

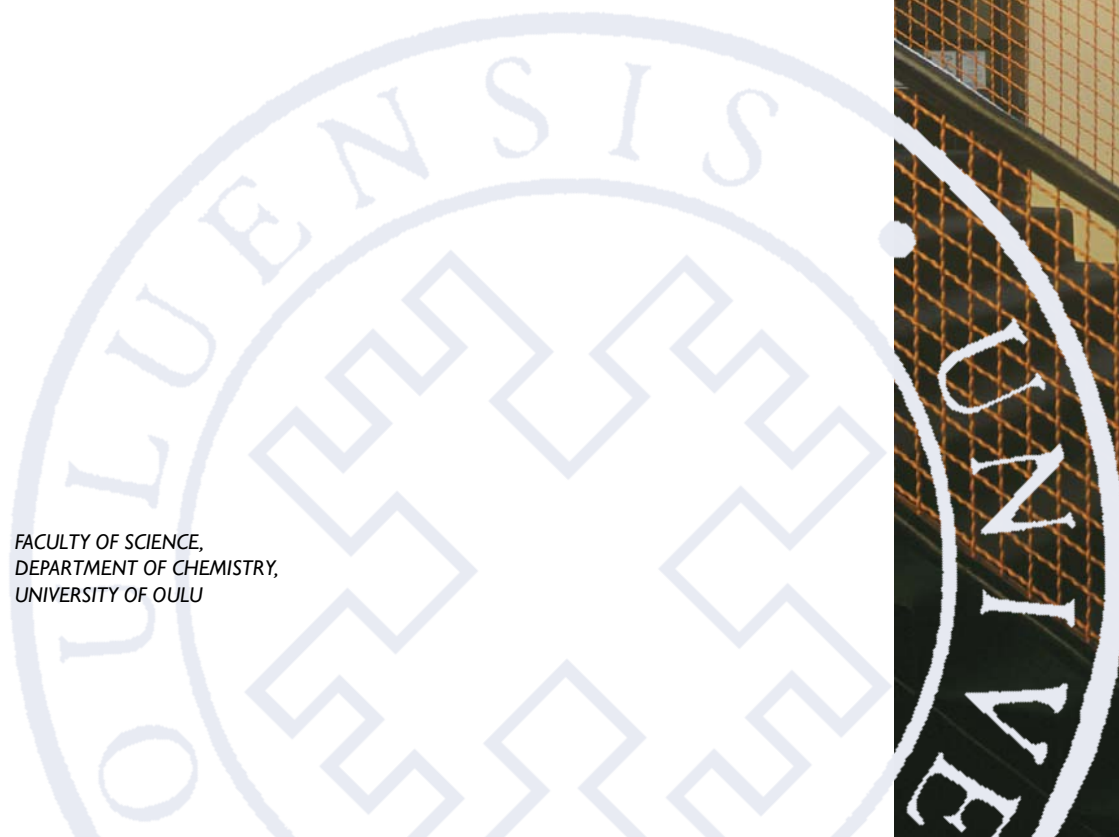
Matti Vaismaa

DEVELOPMENT OF BENIGN
SYNTHESIS OF SOME
TERMINAL α -HYDROXY
KETONES AND ALDEHYDES

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DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF OULU

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MATTI VAISMAA

**DEVELOPMENT OF BENIGN
SYNTHESIS OF SOME TERMINAL
 α -HYDROXY KETONES AND
ALDEHYDES**

Academic dissertation to be presented with the assent of
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Abstract

The synthesis of α -hydroxy aldehydes and hydroxymethyl ketones as well as their interconversion to each other are discussed in this thesis. The literature survey of the monograph reviews the synthetic methods for the preparation of 1,2-bifunctionalized hydroxy aldehydes and ketones. The keto-aldehyde isomerisation reaction catalyzed by Triosephosphate isomerase enzyme (TIM) and organic compounds that interact with the TIM are also introduced. In addition, the microwave heating techniques in organic syntheses are reviewed. The practical work consists of two entities: The synthesis of new substrate candidates and transition state analogues for a mutated monomeric TIM. These compounds are model compounds for the catalytic activity and the structural studies of the mutated monomeric TIM. The synthesis of the sulphonyl α -hydroxy ketone-based substrate candidates consists of four successive syntheses. The microwave-activation was utilized in the preparation of a carbon-sulphur bond and the synthesis of hydroxymethyl ketones. The improved synthesis of the terminal α -hydroxy ketone functionality with microwave activation is presented. The formation of charged compounds was utilized to improve the absorption of microwave energy of reaction mixtures. The design and the synthetic work were carried out in accordance to principles of green chemistry. The second part of the practical work is the development of an organocatalytic α -oxybenzoylation reaction of aldehydes with high enantiomeric selectivity. This novel method generated enantiomerically pure α -hydroxy aldehydes in the stable benzoate-protected form from achiral starting materials under mild conditions at the presence of air and moisture.

Keywords: α -hydroxy aldehyde, α -hydroxy ketone, microwave-assisted synthesis, organocatalysis, triosephosphate isomerase

To my father

Acknowledgements

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Oulu, June 2009

Matti Vaismaa

Symbols and Abbreviations

| | |
|-------------------|--|
| δ | chemical shift |
| Δ | heating |
| AcOH | acetic acid |
| A-TIM | the mutated triosephosphate isomerase |
| bp. | boiling point |
| BPO | dibenzoyl peroxide |
| Bn | benzyl |
| Bu | butyl (<i>n</i> -butyl) |
| Bz | benzoyl |
| conc. | concentrated |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCA | dichloroacetic acid |
| DCM | dichloromethane |
| DCE | 1,2-dichloroethane |
| <i>de</i> | diastereomeric excess |
| DHAP | dihydroxyacetone phosphate |
| DIBAL | diisobutylaluminium hydride |
| DIPEA | diisopropylethylamine |
| DME | 1,2-dimethoxyethane |
| DMF | <i>N,N</i> -dimethylformamide |
| DMSO | dimethylsulphoxide |
| DSC | differential scanning calorimeter |
| <i>ee</i> | enantiomeric excess |
| EI | electron ionization |
| ESI | electrospray ionization |
| Et | ethyl |
| Et ₂ O | diethyl ether |
| EtOAc | ethyl acetate |
| Et ₃ N | triethylamine |
| eV | electron volt |
| equiv. | equivalent |
| FID | flame ionization detector |
| GAP | glyceraldehyde-3-phosphate |
| GC | gas chromatography |
| Glu | glutamic acid, (<i>S</i>)-2-aminopentanedioic acid |

| | |
|----------------|---|
| Hex | hexyl |
| His | histidine, (<i>S</i>)-2-amino-3-(1 <i>H</i> -imidazol-4-yl)propanoic acid |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectra |
| <i>J</i> | coupling constant |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| MS | mass spectrometry |
| mp. | melting point |
| MW | microwave |
| <i>m/z</i> | mass per charge ratio |
| <i>n.d.</i> | not detected, value is under the limit of detection |
| NMR | nuclear magnetic resonance (spectroscopy) |
| PDB | protein data bank (http://www.rcsb.org) |
| PE | petroleum ether |
| 2PG | 2-phosphoglycolic acid |
| Ph | phenyl |
| ppm | parts per million |
| Pr | propyl |
| <i>p</i> -TsOH | <i>para</i> -toluenesulphonic acid |
| rfx | reflux |
| rt | room temperature |
| sat. | saturated |
| TBDMS | <i>tert</i> -butyldimethylsilyl |
| <i>Tb</i> TIM | wtTIM isolated from <i>Trypanosoma brucei brucei</i> |
| TCA | trichloroacetic acid |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIM | Triosephosphate isomerase (TPI is also used in the literature) |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TMSE | <i>tris</i> (trimethylsiloxy)ethylene |
| TOF | time of flight |
| Tol | tolyl, <i>para</i> -methylphenyl |
| UV | ultraviolet |
| wtTIM | wild-type triosephosphate isomerase |

List of original articles

This thesis is based on the following publications which are referred to in the text by their Roman numerals

- I Vaismaa MJP, Yliniemelä SM & Lajunen MK (2007) An improved and green preparation of 3-(alkylthio)propionic acids. *Z Naturforsch B: Chem Sci* 62(10): 1317–1323.
- II Vaismaa MJP, Leskinen MV & Lajunen MK (2009) The microwave-assisted one carbon chain extension in the preparation of terminal α -hydroxy ketones. *Synth Commun* 39(11): 2042–2052.
- III Vaismaa MJP, Yau SC & Tomkinson NCO (2009) Organocatalytic α -oxybenzoylation of aldehydes. *Tetrahedron Lett* 50(26): 3625–3627.

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1 Introduction

In the summer of 2003, our group linked up with the working consortium of protein crystallographers, biochemists and process engineers. There was an urgent need to model compounds for the study of mutated triosephosphate isomerase (A-TIM) [1] that could be used to produce new non-natural α -hydroxy aldehydes from α -hydroxy ketones.

The purpose of our study was to synthesize analogues of dihydroxyacetone phosphate (DHAP) and D-glyceraldehyde phosphate (D-GAP), which are natural substrates of triosephosphate isomerase (TIM), as well as compounds which mimic 2-phosphoglycolic acid (2PG), the most studied transition state analogue of TIM (Fig. 1). With these compounds further information on the triosephosphate isomerase reaction could be gained and furthermore they would help to determine the binding properties and the fine structure of the mutated A-TIM enzyme.

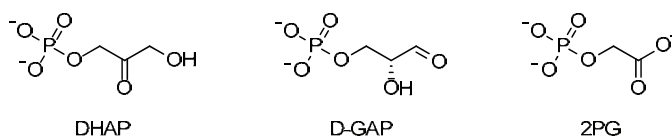


Fig. 1. The substrates and the transition state analogue of TIM.

The work of the consortium focuses on a monomeric *Trypanosoma brucei brucei* triosephosphate isomerase (*Tb*TIM) mutant A-TIM as a target biocatalyst [2]. There were several reasons to choose TIM as the reference enzyme. It is small in size and a stable biomolecule that does not require co-factors. TIM is also easy to crystallize, highly soluble, easily expressed in *Escherichia coli*, and the TIM-barrel is a well-known enzyme fold. For the consortium, the most interesting feature is the TIM-catalyzed reaction where achiral α -hydroxy ketone is transformed to an enantiomerically pure (*R*)- α -hydroxy aldehyde.

1.1 Aims of the work

This study focused on the chemistry and the synthesis of two bi-functional compounds: α -hydroxy aldehydes **1** and terminal α -hydroxy ketones **2**, as well as their interconversion into each other (Fig. 2). The keto-aldehyde tautomerism is a

specific reaction that occurs between α -hydroxy substituted aldehyde **1** and the corresponding ketone **2**. It is also known as a Lobry-de Bruyn-van Ekenstein transformation [3].

The α -hydroxy aldehydes are highly reactive compounds and contain a stereogenic centre at α -carbon, which makes them suitable substances for many biochemical transformations, while α -hydroxy ketones are relatively stable and can be readily synthesized and stored for further use.

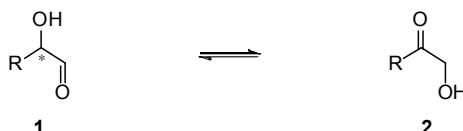


Fig. 2. Keto-aldehyde isomerism between α -hydroxy aldehyde **1 and 1-hydroxy 2-ketone **2** (= hydroxymethyl ketone, terminal α -hydroxy ketone, α -ketol).**

The aim and strategy of the work was to synthesize a library of compounds with an α -hydroxy ketone group based on natural substrates of triosephosphate isomerase, and a library of transition state analogues which mimic 2PG and have a chain length of one carbon atom shorter than the ketone. The work presented in this thesis consists of synthetic chemistry carried out in the laboratory of organic chemistry. The design and computational studies of substrate candidates were conducted in collaboration with the research groups of biochemistry and bioengineering supervised by professors Rik Wierenga and Peter Neubauer, respectively.

The ultimate goal of the consortium was to develop a method to convert an α -hydroxy ketone to an α -hydroxy aldehyde. With the exception of specific reactions of ketones [4], the synthesis of 1,2-functionalized hydroxy ketones utilizes similar synthetic protocols to that of α -hydroxy aldehydes. Often the terminal α -hydroxy ketones also are synthesized via tautomerization of α -hydroxy aldehyde intermediate [5]. Because of these reasons, the literature survey of this thesis mainly focuses on synthetic methods, which gives an α -hydroxy aldehyde product, even though the isolated product was in some cases an α -hydroxy ketone.

As a part of the learning process of the synthesis of α -hydroxy aldehydes the author visited the research group of Doctor Nicholas Tomkinson at Cardiff University. The asymmetric organocatalytic α -oxybenzoylation of aldehydes appeared eco-friendly, interesting and important to become familiar with. The aim of the study was to develop an asymmetric synthesis of α -oxo functionalized

aldehydes. Being a part of the development of a synthetic method, which created α -hydroxy aldehydes in an asymmetric and rather stable form using a non-toxic recyclable catalyst in the presence of air and moisture, was one of highlights of the PhD study.

The results from the annual KETJU seminar organised by the Academy of Finland in 2009 were the emphasis of the importance of inventing a new method of synthesis for α -hydroxy aldehydes and the need to create more environmentally benign one-carbon synthons for homologation reactions.

1.2 Green chemistry

At the beginning of this research project, there were two important aspects in modern synthetic chemistry, which our group was focused on: the concept of green chemistry and synthetic applications using a microwave heating technique. The philosophy of the design, selection and carrying out chemical synthesis were the twelve principles of green chemistry [6]. Green chemistry includes the following precepts: the unnecessary production of chemical waste and the level of its toxicity should be considered and whenever possible minimised. Reactions should be designed in such a way that most of the materials used in syntheses are included into the final product. The toxicity and the environmental impact of the reagents and final products should be low. Wasteful isolation and purification processes should be made less necessary. Energy requirements need to be considered. Bulk chemicals should be readily accessible and preferably renewable. Respectively renewable catalytic processes are better than stoichiometric reactions. Chemical transformations should be easy to monitor and control from the beginning to the end of the reaction. The risk of hazards, chemical accidents and leaks to the environment should be minimized. [6]

Thus, the development of a green method to prepare α -oxy substituted aldehyde and ketones in a stable form has been one goal during this research. Organocatalysis [7] as well as biocatalysis [2] would provide a solution to this. At their best, catalysis will happen with a quantitative conversion and high selectivity in water at ambient temperature creating no toxic waste.

Microwave-assisted organic synthesis [8] can be considered as one way of improving the syntheses or as a concrete application to improve energy efficiency and to decrease the time of the chemical transformation. [9] This also is in accordance with the principles of green chemistry.

2 The synthesis and applications of α -hydroxy aldehydes and their synthetic equivalents

The main product of the reaction of triosephosphate isomerase is an α -hydroxy aldehyde. Thus the exclusive study of α -hydroxy aldehydes and their synthetic equivalents was deemed necessary in order to build a better understanding of this product. How would it act in different conditions, how it could be isolated, or protected *in situ*, or if nothing else, analysed and determined thoroughly.

The α -hydroxy aldehydes and their synthetic equivalents are an interesting subject from the synthetic point of view. They are valuable synthetic intermediates and building blocks for the synthesis of carbohydrates and analogues via chemical or enzymatic aldol reaction. [10] They are also useful precursors of oxiranes, allylic alcohols, 1,2-diols and other structural units in syntheses of natural products [11]. The α -hydroxy carbonyl compounds are structural subunits of natural products including sugars and β -hydroxy- α -amino acids [12].

The synthesis of α -hydroxy aldehydes can be summarized in five main routes (Fig. 3). Firstly, the selective oxidation of primary alcohol **3** provides the α -hydroxy aldehyde functionality. Secondly, the use of reducing agents with α -hydroxy substituted reactant synthons having the oxidation state of carboxylic acid, ester, and amide (**4a**, X = OH, OR, NH₂) or with α -hydroxy nitriles **4b**.

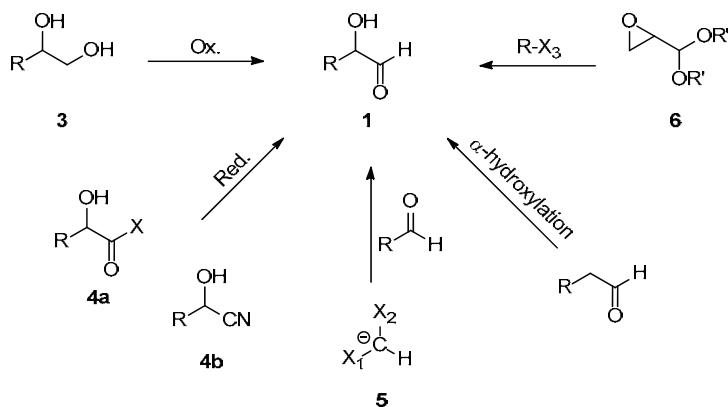


Fig. 3. The synthesis of α -hydroxy aldehydes.

Thirdly, formulation of carbonyl compounds using an anion derived from hetero disubstituted carbanions **5** as a formyl anion equivalent gives α -hydroxy aldehyde

acetals which can be hydrolysed to α -hydroxy aldehydes **1**. The fourth common method is the α -hydroxylation of aldehyde or their enol, which is nowadays widely utilized in organocatalytic reactions. Alternatively, α -hydroxy aldehyde equivalents are obtained, either by the ring opening of a 2,3-epoxy-acetal **6** by various nucleophiles or by substitution of metal halide compounds. [10, 13]

α -Hydroxy aldehydes are very difficult to purify and characterise since they are sensitive to air, moisture and heat. Therefore, the last step in their synthesis has to be efficient and should not generate by-products that need laborious separation. Often reactions have been continued further directly from the non-isolated reaction media containing hydroxy aldehydes or its synthetic equivalents. The protection of the α -hydroxyl group with a bulky substituent or the acetalisation of the free aldehyde functionality can in some cases be used to stabilize the forming product.

Novel methods on the preparation of enantiomerically pure α -hydroxy aldehydes consist of transformations with enzymes, as well as chiral auxiliaries, or chiral starting materials [11]. The problem in this study is that even the mildest reaction conditions generally lead to partial racemisation or isomerism into the achiral α -hydroxy ketone.

The modification of α -hydroxy aldehydes is a primary importance in the synthesis of many biologically active derivatives [14, 15]. Besides naturally occurring aldehydes as (*R*)-glyceraldehyde, (*S*)-lactaldehyde or D-glucose (Fig. 4), it is difficult to obtain other chiral α -hydroxy aldehydes in a large scale.

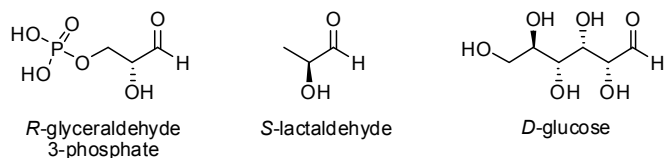


Fig. 4. Some naturally occurring α -hydroxy aldehydes.

2.1 Stability of α -hydroxy aldehydes

α -Hydroxy aldehydes are known to rearrange to α -hydroxy ketones easily (Fig. 5). The inductive effect caused by the adjacent hydroxyl group intensifies electrophilicity of the α -carbon and increases the rate of enolization and

conversion of aldehyde into the more stable keto form. The α -hydroxyl also makes the aldehyde carbon highly reactive, which have been exploited in natural processes. In addition, the α -hydroxy aldehydes are versatile starting materials in synthetic chemistry. The downside of the high reactivity in both natural bioprocesses and organic syntheses is that α -hydroxy aldehydes need to be protected (Fig. 5). In highly diluted solutions some free α -hydroxy aldehydes have been postulated to survive for some days [16]. Generally, it is the most useful to protect the aldehyde functionality than the hydroxyl group in order to prevent further reactions. Aldehyde hydrates and cyclic structures containing hemiacetals are the most common aldehyde protections in biochemical processes. Different acetals and protection of α -hydroxyl group are commonly utilized in synthetic applications. As far as we know there has been no synthetic application published in which α -hydroxy ketones have been used as a starting material towards α -hydroxy aldehydes.

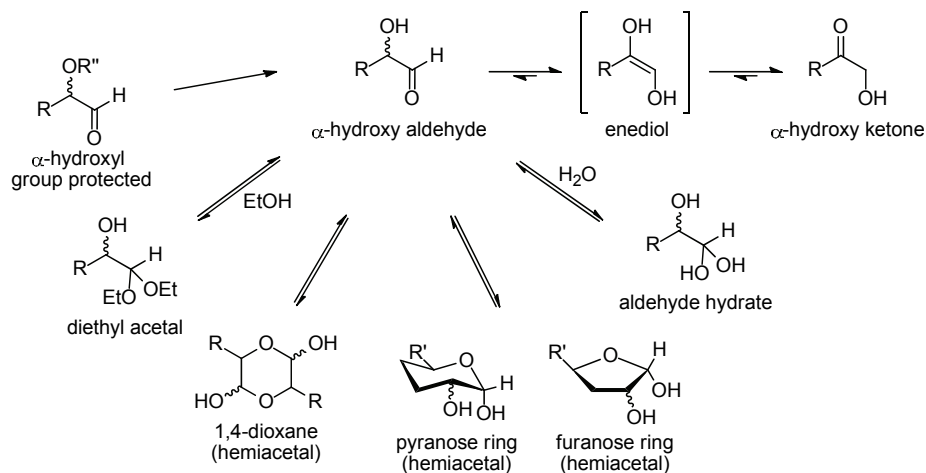


Fig. 5. The protection and natural occurrence of α -hydroxy aldehydes. Herein every transformation except tautomerization to α -hydroxy ketone preserves the chirality on the α -carbon reversibly.

2.2 Analysis of α -hydroxy aldehyde products

α -Hydroxy aldehydes are known to be challenging to handle because of their sensitivity. This causes variable problems to detection, determination and

confirmation of the success of the synthesis. In most of cases, products cannot be analysed directly but reaction intermediates or their derivatives are used to inform the existence of the α -hydroxy aldehyde. Generally, it is more convenient to continue a reaction scheme by one step forward than trying to analyse the labile α -hydroxy aldehyde compounds.

The optical purity of the protected α -hydroxy aldehydes is commonly determined through reduction to more stable 1,2-diols **3** which can then be transferred into a chiral HPLC column. It should be noted that the dimeric derivative (Fig. 5) also give a similar 1,2-diol product after the sodium borohydride reduction as the corresponding monomeric aldehydes [17]. Other methods such as the measurement of the optical rotation or the determination of the enantiomeric ratio based on NMR signals of the Mosher esters [18] have been occasionally used.

α -Hydroxy aldehydes are often synthesized as racemic mixtures. The handling of sensitive compounds has pushed synthetic methods to be as quick and easy to perform. The high yield and optical purity of the reaction are secondary matters after having at least some product in the flask. However, optically pure substances can be obtained through purification. Kinetic resolution is a gentle way of purifying these sensitive compounds. For example, a yeast transketolase catalyzed a kinetic resolution of racemic α -hydroxy aldehydes **1** has been reported (Fig. 6) [19]. Racemic aldehyde **1** reacted with lithium hydroxypyruvate (**7**) in the presence of transketolase enzyme to give 5-substituted 5-deoxy-D-xylose **8** and unreacted (*S*)-2-hydroxy aldehydes **S-1** in high optical purity. Interestingly, it was observed that enantiomerically pure **S-1** did not dimerize as easily as the racemic mixture did.

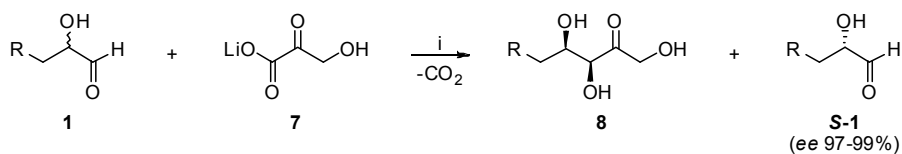


Fig. 6. Reagents: i) Yeast transketolase, Tris-HCl pH 7.6 buffer, 30 °C, 24 - 168 h.

2.3 Functional group transformations to α -hydroxy aldehyde

2.3.1 Reduction of α -hydroxy carbonyl derivatives

There are some common synthetic procedures for the reduction of a carboxylic acid derivative to an aldehyde. Obviously, an easy way to produce optically pure α -hydroxy aldehydes is to start from naturally occurring α -hydroxy carboxylic acids [20] which already have the optimal chirality. On the other hand, the direct reduction of carboxylic acids to aldehydes is not a convenient procedure since the reaction easily overreacts to alcohol. However, the reduction of the chiral α -hydroxy carboxylic acid by lithium aluminium hydride generates optically pure 1,2-diols which could be later oxidized backwards to the corresponding aldehyde. [21] The milder method is the reduction of esters of α -hydroxy carboxylic acid with diisobutylaluminium hydride (DIBAL) [22]. Another reduction used in the synthesis of α -hydroxy aldehydes are the Rosenmund catalytic hydrogenation of an acid chloride derivative with poisoned palladium [23] and the reduction of tertiary amides by various reducing agents [24-27].

2.3.2 Reduction of α -substituted nitriles

A simple synthesis of protected α -hydroxy aldehyde **9a** via the reduction of α -trimethylsiloxy nitrile **10a** [28] with DIBAL has been reported in many articles (Fig. 7). A more detailed study of crucial hydrolysis steps (iii-v) has been published by Oguni *et al.* [29].

Conversions of α -trimethylsiloxy nitrile **10a** and α -*tert*-butyldimethylsiloxy nitrile **10b** to the corresponding aldehydes **9a-b** consist of two steps (Fig. 7 & Fig. 8). At first, the reduction of nitriles **10a-b** with DIBAL gave corresponding imines which were hydrolysed to aldehyde **9a-b** with a treatment of an aqueous acid solution. In a situation when there was no hydrogen bound to an α -carbon, the hydrolysis and the cleavage of the trimethylsilyl protective group were successful even under rather acidic conditions (Table 1). Remarkably, the use of aqueous sulphuric acid in the hydrolysis to **9a-b** did not lead to premature cleavage of silyl ether bonds. Diluted hydrochloric acid was suitable for the deprotection of **9a** to α -hydroxy aldehyde **1**. [29, 30]

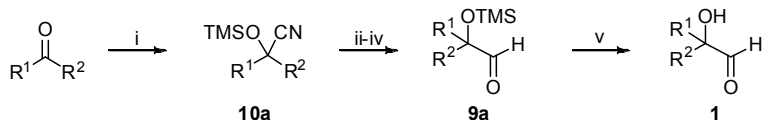


Fig. 7. Reagents: i) TMS-CN, ZnI₂; ii) DIBAL, hexane, 0 °C, 1 h; iii) Et₂O/aq. sat. NH₄Cl; iv) aq. H₂SO₄, 15 °C; v) aq. HCl, 15 °C. See Table 1 for details.

Table 1. Hydrolysis of α -trimethylsiloxy nitriles **10a** to α -hydroxy aldehydes **1**.

| Entry | R ¹ | R ² | H ₂ SO ₄ , M | Time, h | Isol. yield of 9a | HCl, M | Time, h | Isol. yield of 1 |
|-------|--|----------------|------------------------------------|---------|--------------------------|--------|---------|-------------------------|
| 1 | Ph | Ph | 0.8 | 18 | 86 | 9 | 15 | 80 |
| 2 | Ph | Me | 0.65 | 19 | 63 | 3 | 14 | 65 |
| 3 | -CH ₂ (CH ₂) ₃ CH ₂ - | | 0.5 | 19 | 61 | 1 | 5 | 75 |
| 4 | pentyl | pentyl | 0.8 | 19 | 79 | 6 | 14 | 72 |

α -Hydroxy aldehydes containing an α -proton are more reactive and sensitive than aldehydes without an α -proton. Therefore, the nitriles **10b** were reduced to α -siloxy aldehydes **9b** at a lower temperature than previously, and the slightly bulkier *tert*-butyldimethylsilyl protective group was used (Fig. 8). In turn, the treatment of the formed *N*-organoaluminium imine intermediate with cold methanol followed by hydrolysis with 1 M H₂SO₄ solution afforded TBDMS protected α -hydroxy aldehydes **9b** in good yields (Table 2). [30]

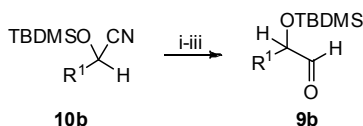


Fig. 8. Reagents: i) DIBAL, toluene; ii) MeOH, 0 °C, 2 h; iii) 1 M H₂SO₄, 18 °C, 3 h.

Table 2. The reduction of α -*tert*-butyldimethylsiloxy nitrile **10b** to the corresponding aldehydes **9b** by DIBAL in different reaction conditions.

| Entry | R ¹ | Temperature, °C | Time, h | Isolated yield of 9b |
|-------|-----------------|-----------------|---------|-----------------------------|
| 1 | Ph | - 78 | 5 | 67 |
| 2 | hexyl | - 78 | 2 | 86 |
| 3 | Cyclo-hexyl | - 40 | 2 | 89 |
| 4 | ^t Bu | - 40 | 2.5 | 80 |

Respectively, the reduction of THP-protected chiral α -hydroxynitriles **11** at $-78\text{ }^\circ\text{C}$ yielded chiral α -tetrahydropyranloxy aldehydes **9c** (Fig. 9). The key step was the preparation of chiral hydroxynitriles **4b** in a high enantiomeric purity by the enzyme catalysed asymmetric addition of hydrogen cyanide to an aldehyde. After tetrahydropyranyl protection, the reduction of **11** was carried out by DIBAL. Some aldehydes **9c** ($R = {}^n\text{Pr}$ or Ph) were stable enough to be purified by column chromatography after which they were isolated in 60% and 57% yield, respectively. The other aldehydes in Fig. 9 were too sensitive to air and moisture and were used directly in the Horner-Wittig reaction. Yields of the final products **12** were good in all cases and the high enantiomeric purity was successfully preserved throughout the reaction sequence. [31]

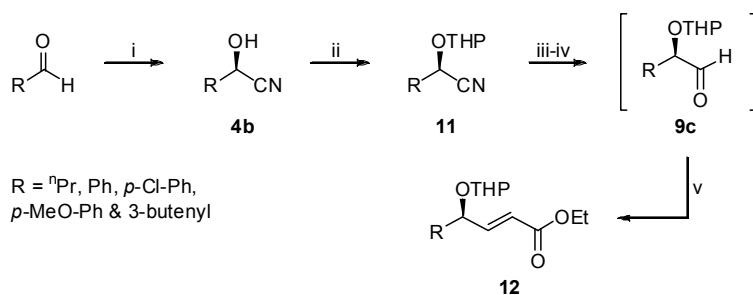


Fig. 9. Reagents: i) HCN, *R*-hydroxynitrile lyase; ii) 2,3-dihydroxyran, *p*-TsOH; iii) DIBAL, Et_2O , $-78\text{ }^\circ\text{C}$; iv) 10% H_2SO_4 , $-15\text{ }^\circ\text{C}$, 10 min; v) lithium diisopropylamide, $\text{Ph}_2\text{POCH}_2\text{CO}_2\text{Et}$, THF, $-78\text{ }^\circ\text{C}$ to rt (ee 86–97%).

2.3.3 Selective oxidation of 1,2-diols

The Swern oxidation [32] and the oxidation using pyridinium chlorochromate [33] or Dess-Martin periodate [34] are mild and well known methods to convert primary alcohol to aldehyde. The clean synthesis of α -hydroxy aldehydes from 1,2-diols **3** usually demands an extra reaction step to protect secondary hydroxyl with a group which later can be easily cleaved. There are also some oxidation methods in which the primary hydroxy group have been oxidized in the presence of the secondary hydroxyl [35-39]. The treatment of the 1,2-diol **3** with a selective oxidizing agent would be a straightforward method to α -hydroxy aldehyde. However, the synthetic reactions did

The oxidative hydroxylation of silyl enol ether **16** with hydrogen peroxide and cetylpyridinium peroxotungstophosphate caused the cleavage of the silyl group and rapid tautomerization to α -hydroxy ketones [13]. When the oxidation of **16** was carried out with *m*-chloroperbenzoic acid instead, silyl *m*-chlorobenzyl acetal **17** was isolated after the hydrolysis (Fig. 11) [42]. The reaction was believed to proceed via an epoxy intermediate as in Fig. 10, but this time followed by a nucleophilic attack of benzoyloxy anion. The reaction of **17** with acetic anhydride followed by hydrolysis generated an α -acetoxy aldehyde **9d** (Table 4).

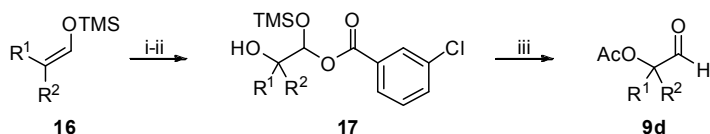


Fig. 11. Reagents: i) *m*-CPBA, DCM, rt, 1 h; ii) H₂O; iii) Ac₂O, Et₃N, 4-pyrrolidino-pyridine (cat.), dry Et₂O, rt, 15 min; H₂O.

The yields of **9d** are presented in Table 4. Acetyl protected products were stable enough to be purified by a vacuum distillation. [42] It is also worth noting that since this reaction has the epoxy intermediate, introduction of enantioselectivity could be possible [43]. Furthermore, because silyl ether and benzyl ester readily hydrolyse in water, the compound **17** could be a valuable α -hydroxy aldehyde equivalent for the TIM studies.

Table 4. The synthesis of protected α -hydroxy aldehydes **17** and **9d** from silyl enol ether **16**.

| Entry | R ¹ | R ² | Yield of 17 , % | Yield of 9d , % ^(a) |
|-------|--|----------------|------------------------|---------------------------------------|
| 1 | Ph | Me | 85 | |
| 2 | PhCH ₂ | H | 72 | 42 |
| 3 | -CH ₂ CH ₂ CH ₂ CH(CO ₂ Et)CH ₂ - | | 93 | 45 |
| 4 | Me | Me | 74 | |
| 5 | Octyl | H | 84 | 46 |
| 6 | -CH ₂ CH ₂ CH=CHCH ₂ - | | 79 | 39 |

a) Yields of direct conversion of **9d** from **16** without isolation of the intermediate **17**. Yields are determined from the distilled products.

Enol acetates **18** were utilized in the synthesis of α -oxo functionalised aldehydes (**9d** & **1** in Fig. 12). In 1996, Kern and Spiteller [16] reported the synthesis of racemic long chain aliphatic α -hydroxy aldehydes [**1**, R = C₅H₁₁, C₁₄H₂₉, (CH₂)₇CO₂Me] through a thermal rearrangement of epoxy enol esters **19** in the presence of a protic acid, followed by enzymatic hydrolysis of the intermediate α -acetoxy aldehydes **9d** (Fig. 12). Some racemic α -hydroxy aldehyde **1** was formed but mostly in dimeric form. Later, it was shown that direct enantioselective enzyme catalysed hydrolysis of **19** provided optically pure α -hydroxy aldehydes *S*-**1** (Table 5) [44]. The reaction was assumed to proceed via the unstable oxiranol intermediate **20**. The good *ee* value of the **1** originated from the lipase catalysed kinetic resolution which left the *R,R*-isomers of **20** unreactive (Table 5, entries 1-2). In turn, different α -substituents (R) affected highly the enzyme's activity and resolution (entries 3-4).

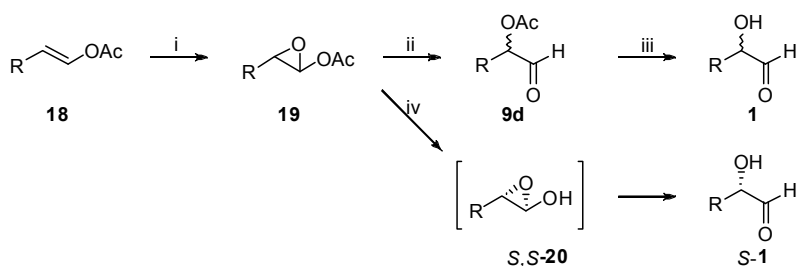


Fig. 12. Synthesis of α -hydroxy aldehyde **1 from enol acetate **18**: Reagents: i) *m*-CPBA, DCM, rt, overnight; ii) *p*-TsOH, no solvents, 80 °C, 5–10 min ; iii) Hog liver esterase (563U), 35 °C overnight; iv) pH 7 phosphate buffer, hexane, see Table 5.**

Table 5. Enzymatic hydrolysis of racemic epoxy ester **19. Conversion and enantiomeric purity of (*S*)- α -hydroxy aldehyde **S-1**. [44]**

| Entry | R | Enzyme ^(a) | Time, h | Conv., % ^(b) | <i>ee</i> , % ^(c) | Opt. purity of the residue 20 , % ^(d) |
|-------|--------------------------------------|-----------------------|---------|-------------------------|------------------------------|---|
| 1 | ⁿ Bu | PSL | 24 | 47 | 75 | 88 |
| 2 | ⁿ Bu | CAL | 4 | 46 | 100 | 89 |
| 3 | Bn | CAL | 1 | 62 | 15 | 46 |
| 4 | CH ₂ CH(OMe) ₂ | CAL | 11 | 64 | 12 | 96 |

a) PSL = *Pseudomonas* lipase (species unknown), CAL = *Candida Antarctica* lipase.

b) Conversion of **S-1** determined by GC.

c) Enantiomeric excess of **S-1** was measured after methylation of **1** to dimethylacetal which was converted to the Mosher's ester and analyzed by ¹⁹F and ¹H NMR.

d) Optical purity of the unreactive residue *R,R*-**20**.

The asymmetric dihydroxylation (AD) [45] of vinyl derivatives **21** containing a good leaving group at terminal carbon have been used in the synthesis of optically pure α -hydroxy aldehydes **1** and corresponding ketones **2** (Fig. 13). [46]

Examples of different vinyl substituents have been reported, in both racemic and asymmetric sense. The dihydroxylation and subsequent rearrangement of α -haloalkenes (**21** where X = Cl or Br) [47] and enol ethers (X = MeO or TBDMSO) [48] have successfully generated α -hydroxy aldehydes **1** under the asymmetric control. α,β -Unsaturated nitriles and phosphonates can also undergo racemic dihydroxylation providing the corresponding base labile cyanohydrins and phosphates [**22**, where X = CN or PO(OR')₂] [49]. However, in most of these cases, only achiral hydroxyketones **2** have been detected after isolation procedures.

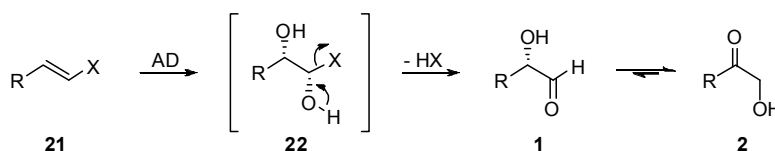


Fig. 13. The one-step procedure of α -hydroxy carbonyl compounds from terminal alkenes via the asymmetric dihydroxylation and the 1,2-elimination. [X = Cl, Br, OR', SO₂R', NO₂, CN, PO(OR')₂; R' = alkyl, aryl, etc.]

Sharpless asymmetric dihydroxylation of vinyl sulphones (**21**, when X = SO₂R') has been introduced to the synthesis of α -hydroxy aldehydes by Evans and Leffray (Fig. 13 & Fig. 14) [46]. Vinyl sulphones are easily accessible from terminal alkenes via cross metathesis with phenyl vinyl sulphone [50] or by iododisulphonation followed by elimination [51]. AD-mixtures are commercially available mixtures of reagents for the Sharpless asymmetric dihydroxylation of alkenes. The mixtures are available in two variations, "AD-mix- α " and "AD-mix- β " containing the ingredient reported by Sharpless [45].

The stability of the non-protected α -hydroxy aldehyde **1** turned out to be the major problem in these type asymmetric dihydroxylation reactions [46]. The dihydroxylation product **1** from vinyl phenyl sulphones **23** were therefore not isolated, but directly converted into the corresponding α,β -unsaturated esters **24-25** using a Horner-Wadsworth-Emmons protocol [52] (Fig. 14) [46] or by a boron-Mannich reaction with β -styrenyl boronic acid and primary amine to give *anti*-1,2-amino alcohols **26** (Fig. 15) [53].

