TALLINN UNIVERSITY OF TECHNOLOGY
DOCTORAL THESIS
31/2020

Oxidative Ring-Cleavage Reactions of Cyclopropanols and their Application for the Synthesis of Bioactive Cyclopeptides

GÁBOR ZOLTÁN ELEK

TAL TECH PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
School of Science
Department of Chemistry and Biotechnology
This dissertation was accepted for the defence of the degree of Doctor of Philosophy in Chemistry 01/06/2020

Supervisor: Prof. Dr. Margus Lopp
School of Science
Tallinn University of Technology
Tallinn, Estonia

Co-supervisor: Dr. Dzmitry G. Kananovich
School of Science
Tallinn University of Technology
Tallinn, Estonia

Opponents: Prof. Dr. Ari Koskinen
Department of Chemistry and Materials Science
Aalto University
Espoo, Finland

Senior Researcher Dr. Uno Mäeorg
Department of Chemistry
University of Tartu
Tartu, Estonia

Defence of the thesis: 28/08/2020, Tallinn

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for doctoral or equivalent academic degree.

Gábor Zoltán Elek

---
signature

European Union
European Regional
Development Fund

Investing
in your future

ISSN 2585-6898 (publication)
ISBN 978-9949-83-572-0 (publication)
ISSN 2585-6901 (PDF)
ISBN 978-9949-83-573-7 (PDF)
Printed by Spin Press

TALLINNA TEHNIKAÜLIKOOL
DOKTORITÖÖ
31/2020

Tsüklopropanoolide oksüdeerivad tsükliavamisreaktsioonid ja nende rakendus bioaktiivsete tsüklopeptiidide sünteesil

GÁBOR ZOLTÁN ELEK

TAL TECH
KIRJASTUS

Contents

List of Publications 6
Author's Contribution to the Publications 7
Introduction 8
Abbreviations 9
1 Literature overview 11
1.1 Aerobic oxidations 11
1.2 Synthetic routes to ketoepoxides (α,β-epoxy ketones) and γ-keto sulfones 13
1.2.1 Synthesis of α,β-epoxy ketones 13
1.2.2 Synthesis of γ-keto sulfones 18
1.3 Cyclopropanols: preparation, structure, reactivity and applications 20
1.3.1 Preparation of cyclopropanols 20
1.3.2 Structure and reactivity of tertiary cyclopropanols 22
1.3.3 Applications of cyclopropane ring cleavage in natural product synthesis 31
1.4 Diversity-oriented synthesis with late-stage modifications 32
1.5 Bioactive peptide targets for natural product synthesis 33
2 Aims of the study 36
3 Results and discussion 37
3.1 Enantioselective one-pot synthesis of α,β-epoxy ketones *via* aerobic oxidation of cyclopropanols (Publication I) 37
3.2 Synthesis of γ-keto sulfones by copper-catalyzed oxidative sulfonylation of tertiary cyclopropanols (Publication II) 45
3.3 Divergent access to histone deacetylase inhibitory cyclopeptides *via* a late-stage cyclopropane ring cleavage strategy. Short synthesis of Chlamydocin (Publication III) 53
Conclusions 63
References 64
Acknowledgements 71
Abstract 72
Lühikokkuvõte 73
Appendix 75
Publication I 75
Publication II 81
Publication III 91
Curriculum vitae 99
Elulookirjeldus 100

List of Publications

The list of author's publications, on the basis of which the thesis has been prepared:

I **G.Z. Elek**, V. Borovkov, M. Lopp, D.G. Kananovich. "Enantioselective One-Pot Synthesis of α,β-Epoxy Ketones via Aerobic Oxidation of Cyclopropanols". *Org. Lett.* **2017**, *19*, 3544-3547.

II Y.A. Konik, **G.Z. Elek**, S. Kaabel, I. Järving, M. Lopp, D.G. Kananovich. "Synthesis of γ-keto sulfones by copper-catalyzed oxidative sulfonylation of tertiary cyclopropanols". *Org. Biomol. Chem.* **2017**, *15*, 8334-8340.

III **G.Z. Elek**, K. Koppel, D.M. Zubrytski, N. Konrad, I. Järving, M. Lopp, D.G. Kananovich. "Divergent Access to Histone Deacetylase Inhibitory Cyclopeptides via Late-Stage Cyclopropane Ring Cleavage Strategy. Short Synthesis of Chlamydocin". *Org. Lett*. **2019**, *21*, 8473-8478.

Author's Contribution to the Publications

Contribution to the papers in this thesis are:

I Carrying out the experiments, major role in manuscript preparation and supporting information compilation (characterisation of intermediates, reaction products)

II Carrying out optimisation experiments, a majority of the scope, participation in manuscript preparation and compilation of supporting information (characterisation of intermediates and reaction products)

III Carrying out the experiments, major role in manuscript preparation and supporting information compilation (characterisation of intermediates, reaction products)

Introduction

The importance of environmentally benign chemical processes dictates the promotion of research on replacing harmful reagents, *inter alia* oxidants, with those exhibiting safety, low cost, excellent chemical performance and selectivity. For this purpose, fine-tuning oxidation conditions might be possible by using a mild, transition metal catalysis inspired by enzymatic reactions of nature. Atmospheric oxygen, as the most abundant and cheapest oxidant, is perhaps the most attractive choice as an oxidation reagent.

Cyclopropane derivatives, due to their internal ring strain, could be considered as preferred substrates in such transformations. A remarkable feature of the cyclopropane chemistry is that mild conditions are required for the cleavage of the cyclopropane ring, tolerated by a wide range of functional groups and making the approach very useful for the synthesis of natural products and bioactive molecules. The most common transformations of cyclopropanols are ring cleavage reactions, which are sensitive to catalysts and can proceed in a chemo- and regioselective manner, depending on the used conditions. Still, there is plenty of room for improvement, for expanding the scope of the methods and for introducing stereoselectivity into the methodology.

In the present work, we expand for the first time on the paradigm of diversity-oriented synthesis operating with pluripotent functional groups on the chemistry of cyclopropanes, thus making it suitable for the synthesis of compound libraries according to drug discovery programmes.

The thesis focuses on the development of environmentally benign, bio-inspired, transition metal-catalysed, aerobic oxidative ring-cleavage methodologies for tertiary cyclopropanols, with their subsequent application for the diversity-oriented synthesis of histone deacetylase inhibitory cyclopeptides.

The obtained results expand the applications of easily available cyclopropanols in organic synthesis, including asymmetric transformations, and demonstrate the potential of the developed approach in drug discovery and medicinal chemistry.

Abbreviations

AA	Amino acid
acac	acetylacetonate
Acyha	2-amino-7-(1-hydroxycyclopropyl)heptanoic acid
AODA	2-amino-8-oxodecanoic acid
AOE	(2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid
ASU	2-aminosuberic acid
BHT	Butylated hydroxytoluene
Boc	*tert*-Butyloxycarbonyl
CBz	benzyloxycarbonyl
CD	Circular dichroism
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DIPEA	N,N-Diisopropylethylamine
DMC	Dimethyl carbonate
DME	Dimethoxyethane
DNA	Deoxyribonucleic acid
dr	diastereomeric ratio
ee	enantiomeric excess
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
FG	Functional Group
FGI	Functional Group Interconversion
Fmoc	Fluorenylmethyloxycarbonyl
HAT	Histone Acetyl Transferase
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HDAC	Histone deacetylase
HOBT	Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
LOC	Limiting Oxygen Concentration
MALDI	Matrix-Assisted Laser Desorption/Ionization
MO	Molecular Orbital
MTBE	Methyl tert-butylether
NEM	N-ethylmorpholine
NHC	Nitrogen-heterocyclic carbene
NMR	Nuclear magnetic resonance
OEP	2,3,7,8,12,13,17,18-octaethylporphyrin
PDL	Poly-D-leucine
PIFA	Phenyliodine bis(trifluoroacetate)
PG	Protecting group

PLL	Poly-L-leucine
SET	Single Electron Transfer
TBAF	Tetra-*n*-butylammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TEA	Triethylamine
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TM	Transition Metal
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
UV	Ultraviolet
VB	Valence Bond
ZBG	Zinc Binding Group
Π_n	Overall yield (over *n* steps)

1 Literature overview

In the development of chemical processes, requirements for their environmentally benign "green" character have continuously increased. Therefore, chemical transformations with higher safety, minimal waste formation and operational simplicity are favoured.[1]

Oxidations are among the most frequently used methods in the chemical industry.[2] Historically, the application of harmful chromates, inorganic manganese salts in stoichiometric quantities, which display high toxicity and poor atom economy, was common.[3] With the emerging need to use "green chemistry" principles, the previously developed protocols have to be replaced by less harmful ones.

Aerobic oxygen is the most eco-friendly oxidizing agent, reacting under mild conditions (including in living organisms), offering broad applicability and not producing detrimental waste products.[4]

The first part of the literature overview introduces the advantages of aerobic oxidations. Implementation opportunities of atmospheric oxidation, in connection with mild oxidative pathways, will be covered in the following section. Then the focus will shift to cyclopropanol chemistry,[5] working on further possible directions of synthetic method development. Finally, synthetic utility of value-added cleavage products will be briefly summarised in the last chapters.

1.1 Aerobic oxidations

Pure molecular oxygen is the best reagent from the point of view of green chemistry: in most cases, the oxidant is fully incorporated into the reaction product, and thus the formation of waste from the oxidant is prevented. Even if O_2 incorporation is not complete, only non-toxic by-products with low molecular weights (e.g. water) are formed, hardly affecting the environmentally benign character of the oxidation. Safety issues have not been fully dealt with because of the need for organic solvents which are flammable and dangerous together with oxygen gas, especially in large-scale manufacturing.[6] However, the concentration of oxygen can be either adjusted by using gaseous mixtures with lower oxygen content or by using natural air (containing 21% oxygen).

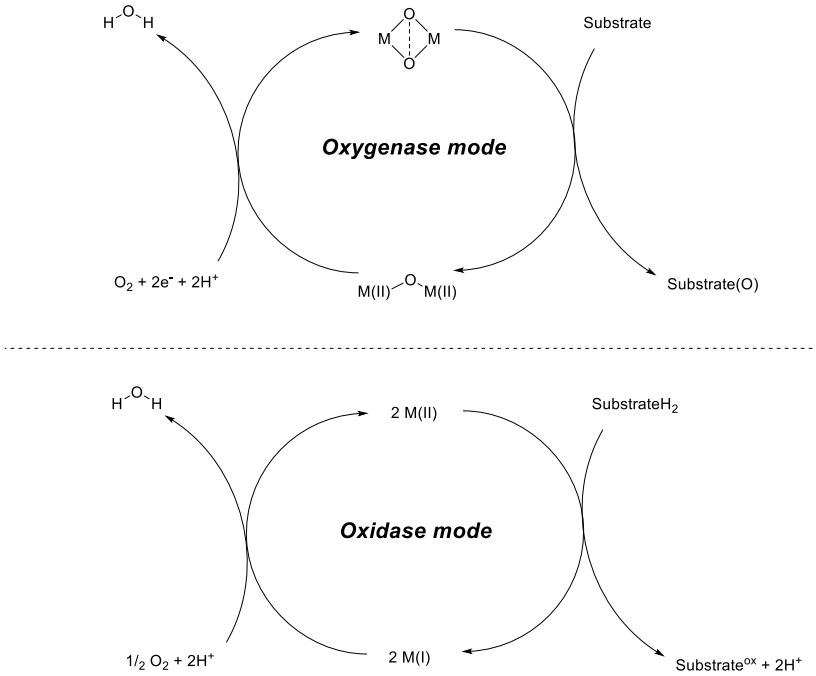
One can claim that aerobic oxygen is the greenest solution for oxidation, since air is the most abundant gas, is inexpensive and is simple to utilise. Despite all of the mentioned advantages, oxidations with air are usually avoided in industry.[7] The optimised scaled-up processes still have difficulties with safety, even with the application of aerobic oxygen, and therefore it is necessary to adjust the limiting oxygen concentration (LOC) often, leading to low reaction rates. Below the LOC limit, no combustion is possible.[8] Large-scale oxidations also require very efficient gas-liquid mixing. So, flow mode oxidative methodologies were developed in order to avoid problems in mass and heat transfer.[9]

For these reasons, increasing attention has been paid to the application of flow chemistry in scale-up processes,[10] increasing the attractiveness of air oxidation processes in general.

A possible drawback of aerobic oxidation is auto-oxidation, which takes place without catalytic assistance.[11] Despite several developed practical processes, general negative features of noncatalytic aerobic oxidation - low reaction rates and a lack of selectivity - remain. Therefore, numerous studies have been devoted to the development of catalytic, aerobic oxidation methodologies aiming for selectivity and shorter reaction times.[12]

The principal classification of the catalytic oxidation methods is based on the catalyst status: homogeneous or heterogeneous. These two distinct groups have both advantages and disadvantages: homogeneous catalysis offers improved accessibility of the dissolved complex that facilitates oxidation, while heterogeneous catalysts are more easily separable from the reaction mixture. A bridging compromise of these two classes can be created with the application of nanocatalysis (catalysts grafted on nanoparticles).[13] Approaches where the design of the catalytic system is inspired by biocatalysts from nature are very promising. There are a great number of well-known natural oxygen carriers in blood and muscle:[14] the cytochromes,[15] containing Fe metal ions, enzymes, containing zinc ions,[16] and metalloproteins, with copper[17] or manganese[18] ions. All offer biomimetic design opportunities to achieve selective oxidative transformation with a broad substrate range.

Catalysed aerobic oxidations can be divided into two main groups, in terms of mechanism (**Scheme 1**). Molecular oxygen can react in the "oxygenase" or "oxidase" mode: named after the natural enzyme catalysed reaction.[19]



***Scheme 1**. Oxygenase and oxidase pathways of aerobic oxidations (M indicates metal)*

Oxygenase-type catalysts are responsible for the direct oxygen atom incorporation into the target molecule. Further classification is possible by considering how many oxygen atoms are inserted. In monooxygenase-type activity, one oxygen atom is converted to the oxidized substrate, whilst the second one is reduced to water. In the case of dioxygenase-type action, the incorporation of dioxygen occurs, with no waste product formation from the oxidant.[20] In contrast to the oxidative behaviour of oxygenase-type processes, oxidase-type reactions result in the formation of reduced by-products (water or peroxide), while the substrate's oxidation does not necessarily incorporate oxygen.[21]

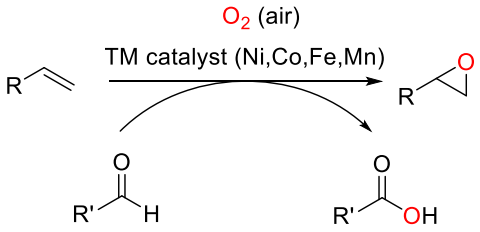
The bio-inspired molecular oxygen-containing manganese porphyrinoid complexes are more stable than their iron-containing counterparts.[22] The range of successful biomimetic oxidations of these complexes includes a number of different epoxidations, allylic oxidations and C-H functionalisation reactions, including traditionally unreactive alkyl and aryl positions and the oxidation of heteroatoms.[23]

In contrast to the above-mentioned methodologies, oxidations catalysed by copper require precise synthetic planning due to the common selectivity (*inter alia,* allylic oxidation vs. epoxidation)[24] and reactivity problems.[25] Therefore, copper-catalysed oxygenations are less commonly used.

