* = 5.6, 7.9 Hz, 1H, SOC*H*), 7.45 (m, 5H, *H*$_{ar}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (q, CH(*C*H$_3$)$_2$), 22.5 (q, CH(*C*H$_3$)$_2$), 23.1 (q, CH(*C*H$_3$)$_2$), 23.2 (q, CH(*C*H$_3$)$_2$), 25.6 (d, *C*H(CH$_3$)$_2$), 25.7 (d, *C*H(CH$_3$)$_2$), 35.3 (t, *C*H$_2$*i*Pr), 38.1 (t, *C*H$_2$*i*Pr), 60.6 (d, SO*C*H), 125.0 (d, C_{ortho}), 129.1 (d, C_{meta}), 130.8 (d, C_{para}), 142.2 (s, C_{ipso}).

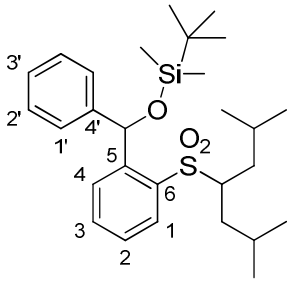
***ortho*- to α-Rearrangement of sulfones 1-2a-r and 1-26 and sulfoxides 1-11a,b (Table 1.3-1.6, General procedure):**

The respective additive (TMEDA, HMPA; 1 mmol, 3 mmol) and base (0.55 mmol) were added to a stirred solution of sulfone **1-2a-r, 1-26** or sulfoxide **1-11a,b** (0.5 mmol) in the respective solvent (5 mL) at –78 °C. After 10 min at –78 °C 1 mL of the solution was taken by a syringe and added to a dry capped vial containing D_2O. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated. The remaining reaction mixture was placed in a bath at –60 °C and kept for 10 min. Another sample (1 mL) was removed and deuterated as described above. The procedure was repeated at defined temperatures –40 °C, –20 °C, 0 °C and r.t. Metalation of **1-2c** was monitored also at different temperature intervals (Table 1.3, entries 6-7). The mass balance was determined to be quantitative for each mixture and the products were analyzed by ^{1}H NMR.

Initial deprotonation and potential transmetalation of sulfones 1-31, 1-34, 1-36, 1-42 and two-fold deprotonation of sulfone 1-2h (Tables 1.7-1.9, Schemes 1.4, 1.7, General procedure):

The additive (TMEDA or HMPA, see Tables 1.7-1.9, Schemes 1.4, 1.7) and *n*BuLi (1.6*M* in hexane, see Tables 1.7-1.9) were added to a stirred solution of sulfone **1-31**, **1-34**, **1-36**, **1-42** or **1-2h** (0.5 mmol) in dry solvent (3-5 mL) at –78 °C. After the given time (Tables 1.7-1.9, Schemes 1.4, 1.7) an aliquot of the solution was removed by a syringe and added to a capped vial containing a few drops of D_2O. The volume of the sample corresponded to the total volume divided by the number of samples taken. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^{1}H NMR spectroscopy. The procedure was repeated at defined temperatures as described in the Tables and Schemes.

2,6-Dimethylhept-4-yl 2-(1-*tert*-butyldimethylsilyloxybenzyl)phenyl sulfone (1-42):



tert-Butyldimethylsilyl chloride (84 mg, 0.56 mmol) was added to a stirred solution of sulfone **1-36** (105 mg, 0.28 mmol) and imidazole (57 mg, 0.84 mmol) in dry DMF (5 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at this temperature for 24 h and water (5 ml) was added. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave 119 mg (87%) of sulfone **1-42** as colorless oil. R_f (EtOAc/hexane 1:5) = 0.67; IR ν_{max} 2966, 2941, 2905, 2866, 1474, 1315, 1304, 1255, 1145, 1124, 1072, 870, 855, 840, 780, 759 cm^{-1}; MS (ESI+) *m/z* (%) 999 (10) [2M+Na$^+$], 511 (100) [M+Na$^+$]; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{28}H_{44}O_3SSiNa^+$: 511.2673; found: 511.2672; ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 3H, Si(C*H*$_3$)$_2$), 0.02 (s, 3H, Si(C*H*$_3$)$_2$), 0.38 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.62 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.77 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.88 (s, 9H, C(C*H*$_3$)$_3$), 1.13 (m, 1H, C*H*(CH$_3$)$_2$), 1.21-1.45 (m, 3H, C*H*$_2$*i*Pr), 1.67 (m, 1H, C*H*(CH$_3$)$_2$), 1.80 (m, 1H, CH*Hi*Pr), 2.59

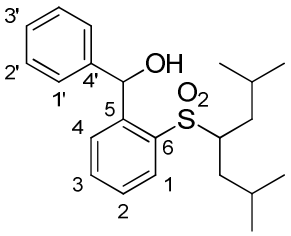
(tt, J = 7.3, 5.0 Hz, 1H, SO_2CH), 7.09 (s, 1H, CHOSi), 7.27 (m, 1H, $H_{3'}$), 7.29 (m, 2H, $H_{2'}$), 7.38 (m, 2H, $H_{1'}$), 7.45 (m, 1H, H_2), 7.72 (m, 1H, H_3), 7.93 (dd, J = 8.0, 1.4 Hz, 1H, H_1), 8.23 (dd, J = 8.0, 1.3 Hz, 1H, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6 (q, Si(CH$_3$)$_2$), 18.2 (s, C(CH$_3$)$_3$), 21.7 (q, CH(CH$_3$)$_2$), 22.4 (q, CH(CH$_3$)$_2$), 23.1 (q, CH(CH$_3$)$_2$), 23.2 (q, CH(CH$_3$)$_2$), 25.3 (d, CH(CH$_3$)$_2$), 25.7 (d, CH(CH$_3$)$_2$), 25.9 (q, C(CH$_3$)$_3$), 36.9 (t, CH$_2$*i*Pr), 38.8 (t, CH$_2$*i*Pr), 61.3 (d, SO$_2$$C$H), 70.6 (d, CHOSi), 127.3 (d, C_2 or $C_{3'}$), 127.7 (d, C_2 or $C_{3'}$), 128.3 (d, $C_{1'}$ or $C_{2'}$), 128.6 (d, $C_{1'}$ or $C_{2'}$), 129.5 (d, C_4), 131.5 (d, C_1), 133.6 (d, C_3), 134.5 (s, C_6), 143.5 (s, $C_{4'}$), 145.5 (s, C_5).

5.2.2. Preparative applications of selected sulfonyl carbanions

ortho-Substituted phenyl sulfones 1-26, 1-34, 1-36, 2-1a-e, 2-2a,b (Table 2.1-2.2, General procedure):

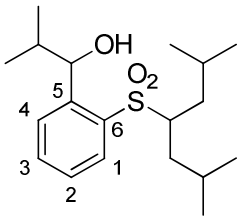
*n*BuLi (0.72 mL, 1.15 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (268 mg, 1 mmol) and TMEDA (0.3 mL, 1.95 mmol) in dry THF (5 mL) at –78 °C under a nitrogen atmosphere. After stirring for 15 min, aldehyde, ketone, TMSCl, I_2, Br_2 or $B(OCH_3)_3$ (1.2 mmol) in THF (2.5 mL) was added dropwise at –78 °C. The reaction mixture was stirred for 3 h until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **1-26, 1-34, 1-36, 2-1a-e** and **2-2a,b**.

2,6-Dimethylhept-4-yl 2-(1-hydroxybenzyl)phenyl sulfone (1-36):



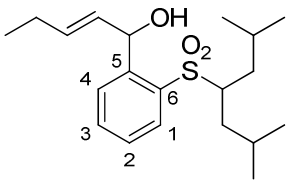
Yield 315 mg (84%) as colorless crystals, m.p. 99-100 °C. R_f (EtOAc/hexane 1:5) = 0.45; IR ν_{max} 3435, 2950, 1468, 1441, 1388, 1371, 1296, 1278, 1141, 1114, 954, 765 cm^{-1}; MS (ESI+) *m/z* (%) 771 (40) $[2M+Na^+]$, 397 (25) $[M+Na^+]$, 392 (100) $[M^++H_2O]$; Anal. calcd for $C_{22}H_{30}O_3S$ (374.54): C 70.55, H 8.07, S 8.56; found: C 70.53, H 8.10, S 8.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.78 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.41 (m, 2H, C*H*H*i*Pr), 1.54 (m, 1H, C*H*(CH$_3$)$_2$), 1.69 (m, 2H, CH*Hi*Pr, C*H*(CH$_3$)$_2$), 1.82 (m, 1H, CH*Hi*Pr), 3.21 (tt, *J* = 7.1, 5.1 Hz, 1H, SO_2C*H*), 3.35 (d, *J* = 4.6 Hz, 1H, O*H*), 6.71 (d, *J* = 4.6 Hz, 1H, C*H*OH), 7.35 (m, 7H, *H*$_2$, *H*$_3$, *H*$_{1'}$, *H*$_{2'}$, *H*$_{3'}$), 7.53 (dd, *J* = 7.6, 1.4 Hz, 1H, *H*$_4$), 8.00 (dd, *J* = 7.9, 1.4 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (q, CH(*C*H$_3$)$_2$), 22.3 (q, CH(*C*H$_3$)$_2$), 23.12 (q, CH(*C*H$_3$)$_2$), 23.14 (q, CH(*C*H$_3$)$_2$), 25.8 (d, *C*H(CH$_3$)$_2$), 25.9 (d, *C*H(CH$_3$)$_2$), 38.1 (t, *C*H$_2$*i*Pr), 38.8 (t, *C*H$_2$*i*Pr), 61.8 (d, SO_2*C*H), 71.1 (d, *C*HOH), 127.5 (d, *C*$_{3'}$), 128.3 (d, *C*$_2$), 128.4 (d, *C*$_{1'}$), 129.2 (d, *C*$_1$), 131.2 (d, *C*$_{2'}$), 132.2 (d, *C*$_4$), 134.9 (d, *C*$_3$), 137.1 (s, *C*$_6$), 142.4 (s, *C*$_{4'}$), 144.9 (s, *C*$_5$).

2,6-Dimethylhept-4-yl 2-(1-hydroxyisobutyl)phenyl sulfone (2-1a):



Yield 306 mg (90%) as colorless crystals, m.p. 44-46 °C. R_f (EtOAc/hexane 1:5) = 0.44; IR ν_{max} 3495, 2960, 1468, 1336, 1295, 1143, 1131, 1026, 744, 723 cm^{-1}; MS (ESI+) *m/z* (%) 363 (100) [M+Na^+]; Anal. calcd for $C_{19}H_{32}O_3S$ (340.52): C 67.02, H 9.47, S 9.42; found: C 67.27, H 9.43, S 9.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (d, *J* = 6.3 Hz, 3H, $CH_2CH(CH_3)_2$), 0.77 (m, 6H, $HOCHCH(CH_3)_2$, $CH_2CH(CH_3)_2$), 0.85 (2×d, *J* = 6.3 Hz, 6H, $CH_2CH(CH_3)_2$), 1.11 (d, *J* = 6.5 Hz, 3H, $HOCHCH(CH_3)_2$), 1.39 (m, 4H, $CH_2CH(CH_3)_2$, CHHiPr), 1.68 (m, 2H, CHHiPr), 2.22 (m, 1H, $HOCHCH(CH_3)_2$), 2.66 (d, *J* = 4.9 Hz, 1H, OH), 3.16 (tt, *J* = 7.3, 4.9 Hz, 1H, SO_2CH), 5.01 (dd, *J* = 4.9, 8.4 Hz, 1H, CHOH), 7.45 (m, 1H, H_2), 7.63 (m, 2H, H_3, H_4), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0 (q, $HOCHCH(CH_3)_2$), 20.1 (q, $HOCHCH(CH_3)_2$), 22.1 (q, $CH_2CH(CH_3)_2$), 22.2 (q, $CH_2CH(CH_3)_2$), 23.0 (q, $CH_2CH(CH_3)_2$), 23.1 (q, $CH_2CH(CH_3)_2$), 25.8 (d, $CH_2CH(CH_3)_2$), 25.9 (d, $CH_2CH(CH_3)_2$), 33.8 (d, $HOCHCH(CH_3)_2$), 38.3 (t, CH_2*i*Pr), 38.7 (t, CH_2*i*Pr), 61.7 (d, SO_2CH), 75.2 (d, CHOH), 127.8 (d, C_2), 128.7 (d, C_1), 131.4 (d, C_4), 134.0 (d, C_3), 136.7 (s, C_6), 144.3 (s, C_5).

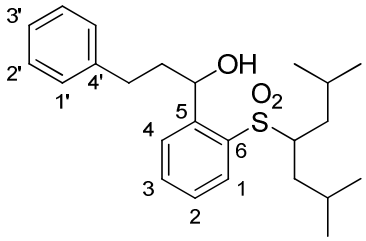
(*E*)-2,6-Dimethylhept-4-yl 2-(1-hydroxypent-2-enyl)phenyl sulfone (2-1b):



Yield 279 mg (79%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.25; IR ν_{max} 3496, 2957, 2931, 1468, 1379, 1289, 1136, 1113, 998, 762 cm^{-1}; MS (ESI+) *m/z* (%) 375 (100) [M+Na^+]; Anal. calcd for $C_{20}H_{32}O_3S$ (352.53): C 68.14, H 9.15, S 9.10; found: C 67.97, H 9.29, S 9.07; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.77 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.81 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.86 (d, *J* = 6.5 Hz, 3H, $CH(CH_3)_2$), 0.97 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.37 (m, 2H, CHHiPr), 1.50 (m, 1H, $CH(CH_3)_2$), 1.56-1.84 (m, 3H, CHHiPr, $CH(CH_3)_2$), 2.07 (m, 2H, CH_2CH_3), 2.95 (broad s, 1H, OH), 3.21 (m, 1H, SO_2CH), 5.70 (dd, *J* = 5.9, 15.4 Hz, 1H, $CH_2CH{=}CH$), 5.88 (dt, *J* = 6.2, 15.4 Hz, 1H, $CH_2CH{=}CH$), 6.00 (m, 1H, CHOH), 7.41 (m, 1H, H_2), 7.59 (m, 1H, H_3), 7.67 (m, 1H, H_4), 7.91 (m, 1H,

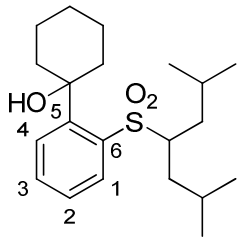
H₁); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (q, CH_2CH_3), 22.0 (q, $CH(CH_3)_2$), 22.2 (q, $CH(CH_3)_2$), 23.0 (q, $CH(CH_3)_2$), 23.1 (q, $CH(CH_3)_2$), 25.4 (t, CH_2CH_3), 25.78 (d, $CH(CH_3)_2$), 25.81 (d, $CH(CH_3)_2$), 38.2 (t, CH_2*i*Pr), 38.7 (t, CH_2*i*Pr), 61.6 (d, SO_2CH), 69.7 (d, CHOH), 127.9 (d, *C₂*), 128.3 (d, *C₁*), 129.8 (d, $CH_2CH=CH$), 131.3 (d, *C₄*), 134.1 (d, *C₃*), 134.9 (d, $CH_2CH=CH$), 135.9 (s, *C₆*), 144.1 (s, *C₅*).

2,6-Dimethylhept-4-yl 2-(1-hydroxy-3-phenylpropyl)phenyl sulfone (2-1c):



Yield 374 mg (93%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.35; IR ν_{max} 3498, 2957, 1468, 1454, 1331, 1295, 1140, 1115, 1058, 747, 725 cm^{-1}; MS (ESI+) *m/z* (%) 425 (100) [$M+Na^+$]; Anal. calcd for $C_{24}H_{34}O_3S$ (402.59): C 71.60, H 8.51, S 7.96; found: C 71.43, H 8.55, S 7.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)_2$), 0.82 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)_2$), 0.87 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)_2$), 0.92 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)_2$), 1.41 (m, 2H, CHHi*Pr*), 1.57 (m, 1H, $CH(CH_3)_2$), 1.62-1.86 (m, 3H, CHHi*Pr*, $CH(CH_3)_2$), 2.13 (m, 1H, CHHCHOH), 2.27 (m, 1H, CHHCHOH), 2.75 (m, 1H, PhCHH), 3.00 (m, 2H, PhCHH, OH), 3.15 (m, 1H, SO_2CH), 5.46 (m, 1H, CHOH), 7.25 (m, 5H, *H₁´*, *H₂´*, *H₃´*), 7.47 (m, 1H, *H₂*), 7.65 (m, 1H, *H₃*), 7.75 (m, 1H, *H₄*), 7.99 (m, 1H, *H₁*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (q, $CH(CH_3)_2$), 22.1 (q, $CH(CH_3)_2$), 22.8 (q, $CH(CH_3)_2$), 22.9 (q, $CH(CH_3)_2$), 25.5 (d, $CH(CH_3)_2$), 25.6 (d, $CH(CH_3)_2$), 32.8 (t, $PhCH_2$), 38.2 (t, CH_2*i*Pr), 38.5 (t, CH_2*i*Pr), 39.4 (t, $PhCH_2CH_2$), 61.5 (d, SO_2CH), 69.2 (d, CHOH), 126.0 (d, *C₃´*), 128.1 (d, *C₂*), 128.5 (d, *C₁*), 128.7 (d, *C₁´*, *C₂´*), 131.2 (d, *C₄*), 133.4 (d, *C₃*), 135.7 (s, *C₆*), 141.5 (s, *C₄´*), 144.9 (s, *C₅*).

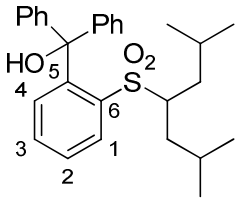
2,6-Dimethylhept-4-yl 2-(1-hydroxycyclohexyl)phenyl sulfone (2-1d):



Yield 312 mg (85%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.44; IR ν_{max} 3495, 2955, 2930, 1468, 1386, 1288, 1267, 1133, 1112, 994, 768, 745 cm^{-1}; MS (ESI+) *m/z* (%) 389 (30)

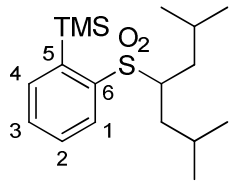
[M+Na^+], 349 (100) [M–OH^-], 223 (20) [M+H^+–OH–CH(*i*Bu)$_2$]; Anal. calcd for $C_{21}H_{34}O_3S$ (366.56): C 68.81, H 9.35, S 8.75; found: C 68.87, H 9.23, S 8.97; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 0.78 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.32 (m, 2H, C*H*H*i*Pr), 1.54 (m, 4H, C*H*(CH$_3$)$_2$, C*H*$_2$), 1.65-1.89 (m, 10H, CH*Hi*Pr, C*H*$_2$), 4.21 (m, 1H, SO_2C*H*), 4.53 (s, 1H, O*H*), 7.30 (ddd, *J* = 8.1, 6.7, 1.8 Hz, 1H, *H*$_2$), 7.48 (m, 2H, *H*$_3$, *H*$_4$), 8.07 (dd, *J* = 8.1, 1.2 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (t, *C*H_2CH_2CH_2COH), 22.3 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 25.7 (t, *C*H_2CH_2COH), 25.9 (d, 2×*C*H(CH$_3$)$_2$), 38.8 (t, 2×*C*H_2*i*Pr), 40.1 (t, *C*H_2COH), 61.9 (d, SO_2*C*H), 75.3 (s, *C*OH), 126.7 (d, *C*$_2$), 129.2 (d, *C*$_1$), 133.1 (d, *C*$_4$), 133.2 (d, *C*$_3$), 136.7 (s, *C*$_6$), 152.2 (s, *C*$_5$).

2,6-Dimethylhept-4-yl 2-(1-hydroxy-1-phenylbenzyl)phenyl sulfone (2-1e):



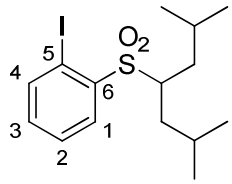
Yield 424 mg (94%) as colorless crystals, m.p. 112-113 °C. R_f (EtOAc/hexane 1:5) = 0.59; IR ν_{max} 3403, 2955, 1467, 1441, 1383, 1291, 1167, 1113, 1072, 1043, 956, 765, 748 cm^{-1}; MS (ESI+) *m/z* (%) 473 (100) [M+Na^+], 329 (40) [M+Na^+–OH–CH(*i*Bu)$_2$], 307 (30) [M+H^+–OH–CH(*i*Bu)$_2$]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{28}H_{34}O_3SNa^+$: 473.2121; found: 473.2120; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.35 (m, 2H, C*H*H*i*Pr), 1.52 (m, 2H, C*H*(CH$_3$)$_2$), 1.74 (m, 2H, CH*Hi*Pr), 3.75 (m, 1H, SO_2C*H*), 6.30 (s, 1H, O*H*), 6.88 (dd, *J* = 7.9, 1.3 Hz, 1H, *H*$_4$), 7.08 (m, 4H, *H*$_{ar}$), 7.23 (m, 6H, *H*$_{ar}$), 7.35 (td, *J* = 7.9, 1.5 Hz, 1H, *H*$_3$), 7.41 (td, *J* = 7.9, 1.3 Hz, 1H, *H*$_2$), 8.14 (dd, *J* = 7.9, 1.5 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3 (q, CH(*C*H$_3$)$_2$), 23.1 (q, CH(*C*H$_3$)$_2$), 25.8 (d, 2×*C*H(CH$_3$)$_2$), 38.4 (t, *C*H_2*i*Pr), 38.5 (t, *C*H_2*i*Pr), 62.6 (d, SO_2*C*H), 83.4 (s, *C*OH), 127.6 (d, *C*$_2$), 127.7 (d, *C*$_{ar}$), 128.1 (d, *C*$_{ar}$), 128.2 (d, *C*$_{ar}$), 132.4 (d, *C*$_3$), 133.7 (d, *C*$_4$), 134.0 (d, *C*$_1$), 137.2 (s, *C*$_6$), 147.4 (s, *C*$_5$), 148.2 (s, *C*$_{ipso}$).

2,6-Dimethylhept-4-yl 2-(trimethylsilyl)phenyl sulfone (1-26):



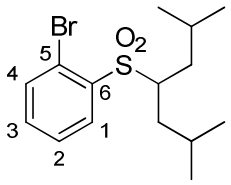
Yield 282 mg (83%) as colorless crystals, m.p. 62-63 °C. R_f (EtOAc/hexane 1:5) = 0.79; IR ν_{max} 2980, 2898, 1312, 1248, 1147, 1112, 844, 746 cm^{-1}; MS (ESI+) *m/z* (%) 363 (100) [M+Na^+]; Anal. calcd for $C_{18}H_{32}O_3SSi$ (340.60): C 63.47, H 9.47, S 9.41, Si 8.25; found: C 63.54, H 9.48, S 9.18, Si 8.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (s, 9H, Si(C*H*$_3$)$_3$), 0.70 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.29-1.58 (m, 4H, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.72 (m, 2H, CH*Hi*Pr), 3.06 (m, 1H, SO_2C*H*), 7.55 (m, 2H, *H*$_2$, *H*$_3$), 7.80 (m, 1H, *H*$_4$), 7.95 (m, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.5 (q, Si(*C*H$_3$)$_3$), 21.8 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 25.6 (d, *C*H(CH$_3$)$_2$), 38.1 (t, *C*H$_2$*i*Pr), 60.7 (d, SO_2*C*H), 129.3 (d, *C*$_2$), 130.8 (d, *C*$_1$), 132.3 (d, *C*$_3$), 136.8 (d, *C*$_4$), 141.2 (s, *C*$_5$), 143.6 (s, *C*$_6$).

2,6-Dimethylhept-4-yl 2-iodophenyl sulfone (1-34):



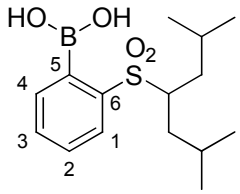
Yield 304 mg (77%) as colorless crystals, m.p. 87-88 °C. R_f (EtOAc/hexane 1:5) = 0.45; IR ν_{max} 2960, 1559, 1541, 1508, 1472, 1457, 1315, 1146, 741, 668, 597 cm^{-1}; MS (ESI+) *m/z* (%) 417 (100) [M+Na^+], 269 (30) [**1-2h**+H^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{15}H_{23}IO_2S$+Na^+: 417.0356; found: 417.0353; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.33 (m, 2H, C*H*H*i*Pr), 1.64 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 3.76 (tt, *J* = 6.9, 4.7 Hz, 1H, SO_2C*H*), 7.19 (m, 1H, *H*$_3$), 7.48 (m, 1H, *H*$_2$), 8.04 (dd, *J* = 7.9, 1.1 Hz, 1H, *H*$_4$), 8.08 (dd, *J* = 7.9, 1.7 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 25.6 (d, *C*H(CH$_3$)$_2$), 38.3 (t, *C*H$_2$*i*Pr), 56.9 (d, SO_2*C*H), 93.1 (s, *C*$_5$), 128.5 (d, *C*$_2$), 132.4 (d, *C*$_1$), 134.2 (d, *C*$_3$), 142.8 (d, *C*$_4$), 143.1 (s, *C*$_6$).

2-Bromophenyl 2,6-dimethylhept-4-yl sulfone (2-2a):



Yield (63%) as a colorless oil, not separable from **1-2h** (31%). R_f (EtOAc/hexane 1:5) = 0.40; MS (ESI+) *m/z* (%): 371/369 (80/80) [M+Na$^+$], 291 (100) [**1-2h**+Na$^+$]; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for $C_{15}H_{23}BrO_2S$+Na$^+$: 369.0494; found: 369.0495; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 1.37 (m, 2H, C*H*H*i*Pr), 1.67 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 3.76 (m, 1H, SO$_2$C*H*), 7.45 (m, 1H, *H*$_3$), 7.55 (m, 1H, *H*$_2$), 7.72 (dd, *J* = 7.7, 1.4 Hz, 1H, *H*$_4$), 8.09 (dd, *J* = 7.7, 1.8 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 25.7 (d, *C*H(CH$_3$)$_2$), 38.5 (t, *C*H$_2$*i*Pr), 57.9 (d, SO$_2$*C*H), 121.0 (s, *C*$_5$), 127.9 (d, *C*$_2$), 132.7 (d, *C*$_1$), 134.6 (d, *C*$_3$), 135.6 (d, *C*$_4$), 138.0 (s, *C*$_6$).

(2-((2,6-Dimethylhept-4-yl)sulfonyl)phenyl)boronic acid (2-2b):

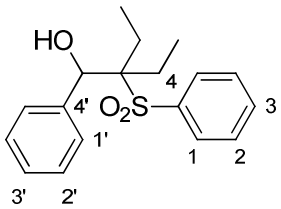


Yield 258 mg (83%) as a colorless solid, m.p. 91-92 °C. R_f (CH_3COOH/EtOAc/hexane 1:1:5) = 0.30; IR ν_{max} 3438, 3282, 3063, 2958, 2929, 2869, 1605, 1593, 1582, 1470, 1387, 1290, 1278, 1141, 1031, 1021, 837, 692 cm^{-1}; MS (ESI–) *m/z* (%): 311/310 (100/25) [M–H$^+$]; HRMS (ESI–) *m/z* [M–H$^+$] calcd for $C_{15}H_{24}BO_4S^-$: 311.1494; found: 311.1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 1.35 (m, 2H, C*H*H*i*Pr), 1.62 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 3.31 (m, 1H, SO$_2$C*H*), 6.57 (broad s, 2H, B(O*H*)$_2$), 7.44-7.73 (m, 2H, *H*$_2$, *H*$_3$), 7.99 (dd, *J* = 1.3, 7.7 Hz, 1H, *H*$_4$), 8.04 (dd, *J* = 1.6, 7.3 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (q, CH(*C*H$_3$)$_2$), 22.9 (q, CH(*C*H$_3$)$_2$), 25.7 (d, *C*H(CH$_3$)$_2$), 38.4 (t, *C*H$_2$*i*Pr), 59.9 (d, SO$_2$*C*H), 129.9 (d, *C*$_1$), 130.4 (d, *C*$_3$ or *C*$_2$), 132.9 (d, *C*$_3$ or *C*$_2$), 137.1 (d, *C*$_4$), 140.5 (s, *C*$_5$), 141.6 (s, *C*$_6$).

(2-Hydroxyalkyl) phenyl sulfones 2-3a-f (General procedure):

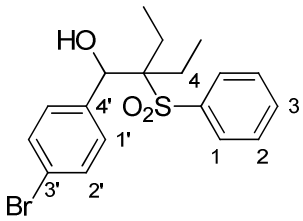
*n*BuLi (0.41 mL, 0.65 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of **1-2p** (106 mg, 0.5 mmol) and TMEDA (0.15 mL, 0.98 mmol) in dry THF (4 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde (0.7 mmol) in THF (2 mL) was added dropwise at –78 °C. The reaction mixture was warmed to 0 °C, stirred at this temperature for 1 h until complete as indicated by TLC and quenched with water. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:50) gave sulfones **2-3a-f**.

2-Ethyl-1-phenyl-2-(phenylsulfonyl)butan-1-ol (2-3a):



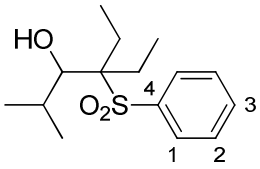
Yield 127 mg (80%) as colorless crystals, m.p. 119-121 °C. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 3488, 2975, 2943, 1447, 1281, 1143, 1073, 722, 691 cm^{-1}; MS (ESI+) *m/z* (%) 341 (100) [$M+Na^+$], 199 (20) [$M+Na^+–PhSO_2H$], 165 (20) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{18}H_{22}O_3S$ (318.43): C 67.89, H 6.96, S 10.07; found: C 67.91, H 7.11, S 9.89; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.12 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.47 (dq, *J* = 7.5, 15.0 Hz, 1H, C*H*HC*H*$_3$), 1.72 (dq, *J* = 7.4, 15.0 Hz, 1H, CH*H*C*H*$_3$), 1.96 (dq, *J* = 7.5, 15.1 Hz, 1H, C*H*HC*H*$_3$), 2.21 (dq, *J* = 7.5, 15.1 Hz, 1H, CH*H*C*H*$_3$), 4.19 (d, *J* = 2.5 Hz, 1H, O*H*), 4.92 (d, *J* = 2.5 Hz, 1H, C*H*OH), 7.22 (m, 5H, *H$_{ar}$*), 7.54 (m, 2H, *H$_2$*), 7.65 (m, 1H, *H$_3$*), 7.90 (m, 2H, *H$_1$*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5 (q, *C*H_3), 9.4 (q, *C*H_3), 19.5 (t, *C*H_2CH$_3$), 24.0 (t, *C*H_2CH$_3$), 74.1 (d, *C*HOH), 76.1 (s, SO_2*C*), 128.1 (d, *C$_{3'}$*), 128.38 (d, *C$_{1'}$*), 128.41 (d, *C$_2$*), 129.0 (d, *C$_{2'}$*), 130.2 (d, *C$_1$*), 133.9 (d, *C$_3$*), 137.5 (s, *C$_{4'}$*), 139.1 (s, *C$_4$*).

1-(4-Bromophenyl)-2-ethyl-2-(phenylsulfonyl)butan-1-ol (2-3b):



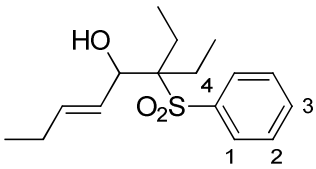
Yield 129 mg (65%) as colorless crystals, m.p. 119-121 °C. R_f (EtOAc/hexane 1:5) = 0.22; IR ν_{max} 3487, 2981, 2940, 1485, 1446, 1281, 1144, 1073, 1010, 725, 690 cm^{-1}; MS (ESI+) *m/z* (%) 419/417 (100/100) [M+Na^+], 165 (40) [$PhSO_2H$+Na^+]; Anal. calcd for $C_{18}H_{21}BrO_3S$ (396.33): C 54.41, H 5.33, S 8.07, Br 20.11; found: C 54.41, H 5.33, S 7.98, Br 20.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.10 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.53 (dq, *J* = 7.4, 14.8 Hz, 1H, C*H*HC*H*$_3$), 1.69 (dq, *J* = 7.4, 14.8 Hz, 1H, C*H*HC*H*$_3$), 1.92 (dq, *J* = 7.5, 15.0 Hz, 1H, CH*H*C*H*$_3$), 2.16 (dq, *J* = 7.5, 15.0 Hz, 1H, CH*H*C*H*$_3$), 4.32 (d, *J* = 2.5 Hz, 1H, O*H*), 4.90 (d, *J* = 2.5 Hz, 1H, C*H*OH), 7.15 (m, 2H, *H*$_{1'}$), 7.39 (m, 2H, *H*$_{2'}$), 7.56 (m, 2H, *H*$_2$), 7.67 (m, 1H, *H*$_3$), 7.90 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.7 (q, *C*H_3), 9.5 (q, *C*H_3), 19.8 (t, *C*H_2CH$_3$), 24.1 (t, *C*H_2CH$_3$), 73.9 (d, *C*HOH), 75.8 (s, SO_2*C*), 122.0 (s, *C*$_{3'}$), 129.1 (d, *C*$_2$), 130.2 (d, *C*$_{1'}$), 130.3 (d, *C*$_1$), 131.3 (d, *C*$_{2'}$), 134.1 (d, *C*$_3$), 137.4 (s, *C*$_{4'}$), 138.3 (s, *C*$_4$).

4-Ethyl-2-methyl-4-(phenylsulfonyl)hexan-3-ol (2-3c):



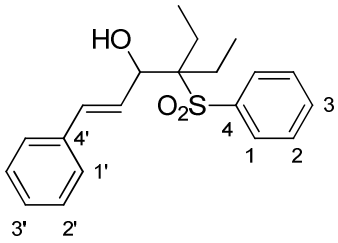
Yield 100 mg (70%) as colorless crystals, m.p. 90-91 °C. R_f (EtOAc/hexane 1:5) = 0.29; IR ν_{max} 3515, 2966, 2886, 1446, 1278, 1120, 1073, 1016, 758, 721, 690 cm^{-1}; MS (ESI+) *m/z* (%) 307 (100) [M+Na^+], 165 (40) [$PhSO_2H$+Na^+]; Anal. calcd for $C_{15}H_{24}O_3S$ (284.41): C 63.34, H 8.51, S 11.27; found: C 63.53, H 8.48, S 11.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (2×t, *J* = 7.5 Hz, 6H, CH$_2$C*H*$_3$), 1.04 (2×d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.54 (dq, *J* = 7.5, 14.8 Hz, 1H, C*H*HC*H*$_3$), 1.83 (dq, *J* = 7.5, 15.1 Hz, 1H, C*H*HC*H*$_3$), 2.03 (dq, *J* = 7.5, 14.8 Hz, 2H, C*H*HC*H*$_3$), 2.21 (m, 1H, C*H*(CH$_3$)$_2$), 3.19 (d, *J* = 7.8 Hz, 1H, O*H*), 3.80 (dd, *J* = 3.0, 7.8 Hz, 1H, C*H*OH), 7.51 (m, 2H, *H*$_2$), 7.61 (m, 1H, *H*$_3$), 7.87 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9 (q, CH$_2$*C*H$_3$), 9.1 (q, CH$_2$*C*H$_3$), 17.6 (q, CH(*C*H$_3$)$_2$), 23.3 (t, *C*H$_2$CH$_3$), 24.3 (q, CH(*C*H$_3$)$_2$), 24.9 (t, *C*H$_2$CH$_3$), 29.5 (d, *C*H(CH$_3$)$_2$), 74.4 (s, SO_2*C*), 77.8 (d, *C*HOH), 128.9 (d, *C*$_2$), 130.2 (d, *C*$_1$), 133.8 (d, *C*$_3$), 138.8 (s, *C*$_4$).

