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Xanthate Transfer**

**GOH KAU KIAT KELVIN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2015**

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Xanthate Transfer**

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ABSTRACT

Formation of carbon-carbon bonds had been by far the most researched and refined objective in organic synthesis. On the contrary, the use of free-radical chemistry in this area had thus been limited to tin-mediated protocols which were gradually losing popularity due to toxicity and purification issues. Xanthates, a class of thiocarbonylthio compounds have found remarkable application in both inter- and intra-molecular tin-free radical additions to simple and un-activated olefins. In this thesis, the use of xanthates is further explored and renewed through combination with other types of radical chemistry previously employed with tin-based initiators. The goal is to develop novel tin-free solutions in the C-C bond formation for the synthesis of highly functionalized molecules which had otherwise been plagued by acid-base problems in ionic chemistry. This concept is briefly demonstrated by a few free-radical alternatives to enolate chemistry involving ketones, lactones and thiolactones.

SUMMARY

- In Chapter 1, a brief history and introduction to free-radical mediated reactions is reviewed, following the rise of radical chemistry through tin-mediated protocols to its subsequent decline. This is then followed by a brief introduction to the chemistry of xanthates as the next new contender for tin-free radical mediated C-C bond synthesis.
- Chapter 2 will introduce the types of manipulation of the xanthate moiety for further transformation of the xanthate adduct to other useful synthetic scaffolds. In this chapter, an accidental discovery led to the development of a novel *O*-secondary alkyl xanthate. This allowed manipulation of the xanthate moiety as a sulfur nucleophile under acid-free condition in the synthesis of 2-sulfolenes. This approach paved an efficient route to acid-sensitive (1*E*,3*E*)-TMS dienes *via* the construction of functionalized TMS 2-sulfolenes. The scope and limitation of this synthetic approach is studied and discussed here.

- In Chapter 3, a brief introduction to radical-mediated synthesis of ketones *via* the use of acyl derivatives is described. This follows the role of acyl derivatives as radical precursors in the synthesis of ketones until their switch to become carbonyl radical acceptors. The integration of keto-xanthates into acyl phosphonate chemistry was found to surpass the conventional halogen atom transfer in this radical cascade. This was brought about by use of the phosphonate radical mediating the xanthate transfer for the synthesis of cyclic 1,5 diketones. This approach could be seen as a radical variant to the conventional ionic-based Robinson-Annulation.

- Finally, Chapter 4 will contain a brief review of alkyl radical addition to carbon-nitrogen unsaturated systems such as the nitrile and oxime ether and their role as indirect carbonyl acceptors. This is then followed by an introduction to the development and use of sulfonyl oxime ethers. A brief overview of α -functionalization of lactones and the importance of the oxime ether group will also

be included. The development of their subsequent extension to heteroatom-substituted sulfonyl oxime ethers as radical carboxylate acceptors for the synthesis of *O*-benzyl oxime ether carboxylate derivatives is described in detail, along with a few novel and unexpected discoveries found in this study.

ABBREVIATIONS

Ac	acetate
AIBN	2,2'-azo bisisobutyronitrile
Ag	silver
AM1	Austin Model 1
Ar	aryl
aq	aqueous
Bu	butyl
BuLi	butyllithium
Bn	benzyl
br	broad
Calcd	calculated
CO	carbon monoxide
°C	degree centigrade
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DHP	dihdropyran
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DNA	deoxyribonucleic acid
d.r.	diastereomeric ratio
DTBP	di-tert-butyl peroxide
EI	positive electron impact ionization
Equiv	equivalent
ESI	electrospray ionization
Et	ethyl
e.V.	electronvolt
g	gram
h	hour(s)
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HRMS	high-resolution mass spectrometry
HWE	Horner–Wadsworth–Emmons
hν	photoirradiation
Hz	hertz
ⁱ Pr	isopropyl
<i>J</i>	coupling constant (NMR)
kcal	kilocalorie(s)
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LUMO	lowest occupied molecular orbital
m-CPBA	meta-chloroperbenzoic acid
M	molarity (mol/L) (concentration)
Me	methyl
mg	milligram

min	minute(s)
mol	mole
mL	millilitre
mmol	millimole
m.p.	melting point
nm	nanometre
NMR	nuclear magnetic resonance
NPhth	phthalimide
OTf	triflate
Ph	phenyl
PhCl	chlorobenzene
Piv	pivaloyl
p-TSA	para-toluenesulfonic acid
ppm	parts per million
RNA	ribonucleic acid
rt	room temperature
SAR	structure-activity relationship
sec	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
TEAI	triethylammonium iodide
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	chlorotrimethylsilane
Ts	tosyl
UV	ultraviolet
V-40	1,1'-azobis(cyclohexane-1-carbonitrile)
Xa	xanthate
Δ	reflux

Chapter I.

Introduction to Free-Radical Mediated Reactions

1.1 History of the first organic free-radical

It was by a stroke of serendipity which led Moses Gomberg to discover the first stable organic free-radical in his synthesis of hexaphenylethane in 1900.¹ However, the notion of a free-radical was met with much resistance as it conflicted with then popular doctrine of the quadrivalency of carbon, which had led to the deduction of many current molecular structures.²

Scheme 1. Formation of the Triphenylmethyl Radical

Fortunately, this was sufficient to spark off various small but progressive steps towards elucidating the identity of this mysterious species. Evidence supporting Gomberg started to accumulate through the work of Paneth and Hofeditz³ who proved that less stabilized alkyl radicals existed as transient and reactive intermediates in the gaseous phase.

1.2 The induction of free-radicals into organic synthesis

Free-radicals in solution phase on the other hand, were largely unknown until 1937, when Hey and Waters described the phenylation of aromatic compounds by benzoyl peroxide as a radical reaction (Scheme 2).⁴ In the same year, Kharasch observed the *anti*-Markovnikov addition of hydrogen bromide to alkenes, presumably *via* a radical chain process as opposed to the ionic pathway which gave the Markovnikov adduct (Scheme 3).⁵

Scheme 2. Phenylation of Benzoyl Peroxide in Benzene

Scheme 3. The Markovnikov and *anti*-Markovnikov Addition of HBr to Alkenes in Presence of Peroxide

These two pioneering discoveries heralded the start of free-radical mediated organic synthesis. Following these discoveries, the mechanism behind free-radical copolymerization was studied by Mayo, Walling and Lewis,⁶ leading to a revolutionary breakthrough in the polymer industry which bore the various important and essential materials used in daily life.

1.3 Rapid development of free-radical mediated organic synthesis towards the end of the 20th century

Notwithstanding these achievements, free-radical chemistry remained a subject of scientific enigma to most organic chemists until the 1960s. In 1973, Kochi compiled a review⁷ of the most significant works describing the formation, structure and reactivity of radicals in the 1950s and 1960s, re-igniting the curiosity of organic chemists to challenge this field of science to develop new applications for synthesis. Towards the end of the 20th century, a few notable works employing the use of free-radicals in organic synthesis include: (i) the combination of a silver salt such as silver nitrate, AgNO_3 and an oxidizing agent such as ammonium persulfate, $(\text{NH}_4)_2\text{S}_2\text{O}_8$ with organic acids resulted in oxidative decarboxylation to liberate alkyl radicals for the free-radical substitution to aromatic compounds by Minisci⁸; (ii) the reduction of alkyl mercury salts to form cyclohexyl free-radicals by Giese⁹; (iii) the use of tin-hydrides with alkyl halides to generate alkyl free-radicals and the manipulation of atom-transfer technique by Curran¹⁰; (iv) the use of allyl stannanes for free-radical allylation by Keck¹² and lastly; (v) the well-known Barton decarboxylation and the Barton-McCombie deoxygenation using the thiohydroxamate ester method by Barton and McCombie¹³.

These classical radical-mediated reactions remained relevant even in modern synthetic routes and methodologies, in particularly, for C-C bond formation (Schemes 3-5).^{14, 15, 16, 17} Purine bases or nucleosides such as **1.1** are basic structural units in RNA and DNA. Radical alkylation at the C6 position *via* the Minisci Reaction offers a mild alternative over ionic pathways for the functionalization of the purine moiety. For example, disproportionation of persulfate anion $\text{S}_2\text{O}_8^{2-}$ by Ag^+ to sulfate dianion SO_4^{2-} and sulfate anion radical $\text{SO}_4^{\cdot-}$ which then react with carboxylates to generate $\text{R}^\cdot$ radical with extrusion of carbon dioxide. This $\text{R}^\cdot$ radical then undergoes a radical substitution

reaction on a protonated purine. Selectivity was achieved due to C-H activation by the neighbouring Ag^+ cation coordinated on the N7 of the purine (Scheme 3). Variations of the R group in functionalized purine **1.2** allow the manipulation of its biological activity by adjustment of the amount of hydrogen bonds.¹⁴

Scheme 3. Alkylation of Purine Nucleosides at C6 *via* the Minisci Reaction

C-C bond formation between alkyl iodides and acrylates can be achieved using the Giese reaction without the need for preparation of the corresponding organometallics which broadly expanded the scope of functionality tolerance. Previously, it was thought that tributyltin chloride was reduced to tributyltin hydride, which dissociates into tributyltin radical under photolysis. The tributyltin radical then abstracts an iodine atom from the alkyl iodide to form the nucleophilic alkyl radical which subsequently adds to methyl acrylate, an electron deficient acceptor and forms a secondary alkyl radical. Tributyltin radical, Bu₃Sn· is regenerated when hydrogen atom is abstracted from Bu₃SnH and propagates the radical chain process (Scheme 4).^{15a} In the tin-free version reported by Ryu,^{15b} the alkyl iodide could dissociate into its corresponding alkyl radical

under photolysis, which then adds to the methyl acrylate to give the radical adduct. α -iodo ester is formed in a reversible halogen atom transfer of an iodine atom from the starting alkyl iodide but the equilibrium is directed by reduction in presence of reducing agent to give the reduced product (Scheme 4).

Scheme 4. The Giese Reaction and its Tin-Free Variation

Barton decarboxylation was utilized to introduce a benzoquinone to the thiohydroxamic ester **1.3** to give quinone **1.4** in the synthesis of ilimaquinone, a marine natural product exhibiting interesting biological and pharmacological properties.¹⁶ Light-induced homolysis of the thiohydroxamic ester **1.3** give alkyl radical **1.3a** which then undergo addition to benzoquinone to give the radical adduct **1.3b**. This in turn abstracts the thiopyridine group from the starting thiohydroxamic ester **1.3** to form quinone **1.3c** and regenerate radical **1.3a** for chain propagation. Quinone **1.3c** is then oxidized to quinone **1.4** in presence of benzoquinone (Scheme 4).

Scheme 5. Barton Decarboxylation in the Synthesis of (-)-Ilimaquinone

However, the most common and highlighted applications involving free-radical mediated synthesis centered around the halogen atom transfer, which was usually engaged in tandem radical cascade for the construction of complex fused ring structures such as Scholarisine A. An elegant synthesis was achieved in a shorter route, stemming from an easily prepared starting material by introduction of a few novel key steps, two of which demonstrated the potential of free-radical mediated reactions.¹⁷ One of them utilizes a Keck allylation on carbonyl-rich bromide **1.5** to give the allylated fused tricycle **1.6** in a tandem radical cascade cyclization. Et₃B-initiated abstraction of bromine atom from bromide **1.5** gave alkyl radical **1.5a** which undergoes intramolecular 6-*exo trig* cyclization to the alkene to generate radical **1.5b** which then adds to allyl tributyltin, liberating Bu₃Sn• to propagate the radical chain process (top of Scheme 6). A second radical-mediated step involves a 1,5-hydrogen atom transfer from radical **1.7a** generated from iodine atom abstraction from iodide **1.7**. Subsequent 5-*exo trig* cyclization and

oxidation gave spiroindolenine **1.8**, the key intermediate to Scholarisine A (bottom of Scheme 6).

Scheme 6. Key Radical Steps in the Synthesis of Scholarisine A¹⁷

In fact, the use of the halogen atom transfer and Bu_3SnH is commonplace in the synthesis of various carbo-polycyclic cores of various natural products such as sativene and cocamphene,¹⁸ norseychellanone,¹⁹ alliacode²⁰ and morphine²¹ (Figure 1) since this method offers a rather mild alternative against ionic processes which do not work with difficult cyclizations or have limited functionality tolerance. Henceforth, these accomplished feats further decorated the use of Bu_3SnH which demonstrated itself as a very effective chain carrier to facilitate a viable chain transfer.

Figure 1. Various Structural Cores achieved by Radical Cyclizations using Bu_3SnH

1.4 The radical chain process - The Tin Hydride Method

Since most free radicals are highly reactive species, they can react with themselves by homo-coupling or disproportionate at rates approaching the diffusion control limit.^{10a} Despite having such a reactivity, direct radical-radical combination are not useful synthetic processes.¹¹ For example, the recombination of radicals would require large stoichiometric amounts of initiators in absence of a chain process and there is no selectivity of product due to lack of manipulation of reaction conditions.¹¹ In addition, the active concentration of free radicals is so low as compared to non-radicals such as the solvents, that reaction between the two are unavoidable.¹¹ Henceforth, it is more useful to consider reactions between radicals and non-radicals for a few reasons.¹¹ Firstly, since the radical character is not diminished during reaction with non-radicals, this allows the use of a catalytic amount of radical initiator. Secondly, the reactions are not diffusion-

controlled, therefore, it is possible to manipulate the reaction by varying substituents on the radical precursors and acceptors. Thirdly, the concentration of non-radicals are easily controlled in experimental manipulation. These could be accomplished by using a chain reaction which is briefly described in Scheme 7.

Tri-*n*-butyltin radical ($\text{Bu}_3\text{Sn}\cdot$) first abstracts a halogen atom or a related functional group X from a radical precursor AX in step 1. This will determine the site of the initial radical according to the location where X is placed on the molecule. The generated radical $\text{A}\cdot$ should have sufficient life-time to form a new intermediate radical $\text{B}\cdot$ *via* either an inter-molecular or intra-molecular reaction in step 2. Both the initial radical $\text{A}\cdot$ and intermediate radical $\text{B}\cdot$ can abstract a hydrogen atom from Bu_3SnH in steps 3 and 4 and this will in turn, regenerate $\text{Bu}_3\text{Sn}\cdot$ to propagate the radical chain from step 1. Steps 3 and 4 are the chain-transfer steps in the radical chain which will control the whole chain process. These are the most important steps in the chain and will determine if the reaction could be self-sustained or collapse in absence of an effective transfer mechanism. They also determine the lifetimes of radicals $\text{A}\cdot$ and $\text{B}\cdot$ and are controlled by the rate constants k_{H} and k_{H}' , which in turn are dependent on the concentration of Bu_3SnH . As such, this can be controlled by dilution control using syringe-pump techniques. Chain termination occurs in step 5 when the radical intermediate is converted to a non-radical product which can no longer participate in the radical chain process. Simply put, for an effective radical chain to manifest, all other reactions and manipulation of the intermediate radicals (e.g. steps 1, 2, 3 and 4) should be faster than the chain-terminating step 5.

Scheme 7. Trialkyltin Hydride-Mediated Radical Reactions

In order to have a successful chain process, the selectivities of the involved radicals have to differ from each other in a controlled manner to be synthetically useful. For example, the alkyl radical $\text{R}\cdot$ in Scheme 8¹¹ can react with an alkene to give a radical adduct *via* k_1 or abstract a hydrogen atom from Bu_3SnH to give the reduced alkane *via* k_2 . Similarly, the generated radical adduct also has possible pathways to either react with another molecule of alkene to give a dimer *via* k_3 or be reduced by hydrogen atom abstraction *via* k_4 . If there is no selectivity between $\text{R}\cdot$ and its radical adduct, ($k_1/k_2 = k_3/k_4$), this can lead to either polymerization ($k_1/k_2 \gg 1$), premature reduction of alkyl radical ($k_1/k_2 \ll 1$) or a mixture of reduced alkane and radical addition product ($k_1/k_2 = 1$).¹¹ In C-C bond formation, $\text{R}\cdot$ radical has to react with the alkene much faster than the reduction process by Bu_3SnH and this can be accomplished by employing low concentration of Bu_3SnH using high dilution techniques to favor k_1 over k_2 .¹¹

Scheme 8. Selectivity Pathways of Radicals in Tin-Hydride Radical Reactions

Selectivity among radicals could be attributed to many factors, which are then further simplified by characterizing two parameters, namely, the kinetic and thermodynamic parameters. Alkyl radicals with electron-donating substituents such as alkyl, alkoxy and amino behave like nucleophiles and react quickly with alkenes bearing electron-withdrawing substituents such as nitrile, ketone and ester and vice versa, electron deficient alkyl radicals behave like electrophiles and react better with electron-rich alkenes. This trend is supported by frontier molecular orbital theory (FMO) which describes the early transition state of such reactions thought to be prevalent in fast radical reactions.^{10a, 11} Radicals have a high lying SOMO (singly occupied molecular orbital) which interact favorably with the LUMO (lowest unoccupied molecular orbital) of the alkene.¹¹ The presence of an electron-withdrawing group lowers the LUMO energy of the alkene, thus, maximizing this interaction by reducing the SOMO-LUMO difference (Figure 2). Radicals that bear electron-withdrawing substituents have comparatively lower SOMO energies such that the SOMO-HOMO interaction is dominant (Figure 2).¹¹

Figure 2. FMO Representations of Nucleophilic Radical and Electron-Poor Alkene (Left) and Electrophilic Radical and Electron-Rich Alkene (Right)

Bond dissociation strength could be used as an estimate to direct site-specific radical formation *via* elimination. For example, a primary radical can add to an alkene or a carbonyl to generate an alkyl adduct or alkoxy radical respectively (Scheme 9). Addition to the alkene involves breaking of a weaker CC π -bond and formation of a stronger CC σ -bond which is thermodynamically favored ($k_1/k_2 \gg 1$).¹¹ This addition reaction is exothermic and can be further enhanced to become synthetically useful by varying substituents on both the incoming radical and alkene as discussed previously in Figure 2. Addition to a carbonyl involves breaking of a strong CO π -bond and formation of a comparatively strong CC σ -bond.¹¹ Due to the small differences in enthalpy between a CO π -bond and CC σ -bond, this addition does not enjoy a similar thermodynamic driving force ($k_3/k_4 \gg 1$) as compared to a reaction with alkenes.¹¹ In addition, the stability of the radical adduct can be used to direct the rearrangement of a radical. An intramolecular 3-*exo trig* attack on an alkene to generate a methylcyclopropyl radical is reversible with fragmentation to give back its starting primary homoallyl radical ($k_5/k_6 = 1$) due to the unfavorable ring strain of cyclopropane ring. However, this can be directed towards the more stable tertiary radical ($k_7/k_8 \gg 1$) (Scheme 9).¹¹

Scheme 9. Selectivity Pathways of Radicals in Elimination and Rearrangement Reactions

1.5 The divergence from organostannanes and a possible alternative solution in organosilanes

The impact of tin is so enormous on radical mediated synthesis that by the start of the 21st century, almost every significant radical mediated methodology involved the use of organostannanes or tin hydrides to some extent.²² However, the same success brought about by tin also resulted in the subsequent reluctance of organic chemists to consider radicals in synthesis. This is briefly shown by a search on Reaxys, a popular database search engine for literature.²³ Publications associated with radicals have been increasing to a maximum in 2011 (Figure 3) while publications in that same subset that involved tin or organostannanes have started to decrease after reaching its peak in 2005 (Figure 4).²³ This shows that although tin is still currently in use, it is gradually excluded or replaced in radical-mediated studies. Trialkyl tin compounds or organostannanes, in particular, those that bear long alkyl chain substituents are extremely toxic²⁴ and the description matches those of the initiators such as Bu_3SnH . The neurotoxicity accompanied by frequent handling and disposal of these organostannanes as well as difficulty in removal of tin residues during isolation by silica-gel column chromatography forced chemists to seek tin-free alternatives or totally abandon the use of free-radical mediated reactions altogether.²⁵ Tin hydride-based methods also suffer from the premature reduction of intermediate radicals,²⁵ limiting the possibility of exploring a greater variety of radical cascade reactions.

Figure 3. List of Publications Containing "Radical" as Keyword from 1995 to 2014

Figure 4. List of Publications Containing "Radical, Tin, Stannane or Sn" as Keyword
from 1995 to 2014

Scheme 10. (TMS)₃SiH-Mediated Radical Addition of Alkyl Iodide

The use of (TMS)₃SiH can also be extended to chalcogen derivatives for use as radical precursors. (TMS)₃Si radicals generated by thermal initiation with AIBN converts selenoester **1.11** to its corresponding acyl radical which then adds to an α,β-unsaturated lactam ester **1.12** to generate a radical adduct, which subsequently abstracts a hydrogen

atom from $(\text{TMS})_3\text{SiH}$ to regenerate $(\text{TMS})_3\text{Si}$ radical for chain propagation.³⁰ Interestingly, due to the stronger Si-H bond in $(\text{TMS})_3\text{SiH}$, hydrogen atom abstraction was slow enough to allow sufficient equilibration of the radical adduct to the more stable *trans* isomer exclusively in 72% yield (Scheme 11).³⁰

Scheme 11. $(\text{TMS})_3\text{SiH}$ -Mediated Radical Addition of Selenoester

Similarly, $(\text{TMS})_3\text{SiH}$ was also found to be a good substitute for Bu_3SnH in mediating radical cascades as shown in Scheme 12.³¹ Iodine atom abstraction from iodide **1.14** gave the aryl radical which then undergoes a 5-*exo trig* cyclization attack from the bottom of the cyclohexene. Subsequently, a second 5-*exo trig* cyclization attack on the azide to generate an aminyl radical which abstract a hydrogen atom from $(\text{TMS})_3\text{SiH}$ to liberate $(\text{TMS})_3\text{Si}$ radical for chain propagation. Stereoselectivity was controlled by the methanesulfonyl aniline side chain of the cyclohexene to give the *cis*-fused ABCE ring system in **1.15**, which is a precursor to aspidospermidine, an indoline alkaloid with known potent biological activity.³¹

Scheme 12. An Example of (TMS)₃SiH-Mediated Radical Cascade

Despite showing promising potential, there are still some drawbacks to the use of (TMS)₃SiH as an effective replacement for Bu₃SnH. Unlike its tin counterpart, (TMS)₃Si adds easily to alkenes and alkynes and is known to be an efficient hydrosilylation agent.²⁵ Therefore, it is mostly competent in fast intramolecular radical cyclization but may prove ineffective in intermolecular radical addition due to strong competition from the hydrosilylation reaction.²⁵ Successful examples^{29, 30} mainly arise from the clever use of activated alkene acceptor and radical precursor pairs. Even so, the exceptional functional group tolerance brought about by the mild conditions offered by radical mediated reactions makes them a powerful tool for C-C bond formation. Thus, this field of synthesis remains one of vital importance, in which, development of new applications, in particularly, tin-free methods can potentially supplement or even replace current ionic pathways that were plagued by functional group compatibility issues.

1.6 The degenerative xanthate transfer: A rising star in tin-free radical mediated synthesis

A decade into the 21st century later, a number of heavy metal-free based methodologies for the generation of alkyl radicals were gaining popularity as reliable and effective synthetic tools.³² Among these next-generation contenders for the tin-free radical mediated synthesis, the use of xanthates by Zard stood out due to its ability to work with un-activated olefins in an intra- and even, inter-molecularly fashion.

Since its inception, developments and applications in free radical mediated reactions were mostly limited to addition to activated olefins or intra-molecular cyclization as seen in previous examples. Only a few reactions were capable of creating a carbon-carbon bond in an intermolecular fashion starting with simple, un-activated olefins. The use of xanthates resolved this longstanding problem (Scheme 13).³³

Once initiation begins, $R\cdot$ radical is formed from the starting xanthate **1.16**. This $R\cdot$ radical can then rapidly add to another molecule of **1.16** to form the stabilized radical adduct **1.17**. Dimerization of two radical units of **1.17** is possible but difficult due to steric hindrance at the bulky radical center. Henceforth, they are likely to do so reversibly without disproportionation. Next, fragmentation of **1.17** can cleave either the C-O bond to give dithioketone **1.18** and a $Et\cdot$ radical or the C-S bond to regenerate $R\cdot$ radical. Cleavage of the stronger C-O bond to generate a high energy ethyl radical is not thermodynamically favorable and thus, it is more likely to regenerate the $R\cdot$ radical and **1.16**. Overall, this shows that the reaction between $R\cdot$ radical and **1.16** is reversible and regenerate. Moreover, such a regenerative effect significantly prolongs the lifetime of the $R\cdot$ radical, making it possible to do additions, even to non-activated alkene **1.18**, forming a new radical adduct **1.20**. This will undergo reversible addition to **1.16** to give another

intermediate radical **1.21** which will then fragmentate again to give addition product **1.22** and the initial $R^\cdot$ radical required to further propagate the chain.

The mechanistic works of each various component of the xanthate transfer builds into a simple yet logical radical chain process. Firstly, the thiocarbonyl group is more radicophilic than any simple olefin, in other words, it rapidly scavenges any reactive radical species such as $R^\cdot$, **1.20** or other radicals derived from the initiator itself. This would mean that radicals formed are rapidly converted into the stabilized radical adducts **1.17** and **1.21**. Secondly, these radical adducts will fragment to give the most stabilized radicals. It is then important to bias the fragmentation of **1.21** preferentially to give **1.22** and $R^\cdot$ radical by designing **1.20** to be less stable than $R^\cdot$ radical. Otherwise, the chain process would be impeded and undesired side reactions will start to manifest. Also, it is important to favor the equilibrium towards regenerating $R^\cdot$ radical so as to prevent a gradual build-up in concentration of **1.20** which can undergo further addition to the olefin, resulting in undesirable telomerization. Finally, as long as the starting xanthate **1.16** is available, the product **1.22** is less preferred to undergo further radical addition and becomes “protected”. The greater the disparity in the relative stabilities of $R^\cdot$ and **1.20**, the easier to channel the direction of the chain to favor the formation of **1.22**, hence, enabling more control over the process.

Scheme 13. The Degenerate Xanthate Transfer Chain Cycle

1.7 Use and application of xanthates

The use of a xanthate is generally more advantageous over the fragile and reactive bromides and iodides for the generation of alkyl radicals.³³ For example, they are comparatively more stable to light degradation, thus allowing for longer storage duration.³³ In some cases, the potassium *O*-ethyl xanthate salt, [EtOC(=S)SK] is cheaper than the halogenating agents and are easy to handle. Furthermore, chlorides, which are rarely involved in free-radical reactions, are easily displaced by xanthates and thus, become potential radical precursors. Also, the use of non heavy-metal initiators such as peroxides, azo derivatives and triethylborane/air combinations work effectively with xanthates similar to that of iodides. More notably, the radical reaction involving xanthates can be run under high concentration and various solvents have been shown to work, including water. Highly functionalized xanthates such as **1.16** are capable of performing efficient inter-molecular additions to various functionalized olefins, allowing facile installation of a carbon bearing both a trifluoromethyl and an amine group to various olefins (Scheme 14).³⁴

Scheme 14. Incorporation of Trifluoromethylamine to Various Functionalized Alkenes

This functional group tolerance is not only limited to the olefin partner but also extends to the xanthate precursors themselves as shown in Scheme 15. Xanthate **1.17** grants access to the trifluoromethyl unit which is an important structural moiety in bioactive molecules,³⁵ while xanthate **1.18** allows incorporation of a Wienreb amide.³⁶ Xanthate **1.19** shows that geminal bis-phosphonates³⁷ are also readily transferred while Xanthate **1.20** give rise to an interesting dithiane derivative.³⁸ Heterocycles are also transferable with this process onto olefins as seen from Xanthates **1.20**, **1.21** and **1.22**.³⁹

Scheme 15. Addition of Various Functionalized Xanthates to Allyl Trimethylsilane

The degenerative nature of the alkyl radical in the xanthate transfer process accompanied with a unique self-regulating process had brought about a true practical solution to the challenges of various radical-mediated synthesis, in particularly, intermolecular C-C bond formation.³³ The broad generality and wide combinations of substrates that could be incorporated in a xanthate reaction also presents an opportunity for the discovery of new and possibly milder types of C-C bond formation which can tolerate multiple functionalities on the same structure. Henceforth, this presents an interesting subject of immense synthetic potential to be studied.

Chapter II.

Manipulation of the Xanthate Moiety as a Latent Sulfur Nucleophile Using Secondary *O*-Alkyl Xanthates: A Chugaev Approach

2.1 Modification of the xanthate group

In general, the xanthate transfer consists of the addition of an alkyl and a thiocarbonylthio (xanthate) group across the alkene, forming a C-C and C-S bond simultaneously as seen in the examples described in Chapter 1 (Schemes 14 and 15). If the C-C bond formation is the only intended transformation of the radical addition, the xanthate group could be removed by means of reduction or elimination. In other instances, the xanthate group can be transformed to other functionalities *via* substitution methods that can be either ionic or radical in nature. All in all, the C-S bond can be further functionalized or removed after the addition is completed and presents tremendous synthetic utility potential.

2.2 Removal of the xanthate group

In most simple radical addition of xanthates to alkenes, the resulting product is still nevertheless a xanthate and can undergo radical initiation to give an alkyl radical. Hydrogen atom abstraction by the intermediate alkyl radical in presence of a suitable hydrogen atom donor such as tris(trimethylsilyl)silane or hypophosphorous acid and its corresponding salts behaves like a pseudo reduction process.⁴⁰ This results in a mild homolytic method for the transformation of a C-S bond to a C-H bond. Conversely, stoichiometric use of lauryl peroxide, DLP and isopropanol could also effect this hydrogen atom abstraction process.⁴¹ DLP is first used as initiator on the xanthate **2.1** to generate the alkyl radical which then abstracts hydrogen atom from isopropanol which acts as the hydrogen donor to give product **2.2**. The liberated hydroxyisopropyl radical is then oxidized to the cation by carboxylic radical generated from initial homolysis of DLP to form the carboxylate anion which in turn, deprotonates the cation to give acetone and

carboxylic acid as byproduct (Scheme 16).⁴² Since this reaction does not have a radical chain process, a stoichiometric amount of DLP is required.

Scheme 16. Synthesis of a Xanthate-Free Product of Pleuromutilin

In some circumstances, elimination of the xanthate group can also result in the introduction of unsaturation into the product. For example, radical addition of acyl xanthate **2.3** to vinyl pinacol boronic ester gave the xanthate **2.4** which then undergoes β -elimination with Et₃N to give unsaturated boronate derivative **2.5** with release of thiolate (Scheme 17). To prevent a Michael-addition type reaction, the thiolate is quickly trapped by methyl iodide and the iodide anion is scavenged by available excess amine to form the insoluble ammonium iodide.⁴³

Scheme 17. Synthesis of Vinyl Boronate from Acyl Xanthate

2.3 Substitution of the xanthate group

Radical acceptors can influence the type of additional transformation of the xanthate addition products as well. Addition to enol ethers such as **2.6** or vinyl acetate gave rise to *O-S* type acetals whereby the C-S bond was suggested to be weakened by an anomeric-type effect and became susceptible towards acid-catalyzed elimination of dithiocarbonate and oxocarbenium formation.^{33, 34, 44} In the first example, Ag^+ activated the dithiocarbonate as a leaving group with the formation of an oxocarbenium as a result of electron transfer from the lone pair electrons on anomeric oxygen atom. This oxocarbenium cation is then attacked with retention of stereochemistry by nucleophilic nitrogen on the pyrimidine activated by desilylation from trifluoromethanesulfonyl anion. The dithiocarbonate then displaces another trimethylsilyl group to form the fluorinated 2'- α -C-nucleoside pyrimidine dione **2.7** with regeneration of Ag^+ for catalytic cycle (top of Scheme 18).⁴⁴ A second example is shown at the bottom of Scheme 13, starting from xanthate **2.8**, addition to vinyl acetate gave an *O-S* type acetal **2.9**. In this instance, *para*-

toluenesulfonic acid, *p*-TSA was used to activate the dithiocarbonate for displacement *via* a transformation to an oxocarbenium from acetate group. This was followed by nucleophilic attack by MeOH. Finally, oxocarbenium formation *via* electron transfer from the methoxy group displaces the acetate for a second methoxy group to give acetal **2.10**.³⁴

Scheme 18. Ionic Substitutions of the Xanthate moiety

More impressively, the xanthate group can be functionalized by radical means as well. In the first example, radical bromination exploits the same strategy used in radical reduction discussed earlier using isopropanol as a hydrogen atom donor. Cumyl peroxide decomposes on heating to acetophenone and methyl radical which liberate alkyl radical from the xanthate, which in turn abstracts a bromine atom from a suitable bromine atom donor such as ethyl 2-bromo-2-methylpropanoate to form bromolactone **2.11** (Scheme 19). The resulting ethyl isobutyrate radical is too stabilized to abstract bromine atom from the product molecule and undergoes dimerization or disproportionation.⁴⁵

Scheme 19. Bromine Exchange of Xanthate Addition Product

In the second substitution example in Scheme 20, a dichlorovinyl group was introduced *via* addition-fragmentation of the xanthate to dichlorovinyl ethyl sulfone which utilized the fragmented ethyl radical to propagate the chain process, generating the vinylated 2-deoxyglucose derivative **2.12**, which could be further converted to an alkyne by Corey-Fuchs reaction or undergo cross-coupling reactions.⁴⁶

Scheme 20. Radical Vinylation of Xanthate

Thirdly, azides such as **2.13** and aldoximes such as **2.14** could be accessed from xanthates *via* radical azidation⁴⁷ and radical formylation⁴⁸ with the corresponding sulfonyl azides or sulfonyl oxime ethers, respectively (Scheme 21). These allowed the incorporation of xanthates and its addition products as useful synthetic precursors towards scaffolds bearing these useful functionalities. Similarly, they rely on the regenerated ethyl or methyl radical as chain relay carriers by fragmentation of their corresponding sulfonyl radicals.

Scheme 21. Radical Azidation and Formylation of the Xanthate Moiety

2.4 Retention of the xanthate group

In previous examples (Schemes 16 to 21), the xanthate group was mostly removed by reduction, elimination or substitution to other functionalities. Methods to utilize the thiocarbonylthio group itself into something of synthetic value are scarce and not well-studied, henceforth, leading to removal. One such rare example is the transformation of a pivalate bearing xanthate **2.15** to a dithiethanone **2.16**. Dithiethanones are potential precursors to thioaldehydes, however, they are uncommon in synthesis and as a result, very little is known about their chemistry and applications.³³ The mechanism is briefly shown in Scheme 22. Titanium tetrachloride activates the pivalate for displacement reaction by the sulfur anion formed from a nucleophilic attack on the thiocarbonyl by the lone pair electrons on oxygen in the xanthate group.⁴⁹

Scheme 22. Synthesis of a Dithiethanone

It is somehow regrettable that despite the increasing number of xanthate radical additions in synthesis, the xanthate group itself remained under-utilized. However, the xanthate group merits strong consideration for further synthetic application because it provides an easy source of sulfur to the molecule.

2.5 Synthesis and application of 2-Sulfolenes

Since the xanthate moiety placed a valuable source of sulfur on the addition product, it could be further exploited with a ketone to generate thiocycles. Thiocycles such as 2,3-dihydrothiophenes could be converted by oxidation to 2-sulfolenes. These could undergo base-induced isomerization to 3-sulfolenes,⁵⁰ which are known but under-utilized precursors to 1,3-dienes⁵¹ due to a lack of convenient synthetic routes to access this class of compounds.⁵² 1,3-dienes have been important synthetic intermediates for reactions such as the Diels-Alder reaction.⁵³ In addition, the silane group itself presents a dynamic synthetic handle which can undergo further transformation into other useful groups such as allylic alcohols,⁵⁴ aldehydes⁵⁵ and also excellent cross-coupling partners such as iodides⁵⁶ and boronate derivatives⁵⁷ (Scheme 23). Therefore, the incorporation of the silane group on a 1,3-diene could potentially further extend its application beyond that of Diels-Alder cycloadditions.

Scheme 23. TMS as a Versatile Synthetic Handle to Various Functional Groups

Traditional preparation of such dienylsilanes depended on carbanion-based methods such as a modification of the Peterson olefination⁵⁸ or Horner-Wadsworth-Emmons-type reactions (Scheme 24).⁵⁹

Scheme 24. Carbanion-based Approach to Alkenyl and Dienyl Silanes

On the other hand, the use of transition-metals such as those in palladium- or nickel-based catalyzed cross-coupling reactions are popular for the preparation of such dienylsilanes (Scheme 25). In spite of that, the coupling partners of these popular cross-coupling reactions are primarily vinyl or dienyl halides,⁶⁰ triflates,⁶¹ and tosylates.⁶² Stereo-selectivity is generally limited though its coupling precursors which usually requires predefined geometrical alkenyl halides⁶⁰, or dithioacetals⁶³ that may not be commercially available or even tedious in preparation. For example, the use of bromo thioethene and Grignard reagents under Ni or Pd-catalysis gave the corresponding dienes in excellent yields and selectivity (Scheme 25).⁶⁰ However, the halide precursors require tedious multiple distillation and further enrichment to separate the *E* and *Z* isomers which would otherwise affect the final geometry of the diene product.⁶⁰

Scheme 25. Pd- and Ni-Catalyzed Cross-Coupling Reactions with Grignard Reagents in Synthesis of Dienyl Silanes.

Alkenyl iodides and triflates can undergo Heck reaction with vinyltrimethylsilane to give the corresponding dienyl silanes (Scheme 26).^{61a} Hallberg observed that regioselectivity of the Heck coupled product was dependent on having a substituent on the carbon bearing the iodide or tosylate and therefore, largely determined by substrate.^{61a} This was in agreement with Heck's observation^{61b} as well. The use of less activated olefins such as vinyl tosylates and phosphates could also be used in Heck reaction.⁶² In this example, dienyl silane could be accessed by a 1,2-isomerization of the

alkene-coordinated palladium (II) hydride intermediate. Despite the excellent regioselectivity observed, the silane was obtained in poor yields as a result of degradation under the reaction conditions (Scheme 26).⁶²

Scheme 26. Pd-Catalyzed Heck Reactions of Vinyl Iodide, Triflates and Tosylates with Vinyltrimethylsilane for the Synthesis of Dienyl Silanes.

Thioacetals can react with Grignard reagents to give alkenes under nickel catalysis (Scheme 27).⁶³ Nickel catalyst first inserts into carbon-sulfur bond which is followed by displacement of sulfur by Grignard reagent to give the corresponding alkylated intermediate. Nickel catalyst may then react with the second carbon-sulphur bond to give a sterically crowded alkylnickel intermediate which would readily undergo p-elimination to give an alkene.⁶³ Despite the excellent reactivity and stereoselectivity shown in this Ni-catalyzed process, the preparation of such geometrically-defined vinyl thioacetals would stem from its corresponding vinyl aldehydes, which also required tedious preparation and purification to separate geometric mixtures like the vinyl halides.

Scheme 27. Ni-Catalyzed Cross-Coupling Reactions of Thioacetals and Trimethylsilyl Grignard Reagent in Synthesis of Dienyne Silanes.

In addition, the use of organometallic reagents such as stannanes,⁶⁴ organozinc⁶⁵ or organotitanium derivatives⁶⁶ have their own share of problems on the preparation of the reagents and perceived toxicity as well. The first example in Scheme 27 shows that undesirable side reactions such as homo-coupling could compete with cross-coupling in Pd-catalyzed Stille coupling of vinyl halides and vinyl organostannanes.⁶⁴ Silyl-substituted zinc complexes could be utilized with allylic halides under Pd-catalyzed conditions to give dienyne silanes (Scheme 28).⁶⁵ This is analogous with the use of Grignard reagents^{60, 63} in terms of preparation of reagents for synthesis. Silyl-substituted titanium complexes with vinyl aldehydes have been reported as well albeit in low yield and poor selectivity (Scheme 28).⁶⁶

Scheme 28. Organometallic Reagents used in Synthesis of Dienyl Silanes.

In general, extremely high stereo-selectivity of the cross-coupling reactions can be achieved by the examples described^{60, 61, 62, 63, 64, 65, 66} however, the tedious preparation of the reagents may prove difficult to access such dienyl silanes. In addition, while under prolonged storage, the direct synthesis of 1,3-dienes is usually plagued by rapid polymerization and is difficult to handle.⁶⁷ In this regard, the bench-stable 2-sulfolenes are a more user-friendly alternative to prepare these dienylsilanes.⁶⁷

2.6 Proposed strategy to manipulate xanthates as a sulfur source

Our first approach to such 2-sulfolenes was previously reported using keto-xanthates **2.17** to install a ketone functionality in the γ -position to the xanthate group in the xanthate adduct **2.19**, which on treatment with ethylene diamine, releases the nucleophilic thiol **2.21** which would then cyclize onto the ketone in presence of a strong acid. This was followed with the elimination of H₂O to generate a 2,3-dihydrothiophene **2.22** (Scheme 29).⁶⁷ However, this method was met with a limitation on the use of alkenes bearing certain sensitive functionality such as the trimethylsilyl (TMS) group. In addition, the former strategy involved a multi-step process to release the thiol from the

xanthate group that in turn, often led to undesired oxidation of the thiol under the acidic or basic aqueous work-up conditions to the disulfide.

Scheme 29. Proposed Routes to 1,3-Dienes from Keto-Xanthate Adducts

An accidental discovery was made while subjecting keto-xanthate type adducts to mass spectrometry.⁶⁸ Significant relative mass peaks matching that of the corresponding 2,3-dihydrothiophene was observed. This led to a hypothesis of possibly fragmenting the xanthate group by heat to liberate thiol from the xanthate for nucleophilic attack on the ketone in absence of acid and base. Unfortunately, the operating temperature of the

observed reaction that happened in the mass spectrometer was extremely high (about 300 °C) to ionize the molecules and was impractical for a laboratory synthesis. The rationale behind this was based on the need for tremendous amount of energy to break the strong C-O bond in *O*-ethyl xanthates. This may be circumvented through the use of secondary *O*-alkyl xanthates by exploiting the Chugaev-type elimination to liberate the free thiol.

The strategy in mind was to enhance the fragmentation of the xanthate to the thiol using *O*-(*sec*-butyl) keto-xanthates **2.20**. On heating to a suitable temperature, xanthate **2.20** undergoes a *retro-ene* type of elimination, followed by release of COS as a gas and the liberated thiol or thiolate anion **2.21** as shown in Scheme 29. This thiol or thiolate then undergoes a nucleophilic attack on the ketone and give the 2,3-dihydrothiophene **2.22** with elimination of water. Since it is more thermodynamically favorable to form a more substituted alkene such as a but-2-ene from a secondary butyl group as compared to ethylene from an ethyl group, this driving force may allow the reaction to occur more readily, hence, the need for lower operating temperatures. This revised process is more efficient and convenient step-wise as compared to the previous process because fragmentation generate the thiol *in-situ* which subsequently attack on the ketone, all in a one-pot process in the absence of acid or base. Subsequently, the 2,3-dihydrothiophene could then be oxidized in the same flask to the 2-sulfolene **2.23** which could be isolated nicely as a solid. This is then subjected to isomerization with DBU to 3-sulfolene **2.24** and give the 1,3-diene **2.25** after extrusion of SO₂ as a gas by a thermal process akin to a reverse cyclo-addition. The geometry of the 1,3-diene is restricted to exclusively the (1*E*,3*E*) conformation due to the concerted syn-elimination of the 3-sulfolenes.⁵¹

2.7 Preliminary Studies

The hypothesis was first tested with TMS keto-xanthate adduct **2.20a**, formed from an acetophenone xanthate **2.18a** and vinyl trimethylsilane in a xanthate addition reaction. Ph₂O was chosen as the solvent due to its high boiling point of 258 °C. As the mixture was heated steadily to 200 °C, effervescence was observed after the 190 °C mark. Using a concentration of 1.0 M of **2.20a** in Ph₂O, the reaction resulted in a multitude of spots on the TLC. Purification by silica-gel column chromatography gave the 2-sulfolene in less than 10% yield, accompanied with large amounts of other uncharacterized impurities (Table 1, Entry 1). Reducing the reaction concentration to 0.5 M improved the yield to 20% (Table 1, Entry 2). These initial results led us to reason that these undesirable side reactions could have arisen from competing intermolecular reactions between the fragmented thiolate or thiol from the xanthate and other ketone or thiocarbonyl of another molecule. A way to circumvent this problem would be to dilute the reaction mixture so that the intra-molecular reaction would be promoted over the inter-molecular reactions to curb the formation of these undesired side products. Indeed, the yields improved on reducing the concentration further (Table 1 Entries 2 to 5). At 0.1 M concentration, the isolated yield dipped partly as a result of loss in product during the recovery from Ph₂O (Table 1, Entry 6). Therefore, the optimized concentration was set at 0.2 M in which the reaction yield was high as well as facilitate reasonable isolation of the product. As planned, the TMS group remained intact using this process and thus, demonstrated this technique to be tolerant of the TMS functionality.

Table 1. Optimization of the One-Pot Reaction to 2-Sulfolene

Entry	Concentration (M) in Ph_2O	Yield (%)
1	1.0	<10
2	0.5	20
3	0.4	57
4	0.3	76
5	0.2	89
6	0.1	81

2.8 Results and Discussion

With this one-pot protocol optimized, a number of TMS xanthate adducts **2.20a–m** from keto-xanthates **2.18a–m** bearing this new *O*-(*sec*-butyl) xanthate group were synthesized in good to excellent yields of 75–98% (Scheme 30).

Scheme 30. Preparation of TMS Xanthate Adducts

^aConditions: To vinyl trimethylsilane (2.0 equiv) and **2.18** in EtOAc (1.0 M in the xanthate) heated to reflux under nitrogen was added 0.05 equiv of dilauroyl peroxide (DLP) every hour until **2.18** was mostly consumed as indicated by TLC. ^bIsolated yields were based on **2.18**. ^c0.10 equiv of DLP was used at hourly intervals.

With numerous of these TMS xanthate adducts **2.20** in hand, we attempted the one-pot reaction to the corresponding 2-sulfolenes. 2-Sulfolenes with *para*-substituted aryls bearing electron-withdrawing **2.23b–c**, or electron-donating substituents **2.23d–e**, a methyl β to the sulfone **2.23f**, fused-naphthalenyl **2.23g**, fused-dihydronaphthalene **2.23h**, a heterocycle such as a fused-piperidine **2.23j**, fused-cyclohexyl **2.23k** and an ethyl ester β to the sulfone **2.23l** were prepared in moderate to excellent yields (Scheme 31, **2.23a–h**,

j, k, l, 63–91%). A particularly interesting example emerged in the 2-sulfolene bearing a thiophene **2.23i**. The use of *m*-CPBA could oxidize either TMS-substituted 2,3-dihydrothiophene or the thiophene. Manipulation of the reaction at a lower temperature of 0 °C, allowed oxidation to occur selectively on the TMS-substituted 2,3-dihydrothiophene instead of the thiophene to give the desired 2-sulfolene **2.23i** in a moderate yield of 58%. It is proposed that the electron pair on the sulfur atom in thiophene could be less active for attack on *m*-CPBA due to partial delocalization into the π -electron system of the aromatic thiophene ring. This is in contrast to the electron pair on the sulfur atom of 2,3-dihydrothiophene which does not constitute such π -electron system due to a lack of aromatic system.