Oxidative reactions are mostly classified according to the functional groups which are oxidised during the transformation. The other classification is made by the oxidation products, thus showing the targets of the transformations. In the present dissertation, the second division is used to highlight the methods connected with the targeted compounds, e.g. epoxides and sulfones.

Previously, the oxidative synthesis of epoxides catalysed by manganese or copper catalysts[26,27] excluded the oxidation methods with aerobic oxygen due to its poor selectivity.[28] To overcome this gap, Mukaiyama et al. have developed a transition metal-catalysed procedure utilising atmospheric dioxygen in the presence of a co-reductant, a secondary alcohol or a bulky aldehyde (**Scheme 2**).[29] The actual oxidant, which is formed in the oxidative cycle, is a transition metal acyl-peroxo complex.[23a] Despite the development of a robust protocol, several necessary improvements have been implemented in order to broaden the substrate scope, including enantioselective variants.[30] Despite all efforts, it was shown that this method is not usable to get ketoepoxides: all attempts appeared to be inefficient,[31] showing a need for a different approach.

To the best of our knowledge, there are no precedents for aerobic oxidations giving sulfones with the desired TM (Mn and Cu) catalysts.



***Scheme 2**. Mukaiyama epoxidation*

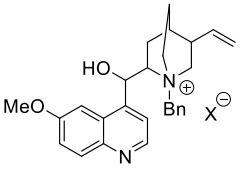
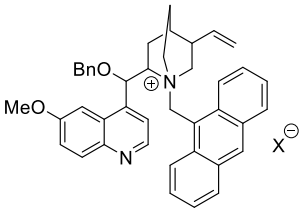
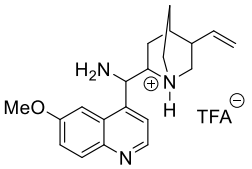
1.2 Synthetic routes to ketoepoxides (α,β-epoxy ketones) and γ-keto sulfones

1.2.1 Synthesis of α,β-epoxy ketones

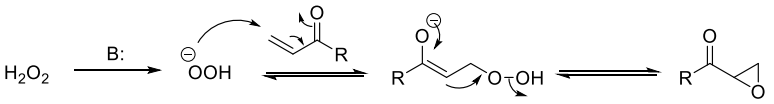
Epoxy ketones are among the most versatile building blocks for the preparation of fine chemicals (pharmaceuticals and agrochemicals) and other valuable compounds, including enantiomeric forms of chiral compounds.[32] In addition to that, the epoxy ketone moiety is a broadly presented structural unit in several natural bioactive products and their synthetic drug leads.[33]

The first methods for the synthesis of enantiomeric epoxy ketones (since the seminal report from the Wynberg group)[34] exploited the reactivity of the electron-deficient enone double bond towards a hydroperoxide anion through a Weitz-Scheffer reaction. This transformation includes a hydroperoxide anion addition (formed by the basic, chiral quaternary ammonium salt) to the activated double bond of the vinyl ketone, giving a β-keto adduct, followed by an intramolecular nucleophilic displacement, leading to the desired epoxy ketone group, although with low enantioselectivity (**Scheme 3**).[35]

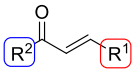
Previous works

Group	***Source of enantioselectivity***	***ee (%)***	***Comments***
Wynberg (1976)		20-35	Low enantioselectivity Only chalcones
Julia-Colonna (1982)	Poly-L-AA	>90	Narrow scope Experimental inconveniences
Lygo (1998)		70-90	Limitations (Alkyl groups)
List (2013)		98-99	Broadened scope Minor limitations (alkyl vinyl ketones)

Weitz-Scheffer epoxidation mechanism:



Summary (Limitations up to date):



R^1 = Aryl, Alkyl, FG-substituent, H?
R^2 = Aryl, EWG, Alkyl, FG-substituent?

Scheme 3*. Previous key works on asymmetric Weitz-Scheffer epoxidation and scope limitations*

Several improvements have been introduced in order to increase the enantioselectivity of the asymmetric epoxidation and to extend the scope of applicable substrates under operationally simple conditions. Successful methodologies were found for chalcone-type or activated α,β-unsaturated ketones by electron-withdrawing groups.[36] The contributions were mainly based on the application of cinchona alkaloid-derived organocatalysts/phase-transfer catalysts[37] or on the utilisation of synthetic enzymes (poly-amino acids).[38] At the outset, Wynberg envisioned the deprotonation possibility with basic cinchona alkaloids, with the hope of an additional asymmetric induction. However, the achieved enantioselectivities were in the range of 20-35% *ee*.[39] A few years later Julià et al. developed a methodology that replaced the alkaloid-derived catalyst with synthetic enzymes, namely poly-L-alanine, and later with several analogues (poly-L-leucine, poly-L-neopentylglycine etc.). The designed oligopeptides were attractive mimics to the metal ion-containing biocatalysts.[38a] This significant improvement raised the enantioselectivity of the oxidation in several cases over 90%. Systematic evaluation of the conditions of the developed protocol (known as Juliá-Colonna epoxidation) predicted future directions for improvement in the field (e.g. the dependence of stereoselectivity on the degree of polymerisation of the synthetic enzyme).[38b] The initial Juliá-Colonna epoxidation was conducted in a tri-phase system, in the presence of an inorganic base and a peroxide in the aqueous segment, an immiscible organic solvent, and eventually the catalyst itself as an insoluble, separate phase. The experimental inconveniences derived from the original tri-phasic conditions (long reaction times and tedious work-up procedures) motivated researchers to develop new variants with the use of soluble/insoluble immobilised catalysts (poly-L-leucine, most abundantly) and conditions employing one organic solvent, in which the enone substrate and the organic base dissolve.[40] To simplify the operational procedure, the original inorganic bases were replaced by amidine-type organic bases, such as DBU by the Roberts group.[41]

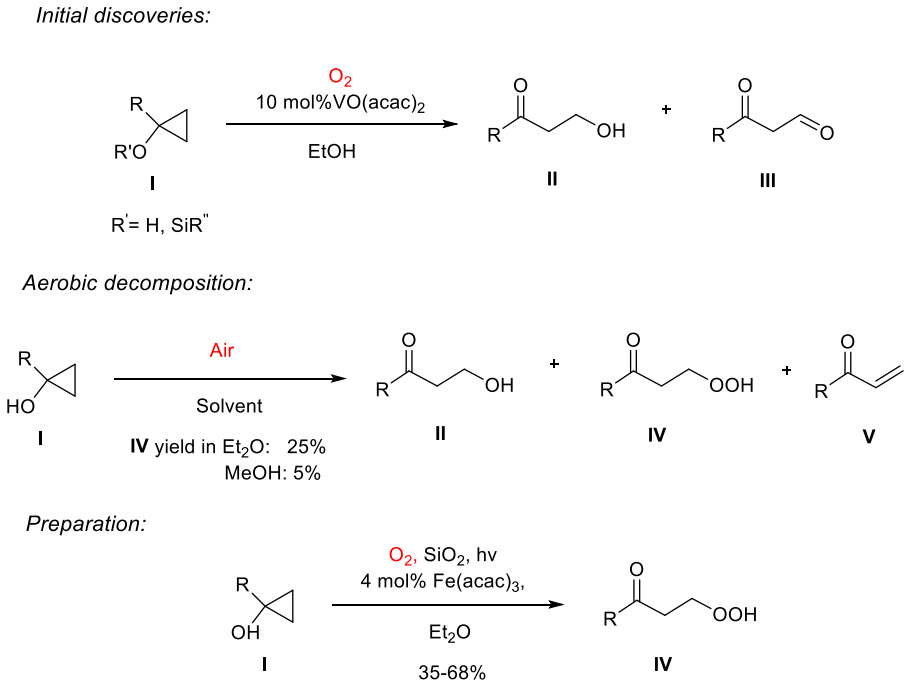
In later research, cinchona-type alkaloid-modified organocatalysts further improved the performance of the epoxidation. Unlike the catalysts used by Wynberg[34,39], the Lygo group introduced phase-transfer catalysts in which the 9-anthracenylmethyl substituent of quinuclidine nitrogen was used instead of the benzyl group. Further changes with the benzyl protection of the secondary alcohol unit widened the scope of epoxidized substrates and increased enantioselectivites up to 90% *ee*.[42] Fine-tuning of the elaborated phase-transfer catalytic protocols (e.g. modifying the applied base) by several research groups[43] resulted in a slight improvement in stereoselectivity (95% *ee*), although a limitation on the substrate scope, especially with those bearing alkyl substituents adjacent to the carbonyl group, still remains a challenge.

Different cinchona alkaloid-derived catalysts were prepared with the secondary alcohol functionality replaced by an amino group suitable for covalent aminocatalysis.[37b] The List group developed asymmetric variants of epoxidation of the carbonyl compounds with a broadened scope of applicable substrates (including an extended list of successful alkyl substituents at the enone double bond[44a], and some functional group-bearing substituents adjacent to the unsaturated motif[44b]).[44] In most cases, the enantiopurities of the desired products were exceptional, but with a varying range of product yields (40-90%), especially in the presence of functional groups. Alkyl vinyl ketone epoxidation failed when using the elaborated method.

The contributions of developed chiral ligand – metal peroxide-based complexes[45] will not be discussed in the present literature overview.

It can be concluded, as a result of intensive research, that vast improvements were made with cinchona alkaloid-based organocatalytic and phase-transfer catalytic reactions in transformations of enones to ketoepoxides, affording enantioselectivity up to 98-99% *ee*, high yields and a broad selection of substrates. A remaining synthetic challenge is to enable the use of enolisable substrates (e.g. alkyl vinyl ketones) and some problematic functional groups R^2. In most studies, R^2 substituents are limited to a small number of aryl and alkyl groups, with no information about substrate tolerance to epoxidation (**Scheme 3**). Among others, simple vinyl alkyl ketones fail to afford the desired epoxide product due to a lack of reactivity[37a,40] or as a result of an accompanying aza-Michael reaction with the organocatalyst itself.[44b]

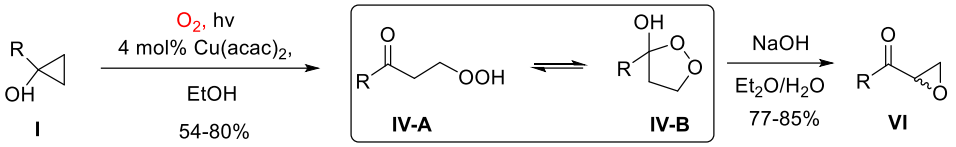
To overcome the problem arising from the insufficient reactivity of the enone double bond, oxidative ring cleavage of the cyclopropanol moiety to afford the peroxyketone intermediate (the same as in Weitz-Scheffer reaction) is envisioned. This transformation could be achieved by oxidation with molecular oxygen. In a seminal work by Kirihara et al., they discovered that vanadyl acetylacetonate ($VO(acac)_2$) catalyses the ring-opening of cyclopropanols with oxygen.[46] This discovery was followed by the investigation of Blanco et al., who noticed the formation of β-peroxyketone (**IV**) among the oxidation products in the reaction catalysed by $Fe(acac)_3$ for the first time (**Scheme 4**).[47]



***Scheme 4**. Seminal works on the preparation of peroxyketones*

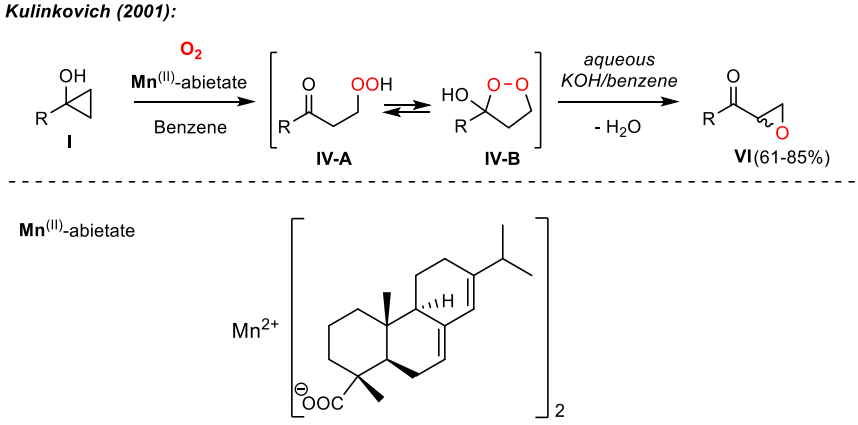
The yields were improved up to 84% by replacing ferric acetylacetonate with cupric acetylacetonate ($Cu(acac)_2$) at the same loadings.[48] It is worth mentioning that a critical point of this transformation is the equilibrium of peroxyketones with their cyclic hemiacetal form. The possibility of synthesizing epoxy ketones directly from β-peroxy adducts according to the Weitz-Scheffer reaction was envisioned by the same authors

(**Scheme 5**). According to the literature source, the scope of the transformation is limited only to bicyclo[n.1.0]alkan-1-ols.



***Scheme 5**. Alternative preparatory pathway to epoxy ketones from cyclopropanols*[48]

Kulinkovich and co-workers substantially improved Blanco's method by finding that Mn(II) salts (abietate or acetylacetonate) are capable of catalysing the desired cyclopropane ring cleavage reaction, as in the case of the previous contributions[47,48] with decreased catalyst loadings (1-1.5 mol%). Furthermore, the developed protocol was merged into a one-pot setup, extending the scope of mono- and disubstituted tertiary cyclopropanols, thus providing an increased overall yield (61-85%) of the resulting aliphatic and arylaliphatic epoxy ketones. The shortcoming of this methodology is the application of flammable and toxic benzene as a solvent under a pure oxygen gas atmosphere.[49] However, this work opened up attractive alternatives for overcoming the problem of the traditionally unreactive alkyl vinyl ketones as epoxidation substrates by using cyclopropanols (**Scheme 6**).