(*E*)-3-Ethyl-3-(phenylsulfonyl)oct-5-en-4-ol (2-3d):



Yield 96 mg (64%) as colorless crystals, m.p. 65-66 °C. R_f (EtOAc/hexane 1:5) = 0.32; IR ν_{max} 3493, 2969, 2939, 1446, 1281, 1131, 1075, 971, 721, 691, 604 cm^{-1}; MS (ESI+) *m/z* (%) 319 (100) [M+Na^+], 165 (30) [$PhSO_2H$+Na^+]; Anal. calcd for $C_{16}H_{24}O_3S$ (296.42): C 64.83, H 8.16, S 10.82; found: C 64.94, H 8.24, S 10.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (m, 9H, C*H*$_3$), 1.61 (dq, *J* = 7.4, 14.8 Hz, 1H, CC*H*HC*H*$_3$), 1.80 (dq, *J* = 7.5, 15.1 Hz, 1H, CC*H*HC*H*$_3$), 1.94 (m, 4H, CCH*H*C*H*$_3$, =CHC*H*$_2$CH$_3$), 3.47 (d, *J* = 6.1 Hz, 1H, O*H*), 4.34 (t, *J* = 6.1 Hz, 1H, C*H*OH), 5.55 (ddt, *J* = 1.4, 6.2, 15.2 Hz, 1H, CH$_2$CH=C*H*), 5.71 (dtd, *J* = 0.8, 7.1, 15.2 Hz, 1H, CH$_2$C*H*=CH), 7.50 (m, 2H, *H*$_2$), 7.60 (m, 1H, *H*$_3$), 7.86 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5 (q, CCH$_2$*C*H$_3$), 8.8 (q, CCH$_2$*C*H$_3$), 13.3 (q, CHCH$_2$*C*H$_3$), 22.0 (t, C*C*H$_2$CH$_3$), 23.6 (t, C*C*H$_2$CH$_3$), 25.5 (t, =CH*C*H$_2$CH$_3$), 73.4 (s, SO$_2$*C*), 74.8 (d, *C*HOH), 126.7 (d, CH$_2$CH=*C*H), 128.8 (d, *C*$_2$), 130.4 (d, *C*$_1$), 133.8 (d, *C*$_3$), 136.9 (d, CH$_2$*C*H=CH), 138.3 (s, *C*$_4$).

(*E*)-4-Ethyl-1-phenyl-4-(phenylsulfonyl)hex-1-en-3-ol (2-3e):



Yield 122 mg (71%) as colorless crystals, m.p. 85-86 °C. R_f (EtOAc/hexane 1:5) = 0.20; IR ν_{max} 3491, 2974, 2943, 2886, 1446, 1361, 1279, 1133, 1073, 969, 755, 721, 690, 604 cm^{-1}; MS (ESI+) *m/z* (%) 367 (100) [M+Na^+], 327 (10) [M–OH^-]; Anal. calcd for $C_{20}H_{24}O_3S$ (344.15): C 69.73, H 7.02, S 9.31; found: C 69.67, H 6.89, S 9.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (m, 6H, C*H*$_3$), 1.77 (dq, *J* = 7.4, 15.0 Hz, 1H, C*H*HC*H*$_3$), 1.88 (dq, *J* = 7.6, 15.1 Hz, 1H, C*H*HC*H*$_3$), 2.04 (m, 2H, CH*H*C*H*$_3$), 3.69 (d, *J* = 6.6 Hz, 1H, O*H*), 4.56 (td, *J* = 1.3, 6.6 Hz, 1H, C*H*OH), 6.28 (dd, *J* = 6.6, 15.8 Hz, 1H, PhCH=C*H*), 6.64 (dd, *J* = 1.3, 15.8 Hz, 1H, PhC*H*=CH), 7.27 (m, 5H, *H*$_{ar}$), 7.48 (m, 2H, *H*$_2$), 7.61 (m, 1H, *H*$_3$), 7.89 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5 (q, *C*H$_3$), 8.7 (q, *C*H$_3$), 22.2 (t, *C*H$_2$CH$_3$), 23.2 (t, *C*H$_2$CH$_3$), 73.6 (s, SO$_2$*C*), 74.6 (d, *C*HOH), 126.7 (d, *C*$_{ar}$), 127.1 (d, PhCH=*C*H), 127.9 (d,

$C_{3'}$), 128.6 (d, C_{ar}), 128.7 (d, C_2), 130.3 (d, C_1), 132.9 (d, Ph*C*H=CH), 133.7 (d, C_3), 136.4 (s, $C_{4'}$), 138.0 (s, C_4).

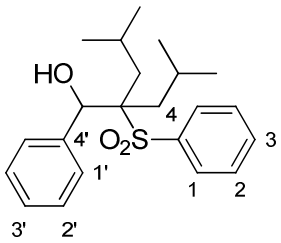
2-Hydroxyalkyl phenyl sulfones 2-4a-g (**General procedure):**

Conditions A: *n*BuLi (0.27 mL, 0.43 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (100 mg, 0.37 mmol) and TMEDA (0.1 mL, 0.65 mmol) in dry THF (4 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the reaction mixture was warmed to 0 °C during 1 h, followed by dropwise addition of the aldehyde (0.44 mmol) in THF (2 mL) at –78 °C. The reaction mixture was warmed to –20 °C, stirred at this temperature until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **2-4a-g**.

Conditions B: *n*BuLi (0.27 mL, 0.43 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (100 mg, 0.37 mmol) and TMEDA (0.1 mL, 0.65 mmol) in dry THF (4 mL) at –20 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde (0.44 mmol) in THF (2 mL) was added dropwise at –78 °C. The reaction mixture was warmed to –20 °C, stirred at this temperature until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **2-4a,d,f,g**.

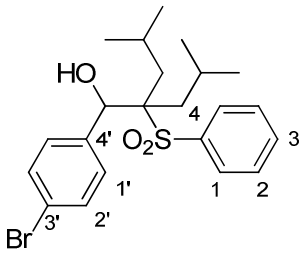
Conditions C: *n*BuLi (0.27 mL, 0.43 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (100 mg, 0.37 mmol) and HMPA (0.4 mL, 2.22 mmol) in dry THF (4 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde (0.44 mmol) in THF (2 mL) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **2-4a-g**.

2-Isobutyl-4-methyl-1-phenyl-2-(phenylsulfonyl)pentan-1-ol (2-4a):



Yield 104 mg (75%, conditions C) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.37; IR ν_{max} 3476, 2961, 2870, 1470, 1446, 1389, 1280, 1123, 1075, 751, 723, 690, 631 cm^{-1}; MS (ESI+) *m/z* (%) 397 (100) [$M+Na^+$], 256 (60) [$M–PhSO_2+Na^+$], 165 (20) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{22}H_{30}O_3S$ (374.54): C 70.55, H 8.07, S 8.56; found: C 70.26, H 8.03, S 8.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.06 (2×d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.37 (dd, *J* = 4.2, 15.0 Hz, 1H, C*H*H*i*Pr), 1.52 (dd, *J* = 6.0, 15.0 Hz, 1H, CH*Hi*Pr), 1.71 (m, 1H, C*H*(CH$_3$)$_2$), 1.88 (dd, *J* = 5.4, 15.4 Hz, 1H, C*H*H*i*Pr), 1.96 (dd, *J* = 4.6, 15.4 Hz, 1H, CH*Hi*Pr), 2.43 (m, 1H, C*H*(CH$_3$)$_2$), 4.00 (d, *J* = 3.3 Hz, 1H, O*H*), 5.16 (d, *J* = 3.3 Hz, 1H, C*H*OH), 7.31 (m, 3H, *H*$_{1'}$, *H*$_{3'}$), 7.36 (m, 2H, *H*$_{2'}$), 7.49 (t, *J* = 7.8 Hz, 2H, *H*$_2$), 7.62 (m, 1H, *H*$_3$), 7.83 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.60 (d, *C*H(CH$_3$)$_2$), 23.63 (d, *C*H(CH$_3$)$_2$), 25.5 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 38.7 (t, *C*H$_2$*i*Pr), 41.8 (t, *C*H$_2$*i*Pr), 76.2 (s, SO$_2$*C*), 76.8 (d, *C*HOH), 128.2 (d, *C*$_{1'}$), 128.6 (d, *C*$_{3'}$), 128.7 (d, *C*$_2$), 129.2 (d, *C*$_{2'}$), 130.5 (d, *C*$_1$), 133.7 (d, *C*$_3$), 138.7 (s, *C*$_{4'}$), 139.4 (s, *C*$_4$).

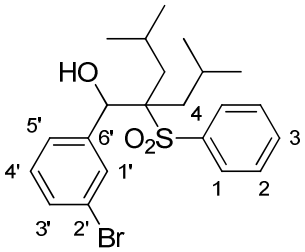
1-(4-Bromophenyl)-2-isobutyl-4-methyl-2-(phenylsulfonyl)pentan-1-ol (2-4b):



Yield 80 mg (48%, conditions C) as a colorless solid, m.p. 109-110 °C. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 3478, 2961, 2931, 2870, 1488, 1472, 1446, 1282, 1125, 1075, 1011, 759, 730, 690 cm^{-1}; MS (ESI+) *m/z* (%) 931/929/927 (15/30/15) [$2M+Na^+$], 477/475 (95/100) [$M+Na^+$], 165 (40) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{22}H_{29}BrO_3S$ (452.43): C 58.27, H 6.45, S 7.07, Br 17.62; found: C 58.56, H 6.39, S 7.32, Br 17.84; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.05 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.36 (dd, *J* = 4.1, 15.0 Hz, 1H, C*H*H*i*Pr), 1.51 (dd, *J* = 6.1, 15.0 Hz,

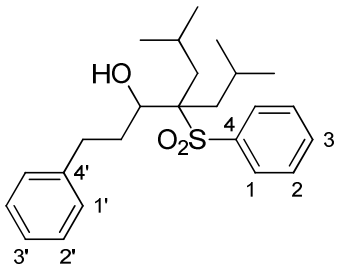
1H, CH*Hi*Pr), 1.67 (m, 1H, C*H*$(CH_3)_2$), 1.83 (dd, *J* = 5.4, 15.4 Hz, 1H, C*H*H*i*Pr), 1.91 (dd, *J* = 4.6, 15.4 Hz, 1H, CH*Hi*Pr), 2.39 (m, 1H, C*H*$(CH_3)_2$), 4.14 (d, *J* = 3.3 Hz, 1H, O*H*), 5.09 (d, *J* = 3.3 Hz, 1H, C*H*OH), 7.24 (m, 2H, *H*$_{1'}$), 7.46 (m, 2H, *H*$_{2'}$), 7.54 (m, 2H, *H*$_2$), 7.66 (m, 1H, *H*$_3$), 7.85 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (d, *C*H$(CH_3)_2$), 24.0 (d, *C*H$(CH_3)_2$), 25.5 (q, CH(*C*$H_3)_2$), 25.9 (q, CH(*C*$H_3)_2$), 26.1 (q, CH(*C*$H_3)_2$), 26.2 (q, CH(*C*$H_3)_2$), 38.9 (t, *C*H_2*i*Pr), 41.8 (t, *C*H_2*i*Pr), 75.9 (s, SO_2*C*), 76.5 (d, *C*HOH), 122.7 (s, *C*$_{3'}$), 128.9 (d, *C*$_2$), 129.1 (d, *C*$_{1'}$), 130.5 (d, *C*$_1$), 131.0 (d, *C*$_{2'}$), 133.9 (d, *C*$_3$), 138.5 (s, *C*$_{4'}$ or *C*$_4$), 138.6 (s, *C*$_{4'}$ or *C*$_4$).

1-(3-Bromophenyl)-2-isobutyl-4-methyl-2-(phenylsulfonyl)pentan-1-ol (2-4c):



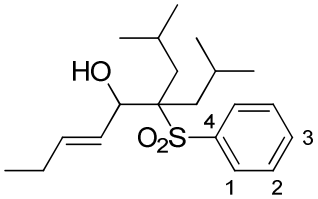
Yield 106 mg (63%, conditions C) as a colorless solid, m.p. 81-82 °C. R_f (EtOAc/hexane 1:5) = 0.39; IR ν_{max} 3488, 2961, 2871, 1668, 1473, 1457, 1447, 1389, 1282, 1129, 1075, 759, 728, 690 cm^{-1}; MS (ESI+) *m/z* (%) 477/475 (100/98) [$M+Na^+$], 165 (40) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{22}H_{29}BrO_3S$ (452.43): C 58.27, H 6.45, S 7.07, Br 17.62; found: C 58.44, H 6.47, S 6.96, Br 17.94; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (2×d, *J* = 6.6 Hz, 6H, CH(C*H*$_3)_2$), 1.07 (2×d, *J* = 6.6 Hz, 6H, CH(C*H*$_3)_2$), 1.39 (dd, *J* = 4.6, 15.0 Hz, 1H, C*H*H*i*Pr), 1.47 (dd, *J* = 5.6, 15.0 Hz, 1H, CH*Hi*Pr), 1.66 (m, 1H, C*H*$(CH_3)_2$), 1.85 (dd, *J* = 5.4, 15.4 Hz, 1H, C*H*H*i*Pr), 1.92 (dd, *J* = 4.6, 15.4 Hz, 1H, CH*Hi*Pr), 2.41 (m, 1H, C*H*$(CH_3)_2$), 4.20 (d, *J* = 3.0 Hz, 1H, O*H*), 5.08 (d, *J* = 3.0 Hz, 1H, C*H*OH), 7.19 (t, *J* = 7.8 Hz, 1H, *H*$_{4'}$), 7.33 (d, *J* = 7.9 Hz, 1H, *H*$_{3'}$), 7.44 (m, 1H, *H*$_{5'}$), 7.51 (t, *J* = 1.7 Hz, 1H, *H*$_{1'}$), 7.56 (t, *J* = 7.7 Hz, 2H, *H*$_2$), 7.67 (m, 1H, *H*$_3$), 7.89 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (d, *C*H$(CH_3)_2$), 23.8 (d, *C*H$(CH_3)_2$), 25.3 (q, CH(*C*$H_3)_2$), 25.6 (q, CH(*C*$H_3)_2$), 25.9 (q, CH(*C*$H_3)_2$), 26.0 (q, CH(*C*$H_3)_2$), 38.5 (t, *C*H_2*i*Pr), 41.7 (t, *C*H_2*i*Pr), 75.5 (s, SO_2*C*), 76.3 (d, *C*HOH), 122.7 (s, *C*$_{2'}$), 127.6 (d, *C*$_{3'}$), 128.7 (d, *C*$_2$), 129.5 (d, *C*$_{4'}$), 130.3 (d, *C*$_1$), 131.5 (d, *C*$_{1'}$), 132.1 (d, *C*$_{5'}$), 133.8 (d, *C*$_3$), 138.2 (s, *C*$_4$), 141.5 (s, *C*$_{6'}$).

4-Isobutyl-6-methyl-1-phenyl-4-(phenylsulfonyl)heptan-3-ol (2-4d):



Yield 123 mg (61%, conditions A) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.46; IR ν_{max} 3509, 3085, 2960, 2925, 1603, 1584, 1496, 1469, 1446, 1388, 1279, 1123, 1075, 1000, 931, 755 cm^{-1}; MS (ESI+) *m/z* (%) 425 (95) [M+Na^+], 283 (100) [M+Na^+–$PhSO_2H$]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{24}H_{34}O_3SNa^+$: 425.2121; found: 425.2120; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.87 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.88 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 0.99 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 1.35 (dd, *J* = 5.6, 15.2 Hz, 1H, C*H*H*i*Pr), 1.60 (dd, *J* = 6.1, 15.3 Hz, 1H, CH*Hi*Pr), 1.70 (dd, *J* = 3.9, 15.3 Hz, 1H, CH*Hi*Pr), 1.86 (m, 1H, C*H*(CH$_3$)$_2$), 1.89-2.09 (m, 4H, C*H*$_2$CHOH, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 2.62 (m, 1H, C*H*HPh), 2.97 (m, 1H, CH*H*Ph), 3.20 (d, *J* = 6.6 Hz, 1H, O*H*), 4.19 (m, 1H, C*H*OH), 7.17 (m, 3H, *H*$_{1'}$, H$_{3'}$), 7.25 (m, 2H, *H*$_{2'}$), 7.49 (t, *J* = 7.7 Hz, 2H, *H*$_2$), 7.58 (m, 1H, *H*$_3$), 7.89 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5 (d, *C*H(CH$_3$)$_2$), 24.0 (d, *C*H(CH$_3$)$_2$), 25.3 (q, CH(*C*H$_3$)$_2$), 25.46 (q, CH(*C*H$_3$)$_2$), 25.50 (q, CH(*C*H$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 33.3 (t, *C*H$_2$Ph), 35.1 (t, *C*H$_2$CHOH), 39.4 (t, *C*H$_2$*i*Pr), 41.2 (t, *C*H$_2$*i*Pr), 72.7 (d, *C*HOH), 77.4 (s, SO_2*C*), 126.0 (d, *C*$_{3'}$), 128.5 (d, *C*$_{2'}$), 128.6 (d, *C*$_{1'}$ or *C*$_2$), 128.7 (d, *C*$_{1'}$ or *C*$_2$), 130.2 (d, *C*$_1$), 133.5 (d, *C*$_3$), 139.2 (s, *C*$_4$), 141.7 (s, *C*$_{4'}$).

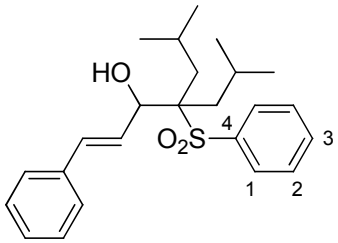
(*E*)-4-Isobutyl-2-methyl-4-(phenylsulfonyl)non-6-en-5-ol (2-4e):



Yield 80 mg (61%, conditions C) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 3489, 2960, 2928, 2871, 1447, 1335, 1284, 1127, 1077, 972, 758, 724, 690 cm^{-1}; MS (ESI+) *m/z* (%) 375 (100) [M+Na^+], 233 (30) [M–$PhSO_2H$+Na^+], 165 (30) [$PhSO_2H$+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{20}H_{32}O_3SNa^+$: 375.1964; found: 375.1964; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3×d+t, *J* = 6.5 Hz, 12H, CH(C*H*$_3$)$_2$, CH$_2$C*H*$_3$), 0.94 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.45 (dd, *J* = 4.5, 15.0 Hz, 1H, CH*Hi*Pr), 1.60 (dd, *J* = 5.6, 15.3 Hz, 1H, C*H*H*i*Pr), 1.72 (dd, *J* = 4.5, 15.3 Hz, 1H, CH*Hi*Pr), 1.79 (dd, *J* = 5.7, 15.0 Hz, 1H, C*H*H*i*Pr),

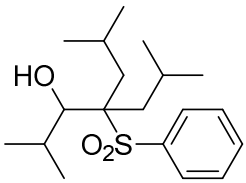
2.00 (m, 4H, C*H*$_2$CH$_3$, C*H*(CH$_3$)$_2$), 2.90 (d, *J* = 5.0 Hz, 1H, O*H*), 4.51 (t, *J* = 4.9 Hz, 1H, C*H*OH), 5.56 (dd, *J* = 5.3, 15.3 Hz, 1H, =C*H*CHOH), 5.72 (dt, *J* = 6.8, 15.3 Hz, 1H, CH$_2$C*H*=), 7.44 (m, 2H, *H$_2$*), 7.54 (m, 1H, *H$_3$*), 7.84 (m, 2H, *H$_1$*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.4 (q, CH$_2$*C*H$_3$), 23.7 (d, *C*H(CH$_3$)$_2$), 23.9 (d, *C*H(CH$_3$)$_2$), 25.4 (q, CH(*C*H$_3$)$_2$), 25.6 (t, *C*H$_2$CH=), 25.7 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 26.0 (q, CH(*C*H$_3$)$_2$), 39.1 (t, *C*H$_2$*i*Pr), 40.9 (t, *C*H$_2$*i*Pr), 74.7 (d, *C*HOH), 75.9 (s, SO$_2$*C*), 127.0 (d, =C*H*CHOH), 128.7 (d, *C$_2$*), 130.7 (d, *C$_1$*), 133.6 (d, *C$_3$*), 137.4 (d, CH$_2$C*H*=), 139.3 (s, *C$_4$*).

(*E*)-4-Isobutyl-6-methyl-1-phenyl-4-(phenylsulfonyl)hept-1-en-3-ol (2-4f):



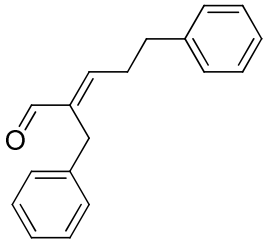
Yield 145 mg (98%, conditions C) as a colorless oil. R$_f$ (EtOAc/hexane 1:5) = 0.32; IR ν_{max} 3479, 2960, 2870, 1447, 1281, 1124, 1075, 972, 752, 724, 691 cm^{-1}; MS (ESI+) *m/z* (%) 824 (20), 423 (100) [M+Na$^+$], 281 (40) [M–PhSO$_2$H+Na$^+$], 165 (10) [PhSO$_2$H+Na$^+$]; Anal. calcd for C$_{24}$H$_{32}$O$_3$S (400.57): C 71.96, H 8.05, S 8.00; found: C 71.74, H 7.77, S 8.27; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (2×d, *J* = 6.6 Hz, 6H, CH(C*H$_3$*)$_2$), 0.92 (d, *J* = 6.7 Hz, 3H, CH(C*H$_3$*)$_2$), 0.99 (d, *J* = 6.6 Hz, 3H, CH(C*H$_3$*)$_2$), 1.58 (dd, *J* = 4.6, 15.0 Hz, 1H, CH*H*i*Pr*), 1.65 (dd, *J* = 5.6, 15.3 Hz, 1H, C*H*H*i*Pr), 1.78 (dd, *J* = 4.5, 15.3 Hz, 1H, CH*H*i*Pr*), 1.92 (dd, *J* = 5.7, 15.0 Hz, 1H, C*H*H*i*Pr), 2.05 (m, 2H, C*H*(CH$_3$)$_2$), 3.18 (s, 1H, O*H*), 4.76 (d, *J* = 6.0 Hz, 1H, C*H*OH), 6.28 (dd, *J* = 6.3, 15.7 Hz, 1H, =C*H*CHOH), 6.63 (dd, *J* = 1.3, 15.7 Hz, 1H, PhC*H*=), 7.15-7.28 (m, 5H, *H$_{ar}$*), 7.40 (t, *J* = 7.8 Hz, 2H, *H$_2$*), 7.53 (m, 1H, *H$_3$*), 7.85 (m, 2H, *H$_1$*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.6 (d, *C*H(CH$_3$)$_2$), 23.9 (d, *C*H(CH$_3$)$_2$), 25.3 (q, CH(*C*H$_3$)$_2$), 25.5 (q, CH(*C*H$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 39.2 (t, *C*H$_2$*i*Pr), 40.6 (t, *C*H$_2$*i*Pr), 74.2 (d, *C*HOH), 76.1 (s, SO$_2$*C*), 126.7 (d, *C$_{ar}$*), 127.3 (d, =C*H*CHOH), 128.0 (d, *C$_{para}$*), 128.5 (d, *C$_{ar}$*), 128.6 (d, *C$_2$*), 130.6 (d, *C$_1$*), 133.4 (d, PhC*H*=), 133.5 (d, *C$_3$*), 136.5 (s, *C$_{ipso}$*), 139.0 (s, *C$_4$*).

4-Isobutyl-2,6-dimethyl-1-phenyl-4-(phenylsulfonyl)heptan-3-ol (2-4g):



Yield 55 mg (44%, conditions C) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.46; IR ν_{max} 3515, 2960, 2931, 2871, 1470, 1446, 1388, 1277, 1122, 1075, 1017, 757, 722, 691, 629 cm^{-1}; MS (ESI+) *m/z* (%) 363 (100) [$M+Na^+$], 221 (30) [$M–PhSO_2H+Na^+$], 165 (20) [$PhSO_2H+Na^+$]; HRMS (ESI+) *m/z* [$M+Na^+$] calcd for $C_{19}H_{32}O_3SNa^+$: 363.1964; found: 363.1964; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J* = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$), 0.93 (d, *J* = 6.5 Hz, 3H, $CH_2CH(CH_3)_2$), 0.95 (d, *J* = 6.5 Hz, 3H, $CH_2CH(CH_3)_2$), 1.02 (d, *J* = 6.6 Hz, 3H, $OHCHCH(CH_3)_2$), 1.07 (2×d, *J* = 6.6 Hz, 6H, $OHCHCH(CH_3)_2$, $CH_2CH(CH_3)_2$), 1.45 (m, 1H, CHHiPr), 1.63 (dd, *J* = 6.4, 15.6 Hz, 1H, CHHiPr), 1.83 (dd, *J* = 3.7, 15.6 Hz, 1H, CHHiPr), 2.03 (m, 3H, CHHiPr, $CH_2CH(CH_3)_2$), 2.15 (m, 1H, $OHCHCH(CH_3)_2$), 2.93 (d, *J* = 6.8 Hz, 1H, OH), 4.11 (dd, *J* = 1.8, 6.8 Hz, 1H, CHOH), 7.52 (m, 2H, H_{meta}), 7.61 (m, 1H, H_{para}), 7.95 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2 (q, $OHCHCH(CH_3)_2$), 23.7 (d, $CH_2CH(CH_3)_2$), 24.1 (d, $CH_2CH(CH_3)_2$), 24.2 (q, $OHCHCH(CH_3)_2$), 25.5 (q, $CH_2CH(CH_3)_2$), 25.9 (q, $CH_2CH(CH_3)_2$), 26.07 (q, $CH_2CH(CH_3)_2$), 26.10 (q, $CH_2CH(CH_3)_2$), 29.5 (d, $OHCHCH(CH_3)_2$), 39.4 (t, CH_2iPr), 41.6 (t, CH_2iPr), 76.9 (d, CHOH), 78.5 (s, SO_2C), 128.8 (d, C_{meta}), 130.4 (d, C_{ortho}), 133.6 (d, C_{para}), 140.0 (s, C_{ipso}).

(*E*)-2-Benzyl-5-phenyl-2-pentenal 2-5:



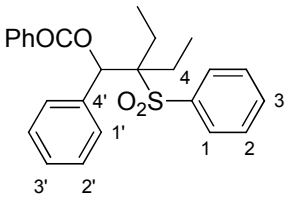
For yields see Table 2.4, colorless oil. R_f (EtOAc/hexane 1:5) = 0.54; IR ν_{max} 3085, 3062, 3027, 1685, 1638, 1602, 1584, 1495, 1453, 1289, 1030, 1002, 698 cm^{-1}; MS (ESI+) *m/z* (%) 525 (25), 273 (100) [$M+Na^+$]; HRMS (ESI+) *m/z* [$M+Na^+$] calcd for $C_{18}H_{18}ONa^+$: 273.1250; found: 273.1251; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (m, 4H, CH_2CH_2Ph), 3.54 (s, 2H, CCH_2Ph), 6.59 (m, 1H, =CH), 7.10 (m, 5H, H_{ar}), 7.18 (m, 3H, H_{ar}), 7.26 (m, 2H, H_{ar}), 9.40 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1 (t, CCH_2Ph), 31.2 (t, CH_2CH_2Ph), 34.4 (t, CH_2CH_2Ph), 126.3 (d, C_{para}), 126.6 (d, C_{para}), 128.52 (d, C_{ar}), 128.55 (d, C_{ar}), 128.7 (d, C_{ar}),

128.8 (d, C_{ar}), 139.3 (s, C_{ipso}), 140.1 (s, C_{ipso}), 143.1 (s, *C*=), 154.8 (d, *C*H=), 194.8 (d, *C*HO).

2-Benzoyloxy sulfones 2-6a-f (General Procedure):

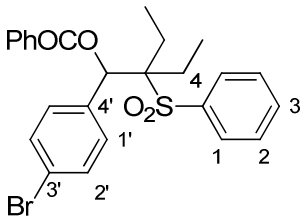
*n*BuLi (0.37 mL, 0.6 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2p** (106 mg, 0.5 mmol) and TMEDA (0.15 mL, 0.98 mmol) in dry THF (5 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde (0.6 mmol) in THF (2 mL) was added dropwise at –78 °C. The reaction mixture was slowly warmed to 0 °C and stirred until complete as indicated by TLC. Benzoyl chloride (75 µL, 0.65 mmol) was added at –78 °C. After 20 min, 3-(dimethylamino)propan-1-ol (88 µL, 0.75 mmol) was added. After 10 min, the reaction was quenched with water. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed successively with 1*M* HCl, 5% $NaHCO_3$ and brine solutions, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave benzoyloxy sulfones **2-6a-f**.

2-Ethyl-1-phenyl-2-(phenylsulfonyl)but-1-yl benzoate (2-6a):



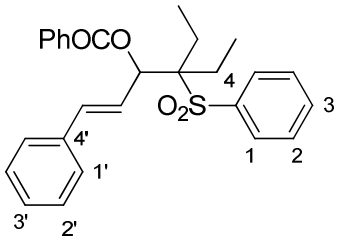
Yield 186 mg (88%) as a colorless solid, m.p. 120-121 °C. R_f (EtOAc/hexane 1:5) = 0.21; IR ν_{max} 2981, 2946, 1724, 1450, 1294, 1264, 1145, 1107, 1089, 1073, 759, 715 cm^{-1}; MS (ESI) *m/z* (%) 445 (100) [M+Na^+], 303 (70) [M–$PhSO_2H$+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{25}H_{26}O_4SNa^+$: 445.1444; found: 445.1443; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.26 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.95 (dq, *J* = 7.5, 15.1 Hz, 1H, C*H*HCH$_3$), 1.98 (dq, *J* = 7.5, 15.1 Hz, 1H, C*H*HCH$_3$), 2.16 (dq, *J* = 7.5, 15.2 Hz, 1H, CH*H*CH$_3$), 2.38 (dq, *J* = 7.4, 15.2 Hz, 1H, CH*H*CH$_3$), 6.51 (s, 1H, C*H*OCOPh), 7.26 (m, 2H, H_{meta}), 7.27-7.30 (m, 3H, $H_{2'}$, $H_{3'}$), 7.34 (m, 3H, H_{para}, H_2), 7.38 (m, 2H, $H_{1'}$), 7.53 (m, 1H, H_3), 7.73 (m, 2H, H_{ortho}), 7.77 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8 (q, *C*H$_3$), 9.0 (q, *C*H$_3$), 22.4 (t, *C*H$_2$CH$_3$), 23.1 (t, *C*H$_2$CH$_3$), 74.2 (s, SO_2*C*), 76.8 (d, *C*HOCOPh), 128.17 (d, $C_{1'}$), 128.24 (d, C_{meta}), 128.3 (d, $C_{2'}$), 128.6 (d, C_2, $C_{3'}$), 129.58 (d, C_{ortho}), 129.63 (d, C_1), 129.72 (s, C_{ipso}), 133.0 (s, C_{para}), 133.1 (d, C_3), 136.8 (s, $C_{4'}$), 138.8 (s, C_4), 164.4 (s, *C*=O).

1-(4-Bromophenyl)-2-ethyl-2-(phenylsulfonyl)butyl benzoate (2-6b):



Yield 218 mg (87%) as colorless crystals, m.p. 150-151 °C. R_f (EtOAc/hexane 1:5) = 0.44; IR ν_{max} 2981, 1725, 1299, 1265, 1146, 1095, 723, 714 cm^{-1}; MS (ESI) *m/z* (%) 638 (40), 525/523 (100/100) [$M+Na^+$], 383/381 (40/40) [$M–PhSO_2H+Na^+$]; Anal. calcd for $C_{25}H_{25}BrO_4S$ (500.44): C 59.88, H 5.03, S 6.39, Br 15.94; found: C 60.06, H 5.11, S 6.22, Br 15.92; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.17 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.93 (m, 3H, C*H*$_2$CH$_3$), 2.28 (dq, *J* = 7.5, 15.0 Hz, 1H, C*H*HCH$_3$), 6.42 (s, 1H, C*H*OCOPh), 7.21 (m, 4H, H_{ar}), 7.29 (m, 3H, H_{ar}), 7.36 (m, 2H, H_{ar}), 7.47 (m, 1H, H_3 or H_{para}), 7.65 (m, 2H, H_{ortho}), 7.68 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.07 (q, *C*H$_3$), 9.12 (q, *C*H$_3$), 21.9 (t, *C*H$_2$CH$_3$), 23.4 (t, *C*H$_2$CH$_3$), 74.1 (s, SO$_2$*C*), 76.3 (d, *C*HOCOPh), 123.0 (s, $C_{3'}$), 128.5 (d, C_{ar}), 128.9 (d, C_{ar}), 129.6 (s, C_{ipso}), 129.7 (d, C_{ar}), 129.8 (d, C_{ar}), 130.1 (d, C_1), 131.6 (d, $C_{2'}$), 133.4 (d, C_3 or C_{para}), 133.5 (d, C_3 or C_{para}), 136.1 (s, $C_{4'}$), 138.8 (s, C_4), 164.5 (s, *C*=O).

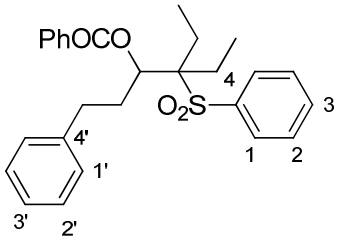
(*E*)-4-Ethyl-1-phenyl-4-(phenylsulfonyl)hex-1-en-3-yl benzoate (2-6c):



Yield 198 mg (88%) as colorless crystals, m.p. 140-142 °C. R_f (EtOAc/hexane 1:5) = 0.26; IR ν_{max} 2980, 2888, 1720, 1449, 1299, 1286, 1263, 1144, 1095, 1070, 1025, 965, 756, 713, 691, 603 cm^{-1}; MS (ESI+) *m/z* (%) 471 (100) [$M+Na^+$], 185 (30) [$M–PhSO_2H–PhCOO^–$]; Anal. calcd for $C_{27}H_{28}O_4S$ (448.58): C 72.29, H 6.29, S 7.15; found: C 72.58, H 6.39, S 7.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (2×t, *J* = 7.5 Hz, 6H, C*H*$_3$), 2.14 (m, 3H, C*H*$_2$CH$_3$), 2.34 (dq, *J* = 7.5, 15.0 Hz, 1H, CH*H*CH$_3$), 6.23 (d, *J* = 7.9 Hz, 1H, C*H*OCOPh), 6.42 (dd, *J* = 7.9, 15.7 Hz, 1H, PhCH=C*H*), 6.81 (d, *J* = 15.7 Hz, 1H, PhC*H*=CH), 7.22-7.45 (m, 9H, H_{ar}), 7.52 (m, 2H, H_3, H_{para}), 7.62 (m, 2H, H_{ortho}), 7.94 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6 (q, *C*H$_3$), 8.8 (q, *C*H$_3$), 22.9 (t, *C*H$_2$CH$_3$), 23.5 (t, *C*H$_2$CH$_3$), 73.4 (s, SO$_2$*C*), 75.6 (d, *C*HOCOPh), 122.8 (d, PhCH=*C*H), 126.9 (d, C_{ar}), 128.1 (d, $C_{3'}$), 128.3 (d, C_{ar}), 128.6 (d,

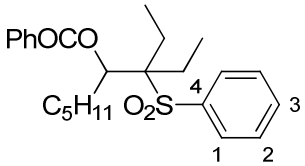
C_{ar}), 128.8 (d, C_{ar}), 129.57 (d, C_{ortho}), 129.64 (s, C_{ipso}), 130.2 (d, C_1), 133.1 (d, C_3 or C_{para}), 133.2 (d, C_3 or C_{para}), 135.9 (s, $C_{4'}$), 136.1 (d, Ph*C*H=), 139.2 (s, C_4), 164.9 (s, *C*=O).