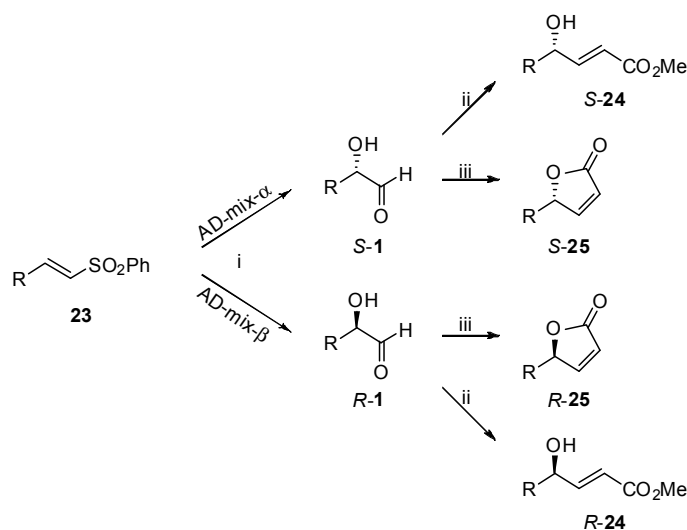


Fig. 14. Reagents: i) AD-mix, $MeSO_2NH_2$, $tBuOH/H_2O$, $25\text{ }^\circ C$, 24 h; ii) $(EtO)_2POCH_2CO_2Me$, NaH , THF, $20\text{ }^\circ C$, 12 h; iii) $(F_3CCH_2O)_2POCH_2CO_2Me$, NaH , THF, $-78\text{ to }20\text{ }^\circ C$, 5 h. [46]

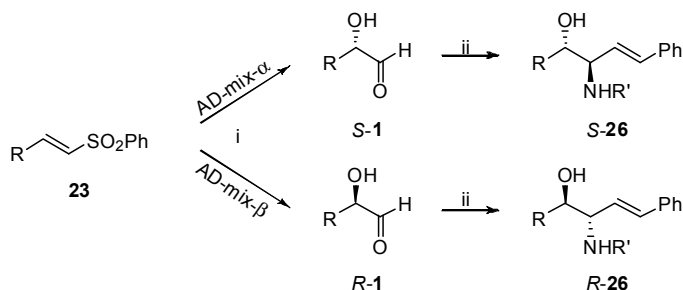


Fig. 15. Reagents: i) AD-mix, $MeSO_2NH_2$, $tBuOH/H_2O$, rt, 24 h; H_2O ; ii) $PhCH_2CH_2B(OH)_2$, NHR' , DCM, rt, 40 h; H_2O (overall yield 35–51%, ee 83–95%). [53]

Recently, the Sharpless asymmetric dihydroxylation of enol benzoates **27** was reported by Ready *et al.* [54] (Fig. 16). They studied the preparation of trisubstituted, stereo-defined enol derivatives as 1-methyl substituted enol benzoates **27**. It was presented earlier in the literature that benzoyl substituents interact favourably in the reaction with commercial AD-mixtures [55]. The asymmetric dihydroxylation of the enol **27** led to a good yield and high enantiomeric purity of the isolated diols **29a-g** (Table 6). The moderate yields can

be accounted for by a steric hindrance around the double bond (entry 3) and a possible side reaction with the additional unsaturated part of the tail (entries 4 & 6). [54]

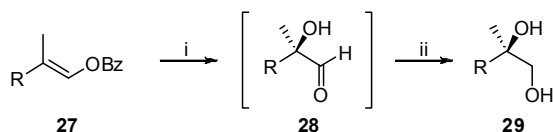


Fig. 16. Reagents: i) AD-mix- β , t BuOH/H₂O, 0 °C, 12 - 24 h; ii) NaBH₄, 0 °C, 2 h; H₂O.

Table 6. The asymmetric dihydroxylation of enol benzoates **27**. Enantioselectivity and the yields after reduction of the non-isolated aldehyde **28a-g** to diol **29a-g**, and after cyclization of **28h** to 7-hydroxy-frontalin (**30**). [54]

| Entry | R | Product | ee of 29 , % ^a | Isol. yield of 29 , % |
|-------|-----------------|------------------------|----------------------------------|--------------------------------|
| 1 | <i>n</i> -decyl | 29a | 96 | 78 |
| 2 | Bn | 29b | 94 | 84 |
| 3 | Ph | 29c | 95 | 75 |
| 4 | | 29d | 96 | 59 |
| 5 | | 29f | 96 | 87 |
| 6 | | 29g | 95 | 75 |
| 7 | | 30 ^b | ee of 30 , 93% | Isol. yield of 30 , 76% |

a) The ee values were determined from monobenzoylated analogues of the diols by HPLC.

b) See Fig. 17.

The additional keto functional group offered the possibility to obtain a one-pot synthesis of hydroxy derivative of the insect phenomenon (+)-frontalin **30** from **27h** through the Sharpless dihydroxylation following the intramolecular acetalisation of (*R*)-2-hydroxy-2-methyl-6-oxoheptanal (**28h**) (Fig. 17). [54]

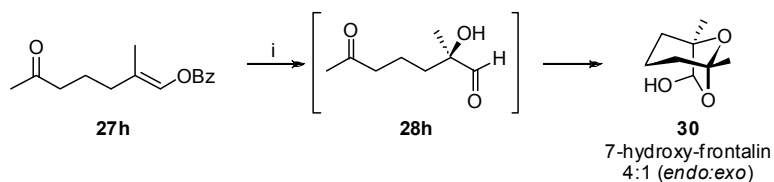


Fig. 17. Reagents: i) AD-mix- β , NaHCO_3 , $^t\text{BuOH}/\text{H}_2\text{O}$, $0\text{ }^\circ\text{C}$, 24 h (85%).

The enantioenriched α -hydroxy aldehydes **28** obtained from the dihydroxylation were useful materials for further synthetic manipulations (Fig. 18). Reactions were carried out using the Sharpless procedure [45] followed by the isolation of the formed α -hydroxy aldehyde **28b** by extraction. The crude product **28b** was not concentrated to dryness, but continued on to suitable reactions. For example, the Ohira-Bestmann homologation of α -hydroxy aldehyde **28b** in methanol provided propargyl alcohol **31** in 77% yields. Reductive amination of **28b** yielded the corresponding amino alcohol **32** (84%). Alternatively, the aldehyde was oxidised to its α -hydroxy methyl ester **33** (92%), or reacted with a Wittig reagent to afford an α,β -unsaturated ester **34**. [54]

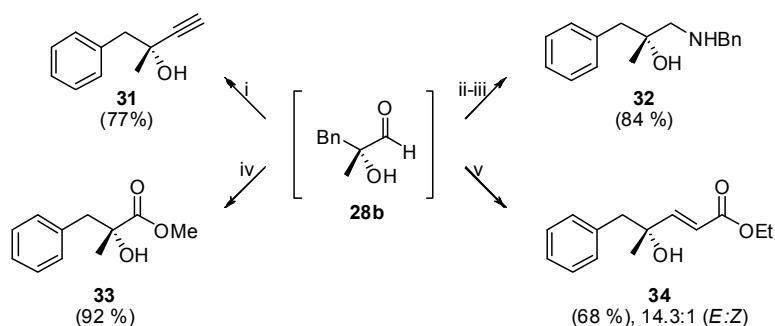


Fig. 18. Reactions of α -hydroxy aldehydes **28b.** Reagents: i) $(\text{MeO})_2\text{POCH}_2\text{COMe}$, K_2CO_3 , MeOH , $0\text{ }^\circ\text{C}$, 1 h; rt, 4 h; ii) BnNH_2 , toluene, 4 Å molecular sieves, $105\text{ }^\circ\text{C}$; iii) NaBH_4 , MeOH $0\text{ }^\circ\text{C}$, 1 h; sat. NaHCO_3 ; iv) KOH , I_2 , MeOH , $0\text{ }^\circ\text{C}$, 3 h; v) $[\text{Bu}_3\text{PCH}_2\text{CO}_2\text{Et}]\text{Br}$, NaHCO_3 , toluene, $90\text{ }^\circ\text{C}$, 3 h. [54]

The Wittig-type phosphonate chemistry can also be used in the actual synthesis of α -hydroxy aldehydes **1** (Fig. 19 & Table 7) [56]. The olefination of a carbonyl compound with tetraethyl methanediphosphonate **35a** afforded a single diethyl

(*E*)-1-alkanephosphonate isomer **36** [57]. This alkene **36** was selectively *syn*-dihydroxylated into the *threo*-diol **37** by the Sharpless procedure at the presence of 4-methyl morpholine 4-oxide [58]. Next, the elimination of the diethyl phosphate group was carried out by refluxing in an alkaline water and methanol solutions [59]. Tertiary α -hydroxy aldehydes **1** ($R^1, R^2 \neq H$) were still stable under these conditions, but aldehydes which can form enolate ($R^2 = H$) tautomerized simultaneously to hydroxymethyl ketones **2** (Table 7). [56]

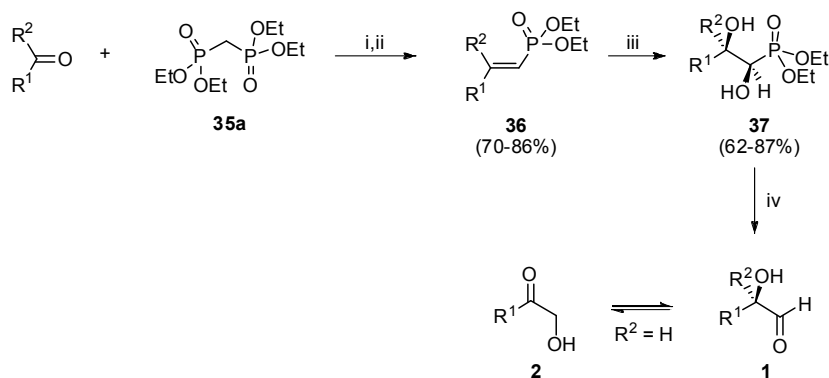


Fig. 19. Reagents: i) NaH, benzene, rfx; ii) H_3O^+ ; iii) 4-methylmorpholine 4-oxide, $^t\text{BuOH}$, H_2O , OsO_4 , rt, 48–96 h; iv) NaHCO_3 , H_2O , MeOH , rfx 1–3 h.

Table 7. The formation of tertiary α -hydroxy aldehydes **1** and hydroxymethyl ketones **2** by retro-addition of diethyl phosphite group.

| Entry | Isolated product | R^1 | R^2 | Yield of elimination, % |
|-------|------------------|-----------------|------------------------------------|-------------------------|
| 1 | 1 | Ph | Me | 65 ^a |
| 2 | 1 | | –(CH ₂) ₅ – | 63 ^a |
| 3 | 2 | Et | H | 82 |
| 4 | 2 | ⁱ Pr | H | 70 |
| 5 | 2 | pentyl | H | 75 |
| 6 | 2 | Ph | H | 84 |
| 7 | 2 | <i>p</i> -BrPh | H | 74 |
| 8 | 2 | <i>p</i> -MeOPh | H | 76 |

a) Enantiomeric excess were not reported.

In the scientific literature, there are some other phosphorus-stabilised carbon nucleophiles mentioned which can be reacted first with carbonyl compounds and then dihydroxylated to give α -hydroxy aldehyde equivalents (Fig. 20) [60].

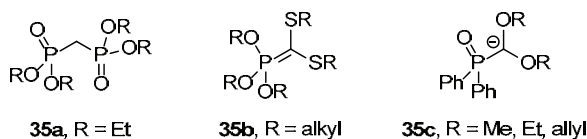


Fig. 20. Phosphorus-substituted one carbon nucleophiles.

In addition, the products **39** in Pummerer rearrangements of vinyl sulphoxides **38** (Fig. 21) collapsed in basic hydrolysis to α -hydroxy aldehydes similarly that the terminal substituted 1,2-diols **22** did after the Sharpless asymmetric dihydroxylation (Fig. 13). The variation in yields not only mirror the effect of steric hindrance of the allylic bond [R = Me (85%), ⁱPr (78%), ^tBu (48%)], but the stability of the product [R = H (62%), CH₂OBn (87%)] also effected the yield. [61]

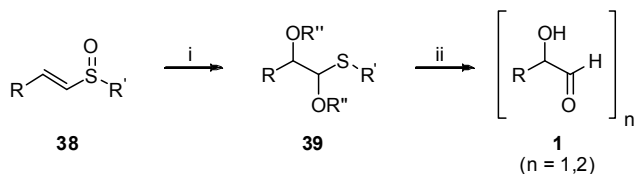


Fig. 21. Reagents: i) R''₂O, DCM, 0 °C, 15 min; NaHCO₃ (aq); ii) Et₃N (0.1 equiv.), MeOH (2.2 equiv.), DCM (0.2 M), 0 °C, 5 min. (R' = Ph, Tol; R'' = CF₃CO)

Ozone can be used to oxidize alkenes to aldehydes. Corey *et al.* have reported an enantioselective conversion of aldehyde **40** to chiral propan-1,2-dienyl carbinols **42** with a propargylborane derivative **41** (Fig. 22 & Table 8) [62]. Later, the allene compound **42** was converted to a protected α -hydroxy aldehyde **9b** by an ozone-assisted oxidation. [63]

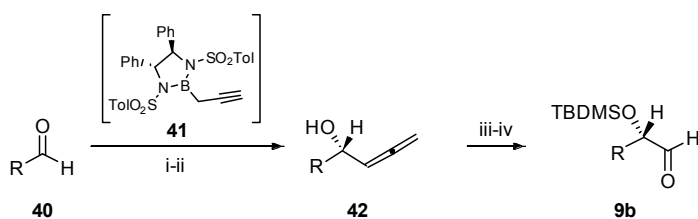


Fig. 22. Reagents: i) DCM, 78 °C, 2 h; ii) H₂O ; iii) TBDMS[SO₂CF₃], 2,6-lutidine, DCM 0 °C - rt; iv) O₃, DCM -78 °C.

Three of the previously synthesized dienylic carbinols **42** were examined in ozonolysis (Table 8). Ozone was passed into the cold solution of silylated **42** until a slight violet colour persisted. After vacuum removal of DCM the essentially pure chiral aldehyde **9b** was obtained in 89–99% yield with the original enantiomeric purity. Two important aspects to stabilise the formed product **9b** were the protection of alcohol **42** and the use of cold temperature (-78 °C) during ozonolysis. The addition of a base has been commonly used in quenching of ozonolysis [64], but this time it caused an unwanted migration of the α -hydroxyl protective group. Without the additional base, the reaction was successful even with the unstable α -hydroxy aldehydes **9b**. [63]

Table 8. The synthesis of chiral propan-1,2-diethyl carbinols **42** and ozone assisted oxidation to aldehyde **9b**.

| Entry | R | Isol. yield of 42 , % | ee of 42 , % | Abs. config. of 42 | Yield of 9b , % |
|-------|------------------|------------------------------|---------------------|---------------------------|------------------------|
| 1 | <i>n</i> -pentyl | 82 | >99 | S | 98 |
| 2 | ⁱ Pr | 74 | >99 | S | |
| 3 | cyclo-Hex | 78 | >99 | S | |
| 4 | ^t Bu | 78 | >99 | S | a) |
| 5 | Ph | 72 | >99 | R | a) |
| 6 | PhCH=CH | 74 | >99 | S | |

a) Between 89 - 99%. Individual values were not given in the original article. [63]

Mechanistically, alkene and ozone form a five-member ring intermediate which splits into two carbonyl compounds. From the green chemistry point of view, the ozonolysis of the unsaturated carbon-carbon bond can be useful because of some its harmless by-products: For example acetone molecule [65] or an additional functional group at the end of the product [66] can be cleaved (Fig. 23).

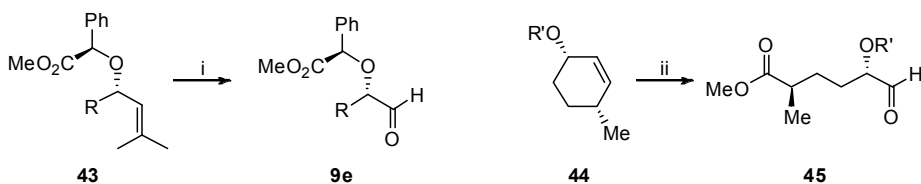


Fig. 23. Reagents: i) O_3 , MeOH, $-78\text{ }^\circ\text{C}$. (R = ^nBu , ^iPr , Ph, Hex, Allyl) [65]; ii) O_3 , NaHCO_3 , DCM-MeOH, 4:1, $-78\text{ }^\circ\text{C}$. (R' = Bz) [66]

2.4 Carbon-carbon chain extension

The transformation of carbonyl compounds **46** to α -hydroxy aldehydes **1** having an additional carbon in the main chain is called homologation, formylation, or simply, carbon chain extension (Fig. 24) [67]. This means an addition of formaldehyde molecule **47** to ketone or aldehyde **46**. The transformation is not straightforward since the direct reaction between two similar carbonyl compounds most likely yields a mixture of products. Ordinarily, the carbon atom in the carbonyl group is less electronegative than the oxygen and therefore the carbonyl carbon reacts as an electrophile. The polarity of the carbonyl functional group however can be inverted [68, 69]. In other words, formaldehyde can be in a masked form (*umpolung*) as compound **5** where the carbon atom is nucleophilic and can attack the electrophilic carbon of the second carbonyl compound **46** [70]. During the last step, the α -hydroxy aldehyde functionality is unmasked to give the wanted product **1**.

The principle of affinity inversion was introduced for the first time in the 1950s in the synthesis of α -hydroxy substituted aldehydes **1** via cyanohydrins **50** (Fig. 24) [71]. Cyanide probably is the most often described carbon nucleophile in organic chemistry textbooks. It is also known that nature utilizes cyanides in the nitrilase-mediated cyanation of aldehydes [60]. The strategy in carbon-carbon bond formation with cyano compounds is relatively easy as carbon is nucleophilic and reacts selectively with the electrophilic carbonyl carbon to form **50**. The conversion of cyanohydrin **50** to α -hydroxy aldehydes requires two sequential reactions, which are the reduction to imine and hydrolysis [72].

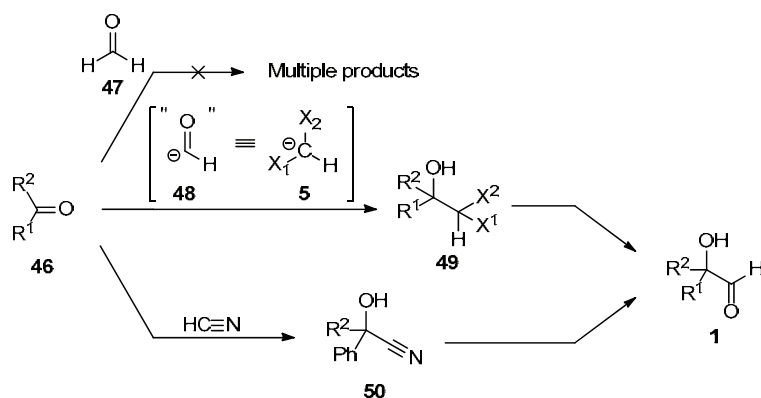


Fig. 24. The synthesis of α -hydroxy aldehydes **1** by a masked formylation reaction (umpolung). (R^1 = alkyl, H; R^2 = alkyl)

Different formyl anion equivalents **48** have been utilized in syntheses [60]. Carbanions **5** derived from the protective ketones and aldehydes are well studied (Fig. 25). After the discovery that a carbanion can be formed from 1,3-dithiane by metalation with *n*-butyllithium [73], dithio carbanions (**5**, X^1 , X^2 = SR) have become the most studied formyl anion equivalents. The deprotection (*unmasking*) of *S,S*-acetals need much stronger reagents than oxygen based acetals [68]. In the stability and the facility of the deprotection *O,S*-acetals are located inbetween acetals and thioacetals. *O,O*- and *O,N*-acetals are more labile toward the hydrolysis than others and, since they lack the slightly electronegative sulphur atom, their umpolung reaction needs further modification [74-77]. An additional substituent in nitrogen atom makes *N*-acetals good chiral auxiliaries for asymmetric syntheses. Furthermore, the replacement of the oxygen atom in the *O,N*-acetal anion with a sulphur makes it possible to form a stable carbanion and increases stereoselectivity of a reaction [78]. Cyclic structures have also shown to increase stability of carbanion intermediate **5** and the corresponding acetal **49**, and are used to add stereoselectivity to the reaction [79]. Unlike *O,O*-acetals, there is only a minor difference in hydrolytic stability between cyclic and acyclic thioacetals. Respectively, oxazolines are more stable than *O,N*-acetals. [80]

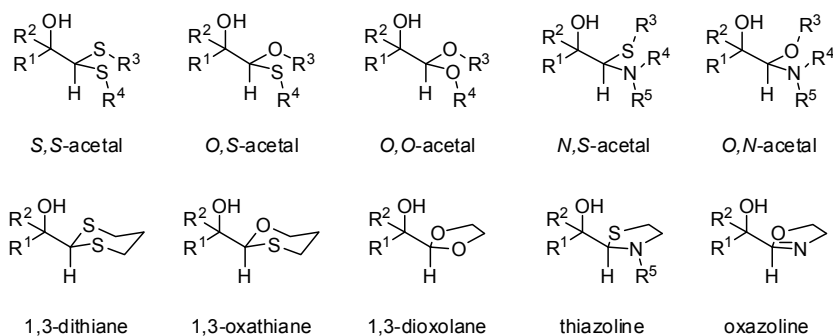


Fig. 25. An example of α -hydroxy aldehyde acetals which have been utilized in the homologation of ketones or aldehydes.

2.4.1 The primary Corey-Seebach's *S,S*-acetals

Thiol, sulphoxide and sulphonyl-based formaldehyde anion equivalents probably are the most used reagents in carbonyl homologation reactions. There are many variables of these in the literature (Fig. 26). [68] According to our knowledge, Corey and Seebach introduced the first carbon nucleophile, lithium derivative of 1,3-dithianes **56** (Fig. 27) [73]. The *S,S*-acetal derivatives **57** mostly gave the stable ketone product (**58**, R = alkyl) instead of an α -hydroxy aldehyde (R = H) [81, 82]. The conversion of *S,S*-acetals to aldehydes was generally carried out by complex formation with a metal ion or by making one sulphur atom more electrophilic by oxidation [72].

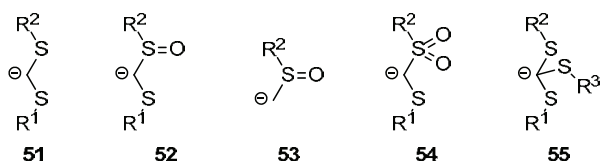


Fig. 26. Thioacetal carbanion variants which were used as a formyl anion equivalent in the synthesis of α -hydroxy aldehydes. Sulphoxide **53** was used in Pummerer-type rearrangement [12, 61] (see Fig. 21). [68]

Disadvantages of *S,S*-acetals are related to their environmental impact. Most thiols and dithiols have an obnoxious odour. Therefore to work with them

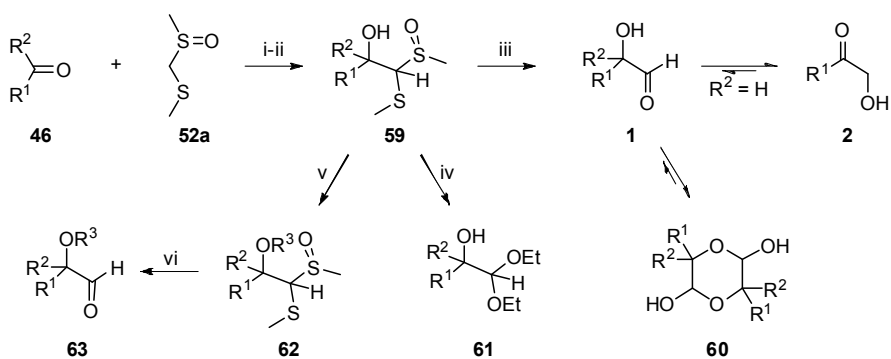


Fig. 28. Reagents: i) ⁿBuLi, THF, -10 °C, 1 h; ii) H₂O; iii) HCl, THF, rt, 1½ h; iv) CH(OEt)₃, EtOH, a drop of conc. H₂SO₄, rt, 4 days; v) NaH, MeI or BnBr, DMSO, rt; vi) CuCl₂, DME, rt, few hours. (R¹ = aryl; R² = aryl, H; or **46** = cyclohexanone).

When the methylsulphoxide group of **52a** was exchanged to a toluenesulphonyl group (see Fig. 29), a smooth hydrolysis of tosylthioacetal derivative **65** to **66** was able to be carried out with silica, by simple acidic hydrolysis or with cupric chloride dihydrate. The photo irradiation with a 254 nm light under neutral or basic conditions was even a milder method to unmask the protected α -hydroxy aldehyde **65**. [85]

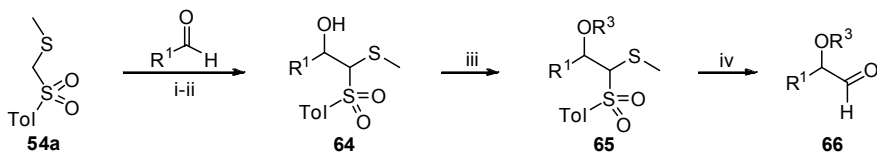


Fig. 29. Reagents: i) ⁿBuLi, THF, -78 °C, 1 h; ii) H₂O; iii) hydroxyl protection; iv) Et₂O, aqueous NaHCO₃, *hν*, 1h. (R¹ = Ph, BnCH₂, BnOCH₂; R² = Et, Ph; R³ = Ac, MeOCH₂, THP).

An interesting feature of the sulphoxide is its chirality that can be utilized in an enantioselective synthesis of α -hydroxy aldehydes (Fig. 30) [86]. A chiral formyl anion equivalent was formed by lithiation of (+)-(*S*)-*p*-tolyl *p*-tolylthiomethyl sulphoxide (**52b**). This further reacted with aryl aldehydes **67a-b**. The observed diastereoisomeric ratios of **68a** were presented to yield from the cyclic transition state stabilized by the chelation through the lithium ion (Fig. 30). The

enantioselectivity derived from the slightly less hindered phenylacetaldehyde (**67b**) was dramatically lower than with benzaldehyde (**67a**).

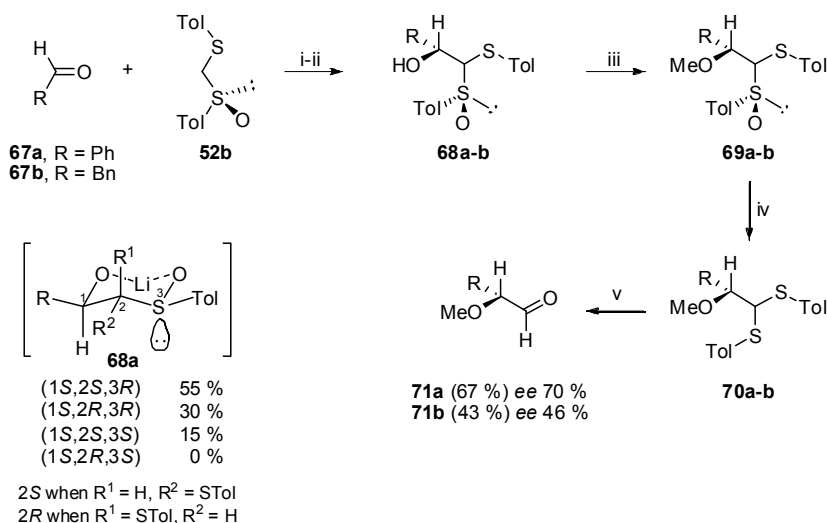


Fig. 30. Reagents: i) ⁿBuLi, THF, -20 °C, 20 min; **67a-b**, -78 °C, 15 min; ii) sat. NH₄Cl; iii) Me₂SO₄, Bu₄NOH, DCM, H₂O, rt, 3 min; iv) **69a**; Ph₃P, NaI, I₂, MeCN, rt, 10 min or **69b**; (Me₂N)₃P, NaI, I₂, MeCN, rt, over night; v) I₂, NaHCO₃, dioxane, H₂O rt, 20 min.

The direct hydrolysis of methyl protected thioacetal *S*-oxide **69a-b** to aldehyde **71a-b** was unsuccessful. The acidic hydrolysis was ineffective and cerium(IV)ammonium nitrate, copper(II)chloride, methylfluorosulphonate, or *O*-mesitylenesulphonylhydroxylamine-assisted hydrolysis led to a mixture of products. Therefore, *S*-oxide **69** was first reduced to dithioacetal **70** which then was hydrolysed to aldehyde **71** having the original orientation at the α-carbon. [86]

The umpolung reactions are not limited only to substitutions of aldehydes or ketones by formyl anion equivalent, but also acid chlorides [87] and esters [88] can be used (Fig. 31 & Fig. 32). In the case of product **73**, the masked α-oxo aldehyde must first be reduced and then unmasked to give α-hydroxy aldehyde **75**. The acid chloride **72** underwent a reaction with lithium salt of optically pure (*S*)-sulphoxide **52b** to give β-oxosulphoxide **73** (Fig. 31) [87]. It is noteworthy that the reduction of the racemic ketone **73** with LiAlH₄ was reported to give a racemic mixture of two diastereomers of β-hydroxysulphoxide **74a** and **74b**. Theoretically it was possible to obtain four different diastereomers (Fig. 31). [89]

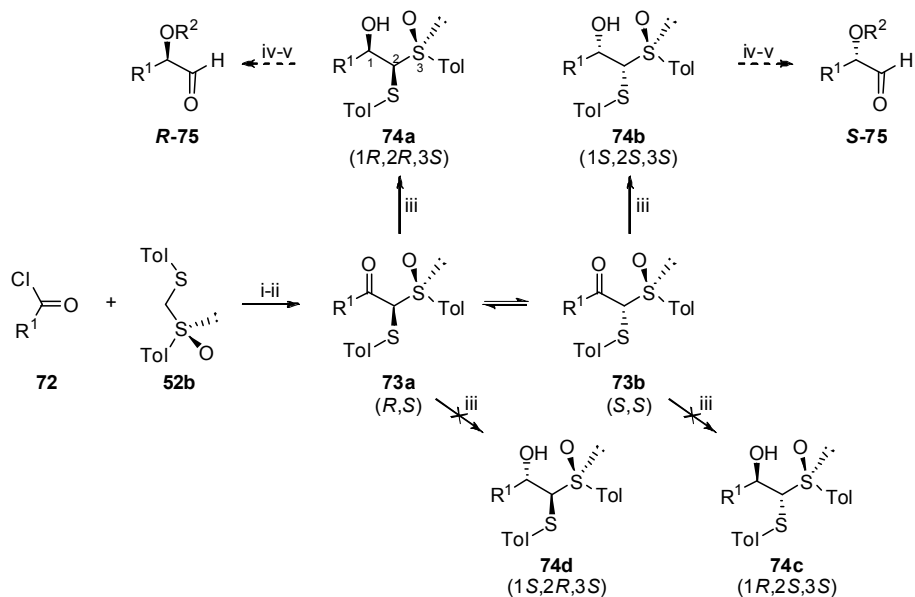


Fig. 31. Reagents: i) $n\text{BuLi}$, THF; ii) H_2O ; iii) LiAlH_4 , Et_2O , THF, $-78\text{ }^\circ\text{C}$; iv-v) same as in Fig. 30. ($\text{R}^1 = \text{Ph}$, $n\text{Hex}$ or $t\text{Bu}$).

The 1,3-asymmetric induction of chiral α,β -substituted ketones **73** during a metal hydride reduction was studied in more detail by Guanti *et al.* (Table 9) [89]. In addition to lithium aluminium hydride, the reduction was carried out by sodium borohydride. A significant change in diastereoisomeric ratios of product **74** was detected when the reduction of the diastereoisomeric mixtures of **73** was carried out with NaBH_4 in aqueous ethanol. The α -hydroxy dithioacetals **74a** and **74b** did not epimerize to each other under these reaction conditions. Therefore, the change in ratios was assumed to be caused by the equilibrium between **73a** and **73b** and their different reactivity toward the reducing agent. This means that the β -tolylsulphoxide substituent of **73** also contributed to the reduction of the carbonyl group. The presence of a protic solvent and alkalic additive at room temperature aided the epimerisation of **73**. As conclusion, the α -arylsulfoxide β -oxosulphoxide **73** can be used to produce optically pure α -hydroxy aldehydes **75**. [89]

Table 9. The reduction of α -tolylthio- β -oxosulphoxides 73a and 73b. [87, 89]

| Entry | R ¹ | Hydride ^a | Solvent (V/V) | Additive | T (°C) | 73a:b ^b | 74a:b:c:d ^b | Yield (%) |
|-------|------------------|----------------------|-----------------------------|-------------------|--------|--------------------|------------------------|-----------|
| 1 | Ph | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 99:1 | 99:1:0:0 | 76 |
| 2 | Ph | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 68:32 | 83:17:0:0 | 64 |
| 3 | Ph | NaBH ₄ | abs. EtOH | | -78 | 99:1 | 94:6:0:0 | 79 |
| 4 | Ph | NaBH ₄ | abs. EtOH | | -78 | 68:32 | 75:25:0:0 | 70 |
| 5 | Ph | NaBH ₄ | EtOH-H ₂ O (7:3) | | rt | 68:32 | 83:17:0:0 | 80 |
| 6 | Ph | NaBH ₄ | EtOH-H ₂ O (7:3) | NaOH ^c | rt | 68:32 | 90:10:0:0 | 80 |
| 7 | ^t Bu | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 1:99 | 1:99:0:0 | 76 |
| 8 | ^t Bu | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 36:64 | 36:64:0:0 | 75 |
| 9 | ^t Bu | NaBH ₄ | EtOH-H ₂ O (7:3) | NaOH ^c | rt | 36:64 | 50:50:0:0 | 80 |
| 10 | ⁿ Hex | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 99:1 | 99:1:0:0 | 76 |
| 11 | ⁿ Hex | LiAlH ₄ | Et ₂ O-THF (7:3) | | -78 | 59:41 | 74:26:0:0 | 60 |
| 12 | ⁿ Hex | NaBH ₄ | abs. EtOH | | rt | 59:41 | 71:18:5:6 | 85 |
| 13 | ⁿ Hex | NaBH ₄ | EtOH-H ₂ O (7:3) | NaOH ^c | -30 | 59:41 | 66:26:2:6 | 81 |

a) 2 equiv. of hydride was used.

b) NMR and HPLC were used for a detection and conformation of diastereoisomers.

c) Additional 0.05 equivalent of NaOH was added.

The reduction of achiral *bis-p*-tolylthiomethyl ketones **77** through fermentation with baker's yeast exclusively yielded a single enantiomer of alcohol **78** (Fig. 32). The rate of reduction was dependent on the length of the carbon chain (R¹) and on the type of the hetero-substituent (Table 10). [88]

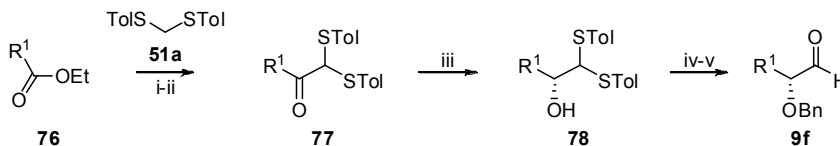


Fig. 32. Reagents: i) ⁿBuLi, THF -78 °C, 30 min; ii) H₂O; iii) *Distillerie Italiane*, glucose, H₂O, EtOH, 27–30 °C, 3–7 days; iv) BnBr, NaH, DMF; v) HgO, BF₃-Et₂O, H₂O, THF 1 h.

Table 10. Enantioselective reduction of 1,1-*bis-p*-tolylthioalkan-2-one (77**) by baker's yeast.**

| Entry | R ¹ | Time | Temp. (°C) | Yield (%) ^a | ee (%) |
|-------|-------------------------------------|----------|------------|------------------------|-----------------|
| 1 | Me | 3.5 days | 27 | 50 | 95 ^b |
| 2 | CF ₃ | 3 days | 27 | 25 | 95 ^c |
| 3 | CH ₂ F | 4 days | 30 | 42 | 95 ^c |
| 4 | MeOCH ₂ OCH ₂ | 6 days | 30 | 50 | 95 ^b |

a) Isolated yield of **78**. Yields were not optimized.

b) Determined by ¹H-NMR complexed with europium(III) *tris*[3-(heptafluoropropylhydroxymethyl-ene)-(+)-camphorato].

c) Determined by ¹H-NMR as Mosher's esters.

2.4.2 Other hetero atoms in formyl anion equivalents

The change of a sulphur atom to oxygen in a formyl anion equivalent destabilizes the negative charge at carbon, which makes the formylation reaction less successful [74, 75, 90, 91]. However, the reaction conditions for the transformation of *S,O*-acetals to aldehydes can be milder than with *S,S*-acetals, which is preferred for sensitive α -hydroxy aldehydes.

The reaction of ketones **46** and 1-chloromethyl phenyl sulphone (**79**) yielded α,β -epoxy sulphones **80** (Fig. 33) [92]. When epoxide **80** was exposed to nucleophilic base (KO^tBu or Ph_3CLi), it gave an intermediate which hydrolysed to α -hydroxy aldehyde **1** under mild alkaline condition [71].

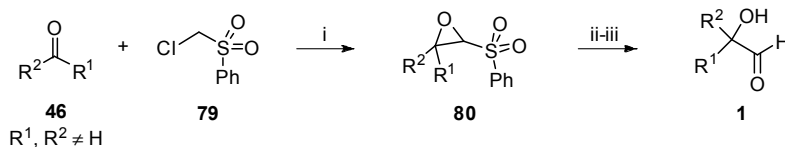


Fig. 33. Reagents: i) $\text{ClCH}_2\text{SO}_2\text{Ph}$, KO^tBu , THF, 10–15 °C, 8–14 h; ii) KO^tBu , THF, H_2O , 25 °C, 3–5 h; iii) H_3O^+ , THF, rt, 48 h.

Other formyl anion equivalents which contain oxygen and sulphur heteroatoms are 1,3-oxathianes (**81**) [93] and α -oxofunctionalized sulphones **82-83** [94, 95]. As seen before, anions are generally formed by the treatment with *n*-butyllithium or lithium diisopropylamide (anion **83**). Nonetheless, the reaction was successful only with a limited number of electrophiles. [72]

Thiazole **84** [96] is an interesting compound with its structural simplicity and use in various natural product syntheses. Anions **81-84** reacted with aldehydes or ketones to give corresponding hydroxy thioacetals which could be unmasked to α -hydroxy aldehydes. Acetals synthesized from α -thio silanes **85** [97] underwent a sila-Pummerer rearrangement [98] at the presence of an oxidant to yield *O*-(trimethylsilyl)thioacetals which can be later hydrolysed to α -hydroxy aldehyde. [72]

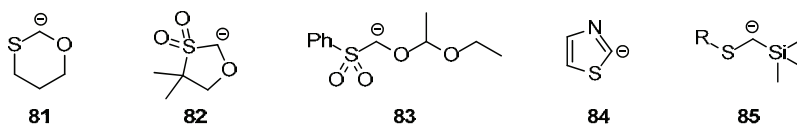


Fig. 34. Examples of formyl anion equivalents with one sulphur atom. The cyclic structure, the additional oxygen at sulphur and large side chain are important for the stabilisation the negative charge at carbanion. [72]

An example of lithiated carbanions which do not contain sulphur is shown in Fig. 35. The reaction of carbonyl compounds with phenylseleno-(trimethylsilyl)methylithium (**86**) [99] or methoxy-(phenyldimethylsilyl)methylithium (**87**) [100] has been reported to give β -hydroxy silanes which were converted to α -hydroxy aldehyde equivalents via sila-Pummerer rearrangement using hydrogen peroxide, *m*-CPBA, or acetic anhydride [72]. Phosphorus-stabilised formyl anion equivalents **88** (see also Fig. 20) have been designed and utilized in Wittig-type olefination [60]. In addition, Katritzky's benzothiazoyl alkanes **89** are good examples of strategically designed nitrogen-based anions for the carbonyl homologation reactions [72, 76, 77, 101].

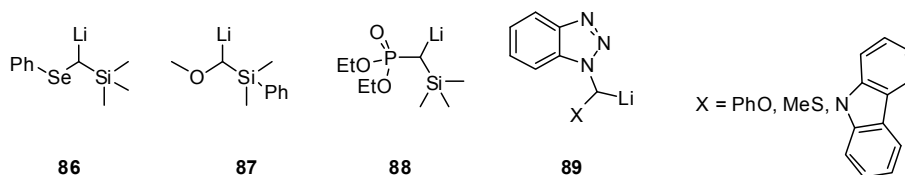


Fig. 35. Lithium formaldehyde equivalents.

Metallation of diheterosubstituted carbon with lithium reagents is the most commonly used method for the formyl anion equivalent, but the lithiation of alkyl stannic derivatives [102-104] or trialkylsilanes [96, 105] can also be used [60].

A thallium(I)-catalyzed reaction of ketones with tosylmethyl isocyanide **90** yielded an excite intermediate **91** (Fig. 36 & Table 11) [106]. 4-Ethoxy-2-oxazoline derivatives **91** formed from ketones at the presence of thallium(I)ethoxide [107]. ^tBuOK and EtONa could be used to replace the toxic thallium compound [108]. The hydrolysis of oxazoline ring **91** proceeded via a rapid ring opening to the formamide acetal intermediate which further hydrolysed

slowly to the final product **1**. In principle, the reaction could yield a racemic mixture of products depending on the side of the attack by isocyanide anion **90**. However, exclusively (*R*)-4-ethoxy-2-oxazoline **91** was observed [106]. The yield and diastereoselectivity of **91** and the yield of aldehyde **1** are presented in Table 11.