***Scheme 6**. Synthesis of epoxy ketones via the Kulinkovich route*

It can be concluded, that the development of the cyclopropanol approach has resulted in a simple methodology for the preparation of different epoxy ketones and the scope of using cyclopropanol precursors has also been broadened. This approach was used in natural product synthesis, e.g. insect pheromones.[50] A problem that remains is that no asymmetric versions have been developed so far that yield chiral epoxy ketones.

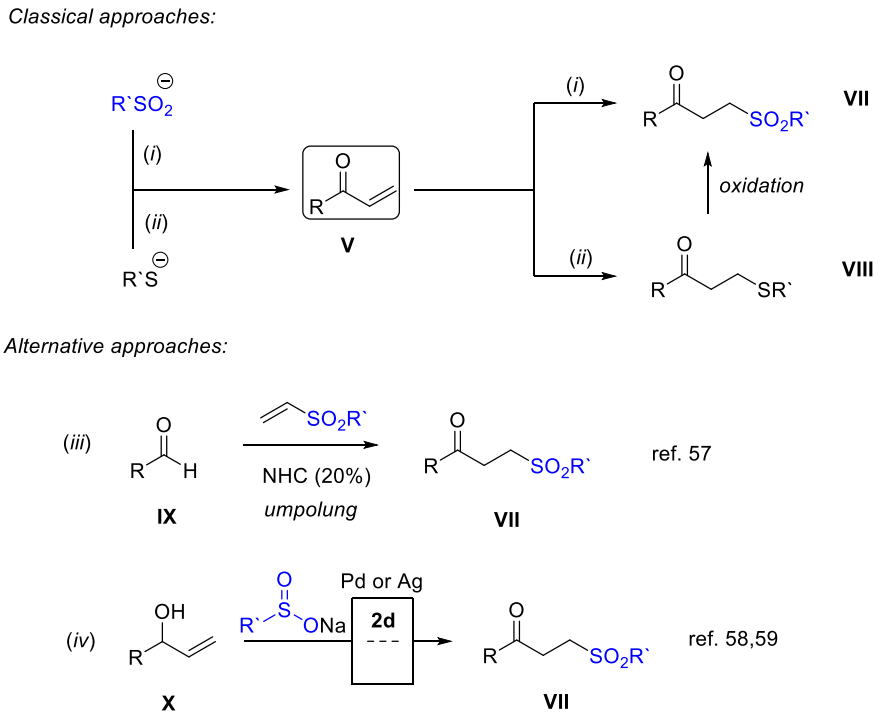
To summarise, several methodologies have been developed to synthesise epoxy ketones, including enantioselective variants, e.g. utilising cinchona alkaloid-derived organocatalysts and synthetic enzymes, although each demonstrated its own drawback, e.g. limited substrate range or low (or absence of) stereoselectivity. Therefore, the aerobic oxidative ring cleavage of cyclopropanols could be a useful supplement to avoid

the shortcomings and scope limitations of these previously described methodologies if an enantioselective cyclopropanol ring cleavage approach to yield enantioenriched peroxyketone intermediates or the corresponding asymmetric epoxides were elaborated.

1.2.2 Synthesis of γ-keto sulfones

Several fine chemicals, including pharmaceuticals and agrochemical agents, bear keto sulfone groups as their key structural fragments. For that reason, a considerable interest in the synthesis of keto sulfones has arisen.[51] The sulfone group is believed to be a carbonyl bioisostere pharmacophore warhead.[52] From a synthetic viewpoint, sulfones are relevant intermediates in C-C bond formation reactions, including the Julia olefination and Ramberg-Bäcklund reaction.[53]

The conventional pathways for the synthesis of keto sulfones (**VII**) usually consist of (*i*) the addition of nucleophilic sulfinate anions to Michael acceptor α,β-unsaturated ketone[54] and (*ii*) the addition of nucleophilic thiol/thiolate species to the same acceptor, followed by the subsequent oxidation of the sulfa-Michael adduct (**VIII**) to sulfone[55,56]. Some other approaches have been developed quite recently, including (*iii*) the Stetter reaction between aldehydes and α,β-unsaturated sulfones,[57] and (*iv*) catalytic transformations (with Pd/Ag catalysis),[58,59] starting with allylic alcohols (*via* the formation of α,β-unsaturated ketone intermediate *in situ*) (**Scheme 7**).



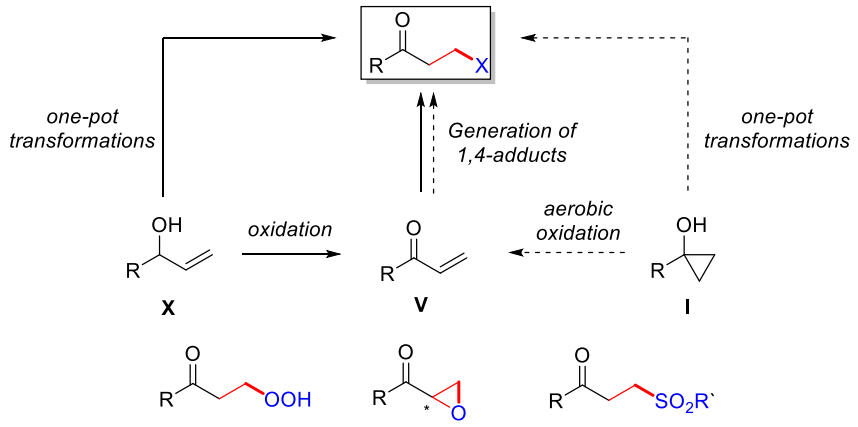
***Scheme 7**. Possible synthetic pathways to sulfones*

First, it should be considered whether the starting sulphur-motif is readily oxidised to sulfone or an additional oxidation step prior to the C-S bond formation is needed. In the above-mentioned pathway (*ii*), the initial reagent is in a reduced state compared to the target sulfone, and therefore additional oxidation is required to complete the synthesis.[55,56,60] In most cases, a co-oxidising agent, peroxide[61] or peracid,[62] is necessary due to the insufficient reactivity of molecular oxygen, in defiance of green chemistry principles.

The pathways (*i*), (*iii*) and (*iv*) are more facile, because there is no need for the additional oxidant. The carbene-catalysed Stetter reaction (*iii*) involves a nucleophilic species (Breslow-intermediate) derived from aldehyde (**IX**)),[63] as a result of "umpolung". This attacks the electrophilic vinyl sulfone and yields the target γ-keto sulfone. A disadvantage of this methodology, despite its elegant chemistry, is the need for an external base to generate carbene from the salt precursor.

The pathway (*i*) via a hetero-Michael addition[64] is a well investigated and documented way to generate β-Michael adducts from α,β-unsaturated ketones, *inter alia* γ-keto sulfones[54]. Eventually, the synthetic route (*iv*) exploits the oxidative potential of transition metal (palladium/silver) catalysis to form enone[58] or similarly oxidised species (in the case of a silver catalyst).[59] While the Pd-catalysed route affords a broader scope, including alkyl-substituted allylic alcohols; with the use of pure oxygen gas, Ag-catalysis operates under aerobic conditions, although with a limited scope involving only aromatic substituents.

A common feature of the above-mentioned reaction pathways is the fact that a vast number of them proceed through the Michael acceptor vinyl ketone (**V**). The enone intermediate is often obtained by the oxidation of allylic alcohol (**X**). Therefore, enone **V** acts as a precursor for a great number of 1,4-adducts (β-Michael adducts). Not only the γ-keto sulfones, but also the previously introduced chiral α,β-epoxy ketones were synthesised following this manner, suggesting the need to explore new routes to keto sulfones from cyclopropanols[65] (**Scheme 8**).

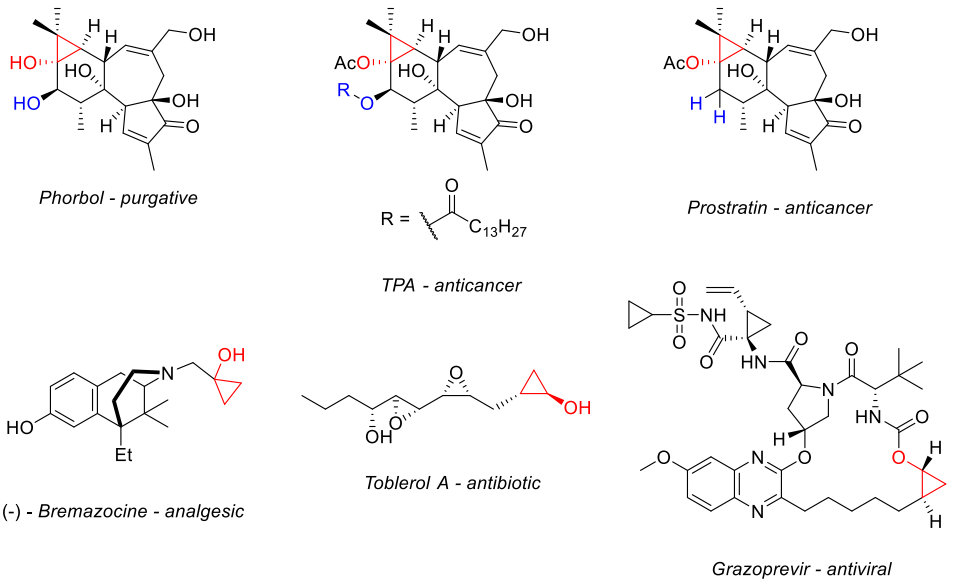


Scheme 8. *Investigated and unexplored synthetic pathways to 1,4-adducts of enones*

1.3 Cyclopropanols: preparation, structure, reactivity and applications

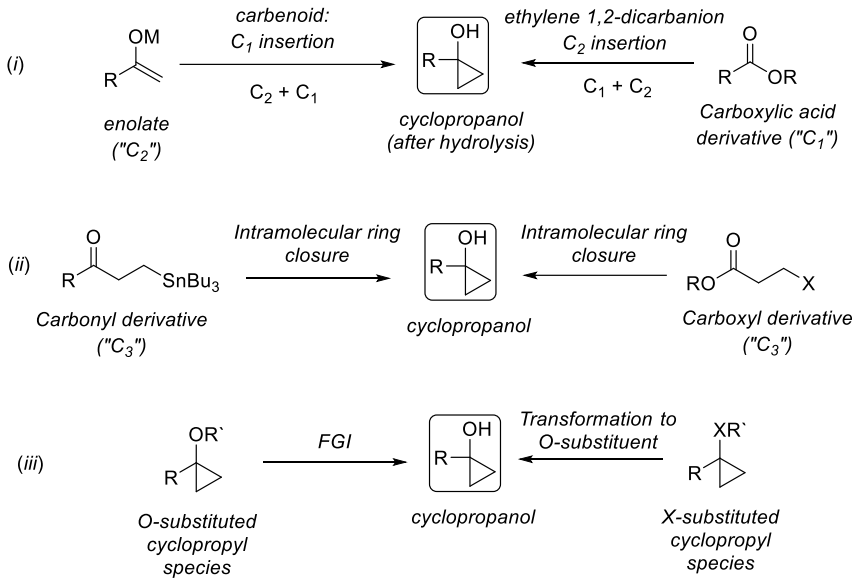
1.3.1 Preparation of cyclopropanols

Cyclopropanes are three-membered carbocycles with elevated energy due to their internal ring strain. Heteroatomic substituents (e.g. OH and OR) at the ring possess a π-electron-donating character and consequently enhanced reactivity with electrophilic reagents and oxidants.[66] Furthermore, the cyclopropanol structural subunits can be found in a number of bioactive natural products (**Scheme 9**).[67] Therefore, the synthesis of cyclopropanols has received notable attention.



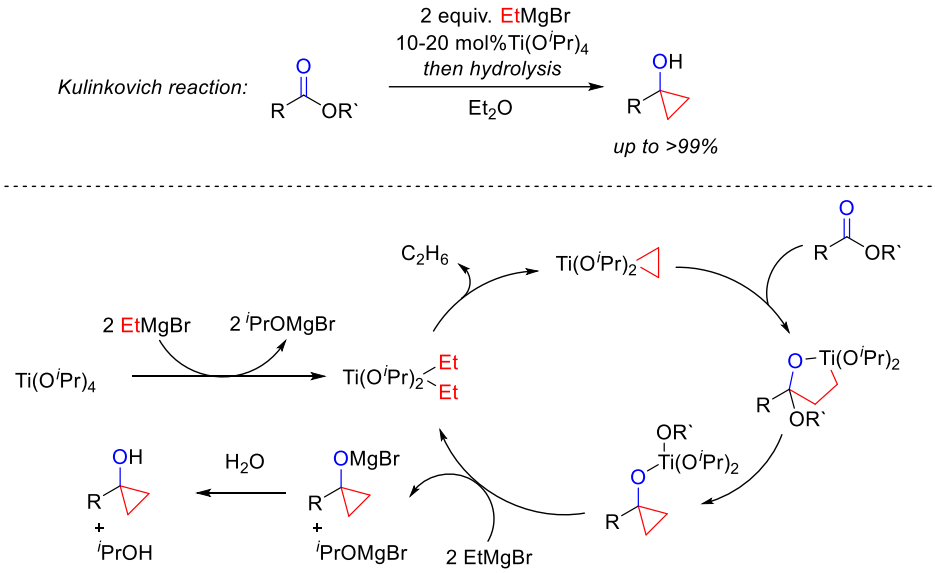
***Scheme 9**. Some natural products containing a cyclopropanol motif*[68]

A great deal of information regarding the synthesis of cyclopropanols has appeared in literature and has been summarised in several comprehensive reviews.[69,67] The preparative procedures can be classified according to the substrate structure and the carbocyclic ring formation method in the following manner: (*i*) cyclopropanation of enol derivatives (C_2+C_1 approach) and carboxylic acid derivatives (C_1+C_2 approach), (*ii*) intramolecular ring closure/contraction, and (*iii*) interconversion of readily available carbocyclic precursors. As a result, a wide variety of starting materials can be used for the synthesis of tertiary cyclopropanols (**Scheme 10**).



Scheme 10. *Synthesis of tertiary cyclopropanols*

The first possibility (*i*) is to employ a two-carbon ("C_2") precursor, usually enol derivatives (e.g. metal enolates) as a starting material. Thus, enolate reacts with a one-carbon ("C_1") carbenoid precursor, yielding cyclopropanols after hydrolysis.[70] The common reaction conditions are analogous to the seminal Simmons-Smith cyclopropanation.[71] Using this convenient methodology, cyclopropanols with multiple substituents in moderate to high yields can be synthesised. According to an alternative approach, "C_1" precursors, such as carboxylic acid derivatives, react with "C_2" precursors (such as corresponding ethyl Grignard reagents), resulting in cyclopropanes via the *in situ* generation of ethylene 1,2-dicarbanion equivalents. A simple and efficient variant of that approach is the Kulinkovich reaction (**Scheme 11**).[72] This protocol involves the use of the mentioned "C_1" and "C_2" precursors in the presence of catalytic amounts of $Ti(O^iPr)_4$. With this methodology, cyclopropanols can be synthesised almost in quantitative yields. The mechanism of this transformation was proposed by Kulinkovich, and involves the *in situ* generation of titanacyclopropane species, performing a stepwise double alkylation of an ester carbonyl group, i.e. acting as a synthetic equivalent of ethylene 1,2-dicarbanion.[73]



***Scheme 11**. Simplified mechanism of the Kulinkovich cyclopropanation*

The Kulinkovich reaction serves as the most successful methodology to synthesise a variety of cyclopropanols from easily available starting materials and demonstrates a simple experimental protocol. Several improved modifications, including asymmetric variants,[74,68] and the increased scope of cyclopropane derivatives[75] have been developed in addition to the original methodology.