4-Ethyl-1-phenyl-4-(phenylsulfonyl)hex-3-yl benzoate (2-6d):



Yield 205 mg (91%) as a colorless solid, m.p. 126-127 °C. R_f (EtOAc/hexane 1:5) = 0.36; IR ν_{max} 2980, 2871, 1719, 1451, 1387, 1302, 1268, 1177, 1143, 1105, 1077, 1026, 758, 712, 693 cm^{-1}; MS (ESI+) *m/z* (%) 473 (100) [$M+Na^+$], 331 (60) [$M–PhSO_2H+Na^+$]; Anal. calcd for $C_{27}H_{30}O_4S$ (450.59): C 71.97, H 6.71, S 7.12; found: C 71.93, H 6.92, S 6.83; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.5 Hz, 3H, CH_3), 1.14 (t, *J* = 7.5 Hz, 3H, CH_3), 1.87 (dq, *J* = 7.5, 15.0 Hz, 1H, CH*H*CH_3), 2.10 (m, 3H, CH_2CH_3), 2.32 (m, 1H, $PhCH_2CHH$), 2.53 (m, 1H, $PhCH_2CHH$), 2.68 (m, 1H, PhC*H*HCH_2), 2.72 (m, 1H, PhCH*H*CH_2), 5.72 (dd, *J* = 1.7, 10.5 Hz, 1H, C*H*OCOPh), 7.23 (m, 3H, $H_{1'}$, $H_{3'}$), 7.32 (m, 2H, $H_{2'}$), 7.39 (t, *J* = 7.8 Hz, 2H, H_{meta}), 7.56 (m, 3H, H_2, H_{para}), 7.66 (m, 3H, H_{ortho}, H_3), 7.88 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3 (q, CH_2CH_3), 8.6 (q, CH_2CH_3), 22.3 (t, CH_2CH_3), 23.4 (t, CH_2CH_3), 32.9 (t, $PhCH_2CH_2$), 33.4 (t, $PhCH_2CH_2$), 73.4 (s, SO_2C), 74.4 (d, *C*HOCOPh), 126.1 (d, $C_{3'}$), 128.4 (d, C_{ar}), 128.6 (d, 2×C_{ar}), 128.7 (d, C_{ar}), 129.4 (s, C_{ipso}), 129.7 (d, C_{ortho}), 130.4 (d, C_1), 133.2 (d, C_3), 133.4 (d, C_{para}), 138.9 (s, C_4), 141.1 (s, $C_{4'}$), 166.0 (s, *C*=O).

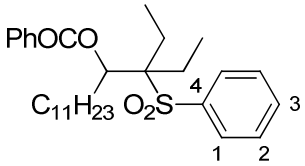
3-Ethyl-3-(phenylsulfonyl)non-4-yl benzoate (2-6e):



Yield 138 mg (66%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.30; IR ν_{max} 2956, 2932, 2859, 1720, 1449, 1301, 1268, 1145, 1105, 1077, 1026, 757, 712, 692 cm^{-1}; MS (ESI+) *m/z* (%) 855 (10) [$2M+Na^+$], 439 (100) [$M+Na^+$]; Anal. calcd for $C_{24}H_{32}O_4S$ (416.57): C 69.20, H 7.74, S 7.70; found: C 69.47, H 7.71, S 8.00; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 6.8 Hz, 3H, $CH_2CH_2CH_3$), 1.10 (2×t, *J* = 7.5 Hz, 6H, CCH_2CH_3), 1.16-1.35 (m, 6H, $(CH_2)_3$), 1.87 (m, 2H, CH_2CHOCOPh), 2.01 (m, 3H, CCH_2CH_3), 2.13 (m, 1H, CCH*H*CH_3), 5.60 (dd, *J* = 1.9, 10.6 Hz, 1H, C*H*OCOPh), 7.30 (t, *J* = 7.5 Hz, 2H, H_{meta}), 7.49 (m, 3H, H_2, H_{para}),

7.54 (m, 2H, H_{ortho}), 7.60 (t, J = 7.5 Hz, 1H, H_3), 7.89 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6 (q, CCH_2CH_3), 8.7 (q, CCH_2CH_3), 14.2 (q, $CH_2CH_2CH_3$), 22.7 (t, CCH_2CH_3), 22.8 (t, CCH_2CH_3), 22.9 (t, CH_3CH_2), 26.7 (t, CH_2), 31.6 (t, $CH_2CH_2CH_3$ or $CH_2CHOCOPh$), 31.8 (t, $CH_2CH_2CH_3$ or $CH_2CHOCOPh$), 73.8 (s, SO_2C), 75.1 (d, $CHOCOPh$), 128.4 (d, C_{meta}), 129.1 (d, C_2), 129.76 (s, C_{ipso}), 129.82 (d, C_{ortho}), 130.3 (d, C_1), 133.2 (d, C_3), 133.5 (d, C_{para}), 139.4 (s, C_4), 166.1 (s, C=O).

3-Ethyl-3-(phenylsulfonyl)pentadec-4-yl benzoate (2-6f):



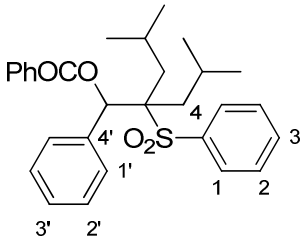
Yield 208 mg (83%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.40; IR ν_{max} 2925, 2854, 1720, 1449, 1302, 1267, 1146, 1077, 1070, 1026, 757, 711, 691 cm^{-1}; MS (ESI+) *m/z* (%) 523 (100) [M+Na$^+$], 359 (20) [M$^+$–PhSO$_2$]; Anal. calcd for $C_{30}H_{44}O_4S$ (500.73): C 71.96, H 8.86, S 6.40; found: C 71.82, H 8.68, S 6.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 6.8 Hz, 3H, $CH_2CH_2CH_3$), 1.10 (2×t, J = 7.5 Hz, 6H, CCH_2CH_3), 1.15-1.34 (m, 18H, $(CH_2)_9$), 1.87 (m, 2H, $CH_2CHOCOPh$), 2.01 (m, 3H, CCH_2CH_3), 2.13 (m, 1H, $CCHHCH_3$), 5.61 (dd, J = 1.9, 10.6 Hz, 1H, $CHOCOPh$), 7.30 (t, J = 7.5 Hz, 2H, H_{meta}), 7.48 (m, 3H, H_2, H_{para}), 7.54 (m, 2H, H_{ortho}), 7.59 (t, J = 7.5 Hz, 1H, H_3), 7.90 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.66 (q, CCH_2CH_3), 8.72 (q, CCH_2CH_3), 14.3 (q, $CH_2CH_2CH_3$), 22.78 (t, CCH_2CH_3), 22.82 (t, CCH_2CH_3), 22.9 (t, CH_3CH_2), 26.9 (t, CH_2), 29.4 (t, CH_2), 29.49 (t, CH_2), 29.53 (t, CH_2), 29.6 (t, CH_2), 29.7 (t, 2×CH_2), 31.5 (t, $CH_2CH_2CH_3$), 32.0 (t, $CH_2CHOCOPh$), 73.6 (s, SO_2C), 74.9 (d, $CHOCOPh$), 128.3 (d, C_{meta}), 129.0 (d, C_2), 129.7 (s, C_{ipso}), 129.8 (d, C_{ortho}), 130.2 (d, C_1), 133.1 (d, C_{para}), 133.4 (d, C_3), 139.3 (s, C_4), 165.9 (s, C=O).

2-Benzoyloxy sulfones 2-6g-i (General Procedure):

*n*BuLi (0.27 mL, 0.43 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (100 mg, 0.37 mmol) and HMPA (0.4 mL, 2.22 mmol) in dry THF (4 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde (0.47 mmol) in THF (1.5 mL) was added dropwise at –78 °C. The reaction mixture was stirred at this temperature until complete as indicated by TLC. Benzoyl chloride (57 µL, 0.49 mmol) was added. After 20 min, the reaction mixture was warmed to room temperature during 20 min

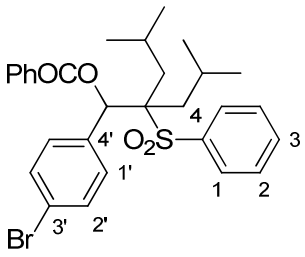
and 3-(dimethylamino)propan-1-ol (65 µL, 0.56 mmol) was added. After 10 min, the reaction was quenched with water. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed successively with 1*M* HCl, 5% $NaHCO_3$ and brine solutions, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave compounds **2-6g-i**.

2-Isobutyl-4-methyl-1-phenyl-2-(phenylsulfonyl)pentyl benzoate (2-6g):



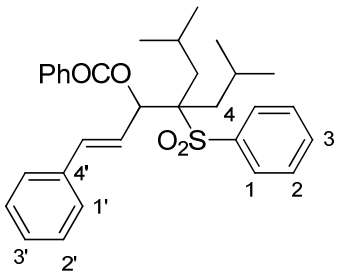
Yield 97 mg (55%) as colorless crystals, m.p. 176-177 °C. R_f (EtOAc/hexane 1:5) = 0.38; IR ν_{max} 2963, 2871, 1725, 1449, 1314, 1298, 1142, 1126, 1105, 1094, 1077, 1069, 1002, 754, 724, 713, 692 cm^{-1}; MS (ESI+) *m/z* (%) 501 (100) [$M+Na^+$], 359 (50) [$M–PhSO_2H+Na^+$]; Anal. calcd for $C_{29}H_{34}O_4S$ (478.64): C 72.77, H 7.16, S 6.70; found: C 72.98, H 6.85, S 6.42; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J* = 6.7 Hz, 3H, CH(C*H*$_3$)$_2$), 1.03 (d, *J* = 6.7 Hz, 3H, CH(C*H*$_3$)$_2$), 1.10 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.12 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.59 (dd, *J* = 3.4, 15.2 Hz, 1H, C*H*H*i*Pr), 2.03 (dd, *J* = 6.4, 15.2 Hz, 1H, CH*H**i*Pr), 2.18 (d, *J* = 5.0 Hz, 2H, CH$_2$*i*Pr), 2.30 (m, 1H, C*H*(CH$_3$)$_2$), 2.45 (m, 1H, C*H*(CH$_3$)$_2$), 6.71 (s, 1H, C*H*OCOPh), 7.18 (t, *J* = 7.8 Hz, 2H, H_{meta}), 7.32 (m, 6H, H_2, H_{ar}), 7.51 (m, 3H, H_{ar}), 7.57 (dd, *J* = 1.2, 8.3 Hz, 2H, H_{ortho}), 7.69 (dd, *J* = 1.1, 8.4 Hz, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7 (d, *C*H(CH$_3$)$_2$), 23.8 (d, *C*H(CH$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 26.3 (q, CH(*C*H$_3$)$_2$), 40.3 (t, *C*H$_2$*i*Pr), 41.5 (t, *C*H$_2$*i*Pr), 76.6 (s, SO$_2$*C*), 77.4 (d, *C*HOCOPh), 128.3 (d, C_{ar}), 128.46 (d, C_{ar}), 128.52 (d, C_{ar}), 128.9 (d, $C_{3'}$), 129.6 (d, C_{ortho}), 129.9 (d, C_{ar}), 130.1 (s, C_{ipso}), 130.2 (d, C_1), 133.0 (d, C_3 or C_{para}), 133.5 (d, C_3 or C_{para}), 136.8 (s, $C_{4'}$), 139.5 (s, C_4), 164.7 (s, *C*=O).

1-(4-Bromophenyl)-2-isobutyl-4-methyl-2-(phenylsulfonyl)pentyl benzoate (2-6h):



Yield 126 mg (61%) as colorless crystals, m.p. 209-210 °C. R_f (EtOAc/hexane 1:5) = 0.50; IR ν_{max} 2964, 2872, 1726, 1451, 1389, 1301, 1264, 1143, 1126, 1093, 1076, 756, 713, 691 cm^{-1}; MS (ESI+) *m/z* (%) 581/579 (60/60) [$M+Na^+$], 439/437 (100/95) [$M–PhSO_2H+Na^+$], 295/293 (50/50) [$M–PhSO_2H–PhCOO^–$], 214 (40) [$M–PhSO_2H–PhCOO^––Br$]; Anal. calcd for $C_{29}H_{33}BrO_4S$ (557.54): C 62.47, H 5.97, S 5.75, Br 14.33; found: C 62.18, H 5.59, S 5.92, Br 14.41; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.01 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.07 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.12 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 1.58 (dd, *J* = 3.7, 15.2 Hz, 1H, C*H*H*i*Pr), 2.02 (dd, *J* = 6.3, 15.2 Hz, 1H, CH*H*i*i*Pr), 2.08 (dd, *J* = 4.5, 15.2 Hz, 1H, CH*H*i*i*Pr), 2.16 (dd, *J* = 5.3, 15.2 Hz, 1H, CH*H*i*i*Pr), 2.30 (m, 1H, C*H*(CH$_3$)$_2$), 2.43 (m, 1H, C*H*(CH$_3$)$_2$), 6.63 (s, 1H, C*H*OCOAr), 7.24 (m, 2H, H_{meta}), 7.36 (m, 4H, $H_{1'}$, H_2), 7.43 (m, 3H, $H_{2'}$, H_{para}), 7.53 (m, 1H, H_3), 7.58 (m, 2H, H_{ortho}), 7.69 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.75 (d, *C*H(CH$_3$)$_2$), 23.84 (d, *C*H(CH$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 25.8 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 26.3 (q, CH(*C*H$_3$)$_2$), 40.4 (t, *C*H$_2$*i*Pr), 41.5 (t, *C*H$_2$*i*Pr), 76.4 (s, SO$_2$*C*), 76.8 (d, *C*HOCOAr), 123.2 (s, $C_{3'}$), 128.58 (d, C_2), 128.64 (d, C_{meta}, $C_{1'}$), 129.6 (d, C_{ortho}), 129.8 (s, C_{ipso}), 130.1 (d, C_1), 131.5 (d, $C_{2'}$), 133.3 (d, C_{para} or C_3), 133.5 (d, C_{para} or C_3), 135.9 (s, $C_{4'}$), 139.3 (s, C_4), 164.7 (s, *C*=O).

(*E*)-4-Isobutyl-6-methyl-1-phenyl-4-(phenylsulfonyl)hept-1-en-3-yl benzoate (2-6i):



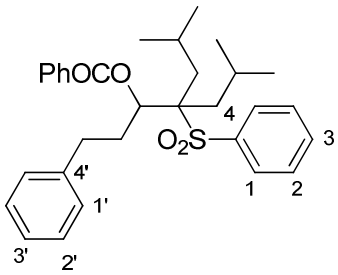
Yield 149 mg (80%) as colorless crystals, m.p. 95-96 °C. R_f (EtOAc/hexane 1:5) = 0.36; IR ν_{max} 3028, 2870, 1721, 1448, 1298, 1262, 1141, 1094, 1078, 752, 727, 712, 691 cm^{-1}; MS (ESI+) *m/z* (%) 527 (100) [$M+Na^+$], 385 (30) [$M–PhSO_2H+Na^+$], 241 (30) [$M–PhSO_2H–PhCOO^–$], 185 (40) [$M–PhSO_2H–PhCOO^––CH_2=C(CH_3)_2$]; Anal. calcd for $C_{31}H_{36}O_4S$ (504.68): C 73.78, H 7.19, S 6.35; found: 73.80, H 7.18, S 6.27; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 0.97 (m, 12H, CH(C*H*$_3$)$_2$), 1.83-2.03 (m, 3H, C*H*$_2$*i*Pr), 2.09 (dd, *J* = 4.9, 15.1 Hz, 1H, C*H*H*i*Pr), 2.20 (m, 2H, C*H*(CH$_3$)$_2$), 6.15 (m, 2H, PhCH=C*H*, C*H*OCOPh), 6.71 (d, *J* = 14.8 Hz, 1H, PhC*H*=CH), 7.06-7.33 (m, 10H, *H*$_{ar}$), 7.38 (m, 3H, *H*$_{ar}$), 7.76 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.8 (d, *C*H(CH$_3$)$_2$), 24.0 (d, *C*H(CH$_3$)$_2$), 25.5 (q, CH(*C*H$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 25.8 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 40.1 (t, *C*H$_2$*i*Pr), 40.6 (t, *C*H$_2$*i*Pr), 75.5 (s, SO$_2$*C*), 76.2 (d, *C*HOCOPh), 122.8 (d, PhCH=*C*H), 127.1 (d, *C*$_{ar}$), 128.4 (d, *C*$_{ar}$), 128.6 (d, *C*$_{ar}$), 128.75 (d, *C*$_{ar}$), 128.81 (d, *C*$_{ar}$), 129.6 (d, *C*$_{ortho}$), 130.0 (s, *C*$_{ipso}$), 130.6 (d, *C*$_1$), 133.1 (d, *C*$_3$ or *C*$_{para}$), 133.2 (d, *C*$_3$ or *C*$_{para}$), 136.1 (s, *C*$_{4'}$), 137.5 (d, Ph*C*H=), 140.0 (s, *C*$_4$), 164.9 (s, *C*=O).

2-Benzoyloxy sulfones 2-6j-l (General Procedure):

*n*BuLi (0.54 mL, 0.86 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (200 mg, 0.74 mmol) and TMEDA (0.3 mL, 2 mmol) in dry THF (6 mL) at –78 °C under a nitrogen atmosphere. The reaction mixture was warmed to –20 °C during 1h and the aldehyde (0.93 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at this temperature until complete as indicated by TLC. Benzoyl chloride (114 µL, 0.96 mmol) was added and the reaction mixture was warmed to room temperature after 20 min. 3-(Dimethylamino)propan-1-ol (130 µL, 1.11 mmol) was added and the reaction was quenched with water after 10 min. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed successively with 1*M* HCl, 5% NaHCO$_3$ and brine solutions, dried over MgSO$_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) provided compounds **2-6j-l**.

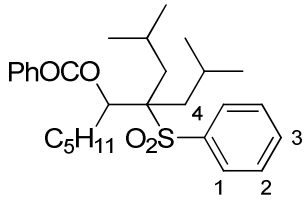
4-Isobutyl-6-methyl-1-phenyl-4-(phenylsulfonyl)hept-3-yl benzoate (2-6j):



Yield 251 mg (67%) as colorless crystals, m.p. 78-79 °C. R$_f$ (EtOAc/hexane 1:5) = 0.39; IR ν_{max} 2961, 2870, 1720, 1602, 1470, 1266, 1230, 1141, 1105, 1070, 1026, 755, 711, 693 cm^{-1}; MS (ESI+) *m/z* (%) 1035 (10) [2M+Na$^+$], 529 (100) [M+Na$^+$], 387 (30) [M–PhSO$_2$H+Na$^+$]; Anal. calcd for C$_{31}$H$_{38}$O$_4$S (506.70): C 73.48, H 7.56, S 6.33; found: C 73.45, H 7.69, S 6.44; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.96 (2×d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.02

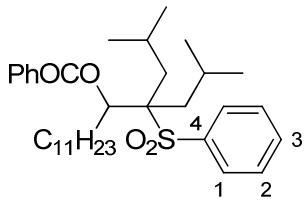
(2×d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.84 (dd, *J* = 4.3, 15.2 Hz, 1H, CH*Hi*Pr), 1.87 (dd, *J* = 4.3, 15.2 Hz, 1H, CH*Hi*Pr), 1.91-2.06 (m, 3H, C*H*HCHOCOPh, C*H*$_2$*i*Pr), 2.11 (m, 1H, C*H*(CH$_3$)$_2$), 2.23 (m, 2H, CH*H*CHOCOPh, C*H*(CH$_3$)$_2$), 2.57 (m, 1H, PhC*H*HCH$_2$), 2.66 (m, 1H, PhCH*H*CH$_2$), 5.89 (dd, *J* = 2.0, 9.9 Hz, 1H, C*H*OCOPh), 7.09 (m, 2H, *H*$_{1'}$), 7.12 (m, 1H, *H*$_{3'}$), 7.21 (m, 2H, *H*$_{2'}$), 7.29 (m, 4H, *H*$_2$, *H*$_{meta}$), 7.41 (t, *J* = 7.8 Hz, 1H, *H*$_{para}$), 7.48 (m, 1H, *H*$_3$), 7.53 (m, 2H, *H*$_{ortho}$), 7.79 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 23.9 (d, *C*H(CH$_3$)$_2$), 24.0 (d, *C*H(CH$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 33.5 (t, *C*H$_2$Ph), 34.9 (t, *C*H$_2$CH$_2$Ph), 39.6 (t, *C*H$_2$*i*Pr), 40.4 (t, *C*H$_2$*i*Pr), 75.3 (d, *C*HOCOPh), 76.1 (s, SO$_2$*C*), 126.1 (d, *C*$_{3'}$), 128.45 (d, *C*$_{ar}$), 128.54 (d, *C*$_{ar}$), 128.7 (d, *C*$_{ar}$), 128.9 (d, *C*$_{ar}$), 129.7 (d, *C*$_{ortho}$), 129.8 (s, *C*$_{ipso}$), 130.4 (d, *C*$_1$), 133.2 (d, *C*$_3$ or *C*$_{para}$), 133.3 (d, *C*$_3$ or *C*$_{para}$), 139.9 (s, *C*$_4$), 141.3 (s, *C*$_{4'}$), 166.0 (s, *C*=O).

4-Isobutyl-2-methyl-4-(phenylsulfonyl)dec-5-yl benzoate (2-6k):



Yield 273 mg (78%) as a colorless oil. R$_f$ (EtOAc/hexane 1:5) = 0.38; IR ν_{max} 3063, 2959, 2929, 2870, 1722, 1602, 1585, 1492, 1450, 1446, 1266, 1079, 1069, 935, 758, 726 cm^{-1}; MS (ESI+) *m/z* (%) 495 (60) [M+Na$^+$], 353 (100) [M–PhSO$_2$H+Na$^+$]; Anal. calcd for C$_{28}$H$_{40}$O$_4$S (472.68): C 71.15, H 8.53, S 6.78; found: 71.38, H 8.53, S 6.65; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.79 (t, *J* = 6.9 Hz, 3H, CH$_2$C*H*$_3$), 0.97 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.00 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.03 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.05 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.10-1.37 (m, 6H, (C*H*$_2$)$_3$), 1.68 (m, 1H, C*H*HCHOCOPh), 1.82-1.99 (m, 4H, CH*H*CHOCOPh, C*H*$_2$*i*Pr), 2.04 (dd, *J* = 4.1, 15.1 Hz, 1H, CH*Hi*Pr), 2.14 (m, 1H, C*H*(CH$_3$)$_2$), 2.22 (m, 1H, C*H*(CH$_3$)$_2$), 5.78 (dd, *J* = 2.0, 10.1 Hz, 1H, C*H*OCOPh), 7.27 (t, *J* = 8.0 Hz, 2H, *H*$_{meta}$), 7.32 (t, *J* = 8.0 Hz, 2H, *H*$_2$), 7.43 (m, 1H, *H*$_{para}$), 7.46 (m, 1H, *H*$_3$), 7.50 (m, 2H, *H*$_{ortho}$), 7.81 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.2 (q, CH$_2$*C*H$_3$), 22.6 (t, CH$_3$*C*H$_2$), 23.8 (d, *C*H(CH$_3$)$_2$), 24.0 (d, *C*H(CH$_3$)$_2$), 25.7 (q, 2×CH(*C*H$_3$)$_2$), 25.8 (q, CH(*C*H$_3$)$_2$), 26.1 (q, CH(*C*H$_3$)$_2$), 26.8 (t, *C*H$_2$), 32.1 (t, *C*H$_2$), 32.6 (t, *C*H$_2$CHOCOPh), 39.6 (t, *C*H$_2$*i*Pr), 40.4 (t, *C*H$_2$*i*Pr), 75.6 (d, *C*HOCOPh), 76.6 (s, SO$_2$*C*), 128.4 (d, *C*$_{meta}$), 128.9 (d, *C*$_2$), 129.7 (d, *C*$_{ortho}$), 130.1 (s, *C*$_{ipso}$), 130.4 (d, *C*$_1$), 133.1 (d, *C*$_3$, *C*$_{para}$), 140.1 (s, *C*$_4$), 165.9 (s, *C*=O).

4-Isobutyl-2-methyl-4-(phenylsulfonyl)hexadec-5-yl benzoate (2-6l):

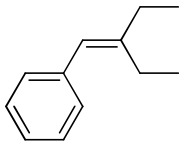


Yield 239 mg (58%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.49; IR ν_{max} 2931, 2923, 2854, 1721, 1450, 1302, 1268, 1175, 1078, 1026, 756, 711, 691 cm^{-1}; MS (ESI+) *m/z* (%) 579 (100) [$M+Na^+$], 437 (40) [$M–PhSO_2H+Na^+$]; Anal. calcd for $C_{34}H_{52}O_4S$ (556.84): C 73.34, H 9.41, S 5.76; found: C 73.47, H 9.47, S 6.04; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 6.9 Hz, 3H, CH_2CH_3), 0.96 (2×d, *J* = 6.5 Hz, 6H, $CH(CH_3)_2$), 1.02 (2×d, *J* = 6.5 Hz, 6H, $CH(CH_3)_2$), 1.06-1.33 (m, 18H, $(CH_2)_9$), 1.66 (m, 1H, CHHCHOCOPh), 1.88 (m, 4H, CHHCHOCOPh, CH_2iPr), 2.02 (dd, *J* = 4.1, 15.1 Hz, 1H, CHHiPr), 2.10 (m, 1H, $CH(CH_3)_2$), 2.19 (m, 1H, $CH(CH_3)_2$), 5.74 (dd, *J* = 2.0, 10.1 Hz, 1H, CHOCOPh), 7.21-7.32 (m, 4H, H_2, H_{meta}), 7.36-7.51 (m, 4H, H_3, H_{para}, H_{ortho}), 7.79 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (q, CH_2CH_3), 22.6 (t, CH_3CH_2), 23.6 (d, $CH(CH_3)_2$), 23.8 (d, $CH(CH_3)_2$), 25.5 (q, 2×$CH(CH_3)_2$), 25.6 (q, $CH(CH_3)_2$), 25.9 (q, $CH(CH_3)_2$), 26.9 (t, CH_2), 29.30 (t, CH_2), 29.33 (t, CH_2), 29.5 (t, CH_2), 29.6 (t, 2×CH_2), 29.7 (t, CH_2), 31.9 (t, CH_2CHOCOPh), 32.5 (t, CH_2), 39.4 (t, CH_2iPr), 40.2 (t, CH_2iPr), 75.4 (d, CHOCOPh), 76.4 (s, SO_2C), 128.1 (d, C_{meta}), 128.6 (d, C_2), 129.5 (d, C_{ortho}), 129.9 (s, C_{ipso}), 130.2 (d, C_1), 132.9 (d, C_3, C_{para}), 140.0 (s, C_4), 165.6 (s, C=O).

Julia olefination with samarium diiodide (General procedure):

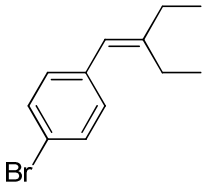
Benzoylated compound **2-6a-c,g-i** (0.16 mmol) was dissolved in THF (1.5 mL) and DMPU (0.73 mL, 6 mmol). After degassing the mixture by three freeze-pump-thaw cycles, a solution of SmI_2 (9.6 mL, 0.96 mmol) was added at 0 °C. After 2 h at room temperature, the reaction mixture was diluted with diethyl ether (2 mL) and decanted from samarium salts, which were washed thoroughly with diethyl ether. The combined organic layers were washed with saturated NH_4Cl solution and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:10) afforded olefins **2-7a-c,g-i.**

(2-Ethylbut-1-en-1-yl)benzene (2-7a):



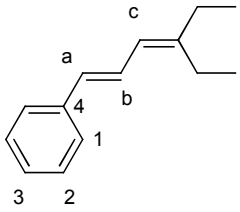
Yield 21 mg (82%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.96; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.14 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 2.22 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 2.28 (q, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_3$), 6.25 (s, 1H, PhC*H*), 7.23 (m, 3H, H_{meta}, H_{para}), 7.32 (m, 2H, H_{ortho}). The spectral data are in agreement with those in the cited literature.[233]

4-Bromo(2-ethylbut-1-en-1-yl)benzene (2-7b):



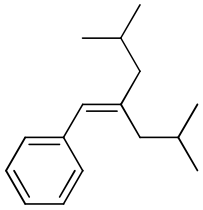
Yield 30 mg (78%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.93; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.09 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 2.18 (m, 4H, C*H*$_2$CH$_3$), 6.13 (s, 1H, ArC*H*), 7.06 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.40 (d, 2H, *J* = 8.3 Hz, 2H, H_{ar}). The spectral data are in agreement with those in the cited literature.[234]

(*E*)-(4-Ethylhexa-1,3-dien-1-yl)benzene (2-7c):



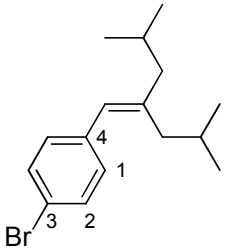
Yield 20 mg (68%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.96; IR ν_{max} 3030, 2967, 2936, 2878, 1682, 1495, 1452, 1399, 1029, 962, 919, 748, 695 cm^{-1}; MS (EI) *m/z* (%) 186 (100) [M$^+$], 157 (40), 145 (50); Anal. calcd for $C_{14}H_{18}$ (186.30): C 90.26, H 9.74; found: C 89.91, H 9.77; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (2×t, *J* = 7.5 Hz, 6H, C*H*$_3$), 2.08 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 2.22 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$), 5.90 (d, *J* = 11.0 Hz, 1H, H_c), 6.39 (d, *J* = 15.5 Hz, 1H, H_a), 6.96 (dd, *J* = 11.0, 15.5 Hz, 1H, H_b), 7.11 (m, 1H, H_3), 7.23 (m, 2H, H_2), 7.33 (m, 2H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (q, *C*H$_3$), 13.7 (q, *C*H$_3$), 24.2 (t, *C*H$_2$CH$_3$), 29.7 (t, *C*H$_2$CH$_3$), 123.2 (d, C_c), 125.5 (d, C_b), 126.1 (d, C_1), 126.9 (d, C_3), 128.5 (d, C_2), 130.0 (d, C_a), 138.2 (s, =*C*(CH$_2$)$_2$), 148.1 (s, C_4).

(2-Isobutyl-4-methylpent-1-en-1-yl)benzene (2-7g):



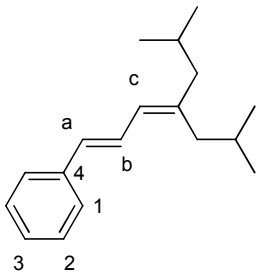
Yield 26 mg (68%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.85; IR ν_{max} 2980, 2956, 2926, 2868, 1462, 1383, 1365, 1164, 1076, 953, 737, 698, 669 cm^{-1}; MS (EI) *m/z* (%) 216 (100) [M^+], 173 (50); HRMS (EI) *m/z* [M^+] calcd for $C_{16}H_{24}^+$: 216.1878; found: 216.1876; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 0.92 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.81 (m, 2H, C*H*(CH$_3$)$_2$), 1.99 (d, *J* = 7.4 Hz, 2H, C*H*$_2$*i*Pr), 2.09 (d, *J* = 7.4 Hz, 2H, C*H*$_2$*i*Pr), 6.30 (s, 1H, C*H*=C), 7.16 (m, 3H, *H*$_{ortho}$, *H*$_{para}$), 7.27 (m, 2H, *H*$_{meta}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.77 (q, CH(*C*H$_3$)$_2$), 22.80 (q, CH(*C*H$_3$)$_2$), 26.6 (d, *C*H(CH$_3$)$_2$), 26.7 (d, *C*H(CH$_3$)$_2$), 39.1 (t, *C*H$_2$*i*Pr), 47.1 (t, *C*H$_2$*i*Pr), 125.9 (d, *C*$_{para}$), 127.5 (d, *C*H=C), 128.1 (d, *C*$_{ortho}$), 129.2 (d, *C*$_{meta}$), 139.1 (s, =*C*(CH$_2$)$_2$), 141.7 (s, *C*$_{ipso}$).

4-Bromo-1-(2-isobutyl-4-methylpent-1-en-1-yl)benzene (2-7h):



Yield 33 mg (71%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.89; IR ν_{max} 2980, 2955, 2926, 2868, 1486, 1463, 1384, 1366, 1260, 1164, 1097, 1072, 1011, 953, 824, 669 cm^{-1}; MS (EI) *m/z* (%) 296/294 (30/30) [M^+], 172 (90) [M^+–Br–*i*Pr], 129 (100) [M^+–Br–2×*i*Pr]; HRMS (EI) *m/z* [M^+] calcd for $C_{16}H_{23}{}^{79}Br^+$: 294.0983; found: 294.0980; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 0.92 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.81 (m, 2H, C*H*(CH$_3$)$_2$), 2.00 (d, *J* = 7.1 Hz, 2H, C*H*$_2$*i*Pr), 2.07 (d, *J* = 7.1 Hz, 2H, C*H*$_2$*i*Pr), 6.23 (s, 1H, C*H*=C), 7.04 (d, *J* = 8.4 Hz, 2H, *H*$_1$), 7.40 (d, *J* = 8.4 Hz, 2H, *H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.75 (q, CH(*C*H$_3$)$_2$), 22.78 (q, CH(*C*H$_3$)$_2$), 26.61 (d, *C*H(CH$_3$)$_2$), 26.63 (d, *C*H(CH$_3$)$_2$), 39.1 (t, *C*H$_2$*i*Pr), 47.1 (t, *C*H$_2$*i*Pr), 119.7 (s, *C*$_3$), 126.3 (d, *C*H=C), 130.9 (d, *C*$_2$), 131.2 (d, *C*$_1$), 138.0 (s, =*C*(CH$_2$)$_2$), 142.7 (s, *C*$_4$).

(*E*)-1-(4-Isobutyl-6-methyl-1-phenyl)hepta-1,3-heptadiene (2-7i):

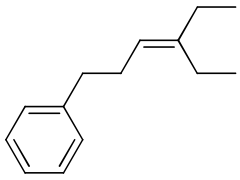


Yield 32 mg (82%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.89; IR ν_{max} 2954, 2925, 2868, 1595, 1497, 1383, 1366, 962, 746, 691 cm^{-1}; MS (EI) *m/z* (%) 242 (50) [M^+], 199 (30) [M^+–*i*Pr], 143 (100) [M^+–*i*Pr–CH_2=$C(CH_3)_2$]; Anal. calcd for $C_{18}H_{26}$ (242.40): C 89.19, H 10.81; found: C 89.16, H 10.88; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 0.88 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.77 (m, 2H, C*H*(CH$_3$)$_2$), 1.93 (d, *J* = 7.3 Hz, 2H, C*H*$_2$*i*Pr), 2.08 (d, *J* = 7.3 Hz, 2H, C*H*$_2$*i*Pr), 6.01 (d, *J* = 11.0 Hz, 1H, *H*$_c$), 6.41 (d, *J* = 15.5 Hz, 1H, *H*$_a$), 6.99 (dd, *J* = 11.0, 15.5 Hz, 1H, *H*$_b$), 7.13 (m, 1H, *H*$_3$), 7.27 (m, 2H, *H*$_2$), 7.31 (m, 2H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 27.0 (d, *C*H(CH$_3$)$_2$), 27.7 (d, *C*H(CH$_3$)$_2$), 40.1 (t, *C*H$_2$*i*Pr), 47.6 (t, *C*H$_2$*i*Pr), 126.0 (d, C$_b$), 126.3 (d, C$_1$), 127.1 (d, *C*$_3$), 127.7 (d, *C*$_c$), 128.8 (d, *C*$_2$), 130.1 (d, C$_a$), 138.2 (s, =*C*(CH$_2$)$_2$), 143.4 (s, *C*$_4$).