Presumable, with aldehydes ($R^2 = H$) the 1,2-elimination of ethanol from **91** would prevent the hydrolysis to the α -hydroxy aldehyde [109].

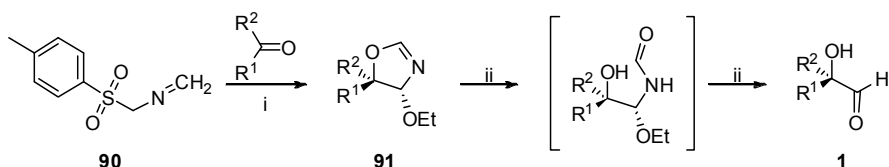


Fig. 36. Reagents: i) TIOEt, EtOH, 1,2-dimethoxyethane, rt; ii) H_3O^+ , THF, rt, over night.

Table 11. The synthesis of α -hydroxy aldehydes **1** from ketones and tosylmethyl isocyanide (**90**). [106, 107]

| Entry | R^1 | R^2 | Yield of 91 , % ^(a) | de of 91 , % ^(b) | Yield of 1 , % |
|-------|-----------------|------------------------------------|---------------------------------------|------------------------------------|-----------------------|
| 1 | ⁿ Pr | ⁿ Pr | 75 | - | 52 |
| 2 | | -(CH ₂) ₅ - | 72 | - | 38 |
| 3 | ^t Bu | Me | 35 | 60 ^c | 70 |
| 4 | Me | <i>p</i> -BrPh | 55 | 68 | 71 |
| 5 | Ph | Me | 60 | 64 | 70 |
| 6 | <i>p</i> -MeOPh | Me | 40 | 70 | - |

a) Isolated yield after distillation.

b) Diastereomeric excess of major (*R,R*)-isomer. Determined by ¹H-NMR.

c) Approximately value since peaks were overlapping.

2.4.3 Chiral formyl anion equivalents

The combination of nitrogen and sulphur heteroatoms in the formyl anion equivalent is ideal because of their applicability to chiral auxiliaries, which is enabled by an extra substituent at nitrogen, and the charge stabilizing effect of sulphur. However, the addition of organolithiums to carbonyl group is not very selective [78, 110]. (*S*)-lithium 4-isopropyl *N*-Boc-thiazolidine (**92**) [78] is one good example of chiral formyl anion synthons (Fig. 37). The formylation of aldehydes ($R = Ph$, ^tBu, cyclo-Hex) with chiral lithium auxiliary **92** afforded diastereomers **93a** and **93b** in ratio 70:30, respectively (Table 12, entries 1-3). The

product from the addition of pivaldehyde (R = ^tBu) and cyclohexancarbaldehyde (R = cyclo-Hex) was noted to cycle to oxazolidinones **94a-b**. [78]

Mechanistically, it was postulated that the *tert*-butoxy carbonyl group improved the stereoselectivity by chelation to the lithium atom (Fig. 38) [78]. This was presented to favour the formation of the carbon-lithium bond of **92** pseudo-equatorially (70% in *S*-configuration at C-2). When the bulky R group was in an *anti* position to the Boc-group, the reaction yielded (*S,R*) and (*R,S*) (**93a** & **93b**) as major and minor conformations (Fig. 37) [78]. In addition, the transfer of the isopropyl substituent of the thiazolidine ring (**96**, Fig. 39) from C-4 to C-5 could increase the selectivity towards the major conformation (Table 12, entry 4). [78]

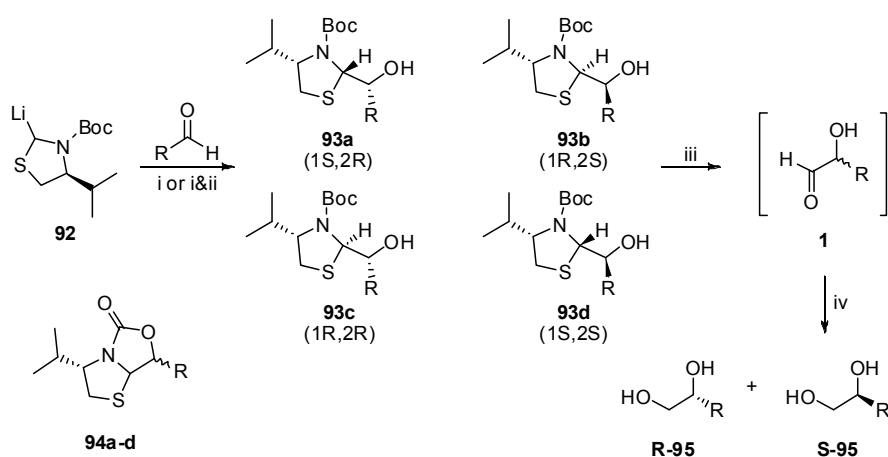


Fig. 37. Reagents: i) THF, -78 °C, 20 min; H₂O rt; ii) Et₂O, KO^tBu, H₂O, rt, over night; iii) HgCl₂, MeCN, H₂O, rt, 6 h; iv) NaBH₄. [78]

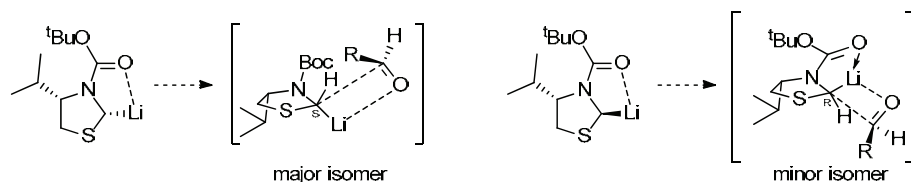


Fig. 38. The proposed structures of transition states by Gawley. [78]

Later, new chiral formyl anion equivalents based on *N,S*-geometry were developed (Fig. 39) [78, 96, 110-112]. The improved diastereoselectivity of **98**

compared to **97** was presented to be likely a consequence of more restricted motion of the isopropyl group because the geminal phenyl groups (Table 12, entries 5-6) [110, 111].

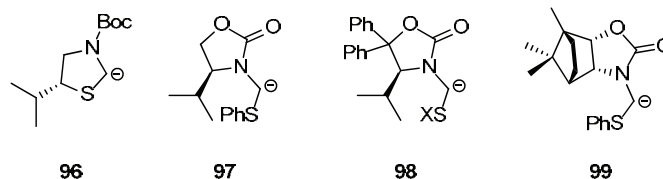


Fig. 39. Chiral formyl anion equivalents containing *N,S*-geometry. [78, 96, 110-112]

Table 12. Yield and diastereoselectivity of chiral formyl anion equivalents based on lithium *N,S*-carbanion.

| Entry | Anion | X | R | Conditions | Yield, % | dr, a:b:c:d ^a | Ref. |
|-------|-----------|-----------------|----------------------|----------------|--------------------|---------------------------------|-------|
| 1 | 92 | | Ph | -78 °C, THF | 87 | 70:30:0:0 | [78] |
| 2 | 92 | | ^t Bu | — [—] | 83 | 70:30:0:0 | [78] |
| 3 | 92 | | cyclo-Hex | — [—] | 83 | 70:30:0:0 | [78] |
| 4 | 96 | | ^t Bu | — [—] | — ^(b) | 85:12:3:0 | [78] |
| 5 | 97 | | Ph | — [—] | — ^(b) | 34:0:0:66 | [110] |
| 6 | 98 | ^t Bu | Ph | — [—] | mix ^(c) | - | [112] |
| 7 | 98 | Me | Ph | — [—] | 86 | 10:0:0:90 | [112] |
| 8 | 98 | Me | Ph | -100 °C, THF | 90 | 7:0:0:93 | [112] |
| 9 | 98 | Me | CH ₂ =CMe | — [—] | 88 | 15:0:0:85 | [112] |
| 10 | 98 | Me | Pr | — [—] | 83 | 30:0:0:70 | [112] |
| 11 | 98 | Me | 2-thiophenyl | — [—] | 92 | 8:0:0:92 | [112] |
| 12 | 99 | | Ph | -100 °C, THF | 77 | 0:14:86:0 | [110] |
| 13 | 99 | | ^t Bu | — [—] | 59 | 0:64:34:0 | [110] |
| 14 | 99 | | cyclo-Hex | — [—] | 74 | 0:24:76:0 | [110] |
| 15 | 99 | | Et | — [—] | 71 | 0:24:76:0 | [110] |

a) Diastereomeric ratio of 1-acetal 2-alcohol intermediate **a:b:c:d** [= (1*S*,2*R*):(1*R*,2*S*):(1*R*,2*R*): (1*S*,2*S*)]

b) Yield was not given.

c) Mixture of products.

The 4-isopropyl-2-oxo-5,5-diphenyloxazolidin-3-yl (methylthio)methane anion (**98**, X = Me) [111, 112] has proven to be the most effective of these type chiral formyl anions (Table 12, entries 7-11). Furthermore, the camphor-derivative of oxazolidinone *S,N*-acetal **99** [110] has an additional useful feature. The diastereomeric products from the addition of **99** to aldehyde could be separated by a simple crystallization.

Unfortunately, the unmasking procedure of these synthesized *N,S*-acetal alcohols (Table 12) were carried out with the assistance of mercury salt, which created toxic waste [78, 96, 110-112].

2.4.4 Alkene anions, imines and enols as formaldehyde equivalents

The unmasking of the aldehyde functionality from its primary acetal intermediate is still a major challenge of thiol-based formylation reagents. Toxic reagents such as mercury salt and iodide reagents are not environmentally benign and the hydrolysis at rather high temperature is problematic for sensitive α -hydroxy aldehydes. The second category of formyl and hydroxy carbonyl anion equivalents has been developed based on α -lithiated alkoxy-, thio- and silyl substituted alkanes **100-102** as well as alkoxyallenes **103** (Fig. 40). Herein, after the reaction with aldehydes or ketones, the mild oxidative cleavage of the alkene intermediate builds up the aldehyde group. [60]

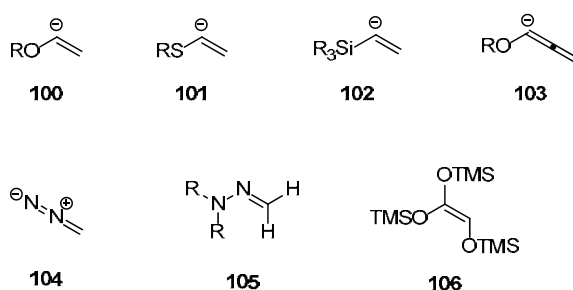


Fig. 40. Formaldehyde equivalents based on heterosubstituted alkenes and allenes.

As mentioned earlier, the unmasked small aldehydes are unfavourable nucleophiles. Single formaldehyde does not form enol, and an enolate is nucleophilic at α -carbon and oxygen. The metallation of allylic carbon by a strong base e.g. butyl lithium forms a reactive carbanion compounds (**100-103** in Fig. 40) [60]. The small and nucleophilic diazomethane (**104**) is a classical reagent for carbonyl homologation [113]. However diazoalkanes commonly are toxic and highly explosive. Other neutral formaldehyde equivalents are formaldehyde dialkylhydrazone **105** and *tris*(trimethylsiloxy)ethylene (TMSE, **106**). Hydrazone **105** attacks aldehyde and forms an imine intermediate **107**. This can be later

ozonated or hydrolysed to aldehyde **9f** (Fig. 41) [114, 115]. The silylated ketene enol **106** reacts with a carbonyl compound yielding a compound that can readily be unmasked by decarboxylation [116]. This reaction, the Wissner hydroxy ketone synthesis [117], is discussed later in further detail.

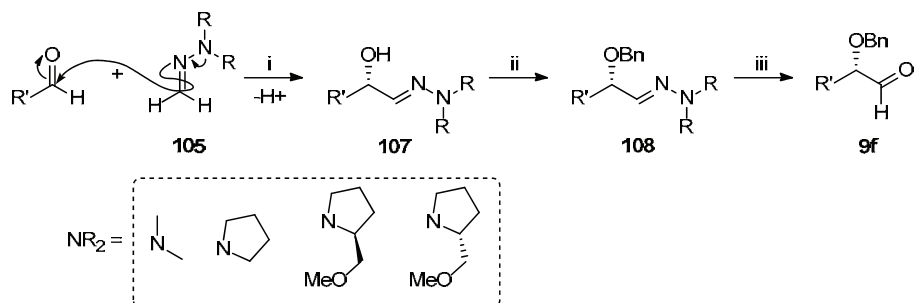


Fig. 41. Reagents: i) DCM, rt, 3–46 h; ii) BnBr, NaH, Bu₄NI, THF; iii) O₃/Me₂S or HCl/H₂O. [114]

When the chiral alkane anion auxiliary controls the stereochemistry, achiral aldehyde or ketone substances can be used [60]. The enantioselectivity of the reaction with dialkylhydrazones **105** was achieved via the unsymmetrical imine (Fig. 41). A first chiral version of a lithiated vinyl species **109** was reported by Braun and Mahler (Fig. 42) [118, 119]. The intermediate **110a** yielded *S*-**1** aldehyde as a predominant product with over 95% diastereoselectivity. In this case, the chelation of methoxyethoxymethyl ether on the lithium atom was presented to help the control of stereoselectivity in reaction with aldehydes.

A highly enantioselective chiral vinyl anion species are also the nucleophilic chiral propargyl borane derivative **41** presented earlier in Fig. 22 [63]. Altogether, a common disadvantage of these reagent-based strategies is that the chiral auxiliaries are irreversibly lost after the unmasking procedures [60].

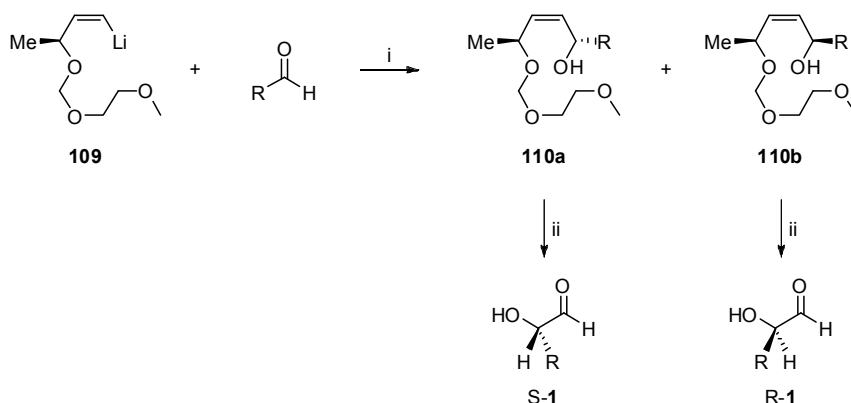


Fig. 42. Chiral formyl anion equivalent based on vinyl lithium. Reagents: i) Et_2O , THF; ii) $\text{O}_3/\text{Me}_2\text{S}$. [119]

2.4.5 Aldehyde cross-condensation

An interesting synthetic method related to carbonyl homologation is an aldehyde-aldehyde condensation catalyzed by *N*-heterocyclic carbenes, which was recently reviewed [120]. Carbenes themselves are highly reactive neutral species possessing a bivalent carbon atom with an electron sextet. Organocatalytic reactions of formaldehyde with another aldehyde or ketone are a modern modification of the *umpolung* strategy. In these reactions, reagents are not used as chiral auxiliaries, but the renewable stereogenic centre is formed by the catalyst.

For the introduction, the catalytic mechanism [121] of the condensation of formaldehyde (**47**) to α -hydroxy aldehyde **117** is presented in Fig. 43 [122]. The reaction was catalyzed by 1,3,4-triphenyl-1,2,4-triazolin-5-ylidene (**111**). The carbene, triazolin-5-ylidene **112**, which was formed *in situ* by the deprotonation of a triazolium salt **111**, underwent a nucleophilic attack with formaldehyde generating a thiazolium salt adduct **113**. The following proton transfer generated an “active aldehyde” in the form of the resonance-stabilized enaminol **114**. This intermediate **114** reacted similarly with the second aldehyde than happens with the common *umpolung* reagents. Finally glucolaldehyde (**117**) eliminated from the intermediates **115** or **116**, which regenerated the carbene catalyst **112** for the next catalytic cycle. The catalyst **112** is so far the most powerful organocatalyst of this type yielding 60% of glycolaldehyde (**117**) as the main product. In addition,

formations of 1,3-dihydroacetone (DHA) or glyceraldehyde (GA) side products were minimal under the reaction of **112**. Presumably, the triazolium ylidene **115** was stable enough to favour the elimination of α -hydroxy aldehyde **117** over the addition of a third formaldehyde molecule. [120]

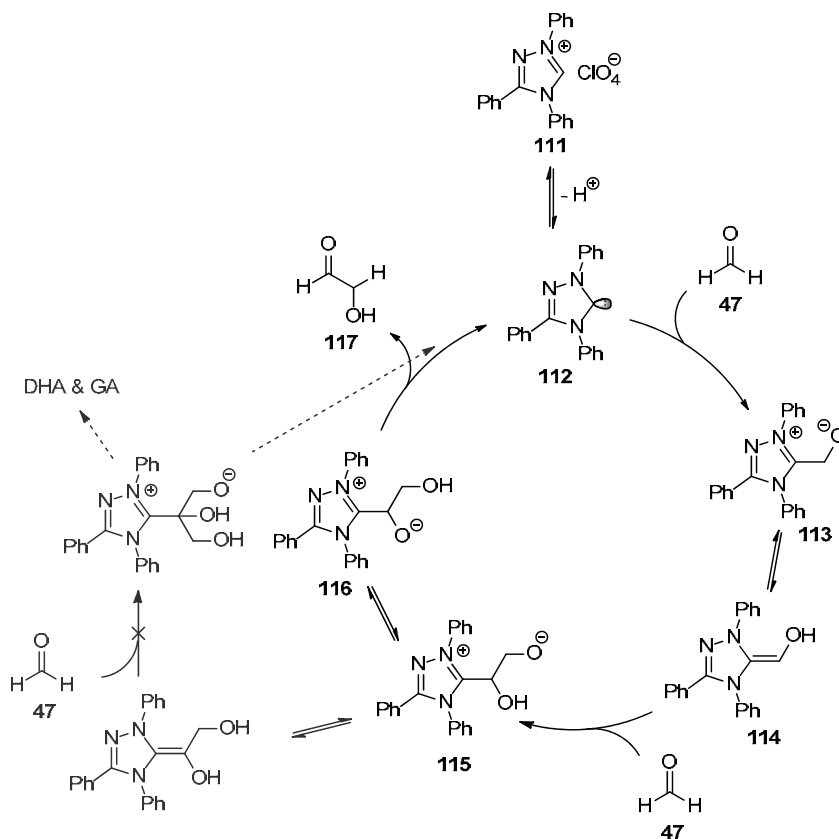


Fig. 43. A mechanism of the carbene-catalysed condensation of formaldehyde. [122]

The logical development of organocatalytic aldehyde condensation was the use of chiral catalysts as asymmetric auxiliaries (Fig. 44). Studies with benzaldehyde derivatives showed that enantiomeric excess and catalytic activities were dependent on the hindrance around the carbene. This catalyst **S-118** provided a *bis*-adduct of benzaldehydes (= benzoin) in 66% yield of *R*-enantiomer with 75% *ee*. [123] This condensation required only a catalyst loading of 1.25 mol % when

a 2.5 mol % of catalyst **111** was used in the previous experiments. Furthermore, both catalysts are highly active organocatalyst. The condensation of aliphatic aldehydes with **118** gave very low yields and poor enantiomeric excesses. [120]

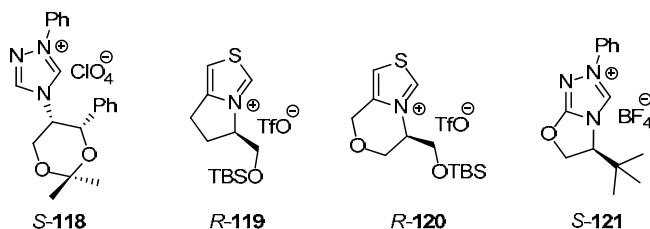


Fig. 44. Chiral heteroazolium salts as precursors of chiral carbenes for asymmetric benzoin condensation. [120]

Novel bicyclic thiazolium derivatives *R*-**119** and *R*-**120** were introduced for the acyloin condensation. The catalyst *R*-**119** yielded 77% of aliphatic butyoin with 14% *ee* and 50% of benzoin with 19% *ee*. The optimized catalyst structure *R*-**120** gave butyoin with the enantiomeric excess of 33% (75% yield). [124] Afterwards, the chiral bicyclic triazolium ylidene *S*-**121** was reported for the organocatalytic benzoin condensation. (*S*)-Benzoin was synthesized with a good enantioselectivity (90% *ee*) and yield (83%). By lowering of the reaction temperature, *ee* increased but at the cost of the catalytic activity. [125]

A selective cross-acyloin condensation of formaldehyde (**47**) with another aldehyde was reported already in 1985 (Fig. 45) [126]. The catalyst 3-ethylbenzothiazolium bromide (**122**) in combination with triethylamine in an alcohol solvent gave the best result in terms of selectivity and catalytic activity (Table 13). The α -hydroxy ketone **2** was isolated as a reaction product. However, it was not reported whether α -hydroxy aldehydes could be produced by this method.

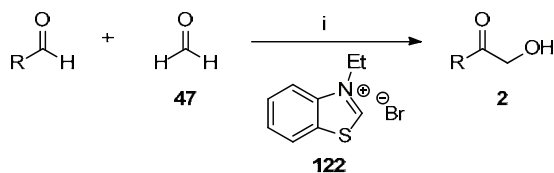


Fig. 45. Reagents: i) **122 (10 mol%), Et₃N, EtOH, 60 °C, 24 h.**

Table 13. The aldehyde cross-condensation with 3-ethylbenzothiazolium bromide (122**) catalyst.^a [126]**

| Entry | R | Converted 47 , % | Selectivity of 2 , % |
|-------|-----------------|-------------------------|-----------------------------|
| 1 | Me | 76 | 100 |
| 2 | Et | 74 | 89 |
| 3 | ⁿ Pr | 93 | 73 |
| 4 | ⁱ Pr | 100 | 100 |
| 5 | cyclo-Hex | 94 | 64 |
| 6 | 2-furyl | 88 | 81 |
| 7 | Ph | 96 | 100 |

a) **47** as paraformaldehyde (5 mmol), aldehyde (5 mmol), **122** (0.5 mmol), Et₃N (0.5 mmol), EtOH (5 mL), 60 °C, 24 h.

2.5 Organocatalytic α -oxo functionalisation of aldehydes

The modern method for the substitution of the α -carbon of aldehyde is an organocatalysis. The term, organocatalysis, describes the acceleration of chemical reactions through the addition of a substoichiometric amount of a small organic compound which does not contain metal atoms in the catalytic site [7]. In general, an organocatalyst acts similarly as an enzyme creating a chiral environment in the reactive site. It activates a nucleophile, or an electrophile, or both; through weak interactions, such as hydrogen bonding, or ion pairing, or much stronger interaction such as a covalent bond formation [127]. The organocatalysis is located between conventional metal-complex-mediated and enzyme-catalysed reactions. Reactions usually happen in organic solvents, but the presence of moisture and air is not harmful, and water can even have a positive effect on the reaction. There are many excellent reviews published in the field of organocatalysis over its short history to bring synthetic chemistry closer to biochemical transformations [7, 128-131].

Mechanistically, organocatalytic α -substitution of aldehyde **123** goes via the intermediate **124** where the α -carbon is activated toward electrophiles (Fig. 46). Dalko and Moisan have characterized four general organocatalytic activation processes in their review [128]. Firstly, the activation of the reaction is based on the nucleophilic/electrophilic properties of the catalysts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/base activation. Secondly, the catalyst is an organic molecule which forms reactive intermediate(s) usually by a covalent bonding with a substance. The chiral catalyst is consumed in the

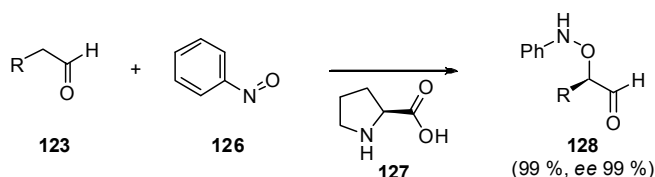


Fig. 47. Proline catalyzed α -aminoxylation of aldehydes.

In 2007, Jørgensen *et al.* reported asymmetric organocatalytic β -oxolation of α,β -unsaturated aldehydes **129** with an *E*-benzaldehyde oxime (**130**) as a hydroxylating agent and a 2-*[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine* catalyst (**131**) (Fig. 48). The product **132** was subsequently reduced to diol to estimate the high enantiomeric excess (95%) and the yield (60–75%) of substitution. A further advantage of oximes **132** is the easy cleavage of the N-O bond, which generates β -hydroxy aldehydes or 1,3-diols. [136]

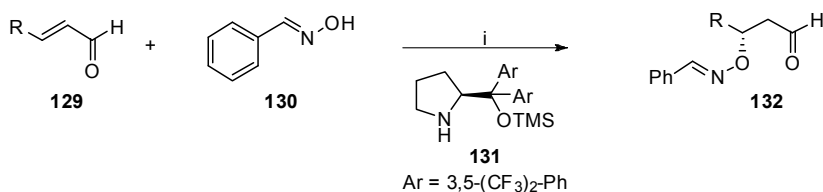


Fig. 48. Reagents: i) **131 (10 mol%), PhCO₂H (10 mol%), toluene, 4 °C, 1 h; (NaBH₄, MeOH).**

A novel enantioselective radical-mediated formation of α -C-O bond with HBF₄ salt of McMillan's imidazolidinone **134** is presented in Fig. 49 [137]. The enamine intermediate **124** (X = NR₂) prepared from aldehyde **123** and organocatalyst **134** was oxidized with NaNO₂/O₂ co-oxidant and FeCl₃ as a single electron transfer reagent. 2,2,6,6-Tetramethylpiperidine-1-oxyl (**133**) worked as a stereoselective radical trap and provided an access to α -oxoaminated aldehydes **135** with moderate yields (58–75%) and 82–90% *ee*. [138]

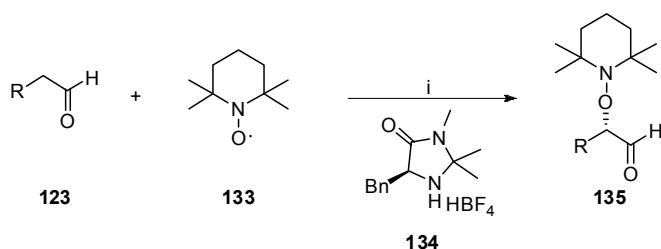


Fig. 49. Reagents: i) **134** (20 mol%), **133** (200 mol%), FeCl₃, NaNO₂, O₂, DMF, -10 °C, 24 h.

Aldehydes can be also hydroxylated with molecular oxygen in the presence of an organocatalyst. The excitation of molecular oxygen by UV light in the presence of tetraphenylporphine (**136**) generated the singlet molecular oxygen ¹O₂ which was the actual reactive species (Fig. 50) [139]. When ¹O₂ reacted with the enamine intermediate **124** (X = NR₂) formed in the reaction of **123** and the catalyst **131**, a stereoselective addition to α-hydroperoxide substituent to **123** took place. *S*-**137** was reduced immediately to diol *S*-**138** to obtain the high enantioselectivity. [140]

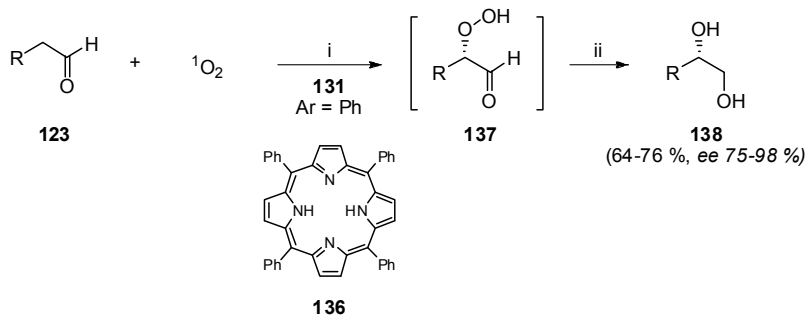


Fig. 50. Reagents: i) **131** (20 mol%), **136** (10 mol%), 0 °C, 6 h; ii) NaBH₄, MeOH.

It is worth noting that solvent has an important role in these type organocatalytic reactions. For example in the α-chlorination of aldehydes with *N*-chlorosuccinimide (NCS) Jørgensen [141] found the most efficient conversion and *ee* of the reaction in chlorinated solvents as dichloroethane, dichloromethane and chloroform when compared to ethanol and THF. In DMSO, the product was reported to racemize.

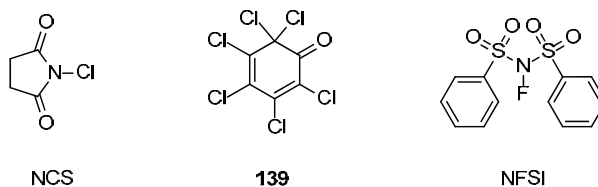


Fig. 51. Examples of α -chlorination (NCS & **139) and α -fluorination (NFSI) reagents used in the organocatalytic α -substitution of aldehydes.**

The MacMillan's group used the perchlorinated quinone (**139**) in an α -chlorination reaction [142], *N*-fluorobenzenesulphonamide (NFSI) for an α -fluorination process [143], and nitrosobenzene (**126**) for an α -oxyamination transformation [133] (Fig. 51). Generally, MacMillan *et al.* used a high excess of reagent, low concentration and low reaction temperatures [133, 142, 143], probably preventing side reactions such as aldol reactions. Furthermore, the MacMillan-type organocatalysts **134** usually gave high enantioselectivity and at least moderate yield in each case so the effect of the solvent was studied systematically [133, 142, 143]. Chloroform was found to be a good choice for the α -chlorination and α -oxidation reactions. Slightly better conversions were obtained in acetonitrile and benzene than with more polar NMP, DMF, DMSO and THF solvents. In addition, α -chlorination occurred well in ethyl acetate and acetone where the reaction was the fastest.

Table 14 presents solvents, which were used in organocatalytic transformations, organised based on increasing polarity as normalised empirical parameter value [144]. The polarity value of the most successful solvent in α -chlorination [142] and α -oxygenation reactions [133] were between 0.22 and 0.35; between ethyl acetate and acetone. The second best solvents as NMP, acetonitrile, benzene and THF, where the α -functionalization usually took place fastest, are next to the most successful solvents in Table 14. In the α -fluorination reaction, *iso*-propanol was used as a co-solvent which increased the polarity of reaction solvents; this meant that the reaction finished quicker using less polar solvents like THF and EtOAc [143]. In addition, it was noted that the cross-aldol reactions yielded the highest yield in polar solvents like MeCN, NMP and DMF [145]. As a conclusion, the α -functionalization of aldehydes were the best in the mid-polar solvent as THF, EtOAc, DCM and acetone, and when the polarity of the solvent was increased, aldol reactions started to take place.

Table 14. Polarity, dielectric constant and dipole moment of some common solvents.
[146]

| Solvent | Normalized empirical parameter, E_T^N ^(a) | Polarity index ^(b) | Dielectric constant, ϵ_r ^(c) |
|--------------------------------------|--|-------------------------------|--|
| Tetramethylsilane (TMS) | 0.00 | | |
| <i>n</i> -Hexane | 0.01 | 0.0 | 1.9 |
| Toluene | 0.10 | 2.3 | 2.4 |
| Benzene | 0.11 | 3.0 | 2.3 |
| 1,4-Dioxane | 0.16 | 4.8 | 2.2 |
| Tetrahydrofuran | 0.21 | 4.2 | 7.6 |
| Ethyl acetate | 0.22 | 4.3 | 6.0 |
| Chloroform | 0.26 | 4.3 | 4.9 |
| Dichloromethane | 0.31 | 3.4 | 8.9 |
| 1,2-Dichloroethene | 0.33 | 3.7 | 10 |
| Acetone | 0.35 | 5.4 | 21 |
| <i>N</i> -Methyl-2-pyrrolidone (NMP) | 0.36 | 6.5 | 32 |
| <i>N,N</i> -Dimethylformamide | 0.39 | 6.4 | 37 |
| Dimethylsulphoxide | 0.44 | 6.5 | 46 |
| Acetonitrile | 0.46 | 6.2 | 36 |
| <i>i</i> -Propanol | 0.55 | 4.3 | 20 |
| Ethanol | 0.65 | 5.2 | 25 |
| Methanol | 0.76 | 6.6 | 33 |
| Water | 1.00 | 9.0 | 78 |

- a) Normalized empirical parameter of solvent polarity, derived from the transition energy at 25 °C of the long-wavelength visible absorption of the standard pyridinium *N*-phenolate betaine dye, $E_T(30)$. Values are dimensionless numbers, normalized by water (1.00) and TMS (0.00). [144]
- b) Order in polarity of some solvents is different than based on empirical parameters. Especially, MeCN is located as less polar solvent than NMP, DMF, and DMSO which would be better suited with the assumption of the classification of the suitable reaction solvent. [147]
- c) Relative permittivity (= dielectric constant) of the pure liquid at 25 °C.

2.6 Other methods in synthesis of α -hydroxy aldehydes

In addition to the methods discussed above, there are some miscellaneous reactions which generate α -hydroxy aldehyde functionality. A cobalt-catalyzed direct formylation of aldehydes with carbon monoxide and hydrosilane produced diethylmethylsilyl protected α -hydroxy aldehydes **9g** (Fig. 52) [148, 149]. In turn, a SnI_2 -induced masked-formylation, in which a mild radical-assisted reaction took place between 1,2-dioxalanes **140** and carbonyl compounds, led to an acetal-protected α -hydroxy aldehyde **141** [74].

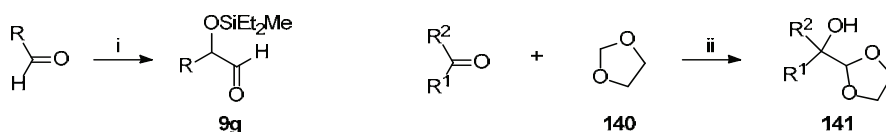


Fig. 52. Alternative formylation reactions. Reagents: i) HSiEt₂Me, CO, Co₂(CO)₈/PPh₃ [148]; ii) Sml₂, PhI, THF-HMPA, rt, 5 min [74].

In 1985, an oxidative cleavage of 3,4-diol with tetraacetoxy palladium was introduced [150] (Fig. 53). Some years later, a symmetric 1,4-diprotected tetradial **142** was reacted with Pd(OAc)₄ to give two equivalents of benzyl or TBDMS protected aliphatic α -hydroxy aldehydes **143** with the same chirality as the starting material. [11, 151]

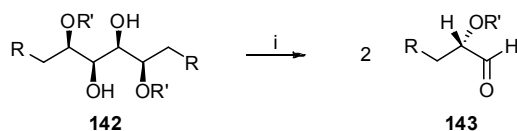


Fig. 53. Reagents: i) Pd(OAc)₄, benzene, rt, 1 h. R' = Bz or TBDMS.

An acetal group is generally used for the protection of the aldehyde functionality. The ring opening of the 2-(diethoxymethyl)oxirane (**144**) with a strong nucleophile R⁻ regioselectively occurred in 3-position and gave a stable α -hydroxy acetal **145** (Fig. 54). Oxirane **144** was obtained from an allylic acetal derivative by oxidation [152]. Nucleophiles like hydrosulphide, cyanide, and benzyloxy anions were successfully reacted in an oxirane ring opening. The subsequent acid-catalysed hydrolysis of diethylacetal **145** yielded α -hydroxy aldehyde **146** as hydrates or dimers. [19]

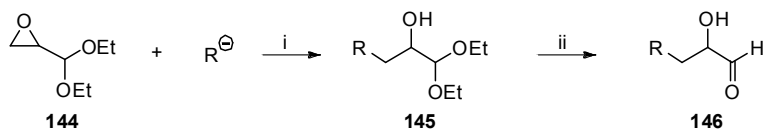


Fig. 54. Reagents: i) R = BnO, SH, CN; H⁺; ii) H⁺, H₂O, 60 °C, 4 h.

2,2-Diethoxyacetaldehyde (**147**) is an interesting small molecule (Fig. 55). It consists of two aldehyde groups of which one is protected. α -Hydroxy acetal **148** was obtained from aldehyde **147** by the Grignard reaction [153]. Acetal **148** was hydrolysed to aldehyde **149**. Furthermore, the Grignard reaction was applied to an asymmetric synthesis of *O*-protected α -hydroxy aldehydes **154** (Fig. 56) [154].

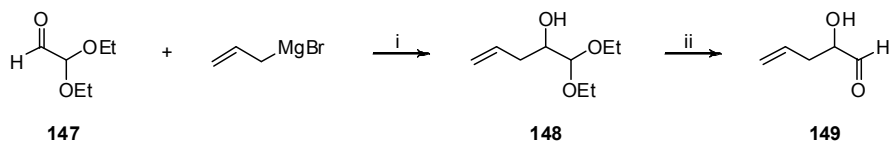


Fig. 55. Reagents: i) Et₂O, -78 °C to rt, 1 h; H₂O (72%); ii) pH 1.0 buffer, rt, 20 h. [153]

The diastereomerically pure (*S*)-2-formyloxazoline **151** was gained when a corresponding stannyl reagent **150** was treated with *n*-butyllithium and reacted with excess dimethylformamide. Respectively, the addition of Grignard reagents to the *bis*-chelate intermediate of **151** precomplexated with strong Lewis acid such as TiCl₄ or MgBr₂ in DCM was reported to give alcohol **152** in high diastereoselectivity (*de* > 96%).

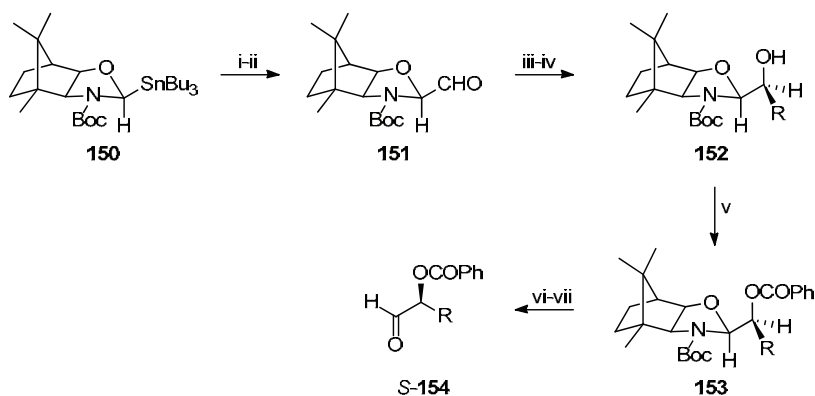


Fig. 56. Reagents: i) ⁿBuLi, THF, -78 °C; ii) DMF; iii) TiCl₄, DCM, -78 °C; iv) RMgBr; v) PhCOCl, pyridine; vi) HCl/EtOAc, 0 °C; vii) THF/H₂O rt. R = ⁿBu, cyclo-Hex, Ph, ^tBu. [154]

The unmasked α -benzyloxy aldehydes **154** were revealed in hydrolysis of *O*-benzoyl protected derivatives **153** with 4 M HCl in ethyl acetate followed by the evaporation and treatment of aqueous THF. The products *S*-**154** were subsequently reduced to diols for the obtaining of enantioselectivity (98%) and good overall yields (63–71%). [154]

In 2005, Tomkinson *et al.* [155] reported an interesting oxo-functionalization of carbonyl compounds with quaternary *O*-acyl hydroxylamine hydrochloride salt **155** (Fig. 57). At first it was described as a chemospecific synthetic method to α -oxybenzylation of aldehydes through the utilization of *N*-*tert*-butyl substituted hydroxylammonium salt **155** (Table 15, entries 1-6 & 8-9) [156]. In addition, it was shown that cyclohexanone did not react during the substitution (entry 7). In turn, aldehydes that had a saturated, unsaturated or aromatic group with a primary or secondary α -carbon reacted well. The reaction was presented to proceed via a [3,3]-sigmatropic rearrangement of enamine intermediate **157** to α -oxysubstituted imine which was subsequently hydrolysed to aldehyde **158** [157]. The reaction was successfully tested also with hydroxylamine reagents **155** leading to acetyl and pivaloyl esters of α -hydroxy valeraldehyde (entries 8-9).

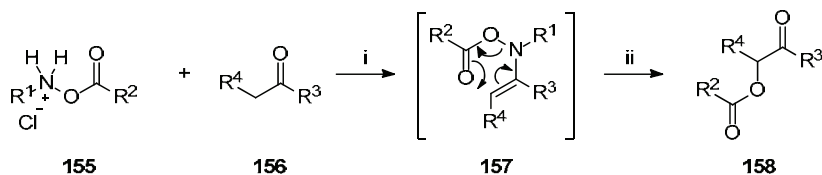


Fig. 57. Treatment of aldehydes or ketones with *N*-alkyl-*O*-acyloylhydroxylamine hydrochloride (155**) provided the α -functionalized product **158**; i) The reaction was carried out in THF [156] or DMSO [155] at 25–50 °C in the presence of water and air; ii) H_2O .**

Further development of the Tomkinson reagent **155** was the replacement of *N*-*tert*-butyl substituent by a methyl group [155]. Now an α -acyloxylation also occurred with ketones in good yields (entries 11-24). The use of DMSO produced a cleaner and faster transformation than with less polar solvents. The α -oxy substitution did not occur in the methyl carbonyl compound e.g., acetone and acetophenone (entries 26-27).