The intramolecular ring closure reactions with three-carbon ("C_3") unit,[76] and the transformations involving the assembled cyclopropane scaffold[77] are outside the scope of present thesis and therefore are not discussed here.

1.3.2 Structure and reactivity of tertiary cyclopropanols

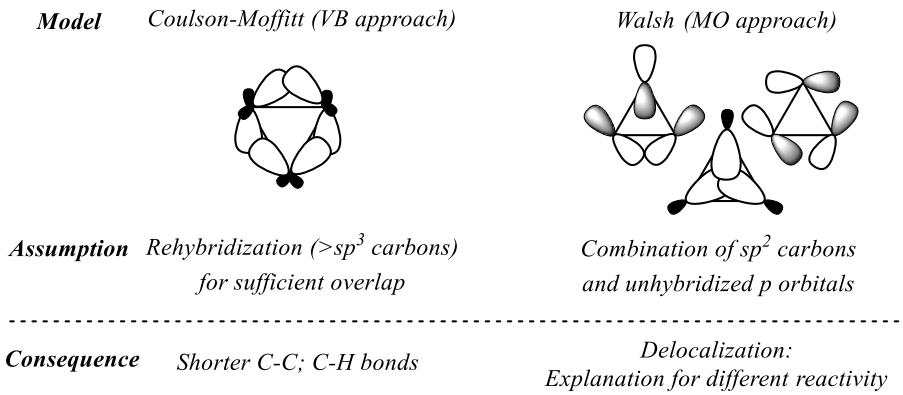
The observation that according to their reactivity cyclopropanes somewhat resemble olefins was linked with their unique structural features.[78] Within the cyclopropane ring, each carbon-carbon covalent bond is capable of reacting as an olefinic double bond.[5] The non-ideal geometry for sp^3 carbons causes a strained structure of the ring and changes the common bonding properties. The behaviour of cyclopropane bonds can be rationalised through the theoretical models of Coulson-Moffitt and Walsh.

The Coulson-Moffitt model describes the consequences of the hybridisation adjustment (rehybridisation) from poorly overlapping sp^3 orbitals. For improved overlapping, an increased *p*-character of the C-C bonds and an increased *s*-character of C-H bonds have to exist. The known chemical properties of cyclopropanes are in good agreement with the described model, manifesting in slightly shorter C-C and C-H bonding in cyclopropane compared to the aliphatic hydrocarbons.[79,80] The additional consequence of the rehybridisation results in elevated energy in the electrons and therefore increased reactivity.

However, the difference between the ring strain of cyclopropane and cyclobutane (~1 kcal/mol) indicates the presence of a possible extra stabilisation in cyclopropanes. The Walsh model proposes the formation of cyclopropane from three sp^2 methylene groups and six unhybridised carbon *p*-orbitals. Consequently, one delocalised MO is

created with high overlap inside the ring, whilst two degenerated orbitals are formed via overlapping outside the carbocycle. Besides that, computational studies confirm that theory and NMR spectroscopy reveal the presence of electron delocalisation as a ring current, shifting nuclear resonance upfield.[81-83]

It may be concluded that cyclopropane bears a non-ideal geometry and has a strained structure, with shortened C-C and C-H bonds compared to the aliphatic hydrocarbons. Delocalisation inside the ring provides extra stabilisation to the ring, and therefore different reactivity than the cyclobutane with similar strain energy (~1 kcal/mol difference). So, the two introduced models complement each other (**Scheme 12**).

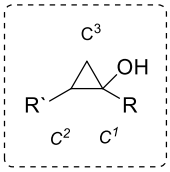


***Scheme 12**. Structural properties of cyclopropanes*

The ring strain is one of the main driving forces dictating the chemical properties of cyclopropanes. The main transformation pathways are the ring cleavage of the three-membered carbocyclic system[84] and/or rearrangement to a larger ring structure with decreased strain energy.[85] Fine-tuning of the reactivity of cyclopropane derivatives can be achieved *via* the attachment of substituents with different electronic natures to the ring. The donor OH-substituent provides enhanced reactivity to cyclopropanols compared to the parent cyclopropanes. Due to its *p*-electron releasing feature, cyclopropanols: (*i*) are susceptible to SET from the lone pair of the oxygen, leading to radical transformations and, (*ii*) have an increased tendency of a heterolytic cleavage of the cyclopropane ring.[66] The reactivity patterns of cyclopropanols are summarised below.

The cyclopropanol ring cleavage reactions can be divided into three groups, in terms of (*i*) which C-C bond of the ring is cleaved, (*ii*) what mechanism is involved in the cleavage step and (*iii*) what mode of activation is used in the ring opening reaction (**Scheme 13**). Due to the enormous number of cyclopropanol ring cleavage reactions discovered so far, only the most elegant and those having direct connection to the dissertation will be discussed here.[69,86,87] The synthetic interest in ring opening reactions is justified by their high regioselectivity, mild reaction conditions and the broad scope of functional group tolerance.

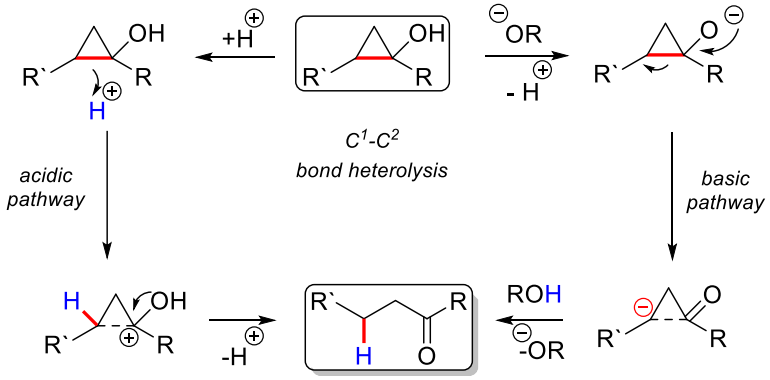
Reactivity patterns of cyclopropane ring cleavage



Mechanism	*Mode of activation*	*Reactive intermediate*	*Scheme*
C^1-C^2 heterolysis	acidic/basic	carbocation/homoenolate	**14**
C^1-C^2 homolysis	radicals/TM	β-oxo radical	**15-17**
C^1-C^3 heterolysis	TM/halogen	homoenolate	**20**
C^1-C^2 + C^1-C^3 cleavage	copper/lead/misc. oxidant	β-oxo radical + homoenolate misc. adduct	**18-19, 21-22, 24**

***Scheme 13**. Summary of cyclopropane ring cleavage reactivity patterns*

The C-C bond cleavage of cyclopropanols with the following rearrangement to carbonyl compounds in acidic or basic media has been known since their first preparation and was reviewed as early as the 1960s-70s.[69,84] The cleavage of the cyclopropane ring occurs in a heterolytic manner, forming either a protonated cyclopropane or a homoenolate, both pathways catalysed either by a base or an acid (**Scheme 14**). The transformation was used for the introduction of a ketone motif to natural product skeletons. Due to very recent advances, the use of mild basic conditions (e.g. $Mg(OMe)_2$ base), leaving more sensitive functional groups intact[88], made the approach even more attractive and suppressed the racemisation of chiral ketone products. It is worth noting that this heterolytic pathway can proceed via cleavage of either C^1-C^2 or C^1-C^3 bonds, and therefore it might give a mixture of products.

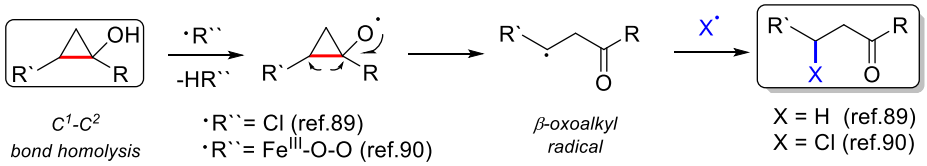


***Scheme 14**. C-C heterolytic bond cleavage mediated by an acid or a base.*

Besides heterolytic pathways of bond cleavage, bond scission *via* homolysis can occur. It has been found in a seminal work that 1,2-disubstituted cyclopropanols are cleaved at the most substituted bond (C^1-C^2) in hot chloroform and CCl_4 yielding ketones.[89] The authors suggested a radical pathway, initiated by the hydrogen atom abstraction to form a cyclopropyloxy radical, which, due to its instability, rearranges to β-oxoalkyl

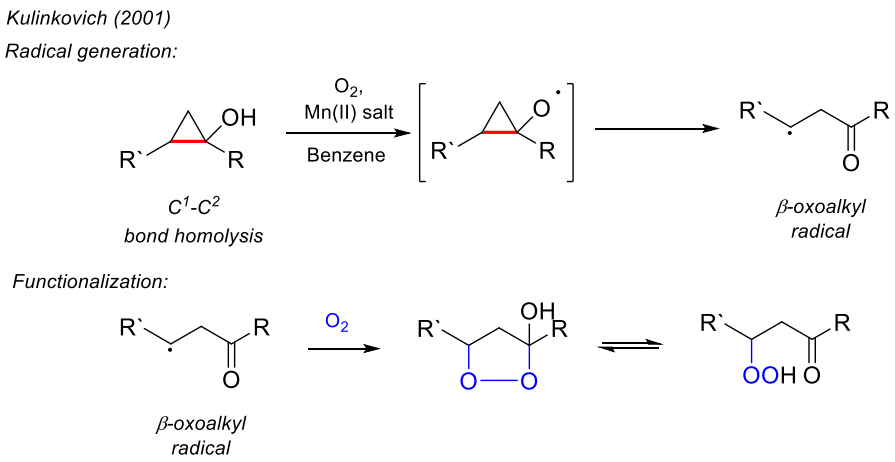
species, susceptible to radical recombination. This observation has opened up new opportunities to obtain functionalised ketones in the β-position (e.g. X=Cl) (**Scheme 15**).[90] Furthermore, transition metal-catalysed radical oxidative cleavage reactions with different catalysts bearing the proper oxidation state (Fe(III), Cr(VI), V(V), Mn(II), Mn(III), Cu(II), Pb salts, etc.) have been investigated.[91]

The homolytic C^1-C^2 bond cleavage reaction has significant biological importance, as the irreversible covalent deactivation of methanol oxidase enzyme presumably occurs by the same mechanism.[92]



***Scheme 15**. C^1-C^2 homolytic bond cleavage mediated by free radicals*

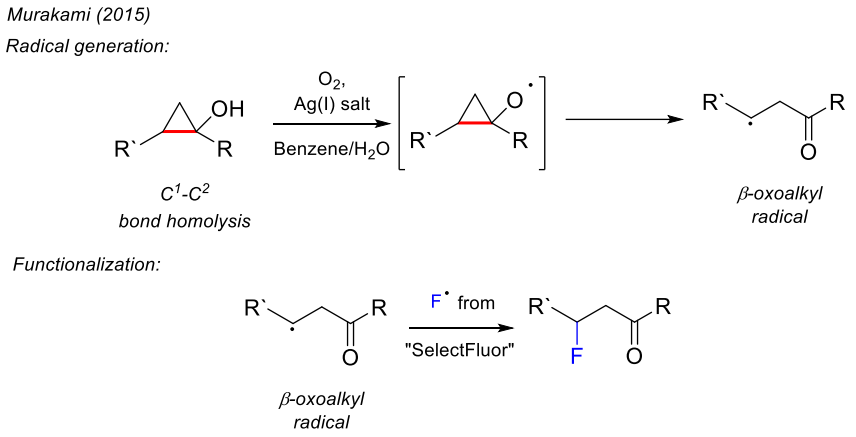
The developed methodology with versatility of accessible intermediates and products has been applied to the synthesis of valuable bicyclic and heterocyclic intermediates in multi-step chemical synthesis.[93] The possibility of the oxidative preparation of peroxy and epoxy ketones with the assistance of Mn-salts was mentioned in the previous chapter (**Scheme 16**).[49,50]



***Scheme 16**. C^1-C^2 bond homolysis with Mn(II)-salts for peroxyketone synthesis*

Significance of Mn(II) and Mn(III) catalysts has been demonstrated in numerous studies on cyclopropanol ring cleavage reactions in order to obtain functionalised β-oxo-adducts.[94] Numerous synthetically useful targets (e.g. 1,6-diketones),[95] as well as important bioactive compounds e.g. oxindoles or phenantridines were obtained.[96]

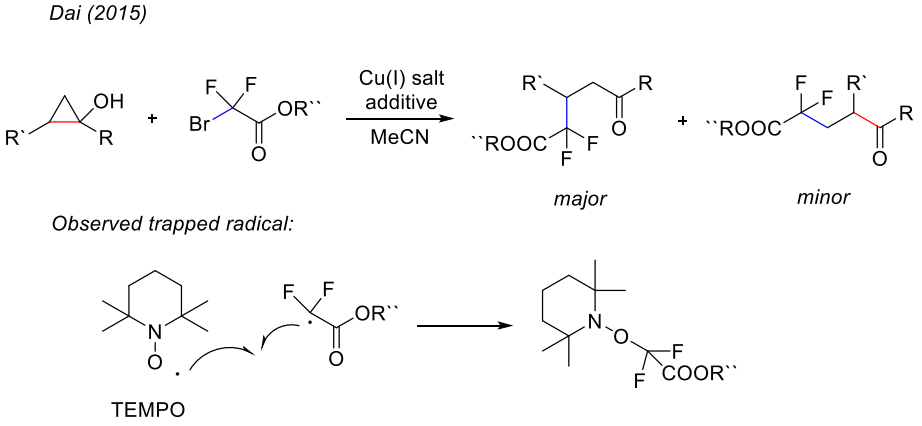
Additionally, a fluorine atom can also be introduced to the β-position of ketone via a silver-mediated C^1-C^2 bond cleavage strategy (**Scheme 17**).[97]