Scheme 31. One-Pot Synthesis of TMS 2-Sulfolenes

^aConditions: In the first step, **2.20** (0.2 M in Ph_2O) was heated to 200 °C under nitrogen for 2h. In the second step, the reaction mixture was cooled to rt and diluted with CH_2Cl_2 (1.5 times the volume of Ph_2O), and this was followed by two additions of *m*-CPBA (1.2 equiv) every 30 min. ^bIsolated yields were based on **2.20**. ^cThe oxidation was done at 0 °C.

Unexpectedly, the TMS xanthate substrate **2.20m** failed to give the desired 2-sulfolene. The characteristic vinyl proton of the supposed 2-sulfolene exhibiting a triplet at the region of 6.6 to 6.7 ppm was not observed from crude ^1H NMR. We were initially puzzled by this deviation since alkyl-substituted TMS keto-xanthate adducts such as **2.20j** and **2.20k** had worked as expected. A closer observation of the structure of **2.20m** showed that the C5 position of the 1-(TMS)-butanone side chain was di-substituted as compared to the C3 position. Deprotonation could happen on either C3 (internal side of dihydrothiophene ring) or C5 (external side of dihydrothiophene ring) to give *tri*-substituted or *tetra*-substituted alkene. Therefore, a likely reason for the failure to form the desired 2-sulfolene would be that the elimination process took place on the external side of the dihydrothiophene formation to give the more stable *tetra*-substituted alkene outside the dihydrothiophene ring instead of internal elimination to a *tri*-substituted alkene within the dihydrothiophene ring. To test this behaviour, we prepared another substrate which would constitute both C3 and C5 positions of the ketone to be mono-substituted. In addition, this TMS xanthate **2.20n** was designed such that it bears a *tert*-butyl group on the left side of the ketone and does not contribute to any likely stability factor during the formation of the alkene by conjugation effects (Scheme 32).

Scheme 32. Formation of *exo*-Alkene is Favoured during Elimination of Water

Result from the test experiment showed that even in such cases, elimination gave exclusively the *exo*-alkene **2.23n'** in 78% yield over the internal alkene (Scheme 32). This

may be attributed to relatively smaller ring strain of having the alkene formation external to the dihydrothiophene ring in comparison to that which is internal. This ring strain might have an effect on the formation of the ring similar to those of carbocycles. To strike a comparison, the smaller heat of formation or (ΔH_f) of methylenecyclopentane of 3.29 kcal/mol as compared to a cyclopentene having a (ΔH_f) of 8.23 kcal/mol would have meant a less favorable formation of the latter.⁶⁹ This is of course, a rough estimation since the ring dealt here is a thiocycle. Consequently, this ring strain can be overcome if the internal alkene formation is more stable such as adopting a *tetra*-substitution as seen in examples **2.23j** and **2.23k** in Scheme 31. Unfortunately, this represents the main limitation of this approach for 2-sulfolene formation.

Regardless, we pushed on and attempted the planned *in-situ* DBU isomerization with thermal extrusion of SO₂ to convert these novel TMS 2-sulfolenes **2.23a – l** to generate our desired TMS 1,3-dienes **2.25**. Disappointingly, the conversion to the **2.25** was low and desilylation was observed. To investigate the root cause of this desilylation, a plan was devised to tackle this problem in stages by first attempting to isomerize the **2.23** to the 3-sulfolene, **2.24** (Scheme 33). To our surprise, when **2.23a** was subjected to DBU in acetonitrile, we observed the formation of desilylated 2-sulfolene **2.23a'** instead of the expected isomerization to the 3-sulfolene **2.24a** (Scheme 33).

Scheme 33. Desilylation of TMS 2-Sulfolene by DBU in Acetonitrile

^aProduct yield ratios were determined by ¹H NMR analysis of isolated mixtures of compounds **2.25a** and **2.25a'**.

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or desilylation ratio (Table 2, entries 2 and 3). Interestingly, the ratio improved to almost 2:1 on introduction of a co-base (Table 2, Entries 4 and 5). The role of the co-base was speculated to either drive the isomerization faster than the desilylation step or neutralize any acid generated which might serve as a proton source for the desilylation process. A marked improvement was observed when using a drying agent such as anhydrous MgSO_4 , increasing the ratio to almost 3:1 (Table 2, Entry 6). The best condition was achieved using dry K_2CO_3 (Table 2, Entry 7). However, inconsistency was observed even under this condition, which largely depended on the extent to which the reaction setup was kept strictly moisture-free. Given that the generated anion alpha to the sulfonyl group is well-stabilized and abstracts a proton from water to regenerate the hydroxide anion, in theory, this undesirable reaction required only 0.5 equiv of water to the TMS 2-sulfolene, **2.23**. As such, the extent of removing such small amounts of water is almost operationally impractical on small reaction scales of 0.5 mmol.

Since meticulous removal of water by physical means proved futile to secure a reliable technique,⁷⁰ this problem could be tackled by introducing a sacrificial electrophile such as trimethylsilyl chloride, TMSCl to trap the problematic hydroxide anion. Indeed, this approach worked effectively to furnish the TMS 1,3-dienes **2.25(a-i)** in the absence of desilylation by-products in moderate to good yields (Scheme 34, 64–88%). TMSCl should react rapidly with residual water, and the released HCl could be irreversibly neutralized with excess anhydrous K_2CO_3 . The latter reagent is also a good dehydrating agent in its own right. Also, the use of excess amount of reagents (5 equiv) was required to drive the reaction to completion in shorter reactions between 45 min to 1 h as well as to deter against possible desilylation under prolonged reaction times.

Scheme 34. Synthesis of TMS (1*E*,3*E*)-Dienes

^aThe reaction was carried out with DBU (10 equiv), TMSCl (10 equiv), and K₂CO₃ (10 equiv) in toluene (5 mL).

A few limitations were noted in this reaction. Substrate bearing a piperidine such as **2.23j** did not react to give the desired diene. Unfortunately, no conclusive solution was made to understand any underlying effects that caused this failure. **2.23k** could not be isolated due to high volatility despite observing complete consumption of the TMS 2-sulfolene by TLC. More notably, the reaction became significantly slow and poor conversions were obtained on substrates bearing a substitution at the 4' position of the TMS 2-sulfolene (**2.23f** and **2.23l**). Using the standard condition of 5 equiv of DBU, TMSCl and K₂CO₃ resulted in only a poor yield of 28% of TMS diene **2.23f**. However, this was improved satisfactorily by increasing the amount of reagents (10 equiv) to give TMS diene **2.25f** in better yield of 64%. Unfortunately, **2.23l** failed to show any reaction at all. From these observations, we attributed this loss in reactivity as a result of steric hindrance.

2.9 Conclusion

In conclusion, we have demonstrated the use of secondary *O*-(2-butyl) xanthate adducts **2.20** to form 2-sulfolenes **2.23** in a one-pot fashion *via* a Chugaev approach. This novel method eliminates tedious multistep workups and, more importantly, avoids acidic conditions to making these 2-sulfolenes. The Chugaev elimination allows us to tap into xanthates as latent sulfur nucleophiles in absence of acids and bases. This generates a more robust protocol tolerant of an acid-sensitive group such as a TMS group adjacent to the sulfone, thus creating a new synthetic pathway to interesting and novel TMS 2-sulfolenes **2.23**. In addition, we were able to convert these TMS 2-sulfolenes to the corresponding (1*E*,3*E*)-TMS dienes **2.25** in the absence of desilylation. From a synthetic point of view, this method offers an advantage in preparation of such TMS dienes over previous methods^{60, 61, 62, 63, 64, 65, 66} since it starts from a simple precursor such as vinyltrimethylsilane.

Chapter III.

The Combination of Keto-Xanthates and Alkenyl Acyl Phosphonates: A Radical Variant to the Robinson Annulation.

3.1 Radical addition to multiple bonds

Since the inception of radical-mediated techniques in synthetic chemistry, most of the studied radical reactions have been directed to addition reactions to multiple bonds of the type (X=Y). Examples of these include the more commonly studied alkenes and alkynes (X and Y = C), and to a lesser extent, nitriles⁷¹ and aldehydes⁷² (X = C, Y = N or O) as well. The notion of involving carbonyls as a radical reaction partner is interesting, since the carbonyl group is widely employed in many other reactions and found in many synthetic intermediates. Henceforth, a radical pathway involving this functionality would uncover greater opportunities for application in radical-mediated synthesis.

3.2 Preparation of ketones *via* radical acylation

There are countless reports pertaining to the preparation of carbonyl groups, in particularly the ketone, a dominating functionality found in many synthetic transformations. An example of a direct method to access the ketone functionality is displayed through the use of organometallic reagents with carboxylic acid derivatives *via* an ionic acylation approach.⁷³ One of the most common choice of organometallic nucleophile employed in such combinations is the use of Grignard reagent and an acid chloride as the acylating agent.⁷⁴ Direct use of Grignard reagents often gave poor yields of ketones and suffer from numerous side reactions such as overaddition to the tertiary alcohol or other condensation products resulting from β -elimination of the magnesium complex formed by the reduction of the acid chloride by the Grignard reagent.⁷⁴ Use of transition-metals like Ni(II) and Fe(III) helped to catalyze and promote the reaction to give clean acylations of the Grignard reagents.⁷⁴ This could also be accomplished by using a tridentate ligand such as bis[2-(*N,N*-dimethylamino)ethyl]ether to moderate the reactivity of the Grignard reagent by chelation to form a more stable organomagnesium

complex.⁷⁴ It was proposed that such a stabilization helped to curb the side reactions and better control the acylation reaction with acid chlorides (Scheme 35).⁷⁴

Scheme 35. Tridentate-promoted Acylation of Grignard Reagents

The use of *N*-methoxy-*N*-methyamides (Weinreb amides) as carboxylate synthons in the synthesis of ketones had mitigated the problem of overaddition by the organometallic nucleophile.⁷⁵ The formation of a stable tetrahedral chelate intermediate hinders a second attack by the nucleophile as shown in Scheme 36. Elimination of the intermediate oxaphosphetane then generates the *N*-methoxy-*N*-methyl enamine which hydrolyzed to the enol and lastly, tautomerize to the ketone.⁷⁵

Scheme 36. Wittig Reaction on Weinreb Amide for Synthesis of Ketone

In the previous two examples, reagents such as organolithiums and Grignards are common nucleophiles used to synthesize ketones from acid chlorides and other acid derivatives. However, these reagents are highly reactive and are not compatible with a wide variety of functionalities.⁷⁶ Therefore, for direct synthesis of more complex ketones, the use of moderately reactive organometallic species such as organozinc compounds allow more tolerance of functional groups.⁷⁶ Organozinc compounds can be easily prepared by insertion of commercial zinc dust in the presence of lithium chloride and

undergo transition metal-catalyzed coupling reactions to give the corresponding ketones (Scheme 37).⁷⁶ The role of lithium chloride was proposed to free the metal surface by generation of a highly soluble lithium chloride-organozinc reagent complex.⁷⁶

Scheme 37. LiCl-promoted Insertion of Zinc into Halides as Organozinc Reagents for the Synthesis of Ketones with Acid Chlorides

Despite many advances in organometallic acylation, its radical counterpart, however, was not as well-studied since the addition of alkyl radicals to the carbonyl group (C=O) was a distressing affair, due to their high reversibility and the high π bond strength of the C=O bond (Scheme 38).⁷⁷

Scheme 38. Radical (*intra*-molecular) Addition to Multiple Bond Systems

Indeed, reports documenting radical-mediated acylation are rare as compared to the common radical addition to olefins. Before 1990, acyl derivatives were more commonly regarded as radical precursors^{71, 72} instead of radical acceptors which would later be further categorized under direct (no further chemical manipulation required) and indirect carbonyl group acceptors. The latter would be covered in the next chapter. Some of these carbonyl group radical precursors include seleno-esters,⁷⁸ carbon monoxide,⁷⁹ and acyl germanes.⁸⁰

3.3 Acyl selenoesters, acyl germanes and carbon monoxide as acyl radical precursors

Interest in radical acylation was rapidly building up after 1990, following reports from Boger and Crich,⁷⁸ Ryu,⁷⁹ Curran,⁸⁰ on the use of seleno-esters, carbon monoxide (CO) and acyl germanes for the synthesis of cyclic ketones under free radical conditions. The idea centered about the use of photo-induced or peroxide-initiated homolytic cleavage of weak carbon-chalcogen bonds such as the C-Se bond in seleno-ester derivative **3.1** to form an acyl radical, followed by trapping in tandem through a series of intra-molecular additions which then led to a fused-cyclic ketone **3.2** (Scheme 39).^{78b} Boger led these early investigations into these type of acyl derivatives as suitable radical precursors with the fast trapping of the highly reactive acyl radical while Crich further explored the effects of substituent and ring size on this radical cyclization.^{78e}

Scheme 39. Tandem Cyclization Starting from a Seleno-ester as a Radical Precursor

At the same time, Ryu also investigated the concept of trapping carbon monoxide with carbon-centered radicals to generate the corresponding reactive acyl radicals which could then be either trapped by reductants to give aldehydes^{79a} or undergo further radical alkylation with an activated alkene like acrylonitrile and allyl tributylstannane in multi-component reactions to generate a ketone such as **3.3** (Scheme 40).^{79b} A few key

considerations for the success of this approach include firstly the use of more reactive alkyl radicals generated from alkyl bromides or iodides and Bu_3SnH and secondly, the fine-tuning of the optimal ratio of CO concentration and amount of Bu_3SnH for a more effective radical chain.^{79a}

Scheme 40. Four-Component Tandem Radical Cascade by Ryu

Ryu's successful employment of acyl radicals as a precursor in synthesis soon drew increasing attention from the synthetic community. In the following year, Kiyooka then extended this approach to acyl germanes as well, proposing a similar mechanism to Boger whereby the homolytic cleavage of the weak C-Ge bond in acyl germane **3.4** resulted in the generation of a reactive acyl radical **3.5** and the partnering germeryl radical in a solvent cage which was then quickly trapped by a fast intra-molecular addition on a proximately-close alkene (Scheme 41).^{80a} This was however, refuted by Curran, who in his own investigations of the acyl germanes, believed that a radical chain isomerization was the key to this observation instead.^{80b}

3.4 β -Elimination from an alkoxy radical

Curran pinpointed the error in Kiyooka's proposal by highlighting one of the experimental data reported in his initial communication as a likely indicator to the subsequent failure to explain the mechanism.^{80b} Firstly, the lifetimes of solvent cages were too short to permit normal radical cyclizations to occur. In addition, assuming that

cyclization did occur by trapping of the acyl radical **3.5**, there was no obvious reaction pathway to explain the observed selectivity in radical-radical coupling and also, both cyclized products **3.6a** and **3.6b** should be comparable in cyclization rates and the observed dramatic differences in yields could not be explained. Curran was convinced that the radical chain mechanism did not involve acyl radicals but instead, was initiated by free germyl radicals from homolytic cleavage of the acyl germane **3.4** and added to the alkene, followed by a 5-*exo* cyclization to generate a β -germylalkoxy radical **3.7**. Subsequently, the alkoxy radical underwent β -fragmentation into the ketone **3.6** with the regeneration of the germyl radical as a chain carrier to propagate the radical cycle (Scheme 41).^{80b} Through a series of experiments, he demonstrated that the introduction of catalytic amounts of germyl radicals was sufficient to propagate the radical chain and gave the ketone in similar yield as well and therefore, proposed that the acyl germanes were akin to a reagent equivalent of a carbonyl group acceptor.⁸⁰

Scheme 41. Curran's and Kiyooka's Proposed Pathway

This counterproposal^{80b} by Curran abruptly changed the outlook for such acyl derivatives as radical precursors and also conceptualized them as potential radical

acceptors as well. More importantly, it also hinted the possibility of these acyl derivatives as a new class of carbonyl equivalent radical partners. This new concept was then quickly noted and explored by Kim.

3.5 Tuning acyl derivatives as suitable radical carbonyl acceptors by β -elimination from an alkoxy radical

Following Curran's hypothesis of acyl derivatives as plausible carbonyl radical acceptors, Kim explored the use of thio- and seleno-esters for the intra-molecular radical cyclization.⁸¹ The general idea was centered about a radical-type forming and fragmentation equilibrium process. Starting with thio-ester **3.8**, halogen atom abstraction with bis(tributyltin), $(\text{Bu}_3\text{Sn})_2$ would generate the corresponding alkyl radical which would undergo a 5-*exo* radical cyclization onto the thio-ester to generate phenylthiyl-alkoxy radical **3.9**. This addition is presumed to be slow and highly reversible due to the factors as discussed earlier.⁷⁷ However, the β -elimination of the phenylthiyl radical from the alkoxy radical **3.9** would be an irreversible process, which would inevitably shift the reaction equilibrium in favor of cyclization to the pentanone over ring opening to the open-chain radical (Scheme 40).⁸¹

Scheme 40. Irreversible β -Fragmentation from an Alkoxy Radical as Driving Force

This was then tested and demonstrated in the synthesis of various ketones from thio-esters. A number of distinct behaviours were observed in the use of such thio-esters as radical acceptors (Table 3).⁸¹ Firstly, this reaction proceeded better using radical leaving groups with substituent that imparted better stability to the leaving radical. For

example, *S*-phenyl thio-esters **3.10b** were found to be better radical acceptors than *S*-alkyl thio-esters **3.10a**, probably as a result of the more stable phenylthiyl radical over the thioalkyl radical (Table 3, Entries 1 and 2). Next, ring size was a significant factor in such radical cyclizations such that the ratio of reduction products obtained was higher in 6-*exo* cyclizations as compared to 5-*exo* cyclizations (Table 3, Entries 2 and 3). Presumably the slower 6-*exo* cyclization allowed the reduction step to compete more effectively.

Table 3. Ring Size and Substituent Effect on Radical Cyclization of Thio-Esters

Entry	R	n	Yield (%)
			3.11a : 3.10a'
1	ⁿ Bu	1	31 : 45
2	Ph	1	87 : 11
3	Ph	2	46 : 33

Open chain products were also observed albeit in lower yields, indicating that β -cleavage of the C-C bond could also compete with β -cleavage of C-S bond. This revealed that β -elimination of the phenylthiyl radical was slow, at least in comparison with other radical steps. This problem was simply addressed by using a different type of leaving radical group which could direct the radical acylation process more favorably towards the desired fragmentation pathway. Seleno-esters were found to be much more efficient as

compared to thio-esters. The weaker C-Se bond accelerated the β -fragmentation and curtailed the problematic C-C cleavage observed as a result of slower C-S bond fragmentation but did not suppress the accompanying reduction step completely (Scheme 42).⁸¹

Scheme 42. Effect of Phenylthio- and PhenylSeleno- Radical Leaving Group

One key observation was evident from these results. The easier the σ -bond fragmentation of C-Y from the intermediate alkoxy radical, the more efficient the reaction. This could be manipulated by varying the substituents on the radical leaving group to stabilize the fragmented radical or changing to another type of radical leaving group (SPh to SePh) which has a weaker bond to the carbonyl group, leading to facile dissociation.

In contrast to thio-esters, carboxylic esters and amides have limited reactivity towards alkyl radicals.⁸² This was presumably attributed to π -bond delocalization of the carbonyl group with non-bonding electrons of heteroatoms such as oxygen and nitrogen, therefore, the effect of such a resonance stabilization increased the energy of the LUMO of the carbonyl, rendering it to become a poor radical acceptor. Hypothetically, in the case of a carboxylic mixed anhydride, the introduction of electron-withdrawing factors should diminish this resonance effect and disrupt the stability brought about by resonance due to electron delocalization, leading to potentially acceptable LUMO energy levels for radical addition to occur. Unfortunately, these carboxylic mixed anhydrides were found to be only moderate radical acceptors in practice and did not function well as carbonyl group acceptors. Subsequently, a number of other radical carbonyl acceptors were explored

based on this concept. Acyl derivatives such as methyl oxalyl chloride⁸³ and S-phenyl chlorothioformate⁸⁴ were found to work well with alkyl radicals as carbonyl radical acceptors as well. Thus, the notion of incorporating electron-withdrawing groups to activate the carbonyl group for successful radical acylation remained relevant.

Among these new carbonyl radical acceptors, the acyl phosphonate stood out in terms of reactivity.⁸⁵ Experiments employing the use of iodo alkenyl acyl derivatives **3.12a–c** bearing an acyl phosphonate, a phenylthio-ester and a phenyl seleno-ester were carried out to observe the relative cyclization proficiencies of these acyl derivatives as carbonyl radical acceptors. As seen from Scheme 43,⁸⁵ the acyl phosphonate derivative **3.12a** gave exclusively cyclohexanone **3.14** in 75% yield while phenylthio-ester derivative **3.12b** gave only bicyclic ketone **3.15** in 92% yield. The generated alkyl radical **3.13** of any of the three acyl derivatives have two possible pathways. Firstly, it could undergo a 5-*exo* ring closure to the alkene and then cyclized to the carbonyl radical acceptor in a second 5-*exo* cyclization to give the fused bicycle **3.15**. Otherwise, **3.13** could also add to the carbonyl radical acceptor *via* a 6-*exo* cyclization, bypassing the expectedly faster 5-*exo* cyclization instead. The efficiency of the acyl phosphonate derivative as a carbonyl radical acceptor was clearly superior over the thio-ester and even the seleno-ester **3.12c** as well.

Scheme 43. A Comparison of the Reactivity of the Acyl Phosphonate, Thio- and Seleno-Ester

3.6 Proposed strategy of radical-mediated synthesis of 1,5-diketones by radical acylation

As mentioned in the first part of this chapter, there are numerous reports pertaining to either ionic and radical synthesis of ketones.⁷³⁻⁸⁵ In particular, 1,5-diketones are valuable synthetic starters in the synthesis of fused-ring systems which form the carbon backbone of many interesting classes of compounds such as alkaloids, steroids and terpenes.⁸⁶ In addition, 1,5-diketones pave an easy route to functionalized pyridines.⁸⁷ Despite that, the installment of two or more ketone functionalities in the same molecular scaffold is no easy feat due to the highly reactive ketone and the acidic hydrogens α to the carbonyl group. The most studied and known synthetic approach to these 1,5-diketones generally exploit the use of enolates and vinyl ketones *via* conjugate addition in the Robinson Annulation.⁸⁸

The history of this conjugate addition has been a constant battle to overcome the limitations that plagued these two requisite precursors; being the uncontrollable polymerization of vinyl ketones and the bothersome control on the reactivity of the anionic enolate.^{86a} Most synthetic solutions were centered about producing more

convenient and milder alternatives of these two precursors, as exemplified by the use of silyl enol ethers under Lewis-acid catalyzed Mukaiyama aldol reactions or enamine-mediated reactions⁸⁹ and Mannich-type bases or α -silylated ketones.⁹⁰ Regardless, due to the approach being ionic in nature, these modifications tend to work under acidic or basic conditions.^{89, 90} Functionalities that are acid- or base-sensitive remained confined to the specific acid- or base-mediated reaction conditions and henceforth, a general protocol to liberate them remained elusive at hand.

On the contrary, radical-based approaches to the synthesis of such 1,5-diketones have not been as rigorously explored in vast contrast to their ionic counterparts. The unique environment in which free radicals worked in makes them impervious to the acidic or basic conditions that would have manifested in an ionic approach. This somewhat makes them a more suitable match to work with acid- or base-sensitive functionalities. Presently, there are only a few reports of radical-mediated synthesis of 1,5-diketones.^{91, 92} However, some of these strategies were based on α -keto radical addition to modified versions of enones, which are coupled with additional oxidation and reduction or tedious protection and deprotection steps to liberate the free diketone in the final product.⁹¹ Therefore, it is highly desirable to develop a facile and direct synthetic route to access highly functionalized 1,5-diketones from simple precursors without the need for additional chemical transformation steps.

In continuation with extending the application of acyl phosphonates as carbonyl radical acceptors, we reasoned that free-radical addition of α -keto radicals to alkenyl acyl phosphonates, followed by an intra-molecular radical cyclization with β -fragmentation of a phosphonate radical from the intermediate alkoxy radical would generate the target 1,5-diketones (Scheme 44). Such an approach would allow for the introduction of a ketone unit and the forming of a second ketone unit on the same scaffold simultaneously by

radical means. These may present an opportunity to include substrates bearing acid- or base-sensitive functionalities that had previously been thwarted by unwanted enolization and deprotonations in a traditional ionic approach.

Scheme 44. Proposed Radical Acylation using α -Keto Radical and Alkenyl Acyl Phosphonate

3.7 Preliminary studies

Initially, synthesis of the alkenyl acyl phosphonate *via* an Arbuzov-type reaction with triethyl phosphite with the corresponding acid chloride derived from hex-5-enoic acid was planned to test the idea. Unfortunately, the low volatility of the resulting acid chloride posed difficulties in the synthesis of the corresponding acyl phosphonate. When the crude acid chloride was reacted with an equimolar quantity of triethyl phosphite, a significant amount of triethyl phosphite remained in the crude mixture, indicating that some of the acid chloride might have been lost during isolation (Scheme 45). Significant loss of the acid chloride was observed during isolation while trying to remove the excess oxalyl chloride in vacuo. The acid chloride could be obtained pure if distilled from a large quantity, however due to unavailability of sufficient amounts of the alkenyl acid, a cheaper alternative was considered.

Scheme 45. Preparation of Acid Chloride from Hex-5-enoic Acid

Next, we decided to decrease the volatility of the acyl chloride by increasing the molecular weight of the acid. Therefore, using allyl diethylmalonate ester and *tert*-butyl 2-bromoacetate, we made the corresponding ester which was then hydrolyzed to the acid followed by conversion to the acid chloride with oxalyl chloride and finally, attempted the Arbuzov-type reaction with triethyl phosphite to give the corresponding acyl phosphonate in quantitative and clean conversion from the acid (Scheme 46).

Scheme 46. Preparation of Alkenyl Acyl Phosphonate for Preliminary Test

The reaction was then tested using similar conditions from a previous report.⁸⁵ α -Keto radical generated from their corresponding α -bromo ketone using hexamethylditin $(\text{Me}_3\text{Sn})_2$ did not give the desired 1,5 diketone but was prematurely reduced to the starting ketone instead. This was in stark contrast to the other functionalized carbon-centered radicals that had found success with the same protocol previously.⁸⁵ Various other systems for the generation of the α -keto radicals, in particularly, tin-free initiator systems

such as azo initiators like AIBN and also the combined use of triethylborane and air which were known to generate the reactive ethyl radical that was required to propagate the radical chain effectively^{32a} (Table 4, Entries 2 and 3). Unfortunately, these methods failed to give the desired 1,5-diketone and reduction was a predominant observation even under these reactions (Table 4).

These results prompted us to re-evaluate our approach for the generation of the α -keto radicals. Notably, the use of α -bromo ketone in all the previously mentioned systems utilized the halogen atom transfer principle,^{10a} therefore, these precursors had some kind of mechanistic similarity. On the other hand, these bromides could also be converted to their corresponding xanthates which would then undergo a different type of mechanism³³ to generate the α -keto radicals. We then decided to test the reaction using keto-xanthates instead. For convenience, the keto-xanthates could be derived from the same halo-ketones used in the previous reactions.

Table 4. Reaction of α -Bromoacetophenone with Alkenyl Acyl Phosphonate under Various Initiator Systems

Entry	Initiator Systems	1,5-Diketone (%)	Reduced ketone (%)	Recovered α -Bromo Ketone (%)
1	(Me ₃ Sn) ₂ /300 nm	< 5	72	22
2	AIBN/reflux	0	19	69
3	Et ₃ B/air/rt	0	61	28

3.8 Results and Discussion

A list of functionalized keto-xanthates **3.23** (Figure 4) were then put to the test with alkenyl acyl phosphonates **3.16** and **3.17**, which would generate the corresponding 5- and 6-membered carbocyclic ketones **3.24** and **3.25**, respectively.

Figure 4. List of Keto-xanthates

Gratifyingly, these functionalized keto-xanthates **3.23a-d** proved to be effective reaction partners and furnished the desired 1,5-diketones in the absence of reduction unlike the previous initiator systems. 5- or 6-membered carbocyclic 1,5-diketones were smoothly synthesized from primary keto-xanthates bearing alkyl **3.24a**, **3.25a**, a chloromethyl **3.24b**, **3.25b** and a benzyl **3.24c**, **3.25c** substituent in good yields of 72 to 80%. Secondary xanthates bearing alkyl substituents **3.24d**, **3.25d** also reacted reasonably well to give moderate yields of 63 and 61%, respectively (Scheme 47). These results demonstrated that the liberated phosphonate radical was able to mediate the xanthate transfer effectively in this radical cascade reaction.

Scheme 47. Synthesis of 5- and 6-Membered Carbocyclic 1,5-Diketones

^aConditions: **3.23** and **3.16** or **3.17** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv DLP every hour until **3.23** was mostly consumed as indicated by TLC; isolated yields were based on **3.23**.

^bDLP was added at 0.3 equiv every hour; diastereomers (1:1) were not separated.

With this success in hand, we decided to test our current approach to synthesize 1,5-diketones from various types of alkenyl acyl phosphonates derived from their corresponding alkenyl acids. Hence, the synthesis of acyl phosphonates **3.18** and **3.19** from the corresponding 2-(allyloxy) acetic acid and 2-(*N*-allyl-4-methylphenylsulfonamido) acetic acid were initiated in the hope that these would possibly

3.20, X = O
3.21, X = NTs

3.28, X = O
3.29, X = NTs

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To our delight, *O*-Allyl acyl phosphonate **3.20** was formed cleanly in almost quantitative yield as seen from the crude ^1H NMR spectrum. The acyl phosphonate was then reacted with various functionalized keto-xanthates **3.23a–f** to give the corresponding benzopyran 1,5-diketones or 3-substituted chroman-4-ones **3.28** in moderate to good yields of 49 to 75% (Scheme 50). In addition, chroman-4-ones are known to self-polymerize under basic conditions during alkylation reactions,^{93a} therefore, this present radical approach offers a comparatively shorter and milder synthetic route in contrast to preceding procedures.^{93b} Yields of benzopyran 1,5-diketones **3.28a–d** were slightly lower but comparable to those of the carbocyclic 1,5-diketones **3.24** and **3.25**. Successful incorporation of keto-xanthates **3.23e** and **3.23f** showed that the ethyl ester functionality was well-tolerated although a notable decline in yield was observed with **3.23f** (Scheme 50). This decline in reactivity was reasoned to be caused by the abnormally strong stabilization of the alkyl radical by having two adjacent electron-withdrawing carbonyl groups due to either induction effect or conjugation. As a consequence, this would impede its addition to the olefin since the reversible fragmentation would be more preferred, resulting in a retarding of the radical chain process as discussed in Chapter 1. Henceforth, we postulate that such keto-xanthates may be less effective as radical precursors, leading to the observed diminished yield (49%).

Scheme 50. Synthesis of Benzopyran 1,5-Diketones

^aConditions: **3.23** and **3.20** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) under argon was added 0.2 equiv DLP every hour until **3.23** was mostly consumed as indicated by TLC; isolated yields were based on **3.23**. ^bDLP was added at 0.3 equiv every hour; diastereomers (1:1) were not separated.

Adding on to this result, as expected, the cleanly formed *N*-allyl acyl phosphonates **3.21** also reacted effectively with functionalized keto-xanthates **3.23a-h**, proving the ability to construct nitrogen-containing heterocycles as well. Tetrahydroquinoline 1,5-diketones **3.29a-e, g, h** were thus obtained in good yields of 61 to 83% with the exception of **3.29f** (Scheme 51). The excessive stability of the intermediate carbon radical, as discussed above, had a deleterious effect on formation as well, resulting in a comparatively lower yield of 40%. The ready formation of compounds **3.29g** and **3.29h** further demonstrates the broad functional group tolerance of this radical process to include phosphonates and pivalates as well (Scheme 51).

Scheme 51. Synthesis of Tetrahydroquinoline 1,5-Diketones

^aConditions: **3.23** and **3.21** (1.5 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) under argon was added 0.2 equiv DLP every hour until **3.23** was mostly consumed as indicated by TLC; isolated yields were based on **3.23**. ^bDLP was added at 0.3 equiv every hour; diastereomers (1:1) were not separated.

A comparison of this radical-based approach with that of the classical conjugate addition using enolate and enone reveals some advantages over the latter. Firstly, it should be noted that keto-xanthates **3.23** were readily synthesized⁹⁴ from commercially available materials as opposed to the corresponding enones used in the ionic synthetic pathway to 1,5-diketones via conjugate addition. For example, vinyl ketones containing an α -chlorine or α -ester group corresponding to keto-xanthates **3.23b**,⁹⁵ **3.23e**⁹⁵ and

3.23f⁹⁶ would pose severe difficulties, particularly in preparation as enone counterparts in ionic conjugate addition. In addition, the presence of particularly acidic hydrogens α to the ketone induced by electron withdrawing groups such as a chlorine atom **3.23b**, an ester **3.23e**, or phosphonate **3.23g** would also pose problems in an acidic or basic medium, leading to uncontrolled mixtures of side products arising from further cyclization or other ionic transformations.⁹⁷ Similarly, ketones bearing α -substituents such as a phenyl **3.23c** or pivalate **3.23h** could also enolize easily due to stabilization by the conjugation effect or lone pair donation from an heteroatom such as oxygen. This would serve to complicate reactions under acidic conditions as well.⁹⁷ A schematic comparison of the radical-mediated versus ionic approach to these 1,5-diketones is described in Figure 5. One can view keto-xanthates such as **3.23b** as a radical surrogate of the enone used in the ionic equivalent of the conjugate addition. Henceforth, this translates to a radical-type modification of the enone and enolate precursors in the conjugate addition of the Robinson Annulation similar to those of their ionic counterparts as discussed earlier.^{89, 90}

Figure 5. A Comparison of Keto-Xanthate **3.23b** as a Radical Surrogate for its Corresponding Enone Equivalent

With a great variety of these functionalized 1,5-diketones in hand, we also attempted to make the corresponding functionalized fused pyridines as well. Treatment of these functionalized 1,5-diketones **3.24**, **3.25**, **3.28** and **3.29** with excess ammonium acetate in refluxing acetic acid led to either functionalized carbocyclic (**3.31** and **3.32**) or

heterocyclic (**3.33–3.36**) fused-ring pyridines, including a tetra-substituted pyridine **3.35** in good yields (76–85%, Scheme 52). Further transformation could be performed on pyridine **3.36** bearing a methylene phosphonate group whereby it could undergo a Horner–Wadsworth–Emmons (HWE) reaction to give vinyl pyridine derivatives.⁹⁸ Fused-ring pyridines such as **3.31–3.36** belong to an important class of aromatic nitrogen heterocycles. These compounds exhibit high bioactivity and are valuable for medicinal research purposes.^{99, 101} The present method offers yet another alternative to access novel variations of structurally similar multi-substituted fused-ring pyridines^{99–101} and thus improves the diversity needed for structure-activity relationship (SAR) studies.

Scheme 52. Synthesis of Functionalized Fused-Ring Pyridines^{a,b}

^aConditions: **3.24a**, **3.25a**, **3.28c**, **3.29c**, **3.29f** and **3.29g** were added NH_4OAc (10 equiv) in refluxing acetic acid (0.2 M in diketone) to give the corresponding pyridines **3.31** to **3.36** respectively.^b Isolated yields.

The successful use of keto-xanthates with the alkenyl acyl phosphonates led us to propose a mechanistic pathway which would involve the use of phosphonate radical **B** to mediate the xanthate transfer in this radical cascade reaction (Scheme 53). Initially, keto-xanthate **3.23** was degenerately converted into α -keto radical **A** by thermal initiation with dilauroyl peroxide (DLP) and then, undergoes an inter-molecular radical addition to the alkenyl acyl phosphonate **3.16**. This was followed by a xanthate transfer to give the xanthate adduct **3.16a**. We did not isolate this xanthate adduct during the course of these experiments but noted the appearance and disappearance of a new spot by TLC. Therefore, we did not rule out the possibility that a step-wise reaction may also have occurred instead of a concerted addition-cyclization process. This xanthate **3.16a** is further reversibly converted into radical intermediate **3.16b** by more DLP and subsequently undergoes a 5-*exo trig* cyclization to give the intermediate alkoxy radical **3.16c**. β -fragmentation from the alkoxy radical of **3.16c** then leads to the 1,5-diketone **3.24** with the extrusion of phosphonate radical **B**, which could then participate in another xanthate exchange with keto-xanthate **3.23** and reintroduce the α -keto radical **A**, thus, propagating the radical chain process. The key to success lies in the degenerate nature of the xanthate exchange, which provided the intermediate radicals with an extended lifetime, even in a concentrated medium. With α -halo ketones, it was possible that formation of a tin or boron enolate in the case of $(\text{Me}_3\text{Sn})_2$ or Et_3B -initiation caused premature reduction of α -keto radical **A**.¹⁰² Currently, this was only observed for the α -keto type radicals used in this context, while other type of radicals have been reported to work efficiently in tin-mediated reactions with alkenyl acyl phosphonates.⁸⁵

Scheme 53. Proposed Mechanism Involving a Phosphonate Radical-Mediated Xanthate Transfer

Ultimately, we remained bothered by our failure to employ acyl phosphonates such as **3.18** and **3.19** in our current protocol and were determined to probe this matter in hopes of revealing the cause and eventually test the scope of this applications for the synthesis of various ketonyl cycles. With the successful synthesis of acylphosphonates **3.16**, **3.17**, **3.20** and **3.21**, it was possible to analyze their phosphorous-proton decoupled NMR spectra, $^{31}\text{P} \{^1\text{H}\}$. Interestingly, it was noted that all successfully synthesized acyl phosphonates had a single major ^{31}P peak within a narrow range from δ -1.8 to -3.8 ppm (Figures 6–9). We believed that this corresponds to the phosphonate group that is adjacent to an electron-withdrawing group such as a carbonyl.

Figure 6. ^{31}P { ^1H } spectrum of crude acyl phosphonate **3.16**

Figure 7. ^{31}P { ^1H } spectrum of crude acyl phosphonate **3.17**

Figure 8. ^{31}P { ^1H } spectrum of crude acyl phosphonate **3.20**

Figure 9. ^{31}P { ^1H } spectrum of crude acyl phosphonate **3.21**

However, in the ^{31}P { ^1H } NMR spectrums of **3.18** and **3.19**, the same characteristic peak was absent (Figures 10 and 11). Instead, there were five major peak signals among some other minor signals in the spectrum. Since all the peak signals lie in the range between 0 to 50 ppm, the structures were likely to correspond to that of

O=P(R)₃.¹⁰³ Interestingly, both of the ³¹P {¹H} NMR spectrums of **3.18** and **3.19** exhibit similar spectrum peak patterns (Figure 10 and 11), leading us to theorize that there was a common structure resulting from having a β-heteroatom to the acylphosphonate. By inspection of the spectrum, four of the peaks (two at -1 ppm and two at +17 ppm) seem to correspond to a pair of doublets instead of four singlets. Indeed, the coupling constants were measured to correspond to each other, indicating possible ³¹P-³¹P coupling to each other, see Figure 10; δ -1.1, (d, *J* = 22.40 Hz), δ 17.7, (d, *J* = 22.40 Hz) and Figure 11; δ -1.2, (d, *J* = 14.90 Hz), δ 17.5, (d, *J* = 14.90 Hz). This helped to narrow down the possible number of major phosphorus compounds to two, whereby one bears a single phosphorus atom at δ +11 while the other might be a multi-phosphorus atom compound bearing two phosphorus atoms as observed by two doublets at δ -1 and +17 ppm respectively.

Figure 10. ³¹P {¹H} Spectrum of Crude Acyl Phosphonate **3.18**

Figure 11. ^{31}P $\{^1\text{H}\}$ Spectrum of Crude Acyl Phosphonate **3.19**

To determine the likely structures, a search in literature on the synthesis of acyl phosphonates was conducted. Acyl phosphonates have been reported to undergo keto-enol tautomerism as well.¹⁰⁴ Although the keto-form is generally accepted as the more stable conformation, electron-donating effects can also stabilize the enol-form as well.¹⁰⁴

Scheme 54. Keto-Enol Tautomerism of Acyl Phosphonates and Effect of Resonance by Conjugation with Lone Pair Electrons of Heteroatom

A report was found to observe that the enol form dominated the keto form of the acyl phosphonate when enol formation is favored by conjugation effects and the ^{31}P chemical shifts of both forms corresponded to those observed in our study.¹⁰⁵ For example, the keto form of acylphosphonate (Figure 12, A) has a shift at δ -3.0 ppm¹⁰⁵

which was closely similar to that of compounds **3.16**, **3.17**, **3.20** and **3.21**. The enol form (Figure 12, B) has a chemical shift at $\delta +12.9$ ppm¹⁰⁵ which seem to closely correspond to the singlet observed at +11 ppm in both $^{31}\text{P}\{^1\text{H}\}$ spectrums of **3.18** and **3.19**. Another report of a diphosphorus compound (Figure 12, C) bearing a PCOP-type of coupling between phosphorus atoms was observed to have a similar chemical shift and coupling constant as the observed pair of doublets as well.¹⁰⁶

Figure 12. ^{31}P Shifts of Compounds Proposed as Similar Structures of Observed $^{31}\text{P}\{^1\text{H}\}$ Spectrums of Crude Acyl Phosphonate **3.19** and **3.19**

Based on these observations and literature data, a possible mechanism was proposed for the formation of the side product (Scheme 55). Keto-enol tautomerism of the acyl phosphonate was favored towards enol formation due to the stabilization effect brought about by conjugation of lone pair on the heteroatom to the enol.^{104, 105} This enol could then attack a diethyl phosphorochloridate which presumably may be formed from triethyl phosphite and excess oxalyl chloride¹⁰⁷ remaining in the reaction to form a hydroxyl *gem*-(bisphosphonate). Attack by the hydroxyl group on one of the phosphonate group would then give rise to an oxaphosphirane intermediate.¹⁰⁸ Reformation of the stable enol as well as release of ring strain could be the driving force to effect the cleavage of the oxaphosphirane ring to give the diphosphorus side product. Consequently,

the planned radical cyclization may not have worked as a result of the formation of such enol acylphosphonate and the side product

Scheme 55. Proposed Explanation for Unsuccessful Attempt of the Radical Acylation with Acylphosphonates **3.18** and **3.19**

A final experiment was then done to ascertain if the cause of this failure indeed lies with the conjugation effect brought about by an α -substituted heteroatom to the carbonyl group. We decided to extend one carbon in between the heteroatom and the carbonyl group. This should then largely eliminate the conjugation effect observed in acyl phosphonates **3.18** and **3.19** as well as enable a 6-*exo* cyclization which had been shown to work with **3.20** and **3.21**.

Scheme 56. Synthesis of Acyl Phosphonate **3.22** from 3-Allyloxy Propanoic Acid

The synthesis of acyl phosphonate **3.22** from 3-(allyloxy) propanoic acid was not as clean as **3.20** or **3.21**. However, a major singlet was observed at δ -3.4 ppm in its ^{31}P $\{^1\text{H}\}$ NMR spectrum. There were also some minor signals resembling a pair of doublet peaks at δ 1.21 (d, $J = 20.05$ Hz) and 19.9 (d, $J = 20.05$ Hz) ppm.

Figure 13. ^{31}P $\{^1\text{H}\}$ Spectrum of Crude Acyl Phosphonate **3.22**

The crude acyl phosphonate **3.22** was then reacted with the keto-xanthates using our current protocol. We were delighted to isolate the desired dihydropyran-type 1,5-diketones **3.30h** in 65% yield and **3.30i** in 54% yield respectively (Scheme 57). These results constitute experimental evidence to support our postulate for the failure of the radical cyclization as a result of conjugation effect by an α -substituted heteroatom to the carbonyl.

Scheme 57. Synthesis of Dihydropyran-type 1,5-Diketones

3.9 Conclusion

In conclusion, we have demonstrated an effective synthetic combination of alkenyl acyl phosphonates and keto-xanthates, leading to a direct and facile access to functionalized 1,5-diketones without the need for further transformation. Radical acylation using acyl phosphonates as radical carbonyl acceptors allowed for a radical-mediated synthetic route to densely functionalized diketones owing to the advantages of operating under milder conditions and better functionality tolerance over the ionic approach. This work also highlighted an example showing the use of keto-xanthates as successful alternatives in place of α -halo ketones, whereby the radical halogen atom transfer process was rendered mostly ineffective. α -Halo ketones are generally unstable and the fast halogen transfer cannot be exploited effectively in this instance. The strategic use of alkenyl acyl phosphonate grants to some extent, synthetic flexibility for the construction of carbocycles or heterocycles in the 1,5-diketones *via* the radical cascade reaction while the keto-xanthate partner allows easy incorporation of a great variety of

functionalities. Moreover, some of the keto-xanthates can be prepared from commercially available substrates easier and faster than the usual ionic precursors required for the synthesis of 1,5-diketones. In addition, these 1,5-diketones can be further elaborated into novel fused-ring pyridines. Lastly, we have also briefly probed into the synthesis of these acyl phosphonates and gained a better understanding of the scope of viable acyl phosphonates that could be applied to this radical approach for 1,5-diketone synthesis.

Chapter IV.

Bis-Sulfonyl Benzyl Oxime Ethers as a Radical/Ionic Bi-Functional Carboxylate Equivalent: An *O*-Benzyl Oxime Ether Derivatization of Lactones and Thiolactones

4.1 Radical cyclization on carbon-nitrogen unsaturated systems

Kinetic studies¹⁰⁹ have shown that the radical addition and cyclization onto C=O bond of carbonyl groups are still relatively slower than that of the C=N bond due to the stronger C=O bond strength and high reversibility. However, acyl derivatives such as thio- and seleno-esters, acyl germanes and other acyl derivatives have been demonstrated as effective direct radical carbonyl acceptors with carbon-centered radicals as described in Chapter 3. Even so, these C=O type acyl derivatives are generally prepared by nucleophilic substitution of highly reactive acid chlorides or bromides with nucleophiles and organometallics, which in turn, are equally sensitive and reactive as their precursors. This can sometimes impose a technical handicap on the preparation and handling of these substrates in synthesis. As such, there has been some interest in developing and studying the use of carbon-nitrogen iminyl type derivatives such as nitriles, oxime ethers, hydrazones and imines as suitable radical acceptors.¹¹⁰ Furthermore, radical addition to these carbon-nitrogen iminyl type derivatives can give an amine or in some cases, an imine or oxime ether which could be easily hydrolyzed to the carbonyl group. Henceforth, they could also be considered as the indirect carbonyl acceptors in contrary to the acyl derivatives. Although a number of such unsaturated carbon-nitrogen systems had been studied in radical reactions, the use of nitriles and oxime ethers had stood out among the list as the two prevailing classes of carbon-nitrogen radical acceptors that had found success as indirect carbonyl radical acceptors.