Table 15. α -Oxylation of aldehydes and ketones **156 with *N*-methyl-*O*-acyloylhydroxylamine hydrochloride (**155**).**

| Entry | R ¹ | R ² | R ³ | R ⁴ | Isolated yield, % | Ref. |
|-------|-----------------|-----------------|-----------------|--|-------------------|--------------------|
| 1 | ^t Bu | Ph | H | Pr | 72 ^(a) | [156] |
| 2 | ^t Bu | Ph | H | ⁱ Pr | 79 ^(a) | - ^(a) - |
| 3 | ^t Bu | Ph | H | CH ₂ =CHCH ₂ - | 76 ^(a) | - ^(a) - |
| 4 | ^t Bu | Ph | H | Bn | 69 ^(a) | - ^(a) - |
| 5 | ^t Bu | Ph | H | Ph | 67 ^(a) | - ^(a) - |
| 6 | ^t Bu | Ph | H | -R ₃ CH- = cyclo-Hex ^(b) | 82 ^(a) | - ^(a) - |
| 7 | ^t Bu | Ph | | -CH ₂ CH ₂ CH ₂ CH ₂ - | - ^(a) | - ^(a) - |
| 8 | ^t Bu | Me | H | ⁱ Pr | 72 ^(a) | - ^(a) - |
| 9 | ^t Bu | ^t Bu | H | ⁱ Pr | 64 ^(a) | - ^(a) - |
| 10 | Me | Ph | H | ⁱ Pr | 92 ^(c) | [155] |
| 11 | Me | Ph | Pr | Et | 90 ^(d) | - ^(a) - |
| 12 | Me | Ph | Me | ⁱ Pr | 73 ^(d) | - ^(a) - |
| 13 | Me | Ph | Me | CH ₂ =CHCH ₂ - | 81 ^(d) | - ^(a) - |
| 14 | Me | Ph | Me | <i>p</i> -OHPHCH ₂ | 83 ^(d) | - ^(a) - |
| 15 | Me | Ph | | -CH ₂ CH ₂ CH ₂ CH ₂ - | 80 ^(c) | - ^(a) - |
| 16 | Me | Ph | | -CH ₂ CH ₂ OCH ₂ - | 79 ^(c) | - ^(a) - |
| 17 | Me | Ph | | -CH ₂ CH ₂ NTsCH ₂ - | 74 ^(c) | - ^(a) - |
| 18 | Me | Ph | Ph | Me | 69 ^(e) | - ^(a) - |
| 19 | Me | Ph | <i>p</i> -MeOPh | Me | 92 ^(f) | - ^(a) - |
| 20 | Me | Ph | <i>p</i> -OHPH | Me | 85 ^(f) | - ^(a) - |
| 21 | Me | Me | | -CH ₂ CH ₂ CH ₂ CH ₂ - | 67 ^(c) | - ^(a) - |
| 22 | Me | ^t Bu | | -CH ₂ CH ₂ CH ₂ CH ₂ - | 69 ^(c) | - ^(a) - |
| 23 | Me | <i>p</i> -MeOPh | | -CH ₂ CH ₂ CH ₂ CH ₂ - | 70 ^(c) | - ^(a) - |
| 24 | Me | ^t Bu | Pr | Et | 58 ^(a) | - ^(a) - |
| 25 | Me | Ph | Me | H | - ^(g) | - ^(a) - |
| 26 | Me | Ph | Ph | H | - ^(g) | - ^(a) - |

a) Reactions were carried out in a 9:1 mixture of THF and water at 50 °C except entry 5 which was done at room temperature.

b) Cyclohexanecarbaldehyde was used as a starting material.

c) DMSO, rt, 4–24 h.

d) DMSO, 50 °C, 24 h.

e) DMSO, 50 °C, 48 h, 1.5 equiv. of **155**.

f) DMSO, 50 °C, 48 h, 2 equiv. of **155**.

g) DMSO, 50 °C, 72 h.

2.7 Concluding remarks of α -hydroxy aldehydes

We can summarize that the highly sensitive α -hydroxy aldehydes should be synthesized as protected forms, either as an acetal derivative or a bulky protective group attached to the α -hydroxyl group. The formation of α -hydroxy aldehyde functionality should preferably be carried out in the last synthetic step after which the

products are immediately further used. The optimum reaction time, temperature and pH are important aspects in order to prevent the decomposition of α -hydroxy aldehyde derivatives.

A development of chiral formyl anion equivalents has nowadays been improved. Meanwhile, along with the increasing enantiomeric purity of the product, the size of the reagents is getting larger. This is unfavourable to the atom economy of the reaction. Novel anion synthons, which do not contain sulphur, have been developed. This eases the handling processes as well as reduces the toxicity of the chemical waste.

The α -substitution of aldehydes with a number of substituents has been extensively developed with organocatalytic methods [135]. In fact the organocatalytic α -oxo substitution would be the most prospective and green method for the preparation of α -hydroxy aldehydes in their relatively stable hydroxyl-protected form. An interesting synthetic method is the carbene-catalyzed formaldehyde cross-condensation [120]. This organocatalytic procedure is a novel and green method for the aldehyde homologation.

The development of the synthesis of α -hydroxy aldehyde as well as the invention of new formaldehyde equivalents are two important challenges in the building of small reactive synthons to be used of the chemical industry [158].

3 The direct synthesis of terminal α -hydroxy ketones

In this study the α -hydroxy ketones, which have the hydroxy ketone structure on the terminal position, are discussed. The previous examples of this literature survey were the synthetic methods which yield α -hydroxy aldehydes or their synthetic equivalents. Generally, most of these reactions have also been adapted for the synthesis of the 1-hydroxy-2-ketone. Thus, the synthetic examples of ketones are not reviewed herein as extensively as aldehydes.

The α -hydroxy ketones can serve as a synthetic unit in the preparation of various chemicals [159]. For example α -hydroxy ketones are used in the synthesis of heterocycles such as imidazoles [160] or imidazolones [161]. In addition, they are a reducing agent for the dyeing of textiles [162] and aroma compounds of food. They can also be important structural components of natural products. [15, 163]

Besides the tautomerization of the α -hydroxy aldehyde, a number of specific reactions for the synthesis of terminal 1-hydroxy-2-ketone functionality have been reported (Fig. 58). The terminal α -hydroxy ketone generally are produced by a catalytic [164] or stoichiometric [165] oxidation of terminal olefins. 1,2-Diols [166-168] or α -halo substituted ketones [169] can be converted into α -hydroxy substituted ketones. The oxidation of oxirane [170-172] and kinetically controlled α -hydroxylation of methylketones [173] can also be used for the synthesis of α -hydroxy ketones. [II]

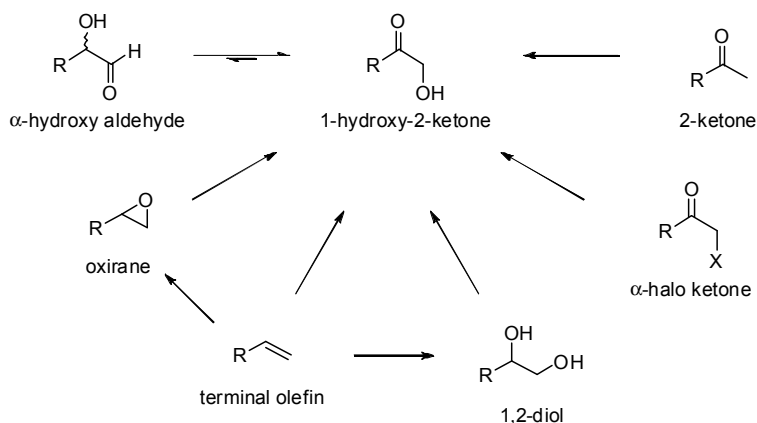


Fig. 58. Functional group transformations to a terminal α -hydroxy ketone.

Keto-aldehyde isomerisation is not limited only to a 1,2-migration of a proton but also an α -substituent can be transferred. The treatment of suitable α -hydroxy aldehydes **159** and ketones **160** with a base, Brønsted or Lewis acid, or simply by heat; led to a 1,2-shift of α -alkyl or aryl substituent Z (Fig. 59). Generally, the reaction is reversible, but α -hydroxy ketones **160** are more stable than aldehydes and therefore the equilibrium remains primarily on the ketone side. [5]

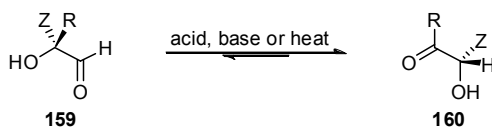


Fig. 59. The rearrangement between α -hydroxy aldehyde and ketone. (Z = alkyl or aryl groups).

Similarly, a catalytic asymmetric rearrangement of α -siloxy aldehydes **161** to optically active α -siloxy ketones **162** happens in the presence of a chiral Lewis acid auxiliary (Fig. 60) [174]. The stereochemistry of the reaction was controlled by a bulky BINOL ligand coordinated to aluminium metal. The transformation was finished by the migration of the silyl group between the hydroxyl groups. It is worth noting that the proposed mechanism partially resembles the mechanism reported with triosephosphate isomerase (Fig. 71).

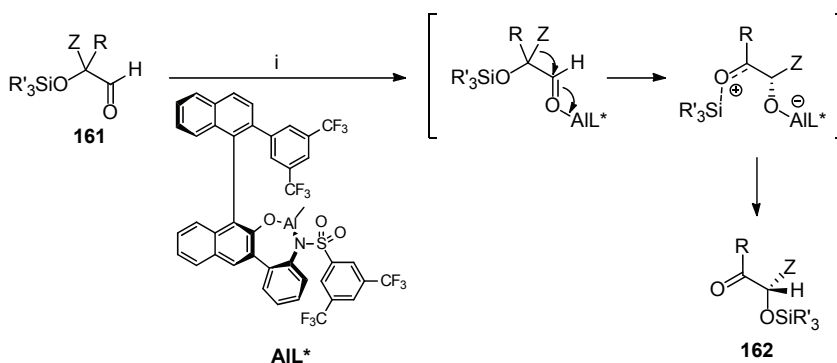


Fig. 60. Reagents: i) AIL*, toluene, $-20\text{ }^{\circ}\text{C}$, 12h. Z = alkyl or aryl.

As shown earlier, the one-carbon chain extension of a carbonyl compound can be achieved using masked formyl anions (Fig. 24) [60] or with reagents like

diazomethane (**104**, Fig. 40) [175]. These reagents however require constant control of the reaction temperature. On the other hand, the reaction between *tris*(trimethylsiloxy)ethylene (**106**) [116] and acid chloride **163** yields compounds **165/166** which have two carbons added at the end of the carbon chain (Fig. 61). However, the decarboxylation of this β -keto acid **166** yields the product of the desired length of the carbon chain. Reagent **106** has a rather stable enol form that can attack the carbonyl group of aldehyde or acid chloride [176, 177]. Furthermore, the reagent alone can be heated to a high temperature by microwaves without any detectable decomposition [II]. Thus, the ketene enol **106** was selected by us for the microwave assisted condensation.

The reaction is known as the Wissner hydroxy ketone synthesis [117]. Earlier Mukaiyama [178] reported that the silylated enol ethers went through an aldol type reaction with ketones or aldehydes. The same methodology was later applied to acid chlorides and silylated ketene acetals by Wissner [177].

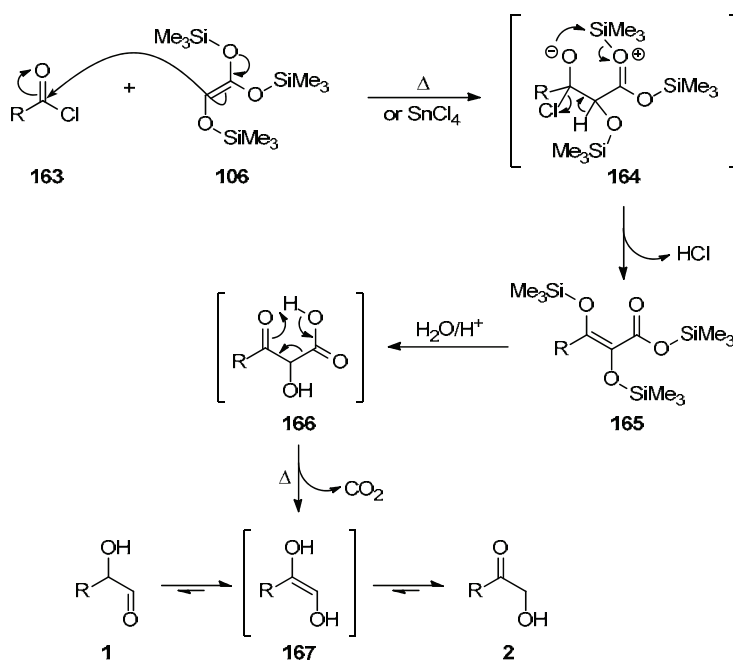

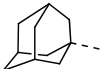


Fig. 61. The presented mechanism of the hydroxymethyl ketone synthesis. [177]

Mechanistically the silylated ketene acetal **106** makes a nucleophilic attack to the carbonyl group either by heating or with the assistance of a Lewis acid (Fig. 61). The formed intermediate **164** undergoes trimethylsilyl transfer and loses hydrogen chloride which is neutralized by the additional molecule of **106**. The silyl β -enol ester **165** was isolated and its structure was verified [177]. The hydrolysis of **165** produced the β -keto acid **166** which further decarboxylates to enediol **167**. Enediol spontaneously tautomerizes to an α -hydroxy ketone **2**. It may be as Wissner [177] pointed out that the α -hydroxy aldehyde **1** are also produced, but the equilibrium is strongly on the side of ketones **2**.

The synthesis of a variety of α -hydroxy ketones was carried out with thermal condensation and under catalytic conditions (Table 16). Both methods gave similar result for less hindered, nonconjugated acid chlorides (entries 1-5). In this study, the thermal procedure was found superior for hindered acid chlorides (entries 6-9). The highly hindered acid chloride failed to react under the studied condition (entry 10). [177] Currently the Lewis acid catalysed procedure has become a widely accepted method for this hydroxy ketone synthesis.

Table 16. The prepared hydroxy methyl ketones by the Wissner hydroxy ketone synthesis. [177]

| Entry | R = | Reaction conditions ^(a) | Yield of isolated product 1 ^(b) |
|-------|---|------------------------------------|---|
| 1 | <i>n</i> -heptyl | 95–100 °C, 4 h | 84 |
| 2 | —" | SnCl ₄ , 1 h | 90 |
| 3 | Bn | 95 °C, 4 h | 81 |
| 4 | —" | SnCl ₄ , 1 h | 76 |
| 5 | Br(CH ₂) ₄ | SnCl ₄ , 1 h | 79 |
| 6 | cyclo-hexyl | 100 °C, 4 h | 71 |
| 7 | —" | SnCl ₄ , 5 h | 48 |
| 8 | Ph | 95 °C, 4 h | 62 |
| 9 |  | 95 °C, 4 h | 69 |
| 10 |  | 95 °C, 4½ h | — ^(c) |

a) Reactions were carried out in the absence of solvents. The stannic chloride catalysed reactions were allowed to exotherm without cooling.

b) Yields were obtained for distilled or recrystallized products.

c) No product was obtained.

4 Microwave-assisted organic synthesis

The use of microwaves in organic syntheses was a topical issue when this PhD research project began. Microwaves represent the range of electromagnetic radiation between infrared and short radio waves within a frequency range from about 300 000 to 300 MHz and a wavelength from 1 m to 5 mm (Fig. 62). It is a low energetic radiation having an effect only on the rotation of molecules and no effect on the chemical bonds or the structure of the molecule. The frequency 2450 MHz (wavelength 12.2 cm, energy 0.0016 eV) is standardized in most household and laboratory scale microwave apparatuses. In addition, the frequencies of 433 MHz, 915 MHz (American only), 5800 MHz and 24125 MHz have been established for scientific, medicinal and industrial use by the International Telecommunication Union. [179, 180]

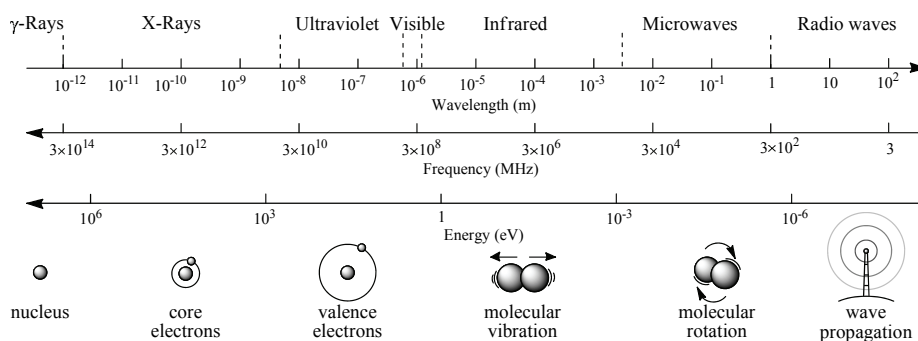


Fig. 62. The electromagnetic spectrum of known radiations showing the wavelength, frequency, energy and particle interaction.

Microwaves as short-wave radiation are generated by a high-powered vacuum tube called a magnetron where the coherent waves are formed and from which radiation is further guided into the heating cavity of the microwave oven or onto the antenna with radar applications [181]. In fact, the development of radar technology during World War II was the reason for the invention of more powerful magnetrons [182]. Later in 1950, the everyday heating application using microwaves was introduced by Percy Spencer at Raytheon Manufacturing Company [183, 184]. The industrial use of microwave heating began shortly after the invention of the microwave oven. The removal of organic sulphur from coal, vulcanisation of rubber, drying and analysis of chemical or food products, solvent extraction application as well as wet ashing or digestion techniques of the

chemical, biological or geological sample are popular microwave-assisted methods [179, 185].

4.1 The triumph of microwave chemistry

Microwave-assisted chemistry has been a significant improvement in the laboratory work of organic chemistry since its introduction to synthesis in 1986 [186, 187]. It took some time until microwave activation was commonly accepted in synthetic use, presumably due to safety and reproducibility issues with domestic microwave ovens. In the late 1990s, after the development of microwave reactors designed for synthetic purposes, where precise temperature, pressure and MW-power could be regulated, the microwave-assisted organic synthesis become an important part of research work (Fig. 63). Organic compounds are synthesized in minutes with the help of microwaves instead of hours or days using conventional heating baths and devices. Besides speeding up laboratory work, microwave chemistry often enables better yields, cleaner products and also gives new possibilities to perform chemical reactions [185].

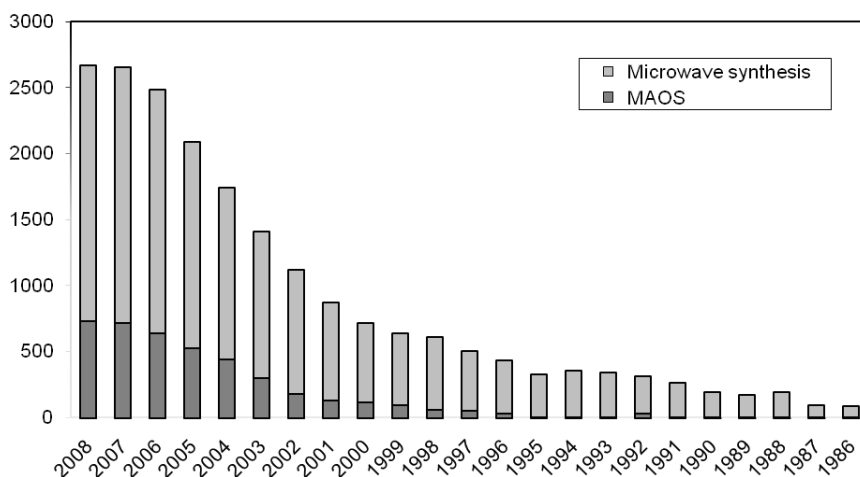


Fig. 63. Publications in the Chemical Abstract's database utilizing a microwave assisted synthesis since the first application in 1986. The figure was created by Scifinder Scholar® 2007 using topic search with keywords microwave synthesis and microwave assisted organic synthesis (MAOS) on 3rd Feb 2009. The exponential growth of publications can be seen also in other figures published. [180, 181, 188-190]

There are many excellent books [179, 181, 185, 191] and extensive reviews written by Gedye [192, 193], Lindström [189], Loupy [190], Kappe [8, 194], Majetich [195], Mingos [196, 197] and their co-authors in the area of microwave assisted organic synthesis. In the preliminary reviews of microwave-assisted organic synthesis in 1988 by Gedye, 1991 by Mingos and 1995 by Majetich; there are extensive studies of their own groups presented emphasising the advantages of MW heating. The reviews of Lindström, Loupy and Kappe are surveys of microwave-assisted synthesis carried out in the literature from the 1980s to the present. The diversity of the modern microwave technique in organic chemistry is extensively covered in these reviews. An updated book including practical microwave-assisted organic synthetic methods has been published recently by Kappe and co-authors [198].

Numerous publications have reported chemical reactions in commercial microwave ovens, but with the lack of information of the actual time, power or temperature. However, along with the expanding knowledge of the benefits of synthetic microwave reactors, current microwave-assisted reactions are reported with more detailed information.

4.2 Microwave activation

Compared with conventional heating technique, where external heat energy is conducted through the walls of the vessel into the reaction mixture, microwave energy directly interacts with the reactive species in the reaction vessel (Fig. 64). Therefore, the temperature gradient of the reaction mixture in the microwave-assisted reaction is homogenous as energy is more rapidly and equally diffused throughout the reaction mixture from multiple spots [185]. In fact, the existence of microwave-induced local temporary “hotspots” [199] is not fully agreed upon. However, it is known that microwave interacts differently with polar and non-polar substances [200]. The glassware for synthetic work is chosen so that it is transparent to microwave radiation, which is advantageous as the walls of the reaction vessel are not overheated as they are when using a conductive heating technique. [179, 185] Overheated surfaces can lead to the decomposition of products, substances or reagents.

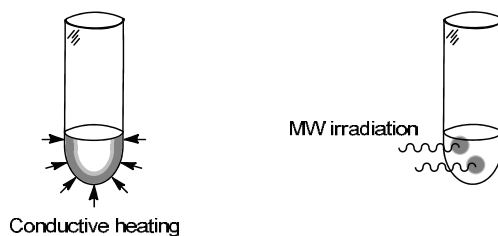


Fig. 64. Energy transfer in a conventional heating technique vs. microwave-assisted heating.

Microwave energy consists of an electronic and a perpendicular magnetic field. Only the interaction of the electronic field with a substance is important in chemical transformations. [179, 185] Molecules of the reaction mixture attempt to orient in accordance with the rapidly changing direction of the electronic field (about 2.4×10^9 changes per second) [201]. Polar molecules as dipoles rotate when trying to follow the applied electronic field, and charged particles start to move along with the field (Fig. 65) [179]. However, every molecule in the system cannot respond instantaneously to the change in direction, because of their motion is slowed down by fluidic resistance and intermolecular interactions. This asynchronous movement causes friction and collisions between molecules which is shown as heat [201]. Less-interactive molecules (e.g. with a small molecular weight, low van der Waals interaction, or no hydrogen bonding) would adjust themselves along with the changing direction of an electronic field more simultaneously without friction and therefore do not heat.

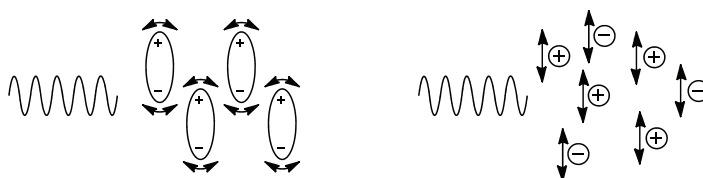


Fig. 65. The electronic field of microwave radiation caused a dipole rotation of polarized molecules and ionic conduction of charged particles.

Ionic molecules with a stronger charge distribution interact more readily with microwaves than dipoles. That can be helpful in organic synthesis when a charged by-product or an inorganic additive increases the absorption of MW radiation. The ability of a reaction mixture to convert MW energy to heat depends on the properties of substance molecules in accordance with the dissipation factor ($\tan \delta$). $\tan \delta$ values for common organic substances are reported in many microwave tables and it is a quantity formulated as the proportion of the substance's dielectric loss factor (ϵ'') to its dielectric constant (ϵ') (Fig. 66). The dielectric constant ϵ' indicates how much of a substance is interacting with the input MW energy and the loss factor ϵ'' is the amount of energy transferred (lost) to heat. [179, 196, 202]

$$\tan \delta = \frac{\epsilon''}{\epsilon'}$$

Fig. 66. The dissipation factor ($\tan \delta$) is related to the substance's dielectric loss factor (ϵ'') and dielectric constant (ϵ').

When MW energy is applied to the reaction, molecules organise more systematically due to the electric field, and after MW radiation has been switched off, the molecules return back to their original random organisation. The time taken for the majority of the molecules to return to their original state after being exposed to MW radiation is called the molecular dielectric relaxation time (τ). [179] This relaxation time is characteristic for substances and dependent on temperature. The higher the temperature the less time is needed for molecules to disorganise. Relaxation time at room temperature for large molecules in viscous solvents can be even 10^{-4} s but small dipoles in diluted media reorient even more quickly at 10^{-10} s. Relaxation time for organic reactions is around a few picoseconds. [189]

The three main dielectric parameters; $\tan \delta$, constant ϵ' and loss factor ϵ'' are all highly dependent on properties of the substances (e.g. polarity, charge, dipole moment, viscosity), but also the temperature, the MW frequency (usually only 2450 MHz used), the volume and the concentration of the sample will affect the ability of the samples to absorb MW energy. [185]

4.3 Microwave apparatuses in synthetic chemistry

The first microwave-assisted syntheses were carried out with domestic microwave ovens. Chemists had problems with safety issues and repeatability of reactions. Organic reactions behaved unpredictably, which sometimes caused explosion inside the microwave oven. The major problem in syntheses with domestic ovens is that microwave energy is distributed unequally inside the relatively large heating cavity. The microwaves entering the cavity start reflecting from the metallic surfaces of the cavity until absorbed in the sample or reflected out to a dummy load collector which is necessary to prevent radiation from entering back to the magnetron. This wall to wall reflection creates a random microwave pattern which is shown in Fig. 67 as a multi-mode cavity [179]. If a sample happens to be in a spot of where the MW energy is multiplied it heats much faster than when located to the side of that spot. This problem has been tried to overcome with the use of mode stirrers or fan-shape paddles and turntables or spinners to unify the energy throughout the cavity [181, 197]. Another problem related to domestic microwave ovens is that the variable powers are produced by periodic switching on and off of the full magnetron power. The broad change in the microwave energy input is believed to be undesirable to the chemical transformation [197].

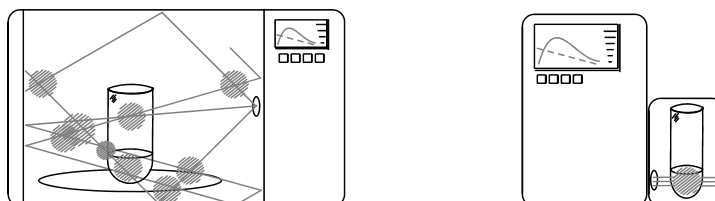


Fig. 67. Simplified picture of the distribution of a high microwave energy concentrate (grey spots) in a multi-mode microwave oven and a single-mode reactor.

Problems with multi-mode apparatuses have contributed to the designing of specific microwave reactors for synthetic use with a consistent microwave energy pattern, which are also known as single-mode reactors (Fig. 67). The unique standing wave is created through the design of an accurate wave guide and heating cavity and the mounting of the reaction vessel at a precise distance from the radiation source. It must be noted that the heating cavity in single mode

reactors is much smaller than with a multimode apparatus. The reaction volume can vary from 0.2 to 50 mL under sealed vessel conditions and can have a maximum ca. 150 mL in an open flask reactor. Most of current commercially available single and multi-mode MW-reactors are featured with efficient magnetic stirrers, a computer-controlled temperature monitoring system utilizing an in-reaction fiber-optic probe or shielded thermocouples or infrared measurement through the vessel wall and software that enables real-time adjusting of MW power output due to absorption, temperature or pressure. In addition, closed microwave reactors are equipped with precise pressure control and safety shielding the cavity. [189]

Biotage AB [203], CEM Corporation [204], Milestone [205], Anton Paar and Plazmatronika are developers of modern synthetic microwave reactors. On the other hand, Biotage's Initiator™ and Discover® reactors by CEM are the only available single-mode reactors. It seems that only the single-mode reactor can lead to repeatable results, at least with small scale reactions, even though the techniques used with a multi-mode microwave reactor have greatly improved [181, 189, 190, 206]. The reactions in this thesis have been carried out using single-mode reactors.

The next step in microwave synthesis is to scale-up the reactors to an industrial batch size, which demands a new type of innovation [207]. As mentioned earlier, the heating assisted by microwaves is a result of MW energy penetration into the sample and then loss as heat. The depth of the penetration is limited since the energy of the microwave radiation is low. The depth of penetration is determined by the depth of the material where microwave power has fallen to one half of its original value [197]. For example, classical solvents such as water and alcohols have a depth of penetration less than 10 cm at room temperature at a 2.45 GHz frequency [181]. A lower frequency (915 MHz) or higher temperature would ease penetration. Generally, microwave batch reactors are equipped with relatively high power magnetrons (> 1000 W) and they provide sufficient heating up to 500 mL volumes. However, these large batches would still be heated unequally and the control of real-time MW power input would be difficult. A manufacture of parallel multimagnetron systems or the modification of the pipe-like reaction vessels are solutions to this issue [181].

An important factor in processing multi-cubic metre batches under microwave heating is the safety aspect, as loss of control may have serious consequences. Especially pressurised closed vessels on a large scale are high risk systems.

The most attractive solution to the scale-up problem is to adapt a continuous flow systems for the microwave technique in such a way that the reaction mixture is pumped through a small vessel [208, 209] or tube inside a cavity [210, 211] to which MW radiation is applied. [207]

4.4 Solvents in microwave-assisted synthesis

In closed microwave-assisted synthesis, the boiling point of the solvent is not as an important factor as it is in the conventional heating method. Thus, selecting the right solvent for synthesis can be based on the solubility and properties of the solvent. Common organic or inorganic solvents (MeOH, EtOH, DMSO, MeCN, DMF, and H₂O) with a high dipole moment and a low molecular weight couple with 2.45 GHz microwave radiation effectively (Table 17). Non-polar solvents such as hexane, toluene and THF have a negligible dielectric loss and $\tan \delta$ values which means they do not heat efficiently in a microwave electronic field [197].

Table 17. Dielectric parameters of some common solvent. [196]

| Solvent | Tan δ | Dielectric loss factor, ϵ'' | Dielectric constant, ϵ' | bp. at 1 bar (°C) | bp. (°C) attained by MW ^a |
|-----------------|--------------|--------------------------------------|----------------------------------|-------------------|--------------------------------------|
| Ethylene glycol | 1.35 | 50.0 | 37.0 | 197 | |
| EtOH | 0.94 | 22.9 | 24.3 | 78 | 155 (1) |
| DMSO | 0.83 | 37.1 | 45.0 | 189 | 250 (1) |
| Formic acid | 0.72 | 42.2 | 58.5 | 100 | |
| DMF | 0.16 | 6.07 | 37.7 | 153 | 250 (1) |
| Water, dist. | 0.12 | 9.89 | 80.4 | 100 | 165 (10) |
| MeCN | 0.06 | 2.33 | 37.5 | 82 | 180 (13) |
| EtOAc | 0.06 | 0.35 | 6.0 | 77 | |
| Acetone | 0.05 | 1.12 | 20.7 | 56 | 150 (7) |
| THF | 0.05 | 0.35 | 7.4 | 66 | 110 (3) |
| DCM | 0.04 | 0.38 | 9.1 | 40 | 110 (5) |
| Toluene | 0.04 | 0.096 | 2.4 | 111 | |
| Hexane | 0.02 | 0.038 | 1.9 | 69 | |

a) InitiatorTM by Biotage. Pressure (bar) is in brackets.

In open vessel reactions, the boiling point of solvent usually limits the use of high temperature. Microwave-assisted synthesis can also be carried out in the absence of solvents or other volatile compounds [212]. The reagent can also be absorbed into solid strongly microwave absorbing inorganic material, e.g., silica or graphite [194]. Also ionic liquids are efficient microwave absorbers [213]. The use of high

temperature with a low pressure is possible because of the ionic structure and non-existent vapour pressure of the ionic liquids.

4.5 Advantages of microwave chemistry

Why does the use of microwave radiation, instead of conventional heating, seem to give better yields and speed up reaction? The review of Mingos *et al.* contains an excellent outline of how the assistance of microwaves improves chemical transformations [196]. It was also shown that the effects of microwave dielectric heating can be examined as a thermal effect which is resultants of differences in temperatures and the distribution of heat in a reaction vessel. There has been some speculation in early literature if microwaves could affect chemical transformations other than in thermodynamic ways, but at the moment, the existence of so called non-thermal microwave effects can be ruled out [193, 201].

The most obvious advantage in microwave heating is the dramatically shortened reaction time. According to present knowledge, the increase of the reaction rate is exclusively due to the possibility to gain a higher temperature through microwave dielectric heating than with conventional heating baths and mantels [201]. This is emphasized in closed well-pressured systems where boiling points of compounds are no longer limited by maximum temperatures [195]. A theoretical approximation, which gives some information on the relationship of the reaction rate and temperature, is the Arrhenius equation of rate constant [194]. It has been used to predict that the rate of the first order reaction would multiply about 10^2 times at every increase of $50\text{ }^\circ\text{C}$ [197]. Respectively, the increase of rate would have been about 10^3 times on second order reactions [197]. All of this can be simplified in such a manner that the time required for the reaction to complete is halved when the reaction temperature increases by $10\text{ }^\circ\text{C}$ [181]. Therefore, it is not surprising that with the possibility to use even 2–3 times higher temperatures ($> 100\text{ }^\circ\text{C}$ above bp.) in the closed microwave-assisted system, the original conventional reaction times are shortened from days to hours or from hours to minutes etc. In addition microwave-assisted systems were able to obtain temperatures of 5–25 $^\circ\text{C}$ above boiling points by a rapid MW heating in open vessels, but only when highly MW absorbing co-substances were added to the solvent [197, 214]. This effect is known as superheating.

Microwave-assisted organic syntheses were generally reported to have some improvements in yields. Obviously, the short reaction time (usually minutes) made it possible to optimize reaction conditions more quickly than with

conventional multi-hours-reactions. On the other hand, the increase of the temperature could also accelerate side reactions. However, the important difference compared to conventional heating is that microwave activation puts energy into the system more uniformly [203]. The more uniform temperature throughout the reaction mixture gives the possibility to obtain less decomposition and fewer side reactions, and therefore, cleaner products [189]. As presented in Fig. 64 the energy is absorbed by reagents themselves, and non-absorbing solvents as well as the vessel's walls remain cool. In addition, in this manner the solvent can act as a heat sink stabilizing sensitive products. On the contrary, very high temperatures can be achieved by exposing metal powders in a microwave field, which is proposed to accelerate organic and inorganic reaction even more [215]. Through the careful design of reaction, reagents can be made more absorbent toward MW energies than the final product.

The advantage of the microwave-assisted synthesis is the efficient, sustainable and ecological use of time and energy. Microwave chemistry allows for the introduction of better conversions and new ways to carry out reactions that are also in accordance with the green chemistry. With the assistance of microwave, organic syntheses can be modified to become greener by considering the use of less toxic solvents since the boiling point or solubility are not limiting factors in reactions. Microwave heating enables the ability to work with less reactive chemicals because their reactivity increases when extra energy is applied to the system. Generally, microwave activation can be used in all reactions that require heating [189].

5 Triosephosphate isomerase

The ultimate aim of this thesis was the investigation and the rational design of new substrates of a modified triosephosphate isomerase (A-TIM) when natural substances were less capable on binding in A-TIM's enlarged active site [1]. The reference enzyme (TIM) catalyses a reversible biochemical transformation in the middle of the glycolytic cascade: the interconversion of dihydroxyacetone phosphate (DHAP) and D-glyceraldehyde phosphate (D-GAP), which is catalyzed exclusively by triosephosphate isomerase (Fig. 68) [216, 217]. It should be noted that some trivial biochemical naming and shortcuts were chosen for the most common natural compounds as they occurred that way in the literature referred.

Despite the fact that the conversion of DHAP into D-GAP is energetically unfavourable, TIM catalyses this reaction to happen about 500 times per second limiting only by the diffusion of the substrate into the active site of the enzyme [216, 218]. This conversion has been proposed to go through the *cis*-enediol intermediate [216, 217, 219], which would be highly unstable without protection provided by the enzyme cage, producing a single enantiomer of glyceraldehyde phosphate. The α -hydroxy substituted aldehydes are known to be highly unstable due to the increased carbonyl group activity by adjacent hydroxyl group [16].

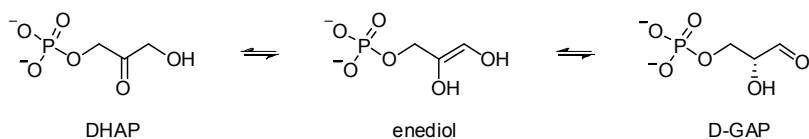


Fig. 68. The interconversion of dihydroxyacetone phosphate and D-glyceraldehyde phosphate goes through an enediol intermediate and is catalysed by the triosephosphate isomerase.

5.1 General

Triosephosphate isomerase is a well-studied natural enzyme. It is noteworthy that nearly all living organisms; including animals, plants, fungi and bacteria, which use glycolysis in their energy production have a TIM in their cell's cytosol. An interesting observation is the similarity of TIM between species, which suggests a similar enzyme being involved already in the primordial stages of life [220-223]. The importance of TIM can also be seen from the medical perspective. In humans,

an insufficient triosephosphate isomerase has been associated with severe neurological disorders and haemolytic anaemia [224] and recently with early childhood death [225]. Another practical example would be to utilize the inhibition of TIM's activity as a cure to malaria caused by protozoan parasites because of their high dependence on glycolysis [226-228]. Better understanding of the function and substrate binding properties of TIM is therefore an important area of research.

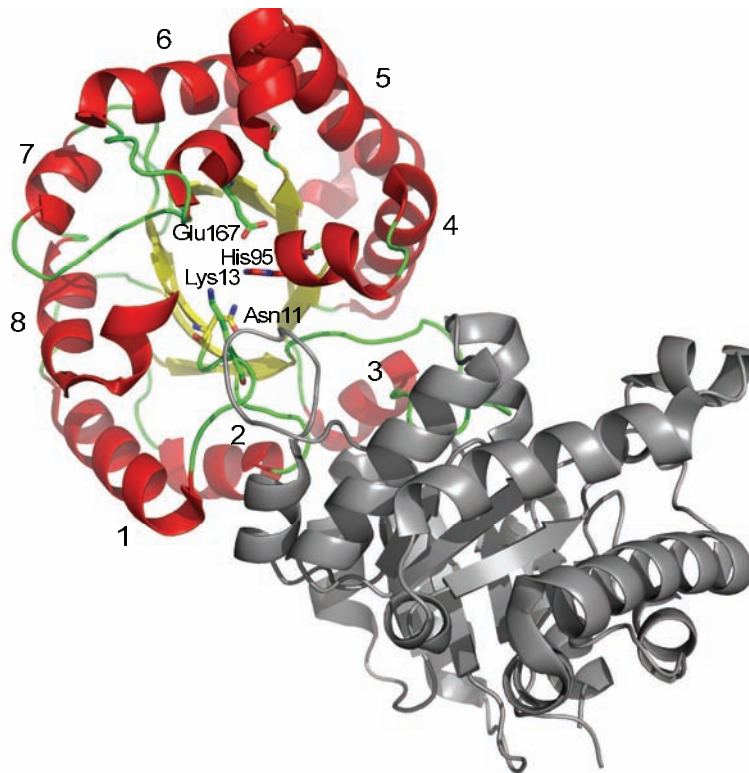


Fig. 69. The picture of the dimeric wild-type *Tb*TIM showing four important substrate binding residues. Each eight $\beta\alpha$ -loops begin at β -sheets, proceed on α -helices and turn back to the core of β -sheets (PDB code 1IIH). Reprinted on permission with Wierenga. [229]

Wild-type triosephosphate isomerase (wtTIM) occur in a dimeric form having two identical subunits, each of which is made up of ca. 250 amino acids (Fig. 69). The three-dimensional structures of both subunits contain eight parallel β -strands (marked in yellow) on the core structure surrounded by eight α -helices (red) on the outside. This structural scaffold is known as an $\alpha\beta$ -barrel, or a TIM-barrel, since it was first discovered in the TIM. The TIM barrel is also by far the most commonly observed protein fold in the database of the protein data bank. [230, 231] The repeating β -strands and α -helices are numbered sequentially from the *N*-terminus to *C*-terminus, as β 1- β 8 and α 1- α 8. The catalytic loops come after the β -strands and are numbered as loop 1 to loop 8. [230]

The catalytic site of TIM is located in the central part of the barrel where the catalytic loops 6, 7 and 8 shape the substrate binding pocket (Fig. 69) [232]. Two important amino acid residues are highlighted as glutamate-167 (167th residue counted from the *N*-terminus of trypanosomal TIM) and histidine-95 which both have been proved to be involved in the catalytic mechanism [217, 232]. Two other residues, lysine-13 [217] and asparagine-11 [217, 233-235] are also located close to the catalytic site and are proposed to interact with a substrate. The orientation of all these residues is important, and the identical sequence of the active site residue occurs in all known triosephosphate isomerases [236]. It is known that a mutation in any of these residues yields a dramatic decrease in the catalytic activity of TIM [217]. Loop 8 as well as loops 6 and 7 interact closely with oxygen atoms of the phosphate group of the substrate and therefore play an important role in placing the substrate in its competent place.