Scheme 17. *Fluorination of* β-position via *C^1-C^2 homolytic bond cleavage*

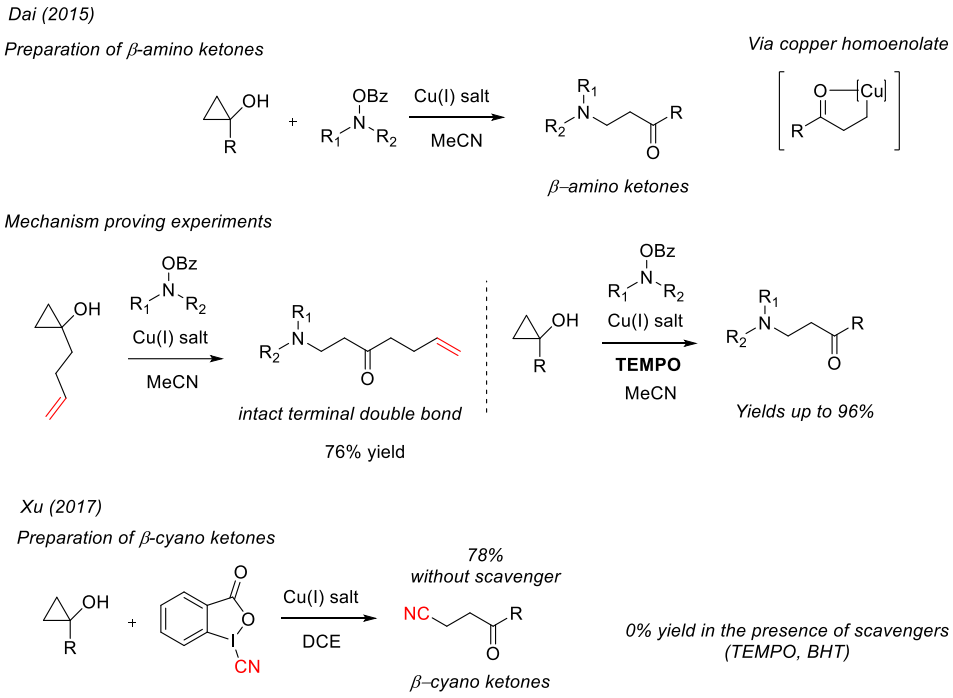
Most of the cleavage reactions which are performed with the assistance of copper salts demonstrate interesting mechanistic features. The nature of the C^1-C^2 bond cleavage was proved by radical trapping experiments with the application of well-known radical scavengers, such as TEMPO or BHT.

As a representative example, Dai and co-workers incorporated fluorinated scaffolds via cross-coupling reactions including copper(I) salts for ring cleavage.[98] The radical nature of the developed methodology was proved with the addition of a TEMPO scavenger (**Scheme 18**). As the diminished reaction rate and lack of conversion does not fully support the radical mechanism, the presence of a TEMPO-fluorinated adduct was observed by ^{19}F NMR spectroscopy. It is important to mention that disubstituted cyclopropanols under the established reaction conditions not only afford C^1-C^2 cleavage products, but also a cross-coupled product in minor quantity. This fact hints that a cleavage at the least substituted bond of the disubstituted cyclopropanol also occurs.



Scheme 18. *Proof of the presence of a radical C^1-C^2 bond cleavage*

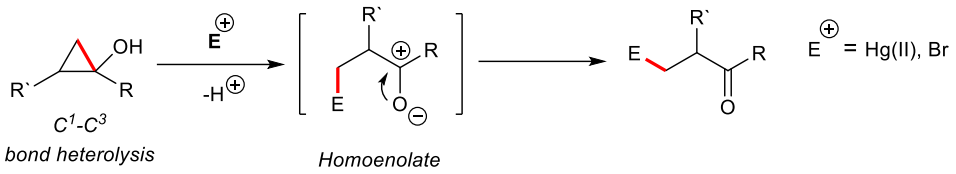
The following copper-catalysed ring cleavage examples provide rough conclusions about the mechanistic nature of the reaction. First, the Dai group studied the transformation to β-amino compounds from cyclopropanols.[99] They proposed a mechanism with the formation of a copper homoenolate intermediate, due to the absence of a radical addition to the terminal double bond. Furthermore, the presence of TEMPO did not inhibit the reaction (**Scheme 19**). The Xu group investigated β-cyano adduct formation from cyclopropanols and concluded that the presence of radical scavengers (TEMPO, BHT etc.) inhibits the reaction (**Scheme 19**).[100]



***Scheme 19**. Copper-mediated cyclopropanol ring cleavage reactions and relevant mechanistic studies*

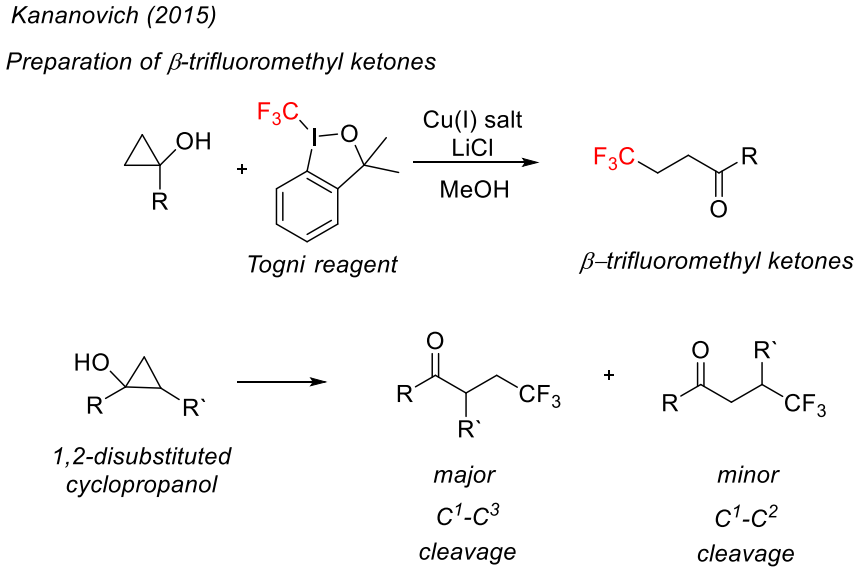
In a later report, Dai's group used cyclopropanol ring cleavage for the synthesis of diverse δ-ketoesters and γ-butyrolactones.[101] However, they have now proposed the possibility of a different, copper-homoenolate intermediate besides the β-oxoalkyl radical, therefore providing an explanation for a non-selective scission mechanism, besides a sole C^1-C^2 bond cleavage. This proposal also supports the participating co-existence of the cleavage of the least substituted bond.

The occurrence of a ring cleavage at the least substituted bond (C^1-C^3) was also discovered in early examples, where the reacting halogen or metal prefers the least substituted site for electrophilic attack (**Scheme 20**).[69] In this manner, regioisomeric β-oxoalkyl ketones can be synthesized.



***Scheme 20**. C¹-C³ heterolytic cleavage*

Kananovich and co-workers developed a copper-catalysed methodology for the C^1-C^3 bond cleavage in cyclopropanols and a direct introduction of the trifluoromethyl group to the β-position of the forming carbonyl compound, by using a Togni reagent.[102] They observed that the cleavage of 1,2-disubstituted cyclopropanols may proceed through two parallel mechanisms: *via* an electrophilic C^1-C^3 cleavage (copper homoenolate), leading to α-alkyl ketone, and *via* a homolytic C^1-C^2 (β-oxoalkyl radical) cleavage, leading to regioisomeric β-CF_3 functionalised ketones (**Scheme 21**).

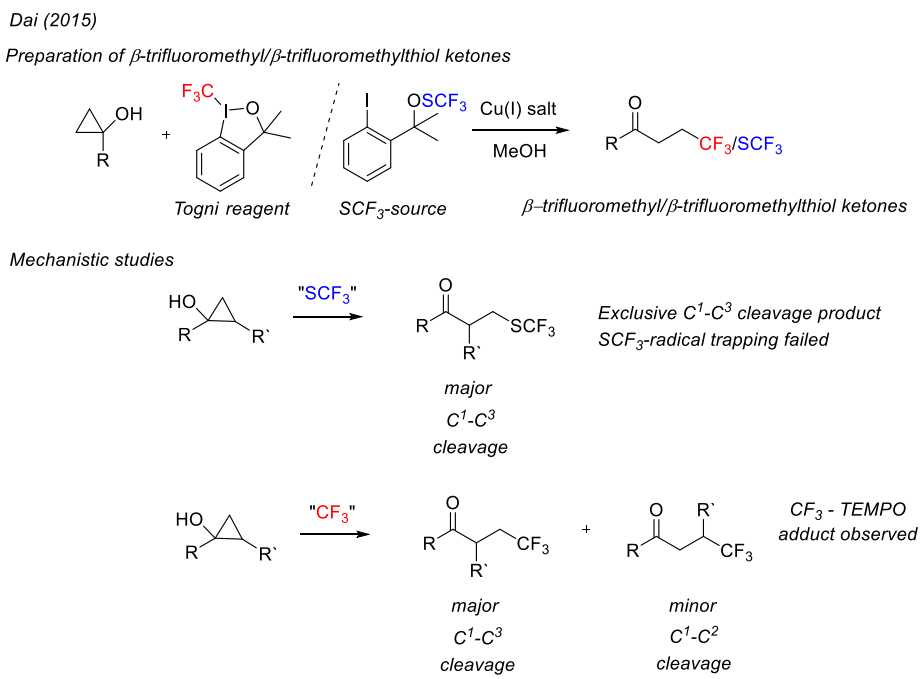


***Scheme 21**. Preparation of CF_3-substituted ketones via a cyclopropane ring cleavage*

The Dai group independently developed the same transformation to access β-trifluoromethyl and additionally β-trifluoromethylthio ketones. SCF_3 transfer was found to be more regioselective in favour of a C^1-C^3 cleavage, while the CF_3 transfer proceeds in a non-selective manner (**Scheme 22**).[103] In the case of trifluoromethyl radicals, interception with a TEMPO scavenger was successful, while in the case of SCF_3 transfer, trapping the SCF_3 radical was unsuccessful.

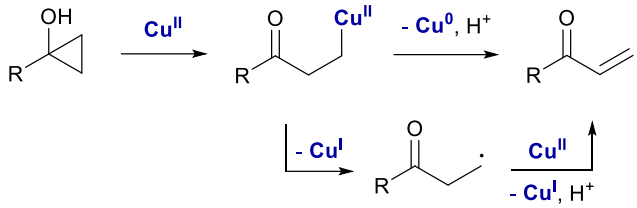
As a further development of the method, Kananovich et al. have demonstrated the possibility of trifluoromethylation of cyclopropanols without the need for an inert atmosphere and by using a more available Langlois reagent (and similar sulfinate salts) as a source of the CF_3 group.[104] According to these experiments and NMR studies, they stated that, although radicals are present, they inefficiently participate in the C^1-C^2

cleavage pathway, but instead take part in the formation of copper (II) or copper (III) species. This verifies the previously proposed mechanism.[102]



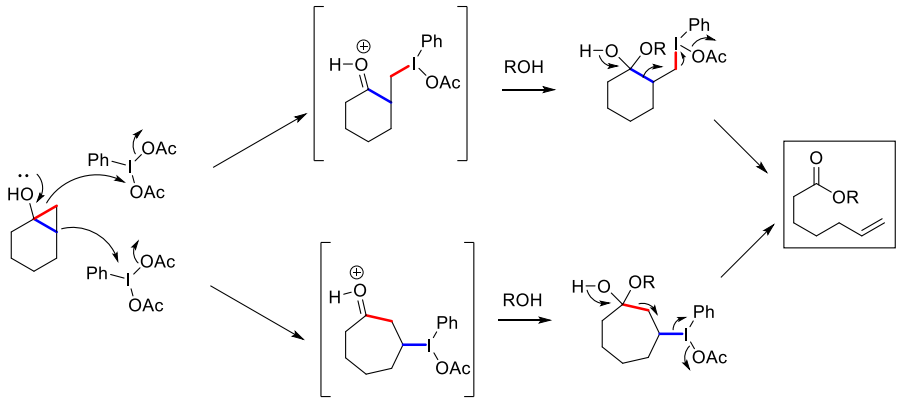
***Scheme 22**. Parallel mechanistic studies on CF_3/SCF_3 functionalisation*

In addition to the acid/base-catalysed cyclopropane ring cleavage, transition metals (Mn, Ag and Hg) were well-described examples showing the difference between homo- and heterolytic mechanisms to demonstrate regioselectivity. However, the cleavage reaction with copper did not proceed in a selective fashion due to the applied conditions. It was observed that both pathways have a β-oxoalkyl radical and a β-metaloketone (homoenolate equivalent) intermediate participating.[98-99, 101-104] Several copper-catalysed electrophilic ring cleavage reactions yielded a vinyl ketone by-product.[101] It was proposed that its generation can be accomplished via one- and two-electron transfer pathways (**Scheme 23**). First, the electrophilic cleavage leads to an organocopper compound, which undergoes Cu-C bond homolysis to generate a β-oxoalkyl radical, which is oxidised by copper(II) species to yield an enone. The second possibility is a reductive elimination of Cu(0) to yield a vinyl ketone. The vinyl ketone's presence as a plausible intermediate instead of being a sole by-product should not be excluded, and was verified in the case of trifluoromethylation, where inefficient reactivity according to classic Michael-addition protocols was reported.[105]



***Scheme 23**. Plausible pathways to generate an enone by-product/intermediate in copper-catalysed cyclopropanol cleavage reactions*

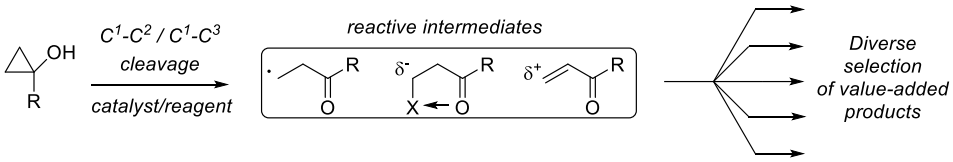
It has also been found that besides the previous examples regarding the non-selective cleavage of cyclopropanols, Pb(IV) acetate cleaves both C^1-C^2 and C^1-C^3 bonds.[106] Considering the toxic impact of Pb salts, it can be replaced by some hypervalent iodine reagents, e.g. $PhI(OAc)_2$, being also capable of oxidative fragmentation of the cyclopropanol and yielding valuable carboxylic acid products or their esters (**Scheme 24**).[107]



***Scheme 24**. Oxidative fragmentation of cyclopropanols with $PhI(OAc)_2$*

Heterolysis of the C-O bond in activated cyclopropanols (where the OH is transformed into a leaving group with increased heterolytic potency, e.g. sulfonate) proceeds usually *via* a C^2-C^3 bond cleavage through an allylic cation intermediate.[108] Only in a special case, when the cyclopropanol bears a strongly electron-donor geminal substituent, may the transformation proceed with the retention of the cyclopropane ring. In this case, nucleophilic displacement occurs.[109,110]