4.2 Nitrile group as indirect carbonyl radical acceptors

Among the carbon-nitrogen type radical acceptors, the nitrile group would seem to come to mind easily since it is analogous to that of an alkyne. Indeed, a search in literature revealed possibly that the first radical addition to a nitrile was reported in 1966 when Shelton and Uzelmeier isolated trace amounts of cyclohexyl(phenyl)methanimine generated from peroxide-induced radical addition of cyclohexyl radicals on benzonitrile (Scheme 58).^{71a}

Scheme 58. Addition of Cyclohexyl Radical to Benzonitrile

A more successful attempt was then reported by Ogibin¹¹¹ in the preparation of cyclopentanone *via* radical cyclization of 5-bromocyanopentane and subsequently, its rate constant was later determined by Ingold (Scheme 59).¹¹²

Scheme 59. 5-*exo* Cyclization to Nitrile and Hydrolysis to Ketone

However, it was Corey who started to popularize the utility of nitriles as indirect carbonyl radical acceptors in his novel strategy for the 5-membered ring annulation of unsaturated ketones with zinc-trimethylchlorosilane (Scheme 60).¹¹³ The α -oxy alkyl radical was generated by single electron transfer (SET) to the ketone **4.1**. Notably, this annulation was only effective for 5-*exo* cyclizations.

Scheme 60. Corey's Zn/TMSCl treatment of nitrile ketone to give a fused cyclic ketone

This strategy was later employed by Mann during his synthesis¹¹⁴ of the diterpenoid skeleton **4.2**, which was a precursor of the key intermediate towards natural compounds such as Aphidicolin,¹¹⁵ a known inhibitor of DNA polymerase¹¹⁶ and potentially an anticancer¹¹⁷ and antiherpes agent.¹¹⁸ Stemodin,¹¹⁹ a related diterpene which was also used for the treatment of venereal disease¹²⁰ also possess a similar core and could benefit from this synthetic route as well (Scheme 61).¹¹⁴

Likewise, Clive also explored the use of thionocarbamates in his annulation of δ -hydroxyl nitriles to bicyclic ketones.¹²¹ In contrast to the conventional use of halides, Clive accomplished the radical reaction by defragmentation of thionocarbamate **4.3** to an alkyl radical which then cyclized onto the nitrile *via 5-exo* mode. The substrate could be easily accessed from simple Michael addition of cyclic enamines to acrylonitrile. Similarly to Corey,¹¹³ all but one of the examples were restricted to 5-*exo* cyclizations as well (Scheme 62).¹²¹

Scheme 61. Radical Addition to Nitrile for Synthesis of Core Structure to Key Intermediate leading to Aphidicolin or Stemodin by Mann

Scheme 62. Radical Cyclization of Thionocarbamate onto Nitrile

Notably, the 6-*exo* cyclization onto nitrile proved sluggish^{113, 114, 121} and was often overwhelmed by the faster 1,5 hydrogen transfer process.¹²² This could be curbed by positioning the reactive sites for the radical reaction in a more rigid system or employ a synthetic structure of more constrained geometry to better promote the 6-*exo* cyclization instead. Fraser-Reid was able to demonstrate this in his synthesis of the core structure of a puffer fish toxin whereby an alkyl radical generated from bromonitrile **4.4** underwent a 6-*exo* cyclization on the nitrile (Scheme 63).¹²³ Fraser-Reid also later explored tandem radical cyclizations with nitrile **4.5** and extended this approach to the total synthesis of tricyclic natural product as well (Scheme 63).¹²⁴

Scheme 63. Fraser-Reid's Use of Nitriles as Indirect Carbonyl Radical Acceptors in 6-*exo*-type and Tandem Radical Cyclizations

4.3 Oxime ethers as indirect carbonyl radical acceptors

It was thought that the oxime ethers were the first to surface in the early literature reports of radical addition of carbon-centered radicals onto carbon-nitrogen unsaturated systems.¹¹⁰ On the contrary, the earliest example of oxime ethers as radical acceptors noted by literature was similarly derived from Corey's work in 1983,¹¹³ alongside the nitriles as well (Scheme 64). Nevertheless, the facile preparation and stability of oxime ethers had greatly spur on synthetic chemists to start taking interest in radical addition to carbon-nitrogen unsaturated systems as a tool for synthesis. Therefore, the oxime ether should be credited as a forerunner of these iminyl-type radical acceptors.

Scheme 64. Corey's Zn/TMSCl Treatment of Aldoxime Ketone to Bicyclic Hydroxyamine

Hart utilized halo- and seleno-type precursors with Bu_3SnH or bis(trimethylstannyl)benzopinacolate to generate the alkyl radical required for cyclization onto *O*-benzyl oxime ether under intra- and inter-molecular fashion.¹²⁵ He was able to synthesize perhydroindan **4.7** in high yield of 85% albeit a 50:50 diastereomeric mixture from iodo-lactone **4.6** *via* intra-molecular radical cyclization to the oxime ether as well as alkoxy amines such as **4.8** from the inter-molecular radical addition to oxime ethers from alkyl iodides (Scheme 65).¹²⁵

Scheme 65. Hart's Approach to Perhydroindans

Following Hart's report in the same journal, Bartlett reported his synthesis of aminocyclopentane and aminocyclohexane derivatives using *O*-benzyl oxime ether to capture alkyl radicals generated by bromides and more importantly, phenyl thionocarbonates such as **4.9**.¹²⁶ Using d-glucose, he was able to easily synthesize the phenyl thionocarbonate oxime ether precursor **4.10** which he cyclized to the subsequent amino cyclopentane derivatives **4.11** in excellent yield and modest stereoselectivities (Scheme 66).¹²⁶

Scheme 66. Bartlett Synthesis of *O*-Benzylamino Cyclopentane Derivatives

The use of phenyl thionocarbonates in Bartlett's work led to an interesting development of exploiting carbohydrates such as d-glucose to synthesize potential oxime ether radical precursors. One such application was employed by Naito who used keto oxime ether **4.12** to generate amino alcohol **4.13**.¹²⁷ These were protected analogues of amino cyclopentitols, which were found to be effective and specific inhibitors against glycosidases.¹²⁸ The trans-isomer of **4.13** could also be further manipulated to give piperidine **4.14** which is a precursor to 1-deoxynojirimycin,¹²⁹ another glycosidase inhibitor as well (Scheme 67).¹²⁷

Carbohydrates such as d-allofuranose could also be utilized under a similar concept. Moore employed this strategy¹³⁰ by using a dithioacetal **4.16** made from a bisisopropylidene derivative **4.15** of d-allofuranose in his synthesis of a protected analogue **4.17** of Mannostatin A,¹³¹ a sugar hydrolase inhibitor (Scheme 68).¹³⁰

Scheme 69. Improved Stereoselectivity through the use of Isopropylidene Acetals by Marco-Contelles

So far, the use of oxime ethers had been often described as radical acceptors for cyclization onto carbon-nitrogen unsaturated systems and therefore, resulted in the formation of amines. This is not surprising since the intermediate aminyl radical readily abstracts a hydrogen atom from available sources such as the tin hydride used to liberate the propagating tributyltin radical. Retention of the C=N bond in such oxime ether radical acceptors was uncommon. One such rare example was reported by Pattenden in an interesting radical cascade for the synthesis of bi- and tricyclic ring systems containing an oxime ether (Scheme 70).¹³³ Initially, tris(trimethylsilyl)silyl radical adds to the alkyne **4.20** to generate a vinyl radical **4.21** which then undergoes a *6-exo* cyclization onto the oxime ether. β -fragmentation of the strained cyclobutane then proceeded from the intermediate aminyl radical **4.22** to generate another secondary carbo radical **4.23** with ring expansion. Next, addition to the vinyl silane *via* a *5-exo* cyclization gave rise to another alkyl radical **4.24** which was then trapped by the oxime ether, forming intermediate aminyl radical **4.25** bearing a cyclopropane. This was then followed by another β -fragmentation of the strained cyclopropane, which led to the formation of a stabilized tertiary carbo radical **4.26** and finally undergo elimination of tris(trimethylsilyl)silyl radical to give α,β -unsaturated bicyclic oxime ether **4.27**. The strong driving force in this cascade reaction was attributed to the energetically favorable release of strain in the subsequent ring expansion, allowing the intermediate aminyl

radical to be quickly assimilated back into the radical cascade reaction before being quenched by proton sources (Scheme 70).¹³³

Scheme 70. Pattenden's Radical Cascade Synthesis of Bicyclic System with Double Ring Expansion

4.4 β -Fragmentation from an aminyl radical using sulfonyl oxime ethers

Indeed, this phenomenon of β -fragmentation from aminyl radicals generated from radical addition to O-benzyl oxime ethers was observed again in Kim's use of phenylsulfonyl oxime ethers as indirect carbonyl radical acceptors.¹³⁴ Kim's approach to employing such oxime ethers as carbonyl radical acceptors emerged from a simple concept. The idea was centered about finding a suitable radical leaving group on the oxime ether to drive the β -fragmentation from the intermediate aminyl radical following the addition of alkyl radicals to the oxime ethers **4.28** and **4.29**. It was found that phenylsulfonyl radicals liberated from **4.29** were more efficient radical leaving groups for

the β -fragmentation from aminyl radicals generated in the radical addition to *O*-benzyl oxime ethers as compared to phenylsulfanyl radicals liberated from **4.28** (Scheme 71).¹³⁴ The introduction of the more electron-withdrawing sulfonyl group was expected to lower the LUMO of the oxime ether radical acceptor, thus, improving the SOMO-LUMO interaction favorably, increasing the rate of addition of alkyl radicals to the oxime ether.¹¹ These oxime ethers were then hydrolyzed to the corresponding aldehyde **4.30a** and ketone **4.30b**.

Scheme 71. Tin Mediated Free-Radical Acylation of Alkyl Iodide

This was also successfully extended to sequential intra-molecular cyclizations (Scheme 72) to give bicycles **4.32** containing the *O*-benzyl oxime ether group from iodo-cyclopentene **4.31**. In addition, three-component radical cascades were found to work as well to form oxime ether-containing carbocycle **4.33** (Scheme 73).¹³⁴ The *O*-benzyl oxime ether could subsequently be hydrolyzed with acid to the corresponding ketone **4.34a** or aldehyde **4.34b** easily.

Scheme 72. Sequential Intra-Molecular Cyclization with Sulfonyl Oxime Ether

Scheme 73. Three-Component Radical Cascade with Sulfonyl Oxime Ether

In the following year, the same radical acylation strategy was improvised further with the use of a bis-sulfonyl oxime ether **4.35**.¹³⁵ This enabled the sequential radical alkylation onto a bis-sulfonyl oxime ether which now acts like a carbonyl equivalent geminal radical acceptor. Preliminary experiments revealed the phenyl bis-sulfonyl oxime ether derivative **4.35a** to be less reactive to radical alkylation as compared to its first radical adduct **4.36a**, despite bearing favorable predictions of reactivity by standard AM1 calculations of LUMO energies.¹³⁵ In contrary, following the first alkyl radical addition, a second uncontrolled alkylation took place as well, rendering the protocol incapable of introducing a different alkyl radical in planned sequence. This was later attributed to sterics brought about by the bulky phenyl group, in which on elimination after the first

radical addition, promoted a second radical addition in the subsequent radical adduct **4.36a** to give dialkylated oxime ether **4.37**. This was then solved by changing to a methyl bis-sulfonyl oxime ether derivative **4.35b**, resolving the steric issue and increasing the reactivity of the radical acceptor as well (Scheme 74).¹³⁵

Scheme 74. Steric effect on sequential alkylation on bis-sulfonyl oxime ether

Further optimization done on the bis-sulfonyl oxime ether resulted in switching of the tetrahydropyran group (THP) for a benzyl group (Bn). A wide range of ketones bearing two different alkyl side chains were successfully synthesized based on this 3-step one pot procedure. The protocol was also extended to sequential intra-molecular radical cyclizations to give bicyclic ketones as well. For example, on a double halo-substituted derivative **4.38**, the iodide is preferentially abstracted by tin to give the first alkyl radical for the radical addition to methyl bis-sulfonyl oxime ether **4.39a**. This is then followed by a second radical addition by the alkyl radical generated from the bromide, which cyclized in tandem on the alkyne and the sulfonyl oxime ether to give the oxime ether bicycle **4.40**, which then hydrolyzed to ketone **4.41**. (Scheme 75).¹³⁵

Scheme 75. Sequential Radical Alkylation of Di-Halo Derivative to Bis-Sulfonyl Oxime Ether

The resounding success of this radical acylation strategy using sulfonyl oxime ethers fueled further development of a tin-free approach by Kim,⁴⁸ in particularly in midst of an increasing disdain for tin-mediated protocols in radical reactions. Capitalizing on the idea of the thermal decomposition of ethylsulfonyl radicals by Zard in which the resulting liberated ethyl radical act as a radical relay to mediate the halogen atom transfer,¹³⁶ Kim hoped to extend this approach to sulfonyl oxime ethers **4.29** as well. In preliminary studies, the ethyl radical was shown to directly attack the sulfonyl oxime ether **4.29b** much faster than the iodine atom transfer process, thus, fiercely contesting the competition with the cyclohexyl radical for the radical addition. This severely limits the protocol of introducing various alkyl groups *via* the use of alkyl iodides as radical precursors in this tin-free method. A stopgap measure was then put in place using methyl sulfonyl oxime ethers **4.29c** instead. This required the use of much elevated temperatures to forcibly decompose the methylsulfonyl radical into the more reactive methyl radical, which more active in iodine atom abstraction as compared to the ethyl radical (Scheme 76).⁴⁸

Scheme 76. Tin-Free Addition of Cyclohexyl Radical to Ethyl- and Methyl-Sulfonyl Oxime Ethers

However, the use of methylsulfonyl oxime ether **4.29c** was only effective for secondary and tertiary carbon-centered radicals generated from alkyl halides. Primary alkyl radicals did not work well at all. This was attributed to the small disparity in energy differences between a methyl radical and primary alkyl radical, resulting in a lack of differentiation between either propagating methyl radical or the primary alkyl radical to add to the oxime. Ultimately, this was resolved by using a more reactive radical precursor such as an alkyl phenyl telluride which proved to accelerate the iodine atom transfer more efficiently than the alkyl iodides (Scheme 77).⁴⁸

Scheme 77. Tin-Free Radical Alkylation of Methylsulfonyl Oxime Ether

To effectively and easily generate primary alkyl radicals, a novel type of primary alkyl radical precursor was developed through the use of alkyl allyl sulfones.¹³⁷ The alkyl sulfonyl radical **4.45** was first generated from addition-fragmentation of alkyl allyl sulfone **4.44** by an azo-initiator such as V-40. This alkyl sulfonyl radical **4.45** could add to the starting alkyl allyl sulfone **4.44** in a degenerate manner or add to allyl phenyl

sulfone to generate phenyl sulfone radical. The latter pathway would in turn, regenerate the alkyl sulfonyl radical on addition to the starting material. The alkyl sulfone radical then fragment reversibly with extrusion of sulfur dioxide into the alkyl radical **4.46** which would then be trapped by the reactive sulfonyl oxime ether **4.29a** to give aldoxime **4.30a** with the extrusion of phenyl sulfone radical used for further propagation of the radical chain (Scheme 78).¹³⁷

Scheme 78. Use of Alkyl Allyl Sulfone as Primary Alkyl Radical Precursors

4.5 A radical carboxylation approach using sulfonyl oxime ethers as carboxylate radical acceptors

Sulfonyl oxime ethers have proven themselves to be efficient carbonyl radical acceptors in the synthesis of various acyclic and cyclic ketones *via* tin-mediated or tin-free procedures as described earlier. However, this approach has thus far been limited to radical carbonylation for the indirect synthesis of ketones and aldehydes. In the same regard, radical carboxylation for the synthesis of esters or thioesters should be possible as well through the use of heteroatom substituted sulfonyl oxime ethers. However, the

introduction of a heteroatom to the sulfonyl oxime ether greatly diminished its effectiveness as a radical acceptor. This was expected since the lone pair electrons could back-donate electron density to the iminyl group, therefore, increasing the LUMO energy of the radical acceptor. The key to success for the sulfonyl oxime ethers was the use of the sulfone group, which was a strongly electron-withdrawing group. This not only lowers the LUMO energy of the oxime ether but also doubles as a stabilized radical leaving group in contrast to the electron-donating phenylsulfanyl group. Therefore, addition of another electron-withdrawing group such as an ethyl ester in **4.48** or sulfone in **4.39a** further increases its ability as a radical acceptor. For example, the replacement of a sulfone group in **4.39a** with a methyl group in **4.47** caused an increase in LUMO energy of the sulfonyl oxime ether by 0.4354 eV (Figure 14).¹³⁵ Evidently, the introduction of electron-donating substituents served to widen the SOMO-LUMO gap, leading to reduced reactivity for the radical addition.

Figure 14. List of Successfully Employed Sulfonyl Oxime Ethers and Effect of Electron-Withdrawing Group on LUMO energy

Experimental results have also provided evidence for this decline in reactivity. For example, the replacement of methyl group with a more electron-donating substituent like a phenylthiyl on the sulfonyl oxime ether led to a decline in reactivity (Scheme 79).¹³⁸ In contrast, having more electron-withdrawing substituents on the sulfonyl oxime ether such

as in the case of the bis-sulfonyl oxime ether **4.39a**, increases its reactivity to radical addition to the extent whereby sequential di-alkylation occurred.

Scheme 79. Effect of Electron-Donating Substituents on alkyl radical addition to Sulfonyl Oxime Ether

Since heteroatom-substituted sulfonyl oxime ethers are relatively poor radical acceptors for tin-mediated intermolecular radical alkylation, this method does not provide a good route to the corresponding carboxylates. An alternative would be to perform radical alkylation to bis-sulfonyl oxime ethers to give the mono-sulfonyl radical adduct **4.49**, followed by acid-promoted hydrolysis of the *O*-benzyl sulfonyl oxime ether to acyl methyl sulfone. This is then attacked with an alcohol like MeOH to generate the desired acyclic ester **4.50** (Scheme 80).¹³⁹

Scheme 80. Tin-Mediated/Acid Hydrolysis Approach to Esters via Bis-sulfonyl Oxime Ethers

Access to cyclic esters such as lactones or thiolactones may be possible by using alcohol or thiol-containing substrates which can cyclize onto the *O*-benzyl sulfonyl oxime

ether *via* nucleophilic displacement of sulfone (Scheme 81).¹⁴⁰ Lactones are commonly found in compounds relating to flavoring in spirits and wine¹⁴¹ or perfumes and food additives.¹⁴² Lactones¹⁴³ and thiolactones¹⁴⁴ are also present in biologically active compounds and also possess potential synthetic utility as intermediates^{145, 146} in synthesis of natural products. While this approach constitutes an indirect way to the lactone group, a direct radical carboxylation has not been explored and may possibly provide a more versatile route to such lactones.¹⁴⁰

Scheme 81. Possible Synthesis of Lactone and Thiolactone using Hydroxyl- and Thiol-Substituted Alkyl Radicals

4.6 Synthesis of heteroatom-tethered sulfonyl *O*-benzyl oxime ethers

During the course of development of these sulfonyl oxime ethers, their synthetic route was improved gradually but have gone unnoticed in face of the amazing feat accomplished by the radical reaction itself. Since the first communication by Kim in 1996,¹³⁴ the sulfonyl oxime ethers **4.29a** were first derived from formaldehyde or acetaldehyde in a 4-step synthesis (Scheme 82). This however limited the side substituent to either a hydrogen or methyl group.

Scheme 82. Synthesis of Phenyl Sulfonyl Oxime Ether from Formaldehyde and Acetaldehyde

The synthesis of bis-sulfonyl oxime ethers however, required a different synthetic route.¹³⁵ Starting from α -nitro sulfone, sequential bromination and *O*-methylation afforded an unstable nitronic ester which rapidly converted to the bromo oxime **4.51** which was the key intermediate for all subsequent sulfonyl oxime ether transformations. The hydroxyl group could be capped with a tetrahydropyran or benzyl group leading to **4.52** and subsequently be treated with either a suitable sodium thiolate or alcoholate to give the heteroatom-substituted sulfonyl oxime ether **4.53**. An excess of sodium methyl thiolate used on **4.52** would give methyl bis-sulfanyl oxime ether **4.54** which is then further oxidized to the methyl bis-sulfonyl oxime ether **4.35b**. This route allows a more flexible manipulation of introducing another substitution next to the phenylsulfonyl group or methylsulfonyl group on the oxime ether. Unfortunately, the precursors were difficult to handle or synthesize and the yield of the final product was gradually reduced in the long synthesis itself. Even so, this was the first synthesis to introduce bis-sulfonyl oxime derivatives **4.35** (Scheme 83).¹³⁵

Scheme 83. Synthesis of Substituted or Bis-sulfonyl Oxime Ethers

A more convenient and flexible route to *O*-benzyl bis-sulfonyl oxime ether **4.39a** was then reported by Kim in 2010.¹⁴⁷ Starting from easily available and commercial *O*-benzyl amine hydrochloride, carbon disulfide and iodomethane, the mixture was then added triethylamine to give the methyl bis-sulfanyl oxime ether **4.55a** which then undergoes oxidation to the bis-sulfonyl oxime ether in two steps (Scheme 84).¹⁴⁷ **4.39a** was then later used as a phosgene surrogate in nucleophilic substitutions.

Scheme 84. 2-Step Synthesis of Methyl Bis-sulfonyl Oxime Ethers

4.7 Proposed strategy for heteroatom-tethered sulfonyl *O*-benzyl oxime ethers as carboxylate radical acceptors for the synthesis of *O*-benzyl oxime ether carboxylate derivatives

Building on our work previously on tin-free radical carbonylation⁴⁸ and our recently reported improved synthetic route to bis-sulfonyl oxime ethers,¹⁴⁷ we envisaged that the use of alkenyl heteroatom-tethered sulfonyl oxime ethers may function as potential carboxylate radical acceptors for the construction of lactone, thiolactone and maybe lactam derivatives. This would then demonstrate bis-sulfonyl *O*-benzyl oxime ethers as an ionic and radical bi-functional carboxylate synthetic equivalent (Scheme 85).

Scheme 85. Bis-Sulfonyl Oxime Ether as Ionic/Radical Bi-Functional Carboxylate Equivalent

The proposed strategy was to introduce an alkyl radical $\text{R}^\cdot$ onto the alkene first by inter-molecular fashion to generate a secondary alkyl radical and then cyclize onto the heteroatom-substituted oxime ether. Although addition to such sulfonyl oxime ethers were not effective under inter-molecular conditions,¹³⁹ the intra-molecular attack was presumed to be faster. β -fragmentation from the intermediate aminyl radical should regenerate the sulfonyl radical with the formation of the cyclized *O*-benzyl oxime lactone

or a "lactoxime" in this instance. The sulfonyl radical then decomposes with extrusion of sulfur dioxide to the alkyl radical which then propagates the radical chain by mediating the halogen atom transfer of the alkyl halide. (Scheme 86).

Scheme 86. Initial Proposed Strategy for Synthesis of *O*-benzyl Oxime Lactone from Alkenyl *O*-tethered Sulfonyl Oxime Ether

This synthetic approach provides a direct route to unusual *O*-benzyl oxime ether derivatives of mono α -alkylated lactones, thiolactones and lactams as well. Current methods that utilized the condensation of *O*-alkyl amines with ketones and aldehydes would be difficult to replicate with the corresponding lactones, thiolactones or lactams. Furthermore, the synthesis of their precursor mono α -alkylated lactones, thiolactones and lactams are not trivial as well. Direct α -alkylation of lactones requires the use of strong bases to generate the ester enolate¹⁴⁸, therefore, the functional group tolerance of such a process is severely limited to simple alkyl electrophiles that do not possess reactive polar sites.¹⁴⁸ Moreover, the generated ester enolate is very reactive, and it is often difficult to achieve control over mono-, di-alkylation and self-condensation. It is often easier to di-

alkylate than mono-alkylate a lactone enolate. A more convenient approach to the synthesis of such functionalized lactones is done *via* condensation of hydroxyl acids,¹⁴⁹ ketone or aldehyde acids^{150, 151} and hydroxyl nitriles¹⁵² or the acid-catalyzed lactonization,¹⁵³ halo-lactonization¹⁵⁴ and seleno-lactonization¹⁵⁵ of alkenyl acids. In addition, oxidation-ring expansion processes such as the well-known Bayer-Villiger reaction¹⁵⁶ of cyclic ketones have been a popular choice to access lactones as well.

However, the manner of cyclization on such a single precursor generally requires the use of fully functionalized analogues of such carboxylic derivatives,¹⁴⁹⁻¹⁵⁵ which may in turn, prove tedious in preparation or bear limited choice of functionality as a result of the intermediate hydrolysis step to the acid or the final condensation step to the target molecule. Even so, most of these lactones are poorly or not functionalized at the alpha position (Figure 15). A brief look at the substrate examples¹⁴⁹⁻¹⁵⁵ in these reactions revealed the preference of substitution at the hydroxyl position instead of the carboxylic acid derivative. It could be surmised that the preparation of such carboxylic acid derivatives bearing more complex substituent near the carboxylate center may not be trivial. Moreover, in Bayer-Villiger reactions of cyclic ketones, the migration of the more substituted group is more favored, therefore, it was not always possible to get the mono alpha-substituted lactones as well.

Figure 15. Common ionic approaches to lactone synthesis

Lactones can be converted to their corresponding thiolactones *via* an oxygen-sulfur transfer using a sulfination agent such as P_2S_5 .¹⁵⁷ However, this usually results in a mixture of thiolactone, thionolactone and dithioester which are difficult to separate cleanly (Figure 16). Similarly to lactones, thiolactones are preferably synthesized by acid-

or base-promoted condensation of their corresponding thiol carboxylic acids,¹⁵⁸ esters,¹⁵⁹ amides,¹⁶⁰ and acid chlorides¹⁶¹ (Figure 16) and face similar challenges for the incorporation of acid or base-sensitive functionalities near the carboxylate center as well.

Figure 16. Common ionic approaches to thiolactone synthesis

4.8 Oxime ether derivatives as important bioactive scaffolds

In addition, these novel carboxylate *O*-benzyl oxime ethers themselves represent an almost unknown or rare class of compounds.¹⁶² The synthesis of oxime and oxime ether derivatives had mostly been confined to their corresponding ketones and aldehydes¹⁶³ while oxime derivatives of lactones and thiolactones remained largely unexplored. Only one example of an oxime ether derivative of lactone had been reported using a Mitsunobu-type reaction.¹⁶² Oxime and oxime ether derivatives of ketones and aldehydes or also known as "ketoximes" and "aldoximes" respectively, have been shown to have interesting biological activity including anti-fungal, anti-bacteria and anti-convulsant properties.¹⁶⁴ These have found various applications in the development of novel pesticides,¹⁶⁵ fungicides¹⁶⁶ and antiepileptic drugs¹⁶⁴ such as those shown in Figure 17. In addition, they also serve as plant growth agents in the agricultural industry.

Figure 17. Examples of Bioactive Oxime Ether Derivatives^{164, 165}

The oxime ether group is regarded as a highly efficient pharmacophore and is a popular moiety to include in drug molecular design as a result of bioisosterism.¹⁶⁷ The presence of such a bioisostere allows possible reduction in toxicity or manipulate the biological activity or alter other desirable properties such as bioavailability without drastically changing the molecular structure. A synthetic route to such carboxylate *O*-benzyl oxime ether derivatives would potentially extend this benefit to existing or future bioactive molecular scaffolds containing lactones and thiolactones as well.^{143, 144}

4.9 Preliminary Studies

We started our investigation on this concept by first preparing the alkenyl *O*-tethered ethyl sulfonyl *O*-benzyl oxime ether **4.56b** as carboxylate radical acceptor. **4.56b** was chosen in consideration of the anticipated poor differentiation of selectivity between primary alkyl radicals and the propagating methyl radical which are of similar HOMO energy levels.⁴⁸ Also, the ethyl radicals could be generated at a lower reflux temperature as compared to methyl radicals from sulfonyl radical decomposition. Hence alkenyl *O*-tethered ethyl sulfonyl *O*-benzyl oxime ether **4.56b** was synthesized in good yield of 75% from reacting sodium homoallylic alkoxide and ethyl bis-sulfonyl *O*-benzyl oxime ether **4.39b** (Scheme 87).

Scheme 87. Synthesis of Alkenyl *O*-tethered Ethyl Sulfonyl *O*-benzyl Oxime Ether

Initial results were disheartening when 2-bromo-1-phenylethanone was first tested using AIBN as radical initiator with **4.56b** in refluxing DCE. Despite the isolation of the desired oxime lactone **4.68a** in low yield of 9%, showing that the reaction does work as proposed, a significant amount of the starting sulfonyl oxime ether **4.56b** was recovered in 28% yield. More surprisingly, the major product isolated was the ethyl sulfone radical adduct of the oxime lactone **4.68aa** in 42% (Scheme 88).

Scheme 88. Preliminary test Using α -Bromo Ketone with Alkenyl *O*-tethered Ethyl Sulfonyl *O*-benzyl Oxime Ether

A repeat of the experiment under tin-mediated conditions with 300 nm lamp gave **4.68aa** in very high yield of 84%, accompanied with the desired oxime lactone **4.68a** in a low yield of 11% (Scheme 89). In this test, the starting alkenyl sulfonyl oxime ether

Since the halogen atom transfer did not prove useful in this reaction, we next turned to xanthates, which had previously been demonstrated to work with alkenyl acyl phosphonates.¹⁶⁹ The use of keto xanthate proved as effective as using tin to mediate the radical reaction however, the ethyl sulfone addition remained dominant (61% yield) with a slight improvement in yield of 27% of the desired oxime lactone formation (Table 5, Entry 1). This result showed that the ethyl sulfone radical addition was also able to compete effectively with the xanthate transfer as well, although not as effectively as it did in the halogen atom transfer. Notably, an increase in the stoichiometric ratio of the keto-xanthate **3.23i** to alkenyl sulfonyl oxime ether **4.56b** improved the yield of the desired oxime lactone to a certain extent (Table 5, Entries 2 and 3) with the ethyl sulfonyl adduct **4.68aa** as the major product.

Table 5. Effect of Ratio of Reagents on Alkyl and Ethyl Sulfone Radical Addition

Entry	3.23i/4.56b (equiv)	% Yield (4.68a/4.68aa)
1	1/1	27/61
2	1.5/1	39/55
3	2/1	43/51
4 ^a	0/1	No reaction

^aThe reaction was done in refluxing chlorobenzene with only DLP over 1 hour.

From these observations, we were led to believe that both the alkyl and ethyl sulfone radical concentration were of comparable significance in the reaction medium to effect the radical addition to form the oxime lactones (Scheme 90). The presumed liberated ethyl radical did not present a problem in this reaction as it did in previous work⁴⁸ on sulfonyl oxime ethers. In addition, a separate experiment was performed by reacting only the alkenyl sulfone oxime ether with DLP in refluxing chlorobenzene for an hour (Table 5, Entry 4). No observable change was observed *via* TLC, indicating that the ethyl sulfone addition might not be caused by unimolecular chain transfer process under peroxide initiation. Therefore, it was possible to manipulate their respective active concentrations in the reaction mixture to direct the radical cycle to propagate towards the desired product. This was demonstrated by varying the stoichiometric ratios between the keto-xanthate **3.23i** and alkenyl sulfonyl oxime ether **4.56b** as seen in Table 5.

Scheme 90. Competition between Alkyl and Ethyl Sulfonyl Radical

However, to significantly direct the radical chain towards the desired oxime lactone, use of a large excess amount of the keto-xanthate would be required. Such wastage would render this application to be impractical for use. Instead, we decided to emulate this ratio difference by diluting the concentration of the alkenyl sulfonyl oxime ether. This was first done with interval addition of a mixture of the alkenyl sulfonyl oxime ether **4.56b** and DLP in DCE to a refluxing solution of the keto-xanthate **3.23i** in DCE. Indeed, a more favorable result was obtained with the desired oxime lactone **4.68a** as the major isolated product (Scheme 91). Unfortunately, this did not suppress the formation of the ethyl sulfone adduct **4.68aa** completely. Syringe-pump techniques proved futile as the addition was too slow to keep the radical chain cycle alive (Scheme 92).

Scheme 91. Interval Addition of Alkenyl Sulfonyl Oxime Ether to Keto-Xanthate

Scheme 91. Syringe-Pump Addition of Alkenyl Sulfonyl Oxime Ether to Keto-Xanthate

Ultimately, the goal was targeted at using the sulfonyl radical to mediate the xanthate transfer to introduce alkyl radicals for this radical carboxylation reaction and not participate in the direct addition. After many experiments, manipulation of the reaction concentration of the keto-xanthate in real-time proved to be inconsistent and did not completely eliminate the ethyl sulfonyl radical addition at all. We then switched our focus to the sulfonyl radical instead of the α -keto radical. Following on a previous report by Zard on the use of isopropyl sulfonyl radical which decomposed readily to the isopropyl radical to act as the relay in the radical chain process,¹⁷⁰ we decided to induct this strategy into the present approach. The alkenyl isopropyl sulfonyl *O*-benzyl oxime ether **4.56c** was then synthesized in good yield of 72% from the bis-sulfonyl precursor **4.39c** as shown in Scheme 93. Unfortunately, secondary iodides did not work well using our present synthetic route as seen from the low yield (27%) of bis-sulfonyl *O*-benzyl oxime ether obtained. This was largely attributed to steric hindrance.

Scheme 93. Synthesis of Alkenyl *O*-tethered Isopropyl Sulfonyl *O*-Benzyl Oxime Ether

Regardless, the alkenyl isopropyl sulfonyl *O*-benzyl oxime ether **4.56c** was put to the test and was successful in eliminating the expected isopropyl sulfone addition pathway. The desired oxime lactone **4.68a** was synthesized in 69% yield without

observing any isopropyl sulfonyl adduct in the radical reaction with keto-xanthate **3.23i** (Scheme 94).

Scheme 94. Reaction of Keto-Xanthate with Alkenyl *O*-tethered Isopropyl Sulfonyl *O*-Benzyl Oxime Ether

In view of the results thus far, we summarized the findings in Scheme 95. In this radical carboxylation approach, there were two possible radical pathways **A** and **B**. The initial and conventional pathway **A** was focused on the addition of the α -keto radical and regeneration of the α -keto radical, in which, this was supposedly mediated by an alkyl radical produced from the decomposition of the liberated sulfonyl radical expelled during β -elimination from the intermediate aminyl radical on the oxime ether. Initial results however, showed that the liberated sulfonyl radicals do not decompose fast enough to mediate the xanthate or halogen atom transfer and therefore, become involved in the addition to the alkenyl sulfonyl oxime ether *via* another radical pathway **B** instead. The differentiation between pathways **A** and **B** could be effectively distinguished by promoting faster decomposition of the sulfonyl radical into a more stabilized radical chain relay such as an isopropyl radical. Henceforth, the key focus in this radical carboxylation is the manipulation of sulfonyl radical decomposition against the direct addition to the alkenyl sulfonyl oxime ether.

Scheme 95. The Sulfonyl Radical as the Cornerstone of the Radical Carboxylation

Approach using Alkenyl Sulfonyl *O*-benzyl Oxime Ethers

Despite achieving success with the alkenyl isopropyl sulfonyl *O*-benzyl oxime ether **4.56c** in the radical carboxylation of xanthates, the synthetic yield was poor and was not favorable at all in preparative scale for further substrate studies. In this regard, we decided to push forward boldly with a new radical chain relay designed based on the difficulties experienced in the course of work with this radical carboxylation approach. Firstly, the new radical chain relay should be a primary alkyl so as to enable facile alkylation of *O*-benzyl iminyl dithiolate using the current synthetic approach to bis-sulfonyl *O*-benzyl oxime ether. Next, this radical relay group should be stable to enable fast decomposition from the sulfonyl radical and finally, it should be selective to attack the more radicophilic sulfur of the xanthate instead of addition to alkene. A possible yet

simple candidate fulfilling these requirements was the benzyl group although it was very rarely reported in radical-mediated strategies.

Nevertheless, this bold plan was put into action by first attempting the synthesis of the alkenyl benzyl sulfonyl *O*-benzyl oxime ether **4.56d**. In addition, synthesis of the bis-sulfonyl precursor **4.39d** was achieved in very high yield of 81% over 2 steps. The high insolubility of this compound in methanol came as a bonus through the easy purification of the compound by simply washing the solid with methanol unlike the other bis-sulfonyl *O*-benzyl oxime ethers like **4.39b** and **4.39c** which generally required silica-gel column chromatography. Finally, alkenyl benzyl sulfonyl *O*-benzyl oxime ether **4.56d** was also obtained in good yield of 78% (Scheme 96).

Scheme 96. Synthesis of Alkenyl *O*-tethered Benzyl Sulfonyl *O*-Benzyl Oxime Ether

To test this reaction, we attempted the radical reaction with the keto-xanthate **3.23i** and the alkenyl benzyl sulfonyl *O*-benzyl oxime ether **4.56d** in hand. It was comforting to obtain similar results with that of the isopropyl sulfonyl oxime derivative and thus, greatly enhanced synthetic preparation for further study of this synthetic approach. Notably, this was the first instance that a benzyl radical has been successfully employed to mediate a xanthate transfer reaction and therefore, presented a very rare occurrence of the use of such species as a radical chain relay (Scheme 97).

Scheme 97. The First Successful Instance of a Benzyl Radical mediating a Xanthate Transfer Reaction

4.10 Results and Discussion

In preparation for expanding the scope of this study, the synthesis of various alkenyl benzyl sulfonyl oxime ethers was attempted for use as precursors to further test this synthetic strategy. In general, the oxy-tethered alkenyl benzyl sulfonyl oxime ethers were easily synthesized using the sodium alkoxides prepared by reacting sodium hydride with various unsaturated alcohols. A series of tests showed that mainly primary alkoxides containing acyclic alkynes (**4.58d**, **4.59d**), allenyl (**4.60d**), methallyl (**4.62d**) and an acyclic 1,3-dioxolane substituted alkene (**4.67d**) were synthesized in good to excellent yields of 67-92% with the benzyl bis-sulfonyl *O*-benzyl oxime ether **4.39d** (Scheme 98). In addition, phenols (**4.57d**, **4.61d**) were similarly obtained in good yields of 80% and 74% respectively with benzyl bis-sulfonyl *O*-benzyl oxime ether **4.39d** as well.

Scheme 98. Synthesis of *O*-tethered Alkenyl Benzyl Sulfonyl *O*-Benzyl Oxime Ethers

Unfortunately, secondary and tertiary alkoxides failed to attack the oxime ether center (Scheme 99).

Scheme 99. Reaction of Secondary and Tertiary Alcohols on Benzyl Bis-Sulfonyl *O*-Benzyl Oxime Ether with Various Bases

In particularly for tertiary alkoxides, the formation of benzaldehyde was always observed. A likely reason could be due to the steric nature of the larger benzyl group, the additional substitution on the nucleophiles caused them to behave as bases instead, and

deprotonate the benzylic hydrogen on the *O*-benzyl oxime ether, leading to the formation of benzaldehyde as observed from crude ^1H NMR spectrum as well as consumption of benzyl bis-sulfonyl *O*-benzyl oxime ether **4.39d** (Scheme 100).

Scheme 100. Proposed Mechanism for Formation of Benzaldehyde during Reaction of Hindered Nucleophiles with **4.39d**

2-Allylaniline (Scheme 101) and substituted amines (Scheme 102) were also found to react poorly as well with benzyl bis-sulfonyl *O*-benzyl oxime ether **4.39d**. The use of strong inorganic bases such as butyllithium (BuLi), lithium diisopropyl amide (LDA), sodium hydride (NaH) and potassium carbonate (K_2CO_3) or non-nucleophilic amine bases like triethylamine (Et_3N) or pyridine with alkenyl amines did not afford any isolable amounts of nitrogen-tethered alkenyl sulfonyl oxime ethers. Like the tertiary and secondary alkoxides, these substituted amine nucleophiles acted more like bases instead when reacted with **4.39d** and generated benzaldehyde as well.

Scheme 101. Reaction of 2-Allyl Aniline on Benzyl Bis-Sulfonyl *O*-Benzyl Oxime Ether with Various Bases

Scheme 102. Reaction of *N*-Benzylbut-3-en-1-amine on Benzyl Bis-Sulfonyl *O*-Benzyl Oxime Ether with Various Bases

Unfortunately, even with the use of primary alkenyl amines with benzyl bis-sulfonyl *O*-benzyl oxime ether **4.39d**, nitrogen-tethered alkenyl sulfonyl oxime ethers were not isolated either. Only when reverted back to using ethyl bis-sulfonyl *O*-benzyl oxime ether **4.39b**, the synthesis was successful albeit a low yield of 22% was observed (Scheme 103).

Scheme 103. Synthesis of *N*-tethered Alkenyl Ethyl Sulfonyl *O*-Benzyl Oxime Ether from Primary Alkenyl Amines

Nevertheless, we attempted the radical reaction with the nitrogen-tethered alkenyl ethyl sulfonyl oxime ether **4.63b** and keto-xanthate **3.23i**. The reaction proceeded smoothly to afford the lactam oxime ether derivative or amidoxime **4.69** exclusively in 65% yield (Scheme 104). We were surprised not to observe the formation of the ethyl sulfone addition product at all. The reason for this discrepancy against the *O*-tethered alkenyl sulfonyl oxime ether analogue remains unknown but due to the difficulty of preparing the volatile primary amine as well as the poor yield resulting from preparing **4.63b**, we decided to place our focus on the other heteroatom-tethered analogues instead. Nonetheless, this result has demonstrated the possibility of accessing such functionalized amidoximes *via* the current approach. Amidoximes derivatives have been known to act as potential antimalaria¹⁷¹ and antitumor agents.¹⁷²

Scheme 104. Reaction of Keto-Xanthate with Alkenyl *N*-tethered Ethyl Sulfonyl *O*-Benzyl Oxime Ether

We next turn our attention to the sulfur-tethered analogues. Initially, the alkenyl thiols were prepared by nucleophilic substitution of their corresponding bromides with potassium thioacetate and later hydrolyzed with aqueous base or reduced with lithium aluminium hydride (LAH). The crude thiols were then subjected to the similar conditions as the formation of alkoxides (Scheme 98) by reaction with sodium hydride and then reacted with the benzyl bis-sulfonyl oxime ether. We have found this synthetic preparation to be tedious and ineffective due to the additional work-up steps which tend to cause unwanted oxidation of the thiols to the disulfides. To bypass the additional work-up steps or hydrolysis and reduction processes, we chanced upon a literature¹⁷³ describing the use of pyrrolidine as a base to generate the thiol *in-situ* from thioacetates and then react with the electrophile introduced subsequently. This concept was inculcated into the current procedure using alkoxides with a slight modification of switching out the sodium hydride for pyrrolidine and reacting with the thioacetates instead. We were delighted to obtain clean and almost quantitative conversions (86–96%) of the alkenyl sulfur-tethered benzyl sulfonyl *O*-benzyl oxime ethers (**4.64d–4.66d**) in one-pot fashion in absence of the need for additional work-up (Scheme 105).

Scheme 105. Synthesis of *S*-tethered Alkenyl Benzyl Sulfonyl *O*-Benzyl Oxime Ether

With a variety of these alkenyl *O*- or *S*-tethered benzyl *O*-benzyl sulfonyl oxime ethers, we then proceeded to test the radical reaction with a diverse range of xanthates bearing many different functionalities. *O*-benzyl oxime ether derivatives of γ -lactones and thiolactones (**4.68** and **4.70**) bearing the various α -substituted alkyl chains containing a variety of functional groups were successfully synthesized from their corresponding butenyl heteroatom-tethered benzyl sulfonyl *O*-benzyl oxime ethers (**4.56d** and **4.64d**) in good to excellent yields (Scheme 106, 58–81%). Some of these functional groups include a ketone (**4.68a** and **4.70a**), a Weinreb amide (**4.68b** and **4.70b**), a phthalimide (**4.68c** and **4.70c**), primary and secondary ethyl esters (**4.68d**, **4.70d** and **4.70f**), and a nitrile (**4.68e** and **4.70e**). Functionalities such as a Weinreb amide or a phthalimide are potential electrophiles for hydroxyl and thiol groups during the ring-closing esterification process to form the lactone or thiolactone. In addition, a nitrile group would also be a potential target during hydrolysis as seen in the preparation of lactones using hydroxyl nitriles as described earlier¹⁵² and would not escape intact. To add on to the mildness of this approach, ester functionalities would avoid the need for re-esterification after lactone or thiolactone formation if the precursor required a pre-hydrolysis step to the carboxylic acid as in the conventional ionic route.

Scheme 106. Synthesis of α -Functionalized *O*-Benzyl Oxime Ether Derivatives of γ -Lactones and Thiolactones

^aConditions: **4.56d** or **4.64d** and xanthate (2 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv DLP every 1.5h (up to 1.2 equiv DLP) until **4.56d** or **4.64d** was mostly consumed as indicated by TLC; isolated yields were based on **4.56d** or **4.64d**. ^bdiastereomers (1:1) were not separated.

O-Benzyl oxime ether derivatives of δ -lactones and thiolactones (**4.71** and **4.72**) were also synthesized from their pentenyl heteroatom-tethered benzyl sulfonyl oxime ethers in good to excellent yields (Scheme 107, 52–82%). Similar to their γ -lactone and thiolactone counterparts, functional groups such as a ketone (**4.71a**), a Weinreb amide (**4.71b** and **4.72b**), a phthalimide (**4.71c** and **4.72c**), primary and secondary ethyl esters (**4.71d** and **4.71f**) or a nitrile (**4.71e** and **4.72c**) In addition to these, new functionalities such as a thiophene ketone (**4.72d**) and even an oxazolidinone group (**4.71g**) were successfully incorporated on alkyl chains at the alpha position (Scheme 104). Special mention has to be noted of the δ -lactone derivatives **4.71** which are also the indirect precursors to mono 3-alkylated dihydrocoumarins. 3,4-dihydrocoumarin derivatives are a privileged sub-class of coumarins which are commonly found in natural products and also exhibit interesting biological activities including anti-herpetic, anti-inflammatory, anti-oxidative, anti-ageing and anti-cancer properties.¹⁷⁴ Recent synthesis of such 3,4-dihydrocoumarins produce the 4-substituted¹⁷⁵ or 3,3-disubstituted derivatives¹⁷⁶ with some restriction to incorporate functionality other than simple alkyl groups or an ethyl ester^{175c} on the 3-position. The current approach therefore complements the existing methods by offering a facile access to such *O*-benzyl oxime ether derivatives of mono 3-substituted 3,4-dihydrocoumarins which would allow for further development in SAR studies as bioisostere analogues. When hydrolyzed, they also lead to the corresponding mono 3-substituted 3,4-dihydrocoumarins with a wide range of diverse functionalities *via* the current synthetic route which is free of transition-metal catalysts or lewis acids or the need for relactonization steps.