Julia olefination with sodium amalgam (General procedure):

Compound **2-6d-f,j-l** (0.134 mmol) was dissolved in THF (1 mL) and methanol (2 mL) under a nitrogen atmosphere. Sodium amalgam (67 mg, 0.31 mmol) was added at –20 °C. After 3 h at this temperature, the reaction mixture was diluted with diethyl ether and decanted from mercury. The organic layer was washed with brine and the aqueous layer was extracted with diethyl ether (3×25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:30) afforded olefins **2-7d-f**,**j-l**.

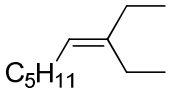
(4-Ethylhex-3-en-1-yl)benzene (2-7d):



Yield 19 mg (76%) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.91; IR ν_{max} 2964, 2929, 2874, 2856, 1496, 1456, 1261, 1082, 1029, 802, 746, 698 cm^{-1}; MS (EI) *m/z* (%) 188 (20)

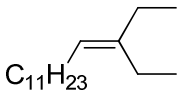
[M^+], 97 (60), 91 (40), 55 (100); HRMS (EI) *m/z* [M^+] calcd for $C_{14}H_{20}^+$: 188.1565; found: 188.1560; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 0.89 (t, *J* = 7.5 Hz, 3H, C*H*$_3$), 1.91 (2×q, *J* = 7.5 Hz, 4H, C*H*$_2$CH$_3$), 2.23 (m, 2H, C*H*$_2$CH=), 2.55 (m, 2H, C*H*$_2$Ph), 5.04 (t, *J* = 7.1 Hz, 1H, C*H*=), 7.09 (m, 3H, H_{ortho}, H_{para}), 7.18 (m, 2H, H_{meta}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1 (q, *C*H$_3$), 13.4 (q, *C*H$_3$), 23.4 (t, *C*H$_2$CH$_3$), 29.4 (t, *C*H$_2$CH$_3$), 29.9 (t, *C*H$_2$CH=), 36.8 (t, *C*H$_2$Ph), 122.0 (d, *C*H=), 125.9 (d, C_{para}), 128.4 (d, C_{ortho}), 128.7 (d, C_{meta}), 142.5 (s, C_{ipso}), 144.0 (s, =*C*(CH$_2$)$_2$).

3-Ethylnon-3-ene (2-7e):



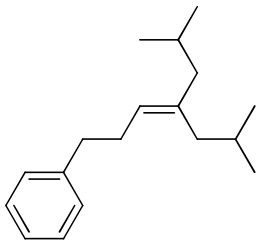
Yield 13 mg (64%) as a colorless volatile liquid. R_f (EtOAc/hexane 1:10) = 0.91; IR ν_{max} 2964, 2929, 2874, 2856, 1456, 1261 cm^{-1}; MS (EI) *m/z* (%) 154 (40) [M^+], 125 (20), 111 (20), 97 (30), 83 (40), 55 (100), 41 (40); Anal. calcd for $C_{11}H_{22}$ (154.29): C 85.63, H 14.37; found: C 85.80, H 14.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, *J* = 6.9 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 0.88 (t, *J* = 7.4 Hz, 3H, CCH$_2$C*H*$_3$), 0.91 (t, *J* = 7.4 Hz, 3H, CCH$_2$C*H*$_3$), 1.21 (m, 6H, (C*H*$_2$)$_3$), 1.83-2.02 (m, 6H, C*H*$_2$CH=, CC*H*$_2$CH$_3$), 5.00 (t, *J* = 7.1 Hz, 1H, C*H*=); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2 (q, CCH$_2$*C*H$_3$), 13.5 (q, CCH$_2$*C*H$_3$), 14.3 (q, CH$_2$CH$_2$*C*H$_3$), 22.9 (t, CH$_3$*C*H$_2$), 23.3 (t, C*C*H$_2$CH$_3$), 27.7 (t, *C*H$_2$CH=), 29.5 (t, *C*H$_2$), 30.1 (t, C*C*H$_2$CH$_3$), 31.9 (t, *C*H$_2$), 123.2 (d, *C*H=), 142.8 (s, =*C*(CH$_2$)$_2$).

3-Ethylpentadec-3-ene (2-7f):



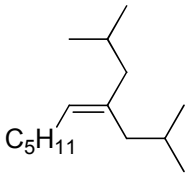
Yield 29 mg (92%) as a colorless liquid. R_f (EtOAc/hexane 1:10) = 0.95; IR ν_{max} 2963, 2925, 2873, 2854, 1664, 1464, 1378 cm^{-1}; MS (CI+) *m/z* (%) 239 (100) [M+H$^+$], 125 (20), 111 (20), 97 (40); HRMS (CI+) *m/z* [M+H$^+$] calcd for $C_{17}H_{35}^+$: 239.2739; found: 239.2738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.8 Hz, 3H, CH$_2$CH$_2$C*H*$_3$), 0.91 (t, *J* = 7.6 Hz, 3H, CCH$_2$C*H*$_3$), 0.94 (t, *J* = 7.4 Hz, 3H, CCH$_2$C*H*$_3$), 1.22 (m, 18H, (C*H*$_2$)$_9$), 1.97 (m, 6H, CC*H*$_2$CH$_3$, C*H*$_2$CH=), 5.03 (t, *J* = 7.0 Hz, 1H, C*H*=); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2 (q, CCH$_2$*C*H$_3$), 13.5 (q, CCH$_2$*C*H$_3$), 14.3 (q, CH$_2$CH$_2$*C*H$_3$), 22.9 (t, CH$_3$*C*H$_2$), 23.4 (t, C*C*H$_2$CH$_3$), 27.8 (t, *C*H$_2$CH=), 29.4 (t, *C*H$_2$), 29.6 (t, *C*H$_2$), 29.7 (t, *C*H$_2$), 29.86 (t, *C*H$_2$), 29.90 (t, 2×*C*H$_2$), 29.93 (t, *C*H$_2$), 30.5 (t, *C*H$_2$), 32.2 (t, *C*H$_2$), 123.2 (d, *C*H=), 142.8 (s, =*C*(CH$_2$)$_2$).

(4-Isobutyl-6-methylhept-3-en-1-yl)benzene (2-7j):



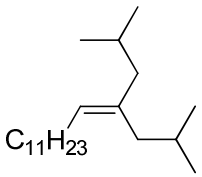
Yield 44 mg (79%) as a colorless liquid. R_f (EtOAc/hexane 1:10) = 0.93; IR ν_{max} 2953, 2926, 2868, 1496, 1462, 1383, 1365, 909, 735, 698 cm^{-1}; MS (EI) *m/z* (%) 244 (10) [M^+], 97 (100), 91 (40), 55 (90); HRMS (EI) *m/z* [M^+] calcd for $C_{18}H_{28}^+$: 244.2191; found: 244.2192; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 0.79 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.63 (m, 2H, C*H*(CH$_3$)$_2$), 1.75 (d, *J* = 7.2 Hz, 2H, C*H*$_2$*i*Pr), 1.79 (d, *J* = 7.3 Hz, 2H, C*H*$_2$*i*Pr), 2.27 (m, 2H, C*H*$_2$CH=), 2.57 (m, 2H, C*H*$_2$Ph), 5.13 (t, *J* = 7.1 Hz, 1H, C*H*=), 7.12 (m, 3H, *H*$_{ortho}$, *H*$_{para}$), 7.21 (m, 2H, *H*$_{meta}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8 (q, CH(*C*H$_3$)$_2$), 22.9 (q, CH(*C*H$_3$)$_2$), 26.4 (d, *C*H(CH$_3$)$_2$), 30.2 (t, *C*H$_2$CH=), 36.8 (t, *C*H$_2$Ph), 39.1 (t, *C*H$_2$*i*Pr), 47.1 (t, *C*H$_2$*i*Pr), 125.9 (d, *C*$_{para}$), 126.6 (d, *C*H=), 128.4 (d, *C*$_{ortho}$), 128.8 (d, *C*$_{meta}$), 138.2 (s, =*C*(CH$_2$)$_2$), 142.8 (s, *C*$_{ipso}$).

4-Isobutyl-2-methyldec-4-ene (2-7k):



Yield 25 mg (89%) as a colorless liquid. R_f (EtOAc/hexane 1:10) = 0.96; IR ν_{max} 2954, 2926, 2868, 1465, 1366, 1166, 1135 cm^{-1}; MS (EI) *m/z* (%) 210 (50) [M^+], 154 (30), 153 (30), 111 (40), 97 (100), 83 (95), 69 (90), 55 (60), 43 (30), 41 (30); HRMS (EI) *m/z* [M^+] calcd for $C_{15}H_{30}^+$: 210.2348; found: 210.2345; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (m, 15H, C*H*$_3$), 1.18 (m, 6H, (C*H*$_2$)$_3$), 1.67 (m, 2H, C*H*(CH$_3$)$_2$), 1.77 (d, *J* = 7.1 Hz, 2H, C*H*$_2$*i*Pr), 1.82 (d, *J* = 7.1 Hz, 2H, C*H*$_2$*i*Pr), 1.95 (m, 2H, C*H*$_2$CH=), 5.10 (t, *J* = 7.2 Hz, 1H, C*H*=); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q, CH$_2$*C*H$_3$), 22.8 (q, CH(*C*H$_3$)$_2$), 22.86 (t, CH$_3$*C*H$_2$), 22.89 (q, CH(*C*H$_3$)$_2$), 26.4 (d, *C*H(CH$_3$)$_2$), 27.0 (d, *C*H(CH$_3$)$_2$), 28.1 (t, *C*H$_2$CH=), 30.1 (t, *C*H$_2$), 31.9 (t, *C*H$_2$), 39.1 (t, *C*H$_2$*i*Pr), 47.1 (t, *C*H$_2$*i*Pr), 127.6 (d, *C*H=), 137.3 (s, =*C*(CH$_2$)$_2$).

4-Isobutyl-2-methylhexadec-4-ene (2-7l):

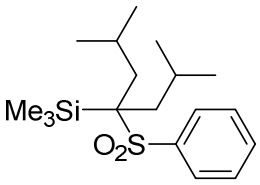


Yield 25 mg (64%) as a colorless liquid. R_f (EtOAc/hexane 1:10) = 0.94; IR ν_{max} 2953, 2923, 2854, 1464, 1382, 1365 cm^{-1}; MS (EI) *m/z* (%) 294 (40) [M^+], 238 (40), 125 (80), 111 (40), 97 (100), 83 (95), 69 (90), 55 (80), 43 (40), 41 (40); HRMS (EI) *m/z* [M^+] calcd for $C_{21}H_{42}^+$: 294.3287; found: 294.3280; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (m, 15H, C*H*$_3$), 1.18 (m, 18H, (C*H*$_2$)$_9$), 1.63 (m, 2H, C*H*(CH$_3$)$_2$), 1.73 (d, *J* = 7.2 Hz, 2H, C*H*$_2$*i*Pr), 1.78 (d, *J* = 7.2 Hz, 2H, C*H*$_2$*i*Pr), 1.90 (m, 2H, C*H*$_2$CH=), 5.06 (t, *J* = 7.2 Hz, 1H, C*H*=); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (q, CH$_2$*C*H$_3$), 22.7 (q, CH(*C*H$_3$)$_2$), 22.78 (q, CH(*C*H$_3$)$_2$), 22.82 (t, CH$_3$*C*H$_2$), 26.3 (d, *C*H(CH$_3$)$_2$), 26.9 (d, *C*H(CH$_3$)$_2$), 28.0 (t, *C*H$_2$CH=), 29.49 (t, *C*H$_2$), 29.51 (t, *C*H$_2$), 29.7 (t, *C*H$_2$), 29.79 (t, 2×*C*H$_2$), 29.80 (t, *C*H$_2$), 30.3 (t, *C*H$_2$), 32.1 (t, *C*H$_2$), 38.9 (t, *C*H$_2$*i*Pr), 46.9 (t, *C*H$_2$*i*Pr), 127.5 (d, *C*H=), 137.1 (s, =*C*(CH$_2$)$_2$).

α-Substituted phenyl sulfones 2-8a-c (**General procedure):**

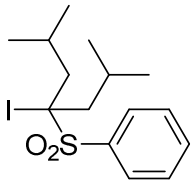
*n*BuLi (0.34 mL, 0.55 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (135 mg, 0.5 mmol) and TMEDA (0.14 mL, 0.88 mmol) in dry THF (5 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the reaction mixture was warmed to 0 °C during 1 h, followed by dropwise addition of trimethylsilyl chloride, iodine or bromine (0.60 mmol) in THF (2 mL) at –78 °C. The reaction mixture was warmed to –20 °C, stirred at this temperature until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **2-8a-c**.

2,6-Dimethyl-4-(trimethylsilyl)hept-4-yl phenyl sulfone (2-8a):



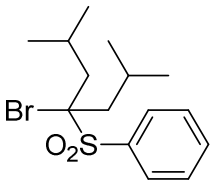
Yield 15 mg (ca 10% in a mixture) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.55; MS (ESI+) *m/z* (%): 363 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{18}H_{32}O_2SSiNa^+$: 363.1785; found: 363.1784.

4-Iodo-2,6-dimethylhept-4-yl phenyl sulfone (2-8b):



Yield 136 mg (69%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.51; IR ν_{max} 3061, 2960, 2930, 2870, 1617, 1584, 1467, 1446, 1307, 1147, 1080, 1024, 754 cm^{-1}; MS (ESI+) *m/z* (%) 417 (100) [M+Na^+], 289 (30) [M–HI+Na^+], 165 (30) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{15}H_{23}IO_2S$ (394.31): C 45.69, H 5.88, S 8.13; found: C 45.55, H 5.81, S 8.43; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.7 Hz, 6H, CH(C*H*$_3$)$_2$), 1.01 (d, *J* = 6.6 Hz, 6H, CH(C*H*$_3$)$_2$), 1.95 (d, *J* = 4.6 Hz, 4H, C*H*$_2$*i*Pr), 2.03 (m, 2H, C*H*(CH$_3$)$_2$), 7.52 (m, 2H, H_{meta}), 7.78 (m, 1H, H_{para}), 7.93 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6 (q, CH(*C*H$_3$)$_2$), 24.7 (q, CH(*C*H$_3$)$_2$), 28.3 (d, *C*H(CH$_3$)$_2$), 47.8 (t, *C*H$_2$*i*Pr), 70.9 (s, SO_2C), 128.5 (d, C_{meta}), 132.0 (d, C_{ortho}), 134.1 (d, C_{para}), 135.1 (s, C_{ipso}).

4-Bromo-2,6-dimethylhept-4-yl phenyl sulfone (2-8c):



Yield 149 mg (86%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.50; IR ν_{max} 3065, 2960, 2928, 2870, 1585, 1468, 1447, 1388, 1320, 1309, 1151, 1081, 1025, 870, 731 cm^{-1}; MS (ESI+) *m/z* (%) 371/369 (100/100) [M+Na^+], 289 (50) [M–HBr+Na^+], 165 (100) [$PhSO_2H+Na^+$]; Anal. calcd for $C_{15}H_{23}BrO_2S$ (347.31): C 51.87, H 6.67, S 9.23, Br 23.01; found: C 51.80, H 6.71, S 9.32, Br 23.30; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 1.01 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$), 2.01 (dd, *J* = 4.7, 14.2 Hz, 2H,

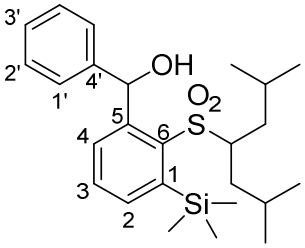
C*H*H*i*Pr), 2.08 (m, 2H, C*H*(CH_3)$_2$), 2.14 (dd, *J* = 4.5, 14.2 Hz, 2H, CH*Hi*Pr), 7.54 (m, 2H, H_{meta}), 7.65 (m, 1H, H_{para}), 7.98 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8 (q, CH(*C*H_3)$_2$), 25.2 (q, CH(*C*H_3)$_2$), 26.4 (d, *C*H(CH_3)$_2$), 46.0 (t, *C*H_2*i*Pr), 85.4 (s, SO_2*C*), 128.8 (d, C_{meta}), 132.0 (d, C_{ortho}), 134.4 (d, C_{para}), 135.5 (s, C_{ipso}).

***ortho,ortho*'-Disubstituted phenyl sulfones 2-9a-h and 1-31 (General procedure):**

Table 2.7: *n*BuLi (0.21 mL, 0.34 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-26** (100 mg, 0.29 mmol) and TMEDA (0.1 mL, 0.67 mmol) in dry THF (3 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, the aldehyde, ketone, trimethylsilyl chloride or iodine (0.38 mmol) in THF (2.5 mL) was added dropwise at –78 °C. The reaction mixture was stirred until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:40) gave sulfones **2-9a-h**, **1-31**.

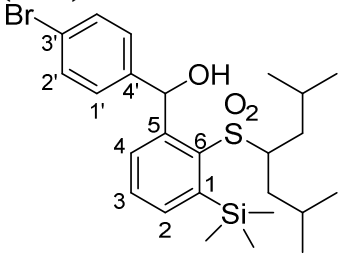
Table 2.8: *n*BuLi (0.75 mL, 1.2 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (268 mg, 1 mmol) and TMEDA (0.3 mL, 1.95 mmol) in dry THF (5 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, trimethylsilyl chloride (1.3 mmol) in THF (2.5 mL) was added dropwise at –78 °C. The reaction mixture was stirred for 10 min and warmed to 0 °C for 15 min. *n*BuLi (0.75 mL, 1.2 mmol, 1.6*M* in hexane) and TMEDA (0.3 mL, 1.95 mmol) was added dropwise at –78 °C. After stirring for 10 min, the aldehyde, trimethylsilyl chloride or iodine (1.3 mmol) was added at –78 °C. The reaction mixture was stirred at this temperature for 2 h until complete as indicated by TLC, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave sulfones **2-9a,c-e,h** and **1-31** (for yields see Table 2.8).

(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)(phenyl)methanol (2-9a):



Yield 106 mg (82%, Table 2.7) as colorless crystals, m.p. 138-139 °C. R_f (EtOAc/hexane 1:10) = 0.24; IR ν_{max} 3479, 2958, 2900, 2870, 1468, 1450, 1295, 1249, 1149, 1134, 1039, 1024, 876, 844, 758, 702 cm^{-1}; MS (ESI+) *m/z* (%) 469 (100) [M+Na^+], 303 (40) [M+H^+–OH–CH(*i*Bu)$_2$]; Anal. calcd for $C_{25}H_{38}O_3SSi$ (446.72): C 67.22, H 8.57, S 7.18; found: C 67.03, H 8.77, S 6.97; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 0.38 (s, 9H, Si(C*H*$_3$)$_3$), 0.62 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.74 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.91 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.98 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.30 (m, 3H, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.45 (m, 1H, CH*Hi*Pr), 1.90 (m, 1H, C*H*(CH$_3$)$_2$), 1.98 (m, 1H, CH*Hi*Pr), 3.54 (m, 1H, SO$_2$C*H*), 5.83 (d, *J* = 5.6 Hz, 1H, O*H*), 6.85 (d, *J* = 5.6 Hz, 1H, C*H*OH), 7.19 (m, 1H, *H*$_{3'}$), 7.30 (m, 2H, *H*$_{2'}$), 7.41 (m, 2H, *H*$_{1'}$), 7.59 (t, *J* = 7.4 Hz, 1H, *H*$_3$), 7.67 (dd, *J* = 1.4, 7.4 Hz, 1H, *H*$_4$), 7.73 (dd, *J* = 1.4, 7.4 Hz, 1H, *H*$_2$); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 2.43 (q, Si(*C*H$_3$)$_3$), 21.1 (q, CH(*C*H$_3$)$_2$), 21.8 (q, CH(*C*H$_3$)$_2$), 22.1 (q, CH(*C*H$_3$)$_2$), 22.3 (q, CH(*C*H$_3$)$_2$), 24.2 (d, *C*H(CH$_3$)$_2$), 25.1 (d, *C*H(CH$_3$)$_2$), 36.5 (t, *C*H$_2$*i*Pr), 39.3 (t, *C*H$_2$*i*Pr), 61.3 (d, SO$_2$*C*H), 68.8 (d, *C*HOH), 125.6 (d, *C*$_{1'}$), 126.1 (d, *C*$_{3'}$), 127.4 (d, *C*$_{2'}$), 131.6 (d, *C*$_3$), 131.8 (d, *C*$_4$), 134.9 (d, *C*$_2$), 139.7 (s, *C*$_6$), 140.9 (s, *C*$_1$), 144.7 (s, *C*$_{4'}$), 145.2 (s, *C*$_5$).

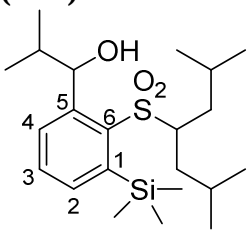
(4-Bromophenyl)(2-((2,6-dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)methanol (2-9b):



Yield 134 mg (88%, Table 2.7) as colorless crystals, m.p. 138-139 °C. R_f (EtOAc/hexane 1:10) = 0.42; IR ν_{max} 3464, 2958, 2870, 1487, 1468, 1388, 1294, 1248, 1148, 1134, 1101, 1038, 1010, 875, 844, 803, 759, 676 cm^{-1}; MS (ESI+) *m/z* (%) 544/542 (100/100) [M^++H_2O], 509/507 (40/40) [M–H_2O+H^+]; Anal. calcd for $C_{25}H_{37}BrO_3SSi$ (525.61): C 57.13, H 7.10, S 6.10, Si 5.34, Br 15.20; found: C 57.26, H 7.16, S 6.16, Si 5.64, Br 14.98; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 0.32 (s, 9H, Si(C*H*$_3$)$_3$), 0.55 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.67

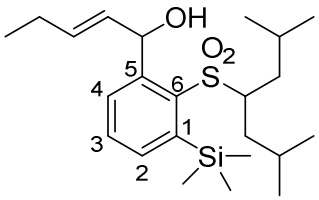
(d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.86 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.93 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 1.16 (m, 1H, C*H*H*i*Pr), 1.25 (m, 2H, CH*Hi*Pr, C*H*(CH$_3$)$_2$), 1.41 (m, 1H, C*H*H*i*Pr), 1.85 (m, 1H, C*H*(CH$_3$)$_2$), 1.93 (m, 1H, CH*Hi*Pr), 3.45 (m, 1H, SO$_2$C*H*), 5.98 (broad s, 1H, O*H*), 6.75 (s, 1H, C*H*OH), 7.30 (d, *J* = 8.2 Hz, 2H, *H*$_{1'}$), 7.42 (d, *J* = 8.2 Hz, 2H, *H*$_{2'}$), 7.55 (m, 1H, *H*$_3$), 7.58 (m, 1H, *H*$_4$), 7.68 (m, 1H, *H*$_2$); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 2.6 (q, Si(*C*H$_3$)$_3$), 21.3 (q, CH(*C*H$_3$)$_2$), 22.0 (q, CH(*C*H$_3$)$_2$), 22.3 (q, CH(*C*H$_3$)$_2$), 22.5 (q, CH(*C*H$_3$)$_2$), 24.4 (d, *C*H(CH$_3$)$_2$), 25.3 (d, *C*H(CH$_3$)$_2$), 36.7 (t, *C*H$_2$*i*Pr), 39.5 (t, *C*H$_2$*i*Pr), 61.6 (d, SO$_2$*C*H), 68.6 (d, *C*HOH), 119.6 (s, *C*$_{3'}$), 128.0 (d, *C*$_{1'}$), 130.1 (d, *C*$_{2'}$), 131.8 (d, *C*$_3$ or *C*$_4$), 132.0 (d, *C*$_3$ or *C*$_4$), 135.3 (d, *C*$_2$), 139.8 (s, *C*$_6$), 141.3 (s, *C*$_1$), 144.4 (s, *C*$_{4'}$), 144.8 (s, *C*$_5$).

1-(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)-2-methylpropan-1-ol (2-9c):



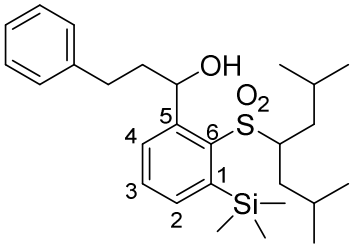
Yield 97 mg (81%, Table 2.7) as a colorless solid, m.p. 133-135 °C. R$_f$ (EtOAc/hexane 1:10) = 0.31; IR ν_{max} 3487, 2595, 2870, 1469, 1388, 1307, 1249, 1150, 1136, 1100, 1034, 940, 873, 844, 761, 677, 605 cm^{-1}; MS (ESI+) *m/z* (%) 847 (10) [2M+Na$^+$], 435 (100) [M+Na$^+$], 395 (90) [M–H$_2$O+H$^+$]; Anal. calcd for C$_{22}$H$_{40}$O$_3$SSi (412.70): C 64.03, H 9.77, S 7.77; found: C 64.15, H 9.64, S 7.55; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 0.31 (s, 9H, Si(C*H*$_3$)$_3$), 0.50 (d, *J* = 6.4 Hz, 3H, CH$_2$CH(C*H*$_3$)$_2$), 0.63 (d, *J* = 6.5 Hz, 3H, OHCHCH(C*H*$_3$)$_2$), 0.65 (d, *J* = 6.5 Hz, 3H, CH$_2$CH(C*H*$_3$)$_2$), 0.89 (d, *J* = 6.4 Hz, 3H, CH$_2$CH(C*H*$_3$)$_2$), 0.94 (d, *J* = 6.5 Hz, 6H, OHCHCH(C*H*$_3$)$_2$, CH$_2$CH(C*H*$_3$)$_2$), 1.07 (m, 1H, C*H*H*i*Pr), 1.18 (m, 2H, C*H*H*i*Pr, CH$_2$C*H*(CH$_3$)$_2$), 1.31 (m, 1H, C*H*H*i*Pr), 1.90 (m, 3H, CH*Hi*Pr, CH$_2$C*H*(CH$_3$)$_2$, OHCHC*H*(CH$_3$)$_2$), 3.34 (m, 1H, SO$_2$C*H*), 4.88 (d, *J* = 7.1 Hz, 1H, O*H*), 5.16 (t, *J* = 7.1 Hz, 1H, C*H*OH), 7.60 (t, *J* = 7.5 Hz, 1H, *H*$_3$), 7.68 (dd, *J* = 1.4, 7.5 Hz, 1H, *H*$_2$), 7.80 (dd, *J* = 1.4, 7.5 Hz, 1H, *H*$_4$); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 2.4 (q, Si(*C*H$_3$)$_3$), 17.7 (q, OHCHCH(*C*H$_3$)$_2$), 18.8 (q, OHCHCH(*C*H$_3$)$_2$), 21.1 (q, CH$_2$CH(*C*H$_3$)$_2$), 21.88 (q, CH$_2$CH(*C*H$_3$)$_2$), 21.93 (q, CH$_2$CH(*C*H$_3$)$_2$), 22.3 (q, CH$_2$CH(*C*H$_3$)$_2$), 24.1 (d, CH$_2$*C*H(CH$_3$)$_2$), 25.2 (d, CH$_2$*C*H(CH$_3$)$_2$), 35.3 (d, OHCH*C*H(*C*H$_3$)$_2$), 36.5 (t, *C*H$_2$*i*Pr), 39.7 (t, *C*H$_2$*i*Pr), 60.8 (d, SO$_2$*C*H), 73.1 (d, *C*HOH), 126.9 (d, *C*$_4$), 131.3 (d, *C*$_3$), 134.5 (d, *C*$_2$), 139.9 (s, *C*$_6$), 141.0 (s, *C*$_1$), 145.8 (s, *C*$_5$).

(*E*)-1-(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)pent-2-en-1-ol (2-9d):



Yield 98 mg (80%, Table 2.7) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.82; IR ν_{max} 3487, 2960, 2871, 1467, 1326, 1295, 1248, 1137, 1101, 969, 862, 844, 760, 673, 558 cm^{-1}; MS (ESI+) *m/z* (%) 447 (100) [M+Na^+], 303 (40) [M+Na^+–OH–CH(*i*Bu)$_2$]; Anal. calcd for $C_{23}H_{40}O_3SSi$ (424.72): C 65.04, H 9.49, S 7.55; found: C 65.26, H 9.55, S 7.24; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 0.31 (s, 9H, Si(C*H*$_3$)$_3$), 0.58 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.71 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.81 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.89 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.91 (t, *J* = 6.3 Hz, 3H, CH$_2$C*H*$_3$), 1.25 (m, 2H, C*H*H*i*Pr), 1.34 (m, 2H, CH*Hi*Pr, C*H*(CH$_3$)$_2$), 1.75 (m, 2H, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.98 (m, 2H, C*H*$_2$CH$_3$), 3.36 (m, 1H, SO$_2$C*H*), 5.20 (broad s, 1H, O*H*), 5.62 (dd, *J* = 5.3, 15.4 Hz, 1H, CH$_2$CH=C*H*), 5.73 (dt, *J* = 6.2, 15.4 Hz, 1H, CH$_2$C*H*=CH), 6.05 (d, *J* = 5.1 Hz, 1H, C*H*OH), 7.60 (t, *J* = 7.6 Hz, 1H, *H*$_3$), 7.69 (dd, *J* = 1.4, 7.6 Hz, 1H, *H*$_2$), 7.77 (dd, *J* = 1.4, 7.6 Hz, 1H, *H*$_4$); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 2.6 (q, Si(*C*H$_3$)$_3$), 12.7 (q, CH$_2$*C*H$_3$), 21.4 (q, CH(*C*H$_3$)$_2$), 21.9 (q, CH(*C*H$_3$)$_2$), 22.3 (q, CH(*C*H$_3$)$_2$), 22.4 (q, CH(*C*H$_3$)$_2$), 24.1 (t, C*H*$_2$CH$_3$), 24.5 (d, *C*H(CH$_3$)$_2$), 25.1 (d, *C*H(CH$_3$)$_2$), 37.2 (t, *C*H$_2$*i*Pr), 39.0 (t, *C*H$_2$*i*Pr), 61.2 (d, SO$_2$*C*H), 68.1 (d, *C*HOH), 131.1 (d, *C*$_4$), 131.6 (d, CH$_2$*C*H=CH), 131.8 (d, *C*$_3$), 132.3 (d, CH$_2$CH=*C*H), 135.0 (d, *C*$_2$), 139.5 (s, *C*$_6$), 141.0 (s, *C*$_1$), 145.5 (s, *C*$_5$).

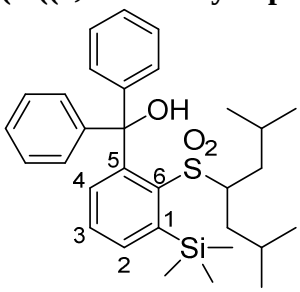
1-(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)-3-phenylpropan-1-ol (2-9e):



Yield 102 mg (74%, Table 2.7) as a colorless solid, m.p. 117-118 °C. R_f (EtOAc/hexane 1:5) = 0.15; IR ν_{max} 3489, 2981, 2904, 2887, 1542, 1523, 1396, 1388, 1381, 1150, 954, 669 cm^{-1}; MS (ESI+) *m/z* (%) 497 (100) [M+Na^+], 331 (30) [M+H^+–OH–CH(*i*Bu)$_2$]; Anal. calcd for $C_{27}H_{42}O_3SSi$ (474.77): C 68.30, H 8.92, S 6.75; found: C 67.99, H 8.80, S 6.93; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ 0.32 (s, 9H, Si(C*H*$_3$)$_3$), 0.52 (d, *J* = 6.2 Hz, 3H,

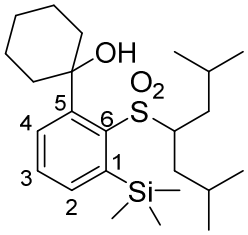
CH(C*H*$_3$)$_2$), 0.66 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 0.91 (d, *J* = 6.4 Hz, 3H, CH(C*H*$_3$)$_2$), 1.20 (m, 3H, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.32 (m, 1H, CH*Hi*Pr), 1.81 (m, 2H, CH*Hi*Pr, C*H*(CH$_3$)$_2$), 1.90 (m, 2H, C*H*$_2$CH$_2$Ph), 2.51 (m, 1H, C*H*HPh), 2.83 (m, 1H, CH*H*Ph), 3.30 (m, 1H, SO$_2$C*H*), 5.19 (d, *J* = 5.4 Hz, 1H, O*H*), 5.49 (m, 1H, C*H*OH), 7.09 (m, 3H, *H$_{ortho}$*, *H$_{para}$*), 7.18 (m, 2H, *H$_{meta}$*), 7.61 (t, *J* = 7.6 Hz, 1H, *H$_3$*), 7.69 (m, 1H, *H$_2$*), 7.89 (m, 1H, *H$_4$*); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 3.1 (q, Si(*C*H$_3$)$_3$), 21.8 (q, CH(*C*H$_3$)$_2$), 22.5 (q, CH(*C*H$_3$)$_2$), 22.7 (q, CH(*C*H$_3$)$_2$), 22.9 (q, CH(*C*H$_3$)$_2$), 24.9 (d, *C*H(CH$_3$)$_2$), 25.7 (d, *C*H(CH$_3$)$_2$), 32.3 (t, *C*H$_2$CH$_2$Ph), 37.3 (t, *C*H$_2$*i*Pr), 39.8 (t, *C*H$_2$*i*Pr), 42.0 (t, *C*H$_2$Ph), 61.4 (d, SO$_2$*C*H), 68.9 (d, *C*HOH), 125.7 (d, *C$_{para}$*), 128.3 (d, *C$_{ortho}$*, *C$_{meta}$*), 130.2 (d, *C$_4$*), 132.4 (d, *C$_3$*), 135.5 (d, *C$_2$*), 139.7 (s, *C$_6$*), 141.7 (s, *C$_1$*), 142.0 (s, *C$_{ipso}$*), 147.5 (s, *C$_5$*).

(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3(trimethylsilyl)phenyl) diphenylmethanol (2-9f):



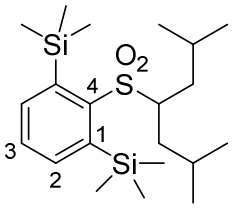
Yield 63 mg (32%, Table 2.7) as a colorless oil. R$_f$ (EtOAc/hexane 1:5) = 0.73; IR ν_{max} 3405, 2957, 2932, 2871, 1447, 1289, 1247, 1128, 1115, 848, 769, 759, 700, 668 cm^{-1}; MS (ESI+) *m/z* (%) 545 (100) [M+Na$^+$]; Anal. calcd for C$_{31}$H$_{42}$O$_3$SSi (522.81): C 71.22, H 8.10, S 6.13; found: C 71.14, H 8.35, S 5.72; HRMS (ESI+) *m/z* [M+Na$^+$] calcd for C$_{31}$H$_{42}$O$_3$SSiNa$^+$: 545.2516; found: 545.2515; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.39 (s, 9H, Si(C*H*$_3$)$_3$), 0.54 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.75 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.88 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.07 (m, 2H, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.18 (m, 1H, CH*Hi*Pr), 1.29 (m, 1H, C*H*H*i*Pr), 1.76 (m, 1H, C*H*(CH$_3$)$_2$), 1.89 (m, 1H, CH*Hi*Pr), 3.96 (m, 1H, SO$_2$C*H*), 6.44 (s, 1H, O*H*), 6.80 (m, 2H, *H$_{ar}$*), 6.86 (m, 1H, *H$_4$*), 7.11 (m, 2H, *H$_{ar}$*), 7.15-7.32 (m, 7H, *H$_3$*, *H$_{ar}$*), 7.80 (dd, *J* = 1.2, 7.5 Hz, 1H, *H$_2$*); ^{13}C NMR (100 MHz, CDCl$_3$) δ 4.1 (q, Si(*C*H$_3$)$_3$), 21.9 (q, CH(*C*H$_3$)$_2$), 22.7 (q, CH(*C*H$_3$)$_2$), 23.17 (q, CH(*C*H$_3$)$_2$), 23.23 (q, CH(*C*H$_3$)$_2$), 25.5 (d, *C*H(CH$_3$)$_2$), 26.1 (d, *C*H(CH$_3$)$_2$), 37.5 (t, *C*H$_2$*i*Pr), 39.8 (t, *C*H$_2$*i*Pr), 64.1 (d, SO$_2$*C*H), 84.2 (s, *C*OH), 127.6 (d, 2×*C$_{ar}$*), 127.7 (d, *C$_{ar}$*), 128.1 (d, *C$_{ar}$*), 128.7 (d, 2×*C$_{ar}$*), 130.7 (d, *C$_3$*), 135.5 (d, *C$_4$*), 136.6 (d, *C$_2$*), 140.7 (s, *C$_6$*), 147.4 (s, *C$_{ipso}$*), 147.8 (s, *C$_1$*), 148.0 (s, *C$_{ipso}$*), 149.1 (s, *C$_5$*).