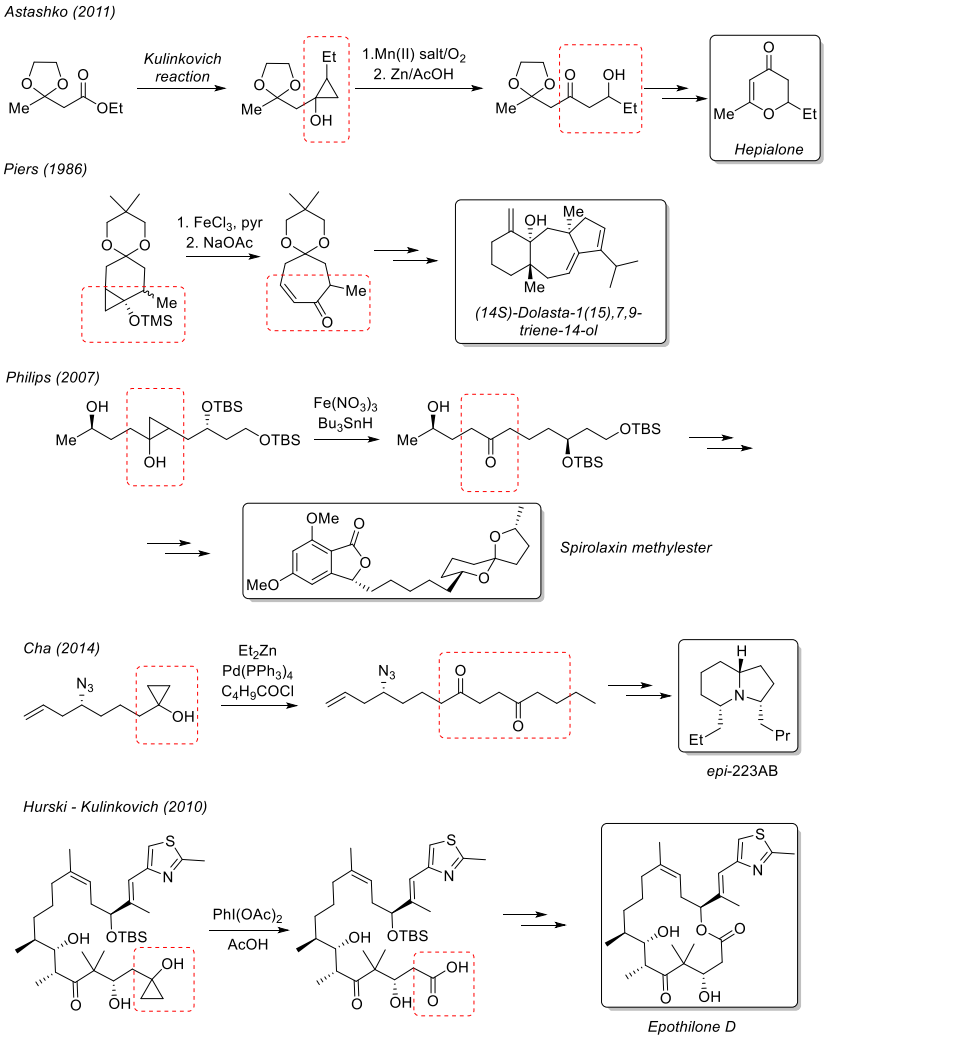
It may be concluded that the chemistry of cyclopropanols offers a broad spectrum of possibilities affording diverse valuable beta-substituted ketones under mild conditions with a wide scope of tolerant functional groups. In the case of ring cleavage reactions regarding 1,2-disubstituted cyclopropanols, conditions must be carefully selected to achieve the necessary regioselectivity. This is the reason why cyclopropane chemistry has become increasingly popular in terms of valuable C_3 synthons in the synthesis of natural products and bioactive compounds (**Scheme 25**).



***Scheme 25**. Cyclopropanols as C_3-synthons in the synthesis of valuable β-functionalised carbonyl compounds*

1.3.3 Applications of cyclopropane ring cleavage in natural product synthesis

The incorporation and subsequent cleavage of the cyclopropane[111]/cyclopropanol[112] motif in the total synthesis of natural products has gained increasing interest. The utility of cyclopropanol ring cleavage reactions has been demonstrated in a broad assortment of key intermediates used in the synthesis of bioactive compounds. (**Scheme 26**).[113-119]



***Scheme 26**. Representative examples of cyclopropanol intermediates in the total synthesis of natural products*

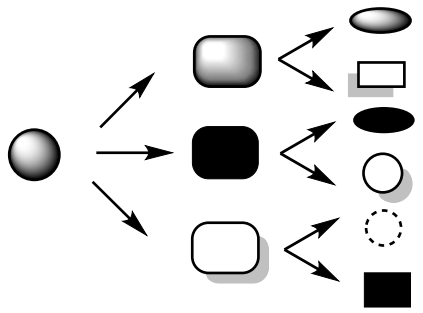
1.4 Diversity-oriented synthesis with late-stage modifications

Quite recently, the engine for drug discovery-driven medicinal chemistry lay in the synthesis of libraries of small molecules bearing moderately diverse structural features.[120] Because of the rather low efficiency of these screenings, the demand has arisen for the broadening of the boundaries of the existing synthetic chemical space via the incorporation of the novel paradigm of a diversity-oriented synthetic approach to endogenous-like bioactive compounds.[121]

The concept relies on creating different aspects and levels of diversity, providing accessibility of various functionalities/scaffolds to the expanded bioactive chemical space. The criteria of diversity are established by four different aspects: (*i*) *appendage diversity* provides variability via different structural moieties within a molecule, (*ii*) *functional group diversity* describes the alteration possibility of the functional groups required to be installed, (iii) *stereochemical diversity* allows the creation of distinct stereoisomers, and (iv) *skeletal diversity* enables the installation or transformation of scaffolds within the molecule.[122] The completion of the diversity criteria can be fulfilled *via* the incorporation and utilisation of pluripotent functional groups in synthetic precursors.

The pluripotency of a functional group describes the ability to be simply transformed into various functional groups. Consequently, these groups are responsible for achieving the above-mentioned aspects of selectivity for accessing a broad bioactive chemical space for diversity-oriented synthesis (**Scheme 27**).

Diversity-oriented synthesis

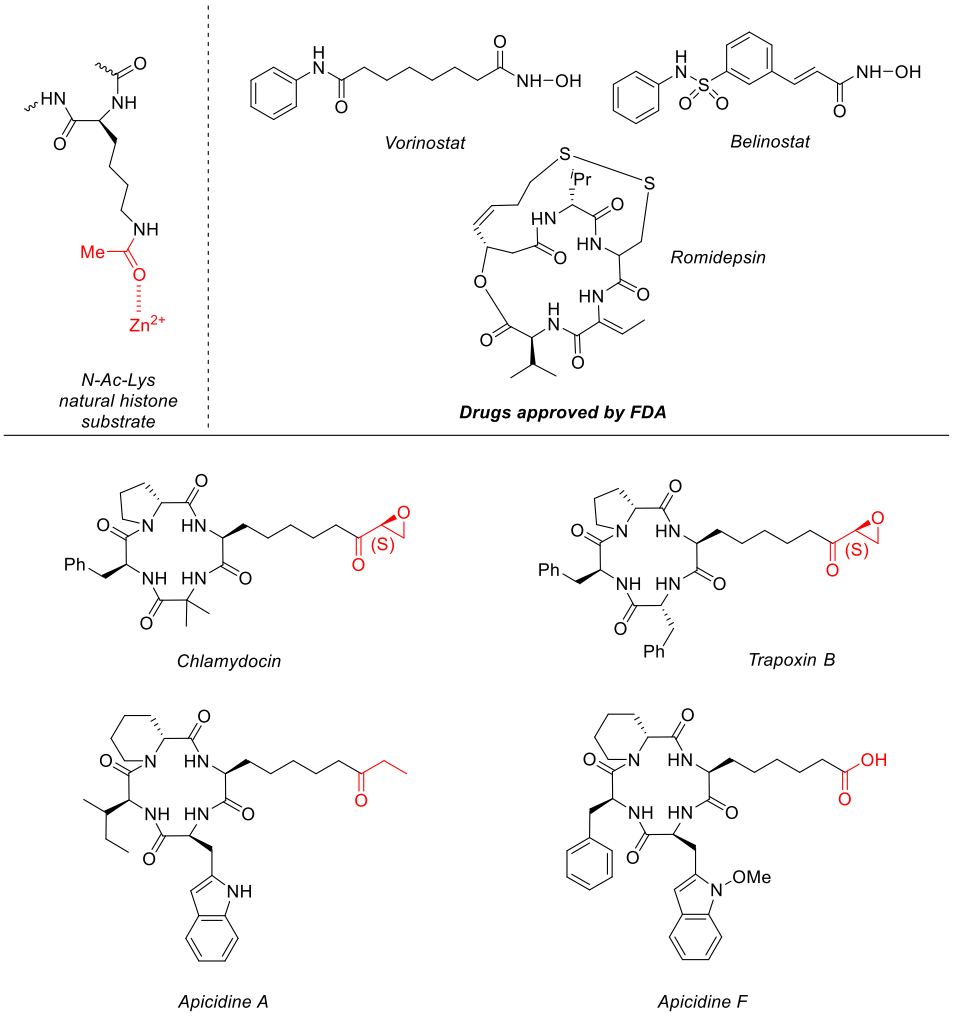


Scheme 27*. Fundamental concepts of the diversity-oriented synthetic approach*

An ideal pluripotent functional group should exhibit unique reactivity, participating only in a selected chemo/regio/stereoselective transformation carried out under mild conditions, having broad functional group tolerance and providing high yields of the desired product. Consequently, there is a continuous need for the development of such functionalities, precursors and reactions, in order to proceed to the idealistic borderless bioactive chemical space of bioactive structures.[123] Due to the above-mentioned pluripotent properties of the cyclopropanol functional group, it should be taken into consideration when creating new chemical strategies and approaches.

1.5 Bioactive peptide targets for natural product synthesis

Natural peptides are the foundation of living world construction. Several synthetic and semi-synthetic peptides exhibit a remarkable bioactive profile in a wide spectrum of properties, thus attracting considerable interest for drug discovery programmes.[124] Fine-tuning of pharmacological properties is accomplished by the modification of the sequence of amino acids or through the installation of several different pharmacophore warheads in the parent peptide scaffold.[125] Due to various demonstrated bioactivities, the cyclic oligopeptides exhibiting histone deacetylase enzyme inhibitory (HDACi) have received multidisciplinary interest (**Scheme 28**).[126]



***Scheme 28**. Inhibitors of the histone deacetylase enzymes*

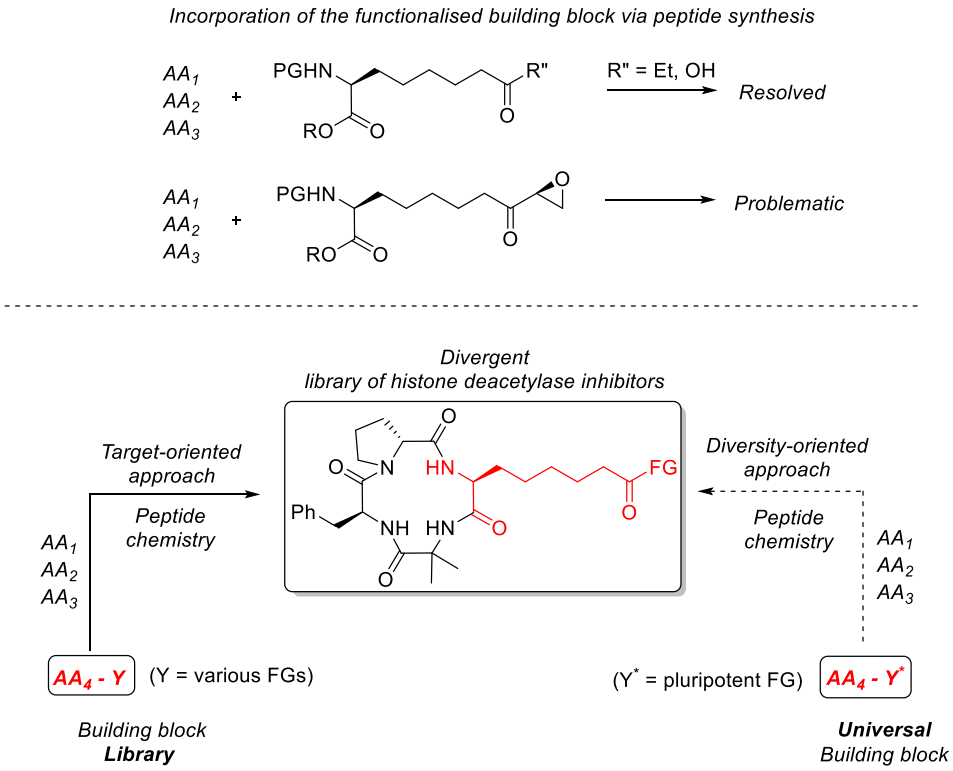
In eukaryotic cells, HDAC enzymes serve as gene expression mediators. DNA in its resting state is packaged as chromatin, and is therefore inaccessible in the replication process, due to the Coulomb interactions between the DNA negative backbone and the positive lysine residues of the histone protein. When accessibility for

the replication-transcription sequence is essential, the previously mentioned attractive interaction can be attenuated by the installation of an acetyl group on the lysine residue with the aid of an HAT enzyme. As the replication is performed, a subsequent HDAC enzyme removes the acetyl function to achieve its original resting state.[127] An imbalance in this highly orchestrated biomachinery results in such severe physiological diseases as cancer, as well as neurological and metabolic disorders.[128]

A set of naturally occurring cyclopeptides has shown inhibitory properties against zinc dependent HDAC enzymes. These products are created by nature as biosynthetic secondary metabolites of different fungal strains. Some examples of this type of compounds are chlamydocin, HC-toxin, trapoxins, WF-3161 and the apicidine family of compounds.[129] Due to their HDAC inhibitory potential, a wide spectrum of bioactivity, ranging from anticancer potency to antiparasitic features, has been found. The structural assembly of these compounds is archetypal, bearing a cyclic cap facilitating the interaction between the inhibitor and the peripheral site of the enzyme catalytic pocket; a hydrophobic spacer sterically adjusts the warhead - the ZBG (Zinc binding group) - into the catalytic pocket. The mimicking properties originate from the structural bioisosteric similarity between the spacer, along with ZBG and the acetylated lysine residue.[130] It is notable that the zinc-binding functionalities are similar in several mentioned inhibitory compounds; the enzyme inhibition may happen in a reversible or irreversible fashion. The epoxy ketone warhead (AOE) suggests an alkylation possibility with any nucleophilic functionality within the catalytic pocket of the enzyme, leading to an irreversible inhibition. On the other hand, the ethyl ketone group (AODA) and carboxylic acid function (ASU) are responsible for the reversible inhibition. So, it is understandable that the carbonyl function has vital significance. Synthetic, analogous compounds, bearing carbonyl-containing hydroxamic acid functionality, were successfully introduced as anticancer drugs and have been approved by the FDA.[128] Despite the initial success, research on selective HDAC inhibitors, especially on the enzyme isoform level, has yet to be undertaken and offers a multidisciplinary challenge for researchers.[131]

When tailoring the bioactivity with a hope of increased selectivity, either modification of the amino acid sequence or alteration of the ZBG warhead (chemical editing) is applied.[132] Several protocols have been developed regarding the non-proteinogenic amino acid building blocks attached to the key fragment (AOE/AODA/ASU), prior to incorporation into the cyclopeptide scaffold.[133,134] The installation of AODA and ASU units *via* standard peptide coupling protocols can be performed smoothly. However, the side-chain with an epoxyketone function with a stereogenic centre in a certain configuration requires an advanced solution due to the incompatibility of the epoxy ketone motif with any conditions used for unmasking N-protection.[135] **(Scheme 29)**. Therefore, the synthesis of natural cyclopeptides bearing the AOE warhead was realised after the cyclic tetrapeptide skeleton was assembled, as a result of a multi-step synthesis.[136] Despite several elegant contributions, they have multiple deficiencies. The preparation of each building block with the preformed warhead is tedious and not time efficient. On the other hand, incorporating the warhead into the later stage of the synthesis leads to only one specific inhibitor.