Scheme 107. Synthesis of α -Functionalized *O*-Benzyl Oxime Ether Derivatives of 3-Substituted Dihydrocoumarins and α -Substituted δ -Thiolactones

^aConditions: **4.57d** or **4.65d** and xanthate (2 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv DLP every 1.5h (up to 1.2 equiv DLP) until **4.57d** or **4.65d** was mostly consumed as indicated by TLC; isolated yields were based on **4.57d** or **4.65d**. ^bdiastereomers (1:1) were not separated.

Following the successful synthesis of various diversely functionalized *O*-benzyl oxime ether derivatives of γ - and δ - lactones and thiolactones, we attempted to try the reaction with other unsaturated systems as well. For instance, the use of propargyl benzyl sulfonyl oxime ethers such as **4.58d** and **4.59d** should in theory, after alkyl radical addition to the alkyne, lead to a vinylic radical (Scheme 108). Vinylic radicals are very

reactive species and have previously been reported to undergo trapping by the oxime ether.¹⁷⁷ Applying this strategy to our current approach would produce the corresponding *O*-benzyl oxime ether derivatives of methylene lactones. Unfortunately, the test xanthate **3.23i** failed to add to the alkyne under inter-molecular conditions although intra-molecular addition of xanthates to alkynes have been reported previously.¹⁷⁸ In this instance, it is believed that the addition of a carbon-centered radical to the alkyne is too slow probably due to weak SOMO-LUMO interactions, which in turn, failed to induce a subsequent radical cyclization onto a weakly activated *O*-tethered benzyl sulfonyl oxime ether. The poor ability of the *O*-tethered benzyl sulfonyl oxime ether to trap the short-lived reactive vinylic radical species would then caused a disruption to the propagation process and stop the radical chain.

Scheme 108. Failed Attempt to Synthesize *O*-Benzyl Oxime Ether Derivatives of Methylene Lactones *via* Trapping of Proposed Intermediate Vinylic Radical

Next, we tested the reaction with stabilized radicals such as an allylic and a benzylic radical by alkyl radical addition to an allenyl *O*-tethered benzyl sulfonyl *O*-benzyl oxime ether **4.60d** and a styrene *O*-tethered benzyl sulfonyl *O*-benzyl oxime ether **4.61d**. Radical addition to the center carbon atom of the allene group should furnish a π -type vinylmethyl radical which on rotation of the CH_2 group, lead to an allylic π -radical that is stabilized by resonance effects.¹⁷⁹ In this example, radical formation could be

directed to either the internal or terminal end of the allyl group which would lead to either a β -lactone *O*-benzyl oxime ether derivative or an unsaturated δ -lactone *O*-benzyl oxime ether derivative (Scheme 109). Likewise, alkyl radical addition on a styrene should generate the stabilized benzylic radical which could possibly be trapped by the oxime ether to give benzofuranones (Scheme 110). Unfortunately, despite observing total consumption of **4.60d**, no characterizable compounds were isolated. Regretably, the reaction of **4.61d** gave messy mixtures of spots as observed by TLC and was presumed to undergo uncontrolled polymerization instead.

Scheme 109. Failed Attempt to Synthesize *O*-Benzyl Oxime Ether Derivatives of either an Alkenyl β -Lactone or 3-Substituted Unsaturated Lactone *via* Trapping of Proposed Intermediate Allylic radical

Scheme 110. Failed Attempt to Synthesize *O*-Benzyl Oxime Ether Derivatives of Benzofuranone *via* Proposed Trapping of Intermediate Benzylic Radical

According to Baldwin's rule, 4-*exo trig* type radical cyclizations are allowed to proceed due to favorable orbital interactions.¹⁸⁰ In this regard, we decided to test if alkyl radical addition to methallyl *O*-tethered benzyl sulfonyl *O*-benzyl oxime ether **4.62d** would be viable using the current strategy to give the corresponding β -lactone *O*-benzyl oxime ether derivative (Scheme 111). Sadly, we were unable to isolate any characterizable product as well.

Scheme 111. Failed Attempt to Synthesize β -Lactone *O*-Benzyl Oxime Ether Derivative

Finally, we attempted to synthesize *O*-benzyl oxime ether derivatives of γ -lactones and thiolactones bearing α - and β -substituents. Reaction of various functionalized keto-xanthates with vinyl heteroatom-tethered benzyl sulfonyl *O*-benzyl oxime ethers bearing 1,3-dioxolane group (**4.66d** and **4.67d**) afforded the α,β -disubstituted γ -lactone or thiolactone *O*-benzyl oxime ether derivatives (**4.73** and **4.74**) in good yields (Scheme 112, 57–78%). As shown in Scheme 109, α -alkylation of ketones bearing a phenyl (**4.73a** and **4.74a**), a methyl (**4.73b** and **4.74b**), a cyclopropyl (**4.73c** and **4.74c**), a *para*-bromo phenyl methylene (**4.74d**), a benzyl (**4.73d**), a methyl phosphonate (**4.73e** and **4.74e**) and secondary ethyl esters (**4.73f** and **4.74f**) were successfully incorporated along with a 1,3-dioxolane at the beta position (Scheme 112). The synthetic potential to derive multi-substituted *O*-benzyl oxime ether derivatives of γ -lactones and thiolactones with the present approach is demonstrated clearly here.

Scheme 112. Synthesis of α -Functionalized *O*-Benzyl Oxime Ether Derivatives of γ -Lactones and Thiolactones Bearing a Beta 1,3-Dioxolane Group

^aConditions: **4.66d** or **4.67d** and xanthate (2 equiv) in anhydrous 1,2-dichloroethane (DCE, 0.5 M in the xanthate) heated to reflux under argon was added 0.2 equiv DLP every 1.5h (up to 1.2 equiv DLP) until **4.66d** or **4.67d** was mostly consumed as indicated by TLC; isolated yields were based on **4.66d** or **4.67d**. ^bdiastereomers (1:1) were not separated. ^cYield in parenthesis is based on recovered starting material.

In addition, having a 1,3-dioxolane group at the β -position constituted a means of forming a ketone by deprotection at the end of the radical reaction. This would supposedly give rise to 1,5 diketones which could be further transformed into fused lactone pyridines or thiolactone pyridines using an ammonia source such as ammonium acetate in refluxing acetic acid (Scheme 113). We were intrigued at this possibility and decided to attempt the reaction. However, when we subjected **4.73b** to the conditions of ammonium acetate in refluxing acetic acid, the 1,3-dioxolane group was found to be resistant towards the acidic environment of the reaction. The *O*-benzyl oxime ether group remained intact as well.

Scheme 113. Attempted Deprotection and Subsequent Pyridine Formation using Ammonium Acetate as Source of Ammonia in refluxing Acetic Acid

An unexpected discovery was made when we switched to ammonium formate in refluxing formic acid. Thieno[2,3-*b*] pyridine **4.76** was isolated in excellent yield of 80% (Scheme 114). The presence of an *O*-ethylene formic ester group as deduced from NMR led to the assumption that the deprotection of the *O*-benzyl oxime ether group could have been faster than the 1,3-dioxolane group.

Scheme 114. Unexpected Formation of Thienopyridine

Based on the structure and reaction conditions, we proposed a likely mechanism for the unexpected formation of this thienopyridine in Scheme 115. Firstly, the *O*-benzyl oxime ether group was hydrolyzed to the keto-thiolactone **A** in the presence of formic acid by water which would be gradually produced from formic acid on heating. Amine condensation of the ketone by ammonia from ammonium formate then led to the intermediate imine which isomerize to the nucleophilic enamine **B**, followed by an intramolecular condensation onto the thiolactone to form a dihydropyridine **C** which quickly aromatize to the pyridine **D**. Next, acid-catalyzed ring-opening of the 1,3-dioxolane group was driven by aromatization to the thienopyridine ring *via* an oxocarbenium intermediate **E** to form the thienopyridine ethylene alcohol **F** which then reacts with formic acid in the bulk solution to give the corresponding formic ester derivative **4.76**.

Scheme 115. Proposed Mechanism for the Formation of Thienopyridine based on Ammonium Formate as Source of Ammonia

We then attempted to selectively deprotect the 1,3-dioxolane group to the ketone in hope that we could accomplish our initial idea of forming *O*-benzyl oxime ether

derivatives of either fused lactone pyridine or thiolactone pyridine. Several deprotection conditions were screened on **4.73a** as shown in Table 6. Despite our efforts, the 1,3-dioxolane group proved tenacious against deprotection to the corresponding ketone. Strangely, the *O*-benzyl oxime ether remained intact as well in all cases.

Table 6. Attempts to Deprotect 1,3-Dioxolane Group

Entry	Conditions ¹⁸¹
1	<i>p</i> -TSA.H ₂ O (1 equiv), acetone / water = 10/1 (0.3 M in acetal), rt, overnight
2	1 M HCl (aq) / THF = 1/1 (0.2 M in acetal), rt, overnight
3	1 M HCl (aq) / THF = 1/1 (0.2 M in acetal), reflux, overnight
4	Acetic acid (0.1 M in acetal), reflux, 48h
5	I ₂ (1 equiv) in acetone (0.25 M in acetal), reflux, overnight
6	TEAI (1.2 equiv), BF ₃ .OEt ₂ (1.2 equiv) in CCl ₃ (0.5 M in acetal), reflux, overnight

Unexpectedly, when **4.73b** was subjected to stirring with formic acid at rt for 24h, we were surprised to obtain the thieno[2,3-*b*] pyridine **4.76** in high yield of 83% (Scheme 116). In contrary to our belief, the ammonia source required for the pyridinization could be obtained from the *O*-benzyl oxime ether nitrogen itself. Use of 1,5 keto-oxime

derivatives in pyridinization are rare and usually involve the use of *O*-acetyl oxime ethers to facilitate the easy liberation of the imine for condensation with ketone.^{182, 183} The use of ammonium acetate as ammonia source in refluxing acetic acid has been known to induce the pyridinization of 1,5 keto *O*-acetyl oxime ether.¹⁸² More recently, a tandem copper redox and iminium activation strategy had been employed on *O*-acetyl oxime ethers for the synthesis of pyridines, relying on the oxime as the nitrogen source itself.¹⁸³ Thus, to the best of our knowledge, the use of the *O*-benzyl oxime ether group itself as an ammonia source for pyridinization is unprecedented.

Scheme 116. Thienopyridine Formation in Absence of Ammonium Formate

Excited by this finding, we decided to react another *O*-benzyl oxime ether derivative of a γ -thiolactone bearing a 1,5 ketone group **4.70f** in hope to obtain dihydrothieno[2,3-*b*] pyridines. Unfortunately, the reaction did not work at all and **4.70f** was recovered in full unchanged (Scheme 117).

Scheme 117. Failed Attempt at Thienopyridine formation from *O*-Benzyl Oxime Ether Derivative of γ -Thiolactone

These combined observations then led us to postulate a revised mechanism for the formation of the thieno[2,3-*b*] pyridine from 1,5 keto *O*-benzyl oxime ethers. Firstly, acid

activation of one of the oxygen atoms of the 1,3-dioxolane acetal resulted in ring-opening to an oxocarbenium carbonyl **A** bearing an ethylene alkoxide. This alkoxide is able to reversibly attack the oxonium to regenerate the 1,3-dioxolane group. However, in presence of formic acid which acts as a formylating agent, the alkoxide is rapidly trapped to form formic ester **B**. This is then followed by the elimination of water which in turn, abstracts a methylene proton on the tetrahydrothiophene on **B** to form dihydrothiophene **C** (Scheme 118). Subsequently, the oxime group on the dihydrothiophene is reversibly isomerized in favor of its enamine form, which is driven forward by the aromatization of thiophene **D**. The nucleophilic enamine would then condense onto the ketone to form dihydropyridine **E** which then undergoes autoxidation to the pyridine, similarly promoted by the strong driving force of rearomatization to give thieno[2,3-b] pyridine **4.76**.

Scheme 118. Revised Proposed Mechanism for the Formation of Thienopyridine based on Oxime Ether as Ammonia Source, Driven by Formylation of 1,3-Dioxolane in Formic Acid.

Some key considerations of this proposed mechanism to explain the formation of thienopyridine were derived from the experimental observations that include: (a) the specific use of formic acid as an effective formylating agent; (b) the unusual nucleophilicity of the heteroatom tethered oxime nitrogen and (c) the need for a 1,3-dioxolane group to initiate the rearomatization of the dihydrothiophene to thiophene which in turn, favors the formation of the enamine formation from the oxime.

Fused heterocycles such as the thieno[2,3-*b*] pyridine and their other heteroatom analogue derivatives are commonly regarded as isosteric to quinoline derivatives, which are well-known moieties in bioactive molecules.¹⁸⁴ However, the synthesis of thieno[2,3-*b*] pyridines is comparatively rare^{185b, 186} while the *O*-analogues, the furo[2,3-*b*] pyridines have been more commonly prepared although they remained a rare occurrence in nature.¹⁸⁷ Furthermore, furo[2,3-*b*] pyridines are also present in bioactive scaffolds such as L-754,394, a potent HIV protease enzyme inhibitor (Figure 18) and thus remain an attractive target for cancer studies.¹⁸⁸ Due to insufficient time for further investigation on our end, we decided to halt the study here. It should be re-emphasized that the potential of this synthetic approach to possibly synthesize both the furo- and thieno[2,3-*b*] pyridines from *O*-benzyl oxime ether derivatives would significantly aid in their preparation and future study as important bioisoteres for SAR studies.

Figure 18. Structure of L-754,394, a Potent HIV Protease Enzyme Inhibitor

4.11 Conclusion

In conclusion, alkyl bis-sulfonyl *O*-benzyl oxime ethers have been utilized as an ionic and radical bifunctional carboxylate synthetic equivalent. The use of heteroatom alkenyl precursors allowed for the synthesis of novel *O*-benzyl oxime ether derivatives of various lactone and thiolactone or "lactoxime" and "thiolactoxime". In addition the present approach could possibly be extended to synthesize amidoximes. Nucleophilic substitution of alkyl bis-sulfonyl *O*-benzyl oxime ethers with substituted alkenyl alkoxide or thiol can incorporate substituents at the β -position while the xanthate radical addition allows facile incorporation of a diverse range of functionalities for the α -alkylation of these new entities as well. Overall, this work constitutes a novel strategy for the *O*-benzyl oxime ether derivatization of lactones, thiolactones and possibly lactams which are commonly found in structurally bioactive molecules and may find useful application as bioisosteres in SAR studies. Finally, a few unexpected discoveries were made in this study, including the first instance of a benzyl radical acting as a radical chain relay in the xanthate transfer as well as the unusual use of *O*-benzyl oxime ether as an ammonia source for the pyridinization in formic acid, resulting in a rare formation of thieno[2,3-*b*]pyridines.

PUBLICATIONS

- "Free-Radical Variant for the Synthesis of Functionalized 1,5-Diketones."

Goh, K. K. K.; Kim, S.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 4818.

- "A Synthesis of (1E,3E)-TMS Dienes from Keto-Xanthates via Chugaev-type

Elimination." **Goh, K. K. K.**; Kim, S.; Zard, S. Z. *J. Org. Chem.* **2013**, *78*,

12274.

Chapter 5. Experimental Section

5.1 General Methods.

A variety of chemical reagents were commercially purchased and used without further purification. Analytical TLC was carried out on pre-coated plates and visualized with UV light or stained with potassium permanganate, acidic anisaldehyde or cerium molybdate. ^1H , ^{13}C and ^{31}P NMR spectra were measured at 298 K on a Bruker Avance III 400 Fourier Transform NMR spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of TMS. The signals observed were described as: s (singlet), d (doublet), dt (doublet of triplets), dd (doublet of doublets), ddt (doublet of doublet of triplets), tt (triplets of triplets), t (triplet), q (quartet), m (multiplet). The number of protons (n) for a given resonance was indicated as nH. Coupling constants are reported as J value in Hz. ^{13}C NMR is reported as δ (ppm) in downfield from TMS and relative to the signal of chloroform-d (δ 77.00, triplet). High resolution mass spectrometry (For compounds 2.18, 2.20, 2.23 and 2.25) were obtained using a Q-tof high resolution mass spectrometer and recorded by positive electron impact ionization (EI^+) at 70 e.V. on a double-focusing high mass spectrometer (JEOL JMS-GCmate II mass spectrometer) at Ecole Polytechnique. In the event that HRMS could not be resolved, low resolution mass spectra (m/z) was recorded by chemical ionization (CI/NH_3) on a Hewlett-Packard HP 5989B mass spectrometer and only reported of molecular species ($[\text{M}+\text{H}]^+$, $[\text{M}+\text{NH}_4]^+$) and other major fragments. High resolution mass spectrometry for all other compounds except those mentioned earlier were recorded using Q-Tof Premier LC HR mass spectrometer at Nanyang Technological University of Singapore. The quoted masses are accurate to ± 5 ppm. Melting point was determined using OptiMelt from SRS Stanford Research Systems. The chemical naming of the molecules that appear in the following pages were generated with the use of ChemBioDraw Ultra 12.0.

5.2 Manipulation of the Xanthate Moiety as a Latent Sulfur Nucleophile Using Secondary *O*-Alkyl Xanthates: A Chugaev Approach.

Preparation of *O*-sec-butyl xanthate potassium salt. To a solution of potassium tert-butoxide (56.1 g, 500 mmol, 1.0 equiv) in THF (170 mL) under nitrogen at 0 °C was added 2-butanol (40.7 g, 550 mmol, 1.1 equiv). The reaction mixture was stirred for 1 hour while warming to rt. The mixture is cooled again to 0 °C and carbon disulfide (43 g, 550 mmol, 1.1 equiv) was added dropwise while stirring. The reaction mixture was stirred overnight while warming to rt. The yellow suspension obtained was diluted with Et₂O (170 mL) and filtered. The obtained yellow residue was washed with more Et₂O (3 x 150 mL). The residue obtained was further dried in vacuo to give a white solid (85 g, 450 mmol, 90% yield) which required no further purification.

potassium *O*-sec-butyl carbonodithioate; 85 g, 90% yield, white solid; ¹H NMR (CD₃OD, 400 MHz): δ 5.46 (m, 1H), 1.67 (m, 2H), 1.26 (d, 3H, *J* = 6.2 Hz), 0.94 (t, 3H, *J* = 7.5 Hz) ppm; ¹³C NMR (CD₃OD, 100 MHz): δ 81.4, 30.0, 19.4, 10.3 ppm; **m.p.** 241–243 °C; **HRMS (ESI)** *m/z* Calculated for [M+H]⁺ C₅H₁₀OS₂K 188.9810, found 188.9811.

General procedure 5.2.1 for the preparation of *O*-sec-butyl keto-xanthates 2.18. To a magnetically stirred solution of the corresponding bromide or chloride (10 mmol) in acetone at 0 °C under a nitrogen flow was added portionwise potassium *O*-sec-butyl carbonodithioate (1.5 equiv). The resulting suspension was stirred for 2h while warming

to rt under a nitrogen atmosphere and then concentrated under reduced pressure. CH_2Cl_2 was added to the crude mixture to precipitate the excess potassium *O*-*sec*-butyl carbonodithioate salt which was washed with additional CH_2Cl_2 . The combined filtrate was then concentrated under reduced pressure and purified by flash column chromatography (silica gel, EtOAc-petroleum ether) to give the titled xanthates.

***O*-*sec*-butyl *S*-(2-oxo-2-phenylethyl) carbonodithioate (2.18a)**; 2.36 g, 88% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 8.02 (dd, 2H, $J = 8.3$ Hz, $J = 1.2$ Hz), 7.59–7.63 (m, 1H), 7.50 (t, 2H, $J = 7.6$ Hz), 5.55–5.62 (m, 1H), 4.64 (s, 2H), 1.61–1.81 (m, 2H), 1.33 (d, 3H, $J = 6.2$ Hz), 0.92 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.7, 192.4, 135.8, 133.7, 128.8, 128.4, 83.4, 43.2, 28.4, 18.6, 9.5 ppm; **HRMS** (EI^+ , $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}_2$ $[\text{M}]^+$) calcd.; 268.0592, found 268.0589.

***O*-*sec*-butyl *S*-(2-(4-fluorophenyl)-2-oxoethyl) carbonodithioate (2.18b)**; 2.60 g, 91% yield, white solid; ^1H NMR (CDCl_3 , 400 MHz): δ 8.04–8.07 (m, 2H), 7.14–7.19 (m, 2H), 5.54–5.62 (m, 1H), 4.61 (s, 2H), 1.62–1.80 (m, 2H), 1.33 (d, 3H, $J = 6.3$ Hz), 0.93 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.6, 190.9, 166.0 (d, $J_{\text{CF}} = 256.0$ Hz), 132.2 (d, $J_{\text{CF}} = 3.0$ Hz), 131.1 (d, $J_{\text{CF}} = 9.4$ Hz), 115.9 (d, $J_{\text{CF}} = 22.0$ Hz), 83.6, 43.1, 28.4,

18.6, 9.5 ppm; **m.p.** 37-39 °C; **HRMS** (EI^+ , $\text{C}_{13}\text{H}_{15}\text{FO}_2\text{S}_2$ $[\text{M}]^+$) calcd.; 286.0497, found 286.0485.

O-sec-butyl S-2-(4-bromophenyl)-2-oxoethyl carbonodithioate (2.18c); 2.98 g, 86% yield, white solid; ^1H NMR (CDCl_3 , 400 MHz): δ 7.88 (d, 1H, J = 8.4 Hz), 7.64 (d, 1H, J = 8.3 Hz), 5.55–5.61 (m, 1H), 4.59 (s, 2H), 1.62–1.80 (m, 2H), 1.32 (d, 3H, J = 6.2 Hz), 0.92 (t, 3H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.5, 191.5, 134.4, 132.1, 129.9, 129.0, 83.6, 43.0, 28.4, 18.6, 9.5 ppm; **m.p.** 48-50 °C; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{15}\text{BrO}_2\text{S}_2$ 345.9697, found 345.9700.

O-sec-butyl S-2-oxo-2-p-tolylethyl carbonodithioate (2.18d); 2.68 g, 95% yield, orange oil; ^1H NMR (CDCl_3 , 400 MHz): δ ppm 7.92 (d, 2H, J = 8.3 Hz), 7.30 (d, 2H, J = 8.0 Hz), 5.55–5.63 (m, 1H), 4.62 (s, 2H), 2.43 (s, 3H), 1.62–1.80 (m, 2H), 1.32 (d, 3H, J = 6.3 Hz), 0.92 (t, 3H, J = 7.5 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.8, 192.0, 144.7, 133.3, 129.4, 128.6, 83.4, 43.2, 28.4, 21.7, 18.6, 9.5 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}_2$ 282.0748, found 282.0749.

O-sec-butyl S-2-(4-methoxyphenyl)-2-oxoethyl carbonodithioate (2.18e); 2.95 g, 99% yield, orange oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.99–8.01 (m, 2H), 6.95–6.97 (m, 2H), 5.52–5.62 (m, 1H), 4.60 (s, 2H), 3.89 (s, 3H), 1.61–1.81 (m, 2H), 1.32 (d, 3H, $J = 6.3$ Hz), 0.92 (t, 3H, $J = 7.5$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 212.9, 190.9, 164.0, 130.8, 128.8, 113.9, 83.3, 55.5, 43.0, 28.4, 18.6, 9.5 ppm; **HRMS (EI^+)** m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{18}\text{O}_3\text{S}_2$ 298.0697, found 298.0702.

O-sec-butyl S-1-oxo-1-phenylpropan-2-yl carbonodithioate (2.18f); 2.43 g, 86% yield, orange oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 8.02 (d, 2H, $J = 8.1$ Hz), 7.60 (t, 1H, $J = 7.4$ Hz), 7.49 (t, 2H, $J = 7.6$ Hz), 5.57–5.62 (m, 1H), 5.43–5.49 (m, 1H), 1.57–1.74 (m, 5H), 1.31 (d, 1.5H, $J = 6.3$ Hz), 1.30 (d, 1.5H, $J = 6.2$ Hz), 0.90 (t, 3H, $J = 7.4$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 196.8, 135.0, 133.6, 128.7, 128.6, 128.6, 83.4, 49.5, 49.5, 28.4, 28.4, 18.7, 18.6, 17.0, 17.0, 9.6 ppm; **HRMS (EI^+)** m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}_2$ 282.0748, found 282.0746.

***O*-sec-butyl *S*-2-(naphthalen-2-yl)-2-oxoethyl carbonodithioate (2.18g);** 3.12 g, 98% yield, yellow oil; **¹H NMR** (CDCl₃, 400 MHz): δ 8.57 (s, 1H), 8.06 (dd, 1H, *J* = 1.7 Hz, *J* = 8.6 Hz), 8.00 (d, 1H, *J* = 8.1 Hz), 7.91 (dd, 2H, *J* = 12.0 Hz, *J* = 8.4 Hz), 7.61 (dtd, 1H, *J* = 14.8 Hz, *J* = 7.0 Hz, *J* = 1.2 Hz), 5.57–5.64 (m, 1H), 4.78 (s, 2H), 1.60–1.83 (m, 2H), 1.33 (d, 3H, *J* = 6.3 Hz), 0.93 (t, 3H, *J* = 7.5 Hz) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 212.8, 192.4, 135.8, 133.1, 132.4, 130.3, 129.7, 128.8, 128.7, 127.8, 127.0, 123.9, 83.5, 43.3, 28.4, 18.6, 9.5 ppm; **HRMS (EI⁺)** *m/z* Calculated for [M]⁺ C₁₇H₁₈O₂S₂ 318.0748, found 318.0737.

***O*-sec-butyl *S*-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl carbonodithioate (2.18h);** 1.74 g, 59% yield, orange oil; **¹H NMR** (CDCl₃, 400 MHz): diastereomers = 1/1: δ 8.05 (d, 1H, *J* = 7.8 Hz), 7.51 (dt, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz), 7.33 (t, 1H, *J* = 7.6 Hz), 7.26 (d, 1H, *J* = 7.6 Hz), 5.60–5.67 (m, 1H), 4.76–4.80 (m, 1H), 3.06–3.22 (m, 2H), 2.62–2.69 (m, 1H), 2.26–2.41 (m, 1H), 1.63–1.84 (m, 2H), 1.35 (d, 1.5H, *J* = 6.3 Hz), 1.34 (d, 1.5H, *J* = 6.2 Hz), 0.95 (t, 1.5H, *J* = 7.5 Hz), 0.94 (t, 1.5H, *J* = 7.4 Hz) ppm; **¹³C NMR** (CDCl₃, 100 MHz): diastereomers = 1/1: δ 212.4, 212.3, 192.7, 143.4, 133.9, 131.9, 128.7, 128.0, 126.9, 83.2, 83.2, 56.8, 56.7, 30.4, 29.1, 28.4, 18.6, 18.6, 9.5 ppm; **HRMS (EI⁺)** *m/z* Calculated for [M]⁺ C₁₅H₁₈O₂S₂ 294.0748, found 294.0737.

***O*-sec-butyl *S*-2-oxo-2-(thiophen-2-yl)ethyl carbonodithioate (2.18i)**; 2.06 g, 75% yield, reddish-brown oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.87 (dd, 1H, $J = 3.8$ Hz, $J = 1.0$ Hz), 7.71 (dd, 1H, $J = 1.0$ Hz, $J = 4.9$ Hz), 7.17 (dd, 1H, $J = 4.9$ Hz, $J = 3.9$ Hz), 5.54–5.62 (m, 1H), 4.53 (s, 2H), 1.61–1.80 (m, 2H), 1.32 (d, 3H, $J = 6.3$ Hz), 0.91 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.3, 185.3, 142.6, 134.6, 132.8, 128.3, 83.6, 42.9, 28.4, 18.6, 9.5 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{11}\text{H}_{14}\text{O}_2\text{S}_3$ 274.0156, found 274.0157.

***O*-sec-butyl *S*-4-oxo-1-tosylpiperidin-3-yl carbonodithioate (2.18j)**; 3.53 g, 88% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 2 diastereomers = 1/1: δ 7.67 (d, 2H, $J = 8.2$ Hz), 7.32 (d, 2H, $J = 8.1$ Hz), 5.52–5.60 (m, 1H), 4.60–4.66 (m, 1H), 4.26–4.32 (m, 1H), 3.94–3.98 (m, 1H), 2.88–2.97 (m, 2H), 2.68–2.76 (m, 1H), 2.59 (td, 1H, $J = 14.7$ Hz, $J = 3.4$ Hz), 2.40 (s, 3H), 1.60–1.84 (m, 2H), 1.33 (d, 1.5H, $J = 6.3$ Hz), 1.31 (d, 1.5H, $J = 6.3$ Hz), 0.91 (t, 1.5H, $J = 7.7$ Hz) 0.89 (t, 1.5H, $J = 7.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 2 diastereomers = 1/1: δ 209.9, 209.8, 200.2, 200.1, 144.2, 133.3, 129.9, 127.3, 83.6, 56.5, 56.4, 50.8, 45.8, 40.5, 28.2, 21.4, 18.5, 18.4, 9.5, 9.4 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{S}_3$ 401.0789, found 401.0788.

***O*-sec-butyl *S*-2-oxocyclohexyl carbonodithioate (2.18k)**; 2.27 g, 92% yield, orange oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 5.53–5.61 (m, 1H), 4.51 (dd, 1H, J = 11.1 Hz, J = 5.6 Hz), 2.61 (td, 1H, J = 12.2 Hz, J = 3.6 Hz), 2.41–2.51 (m, 2H), 1.62–2.10 (m, 7H), 1.32 (d, 1.5H, J = 6.3 Hz), 1.31 (d, 1.5H, J = 6.3 Hz), 0.92 (t, 1.5H, J = 7.4 Hz), 0.91 (t, 1.5H, J = 7.4 Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 212.4, 205.0, 82.8, 82.8, 59.3, 59.2, 41.6, 34.3, 34.3, 28.4, 28.4, 27.4, 25.1, 18.6, 18.5, 9.4 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{11}\text{H}_{18}\text{O}_2\text{S}_2$ 246.0748, found 246.0738.

Ethyl 2-(*sec*-butoxycarbonothioylthio)-3-oxo-3-phenylpropanoate (2.18l); 2.55 g, 75% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 2 diastereomers = 7/3 (enol/keto): δ 14.18 (d, 0.7H, J = 14.1 Hz), 8.04–8.06 (m, 0.5H), 7.36–7.65 (m, 4.5H), 6.26 (d, 0.3H, J = 1.6 Hz), 5.53–5.61 (m, 1H), 4.32 (q, 1.4H, J = 7.1 Hz), 4.23 (q, 0.6H, J = 7.1 Hz), 1.61–1.80 (m, 2H), 1.28–1.34 (m, 5.1H), 1.22 (t, 0.9H, J = 7.2 Hz), 0.85–0.94 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 2 diastereomers = 7/3 (enol/keto): δ 210.5, 210.4, 189.9, 189.9, 172.6, 165.8, 165.8, 134.8, 134.1, 130.8, 129.1, 129.1, 128.8, 128.5, 128.4, 127.8, 84.3, 84.2, 82.9, 82.8, 62.8, 62.1, 59.6, 59.5, 28.5, 28.4, 18.6, 18.6, 14.1, 13.9, 9.5 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{16}\text{H}_{20}\text{O}_4\text{S}_2$ 340.0803, found 340.0808.

O-sec-butyl S-(2-(((5S,10S,13S)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-oxoethyl) carbonodithioate (2.18m); 4.47 g, 96% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 2 diastereomers = 1/1: δ 5.52–5.60 (m, 1H), 3.99 (d, 1H, $J = 3.6$ Hz), 3.96 (d, 1H, $J = 2.0$ Hz), 3.58 (tt, 1H, $J = 11.04$ Hz, 4.72 Hz), 2.75 (t, 0.5H, $J = 8.9$ Hz), 2.74 (t, 0.5H, $J = 8.8$ Hz), 2.10–2.21 (m, 1H), 2.00–2.04 (m, 1H), 1.35–1.81 (m, 13H), 1.32 (d, 1.5H, $J = 6.2$ Hz), 1.32 (d, 1.5H, $J = 6.3$ Hz), 1.09–2.09 (m, 7H), 0.98 (dt, 1H, $J = 3.7$ Hz, $J = 13.4$ Hz), 0.92 (t, 3H, $J = 7.5$ Hz), 0.85–0.95 (m, 1H), 0.80 (s, 3H), 0.65–0.73 (m, 1H), 0.63 (s, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): 2 diastereomers = 1/1: δ 213.1, 203.5, 83.3, 71.2, 62.4, 62.4, 56.7, 54.1, 47.1, 44.8, 44.8, 39.0, 38.1, 36.9, 35.5, 35.5, 31.9, 31.4, 28.5, 28.4, 24.4, 23.4, 21.2, 18.6, 13.6, 12.3, 9.5 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{26}\text{H}_{42}\text{O}_3\text{S}_2$ 466.2575, found 466.2576.

O-sec-butyl S-4,4-dimethyl-2-oxopentyl carbonodithioate (2.18n); 2.41 g, 92% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 5.53–5.62 (m, 1H), 3.96 (s, 2H), 2.49 (s, 2H), 1.65–1.84 (m, 2H), 1.34 (d, 3H, $J = 6.2$ Hz), 1.04 (s, 9H), 0.93 (t, 3H, $J = 7.5$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 212.9, 202.5, 83.5, 53.9, 47.1, 31.2, 29.6, 28.4, 18.6, 9.5 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{12}\text{H}_{22}\text{O}_2\text{S}_2$ 262.1061, found 262.1060.

General procedure 5.2.2 for the addition of xanthates 2.18 to vinyltrimethylsilane for the synthesis of TMS xanthate adducts 2.20. A solution of the corresponding xanthate (5 mmol, 1.0 equiv) and vinyl trimethylsilane (2.0 equiv) in EtOAc was refluxed under a nitrogen atmosphere for 10 min. Lauroyl peroxide, DLP (5 mol%) was then added every

hour until complete consumption of the xanthate as indicated by TLC analysis. The resulting solution was concentrated under reduced pressure and the crude mixture was purified by flash column chromatography (silica gel, Et₂O-petroleum ether = 10/90) to give the titled TMS xanthate adducts.

O-sec-Butyl S-4-oxo-4-phenyl-1-(trimethylsilyl)butyl Carbonodithioate (2.20a); 1.69 g, 92% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): diastereomers = 1/1: δ 7.93 (d, 2H, *J* = 7.8 Hz), 7.54 (t, 1H, *J* = 7.4 Hz), 7.44 (t, 2H, *J* = 7.7 Hz), 5.56–5.64 (m, 1H), 3.25–3.29 (m, 1H), 3.13–3.19 (m, 2H), 2.29–2.39 (m, 1H), 1.56–1.90 (m, 3H), 1.33 (d, 1.5H, *J* = 6.3 Hz), 1.27 (d, 1.5H, *J* = 6.3 Hz), 0.93 (t, 1.5H, *J* = 7.4 Hz), 0.90 (t, 1.5H, *J* = 7.5 Hz), 0.15 (s, 4.5H), 0.15 (s, 4.5H) ppm; ¹³C NMR (CDCl₃, 100 MHz): diastereomers = 1/1: δ 216.1, 199.8, 136.9, 133.0, 128.5, 128.0, 83.0, 37.0, 36.3, 28.5, 25.3, 18.7, 9.6, -2.6 ppm; **HRMS (EI⁺)** *m/z* Calculated for [M]⁺ C₁₈H₂₈O₂S₂Si 368.1300, found 368.1305.

O-sec-Butyl S-4-(4-fluorophenyl)-4-oxo-1-(trimethylsilyl)butyl Carbonodithioate (2.20b); 1.89 g, 98% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): diastereomers = 1/1: δ 7.93–7.96 (m, 2H), 7.11 (t, 2H, *J* = 8.6 Hz), 5.55–5.64 (m, 1H), 3.26 (dd, 1H, *J* = 11.1 Hz, *J* = 3.5 Hz), 3.05–3.15 (m, 2H), 2.28–2.37 (m, 1H), 1.59–1.87 (m, 3H), 1.33 (d,

1.5H, $J = 6.3$ Hz), 1.27 (d, 1.5H, $J = 6.3$ Hz), 0.92 (t, 1.5H, $J = 7.5$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.14 (s, 4.5H), 0.14 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 216.2, 198.1, 165.6 (d, $J_{\text{CF}} = 254.5$ Hz), 133.3, 130.6 (d, $J_{\text{CF}} = 9.2$ Hz), 115.6 (d, $J_{\text{CF}} = 21.8$ Hz), 83.0, 36.9, 36.3, 28.5, 25.2, 18.7, 9.6, -2.6 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{18}\text{H}_{27}\text{FO}_2\text{S}_2\text{Si}$ 386.1206, found 386.1209.

O-sec-Butyl S-4-(4-bromophenyl)-4-oxo-1-(trimethylsilyl)butyl Carbonodithioate (2.20c); 2.17 g, 97% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 7.79 (dd, 2H, $J = 8.4$ Hz, $J = 1.2$ Hz), 7.58 (d, 1H, $J = 8.6$ Hz), 5.53–5.67 (m, 1H), 3.26 (dd, 1H, $J = 11.1$ Hz, $J = 3.5$ Hz), 3.01–3.23 (m, 2H), 2.29–2.39 (m, 1H), 1.57–1.85 (m, 3H), 1.33 (d, 1.5H, $J = 6.3$ Hz), 1.28 (d, 1.5H, $J = 6.3$ Hz), 0.92 (t, 1.5H, $J = 7.5$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.13 (s, 4.5H), 0.13 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 216.0, 198.5, 135.4, 131.7, 129.4, 127.9, 82.9, 36.8, 36.6, 36.1, 28.4, 25.0, 24.8, 18.6, 9.5, -2.7 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{18}\text{H}_{27}\text{BrO}_2\text{S}_2\text{Si}$ 446.0405, found 446.0384.

O-sec-Butyl S-4-oxo-4-p-tolyl-1-(trimethylsilyl)butyl Carbonodithioate (2.20d); 1.79 g, 94% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 7.83 (d,

2H, $J = 8.0$ Hz), 7.24 (d, 2H, $J = 8.0$ Hz), 5.58–5.63 (m, 1H), 3.26 (dd, 1H, $J = 10.9$ Hz, $J = 3.5$ Hz), 3.11–3.15 (m, 2H), 2.40 (s, 3H), 2.28–2.38 (m, 1H), 1.61–1.89 (m, 3H), 1.33 (d, 1.5H, $J = 6.3$ Hz), 1.27 (d, 1.5H, $J = 6.3$ Hz), 0.93 (t, 1.5H, $J = 7.4$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.14 (s, 4.5H), 0.14 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 211.9, 199.4, 143.7, 134.4, 129.2, 128.1, 82.9, 36.9, 36.3, 28.5, 25.4, 25.1, 21.6, 18.7, 9.6, -2.6 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{19}\text{H}_{30}\text{O}_2\text{S}_2\text{Si}$ 382.1456, found 382.1472.

O-sec-Butyl S-4-(4-methoxyphenyl)-4-oxo-1-(trimethylsilyl)butyl Carbonodithioate (2.20e); 1.89 g, 95% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 7.92 (d, 2H, $J = 8.8$ Hz), 6.92 (d, 2H, $J = 8.8$ Hz), 5.56–5.64 (m, 1H), 3.86 (s, 3H), 3.26 (dd, 1H, $J = 10.9$ Hz, $J = 3.5$ Hz), 3.08–3.14 (m, 2H), 2.27–2.37 (m, 1H), 1.61–1.88 (m, 3H), 1.34 (d, 1.5H, $J = 6.3$ Hz), 1.27 (d, 1.5H, $J = 6.2$ Hz), 0.93 (t, 1.5H, $J = 7.4$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.14 (s, 4.5H), 0.14 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 216.1, 198.3, 163.4, 130.3, 130.0, 113.7, 82.9, 55.4, 36.7, 36.4, 28.5, 25.5, 18.7, 9.6, -2.6 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{19}\text{H}_{30}\text{O}_3\text{S}_2\text{Si}$ 398.1406, found 398.1406.

***O*-sec-Butyl S-3-methyl-4-oxo-4-phenyl-1-(trimethylsilyl)butyl Carbonodithioate (2.20f)**; 1.78 g, 93% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1/1/1: δ 7.92–7.98 (m, 2H), 7.52–7.56 (m, 1H), 7.40–7.48 (m, 2H), 5.36–5.67 (m, 1H), 3.70–3.85 (m, 1H), 3.07–3.42 (m, 1 H), 1.92–2.52 (m, 1H), 1.41–1.90 (m, 3H), 1.35 (dd, 2H, J = 15.1 Hz, J = 6.3 Hz), 1.24 (dd, 2.5H, J = 13.8 Hz, J = 6.5 Hz), 1.17 (dd, 1.5H, J = 7.2 Hz, J = 1.5 Hz), 0.95 (m, 1.5H), 0.86 (t, 0.75H, J = 7.4 Hz), 0.73 (t, 0.75H, J = 7.5 Hz), 0.13 (s, 2.25H), 0.12 (s, 2.25H), 0.09 (s, 2.25H), 0.09 (s, 2.25H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1/1/1: δ 215.9, 215.0, 203.9, 203.4, 136.5, 135.9, 132.9, 128.6, 83.1, 82.8, 38.9, 35.2, 34.5, 34.1, 33.7, 33.0, 28.6, 28.4, 28.2, 19.5, 18.7, 18.5, 18.1, 16.6, 9.6, -3.0, ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{19}\text{H}_{30}\text{O}_2\text{S}_2\text{Si}$ 382.1456, found 382.1461.

***O*-sec-Butyl S-4-(naphthalen-2-yl)-4-oxo-1-(trimethylsilyl)butyl Carbonodithioate (2.20g)**; 1.67 g, 80% yield, white solid; **m.p.** 71–75 °C; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 8.45 (s, 1H), 8.02 (dd, 1H, J = 8.6 Hz, J = 1.7 Hz), 7.95 (d, 1H, J = 7.9 Hz), 7.87 (dd, 2H, J = 8.1 Hz, J = 6.1 Hz), 7.52–7.62 (m, 2H), 5.56–5.63 (m, 1H), 3.26–3.34 (m, 3H), 2.36–2.45 (m, 1H), 1.56–2.04 (m, 3H), 1.32 (d, 1.5H, J = 6.3 Hz), 1.26 (d, 1.5H, J = 6.2 Hz), 0.91 (t, 1.5H, J = 7.5 Hz), 0.88 (t, 1.5H, J = 7.5 Hz), 0.18 (s, 4.5H), 0.17 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 216.2, 199.7, 135.5, 134.2, 132.5, 129.7, 129.5, 128.3, 127.7, 126.7, 123.8, 83.0, 37.0, 36.3, 28.5, 25.4, 18.7, 9.6, -2.6 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{22}\text{H}_{30}\text{O}_2\text{S}_2\text{Si}$ 418.1456, found 418.1458.

O-sec-Butyl S-2-(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-1-(trimethylsilyl)ethyl Carbonodithioate (2.20h); 1.50 g, 75% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): diastereomers = 1/1/1/1: δ 8.00 (t, 1H, $J = 7.5$ Hz), 7.44 (t, 1H, $J = 7.4$ Hz), 7.21–7.35 (m, 1H), 7.22 (d, 1H, $J = 7.6$ Hz), 5.53–5.65 (m, 1H), 3.32–3.63 (m, 1H) 2.95–3.11 (m, 2H), 2.59–2.75 (m, 1H), 2.40–2.56 (m, 2H), 1.63–2.17 (m, 4H), 1.28–1.36 (m, 3H), 0.89–0.95 (m, 3H), 0.16 (s, 2.25H), 0.16 (s, 2.25H), 0.13 (s, 2.25H), 0.13 (s, 2.25H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): diastereomers = 1/1/1/1: δ 216.8, 200.4, 144.0, 143.7, 133.1, 132.8, 132.5, 128.6, 127.3, 126.4, 83.0, 82.6, 46.1, 45.5, 35.5, 33.7, 32.5, 32.1, 30.6, 29.5, 28.9, 28.5, 18.7, 9.6, -2.8 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{20}\text{H}_{30}\text{O}_2\text{S}_2\text{Si}$ 394.1456, found 394.1464.

O-sec-Butyl S-4-oxo-4-(thiophen-2-yl)-1-(trimethylsilyl)butyl Carbonodithioate (2.20i); 1.55 g, 83% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 7.68 (ddd, 1H, $J = 3.6$ Hz, $J = 2.3$ Hz, $J = 1.1$ Hz), 7.61 (dd, 1H, $J = 4.9$ Hz, $J = 1.0$ Hz), 7.10–7.12 (m, 1H), 5.56–5.64 (m, 1H), 3.25 (dd, 1H, $J = 11.1$ Hz, $J = 3.4$ Hz), 3.07–3.13 (m, 2H), 2.29–2.37 (m, 1H), 1.58–1.90 (m, 3H), 1.33 (d, 1.5H, $J = 6.3$ Hz), 1.27 (d, 1.5H, $J = 6.3$ Hz), 0.93 (t, 1.5H, $J = 7.5$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.14 (s, 4.5H), 0.13 (s,

4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 215.9, 192.7, 144.2, 133.4, 131.8, 128.0, 83.0, 37.7, 36.2, 28.5, 25.5, 18.7, 9.6, -2.7 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{16}\text{H}_{26}\text{O}_2\text{S}_3\text{Si}$ 374.0864, found 374.0868.