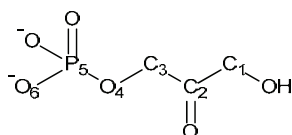


Fig. 70. The structure of DHAP illustrates the atom numbering map of the substrate. The atoms of the molecule can be generally numbered systematically from 1 to 5 at the main structural backbone. In addition, O1 and O2 refer to the oxygen atoms bond to C1 and C2, respectively.

TIM is described as a perfect enzyme since its catalytic rates are comparable to the diffusion encounter rate and it increases the rate of conversion of DHAP to D-GAP by a billion times [216]. It is also worthy to note that TIM does not need

additional co-factors or metal ions to act. Even though the principle of the TIM reaction is well understood, chemical details of the mechanism are still controversial [234]. The “classical” mechanism by Knowles [237] (Fig. 71) has been the most commonly agreed upon reaction pathway for the isomerase [234]. There are additionally other mechanisms presented in the scientific literature [234].

The conversion has been shown to drive forward by the glutamate-167 anion, also referred to as the catalytic base [217]. It is expected that the glutamate can act by abstracting the topmost proton (marked in red, Fig. 71) from the C1 carbon of the DHAP. Histidine-95 is neutral at natural pH and acts as conjugated acid pushing its proton toward carbonyl oxygen either covalently (Fig. 71) or by hydrogen bonding. [237, 238] In the absence of an enzyme, the formation of a labile enediol(ate) intermediate would be an energetically unfavoured process because of the high pK_a of the sp^3 hybridized C1 carbon. The intermediate also most easily reacts back to DHAP. However, the well-designed placement of functional groups in the substrate binding site stabilizes the intermediate so that the transfer of the proton from C1 to the C2 carbon is made possible. The cleavage of a proton from the primary OH group with the help of histidine-95 anion finalises the tautomerization to α -hydroxy aldehyde. [234, 237]

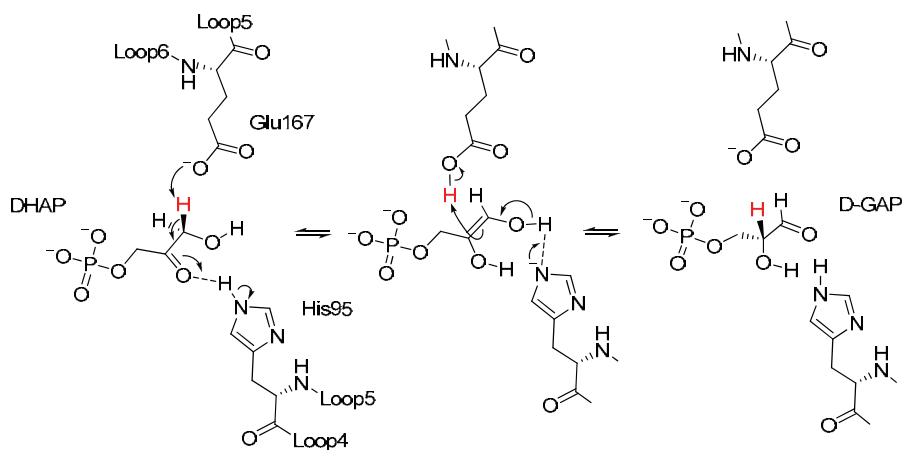


Fig. 71. The “classical” mechanism of the triosephosphate isomerase.

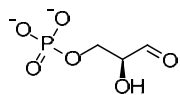
The mechanism of TIM has been extensively studied with NMR and X-ray crystallography using isotope labelling or binding non-natural analogues of natural substrates [217, 234]. In addition, site selective mutagenesis has been applied to TIM to show the importance and function of catalytic glutamate [239] and histidine [237] residues. The lifelong work carried out by the group of Jeremy Knowles is greatly acknowledged [240].

5.2 Non-natural substrates of triosephosphate isomerase

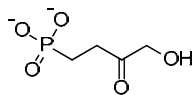
In addition to DHAP and D-GAP (Fig. 68), there are many publications on the analogues of these natural substrates and their interactions with TIMs in the literature. The following Fig. 72 presents a preliminary summary of the most studied non-natural substrates [241]. In principle, these substrate candidates can be grouped into three groups: analogues of the natural substrates (**168-173**); reversible binding inhibitors (**174-179**) and covalently binding inhibitors (**180-182**). Two compounds; 2-phosphoglycolate (**178**, 2PG) [242] and 2-phosphoglycolohydroxamate (**179**, PGH) are published to represent the binding symmetry of enediol transition state.

The compounds **168-179** of the first two categories bind reversibly into TIM, which can be used to study the functionality and activity of the enzyme. The ketone or aldehyde functionality containing substrate analogues **168-173** also assist with the study of catalytic activity of TIM. The non-covalent interaction, on the other hand, can be so strong that it can inhibit the enzyme. The known two transition state analogues **178-179** binds more strongly to the active site of the enzyme than the substrate mimics do [243] making them most suitable for structural studies. The unexpected function of the uncharged histidine of the catalytic site has been discovered with the complex of **179** by NMR [244] and X-ray crystallography [245]. In turn, the covalently binding “suicide inhibitor” **180-182** forms an irreversible bond to the residue of the active site, which has been used to show valuable information of the residues themselves. For example, the functionality of the catalytic glutamate-167 residue has been revealed by covalently binding of 1-halo-3-hydroxyacetone phosphates **180** [246].

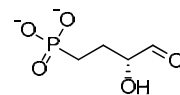
Analogues of natural substrates



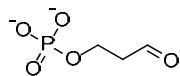
168 (L-GAP)



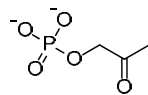
169



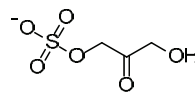
170



171

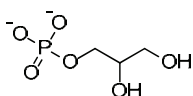


172

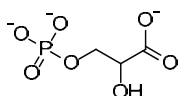


173 (DHAS)

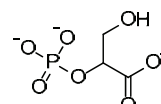
Competitive inhibitors



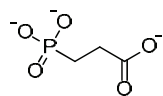
174 (G3P)



175 (3PGA)

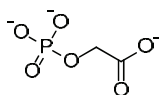


176 (2PGA)

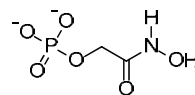


177 (3PP)

Transition state analogues

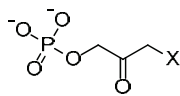


178 (2PG)

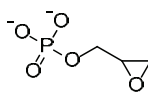


179 (PGH)

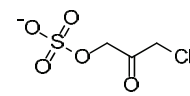
Irreversible inhibitors



180 (X = I, Br, Cl)



181



182

Fig. 72. The non-natural substrates of TIM; the analogues of the natural substrates (168-173) contain ketone or aldehyde functionality, the competitive inhibitors (174-179) interact with the active site of TIM by hydrogen bonding, and the irreversible inhibitors (180-182) form a covalent ester bond with the catalytic glutamate residue.

The dissociation constant of the enzyme-inhibitor complex K_i is generally used to estimate the binding affinity of non-natural substrates (inhibitors) [242]. K_i of the competitive inhibitors is the respective dissociation constant [247]. This is determined by comparing the Michael-Menten's kinetics with and without inhibition (Fig. 73) [248].

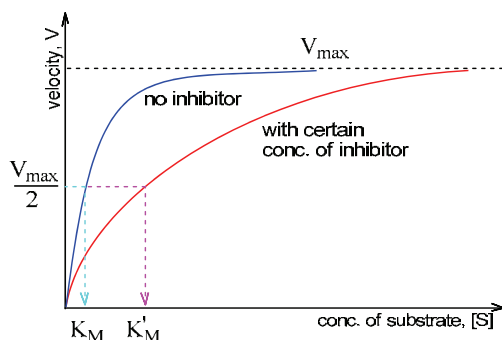


Fig. 73. The effect of competitive inhibition on enzyme kinetics. The top curve represents the reaction's velocity at function of concentration of natural substrate, and the lower curve shows the same reaction with an additional inhibitor. Concentration of inhibitor is constant.

Generally, the dissociation constants of substrate candidates **168-173** have been determined lower than the dissociation constants of the natural substrates [249-251]. There are many small differences in **168-173** that affect the binding of the natural enzyme (Fig. 72). This also should be considered in designing the new substrates for mutated non-natural TIM, which is the area of interest in this study.

TIM has a really high selectivity to the specific chiral conformation. It was defined with the decrease of 10^6 in rate constants when L-GAP (**168**) was used instead of D-GAP [250]. In turn, the change of D-GAP to 1-hydroxy-4-phosphono-butanal (**170**) decreased the rate of conversion much less [249]. Another similar decrease of the affinity was also seen by exchanging 2-phosphoglycolate (**178**) to 3-phosphono-propionate (**177**) [252]. However, the interaction of the O4 oxygen of the phosphate ester (Fig. 70) with the surrounding residues could be assumed to be insignificant [229, 253].

Triosephosphate isomerase catalysed interconversion cannot happen between 3-hydroxypropionaldehyde phosphate (**171**) and monohydroxyacetone phosphate (**172**) due the lack of an adjacent hydroxyl group. However, the first step of the

catalytic reaction path has shown to give an enolate intermediate (Fig. 71). The exchange rate of methyl protons were ca. thousand fold slower with methylketone **172** than with DHAP. Presumably, the reason for that could be the higher pK_a of the vicinal methyl groups of **172**. [251] It was also noted that aldehyde **171** was too labile under the conditions needed to study enzymatic reaction. Furthermore, the racemate of glycerol-3-phosphate (**174**) was one of the first non-natural substrates studied with wtTIMs (chicken, rabbit and *Tb*TIM), and it had similar affinity than DHAP [254].

The phosphate functionality is an important factor on the binding of the substrate molecule. However both sulphate (SO_4^{2-}) and phosphate (HPO_4^{2-}) were determined to have a similar binding strength to *Tb*TIM [254]. This is likely the result from the same strong charge distribution of the anions since wtTIM was observed to lose some catalytic activity with dihydroxyacetone sulphate (**173**) when compared to DHAP [249].

5.3 Toward new enzyme catalyst

According to the hypothesis of our consortium it is possible to design new enzymes on the scaffold of TIM that are capable of catalyzing the conversion of α -hydroxy ketone compounds into the specific, chiral α -hydroxy aldehyde analogues.

The wild-type TIM has very narrow substrate specificity, as the only known substrates being DHAP and D-GAP. When specific mutations were carried out this selectivity toward α -hydroxy carbonyl compounds was started to change (Fig. 74). [1, 232] The starting point of the protein engineering effort was a mutated, monomeric protein, derived from *Trypanosoma brucei brucei* TIM (*Tb*TIM) [232]. The dimeric interface was disrupted by deleting residues in the loop-3, which made TIM a monomeric protein. Further small changes were made in loop 1 and loop 4. The extended groove in the binding pocket was created by compressing loop-8 around the phosphate binding site. This protein (ml8bTIM) was further mutated (V233A) to restore its binding properties [1]. This novel protein is now called A-TIM.

A-TIM can bind new substrate analogues which cannot otherwise be bound. The modification was such that the substrate binding site would not only be restricted to interact with the phosphate group analogue, but different functionality could also be used. For example citric acid has been fitted into the binding site [1]. The monomeric form of TIM is also a manageable size for NMR spectroscopy and X-ray

diffraction experiments. The finding of a perfect match for substrate and A-TIM was appointed as a goal for our project.

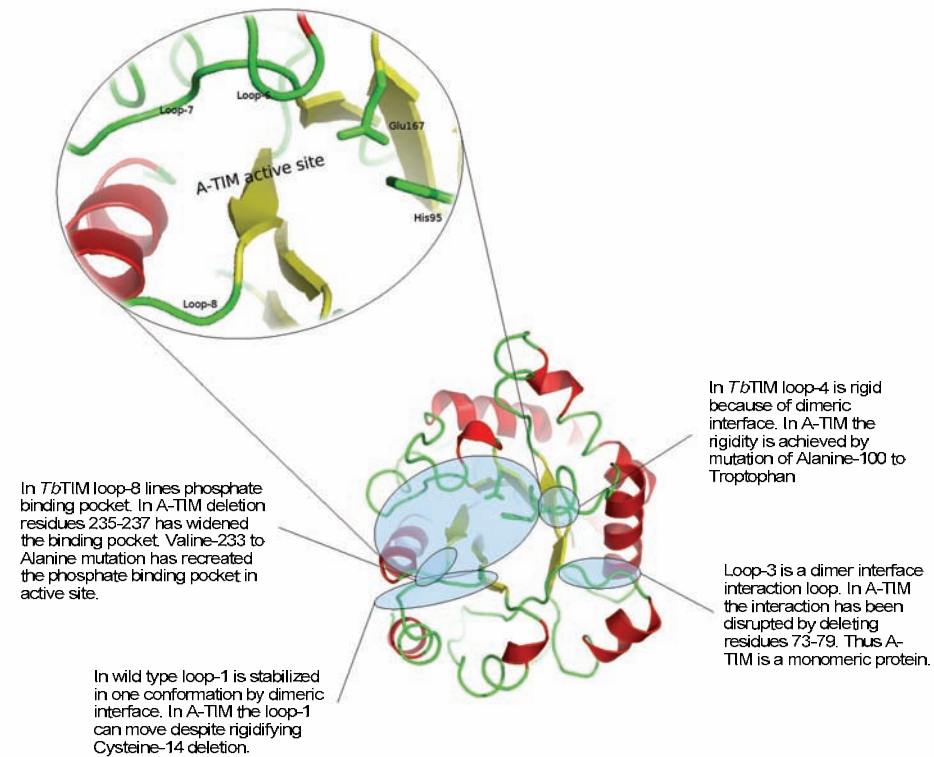


Fig. 74. The differences between wild type *Tb*TIM and A-TIM [1, 232]. The picture is modified from the poster presented at the INPEC meeting. The picture was created using Pymol. Reprinted with permission by Salin. [255]

6 Results and discussion

6.1 Design and synthesis of transition state analogues and substrate analogues based on mutated triosephosphate isomerase

The starting point of our study was the structural dimensions of the extended substrate binding pocket of TIM [232]. In addition it was known that dihydroxyacetone phosphate and glyceraldehyde phosphate are relatively unstable compounds, and the synthesis of an exact structural analogue of these substances is not trivial [15, 256]. The shape and size of the modified binding site of A-TIM sets several requirements for substrate candidates (Fig. 75). The fitting of the candidate was preliminary estimated through visual inspection and computational approaches.

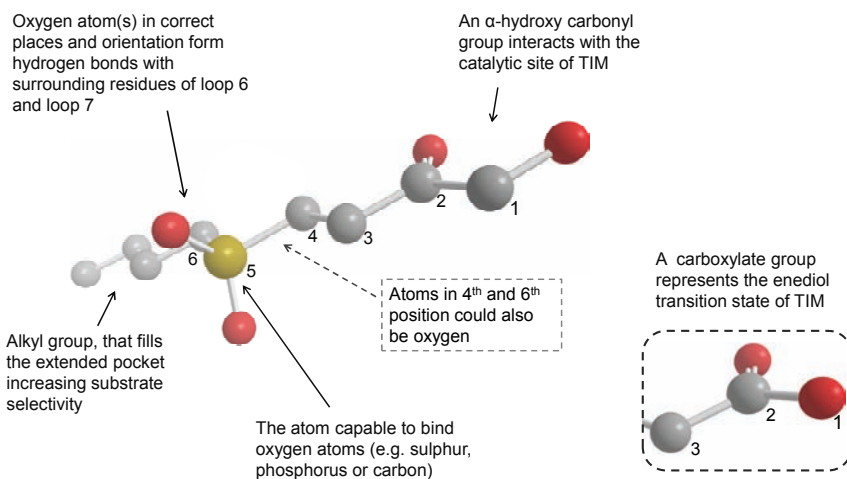


Fig. 75. Schematic presentation of the requirements for non-natural substrate candidates and corresponding transition state analogues. The insert shows the carboxylate group of the transition state analogue.

The structure of the substrate analogue has to contain an α -hydroxy ketone or aldehyde unit at the end of its skeleton in order to interact with catalytic residues. Respectively, the transition state analogue has a carboxylic acid group which binds to the catalytic site. Thus the enzymatic conversion could be expected only

with the α -hydroxy carbonyl compound. The centre atom (5th in the chain) has to be capable of binding an oxygen atom needed to anchor a substrate molecule in its place between loops 6 and 7 as phosphate does in the wild type system. Besides phosphate, sulphate and carbonyl would fulfil this requirement. According to the earlier results [253], the replacement of the oxygen atom at position 4 by a carbon would not have an effect on the binding strength between substrate and A-TIM, but it makes the substrate candidate more stable and prevents the elimination reaction [257]. The elimination of the phosphate group is a major problem during the triosephosphate isomerase.

In addition, substrate should contain a tail which could slide into the extended hydrophobic groove of the A-TIM. The size of this pocket would be interesting to determine; therefore the compounds that have been synthesized have an alkyl chain of variable length. In a collaborative affair with the group of Wierenga the exact fitting into the extended pocket was advanced to increase substrate binding and possibly improving the catalytic activity of the enzyme.

6.1.1 The development of the synthetic proposal

At the first stage, the sulphonyl functionalized α -hydroxy ketones were chosen for the substrate candidates because hydroxy ketones are more stable than corresponding aldehydes [251]. The corresponding phosphate functionality would be less tolerant towards aqueous conditions [15], and the 4-carboxyl derivatized substrate candidates would be synthesized by other persons [258]. While the synthesis of 4-alkylsulphonyl-2-hydroxybutan-2-ones **183** has not been previously described, it was decided that the synthetic methods should follow the principles of green chemistry when possible. Furthermore, the microwave-assisted organic synthesis interested us.

The preliminary synthetic proposal was that the α -hydroxy carbonyl functionality could be synthesized first (Fig. 76). The *S*-alkylation of this compound with different alkyl thiols would result with a number of thioethers **184**, which have an α -hydroxy carbonyl group at the correct position and the alkyl tail at variable length. The oxidation of the sulphur atom would give the target compound **183**.

After the unsuccessful results of the quite unpleasant synthesis of α -hydroxy ketone **185** from but-2-yne-1,4-diol with mercury sulphate [259], it was considered that the Wissner hydroxy ketone synthesis (Fig. 61) [177] could be applied to our purpose. Unfortunately, after many attempts to convert the

corresponding acid chlorides to hydroxy ketones with TMSE **106**, the compounds **185-187** were still unacceptable to us. Ketones **185-186** could not be isolated from the reaction mixture because of the multiple side reactions. A minimal amount of mercapto ketone **187** was detected when the thiol group was left unprotected. However, difficulties were faced when protective groups were studied [80].

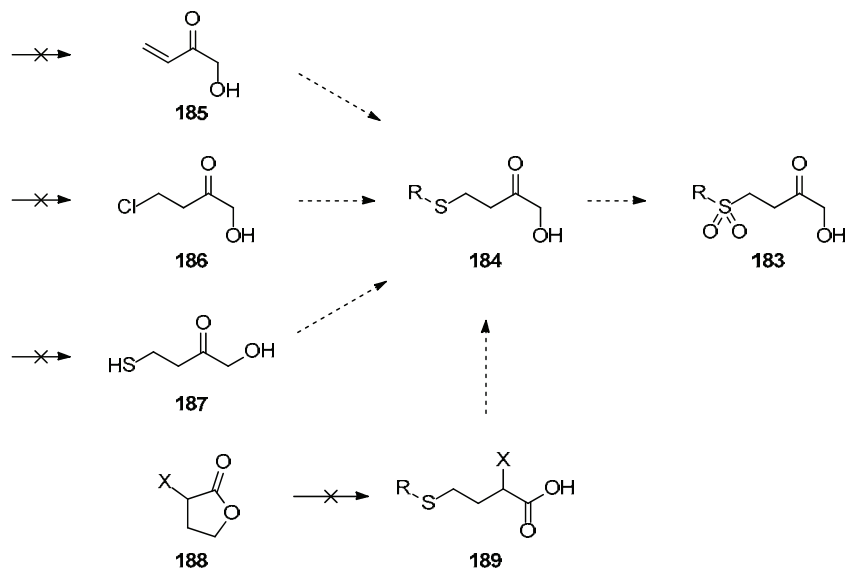


Fig. 76. Reaction pathways towards an α -hydroxy ketone **183** that could not be completed.

The next strategy to overcome the problem related to the stability of α -hydroxy carbonyl compounds was to the use of 3-hydroxy-dihydrofuranone (**188**, X = OH) [260] as the target molecule for *S*-alkylation. This reaction would create α -hydroxy carboxylic acid (**189**, X = OH). Acid **189** could be mildly reduced with DIBAL [261] to α -hydroxy aldehyde followed by the tautomerization into a corresponding α -hydroxy ketone **184**. However, a further study of this idea was competed after reactions with a base or Lewis acid-assistance [262], which poorly yielded any product **189** (X = H, R = *n*-butyl).

Later it was proposed that the already successful synthetic route with the butyl derivative **183b** could be used for the synthesis of a library of variable α -hydroxy ketone derivatives **183** (Fig. 77).

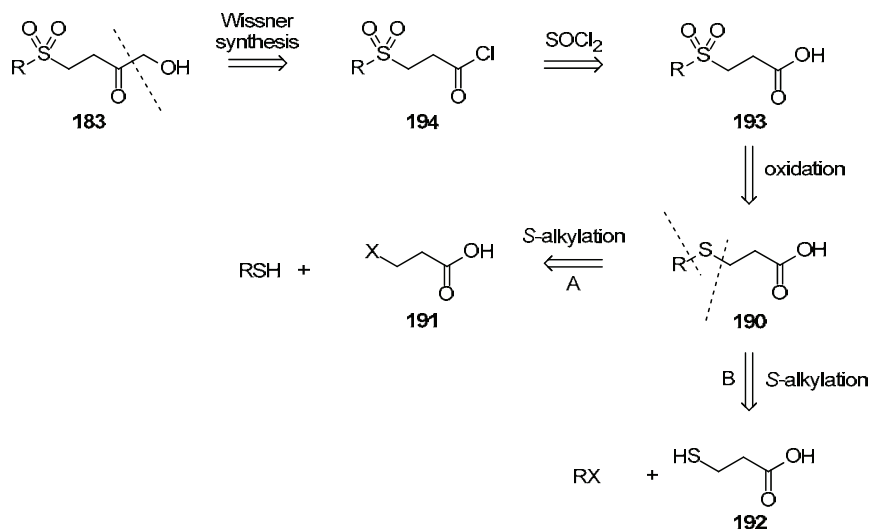


Fig. 77. The retrosynthetic analysis of alkylsulphonyl α -hydroxy ketones **183.**

The compounds are synthesized individually and the sensitive α -hydroxy ketone part is formed in the last step which is the Wissner hydroxy ketone synthesis. The reaction path starts from the thioether **190** which can be synthesised by two alternative routes. Propionic acid **191** with a good leaving group at β -position can be substituted by alkylthiol (route A), or 3-mercaptopropionic acid (**192**) can be *S*-alkylated with a variety of alkyl halides (route B) [1]. The oxidation of thioether **190** to sulphonyl **193** and the formation of acid chloride **194** are two straightforward procedures. The last reaction takes place between the acid chloride **194** and silylated ketone acetal **106** [177].

The presented reaction route does not need any protection of functional groups. The substitution by a soft nucleophile like thiol is a thermodynamically favoured process and therefore, microwave-assistance would favour *S*-alkylation to **192** over esterification [185]. With the acid **193**, there is also a minimal risk of over oxidation. The sensitive α -hydroxy ketone part is synthesized in the last step. When necessary, the tail part of the molecule can contain functional groups like hydroxyl or an amino group. These functionalities could be protected already before the *S*-alkylation. Another advantage of the presented pathway is that both the transition state analogue **193** and the substrate analogue **183** will be produced.

6.1.2 Microwave-assisted S-alkylation

In addition to β -alkylthio carboxylic acids **192** being the intermediates towards sulphonyl α -hydroxy ketones **183** (Fig. 77), they are interesting compounds due their many industrial applications [263]. They have been used as additives to improve resistance toward heat and oxidants, as well as to increase lubrication, antibacterial and detergent properties in different applications [I].

Two common methods to form a thioether group in a carbon chain are the S_N2 displacement of the good leaving group with a thiol or a polar addition of an alkanethiol to an unsaturated carbon. [264] Typically, alkylations of this kind are carried out in the presence of a stoichiometric amount of a base which activates the sulphur nucleophile and neutralizes the leaving group. Our first choice was a substitution of a β -halo-substituted carboxylic acid with different alkyl thiols using sodium hydroxide as a base [I]. From the environmental point of view the formation of non-toxic sodium halide as a by-product was a positive aspect. The reaction was also readily applicable to microwave heating. In addition, microwave energy is absorbed very efficiently into a reaction mixture at the presence of charged particles.

The microwave-assisted substitution of 3-chloropropionic acid (**191**, X = Cl) with a slight excess of alkanethiol moderately yielded 3-(alkylthio)propionic acids **190** in 10 min (Fig. 78) [I]. The reaction mixture also contained small quantities of side products as *S*-dialkylsulphide **195** and *S,S'*-dialkyldisulphide **196**, and some ester **197**. The problem was that the thiols tend to form these offensive sulphides and disulphides even under mildly basic conditions [264].

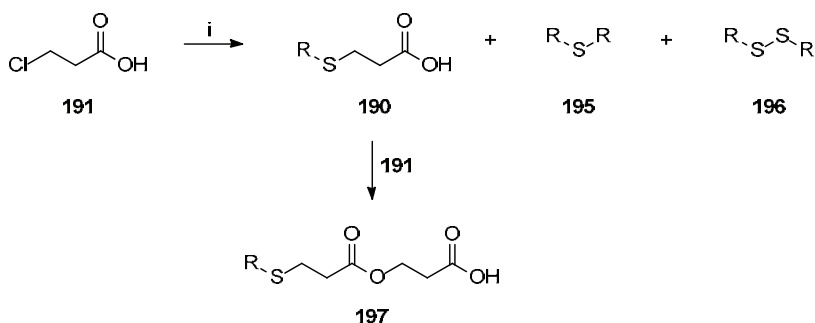


Fig. 78. The side products in the synthesis of 3-(alkylthio)propionic acid **190** from 3-chloropropionic acid (**191**); Reagents: i) RSH, NaOH, EtOH, MW irr. 70 °C, 10 min. R = *n*-butyl, *n*-pentyl, *n*-hexyl & benzyl.

When the functionality of the starting compounds was interchanged so that 3-mercaptopropionic acid (**192**) and alkyl halides were used instead of **191** and alkanethiol (Fig. 79) the formation of rather unpleasant and volatile side products were decreased. Thiol **192** reacted with butylchloride or butylbromide in 3 M solution of ethanol at the presence of two equivalents of solid NaOH. The graphical examination of the product mixture as a function of reaction time is presented in Fig. 80. [I]

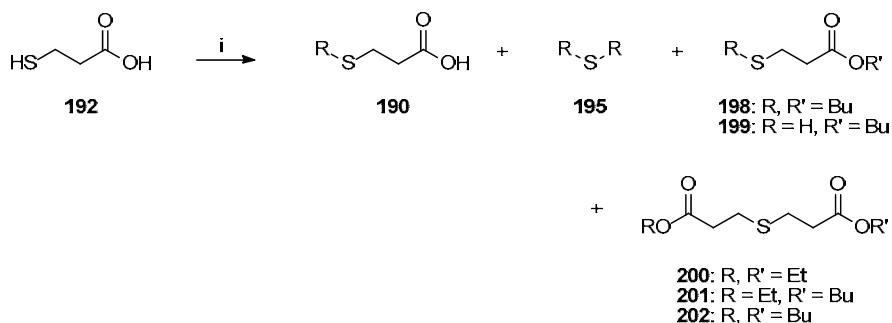


Fig. 79. Products of the microwave-assisted S-alkylation of 192; Reagents: i) R-X, NaOH, EtOH, MW irr.

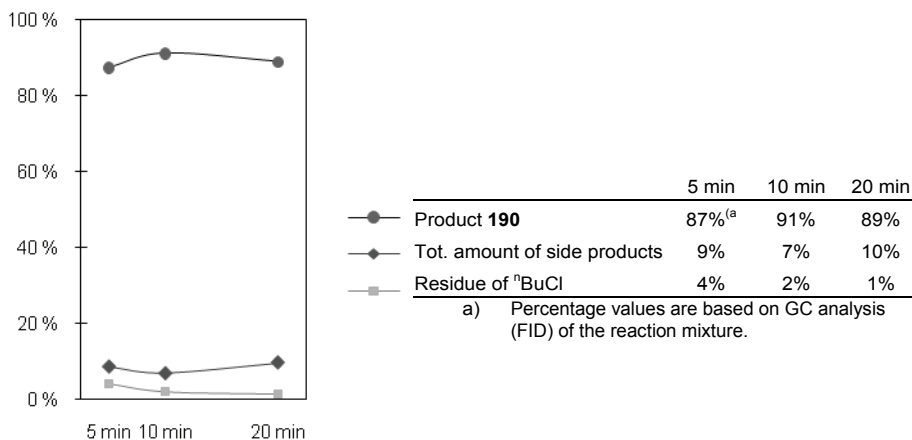


Fig. 80. The microwave-assisted S-alkylation of 192 at 100 °C as a function of the reaction time.

Table 18 shows the influence of the reaction temperature on the selectivity of S-alkylation. When chloride was the leaving group, the S-alkylation did not to happen

until the temperature was high enough (entries 2 & 3). With the initial microwave power of 100–200 W, the temperature of the reaction was about 20 °C higher than the adjusted value because of the reaction was exothermic at its inception. This was likely because the acid-base reaction when the sodium salt of **192** formed. After 2 min when the temperature decreased, the MW irradiation continued with the constant power of 15–25 W for the rest of the time. The analysis of the reaction mixture showed that the *S*-alkylation had not been completed within the 2 min time, but that the 10 min reaction time was optimal (Fig. 80). The temperature of 120 °C was found to be best for alkyl chlorides and 80 °C for bromides, respectively (Table 18). The substitutions with butyl bromide yielded more ester side products **198** and **199** than the corresponding chloride (entries 5-7) that can be seen to have systematically lower yields (Table 18, entries 9-12). [I]

Table 18. The microwave assisted *S*-alkylation. The effect of the reaction temperature and halide to the yield of main product **190 and the quantity of side product.**

| Entry | R-X | T, °C ^a | Components in the reaction mixture, % ^b | | | | | ⁿ BuSH | Isolated yield of 190 , % |
|-------|-------------------|--------------------|--|------------|------------|------------|----------------|-------------------|----------------------------------|
| | | | 190 | 195 | 198 | 199 | 200-202 | | |
| 1 | ⁿ BuCl | rt ^c | 3 | 1 | | | | - | |
| 2 | ⁿ BuCl | 70 | | | | | | 0 ^d | |
| 3 | ⁿ BuCl | 80 | 99 | | | | | 77 | |
| 4 | ⁿ BuCl | 100 | 98 | | | | 2 | 77 | |
| 5 | ⁿ BuCl | 120 | 98 | | 1 | | 1 | 84 | |
| 6 | ⁿ BuCl | 140 | 93 | 2 | 4 | | 1 | 83 | |
| 7 | ⁿ BuCl | 160 | 75 | 7 | 14 | | 1 | 69 | |
| 8 | ⁿ BuBr | 70 | 97 | 1 | 2 | | | 60 | |
| 9 | ⁿ BuBr | 80 | 96 | 1 | 3 | | | 72 | |
| 10 | ⁿ BuBr | 100 | 87 | 2 | 11 | | | 78 | |
| 11 | ⁿ BuBr | 120 | 54 | 13 | 30 | 3 | | 59 | |
| 12 | ⁿ BuBr | 160 | 21 | 17 | 22 | 34 | 4 | 2 | |

a) The set maximum temperature. Reaction time was 10 min.

b) Compounds were identified by GC-MS (EI). [265, 266] Percentage values are based on GC analysis (FID).

c) 24 h without heating.

d) Only the starting material **192** was recovered.

The formation of sulphides **195** and **200** was interesting since it could not be explained by a direct reaction between the reactants (Table 18, entries 6-12). The acid **190** could form an intermediate **203** where the β -carboxylate group would stabilize the negative charge on sulphur (Fig. 81) [267]. External heat or the nucleophilic attack by a thiolate anion could trigger the cleavage of the C–S bond, which led to the formation of butanethiol and other side products [I].

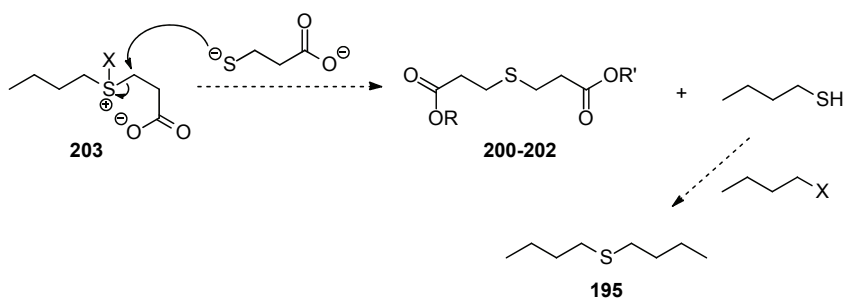

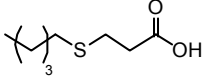

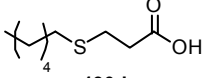

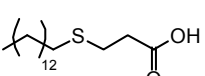

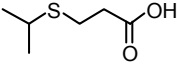

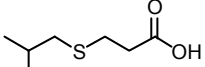

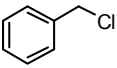
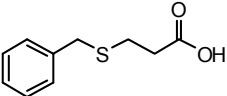

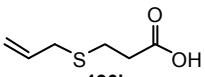

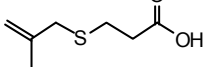

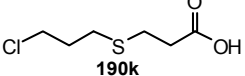

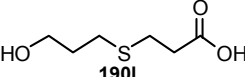



Fig. 81. A possible path for the formation of side products in the microwave-assisted thio-alkylation of 3-mercaptopropionic acid (192**). (X = Cl, Br; R = H, Et, Bu; R' = H, Et, Bu)**

The *S*-alkylation of **192** with the halides (Table 19) gave similar results as the experiments carried out with butyl halides (Table 18). The reaction with simple primary or secondary halides selectively yielded the desired product **190** at selected temperatures. In this study, alkyl chlorides were mostly used, but when its boiling point was close to room temperature, the corresponding bromide and 80 °C reaction temperature were used instead (Table 19, entries 1, 6 & 12). Aryl, allyl and tertiary halides can form a stable carbocation and therefore, favour the S_N1 type reaction with a nucleophile resulting in the increasing formation of the ester **198** even at lower temperatures (entries 9-14). The alkylation with a tertiary butyl chloride was carried out in order to understand what would happen when the S_N2 type substitution is an unfavourable process, (Table 19, entries 9-10). In these experiments, the main product was not the *tert*-butyl thioether but *iso*-butylthiopropionic acid (**190g**). Most likely, *tert*-butyl chloride under basic conditions formed the elimination product, 2-methylpropene, which subsequently reacted with **192** yielding **190g**. [1]

Table 19. Products and yields of microwave-assisted synthesis of 3-(alkylthio)propionic acids **190 under basic conditions in ethanol. [1]**

| Entry | R-X | Product | Temp., °C | Yield, % ^(a) | Ratio of 190:198 ^(b) |
|-------|-----|---------|-----------|-------------------------|--|
| 1 | | | 80 | 94 | 99:1 |
| 2 | | | 120 | 84 | 99:1 |

| Entry | R-X | Product | Temp., °C | Yield, % ^(a) | Ratio of 190:198 ^(b) |
|-------|---|--|-----------|-------------------------|--|
| 3 |  |  190c | 120 | 91 | <i>n.d.</i> |
| 4 |  |  190d | 120 | 94 | 99:1 |
| 5 |  |  190e | 120 | 77 | 99:1 |
| 6 |  |  190f | 80 | 97 | 99:1 |
| 7 | — ^(c) — | 190f | 120 | 91 | 89:1 |
| 8 |  |  190g | 120 | 90 | 99:1 |
| 9 |  | 190g | 80 | 10-20 ^(d) | 98:2 ^(c) |
| 10 | — ^(c) — | 190g | 120 | 72 | 96:4 ^(c) |
| 11 |  |  190h | 120 | 72 | 79:21 |
| 12 |  |  190i | 80 | 85 | 94:6 |
| 13 | — ^(c) — | 190i | 120 | 53 | 91:9 |
| 14 |  |  190j | 120 | 85 | 96:4 |
| 15 |  |  190k | 80 | 90 | 95:5 |
| 16 |  |  190l | 80 | 57 | 90:10 |
| 17 |  | 190l | 120 | 73 | 96:4 |

| Entry | R-X | Product | Temp., °C | Yield, % ^(a) | Ratio of 190:198 ^(b) |
|-------|-----|---------|-----------|-------------------------|--|
| 18 | | | 120 | 82 | 98:2 |
| 19 | | | 120 | 90 | 99:1 |
| 20 | | | 120 | 32 ^(d) | <i>n.d.</i> |

a) The isolated yield of **190a-o**.

b) The ratio of the acid **190a-o** vs. its ester **198a-o** based on ¹H NMR of the crude product.

c) *Tert*-butyl ester of **190g**.

d) Estimated from the mixture of the crude product.

A tolerance of functional groups was studied with a selection of substituted halides (Table 19, entries 15-20). In the case of bromo and chloro disubstituted alkyl halide, the *S*-alkylation took place with a good selectivity to the bromo substituted end, yielding the compound **190k**. Ether or cyano substituents tolerated the reaction conditions well (entries 18-19). [I] However, the formation of the *S-p*-methoxybenzyl ether succeeded only poorly (entry 20). We thought that this would have served as the protective group of thiol. In turn, the free hydroxyl group was stable during the reaction (entries 16-17).

The synthesis of DHAP analogues bearing a polar group at the end of a side chain might be interesting for the triosephosphate isomerase studies. It was assumed that a hydrophilic functionality placed on the side chain of the substrate would ease its access into the extended groove. In addition, the water molecule, which is located on the bottom of the pocket, could be replaced by a terminal hydroxyl or an amino substituent.

6.1.3 Oxidation of thioethers

The oxidation of the alkylthiopropionic acids **190** took place easily. The mild oxidant, *m*-chloroperbenzoic acid, successfully oxidized **190** to 3-alkylsulphonylpropionic acid **193**, but the isolation of the product from the reaction mixture was laborious. On the contrary, the oxidation of **190** with hydrogen peroxide in an aqueous acetic acid solution was fast and gave a product mixture from which the product **193** was easy to isolate. Even though this oxidation was exothermic, the solution of **190** and concentrated acetic acid was heated at 35 °C

before the addition of H₂O₂. The instant reaction produced the desired sulphonyl derivative **193**, as the only non-volatile substance; in quantitative yield in 20 min. Hydrogen peroxide is one of the most useful oxidants because it does not produce any waste except water.

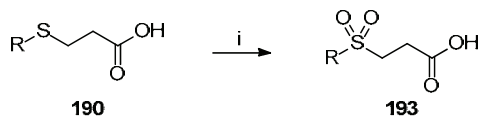


Fig. 82. The synthesis of sulphonylpropionic acid derivatives 193; Reagents: i) 30% H₂O₂, AcOH, rfx, 20 min.

The transition state analogue, 2-phosphoglycolic acid (**178**), has a strong interaction with TIM [243]. Therefore the binding studies of 3-sulphonylpropionic acid derivatives **193** would give a preliminary result to how the modification of the alkyl chain might influence the binding of TIM. The results of the binding studies with A-TIM are going to be published later.