1-(2-((2,6-Dimethylhept-4-yl)sulfonyl)-3-(trimethylsilyl)phenyl)cyclohexanol (2-9g):



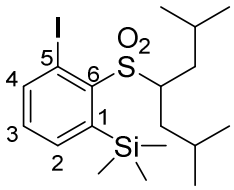
Yield 24 mg (20%, Table 2.7) as colorless crystals, m.p. 125-126 °C. R_f (EtOAc/hexane 1:5) = 0.91; IR ν_{max} 3478, 2980, 2971, 1463, 1295, 1249, 1140, 1135, 1036, 1024, 873, 844, 756 cm^{-1}; MS (ESI+) *m/z* (%) 461 (100) [$M+Na^+$], 421 (30) [$M–H_2O+H^+$]; Anal. calcd for $C_{24}H_{42}O_3SSi$ (438.74): C 65.70, H 9.65, S 7.31; found: C 65.59, H 9.65, S 7.02; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37 (s, 9H, Si(C*H*$_3$)$_3$), 0.54 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.68 (d, *J* = 6.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.96 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.99 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.05-1.30 (m, 4H, C*H*$_2$, C*H*H*i*Pr, C*H*(CH$_3$)$_2$), 1.36 (m, 1H, C*H*H*i*Pr), 1.57 (m, 3H, C*H*$_2$), 1.76 (m, 2H, C*H*$_2$, CH*Hi*Pr), 1.95 (m, 5H, C*H*(CH$_3$)$_2$, C*H*$_2$COH), 2.13 (m, 1H, CH*Hi*Pr), 4.41 (m, 1H, SO$_2$C*H*), 4.66 (s, 1H, O*H*), 7.47 (m, 1H, *H*$_3$), 7.58 (m, 1H, *H*$_4$), 7.77 (m, 1H, *H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.4 (q, Si(*C*H$_3$)$_3$), 21.9 (q, CH(*C*H$_3$)$_2$), 22.0 (t, *C*H$_2$CH$_2$), 22.1 (t, *C*H$_2$CH$_2$), 22.8 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 23.2 (q, CH(*C*H$_3$)$_2$), 25.5 (d, *C*H(CH$_3$)$_2$), 25.7 (t, *C*H$_2$CH$_2$), 26.2 (d, *C*H(CH$_3$)$_2$), 37.6 (t, *C*H$_2$*i*Pr), 38.5 (t, *C*H$_2$*i*Pr), 40.3 (t, COH*C*H$_2$), 43.0 (t, COH*C*H$_2$), 63.6 (d, SO$_2$C*H*), 76.1 (s, COH), 130.8 (d, *C*$_4$), 131.5 (d, *C*$_3$), 135.7 (d, *C*$_2$), 140.7 (s, *C*$_6$), 146.1 (s, *C*$_1$), 151.7 (s, *C*$_5$).

2,6-Dimethylhept-4-yl 2,6-bis(trimethylsilyl)phenyl sulfone (1-31):



Yield 104 mg (87%, Table 2.7) as a colorless oil. R_f (EtOAc/hexane 1:10) = 0.82; IR ν_{max} 2958, 2900, 1469, 1310, 1247, 1155, 1129, 844, 757, 624 cm^{-1}; MS (ESI+) *m/z* (%) 435 (100) [$M+Na^+$]; Anal. calcd for $C_{21}H_{40}O_2SSi_2$ (412.78): C 61.10, H 9.77, S 7.77; found: C 60.79, H 9.95, S 7.57; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42 (s, 18H, Si(C*H*$_3$)$_3$), 0.59 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 0.80 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$), 1.21 (m, 2H, C*H*H*i*Pr), 1.50 (m, 2H, C*H*(CH$_3$)$_2$), 1.58 (m, 2H, CH*Hi*Pr), 2.95 (m, 1H, SO$_2$C*H*), 7.52 (t, *J* = 7.5 Hz, 1H, *H*$_3$), 7.88 (d, *J* = 7.5 Hz, 2H, *H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.9 (q, Si(*C*H$_3$)$_3$), 22.0 (q, CH(*C*H$_3$)$_2$), 23.3 (q, CH(*C*H$_3$)$_2$), 25.5 (d, *C*H(CH$_3$)$_2$), 38.1 (t, *C*H$_2$*i*Pr), 61.6 (d, SO$_2$*C*H), 131.0 (d, *C*$_3$), 138.0 (d, *C*$_2$), 143.2 (s, *C*$_1$, *C*$_4$).

2,6-Dimethylhept-4-yl 2-iodo-6-(trimethylsilyl)phenyl sulfone (2-9h):

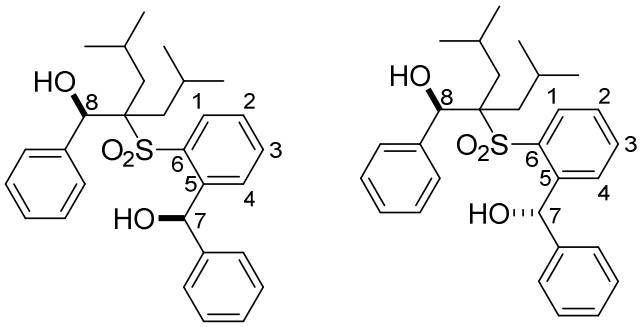


Yield 92 mg (68%, Table 2.7) as colorless crystals, m.p. 99-100 °C. R_f (EtOAc/hexane 1:5) = 0.70; IR ν_{max} 2980, 2960, 2905, 1541, 1508, 1457, 1314, 1150, 848, 750 cm^{-1}; MS (ESI+) *m/z* (%) 484 (100) $[M^+ + H_2O]$; Anal. calcd for $C_{18}H_{31}IO_2SSi$ (466.49): C 46.34, H 6.70, S 6.87, I 27.20; found: C 46.56, H 6.64, S 6.59, I 26.99; ^{1}H NMR (400 MHz, DMSO, 80 °C) δ –0.16 (s, 9H, Si(C*H*$_3$)$_3$), 0.27 (broad s, 6H, CH(C*H*$_3$)$_2$), 0.35 (broad s, 6H, CH(C*H*$_3$)$_2$), 0.83 (m, 4H, C*H*$_2$*i*Pr), 1.11 (broad s, 2H, C*H*(CH$_3$)$_2$), 3.58 (m, 1H, SO$_2$C*H*), 6.79 (t, *J* = 7.6 Hz, 1H, *H*$_3$), 7.36 (dd, *J* = 7.6, 1.2 Hz, 1H, *H*$_4$), 7.77 (dd, *J* = 7.9, 1.2 Hz, 1H, *H*$_2$); ^{13}C NMR (100 MHz, DMSO, 80 °C) δ 2.4 (q, Si(*C*H$_3$)$_3$), 21.5 (q, CH(*C*H$_3$)$_2$), 22.2 (q, CH(*C*H$_3$)$_2$), 24.6 (d, *C*H(CH$_3$)$_2$), ~39.1 (t, *C*H$_2$*i*Pr, overlap with DMSO), 56.8 (d, SO$_2$*C*H), 96.2 (s, *C*$_5$), 132.6 (d, *C*$_3$), 136.1 (d, *C*$_4$), 144.0 (s, *C*$_6$), 144.3 (d, *C*$_2$), 144.9 (s, *C*$_1$).

***ortho*,α-Bis(1-hydroxyalkyl)-2,6-dimethylhept-4-yl phenyl sulfones 2-10a-d (General procedure):**

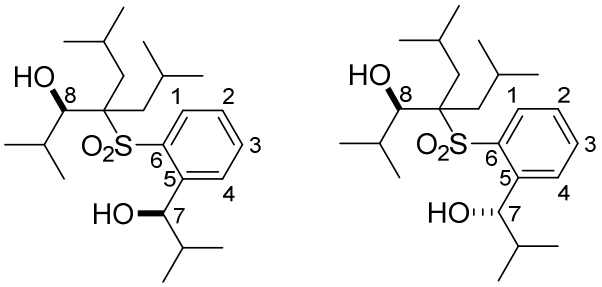
*n*BuLi (0.34 mL, 0.55 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (67 mg, 0.25 mmol) and TMEDA (0.15 mL, 0.98 mmol) in dry THF (2 mL) at –40 °C under a nitrogen atmosphere. After stirring for 30 min, the aldehyde (0.28 mmol) was added in THF (0.5 mL) at –78 °C. The reaction mixture was stirred at this temperature for 3 h, quenched with water and warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20 gradient to 1:5) gave sulfones **2-10a-d**.

4-(1-Hydroxybenzyl)-2,6-dimethylhept-4-yl 2-(1-hydroxybenzyl)phenyl sulfone (2-10a):



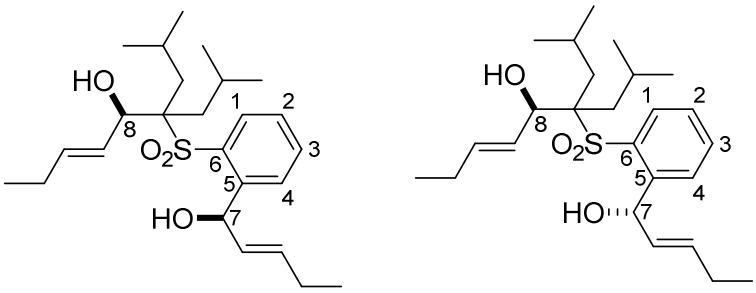
Yield 16 mg (14%) as a 10:1 mixture of unassigned diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.26; IR ν_{max} 3511, 2972, 2935, 2879, 1451, 1395, 1285, 1194, 1139, 1112, 1064, 1022, 912, 853, 821, 769, 735, 706 cm^{-1}; MS (ESI+) *m/z* (%) 503 (80) [M+Na^+], 271 (100) [PhCH(OH)$C_6H_4SO_2$H+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{29}H_{36}O_4SNa^+$: 503.2227; found: 503.2227; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer: δ 0.81 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 0.82 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.01 (dd, *J* = 6.6, 14.4 Hz, 1H, C*H*H*i*Pr), 1.06 (dd, *J* = 6.5, 14.4 Hz, 1H, CH*Hi*Pr), 1.11 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 1.18 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.48 (m, 1H, C*H*(CH$_3$)$_2$), 2.02 (dd, *J* = 5.5, 15.6 Hz, 1H, C*H*H*i*Pr), 2.15 (dd, *J* = 4.4, 15.6 Hz, 1H, CH*Hi*Pr), 2.51 (m, 1H, C*H*(CH$_3$)$_2$), 3.46 (broad s, 1H, C_7HO*H*), 3.78 (broad s, 1H, C_8HO*H*), 5.41 (s, 1H, C*H*$_8$OH), 7.01 (s, 1H, C*H*$_7$OH), 7.16-7.52 (m, 12H, *H*$_{ar}$), 7.56 (m, 1H, *H*$_4$), 8.00 (m, 1H, *H*$_1$); detectable signals of minor diastereomer: δ 5.63 (s, 1H, C_8*H*OH), 8.04 (m, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ 23.7 (d, *C*H(CH$_3$)$_2$), 24.1 (d, *C*H(CH$_3$)$_2$), 25.5 (q, CH(*C*H$_3$)$_2$), 26.0 (q, CH(*C*H$_3$)$_2$), 26.17 (q, CH(*C*H$_3$)$_2$), 26.19 (q, CH(*C*H$_3$)$_2$), 38.0 (t, *C*H$_2$*i*Pr), 42.0 (t, *C*H$_2$*i*Pr), 70.4 (d, *C*H$_7$OH), 77.1 (d, *C*$_8$HOH), 78.0 (s, SO_2*C*), 126.5 (d, *C*$_{ar}$), 127.4 (d, *C*$_{ar}$), 127.9 (d, *C*$_{ar}$), 128.43 (d, *C*$_{ar}$), 128.44 (d, *C*$_{ar}$), 128.9 (d, *C*$_{ar}$), 129.0 (d, *C*$_{ar}$), 131.4 (d, *C*$_{ar}$), 132.8 (d, *C*$_1$), 134.3 (d, *C*$_4$), 137.2 (s, *C*$_6$), 139.3 (s, *C*$_{ipso}$), 142.5 (s, *C*$_{ipso}$), 146.6 (s, *C*$_5$); detectable signals of minor diastereomer: δ 23.1 (d, *C*H(CH$_3$)$_2$), 23.8 (d, *C*H(CH$_3$)$_2$), 25.4 (q, CH(*C*H$_3$)$_2$), 25.7 (q, CH(*C*H$_3$)$_2$), 25.8 (q, CH(*C*H$_3$)$_2$), 26.4 (q, CH(*C*H$_3$)$_2$), 38.1 (t, *C*H$_2$*i*Pr), 41.5 (t, *C*H$_2$*i*Pr), 70.1 (d, *C*H$_7$OH), 76.5 (d, *C*$_8$HOH), 78.7 (s, SO_2*C*), 126.2 (d, *C*$_{ar}$), 126.8 (d, *C*$_{ar}$), 127.3 (d, *C*$_{ar}$), 127.44 (d, *C*$_{ar}$), 128.5 (d, *C*$_{ar}$), 128.76 (d, *C*$_{ar}$), 128.79 (d, *C*$_{ar}$), 131.2 (d, *C*$_{ar}$), 132.3 (d, *C*$_1$), 134.1 (d, *C*$_{ar}$),

4-(1-Hydroxyisobutyl)-2,6-dimethylhept-4-yl 2-(1-hydroxyisobutyl)phenyl sulfone (2-10b):



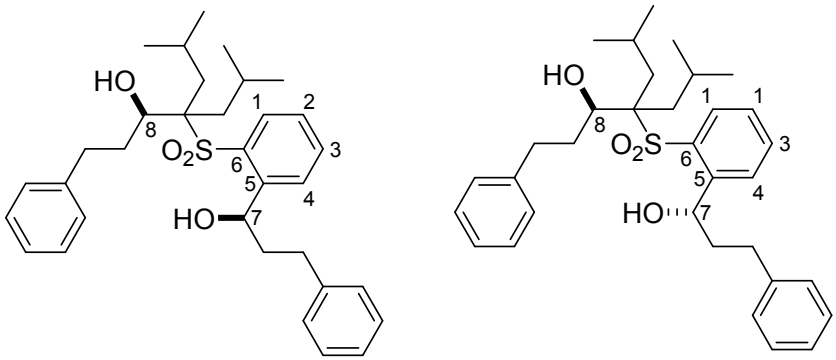
Yield 9 mg (9%) as a 1:1 mixture of unassigned diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.28; IR ν_{max} 3513, 2971, 2937, 2880, 1473, 1395, 1290, 1250, 1194, 1122, 1019, 936, 770, 718 cm^{-1}; MS (ESI+) *m/z* (%) 435 (70) [M+Na^+], 237 (100) [$(CH_3)_2CHCH(OH)C_6H_4SO_2H$+$Na^+$]; HRMS (ESI+) *m/z* [M+$Na^+$] calcd for $C_{23}H_{40}O_4SNa^+$: 435.2540; found: 435.2540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.9 Hz, 3H, OHCHCH(C*H*$_3$)$_2$), 0.75 (d, *J* = 6.8 Hz, 3H, OHCHCH(C*H*$_3$)$_2$), 0.80-1.15 (m, 36H, CH(C*H*$_3$)$_2$) 1.18 (d, *J* = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$), 1.19 (d, *J* = 6.4 Hz, 3H, OHCHCH(C*H*$_3$)$_2$), 1.46 (m, 2H, C*H*$_2$*i*Pr), 1.51-1.63 (m, 3H, C*H*$_2$*i*Pr), 1.77 (dd, *J* = 6.0, 15.7 Hz, 1H, C*H*H*i*Pr), 1.89 (dd, *J* = 4.9, 15.6 Hz, 1H, CH*H*i*Pr), 1.93-2.05 (m, 4H, CH_2*C*H(CH$_3$)$_2$), 2.07-2.19 (m, 4H, HOCHC*H*(CH$_3$)$_2$), 2.35 (dd, *J* = 5.9, 15.3 Hz, 1H, CH*H*i*Pr), 2.45 (d, *J* = 9.5 Hz, 1H, CH_8O*H*), 2.97 (m, 2H, CH_7O*H*), 3.53 (d, *J* = 7.5 Hz, 1H, CH_8O*H*), 3.99 (dd, *J* = 2.0, 7.5 Hz, 1H, C*H*$_8$OH), 4.59 (dd, *J* = 1.9, 9.4 Hz, 1H, C*H*$_8$OH), 5.16 (dd, *J* = 5.1, 7.9 Hz, 1H, C*H*$_7$OH), 5.51 (dd, *J* = 2.8, 9.0 Hz, 1H, C*H*$_7$OH), 7.37 (ddd, *J* = 1.4, 7.2, 8.1 Hz, 1H, *H*$_2$), 7.43 (ddd, *J* = 1.9, 6.8, 8.1 Hz, 1H, *H*$_2$), 7.57-7.73 (m, 4H, *H*$_3$, *H*$_4$), 7.89 (dd, *J* = 1.4, 8.0 Hz, 1H, *H*$_1$), 7.93 (dd, *J* = 1.3, 8.0 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (q, HOCHCH(*C*H$_3$)$_2$), 17.2 (q, HOCHCH(*C*H$_3$)$_2$), 19.1 (q, HOCHCH(*C*H$_3$)$_2$), 19.3 (q, HOCHCH(*C*H$_3$)$_2$), 19.7 (q, HOCHCH(*C*H$_3$)$_2$), 19.9 (q, HOCHCH(*C*H$_3$)$_2$), 23.4 (q, CH_2CH(*C*H$_3$)$_2$), 23.6 (q, CH_2CH(*C*H$_3$)$_2$), 23.81 (q, CH_2CH(*C*H$_3$)$_2$), 23.84 (q, CH_2CH(*C*H$_3$)$_2$), 24.0 (q, HOCHCH(*C*H$_3$)$_2$), 24.4 (q, HOCHCH(*C*H$_3$)$_2$), 25.5 (2×d, CH_2*C*H(CH$_3$)$_2$), 25.8 (2×d, CH_2*C*H(CH$_3$)$_2$), 26.0 (q, CH_2CH(*C*H$_3$)$_2$), 26.1 (q, CH_2CH(*C*H$_3$)$_2$), 26.3 (q, CH_2CH(*C*H$_3$)$_2$), 26.4 (q, CH_2CH(*C*H$_3$)$_2$), 29.5 (d, HOCH*C*H(CH$_3$)$_2$), 30.0 (d, HOCH*C*H(CH$_3$)$_2$), 35.7 (d, HOCH*C*H(CH$_3$)$_2$), 35.8 (d, HOCH*C*H(CH$_3$)$_2$), 38.4 (t, *C*H$_2$*i*Pr), 39.7 (t, *C*H$_2$*i*Pr), 40.7 (t, *C*H$_2$*i*Pr), 41.3 (t, *C*H$_2$*i*Pr), 74.3 (d, *C*$_7$HOH), 76.4 (d, *C*$_7$HOH), 77.0 (d, *C*$_8$HOH), 77.1 (d, *C*$_8$HOH), 79.1 (s, SO_2*C*), 79.7 (s, SO_2*C*), 126.6 (d, *C*$_2$), 127.4 (d, *C*$_2$), 128.9 (d, *C*$_3$ or *C*$_4$), 129.4 (d, *C*$_3$ or *C*$_4$), 132.2 (d, *C*$_1$), 132.8 (d, *C*$_1$), 133.7 (d, *C*$_3$ or *C*$_4$), 133.8 (d, *C*$_3$ or *C*$_4$), 136.9 (s, *C*$_6$), 137.9 (s, *C*$_6$), 145.6 (s, *C*$_5$), 147.5 (s, *C*$_5$).

(*E*,*E*)-4-(1-Hydroxypent-2-enyl)-2,6-dimethylhept-4-yl 2-(1-hydroxypent-2-enyl)phenyl sulfone (2-10c):



Yield 15 mg (14%) as a 1:1 mixture of unassigned diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.26; IR ν_{max} 3534, 3510, 2972, 2937, 2881, 1470, 1443, 1392, 1287, 1139, 1112, 1063, 1019, 974, 770, 717 cm^{-1}; MS (ESI+) *m/z* (%) 895 (100) [2M+Na^+], 459 (100) [M+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{25}H_{40}O_4SNa^+$: 459.2540; found: 459.2540; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.6 Hz, 3H, CH(C*H*$_3$)$_2$), 0.98-1.08 (m, 30H, CH_2CH_3, CH(C*H*$_3$)$_2$), 1.12 (d, *J* = 6.5 Hz, 3H, CH(C*H*$_3$)$_2$), 1.60 (dd, *J* = 5.8, 15.1 Hz, 2H, C*H*H*i*Pr), 1.65-1.81 (m, 4H, C*H*$_2$*i*Pr), 1.88 (dd, *J* = 4.6, 15.2 Hz, 1H, C*H*H*i*Pr), 1.96 (dd, *J* = 5.6, 14.8 Hz, 1H, CH*Hi*Pr), 2.05-2.26 (m, 12H, C*H*(CH$_3$)$_2$, C*H*$_2$CH$_3$), 2.53 (d, *J* = 6.4 Hz, 1H, CH$_8$O*H*), 2.64 (d, *J* = 5.0 Hz, 1H, CH$_8$O*H*), 2.86 (broad s, 1H, CH$_7$O*H*), 2.95 (d, *J* = 4.0 Hz, 1H, CH$_7$O*H*), 4.70 (t, *J* = 5.2 Hz, 1H, C*H*$_8$OH), 5.00 (t, *J* = 6.4 Hz, 1H, C*H*$_8$OH), 5.72 (m, 3H, CH$_2$CH=C*H*, CH$_2$C*H*=CH), 5.83 (m, 3H, CH$_2$CH=C*H*, CH$_2$C*H*=CH), 5.97 (m, 2H, CH$_2$C*H*=CH), 6.24 (m, 1H, C*H*$_7$OH), 6.43 (d, *J* = 5.1 Hz, 1H, C*H*$_7$OH), 7.42 (m, 2H, *H*$_2$), 7.62 (m, 2H, *H*$_3$), 7.71 (m, 2H, *H*$_4$), 7.90 (dd, *J* = 1.3, 8.1 Hz, 1H, *H*$_1$), 7.93 (dd, *J* = 1.4, 8.1 Hz, 1H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (2×q, CH$_2$*C*H$_3$), 13.47 (q, CH$_2$*C*H$_3$), 13.53 (q, CH$_2$*C*H$_3$), 23.68 (d, *C*H(CH$_3$)$_2$), 23.73 (d, *C*H(CH$_3$)$_2$), 23.8 (d, *C*H(CH$_3$)$_2$), 23.9 (d, *C*H(CH$_3$)$_2$), 25.3 (q, CH(*C*H$_3$)$_2$), 25.4 (q, CH(*C*H$_3$)$_2$), 25.46 (t, *C*H$_2$CH$_3$), 25.50 (t, *C*H$_2$CH$_3$), 25.57 (t, *C*H$_2$CH$_3$), 25.61 (t, *C*H$_2$CH$_3$), 25.73 (q, CH(*C*H$_3$)$_2$), 25.74 (q, CH(*C*H$_3$)$_2$), 25.9 (q, CH(*C*H$_3$)$_2$), 26.01 (q, CH(*C*H$_3$)$_2$), 26.02 (q, CH(*C*H$_3$)$_2$), 26.03 (q, CH(*C*H$_3$)$_2$), 39.0 (t, *C*H$_2$*i*Pr), 39.3 (t, *C*H$_2$*i*Pr), 40.7 (t, *C*H$_2$*i*Pr), 40.8 (t, *C*H$_2$*i*Pr), 69.2 (d, *C*$_7$HOH), 69.7 (d, *C*$_7$HOH), 74.2 (d, *C*$_8$HOH), 74.6 (d, *C*$_8$HOH), 77.6 (s, SO$_2$*C*), 77.8 (s, SO$_2$*C*), 127.0 (d, CH$_2$CH=*C*H or *C*$_2$), 127.07 (d, CH$_2$CH=*C*H or *C*$_2$), 127.11 (d, CH$_2$CH=*C*H or *C*$_2$), 127.5 (d, CH$_2$CH=*C*H or *C*$_2$), 129.8 (d, CH$_2$CH=*C*H or *C*$_1$), 129.88 (d, CH$_2$CH=*C*H or *C*$_1$), 129.92 (d, CH$_2$CH=*C*H or *C*$_1$), 130.18 (d, CH$_2$CH=*C*H or *C*$_1$), 132.3 (d, *C*$_4$), 132.8 (d, *C*$_4$), 133.6 (d, CH$_2$*C*H=CH or *C*$_3$), 133.8 (d, CH$_2$*C*H=CH or *C*$_3$), 133.9 (d, CH$_2$*C*H=CH or *C*$_3$), 134.0 (d, CH$_2$*C*H=CH or *C*$_3$), 137.5 (s, *C*$_6$), 137.56 (s, *C*$_6$), 137.62 (d, CH$_2$*C*H=CH), 137.8 (d, CH$_2$*C*H=CH), 145.7 (s, *C*$_5$), 146.3 (s, *C*$_5$).

4-(1-Hydroxy-3-phenylpropyl)-2,6-dimethylhept-4-yl 2-(1-hydroxy-3-phenylpropyl) phenyl sulfone (2-10d):



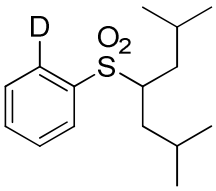
Yield 12 mg (max. 9%, in a mixture with inseparable impurities) as a 1:1 mixture of unassigned diastereomers a as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.25; MS (ESI+) *m/z* (%) 559 (100) [M+Na^+], 299 (20) [$PhCH_2CH_2CH(OH)C_6H_4SO_2H+Na^+$]; HRMS (ESI+) *m/z* [M+$Na^+$] calcd for $C_{33}H_{44}O_4SNa^+$: 559.2852; found: 559.2853; ^{1}H NMR (400 MHz, $CDCl_3$) assignable signals: δ 4.11 (m, 1H, C*H*OH), 4.42 (m, 1H, C*H*OH), 5.52 (m, 1H, C*H*OH), 5.77 (m, 1H, C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.0 (d, *C*HOH), 70.5 (d, *C*HOH), 73.1 (d, *C*HOH), 72.8 (d, *C*HOH), 77.3 (s, SO_2C), 77.8 (s, SO_2C), 146.7 (s, C_5), 147.4 (s, C_5).

5.2.3 Elucidation of the mechanism of the *ortho*→α transmetalation

***Ortho*-deuteration of sulfones 1-2h and 1-19h (General procedure):**

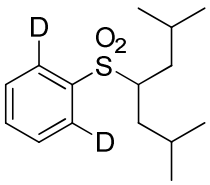
*n*BuLi (0.75 mL, 1.15 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** or **1-19h** (1 mmol) and TMEDA (0.3 mL, 1.95 mmol) in dry THF (5 mL) at –78 °C under a nitrogen atmosphere. After stirring for 10 min, D_2O (0.5 mL) was added. The reaction mixture was warmed to room temperature and diluted with water (2 mL). The layers were separated and the aqueous was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave deuterated sulfones **1-19h** or **3-3**.

2,6-Dimethylhept-4-yl 2-deuterophenyl sulfone (1-19h):



Yield 266 mg (98%; 96% *ortho*-D) as colorless crystals, m.p. 48-49 °C. R_f (EtOAc/hexane 1:5) = 0.47; IR ν_{max} 2968, 2933, 2879, 1472, 1444, 1439, 1374, 1316, 1300, 1154, 1128, 1085, 914, 784, 760, 733 cm^{-1}; MS (ESI+) *m/z* (%) 270 (100) [$M+H^+$], 144 [$ArSO_2H+H^+$]; HRMS (CI+) *m/z* [$M+H^+$] calcd for $C_{15}H_{24}D_2O_2S^+$: 270.1638; found: 270.1632; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$), 0.82 (d, *J* = 6.2 Hz, 6H, $CH(CH_3)_2$), 1.24 (m, 2H, C*H*H*i*Pr), 1.64 (m, 4H, C*H*$(CH_3)_2$, CH*H*iPr), 2.96 (m, 1H, SO_2CH), 7.50 (m, 2H, H_{meta}), 7.58 (m, 1H, H_{para}), 7.81 (m, 1H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (q, $CH(CH_3)_2$), 23.0 (q, $CH(CH_3)_2$), 25.7 (d, $CH(CH_3)_2$), 38.7 (t, CH_2iPr), 61.1 (d, SO_2CH), 129.0 (d, C_{ortho}), 129.1 (d, C_{meta}), 133.6 (d, C_{para}), 138.0 (s, C_{ipso}).

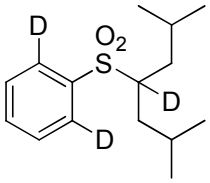
2,6-Dimethylhept-4-yl 2,6-dideuterophenyl sulfone (3-3):



Yield 265 mg (98%; 92% *ortho*-D) as colorless crystals, m.p. 48-49 °C. R_f (EtOAc/hexane 1:5) = 0.46; IR ν_{max} 3063, 2958, 2935, 1573, 1432, 1387, 1369, 1314, 1296, 1213, 1152, 771

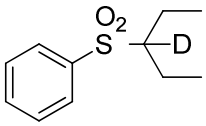
cm^{-1}; MS (ESI+) *m/z* (%) 563 (20) [2M+Na^+], 293 (100) [M+Na^+]; HRMS (ESI+) *m/z* [M+H^+] calcd for $C_{15}H_{23}D_2O_2S^+$: 271.1695; found: 271.1697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$), 0.81 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.21 (m, 2H, C*H*H*i*Pr), 1.60 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 2.93 (m, 1H, SO_2C*H*), 7.48 (m, 2H, H_{meta}), 7.58 (m, 1H, H_{para}), 7.80 (m, 8% H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (q, CH(*C*H$_3$)$_2$), 22.9 (q, CH(*C*H$_3$)$_2$), 25.6 (d, *C*H(CH$_3$)$_2$), 38.6 (t, *C*H$_2$*i*Pr), 61.0 (d, SO_2*C*H), 128.9 (d, C_{meta}), 133.5 (d, C_{para}), 137.9 (s, C_{ipso}).

(4-Deutero-2,6-dimethylhept-4-yl) 2,6-dideuterophenyl sulfone (3-4):



*n*BuLi (2.7 mL, 4.3 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **3-3** (992 mg, 3.7 mmol) and TMEDA (1 mL, 6.5 mmol) in dry THF (4 mL) at –20 °C under a nitrogen atmosphere. After stirring for 10 min, D_2O (0.5 mL) was added at –78 °C. The reaction mixture was warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by short column chromatography (EtOAc/hexane 1:20) gave 901 mg (90%) **3-4** (96% *ortho*-D, 100% α-D) as colorless crystals, m.p. 48-49 °C. R_f (EtOAc/hexane 1:5) = 0.48; IR ν_{max} 2967, 2941, 2879, 1473, 1437, 1312, 1299, 1154, 1114, 838, 760, 724 cm^{-1}; MS (ESI+) *m/z* (%) 565 (20) [2M+Na^+], 294 (100) [M+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{15}H_{21}D_3O_2SNa^+$: 294.1578; found: 294.1579; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.1 Hz, 6H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 1.26 (m, 2H, C*H*H*i*Pr), 1.66 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 7.53 (m, 2H, H_{meta}), 7.61 (m, 1H, H_{para}), 7.85 (m, 4% H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (q, CH(*C*H$_3$)$_2$), 23.0 (q, CH(*C*H$_3$)$_2$), 25.7 (d, *C*H(CH$_3$)$_2$), 38.7 (t, *C*H$_2$*i*Pr), 129.0 (d, C_{meta}), 133.6 (d, C_{para}), 138.1 (s, C_{ipso}).

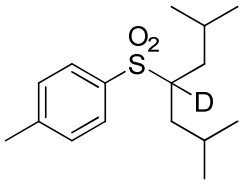
3-Deuteropent-3-yl phenyl sulfone (1-20p):



*n*BuLi (0.41 mL, 0.65 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2p** (106 mg, 0.5 mmol) and TMEDA (0.15 mL, 0.98 mmol) in dry THF (4 mL) at

–78 °C under a nitrogen atmosphere. After stirring for 10 min, D_2O (0.5 mL) was added. The reaction mixture was warmed to room temperature and diluted with water (3 mL). The layers were separated and the aqueous was extracted with diethyl ether (3×15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by short column chromatography (EtOAc/hexane 1:20) gave 105 mg (99%) **1-20p** (100% D) as colorless crystals, m.p. 47-48 °C. R_f (EtOAc/hexane 1:5) = 0.57; IR ν_{max} 2980, 2949, 2890, 1467, 1451, 1305, 1158, 1140, 1084, 736, 726, 694, 612 cm^{-1}; MS (ESI+) *m/z* (%) 236 (100) [M+Na^+]; HRMS (ESI+) *m/z* [M+Na^+] calcd for $C_{11}H_{15}DO_2SNa^+$: 236.0826; found: 236.0825; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.5 Hz, 6H, C*H*$_3$), 1.69 (dq, *J* = 7.5, 15.1 Hz, 2H, C*H*HCH$_3$), 1.87 (dq, *J* = 7.5, 15.1 Hz, 2H, CH*H*CH$_3$), 7.26 (m, 2H, H_{meta}), 7.62 (m, 1H, H_{para}), 7.89 (m, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3 (q, *C*H$_3$), 20.4 (t, *C*H$_2$CH$_3$), 66.8 (s (d, *J* = 20.7 Hz) SO$_2$*C*D), 128.9 (d, C_{ortho}), 129.3 (d, C_{meta}), 133.6 (d, C_{para}), 138.6 (s, C_{ipso}).