O-sec-butyl S-2-(4-oxo-1-tosylpiperidin-3-yl)-1-(trimethylsilyl)ethyl carbonodithioate (2.20j); 3.31 g, 90% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 4 diastereomers = 1/1/1/1: δ 7.68 (d, 2H, $J = 7.3$ Hz), 7.33 (d, 2H, $J = 8.0$ Hz), 5.59–5.68 (m, 1H), 3.82 (ddt, 1H, $J = 12.0$ Hz, $J = 5.2$ Hz, $J = 1.7$ Hz), 3.59–3.69 (m, 1H), 3.21 (ddd, 1H, $J = 12.8$ Hz, $J = 5.0$ Hz, $J = 3.3$ Hz), 3.06–3.14 (m, 1H), 2.73–2.90 (m, 2H), 2.46–2.52 (m, 2H), 2.42 (s, 3H), 1.92–2.00 (m, 1H), 1.66–1.89 (m, 3H), 1.37 (t, 3H, $J = 6.5$ Hz), 0.96 (t, 3H, $J = 7.5$ Hz), 0.10 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 4 diastereomers = 1/1/1/1: δ 215.7, 215.7, 207.7, 207.7, 143.9, 143.8, 133.8, 133.7, 129.8, 127.5, 83.4, 83.4, 50.0, 49.9, 47.2, 47.2, 46.2, 46.2, 40.0, 39.9, 33.1, 33.1, 28.5, 28.4, 27.4, 27.1, 21.5, 18.7, 18.5, 9.6, 9.6, -2.9, -3.0 ppm; MS ($\text{IC} + \text{NH}_4$) m/z Calculated for $[\text{M} + \text{H}]^+$ $\text{C}_{22}\text{H}_{35}\text{NO}_4\text{S}_3\text{Si}$ 502, found 502, $[\text{M} + \text{NH}_4]^+$ 519, found 519, $[(\text{M} + \text{H}) - \text{CH}_3\text{CHCHCH}_3]^+$ 446, found 446, $[(\text{M} + \text{NH}_4) - \text{CH}_3\text{CHCHCH}_3]^+$ 463, found 463, $[\text{M} - \text{SCSO}(\text{CH}_3)\text{CHCH}_2\text{CH}_3]^+$ 352, found 352, $[(\text{M} + \text{NH}_3) - \text{SCSO}(\text{CH}_3)\text{CHCH}_2\text{CH}_3]^+$ 368, found 368.

***O*-sec-Butyl *S*-2-(2-oxocyclohexyl)-1-(trimethylsilyl)ethyl Carbonodithioate (2.20k);**

1.51 g, 87% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1/1/1: δ 5.58–5.66 (m, 1H), 3.15–3.30 (m, 1H), 2.26–2.46 (m, 4H), 1.53–2.09 (m, 7H), 1.22–1.46 (m, 4H), 0.79–1.03 (m, 4H), 0.12 (s, 2.25H), 0.12 (s, 2.25H), 0.09 (s, 2.25H) 0.09 (s, 2.25H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1/1/1: δ 213.3, 212.8, 194.8, 82.8, 48.9, 48.2, 42.7, 42.2, 35.8, 35.5, 33.4, 33.2, 31.2, 30.9, 28.6, 27.9, 25.6, 25.2, 18.7, 9.6, -2.9 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{16}\text{H}_{30}\text{O}_2\text{S}_2\text{Si}$ 346.1456, found 346.1456.

ethyl 2-benzoyl-4-((sec-butoxycarbonothioyl)thio)-4-(trimethylsilyl)butanoate (2.20l);

3.78 g, 86% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 4 diastereomers = 1/1/1/1: δ 7.99 (t, 1H, $J = 7.3$ Hz), 7.52–7.60 (m, 1H), 7.41–7.49 (m, 2H), 5.35–5.66 (m, 1H), 4.65–4.71 (m, 1H), 4.05–4.24 (m, 2H), 3.39 (ddd, 0.5H, $J = 12.8$ Hz, $J = 3.7$ Hz, $J = 2.3$ Hz), 3.16 (td, 0.5H, $J = 12.8$ Hz, $J = 2.5$ Hz), 2.78 (ddd, 0.5H, $J = 14.2$ Hz, $J = 10.0$ Hz, $J = 2.7$ Hz), 2.63 (dddd, 0.5H, $J = 14.8$ Hz, $J = 10.2$ Hz, $J = 4.3$ Hz, $J = 2.3$ Hz), 1.40–1.92 (m, 3H), 1.04–1.36 (m, 6H), 0.75–0.96 (m, 3H), 0.14 (s, 2.25H), 0.14 (s, 2.25H), 0.12 (s, 2.25H), 0.11 (s, 2.25H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 4 diastereomers = 1/1/1/1: δ 215.7, 195.8, 194.1, 169.8, 169.5, 136.5, 136.5, 135.4, 135.3, 133.6, 133.5, 133.3, 133.3, 128.9, 128.7, 128.5, 128.5, 83.3, 83.3, 83.1, 83.0, 61.5, 61.4, 52.3, 52.2, 51.8, 35.7, 35.6, 35.0, 34.8, 30.6, 30.2, 29.2, 29.1, 28.5, 28.5, 28.4, 28.3, 18.7, 18.6, 18.5, 18.2, 14.0, 13.9, 9.6, 9.5, 9.4, -3.0, -3.0, -3.0 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{21}\text{H}_{32}\text{O}_4\text{S}_2\text{Si}$ 440.1511, found 440.1510.

O-sec-butyl-S-4-((10S,13S)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-4-oxo-1-(trimethylsilyl)butylcarbonodithioate

(2.20m); 4.36 g, 77% yield, viscous yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 4 diastereomers = 1/1/1/1: δ 5.59–5.67 (m, 1H), 3.55–3.63 (m, 1H), 3.11–3.16 (m, 1H), 2.45–2.55 (m, 2H), 2.26–2.40 (m, 1H), 2.09–2.18 (m, 2H), 1.91–1.95 (m, 1H), 1.77–1.82 (m, 2H), 1.55–1.72 (m, 8H), 1.16–1.45 (m, 12H), 1.07–1.14 (m, 2H), 0.86–0.99 (m, 5H), 0.79 (s, 3H), 0.63–0.68 (m, 1H), 0.55–0.60 (m, 3H), 0.10 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): 4 diastereomers = 1/1/1/1: δ 211.3, 211.0, 211.0, 82.9, 71.2, 63.3, 63.1, 56.7, 56.7, 54.2, 44.8, 44.4, 44.3, 42.7, 42.6, 42.4, 42.4, 39.1, 39.1, 39.0, 39.0, 38.1, 36.9, 36.3, 36.2, 36.1, 36.1, 35.5, 35.4, 32.0, 31.4, 28.6, 24.5, 24.4, 24.3, 22.9, 22.9, 22.8, 22.7, 21.2, 21.2, 18.8, 18.7, 13.6, 12.3, 9.6, -2.6, -2.7 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{31}\text{H}_{54}\text{O}_3\text{S}_2\text{Si}$ 566.3284, found 566.3271.

O-sec-Butyl S-6,6-dimethyl-4-oxo-1-(trimethylsilyl)heptyl Carbonodithioate (2.20n);

1.43 g, 79% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): diastereomers = 1/1: δ 5.55–

5.63 (m, 1H), 3.08–3.12 (m, 1H), 2.50–2.54 (m, 2H), 2.24 (s, 2H), 2.04–2.12 (m, 1H), 1.55–1.81 (m, 3H), 1.31 (d, 1.5H, $J = 6.3$ Hz), 1.31 (d, 1.5H, $J = 6.3$ Hz), 0.95 (s, 9H), 0.91 (t, 1.5H, $J = 7.4$ Hz), 0.90 (t, 1.5H, $J = 7.5$ Hz), 0.06 (s, 4.5H), 0.06 (s, 4.5H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 216.1, 210.1, 82.7, 55.0, 43.1, 36.0, 30.8, 29.6, 28.5, 24.3, 18.7, 9.5, -2.7 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{34}\text{O}_2\text{S}_2\text{Si}$ 362.1769, found 362.1774.

General procedure 5.2.3 for the one-pot synthesis of 2-sulfolenes 2.23. TMS xanthate adduct (2 mmol, 1.0 equiv) in Ph_2O (10 mL) under nitrogen atmosphere was heated to 200–210 °C for 2h, then cooled to rt. CH_2Cl_2 (20 mL) was added, followed by two successive additions of *m*-CPBA (1.2 equiv, 70–75%) every 30 min at rt and then quenched with $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with CH_2Cl_2 . The combined organic layers were washed with NaHCO_3 , dried over anhydrous MgSO_4 and concentrated under reduced pressure, followed by purification with flash column chromatography (silica gel, EtOAc-petroleum ether = 25/75) to give the titled 2-sulfolenes.

5-Phenyl-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23a); 474 mg, 89% yield, white solid; **m.p.** 113–114 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 7.66–7.69 (m, 2H), 7.38–7.41 (m, 3H), 6.77 (t, 1H, $J = 3.0$ Hz), 2.82–3.03 (m, 2H), 2.75–2.79 (m, 1H), 0.30 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.8, 132.0, 129.3, 128.7, 127.8, 126.6,

50.1, 27.1, -2.9 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{18}\text{O}_2\text{SSi}$ 266.0797, found 266.0792.

5-phenyl-2,3-dihydrothiophene 1,1-dioxide (2.23a'); 322 mg, 83% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.58–7.61 (m, 2H), 7.32–7.35 (m, 3H), 6.68 (t, 1H, J = 3.5 Hz), 3.34–3.38 (m, 2H), 2.87–2.91 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.0, 131.6, 129.8, 129.0, 127.5, 126.8, 48.9, 23.6 ppm. The spectra obtained was in agreement with literature.¹⁸⁹

5-(4-Fluorophenyl)-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23b); 472 mg, 83% yield, white solid; **m.p.** 138–140 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 7.66 (dd, 2H, J = 8.7 Hz, J = 5.3 Hz), 7.08 (t, 2H, J = 8.7 Hz), 6.72 (t, 1H, J = 2.9 Hz), 2.91–3.02 (m, 2H), 2.76–2.83 (m, 1H), 0.29 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.4 (d, J_{CF} = 249.9 Hz), 144.2, 131.7, 128.8 (d, J_{CF} = 8.4 Hz), 124.1 (d, J_{CF} = 3.4 Hz), 116.0 (d, J_{CF} = 21.9 Hz), 50.1, 27.2, -2.7 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{17}\text{FO}_2\text{SSi}$ 284.0703, found 284.0704.

5-(4-Bromophenyl)-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23c); 539 mg, 78% yield, yellow solid; **m.p.** 167–170 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.50–7.55 (m, 4H), 6.77–6.78 (m, 1H), 2.91–3.01 (m, 2H), 2.73–2.82 (m, 1H), 0.29 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 144.2, 132.4, 132.1, 128.2, 126.9, 123.8, 50.2, 27.3, -2.7 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{17}\text{BrO}_2\text{SSi}$ 343.9902, found 343.9898.

5-(p-Tolyl)-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23d); 393 mg, 70% yield, white solid; **m.p.** 135–140 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.57 (d, 2H, J = 8.2 Hz), 7.20 (d, 2H, J = 7.9 Hz), 6.72 (t, 1H, J = 3.1 Hz), 2.91–3.01 (m, 2H), 2.72–2.86 (m, 1H), 2.36 (s, 3H), 0.30 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 145.1, 139.6, 130.8, 129.6, 126.6, 125.0, 50.2, 27.1, 21.3, -2.7 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{O}_2\text{SSi}$ 280.0953, found 280.0952.

5-(4-Methoxyphenyl)-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23e); 522 mg, 88% yield, yellow solid; **m.p.** 117–122 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.59

(d, 2H, $J = 8.5$ Hz), 6.88 (d, 2H, $J = 8.5$ Hz), 6.63 (s, 1H), 3.77 (s, 3H), 2.87–2.96 (m, 2H), 2.72–2.79 (m, 1H), 0.26 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.4, 144.4, 129.8, 128.0, 120.2, 114.2, 55.2, 50.0, 26.9, -2.8 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{O}_3\text{SSi}$ 296.0902, found 296.0907.

4-Methyl-5-phenyl-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23f); 511 mg, 91% yield, white solid; **m.p.** 127–128 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 7.39–7.44 (m, 5H), 2.87–2.90 (m, 2H), 2.67–2.74 (m, 1H), 1.95 (s, 3H), 0.29 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 143.6, 139.1, 129.4, 128.9, 128.5, 128.0, 49.5, 32.7, 17.2, -2.7 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{O}_2\text{SSi}$ 280.0953, found 280.0943.

5-(Naphthalen-2-yl)-2-(trimethylsilyl)-2,3-dihydrothiophene 1,1-Dioxide (2.23g); 519 mg, 82% yield, white solid; **m.p.** 132–135 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 8.29 (s, 1H), 7.82–7.88 (m, 3H), 7.66 (dd, 1H, $J = 8.6$ Hz, $J = 1.6$ Hz), 7.46–7.52 (m, 2H), 6.90 (t, 1H, $J = 3.0$ Hz), 2.95–3.01 (m, 2H), 2.77–2.85 (m, 1H), 0.33 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 145.2, 133.5, 133.1, 131.9, 128.7, 128.7, 127.6, 126.9, 126.6, 126.2, 125.1, 124.0, 50.3, 27.3, -2.7 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{20}\text{O}_2\text{SSi}$ 316.0953, found 316.0955.

2-(Trimethylsilyl)-2,3,4,5-tetrahydronaphtho[1,2-b]thiophene 1,1-Dioxide (2.23h); 369 mg, 63% yield, light yellow solid; **m.p.** 138–141 °C; **¹H NMR** (CDCl₃, 400 MHz): δ 7.71–7.73 (m, 1H), 7.16–7.26 (m, 3H), 2.90–2.99 (m, 4H), 2.73–2.80 (m, 1H), 2.49 (t, 2H, *J* = 8.2 Hz), 0.29 (s, 9H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 145.7, 136.6, 134.5, 128.7, 127.9, 127.0, 125.6, 122.8, 50.8, 31.0, 27.3, 26.3, -2.7 ppm; **HRMS (EI⁺)** *m/z* Calculated for [M]⁺ C₁₅H₂₀O₂SSi 292.0953, found 292.0952.

5-(Trimethylsilyl)-4,5-dihydro-[2,2'-bithiophene] 1,1-Dioxide (2.23i); 316 mg, 58% yield, yellowish-green solid; **m.p.** 119–121 °C; **¹H NMR** (CDCl₃, 400 MHz): δ 7.55 (d, 1H, *J* = 3.2 Hz), 7.34 (d, 1H, *J* = 5.0 Hz), 7.04–7.06 (m, 1H), 6.64 (t, 1H, *J* = 3.3 Hz), 2.89–3.02 (m, 2H), 2.76–2.82 (m, 1H), 0.29 (s, 9H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 139.8, 129.8, 129.1, 128.0, 126.9, 126.7, 49.9, 27.5, -2.7 ppm; **HRMS (EI⁺)** *m/z* Calculated for [M]⁺ C₁₁H₁₆O₂S₂Si 272.0361, found 272.0357.

5-tosyl-2-(trimethylsilyl)-2,3,4,5,6,7-hexahydrothieno[3,2-c]pyridine 1,1-dioxide (2.23j); 646 mg, 81% yield, white solid; **m.p.** 71–75 °C; **¹H NMR** (CDCl₃, 400 MHz): δ

7.64 (d, 2H, $J = 8.0$ Hz), 7.31 (d, 2H, $J = 7.9$ Hz), 3.72 (s, 2H), 3.21–3.33 (m, 2H), 2.69–2.75 (m, 2H), 2.52–2.57 (m, 1H), 2.47 (s, br, 2H), 2.40 (s, 3H), 0.20 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.2, 139.8, 136.1, 133.0, 129.9, 127.3, 49.3, 46.1, 42.0, 29.1, 21.4, 19.2, -2.9 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{25}\text{NO}_4\text{S}_2\text{Si}$ 399.0994, found 399.0993.

2-(Trimethylsilyl)-2,3,4,5,6,7-hexahydrobenzo[b]thiophene 1,1-Dioxide (2.23k); 386 mg, 79% yield, white solid; **m.p.** 89–90 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 2.70–2.74 (m, 2H), 2.50–2.60 (m, 1H), 2.35 (s, 2H), 2.14 (s, 2H), 1.69–1.76 (m, 4H), 0.25 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 144.3, 136.6, 48.7, 31.4, 27.1, 21.2, 21.0, 17.9, -3.0 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{11}\text{H}_{20}\text{O}_2\text{SSi}$ 244.0953, found 244.0961.

ethyl 2-phenyl-5-(trimethylsilyl)-4,5-dihydrothiophene-3-carboxylate 1,1-dioxide (2.23l); 506 mg, 75% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.38–7.47 (m, 5H), 4.12 (q, 2H, $J = 7.1$ Hz), 3.14–3.23 (m, 1H), 2.91–3.00 (m, 2H), 1.05 (t, 3H, $J = 7.1$ Hz), 0.33 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.9, 149.6, 133.6, 129.6, 129.0, 128.0, 126.8, 61.5, 49.3, 27.9, 13.4, -2.8 ppm; HRMS (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{16}\text{H}_{22}\text{O}_4\text{SSi}$ 338.1008, found 338.1004.

2-(2,2-Dimethylpropylidene)-5-(trimethylsilyl)tetrahydrothiophene 1,1-Dioxide (2.23n'); 406 mg, 78% yield, white solid; **m.p.** 103–105 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 6.33 (s, 1H), 2.77–2.87 (m, 1H), 2.58–2.68 (m, 2H), 2.27, 2.20 (ABq, 2H, $J_{\text{AB}} = 14.9$ Hz), 0.95 (s, 9H), 0.20 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 143.8, 134.0, 48.1, 37.3, 30.9, 29.5, 27.3, -2.9 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{12}\text{H}_{24}\text{O}_2\text{SSi}$ 260.1266, found 260.1265.

General procedure 5.2.4 for the synthesis of TMS 1,3-dienes 2.25. A mixture of K_2CO_3 (5.0 equiv), DBU (5.0 equiv) in toluene (5 mL) was refluxed under nitrogen. Trimethylsilyl chloride (5.0 equiv) was added, followed by 2-sulfolene (0.5 mmol, 1.0 equiv) to the refluxing mixture and stirred for 1h. The crude reaction mixture was cooled to rt and passed through a short silica plug, washing with petroleum ether (60 mL) and the filtrate was concentrated under reduced pressure to afford the titled TMS dienes.

Trimethyl((1E,3E)-4-phenylbuta-1,3-dienyl)silane (2.25a); 84 mg, 83% yield, colorless oil. $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.41 (d, 2H, $J = 8.2$ Hz), 7.32 (t, 2H, $J = 7.1$ Hz), 7.23 (t, 1H, $J = 7.2$ Hz), 6.80 (dd, 1H, $J = 15.5$ Hz, $J = 10.0$ Hz), 6.69 (dd, 1H, $J = 17.9$ Hz, $J = 10.0$ Hz), 6.59 (d, 1H, $J = 15.3$ Hz), 6.01 (d, 1H, $J = 18.0$ Hz), 0.13 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 144.1, 137.2, 135.0, 132.9, 131.7, 128.6, 127.6, 126.5, -1.3 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{18}\text{Si}$ 202.1178, found 202.1174. This

compound has been reported previously.⁶⁰ The spectra is in agreement with literature values.

((1E,3E)-4-(4-Fluorophenyl)buta-1,3-dienyl)trimethylsilane (2.25b); 85 mg, 77% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.37 (dd, 2H, $J = 8.7$ Hz, $J = 5.5$ Hz), 7.02 (t, 2H, $J = 8.7$ Hz), 6.71 (dd, 1H, $J = 14.8$ Hz, $J = 10.0$ Hz), 6.67 (dd, 1H, $J = 16.9$ Hz, $J = 10.0$ Hz), 6.54 (d, 1H, $J = 14.9$ Hz), 6.01 (d, 1H, $J = 17.1$ Hz), 0.14 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 162.3 (d, $^1J_{\text{CF}} = 247.3$ Hz), 143.9, 135.0, 133.4 (d, $^4J_{\text{CF}} = 3.3$ Hz), 131.6, 131.4 (d, $^5J_{\text{CF}} = 2.4$ Hz), 128.0 (d, $^3J_{\text{CF}} = 7.9$ Hz), 115.6 (d, $^2J_{\text{CF}} = 21.7$ Hz), -1.3 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{17}\text{FSi}$ 220.1084, found 220.1085. This compound has been reported previously.¹⁹⁰ The spectra is in agreement with literature values.

((1E,3E)-4-(4-Bromophenyl)buta-1,3-dienyl)trimethylsilane (2.25c); 102 mg, 72% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.45 (d, 2H, $J = 8.4$ Hz), 7.27 (d, 2H, $J = 8.4$ Hz), 6.78 (dd, 1H, $J = 15.3$ Hz, $J = 10.1$ Hz), 6.68 (dd, 1H, $J = 17.9$ Hz, $J = 10.1$ Hz), 6.51 (d, 1H, $J = 15.3$ Hz), 6.05 (d, 1H, $J = 17.8$ Hz), 0.15 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 143.7, 136.1, 135.9, 132.3, 131.7, 131.4, 127.9, 121.3, -1.3 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{13}\text{H}_{17}\text{BrSi}$ 280.0283, found 280.0286.

Trimethyl((1E,3E)-4-*p*-tolylbuta-1,3-dienyl)silane (2.25d); 80 mg, 74% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.33 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 7.9 Hz), 6.77 (dd, 1H, J = 14.9 Hz, J = 9.9 Hz), 6.70 (dd, 1H, J = 17.5 Hz, J = 9.9 Hz), 6.58 (d, 1H, J = 14.9 Hz), 6.00 (d, 1H, J = 17.6 Hz), 2.36 (s, 3H), 0.15 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 144.3 (CH), 137.5, 134.4, 134.2, 132.9, 130.7, 129.3, 126.4, 21.2, -1.2 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{Si}$ 216.1334, found 216.1335. This compound has been reported previously.¹⁹¹ The spectra is in agreement with literature values.

((1E,3E)-4-(4-methoxyphenyl)buta-1,3-dienyl)trimethylsilane (2.25e); 90 mg, 78% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.35 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.8 Hz), 6.64–6.72 (m, 2H), 6.51–6.58 (m, 1H), 5.91–5.99 (m, 1H), 3.82 (s, 3H), 0.13 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 159.3, 144.3, 133.4, 132.5, 130.0, 129.7, 127.7, 114.1, 55.2, -1.2 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{OSi}$ 232.1283, found 232.1285; This compound has been reported previously.¹⁹¹ (multiplet was observed even on 500 MHz spectrometer from reference 191). The spectra is in agreement with literature values.

Trimethyl((1*E*,3*E*)-3-methyl-4-phenylbuta-1,3-dienyl)silane (2.25f); 69 mg, 64% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.32–7.39 (m, 4H), 7.23–7.27 (m, 1H), 6.76 (d, 1H, $J = 18.9$ Hz), 6.61 (s, 1H), 6.00 (d, 1H, $J = 18.8$ Hz), 2.04 (d, 3H, $J = 1.0$ Hz), 0.17 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 148.8, 137.9, 137.1, 132.3, 129.2, 128.5, 128.1, 126.6, 13.4, -1.1 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{14}\text{H}_{20}\text{Si}$ 216.1334, found 216.1341.

Trimethyl((1*E*,3*E*)-4-(naphthalen-2-yl)buta-1,3-dienyl)silane (2.25g); 110 mg, 87% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.78–7.81 (m, 4H), 7.64 (dd, 1H, $J = 8.6$ Hz, $J = 1.5$ Hz), 7.42–7.49 (m, 2H), 6.94 (dd, 1H, $J = 15.6$ Hz, 9.9 Hz), 6.73–6.80 (m, 2H), 6.08 (d, 1H, $J = 18.6$ Hz), 0.16 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 144.1, 135.2, 134.7, 133.6, 133.0, 133.0, 132.0, 128.2, 128.0, 127.7, 126.7, 126.3, 125.9, 123.5, -1.2 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{17}\text{H}_{20}\text{Si}$ 252.1334, found 252.1326.

(*E*)-2-(3,4-Dihydronaphthalen-2-yl)vinyl)trimethylsilane (2.25h); 100 mg, 88% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.10–7.20 (m, 4H), 6.78 (d, 1H, $J = 19.0$ Hz), 6.52 (s, 1H), 6.06 (d, 1H, $J = 18.9$ Hz), 2.89 (t, 2H, $J = 8.1$ Hz), 2.52 (t, 2H, $J = 8.1$ Hz), 0.18 (s, 9H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 145.3, 138.7, 135.8, 134.7, 128.7, 128.2, 127.2, 127.0, 126.6, 126.5, 27.8, 22.4, -1.1 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{15}\text{H}_{20}\text{Si}$ 228.1334, found 228.1328.

Trimethyl((1E,3E)-4-(thiophen-2-yl)buta-1,3-dienyl)silane (2.25i); 75 mg, 72% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.17 (d, 1H, $J = 4.3$ Hz), 6.97–7.00 (m, 2H), 6.58–6.74 (m, 3H), 5.96–6.03 (m, 1H), 0.13 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 143.5, 142.6, 134.9, 131.4, 127.6, 126.2, 125.6, 124.6, -1.3 ppm; **HRMS** (EI^+) m/z Calculated for $[\text{M}]^+$ $\text{C}_{11}\text{H}_{16}\text{SSi}$ 208.0742, found 208.0747.

5.3 The Combination of Keto-Xanthates and Alkenyl Acyl Phosphonates: A Radical Variant to the Robinson Annulation.

Preparation of 3,3-bis(ethoxycarbonyl)hex-5-enoic acid.

3,3-bis(ethoxycarbonyl)hex-5-enoic acid; 1.86 g, 72% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 11.11 (br s, 1H), 5.62–5.73 (m, 1H), 5.12–5.15 (m, 2H), 4.21 (q, 4H, $J = 7.1$ Hz), 3.00 (s, 2H), 2.79 (d, 2H, $J = 7.5$ Hz), 1.25 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C

NMR (CDCl₃, 100 MHz): δ 176.2, 169.6, 131.7, 119.7, 61.6, 54.9, 37.4, 36.7, 13.6 ppm;

HRMS (ESI, C₁₂H₁₉O₆ (M+H)⁺): calcd.: 259.1182; found: 259.1183.

This compound was synthesized according to known literature¹⁹² and the ¹H NMR spectrum obtained is in agreement with the literature ¹H NMR spectrum.

Preparation of 3,3-bis(ethoxycarbonyl)hept-6-enoic acid.

3,3-bis(ethoxycarbonyl)hept-6-enoic acid; 2.21 g; 95% yield; pale yellow oil; ¹H NMR (CDCl₃, 400 MHz): δ 7.77 (brs, 1H), 5.73–5.80 (m, 1H), 5.01 (ddd, 2H, J = 13.7 Hz, J = 11.5 Hz, J = 1.3 Hz), 4.21 (q, 4H, J = 7.1 Hz), 3.03 (s, 2H), 1.99–2.14 (m, 4H), 1.25 (t, 3H, J = 7.1 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 176.0, 170.2, 137.0, 115.4, 61.8, 55.1, 37.3, 32.4, 28.7, 13.8 ppm; **HRMS** (ESI, C₁₃H₂₁O₆ (M+H)⁺): calcd.: 273.1338; found: 273.1339. This compound was synthesized using a known procedure adapted from reference¹⁹²

3 Step-synthesis of alkenyl acid. To a suspension of NaH (480 mg, 12 mmol, 1.2 equiv, 60% weight in mineral oil) in anhydrous THF (20 mL) at 0 °C was added diethylmalonate (1.6 g, 10 mmol, 1.0 equiv) dropwise. On complete addition, the reaction mixture was stirred for 1 h while warming to rt. The reaction mixture was cooled to 0 °C and *tert*-Butyl bromoacetate (2.1 g, 10.7 mmol, 1.07 equiv) was then added dropwise to the stirring mixture. which was stirred overnight (17h) at rt. Saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with Et₂O (20 mL) three times. The organic extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give the crude alkyl diethylmalonate which was used in the next step without further purification.

To a suspension of NaH (480 mg, 12 mmol, 1.2 equiv, 60% weight in mineral oil) in anhydrous THF (20 mL) at rt was added the crude alkyl diethylmalonate dropwise. On complete addition, the reaction mixture was stirred for 1h. 4-Bromo-1-butene (1.6 g, 12 mmol, 1.2 equiv) was then added dropwise to the stirring mixture. which was then heated and stirred at 60 °C overnight. Saturated ammonium chloride solution (10 mL) was added and the mixture was extracted with Et₂O (20 mL) three times. The organic extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a colorless oil which was purified by flash column chromatography to give dialkylated ester (2.8 g, 8.6 mmol, 86%) as a colorless oil.

To a solution of the dialkylated ester in CH_2Cl_2 (20 mL) at rt was added trifluoroacetic acid (9.8 g, 86 mmol, 10 equiv) and stirred overnight (17h). The reaction mixture was evaporated under reduced pressure and diluted with CH_2Cl_2 (20 mL) and 1 M HCl (15 mL). The organic layer was separated and the mixture was further extracted with CH_2Cl_2 . The combined organic extract was then dried over anhydrous sodium sulfate, concentrated under reduced pressure to give the crude alkenyl acid 3-sm-acid in quantitative yield. The crude acid was reasonably pure by inspection of NMR.

2-(allyloxy)benzoic acid; 99% yield; white crystalline solid; ^1H NMR (CDCl_3 , 400 MHz): δ 10.59 (brs, 1H), 8.14, (dd, 1H, $J=7.8$ Hz, $J=1.7$ Hz), 7.52–7.56 (m, 1H), 7.05–7.13 (m, 2H), 6.04–6.14 (m, 1H), 5.40–5.52 (m, 2H), 4.79, (d, 2H, $J=5.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.6, 157.2, 134.9, 133.8, 130.9, 122.3, 120.5, 117.9, 113.0, 70.7 ppm. This compound was synthesized according to known literature¹⁹³ and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.

2-(N-allyl-4-methylphenylsulfonamido)benzoic acid; 93% yield; brown solid; ^1H NMR (CDCl_3 , 400 MHz): δ 11.63 (brs, 1H), 7.98–8.00 (m, 1H), 7.54, (d, 2H, $J=8.2$ Hz), 7.41–7.50 (m, 2H), 7.26, (d, 2H, $J=8.2$ Hz), 6.98, (d, 2H, $J=7.3$ Hz), 5.87–5.97 (m, 1H), 5.28 (s, 1H), 5.04–5.08 (m, 2H), 4.30, (d, 2H, $J=4.8$ Hz), 2.38 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.6, 143.7, 138.1, 135.7, 132.9, 132.8, 131.8, 131.3, 131.2, 129.4, 128.4,

127.6, 119.3, 54.7, 21.4 ppm. This compound was synthesized according to known literature¹⁹³ and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.

General procedure 5.3.1 for the synthesis of alkenyl acylphosphonates.

Step 1. Preparation of alkenyl acid chlorides from alkenyl acids

An oven-dried round bottom flask equipped with a magnetic stirbar was charged with the corresponding alkenyl acid (5.0 mmol, 1.0 equiv). The reaction flask was then cooled in an ice-bath, followed by dropwise addition of oxalyl chloride (10.0 mmol, 2.0 equiv) while stirring. Dimethylformamide (DMF) (3 drops) was added to the stirring mixture and vigorous effervescence was observed. After 1h, the ice-bath was removed and the reaction mixture was stirred overnight (17h) while warming to rt. The volatiles were removed under reduced pressure to give the crude acid chloride which was used in the next step without further purification.

Step 2. Preparation of alkenyl acylphosphonates from alkenyl acid chlorides.

To a pre-cooled (ice-bath) round bottom flask equipped with a magnetic stirbar containing the crude alkenyl acid chloride was added triethyl phosphite (5.0 mmol, 1.0 equiv) while stirring. After 30 min, the ice-bath was removed and the reaction was then

stirred overnight (17h) while gradually warming to rt. Any volatiles were removed under reduced pressure and the crude alkenyl acylphosphonate was used without further purification.

diethyl 2-allyl-2-(2-(diethoxyphosphoryl)-2-oxoethyl)malonate (3.16); pale yellow oil;

^1H NMR (CDCl_3 , 400 MHz): δ 5.60–5.71 (m, 1H), 5.06–5.13 (m, 2H), 4.17–4.26 (m, 8H), 3.50 (d, 2H, $J = 2.6$ Hz), 2.76 (d, 2H, $J = 7.5$ Hz), 1.37 (t, 6H, $J = 7.1$ Hz), 1.25 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.7 (d, $J_{\text{cp}} = 173.9$ Hz), 169.5, 132.0, 119.8, 63.9 (d, $J_{\text{cp}} = 7.2$ Hz), 61.7, 54.7, 54.7, 49.0, 45.3 (d, $J_{\text{cp}} = 57.5$ Hz), 37.5, 16.2 (d, $J_{\text{cp}} = 5.6$ Hz), 13.8 ppm; ^{31}P NMR (162 MHz, CDCl_3) δ -3.7 ppm; **HRMS** (ESI, $\text{C}_{16}\text{H}_{28}\text{O}_8^{31}\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 379.1532; found: 379.1520.

1-ethyl 3-methyl 2-(but-3-en-1-yl)-2-(2-(diethoxyphosphoryl)-2-oxoethyl)malonate

(3.17); orange oil; ^1H NMR (CDCl_3 , 400 MHz): δ 5.69–5.79 (m, 1H), 4.96–5.05 (m, 2H), 4.10–4.28 (m, 8H), 3.52 (d, 2H, $J = 2.4$ Hz), 2.06–2.11 (m, 2H), 1.97–2.03 (m, 2H), 1.38 (t, 6H, $J = 7.1$ Hz), 1.25 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.6 (d, $J_{\text{cp}} = 161.8$ Hz), 208.5, 206.8, 169.8, 136.8, 115.3, 63.9 (d, $J_{\text{cp}} = 7.2$ Hz), 61.6, 54.7, 54.7, 51.0, 45.5 (d, $J_{\text{cp}} = 57.3$ Hz), 32.5, 28.8, 16.2 (d, $J_{\text{cp}} = 5.6$ Hz), 13.8 ppm; ^{31}P NMR (162 MHz, CDCl_3) δ -3.6 ppm; **HRMS** (ESI, $\text{C}_{17}\text{H}_{30}\text{O}_8^{31}\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 393.1678; found: 393.1689.

diethyl (2-(allyloxy)benzoyl)phosphonate (3.20); yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 7.92 (dd, 1H, $J = 7.8$ Hz, $J = 1.4$ Hz), 7.48–7.52 (m, 1H), 6.98–7.05 (m, 2H), 6.08–6.17 (m, 1H), 5.29–5.49 (m, 2H), 4.69 (d, 2H, $J = 5.1$ Hz), 4.20–4.27 (m, 4H), 1.35 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 200.0 (d, $J_{\text{cp}} = 179.5$ Hz), 158.4, 135.9, 135.0, 134.4, 132.5, 131.8, 127.2, 126.6, 120.6, 117.7, 113.2, 69.7, 63.6 (d, $J_{\text{cp}} = 7.5$ Hz), 16.2 (d, $J_{\text{cp}} = 5.8$ Hz) ppm; ^{31}P NMR (162 MHz, CDCl_3) δ -1.9 ppm; **HRMS** (ESI, $\text{C}_{14}\text{H}_{20}\text{O}_5^{31}\text{P} (\text{M}+\text{H})^+$): calcd.: 299.1048; found: 299.1047.

diethyl (2-(N-allyl-4-methylphenylsulfonamido)benzoyl)phosphonate (3.21); orange oil; ^1H NMR (CDCl_3 , 400 MHz): δ 8.26–8.28 (m, 1H), 7.40–7.49 (m, 4H), 7.23 (d, 2H, $J = 8.4$ Hz), 6.85–6.87 (m, 1H), 5.89–5.99 (m, 1H), 5.00–5.05 (m, 2H), 4.24–4.29 (m, 4H), 2.42 (s, 3H), 1.33–1.39 (m, 6H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 200.2 (d, $J_{\text{cp}} = 179.5$ Hz), 171.1, 143.4, 137.8, 137.2, 137.1, 137.1, 136.1, 133.1, 132.7, 131.5, 130.7, 130.7, 129.4, 128.1, 127.8, 119.0, 64.3 (d, $J_{\text{cp}} = 6.1$ Hz), 60.3, 54.7, 21.5, 16.3 (d, $J_{\text{cp}} = 5.9$ Hz), 14.2 ppm; ^{31}P NMR (162 MHz, CDCl_3) δ -3.1 ppm; **HRMS** (ESI, $\text{C}_{21}\text{H}_{27}\text{NO}_6\text{S}^{31}\text{P} (\text{M}+\text{H})^+$): calcd.: 452.1297; found: 452.1291.

diethyl (3-(allyloxy)propanoyl)phosphonate (3.22); yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 5.83–5.95 (m, 1H), 5.16–5.31 (m, 2H), 4.17–4.29 (m, 4H), 3.95–4.03 (m, 2H), 3.71–3.79 (m, 2H), 3.11 (t, 2H, $J=6.2$ Hz), 1.32–1.39 (m, 6H) ppm; ^{31}P NMR (162 MHz, CDCl_3) δ -3.4 ppm. **HRMS** (ESI, $\text{C}_{10}\text{H}_{20}\text{O}_5\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 251.1043; found: 251.1043.

O-ethyl S-(2-oxopropyl) carbonodithioate (3.23a); yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 4.64 (q, 2H, $J=7.1$ Hz), 4.00 (s, 2H), 2.33 (s, 3H), 1.42 (t, 3H, $J=7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 213.2, 201.1, 70.8, 46.0, 29.1, 13.7 ppm. **This compound was synthesized according to known literature¹⁹⁴ and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.**

S-(3-chloro-2-oxopropyl) O-ethyl carbonodithioate (3.23b); white solid; ^1H NMR (CDCl_3 , 400 MHz): δ 4.62 (q, 2H, $J=6.6$ Hz), 4.30 (s, 2H), 4.13 (s, 2H), 1.41 (t, 3H, $J=6.6$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.7, 195.6, 71.2, 47.8, 42.8, 13.7 ppm. **This compound was synthesized according to known literature^{94a} and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.**

***S*-(3-(4-bromophenyl)-2-oxopropyl) *O*-ethyl carbonodithioate (3.23c)**; 2.20 g; 65% yield; white solid; **m.p.** 62-64 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.46 (d, 2H, $J=8.4\text{Hz}$), 7.11 (d, 2H, $J=8.3\text{ Hz}$), 4.62 (q, 2H, $J=7.1\text{ Hz}$), 4.01 (s, 2H), 3.86 (s, 2H), 1.40 (t, 3H, $J=7.1\text{ Hz}$) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 213.1, 200.2, 132.2, 131.9, 131.3, 121.4, 71.0, 48.1, 45.0, 13.7 ppm; **HRMS** (ESI, $\text{C}_{12}\text{H}_{14}\text{O}_2\text{S}_2\text{Br}$ ($\text{M}+\text{H}$) $^+$): calcd.: 332.9619; found: 332.9620. **This compound was synthesized using a procedure adapted from reference.**¹⁹⁵

To a solution of 1-(4-bromophenyl)propan-2-one (2.1 g, 10.0 mmol, 1 equiv) in glacial AcOH (15 mL) was added concentrated HBr (7.5 mL) and a solution of Br_2 (0.6 mL, 11.6 mmol, 1.2 equiv) in glacial AcOH (10 mL), and the resulting mixture was stirred at rt for 3h. Acetone (20 mL) was then added, and stirring continued for a further 17 h. The reaction mixture was then concentrated, and extracted with CH_2Cl_2 . The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a black oil which was used in the next step without purification. Potassium *O*-ethyl Xanthate (2.1 g, 13.0 mmol, 1.3 equiv) was added portionwise to the crude bromide in acetone (20 mL) at 0 °C under a nitrogen atmosphere and then stirred at rt for 2h. The reaction mixture was then concentrated, the residue taken up in Et_2O and filtrated through CeliteTM. The solvent was evaporated, and the residue was purified by flash column chromatography (Hexane: Ethyl Acetate 9:1), and the desired xanthate was obtained as a white solid.

***O*-ethyl *S*-(3-oxopentan-2-yl) carbonodithioate (3.23d)**; 1.50 g, 72% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 4.64 (q, 2H, $J = 7.2$ Hz), 4.47 (q, 1H, $J = 7.3$ Hz), 2.55–2.78 (m, 2H), 1.48 (d, 3H, $J = 7.3$ Hz), 1.42 (t, 3H, $J = 7.1$ Hz), 1.09 (t, 3H, $J = 7.3$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.6, 207.4, 70.5, 53.1, 33.3, 15.7, 13.6, 7.8 ppm; **HRMS** (ESI, $\text{C}_8\text{H}_{15}\text{O}_2\text{S}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 207.0513; found: 207.0511. **This compound was synthesized using a procedure adapted from reference.¹⁹⁶**

Potassium *O*-ethyl Xanthate (2.1g, 13 mmol, 1.3 equiv) was added portionwise to 2-bromopentan-3-one (1.7 g, 10.0 mmol, 1.0 equiv) in acetone (20 mL) at 0 °C under a nitrogen atmosphere and then stirred at rt for 2 h. The reaction mixture was then concentrated under reduced pressure, the residue obtained was added water (40 mL), followed by extraction with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography and the desired xanthate was obtained as a yellow oil.

ethyl 4-((ethoxycarbonothioyl)thio)-3-oxobutanoate (3.23e); yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 4.64 (q, 2H, $J = 7.1$ Hz), 4.21 (q, 2H, $J = 7.1$ Hz), 4.12 (s, 2H), 3.65 (s, 2H), 1.42 (t, 3H, $J = 7.1$ Hz), 1.29 (t, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.7, 196.0, 166.6, 70.9, 61.5, 48.0, 45.2, 14.0, 13.6 ppm. **This compound was synthesized according to known literature^{94b} and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.**

ethyl 2-((ethoxycarbonothioyl)thio)-3-oxobutanoate (3.23f); 2.00 g, 80% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 4.61–4.71 (m, 3H), 4.21–4.31 (m, 2H), 2.23 (s, 3H), 1.41 (t, 3H, $J = 7.1$ Hz), 1.28 (t, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 213.6, 184.7, 171.7, 93.2, 70.4, 61.5, 20.6, 14.0, 13.7 ppm; **HRMS** (ESI, $\text{C}_9\text{H}_{15}\text{O}_4\text{S}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 251.0412; found: 251.0406. **This compound was synthesized using a procedure adapted from reference¹⁹⁶**

Potassium *O*-ethyl Xanthate (2.1 g, 13 mmol, 1.3 equiv) was added portionwise to ethyl 2-chloro acetoacetate (1.7 g, 10 mmol, 1.0 equiv) in acetone (20 mL) at 0 °C under a nitrogen atmosphere and then stirred at rt for 2 h. The reaction mixture was then concentrated under reduced pressure, the residue was added water (40 mL), followed by extraction with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography and the desired xanthate was obtained as a yellow oil.

S-(3-(diethoxyphosphoryl)-2-oxopropyl) O-ethyl carbonodithioate (3.23g); yellow oil; ^1H NMR (CDCl_3 , 400 MHz): δ 4.59 (q, 2H, $J = 7.1$ Hz), 4.10–4.14 (m, 6H), 4.21 (d, 2H, $J_{\text{PH}} = 22.4$ Hz), 1.37 (t, 3H, $J = 7.1$ Hz), 1.30 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.8, 194.8 (d, $J_{\text{CP}} = 5.9$ Hz), 70.8, 62.7 (d, $J_{\text{CP}} = 6.4$ Hz), 46.1, 41.5 (d, $J_{\text{CP}} = 127.5$ Hz), 16.2 (d, $J_{\text{CP}} = 6.2$ Hz), 13.6 ppm. **This compound was synthesized**

according to known literature¹⁹⁷ and the ^1H NMR spectrum obtained is in agreement with the literature ^1H NMR spectrum.

Synthesis of Pivalate-bearing xanthate starting from hydroxyl ketone.

3-((ethoxycarbonothioyl)thio)-2-oxopropyl pivalate (3.23h); 1.72 g; 62% yield; red solid; **m.p.** 37-39 °C; ^1H NMR (CDCl_3 , 400 MHz): δ 4.84 (s, 2H), 4.64 (q, 2H, $J = 7.1$ Hz), 4.02 (s, 2H), 1.42 (t, 3H, $J = 7.1$ Hz), 1.27 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 212.6, 197.1, 177.7, 71.0, 67.6, 42.2, 38.7, 27.1, 13.6 ppm; **HRMS** (ESI, $\text{C}_{11}\text{H}_{19}\text{O}_4\text{S}_2$ ($\text{M}+\text{H}^+$)): calcd.: 279.0725; found: 279.0724. **This compound was synthesized using the following procedure.**

3 Step-synthesis of 3-((ethoxycarbonothioyl)thio)-2-oxopropyl pivalate 3.23h. To a solution of hydroxyacetone (740 mg, 10.0 mmol, 1.0 equiv) and pyridine (1.2 g, 15.0 mmol, 1.5 equiv) in diethyl ether (20 mL) at 0 °C was added trimethylacetyl chloride (1.8 g, 15.0 mmol, 1.5 equiv) dropwise. After the addition was complete, the reaction mixture was stirred overnight while warming to rt. The reaction mixture was then filtered and the filtrate evaporated under reduced pressure to give a colorless oil which was used in the next step without purification.

Next, the crude pivalate was dissolved in diethyl ether (20 mL) and cooled in an ice-bath. Bromine (1.6 g, 10.0 mmol, 1.0 equiv) was added dropwise to the stirring mixture. The reaction mixture was then stirred for 5h while warming to rt. The crude mixture was evaporated under reduced pressure to give the bromo keto-pivalate which was used in the next step without purification.

Potassium *O*-ethyl Xanthate (2.1 g, 13 mmol, 1.3 equiv) was added portionwise to the crude bromo keto-pivalate in acetone (20 mL) at 0 °C under a nitrogen atmosphere and then stirred at rt for 2h. The reaction mixture was then concentrated under reduced pressure, the residue was added water (40 mL), followed by extraction with CH₂Cl₂ (3 x 30 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography and the desired xanthate was obtained as a red solid.