6.1.4 Conversion of carboxylic acids to hydroxymethyl ketones

The final step in our synthetic plan was the conversion of selected γ -sulphonylpropionic acids **193** to corresponding α -hydroxy ketones **183** (Fig. 77). Based on binding studies of **193** the most interesting substrate candidates were chosen. At the beginning of the project the importance of sulphonyl substituted hydroxymethyl ketone **183** was unclear from a synthetic chemistry point of view. However, the analogy to DHAP, which widely interacts in biological processes, makes **183** a useful starting material for medicinal applications [15].

Microwave-assisted synthesis was one of the objectives of this thesis. There were only few examples of microwave assisted formation of terminal α -hydroxy ketones in the literature [169, 268]. Neither the microwave-assisted carbon chain extension of the carbonyl compound by one terminal carbon was known.

According to the basic principle shown in Fig. 61, vacuum-dried acid **193** was first need to be converted to acid chloride **194** (Fig. 83). This reaction was carried out by refluxing with thionyl chloride for 2 hours. The excess thionyl chloride was removed by co-evaporation with toluene and keeping it in a vacuum. The quantitative conversion of **194** was confirmed by ¹H NMR.

The totally silylated glycolic acid, TMSE (**106**) was synthesized according to the literature [177] and used in a microwave-assisted reaction with acid chloride

194 (Fig. 83). The microwave power of 250 W and the maximum temperature of 200 °C were applied to the mixture of reagents in the absence of a solvent in a closed reactor for 10 min. Then the reaction was rapidly cooled to room temperature. The simultaneous cleavage of trimethylsilyl groups and the decarboxylation were carried out with the addition of 0.6 M hydrochloric acid and THF followed by heating at 90 °C for 45 min in an open vessel.

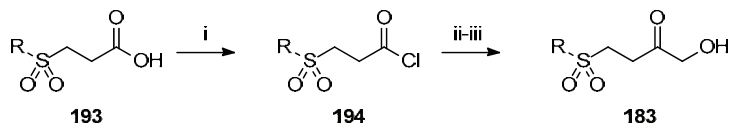


Fig. 83. The synthesis of 4-alkylsulphonyl α -hydroxy butanone **183**. Reagents: i) SOCl_2 , (toluene), 70–80 °C, 2 h; ii) **106**, MW 200 °C, 10 min; iii) HCl/H₂O/THF, 90 °C, 45 min.

6.1.5 Concluding remarks

The synthesis of carboxylic acid derivatives **193** and hydroxy ketones **183** together gave a valuable set of model compounds for triosephosphate isomerase studies.

The fast and green method of synthesis of 4-alkylsulphonyl-1-hydroxy-butan-2-one **183** was developed. The full four step synthetic route with isolations and purifications can be performed during one working day. The use of microwave heating and less toxic solvents and reagents go along with the ideology of green chemistry. However, the excess use of TMSE during the hydroxy methyl ketone synthesis was a major drawback of this route.

6.2 The improved microwave-assisted synthesis of hydroxy methyl ketones

During our studies, it was noticed that the use of microwave activation greatly enhanced the efficiency of the Wissner hydroxy ketone synthesis (Table 20, entries 1-2). We therefore became interested in the further study of this reaction [II].

Besides accelerating condensation by microwave heating, we studied how the reaction system could be improved by additional HCl scavengers (Fig. 84) [II]. There was a need for excess use of the TMSE reagent **106** in the original reaction since an equivalent was consumed in the neutralisation of hydrochloride [177].

Therefore we thought that the tertiary amine, like triethylamine could protect **106** from decomposition (Table 20). Earlier it was also shown to increase the reactivity of the carbonyl compound **204** [269].

Table 20. The effects of variable reaction conditions and components on the reaction of octanoyl chloride (204a**) with TMSE (**106**). [I]**

| Entry | Reaction conditions | 106 , equiv. | Temp., °C | Time | Conv. of 208a , % ^(a) |
|-------|---|---------------------|-----------|---------------------|---|
| 1 | Oil bath heating, no additives, no solvent | 2.2 | 110 | 4 h | 73 |
| 2 | MW activation, no additives, no solvent | 2.2 | 180 | 10 min | 98 |
| 3 | Et ₃ N(1.0 equiv.), THF | 1.1 | - 10 | 5 min | > 24 ^(b) |
| 4 | Et ₃ N (1.0 equiv.), THF | 1.1 | rt | 24 h | 74 |
| 5 | Et ₃ N (1.0 equiv.), THF | 1.1 | rt | 72 h | 76 |
| 6 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 100 | 5 min | 91 |
| 7 | MW, pyridine (1.0 equiv.), THF | 1.1 | 100 | 5 min | 16 |
| 8 | MW, 1-methylimidazole (1.0 equiv.), THF | 1.1 | 100 | 5 min | - |
| 9 | MW, DIPEA (1.0 equiv.), THF | 1.1 | 100 | 5 min | > 50 ^(b) |
| 10 | MW, DBU (1.0 equiv.), THF | 1.1 | 100 | 5 min | - |
| 11 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 80 | 5 min | > 79 ^(b) |
| 12 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 120 | 5 min | 74 |
| 13 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 100 | 90 s ^(c) | > 54 ^(b) |
| 14 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 100 | 10 min | 90 |
| 15 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 100 | 15 min | 78 |
| 16 | MW, Et ₃ N (1.0 equiv.), toluene | 1.1 | 100 | 10 min | 84 |
| 17 | MW, Et ₃ N (1.0 equiv.), CH ₂ Cl ₂ | 1.1 | 100 | 5 min | 67 |
| 18 | MW, Et ₃ N (1.0 equiv.), THF | 1.5 | 100 | 5 min | 89 |
| 19 | MW, Et ₃ N (2.0 equiv.), THF | 1.1 | 100 | 5 min | 87 |
| 20 | MW, Et ₃ N (1.0 equiv.), THF | 1.1 | 100 | 5 min | 89 |
| 21 | MW, THF, Et ₃ N (1.0 equiv.) ^(d) | 1.1 | 100 | 5 min | 84 |

a) Conversion of **208a** is based on the GC analysis of the reaction mixture after decarboxylation using decane as an internal standard.

b) A part of **208a** further reacted with the octanoic acid derivative and formed 2-oxononyl octanoate as a side-product (GC-MS). Look also [270]

c) It took 90 s to achieve the temperature of 100 °C on an absorption level high by Biotage Initiator™ microwave reactor in 2 mL vial.

d) Enolate **106** was added into the solution of **204a** in THF before Et₃N.

The mechanism of this modified hydroxy ketone synthesis is different from the previous (see Fig. 61). At first, triethylamine abstracted α -proton from the acid chloride **204** leading to the cleavage of the chloride ion [271]. The unstable ketene intermediate **205** formed and directly reacted with the nucleophilic enolate **106** under microwave heating (Fig. 84). In addition, the formed Et₃NHCl salt increased the absorption of microwave energy by ionic conduction. [II]

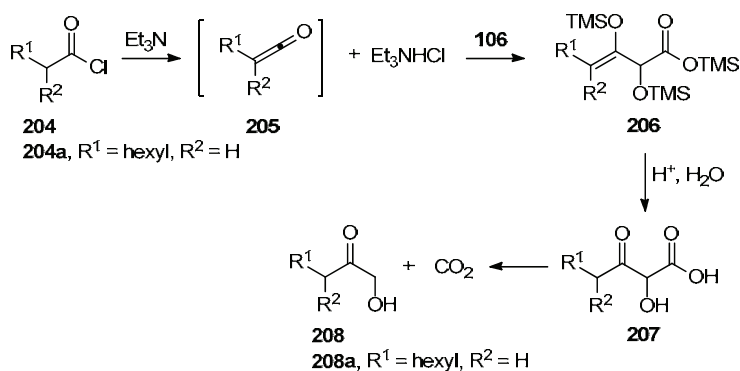


Fig. 84. The activating and protective effect of triethylamine in the condensation of octanoyl chloride (204a**) with TMSE (**106**): The formation of the ketene **205** and the capture of HCl.**

The formation of ketene **205** was an exothermic reaction and was carried out at $-10\text{ }^\circ\text{C}$. The formation of the product **208a** already started at $-10\text{ }^\circ\text{C}$ after a short period of time (Table 20, entry 3). The reaction happened at room temperature but the microwave assistance substantially increased the yield and shortened the reaction time (entries 4-6). The silylated β -enol ester **206** simultaneously hydrolysed and decarboxylated when the 2 M hydrochloric acid was added upon heating in a water bath for 30 min. [II]

The intermediate **206a** (Fig. 84) formed at the presence of triethylamine, resulted the same molecular mass ion as **165a** ($\text{R} = \text{heptyl}$, Fig. 61) in EI-MS, albeit a slightly different fragmentation pattern. Secondly, acid chlorides that could not form ketene seemed not to react (Table 21, entries 6-7). These results suggested that this time intermediate **206** was a kinetic enolate and the reaction proceeded via a ketene intermediate **205** (Fig. 84). [III]

The optimum reaction conditions for the microwave assisted hydroxy ketone synthesis at the present of triethylamine were $100\text{ }^\circ\text{C}$ for 5 min (Table 20) [II]. Reactions with variable acid chlorides **204a-k** were carried out with the stoichiometric amounts of triethylamine, acid chloride **204** and TMSE (**106**) in dry THF under microwave heating followed by the addition of 2 M HCl solution and stirring at ambient temperature for 30 min (Fig. 85 & Table 21).

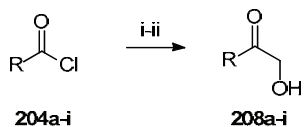
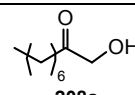
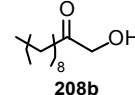
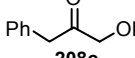
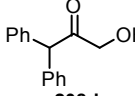
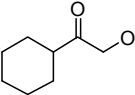
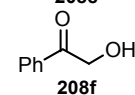
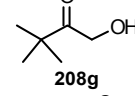
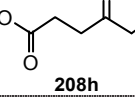
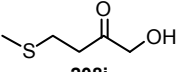
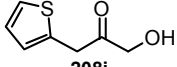


Fig. 85. Reagents: i) **106**, Et₃N, THF, -10° 5 min; MW 100 °C, 5 min; ii) HCl/H₂O, rt, 30 min.

Table 21. The products, yields and reaction conditions for the microwave-assisted synthesis of α -hydroxy ketones **208a-j** from acid chlorides **204a-j** and TMSE (**106**). [II]

| Entry | Product | Max. power and time ^(a) | Max. press.,bar | Cont. power, W ^(b) | Yield, % ^(c) |
|-------|--|------------------------------------|-----------------|-------------------------------|-------------------------|
| 1 |  208a | 250 W, 120 s | 1.3 | 60 | 88 |
| 2 |  208b | 250 W, 105 s | 0.8 | 50 | 75 |
| 3 |  208c | 250 W, 150 s | 2.5 | 200→75 | 71 |
| 4 |  208d | 220 W, 90 s | 1.3 | 100 | 70 |
| 5 |  208e | 250 W, 180 s | 0 | 220→140 | - ^(d) |
| 6 |  208f | 250 W, 150 s | 1.3 | 145 | 6 ^(e) |
| 7 |  208g | 250 W, >300 s ^(f) | 0.4 | - | - |
| 8 |  208h | 215 W, 100 s | 1.7 | 40 | 63 |

| Entry | Product | Max. power and time ^(a) | Max. press.,bar | Cont. power, W ^(b) | Yield, % ^(c) |
|-------|--|------------------------------------|-----------------|-------------------------------|-------------------------|
| 9 |  208i | 250 W, 150 s | 0.7 | 120 | 82 |
| 10 |  208j | 250 W, 150 s | 1.4 | 150→75 | 81 |

- a) The time and the maximum microwave power which was applied to the reaction to gain the temperature of 100 °C.
b) The microwave power required to maintain the temperature of the reaction mixture on 100 °C.
c) The yield of the isolated product. Reactions were carried out on 1 g scale in 20 mL vials.
d) Mixture of products.
e) Conversions were estimated from ¹H-NMR spectra of the crude product mixture.
f) The desired temperature was not reached on 300 s.

Acid chlorides with a primary or secondary carbon at the α -position were milky white mixtures also after microwave irradiation and yielded α -hydroxy substituted ketones **208** in moderate yields (Table 21, entries 1-4 & 8-10). The acid chlorides without α -protons did not produce white, milky mixtures at the beginning of the reaction; thus the ketene intermediate did not form and the reaction hardly occurred within the given reaction time (Table 21, entries 6-7). Additional microwave energy was used with cyclohexanecarbonyl chloride (**204e**) (entry 5), but this time the formation of the reaction intermediate was poor and the reaction did not occur. [II]

6.2.1 Concluding remarks

The improved synthesis of hydroxymethyl ketones from carboxylic chlorides and *tris*(trimethylsiloxy)ethylene (**106**) was developed. The original Wissner hydroxy ketone synthesis was modified by shortening the reaction time from 4 h to 5 min with the assistance of microwave activation and the use of triethylamine as an HCl scavenger.

6.3 The synthesis of α -hydroxy aldehyde by multistep reaction pathway from an α -hydroxy ketone

As a case study the α -hydroxy ketone was converted to the corresponding α -hydroxy aldehyde using a series of conventional synthetic reactions. The α -hydroxy aldehyde **209** was required for the activity studies of A-TIM as a reference compound to the NMR and mass spectrometric measurements. A number of α -hydroxy ketones were available in our laboratory. Therefore the

reaction path towards α -hydroxy aldehyde **209** was designed based on the ketone **183** (Fig. 86). In addition, the 4-(hexylsulphonyl)-1-hydroxybutan-2-one (**183d**) had proven be the most promising substrate candidate of A-TIM. At first this compound **183d** was introduced to the synthetic manipulation of the 1,2-hydroxy carbonyl functionality to generate a monoprotected 1,2-diol **210**. Next the oxidation of the primary alcohol **210** to the aldehyde **211** was carried out using the Swern procedure [32]. In fact, the key intermediate of the synthetic route in Fig. 86 was the mild formation of protected α -hydroxy aldehyde followed by a mild deprotection procedure carried out in cold temperature. In this study the palladium-catalysed hydrogenation of the benzyl ether was investigated.

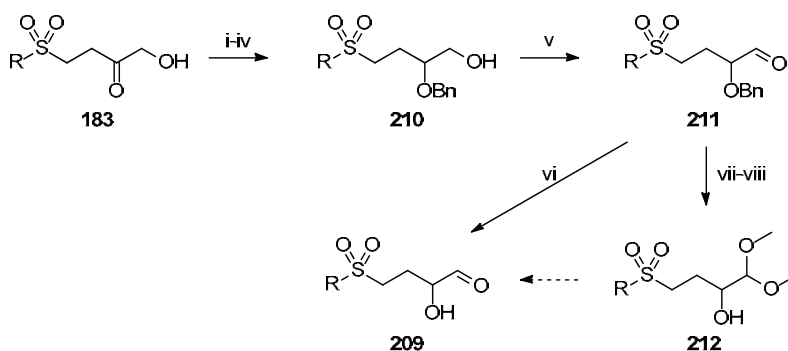


Fig. 86. A synthetic route to converts α -hydroxy ketone to α -hydroxy aldehyde (R = hexyl). i) TBDMSCl, imidazole, DCM, rt, 48 h; ii) NaBH₄, EtOH, -12 °C, 2 h; rt, 1 h; iii) NaH, BnBr, TBAI, THF, rt, 60 h; iv) EtOH, 1.5% HCl, rt, 16 h; v) (COCl)₂, DMSO, Et₃N, DCM, -78 °C, 2 h; vi) Pd/C, H₂, THF, 3 °C, 27 h, vii) dry MeOH, rt, 2 h; viii) Pd/C, H₂, MeOH, 3 °C, 48 h.

It was important to remove the residues of the sulphur by-product completely after the Swern oxidation in order to avoid poisoning of the palladium catalyst. In our study, the benzyl protected α -hydroxy aldehyde **211** enabled the use of flash chromatographic purification. Two alternative strategies for the cleavage of the benzyl protection of **211** were investigated. Firstly, the unprotected α -hydroxy aldehyde **209** was generated when hydrogenation was carried out in an aprotic solvent, THF. After the removal of the catalyst and solvent at cold temperature, the crude product was dissolved in CDCl₃ and immediately analysed by NMR and MS. However no aldehyde **209** was detected. The product had converted back to the α -hydroxy ketone **183d** and other undefined products over the course of the

experiment. The hydrogenation of **211** was then carried out in methanol. At this time the dimethylacetal formed and the hydrogenation yielded α -hydroxy acetal **212**. It was tested if this product could be analysed with NMR or MS measurements. Preliminary results showed that the crude product **212** was a mixture of mono, di- and trimethylated hydroxy aldehydes.

6.4 Asymmetric organocatalytic α -oxybenzoylation of aldehydes

The α -oxo functionalization of aldehydes was studied at Cardiff University. [III] Inspired by the extensive research of the organocatalytic α -functionalization of aldehydes carried out by the groups of MacMillan [133, 142, 143, 145, 272] and Jørgensen [141, 273], and the earlier discoveries published by Tomkinson *et al.* [155, 156, 274], we were encouraged to investigate the reaction of dibenzoyl peroxide (**214**) in the organocatalytic α -oxybenzoylation of carbonyl compounds (Fig. 87). It has previously been shown that enamine form α -addition products when reacted with sulphonyl peroxides [275] or BPO [276, 277]. It was envisaged that a chiral enamine intermediate **213**, formed in the reaction with a secondary amine and aldehyde **123**, could react with BPO to form the α -functionalised aldehyde **215** following hydrolysis.

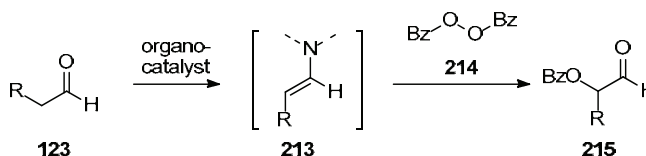


Fig. 87. The concept of the organocatalytic α -oxybenzoylation of aldehydes.

6.4.1 Initial experiments

To test our hypothesis, a one-pot reaction between *iso*-valeraldehyde (**123a**), L-proline (**127**) and BPO was carried out at room temperature (Fig. 88). No formation of desired oxobenzoyl substituted product **215a** was observed (based on ¹H NMR), however, we were encouraged by the fact that other unwanted side products (e.g. from a self aldol reaction) had neither formed [III]. To our delight, when the methyl ester of L-proline hydrochloride (**25**) was used as the

organocatalyst instead, the reaction resulted in the slow formation of the α -oxobenzoylated *iso*-valeraldehyde **215a**.

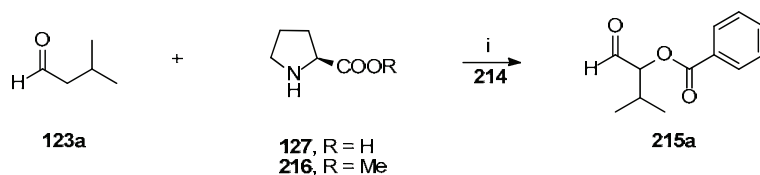


Fig. 88. The first experiment towards the organocatalytic α -oxobenzoylation of aldehydes. i) 20 mol % of **127** \times HCl or **216**, 1 equiv. of **214**, CDCl_3 or THF, rt, 48 h.

Significant improvements in both the rate and overall yield for the transformation was observed when the MacMillan imidazolidinone **217** [137] was used as the reaction catalyst. This time, a 13% yield of **215a** was isolated after 48 h reaction in THF with 20 mol % loading of the catalyst **217**. Of particular importance was the exceptional *ee* (97%) of the product **215a**, which encouraged us to carry out further investigation.

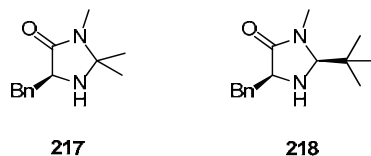


Fig. 89. MacMillan imidazolidinones.

The MacMillan imidazolidinones **217** and **218** are well established organocatalysts for the acceleration of enamine and iminium ion catalysed transformations (Fig. 89) [278]. They are derived from phenyl alanine and catalyse a variety of reactions with good activity and excellent enantioselectivity [130, 279]. Another advantage in use of imidazolidinones is that their preparation is relatively easy and inexpensive. It is based on amide formation of the methyl ester of L-phenylalanine followed by the ring closing to a five-member heterocycle [137]. The second generation catalyst **218** was created to improve efficiency of iminium formation by having a less hindered lone electron pair at the secondary nitrogen [280]. Imidazolidinones **217-218** have been shown to catalyze various reactions among others α -functionalization of aldehydes [133, 142, 143, 145] as well as Michael type alkylation [280, 281] and Diels-Alder cycloaddition reactions [137] of α,β -unsaturated aldehydes.

Another experiment was carried out monitoring the reaction by ^1H NMR (Fig. 90 & Fig. 91). It was hoped that the formation of possible intermediates and side products, which would shut down the catalytic cycle, could be detected using this method. After 1.5 hours, the reaction stopped at around 15% conversion to the desired product **215b**. No visible reason for the shut-down of this catalytic cycle was apparent. However, there were other noteworthy changes shown within the spectrum. Firstly, there was the broad singlet which moved downfield over the course of the experiment. This was attributed to water being introduced to the reaction mixture from the BPO. The movement of this peak from left to right could arise from a decreasing pH during the reaction. Secondly, the benzylic protons of the catalyst **217** moved toward each other in the spectrum, which is a consequence of protonation of the secondary amine. In fact, when imidazolidinone **217** was added into a solution of benzoic acid (**219**) in CDCl_3 , benzyl signals of **217** shifted in a similar manner.

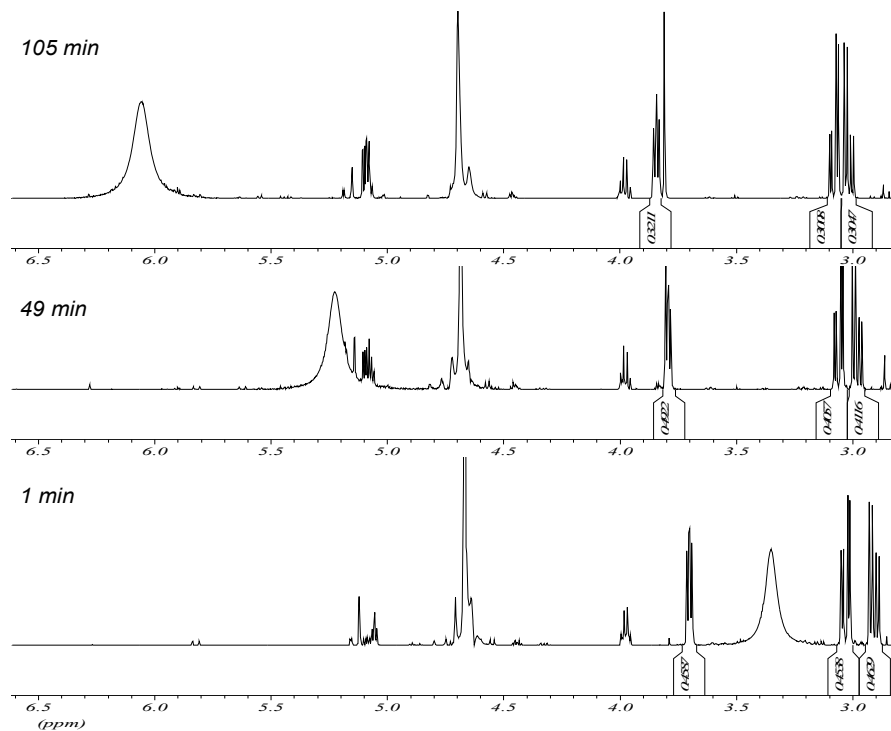


Fig. 90. The α -oxygenation reaction in an NMR tube. The spectra are recorded at 1 min, 49 min and 105 min.

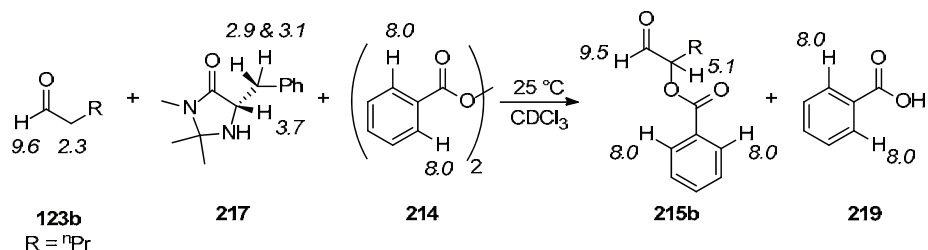


Fig. 91. The α -oxybenzoylation of valeraldehyde (**123b**) in an NMR-tube. Chemical shifts of the characteristic protons are given in ppm. 20 mol% of organocatalyst **217** was used.

6.4.2 Theory of the catalytic process

It was proposed that the catalytic cycle shown in Fig. 92 was operating in the α -oxygenation reaction [135]. The first step involved the reaction between aldehyde **123** and imidazolidinone **217** leading to the formation of *trans*-enamine **220**. The α -position is now activated toward the electrophiles like BPO (**214**). There are two feasible ionic mechanisms for the formation of the C–O bond [III]. BPO can either react directly with the enamine **220** to give the proposed intermediate **221**. An alternative possibility is that the reaction goes via the formation of the *N*-oxo adduct **222** followed by [3,3]-sigmatropic rearrangement [156] (Fig. 93). Both routes would give the α -oxybenzoyl substituted iminium ion **221** as an intermediate. Finally, hydrolysis of this iminium ion would give the observed product **215** and release the catalyst **217** back into the catalytic cycle. Within this proposed mechanism, benzoic acid **219** would be produced as the only by-product.

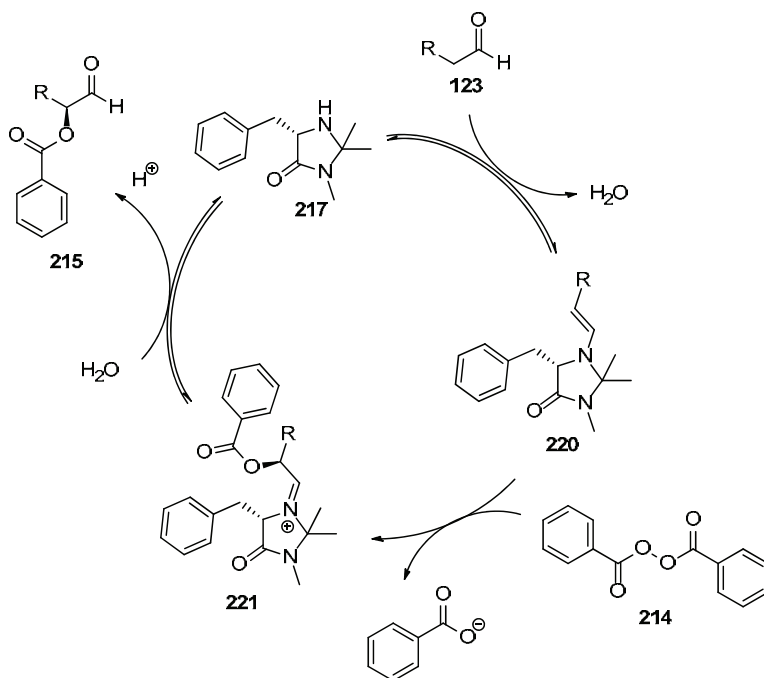


Fig. 92. The proposed catalytic cycle of the MacMillan imidazolidinone **217** catalyzed α -oxybenzoylation of aldehydes.

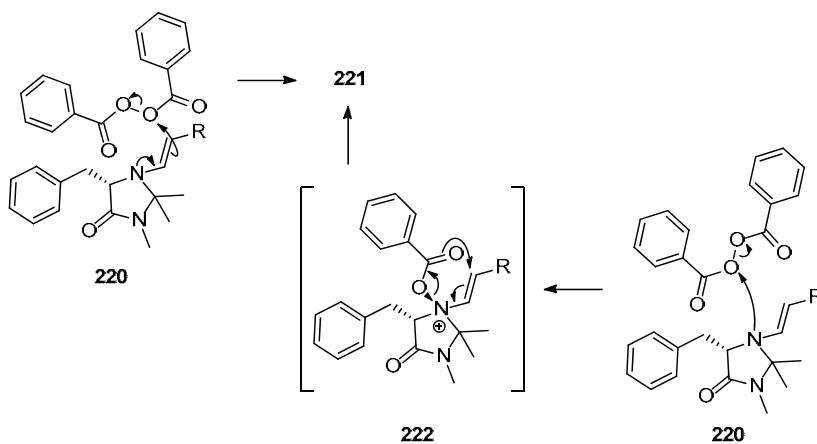


Fig. 93. Two possible mechanistic pathways for the C-O bond formation. The benzyl group next to the nitrogen centre controls the absolute stereochemistry of the product.

6.4.3 The choice of solvent

In a number of organocatalytic transformations, reaction solvents have been shown to significantly affect the rate of the reaction and the stability of the aldehyde which both influences observed yield. Therefore our reaction was at first carried out in different solvents. Toluene, THF, EtOAc, chloroform, acetone, acetonitrile, and the mixture of methanol and THF were tested (Table 22). Our system had additional water from the BPO reagent, which affected the polarity of the solvent system. Although when the reaction was carried out with dried BPO in anhydrous THF, the conversion of the product **215b** was not significantly different (entries 8-9). Table 22 shows that THF, EtOAc, acetone, and toluene led to a better conversion than chloroform or acetonitrile.

As a conclusion, THF and toluene are recommended for the α -oxybenzoylation reaction. However, acetone might also be a good choice even though it contains the ketone group. Based on these experiments THF was selected as the solvent of choice for further studies. It was also decided that the commercial BPO should be used even though it is 75% (w/w) mixture of water.

Table 22. The effect of solvent. Valeraldehyde (123b**) was added into a 0.2 M solution of **217** and BPO at -10 °C and the mixture was left at 5 °C for a day.**

| Entry | Solvent(s) | Conversion of 215b , % ^(a) | Aldehyde 123b left, % ^(a) |
|------------------|------------------------|--|---|
| 1 | Toluene | 15 | 50 |
| 2 | THF | 19 | 52 |
| 3 | EtOAc | 10 | 57 |
| 4 | CHCl ₃ | 5 | 85 |
| 5 | Acetone | 22 | 49 |
| 6 | MeCN ^(b) | 8 | 50 |
| 7 | THF/MeOH | - | 84 |
| 8 ^(c) | THF | 22 | 6 |
| 9 ^(c) | Dry THF ^(d) | 23 | 3 |

a) Values were calculated from ¹H NMR using *p*-dimethoxybenzene standard.

b) BPO dissolved poorly.

c) Reaction was carried out at room temperature.

d) Dried BPO were used.

6.4.4 The effect of reaction concentration, temperature and time

Concentration and temperature of the reaction affect the rate of organocatalytic transformation as well as the rate of side reactions. The low temperature and concentration would be suitable as the side reactions of aldehydes are slowed

down. Another problem is the racemisation of the product over time. Accordingly, some reactions reported in the literature were accelerated by utilizing the overstoichiometric amount of reagent [143] or aldehyde [133]. However, we decided that the α -oxybenzoylation reaction should be carried out without excess of aldehyde or BPO.

It is also worthy of note that the electrophile reagent had an effect on the reaction rate. The α -chlorination reaction with *N*-chlorosuccinimide (NCS) proceeded at room temperature [141], when the reaction with more reactive chlorinated quinone **139** was carried out at -30 °C [142]. The reaction times were close to the same (1–10 h & 6–12 h, respectively).

Two other α -functionalization reactions studied by MacMillan *et al.* were modified probably to accelerate the reaction so that the aldehydes would not decompose. The α -oxyamination reaction was carried out at 4 °C for 4 h using three times the excess of aldehyde and high concentration (6.0 M) [133]. Correspondingly, the five times excess of *N*-fluorobenzenesulphonamide (NFSI) was added into the 0.2 M solution of aldehyde in *iso*-propanol and THF to improve the yield of α -fluoro aldehyde [143]. The latter reaction reached completion in 10–12 h at -10 °C.

As a conclusion three options were investigated for improvement of our reaction; the reaction was carried out at different temperatures, in variable concentrations and the reaction was accelerated by adding the excess of BPO or aldehyde (Table 23). As mentioned earlier, the latter option would not be the preferable solution.

Table 23. The effect of temperature, concentration and time on the α -oxybenzoylation of aldehydes. Reactions were carried out in THF with 20 mol % of organocatalyst **217.**

| Entry | Conc. of 123b , M | Temp., °C | Time, h | Conv. of 215b % ^(a) | Aldehyde 123b left % ^(a) |
|-------|----------------------------|-----------|---------|---------------------------------------|--|
| 1 | 0.5 | 35 | 5 | – ^(b) | – ^(b) |
| 2 | 0.5 | 25 | 19 | 17 | 15 |
| 3 | 0.5 | 5 | 24 | 34 (24, 97% ee) ^(c) | 31 |
| 4 | 0.2 | 5 | 24 | 25 | 21 |
| 5 | 1.0 | 5 | 70 | 35 | 28 |
| 6 | 0.2 | -20 | 70 | 1 | 87 |
| 7 | 0.5 (3×BPO) ^(d) | 25 | 6 | 24 | 31 |
| 8 | 1.0 (5×aldehyde) | 25 | 1 | 29 | 255 |
| 9 | 0.5 (100 mol% 217) | 5 | 24 | 23 | 6 |

a) Conversions have been calculated as before (Table 22).

b) Lots of side products.

c) The product was isolated in 24% yield and reduced to diol to indicate 97% ee.

d) The excess of BPO did not dissolve completely.

Table 23 presents our investigation of the optimization of temperature and the concentration for the α -oxybenzoylation reaction. The reaction hardly took place at -20 °C and heating it to 35 °C led to the decomposition of the aldehydes (entries 1 & 6). The α -oxybenzoylation reaction was good at room temperature and 5 °C (entries 2-3). In fact, α -oxobenzoyl valeraldehyde (**215b**) was isolated in 24% yield and with excellent 97% *ee* (as the detection limit of the UV detector of the HPLC), which encouraged us to believe the possibility of a catalytic reaction. In addition, 0.5 M concentration was found optimal (entries 3-5). After testing the excess amount of reagents as well as the stoichiometric loading of an organocatalyst **217**, it was clear that there was something preventing or slowing down the reaction (entries 7-9). Extending the reaction time even further did not yield more products. However, side reactions of aldehyde happened over time. The BPO seemed to remain unreactive.

6.4.5 Remarks of the reagents addition order

It was extensively proven that the α -oxybenzoylation reaction did not occur if one of the reactive compounds was missing. Therefore, the addition order of the reagent should not affect the overall reaction. On the other hand, the first reaction in the catalytic cycle is a formation of enamine **220** from aldehyde and imidazolidinone **217** followed by the addition of BPO (Fig. 92). Without BPO, the formation of enamine **220** was not observed even when a catalytic amount of benzoic acid was added. It was decided that similar conditions should exist at the beginning of every catalytic cycle; therefore the aldehyde was added into the reaction mixture last. On the other hand, when aldehyde or BPO was added to the reaction mixture in portions (20 mol % at time) in 2 hours intervals, the conversion to α -oxybenzoyl aldehyde was again about 20%. In the literature, the aldehyde [133, 142, 143] or the reagent [141] was the last component to be added into reaction.

6.4.6 Effect of pH

So far, the α -oxybenzoylation reaction did not proceed more than a little over the first catalytic turnover. The difference in reaction mixture compared with the beginning and the end of the first catalytic cycle was a change in pH. In fact there was benzoic acid (**219**) forming during the reaction. At the beginning of the reaction the pH was 8 and after 1 day the pH was close to 4. Under more acidic

conditions aldehydes probably started to decompose as well as the activity of amine organocatalyst was inhibited by the formation of benzoate salt. Although, the transfer of this salt into the water phase was only minor since a quantitative presence of the catalyst **217** in an organic phase was determined by ¹H NMR. In addition, a near 20% conversion was observed when an additional 20 mol % of benzoic acid was added into the reaction at the beginning (Table 25, entry 5).

The next step was studying if the increasing quantity of benzoic acid was the problem. Therefore the compounds, which would neutralise the acid, were investigated. Organic amines were too reactive towards BPO [282] and inorganic salts were difficult to handle with a detrimental effect on the determination of the conversion. Thus aqueous buffer solutions were studied so that the benzoic acid would be transferred into the aqueous phase, maintaining the conditions of the organic phase constant. Results are presented in Table 24. Reactions were carried out in closed test tubes at 5 °C with continuous stirring. 20 mol % of catalyst **217** was loaded and valeraldehyde (**123b**) was added into the cooled solution. The aqueous buffer solution was added last.

Table 24. The effect of aqueous buffers in the α-oxybenzoylation.

| Entry | Reaction solvent system ^a | Conv. of 215b , % ^b | Valeraldehyde (123b) left % ^b |
|-------|--|---------------------------------------|---|
| 1 | 0.5 M Toluene/pH 8.0 buffer ^c | 3 | 75 |
| 2 | 0.5 M Toluene/pH 7.4 buffer ^c | 6 | 57 |
| 3 | 0.5 M Toluene/pH 7.0 buffer ^c | 3 | 69 |
| 4 | 0.5 M Toluene/pH 6.5 buffer ^c | 7 | 61 |
| 5 | 0.5 M Toluene/pH 6.0 buffer ^c | 20 | 58 |
| 6 | 0.5 M Toluene/pH 5.4 buffer ^d | 26 | 56 |
| 7 | 0.5 M Toluene/pH 5.0 buffer ^c | 22 | 60 |

a) The reaction was carried out at rt for 1 day. 20 mol % of catalyst **217** was used.

b) Conversions were calculated from internal standard as in Table 22.

c) 1.5 mL of 0.2 M NaH₂PO₄/Na₂HPO₄ buffer solution was used (for 0.3 mmol of valeraldehyde).

d) 1.5 mL of 0.2 M Na₂HPO₄/citric acid buffer solution was used (0.3 mmol scale).

We decided that the reaction mixture should be biphasic, thus toluene was selected to be the organic solvent. A sodium phosphate buffer was used since its buffer area; from pH 8.0 to 6.0, was close to the determined pH of the reaction mixture. The highest conversion was when the pH of the buffer solution was 5.4 (entry 6, Table 24). In addition, valeraldehyde (**123b**) was more stable under buffered conditions than in non-buffered reactions (Table 23 vs. Table 24). However, the conversion to the product **215** was close to same as those under non-buffered conditions (Table 23). Additionally, this pH would not bind benzoic

acid out of the organic reaction phase. As a conclusion, the α -oxybenzoylation reaction proceeded under the acid condition.

6.4.7 The investigation of co-acids

The first step during the formation of the enamine **220** is the acid catalyzed condensation of carbonyl to the iminium ion which then forms the enamine intermediate **220** [135]. Therefore, the effect of an additional co-acid to the α -oxybenzoylation reaction was investigated (Table 25). Reactions were carried out in THF (0.5 M) with 20 mol% of the catalyst **217** and the same amount of co-acid. After 16 hours at room temperature, the conversion to the α -oxybenzoyl aldehyde was determined by ^1H NMR. At this point, the selection of acids was not extensive. However, it was seen that strong acids slowed down the desired reaction. Later the development of a co-acid was further investigated [III].

Table 25. The α -oxybenzoylation of decanal (123c**) at the presence of additional co-acids.^a**

| Entry | co-acid ^b | pK _a ^c | Conversion of 215c , % ^d | Decanal (123c) left, % ^d |
|-------|----------------------|------------------------------|--|--|
| 1 | none | - | 21 (13, ee 97%) | 17 |
| 2 | HCl | -7 | - | 52 |
| 3 | <i>p</i> -TsOH | -0.43 | - | - |
| 4 | TFA | 0.52 | 5 | 21 |
| 5 | BzOH | 4.19 | 14 | 4 |
| 6 | AcOH | 4.76 | 21 | 11 |

a) Reactions were carried out with 20 mol% of **217** in THF (0.5 M) at rt for 16 h.

b) 20 mol% of co-acid used.

c) The dissociation constant. [283]

d) Conversion was calculated from ^1H NMR spectrum.

6.4.8 Further developments

After spending half a year in Cardiff, it was time to return back to Oulu even though the development of the organocatalysis with BPO especially, was at an interesting stage. Therefore, it was decided to continue the experiments in close contact with the Cardiff group. Nevertheless, two directions of the developments were set. The first experiment carried out in the facilities at the University of Oulu was to adjust the reaction temperature to -3 °C since the problem in earlier experiments was the constantly decomposition of the product or the aldehyde reagent over the time (Table 26). By lowering the temperature it was hoped to

stabilize the reaction mixture and make possible longer reaction times. The group at Cardiff focused on continuing the investigation of additives which would increase the reaction rate.