(4-Deutero-2,6-dimethylhept-4-yl) 4-methylphenyl sulfone (1-20i):



*n*BuLi (2.7 mL, 4.3 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2i** (1.04 g, 3.7 mmol) and TMEDA (1 mL, 6.5 mmol) in dry THF (4 mL) at –20 °C under a nitrogen atmosphere. After stirring for 10 min, D_2O (0.5 mL) was added. The reaction mixture was warmed to room temperature. The layers were separated and the aqueous was extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by short column chromatography (EtOAc/hexane 1:20) gave 1.04 g (99%) **1-20i** (100% D) as colorless crystals, m.p. 77-78 °C. R_f (EtOAc/hexane 1:5) = 0.76; IR ν_{max} 2967, 2939, 2878, 1600, 1472, 1391, 1374, 1315, 1303, 1291, 1144, 1135, 1089, 822, 731, 722, 696 cm^{-1}; MS (CI+) *m/z* (%) 284 (80) [M+H^+], 185 (40) [M–H_2C=C(CH$_3$)$_2$–*i*Pr+H^+], 157 (100) [$CH_3C_5H_4SO_2H_2^+$]; HRMS (EI) *m/z* [M^+] calcd for $C_{16}H_{25}DO_2S^+$: 283.1716; found: 283.1715; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, *J* = 6.2 Hz, 6H, CH(C*H*$_3$)$_2$), 0.82 (d, *J* = 6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 1.22 (m, 2H, C*H*H*i*Pr), 1.64 (m, 4H, C*H*(CH$_3$)$_2$, CH*Hi*Pr), 2.39 (s, 3H, C*H*$_3$C$_6$H$_4$), 7.25 (d, *J* = 8.0 Hz, 2H, H_{meta}), 7.68 (d, *J* = 8.0 Hz, 2H, H_{ortho}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (q, *C*H$_3$C$_6$H$_4$), 22.0 (q, CH(*C*H$_3$)$_2$), 22.9 (q, CH(*C*H$_3$)$_2$), 25.6 (d,

*C*H(CH_3)$_2$), 38.6 (t, *C*H$_2$*i*Pr), 129.0 (d, C_{ortho}), 129.6 (d, C_{meta}), 135.0 (s, C_{ipso}), 144.3 (s, C_{para}).

Experimental data of kinetic studies and cross-over experiments

Kinetic study of the transmetalation of 1-2h:

TMEDA (0.3 mL, 2 mmol) and *n*BuLi (0.72 mL, 1.15 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **1-2h** (268 mg, 1 mmol) in dry THF (12 mL) at the given temperature (Tables 5.3-5.7). After the given time an aliquot of the solution was removed by a syringe and added to a capped dry vial containing a few drops of D_2O. The volume of the sample corresponded to the total volume divided by the number of taken samples. The product was extracted with ether (2 mL). The organic extract was dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^{1}H NMR spectroscopy. The procedure was repeated. The raw data are listed in Tables 5-3-5.7. For generation of Figure 3.1, the individual data points were transformed from real percentage of deuterated **1-19h**/**1-20h** to ideal 100% deuteration degree; e.g. isolated **1-19h**/**1-20h** with a 95% deuteration degree, ratio 9.6:1, which corresponds to 86% **1-19h** and 9% **1-20h** was transformed to 100% D content at a 9.6:1 ratio = 90.5% **1-19h** and 9.5% **1-20h**. The values in the tables are the average values calculated from at least three kinetic measurements at every temperature.

Table 5.3. Kinetic trace at –30 °C.

Entry	Time [min]	**1-19h** [%]	**1-20h** [%]
1	0.5	86.1	13.9
2	1	78.7	21.3
3	2	72.5	27.5
4	3	66.1	33.9
5	4	55.8	44.2
6	5	47.4	52.6
7	6	41.4	58.6
8	8	30.8	69.2
9	11	23.8	76.2
10	15	14.9	85.1
11	20	3.9	96.1
12	26	3.3	96.7

Table 5.4. Kinetic trace at –35 °C.

Entry	Time [min]	**1-19h** [%]	**1-20h** [%]
1	0.5	87.2	12.8
2	1	80.0	20.0
3	2	75.8	24.2
4	4	70.4	29.6
5	6	60.1	39.9
6	8	49.0	51.0
7	11	39.1	60.9
8	15	25.9	74.1
9	20	18.7	81.3
10	27	15.1	84.9
11	35	11.1	88.9
12	45	5.7	94.3

Table 5.5. Kinetic trace at –40 °C.

Entry	Time [min]	**1-19h** [%]	**1-20h** [%]
1	1	89.0	11.0
2	2	86.3	13.7
3	3.5	82.2	17.8
4	6	75.7	24.3
5	9	68.9	31.1
6	14	53.1	46.9
7	21	38.9	61.1
8	30	22.7	77.3
9	45	13.8	86.2
10	65	8.3	91.7
11	90	5.7	94.3
12	120	3.6	96.4

Table 5.6. Kinetic trace at –45 °C.

Entry	Time [min]	**1-19h** [%]	**1-20h** [%]
1	1	93.5	6.5
2	2.5	90.8	9.2
3	5	87.4	12.6
4	9	79.1	20.9
5	14	64.2	35.8
6	20	58.7	41.3
7	29	49.6	50.4
8	40	38.8	61.2
9	56	29.6	70.4
10	75	11.5	88.5
11	108	6.1	93.9
12	145	4.4	95.6

Table 5.7. Kinetic trace at –50 °C.

Entry	Time [min]	**1-19h** [%]	**1-20h** [%]
1	1	91.8	8.2
2	3	91.4	8.6
3	6	88.1	11.9
4	10	85.3	14.7
5	15	80.0	20.0
6	21	75.5	24.5
7	32	64.4	35.6
8	46	51.1	48.9
9	68	27.4	72.6
10	98	20.8	79.2
11	135	9.7	90.3
12	180	6.3	93.7

Table 5.8. Concentration dependence of the transmetalation of **1-*o*-17h** at –40 °C.

Entry	T [°C]	T [min]	Ratio **1-19h**/**1-20h** at 0.125 mol/L THF	Ratio **1-19h**/**1-20h** at 0.031 mol/L THF
1	–40	1	88:10	86:12
2	–40	5	82:17	86:13
3	–40	15	50:48	66:30
4	–40	30	16:75	39:57

Determination of the intramolecular kinetic isotope effect (Scheme 3.4):

*n*BuLi (62 µL, 0.1 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-19h** (30 mg, 0.11 mmol) and TMEDA (0.03 mL, 0.2 mmol) in dry THF (1 mL) at –78 °C under a nitrogen atmosphere. After stirring for 5 min, a sample removed by a syringe was quenched with water and a second sample with D_2O (0.5 mL). The products were extracted with diethyl ether (2 mL). The organic extracts were dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^1H NMR spectroscopy.

Transmetalation of deuterated compounds 3-3, 3-4, 1-20p and 1-20i (Tables 3.1-3.3, Scheme 3.5, General procedure):

TMEDA (0.15 mL, 1 mmol) and *n*BuLi (0.344 mL, 0.55 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **3-3, 3-4, 1-20p** and **1-20i** (0.5 mmol) in dry THF (3-5 mL) at –78 °C. After the given time (Tables 3.1-3.3, Scheme 3.5) an aliquot of the solution was removed by a syringe and added to a capped vial containing a few drops of D_2O or H_2O. The volume of the sample corresponded to the total volume divided by the number of samples taken. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^1H NMR spectroscopy. The procedure was repeated as described in the Tables and Schemes.

Proton or deuterium transfer from 1-2p or 1-20p to 1-*o*-17h (Tables 3.4-3.5, General procedure):

TMEDA (0.15 mL, 1 mmol) and *n*BuLi (0.344 mL, 0.55 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **1-2h** (134 mg, 0.5 mmol) in dry THF (3-4 mL) at –78 °C. The second component **1-2p** or **1-20p** was added after 5 min. After the given time (Tables 3.4-3.5) an aliquot of the solution was removed by a syringe and added to a vial containing a few drops of D_2O or H_2O. The volume of the sample corresponded to the total volume divided by number of taken samples. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^1H NMR spectroscopy. The procedure was repeated as described in the Tables.

***ortho*- to α-Transmetalation of 1-2h using 0.5 equivalents of base and deuteration (Table 3.6):**

TMEDA (0.07 mL, 0.5 mmol) and *n*BuLi (156 μL, 0.25 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **1-2h** (134 mg, 0.5 mmol) in THF (5 mL) at –78 °C. After 10 min at –78 °C a sample of the solution (1 mL) was taken by a syringe and added to a dry capped vial containing a few drops of D_2O. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated. The remaining reaction mixture was placed in a bath at –60 °C and kept for 10 min. Another sample (1 mL) was removed and deuterated as described above. The procedure was repeated at –40 °C, –20 °C and 0 °C. The mass balance was determined to be quantitative for each mixture and the product mixtures of **1-19h** and/or **1-20h** were analyzed by ^1H NMR spectroscopy.

Crossover reaction between 1-2h and 1-20i (Table 3.7):

TMEDA (0.15 mL, 1 mmol) and *n*BuLi (0.363 mL, 0.58 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **1-2h** (86 mg, 0.33 mmol) and **1-20i** (45 mg, 0.165 mmol) in dry THF (3 mL) at –78 °C. After 10 min an aliquot of the solution was removed by a syringe and added to a capped vial containing a few drops of D_2O or H_2O. The sample volume corresponded to the total volume divided by the number of samples taken. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered, evaporated and the residue was analyzed by ^{1}H NMR spectroscopy.

***ortho*- to α-Transmetalation of 1-*o*-17i in presence of 1-*o*,α-45 (Table 3.8):**

The two deprotonations were performed in separated flasks. *n*BuLi (0.164 mL, 0.26 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2h** (34 mg, 0.13 mmol) and TMEDA (0.1 mL, 0.65 mmol) in dry THF (1 mL) at –40 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at this temperature and cooled to –78 °C. In the meantime, *n*BuLi (0.247 mL, 0.39 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfone **1-2i** (106 mg, 0.38 mmol) and TMEDA (0.1 mL, 0.65 mmol) in dry THF (3 mL) at –78 °C under a nitrogen atmosphere in another flask. The reaction mixture containing **1-*o*,α-45** was added by cannula to the flask with *ortho*-deprotonated sulfone **1-2i** at –78 °C. After 10 min at this temperature, a sample (1 mL) was taken by a syringe and added to a dry capped vial containing a few drops of D_2O. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated. The remaining reaction mixture was placed in a bath at –60 °C and kept for 10 min. Another sample (1 mL) was removed and deuterated as described above. The procedure was repeated at –40 °C, –20 °C and 0 °C. The mass balance was determined to be quantitative for each mixture and the products were analyzed by ^{1}H NMR spectroscopy.

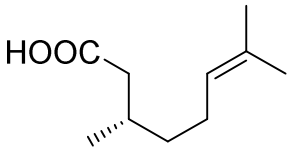
Proton transfer from 1-*o*,α-45 to 1-2i (Table 3.9):

TMEDA (0.15 mL, 1 mmol) and *n*BuLi (275 µl, 0.44 mmol, 1.6*M* in hexane) were added to a stirred solution of sulfone **1-2h** (54 mg, 0.2 mmol) in THF (3 mL) at –40 °C. After 30 min 0.5 mL of the solution was taken by a syringe and added to a dry capped vial containing a few drops of D_2O. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated. The reaction mixture was cooled to –78 °C and sulfone **1-2i** (47 mg, 0.17 mmol) was added. After stirring for 10 minutes 0.5 mL of the

solution was removed by a syringe and added to a dry capped vial containing a few drops of D_2O. The product was extracted with diethyl ether (2 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated. The remaining reaction mixture was placed in a bath at –60 °C and kept for 10 min. Another sample (0.5 mL) was removed and deuterated as described above. The procedure was repeated at –40 °C, –20 °C and 0 °C. The mass balance was determined to be quantitative for each mixture and the product mixtures were analyzed by ^1H NMR spectroscopy.

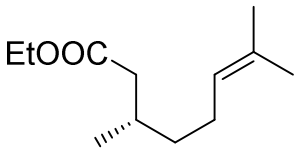
5.2.4 Application of the transmetalation in total syntheses

(*S*)-(-)-Citronellic acid (4-10):



Pyridinium dichromate (PDC, 13.6 g, 36 mmol) was added to a stirred solution of (*S*)-(–)-citronellol **4-6** (3.12 g, 20 mmol) in dry DMF (60 mL) under a nitrogen atmosphere at 0 °C. After stirring at room temperature for 24 h, the reaction mixture was quenched with 1*M* aqueous HCl and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with brine (5×100 mL), dried over $MgSO_4$, filtered and evaporated. Purification by column (EtOAc/hexane 1:10, gradient to 1:2) gave 2.55 g (75%) of acid **4-10** as a colorless liquid. R_f (EtOAc/hexane 1:5) = 0.44; $[\alpha]_D^{20}$: –8.3 (c 4.384 g/100 mL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.30 (m, 2H, $CH_3CHCH_2CH_2$), 1.60 (s, 3H, CH=CC*H*$_3$), 1.68 (d, *J* = 1.2 Hz, 3H, CH=CC*H*$_3$), 1.98 (m, 3H, $CH_3CHCH_2CH_2$), 2.14 (dd, *J* = 8.1, 14.7 Hz, 1H, C*H*HC=O), 2.36 (dd, *J* = 5.7, 14.7 Hz, 1H, CH*H*C=O), 5.07 (m, 1H, C*H*=C$(CH_3)_2$); The data are in agreement with those in the literature.[235]

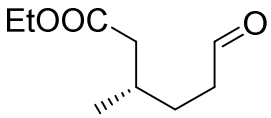
Ethyl (*S*)-(-)-citronellate (4-11):



Sodium hydride (310 mg, 7.8 mmol, 60% in mineral oil) was added to dry DMF (25 mL) at 0 °C under nitrogen atmosphere. (*S*)-(–)-Citronellic acid **4-10** (1.01 g, 5.9 mmol) was added to the solution, stirring was continued for 10 min and ethyl bromide (1.13 mL, 14.75 mmol) was added. The reaction mixture was stirred at room temperature for 24 h, quenched with water and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (EtOAc/hexane 1:20) gave 1.07 g (91%) of ester **4-11** as a colorless liquid. R_f (EtOAc/hexane 1:10) = 0.72; $[\alpha]_D^{20}$: –4.8 (c 1.720 g/100 mL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.33 (m, 2H, $CH_3CHCH_2CH_2$), 1.57 (s, 3H, =CC*H*$_3$), 1.65 (d, *J* = 1.2 Hz, 3H, =CC*H*$_3$), 1.97 (m, 3H, $CH_3CHCH_2CH_2$), 2.08 (dd, *J* = 8.2, 14.6 Hz, 1H,

C*H*HC=O), 2.28 (dd, *J* = 5.9, 14.6 Hz, 1H, CH*H*CO=O), 4.11 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 5.07 (m, 1H, C*H*=C(CH$_3$)$_2$). The data are in agreement with those in the cited literature.[236]

Ethyl (*S*)-3-Methyl-6-oxohexanoate (4-5):



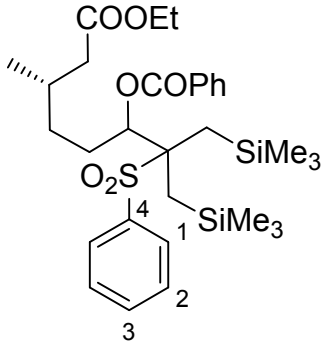
Ozone was bubbled through a mixture of ethyl citronellate **4-11** (103 mg, 0.52 mmol) in dry DCM (3 mL) at –78 °C until a light blue colour persisted. Nitrogen was bubbled through the solution for 20 min to remove excess ozone and dimethyl sulfide (0.1 mL) was added. After 30 min, the mixture was warmed to room temperature. The volatile components were evaporated and the residue was partioned between water (5 mL) and diethyl ether (5 mL). The aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over MgSO$_4$, filtered and the solvent was evaporated. Purification by column chromatography (EtOAc/hexane 1:20) gave 76 mg (85%) of aldehyde **4-5** as a colorless liquid. R$_f$ (EtOAc/hexane 1:2.5) = 0.40; $[\alpha]_D^{20}$: –6.6 (c 1.459 g/100 mL); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.96 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.52 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.69 (m, 1H, CH$_3$CHCH*H*CH$_2$), 1.96 (m, 1H, C*H*CH$_3$), 2.15 (dd, *J* = 7.5, 15.0 Hz, 1H, C*H*HC=O), 2.27 (dd, *J* = 6.3, 15.0 Hz, 1H, CH*H*C=O), 2.44 (m, 2H, C*H*$_2$CHO), 4.11 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 9.75 (s, 1H, C*H*O). The data are in agreement with those in the literature.[236]

Preparation of 2-benzoyloxy sulfones 4-13a,c (General Procedure):

n-BuLi (1.4 mL, 2.23 mmol or 1.6 mL, 2.57 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of sulfones **1-2a** or **1-2c** (1.88 mmol) and TMEDA (0.35 mL, 2.23 mmol or 0.4 mL, 2.57 mmol) in dry DME (12 mL) for **4-13a** or diethyl ether (12 mL) for **4-13c**, respectively, at –78 °C under a nitrogen atmosphere. The reaction mixture was warmed to room temperature during 2 h for **4-13a** or to 0 °C for 30 min for **4-13c** and the aldehyde **4-5** (357 mg, 2.07 mmol) in DME (1.5 mL) or diethyl ether (1.5 mL), respectively, was added dropwise at –78 °C. The reaction mixture was stirred at this temperature for 15 min until complete as indicated by TLC. Benzoyl chloride (268 µL, 2.26 mmol) was added and the reaction mixture was warmed to room temperature after 20 min. 3-(Dimethylamino)propan-1-ol (292 µL, 2.5 mmol) was added and the reaction was quenched with water after 10 min. The layers were separated and the aqueous was extracted with diethyl ether (3×40 mL). The

combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated. Purification by column chromatography (EtOAc/hexane/Et_3N 1:20:0.05) gave benzoyloxy sulfones **4-13a,c**. Side product **4-14a** was isolated followed by side product **4-15**, formed in case of decomposition on silicagel.

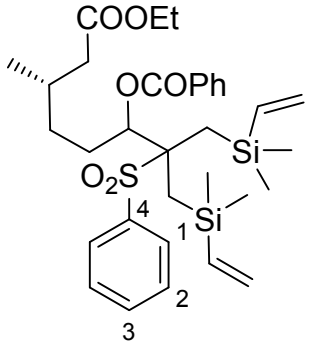
Ethyl (3*S*)-6-benzoyloxy-3-methyl-7-(phenylsulfonyl)-7-(trimethylsilylmethyl)-8-(trimethylsilyl)octanoate (4-13a):



Yield 989 mg (87%) as an inseparable 1:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.31; IR ν_{max} 3091, 3072, 3065, 2957, 2932, 2907, 2875, 1719, 1602, 1585, 1452, 1447, 1393, 1373, 1315, 1296, 1271, 1265, 1251, 1177, 1162, 1134, 1106, 1095, 1080, 1070, 1026, 843, 711, 690 cm^{-1}; MS (ESI+) *m/z* (%) 627 (5) [$M+Na^+$], 485 (100) [$M–PhSO_2H+Na^+$], 269 (20) [$M^+–PhSO_2–PhCO_2–TMS$]; Anal. calcd for $C_{31}H_{48}O_6SSi$ (604.95): C 61.55, H 8.00, S 5.30; found: C 61.82, H 8.14, S 5.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 36H, Si(C*H*$_3$)$_3$), 0.82 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 0.87 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 1.11 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.18 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.19-1.37 (m, 10H, C*H*$_2$CH$_2$CHO, C*H*$_2$Si(CH$_3$)$_3$, C*H*$_2$CHO), 1.45 (A part of AB system, *J* = 14.6 Hz, 1H, C*H*HSi(CH$_3$)$_3$), 1.47 (A part of AB system, *J* = 14.6 Hz, 1H, CH*H*Si(CH$_3$)$_3$), 1.63 (m, 3H, C*H*HCHO, C*H*$_2$Si(CH$_3$)$_3$), 1.86 (m, 3H, C*H*CH$_3$, CH*H*CHO), 1.98 (dd, *J* = 5.7, 14.7 Hz, 1H, C*H*HC=O), 2.02 (dd, *J* = 8.2, 14.7 Hz, 1H, C*H*HC=O), 2.15 (dd, *J* = 7.3, 14.7 Hz, 1H, CH*H*C=O), 2.17 (dd, *J* = 6.0, 14.7 Hz, 1H, CH*H*C=O), 3.98 (m, 2H, OC*H*$_2$CH$_3$), 4.05 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 5.43 (dd, *J* = 2.9, 10.2 Hz, 2H, C*H*OCOPh), 7.23 (m, 4H, *H*$_{meta}$), 7.32 (m, 10H, *H*$_2$, *H*$_{para}$, *H*$_{ortho}$), 7.44 (m, 2H, *H*$_3$), 7.85 (m, 4H, *H*$_1$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1.6 (q, Si(*C*H$_3$)$_3$), 1.7 (q, Si(*C*H$_3$)$_3$), 14.3 (q, OCH$_2$*C*H$_3$), 14.4 (q, OCH$_2$*C*H$_3$), 19.7 (q, CH*C*H$_3$), 19.8 (q, CH*C*H$_3$), 20.56 (t, *C*H$_2$Si(CH$_3$)$_3$), 20.60 (t, *C*H$_2$Si(CH$_3$)$_3$), 21.57 (t, *C*H$_2$Si(CH$_3$)$_3$), 21.61 (t, *C*H$_2$Si(CH$_3$)$_3$), 29.6 (t, *C*H$_2$CHO), 29.7 (t, *C*H$_2$CHO), 30.6 (d, *C*HCH$_3$), 30.7 (d, *C*HCH$_3$), 33.7 (t, *C*H$_2$CH$_2$CHO), 33.8 (t, *C*H$_2$CH$_2$CHO), 41.78 (t, *C*H$_2$C=O), 41.81 (t, *C*H$_2$C=O), 60.30 (t, O*C*H$_2$CH$_3$), 60.34 (t, O*C*H$_2$CH$_3$), 76.78 (s, SO$_2$*C*),

76.81 (s, SO_2C), 77.1 (d, 2×*C*HOCO), 128.19 (d, C_{meta}), 128.20 (d, C_{meta}), 128.95 (d, C_{ortho} or C_2), 128.96 (d, C_{ortho} or C_2), 129.4 (s, C_{ipso}), 129.5 (s, C_{ipso}), 129.52 (d, C_{ortho} or C_2), 129.54 (d, C_{ortho} or C_2), 130.3 (d, 2×C_1), 132.9 (d, 2×C_3), 133.1 (d, 2×C_{para}), 139.3 (s, C_4), 139.4 (s, C_4), 165.8 (s, O*C*OPh), 165.9 (s, O*C*OPh), 172.89 (s, *C*OOEt), 172.92 (s, *C*OOEt).

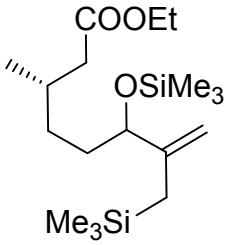
Ethyl (3*S*)-6-benzoyloxy-3-methyl-7-(phenylsulfonyl)-7-(dimethyl(vinyl)silylmethyl)-8-(dimethyl(vinyl)silyl)octanoate (4-13c):



Yield 650 mg (55%) as an inseparable 1:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.40; IR ν_{max} 3059, 2965, 2937, 2865, 1728, 1453, 1409, 1377, 1303, 1270, 1255, 1180, 1139, 1098, 1084, 1073, 1030, 1013, 957, 832, 760, 713, 693 cm^{-1}; MS (ESI+) *m/z* (%) 651 (30) [$M+Na^+$], 509 (100) [$M–PhSO_2H+Na^+$]; HRMS (ESI) *m/z* [$M+Na^+$] calcd for $C_{33}H_{48}O_6SSi_2Na^+$: 651.2602; found: 651.2604; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6 H, Si(CH_3)$_2$), 0.29 (s, 6H, Si(CH_3)$_2$), 0.30 (s, 6 H, Si(CH_3)$_2$), 0.31 (s, 6H, Si(CH_3)$_2$), 0.85 (d, *J* = 6.6 Hz, 3H, CHCH_3), 0.89 (d, *J* = 6.6 Hz, 3H, CHCH_3), 1.13 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3), 1.21 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH_3), 1.19-1.34 (m, 8H, CH_2CH$_2$CHO, CH_2Si, CH_2CHO), 1.45 (m, 2H, CH_2Si), 1.57 (A part of AB system, *J* = 14.6 Hz, 1H, CH_2Si), 1.59 (A part of AB system, *J* = 14.7 Hz, 1H, CH_2Si), 1.72 (m, 3H, CH_2Si, C*H*HCHO), 1.87 (m, 3H, CH*H*CHO, C*H*CH$_3$), 2.00 (dd, *J* = 4.1, 8.2 Hz, 1H, C*H*HC=O), 2.04 (dd, *J* = 4.2, 8.2 Hz, 1H, C*H*HC=O), 2.17 (dd, *J* = 6.0, 8.8 Hz, 1H, CH*H*C=O), 2.22 (m, 1H, CH*H*C=O), 4.01 (m, 2H, OCH_2CH$_3$), 4.08 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 5.45 (m, 2H, C*H*OCOPh), 5.76 (dd, *J* = 3.7, 20.2 Hz, 2H, SiCH=C*H*H), 5.78 (dd, *J* = 3.6, 20.5 Hz, 2H, SiCH=C*H*H), 6.02 (m, 2H, SiCH=CH*H*), 6.28 (dd, *J* = 14.4, 20.2 Hz, 1H, SiC*H*=CHH), 6.30 (dd, *J* = 14.5, 20.3 Hz, 1H, SiC*H*=CHH), 6.42 (dd, *J* = 14.3, 20.3 Hz, 1H, SiC*H*=CHH), 6.44 (dd, *J* = 14.4, 20.2 Hz, 1H, SiC*H*=CHH), 7.26 (m, 4H, H_{meta}), 7.34 (m, 10H, H_2, H_{para}, H_{ortho}), 7.47 (m, 2H, H_3), 7.89 (m, 4H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.64 (q, Si(*C*H$_3$)$_2$), –0.62 (q, Si(*C*H$_3$)$_2$), –0.55 (q, Si(*C*H$_3$)$_2$), –0.54 (q, Si(*C*H$_3$)$_2$), –0.27 (q, Si(*C*H$_3$)$_2$), –0.26 (q, Si(*C*H$_3$)$_2$), –0.25 (q, Si(*C*H$_3$)$_2$), –0.24 (q, Si(*C*H$_3$)$_2$), 14.3 (q, OCH$_2$*C*H$_3$),

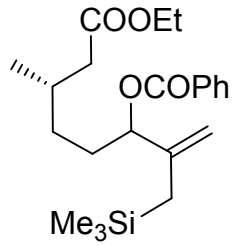
14.4 (q, OCH_2CH_3), 19.7 (q, $CHCH_3$), 19.8 (q, $CHCH_3$), 19.96 (t, CH_2Si), 19.97 (t, CH_2Si), 21.1 (t, CH_2Si), 21.2 (t, CH_2Si), 29.5 (t, CH_2CHO), 29.7 (t, CH_2CHO), 30.6 (d, $CHCH_3$), 30.8 (d, $CHCH_3$), 33.5 (t, CH_2CH_2CHO), 33.6 (t, CH_2CH_2CHO), 41.8 (t, CH_2COO), 41.9 (t, CH_2COO), 60.29 (t, OCH_2CH_3), 60.33 (t, OCH_2CH_3), 76.51 (s, SO_2C), 76.54 (s, SO_2C), 77.1 (d, CHOCOPh), 77.4 (d, CHOCOPh), 128.17 (d, C_{meta}), 128.19 (d, C_{meta}), 128.96 (d, C_{ortho} or C_2), 128.97 (d, C_{ortho} or C_2), 129.42 (s, C_{ipso}), 129.45 (s, C_{ipso}), 129.5 (d, C_{ortho} or C_2), 129.6 (d, C_{ortho} or C_2), 130.4 (d, 2×C_1), 132.0 (t, 2×SiCH=CH_2), 133.0 (d, 2×C_{para}), 133.1 (d, 2×C_3), 139.2 (s, C_4), 139.3 (s, C_4), 140.32 (d, SiCH=CH_2), 140.33 (d, SiCH=CH_2), 165.8 (s, OCOPh), 165.9 (s, OCOPh), 172.9 (s, COOEt), 173.0 (s, COOEt).

Ethyl (3*S*)-3-methyl-7-(trimethylsilylmethyl)-6-((trimethylsilyl)oxy)oct-7-enoate (4-14a):



Yield 88 mg (13%) as an inseparable 1:1 mixture of unassigned diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.83; IR ν_{max} 3094, 3076, 2984, 2958, 2932, 2906, 2874, 2857, 1726, 1636, 1478, 1462, 1447, 1416, 1393, 1382, 1372, 1261, 1251, 1113, 1090, 1047, 1031, 890, 842, 693 cm^{-1}; MS (ESI+) *m/z* (%) 381 (100) [$M+Na^+$], 359 (30) [$M+H^+$], 269 (10) [M^+–OTMS]; HRMS (ESI) *m/z* [$M+H^+$] calcd for $C_{18}H_{39}O_3Si_2^+$: 359.2432; found: 359.2433; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 18H, Si(CH_3)$_3$), 0.09 (s, 18H, OSi(CH_3)$_3$), 0.92 (d, *J* = 6.6 Hz, 3H, CHCH_3), 0.93 (d, *J* = 6.7 Hz, 3H, CHCH_3), 1.21-1.63 (m, 8H, CH_2CH_2), 1.25 (2×t, *J* = 7.1 Hz, 6H, OCH_2CH_3), 1.35 (2×d, *J* = 14.5 Hz, 2H, CHHSi(CH_3)$_3$), 1.53 (2×d, *J* = 14.5 Hz, 2H, CHHSi(CH_3)$_3$), 1.94 (m, 2H, C$H$$CH_3$), 2.09 (2×dd, *J* = 8.4, 14.5 Hz, 2H, CHHC=O), 2.29 (2×dd, *J* = 5.8, 14.5 Hz, 2H, CHHC=O), 3.90 (2×t, *J* = 6.0 Hz, 2H, CHOSi(CH_3)$_3$), 4.12 (2×q, *J* = 7.1 Hz, 4H, OCH_2CH_3), 4.62 (2×s, 2H, CHH=), 4.87 (2×s, 2H, CHH=); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.7 (q, Si(CH_3)$_3$), 0.4 (q, Si(CH_3)$_3$), 14.4 (q, OCH_2CH_3), 19.8 (q, $CHCH_3$), 20.0 (q, $CHCH_3$), 21.35 (t, CH_2Si), 21.44 (t, CH_2Si), 30.57 (d, $CHCH_3$), 30.59 (d, $CHCH_3$), 32.8 (t, CH_2CH_2CHOSi), 32.9 (t, CH_2CH_2CHOSi), 33.55 (t, CH_2CH_2CHOSi), 33.64 (t, CH_2CH_2CHOSi), 42.0 (t, CH_2C=O), 42.2 (t, CH_2C=O), 60.2 (t, OCH_2CH_3), 76.7 (d, CHOSi), 76.8 (d, CHOSi), 108.3 (t, CH_2=), 108.4 (t, CH_2=), 148.89 (s, =C), 148.94 (s, =C), 173.4 (s, C=O).

Ethyl (3*S*)-6-benzoyloxy-3-methyl-7-(trimethylsilylmethyl)oct-7-enoate (4-15):



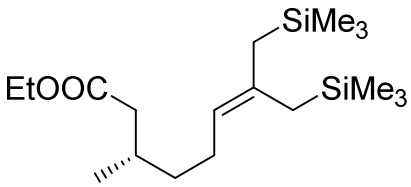
Formed by decomposition on silica gel as an inseparable 1:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.58; IR ν_{max} 3092, 3073, 2986, 2958, 2931, 2875, 2857, 1725, 1717, 1638, 1602, 1585, 1492, 1478, 1462, 1451, 1419, 1393, 1382, 1373, 1315, 1275, 1265, 1251, 1177, 1114, 1097, 1070, 1036, 1027, 999, 888, 853, 845, 712, 690 cm^{-1}; MS (ESI+) *m/z* (%) 413 (100) [M+Na^+], 269 (5) [M–$PhCOO^-$]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{22}H_{34}O_4SiNa^+$: 413.2119; found: 413.2121; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 9H, Si(C*H*$_3$)$_3$), 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 0.95 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 0.97 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.22 (2×t, *J* = 7.1 Hz, 6H, OCH$_2$C*H*$_3$), 1.24-1.43 (m, 4H, CH$_2$C*H*$_2$CHCH$_3$), 1.47 (d, *J* = 14.0 Hz, 2H, *CH*$_2$Si(CH$_3$)$_3$), 1.61 (d, *J* = 13.9 Hz, 2H, C*H*$_2$Si(CH$_3$)$_3$), 1.69-1.87 (m, 4H, C*H*$_2$CH$_2$CHCH$_3$), 1.98 (m, 2H, C*H*CH$_3$), 2.12 (2×dd, *J* = 8.3, 14.5 Hz, 2H, C*H*HC=O), 2.29 (2×dd, *J* = 5.7, 14.5 Hz, 2H, CH*H*C=O), 4.09 (2×q, *J* = 7.1 Hz, 4H, OC*H*$_2$CH$_3$), 4.72 (2×s, 2H, C*H*H=), 4.95 (2×s, 2H, CH*H*=), 5.33 (m, 2H, C*H*OCOPh), 7.44 (m, 4H, *H*$_{meta}$), 7.55 (t, *J* = 7.4 Hz, 2H, *H*$_{para}$), 8.07 (m, 4H, *H*$_{ortho}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ –1.0 (q, Si(*C*H$_3$)$_3$), 14.4 (q, OCH$_2$*C*H$_3$), 19.7 (q, CH*C*H$_3$), 19.9 (q, CH*C*H$_3$), 22.96 (t, *C*H$_2$Si(*C*H$_3$)$_3$), 23.02 (t, *C*H$_2$Si(*C*H$_3$)$_3$), 30.4 (d, *C*HCH$_3$), 30.5 (d, *C*HCH$_3$), 30.8 (t, 2×*C*H$_2$CH$_2$CHOCOPh), 32.39 (t, CH$_2$*C*H$_2$CHOCOPh), 32.44 (t, CH$_2$*C*H$_2$CHOCOPh), 41.9 (t, *C*H$_2$C=O), 42.0 (t, *C*H$_2$C=O), 60.3 (t, O*C*H$_2$CH$_3$), 77.4 (d, *C*HOCOPh), 77.6 (d, *C*HOCOPh), 108.9 (t, *C*H$_2$=), 109.0 (t, *C*H$_2$=), 128.5 (d, *C*$_{meta}$), 129.7 (d, *C*$_{ortho}$), 130.8 (s, *C*$_{ipso}$), 133.0 (d, *C*$_{para}$), 145.2 (s, =*C*), 145.30 (s, =*C*), 165.81 (s, O*C*OPh), 165.83 (s, O*C*OPh), 173.1 (s, *C*=O), 173.2 (s, *C*=O).

Julia olefination with sodium amalgam (General procedure):

Benzoyloxy sulfones **4-13a,c** (0.739 mmol) were dissolved in dry THF (5 mL) and dry ethanol (10 mL) under a nitrogen atmosphere. Sodium amalgam (369 mg, 1.7 mmol) was added at –20 °C. After 3 h at this temperature, the reaction mixture was diluted with diethyl ether (15 mL) and decanted from mercury. The organic layer was washed with brine and the aqueous layer was extracted with diethyl ether (3×40 mL). The combined organic extracts

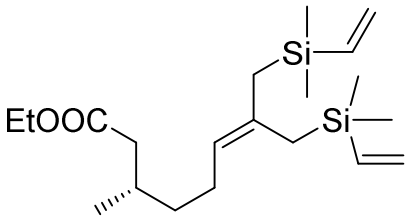
were dried over Na_2SO_4, filtered and evaporated. Purification by column chromatography (EtOAc/hexane 1:50) afforded olefins **4-4a,c**.