***O*-ethyl S-(2-oxo-2-phenylethyl) carbonodithioate (3.23i); yellow oil; ¹H NMR (CDCl₃, 400 MHz): δ 8.03 (d, 2H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 4.61–4.67 (m, 4H), 1.40 (t, 3H, *J* = 7.1 Hz) ppm; This compound was synthesized using a procedure from reference¹⁹⁶ and the ¹H NMR spectrum obtained is in agreement with the literature ¹H NMR spectrum.**

General procedure 5.3.2 for the radical reaction between alkenylacylphosphonates 3.16, 3.17, 3.20, 3.21 and 3.22 with keto-xanthates 3.23. An oven-dried Schlenk tube

with a side arm for gas inlet containing a magnetic stirbar was charged with keto-xanthate (0.5 mmol, 1 equiv), alkenyl acylphosphonate (0.75 mmol, 1.5 equiv) in 1 mL dichloroethane (DCE, 0.5M in keto-xanthate) and refluxed under Argon for 10 minutes. Dilauroyl peroxide (DLP, 0.1 mmol, 0.2 equiv) was then added every hour until most of the keto-xanthate has been consumed as monitored by TLC. The mixture is then cooled to rt and the solvent evaporated under reduced pressure. The crude product was then purified *via* flash column chromatography to afford the desired 1,5-diketones.

diethyl 3-oxo-4-(3-oxobutyl)cyclopentane-1,1-dicarboxylate (3.24a); 119 mg; 80% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 4.23 (q, 2H, $J = 7.1$ Hz), 4.23 (q, 2H, $J = 7.1$ Hz), 2.92–2.98 (m, 1H), 2.80 (ddd, 1H, $J = 13.2$ Hz, $J = 8.6$ Hz, $J = 2.1$ Hz), 2.73 (d, 1H, $J = 19.0$ Hz), 2.51–2.71 (m, 2H), 2.32–2.41 (m, 1H), 2.15 (s, 3H), 2.01 (dd, 1H, $J = 13.0$ Hz, $J = 12.2$ Hz), 1.93 (ddd, 1H, $J = 14.9$ Hz, $J = 8.4$ Hz, $J = 4.2$ Hz), 1.66 (ddd, 1H, $J = 14.2$ Hz, $J = 7.9$ Hz, $J = 7.0$ Hz), 1.28 (t, 3H, $J = 7.1$ Hz) 1.27 (t, 3H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 214.8, 207.6, 170.7, 170.4, 62.0, 61.9, 54.7, 46.3, 44.8, 40.6, 36.1, 29.7, 23.4, 13.8, 13.8 ppm; **HRMS** (ESI, $\text{C}_{15}\text{H}_{23}\text{O}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 299.1495; found: 299.1494.

diethyl 3-(4-chloro-3-oxobutyl)-4-oxocyclopentane-1,1-dicarboxylate (3.24b); 120 mg; 72% yield; light yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 4.23 (q, 2H, $J = 7.1$ Hz), 4.23 (q, 2H, $J = 7.1$ Hz), 4.10 (s, 2H), 2.92–2.98 (m, 1H), 2.72–2.85 (m, 4H), 2.31–2.47 (m, 1H), 1.93–2.05 (m, 2H), 1.72 (td, 1H, $J = 22.0$ Hz, $J = 6.9$ Hz), 1.27 (t, 3H, $J = 7.1$ Hz), 1.27 (t, 3H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 214.7, 201.7, 170.8, 170.4, 62.1, 62.0, 54.7, 48.0, 46.1, 44.8, 36.8, 36.2, 23.4, 13.9, 13.9 ppm; **HRMS** (ESI, $\text{C}_{15}\text{H}_{22}\text{ClO}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 333.1105; found: 333.1100.

diethyl 3-(4-(4-bromophenyl)-3-oxobutyl)-4-oxocyclopentane-1,1-dicarboxylate (3.24c); 175 mg; 77% yield; yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.44 (d, 2H, $J = 8.3$ Hz), 7.07 (d, 2H, $J = 8.4$ Hz), 4.22 (q, 2H, $J = 7.0$ Hz), 4.21 (q, 2H, $J = 7.0$ Hz), 3.65 (s, 2H), 2.91–2.96 (m, 1H), 2.53–2.77 (m, 4H), 2.28–2.37 (m, 1H), 1.97 (dd, 1H, $J = 13.0$ Hz, $J = 12.1$ Hz), 1.91 (ddd, 1H, $J = 12.8$ Hz, $J = 11.2$ Hz, $J = 6.5$ Hz), 1.64 (dt, 1H, $J = 14.3$ Hz, $J = 7.0$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz), 1.26 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 214.9, 206.5, 170.8, 170.5, 132.9, 131.7, 131.0, 121.0, 62.1, 62.0, 54.7, 49.1, 46.2, 44.8, 39.2, 36.2, 23.5, 13.9, 13.9 ppm; **HRMS** (ESI, $\text{C}_{21}\text{H}_{26}\text{BrO}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 453.0913; found: 453.0927.

diethyl 3-(2-methyl-3-oxopentyl)-4-oxocyclopentane-1,1-dicarboxylate (3.24d); 103 mg; 63% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): (1:1 mixture of diastereomers) 4.23 (q, 4H, $J = 7.1$ Hz), 2.94 (dd, 1H, $J = 19.0$ Hz, $J = 5.4$ Hz), 2.71–2.85 (m, 3H), 2.40–2.59 (m, 2H), 2.25–2.36 (m, 1.5H), 2.15 (ddd, 0.5H, $J = 14.0$ Hz, $J = 7.9$ Hz, $J = 6.1$ Hz), 1.97 (dt, 1H, $J = 12.5$ Hz, $J = 4.7$ Hz), 1.70 (m, 1H), 1.27 (t, 3H, $J = 7.1$ Hz), 1.26 (t, 3H, $J = 7.1$ Hz), 1.09 (dd, 3H, $J = 7.2$ Hz, $J = 9.6$ Hz), 1.05 (t, 3H, $J = 7.3$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): (1:1 mixture of diastereomers) δ 215.2, 214.7, 214.4, 214.2, 170.9, 170.8, 170.6, 170.6, 62.1, 62.1, 54.9, 45.6, 45.5, 44.8, 44.7, 43.7, 43.7, 36.8, 36.7, 34.4, 34.0, 32.9, 32.8, 17.2, 16.9, 13.9, 13.9, 7.7, 7.7 ppm; **HRMS** (ESI, $\text{C}_{17}\text{H}_{27}\text{O}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 327.1808; found: 327.1808.

Diethyl 3-oxo-4-(3-oxobutyl)cyclohexane-1,1-dicarboxylate (3.25a); 125 mg; 80% yield; yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 4.15–4.24 (m, 4H), 2.94 (dd, 1H, $J = 14.6$ Hz, $J = 2.2$ Hz), 2.50–2.56 (m, 3H), 2.43 (ddd, 1H, $J = 14.0$ Hz, $J = 6.1$ Hz, $J = 3.8$ Hz), 2.28 (dt, 1H, $J = 11.7$ Hz, $J = 5.7$ Hz), 2.16–2.20 (m, 1H), 2.13 (s, 3H), 2.04 (ddd, 1H, $J = 14.1$ Hz, $J = 10.1$ Hz, $J = 4.2$ Hz), 1.95 (dt, 1H, $J = 14.2$ Hz, $J = 7.6$ Hz), 1.35–1.64 (m, 2H), 1.25 (t, 3H, $J = 7.1$ Hz), 1.24 (t, 3H, $J = 7.1$ Hz), ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 208.6, 207.6, 170.2, 61.8, 57.5, 48.1, 45.2, 40.8, 29.8, 29.6, 28.2, 23.4, 13.9, 13.9 ppm; **HRMS** (ESI, $\text{C}_{16}\text{H}_{25}\text{O}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 313.1651; found: 313.1661.

diethyl 4-(4-chloro-3-oxobutyl)-3-oxocyclohexane-1,1-dicarboxylate (3.25b); 130 mg; 75% yield; light yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 4.15–4.26 (m, 4H), 4.11 (s, 2H), 2.94 (dd, 1H, $J = 14.6\text{ Hz}$, $J = 2.3\text{ Hz}$), 2.68 (m, 2H), 2.53 (dd, 1H, $J = 14.6\text{ Hz}$, $J = 1.0\text{ Hz}$), 2.40–2.46 (m, 1H), 2.31 (dt, 1H, $J = 11.6\text{ Hz}$, $J = 5.3\text{ Hz}$), 2.18 (ddd, 1H, $J = 14.1\text{ Hz}$, $J = 12.8\text{ Hz}$, $J = 4.0\text{ Hz}$), 1.94–2.09 (m, 2H), 1.47–1.69 (m, 2H), 1.25 (t, 3H, $J = 7.1\text{ Hz}$) 1.24 (t, 3H, $J = 7.1\text{ Hz}$) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 207.3, 202.1, 170.1, 170.0, 61.7, 57.3, 48.1, 47.8, 45.2, 36.9, 29.6, 28.2, 23.2, 13.8, 13.8 ppm; **HRMS** (ESI, $\text{C}_{16}\text{H}_{24}\text{ClO}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 347.1261; found: 347.1276.

diethyl 4-(4-(4-bromophenyl)-3-oxobutyl)-3-oxocyclohexane-1,1-dicarboxylate (3.25c); 170 mg; 73% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ 7.43 (d, 2H, $J = 8.3\text{ Hz}$), 7.06 (d, 2H, $J = 8.3\text{ Hz}$), 4.12–4.28 (m, 4H), 3.64 (s, 2H), 2.91 (dd, 1H, $J = 14.6\text{ Hz}$, $J = 1.8\text{ Hz}$), 2.48–2.57 (m, 3H), 2.40 (dd, 1H, $J = 14.2\text{ Hz}$, $J = 1.9\text{ Hz}$), 2.22 (dt, 1H, $J = 11.9\text{ Hz}$, $J = 5.9\text{ Hz}$), 2.10–2.17 (m, 1H), 1.91–1.99 (m, 2H), 1.57 (td, 1H, $J = 14.0\text{ Hz}$, $J = 7.2\text{ Hz}$), 1.43–1.47 (m, 1H), 1.21–1.27 (m, 6H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 207.3, 207.0, 170.0, 170.0, 133.0, 131.5, 131.0, 120.7, 61.6, 57.3, 48.9, 47.8, 45.1, 39.3, 29.4, 28.1, 23.3, 13.8, 13.7 ppm; **HRMS** (ESI, $\text{C}_{22}\text{H}_{28}\text{BrO}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 467.1070; found: 467.1069.

diethyl 4-(2-methyl-3-oxopentyl)-3-oxocyclohexane-1,1-dicarboxylate (3.25d); 104 mg; 61% yield; yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): (1:1 mixture of diastereomers) δ 4.15–4.24 (m, 4H), 2.93 (ddd, 1H, $J = 14.4$ Hz, $J = 7.0$ Hz, $J = 2.1$ Hz), 2.64–2.75 (m, 1H), 2.28–2.58 (m, 4H), 2.12–2.26 (m, 2H), 2.03 (tt, 1H, $J = 13.8$ Hz, $J = 4.5$ Hz), 1.77 (ddd, 0.5H, $J = 13.6$ Hz, $J = 7.9$ Hz, $J = 5.4$ Hz), 1.55 (ddd, 0.5H, $J = 11.7$ Hz, $J = 7.6$ Hz, $J = 4.0$ Hz), 1.38–1.50 (m, 2H), 1.23–1.27 (m, 6H), 1.07 (dd, 3H, $J = 7.1$ Hz, $J = 2.4$ Hz), 1.03 (dt, 3H, $J = 7.3$ Hz, $J = 4.3$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): (1:1 mixture of diastereomers) δ 215.0, 214.7, 207.8, 207.5, 170.1, 61.7, 61.7, 57.5, 57.5, 47.0, 46.8, 45.2, 45.1, 43.7, 43.4, 34.4, 33.7, 32.7, 32.5, 29.5, 29.5, 28.9, 28.7, 17.4, 16.9, 13.8, 7.6, 7.6 ppm; **HRMS** (ESI, $\text{C}_{18}\text{H}_{29}\text{O}_6$ ($\text{M}+\text{H}$) $^+$): calcd.: 314.1964; found: 314.1964.

3-(3-oxobutyl)chroman-4-one (3.28a); 77 mg; 71% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.86 (dd, 1H, $J = 7.9$ Hz, $J = 1.7$ Hz), 7.46 (ddd, 1H, $J = 8.7$ Hz, $J = 7.2$ Hz, $J = 1.8$ Hz), 6.99–7.03 (m, 1H), 6.95 (d, 1H, $J = 8.4$ Hz), 4.51 (dd, 1H, $J = 11.5$ Hz, $J = 4.4$ Hz), 4.27 (dd, 1H, $J = 11.5$ Hz, $J = 8.4$ Hz), 2.64–2.72 (m, 3H), 2.16 (s, 3H), 2.00–2.09 (m, 1H), 1.79–1.88 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 207.7, 194.2, 161.3, 135.8, 127.2, 121.3, 120.3, 117.6, 70.8, 44.8, 40.6, 29.9, 20.6 ppm; **HRMS** (ESI, $\text{C}_{13}\text{H}_{15}\text{O}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 219.1021; found: 219.1020.

3-(4-chloro-3-oxobutyl)chroman-4-one (3.28b); 77 mg; 61% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.86 (dd, 1H, $J = 7.9$ Hz, $J = 1.7$ Hz), 7.48 (ddd, 1H, $J = 8.8$ Hz, $J = 7.2$ Hz, $J = 1.8$ Hz), 7.00–7.04 (m, 1H), 6.96 (d, 1H, $J = 8.4$ Hz), 4.52 (dd, 1H, $J = 11.5$ Hz, $J = 4.4$ Hz), 4.28 (dd, 1H, $J = 11.5$ Hz, $J = 8.4$ Hz), 4.11 (s, 2H), 2.82 (t, 2H, $J = 7.2$ Hz), 2.71 (ddd, 1H, $J = 13.5$ Hz, $J = 8.6$ Hz, $J = 5.0$ Hz), 2.05–2.14 (m, 1H), 1.90 (dtd, 1H, $J = 12.9$ Hz, $J = 7.5$ Hz, $J = 5.4$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 201.9, 194.1, 161.4, 136.0, 127.3, 121.5, 120.3, 117.7, 70.8, 48.2, 44.6, 37.0, 20.6 ppm; HRMS (ESI, $\text{C}_{13}\text{H}_{14}\text{ClO}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 253.0631; found: 253.0630.

3-(4-(4-bromophenyl)-3-oxobutyl)chroman-4-one (3.28c); 140 mg; 75% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.85 (dd, 1H, $J = 7.9$ Hz, $J = 1.7$ Hz), 7.42–7.48 (m, 3H), 7.06 (d, 2H, $J = 8.4$ Hz), 6.98–7.02 (m, 1H), 6.93 (d, 1H, $J = 8.4$ Hz), 4.46 (dd, 1H, $J = 11.5$ Hz, $J = 4.4$ Hz), 4.21 (dd, 1H, $J = 11.5$ Hz, $J = 8.5$ Hz), 3.66 (s, 2H), 2.60–2.69 (m, 3H), 2.02 (qd, 1H, $J = 8.3$ Hz, $J = 6.9$ Hz), 1.81 (dtd, 1H, $J = 13.0$ Hz, $J = 7.5$ Hz, $J = 5.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 206.6, 194.2, 161.3, 135.8, 132.8, 131.7, 131.1, 127.2, 121.3, 121.0, 120.3, 117.6, 70.7, 49.1, 44.7, 39.3, 20.7 ppm; HRMS (ESI, $\text{C}_{19}\text{H}_{18}\text{BrO}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 373.0439; found: 373.0443.

3-(2-methyl-3-oxopentyl)chroman-4-one (3.28d); 80 mg; 65% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): (**top diastereomer**) 7.87 (dd, 1H, $J = 7.9$ Hz, $J = 1.7$ Hz), 7.45–7.49 (m, 1H), 6.99–7.03 (m, 1H), 6.95 (d, 1H, $J = 8.3$ Hz), 4.48 (dd, 1H, $J = 11.5$ Hz, $J = 4.3$ Hz), 4.25 (dd, 1H, $J = 11.5$ Hz, $J = 7.5$ Hz), 2.80–2.86 (m, 1H), 2.47–2.61 (m, 3H), 1.75–1.90 (m, 2H), 1.11 (d, 3H, $J = 7.1$ Hz), 1.07 (t, 3H, $J = 7.3$ Hz) ppm; (**bottom diastereomer**) 7.86 (dd, 1H, $J = 7.9$ Hz, $J = 1.6$ Hz), 7.45–7.49 (m, 1H), 7.00–7.04 (m, 1H), 6.95 (d, 1H, $J = 8.4$ Hz), 4.50 (dd, 1H, $J = 11.5$ Hz, $J = 4.5$ Hz), 4.22 (dd, 1H, $J = 11.5$ Hz, $J = 8.7$ Hz), 2.79 (dd, 1H, $J = 14.0$ Hz, $J = 7.0$ Hz), 2.64–2.76 (m, 1H), 2.41–2.59 (m, 2H), 2.24–2.31 (m, 1H), 1.41–1.48 (m, 1H), 1.17 (d, 3H, $J = 7.0$ Hz), 1.04 (t, 3H, $J = 7.3$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): (**top diastereomer**) δ 214.7, 194.5, 161.4, 135.9, 127.3, 121.4, 120.3, 117.7, 71.2, 44.0, 43.5, 34.9, 29.9, 17.9, 7.7 ppm; (**bottom diastereomer**) δ 214.1, 194.2, 161.3, 135.8, 127.3, 121.4, 120.5, 117.7, 70.9, 43.7, 43.5, 33.9, 29.4, 16.9, 7.8 ppm; HRMS (ESI, $\text{C}_{15}\text{H}_{19}\text{O}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 247.1334; found: 247.1345.

ethyl 3-oxo-5-(4-oxochroman-3-yl)pentanoate (3.28e); 90 mg; 62% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.86 (dd, 1H, $J = 7.9$ Hz, $J = 1.7$ Hz), 7.47 (ddd, 1H, $J = 8.7$ Hz, $J = 7.2$ Hz, $J = 1.7$ Hz), 6.99–7.03 (m, 1H), 6.95 (d, 1H, $J = 8.4$ Hz), 4.52 (dd, 1H, $J = 11.5$ Hz, $J = 4.5$ Hz), 4.26 (dd, 1H, $J = 11.5$ Hz, $J = 8.8$ Hz), 4.19 (q, 2H, $J = 7.1$ Hz), 3.46 (s, 2H), 2.79 (t, 2H, $J = 7.1$ Hz), 2.67–2.75 (m, 1H), 2.07 (dt, 1H, $J = 15.0$ Hz, $J = 6.9$

Hz), 1.86 (dtd, 1H, $J = 13.0$ Hz, $J = 7.4$ Hz, $J = 5.6$ Hz), 1.27 (t, 3H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl₃, 100 MHz): δ 201.9, 194.1, 167.0, 161.3, 135.9, 127.2, 121.3, 120.3, 117.7, 70.7, 61.3, 49.2, 44.6, 40.2, 20.4, 14.0 ppm; HRMS (ESI, C₁₆H₁₉O₅ (M+H)⁺): calcd.: 291.1232; found: 291.1224.

ethyl 3-oxo-2-((4-oxochroman-3-yl)methyl)butanoate (3.28f); 71 mg; 49% yield; colorless oil; ^1H NMR (CDCl₃, 400 MHz): (1:1 mixture of diastereomers) 7.86 (td, 1H, $J = 7.9$ Hz, $J = 1.8$ Hz), 7.46–7.50 (m, 1H), 7.02 (t, 1H, $J = 7.5$ Hz), 6.96 (d, 1H, $J = 8.4$ Hz), 4.52 (ddd, 1H, $J = 11.4$ Hz, $J = 4.6$ Hz, $J = 1.0$ Hz), 4.16–4.29 (m, 3H), 3.88 (ddd, 1H, $J = 5.3$ Hz, $J = 9.1$ Hz, $J = 24.0$ Hz), 2.62–2.78 (m, 2H), 2.21–2.35 (m, 4H), 2.14 (ddd, 0.5H, $J = 11.3$ Hz, $J = 8.3$ Hz, $J = 3.8$ Hz), 1.99 (ddd, 0.5H, $J = 14.1$ Hz, $J = 9.4$ Hz, $J = 4.5$ Hz), 1.24–1.31 (m, 3H) ppm; ^{13}C NMR (CDCl₃, 100 MHz): (1:1 mixture of diastereomers) δ 202.8, 202.3, 194.1, 194.0, 169.3, 169.0, 161.5, 161.4, 136.1, 136.0, 127.3, 127.3, 121.5, 120.4, 120.3, 117.8, 117.8, 70.9, 70.8, 61.7, 57.5, 56.5, 43.5, 43.3, 29.6, 25.0, 14.1, 14.0 ppm; HRMS (ESI, C₁₆H₁₉O₅ (M+H)⁺): calcd.: 291.1232; found: 292.1226.

3-(3-oxobutyl)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (3.29a); 147 mg; 79% yield; yellow oil; ^1H NMR (CDCl₃, 400 MHz): 7.94 (dd, 1H, $J = 7.9$ Hz, $J = 1.6$ Hz), 7.82 (d, 1H, $J = 8.1$ Hz), 7.63 (d, 2H, $J = 8.3$ Hz), 7.50–7.54 (m, 1H), 7.26 (d, 2H, $J = 8.3$ Hz),

7.18–7.22 (m, 1H), 4.39 (dd, 1H, $J = 13.9$ Hz, $J = 4.7$ Hz), 3.79 (dd, 1H, $J = 13.9$ Hz, $J = 11.4$ Hz), 2.59 (dt, 2H, $J = 7.4$ Hz, $J = 2.0$ Hz), 2.34–2.44 (m, 4H), 2.16 (s, 3H), 1.97–2.05 (m, 1H), 1.69 (dt, 1H, $J = 14.2$ Hz, $J = 7.2$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 207.4, 194.9, 144.5, 142.2, 136.6, 134.6, 130.0, 128.1, 126.9, 124.8, 124.4, 122.5, 50.6, 44.3, 40.5, 29.9, 21.5 ppm; HRMS (ESI, $\text{C}_{20}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 372.1270; found: 372.1271.

3-(4-chloro-3-oxobutyl)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (3.29b); 146 mg; 72% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.93 (dd, 1H, $J = 1.6$ Hz, $J = 7.9$ Hz), 7.82 (d, 1H, $J = 8.1$ Hz), 7.64 (d, 2H, $J = 8.2$ Hz), 7.50–7.55 (m, 1H), 7.27 (d, 2H, $J = 8.2$ Hz), 7.19–7.23 (m, 1H), 4.39 (dd, 1H, $J = 13.9$ Hz, $J = 4.7$ Hz), 4.09 (s, 2H), 3.80 (dd, 1H, $J = 13.9$ Hz, $J = 11.3$ Hz), 2.77 (dt, 2H, $J = 7.3$ Hz, $J = 3.5$ Hz), 2.36–2.44 (m, 4H), 1.99–2.08 (m, 1H), 1.74 (dt, 1H, $J = 13.7$ Hz, $J = 7.3$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 201.6, 194.8, 144.6, 142.2, 136.6, 134.7, 130.1, 128.1, 126.9, 124.9, 124.3, 122.5, 50.6, 48.1, 44.0, 36.8, 21.5, 21.5 ppm; HRMS (ESI, $\text{C}_{20}\text{H}_{21}\text{NO}_4\text{SCl}$ ($\text{M}+\text{H}$) $^+$): calcd.: 406.0880; found: 406.0880.

3-(4-(4-bromophenyl)-3-oxobutyl)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (3.29c);

213 mg; 81% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.92 (dd, 1H, $J = 7.9$ Hz, $J = 1.6$ Hz), 7.79 (d, 1H, $J = 8.3$ Hz), 7.61 (d, 2H, $J = 8.3$ Hz), 7.45–7.57 (m, 1H), 7.45 (d, 2H, $J = 8.4$ Hz), 7.17–7.22 (m, 3H), 7.08 (d, 2H, $J = 8.4$ Hz), 4.34 (dd, 1H, $J = 13.8$ Hz, $J = 4.7$ Hz), 3.75 (dd, 1H, $J = 13.8$ Hz, $J = 11.2$ Hz), 3.66 (s, 2H), 2.63 (t, 2H, $J = 7.2$ Hz), 2.35–2.43 (m, 4H), 1.99 (dt, 1H, $J = 14.1$ Hz, $J = 7.1$ Hz), 1.68 (dt, 1H, $J = 14.0$ Hz, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 206.3, 194.8, 144.5, 142.2, 136.6, 134.6, 132.9, 131.8, 131.1, 130.0, 128.1, 126.9, 124.8, 124.3, 122.3, 121.1, 50.6, 49.1, 44.2, 39.1, 21.5 (2 peaks overlap) ppm; **HRMS** (ESI, $\text{C}_{26}\text{H}_{25}\text{NO}_4\text{SBr}$ ($\text{M}+\text{H}$) $^+$): calcd.: 526.0688; found: 526.0695.

3-(2-methyl-3-oxopentyl)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (3.29d);

134 mg; 67% yield; yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): (1:1 mixture of diastereomers) 7.93 (dd, 1H, $J = 7.8$ Hz, $J = 1.5$ Hz), 7.83 (t, 1H, $J = 8.3$ Hz), 7.61 (dd, 2H, $J = 13.5$ Hz, $J = 8.3$ Hz), 7.50–7.54 (m, 1H), 7.18–7.28 (m, 3H), 4.41 (dd, 0.5H, $J = 13.9$ Hz, $J = 4.8$ Hz), 4.33 (dd, 0.5H, $J = 13.9$ Hz, $J = 4.7$ Hz), 3.81 (dd, 0.5H, $J = 13.9$ Hz, $J = 10.7$ Hz), 3.71 (dd, 0.5H, $J = 13.9$ Hz, $J = 11.7$ Hz), 2.76–2.84 (m, 1H), 2.43–2.59 (m, 2H), 2.39 (s, 3H), 2.18–2.38 (m, 2H), 1.67–1.76 (m, 1H), 1.05–1.09 (m, 6H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): (1:1 mixture of diastereomers) δ 214.1, 213.8, 195.3, 194.9, 144.5, 144.4, 142.2, 142.1, 136.7, 136.6, 134.5, 134.5, 130.0, 128.1, 128.1, 126.9, 124.9, 124.8, 124.5, 124.3, 122.7, 122.5, 50.9, 50.8, 43.4, 43.3, 43.2, 42.9, 34.5, 33.8, 30.6, 30.4, 21.5, 17.3, 17.1, 7.7, 7.7 ppm; **HRMS** (ESI, $\text{C}_{22}\text{H}_{26}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 400.1583; found: 400.1578.

ethyl 3-oxo-5-(4-oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)pentanoate (3.29e); 135 mg; 61% yield; yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.93 (dd, 1H, $J = 7.9$ Hz, $J = 1.6$ Hz), 7.82 (d, 1H, $J = 8.4$ Hz), 7.63 (d, 2H, $J = 8.4$ Hz), 7.50–7.54 (m, 1H), 7.26 (d, 2H, $J = 8.4$ Hz), 7.18–7.24 (m, 1H), 4.41 (dd, 1H, $J = 13.9$ Hz, $J = 4.8$ Hz), 4.21 (q, 2H, $J = 7.2$ Hz), 3.78 (dd, 1H, $J = 13.9$ Hz, $J = 11.5$ Hz), 3.45 (d, 2H, $J = 1.1$ Hz), 2.73 (t, 2H, $J = 7.1$ Hz), 2.38–2.45 (m, 4H), 1.98–2.07 (m, 1H), 1.71 (dt, 1H, $J = 7.2$ Hz, $J = 13.9$ Hz), 1.28 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 201.6, 194.8, 167.0, 144.5, 142.2, 136.6, 134.6, 130.1, 128.1, 126.9, 124.8, 124.4, 122.5, 61.4, 50.6, 49.2, 44.1, 40.0, 21.5, 21.3, 14.1 ppm; **HRMS** (ESI, $\text{C}_{23}\text{H}_{26}\text{NO}_6\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 441.1481; found: 441.1479.

ethyl 3-oxo-2-((4-oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)methyl)butanoate (3.29f); 89 mg; 40% yield; colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): (6:4 mixture of diastereomers) 7.82–7.97 (m, 2H), 7.51–7.63 (m, 3H), 7.19–7.27 (m, 3H), 4.47 (dd, 0.4H, $J = 13.9$ Hz, $J = 4.9$ Hz), 4.41 (dd, 0.6H, $J = 13.8$ Hz, $J = 4.7$ Hz), 4.12–4.30 (m, 2H), 3.69–3.88 (m, 2H), 2.34–2.45 (m, 4H), 2.28 (s, 1.5H), 2.27 (s, 1.5H), 1.82–2.22 (m, 2H), 1.28–1.32 (m, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): (6:4 mixture of diastereomers) δ 202.3, 202.1, 194.9, 169.1, 168.9, 144.5, 142.2, 136.6, 136.5, 134.7, 130.1, 130.0, 128.1, 127.0, 126.9, 124.9, 124.3, 122.8, 122.7, 61.6, 57.4, 56.6, 50.8, 50.7, 42.8, 42.6, 29.7,

29.0, 25.9, 25.8, 21.5, 14.0, 14.0 ppm; **HRMS** (ESI, $C_{23}H_{26}NO_6S$ ($M+H$)⁺): calcd.: 444.1481; found: 444.1482.

diethyl (2-oxo-4-(4-oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)butyl)phosphonate (3.29g); 210 mg; 83% yield; yellow oil; **¹H NMR** ($CDCl_3$, 400 MHz): 7.93 (dd, 1H, $J = 7.8$ Hz, $J = 1.6$ Hz), 7.81 (d, 1H, $J = 8.4$ Hz), 7.64 (d, 2H, $J = 8.3$ Hz), 7.49–7.54 (m, 1H), 7.27 (d, 2H, $J = 8.3$ Hz), 7.19 (t, 1H, $J = 7.6$ Hz), 4.41 (dd, 1H, $J = 13.8$ Hz, $J = 4.7$ Hz), 4.12–4.20 (m, 4H), 3.78 (dd, 1H, $J = 13.8$ Hz, $J = 11.4$ Hz), 3.03–3.17 (m, 2H), 2.80 (dt, 2H, $J = 7.3$ Hz, $J = 2.0$ Hz), 2.43–2.47 (m, 1H), 2.39 (s, 3H), 2.00–2.08 (m, 1H), 1.71 (dt, 1H, $J = 14.2$ Hz, $J = 7.0$ Hz), 1.34 (dt, 6H, $J = 7.1$ Hz, $J = 1.4$ Hz) ppm; **¹³C NMR** ($CDCl_3$, 100 MHz): δ 200.8 (d, $J_{cp} = 6.4$ Hz), 194.6, 144.4, 142.1, 136.5, 134.5, 130.0, 128.0, 126.8, 124.7, 124.3, 122.3, 62.5 (d, $J_{cp} = 6.5$ Hz), 50.4, 44.1, 42.3 (d, $J_{cp} = 127.2$ Hz), 40.8, 21.4, 21.2, 16.2 (d, $J_{cp} = 6.2$ Hz) ppm; **³¹P NMR** (162 MHz, $CDCl_3$) δ 19.7 ppm; **HRMS** (ESI, $C_{24}H_{31}NO_7S^{31}P$ ($M+H$)⁺): calcd.: 508.1559; found: 508.1556.

2-oxo-4-(4-oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)butyl pivalate (3.29h); 160 mg; 68% yield; yellow oil; **¹H NMR** ($CDCl_3$, 400 MHz): 7.93 (dd, 1H, $J = 7.8$ Hz, $J = 1.5$ Hz), 7.82 (d, 1H, $J = 8.4$ Hz), 7.63 (d, 2H, $J = 8.3$ Hz), 7.50–7.54 (m, 1H), 7.26 (d, 2H, $J = 8.3$ Hz), 7.20 (t, 1H, $J = 7.6$ Hz), 4.64 (d, 2H, $J = 2.1$ Hz), 4.40 (dd, 1H, $J = 13.9$ Hz, J

=4.7 Hz), 3.78 (dd, 1H, J = 13.9 Hz, J = 11.4 Hz), 2.60 (t, 2H, J = 7.2 Hz), 2.37–2.46 (m, 4H), 1.99–2.08 (m, 1H), 1.68–1.77 (m, 1H), 1.28 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 203.1, 194.8, 177.8, 144.5, 142.2, 136.6, 134.6, 130.0, 128.1, 126.9, 124.8, 124.3, 122.5, 67.8, 50.6, 44.1, 38.7, 35.8, 27.1, 21.5, 21.0 ppm; HRMS (ESI, $\text{C}_{25}\text{H}_{30}\text{NO}_6\text{S}$ ($\text{M}+\text{H}^+$): calcd.: 472.1794; found: 472.1809.

2-oxo-4-(4-oxotetrahydro-2H-pyran-3-yl)butyl pivalate (3.30h); 60 mg; 65% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 4.61 (s, 2H), 4.11–4.21 (m, 2H), 3.73 (dt, 1H, J = 11.0 Hz, J = 3.5 Hz), 3.39 (dd, 1H, J = 11.1 Hz, J = 9.9 Hz), 2.38–2.64 (m, 5H), 1.91–2.00 (m, 1H), 1.50–1.58 (m, 1H), 1.26 (s, 9H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.2, 203.6, 177.9, 72.7, 68.6, 67.8, 50.4, 42.5, 38.7, 36.1, 27.1, 19.2 ppm; HRMS (ESI, $\text{C}_{13}\text{H}_{21}\text{O}_5$ ($\text{M}+\text{H}^+$): calcd.: 257.1389; found: 257.1390.

3-(3-oxo-3-phenylpropyl)dihydro-2H-pyran-4(3H)-one (3.30i); 25 mg; 54% yield; colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.95–7.97 (m, 2H), 7.54–7.58 (m, 1H), 7.46 (t, 2H, J = 7.6 Hz), 4.18–4.24 (m, 2H), 3.75 (dt, 1H, J = 11.1 Hz, J = 3.4 Hz), 3.46 (dd, 1H, J = 11.1 Hz, J = 9.9 Hz), 3.17 (ddd, 1H, J = 17.4 Hz, J = 8.1 Hz, J = 5.9 Hz), 3.02 (ddd, 1H, J = 17.4 Hz, J = 7.9 Hz, J = 6.9 Hz), 2.58–2.71 (m, 2H), 2.43 (td, 1H, J = 14.1 Hz, J = 3.3 Hz), 2.06–2.17 (m, 1H), 1.64–1.72 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.5,

199.5, 136.7, 133.1, 128.6, 128.0, 72.9, 68.7, 50.9, 42.6, 36.0, 20.3 ppm; **HRMS** (ESI, $C_{14}H_{17}O_3$ ($M+H$)⁺): calcd.: 233.1178; found: 233.1175.

General procedure 5.3.3 for the synthesis of pyridines from 1,5-diketones. A round bottom flask containing a magnetic stirbar was charged with 1,5-diketone (0.2 mmol, 1.0 equiv), ammonium acetate (2.0 mmol, 10 equiv) in 1.0 mL acetic acid and heated to 120 °C for 3h. The reaction mixture was cooled to rt before evaporation of the solvents under reduced pressure. CH_2Cl_2 (10 mL) was added and the reaction mixture was washed with saturated sodium bicarbonate solution (5 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was then purified *via* flash column chromatography to afford the desired pyridines.

diethyl 2-methyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (3.31); 45 mg; 81% yield; black oil; ¹H NMR (CDCl₃, 400 MHz): 7.39 (d, 1H, *J* = 7.8 Hz), 6.94 (d, 1H, *J* = 7.8 Hz), 4.22 (q, 4H, *J* = 7.1 Hz), 3.66 (s, 2H), 3.54 (s, 2H), 2.51 (s, 3H), 1.26 (t, 6H, *J* = 7.1 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 171.3, 160.3, 157.2, 132.4, 130.2, 121.4, 61.9, 58.2, 41.7, 38.1, 23.9, 14.0 ppm; **HRMS** (ESI, $C_{15}H_{20}NO_4$ ($M+H$)⁺): calcd.: 278.1392; found: 278.1385.

diethyl 2-methyl-5,6-dihydroquinoline-7,7(8H)-dicarboxylate (3.32); 44 mg; 76% yield; black oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.26 (d, 1H, $J = 7.7$ Hz), 6.92 (d, 1H, $J = 7.7$ Hz), 4.19 (q, 4H, $J = 7.1$ Hz), 3.38 (s, 2H), 2.76 (t, 2H, $J = 6.7$ Hz), 2.50 (s, 3H), 2.32 (t, 2H, $J = 6.7$ Hz), 1.22 (t, 6H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 171.0, 155.8, 153.0, 137.0, 126.7, 121.2, 61.5, 53.8, 37.1, 27.6, 24.7, 23.7, 14.0 ppm; **HRMS** (ESI, $\text{C}_{16}\text{H}_{22}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$): calcd.: 292.1549; found: 292.1554.

2-(4-bromobenzyl)-5H-chromeno[4,3-b]pyridine (3.33); 56 mg; 80% yield; black oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 8.25 (dd, 1H, $J = 7.7$ Hz, $J = 1.6$ Hz), 7.42 (d, 2H, $J = 8.3$ Hz), 7.28–7.32 (m, 2H), 7.20 (d, 2H, $J = 8.3$ Hz), 7.10 (dt, 1H, $J = 7.6$ Hz, $J = 1.0$ Hz), 6.94–6.96 (m, 2H), 5.17 (s, 2H), 4.13 (s, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 160.0, 156.4, 148.1, 138.6, 132.6, 131.6, 131.2, 130.9, 124.7, 123.6, 123.2, 122.3, 121.6, 120.3, 116.9, 67.8, 44.0 ppm; **HRMS** (ESI, $\text{C}_{19}\text{H}_{15}\text{NOBr}$ ($\text{M}+\text{H}$) $^+$): calcd.: 352.0337; found: 352.0338.

2-(4-bromobenzyl)-6-tosyl-5,6-dihydrobenzo[h][1,6]naphthyridine (3.34); 83 mg; 82% yield; black oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 8.18 (dd, 1H, $J = 7.7$ Hz, $J = 1.5$ Hz), 7.79 (d, 1H, $J = 8.0$ Hz), 7.38–7.50 (m, 4H), 7.21 (d, 1H, $J = 7.7$ Hz), 7.10 (d, 2H, $J = 8.3$ Hz), 7.04 (d, 2H, $J = 8.3$ Hz), 6.78 (dd, 3H, $J = 17.2$ Hz, $J = 8.0$ Hz), 4.88 (s, 2H), 3.97 (s, 2H), 2.11 (s, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 159.4, 148.6, 143.2, 138.4, 137.2, 135.0, 133.7, 131.6, 130.7, 130.0 (2 carbon peak overlap), 128.7, 127.5, 127.1, 125.2, 123.9, 121.5, 120.3, 120.0, 48.8, 43.7, 21.3 ppm; **HRMS** (ESI, $\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_2\text{SBr}$ ($\text{M}+\text{H}$) $^+$): calcd.: 505.0585; found: 505.0578.

2-(4-bromobenzyl)-5H-chromeno[4,3-b]pyridine (3.35); 72 mg; 85% yield; black oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 8.19 (dd, 1H, $J = 7.8$ Hz, $J = 1.3$ Hz), 7.79 (t, 2H, $J = 3.8$ Hz), 7.51 (dt, 1H, $J = 7.8$ Hz, $J = 1.5$ Hz), 7.41 (t, 1H, $J = 7.5$ Hz), 7.03 (d, 2H, $J = 8.1$ Hz), 6.79 (d, 2H, $J = 8.1$ Hz), 4.91 (s, 2H), 4.40 (q, 2H, $J = 7.1$ Hz), 2.72 (s, 3H), 2.16 (s, 3H), 1.45 (t, 3H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 166.1, 159.0, 150.7, 143.7, 137.9, 135.4, 134.6, 130.8, 129.7, 128.8, 127.6, 127.1, 125.7, 123.7, 123.1, 61.3, 48.5, 24.6, 21.2, 14.3 ppm; **HRMS** (ESI, $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 423.1379; found: 423.1380.

diethyl ((6-tosyl-5,6-dihydrobenzo[h][1,6]naphthyridin-2-yl)methyl)phosphonate (3.36); 80 mg; 82% yield; black oil; ^1H NMR (CDCl_3 , 400 MHz): 8.15 (dd, 1H, $J = 7.8$ Hz, $J = 1.6$ Hz), 7.79 (dd, 1H, $J = 8.0$ Hz, $J = 0.8$ Hz), 7.46 (dt, 1H, $J = 7.8$ Hz, $J = 1.6$ Hz), 7.37 (dt, 1H, $J = 7.6$ Hz, $J = 1.1$ Hz), 7.30 (d, 1H, $J = 7.8$ Hz), 7.11 (dd, 1H, $J = 7.8$ Hz, $J = 2.3$ Hz), 7.06 (d, 2H, $J = 8.2$ Hz), 6.81 (d, 2H, $J = 8.2$ Hz), 4.92 (d, 2H, $J = 1.6$ Hz), 4.04–4.11 (m, 4H), 3.32 (d, 2H, $J = 21.9$ Hz), 2.18 (s, 3H), 1.26 (t, 6H, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 151.8 (d, $J_{\text{cp}} = 8.3$ Hz), 148.6 (d, $J_{\text{cp}} = 2.3$ Hz), 143.5, 137.2, 134.9, 133.6 (d, $J_{\text{cp}} = 2.5$ Hz), 130.0 (2 carbon peak overlap), 128.7, 127.2, 127.0, 125.0, 124.3 (d, $J_{\text{cp}} = 3.3$ Hz), 122.8 (d, $J_{\text{cp}} = 4.9$ Hz), 62.2 (d, $J_{\text{cp}} = 6.4$ Hz), 48.7, 36.0 (d, $J_{\text{cp}} = 134.9$ Hz), 21.2, 16.3 (d, $J_{\text{cp}} = 6.2$ Hz) ppm; ^{31}P NMR (162 MHz, CDCl_3) δ 24.7 ppm; **HRMS** (ESI, $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_5\text{S}^{31}\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 487.1457; found: 487.1458.

5.4 Bis-Sulfonyl Benzyl Oxime Ethers as a Radical/Ionic Bi-Functional Carboxylate Equivalent: An *O*-Benzyl Oxime Ether Derivatization of Lactones and Thiolactones

General procedure 5.4.1 for the synthesis of alkyl bis-sulfanyl *O*-benzyl oxime ethers.

A round bottom flask containing a magnetic stirbar was added *O*-benzylhydroxylamine hydrochloride (16 g, 10 mmol, 1.0 equiv) and sealed with a septum. The flask was then purged of air and kept under a nitrogen atmosphere. Dichloromethane (20 mL) was added

via syringe into the flask, followed by carbon disulfide (3 mL, 50 mmol, 5 equiv) and the reaction mixture was cooled to 0 °C in an ice bath. Triethylamine (7 mL, 50 mmol, 5 equiv) was added *via* syringe and the reaction mixture was left to stir for another 20 min at 0 °C. Finally, alkyl iodide (50 mmol, 5 equiv) was added *via* syringe into the stirring mixture slowly and the reaction was stirred overnight (16h) while warming to rt. The crude mixture was filtered and evaporation of the filtrate under reduced pressure gave a crude yellow or orange oil which was purified by flash chromatography (silica gel, EtOAc-Hexane) to give the titled alkyl bis-sulfanyl *O*-benzyl oxime ethers.

diethyl benzyloxycarbonimidodithioate (4.55b); 2.37 g, 93% yield, yellow oil; ^1H **NMR** (CDCl_3 , 400 MHz): 7.25–7.38 (m, 5H), 5.14 (s, 2H), 2.92–2.98 (m, 4H), 1.30 (t, 3H, $J = 7.4$ Hz), 1.25 (t, 3H, $J = 7.4$ Hz) ppm; ^{13}C **NMR** (CDCl_3 , 100 MHz): δ 151.2, 137.8, 128.2, 128.0, 127.6, 76.4, 26.9, 25.2, 15.0, 13.8 ppm; **HRMS** (ESI, $\text{C}_{12}\text{H}_{18}\text{NOS}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 256.0830; found: 256.0825.

diisopropyl benzyloxycarbonimidodithioate (4.55c)^a; 0.76 g, 27% yield, yellow oil; ^1H **NMR** (CDCl_3 , 400 MHz): 7.26–7.37 (m, 5H), 5.15 (s, 2H), 3.60–3.73 (m, 2H), 1.33 (d, 6H, $J = 6.8$ Hz), 1.28 (d, 6H, $J = 6.8$ Hz) ppm; ^{13}C **NMR** (CDCl_3 , 100 MHz): δ 150.5, 138.0, 128.2, 128.1, 127.7, 76.5, 38.1, 36.4, 24.0, 22.7 ppm; **HRMS** (ESI, $\text{C}_{14}\text{H}_{21}\text{NOS}_2$

(M+H)⁺: calcd.: 284.1143; found: 284.1143. ^a2-iodopropane (17 g, 100 mmol, 10 equiv) was used.

dibenzyl benzyloxycarbonimidodithioate (4.55d); 3.61 g, 95% yield, yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.22–7.40 (m, 15H), 5.16 (s, 2H), 4.14 (s, 2H), 4.14 (s, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 150.6, 137.7, 136.5, 136.1, 129.2, 129.0, 128.6, 128.5, 128.3, 128.1, 127.8, 127.5, 127.4, 76.6, 37.2, 35.5 ppm; HRMS (ESI, C₂₂H₂₁NOS₂ (M+H)⁺: calcd.: 380.1143; found: 380.1146.

General procedure 5.4.2 for the synthesis of alkyl bis-sulfonyl *O*-benzyl oxime ethers.