Table 26. The organocatalytic α -oxybenzoylation of aldehydes at -3 °C.^a

| Entry | Note | Temp., °C | Time, h | Conv. of 215b % ^b | Valeraldehyde (123b) left % ^b |
|-------|---------------------|-----------|---------|-------------------------------------|---|
| 1 | | -3 | 40 | 35 (24) ^c | 39 |
| 2 | | -3 | 161 | 50 (42) ^c | 21 |
| 3 | 2×BPO | -3 | 40 | 41 | 40 |
| 4 | 2× 123b | -3 | 40 | 54 | 117 |
| 5 | 100 mol% 217 | -3 | 40 | 54 | 10 |

- a) 20 mo% of organocatalyst **217** was loaded.
 b) Conversions have been calculated as before (Table 22).
 c) The isolated yield of product is in bracket.

As a conclusion from the lowered temperature reactions (Table 26) it was proven for the first time that the reaction is truly catalytic. This was however only the beginning of the breakthrough as Jacky and Nick were discovering the remarkable effect of additional co-acids [III]. The result in Table 27 showed that additional *p*-nitrobenzoic acid yielded α -oxybenzoyl valeraldehyde (**215b**) over three times of a catalytic turnover (72%) and high enantiomeric selectivity (*ee* 93%) (Table 27, entry 6). In the literature, the enamine catalysed reactions are clearly indicated to be dependent on the optimum co-catalyst [137, 142, 143, 284, 285]. The acid strength of *p*-nitrobenzoic acid is weaker than in those of the literature examples. However it is yet under debate how the co-acid generally participates in the enamine catalytic reactions [135].

Table 27. The development of α -oxybenzoylation utilizing co-acids. [III]

| Entry | Co-acid | pK _a ^a | Isolated yield of 215b , % | <i>ee</i> , % ^b |
|-------|---|------------------------------|-----------------------------------|----------------------------|
| 1 | HCl | -7 | - | - |
| 2 | <i>p</i> -TsOH | -0.43 | - | - |
| 3 | TCA | 0.66 | 25 | 92 |
| 4 | DCA | 1.35 | 35 | 92 |
| 5 | <i>m</i> -NO ₂ PhCO ₂ H | 3.46 | 54 | 90 |
| 6 | <i>p</i> -NO ₂ PhCO ₂ H | 3.43 | 72 | 93 |
| 7 | <i>m</i> -ClPhCO ₂ H | 3.84 | 22 | 94 |

- a) The dissociation constant. [283]
 b) Determined after NaBH₄ reduction to diol by HPLC.

6.4.9 Concluding remarks of α -oxybenzoylation of aldehydes

As a conclusion we have developed a catalytic asymmetric α -oxybenzoylation reaction of aldehydes. At the beginning, the reaction did not proceed more than little over the first catalytic turnover. The only difference observed in the reaction mixture compared between the start and the end point was a change in pH when the benzoic acid was formed. Under acidic conditions the aldehyde started to decompose or the amine catalyst was inhibited by the acid.

The optimum reaction conditions were investigated. Examining the literature [133, 142, 143, 145] the organocatalytic α -functionalization of aldehydes occurred the fastest in less polar solvents, and when the polarity of the solvent was increased aldol reactions happened. Concentration also had a similar effect; low concentration gives cleaner product mixtures. Reactions also became slower when the temperature was lowered. However, the low reaction temperature was shown to increase the stability of aldehydes leading to a higher yield when the reaction time was extended. In this study the organocatalytic reaction was carried out at -3 °C for seven days when it yielded 42% of α -oxobenzoyl aldehyde. THF was used as a solvent.

The co-acid was found to have a dramatic effect on the reaction rate. The use of 20 mol % of *p*-nitrobenzoic acid with 20 mol % of imidazolidinone catalyst led to the formation of α -oxobenzoylated valeraldehyde in 72% yield and excelled 93% *ee*. The reaction was carried out at room temperature for 24 h. Other aldehydes tested yielded aldehydes with aromatic, alkane, alkene and TBDMS hydroxyl protective group functionality within 50–71% yield and 93–95% *ee*. Remarkably, the benzoate protected α -hydroxy aldehyde products were stable to be exploited in further reactions [III]. The credits to this work belong to Sze Chak Yau.

7 Conclusions

There has been an extensive review of the synthetic method towards α -hydroxy substituted aldehydes. It is important to understand that the problems related to the sensitivity of the α -hydroxy aldehydes, which is also the analytical problem to observe whenever a sensitive product is formed or not. The most interesting methods are mild and high-yielding procedures which are directly applicable to further reactions. The research of TIM isomerase reaction could be considered as an important part of the multienzymatic cascade rather than a single transformation.

Chemical transformations should be carried out by keeping in mind its impact on the environment. Important synthetic aspects are more active conversions of the substances to the products, minimisation of the formation of toxic chemical waste in the form of solvent waste, unnecessary side products and residues of reactants. The input of external heat has been a general way to activate of chemical transformation but it is also the greatest consumer of energy sources in the chemical industry. The energy efficiency in heating and time saving are two important benefits gained when microwave assistance is used in reactions instead of convectional heating baths. The green ways to carry out reactions also are biocatalytic transformations and the use of organocatalytic methods that both are novel solutions for the environmentally benign chemical industry.

In this study, the four-step synthesis of substituted 4-alkylsulphonyl-1-hydroxy-butan-2-one **183** was developed. The use of microwave activation in the endothermic reactions substantially improved the yield of the products and shortened the reaction time. Consequently, the short reaction time decreased the formation of side products and hence purification was easier at every step. This saved so much time that the carrying out of the full reaction pathway was cut down from several days to a workday. The reaction steps were planned and performed by using ecoefficient reagents which produced harmless chemical waste. All reactions of the synthetic path were simple to carry out and yielded one major product.

The presented microwave-assisted *S*-alkylation of 3-mercaptopropionic acid with variable alkyl halides was an efficient and green method. The interchange of the functionality of the reactive components increased the selectivity of *S*-alkylation. The use of microwave activation was advantageous compared to the conventional heating technique. Besides shortening the reaction time, the purity of products also improved.

In addition, the carboxylic acid functionality helped the separation of the product from the reaction mixture as well as it made compounds less offensive.

An improved and fast synthesis for the preparation of hydroxymethyl ketones by the one-carbon chain extension using microwave heating was developed. In the literature, there are not many synthetic methods which utilise microwave-assistance in the synthesis of terminal α -hydroxy ketones. The method was further improved by the use of triethylamine. The base accelerated the reaction rate and made the excess use of enol reagent unnecessary. It also intensified the transfer of microwave energy into the reaction mixture by salt formation. In reference to future development, it would be interesting to test esters [286] or aldehydes to replace carboxylic chloride in the microwave-assisted reaction with TMSE.

The new organocatalytic asymmetric α -oxybenzoylation of aldehydes is a good addition to the α -oxygenation processes. The organocatalytic oxobenzoylation reaction is a mild, efficient, and simple method to generate α -hydroxy aldehydes in a relative stable form from commercially available chemicals with high levels of asymmetric induction. In addition to α -benzoyl esters being highly stable, the benzoyl group can easily be deprotected by a simple hydrolysis. The investigation of this reaction will be continued.

As a final conclusion the synthesized 4-alkylsulphonyl-1-hydroxy-butan-2-one **183** and the corresponding sulphonyl propionic acids **193** were further used in the experiments with triosephosphate isomerase. Later, the collaborative papers based on the docking and the catalytic activity studies of A-TIM with the compounds **183** and **190** will be published by our consortium of chemists, biochemists and bioprocess engineers.

8 Experimental

8.1 General

Commercial reagents (Acros, Aldrich, Fluka, Merck, TCI) were used without further purification except aldehydes (decanal, valeraldehyde, *iso*-valeraldehyde) were fractional distilled. Dry BPO was obtained by precipitation from CHCl_3 with MeOH and drying in vacuum. THF was freshly distilled over metallic sodium using benzophenone indicator. Pyridine was distilled over CaH and stored over molecular sieves. Thionyl chloride was fractional distilled from quinoline collecting the mid-fraction (bp. 78–80 °C). Dry toluene was obtained by distillation over metallic sodium and petroleum ether (bp. 40–60 °C) was dried over molecular sieves (4 Å).

Unless aqueous, all reactions were carried out in oven-dried (100 °C, over night) equipment under inert atmosphere (N_2). Microwave-assisted synthesis were carried out in Biotage's SmithCreator™ or Initiator™ microwave reactors with a single mode cavity in closed vials adopted with an aluminium open-top seal with a septum and a Teflon-coated stirring bar.

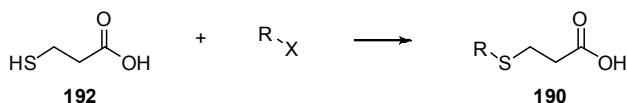
Solvents were evaporated with a Büchi rotary evaporator (water aspirator) followed by the removal of trace volatiles using a vacuum oil pump. Aluminium-backed plates coated with Kieselgel 60 F₂₅₄ silica were used for analytical TLC. TLC plates were visualised with UV light (254 nm) or ether with anisaldehyde/glacial acetic acid/conc. H_2SO_4 in EtOH (5:1:5:89) or with 1% permanganate solution ($\text{KMnO}_4/\text{NaOH}/\text{H}_2\text{O}$). Flash chromatography was carried out using Merck Kieselgel 60 silica (230-400 mesh) and visualized by TLC.

Melting points were measured with a differential scanning calorimeter on a Mettler apparatus. ^1H and ^{13}C NMR spectra were recorded at Bruker DPX 200 (Oulu) and Bruker DPX 400 (Cardiff) spectrometers and reported in parts per million from internal tetramethylsilane (δ 0.00 ppm) or solvent residue (*d*₆-DMSO, δ_{H} 2.50 ppm, δ_{C} 39.52 ppm; CDCl_3 , δ_{H} 7.26 ppm, δ_{C} 77.16 ppm). Data is reported as follows: chemical shift [integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, interpretation]. EI mass spectra (GC-MS) were recorded at 70 eV ionization energies using HP 5973 mass spectrometer and HP 6890 series GC system with DB-624 column by the Oulu University Mass Spectrometry Laboratory. Data is reported as follows: the mass of the ion (possible ion interpretation, relative intensity). High resolution

mass spectra (HRMS) were recorded either negative ($M-H^+$) or positive ($M+Na^+$) ESI by Micromass LCT equipped with TOF detector *N*-(*N*-butyl)benzenesulphonamide as a lock mass. According to 1H NMR all new compounds were higher than 95% pure.

8.2 Microwave-assisted thioalkylation of 3-mercaptopropionic acid

8.2.1 Preparation of 3-alkylthiopropionic acids



Typical procedure. 3-Mercaptopropionic acid (**192**) (1.00 g, 9.4 mmol) and 2 mL of ethanol (absolute) were placed into a 7 mL reactor vial. Halide (R-X, 1.1 equiv.), NaOH (0.75 g, 18.8 mmol) and an additional 1 mL of absolute ethanol were added into the solution followed by a microwave irradiation of 10 min within the temperature appointed (80 °C for bromides or 120 °C for chlorides). After the reaction was quenched by 20 mL of 2 M HCl, the reaction mixture was extracted by 20 mL of dichloromethane or ethyl acetate. The separated water phase was washed with an additional 20 mL of dichloromethane or ethyl acetate. Organic fractions were combined, dried (Na_2SO_4), filtered and concentrated. [I]

3-(Propylthio)propionic acid (190a). [287] Yield 94% (colourless oil, 1.31 g, 8.8 mmol); 1H NMR (200 MHz, $CDCl_3$, ppm) δ_H 10.92 (1H, br s, OH), 2.9-2.6 (4H, m, SCH_2CH_2CO), 2.53 (2H, t, $J = 7.3$ Hz, $CH_3CH_2CH_2S$), 1.62 (2H, m, $J = 7.3$ Hz, CH_3CH_2), 0.99 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ_C 178.5 (C=O), 34.8, 34.2, 26.6, 22.9, 13.5 (CH_3); HRMS (ESI) $m/z = 147.0516$ (calcd. 147.0480 for $C_6H_{11}O_2S$).

3-(Butylthio)propionic acid (190b). [263] Yield 84% (colourless oil, 1.28 g, 7.9 mmol); 1H NMR (200 MHz, $CDCl_3$, ppm) $\delta = 10.73$ (1H, br s, OH), 2.9-2.6 (4H, m, SCH_2CH_2CO), 2.55 (2H, t, $J = 7.3$ Hz, $(CH_2)_2CH_2S$), 1.75-1.30 (4H, m, $CH_3CH_2CH_2$), 0.92 (3H, t, $J = 7.2$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, ppm) δ_C 178.5 (C=O), 34.8, 31.9, 31.6, 26.6, 22.0, 13.7 (CH_3); HRMS (ESI) m/z 161.0642 (calcd. 161.0636 for $C_7H_{13}O_2S$).

3-(Pentylthio)propionic acid (190c). [288] The reaction was carried out as a typical procedure. It was, however, quenched by 10 mL of water and subsequently washed by 10 mL of dichloromethane to remove alkyl halide residues. The water

phase was acidified with 2 M HCl, and extracted with dichloromethane as earlier. Organic fractions were combined, dried (Na₂SO₄), filtered and concentrated. Yield 91% (colourless oil, 1.51 g, 8.6 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 10.5 (1H, br s, OH), 2.79 (2H, ddd, *J* = 1.2, 2.5, 6.3, 8.8 Hz, SCH₂CH₂CO), 2.66 (2H, ddd, *J* = 1.2, 2.5, 6.3, 8.8 Hz, SCH₂CH₂CO), 2.54 (2H, t, *J* = 7.4 Hz, (CH₂)₃CH₂S), 1.8-1.5 (2H, m, CH₂CH₂CH₂S), 1.5-1.2 (4H, m, CH₃(CH₂)₂), 0.90 (3H, t, *J* = 7.5 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 178.5 (C=O), 34.8, 32.3, 31.1, 29.3, 26.7, 22.4, 14.1 (CH₃).

3-(Hexylthio)propionic acid (190d). [289] Yield 94% (colourless oil, 1.69 g, 8.9 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.66 (1H, br s, OH), 2.9-2.6 (4H, m, SCH₂CH₂CO), 2.54 (2H, t, *J* = 7.3 Hz, (CH₂)₄CH₂S), 1.7-1.5 (2H, m, CH₂CH₂CH₂S), 1.5-1.2 (6H, m, CH₃CH₂CH₂CH₂), 0.89 (3H, t, *J* = 6.6 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 178.6 (C=O), 34.8, 32.2, 31.4, 29.5, 28.5, 26.6, 22.6, 14.0 (CH₃); HRMS (ESI) *m/z* 189.0930 (calcd. 189.0949 for C₉H₁₇O₂S).

3-(Tetradecylthio)propionic acid (190e). [290] Yield 77% (white crystals, 2.26 g, 7.5 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 10.93 (1H, br s, OH), 2.79 (2H, ddd, *J* = 1.1, 2.5, 6.0, 8.1 Hz, SCH₂CH₂CO), 2.66 (2H, ddd, *J* = 1.1, 2.5, 6.0, 8.1 Hz, SCH₂CH₂CO), 2.53 [2H, t, *J* = 7.3 Hz, CH₃(CH₂)₁₂CH₂S], 1.58 [2H, m, *J* = 7.3 Hz, CH₃(CH₂)₁₁CH₂CH₂S], 1.45-1.15 [22H, m, CH₃(CH₂)₁₁], 0.88 (3H, t, *J* = 6.5 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 178.3 (C=O), 34.8, 32.3, 32.1, 29.83, 29.82, 29.79 (2xC), 29.74, 29.66 (2xC), 29.5, 29.4, 29.0, 26.7, 22.8, 14.3 (CH₃); HRMS (ESI⁺) *m/z* 325.2162 (calcd. 325.2177 for C₁₇H₃₄NaO₂S).

3-(Isopropylthio)propionic acid (190f). [291] Yield 97% (colourless oil, 1.34 g, 9.1 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.54 (1H, br s, OH), 2.96 (1H, m, *J* = 6.7 Hz, CHS), 2.9-2.6 (m, 4H, SCH₂CH₂CO), 1.28 (6H, d, *J* = 6.7 Hz, 2×CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 178.5 (C=O), 35.0, 34.8, 25.0, 23.3 (2×CH₃); HRMS (ESI) *m/z* 147.0507 (calcd. 147.0480 for C₆H₁₁O₂S).

3-(Isobutylthio)propionic acid (190g). [292] Yield 90% (colourless oil, 1.42 g, 8.8 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.60 (1H, br s, OH), 2.9-2.6 (4H, m, SCH₂CH₂CO), 2.43 (2H, d, *J* = 6.8 Hz, CHCH₂S), 1.80 (1H, m, *J* = 6.6, 6.8 Hz, CH), 0.99 (6H, d, *J* = 6.6 Hz, 2×CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 178.6 (C=O), 41.5, 34.9, 28.6, 27.2, 22.0 (2×CH₃); HRMS (ESI) *m/z* 161.0625 (calcd. 161.0636 for C₇H₁₃O₂S).

3-(Benzylthio)propionic acid (190h). [263] The reaction was carried out as described with **190c**. Yield 72% (white crystals, 1.33 g, 6.8 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 10.23 (1H, br s, OH), 7.4-7.1 [5H (+CHCl₃), m, arom. Hs], 3.72 (2H, s, PhCH₂S), 2.8-2.5 (4H, m, SCH₂CH₂CO); ¹³C NMR (50 MHz, CDCl₃,

ppm) δ_c 178.1 (C=O), 137.9, 128.8 (2 \times arom. C), 128.6 (2 \times arom. C), 127.1, 36.3, 34.3, 25.8; HRMS (ESI) m/z 195.0475 (calcd. 195.0480 for C₁₀H₁₁O₂S).

3-(Prop-2-enylthio)propionic acid (190i). [293] Yield 85% (colourless oil, 1.16 g, 7.9 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.73 (1H, br s, OH), 5.9-5.6 (1H, m, CH), 5.2-5.05 (2H, m, CH₂CH), 3.16 (2H, td, J = 1.1, 7.2 Hz, CHCH₂S), 2.9-2.6 (4H, m, CH₂CH₂CO); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 178.5 (C=O), 134.0, 117.4, 34.8, 34.4, 25.1; HRMS (ESI) m/z 145.0356 (calcd. 145.0323 for C₆H₉O₂S).

3-[(2-Methyl-prop-2-enyl)thio]propionic acid (190j). Yield 85% (colourless oil, 1.28 g, 8.0 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 10.63 (1H, br s, OH), 4.87 (1H, fragmented s, J = 1.4 Hz, CH₂C *cis* to CH₃), 4.84 (1H, fragmented s, J = 0.96 Hz, CH₂C *cis* to CH₂), 3.14 (2H, fragmented s, J = 0.96 Hz, CCH₂S), 2.8-2.6 (4H, m, SCH₂CH₂CO), 1.82 (3H, fragmented s, J = 1.4 Hz, 0.86 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 178.6 (C=O), 141.0 (quaternary C), 113.6, 39.4, 34.3, 25.3, 20.5 (CH₃); HRMS (ESI) m/z 159.0499 (calcd. 159.0480 for C₇H₁₁O₂S).

3-(3-Chloropropylthio)propionic acid (190k). [294] The reaction was carried out as described with **190c**. Yield 90% (white crystals, 1.58 g, 8.7 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.04 (1H, br s, OH), 3.66 (2H, t, J_{av} = 6.4 Hz, CH₂Cl), 2.85-2.55 (6H, m, CH₂SCH₂CH₂CO), 2.05 (2H, m, J_{av} = 6.4 Hz, CH₂CH₂CH₂); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 178.3 (C=O), 43.4, 34.7, 32.0, 29.1, 26.7; HRMS (ESI⁺) m/z 205.0062 (calcd. 205.0066 for C₆ClH₁₁NaO₂S).

3-(3-Hydroxypropylthio)propionic acid (190l). [295] The reaction and isolation procedure were performed as described in the typical procedure except that diethyl ether (4 \times 20 mL) was used for extraction and the acidic water phase was saturated with NaCl. Yield 57% (colourless oil, 0.89 g, 5.4 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 3.73 (2H, t, J_{av} = 6.6 Hz, CH₂OH), 2.90-2.55 (6H, m, CH₂SCH₂CH₂CO), 1.84 (2H, m, J_{av} = 6.6 Hz, CH₂CH₂CH₂); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 176.3 (C=O), 61.2, 34.6, 31.7, 28.5, 26.7; HRMS (ESI) m/z 163.0448 (calcd. 163.0429 for C₆H₁₁O₃S).

3-[(3-Cyanopropyl)thio]propionic acid (190m). The reaction was performed as described with **190c**. Organic fractions were combined, dried (Na₂SO₄), filtered and concentrated yielding colourless oil (1.33 g, 7.7 mmol, 82%); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.42 (1H, br s, OH), 2.85-2.6 (6H, m, CH₂SCH₂CH₂CO), 2.53 (2H, t, J = 7.0 Hz, CNCH₂), 1.95 (2H, m, J = 7.0 Hz, CH₂CH₂CH₂); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 177.8 (C=O), 119.1 (CN), 34.4, 30.5, 26.3, 24.9, 15.9; HRMS (ESI) m/z 172.0420 (calcd. 172.0432 for C₇H₁₀NO₂S).

3-(2-Methoxyethylthio)propionic acid (190n). Yield 90% (pale yellow oil, 1.55 g, 8.5 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 11.49 (1H, br s, OH), 3.59 (2H, t,

$J = 6.6$ Hz, CH₂O), 3.38 (3H, s, CH₃), 2.9-2.6 (4H, m, SCH₂CH₂CO), 2.74 (2H, t, $J = 6.6$ Hz, OCH₂CH₂S); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 177.5 (C=O), 72.0, 58.5, 34.6, 31.3, 26.9; HRMS (ESI) m/z 163.0400 (calcd. 163.0395 for C₆H₁₁O₃S).

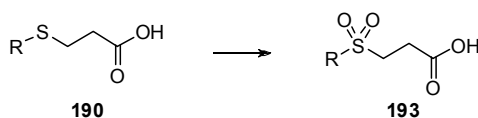
3-(4-Methoxybenzylthio)propanoic acid (190o). [296] The reaction was performed as described with **190c**. Yield 32%; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.24 (2H, d, $J = 8.0$ Hz, arom. Hs), 6.86 (2H, d, $J = 8.0$ Hz, arom. Hs), 3.80 (3H, s, OCH₃), 3.70 (2H, s, PhCH₂), 2.64 (4H, m, SCH₂CH₂).

8.2.2 GC-MS analysis of side products of the microwave-assisted S-alkylation.

The product mixture of the reaction between 3-mercaptopropionic acid (**192**) and *n*-butyl halide was analyzed by GC-MS (EI) [265, 266]. *S*-dibutylsulphide (**195**); Rt 4.6 min; $m/z = 146$ (M⁺, 66%), 117 (M⁺-CH₂CH₃, 8), 103 (M⁺-CH₂CH₂CH₃, 16), 90 (BuSH⁺, 29), 75 (6), 61 (CH₂SCH₂⁺, 100), 56 (96), 47 (13), 41 (52). Butyl 3-mercaptopropanoate (**199**); Rt 6.0 min; $m/z = 162$ (M⁺, 26%), 160 (M⁺-2, 15), 132 (5), 115 (5), 106 (54), 89 (70), 88 (100), 73 (31), 61 (81), 57 (68), 56 (68), 55 (62), 41 (94). *S,S'*-dibutyl disulphide (**196**); $m/z = 178$ (M⁺, 58%), 122 (BuSSH⁺, 41), 87 (9), 57 (CH₃CH₂CHCH₂⁺, 100), 41 (65). 3-(Butylthio)propionic acid (**190a**); Rt 8.1 min; $m/z = 162$ (M⁺, 58%), 145 (M⁺-OH, 1), 133 (M⁺-CH₃CH₂, 2), 119 (M⁺-CH₃CH₂CH₂, 10), 106 (23), 89 (BuS⁺, 100), 77 (8), 73 (8), 61 (42), 56 (40) 55 (40), 45 (33), 41 (38). Butyl 3-(butylthio)propanoate (**198**); Rt 9.3 min; $m/z = 218$ (M⁺, 43%), 162 (33), 145 (33), 129 (8), 116 (48), 106 (40), 89 (100), 74 (54), 61 (77), 57 (76), 55 (73), 47 (21), 45 (87). Ethyl 3-[(3-butoxy-3-oxopropyl)thio]propanoate (**201**); Rt 11.5 min; $m/z = 262$ (M⁺, 2%), 206 (2), 188 (2), 160 (5), 143 (8), 133 (6), 114 (10), 105 (19), 89 (9), 87 (10), 73 (16), 60 (30), 55 (73), 45 (51), 41 (100). Diethyl 3,3'-thiobispropanoate (**200**); Rt 11.9 min; $m/z = 234$ (M⁺, 1%), 165 (2), 143 (2), 132 (22), 114 (15), 105 (8), 89 (20), 73 (17), 55 (45), 45 (83), 41 (100). Dibutyl 3,3'-thiobispropanoate (**202**); Rt 13.0 min; $m/z = 290$ (M⁺, 1%), 217 (1), 188 (3), 161 (1), 143 (5), 132 (4), 114 (8), 105 (13), 89 (9), 73 (8), 57 (36), 55 (44), 41 (100).

3-(3-(Butylthio)propanoyloxy)propanoic acid (**197**) formed in the preparation of **190b** was identified from the crude product mixture. ¹H NMR (200 MHz, CDCl₃) showed a triplet at δ = 4.38 ppm (2H, t, $J = 6.3$ Hz, COOCH₂CH₂COOH) and MS-EI (silylated with HMDS) $m/z = 306$ [M⁺+TMS, 4%], 218 (3), 163 (9), 145 (38), 129 (88), 116 (100), 103 (57), 101 (36), 88 (31), 75 (72), 73 (86), 61 (76), 55 (75), 41 (24).

8.3 Oxidation of 3-alkylthiopropionic acid to 3-alkylsulphonylpropionic acid



Typical procedure. 2 mL of cold 30% hydrogen peroxide (19 mmol, 3.0 equiv.) was injected into a warm solution (30 - 35 °C) of **190** (6.4 mmol, 1.0 equiv.) in 5 mL of acetic acid in a two-neck round-bottomed flask equipped with a condenser, a stirring bar and a thermometer. The reaction was highly exothermic and temperature of the reaction mixture shortly increased to the maximum 80 °C after which it decreased to around 70 °C. Temperature was maintained at 105 °C for an additional 20 min. 50 mL of water was added and solvents were evaporated under reduced pressure and high vacuum yielding pure **193**.

3-(Propylsulphonyl)propionic acid (193a). [297] Quantitative yield (white powder, 1.18 g, 6.5 mmol); mp. 90.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 8.17 (1H, br s, OH), 3.31 (2H, t, *J* = 7.3 Hz, SO₂CH₂CH₂CO), 3.05-2.9 (4H, m, CH₂SO₂CH₂CH₂CO), 1.91 (2H, m, CH₃CH₂), 1.10 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 175.6 (C=O), 55.3, 47.7, 26.6, 16.0, 13.3 (CH₃); HRMS (ESI) *m/z* 179.0396 (calcd. 179.0378 for C₆H₁₁O₄S).

3-(Butylsulphonyl)propionic acid (193b). [297] Quantitative yield (white powder, 1.23 g, 6.4 mmol); mp. 92 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.96 (1H, br s, OH), 3.31 (2H, t, *J*_{av} = 7.3 Hz, SO₂CH₂CH₂CO), 3.3-2.85 (4H, m, CH₂SO₂CH₂CH₂CO), 1.9-1.85 (2H, m, CH₃CH₂CH₂), 1.49 (2H, m, *J*_{av} = 7.3 Hz, CH₃CH₂), 0.97 (3H, t, *J*_{av} = 7.3 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 174.9 (C=O), 53.4, 47.7, 26.6, 24.0, 21.7, 13.5 (CH₃); HRMS (ESI) *m/z* 193.0508 (calcd. 193.0535 for C₇H₁₃O₄S).

3-(Pentylsulphonyl)propionic acid (193c). [288] Yield 81% (white crystals, 0.96 g, 4.7 mmol); ¹H NMR (200 MHz, *d*6-DMSO, ppm) δ_H 12.5 (1H, br s, OH), 3.30 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO), 3.11 (2H, t, *J* = 7.9 Hz, (CH₂)₃CH₂SO₂), 2.66 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO), 1.8-1.5 (2H, m, CH₂CH₂CH₂SO₂), 1.5-1.2 (4H, m, CH₃(CH₂)₂), 0.87 (3H, t, *J* = 7.1 Hz, CH₃); HRMS (ESI⁺) *m/z* 231.0688 (calcd. 231.0667 for C₈H₁₆NaO₄S).

3-(Hexylsulphonyl)propionic acid (193d). [298] Yield 97% (white powder, 1.38 g, 6.2 mmol); mp. 113.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 6.24 (1H, br s, OH), 3.30 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 3.1-2.9 (4H, m, CH₂SO₂CH₂CH₂CO), 1.86 (2H, m, CH₃(CH₂)₃CH₂), 1.55-1.3 (2H, m,

CH₃(CH₂)₂CH₂), 1.45-1.2 (4H, m, CH₃(CH₂)₂), 0.90 (3H, t, *J* = 6.5 Hz, CH₃); ¹³C NMR (50 MHz, *d6*-DMSO, ppm) δ_c 171.9 (C=O), 51.7, 47.6, 30.8, 27.4, 36.8, 21.9, 21.2, 13.9 (CH₃); HRMS (ESI⁻) *m/z* 221.0849 (calcd. 221.0848 for C₉H₁₇O₄S).

3-(Isopropylsulphonyl)propionic acid (193f). [299] Yield 96% (white powder, 1.12 g, 6.2 mmol); mp. 75 °C; ¹H NMR (200 MHz, *d6*-DMSO, ppm) δ_H 5.50 (1H, br s, OH), 3.31 [(2H, t, *J* = 7.3 Hz, SO₂CH₂CH₂CO) and (1H, m, *J* = 6.8 Hz, CH)], 2.67 (2H, t, *J* = 7.3 Hz, SO₂CH₂CH₂CO), 1.25 (6H, d, *J* = 6.8 Hz, 2×CH₃); ¹³C NMR (50 MHz, *d6*-DMSO, ppm) δ_c 172.8 (C=O), 52.8, 45.4, 27.3, 15.8 (2×CH₃); HRMS (ESI⁻) *m/z* 179.0362 (calcd. 179.0378 for C₆H₁₁O₄S).

3-(Isobutylsulphonyl)propionic acid (193g). [300] Yield 97% (white powder, 1.21 g, 6.2 mmol); mp. 97 °C; ¹H NMR (200 MHz, *d6*-DMSO, ppm) δ_H 3.34 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 3.22 (2H, d, *J* = 6.7 Hz, CHCH₂), 2.70 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 2.23 (1H, m, *J* = 6.7 Hz, CH), 1.07 (6H, d, *J* = 6.7 Hz, 2×CH₃); ¹³C NMR (50 MHz, *d6*-DMSO, ppm) δ_c 172.9 (C=O), 59.9, 49.8, 27.8, 24.0, 23.5 (2×CH₃); HRMS (ESI⁻) *m/z* 193.0539 (calcd. 193.0535 for C₇H₁₃O₄S).

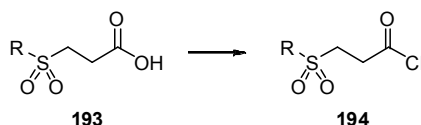
3-(Benzylsulphonyl)propionic acid (193h). [301] Yield 94% (white powder, 1.29 g, 6.0 mmol); mp. 177 °C (lit. 177–178 °C) [301]; ¹H NMR (200 MHz, *d6*-DMSO, ppm) δ_H 7.45-7.3 (5H, m, arom. Hs), 4.53 (2H, s, PhCH₂), 3.27 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO), 2.66 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO); ¹³C NMR (50 MHz, *d6*-DMSO, ppm) δ_c 172.7 (C=O), 58.8, 47.8, 27.5; HRMS (ESI⁻) *m/z* 227.0388 (calcd. 227.0378 for C₁₀H₁₁O₄S).

3-(Propenylsulphonyl)propionic acid (193i). Quantitative yield (pale yellow oil, 1.14 g, 6.4 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H ~6.6 (1H, br s, OH), 6.1-5.8 (1H, m, CH), 5.6-5.4 (2H, m, CH₂CH), 3.78 (2H, d, *J* = 7.3 Hz, CHCH₂SO₂), 3.32 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO), 2.92 (2H, t, *J* = 7.5 Hz, SO₂CH₂CH₂CO); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 174.8 (C=O), 125.2, 124.6, 58.4, 46.2, 26.4; HRMS (ESI⁻) *m/z* 177.0218 (calcd. 177.0222 for C₆H₉O₄S).

3-[(2-Methyl-prop-2-enyl)sulphonyl]propionic acid (193j). Quantitative yield (white powder, 1.24 g, 6.5 mmol); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 5.26 (1H, fragmented s, *J* = 1.5 Hz, CH₂C *cis* to CH₃), 5.14 (1H, fragmented s, *J* = 0.96 Hz, CH₂C *cis* to CH₂), 3.74 (2H, s, CCH₂SO₂), 3.36 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 2.93 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 2.00 (3H, fragmented s, *J* = 1.5, 0.96 Hz, CH₃); ¹³C NMR (*d6*-DMSO, ppm) δ_c 171.8 (C=O), 134.2, 120.1, 59.8, 46.9, 26.6, 22.6; HRMS (ESI⁻) *m/z* 191.0386 (calcd 191.0378 for C₇H₁₁O₄S)

3-(3-Chloropropylsulphonyl)propionic acid (193k). Yield 92% (white powder, 1.09 g, 5.1 mmol); ^1H NMR (200 MHz, *d6*-DMSO, ppm) δ_{H} , 3.75 (2H, t, $J = 6.5$ Hz, CH_2Cl), 3.4-3.1 (4H, m, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 2.68 (2H, t, $J = 7.4$ Hz, $\text{ClCH}_2\text{CH}_2\text{CH}_2$), 2.14 (2H, m, ClCH_2CH_2); ^{13}C NMR (50 MHz, *d6*-DMSO, ppm) δ_{C} 171.9 (C=O), 49.4, 47.9, 43.5, 26.8, 25.0; HRMS (ESI⁺) m/z 236.9942 (calcd. 236.9964 for $\text{C}_6\text{ClH}_{11}\text{NaO}_4\text{S}$).

8.4 The synthesis of acid chlorides



Typical procedure. A solution of **193** (1.1-2.8 mmol, 1.0 equiv.) and thionyl chloride (6.0 equiv.) was refluxed under anhydrous conditions for 2 h after which the mixture was poured into 20 mL of toluene and the residue of SOCl_2 was evaporated under reduced pressure and high vacuum yielding a yellowish powder in a good yield. Conversion of **194** was confirmed by ^1H NMR.

3-(Propylsulphonyl)propionyl chloride (194a). Yield 96% (pale yellow powder, 0.38 g, 1.9 mmol); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 3.49 (2H, ddd, $J = 0.80, 1.6, 6.4, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.32 (2H, ddd, $J = 0.80, 1.6, 6.4, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.02 (2H, fragmented t, $\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{SO}_2$), 1.65 (2H, m, CH_3CH_2), 1.11 (3H, t, $J = 7.4$ Hz, CH_3); ^{13}C NMR δ_{C} 171.9 (C=O), 55.6, 47.6, 39.0, 15.9, 13.2 (CH_3).

3-(Butylsulphonyl)propionyl chloride (194b). Yield 88% (pale yellow powder, 0.39 g, 1.8 mmol); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 3.49 (2H, ddd, $J = 1.2, 1.7, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.31 (2H, ddd, $J = 1.2, 1.7, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.02 (2H, fragmented t, $J = 8.1$ Hz, $\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{SO}_2$), 1.85 (2H, m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.67 (2H, m, $J = 7.3$ Hz, CH_3CH_2), 0.98 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR δ_{C} 171.7 (C=O), 53.8, 47.6, 39.0, 24.0, 21.7, 13.5 (CH_3).

3-(Hexylsulphonyl)propionyl chloride (194d). Yield 97% (pale yellow powder, 0.42 g, 1.7 mmol); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 3.48 (2H, ddd, $J = 1.2, 1.8, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.31 (2H, ddd, $J = 1.2, 1.8, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.02 (2H, fragmented t, $J = 8.1$ Hz, $\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{SO}_2$), 1.87 (2H, m, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2$), 1.55-1.3 (2H, m, one of $\text{CH}_3(\text{CH}_2)_3$), 1.45-1.2 (4H, m, two of $\text{CH}_3(\text{CH}_2)_3$ s), 0.90 (3H, t, $J = 6.5$ Hz, CH_3).

3-(Isopropylsulphonyl)propionyl chloride (194f). Yield 96% (pale brown powder, 0.52 g, 2.6 mmol); $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 3.49 (2H, ddd, $J = 1.5, 6.9, 8.1$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.28 (2H, ddd, $J = 1.5, 6.9, 8.1$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.15 (1H, m, $J = 6.9$ Hz, CH), 1.44 (6H, d, $J = 6.9$ Hz, $2\times\text{CH}_3$).

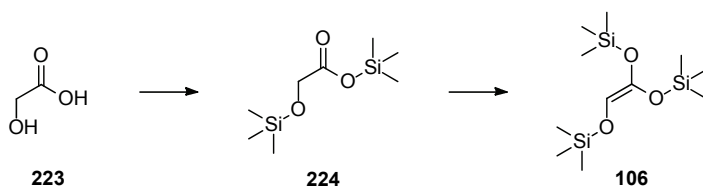
3-(Isobutylsulphonyl)propionyl chloride (194g). Yield 88% (pale yellow powder, 0.48 g, 2.3 mmol); $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 3.48 (2H, ddd, $J = 1.2, 1.8, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.31 (2H, ddd, $J = 1.2, 1.8, 6.6, 7.9$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 2.93 (2H, d, $J = 6.6$ Hz, CHCH_2), 2.40 (1H, m, $J = 6.6$ Hz, CH), 1.15 (6H, d, $J = 6.6$ Hz, $2\times\text{CH}_3$).

3-(Benzylsulphonyl)propionyl chloride (194h). Yield 92% (white powder, 0.45 g, 1.8 mmol); $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 7.5-7.35 (5H, m, arom. Hs) 4.30 (2H, s, PhCH_2), 3.33 (2H, ddd, $J = 1.2, 2.2, 6.3, 8.1$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.19 (2H, ddd, $J = 1.2, 2.2, 6.3, 8.1$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$).

3-(Propenylsulphonyl)propionyl chloride (194i). Yield 72% (brown powder, 0.41 g, 2.1 mmol); $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 6.1-5.8 (1H, m, CH), 5.56 (1H, qd, $J = 10.2, 0.92$ Hz, CH_2CH , *cis*), 5.52 (1H, qd, $J = 16.9, 1.2$ Hz, CH_2CH , *trans*), 3.78 (2H, d, $J = 7.3$ Hz, CHCH_2S), 3.46 (2H, ddd, $J = 1.2, 2.2, 6.2, 8.0$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.32 (2H, ddd, $J = 1.2, 2.2, 6.2, 8.0$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$).

3-(3-chloropropylsulphonyl)propionyl chloride (194k). Yield 87% (pale yellow powder, 0.49 g, 2.0 mmol); $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 3.72 (2H, t, $J = 6.0$ Hz, CH_2Cl), 3.50 (2H, ddd, $J = 1.2, 2.3, 6.3, 8.7$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.36 (2H, ddd, $J = 1.2, 2.3, 6.3, 8.7$ Hz, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CO}$), 3.23 (2H, m, $\text{ClCH}_2\text{CH}_2\text{CH}_2$), 2.35 (2H, m, ClCH_2CH_2).

8.5 The preparation of *tris*(trimethylsiloxy)ethylene



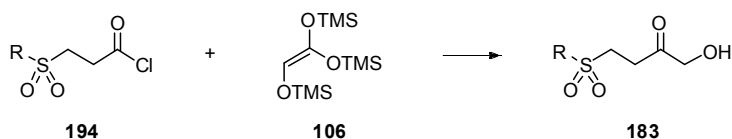
To a stirred solution of glycolic acid (**223**, 15.0 g, 0.20 mol, 1.0 equiv.) in 60 mL of pyridine was added under nitrogen 33.06 g of 1,1,1,3,3,3-hexamethyldisilazane (0.21 mol, 1.0 equiv.) over a 30-min period during which time slurry formed and temperature reached a maximum 55 °C. After 30 min of stirring at ambient temperature 11.42 g of trimethylsilyl chloride (0.10 mol, 0.5 equiv.) was added

drop wise and the mixture was stirred additional 1 h after which it was filtered through Celite and dissolved in 100 mL of petroleum ether and filtered again. The filtrate was concentrated and distilled at 77–79 °C (11 mm) [lit. 78–80 °C (12 mm)] [177] to give trimethylsilyl 2-trimethylsiloxy-acetate (**224**, 34.76 g, 80%, colourless oil). ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.02 (2H, s, CH₂), 0.16 [9H, s, CO₂Si(CH₃)₃], 0.02 [9H, s, CH₂OSi(CH₃)₃]; ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 171.8 (C=O), 61.5 (CH₂), -0.49 (3C), -0.70 (3C); *m/z* (EI) 205 (M⁺-Me, 7%), 190 (M⁺-2×Me, 1), 177 (10), 161 (6), 147 (M⁺-SiMe₃, 100), 133 (9), 117 (2), 103 (4), 88 (2), 73 (88), 66 (13), 59 (6), 52 (2), 45 (15).