To overcome these drawbacks, a diversity-oriented synthesis approach would be valuable. This means that a universal amino acid building block is required with a non-vulnerable pluripotent functional group. This should be incorporated into the peptide scaffold. Once the skeleton is built, the universal scheme can be exploited to synthesise a large number of potent HDAc inhibitory peptides. (**Scheme 29**).



Scheme 29. *Comparison of distinct strategies for the synthesis of HDAc inhibitors*

2 Aims of the study

The general aim of this doctoral work was to broaden the scope of bio-inspired, transition metal-catalysed, environmentally friendly, oxidative cleavage methodologies of tertiary cyclopropanols and apply them in the synthesis of fragments of molecules or bioactive compounds of interest, including HDAc inhibitory cyclopeptide natural products. In order to develop a diversity-oriented approach, the pluripotent cyclopropanol functional group has to be transformed at a late stage of the synthetic sequence.

The specific aims are the following:

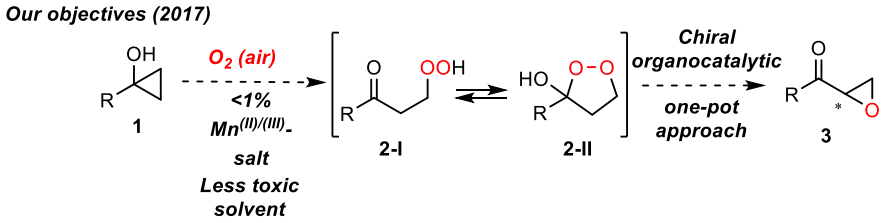
- Develop a simple, one-pot catalytic oxidative cleavage - epoxidation methodology starting from cyclopropanols to obtain chiral epoxy ketones in an enantioselective manner.
- Investigate a copper-catalysed, chemo- and/or regioselective aerobic oxidative ring cleavage of cyclopropanols to extend the scope of accessible β-oxo adducts.
- Apply the developed synthetic methodologies to the total synthesis of bioactive cyclopeptides. Evaluate the utility of cyclopropanol functionality as a pluripotent group satisfying the requirements of diversity-oriented synthesis.

3 Results and discussion

3.1 Enantioselective one-pot synthesis of α,β-epoxy ketones *via* aerobic oxidation of cyclopropanols (Publication I)

The starting point for this research was the non-asymmetric procedure for the synthesis of α,β-epoxy ketones (via peroxyketones) from cyclopropanols developed by Kulinkovich et al.[49] The procedure had minor drawbacks, such as relatively high catalyst loadings (1-1.5%) and the use of benzene in combination with pure oxygen gas. Furthermore, in that seminal study enantioselective synthesis was not tried.

We were motivated by the challenging problem of enantioselectivity and the desire to overcome the previously mentioned shortcomings. The logic of our synthetic approach: the cleavage product (**2**) is formally the intermediate of the Weitz-Scheffer epoxidation, and therefore similar organocatalytic approaches might furnish the chiral epoxyketone (**3**) product, along with resolved substrate incompatibility issues. This approach was investigated and consisted of three elementary steps. First, an aerobic oxidation protocol had to be improved with the elimination of harmful benzene solvent and flammable, high oxygen content. After obtaining the desired peroxyketone (**2-I**) and its tautomer (**2-II**) from cyclopropanol (**1**), the asymmetric epoxidation step of the peroxyketone also had to be developed, yielding enantiomerically enriched epoxy ketone (**3**). When the two separate reactions had been optimised, a combination of these in a one-pot system could be developed (**Scheme 30**).



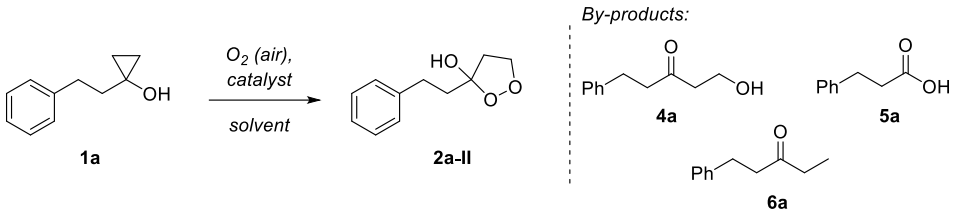
***Scheme 30**. Initial statement of objectives for an enantioselective epoxy ketone synthesis*

The optimisation of the oxidation step was carried out on the model compound 1-(2-phenylethyl)-cyclopropanol (**1a**) with the possibility of UV detection of the products. Air was always used as the oxygen source. Cyclopropanols were synthesised via the Kulinkovich cyclopropanation protocol. We screened different transition metal complexes (which could act as oxygen carriers) at room temperature in dimethyl carbonate (DMC), which is an environmentally benign solvent.[1] The reaction outcome was analysed by ^{1}H NMR.

We also tested metalloporphyrin complexes at the outset, since they are excellent models for biomimetic transition metal catalysis (**Table 1**). Manganese, iron and cobalt were applied as transition metal ions within the porphyrin scaffold. The intermediate **2a-II** was obtained in 95% yield with decreased catalyst loading (0.5 mol%), with Mn porphyrin as a catalyst. However, the reaction was slow (it required one day for full conversion of the starting material), presumably due to the decreased accessibility of manganese, caused by the steric hindrance from the porphyrin ligand. In the case of the

iron and cobalt porphyrin complexes, no target product formation was observed (entries 3-4).

***Table 1**. Condition screening for the optimisation of the aerobic oxidation of cyclopropanol **1a**[a]*



Entry	Catalyst	Catalyst loading [%]	Solvent	T [°C]	Time [h]	**2a-II** Yield [%][b]
1	MnCl(OEP)	0.5	DMC	20	24	95
2	MnCl(OEP)	0.5	THF	20	77	10
3	FeCl(OEP)	0.5	DMC	20	48	0
4	Co(OEP)	0.5	DMC	20	48	0
5	$Mn(OAc)_2$	0.5	Benzene	20	5	90
6	$Mn(OAc)_2$	0.5	DMC	20	3	90
7	$Mn(OAc)_2$	0.5	THF	20	3	90
8	$Mn(OAc)_2$	0.5	EtOAc	20	3	55
9	$Mn(OAc)_2$	0.5	*i*-PrOH	20	3	30
10	$Mn(acac)_3$	0.5	DMC	20	1	95
11	$Mn(acac)_3$	0.5	THF	20	1	90
12	$Mn(acac)_3$	0.5	2-MeTHF	20	1	90
13	$Mn(acac)_3$	0.05	DMC	20	3	95
14	$Mn(acac)_3$	0.05	THF	20	3	93
15	**$Mn(acac)_3$**	**0.5**	**THF**	**0**	**1.5**	**95**

[a] Conditions: **1a** (0.5 mmol) and a specified amount of catalyst were dissolved in 0.5 mL of a solvent and stirred in air (open vial) until full conversion of the starting material (TLC monitoring). [b]Yield was determined by the ^{1}H NMR analysis of crude reaction mixture based on **2a-II** as it is the major tautomer, compared to **2a-I** (~10:1).

To increase the oxidation rate, a simplified and easily available catalyst – manganese(II) acetate salt, with reduced steric hindrance – was tested. Several solvents were screened (entries 5-9). To model the original Kulinkovich procedure, we also used benzene as a solvent. Oxidation in benzene (entry 5) resulted in a 90% yield of **2a-II**, with only a 10% content of by-products **4a-6a**. We investigated less toxic DMC and THF. The importance of THF as a solvent was due to the compatibility with the subsequent asymmetric epoxidation step (see below). To our delight, their performance was similar (entries 6-7), and had a shortened reaction time (3 hours). We observed smaller yields (30-55%) of our target product in more polar solvents, e.g. ethyl acetate and isopropanol (entries 8-9).

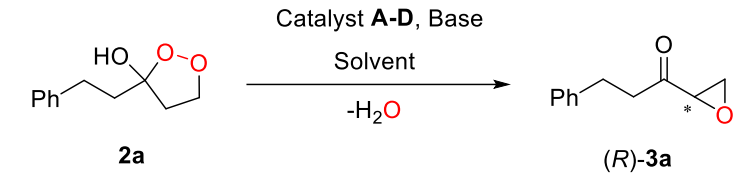
We noticed, that Mn(II) salts showed no conversion of starting material in the initial phase of the reaction (around 1-2 h), but afterwards cleavage occurred rapidly (~1h). This indicates the assumed participation of Mn(III) species accumulated in the initial phase.

Experiments using readily available manganese(III) acetylacetonate salt were performed. In our case, DMC with manganese(III) acetylacetonate at a similar catalytic loading resulted in an increased yield (95%) of the product (entry 10) with a striking shortening of the reaction time (1h), verifying our previous assumption. The oxidative cleavage reaction in THF also proceeded fast, but the yield of **2a-II** remained around 90% (entry 11). The more environmentally friendly solvent 2-MeTHF performed similarly (entry 12). To suppress the formation of oxidation by-products, the amount of catalyst was decreased by a factor of ten to 0.05 mol%. In DMC and THF the reaction was slower and **2a-II** was formed in the same (DMC; entry 13) or lower (THF; entry 14) yield. We also checked the possibility of decreasing by-product formation by cooling down the reaction mixture. Finally, within 1.5 hours, with 0.5% of the catalyst loading, 95% of the required peroxide product was obtained at 0°C degrees (entry 15), opening a pathway for the subsequent optimisation of enantioselective epoxidation.

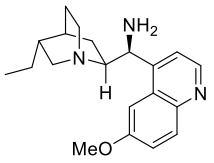
Before performing studies regarding the epoxidation protocol, the isolation and spectral characterisation of **2** (as a mixture of tautomers) was completed, with the structure confirmed by 2D NMR techniques (COSY, HSQC). It is important to mention that thermal instability was noticed during the solvent removal and occasional sensitivity to silica gel was preliminarily reported.[49] To circumvent the problem of potential decomposition, the development of a one-pot procedure was a rational solution.

We expected to perform the transformation of peroxyketone to ketoepoxide in an enantioselective manner by using organocatalysts (Table 2). Our initial selection of catalysts was cinchona-alkaloid-derived primary amine **A** (as a trifluoroacetic acid salt),[44] multifunctional thiourea **B** and squaramide **C.** Whereas **A** was assumed to facilitate the Weitz-Scheffer epoxidation via covalent iminium activation of the carbonyl motif, **B** and **C** were believed to aid predominantly via non-covalent hydrogen bonding interactions. Unfortunately, all of them failed to produce epoxy ketone **3a** (entry 1). In contrast to these failed results, commercial poly-L-leucine (7.5 mol%) after immobilisation on SiO_2 yielded enantiomerically enriched epoxy ketone **3a** in 86% ee (1 h; room temperature; entry 2) in the presence of a stoichiometric amount of DBU according to Juliá-Colonna[38] conditions and improvements.[40] The cited studies focused on chalcone epoxidation; our contribution to the topic is the first formal asymmetric epoxidation of previously challenging, prochiral aliphatic vinyl ketones with PLL. By decreasing the catalyst loading to 2.5 mol% (entry 3), a decrease of ee to 34% was observed. When changing the solvent from THF to MeTHF, MTBE, toluene, DMC and CH_2Cl_2 a wide range of enantioselectivities was observed, showing that the solvents highly affected the asymmetric induction (entries 4-11). As a general trend, when the polarity of the solvent was increased, the stereoselectivity was reduced, although specific solvent-catalyst interactions must also be taken into account (e.g. entries 9, 11).