A round bottom flask containing a magnetic stirbar equipped with a reflux condenser was added alkyl bis-sulfanyl *O*-benzyl oxime ether (7 mmol, 1.0 equiv) and acetic acid (15 mL) and heated to reflux. 30% hydrogen peroxide (10 mL) was then slowly added and the reaction was stirred at reflux for 4h. A second portion of hydrogen peroxide (10 mL) was then added and the reaction was stirred at reflux for another 4h. After the reaction was cooled to rt, CH₂Cl₂ (50 mL) was added and the resulting mixture was washed once with saturated aqueous Na₂S₂O₃ (20 mL) and then thrice with saturated aqueous sodium bicarbonate (20 mL). The organic layer was separated and evaporated under reduced pressure to give a crude yellow oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give the titled alkyl bis-sulfonyl *O*-benzyl oxime ethers.

bis(ethylsulfonyl)methanone *O*-benzyl oxime (4.39b); 1.77 g, 79% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.36–7.40 (m, 5H), 5.50 (s, 2H), 3.46 (q, 2H, $J = 7.5$ Hz), 3.32 (q, 2H, $J = 7.5$ Hz), 1.37 (t, 3H, $J = 7.5$ Hz), 1.32 (t, 3H, $J = 7.5$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 150.3, 134.1, 129.4, 128.9, 128.9, 81.8, 51.4, 50.0, 6.9, 6.2 ppm; **HRMS** (ESI, $\text{C}_{12}\text{H}_{17}\text{NO}_5\text{S}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 320.0626; found: 320.0618.

bis(isopropylsulfonyl)methanone *O*-benzyl oxime (4.39c); 0.56 g, 81% yield (based on 2 mmol of diisopropyl benzyloxycarbonimidodithioate (4.55c)), yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.34–7.42 (m, 5H), 5.51 (s, 2H), 3.81–3.87 (m, 1H), 3.53–3.60 (m, 1H), 1.37 (t, 6H, $J = 6.9$ Hz), 1.32 (t, 6H, $J = 6.9$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 149.8, 134.2, 129.2, 128.8, 128.8, 81.6, 57.1, 55.7, 14.7, 14.2 ppm; **HRMS** (ESI, $\text{C}_{14}\text{H}_{21}\text{NO}_5\text{S}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 348.0939; found: 348.0945.

bis(benzylsulfonyl)methanone *O*-benzyl oxime (4.39d); 2.64 g, 85% yield, white solid; **m.p.** 153–155 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz): 7.10–7.30 (m, 15H), 5.19 (s, 2H), 4.42 (s, 2H), 4.33 (s, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 149.3, 134.0, 131.3, 129.7, 129.3, 129.2, 129.0, 128.9, 128.8, 125.6, 124.7, 81.9, 62.6, 61.1 ppm; **HRMS** (ESI, $\text{C}_{22}\text{H}_{21}\text{NO}_5\text{S}_2$ ($\text{M}+\text{H}$) $^+$): calcd.: 444.0939; found: 444.0919

General procedure 5.4.3 for nucleophilic addition of unsaturated alcohols to bis-sulfonyl *O*-benzyl oxime ethers. An oven-dried round bottom flask containing a magnetic stirbar was charged with sodium hydride (300 mg, 12.5 mmol, 1.5 equiv, 60% by weight in mineral oil) and anhydrous THF (5 mL) under a nitrogen atmosphere. To the stirring suspension mixture was added unsaturated alcohol (5 mmol, 1 equiv) dropwise *via* syringe and the resulting mixture was stirred over 1h at rt. A second oven-dried round bottom flask was then charged with the appropriate alkyl bis-sulfonyl *O*-benzyl oxime ether (6 mmol, 1.2 equiv) and anhydrous THF (10 mL) under a nitrogen atmosphere and cooled to 0 °C in an ice bath. To the stirring mixture in the second round bottom flask at 0 °C was cannulated the mixture from the first flask dropwise. The reaction mixture was then stirred for a further 3h at 0 °C. Saturated ammonium chloride solution (20 mL) was then added to quench the reaction. The resulting mixture was then extracted with EtOAc (30 mL x 3) and the combined organic extract was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure to give a crude oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give the titled alkenyl *O*-tethered sulfonyl *O*-benzyl oxime ethers.

but-3-en-1-yl *N*-benzyloxy(ethylsulfonyl)methanimidate (4.56b); 1.12 g, 15% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.34–7.38 (m, 5H), 5.78 (tdd, 1H, $J = 17.0$ Hz, $J = 10.2$ Hz, $J = 6.7$ Hz), 5.08–5.15 (m, 4H), 4.53 (t, 2H, $J = 6.8$ Hz), 3.19 (q, 2H, $J = 7.4$ Hz), 2.49 (tq, 2H, $J = 6.8$ Hz, $J = 1.3$ Hz), 1.30 (t, 3H, $J = 7.4$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 150.8, 136.0, 132.8, 128.7, 128.6, 128.5, 118.0, 78.2, 74.2, 47.5, 34.1, 6.8 ppm; **HRMS** (ESI, $\text{C}_{14}\text{H}_{20}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 298.1113; found: 298.1106.

but-3-en-1-yl N-benzyloxy(isopropylsulfonyl)methanimidate (4.56c); 224 mg, 72% yield (based on 1 mmol of but-3-en-1-ol), colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.32–7.39 (m, 5H), 5.77 (tdd, 1H, $J = 17.0$ Hz, $J = 10.3$ Hz, $J = 6.7$ Hz), 5.07–5.16 (m, 4H), 4.51 (t, 2H, $J = 6.8$ Hz), 3.41 (td, 1H, $J = 13.8$ Hz, $J = 6.9$ Hz), 2.45–2.51 (m, 2H), 1.32 (d, 6H, $J = 6.9$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 150.5, 136.1, 132.9, 128.6, 128.5, 118.0, 78.3, 74.3, 53.2, 34.1, 14.8 ppm; **HRMS** (ESI, $\text{C}_{15}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 312.1270; found: 312.1268.

but-3-en-1-yl N-benzyloxy(benzylsulfonyl)methanimidate (4.56d); 1.40 g, 78% yield, light yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.23–7.39 (m, 10H), 5.73 (tdd, 1H, $J = 17.1$ Hz, $J = 10.3$ Hz, $J = 6.7$ Hz), 5.06–5.11 (m, 4H), 5.06–5.11 (m, 4H), 4.40 (s, 2H), 4.38 (t, 2H, $J = 6.9$ Hz), 2.41 (tq, 2H, $J = 6.8$ Hz, $J = 1.3$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 151.0, 136.1, 132.8, 131.2, 129.1, 129.0, 128.7, 128.6, 128.5, 126.3, 117.9, 78.2, 74.1, 59.2, 34.0 ppm; **HRMS** (ESI, $\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 360.1270; found: 360.1269.

2-allylphenyl N-benzyloxy(benzylsulfonyl)methanimidate (4.57d); 1.69 g, 80% yield, colorless crystal; **m.p.** 60–61 $^{\circ}\text{C}$; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.32–7.34 (m, 3H), 7.23–7.29 (m, 5H), 7.16–7.18 (m, 1H), 7.06–7.11 (m, 2H), 6.99–7.01 (m, 2H), 6.85–6.87 (m,

1H), 5.93 (tdd, 1H, $J = 17.1$ Hz, $J = 10.9$ Hz, $J = 6.5$ Hz), 5.02–5.07 (m, 2H), 4.93 (s, 2H), 4.39 (d, 1H, $J = 12.6$ Hz), 4.29 (d, 1H, $J = 12.6$ Hz), 3.43 (d, 2H, $J = 6.4$ Hz) ppm; ^{13}C NMR (CDCl₃, 100 MHz): δ 152.6, 148.8, 135.8, 131.2, 130.4, 129.2, 129.1, 128.9, 128.5, 128.4, 128.4, 127.3, 126.1, 124.7, 116.2, 115.5, 78.4, 59.8, 33.9 ppm; HRMS (ESI, C₂₄H₂₄NO₄S (M+H)⁺): calcd.: 422.1426; found: 422.1419.

but-3-yn-1-yl N-benzyloxy(benzylsulfonyl)methanimidate (4.58d); 1.20 g, 67% yield, colorless oil; ^1H NMR (CDCl₃, 400 MHz): 7.17–7.34 (m, 10H), 5.03 (s, 2H), 4.35 (s, 2H), 4.34 (t, 2H, $J = 7.0$ Hz), 2.46 (dt, 2H, $J = 7.0$ Hz, $J = 2.7$ Hz), 1.93 (t, 1H, $J = 2.7$ Hz) ppm; ^{13}C NMR (CDCl₃, 100 MHz): δ 150.4, 135.9, 131.2, 129.1, 128.8, 128.6, 128.6, 126.2, 78.9, 78.4, 72.1, 70.6, 59.3, 20.0 ppm; HRMS (ESI, C₁₉H₂₀NO₄S (M+H)⁺): calcd.: 358.1113; found: 358.1112

pent-4-yn-1-yl N-benzyloxy(benzylsulfonyl)methanimidate (4.59d); 1.32 g, 71% yield, colorless oil; ^1H NMR (CDCl₃, 400 MHz): 7.22–7.41 (m, 10H), 5.10 (s, 2H), 4.45 (t, 2H, $J = 6.1$ Hz), 4.40 (s, 2H), 2.27 (dt, 2H, $J = 7.0$ Hz, $J = 2.7$ Hz), 1.92 (t, 1H, $J = 2.7$ Hz), 1.80–1.86 (m, 2H) ppm; ^{13}C NMR (CDCl₃, 100 MHz): δ 151.0, 136.1, 131.2, 129.0, 128.8, 128.6, 128.6, 126.3, 82.7, 78.2, 73.6, 69.1, 59.4, 28.5, 14.6 ppm; HRMS (ESI, C₂₀H₂₂NO₄S (M+H)⁺): calcd.: 372.1270; found: 372.1266.

buta-2,3-dien-1-yl N-benzyloxy(benzylsulfonyl)methanimidate (4.60d); 1.32 g, 74% yield, light yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.24–7.40 (m, 10H), 5.26–5.33 (m, 1H), 5.10 (s, 2H), 4.80–4.87 (m, 4H), 4.40 (s, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 210.6, 150.5, 136.0, 131.2, 129.0, 128.7, 128.6, 128.5, 126.3, 86.0, 78.3, 76.8, 72.7, 59.2 ppm; **HRMS** (ESI, $\text{C}_{19}\text{H}_{20}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 358.1113; found: 358.1114.

4-bromo-2-vinylphenyl N-benzyloxy(benzylsulfonyl)methanimidate (4.61d); 1.80 g, 74% yield, white solid; **m.p.** 83–85 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.57 (d, 1H, J = 2.4 Hz), 7.09–7.40 (m, 11H), 6.73 (dd, 1H, J = 11.1 Hz, J = 17.6 Hz), 6.40 (d, 1H, J = 8.7 Hz), 5.67 (d, 1H, J = 17.6 Hz), 5.32 (d, 1H, J = 11.1 Hz), 5.07 (s, 2H), 4.48 (s, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 150.8, 148.4, 135.7, 131.3, 131.2, 129.5, 129.4, 129.3, 128.9, 128.7, 128.6, 128.5, 126.6, 117.8, 117.7, 117.4, 78.6, 60.0 ppm; **HRMS** (ESI, $\text{C}_{23}\text{H}_{21}\text{NO}_4\text{SBr}$ ($\text{M}+\text{H}$) $^+$): calcd.: 486.0375; found: 486.0375.

2-methylallyl N-benzyloxy(benzylsulfonyl)methanimidate (4.62d); 1.20 g, 67% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.21–7.39 (m, 10H), 5.09 (s, 2H), 4.96 (d, 2H, J = 15.8 Hz), 4.72 (s, 2H), 4.39 (s, 2H), 1.72 (s, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 150.8, 139.2, 136.0, 131.2, 128.9, 128.6, 128.6, 128.5, 126.3, 115.3, 78.1, 78.1, 59.3, 19.0 ppm; **HRMS** (ESI, $\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 360.1270; found: 360.1259.

Following general procedure 5.4.3 using bis-sulfonyl *O*-benzyl oxime ether **4.39d** and (2-vinyl-1,3-dioxolan-2-yl)methanol²⁰¹ to synthesize **(2-vinyl-1,3-dioxolan-2-yl)methyl N-benzyloxy(benzylsulfonyl)methanimidate (4.67d)**; 1.92 g, 92% yield, yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.24–7.38 (m, 10H), 5.78 (dd, 1H, *J* = 17.2 Hz, *J* = 10.6 Hz), 5.52 (dd, 1H, *J* = 17.2 Hz, *J* = 1.4 Hz), 5.27 (dd, 1H, *J* = 10.4 Hz, *J* = 1.6 Hz), 5.09 (s, 2H), 4.41 (d, 4H, *J* = 8.1 Hz), 3.86–4.02 (m, 4H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 150.7, 136.0, 134.0, 131.1, 128.9, 128.7, 128.5, 128.5, 128.4, 126.3, 118.2, 106.2, 78.2, 74.9, 65.4, 59.5 ppm; HRMS (ESI, C₂₁H₂₄NO₆S (M+H)⁺): calcd.: 418.1324; found: 418.1315.

Synthesis of N'-(benzyloxy)-N-(but-3-en-1-yl)-1-(ethylsulfonyl)methanimidamide (4.63b). Homoallyl amine (213 mg, 3 mmol, 1 equiv) prepared from known literature¹⁹⁸ was added to a solution of bis(ethylsulfonyl)methanone *O*-benzyl oxime, **4.39b** (1.44 g, 4.5 mmol, 1.5 equiv) in anhydrous THF (10 mL) and stirred for 24h at rt. The reaction mixture was diluted with EtOAc (15 mL) followed by the addition of saturated aqueous sodium bicarbonate solution (10 mL). The phases were separated and the aqueous layer was further extracted with ethyl acetate (10 mL x 3). The combined organic extract was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to give a crude yellow oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give **4.63b** as a yellow oil.

N'-(benzyloxy)-N-(but-3-en-1-yl)-1-(ethylsulfonyl)methanimidamide (4.63b); 326 mg, 22% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.31–7.37 (m, 5H), 5.72 (tdd, 1H, $J = 16.9$ Hz, $J = 9.7$ Hz, $J = 6.9$ Hz), 4.99–5.11 (m, 5H), 3.61 (q, 2H, $J = 6.6$ Hz), 3.24 (q, 2H, $J = 7.4$ Hz), 2.30 (q, 2H, $J = 6.8$ Hz), 1.27 (t, 2H, $J = 7.4$ Hz), ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 149.6, 137.1, 134.3, 128.6, 128.5, 128.5, 128.3, 128.3, 128.0, 117.9, 76.9, 48.0, 43.2, 35.0, 6.9 ppm; **HRMS** (ESI, $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 297.1273; found: 297.1268

General procedure 5.4.4 for the improved synthesis of *S*-tethered alkenyl sulfonyl *O*-benzyl oxime ethers. A round bottom flask containing a magnetic stirbar was charged with alkenyl thioacetate (5 mmol, 1.0 equiv) and anhydrous THF (15 mL) under a nitrogen atmosphere. Pyrrolidine (0.41 mL, 5 mmol, 1.0 equiv) was added to the flask and stirred for 1h at rt. The reaction mixture was then cooled to 0 °C with an ice-bath, followed by addition of bis(benzylsulfonyl)methanone *O*-benzyl oxime, **4.39d** (2.66 g, 6 mmol, 1.2 equiv) and stirred for another 3h at 0 °C. The reaction mixture was then concentrated under reduced pressure to give a crude oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give the titled alkenyl *S*-tethered sulfonyl *O*-benzyl oxime ethers.

but-3-en-1-yl N-benzyloxy(benzylsulfonyl)methanimidothioate (4.64d); 1.78 g, 95% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.13–7.33 (m, 10H), 5.60 (tdd, 1H, $J = 16.4$ Hz, $J = 9.7$ Hz, $J = 6.6$ Hz), 5.20 (s, 2H), 4.92–4.97 (m, 2H), 4.43 (s, 2H), 3.09 (t, 2H, $J = 7.4$ Hz), 2.19 (q, 2H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 152.9,

135.9, 134.9, 131.4, 128.9, 128.6, 128.6, 128.6, 126.5, 117.1, 78.5, 59.4, 33.8, 31.2 ppm;

HRMS (ESI, $C_{19}H_{22}NO_3S_2$ ($M+H$)⁺): calcd.: 376.1041; found: 376.1042.

pent-4-en-1-yl N-benzyloxy(benzylsulfonyl)methanimidothioate (4.65d); 1.87 g, 96% yield, colorless oil; **¹H NMR** ($CDCl_3$, 400 MHz): 7.12–7.33 (m, 10H), 5.59 (tdd, 1H, J = 17.0 Hz, J = 10.2 Hz, J = 6.7 Hz), 5.19 (s, 2H), 4.86–4.92 (m, 2H), 4.43 (s, 2H), 3.00–3.04 (m, 2H), 1.97 (q, 2H, J = 7.0 Hz), 1.49–1.57 (m, 2H) ppm; **¹³C NMR** ($CDCl_3$, 100 MHz): δ 152.9, 136.8, 135.9, 131.4, 128.9, 128.6, 128.6, 128.5, 126.5, 115.6, 78.5, 59.4, 32.2, 31.5, 28.9 ppm; **HRMS** (ESI, $C_{20}H_{24}NO_3S_2$ ($M+H$)⁺): calcd.: 390.1198; found: 390.1201.

Following general procedure 5.4.3 using bis-sulfonyl *O*-benzyl oxime ether **4.39d** and the thioacetate of 2-(bromomethyl)-2-vinyl-1,3-dioxolane²⁰³ to synthesize **(2-vinyl-1,3-dioxolan-2-yl)methyl N-benzyloxy(benzylsulfonyl)methanimidothioate (4.66d)**; 1.86 g, 86% yield, yellow oil; **¹H NMR** ($CDCl_3$, 400 MHz): 7.21–7.36 (m, 10H), 5.70 (dd, 1H, J = 17.1 Hz, J = 10.5 Hz), 5.42 (dd, 1H, J = 17.1 Hz, J = 1.5 Hz), 5.27 (s, 2H), 5.18 (dd, 1H, J = 10.5 Hz, J = 1.5 Hz), 4.48 (s, 2H), 3.79–3.96 (m, 4H), 3.49 (s, 2H) ppm; **¹³C NMR** ($CDCl_3$, 100 MHz): δ 152.7, 135.8, 135.7, 131.2, 128.7, 128.5, 128.5, 128.4, 126.5, 117.0, 78.4, 65.2, 59.4, 38.5 ppm; **HRMS** (ESI, $C_{21}H_{24}NO_5S_2$ ($M+H$)⁺): calcd.: 434.1096; found: 434.1103

General procedure 5.4.5 for the radical reaction between alkenyl *O*-, *N*- or *S*-tethered sulfonyl *O*-benzyl oxime ethers with keto-xanthates. An oven-dried Schlenk tube with a side arm for gas inlet containing a magnetic stirbar was charged with keto-xanthate (1 mmol, 2 equiv), alkenyl sulfonyl *O*-benzyl oxime ether (0.5 mmol, 1 equiv) in 1 mL dichloroethane (DCE, 0.5M in oxime ether) and refluxed under Argon for 10 minutes. Dilauroyl peroxide (DLP, 0.1 mmol, 0.2 equiv) was then added every 1.5h over 10h (0.6 mmol, 1.2 equiv total DLP added) by which most of the oxime ether has been consumed as monitored by TLC. The mixture is then cooled to rt and the solvent evaporated under reduced pressure. The crude product was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give the titled *O*-benzyl oxime ether derivatives.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.56d** and xanthate **3.23i** to synthesize **3-(2-((benzyloxy)imino)tetrahydrofuran-3-yl)-1-phenylpropan-1-one (4.68a)**; 113 mg, 70% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.91–7.93 (m, 2H), 7.58 (t, 1H, $J = 7.4$ Hz), 7.46 (t, 2H, $J = 7.7$ Hz), 7.23–7.40 (m, 5H), 4.99 (s, 2H), 4.36–4.41 (m, 1H), 4.22–4.28 (m, 1H), 3.12–3.16 (m, 2H), 2.84–2.92 (m, 1H), 2.33 (dtd, 1H, $J = 12.5$ Hz, $J = 7.1$ Hz, $J = 5.2$ Hz), 2.03 (q, 2H, $J = 7.2$ Hz), 1.85–1.94 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 199.5, 160.7, 138.0, 136.7, 132.9, 128.4, 128.3, 128.1, 128.0, 127.5, 76.1, 70.2, 38.2, 35.7, 30.5, 25.8 ppm; **HRMS** (ESI, $\text{C}_{20}\text{H}_{22}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 324.1600; found: 324.1599.

3-((ethylsulfonyl)methyl)dihydrofuran-2(3H)-one O-benzyl oxime; yellow oil (4.68a');

¹H NMR (CDCl₃, 400 MHz): 7.27–7.37 (m, 5H), 4.96 (s, 2H), 4.46 (dt, 1H, *J* = 8.6 Hz, *J* = 2.0 Hz), 4.24 (ddd, 1H, *J* = 10.5 Hz, *J* = 9.0 Hz, *J* = 5.9 Hz), 3.51 (dd, 1H, *J* = 14.0 Hz, *J* = 3.5 Hz), 3.39 (ddt, 1H, *J* = 11.0 Hz, *J* = 7.9 Hz, *J* = 3.5 Hz), 3.03 (dq, 2H, *J* = 7.4 Hz, *J* = 2.5 Hz), 2.92 (dd, 1H, *J* = 14.0 Hz, *J* = 10.0 Hz), 2.61–2.68 (m, 1H), 2.05–2.16 (m, 1H), 1.38 (t, 3H, *J* = 7.4 Hz) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 158.2, 137.5, 128.3, 127.8, 76.4, 70.9, 53.4, 52.9, 48.5, 33.5, 30.7, 6.5 ppm; **HRMS** (ESI, C₁₄H₂₀NO₄S (M+H)⁺): calcd.: 298.1113; found: 298.1119.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.63b** and xanthate **3.23i** to synthesize **3-(2-((benzyloxy)imino)pyrrolidin-3-yl)-1-phenylpropan-1-one (4.69)**; 42 mg, 65% yield (based on 0.2 mmol of N'-(benzyloxy)-N-(but-3-en-1-yl)-1-(ethylsulfonyl)methanimidamide, **4.63b**), yellow oil; **¹H NMR** (CDCl₃, 400 MHz): 7.94 (d, 2H, *J* = 7.3 Hz), 7.55 (t, 1H, *J* = 7.3 Hz), 7.43 (t, 2H, *J* = 7.7 Hz), 7.35–7.38 (m, 2H), 7.29 (t, 2H, *J* = 7.4 Hz), 7.23–7.26 (m, 1H), 5.11 (br s, 1H), 4.94 (s, 2H), 3.35–3.40 (m, 1H), 3.26–3.32 (m, 1H), 3.05–3.23 (m, 2H), 2.70–2.78 (m, 1H), 2.18–2.27 (m, 1H), 1.90–2.07 (m, 2H), 1.72–1.80 (m, 1H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 200.2, 160.3, 138.5, 136.9, 132.9, 128.5, 128.2, 128.2, 127.6, 75.3, 43.2, 38.8, 36.2, 29.7, 26.8 ppm; **HRMS** (ESI, C₂₀H₂₃N₂O₂ (M+H)⁺): calcd.: 323.1760; found: 323.1761.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.56d** and *O*-ethyl *S*-(2-(methoxy(methyl)amino)-2-oxoethyl) carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)tetrahydrofuran-3-yl)-N-methoxy-N-methylpropanamide (4.68b)**; 112 mg, 73% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.24–7.39 (m, 5H), 4.98 (s, 2H), 4.33–4.38 (m, 1H), 4.22 (dd, 1H, *J* = 15.3 Hz, *J* = 8.2 Hz), 3.60 (s, 3H), 3.16 (s, 3H), 2.79–2.87 (m, 1H), 2.60 (br t, 2H, *J* = 6.9 Hz), 2.27–2.35 (m, 1H), 1.82–2.00 (m, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 173.7, 160.9, 138.0, 128.2, 128.2, 127.6, 76.1, 70.3, 61.1, 38.4, 32.1, 30.6, 29.3, 26.4 ppm; HRMS (EI, C₁₆H₂₃N₂O₄ (M⁺)): calcd.: 307.1658; found: 307.1661.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.56d** and *S*-((1,3-dioxoisindolin-2-yl)methyl) *O*-ethyl carbonodithioate¹⁹⁹ to synthesize **2-(2-(2-((benzyloxy)imino)tetrahydrofuran-3-yl)ethyl)isoindoline-1,3-dione (4.68c)**; 109 mg, 60% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.84 (dd, 2H, *J* = 5.4 Hz, *J* = 3.1 Hz), 7.72 (dd, 2H, *J* = 5.4 Hz, *J* = 3.1 Hz), 7.25–7.37 (m, 5H), 4.88 (d, 2H, *J* = 4.0 Hz), 4.38 (dt, 1H, *J* = 8.4 Hz, *J* = 3.4 Hz), 4.20 (dt, 1H, *J* = 9.1 Hz, *J* = 6.4 Hz), 3.73–3.88 (m, 2H), 2.78–2.86 (m, 1H), 2.40–2.48 (m, 1H), 2.15–2.24 (m, 1H), 1.87–1.97 (m, 1H), 1.74–1.82 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 168.3, 160.3, 137.7, 134.0, 132.1, 128.5, 128.2, 127.6, 123.2, 76.3, 70.3, 37.2, 36.1, 30.7, 30.3 ppm; HRMS (ESI, C₂₁H₂₁N₂O₄ (M+H)⁺): calcd.: 365.1501; found: 365.1501.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.56d** and ethyl 2-((ethoxycarbonothioyl)thio)acetate¹⁹³ to synthesize **ethyl 3-(2-((benzyloxy)imino)tetrahydrofuran-3-yl)propanoate; colorless oil (4.68d)**; 101 mg, 69% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.25–7.40 (m, 5H), 4.97 (s, 2H), 4.32–4.37 (m, 1H), 4.17–4.23 (m, 1H), 4.13 (q, 2H, *J* = 7.1 Hz), 2.76–2.84 (m, 1H), 2.37–2.51 (m, 2H), 2.24–2.32 (m, 1H), 1.97–2.06 (m, 1H), 1.77–1.86 (m, 2H), 1.26 (t, 3H, *J* = 7.1 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 173.0, 160.4, 137.8, 128.5, 128.3, 128.2, 127.6, 76.3, 70.2, 60.4, 38.3, 31.8, 30.2, 26.7, 14.2 ppm; HRMS (ESI, C₁₆H₂₂NO₄ (M+H)⁺): calcd.: 292.1549; found: 292.1554.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.56d** and *S*-(cyanomethyl) *O*-ethyl carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)tetrahydrofuran-3-yl)propanenitrile; yellow oil (4.68e)**; 92 mg, 75% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.19–7.32 (m, 5H), 4.89 (s, 2H), 4.30 (dt, 1H, *J* = 8.4 Hz, *J* = 3.8 Hz), 4.15 (dt, 1H, *J* = 8.9 Hz, *J* = 6.6 Hz), 2.77–2.85 (m, 1H), 2.43–2.47 (m, 2H), 2.24–2.32 (m, 1H), 1.87–1.96 (m, 1H), 1.74–1.83 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 159.5, 137.7, 128.5, 128.2, 127.8, 119.2, 76.4, 70.2, 37.8, 30.2, 27.4, 15.0 ppm; HRMS (ESI, C₁₄H₁₇N₂O₂ (M+H)⁺): calcd.: 245.1290; found: 245.1289.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and xanthate **3.23i** to synthesize **3-(2-((benzyloxy)imino)tetrahydrothiophen-3-yl)-1-phenylpropan-1-one (4.70a)**; 121 mg, 71% yield, light yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.85–7.87 (m, 2H), 7.55 (t, 1H, $J=7.4$ Hz), 7.42 (t, 2H, $J=7.7$ Hz), 7.21–7.37 (m, 5H), 5.12 (s, 2H), 3.00–3.16 (m, 4H), 2.90 (td, 1H, $J=13.6$ Hz, $J=6.7$ Hz), 2.25–2.35 (m, 1H), 1.90–2.06 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 199.8, 163.8, 138.2, 136.8, 132.9, 128.5, 128.2, 128.0, 127.7, 127.5, 76.0, 44.8, 35.7, 34.6, 30.9, 25.8 ppm; HRMS (ESI, $\text{C}_{20}\text{H}_{22}\text{NO}_2\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 340.1371; found: 340.1371.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and *O*-ethyl *S*-(2-(methoxy(methyl)amino)-2-oxoethyl) carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)tetrahydrothiophen-3-yl)-N-methoxy-N-methylpropanamide (4.70b)**; 108 mg, 67% yield, light yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.24–7.37 (m, 5H), 5.13 (s, 2H), 3.57 (s, 3H), 3.08–3.18 (m, 4H), 2.98–3.05 (m, 1H), 2.82–2.85 (m, 1H), 2.57 (br s, 2H), 2.29 (qd, 1H, $J=12.6$ Hz, $J=6.3$ Hz), 1.82–2.00 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.8, 138.1, 128.2, 127.7, 127.5, 76.0, 61.1, 44.9, 34.5, 32.2, 30.8, 29.3, 26.4 ppm; HRMS (ESI, $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 323.1429; found: 323.1429.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and *S*-((1,3-dioxoisindolin-2-yl)methyl) *O*-ethyl carbonodithioate¹⁹⁹ to synthesize **2-(2-(2-((benzyloxy)imino)tetrahydrothiophen-3-yl)ethyl)isoindoline-1,3-dione (4.70c)**; 110 mg, 58% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.84 (dd, 2H, *J* = 5.4 Hz, *J* = 3.0 Hz), 7.70 (dd, 2H, *J* = 5.4 Hz, *J* = 3.0 Hz), 7.24–7.36 (m, 5H), 5.05 (s, 2H), 3.74–3.89 (m, 2H), 2.99–3.11 (m, 2H), 2.82 (tt, 1H, *J* = 8.3 Hz, *J* = 6.0 Hz), 2.42–2.50 (m, 1H), 2.23 (dtd, 1H, *J* = 13.7 Hz, *J* = 7.9 Hz, *J* = 5.8 Hz), 1.86–1.96 (m, 1H), 1.74–1.83 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 168.3, 163.1, 137.9, 134.3, 133.9, 132.1, 128.2, 127.9, 127.6, 123.5, 123.2, 76.1, 43.6, 36.2, 34.1, 30.9, 30.7 ppm; HRMS (ESI, C₂₁H₂₁N₂O₃S (M+H)⁺): calcd.: 381.1273; found: 381.1274.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and ethyl 2-((ethoxycarbonothioyl)thio)acetate¹⁹³ to synthesize **ethyl 3-(2-((benzyloxy)imino)tetrahydrothiophen-3-yl)propanoate; colorless oil (4.70d)**; 100 mg, 65% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.26–7.40 (m, 5H), 5.13 (s, 2H), 4.12 (q, 2H, *J* = 7.1 Hz), 2.98–3.12 (m, 2H), 2.78–2.85 (m, 1H), 2.23–2.44 (m, 3H), 1.98–2.07 (m, 1H), 1.74–1.90 (m, 2H), 1.25 (t, 3H, *J* = 7.1 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 173.3, 163.3, 137.9, 128.2, 127.9, 127.6, 76.1, 60.3, 44.9, 34.2, 31.8, 30.8, 26.8, 14.2 ppm; HRMS (ESI, C₁₆H₂₂NO₃S (M+H)⁺): calcd.: 308.1320; found: 308.1318.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and *S*-(cyanomethyl) *O*-ethyl carbonodithioate¹⁹³ to synthesize **3-((2-((benzyloxy)imino)tetrahydrothiophen-3-yl)propanenitrile (4.70e)**; 105 mg, 81% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.28–7.35 (m, 5H), 5.12 (s, 2H), 3.01–3.09 (m, 2H), 2.88 (tt, 1H, *J* = 8.3 Hz, *J* = 6.1 Hz), 2.42–2.50 (m, 2H), 2.33 (dt, 1H, *J* = 12.1 Hz, *J* = 5.8 Hz), 1.96–2.05 (m, 1H), 1.78–1.89 (m, 2H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 162.2, 137.8, 128.3, 128.0, 127.7, 119.4, 76.3, 44.3, 34.1, 30.7, 30.7, 27.4, 14.9 ppm; HRMS (ESI, C₁₄H₁₇N₂OS (M+H)⁺): calcd.: 261.1062; found: 261.1063.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.64d** and xanthate **3.23f** to synthesize **ethyl 2-((2-((benzyloxy)imino)tetrahydrothiophen-3-yl)methyl)-3-oxobutanoate (4.70f)**; 103 mg, 59% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): diastereomers = 1/1: 7.26–7.38 (m, 5H), 5.12–5.13 (m, 2H), 4.12–4.22 (m, 2H), 3.85 (ddd, 1H, *J* = 12.8 Hz, *J* = 8.8 Hz, *J* = 5.8 Hz), 2.98–3.15 (m, 2H), 2.72–2.80 (m, 1H), 2.23–2.34 (m, 1H), 2.12–2.14 (m, 3H), 1.94–2.11 (m, 2H), 1.83–1.91 (m, 1H), 1.24–1.29 (m, 3H) ppm; ¹³C NMR (CDCl₃, 100 MHz): diastereomers = 1/1: δ 203.5, 202.9, 169.5, 169.2, 163.3, 163.3, 138.2, 138.0, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.6, 76.2, 76.0, 61.4, 57.2, 55.7, 43.4, 42.8, 34.9, 34.6, 30.8, 30.8, 30.4, 29.8, 29.4, 28.9, 14.0, 14.0 ppm; HRMS (ESI, C₁₈H₂₄NO₄S (M+H)⁺): calcd.: 350.1426; found: 350.1425.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and xanthate **3.23i** to synthesize **3-(2-((benzyloxy)imino)chroman-3-yl)-1-phenylpropan-1-one (4.71a)**; 158 mg, 82% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.82 (dd, 2H, $J = 8.3$ Hz, $J = 1.2$ Hz), 7.54 (t, 1H, $J = 7.4$ Hz), 7.39–7.44 (m, 4H), 7.24–7.32 (m, 3H), 7.18–7.20 (m, 1H), 7.10 (d, 2H, $J = 8.1$ Hz), 7.00 (dt, 1H, $J = 7.4$ Hz, $J = 1.1$ Hz), 5.06 (s, 2H), 2.99–3.07 (m, 3H), 2.71–2.78 (m, 2H), 1.92 (dd, 2H, $J = 14.1$ Hz, $J = 6.9$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 199.5, 151.9, 150.8, 138.1, 136.8, 132.9, 129.0, 128.5, 128.2, 128.1, 128.1, 128.0, 127.6, 123.3, 121.7, 116.3, 76.1, 35.8, 33.9, 30.5, 25.1 ppm; **HRMS** (ESI, $\text{C}_{25}\text{H}_{24}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$): calcd.: 386.1756; found: 386.1758.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and *O*-ethyl *S*-(2-(methoxy(methyl)amino)-2-oxoethyl) carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)chroman-3-yl)-N-methoxy-N-methylpropanamide (4.71b)**; 111 mg, 60% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.42 (d, 2H, $J = 7.0$ Hz), 7.34 (t, 2H, $J = 7.3$ Hz), 7.26–7.29 (m, 1H), 7.17–7.21 (m, 1H), 7.07–7.10 (m, 2H), 6.99 (dt, 1H, $J = 7.4$ Hz, $J = 1.0$ Hz), 5.09 (s, 2H), 3.54 (s, 3H), 3.12 (s, 3H), 3.02 (dd, 1H, $J = 17.7$ Hz, $J = 7.1$ Hz), 2.69–2.75 (m, 2H), 2.52 (d, 1H, $J = 5.8$ Hz), 1.75–1.89 (m, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 152.0, 150.8, 138.1, 129.0, 128.2, 128.1, 128.0, 127.6, 123.2, 121.7, 116.2, 76.2, 61.0, 33.9, 32.2, 30.3, 29.2, 25.6 ppm; **HRMS** (ESI, $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$): calcd.: 369.1814; found: 369.1808.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and *S*-((1,3-dioxoisindolin-2-yl)methyl) *O*-ethyl carbonodithioate¹⁹⁹ to synthesize **2-(2-(2-((benzyloxy)imino)chroman-3-yl)ethyl)isoindoline-1,3-dione (4.71c)**; 147 mg, 69% yield, yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.83 (dd, 2H, *J* = 5.3 Hz, *J* = 3.1 Hz), 7.70 (dd, 2H, *J* = 5.3 Hz, *J* = 3.1 Hz), 7.44 (d, 2H, *J* = 7.4 Hz), 7.34 (t, 2H, *J* = 7.4 Hz), 7.26–7.29 (m, 1H), 7.20 (t, 1H, *J* = 7.8 Hz), 7.10 (t, 2H, *J* = 7.0 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 5.05 (s, 2H), 3.72–3.88 (m, 2H), 3.05 (dd, 1H, *J* = 15.4 Hz, *J* = 4.7 Hz), 2.69–2.82 (m, 2H), 2.09–2.17 (m, 1H), 1.73–1.79 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 168.2, 151.6, 151.0, 137.8, 134.3, 133.9, 132.1, 128.8, 128.4, 128.3, 128.2, 127.7, 123.6, 123.3, 123.2, 121.7, 116.4, 76.4, 35.8, 32.5, 29.8, 29.5 ppm; HRMS (ESI, C₂₆H₂₃N₂O₄ (M+H)⁺): calcd.: 427.1658; found: 427.1652.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and ethyl 2-((ethoxycarbonothioyl)thio)acetate¹⁹³ to synthesize **ethyl 3-(2-((benzyloxy)imino)chroman-3-yl)propanoate (4.71d)**; 118 mg, 67% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.42 (t, 2H, *J* = 7.5 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.27–7.31 (m, 1H), 7.20 (t, 1H, *J* = 7.7 Hz), 7.08 (d, 2H, *J* = 7.9 Hz), 7.00 (t, 1H, *J* = 7.4 Hz), 5.08 (s, 2H), 4.10 (q, 2H, *J* = 7.1 Hz), 2.99–3.02 (m, 1H), 2.65–2.73 (m, 2H), 2.38 (t, 2H, *J* = 7.6 Hz), 1.86–1.91 (m, 1H), 1.71–1.78 (m, 2H), 1.27 (t, 3H, *J* = 7.1 Hz) ppm; ¹³C NMR

(CDCl₃, 100 MHz): δ 173.0, 151.5, 150.8, 137.9, 129.0, 128.4, 128.3, 128.1, 127.7, 123.3, 121.5, 116.3, 76.4, 60.4, 33.8, 31.6, 30.0, 25.9, 14.2 ppm; **HRMS** (ESI, C₂₁H₂₄NO₄ (M+H)⁺): calcd.: 354.1705; found: 354.1707.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and *S*-(cyanomethyl) *O*-ethyl carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)chroman-3-yl)propanenitrile (4.71e)**; 119 mg, 78% yield, colorless oil; **¹H NMR** (CDCl₃, 400 MHz): 7.29–7.43 (m, 5H), 7.19–7.24 (m, 1H), 7.09 (d, 2H, *J* = 8.1 Hz), 6.99–7.03 (m, 1H), 5.07 (s, 2H), 2.98 (dd, 1H, *J* = 15.0 Hz, *J* = 4.5 Hz), 2.65–2.78 (m, 2H), 2.36 (t, 2H, *J* = 7.3 Hz), 1.88–1.97 (m, 1H), 1.71–1.80 (m, 1H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 150.6, 150.4, 137.7, 128.8, 128.4, 128.4, 128.3, 127.9, 123.5, 121.0, 119.2, 116.3, 76.4, 33.6, 29.9, 26.8, 14.8 ppm; **HRMS** (ESI, C₁₉H₁₉N₂O₂ (M+H)⁺): calcd.: 307.1447; found: 307.1449.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and ethyl 2-((ethoxycarbonothioyl)thio)propanoate²⁰⁰ to synthesize **ethyl 3-(2-((benzyloxy)imino)chroman-3-yl)-2-methylpropanoate (4.71f)**; 134 mg, 73% yield, yellow oil; **¹H NMR** (CDCl₃, 400 MHz): diastereomers = 1/1: 7.42–7.44 (m, 2H), 7.28–7.37 (m, 3H), 7.19 (t, 1H, *J* = 7.7 Hz), 7.07–7.09 (m, 2H), 6.99 (dt, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz), 5.08 (s, 2H), 4.06–4.13 (m, 2H), 3.00 (ddd, 1H, *J* = 20.7 Hz, *J* = 15.5 Hz, *J* = 5.0 Hz),

2.50–2.76 (m, 3H), 1.99–2.07 (m, 0.5H), 1.71–1.78 (m, 0.5H), 1.57–1.64 (m, 0.5H), 1.37–1.44 (m, 0.5H), 1.23 (dd, 3H, $J = 15.1$ Hz, $J = 7.2$ Hz), 1.11 (dd, 3H, $J = 11.3$ Hz, $J = 7.1$ Hz) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 176.3, 176.0, 151.8, 151.5, 150.8, 137.9, 137.9, 131.2, 128.9, 128.9, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7, 123.2, 123.2, 121.6, 121.4, 116.3, 116.2, 76.3, 76.3, 60.3, 60.3, 37.2, 36.8, 34.6, 34.1, 32.7, 32.0, 30.4, 29.8, 17.9, 17.0, 14.2, 14.1 ppm; HRMS (ESI, $\text{C}_{22}\text{H}_{26}\text{NO}_4$ ($\text{M}+\text{H}$) $^+$): calcd.: 368.1862; found: 368.1862.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.57d** and *O*-ethyl *S*-(2-oxo-2-(2-oxooxazolidin-3-yl)ethyl) carbonodithioate²⁰¹ to synthesize **3-(3-(2-((benzyloxy)imino)chroman-3-yl)propanoyl)oxazolidin-2-one** (**4.71g**); 124 mg, 63% yield, yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.42–7.44 (m, 2H), 7.33–7.37 (m, 2H), 7.26–7.30 (m, 1H), 7.17–7.22 (m, 1H), 7.07–7.10 (m, 2H), 6.99 (dt, 1H, $J = 7.4$ Hz, $J = 1.1$ Hz), 5.08 (s, 2H), 4.36 (d, 2H, $J = 8.1$ Hz), 3.91–3.95 (m, 2H), 2.94–3.11 (m, 3H), 2.68–2.80 (m, 3H), 1.91–2.00 (m, 1H), 1.73–1.82 (m, 1H), ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 172.6, 153.3, 151.7, 150.8, 137.9, 128.9, 128.2, 128.2, 128.1, 127.6, 123.2, 121.6, 116.3, 76.3, 62.0, 42.4, 33.6, 32.5, 30.0, 25.1 ppm; HRMS (ESI, $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_5$ ($\text{M}+\text{H}$) $^+$): calcd.: 395.1607; found: 395.1609.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.65d** and *O*-ethyl *S*-(2-(methoxy(methyl)amino)-2-oxoethyl) carbonodithioate¹⁹³ to

synthesize **3-(2-((benzyloxy)imino)tetrahydro-2H-thiopyran-3-yl)-N-methoxy-N-methylpropanamide (4.72a)**; 131 mg, 78% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.23–7.39 (m, 5H), 5.14 (s, 2H), 3.53 (s, 3H), 3.13 (s, 3H), 2.85–2.92 (m, 1H), 2.77 (td, 1H, $J = 12.9$ Hz, $J = 4.9$ Hz), 2.57–2.63 (m, 1H), 2.47 (br s, 2H), 2.05–2.12 (m, 1H), 1.78–2.01 (m, 4H), 1.64–1.72 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 154.8, 138.1, 128.7, 128.2, 127.7, 127.5, 75.9, 61.0, 38.5, 32.2, 29.6, 29.0, 27.9, 27.2, 21.8 ppm; HRMS (ESI, $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 337.1586; found: 337.1588.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.65d** and *S*-((1,3-dioxoisindolin-2-yl)methyl) *O*-ethyl carbonodithioate¹⁹⁹ to synthesize **2-(2-(2-((benzyloxy)imino)tetrahydro-2H-thiopyran-3-yl)ethyl)isindoline-1,3-dione (4.72b)**; 103 mg, 52% yield, light yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.83 (dd, 2H, $J = 5.4$ Hz, $J = 3.0$ Hz), 7.70 (dd, 2H, $J = 5.4$ Hz, $J = 3.0$ Hz), 7.24–7.38 (m, 5H), 5.11 (s, 2H), 3.65–3.82 (m, 2H), 2.84–2.91 (m, 1H), 2.74–2.78 (m, 1H), 2.60–2.65 (m, 1H), 2.25 (tdd, 1H, $J = 14.0$ Hz, $J = 8.5$ Hz, $J = 7.1$ Hz), 1.94–2.02 (m, 3H), 1.79 (tdd, 1H, $J = 14.1$ Hz, $J = 8.6$ Hz, $J = 5.7$ Hz), 1.62–1.70 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 168.3, 154.2, 137.9, 133.8, 132.2, 128.2, 128.0, 127.5, 123.1, 76.0, 37.1, 36.1, 31.6, 28.4, 27.0, 22.3 ppm; HRMS (ESI, $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 395.1429; found: 395.1428.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.65d** and *S*-(cyanomethyl) *O*-ethyl carbonodithioate¹⁹³ to synthesize **3-(2-((benzyloxy)imino)tetrahydro-2H-thiopyran-3-yl)propanenitrile (4.72c)**; 97 mg, 71% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.28–7.36 (m, 5H), 5.12 (s, 2H), 2.86–2.93 (m, 1H), 2.73–2.79 (m, 1H), 2.63 (tt, 1H, *J* = 8.5 Hz, *J* = 4.2 Hz), 2.27 (t, 2H, *J* = 7.3 Hz), 2.06–2.15 (m, 1H), 1.88–1.99 (m, 3H), 1.70–1.78 (m, 1H), 1.58–1.66 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 153.3, 137.8, 128.3, 128.0, 127.8, 119.7, 76.1, 37.9, 28.9, 28.8, 27.0, 22.2, 15.0 ppm; HRMS (ESI, C₁₅H₁₉N₂OS (M+H)⁺): calcd.: 275.1218; found: 275.1218.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.65d** and *O*-ethyl *S*-(2-oxo-2-(thiophen-2-yl)ethyl) carbonodithioate^{68b} to synthesize **3-(2-((benzyloxy)imino)tetrahydro-2H-thiopyran-3-yl)-1-(thiophen-2-yl)propan-1-one (4.72d)**; 95 mg, 53% yield, yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.59 (dd, 1H, *J* = 4.9 Hz, *J* = 1.1 Hz), 7.44 (dd, 1H, *J* = 3.8 Hz, *J* = 1.1 Hz), 7.21–7.36 (m, 5H), 7.06 (dd, 1H, *J* = 4.9 Hz, *J* = 3.8 Hz), 5.13 (s, 2H), 2.85–2.92 (m, 3H), 2.75–2.80 (m, 1H), 2.62 (tt, 1H, *J* = 8.5 Hz, *J* = 4.3 Hz), 2.27 (t, 2H, *J* = 7.3 Hz), 2.11–2.20 (m, 1H), 1.88–2.02 (m, 4H), 1.65–1.73 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 193.2, 154.6, 144.3, 138.2, 133.3, 132.0, 128.2, 127.9, 127.7, 127.5, 75.8, 36.5, 36.9, 29.2, 27.8, 27.2, 21.9 ppm; HRMS (ESI, C₁₉H₂₂NO₂S₂ (M+H)⁺): calcd.: 360.1092; found: 360.1093.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and xanthate **3.23i** to synthesize **3-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)-1-phenylpropan-1-one (4.73a)**; 149 mg, 75% yield, light yellow oil; ^1H NMR (CDCl_3 , 400 MHz): 7.83–7.86 (m, 2H), 7.54 (t, 1H, $J = 7.4$ Hz), 7.42 (t, 2H, $J = 7.7$ Hz), 7.21–7.34 (m, 5H), 5.10 (s, 2H), 4.02–4.05 (m, 4H), 3.16–3.24 (m, 2H), 2.99–3.08 (m, 2H), 2.85 (dd, 1H, $J = 10.3$ Hz, $J = 3.8$ Hz), 2.15–2.24 (m, 1H), 1.79–1.88 (m, 1H), 2.23 (dtd, 1H, $J = 13.7$ Hz, $J = 7.9$ Hz, $J = 5.8$ Hz), 1.86–1.96 (m, 1H), 1.74–1.83 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 199.7, 158.5, 138.0, 136.9, 132.8, 128.4, 128.2, 128.0, 127.8, 127.6, 114.8, 76.0, 65.6, 65.0, 49.1, 37.3, 35.4, 22.0 ppm; HRMS (ESI, $\text{C}_{20}\text{H}_{26}\text{NO}_6\text{S}$ ($\text{M}+\text{H}^+$)): calcd.: 408.1481; found: 408.1484.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and xanthate **3.23a** to synthesize **4-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)butan-2-one (4.73b)**; 99 mg, 59% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.26–7.36 (m, 5H), 5.12 (s, 2H), 4.01 (s, 4H), 3.17 (d, 1H, $J = 11.5$ Hz), 3.00 (d, 1H, $J = 11.5$ Hz), 2.72 (dd, 1H, $J = 10.2$ Hz, $J = 4.1$ Hz), 2.46–2.58 (m, 2H), 1.94–2.03 (m, 4H), 1.58–1.67 (m, 1H), 1.74–1.83 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 208.3, 158.4, 137.9, 128.2, 127.8, 127.6, 114.8, 76.0, 65.5, 64.8, 48.7, 40.0, 37.1, 29.9, 21.6 ppm; HRMS (ESI, $\text{C}_{17}\text{H}_{22}\text{NO}_4\text{S}$ ($\text{M}+\text{H}^+$)): calcd.: 336.1270; found: 336.1272.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and *S*-(2-cyclopropyl-2-oxoethyl) *O*-ethyl carbonodithioate⁹² to synthesize **3-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)-1-cyclopropylpropan-1-one (4.73c)**; 130 mg, 72% yield, colorless oil; ¹H NMR (CDCl₃, 400 MHz): 7.26–7.37 (m, 5H), 5.13 (s, 2H), 4.01 (s, 4H), 3.17 (d, 1H, *J* = 11.4 Hz), 3.01 (d, 1H, *J* = 11.4 Hz), 2.70–2.77 (m, 2H), 2.58–2.66 (m, 1H), 1.98–2.07 (m, 1H), 1.76–1.82 (m, 1H), 1.61–1.71 (m, 1H), 0.95–0.98 (m, 2H), 0.80–0.83 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 210.3, 158.5, 137.9, 128.2, 127.9, 127.6, 114.8, 76.0, 65.6, 64.9, 48.9, 39.7, 37.2, 21.8, 20.5, 10.5 ppm; HRMS (ESI, C₁₉H₂₄NO₄S (M+H)⁺): calcd.: 362.1426; found: 362.1425.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and *O*-ethyl *S*-(2-oxo-3-phenylpropyl) carbonodithioate¹⁹⁴ to synthesize **4-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)-1-phenylbutan-2-one (4.73d)**; 117 mg, 57% yield, light yellow oil; ¹H NMR (CDCl₃, 400 MHz): 7.22–7.35 (m, 8H), 7.12–7.15 (m, 2H), 5.10 (s, 2H), 3.95–3.98 (m, 4H), 3.55 (s, 2H), 3.14 (d, 1H, *J* = 11.4 Hz), 2.98 (d, 1H, *J* = 11.4 Hz), 2.51–2.72 (m, 3H), 1.94–2.02 (m, 1H), 1.56–1.66 (m, 1H) ppm; ¹³C NMR (CDCl₃, 100 MHz): δ 207.8, 158.4, 138.0, 134.3, 129.4, 128.6, 128.3, 127.8, 127.6, 126.9, 114.8, 76.0, 65.5, 64.9, 50.0, 48.6, 38.6, 37.2, 21.5 ppm; HRMS (ESI, C₂₃H₂₆NO₄S (M+H)⁺): calcd.: 412.1583; found: 412.1584.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and xanthate **3.23g** to synthesize **diethyl (4-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)-2-oxobutyl) phosphonate (4.73e)**; 165 mg, 70% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.20–7.28 (m, 5H), 5.04 (s, 2H), 3.94–4.10 (m, 10H), 2.87 (d, 2H, $J = 22.5$ Hz), 2.59–2.76 (m, 3H), 1.90–1.96 (m, 1H), 1.58–1.66 (m, 1H), 1.25 (t, 6H, $J = 7.1$ Hz) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 201.4 (d, $^2J_{\text{CP}} = 6.3\text{ Hz}$), 158.3, 137.9, 128.2, 127.8, 127.6, 114.7, 76.0, 65.5, 64.9, 62.4 (d, $^2J_{\text{CP}} = 3.8$ Hz), 62.3 (d, $^2J_{\text{CP}} = 3.3$ Hz), 48.6, 42.2 (d, $J_{\text{CP}} = 128.0$ Hz), 40.8, 37.2, 21.3, 16.3, 16.2 ppm; $^{31}\text{P NMR}$ (162 MHz, CDCl_3) δ 20.1 ppm; **HRMS** (ESI, $\text{C}_{21}\text{H}_{31}\text{NO}_7\text{PS}$ ($\text{M}+\text{H}$) $^+$): calcd.: 472.1559; found: 472.1559.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.66d** and xanthate **3.23f** to synthesize **ethyl 2-((8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)methyl)-3-oxobutanoate (4.73f)**; 139 mg, 68% yield, light yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): diastereomers = 1/1: 7.26–7.37 (m, 5H), 5.12–5.13 (m, 2H), 4.08–4.23 (m, 2H), 3.97–4.06 (m, 4H), 3.88 (ddd, 1H, $J = 19.5$ Hz, $J = 10.3$ Hz, $J = 4.3$ Hz), 3.13–3.23 (m, 1H), 2.99–3.04 (m, 1H), 2.75 (ddd, 1H, $J = 15.2$ Hz, $J = 10.7$ Hz, $J = 4.0$ Hz), 2.19–2.37 (m, 1H), 2.10–2.13 (m, 3H), 1.77–1.92 (m, 1H), 1.24–