The reaction was continued. Over 1 h at -10 °C (crushed ice-NaCl-EtOH - bath), 67 mL of 2.5 M *n*-butyl lithium (0.17 mol, 1.2 equiv.) in hexane was added with stirring under nitrogen into a solution of 31.2 g of 1,1,1,3,3,3-hexamethyldisilazane (0.19 mol, 1.3 equiv) and 150 mL of THF. The solution was stirred at 45 °C for 30 min after which it was cooled to -78 °C (CO₂-acetone). 30.9 g of **224** (0.14 mol, 1.0 equiv.) was added dropwise over 40-min period and the solution was stirred at -78 °C for additional 30 min. 25.8 g of chlorotrimethylsilyl (0.24 mol, 1.7 equiv.) was added into the cooled solution during 15 min. After the solution warmed to room temperature it was poured into 200 mL of petroleum ether, filtrated through Celite, concentrated, dissolved in 100 mL of petroleum ether and filtrated again. Solvent was evaporated, and the residue was distilled (91–96 °C, 10 mm) [lit. 54–56 °C (0.1 mm)] [177] to yield 34.9 g (85%) of TMSE (**106**) as colourless oil. ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 5.22 (1H, s, CH), 0.04 (9H, s, Si(CH₃)₃), 0.01 (9H, s, Si(CH₃)₃), -0.3 (9H, s, Si(CH₃)₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 145.1, 106.5, 0.8 (3C), 0.06 (3C), -0.4 (3C); *m/z* (EI) 292 (M⁺, 11%), 221 (6), 189 (1), 147 (26), 130 (4), 117 (1), 102 (32), 73 (100), 59 (2), 45 (12).

8.6 Microwave-assisted synthesis of α-hydroxy ketones

8.6.1 The synthesis of 4-alkylsulphonyl-1-hydroxybutan-2-ones



Typical procedure. Acid chloride **194** (1.6-1.9 mmol, 1.0 equiv.) and **106** (2.15 equiv.) were placed in a 5 mL closed tube and heated at 200 °C using microwave

irradiation for 10 min. A solution of 0.6 M HCl and THF (0.25 equiv. as HCl) was added followed by heating at 80–90 °C for 45 min. 2 mL of water was added and the mixture was saturated with NaCl, extracted four times with 5 mL of dichloromethane. The organic phase was dried (Na₂SO₄), filtrated and concentrated yielding **183**.

1-Hydroxy-4-(propylsulphonyl)butan-2-one (183a). Purified by dry-column chromatography (dry flash) [302] using ethyl acetate elution (white powder, 0.09 g, 0.5 mmol, 31%); mp. 80.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.37 (2H, s, CH₂OH), 3.35 (2H, t, *J*_{av} = 7.2 Hz, SO₂CH₂CH₂CO), 3.1-2.9 (4H, 2×t, CH₂SO₂CH₂CH₂CO), 2.0-1.8 (2H, m, CH₃CH₂), 1.11 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 206.2 (C=O), 68.4 (C-OH), 55.7, 46.5, 30.3, 16.0, 13.3 (CH₃); HRMS (ESI⁺) *m/z* 217.0513 (calcd. 217.0511 for C₇H₁₄NaO₄S).

4-(Butylsulphonyl)-1-hydroxybutan-2-one (183b). Purified by dry flash (EtOAc) (white powder, 0.17 g, 0.8 mmol, 50%); mp. 78 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.36 (2H, s, CH₂OH), 3.35 (2H, t, *J*_{av} = 7.1 Hz, SO₂CH₂CH₂CO), 3.1-2.9 (4H, 2×t, CH₂SO₂CH₂CH₂CO), 1.95-1.75 (2H, m, CH₃CH₂CH₂), 1.49 (2H, m, *J*_{av} = 7.3 Hz, CH₃CH₂), 0.98 (3H, t, *J*_{av} = 7.3 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 206.5 (C=O), 68.5 (C-OH), 53.9, 46.6, 30.4, 24.2, 21.9, 13.8 (CH₃); *m/z* (EI) 207 (M⁺-1, <1%), 177 (M⁺-CH₂OH, 2), 152 (3), 122 (6), 105 (22), 87 (2), 70 (3), 64 (7), 55 (100), 41 (26); HRMS (ESI⁺) *m/z* 231.0681 (calcd. 231.0667 for C₈H₁₆NaO₄S).

1-Hydroxy-4-(pentylsulphonyl)butan-2-one (183c). Purified by dry flash (EtOAc) (white powder, 0.31 g, 1.6 mmol, 57%); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.37 (2H, d, *J* = 5.0 Hz, CH₂OH), 3.35 (2H, t, *J* = 7.1 Hz, SO₂CH₂CH₂CO), 3.1-2.9 (4H, 2×t, CH₂SO₂CH₂CH₂CO), 2.50 (1H, t, *J* = 5.0 Hz, OH), 1.95-1.75 (2H, m, CH₃(CH₂)₂CH₂), 1.55-1.25 (4H, m, CH₃(CH₂)₂), 0.98 (3H, t, *J* = 7.0 Hz, CH₃).

4-(Hexylsulphonyl)-1-hydroxybutan-2-one (183d). Purified by dry flash (EtOAc) (white powder, 0.25 g, 1.0 mmol, 68%); mp. 96 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.36 (2H, s, CH₂OH), 3.34 (2H, t, *J* = 7.1 Hz, SO₂CH₂CH₂CO), 3.1-2.9 (4H, 2×t, CH₂SO₂CH₂CH₂CO), 1.95-1.75 (2H, m, CH₃(CH₂)₃CH₂), 1.55-1.3 (2H, m, CH₃(CH₂)₂CH₂), 1.45-1.25 (4H, m, CH₃(CH₂)₂), 0.90 (3H, t, *J* = 6.5 Hz, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_c 206.2 (C=O), 68.4 (C-OH), 54.1, 46.4, 31.3, 30.3, 28.2, 22.4, 22.1, 14.1 (CH₃); HRMS (ESI⁺) *m/z* 259.0962 (calcd. 259.0980 for C₁₀H₂₀NaO₄S).

1-Hydroxy-4-(isopropylsulphonyl)butan-2-one (183f). Purified by dry flash (EtOAc) (white powder, 0.13 g, 0.7 mmol, 35%); mp. 55.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.37 (2H, s, CH₂OH), 3.32 (2H, t, *J*_{av} = 7.2 Hz, SO₂CH₂CH₂CO), 3.12 (1H, m, *J* = 6.9 Hz, CH), 3.00 (2H, t, *J*_{av} = 7.2 Hz, SO₂CH₂CH₂CO), 1.43 (6H, d, *J* = 6.9 Hz, 2×CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 206.5 (C=O), 68.4 (C-OH), 54.1, 43.0, 29.7, 15.4 (2×CH₃); HRMS (ESI⁺) *m/z* 217.0497 (calcd. 217.0511 for C₇H₁₄NaO₄S).

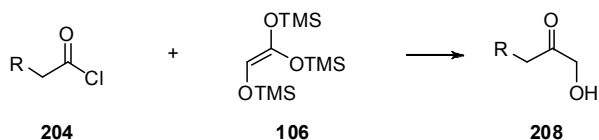
1-Hydroxy-4-(isobutylsulphonyl)butan-2-one (183g). Purified by dry flash (EtOAc) (white powder, 0.14 g, 0.7 mmol, 35%); mp. 73.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.37 (2H, s, CH₂OH), 3.35 (2H, t, *J*_{av} = 7.2 Hz, SO₂CH₂CH₂CO), 2.99 (2H, t, *J*_{av} = 7.2 Hz, SO₂CH₂CH₂CO), 2.93 (2H, d, *J* = 6.7 Hz, CHCH₂), 2.39 (1H, m, *J* = 6.7 Hz, CH), 1.15 (6H, d, *J* = 6.7 Hz, 2×CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 206.3 (C=O), 68.4 (C-OH), 61.5, 47.8, 30.3, 23.8, 22.9 (2×CH₃); HRMS (ESI⁺) *m/z* 231.0650 (calcd. 231.0667 for C₈H₁₆NaO₄S).

4-(Benzylsulphonyl)-1-hydroxybutan-2-one (183h). Purified by dry flash (toluene:EtOAc:MeOH) (white powder, 0.12 g, 0.5 mmol, 33%); mp. 123 °C; ¹H NMR (200 MHz, *d*₆-DMSO, ppm) δ_H 7.45-7.3 (5H, m, arom. Hs), 5.30 (1H, br s, OH), 4.54 (2H, s, PhCH₂), 4.11 (2H, s, CH₂OH), 3.26 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO), 2.91 (2H, t, *J* = 7.4 Hz, SO₂CH₂CH₂CO); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 208.1 (C=O), 67.4 (C-OH), 57.9, 45.5, 30.1; HRMS (ESI⁺) *m/z* 265.0538 (calcd. 265.0511 for C₁₁H₁₄NaO₄S).

1-Hydroxy-4-(propenylsulphonyl)butan-2-one (183i). Purified by dry flash (EtOAc) (light yellow crystals, 0.08 g, 0.4 mmol, 33%); mp. 43 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 6.1-5.8 (1H, m, CH), 5.6-5.4 (2H, m, CH₂CH), 4.36 (2H, s, CH₂OH), 3.77 (2H, d, *J* = 7.4 Hz, CHCH₂SO₂), 3.36 (2H, t, *J* = 7.1 Hz, SO₂CH₂CH₂CO), 2.98 (2H, t, *J* = 7.1 Hz, SO₂CH₂CH₂CO); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 206.4 (C=O), 125.4, 124.6, 68.3 (C-OH), 58.6, 45.2, 30.2; HRMS (ESI⁺) *m/z* 215.0359 (calcd. 215.0354 for C₇H₁₂NaO₄S).

4-(3-chloropropylsulphonyl)-1-hydroxybutan-2-one (183k). Crude yield 70%; mp. 70.5 °C; ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.37 (2H, s, CH₂OH), 3.71 (2H, t, *J*_{av} = 6.1 Hz, CH₂Cl), 3.40 (2H, t, *J* = 7.0 Hz, SO₂CH₂CH₂CO), 3.22 (2H, td, *J*_{av} = 7.5 Hz & *n.d.*, ClCH₂CH₂CH₂), 3.01 (2H, t, *J* = 7.0 Hz, SO₂CH₂CH₂CO), 2.35 (2H, m, *J*_{av} = 7.5, 6.1 Hz, ClCH₂CH₂CH₂); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 206.2 (C=O), 68.3 (C-OH), 51.0, 47.1, 42.9, 30.4, 25.1; HRMS (ESI⁺) *m/z* 251.0116 (calcd. 251.0121 for C₇ClH₁₃NaO₄S).

8.6.2 The microwave-assisted synthesis of α -hydroxy ketone with TMSE in the presence of triethylamine



General synthetic procedure. [III] Acid chloride (**204**, 1.0 equiv.), tris(trimethylsilyloxy)ethylene (**106**, 1.1 equiv.), and triethylamine (1.0 equiv.) were successively added by syringe into THF (1 M) in a closed reactor vessel at $-10\text{ }^{\circ}\text{C}$. The reaction mixture was stirred at $-10\text{ }^{\circ}\text{C}$ for an additional 5 min after which microwave power was introduced (absorption level high, fixed hold time off, pre-stirring 10 s). Temperature and the total irradiation time were controlled. Aqueous HCl (2 M) was added and the reaction mixture was heated at $80\text{--}85\text{ }^{\circ}\text{C}$ for 30 min (**208a-e**) or at room temperature for 30 min (**208f-j**). At this point, for the determination of conversion, decane standard (0.1 equiv.) was added to the reaction mixture and GC samples were taken from the THF phase. The water phase of the reaction was saturated by NaCl and washed three times with Et_2O (**208a-b**, **208f-g** & **208j**) or EtOAc (**208c-e** & **208h-i**). Organic phases were combined, washed with saturated NaHCO_3 solution and brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by column chromatography.

1-Hydroxynonan-2-one (208a). [177] Purified by LC (Et_2O :petroleum ether-60:40); Rf 0.44; white crystals; mp. $31\text{ }^{\circ}\text{C}$: yield 88% (0.86 g); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 4.25(2H, s, CH_2OH), 3.2-3.0 (1H, br s, OH), 2.41 (2H, t, $J = 7.5\text{ Hz}$, CH_2CO), 1.64 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 1.4-1.1 (8H, m, $\text{CH}_3(\text{CH}_2)_4$), 0.88 (3H, t, $J = 6.4\text{ Hz}$, CH_3); ^{13}C NMR (50 MHz, CDCl_3 , ppm) δ_{C} 210.1 (CO), 68.2 (CH_2OH), 38.6, 31.7, 29.3, 29.1, 23.9, 22.7, 14.2; HRMS (ESI^+): m/z 181.1207 (calcd. 181.1204 for $\text{C}_9\text{H}_{18}\text{NaO}_2$).

1-Hydroxyundecan-2-one (208b). [303] Purified by LC (Et_2O :PE-55:45); Rf 0.45; white crystals; mp. $49\text{ }^{\circ}\text{C}$ (lit. $47\text{--}49\text{ }^{\circ}\text{C}$) [304]; yield 75% (0.73 g); ^1H NMR (200 MHz, CDCl_3 , ppm) δ_{H} 4.24 (2H, s, CH_2OH), 3.3-2.9 (1H, br s, OH), 2.41 (2H, t, $J = 7.5\text{ Hz}$, CH_2CO), 1.63 (2H, m, $\text{CH}_2\text{CH}_2\text{CO}$), 1.5-1.0 (12H, m, $\text{CH}_3(\text{CH}_2)_6$), 0.88 (3H, t, $J = 6.5\text{ Hz}$, CH_3); ^{13}C NMR (50 MHz, CDCl_3 , ppm) δ_{C} 210.1 (CO), 68.2 (CH_2OH), 38.6, 32.0, 29.5, 29.4, 29.4, 29.3, 23.9, 22.8, 14.2; HRMS (ESI^+): m/z 209.1538 (calcd. 209.1517 for $\text{C}_{11}\text{H}_{22}\text{NaO}_2$).

1-Hydroxy-3-phenylpropan-2-one (208c). [177] Purified by LC (Et₂O:PE; yield 71% (0.69 g); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.5-7.1 (5H, m, Ar-H's), 4.29 (2H, s, CH₂OH), 3.73 (2H, s, CH₂Ar), 3.02 (1H, br s, OH); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 207.4 (CO), 132.8, 129.4 (2C), 129.1 (2C), 127.7, 67.8 (CH₂OH), 46.0; HRMS (ESI⁺): *m/z* 173.0573 (calcd. 173.0578 for C₉H₁₀NaO₂).

3-Hydroxy-1,1-diphenylpropan-2-one (208d). [305] Purified by LC (Et₂O:PE-60:40); Rf 0.33; white crystals; mp. 56 °C; yield 70% (0.69 g); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.4-7.1 (10H, m, Ar-H's), 5.09 (1H, s, CH), 4.36 (2H, s, CH₂) 3.19 (1H, br s, OH); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 208.3 (CO), 137.5 (2C), 129.0 (4C), 128.8 (4C), 127.7 (2C), 68.3 (CH₂OH), 60.2; HRMS (ESI⁺): *m/z* 249.0897 (calcd. 249.0891 for C₁₅H₁₄NaO₂).

Methyl 5-hydroxy-4-oxopentanoate (208h). [306] Purified by LC (Et₂O); Rf 0.27; colourless oil; yield 63% (0.36 g); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.33 (2H, s, CH₂OH), 3.69 (3H, s, CH₃), 2.71 (4H, s, CH₂CH₂); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 208.3 (CO), 172.9 (COO), 68.3 (CH₂OH), 52.1, 32.9, 27.6; HRMS (ESI⁺): *m/z* 169.0470 (calcd. 169.0477 for C₆H₁₀NaO₄).

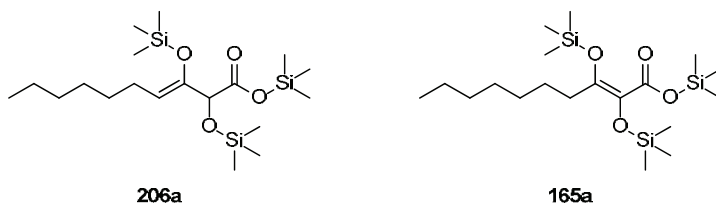
1-Hydroxy-4-(methylthio)butan-2-one (208i). [307] Purified by LC (EtOAc:hexane-55:45); Rf 0.52; white crystals; mp. 46 °C; yield 82% (0.79 g); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 4.29 (2H, s, CH₂OH), 3.09 (1H, br s, OH), 2.9-2.6 (4H, 2×dd, AB-sys., *J* = 10.4, 4.5 Hz, CH₂CH₂), 2.13 (3H, s, CH₃); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 208.3 (CO), 68.7 (CH₂OH), 38.3, 27.8, 15.9; HRMS (ESI⁺): *m/z* 157.0296 (calcd. 157.0299 for C₅H₁₀NaO₂S).

1-Hydroxy-3-(thiophen-2-yl)propan-2-one (208j). Purified by LC (Et₂O: petroleum ether-60:40); Rf 0.31; red oil; yield 81% (0.79 g); ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.24 (1H, dd, *J* = 5.1, 1.3 Hz, CHS), 6.98 (1H, dd, *J* = 5.1, 3.5 Hz, CHC), 6.92 (1H, m, *J* = 3.5, 1.3 Hz, SCHCHCHC), 4.34 (2H, s, CH₂OH), 3.93 (2H, s, CH₂CO), 3.09 (1H, br s, OH); ¹³C NMR (50 MHz, CDCl₃, ppm) δ_C 206.2 (CO), 133.5 (quaternary C), 127.4, 127.3, 125.7, 67.6 (CH₂OH) 39.5 (CH₂); HRMS (ESI⁺): *m/z* 179.0159 (calcd. 179.0143 for C₇H₈NaO₂S).

8.6.3 GC-MS analysis of intermediates of the microwave-assisted hydroxy ketone synthesis

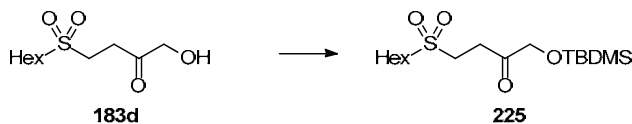
The intermediates from both microwave-assisted hydroxy methyl ketones syntheses were similarly analysed by GC-MS (EI, 70eV). The reaction between octanoyl chloride (**204a**) and TMSE at the presence of triethylamine gave the spectra of trimethylsilyl 2,3-bis(trimethylsilyloxy)dec-3-enoate (**206a**), *m/z* (%) =

418 (0.5%) [M^+], 403 (3) [M^+-Me], 375 (2), 328 (2), 313 (3), 301 (60) [$M^+-COOSiMe_3$], 257 (36), 217 (7), 199 (4), 147 (45), 133 (9), 103 (8), 73 (100) [$SiMe_3^+$]. When the reaction was carried out with two equivalent of TMSE without an additional base, the EI-spectra of the intermediate, trimethylsilyl 2,3-bis(trimethylsilyloxy)dec-2-enoate (**165a**), was following; m/z (%) = 418 (16%) [M^+], 403 (4) [M^+-Me], 375 (4), 333 (1), 301 (22) [$M^+-COOSiMe_3$], 285 (1), 244 (1), 217 (8), 147 (37), 129 (10), 103 (7), 73 (100) [$SiMe_3^+$].



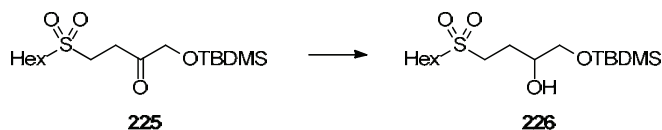
8.7 The transformation of 4-(hexylsulphonyl)-1-hydroxybutan-2-one to 4-(hexylsulphonyl)-2-hydroxybutanal

8.7.1 1-(*tert*-Butyldimethylsilyloxy)-4-(hexylsulphonyl)butan-2-one



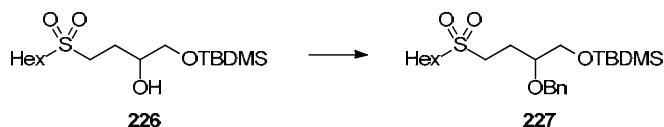
4-(Hexylsulphonyl)-1-hydroxybutan-2-one (**183d**, 1.0 g, 4.4 mmol) was added into solution of *tert*-butyldimethylchlorosilane (0.9 g, 5.7 mmol) and imidazole (0.7 g, 10.9 mmol) in 32 mL dichloromethane at 0 °C. The reaction mixture was stirred at rt for 48 h after which it was quenched with the addition of water (35 mL). This mixture was extracted with DCM (3 × 15 mL), which was washed with brine, dried (Na_2SO_4), filtered, and concentrated. White crystals (**225**, 1.3 g, 3.5 mmol, 85%) were obtained after flash purification (EtOAc:PE-60:40). 1H NMR (200 MHz, $CDCl_3$, ppm) δ_H 4.24 (2H, s, CH_2OSi), 3.27 (2H, t, $J = 6.7$ Hz, $SO_2CH_2CH_2CO$), 3.12 (2H, t, $J = 6.7$ Hz, $SO_2CH_2CH_2CO$), 2.99 (2H, t, $J = 7.9$ Hz, $CH_2CH_2CH_2SO_2$), 2.0-1.7 (2H, m, $CH_2CH_2CH_2SO_2$), 1.6-1.3 (2H, m, $CH_2CH_2CH_2SO_2$), 1.5-1.2 (4H, m, $CH_3CH_2CH_2$), 0.93 (9H, s, $SiC(CH_3)_3$), 0.90 (3H, t, $J = \sim 6.0$ Hz, CH_3), 0.11 (6H, s, $Si(CH_3)_2$); HMRS (ESI $^+$): m/z 373.1859 (calcd. 373.1845 for $C_{16}H_{34}NaO_4SSi$).

8.7.2 1-(*tert*-Butyldimethylsilyloxy)-4-(hexylsulphonyl)butan-2-ol



The solution of ketone (**225**, 1.2 g, 3.6 mmol) in 8 mL ethanol was added dropwise into the ethanol (12 mL) solution of NaBH₄ (0.14 g, 3.6 mmol) at -12 °C. The reduction was carried out at -12 °C for 2 h and at rt for an additional 1 h after which reaction was quenched with the addition of water (30 mL). This mixture was extracted with DCM (3 × 15 mL). The combined organic phase was washed with saturated aqueous NaHCO₃-solution and brine, dried (Na₂SO₄), filtered, and concentrated. White crystals **226** (0.6 g, 1.7 mmol, 48%) were obtained after flash purification (EtOAc:PE, solvent gradient from 20:80 to 40:60). ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 3.9-3.7 (1H, m, CH), 3.67 (1H, dd, one of CH₂OSi), 3.47 (1H, dd, one of CH₂OSi), 3.3-3.1 (2H, 2×m, SO₂CH₂CH₂CH), 2.98 (2H, dd, *J* = 7.9, 8.0 Hz CH₂CH₂CH₂SO₂), 2.53 (1H, d, *J* = 4.0 Hz, OH), 2.1-1.7 (4H, m, CH₂CH₂SO₂CH₂CH₂), 1.6-1.3 (2H, m, CH₂CH₂CH₂SO₂), 1.5-1.2 (4H, m, CH₃CH₂CH₂), 0.91 (9H, s, SiC(CH₃)₃), 0.90 (3H, t, *J* = ~6.0 Hz, CH₃), 0.08 (6H, s, Si(CH₃)₂); HMRS (ESI⁺): *m/z* 375.1993 (calcd. 375.2001 for C₁₆H₃₆NaO₄SSi).

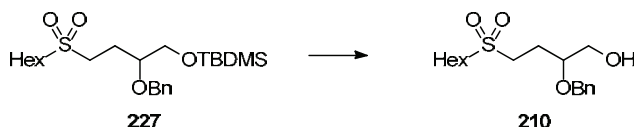
8.7.3 2-Benzyloxy-1-(*tert*-butyldimethylsilyloxy)-4-(hexylsulphonyl)butane



The solution of alcohol (**226**, 0.36 g, 1.0 mmol) in 2 mL of THF was injected into the mixture of NaH (60% in mineral oil, 0.14 g, 3.3 mmol) and THF (5 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. Benzyl bromide (0.3 g, 1.8 mmol) and tetrabutylammonium iodide (0.02 g, 0.04 mmol) were added at a cooled reaction mixture at 0 °C. The reaction was finished after stirring for 60 h at rt. 10 mL of water was added and the mixture was extracted with DCM (3×10 mL). Organic phases were combined, dried (Na₂SO₄), filtered and concentrated to obtain clean product **227** (white crystals, 0.5 g, 1.0 mmol) in quantitative yield. ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.40-7.2 (5H, m, arom. Hs), 4.7-4.4 (2H,

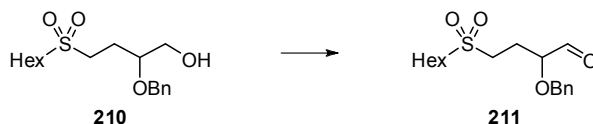
2×d, OCH₂Ph), 3.8-3.5 (3H, 2×m, CH₂CHOCH₂OSi), 3.2-2.9 (2H, m, SO₂CH₂CH₂CH), 2.90 (2H, dd, *J* = 7.9, 8.0 Hz, CH₂CH₂CH₂SO₂), 2.3-1.6 (4H, 2×m, CH₂CH₂SO₂CH₂CH₂), 1.5-1.1 (6H, m, CH₃CH₂CH₂CH₂), 0.90 (9H, s, SiC(CH₃)₃), 0.87 (3H, t, CH₃), 0.06 (6H, s, Si(CH₃)₂); HMRS (ESI⁺): *m/z* 465.2450 (calcd. 465.2471 for C₂₃H₄₂NaO₄SSi).

8.7.4 2-Benzyloxy-4-(hexylsulphonyl)butan-1-ol



The TBDMS protective group was cleaved by dissolving **227** (0.60 g, 1.45 mmol) in the mixture of ethanol (30 mL) and aqueous 1.5% HCl followed by stirring at rt overnight. Solvents were evaporated and the residue was dissolved in EtOAc (25 mL), washed with 25 mL of brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The primary alcohol **210** was obtained after flash chromatography (EtOAc:PE-45:55) as white crystals (0.22 g, 0.7 mmol, 50%). ¹H NMR (200 MHz, CDCl₃, ppm) δ_H 7.5-7.2 (5H, m, arom. Hs), 4.56 (2H, s, OCH₂Ph), 3.93 (1H, very br s, CH), 3.54 (1H, dd, *J* = 9.4, 3.5 Hz, one of CH₂OH), 3.38 (1H, dd, *J* = 9.4, 6.9 Hz, one of CH₂OH), 3.3-3.0 (2H, m, SO₂CH₂CH₂CH), 2.96 (2H, dd, *J* = 7.9, 8.0 Hz, CH₂CH₂CH₂SO₂), 2.55 (1H, br s, OH), 2.2-1.7 (4H, 2×m, CH₂CH₂SO₂CH₂CH₂), 1.5-1.2 (6H, m, CH₃CH₂CH₂CH₂), 0.89 (3H, t, *J* = 7.0 Hz, CH₃); HMRS (ESI⁺): *m/z* 351.1614 (calcd. 351.1606 for C₁₇H₂₈NaO₄S).

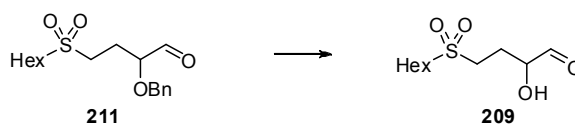
8.7.5 2-Benzyloxy-4-(hexylsulphonyl)butanal



The reaction was carried out under inert atmosphere (N₂). The solution of oxalyl chloride (77 mg, 0.6 mmol) in 0.5 mL of DCM was slowly added into the mixture of DMSO (85 mg, 1.2 mmol) and DCM (0.5 mL) with continuous stirring at -78 °C. After 10 min, the alcohol **210** (180 mg, 0.55 mmol) dissolved in 1 mL of

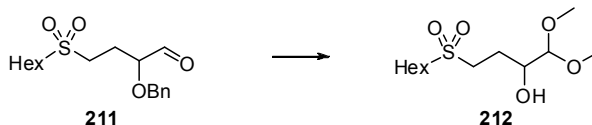
DCM was added dropwise. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h after which triethylamine (278 mg, 2.75 mmol) was added. The reaction was let to warm to room temperature. Equal volumes (10 mL) of water and DCM were poured into the reaction mixture. The organic phase was collected and the aqueous phase was washed with an additional DCM ($2\times 10\text{ mL}$). The combined organic phase was washed once with water (20 mL) and brine (20 mL) after which it was dried (Na_2SO_4), filtered and concentrated. The aldehyde **211** was obtained as white crystals (110 mg, 0.3 mmol, 61%) after the flash chromatographic purification (EtOAc:PE-55:45). $^1\text{H NMR}$ (200 MHz, CDCl_3 , ppm) δ_{H} 9.67 (1H, s, CHO), 7.5-7.2 (5H, m, arom. Hs), 4.67 (2H, q, $J = 11.6\text{ Hz}$, OCH_2Ph), 4.01 (1H, m, CH), 3.2-2.7 (4H, 2 \times t, $\text{CH}_2\text{SO}_2\text{CH}_2$), 2.4-2.0 (2H, m, $\text{SO}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.9-1.6 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_2$), 1.5-1.2 (6H, m, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 0.90 (3H, t, $J = 7.0\text{ Hz}$, CH_3); HMRS (ESI^+): m/z 349.1479 (calcd. 349.1449 for $\text{C}_{17}\text{H}_{26}\text{NaO}_4\text{S}$).

8.7.6 4-(Hexylsulphonyl)-2-hydroxybutanal



The benzyl protected hydroxy butanal **211** (40 mg, 0.12 mmol) was dissolved in THF (1.5 mL). The catalyst Pd/C (10%, 78 mg) was added at $0\text{ }^{\circ}\text{C}$ and hydrogen atmosphere was placed. The hydrogenation reaction was carried out at $3\text{ }^{\circ}\text{C}$ for 27 h. Solid materials was removed by filtering through Acrodisc GHP membrane ($0.45\text{ }\mu\text{m}$) and solvent was removed by nitrogen stream at $-80\text{ }^{\circ}\text{C}$. White crystals (27 mg) were obtained. $^1\text{H NMR}$ and MS analyses showed a mixture of compounds.

8.7.7 4-(Hexylsulphonyl)-1,1-dimethoxybutan-2-ol

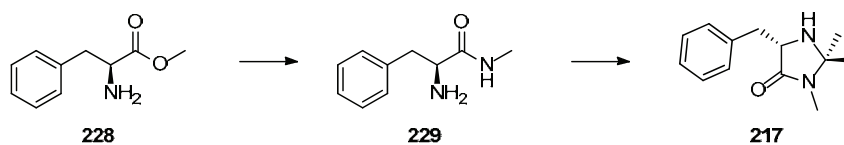


In order to form dimethylacetal, aldehyde **211** (50 mg, 0.15 mmol) and dry methanol (1.5 mL) were first stirred at rt under N_2 -atmosphere for 2 h. This

intermediate was subsequently continued to hydrogenation by addition of Pd/C (10%, 80 mg) and replacement to H₂ atmosphere. The reaction mixture was stirred at 3 °C for 48 h after which solid material was removed by filtering through Acrodisc GHP membrane (0.45 μm). The filtrate was placed at -16 °C and equipped with nitrogen stream for removal of the residual methanol. The product was obtained as white crystals (36 mg). ¹H NMR and MS analyses showed a mixture of compounds.

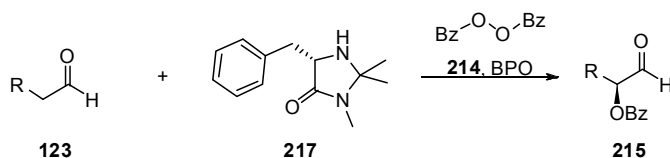
8.8 The organocatalytic α-oxybenzoylation of aldehydes

8.8.1 The preparation of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one



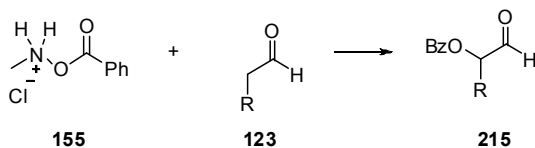
Imidazolidinone **217** was synthesized according to the literature [137]. The solution of MeNH₂ (8.0 M in ethanol, 14 mL) and (*S*)-phenylalanine methyl ester hydrochloride (**228**, 5.0 g, 21.8 mmol) was stirred at room temperature for 20 h. The reaction was quenched by addition of Et₂O (100 mL) followed by the evaporation of volatile components under vacuum. The addition of Et₂O and evaporation was repeated three times to remove excess of MeNH₂ until (*S*)-phenylalanine *N*-methyl amide hydrochloride (**229**) was obtained as a white solid. This amine hydrochloride was treated with saturated aqueous of NaHCO₃ (40 mL) and free amine was extracted with DCM (3 × 40 mL), dried (MgSO₄), filtered, and concentrated. Methanol (50 mL), acetone (16 mL) and *p*-TsOH hydrate (420 mg, 2.2 mmol) were added to this residue and the reaction mixture was refluxed at 65 °C for 62 h, cooled to room temperature and concentrated *in vacuo*. The residue of yellowish oil was purified by column chromatography (EtOAc:PE-95:5) to give **217** as a colourless oil (3.72 g, 17.0 mmol, 78%). IR (CDCl₃) 1718, 1271, 1112 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, ppm) δ_H 7.13-7.26 (5H, m, ArH), 3.73 (1H, dd, *J* = 4.5 Hz, 6.8 Hz, COCH), 3.08 (1H, dd, *J* = 4.5 Hz, 14.1 Hz, PhCHH), 2.94 (1H, dd, *J* = 6.8 Hz, 14.1 Hz, PhCHH), 2.67 (3H, s, NCH₃), 1.19 (3H, s, CH₃CCH₃), 1.09 (3H, s, CH₃CCH₃); HRMS (ESI⁺) *m/z* 219.1491 (calcd. 219.1492 for C₁₃H₁₉N₂O).

8.8.2 General procedure for the organocatalytic α -oxybenzoylation of aldehydes.



BPO (**214**, 100 mol %) was dissolved in THF (containing 8.3 mol % of *p*-methoxybenzene as an internal standard) and cooled to $-10\text{ }^\circ\text{C}$ (acetone/ice bath). Imidazolidinone **217** (20 mol %), (additives) and aldehyde **123** (100 mol %) were added into this mixture. Reactions were usually carried out on a 0.58 mmol scale. After the appointed time a sample was taken, CDCl_3 was added and the ^1H NMR spectrum was recorded. The reaction was quenched by adding EtOAc and saturated aqueous NaHCO_3 solution. Layers were separated and the aqueous layer was extracted twice with EtOAc. Organic phases were combined, dried (MgSO_4), filtrated, and concentrated *in vacuo*. The product **215** was purified by column chromatography and compared with the authentic sample.

8.8.3 The synthesis of α -oxybenzoyl aldehydes using *O*-benzoyl-*N*-methyl hydroxylamine hydrochloride



Control samples were used to determine the conversion and *ee* of the developed organocatalytic method. α -Oxybenzoyl aldehydes **215** were synthesized by applying the literature method [155]. The 0.5 M solution of aldehyde **123** (100 mol %) and *O*-benzoyl-*N*-methyl hydroxylamine hydrochloride (**155**, 100 mol %) in DMSO was stirred at room temperature for 18 h after which the reaction mixture was treated with brine. The product was extracted three times with EtOAc, dried (MgSO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography. After the reduction to diol the 1:1 ratio of enantiomers **215** was determined by HPLC.

3-methyl-1-oxobutan-2-yl benzoate (215a). [155] Yield 25%; Rf 0.39 (Et₂O:PE-30:70); ¹H NMR (400 MHz, CDCl₃, ppm) δ_H 9.59 (1H, s, CHO), 8.04 (2H, d, *J* = 7.7 Hz, ArH), 7.54 (1H, t, *J* = 7.7 Hz, ArH), 7.42 (2H, t, *J* = 7.7 Hz, ArH), 5.01 (1H, dd, *J* = 0.7 Hz, 3.8 Hz, CHOBz), 2.4-2.3 (1H, m, CH), 1.1-1.0 (6H, 2×d, 2×CH₃); ¹³C NMR (100 MHz, CDCl₃, ppm) δ_C 199.3 (1C), 166.6 (1C), 133.9 (1C), 130.2 (2C), 129.7 (1C), 129.0 (2C), 83.0 (1C), 29.7 (1C), 19.3 (1C), 17.7 (1C).

1-oxopentan-2-yl benzoate (215b). [155] Yield 63%; Rf 0.45 (EtOAc:PE-20:80); ¹H NMR (400 MHz, CDCl₃, ppm) δ_H 9.64 (1H, s, CHO), 8.10 (2H, d, *J* = 7.5 Hz, ArH), 7.61 (1H, t, *J* = 7.5 Hz, ArH), 7.48 (2H, t, *J* = 7.5 Hz, ArH), 5.23 (1H, dd, CHOBz), 2.0-1.8 (2H, m, CH₂CH₂), 1.7-1.5 (2H, m, CH₂CH₃), 1.00 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃, ppm) δ_C 198.8 (1C), 166.3 (1C), 133.7 (1C), 130.0 (2C), 129.3 (1C), 128.7 (2C), 78.7 (1C), 31.0 (1C), 18.5 (1C), 13.9 (1C).

1-oxodecan-2-yl benzoate (215c). [155] Yield 56%; Rf 0.31 (Et₂O:PE-30:70); ¹H NMR (400 MHz, CDCl₃, ppm) δ_H 9.64 (1H, s, CHO), 8.10 (2H, d, *J* = 7.6 Hz, ArH), 7.61 (1H, t, *J* = 7.6 Hz, ArH), 7.48 (2H, t, *J* = 7.6 Hz, ArH), 5.22 (1H, dd, CHOBz), 2.0-1.8 (2H, m, CCH₂), 1.6-1.4 (2H, m), 1.4-1.3 (2H, m), 1.3-1.2 (8H, m) 0.87 (3H, t, *J* = 6.5 Hz, CH₃).

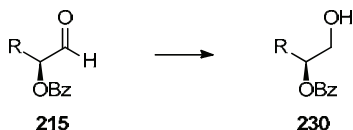
8.8.4 The determination of reaction conversion

Two different analysis methods were considered for monitoring the conversion to α-oxobenzoyl aldehydes **215**. ¹H NMR was used in early experiments for the comparison of the reaction rate from starting material to the product. However, GC-MS (EI) can be used without a removal of reaction solvents (singlet of DCM solvent overlaps with product's signal in ¹H NMR). GC analysis, on the other hand, is suited for volatile products (benzoyl substituent usually increases the boiling point) and the NMR method is suitable for high boiling aldehydes (reactants) since the reaction solvents generally are evaporated before recording. The high boiling point of α-oxobenzoyl-valeraldehyde (**215a**) proved to be a problem in GC-MS analysis as well as the low boiling point of α-oxobenzoyl-decanaldehyde (**215c**) for accurate NMR analysis. Therefore *p*-dimethoxybenzene was used as the internal standard during the measurement of the conversion with NMR.

A general procedure for the analysis of the conversion was following: the standard in a reaction solvent (usually 8.3 mol % = 1/12 part of amount of

aldehyde **123**) was injected into the reaction mixture at the beginning. A sample was taken and dissolved in CDCl₃ and ¹H NMR spectra was recorded. The ratio of integrals of aromatic protons of *p*-dimethoxybenzene and the α-proton of the product **215** was used for the estimation of the conversion.

8.8.5 The determination of enantiomeric excess of α-oxy-benzoylated aldehydes



Aldehyde **215** was dissolved in EtOH and cooled to -10 °C (acetone/ice bath). A solution of NaBH₄ (0.5 M, 120 mol %) was added and stirred at -10 °C for 1 h. After the addition of brine, the product was extracted into EtOAc, dried (MgSO₄), filtered, and concentrated *in vacuo*. The diol **230** was purified by column chromatography. The following HPLC settings were used for 2-benzoyloxydecane-1-ol (**230c**): Rt₁ 37 and Rt₂ 40 min, chiralcel OJ, 1% IPA in hexane, flow rate 0.5 mL/min, 254 nm, and for 2-benzoyloxy-pentane-1-ol (**230b**): Rt₁ 40.5 and Rt₂ 46.2 min, chiralcel OJ, 0.5% IPA in hexane, flow rate 0.5 mL/min, 254 nm. Enantiomeric excess was calculated from the integrated signal values of enantiomers **230**.

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