Ethyl (*S*)-3-methyl-8-(trimethylsilyl)-7-((trimethylsilyl)methyl)oct-6-enoate (4-4a):



Yield 218 mg (86%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.89; $[\alpha]_D^{20}$: –1.1 (c 1.116 g/100 mL); IR ν_{max} 2986, 2957, 2927, 2876, 2854, 1726, 1645, 1478, 1462, 1447, 1415, 1394, 1382, 1371, 1352, 1259, 1248, 1115, 1095, 1032, 855, 840, 699 cm^{-1}; MS (ESI+) *m/z* (%) 365 (100) $[M+Na^+]$; HRMS (ESI) *m/z* $[M+Na^+]$ calcd for $C_{18}H_{38}O_2Si_2Na^+$: 365.2303; found: 365.2303; ^1H NMR (400 MHz, $CDCl_3$) δ –0.01 (s, 9H, Si(C*H*$_3$)$_3$), 0.02 (s, 9H, Si(C*H*$_3$)$_3$), 0.94 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 1.18-1.34 (m, 2H, C*H*$_2$CH$_2$CH=C), 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.38 (s, 2H, C*H*$_2$Si(CH$_3$)$_3$), 1.44 (AB system, *J* = 13.5 Hz, 2H, C*H*$_2$Si(CH$_3$)$_3$), 1.81-2.02 (m, 3H, C*H*CH$_3$, C*H*$_2$CH=C), 2.09 (dd, *J* = 8.6, 14.4 Hz, 1H, C*H*HC=O), 2.30 (dd, *J* = 5.8, 14.4 Hz, 1H, CH*H*C=O), 4.12 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.75 (t, *J* = 7.0 Hz, 1H, C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ –1.0 (q, Si(*C*H$_3$)$_3$), –0.5 (q, Si(*C*H$_3$)$_3$), 14.5 (q, OCH$_2$*C*H$_3$), 19.8 (q, CH*C*H$_3$), 23.9 (t, *C*H$_2$Si(*C*H$_3$)$_3$), 26.3 (t, *C*H$_2$CH=C), 29.5 (t, *C*H$_2$Si(*C*H$_3$)$_3$), 30.3 (d, *C*HCH$_3$), 37.5 (t, *C*H$_2$CH$_2$CH=C), 42.1 (t, *C*H$_2$C=O), 60.2 (t, O*C*H$_2$CH$_3$), 119.4 (d, *C*H=C), 134.4 (s, CH=*C*), 173.4 (s, *C*=O).

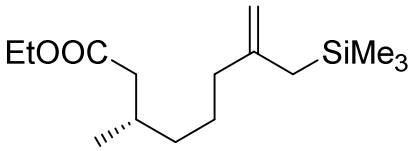
Ethyl (*S*)-8-(dimethyl(vinyl)silyl)-7-((dimethyl(vinyl)silyl)methyl)-3-methyloct-6-enoate (4-4c):



Yield 201 mg (76%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.77; $[\alpha]_D^{20}$: –3.2 (c 0.437 g/100 mL); IR ν_{max} 3058, 2967, 2936, 2864, 1743, 1467, 1409, 1375, 1291, 1252, 1194, 1159, 1100, 1071, 1038, 1012, 953, 835, 759, 619 cm^{-1}; MS (ESI+) *m/z* (%) 389 (100) $[M+Na^+]$; HRMS (ESI) *m/z* $[M+Na^+]$ calcd for $C_{20}H_{38}O_2Si_2Na^+$: 389.2303; found: 389.2303; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H, Si(C*H*$_3$)$_2$), 0.09 (s, 6H, Si(C*H*$_3$)$_2$), 0.93 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.16-1.34 (m, 2H, C*H*$_2$CH$_2$CH=C), 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$),

1.44 (s, 2H, CH_2Si(CH$_3$)$_2$), 1.50 (AB system, *J* = 13.6 Hz, 2H, CH_2Si(CH$_3$)$_2$), 1.81-2.02 (m, 3H, C*H*CH$_3$, CH_2CH=C), 2.10 (dd, *J* = 8.4, 14.5 Hz, 1H, C*H*HC=O), 2.30 (dd, *J* = 5.7, 14.6 Hz, 1H, CH*H*C=O), 4.12 (q, *J* = 7.1 Hz, 2H, OCH_2CH$_3$), 4.80 (t, *J* = 7.0 Hz, 1H, C*H*=CCH$_2$Si), 5.65 (dd, *J* = 3.9, 20.3 Hz, 1H, SiCH=C*H*H), 5.67 (dd, *J* = 3.9, 20.2 Hz, 1H, SiCH=C*H*H), 5.92 (dd, *J* = 3.8, 14.6 Hz, 1H, SiCH=CH*H*), 5.94 (dd, *J* = 3.8, 14.7 Hz, 1H, SiCH=CH*H*), 6.13 (dd, *J* = 14.8, 20.4 Hz, 1H, SiC*H*=CHH), 6.17 (dd, *J* = 14.7, 20.2 Hz, 1H, SiC*H*=CHH); ^{13}C NMR (100 MHz, CDCl$_3$) δ –2.9 (q, Si(*C*H$_3$)$_2$), –2.5 (q, Si(*C*H$_3$)$_2$), 14.5 (q, OCH$_2$*C*H$_3$), 19.8 (q, CH*C*H$_3$), 22.8 (t, *C*H$_2$Si(CH$_3$)$_2$), 26.3 (t, *C*H$_2$CH=C), 28.3 (t, *C*H$_2$Si(CH$_3$)$_2$), 30.2 (d, *C*HCH$_3$), 37.4 (t, *C*H$_2$CH$_2$CH=C), 42.1 (t, *C*H$_2$C=O), 60.2 (t, O*C*H$_2$CH$_3$), 120.4 (d, *C*H=C), 131.5 (t, SiCH=*C*H$_2$), 133.5 (s, CH=*C*), 139.6 (d, Si*C*H=CH$_2$), 173.4 (s, *C*=O).

Ethyl (*S*)-3-methyl-7-((trimethylsilyl)methyl)oct-7-enoate (4-16):

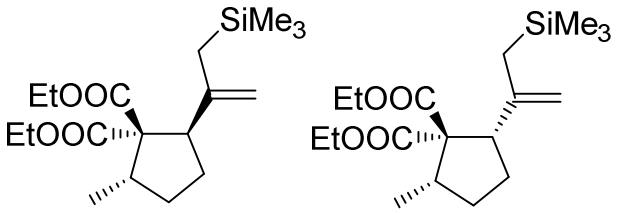


Compound **4-16** was confirmed by significant signals of two hydrogen atoms of 1,1-disubstituted double bond in NMR and HRMS: HRMS (ESI) *m/z* [M+Na$^+$] calcd for C$_{15}$H$_{30}$O$_2$SiNa$^+$: 293.1907; found: 293.1908; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.57 (m, 1H, C=C*H*H), 4.50 (m, 1H, C=CH*H*);

Alkoxycarbonylation/oxidative radical cyclization/carbocation desilylation (General procedure):

*n*BuLi (1.14 mL, 1.82 mmol, 1.6*M* in hexane) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.31 mL, 1.82 mmol) in dry DME (20 mL) at –78 °C under a nitrogen atmosphere. After stirring for 30 min, olefins **4-4a** or **4-4c** (0.70 mmol) in DME (0.5 mL) were added dropwise at –78 °C. After stirring for 30 min, ethyl chloroformate (0.08 mL, 0.84 mmol) was added. After completion of the carboxylation, ferrocenium hexafluorophosphate (534 mg, 1.61 mmol) was added in portions at 0 °C until a blue color of the mixture persisted. The reaction mixture was stirred for aditional 30 min and quenched with a few drops of saturated NH$_4$Cl solution. The mixture was diluted with diethyl ether (25 mL) and filtered through a pad of silica gel. The solvent was evaporated and purification of the residue by column chromatography (EtOAc/hexane 1:200) afforded cyclopentanes **4-3a,c**. Compound **4-18a** generated by incomplete reaction was isolated.

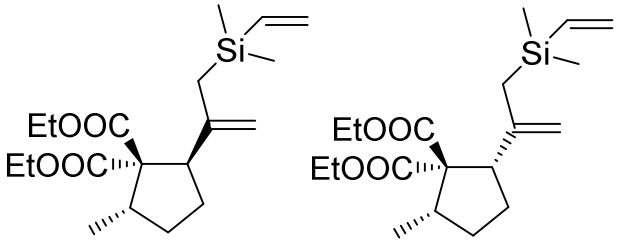
Diethyl (2*S*,5*S*)-2-methyl-5-(3-(trimethylsilyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate, diethyl (2*S*,5*R*)-2-methyl-5-(3-(trimethylsilyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (4-3a):



major - *trans* minor - *cis*

Yield 198 mg (83%) as an inseparable 10:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.56; IR ν_{max} 3083, 2982, 2958, 2931, 2906, 2875, 2856, 1741, 1716, 1629, 1475, 1463, 1447, 1420, 1390, 1380, 1368, 1258, 1249, 1115, 1095, 1044, 1023, 880, 857, 841, 695 cm^{-1}; MS (CI+) *m/z* (%) 341 (95) [M+H$^+$], 325 (100) [M$^+$–CH_3], 295 (30) [M$^+$–OEt]; Anal. calcd for $C_{18}H_{32}O_4Si$ (340.54): C 63.49, H 9.47; found: C 63.80, H 9.75; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer (*trans*): δ 0.01 (s, 9H, $Si(CH_3)_3$), 0.95 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.20 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.23 (m, 1H, $CH_3CHCHHCH_2$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.51 (dd, *J* = 13.3, 0.9 Hz, 1H, C*H*H$Si(CH_3)_3$), 1.61 (dd, *J* = 13.3, 1.0 Hz, 1H, CH*H*$Si(CH_3)_3$), 1.67 (m, 1H, CH_3CHCH_2CHH), 1.94 (m, 2H, $CH_3CHCHHCHH$), 2.91 (m, 1H, C*H*CH_3), 3.29 (dd, *J* = 7.5, 9.6 Hz, 1H, CH_2=CC*H*CH_2), 3.93 (dq, *J* = 10.8, 7.2 Hz, 1H, OCH_2CH_3), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H, OCH_2CH_3), 4.13 (dq, *J* = 10.8, 7.1 Hz, 1H, OCH_2CH_3), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H, OCH_2CH_3), 4.57 (q, *J* = 1.1 Hz, 1H, C=CH_2), 4.60 (t, *J* = 1.0 Hz, 1H, C=CH_2); minor diastereomer (*cis*), detectable signals: δ 2.29 (m, 1H, C*H*CH_3), 3.20 (dd, *J* = 10.6, 8.8 Hz, 1H, CH_2=CC*H*CH_2), 4.61 (s, C=CH_2), 4.71 (d, *J* = 1.1 Hz, 1H, C=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (*trans*): δ 1.3 (q, $Si(CH_3)_3$), 14.1 (q, OCH_2CH_3), 14.3 (q, OCH_2CH_3), 17.1 (q, $CHCH_3$), 29.1 (t, $CH_2Si(CH_3)_3$), 31.3 (t, $CH_2CHC=CH_2$), 33.1 (t, $CH_2CH_2CHC=CH_2$), 41.2 (d, $CHCH_3$), 52.2 (d, CH_2=C*C*H), 60.7 (t, OCH_2CH_3), 60.9 (t, OCH_2CH_3), 68.1 (s, *C*C=O), 108.3 (t, C=*C*H_2), 148.9 (s, *C*=CH_2), 171.1 (s, *C*=O), 172.0 (s, *C*=O); minor diastereomer (*cis*): δ 2.3 (q, $Si(CH_3)_3$), 14.20 (q, OCH_2CH_3), 14.25 (q, OCH_2CH_3), 15.6 (q, $CHCH_3$), 27.6 (t, $CH_2Si(CH_3)_3$), 29.8 (t, $CH_2CHC=CH_2$), 31.5 (t, $CH_2CH_2CHC=CH_2$), 45.1 (d, $CHCH_3$), 53.0 (d, CH_2=C*C*H), 60.3 (t, OCH_2CH_3), 61.1 (t, OCH_2CH_3), 67.8 (s, *C*C=O), 108.7 (t, C=*C*H_2), 146.6 (s, *C*=CH_2), 169.3 (s, *C*=O), 172.6 (s, *C*=O).

Diethyl (2*S*,5*S*)-2-methyl-5-(3-(dimethyl(vinyl)silyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate, diethyl (2*S*,5*R*)-2-methyl-5-(3-(dimethyl(vinyl)silyl)prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (4-3c):

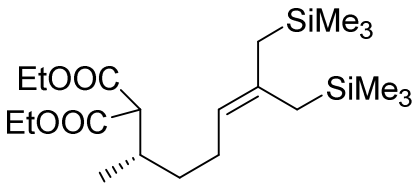


major - *trans* minor - *cis*

Yield 194 mg (79%) as a an inseparable 20:1 mixture of diastereomers as colorless oil. R_f (EtOAc/hexane 1:5) = 0.63; IR ν_{max} 2967, 2939, 2883, 1728, 1636, 1467, 1409, 1299, 1252, 1212, 1184, 1118, 1099, 1075, 1048, 1013, 953, 879, 837, 760 cm^{-1}; MS (CI+) *m/z* (%) 353 (100) [M+H^+], 337 (50) [M^+–CH_3], 325 (40) [M^+–CH=CH_2], 307 (40) [M^+–OEt], 279 (30) [M^+–COOEt]; HRMS (CI) *m/z* [M+H^+] calcd for $C_{19}H_{33}O_4Si^+$: 353.2148; found: 353.2136; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer (*trans*): δ = 0.09 (s, 3H, Si(C*H*$_3$)$_2$), 0.10 (s, 3H, Si(C*H*$_3$)$_2$), 0.95 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.20 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.22 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.25 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.61 (d, *J* = 13.3 Hz, 1H, C*H*HSi(CH$_3$)$_2$), 1.64 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.68 (d, *J* = 13.3 Hz, 1H, CH*H*Si(CH$_3$)$_2$), 1.92 (m, 2H, CH$_3$CHCH*H*CH*H*), 2.91 (dquint, *J* = 10.8, 6.9 Hz, 1H, C*H*CH$_3$), 3.29 (dd, *J* = 7.4, 9.7 Hz, 1H, CH$_2$=CC*H*CH$_2$), 3.94 (dq, *J* = 10.8, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.12 (dq, *J* = 10.8, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 4.13 (dq, *J* = 10.8, 7.0 Hz, 1H, OC*H*$_2$CH$_3$), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.60 (d, *J* = 1.1 Hz, 1H, C=C*H*H), 4.62 (d, *J* = 0.9 Hz, 1H, C=CH*H*), 5.67 (dd, *J* = 3.9, 20.3 Hz, 1H, CH=C*H*H), 5.95 (dd, *J* = 3.9, 14.6 Hz, 1H, CH=CH*H*), 6.17 (dd, *J* = 14.6, 20.3 Hz, 1H, C*H*=CHH); minor diastereomer (*cis*), detectable signals: δ = 1.05 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 2.28 (t, *J* = 9.1 Hz, 1H, C*H*CH$_3$), 3.29 (dd, *J* = 10.6, 8.8 Hz, 1H, =CC*H*CH$_2$), 4.64 (s, C=C*H*$_2$), 4.74 (d, *J* = 1.1 Hz, 1H, C=C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (*trans*): δ −3.4 (q, Si(*C*H$_3$)$_2$), −3.2 (q, Si(*C*H$_3$)$_2$), 14.0 (q, OCH$_2$*C*H$_3$), 14.2 (q, OCH$_2$*C*H$_3$), 17.0 (q, CH*C*H$_3$), 27.8 (t, *C*H$_2$Si(CH$_3$)$_2$), 31.1 (t, *C*H$_2$CHC=CH$_2$), 32.9 (t, *C*H$_2$CH$_2$CHC=CH$_2$), 41.1 (d, *C*HCH$_3$), 52.0 (d, =C*C*H), 60.6 (t, O*C*H$_2$CH$_3$), 60.8 (t, O*C*H$_2$CH$_3$), 67.9 (s, *C*CO$_2$), 108.8 (t, C=*C*H$_2$), 131.73 (t, CH=*C*H$_2$), 138.8 (d, *C*H=CH$_2$), 148.4 (s, *C*=CH$_2$), 171.0 (s, *C*=O), 171.8 (s, *C*=O); minor diastereomer (*cis*): δ − 2.5 (q, Si(*C*H$_3$)$_2$), − 2.3 (q, Si(*C*H$_3$)$_2$), 14.08 (q, OCH$_2$*C*H$_3$), 14.14 (q, OCH$_2$*C*H$_3$), 15.5 (q, CH*C*H$_3$), 26.3 (t, *C*H$_2$Si(CH$_3$)$_3$), 28.6 (t,

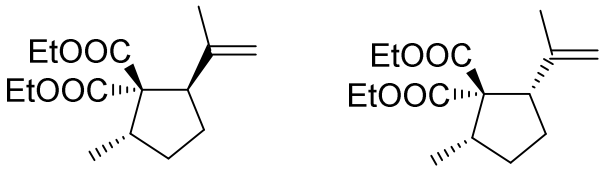
*C*H$_2$CHC=CH$_2$), 31.5 (t, *C*H$_2$CH$_2$CHC=CH$_2$), 44.9 (d, *C*HCH$_3$), 52.8 (d, CH$_2$=C*C*H), 60.2 (t, O*C*H$_2$CH$_3$), 61.0 (t, O*C*H$_2$CH$_3$), 67.6 (s, *C*CO$_2$), 109.1 (t, C=*C*H$_2$), 131.65 (t, CH=C*H$_2$*), 138.9 (d, *C*H=CH$_2$), 146.0 (s, *C*=CH$_2$), 169.1 (s, *C*=O), 172.5 (s, *C*=O).

Diethyl (*S*)-2-(7-(trimethylsilyl)-6-((trimethylsilyl)methyl)hept-5-en-2-yl)malonate (4-18a):



Yield 17 mg (6%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.49; $[\alpha]_D^{20}$: +7.0 (c 0.358 g/100 mL); IR ν_{max} 2964, 2938, 2839, 1740, 1469, 1373, 1251, 1156, 1101, 1071, 1039, 855, 771, 700 cm^{-1}; MS (ESI+) *m/z* (%) 437 (100) [M+Na$^+$]; HRMS (ESI) *m/z* [M+Na$^+$] calcd for $C_{21}H_{42}O_4Si_2Na^+$: 437.2514; found: 437.2513; ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.02 (s, 9H, Si(C*H*$_3$)$_3$), 0.01 (s, 9H, Si(C*H*$_3$)$_3$), 0.98 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 1.15-1.31 (m, 2H, C*H*HCH$_2$CH=C, C*H*$_2$Si(CH$_3$)$_3$), 1.24 (t, *J* = 7.1 Hz, 6H, OCH$_2$C*H*$_3$), 1.33-1.47 (m, 4H, CH*H*CH$_2$CH=C, C*H*$_2$Si(CH$_3$)$_3$), 1.88 (m, 1H, C*H*HCH=C), 1.95 (m, 1H, CH*H*CH=C), 2.26 (m, 1H, C*H*CH$_3$), 3.23 (d, *J* = 7.9 Hz, 1H, C*H*C=O), 4.18 (q, *J* = 7.1 Hz, 4H, OC*H*$_2$CH$_3$), 4.73 (t, *J* = 6.9 Hz, 1H, C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ –0.7 (q, Si(*C*H$_3$)$_3$), –0.2 (q, Si(*C*H$_3$)$_3$), 14.57 (q, OCH$_2$*C*H$_3$), 14.59 (q, OCH$_2$*C*H$_3$), 17.3 (q, CH*C*H$_3$), 24.1 (t, *C*H$_2$Si(CH$_3$)$_3$), 26.5 (t, *C*H$_2$CH=C), 29.8 (t, *C*H$_2$Si(CH$_3$)$_3$), 33.6 (d, *C*HCH$_3$), 35.3 (t, *C*H$_2$CH$_2$CH=C), 58.2 (d, *C*HC=O), 61.47 (t, O*C*H$_2$CH$_3$), 61.54 (t, O*C*H$_2$CH$_3$), 119.3 (d, *C*H=C), 135.1 (s, CH=*C*), 169.3 (s, *C*=O), 169.5 (s, *C*=O).

Diethyl (2*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate and diethyl (2*S*,5*S*)-2-methyl-5-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (4-2):

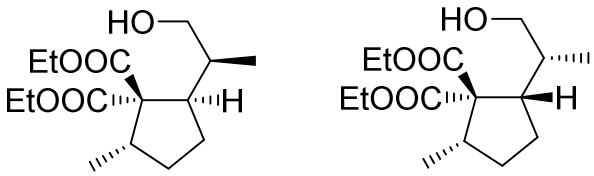


major - *trans* minor - *cis*

$BF_3 \cdot OEt_2$ (130 μL, 1.03 mmol) was added dropwise to silylated ester **4-3a** (320 mg, 0.94 mmol) in dry DCM (19 mL) at –20 °C under a nitrogen atmosphere. The reaction mixture was stirred at this temperature overnight. The reaction was quenched by adding a few drops of saturated $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted three

times with diethyl ether. The combined organic extracts were dried over $MgSO_4$, filtered and evaporad. Purification by column chromatography (EtOAc/hexane 1:100) afforded 227 mg (90%) of **4-2** as an inseparable 10:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.41; IR ν_{max} 2982, 2928, 2959, 2873, 2855, 1717, 1646, 1636, 1465, 1457, 1448, 1437, 1419, 1394, 1374, 1369, 1252, 1113, 1094, 1032, 894, 849, 840 cm^{-1}; MS (ESI+) *m/z* (%) 291 (100) [$M+Na^+$]; Anal. calcd for $C_{15}H_{24}O_4$ (268.35): C 67.14, H 9.01; found: C 67.39, H 9.20; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer (*trans*): δ 0.90 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.13 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.19 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.22 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.62 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.65 (d, *J* = 0.7 Hz, 3H, CH$_2$=CC*H*$_3$), 1.81-1.99 (m, 2H, CH$_3$CHCH*H*CH*H*), 2.85 (dquint, *J* = 10.3, 7.0 Hz, 1H, C*H*CH$_3$), 3.33 (dd, *J* = 8.7, 8.1 Hz, 1H, CH$_2$=CC*H*CH$_2$), 3.93 (dq, *J* = 10.7, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H, OC*H*$_2$CH$_3$), 4.67 (s, 1H, C=C*H*$_2$), 4.70 (s, 1H, C=C*H*$_2$); minor diastereomer (*cis*), detectable signals: δ 1.09 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.16 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.20 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.67 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.69 (s, 3H, CH$_2$=CC*H*$_3$), 1.80 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.87 (m, 1H, CH$_3$CHCH*H*CH$_2$), 1.95 (m, 1H, CH$_3$CHCH$_2$CH*H*), 2.30 (m, 1H, C*H*CH$_3$), 3.17 (dd, *J* = 10.7, 8.7 Hz, 1H, CH$_2$=CC*H*CH$_2$), 3.98-4.22 (m, 4H, OC*H*$_2$CH$_3$), 4.73 (s, C=C*H*$_2$), 4.74 (s, C=C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (*trans*): δ 14.0 (q, OCH$_2$*C*H$_3$), 14.24 (q, OCH$_2$*C*H$_3$), 17.3 (q, CH*C*H$_3$), 23.1 (q, CH$_2$=C*C*H$_3$), 29.9 (t, *C*H$_2$CHC=CH$_2$), 32.9 (t, *C*H$_2$CH$_2$CHC=CH$_2$), 40.9 (d, *C*HCH$_3$), 52.2 (d, CH$_2$=C*C*H), 60.8 (t, O*C*H$_2$CH$_3$), 60.9 (t, O*C*H$_2$CH$_3$), 67.6 (s, *C*CO$_2$), 112.5 (t, *C*H$_2$=C), 146.2 (s, CH$_2$=*C*), 171.1 (s, *C*=O), 171.5 (s, *C*=O); minor diastereomer (*cis*): δ 14.1 (q, OCH$_2$*C*H$_3$), 14.16 (q, OCH$_2$*C*H$_3$), 15.5 (q, CH*C*H$_3$), 23.3 (q, CH$_2$=C*C*H$_3$), 27.9 (t, *C*H$_2$CHC=CH$_2$), 30.9 (t, *C*H$_2$CH$_2$CHC=CH$_2$), 44.7 (d, *C*HCH$_3$), 53.5 (d, CH$_2$=C*C*H), 60.3 (t, O*C*H$_2$CH$_3$), 61.0 (t, O*C*H$_2$CH$_3$), 66.9 (s, *C*CO$_2$), 112.4 (t, *C*H$_2$=C), 144.8 (s, CH$_2$=*C*), 169.3 (s, *C*=O), 172.2 (s, *C*=O).

Diethyl (2*R*,5*S*)-2-((*S*)-1-hydroxypropan-2-yl)-5-methylcyclopentane-1,1-dicarboxylate and diethyl (2*S*,5*S*)-2-((*R*)-1-hydroxyprop-2-yl)-5-methylcyclopentane-1,1-dicarboxylate (4-25):

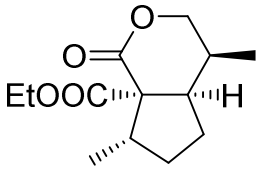


major - *trans* minor - *cis*

9-BBN (2.26 mL, 1.13 mmol, 0.5*M* in THF) was added dropwise to a mixture of olefin **4-2** (127 mg, 0.47 mmol) in dry THF (0.25 mL) at 0 °C under a nitrogen atmosphere. After stirring the mixture at room temperature for 15 h, the starting material was consumed as indicated by TLC. 10% NaOH solution (1.5 mL) was added slowly at 0 °C. After stirring for 15 min, 30% H_2O_2 solution (1.5 mL) was added dropwise to the reaction mixture. The mixture was stirred for 50 min and saturated NH_4Cl (10 mL) was added, the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 10% $Na_2S_2O_3$ solution (3 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated and purification by column chromatography (EtOAc/hexane 1:30, gradient to 1:10) gave 111 mg (83%) of alcohol **4-25** as an in principle separable 10:1 mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.39; IR ν_{max} 3440, 2972, 2944, 2885, 1723, 1467, 1372, 1302, 1254, 1188, 1117, 1099, 1071, 1037, 865, 763 cm^{-1}; MS (ESI+) *m/z* (%) 309 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{15}H_{26}O_5Na^+$: 309.1673; found: 309.1673; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer (*trans*): δ 0.85 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHC), 0.99 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH$_2$O), 1.10-1.32 (m, 7H, C*H*$_3$CH$_2$O, CH$_3$CHC*H*HCH$_2$), 1.36 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.63 (m, 1H, CH$_3$C*H*CH$_2$O), 1.86 (m, 1H, CH$_3$CHCH$_2$CH*H*), 2.09 (m, 1H, CH$_3$CHCH*H*CH$_2$), 2.65 (dt, *J* = 7.3, 11.7 Hz, 1H, CH$_2$C*H*CHCH$_3$), 2.77 (sext, *J* = 7.2 Hz, 1H, CH$_3$C*H*C), 3.36 (dd, *J* = 6.8, 10.8 Hz, 1H, C*H*HOH), 3.54 (dd, *J* = 4.4, 10.8 Hz, 1H, CH*H*OH), 4.08 (m, 2H, CH$_3$C*H*$_2$O), 4.20 (m, 2H, CH$_3$C*H*$_2$O); minor diastereomer (*cis*), detectable signals: δ 0.97 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHC), 1.08 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH$_2$O), 2.27 (m, 1H, CH$_3$C*H*C), 2.57 (m, 1H, CH$_2$C*H*CHCH$_3$), 3.37 (m, 1H, C*H*HOH), 3.56 (m, 1H, CH*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer (*trans*): δ 14.1 (q, *C*H$_3$CH$_2$O), 14.23 (q, *C*H$_3$CH$_2$O), 16.8 (q, *C*H$_3$CHCH$_2$O), 18.8 (q, *C*H$_3$CHC), 27.5 (t, CH$_3$CHCH$_2$*C*H$_2$), 32.5 (t, CH$_3$CH*C*H$_2$CH$_2$), 37.6 (d, *C*HCH$_2$O), 41.1 (d, CH$_3$*C*HC), 47.7 (d, CH$_2$*C*HCHCH$_3$), 61.07 (t, CH$_3$*C*H$_2$O), 61.09 (t, CH$_3$*C*H$_2$O), 66.5 (t, *C*H$_2$OH), 66.7 (s, *C*CO$_2$), 171.7 (s, *C*=O), 172.0 (s, *C*=O); minor

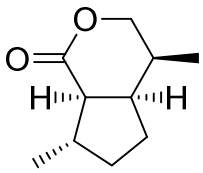
diastereomer (*cis*): δ 14.15 (q, *C*H_3CH_2O), 14.20 (q, *C*H_3CH_2O), 15.3 (q, *C*H_3CHCH_2O), 16.6 (q, *C*H_3CHC), 27.8 (t, $CH_3CHCH_2CH_2$), 31.0 (t, $CH_3CHCH_2CH_2$), 38.6 (d, *C*HCH_2O), 45.3 (d, CH_3CHC), 50.2 (d, $CH_2CHCHCH_3$), 60.5 (t, CH_3CH_2O), 61.10 (t, CH_3CH_2O), 65.9 (t, *C*H_2OH), 66.9 (s, *C*CO_2), 169.9 (s, *C*=O), 172.6 (s, *C*=O).

Ethyl (4*S*,4a*R*,7*S*,7a*R*)-4,7-dimethyl-1-oxohexahydrocyclopenta[c]pyran-7a(1*H*)-carboxylate (4-26):



p-TsOH (6 mg, 0.030 mmol) was added to a diastereomeric mixture of alcohol **4-25** (29 mg, 0.1 mmol) and $CDCl_3$ (0.5 mL). The reaction mixture was directly monitored in the NMR tube. The reaction was completed after 1 h and a few drops of saturated Na_2CO_3 solution were added. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (diethyl ether/pentane 1:30, gradient to 1:10) giving 23 mg (96%) of lactone **4-26** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.31; $[\alpha]_D^{20}$: +23.3 (c 0.300 g/100 mL); IR ν_{max} 2966, 2933, 2863, 1749, 1732, 1467, 1382, 1257, 1237, 1208, 1176, 1126, 1043, 1017 cm^{-1}; MS (ESI+) *m/z* (%) 263 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{13}H_{20}O_4Na^+$: 263.1254; found: 263.1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH$_2$O), 1.12 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CHC), 1.25 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$O), 1.40 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.47 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.78 (m, 2H, CH$_3$CHCH*H*CH*H*), 2.32 (m, 1H, CH$_3$C*H*CH$_2$O), 2.47 (m, 1H, CH$_3$C*H*C), 2.96 (dt, *J* = 7.2, 10.9 Hz, 1H, CH$_2$C*H*CHCH$_3$), 4.08 (d, *J* = 5.1 Hz, 2H, CHC*H*$_2$O), 4.17 (dq, *J* = 7.1, 10.9 Hz, 1H, CH$_3$C*H*HO), 4.19 (dq, *J* = 7.0, 10.9 Hz, 1H, CH$_3$CH*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (q, *C*H_3CHCH_2O), 14.3 (q, *C*H_3CH_2O), 15.7 (q, *C*H_3CHC), 26.5 (t, $CH_3CHCH_2CH_2$), 29.7 (d, *C*HCH_2O), 33.4 (t, $CH_3CHCH_2CH_2$), 44.2 (d, CH_3CHC), 47.3 (d, $CH_2CHCHCH_3$), 61.5 (s, *C*C=O), 61.8 (t, CH_3CH_2O), 72.0 (t, CH*C*H$_2$O), 171.1 (s, *C*=O), 172.0 (s, *C*=O).

Dihydronepetalactone, (4*S*,4a*R*,7*S*,7a*R*)-4,7-dimethylhexahydrocyclopenta[c]pyran-1(3*H*)-one (4-1a):

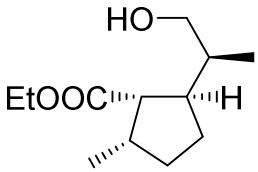


Scheme 4.8: A carefully nitrogen-flushed mixture of lactone **4-26** (5 mg, 0.02 mmol), anhydrous LiCl (1.5 mg, 0.036 mmol), water (1.25 μL, 0.069 mmol) and DMSO (0.2 mL) was heated to 160 °C for 3 h. After cooling to room temperature, saturated $NaHCO_3$ (2 mL) and water (2 mL) were added. The aqueous layer was extracted with diethyl ether (3×2 mL), and the organic extract was washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/pentane 1:30, gradient to 1:1) affording 2.7 mg (49%) of dihydronepetalactone **4-1a**, which was inseparable from starting lactone **4-26**, as a colorless oil, and alcohol **4-27**.

Scheme 4.12: A carefully nitrogen-flushed mixture of carboxylic acid **4-36** (15 mg, 0.07 mmol) and DMSO (0.2 mL) was heated to 130 °C for 5 hours. After cooling to room temperature, water (3 mL) was added. The aqueous layer was extracted with diethyl ether (3×3 mL) and the organic extract was washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (diethyl ether/pentane 1:30, gradient to 1:1) affording 10 mg (85%) of dihydronepetalactone **4-1a** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.30; $[\alpha]_D^{20}$: +66.9 (c 0.121 g/100 mL); IR ν_{max} 2966, 2935, 2864, 2363, 2348, 1742, 1467, 1383, 1251, 1209, 1175, 1122, 1085, 1062, 968, 851, 830, 807, 670 cm^{-1}; MS (ESI+) *m/z* (%) 191 (100) [M+Na^+]; HRMS (EI) *m/z* [M^+] calcd for $C_{10}H_{16}O_2^+$: 168.1150; found: 168.1151; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCH$_2$O), 1.14-1.25 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.20 (d, *J* = 6.4 Hz, 3H, C*H*$_3$CHCHC=O), 1.43 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.75 (m, 1H, CH$_3$CHCH$_2$CH*H*), 1.93 (m, 1H, CH$_3$CHCH*H*CH$_2$), 2.00 (m, 1H, CH$_3$C*H*CHC=O), 2.23 (m, 1H, CH$_3$C*H*CH$_2$O), 2.43 (dd, *J* = 9.3, 10.8 Hz, 1H, C*H*C=O), 2.52 (m, 1H, CH$_2$C*H*CHCH$_3$), 4.02 (ddd, *J* = 1.6, 3.9, 11.1 Hz, 1H, C*H*HO), 4.08 (dd, *J* = 10.4, 11.0 Hz, 1H, CH*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (q, *C*H$_3$CHCH$_2$O), 19.5 (q, *C*H$_3$CHCHC=O), 26.5 (t, CH$_3$CHCH$_2$*C*H$_2$), 31.2 (d, *C*HCH$_2$O), 35.2 (t, CH$_3$CH*C*H$_2$CH$_2$), 40.6 (d, CH$_2$*C*HCHCH$_3$), 41.7 (d, CH$_3$*C*HCHC=O), 50.7 (d, *C*HC=O), 70.1 (t, *C*H$_2$O), 174.5

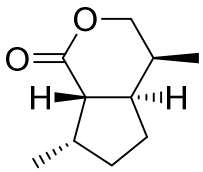
(s, *C*=O). The data are in agreement with those in the cited literature for racemic dihydronepetalactone.[42]

Ethyl (1*S*,2*R*,5*S*)-2-((*S*)-1-hydroxyprop-2-yl)-5-methylcyclopentane-1-carboxylate (4-27):



Yield 0.5 mg (11%) as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.15; IR ν_{max} 3525, 3498, 3420, 3371, 2967, 2935, 2864, 1738, 1466, 1382, 1241, 1189, 1158, 1039 cm^{-1}; MS (ESI+) *m/z* (%) 237 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{12}H_{22}O_3Na^+$: 237.1461; found: 237.1461; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 3H, $HOCH_2CHCH_3$), 0.93 (d, *J* = 7.0 Hz, 3H, $CH_3CHCH_2CH_2$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.33-1.47 (m, 2H, $CH_3CHCHHCHH$), 1.73 (m, 2H, $HOCH_2CHCH_3$, OH), 1.79 (m, 1H, $CH_3CHCHHCH_2$), 1.94 (m, 1H, CH_3CHCH_2CHH), 2.35 (m, 1H, $CH_3CHCH_2CH_2$), 2.55 (m, 1H, $CH_3CHCH_2CH_2CH$), 2.64 (t, *J* = 8.8 Hz, 1H, CHC=O), 3.44 (AB part of ABX system, *J* = 6.5, 6.7, 11.4 Hz, 2H, CH_2OH), 4.17 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (q, $HOCH_2CHCH_3$), 14.5 (q, OCH_2CH_3), 16.4 (q, $CH_3CHCH_2CH_2$), 29.9 (t, $CH_3CHCH_2CH_2$), 34.6 (t, $CH_3CHCH_2CH_2$), 38.0 (d, $CH_3CHCH_2CH_2$), 39.8 (d, $HOCH_2CHCH_3$), 42.5 (d, $CH_3CHCH_2CH_2CH$), 50.0 (d, CHC=O), 60.5 (t, CH_2OH), 66.9 (t, OCH_2CH_3), 176.3 (s, *C*=O).