1.28 (m, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 203.4, 202.9, 169.3, 169.1, 158.1, 158.0, 138.0, 137.8, 128.3, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 127.6, 127.6, 114.6, 76.2, 76.0, 65.6, 65.5, 64.8, 61.4, 61.3, 56.2, 54.9, 47.5, 46.9, 37.3, 37.2, 30.4, 29.2, 25.8, 25.5, 14.0, 14.0 ppm; HRMS (ESI, $\text{C}_{20}\text{H}_{26}\text{NO}_6\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 408.1481; found: 408.1483.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and xanthate **3.23i** to synthesize **3-(8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)-1-phenylpropan-1-one (4.74a)**; 149 mg, 78% yield, colorless oil; ^1H NMR (CDCl_3 , 400 MHz): 7.88–7.90 (m, 2H), 7.55 (t, 1H, $J = 7.4$ Hz), 7.43 (t, 2H, $J = 7.7$ Hz), 7.21–7.37 (m, 5H), 4.96 (s, 2H), 4.13 (dd, 2H, $J = 26.9$ Hz, $J = 9.5$ Hz), 3.92–4.02 (m, 4H), 3.20–3.25 (m, 1H), 3.07–3.12 (m, 1H), 2.88 (dd, 1H, $J = 9.7$ Hz, $J = 4.8$ Hz), 2.07–2.16 (m, 1H), 1.86–1.94 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 199.5, 158.4, 137.8, 136.8, 132.9, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 112.2, 76.2, 75.0, 65.2, 64.9, 44.4, 35.1, 20.6 ppm; HRMS (ESI, $\text{C}_{22}\text{H}_{24}\text{NO}_5$ ($\text{M}+\text{H}$) $^+$): calcd.: 382.1654; found: 382.1653.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and xanthate **3.23a** to synthesize **4-(8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)butan-2-one (4.74b)**; 105 mg, 66% yield, colorless oil; ^1H

NMR (CDCl₃, 400 MHz): 7.26–7.39 (m, 5H), 4.98 (s, 2H), 4.10 (dd, 2H, J = 23.0 Hz, J = 9.5 Hz), 3.93–4.04 (m, 4H), 2.76 (dd, 1H, J = 9.5 Hz, J = 5.2 Hz), 2.49–2.68 (m, 2H), 2.06 (s, 3H), 1.88–1.97 (m, 1H), 1.66–1.71 (m, 1H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 208.2, 158.4, 137.9, 128.4, 128.2, 127.7, 112.2, 76.3, 75.1, 65.2, 64.9, 44.2, 40.0, 29.9, 20.2 ppm; **HRMS** (ESI, C₁₇H₂₂NO₅ (M+H)⁺): calcd.: 320.1498; found: 320.1498.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and *S*-(2-cyclopropyl-2-oxoethyl) *O*-ethyl carbonodithioate⁹² to synthesize **3-(8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)-1-cyclopropylpropan-1-one (4.74c)**; 128 mg, 74% yield, colorless oil; **¹H NMR** (CDCl₃, 400 MHz): 7.25–7.40 (m, 5H), 4.99 (s, 2H), 4.10 (dd, 2H, J = 23.1 Hz, J = 9.5 Hz), 3.93–4.04 (m, 4H), 2.62–2.82 (m, 3H), 1.91–2.00 (m, 1H), 1.80–1.87 (m, 1H), 1.68–1.78 (m, 1H), 0.97–1.01 (m, 2H), 0.82–0.86 (m, 2H) ppm; **¹³C NMR** (CDCl₃, 100 MHz): δ 210.2, 158.5, 137.9, 128.4, 128.2, 127.7, 112.3, 76.3, 75.1, 65.3, 64.9, 44.3, 39.6, 20.5, 10.5, 10.5 ppm; **HRMS** (ESI, C₁₉H₂₄NO₅ (M+H)⁺): calcd.: 346.1654; found: 346.1650.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and xanthate **3.23c** to synthesize **4-(8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)-1-(4-bromophenyl)butan-2-one (4.74d)**; 152 mg, 64%

yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.43 (d, 2H, $J = 8.4\text{ Hz}$), 7.28–7.39 (m, 5H), 7.01 (d, 2H, $J = 8.4\text{ Hz}$), 4.96 (s, 2H), 4.09 (dd, 2H, $J = 22.6\text{ Hz}$, $J = 9.6\text{ Hz}$), 3.91–3.97 (m, 4H), 3.53 (s, 2H), 2.73 (dd, 1H, $J = 9.7\text{ Hz}$, $J = 5.1\text{ Hz}$), 2.57–2.66 (m, 2H), 1.87–1.95 (m, 1H), 1.65–1.73 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 207.0, 158.3, 138.0, 133.1, 131.7, 131.1, 128.3, 128.2, 127.7, 120.9, 112.2, 76.2, 75.0, 65.2, 64.9, 49.1, 44.0, 38.5, 20.2 ppm; **HRMS** (ESI, $\text{C}_{23}\text{H}_{25}\text{NO}_5\text{Br}$ ($\text{M}+\text{H}$) $^+$): calcd.: 474.0916; found: 474.0918.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and xanthate **3.23g** to synthesize **diethyl (4-(8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)-2-oxobutyl) phosphonate (4.74e)**; 175 mg, 77% yield, yellow oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): 7.25–7.39 (m, 5H), 4.97 (s, 2H), 3.92–4.17 (m, 10H), 3.00 (d, 2H, $J = 22.6\text{ Hz}$), 2.75–2.83 (m, 3H), 1.90–1.97 (m, 1H), 1.73–1.80 (m, 1H), 1.33 (t, 6H, $J = 7.1\text{ Hz}$) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ 201.3 (d, $^2J_{\text{CP}} = 6.3\text{ Hz}$), 158.2, 137.8, 128.3, 128.2, 127.6, 112.1, 76.2, 75.0, 65.2, 64.9, 62.5 (d, $^2J_{\text{CP}} = 2.9\text{ Hz}$), 62.5 (d, $^2J_{\text{CP}} = 3.0\text{ Hz}$), 43.9, 42.2 (d, $J_{\text{CP}} = 128.0\text{ Hz}$), 40.6, 19.9, 16.2, 16.2 ppm; $^{31}\text{P NMR}$ (162 MHz, CDCl_3) δ 20.1 ppm; **HRMS** (ESI, $\text{C}_{21}\text{H}_{31}\text{NO}_8\text{P}$ ($\text{M}+\text{H}$) $^+$): calcd.: 456.1787; found: 456.1786.

Following general procedure 5.4.5 using alkenyl heteroatom sulfonyl *O*-benzyl oxime ether **4.67d** and xanthate **3.23f** to synthesize **ethyl 2-((8-((benzyloxy)imino)-1,4,7-trioxaspiro[4.4]nonan-9-yl)methyl)-3-oxobutanoate (4.74f)**; 129 mg, 66% yield, colorless oil; $^1\text{H NMR}$ (CDCl_3 , 400 MHz): diastereomers = 1/1: 7.26–7.40 (m, 5H), 4.97 (s, 2H), 3.93–4.21 (m, 8H), 3.02–3.35 (m, 1H), 2.69–2.86 (m, 1H), 2.11–2.17 (m, 4H), 1.85–1.96 (m, 1H), 1.25–1.29 (m, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): diastereomers = 1/1: δ 203.3, 202.9, 169.2, 169.1, 158.0, 157.9, 137.9, 137.8, 137.4, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.7, 127.7, 112.1, 112.0, 76.4, 76.3, 75.1, 75.0, 65.3, 65.2, 65.2, 65.0, 61.4, 61.4, 55.9, 54.9, 43.0, 42.5, 30.3, 29.3, 29.2, 24.3, 24.2, 14.0 ppm; **HRMS** (ESI, $\text{C}_{20}\text{H}_{26}\text{NO}_7$ ($\text{M}+\text{H}$) $^+$): calcd.: 392.1709; found: 392.1710.

Synthesis of thieno[2,3-b]pyridine using ammonium formate and formic acid (Scheme 106). 4-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)butan-2-one, **4.73b** (67 mg, 0.2 mmol, 1 equiv). ammonium formate (126 mg, 2 mmol, 10 equiv) and formic acid (0.6 mL) was added to a 4 mL vial and stirred at reflux for 6h. After cooling to rt, the reaction mixture was then diluted with diethyl ether (15 mL) and washed with saturated aqueous sodium bicarbonate (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give the thieno[2,3-b]pyridine **4.76**.

Synthesis of thieno[2,3-b]pyridine using only formic acid (Scheme 108). 4-(8-((benzyloxy)imino)-1,4-dioxo-7-thiaspiro[4.4]nonan-9-yl)butan-2-one, **4.73b** (67 mg, 0.2 mmol, 1 equiv) and formic acid (0.6 mL) was added to a 4 mL vial and stirred for 24h at rt. The reaction mixture was then diluted with diethyl ether (15 mL) and washed with

saturated aqueous sodium bicarbonate (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude oil which was then purified by flash chromatography (silica gel, EtOAc-Hexane) to give thieno[2,3-b]pyridine **4.76**.

2-((6-methylthieno[2,3-b]pyridin-3-yl)oxy)ethyl formate (4.76); 39 mg, 83% yield, light orange oil; ^1H NMR (CDCl_3 , 400 MHz): 8.14 (s, 1H), 7.95 (d, 1H, $J = 8.2$ Hz), 7.17 (d, 1H, $J = 8.2$ Hz), 6.28 (s, 1H), 4.60–4.62 (m, 2H), 4.33–4.35 (m, 2H), 2.68 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 160.7, 157.1, 147.9, 130.2, 129.0, 123.4, 119.3, 95.6, 67.2, 61.9, 24.5 ppm; HRMS (ESI, $\text{C}_{11}\text{H}_{12}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$): calcd.: 238.0538; found: 238.0535.

Chapter 6. References

1. (a) Gomberg, M.; *J. Am. Chem. Soc.* **1900**, 22, 757; (b) Gomberg M.; *Chem. Ber.* **1900**, 33, 3150.
2. Davies, D. I.; Parrott, M. J. *Free Radicals in Organic Synthesis*, Springer-Verlag, Berlin, 1978.
3. Paneth, F.; Hofeditz, W.; *Chem. Ber.* **1929**, 62, 1335.
4. Hey, D. H.; Waters, W. A. *Chem. Rev.* **1937**, 21, 169.
5. Kharasch, M. S.; Margolis, E. T.; Mayo, F. R. *J. Org. Chem.* **1937**, 2, 393.
6. (a) Mayo, F. R.; Lewis, F. M. *J. Am. Chem. Soc.* **1944**, 66, 1594; (b) Mayo, F. R.; Lewis, F. M.; Walling, C. *Discuss. Faraday Soc.* **1947**, 2, 285.
7. Kochi, J. K., Eds.; In *Free Radicals*, Vols. 1 and 2, Wiley, New York, 1973.
8. (a) Minisci, F.; Zammori, R.; Bernadi, R.; Cecere, M.; Galli, R. *Tetrahedron* **1970**, 26, 4153; (b) Citterio, A.; Minisci, F.; Arnoldi, A.; Pagano, R.; Parravicini, A.; Porta, O. J. *Chem. Soc. Perkin Trans. 2* **1978**, 519; (c) Citterio, A.; Arnoldi, A.; Minisci, F. *J. Org. Chem.* **1979**, 44, 2674.
9. Giese, B.; Meister, J. *Chem. Ber.* **1977**, 110, 2558; *Angew. Chem.* **1977**, 89, 178; *Angew. Chem. Int. Ed. Engl.* **1977**, 10, 178.
10. (a) Curran, D. P. *Synthesis* **1988**, 417-439, 489-513; (b) Curran, D. P. In *Comprehensive Organic Chemistry: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B., Fleming, I., Eds.; Vol. 4, Chapters 4.1 and 4.2, Pergamon, New York, 1991.
11. For a list of comprehensive literature on the use of free-radicals in synthesis, the following reviews are highly recommended: Giese, B. In *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon Press, Oxford, 1986; Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 753; see ref 10 (a).

12. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
13. (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc. Chem. Commun.* **1983**, 939; (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1574.
14. Xia, R.; Xie, M. -S.; Niu, H. -Y.; Qu, G. -R.; Guo, H. -M. *Org. Lett.* **2014**, *16*, 444.
15. (a) Giese, B.; Gonzàlez-Gòmez, J. A.; Witzel, T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 69; (b) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005.
16. Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 819.
17. Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964.
18. Bakuzi, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261.
19. Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927
20. Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4413
21. Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688
22. Davies, A. G. In *Organotin Chemistry*, WILEY-VCH, Weihelm, 1997.
23. A recent search on Reaxys was performed on 13 Jan 2015 in response to a reviewer's comment.
24. Wong, P. T. S.; Chau, Y. K.; Kramar, O.; Bengert, G. A. *Can. J. Fish. Aquat. Sci.* **1984**, *41*, 1570.
25. Baguley, P. A.; Walton, J. C. *Angew. Chem. Int. Ed.* **1998**, *37*, 3072.
26. (a) Barton, D.H.R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1991**, *32*, 7187; (b) Kopping, B.; Chatgililoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994; (c) Nishiyama, K.; Oba, M. *Tetrahedron Lett.* **1993**, *34*, 3745; (d) Chatgililoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* **1993**, *58*, 249; (e) Barton, D.H.R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron* **1993**, *49*, 7193.

27. (a) Pike, P.; Hershberger, S.; Hershberger, J.; *Tetrahedron Lett.* **1985**, 26, 6289; (b) Pike, P.; Hershberger, S.; Hershberger, J.; *Tetrahedron* **1988**, 44, 6295; (c) Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, 34, 591; (d) Chatgililoglu, C.; Ballestri, M. *Organometallics* **1995**, 14, 5017.
28. Chatgililoglu, C. In *Organosilanes in Radical Chemistry*, John-Wiley & Sons Ltd, Chichester, West Sussex PO19 8SQ, England, 2004.
29. Schneider, H.; Fiander, H.; Harrison, K. A.; Watson, M.; Burton, G. W.; Arya, P. *Bioorg. Med. Chem. Lett.* **1996**, 6, 637.
30. Bennasar, M. -L.; Roca, T.; Gria, R.; Bassa, M.; Bosch, J. *J. Org. Chem.* **2002**, 67, 6268.
31. Kizil, M.; Murphy, J. A.; *J. Chem. Soc. Chem. Commun.* **1995**, 1409.
32. (a) Renauld, P. In *Radicals in Organic Synthesis*, Vols. 1 and 2, Sibi, M. P., Eds.; Wiley-VCH, Weinheim, 2001; (b) Zard, S. Z. *Radicals Reactions in Organic Synthesis*, Oxford University Press, Oxford, 2003.
33. Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, 12, 6002.
34. Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, 5, 2655.
35. Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, 46, 455.
36. Briggs, M. E.; Zard, S. Z. *Synlett* **2005**, 334.
37. Gagosz, F.; Zard, S. Z. *Synlett* **2003**, 387.
38. Greef, M. D.; Zard, S. Z. *Tetrahedron* **2004**, 60, 7781.
39. Biadatti, T.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, 39, 19.
40. Boivin, J.; Jrad, R.; Jugé, S.; Nguyen, V. T. *Org. Lett.* **2003**, 5, 1645.
41. Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, 37, 5877.
42. Bacqué, E.; Pautrat, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2312.

43. (a) Lopez-Ruiz, H.; Zard, S. Z. *Chem. Commun.* **2001**, 2618; (b) Heinrich, M. R.; Sharp, L.; Zard, S. Z. *Chem. Commun.* **2005**, 3077.
44. Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, 71, 2352.
45. Barbier, F.; Pautrat, F.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Synlett* **2002**, 811.
46. Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1999**, 38, 1943.
47. (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2000**, 122, 6496; (b) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, 123, 4717; (c) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2002**, 4, 4257; (d) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, 69, 2755; (e) Panchaud, P.; Renaud, P. *J. Org. Chem.* **2004**, 69, 3205; (f) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, 7, 2587.
48. Kim, S.; Song, H.-J.; Choi, T.-L.; Yoon, J.-Y. *Angew. Chem. Int. Ed.* **2001**, 40, 2524.
49. Quiclet-Sire, B.; Sanchez-Jimenez, G.; Zard, S. Z. *Chem. Commun.* **2003**, 1408.
50. (a) Chou, T.-S.; Chang, S.-Y. *J. Org. Chem.* **1992**, 57, 5015; (b) Broaddus, C. D. *J. Am. Chem. Soc.* **1966**, 88, 3863.
51. (a) Mock, W. L. *J. Am. Chem. Soc.* **1975**, 97, 3666; (b) Kellogg, R. M.; Prins, W. L. *J. Org. Chem.* **1974**, 39, 2366; (c) Macgregor, S. D.; Lemal, D. M. *J. Am. Chem. Soc.* **1966**, 88, 2858; (d) Mock, W. L. *J. Am. Chem. Soc.* **1966**, 88, 2857; (e) Leonard, J.; Hague, A. B.; Knight, J. A. In *Organosulfur Chemistry, Synthetic and Stereochemical Aspects*; Page, P. Eds.; Academic Press, London, 1997; (f) Chou, T. S.; Tso, H. H. *Org. Prep. Proc. Int.* **1989**, 21, 257.
52. Yang, T.-K.; Chu, H.-Y.; Lee, D.-S.; Jiang, Y.-Z.; Chou, T.-S. *Tetrahedron Lett.* **1996**, 37, 4537 and references there cited.
53. Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

54. Aikawa, K.; Hioki, Y.; Mikami, K. *J. Am. Chem. Soc.* **2009**, *131*, 13922.
55. Yamamoto, K.; Ohta, M.; Tsuji, J. *Chem. Lett.* **1979**, 713.
56. (a) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647; (b) Alimardanov, A.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 3839.
57. Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *J. Chem. Soc. Chem. Commun.* **1995**, 2523.
58. (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780; (b) McNulty, J.; Das, P. *Chem. Commun.* **2008**, *44*, 1244.
59. Lee, B. S.; Gil, J. M.; Oh, D. Y. *Tetrahedron Lett.* **2001**, *42*, 2345.
60. (a) Andreini, B. P.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1988**, *29*, 2239; (b) Fianese, V.; Marchese, G.; Mascolo, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1988**, *29*, 3705.
61. (a) Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909. (b) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898.
62. Hansen, A. L.; Ebran, J. -P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3349.
63. Ni, Z. -J.; Yang, P. -F.; Ng, D. K. P.; Tzeng, Y. -L.; Luh, T. -Y. *J. Am. Chem. Soc.* **1990**, *112*, 9356.
64. Stille, J. K.; Groht, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
65. Matsubara, S.; Otake, Y.; Morikawa, T.; Utimoto, K. *Synlett* **1998**, 1315.
66. Petasis, N. A.; Akritopoulou, I. *Synlett* **1992**, 665.
67. Lusinch, M.; Stanbury, T. V.; Zard, S. Z. *Chem. Commun.* **2002**, *36*, 1532.
68. A great deal of acknowledgement should be credited to Dr. Quiclet-Sire, B. who first observed this phenomenon. She was also mainly involved in some other projects involving

- the Chugaev fragmentation of xanthates at the same time as this work; (a) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 5886; (b) Jullien, H.; Quiclet-Sire, B.; Tétart, T.; Zard, S. Z. *Org. Lett.* **2014**, *16*, 302.
69. Wiberg, K. B. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312.
70. It should be noted that the use of dried 3Å molecular sieves could also be an effective physical treatment to remove water. Although physical means to remove water has been shown to work well as seen from Table 2, entry 7, the author has found it to be inconsistent and gave unreproducible results. The author would like to thank the referee of this thesis for the kind suggestion.
71. (a) Shelton, J. R.; Uzelmeier, C. W. *J. Am. Chem. Soc.* **1966**, *88*, 5222; (b) Ogibin, Yu. N.; Troyanski, E. I.; Nikishin, G. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 1461; (c) Ogibin, Yu. N.; Troyanski, E. I.; Nikishin, G. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 843; (d) Bae, D. H.; Engel, P. S.; Hoque, A. K. M. M.; Keys, D. E.; Lee, W.-K.; Shaw, R. W.; Shine, H. J. *J. Am. Chem. Soc.* **1985**, *107*, 2561; (e) Engel, P. S.; Lee, W.-K.; Marschke, G. E.; Shine, H. J. *J. Org. Chem.* **1987**, *52*, 2813; (f) Karatsu, T.; Ichino, Y.; Kitamura, A.; Owens, W. H.; Engel, P. S. *J. Chem. Res. (S)* **1995**, 440. (g) de Lijser, H. J. P.; Arnold, D. R. J. *J. Phys. Chem. A* **1998**, *102*, 5592.
72. (a) Muramatsu, H.; Inukai, K. *J. Org. Chem.* **1962**, *27*, 1572; (b) Flies, F.; Laland, R.; Maillard, B. *Tetrahedron Lett.* **1976**, 439; (c) Maillard, B.; Gardat, C.; Bourgeois, M.-J. *J. Organomet. Chem.* **1982**, *236*, 61; (d) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102; (e) Tsang, R.; Dichon, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484; (f) Fraser-Reid, B.; Vite, G. D.; Yeung, B.-W. A.; Tsang, R. *Tetrahedron Lett.* **1988**, *29*, 1645.

73. O'Neill, B. T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press, New York, 1991, Vol. 1, 397.
74. Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, 7, 5593.
75. Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, 7, 1427.
76. Krasovskiy, A.; Malakhov, V.; Gauryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, 45, 6040.
77. a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, 111, 230; (b) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, 111, 2674; (c) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, 113, 5791.
78. (a) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, 53, 3377; (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, 112, 4003; (c) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, 112, 4008; (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, 57, 1429; (e) Crich, D.; Eustace, K. A.; Fortt, S. M.; Ritchie, T. J. *Tetrahedron* **1990**, 46, 2135.
79. (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, 112, 1295; (b) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, 115, 1187; (c) Ryu, I.; Sonoda, N. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1050; (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, 96, 177; (e) Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, 99, 1991; (f) Ryu, I.; *Chem. Soc. Rev.* **2001**, 30, 16.

80. (a) Kiyooka, S. -I.; Kaneko, Y.; Matsue, H.; Hamada, M.; Fujiyama, R. *J. Org. Chem.* **1990**, *55*, 5562; (b) Curran, D. P.; Liu, H. *J. Org. Chem.* **1991**, *56*, 3463.
81. Kim, S.; Jon, S. Y. *Chem. Commun.* **1996**, 1335.
82. Kim, S.; Jon, S. Y.; Do, J. Y.; Song, H.-J.; Kim, S. S. *Tetrahedron Lett.* **2000**, *41*, 8127.
83. Kim, S.; Jon, S. Y. *Tetrahedron Lett.* **1998**, *39*, 7317.
84. Kim, S.; Jon, S. Y. *Chem. Commun.* **1998**, 815.
85. Kim, S.; Cho, C. H.; Lim, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9574.
86. (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3; (b) Gawley, R. E. *Synthesis* **1976**, 777.
87. (a) Pchelintseva, N. V.; Chalaya, S. N.; Kharchenko, V. G. *Zh. Org. Khim.* **1990**, *26*, 1904; *Chem. Abstr.* **1991**, *115*, 71334; (b) Owton, W. M.; Gallagher, P. T.; Brunavs, M. *Synth. Commun.* **1992**, *22*, 351.
88. (a) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285; (b) Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.
89. Selected examples of the modification of the enolate: (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207; (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779; (c) Takahashi, A.; Yanai, H.; Taguchi, K. *Chem. Commun.* **2008**, *44*, 2385.
90. Selected examples of the modifications of the enone: (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152; (b) Brewster, J. H.; Eliel, E. L. In *Organic Reactions*; Adams, R., Eds; John Wiley and Sons: New York, 1953; Vol. 7, 99-197.
91. (a) Briggs, M. E.; Qacemi, M. E.; Kalai, C.; Zard, S. Z. *Tetrahedron Lett.* **2004**, *45*, 6017; (b) Boivin, J.; Carpentier, F.; Jrad, R. *Synthesis* **2006**, 1664.

92. A recently published paper from Zard on radical-mediated 1,5-diketone synthesis; Debien, L.; Zard, S. Z. *J. Am. Chem. Soc.* **2013**, *135*, 3808.
93. (a) Padfield, E. M.; Tomlinson, M. L. *J. Chem. Soc.* **1950**, 2272. A 5-step synthesis to a similar benzopyran 1,5-diketones has been reported; (b) Venkateswararao, E.; Sharma, V. K.; Lee, K- C.; Roh, E.; Kim, Y.; Jung, S- H. *Bioorg. Med. Chem.* **2013**, *21*, 2544.
94. Keto-xanthates **68b**, **68e** and **68f** were readily synthesized in one step from 1,3-dichloroacetone, ethyl 4-chloroacetoacetate and ethyl 2-chloroacetoacetate; (a) Greef, M. D.; Zard, S. Z. *Org. Lett.* **2007**, *9*, 1773; (b) Tate, E. Z.; Zard, S. Z. *Tetrahedron Lett.* **2002**, *43*, 4683.
95. For example, the preparation of the vinyl ketone equivalent of keto-xanthate **68e** proceeds in only 43% over 2 steps; Ghosh, S.; Rivas, F.; Fischer, D.; Gonzalez, M. A.; Theodorakis, E. A. *Org. Lett.* **2004**, *6*, 941.
96. In another example, the preparation of the vinyl ketone equivalent of keto-xanthate **68f** proceeded in a low yield of 22%; Cocker, W.; McMurry, T. B. H. *J. Chem. Soc.* **1955**, 4430.
97. Smith, M. B.; *Organic Chemistry: An Acid-Base Approach*; CRC Press: Boca Raton, FL, 2011.
98. (a) Chackalamannil, S.; Wang, Y.; Greenlee, W. J.; Hu, Z.; Xia, Y; Ahn, H. -S.; Boykow, G.; Hsieh, Y.; Palamanda, J.; Agans-Fantuzzi, J.; Kurowski, S.; Graziano, M.; Chinatala, M. *J. Med. Chem.* **2008**, *51*, 3061; (b) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326.
99. Rizk, T.; Bilodeau, E. J. -F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325.

-
100. Stolle, W. A.W.; Frissen, A. E.; Marcelis, A. T. M.; Van der Plas, H. C. *J. Org. Chem.* **1992**, *57*, 3000.
101. Cailly, T.; Begtrup, M. *Tetrahedron* **2010**, *66*, 1299.
102. Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2006**, *45*, 6520.
103. Gorenstein, D. G., Eds.; In *Phosphorous-31 NMR: Principles and Applications*. Elsevier Science: Amsterdam, 1984.
104. Tam, C. C.; Mattocks, K. L.; Tishler, M. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 3301.
105. Sun, Y. -W.; Zhu, P. -L.; Xu, Q.; Shi, M. *Tetrahedron* **2012**, *68*, 9924.
106. Costisella, B.; Keitel, T.; Gross, H. *Tetrahedron* **1981**, *37*, 1227.
107. Pudowik, P.; *Zh. Obshch. Khim.* **1959**, *29*, 507.
108. Szajnman, S. H.; Linares, G. G.; Moro, P.; Rodriguez, J. B. *Eur. J. Org. Chem.* **2005**, 3687.
109. Kim, S.; Yoon, K. S.; Kim, Y. S. *Tetrahedron* **1997**, *53*, 73.
110. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.
111. Ogibin, Y. N.; Troyanskii, E. I.; Nikishin, G. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 1461.
112. Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831.
113. Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
114. Hegarty, P.; Mann, J. *Tetrahedron* **1995**, *51*, 9079.
115. Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. *J. Chem. Soc. Perkin Trans I* **1973**, 2841.
116. Ikegami, S.; Taguchi, T.; Ohashi, M. *Nature* **1978**, *275*, 458.

117. Douros, J.; Suffness, M.; In *New Anticancer Drugs*; Carter, S. K.; Sakurai, Y.; Eds.; Springer-Verlag: Berlin, 1980, 29.
118. Pedrali-Noy, G.; Spadari, S. *J. Virol* **1980**, *36*, 457.
119. Manchand, P. S.; White, J. D.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 2705.
120. Toyota, M.; Seishi, T.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 3673.
121. Clive, D. L. J.; Beaulieu, P. L.; Set, L. *J. Org. Chem.* **1984**, *49*, 1313.
122. Chenera, B.; Chuang, C. -P.; Hart, D. J.; Hsu, L. -Y. *J. Org. Chem.* **1985**, *50*, 5409.
123. Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666.
124. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.
125. Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631.
126. Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.
127. Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253.
128. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
129. Ikota, N. *Heterocycles* **1989**, *29*, 1469.
130. Ingall, A. H.; Moore, P. R.; Roberts, S. M. *Tetrahedron Asymmetry* **1994**, *5*, 2155.
131. (a) Aoyagi, T., Yamamoto, T.; Kojiri, K.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883; (b) Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008.
132. Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Grau, A. *Tetrahedron Asymmetry* **1991**, *2*, 961.
133. Pattenden, G.; Schultz, D. J. *Tetrahedron Lett.* **1993**, *34*, 6787.

134. Kim, S.; Lee, I. Y.; Yoon, J. -Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138.
135. Kim, S.; Yoon, J. -Y. *J. Am. Chem. Soc.* **1997**, *119*, 5982.
136. (a) Guyader, F. L.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *J. Am. Chem. Soc.* **1997**, *119*, 7410; (b) Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **1998**, *37*, 2864.
137. Kim, S.; Lim, C. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3265.
138. Kim, S.; Cheong, J. H. *Chem. Commun.* **1998**, 1143.
139. Kim, S. *Adv. Synth. Catal.* **2004**, *346*, 19.
140. The synthesis of cyclic lactone and thiolactone should be possible using hydroxyl or thiol substituents on the alkyl radical involved in the radical addition to *O*-benzyl sulfonyl oxime ether. The author would like to thank one of the referee who reviewed this thesis for his invaluable opinion.
141. (a) Ribereau-Gayon, P.; Sapis, J. C. *C. R. Acad. Sci. Hebd. Seances Acad. Sci. D.* **1965**, *261*, 1915; (b) Waterhouse, A. L.; Towey, J. P. *J. Agric. Food Chem.* **1994**, *42*, 1971.
142. Canan Koch, S. S.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725.
143. Seitz, M.; Reiser, D. *Curr. Opin. Chem. Bid.* **2005**, *9*, 285.
144. Wang, C. -L. J.; Salvino, J. M. *Tetrahedron Lett.* **1984**, *25*, 5243.
145. Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1981**, *16*, 449.
146. (a) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358; (b) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504. (c) Finkelstein, M. B.; Dekant, W.; Kende, A. S.; Anders, M. W. *J. Am. Chem. Soc.* **1995**, *117*, 9590.
147. Kim, S.; Kamaldin, N. A. B.; Kang, S.; Kim, S. *Chem. Commun.* **2010**, *46*, 7822.

148. Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318; (b) Schlessinger, R. H.; Herrmann, J. L. *J. Chem. Soc. Chem. Commun.* **1973**, 71; (c) Jedlinski, Z.; Kowalczak, M.; Kurcok, P.; Grzegorzec, M.; Ermel, J. *J. Org. Chem.* **1987**, *52*, 4601.
149. (a) Regen, S. L.; Kimura, Y. *J. Am. Chem. Soc.* **1982**, *104*, 2064; (b) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558; (c) Nicolaou, K. C.; Bunnage, M. E.; McGany, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599.
150. (a) Piers, E.; Geraghty, M. B. *Can. J. Chem.* **1973**, *51*, 2166; (b) Wineburg, J. P.; Abrams, C.; Swern, D. *J. Heterocycl. Chem.* **1975**, *12*, 749.
151. Pettit, G. R.; Fessler, D. C.; Paull, K. D.; Hofer, P.; Knight, J. C. *J. Org. Chem.* **1970**, *35*, 1398.
152. Kula, J.; Sikora, M.; Sadowska, H.; Piwowarski, J. *Tetrahedron* **1996**, *52*, 11321.
153. King, G. S.; Waight, E. S. *J. Chem. Soc. Perkin Trans I* **1974**, 1499.
154. (a) Jew, S. S.; Terashima, S.; Koga, K. *Tetrahedron* **1979**, *35*, 2337; (b) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273.
155. (a) Pearson, A. J.; Ray, T.; Richards, I. C.; Clardy, J.; Silveira, L. *Tetrahedron Lett.* **1983**, *24*, 827; (b) Fujita, K.-I.; Murata, K.; Iwaoka, M.; Tomoda, S. *Tetrahedron* **1997**, *53*, 2029; (c) Tiecco, M.; Testafeni, L.; Bagnoli, L.; Marini, F.; Tempenni, A.; Tomassini C.; Santi, C. *Tetrahedron Lett.* **2000**, *41*, 3241; (d) Fujita, K.-I.; Hashimoto, S.; Oishi, A.; Taguchi, Y. *Tetrahedron Lett.* **2003**, *44*, 3793; (e) Aprile, C.; Gruttadauria, M.; Amato, M. E.; D'Anna, F.; Lo Meo, P.; Riela, S.; Noto, R. *Tetrahedron* **2003**, *59*, 2241.

156. (a) Strukul, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1198; (b) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737; (c) Yamamoto, T.; Ogura, M.; Amano, A.; Adachi, K.; Hagiwara, T.; Kanisawa, T. *Tetrahedron Lett.* **2002**, *43*, 9081; (d) Zhai, H.; Chen, Q.; Zhao, J.; Luo, S.; Jia, X. *Tetrahedron Lett.* **2003**, *44*, 2893; (e) ten Brink, G. -J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.
157. (a) Scheibye, S.; Kristensen, J.; Lawesson, S. -O. *Tetrahedron* **1979**, *35*, 1339; (b) Schmarr, H. -G.; Eisenreich, W.; Engel, K. -H. *J. Agric. Food Chem.* **2001**, *49*, 5923.
158. (a) Korte, F.; Christoph, H. *Chem. Ber.* **1961**, *94*, 1966; (b) Pattenden, G.; Shuker, A. J. *Tetrahedron Lett.* **1991**, *32*, 6625; (c) Martens, J.; Kintscher, J.; Arnold, W. *Synthesis* **1991**, 497; (d) Vegh, D.; Morel, J.; Decroix, B.; Zilupsky, P. *Synth. Commun.* **1992**, *22*, 2057; (e) Pal, R.; Murty, K. V. S. N.; Mal, D. *Synth. Commun.* **1993**, *23*, 1555; (f) Garbiras, B. J.; Marburg, S. *Synthesis* **1999**, 270; (g) Polec, I.; Lutsen, L.; Vanderzande, D.; Gelan, J. *Eur. J. Org. Chem.* **2002**, 1033.
159. (a) Krasnov, V. P.; Zholanova, E. A.; Biyushkin, V. N.; Kravtsov, V. K. *Zh. Org. Khim.* **1999**, *35*, 597; (b) Li, A. -H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X.-D.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 706; (c) Jeong, L. S.; Kim, H. O.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Chun, M. W.; Lee, C. -K. *J. Med. Chem.* **2001**, *44*, 806.
160. (a) Dafforn, G. A.; Koshland Jr., D. E. *J. Am. Chem. Soc.* **1977**, *99*, 7246; (b) McDonald, R. S.; Patterson, P.; Rodwell, J.; Whalley, A. *Can. J. Chem.* **1992**, *70*, 62.
161. Bhar, D.; Chandrasekaran, S. *Tetrahedron* **1997**, *53*, 11835.
162. (a) Takahashi, H.; Iwai, Y.; Hitomi, Y.; Ikegami, S. *Org. Lett.* **2002**, *4*, 2401; (b) Xavier, N. M.; Rauter, A. P.; Queneau, Y. *Top Curr. Chem.* **2010**, *295*, 19.
163. van Dijk, J.; Zwagemakers, J. M. A. *J. Med. Chem.* **1977**, *20*, 1199.

164. Karakurta, A.; Dalkaraa, S.; Ozalp, M.; Ozbey, S.; Kendi, E.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 421.
165. Hu, Z. B.; Luo, H. -A.; Wang, X. -G.; Huang, M. -Z.; Huang, L.; Pang, H. -L.; Mao, C. -H.; Pei, H.; Huang, C. -Q.; Sun, J.; Liu, P. -L.; Liu, A. -P. *Bull. Korean Chem. Soc.* **2014**, *35*, 1073.
166. (a) Rossello, A.; Bertini, S.; Lapucci, A.; Macchia, M.; Martinelli, A.; Rapposelli, S.; Herreros, E.; Macchia, B. *J. Med. Chem.* **2002**, *45*, 4903; (b) Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307; (c) Hofmann, M.; Langewald, J.; Kuhn, D. G.; Oloumi-Sadeghi, H.; Braun, F. J.; Culbertson, D. L. *PCT Int. Appl. WO* 2006125637, **2006**; *Chem. Abstr.* **2006**, *145*, 501089; (d) Ramalingan, C.; Park, Y. T.; Kabilan, S. *Eur. J. Med. Chem.* **2006**, *41*, 683.
167. Sun, R.; Lu, M.; Chen, L.; Li, Q.; Song, H.; Bi, F.; Huang, R.; Wang, Q. *J. Agric. Food Chem.* **2008**, *56*, 11376.
168. (a) The author would like to thank and acknowledge the referee of this thesis for highlighting this mechanistic possibility. (b) Kang, S. -K.; Ko, B.-S.; Ha, Y.-H. *J. Org. Chem.* **2001**, *66*, 3630.
169. Goh, K. K. K.; Kim, S.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 4818.
170. Charrier, N.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 9443.
171. Ouattara, M.; Wein, S.; Denoyelle, S.; Ortial, S.; Durand, T.; Escale, R.; Vial, H.; Vo-Hoang, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 624.
172. Hazeldine, S.; Pachaiyappan, B.; Steinbergs, N.; Nowotarski, S.; Hanson, A. S.; Casero Jr, R. A.; Woster, P. M. *J. Med. Chem.* **2012**, *55*, 7378.
173. Yelm, K. E. *Tetrahedron Lett.* **1999**, *40*, 1101.

174. For a short perspective on coumarin derivatives and their synthesis and applications, see:
Gu, Y.; Xue, K. *Tetrahedron Lett.* **2010**, *51*, 192 and references 1 to 3 cited within.
175. Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086; (b)
Girotti, R.; Marrocchi, A.; Minuti, L.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.*
2006, *71*, 70; (c) Shaabani, A.; Soleimani, E.; Rezayan, A. H.; Sarvary, A.; Khavasi, H. R.
Org. Lett. **2008**, *10*, 2581.
176. Barluenga, J.; Andina, F.; Aznar, F. *Org. Lett.* **2006**, *8*, 2703.
177. Marco-Contelles, J.; Balme, G.; Bouyssi, D.; Destabel, C.; Henriet-Bernard, C. D.;
Grimaldi, J.; Hatem, J. M. *J. Org. Chem.* **1997**, *62*, 1202.
178. (a) Elheshi, A. M.; Maslak, V.; Saicic, R. N. *J. Serb. Chem. Soc.* **2007**, *72*, 1173; (b)
Kaim, L. E.; Grimaud, L.; Miranda, L. D.; Vieu, E.; Cano-Herrera, M. -A.; Perez-Labrada,
K. *Chem. Commun.* **2010**, *46*, 2489.
179. Roth, W. R.; Ruf, G.; Ford, P. W. *Chem. Ber.* **1974**, *107*, 48.
180. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.
181. (a) Cohen, T.; Zhang, B.; Cherkauskas, J. P. *Tetrahedron* **1994**, *50*, 11569; (b) Sun, J.;
Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; (c) Mandal,
A. K.; Shrotri, P. Y.; Ghogare, A. D. *Synthesis* **1986**, 221.
182. Denisenko, M. V.; Odinokova, L. E.; Denisenko, V. A.; Uvarova, N. I. *Zh. Org. Khim.*
1991, *27*, 2174.
183. Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756
184. Yate, F. S. "Comprehensive Heterocyclic Chemistry", Katritzky, A. R. ed., Pergamon
Press, Oxford, 1984.

185. (a) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409; (b) Beutner, G. L.; Kuethe, J. T.; Yasuda, N. *Tetrahedron Lett.* **2009**, *50*, 781.
186. (a) Zhiryakov, V. G.; Abramenko, P. I. *Khim. Geterotsikl. Soedin.* **1965**, *1*, 334 (b) Klemm, C. H.; Lopfenstein, C. E.; Zell, R.; McCoy, D. R.; Klemm, R. A. *J. Org. Chem.* **1969**, *34*, 347.
187. Shiotani, S. *Heterocycles* **1997**, *45*, 975.
188. Chang, M. -Y.; Tai, H. -Y. *Heterocycles* **2001**, *83*, 2373.
189. Ren, X. -F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468.
190. Shen, Y.; Wang, T. *Tetrahedron Lett.* **1990**, *31*, 543.
191. Babudri, F.; Farinola, G. M.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron* **1998**, *54*, 1085.
192. Crich, D.; Hao, X. *J. Org. Chem.* **1997**, *62*, 5982.
193. Barczak, N.T.; Jarvo, E.R. *Chem. Eur. J.* **2011**, *17*, 12912.
194. Liautard, V.; Robert, F.; landais, Y. *Org. Lett.* **2011**, *13*, 2658.
195. Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 1653.
196. Guignard, R. F. *Synlett* **2013**, *24*, 157.
197. Corbet, M.; Greef, M. d.; Zard, S.Z. *Org. Lett.* **2008**, *10*, 253.
198. McNaughton, B. R.; Bucholtz, K. M.; Camaano-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733.
199. Huang, Z.; Jiaxi, X. *Tetrahedron* **2013**, *69*, 1050.
200. Reyes-Gutierrez, P. E.; Torres-Ochoa, R. O.; Martinez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388.
201. Bacque, E.; Pautrat, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2312.

202. Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482.

203. Westerlund, A.; Carlson, R. *Synth. Commun.* **1999**, *29*, 4035.

Appendix: NMR spectra for Chapter 5

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