(4*S*,4a*R*,7*S*,7a*S*)-4,7-Dimethylhexahydrocyclopenta[c]pyran-1(3*H*)-one (4-1b):



Prepared in analogy to the lactonization of **4-25** in presence of a catalytic amount of *p*-TsOH. The reaction mixture of **4-27** (2 mg, 0.009 mmol) was warmed to 40 °C for 4 days affording after evaporation of the solvent 0.8 mg (56%) of lactone **4-1b** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.32; IR ν_{max} 2965, 2933, 2863, 1742, 1467, 1457, 1383, 1251, 1165, 1086, 826, 806, 671 cm^{-1}; MS (ESI+) *m/z* (%) 191 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{10}H_{16}O_2Na^+$: 169.1223; found: 169.1223; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.7 Hz, 3H, CH_3CHCH_2O), 0.97 (d, *J* = 7.1 Hz, 3H, $CH_3CHCHC=O$), 1.26 (m,

1H, $CH_3CHCHHCH_2$), 1.34 (m, 1H, CH_3CHCH_2CHH), 1.68 (m, 1H, CH_3CHCH_2CHH), 1.94 (m, 1H, $CH_3CHCHHCH_2$), 2.21 (m, 1H, $CH_2CHCHCH_3$), 2.26 (m, 1H, $CHCH_2O$), 2.32 (m, 1H, CHC=O), 2.45 (m, 1H, $CH_3CHCHC=O$), 3.96 (dd, *J* = 3.7, 11.4 Hz, 1H, CHHO), 4.31 (dd, *J* = 4.8, 11.4 Hz, 1H, CHHO). The data are in agreement with those in the cited literature.[211]

(4*S*,4a*R*,7*S*,7a*R*)-4,7-Dimethyl-1-oxohexahydrocyclopenta[c]pyran-7a(1*H*)-carboxylic acid (4-36):

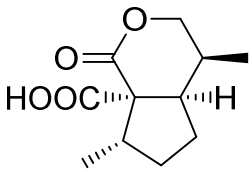
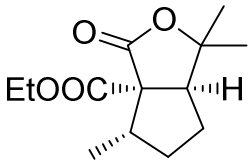


Table 4.1, entry 8: Potassium trimethylsilanolate (200 mg, 1.5 mmol) was added to alcohol **4-25** (45 mg, 0.15 mmol) and dry THF (5 mL) under an argon atmosphere. The reaction mixture was refluxed for 1 day and a few drops of HCl (1*M*) were added after cooling. The mixture was diluted with water, the layers were separated and the aqueous was extracted with DCM (3×5 mL). The organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure affording 96% of crude 1:1 mixture of 16 mg of acid **4-36** and 12 mg of dihydronepetalactone **4-1a**.

Table 4.1, entry 4: Potassium hydroxide (500 mg, 8.9 mmol) was dissolved in water (5 mL) and was added to a mixture of alcohol **17** (40 mg, 0.14 mmol) and methanol (5 mL). The reaction mixture was heated to reflux for a week. After completion, it was acidified by HCl (1*M*) to pH = 1. Methanol was evaporated under reduced pressure and DCM was added. The layers were separated and the aqueous was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Evaporation gave 28 mg (93%) of crude acid **4-36** as a colorless oil. MS (ESI+) *m/z* (%) 235 (40) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{11}H_{16}O_4Na^+$: 235.0941; found: 235.0941; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 7.0 Hz, 3H, CH_3CHCH_2O), 1.15 (d, *J* = 6.9 Hz, 3H, CH_3CHC), 1.56 (m, 1H, CH_3CHCH_2CHH), 1.69 (m, 1H, $CH_3CHCHHCH_2$), 1.85 (m, 1H, $CH_3CHCHHCH_2$), 1.94 (m, 1H, CH_3CHCH_2CHH), 2.21 (m, 1H, CH_3CHC), 2.25 (m, 1H, CH_3CHCH_2O), 3.33 (m, 1H, $CH_2CHCHCH_3$), 4.20 (ddd, *J* = 1.9, 4.2, 11.2 Hz, 1H, CHHO), 4.27 (dd, *J* = 11.2, 11.3 Hz, 1H, CHHO), 12.04 (broad s, 1H, COOH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0 (q, CH_3CHCH_2O), 15.2 (q, CH_3CHC), 25.4 (t, $CH_3CHCH_2CH_2$), 31.2 (d,

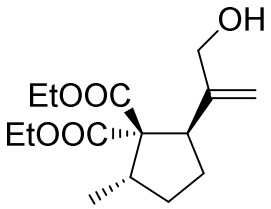
CH_3CHCH_2O), 32.8 (t, $CH_3CHCH_2CH_2$), 44.6 (d, $CH_2CHCHCH_3$), 48.7 (d, CH_3CHC), 60.9 (s, *C*C=O), 71.4 (t, CH_2O), 170.8 (s, *C*OOH), 177.5 (s, *C*$OOCH_2$).

Ethyl (3a*R*,4*S*,6a*S*)-1,1,4-trimethyl-3-oxotetrahydro-1H-cyclopenta[c]furan-3a(3*H*)-carboxylate (4-45):



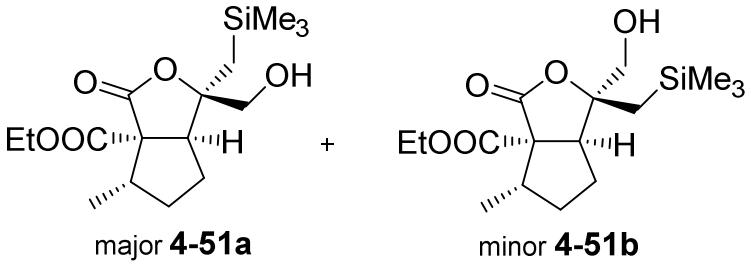
To a solution of allylsilane **4-3c** (5 mg, 0.014 mmol) in a mixture of DCM (0.4 mL) and trifluoroacetic acid (0.1 mL), KHF_2 (2.2 mg, 0.028 mmol) was added. The reaction mixture was refluxed for 3 h, cooled to room temperature and poured into ice-water. After extraction with diethyl ether, the combined organic layers were washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated. Purification by column chromatography (diethyl ether/pentane 1:30, gradient to 1:1) gave 2.5 mg (73%) of lactone **4-45** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.42; IR ν_{max} 2966, 2934, 2864, 1782, 1734, 1467, 1381, 1275, 1247, 1167, 1130, 1099, 1085, 1028, 963, 917, 825, 670 cm^{-1}; MS (ESI+) *m/z* (%) 263 (100) [$M+Na^+$]; HRMS (ESI) *m/z* [$M+Na^+$] calcd for $C_{13}H_{20}O_4Na^+$: 263.1254; found: 263.1254; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 7.0 Hz, 3H, $CHCH_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.31 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.43 (m, 1H, $CH_3CHCHHCH_2$), 1.63 (m, 1H, CH_3CHCH_2CHH), 1.81-1.93 (m, 2H, $CH_3CHCHHCHH$), 2.57 (m, 1H, CH_2CHCH_3), 3.04 (t, *J* = 8.3 Hz, 1H, $CHC(CH_3)_2$), 4.20 (m, 2H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (q, OCH_2CH_3), 16.2 (q, $CHCH_3$), 24.1 (q, $C(CH_3)_2$), 27.8 (t, $CH_3CHCH_2CH_2$), 29.8 (q, $C(CH_3)_2$), 35.5 (t, $CH_3CHCH_2CH_2$), 44.4 (d, $CHCH_3$), 54.5 (d, $CHC(CH_3)_2$), 62.1 (t, OCH_2CH_3), 63.5 (s, *C*C=O), 83.7 (s, $C(CH_3)_2$), 169.9 (s, $COOCH_2CH_3$), 175.5 (s, $COOC(CH_3)_2$).

Diethyl (2*R*,5*S*)-2-(hydroxyprop-2-en-2-yl)-5-methylcyclopentane-1,1-dicarboxylate (4-9):



*m*CPBA (6.7 mg, 0.039 mmol) and $NaHCO_3$ (4.4 mg, 0.053 mmol) were added to a mixture of olefin **4-3a** (9 mg, 0.026 mmol) and DCM (2 mL). The reaction mixture was stirred for 2 h and aqueous sulfuric acid in THF (0.14 mL in 0.45 mL THF) was added. After 1 h, water (2 mL) was added. The mixture was extracted with DCM, the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Purification by column chromatography (diethyl ether/pentane 1:30, gradient to 1:10) gave 0.4 mg (5%) of allylic alcohol **4-9** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.15; IR ν_{max} 3501, 3419, 3371, 2965, 2934, 2863, 1729, 1467, 1454, 1372, 1257, 1197, 1142, 1099, 1075, 1029, 843 cm^{-1}; MS (ESI+) *m/z* (%) 307 (100) [M+Na^+]; HRMS (ESI) *m/z* [M+Na^+] calcd for $C_{15}H_{24}O_5Na^+$: 307.1516; found: 307.1517; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.15 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 1.54 (broad s, 1H, OH), 1.75 (m, 1H, C*H*$_2$), 1.84 (m, 1H, C*H*$_2$), 2.06 (m, 2H, C*H*$_2$), 2.94 (m, 1H, C*H*CH$_3$), 3.41 (dd, *J* = 6.9, 11.4 Hz, 1H, CH$_2$=CC*H*CH$_2$), 3.95 (m, 2H, OC*H*$_2$CH$_3$, C*H*HOH), 4.10 (m, 3H, OC*H*$_2$CH$_3$, CH*H*OH), 4.24 (m, 1H, OC*H*$_2$CH$_3$), 4.82 (s, 1H, C=C*H*H), 5.01 (s, 1H, C=CH*H*).

Ethyl (1*R*,3a*R*,4*S*,6a*S*)-1-(hydroxymethyl)-4-methyl-3-oxo-1-((trimethylsilyl)methyl)tetrahydro-1H-cyclopenta[c]furan-3a(3*H*)-carboxylate (4-51a), ethyl (1*S*,3a*R*,4*S*,6a*S*)-1-(hydroxymethyl)-4-methyl-3-oxo-1-((trimethylsilyl)methyl)tetrahydro-1H-cyclopenta[c]furan-3a(3*H*)-carboxylate (4-51b):

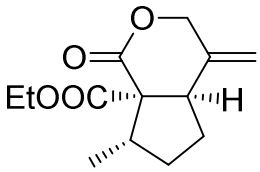


major **4-51a** minor **4-51b**

Conditions C: N-methylmorpholine *N*-oxide (155 mg, 1.32 mmol), OsO_4 (225 μL, 0.018 mmol, 2.5 wt% in *t*BuOH) and pyridine (1 drop) were added subsequently to a solution of silylated olefin **4-3a** (150 mg, 0.44 mmol) in acetone/water/*t*-butanol mixture 1:1:1 (3 mL)

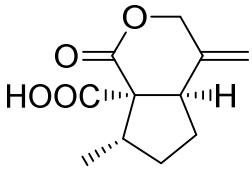
at room temperature. The reaction mixture was stirred for 16 h, concentrated and diluted with water. The mixture was extracted with DCM, the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 1:30, gradient to 1:2.5) giving 121 mg (84%) of alcohol **4-51** as a 6:1 in principle separable mixture of diastereomers as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.34 (major diastereomer), 0.30 (minor diastereomer); IR ν_{max} 3523, 3489, 2964, 2934, 2863, 1776, 1734, 1466, 1373, 1303, 1253, 1189, 1140, 1082, 1033, 996, 919, 846, 695 cm^{-1}; MS (ESI+) *m/z* (%) 679 (20) [2M+Na^+], 351 (100) [M+Na^+]; Anal. calcd for $C_{16}H_{28}O_5Si$ (328.48): C 58.50, H 8.59; found: C 58.71, H 8.69; ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer: δ 0.11 (s, 9H, Si(C*H*$_3$)$_3$), 0.98 (d, *J* = 14.8 Hz, 1H, C*H*HSi(CH$_3$)$_3$), 1.08 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 1.23 (d, *J* = 14.9 Hz, 1H, CH*H*Si(CH$_3$)$_3$), 1.30 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.48 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.59 (broad s, 1H, O*H*), 1.72 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.82 (m, 1H, CH$_3$CHCH*H*CH$_2$), 1.94 (m, 1H, CH$_3$CHCH$_2$CH*H*), 2.52 (m, 1H, CH$_3$C*H*), 3.26 (t, *J* = 8.5 Hz, 1H, C*H*CCH$_2$), 3.53 (d, *J* = 11.9 Hz, 1H, C*H*HOH), 3.62 (d, *J* = 11.9 Hz, 1H, CH*H*OH), 4.23 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$); minor diastereomer: δ 0.09 (s, 9H, Si(C*H*$_3$)$_3$), 1.05 (d, *J* = 14.7 Hz, 1H, C*H*HSi(CH$_3$)$_3$), 1.06 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH), 1.25 (d, *J* = 14.7 Hz, 1H, CH*H*Si(CH$_3$)$_3$), 1.33 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.48 (m, 1H, CH$_3$CHC*H*HCH$_2$), 1.59 (broad s, 1H, O*H*), 1.72 (m, 1H, CH$_3$CHCH$_2$C*H*H), 1.82 (m, 1H, CH$_3$CHCH*H*CH$_2$), 1.94 (m, 1H, CH$_3$CHCH$_2$CH*H*), 2.65 (m, 1H, CH$_3$C*H*), 3.23 (t, *J* = 7.9 Hz, 1H, C*H*CCH$_2$), 3.60 (d, *J* = 12.0 Hz, 1H, C*H*HOH), 3.80 (d, *J* = 12.0 Hz, 1H, CH*H*OH), 4.24 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ 0.4 (q, Si(*C*H$_3$)$_3$), 14.36 (q, OCH$_2$*C*H$_3$), 16.1 (q, *C*H$_3$CH), 21.7 (t, *C*H$_2$Si(CH$_3$)$_3$), 29.0 (t, CH$_3$CHCH$_2$*C*H$_2$), 35.0 (t, CH$_3$CH*C*H$_2$CH$_2$), 45.6 (d, *C*HCH$_3$), 51.9 (d, *C*HCCH$_2$), 61.8 (t, O*C*H$_2$CH$_3$), 66.8 (s, *C*C=O), 70.1 (t, *C*H$_2$OH), 88.73 (s, *C*CH$_2$), 170.0 (s, *C*=O), 175.6 (s, *C*=O); detectable signals of minor diastereomer: δ 0.1 (q, Si(*C*H$_3$)$_3$), 14.38 (q, OCH$_2$*C*H$_3$), 15.9 (q, *C*H$_3$CH), 26.4 (t, *C*H$_2$Si(CH$_3$)$_3$), 28.5 (t, CH$_3$CHCH$_2$*C*H$_2$), 35.6 (t, CH$_3$CH*C*H$_2$CH$_2$), 44.0 (d, *C*HCH$_3$), 53.6 (d, *C*HCCH$_2$), 62.2 (t, O*C*H$_2$CH$_3$), 66.1 (t, *C*H$_2$OH), 88.75 (s, *C*CH$_2$).

Ethyl (4a*R*,7*S*,7a*R*)-7-methyl-4-methylene-1-oxohexahydrocyclopenta[c]pyran-7a(1*H*)-carboxylate (4-8):



$BF_3 \cdot OEt_2$ (9.3 µL, 0.074 mmol) was added dropwise to **4-51** (20 mg, 0.062 mmol) in dry DCM (1 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by adding a few drops of saturated $NaHCO_3$ solution and diluted with water. The aqueous layer was extracted three times with diethyl ether and the organic extract was dried over $MgSO_4$. Purification by column chromatography (diethyl ether/pentane 1:5, gradient to 1:1) gave 13 mg (86%) of lactone ester **4-8** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.35; $[\alpha]_D^{20}$: –15.9 (c 0.270 g/100 mL); IR ν_{max} 2967, 2933, 2863, 1734, 1467, 1456, 1383, 1250, 1166, 671 cm^{-1}; MS (ESI+) *m/z* (%) 261 (100) [M+Na^+]; Anal. calcd for $C_{13}H_{18}O_4$ (238.28): C 65.53, H 7.61; found: C 65.69, H 7.69; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH), 1.23 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.38 (m, 2H, CH$_3$CHC*H*HCH$_2$, CH$_3$CHCH$_2$C*H*H), 1.85 (m, 1H, CH$_3$CHCH*H*CH$_2$), 2.14 (m, 1H, CH$_3$CHCH$_2$CH*H*), 2.84 (m, 1H, CH$_3$C*H*), 3.62 (m, 1H, C*H*C=CH$_2$), 4.18 (dq, *J* = 7.1, 10.7 Hz, 1H, CH$_3$C*H*HO), 4.20 (dq, *J* = 7.2, 10.7 Hz, 1H, CH$_3$CH*H*O), 4.45 (dt, *J* = 0.7, 12.2 Hz, 1H, OC*H*HC=CH$_2$), 4.47 (dtd, *J* = 0.5, 1.3, 12.3 Hz, 1H, OCH*H*C=CH$_2$), 4.98 (d, *J* = 2.6 Hz, 1H, C*H*H=C), 5.08 (m, 1H, CH*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3 (q, OCH$_2$*C*H$_3$), 16.5 (q, *C*H$_3$CH), 31.2 (t, CH$_3$CHCH$_2$*C*H$_2$), 33.5 (t, CH$_3$CH*C*H$_2$CH$_2$), 42.6 (d, *C*HCH$_3$), 47.4 (d, *C*HC=CH$_2$), 62.3 (t, O*C*H$_2$CH$_3$), 63.2 (s, *C*C=O), 71.8 (t, O*C*H$_2$C=CH$_2$), 113.7 (t, *C*H$_2$=C), 141.6 (s, CH$_2$=*C*), 170.5 (s, *C*=O), 171.5 (s, *C*=O).

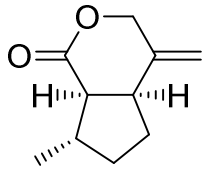
(4a*R*,7*S*,7a*R*)-7-Methyl-4-methylene-1-oxohexahydrocyclopenta[c]pyran-7a(1*H*)-carboxylic acid (4-52):



Potassium hydroxide (1 g, 17.8 mmol) was dissolved in water (2 mL) and added to a mixture of lactone ester **4-8** (40 mg, 0.17 mmol) and methanol (2 mL). The reaction mixture was heated to reflux for 48 h. After completion, it was acidified by hydrochloric acid (1*M*) to

pH = 1. Methanol was evaporated under reduced pressure and DCM was added. The layers were separated and the aqueous was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. Evaporation gave 34 mg (96%) of crude acid **4-52** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.00; MS (EI) *m/z* (%) 211 (10) [M+H$^+$], 192 (50) [M$^+$–H_2O], 165 (100) [M$^+$–COOH], 121 (50) [M$^+$–COOH–COO], 82 (30) [M$^+$–$COOCH_2C{=}CH_2$ –COOH], 67 (50) [M$^+$–$COOCH_2C{=}CH_2$ –Me–COOH]; HRMS (EI) *m/z* [M+H$^+$] calcd for $C_{11}H_{15}O_4^+$: 211.0970; found: 211.0971; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CH), 1.54 (m, 2H, CH_3CHC*H*HC*H*H), 1.86 (m, 1H, CH_3CHCH*H*CH_2), 2.23 (m, 1H, CH_3CHCH_2CH*H*), 2.58 (m, 1H, CH_3C*H*), 3.67 (t, *J* = 8.3 Hz, 1H, C*H*$C{=}CH_2$), 4.59 (dd, *J* = 1.0, 12.3 Hz, 1H, C*H*HO), 4.74 (d, *J* = 12.3 Hz, 1H, CH*H*O), 5.05 (m, 1H, C*H*H=C), 5.09 (d, *J* = 0.8 Hz, 1H, CH*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7 (q, *C*H_3CH), 32.1 (t, CH_3CHCH_2*C*H_2), 33.2 (t, CH_3CH*C*H_2CH_2), 45.9 (d, CH_3*C*H), 47.1 (d, *C*HC=CH_2), 71.6 (t, *C*H_2O), 115.0 (t, *C*H_2=C), 140.3 (s, CH_2=*C*), 172.4 (s, *C*OOH), 174.1 (s, *C*$OOCH_2$).

Dolicholactone, (4aS,7S,7aR)-7-methyl-4-methylenehexahydrocyclopenta[c]pyran-1(3*H*)-one (4-7):



A carefully nitrogen-flushed mixture of carboxylic acid **4-52** (11 mg, 0.02 mmol) and DMSO (0.2 mL) was heated to 110 °C for 4 h. After cooling to room temperature, water (2 mL) was added. The aqueous layer was extracted with diethyl ether (3×3 mL) and the organic extract was washed with brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 1:30, gradient to 10:1) affording 7.9 mg (91%) of dolicholactone **4-7** as a colorless oil. R_f (EtOAc/hexane 1:5) = 0.29; $[\alpha]_D^{20}$: +44.0 (c 0.270 g/100 mL); IR ν_{max} 2969, 2934, 2862, 1738, 1466, 1382, 1297, 1268, 1188, 1024, 972, 801 cm^{-1}; MS (EI) *m/z* (%) 166 (10) [M$^+$], 138 (20) [M$^+$–CO], 121 (20) [M$^+$–COOH], 82 (70) [M$^+$–$COOCH_2C{=}CH_2$], 67 (10) [M$^+$–$COOCH_2C{=}CH_2$–Me]; HRMS (EI) *m/z* [M$^+$] calcd for $C_{10}H_{14}O_2^+$: 166.0993; found: 166.0994; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH), 1.16 (m, 1H, CH_3CHC*H*HCH_2), 1.45 (m, 1H, CH_3CHCH_2C*H*H), 1.89 (m, 1H, $CHCH_3CH$*H*CH_2), 2.05 (m, 1H, CH_3CHCH_2CH*H*), 2.29 (m, 1H, CH_3C*H*), 2.45 (dd, *J* = 8.5, 10.7 Hz, 1H, C*H*C=O), 3.05

(m, 1H, C*H*C=CH_2), 4.53 (dd, *J* = 1.0, 12.0 Hz, 1H, C*H*HO), 4.61 (dd, *J* = 0.6, 12.0 Hz, 1H, CH*H*O), 4.97 (m, 1H, C*H*H=C), 5.04 (m, 1H, CH*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (q, *C*H_3CH), 32.5 (t, CH_3CHCH_2*C*H_2), 34.7 (t, CH_3CH*C*H_2CH_2), 39.4 (d, CH_3*C*H), 42.1 (d, *C*HC=CH_2), 51.2 (d, *C*HC=O), 71.0 (t, *C*H_2O), 113.5 (t, *C*H_2=C), 142.3 (s, CH_2=*C*), 174.0 (s, *C*=O). The data are in agreement with those in the cited literature.[36]

5.3. Crystallographic data

Single-crystal X-ray diffraction data for **1-2h**, **1-2l** and **1-2p** were obtained using a Nonius KappaCCD diffractometer equipped with a Bruker ApexII-CCD detector by monochromatized MoKα radiation (λ = 0.71073 Å) at 150(2) K. The structures were solved by direct methods and refined by full-matrix least squares based on F^2 (SHELXS; SHELXL97[237]). The hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom). The crystallographic data are summarized in Table S3. Crystallographic data (excluding structure factors) for the structures **1-2p**, **1-2h** and **1-2l** have been deposited at the Cambridge Crystallographic Data Centre with CCDC numbers **CCDC 915126**, **915127** and **915128,** respectively. Copies of the data can be obtained, free of charge by application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 5.9. Crystal data, data collection and refinement parameters for **1-2p**, **1-2h** and **1-2l**.

Compound		**1-2p (CCDC 915126)**	**1-2h (CCDC 915127)**	**1-2l (CCDC 915128)**
Empirical formula		$C_{11}H_{16}O_2S$	$C_{15}H_{24}O_2S$	$C_{13}H_{20}O_2S$
M_r		212.30	268.40	240.35
Crystal habit		colorless, prism	colorless, prism	colorless, plate
Crystal size [mm]		0.53 × 0.41 × 0.11	0.55 × 0.46 × 0.44	0.50 × 0.16 × 0.07
Crystal system		Monoclinic	Monoclinic	orthorhombic
Space group		*Pna* (No. 7)	$P2_1$ (No. 4)	$Pna2_1$ (No. 33)
Unit cell dimensions	a [Å]	5.6949 (2)	6.0029 (2)	15.1216 (13)
	b [Å]	14.2806 (5)	14.7139 (5)	6.1361 (5)
	c [Å]	14.0984 (5)	8.8744 (3)	14.0327 (10)
	α [°]			
	β [°]	89.9970 (10)	107.3670 (10)	
	γ [°]			
Volume [Å^3]		1146.57 (7)	748.11 (4)	1302.06 (18)
Z		4	2	4
D_x [Mg m^{-3}]		1.230	1.192	1.226
μ [mm^{-1}]		0.26	0.21	0.23
θ_{max} [°]		27.5	27.5	26.0
Reflections measured		7345	5140	10310
Unique reflections/observed reflections		3713/3651 [$I > 2\sigma(I)$]	3367/3259 [$I > 2\sigma(I)$]	2537/2073 [$I > 2\sigma(I)$]
R_{int}[a]		0.015	0.013	0.050
Parameters refined		258	167	149
$R(F)$[b], [$F^2 > 2\sigma(F^2)$]		0.028	0.025	0.039
$wR(F^2)$[c]		0.072	0.066	0.077
S[d]		0.96	1.01	1.04
$\Delta\rho_{max}$; $\Delta\rho_{min}$ [e Å^{-3}]		0.38; -0.18	0.25; -0.18	0.22; -0.35

[a] $R_{int} = \left|\sum F_0^2 - F_{0,mean}^2\right| / \sum F_0^2$, [b] $R(F) = \sum \|F_0| - |Fc\| / \sum |F_0|$, [c] $wR(F^2) = \left[\sum\left(w\left(F_0^2 - F_c^2\right)^2\right) / \left(\sum w\left(F_0^2\right)^2\right)\right]^{1/2}$, weighting scheme: $w = [\sigma^2(F_o^2) + (w_1P)^2 + w_2P]^{-1}$, where $P = \_[\max(F_o^2, 0) + 2F_c^2]/3$, [d] $S = [\sum(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{1/2}$

5.4. Copies of ^{1}H and ^{13}C NMR spectra

Examples of ^{1}H NMR spectra of the transmetalation reactions

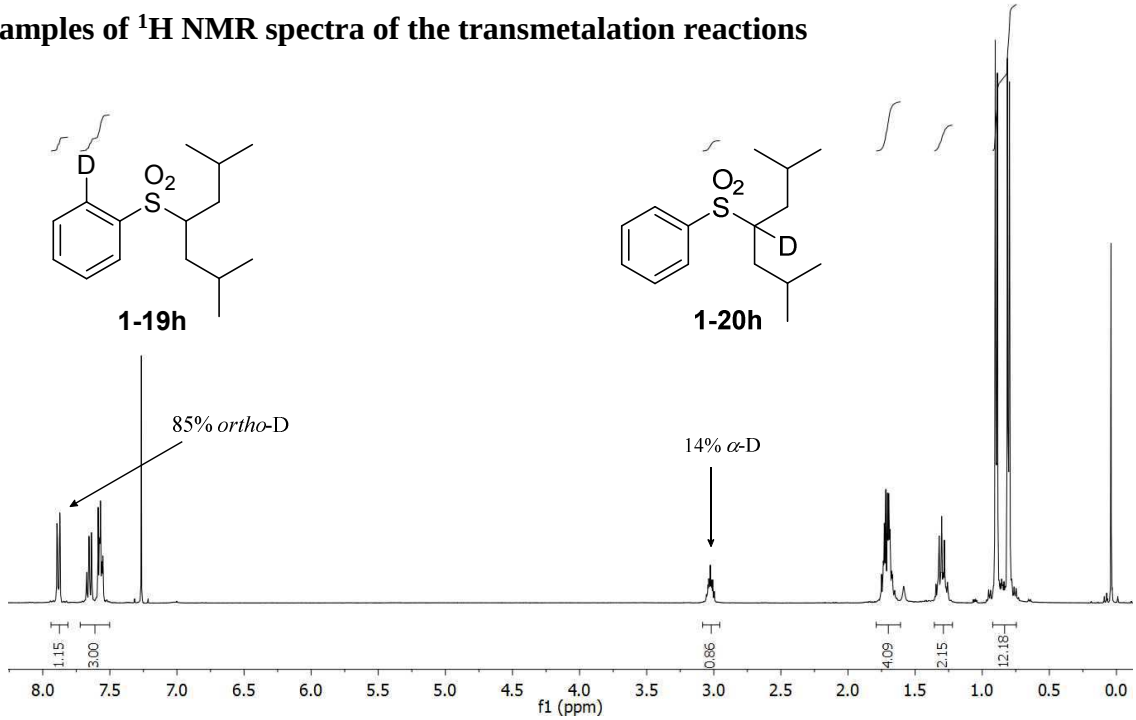


Figure 5.1. Example of ^{1}H NMR spectra of initial deprotonation of **1-2h** at –78 °C.

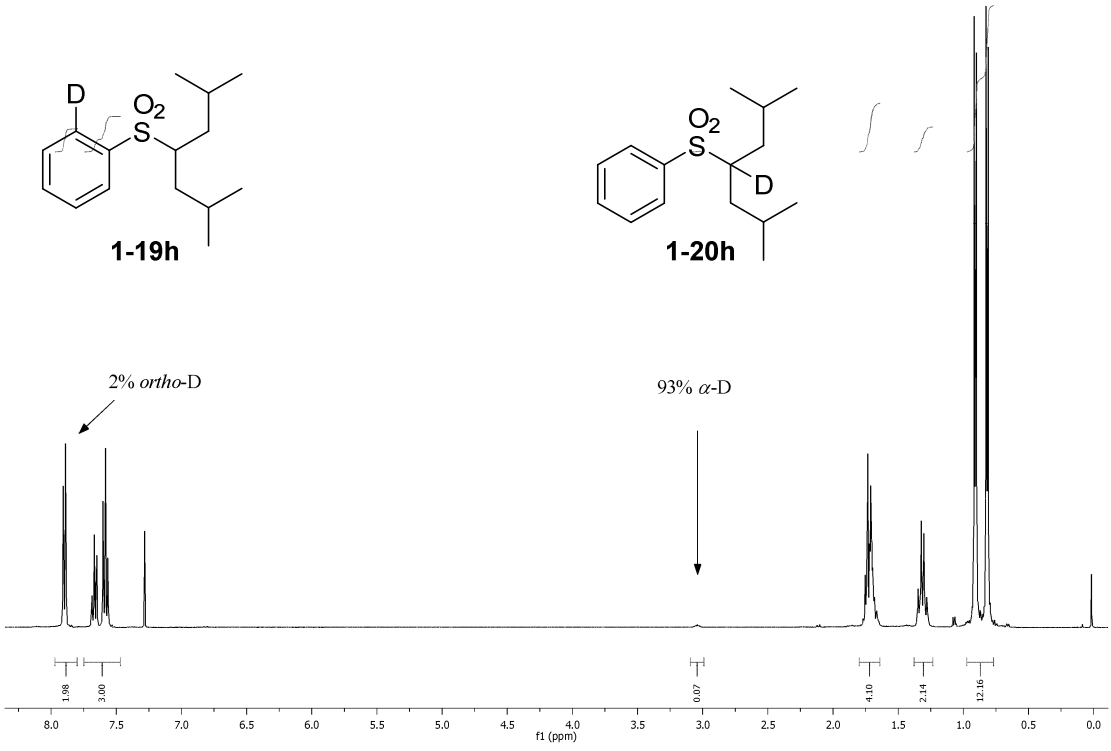


Figure 5.2. Example of ^{1}H NMR spectra after the trasmetalation of **1-*o*-17h** at –20 °C.

6. Abbreviations

$B_{AC}2$	basic acyl cleavage
$B_{AL}2$	basic alkyl cleavage
9-BBN	9-borabicyclo[3.3.1]nonane
brsm	based on recovered starting material
cat.	catalytic amount
CI	chemical ionization
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DoM	directed *ortho*-metalation
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulfoxide
DMVS	dimethylvinylsilyl
EI	electron ionization
equiv.	equivalent(s)
ESI	electrospray ionization
GC	gas chromatography
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
IBX	2-iodoxybenzoic acid
IR	infrared spectrum
KHMDS	potassium hexamethyldisilazide
KIE	kinetic isotope effect
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
*m*CPBA	*meta*-chloroperoxybenzoic acid
m.p.	melting point
MS	mass spectrometry
MW	microwave

*n*BuLi	*n*-butyllithium
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
PDC	pyridinium dichromate
pK_a	log(K_a), where K_a is acid dissociation constant
*p*TsOH	*para*-toluenesulfonic acid
Py	pyridine
R_f	retention factor
r.t.	room temperature
SET	single electron transfer
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
*t*BuLi	*tert*-butyllithium
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethyl-1,2-ethylendiamine
TMS	trimethylsilyl

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8. List of Publications and Conference Contributions

Publications

- L. Řehová, U. Jahn: "Elucidation of the Reaction Mechanism of *ortho*→α Transmetalation Reactions of Alkyl Aryl Sulfone Carbanions" *Eur. J. Org. Chem.* 2014, 4610-4623.
- L. Řehová, I. Císařová, U. Jahn: "The Divergent Reactivity of Alkyl Aryl Sulfones with Bases: Selective Functionalization of *ortho*-Aryl and α-Alkyl Units Enabled by a Unique Carbanion Transmetalation" *Eur. J. Org. Chem.* 2014, 1461-1476.
- V. Kozmík, A. Henke, L. Řehová, M. Kurfurst, M. Slabochová, J. Svoboda, V. Novotná, M. Glogarová: "Liquid Crystalline Benzothiophene Derivatives. Part 2: 2,5-Disubstituted Benzothiophenes" *Liquid Crystals* 2011, *38*, 1245-1261.

Conference contributions

- **2010-2014** Advances in Organic, Bioorganic and Pharmaceutical Chemistry, Czech Republic, *posters*
- **2013** ESOC, 18th European Symposium on Organic Chemistry, Marseille, France, *poster*
- **2013** Vltava 2013, 4th French-Czech Chemistry Meeting, Prague, Czech Republic, *oral communication*
- **2012** French-Czech Meeting on the Chemistry of Biomolecules organised by IBMM Teams, Montpellier, France, *poster*
- **2012** Challenges in Organic Chemistry and Chemical Biology (ISACS7), Edinburgh, United Kingdom, *poster*
- **2011** XXIII Conference on Advances in Organic Chemistry Synthesis (CAOS 2011), Hradec Králové, Czech Republic, *poster*