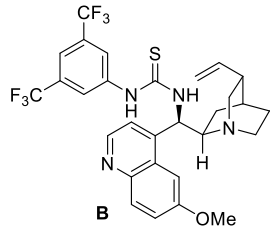
***Table 2**. Optimisation experiments of the asymmetric transformation of peroxide **2a** to ketoepoxide **3a**[a]*



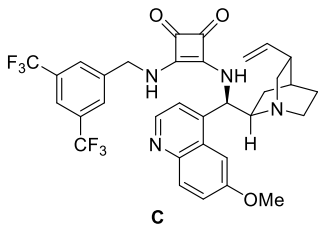
Catalysts:



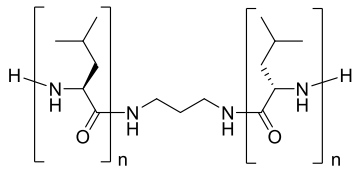
A



B



C



D (PLL on SiO_2)

Entry	Catalyst (mol%)	Solvent	Base	Temperature [°C]	Time [h]	ee[b] [%]
1	**A**-**C**(20%)	DMC	-	20	50	[c]
2	**D** (7.5%)[d]	THF	DBU	20	1	86
3	**D** (2.5%)	THF	DBU	20	1	34
4	**D** (7.5%)	2-MeTHF	DBU	20	1	88
5	**D** (7.5%)	MTBE	DBU	20	1	64
6	**D** (7.5%)	DME	DBU	20	1	68
7	**D** (7.5%)	Dioxane	DBU	20	1	32
8	**D** (7.5%)	Toluene	DBU	20	1	74
9	**D** (7.5%)	CH_2Cl_2	DBU	20	1	58
10	**D** (7.5%)	DMC	DBU	20	1	48
11	**D** (7.5%)	CH_3CN	DBU	20	1	16
12	**D** (7.5%)	THF	DIPEA	20	12	70
13	**D** (7.5%)	THF	TMP	20	12	78
14	**D** (7.5%)	THF	DBU	40	1	66
15	**D** (7.5%)	THF	DBU	-25	24[e]	94

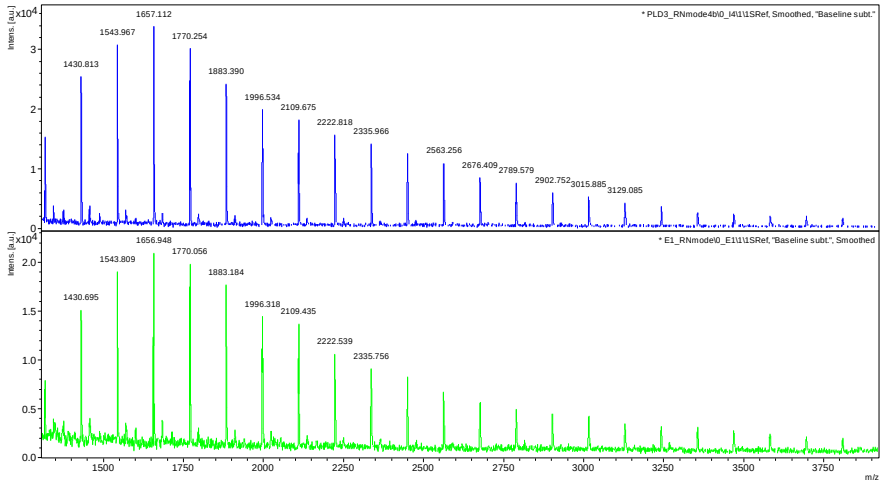
[a]The yield of epoxy ketone **3a** for all reactions was considered to be quantitative according to NMR. [b] Enantiomeric excess was determined by HPLC analysis using an AD-H column. [c] No epoxide **3a** formed. [d] Calculated according to the average molecular weight of PLL polymer. [e] The reaction mixture was stirred in a freezer at -25°C for 24 hours.

Replacing DBU with weaker non-nucleophilic bases (DIPEA and TMP) resulted in a slight decrease in the enantioselectivity, which might be due to the background racemic reaction occurring with an increased reaction time (entries 12-13). The transformation was sensitive to temperature: gentle heating to 40°C caused the ee to drop to 66% (entry 14). In contrast, performing the reaction at -25°C for 24 hours caused a remarkable selectivity increase to 94% ee (entry 15). The obtained results inspired us to attempt to combine the separately developed oxidation and epoxidation steps into a one-pot protocol.

As DMC performed the best in the oxidation and in THF had the highest obtained enantioselectivity, we decided that THF should be used in the combined one-pot protocol, since achieving high enantioselectivity was more crucial. To our delight, using the combined experimental procedure (see Article I), enantiomerically pure epoxy ketone **3a** was obtained in a 77% isolated yield.

To get a reliable synthetic methodology, a characterisation of the applied polypeptide catalyst was necessary, as the enantioselectivity was highly dependent on the length of the polymer chain.[38b] The polymers (PLL and PDL, containing L- and D-Leu amino acid monomeric units, respectively) were synthesised according to the literature procedures.[137] After immobilisation on silica gel[40] the enantioselectivity was evaluated by chiral HPLC analysis after the cleavage of **1a**. To our delight, the prepared catalytic samples afforded the same results obtained with the commercial PLL sample.

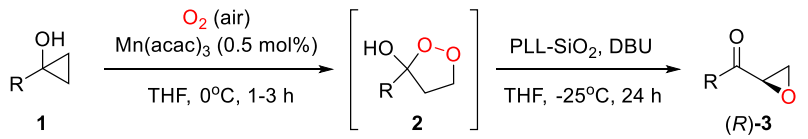
The PLL samples were analysed by matrix-assisted laser desorption/ionisation mass spectrometry (MALDI).[138] We found, that the degree of polymerisation was 17-18 and the average molecular weight was 2000-2100 Daltons (**Scheme 31**).

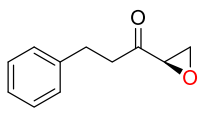


***Scheme 31**. MALDI MS spectra of prepared (upper, blue) and commercial (lower, green) PLL samples (measured by Dr. Karin Valmsen, TalTech)*

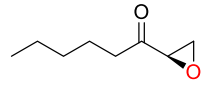
Having the optimised conditions in hand, the next goal was to evaluate the compatibility of the reaction conditions with different functional groups in the substrate, and to determine the scope and limitations of our method. Therefore, the structural diversity of the starting cyclopropanols became the focus of interest. The obtained results demonstrate the high synthetic potential of the method for a broad range of

structures containing aliphatic, aromatic, aryl-substituted aliphatic moieties, together with various functional groups (**Scheme 32**).

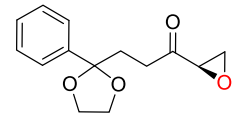




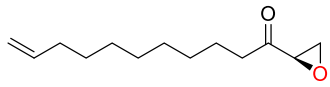
3a (77%; 94% ee)



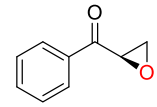
3b (82%; 86% ee)



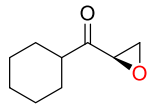
3c (76%; 94% ee)



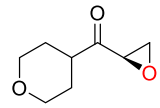
3d (83%; 95% ee)



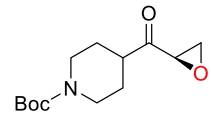
3e (73%; 84% ee)



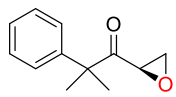
3f (84%; 97% ee)



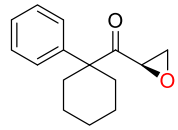
3g (78%; 94% ee)



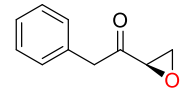
3h (76%; 88% ee)



3i (82%; 97% ee)

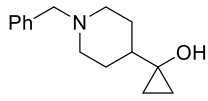


3j (68%; 96% ee)

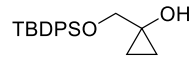


3k (58%; 80% ee)

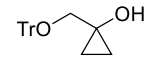
Inefficient substrates:



1l



1m

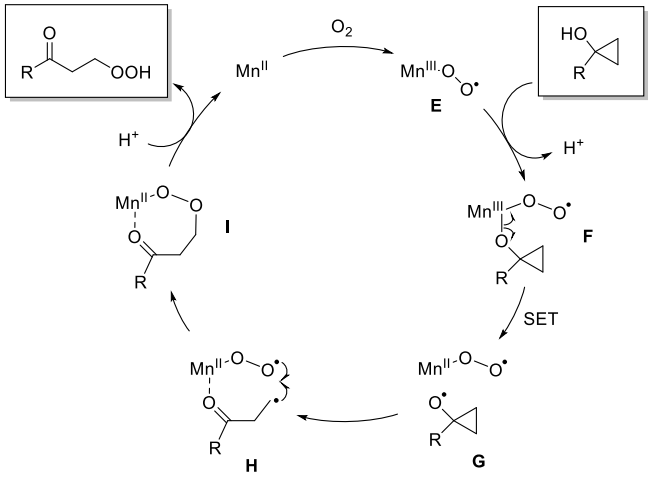


1n

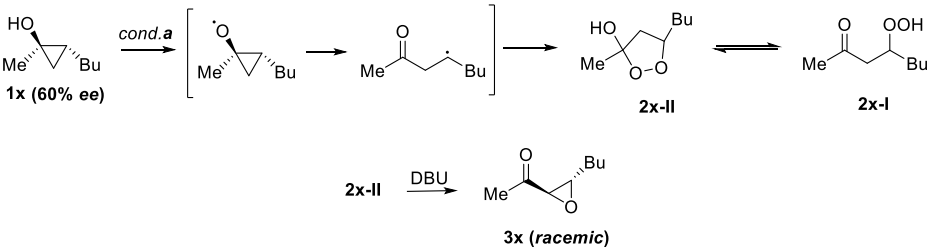
Scheme 32*. Scope of the asymmetric transformation of cyclopropanols to epoxyketones*

Aliphatic epoxyketones **3a**, **3b** and **3k** were synthesised in good yield and enantioselectivity (yields 77%, 82% and 58%; ee 94%, 86% and 80%, respectively). However, in the case of benzyl cyclopropanol (**1k**), an additional quenching step with acetic acid was needed, presumably due to the highly enolisable α-hydrogens adjacent to the aromatic ring. Functional groups in the initial cyclopropanol **1,** such as a protected keto group (**1c**), and a double bond in the chain (**1d**) did not influence the transformation, resulting in epoxyketones in excellent stereoselectivity (95 and 96% ee, respectively). Aromatic cyclopropanol **1e** provided the target epoxide **3e** in 73% yield with 84% ee. Also, the cyclopropanols with secondary α-carbon (**1f**; **1g**) gave epoxides (**3f; 3g**) with good enantioselectivity (97 and 94% ee) and yield (84 and 78%). Hindered tertiary α-carbon did not spoil the reaction outcomes (**3i,** 82% yield and 97% ee; and **3j,** 68% yield and 96% ee). The Boc-protected amide functionality in **1h** aimed at modelling synthetic utilisation with simple peptides, resulting in epoxy ketone **3h** in 76% yield and 88% ee, but an elevated amount of manganese(III) salt was required (2 mol%). The main limitation of the method was that amine functionalities were not tolerated, since they very likely blocked the oxidative cleavage step, presumably due to stronger coordination of amine function to manganese ions in comparison with cyclopropanol (see below). To conclude, according to the developed method, a broad variety of prochiral cyclopropanol substrates can be transformed with a poly-L-leucine catalyst to chiral epoxy ketones in good-to-excellent enantioselectivities and high yields. The reaction protocol is also operationally simple; after filtration of the reaction mixture, a wide spectrum of pure epoxide compounds can be easily obtained.

Some experiments were performed to investigate the mechanism of the developed reaction. A radical mechanism *via* β-oxoalkyl radical species has been proposed by Kulinkovich,[139] and is quite common with manganese(III) salts.[94-96] We found that basic nitrogen-bearing additives with a lone electron pair (pyridine and N-methyl imidazole) or similar motifs in the substrates, e.g. **1l**, blocked the oxidative cleavage step, presumably due to the inactivation of the manganese ion by a nitrogen coordinative binding, compared to the weaker, cyclopropanol binding, thus preventing the metal-substrate interaction and consequently a single electron transfer. The SET mechanism was additionally proved by using chiral disubstituted cyclopropanols (**Scheme 33**), which afforded β-oxoalkyl peroxy adduct, thus confirming C^1-C^2 homolytic cleavage. As expected, the obtained epoxide was isolated as a racemic mixture, due to the facile inversion of the configuration of the stereogenic carbon in the formed β-oxoalkyl radical. These findings confirm the presence of radicals, proving the plausible reaction mechanism (**Scheme 33**).



Mechanism proving experiment:

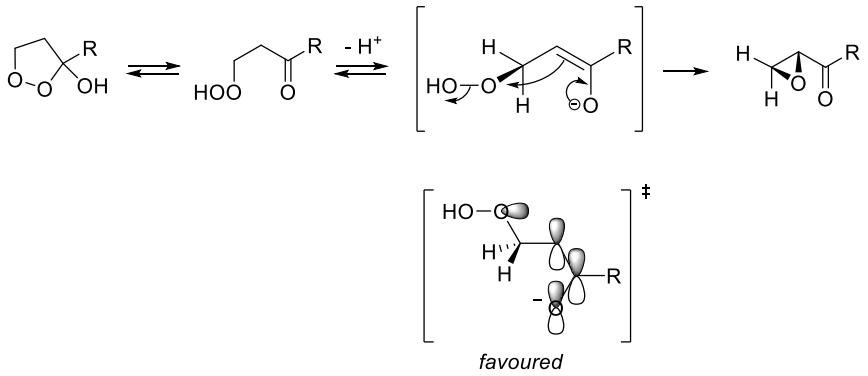


***Scheme 33**. Plausible mechanism for the aerobic Mn-mediated oxidation of cyclopropanols*

Manganese(II) (in situ generated from a Mn^{III} salt) combined with the radical dioxygen, forming a metal peroxy species (**E**),[23b] which coordinated cyclopropanol substrate to provide the precursor of a cyclopropyloxy radical (**F**). Due to the instability of cyclopropyloxy free radical (**G**), it readily cleaved to the β-oxoalkyl radical species (**H**). The newly formed peroxy-radical recombined with radical peroxo species (though the capture of molecular oxygen also cannot be ruled out), forming a peroxoketone-chelated Mn(II) complex (**I**), which eventually released free manganese(II) for the next catalytic cycle and the peroxoketone product.

To understand the mechanism of the subsequent epoxy ketone formation step with PLL, stereochemistry has to be considered. A comparison of the optical rotations of **3e** and **3i** with their previously determined values, absolute stereochemistry of the products and (*R*)-configuration of the chiral centre were assigned (for **3e**: $[\alpha]_D^{25}$ = +39.9 (*c* 1.10, DCM, 84% ee) *vs*. (lit. $[\alpha]_D^{15}$ = +54.95 (*c* 0.74, DCM))) and (for **3i**: $[\alpha]_D^{25}$ = +45.7 (*c* 1.14, chloroform, 80% ee) *vs*. (lit. $[\alpha]_D$ = -47.5 (*c* 1.14, chloroform, for (*S*)-enantiomer))).[140] Thus, we can state that epoxidation with poly-L-leucine resulted in (*R*)-enantiomers, as in Juliá-Colonna epoxidation.[38] The high stereoselectivity of poly-L-leucine was rationalised by two alternative models, proposed by Roberts[141a,b] and later by Berkessel[141c,d]. A common feature of these models is the existence of an oxy-anion hole as the catalytic binding pocket in the helical structure of the poly-L-leucine. The prochiral

peroxyenolate intermediate can fit in it, providing the favoured *re* transition state, leading to (*R)*-epoxy ketones (**Scheme 34**). The differences in the models are connected to the non-covalent participation of the N-terminus of the synthetic enzyme. According to Kelly and Roberts, the N-terminus supplies only a marginal contribution, while according to Berkessel the hydrogen bonding model suggests the participation of substrate N-terminus binding. The latter was also confirmed by our own docking studies (carried out by Larisa Ivanova, University of Tartu).



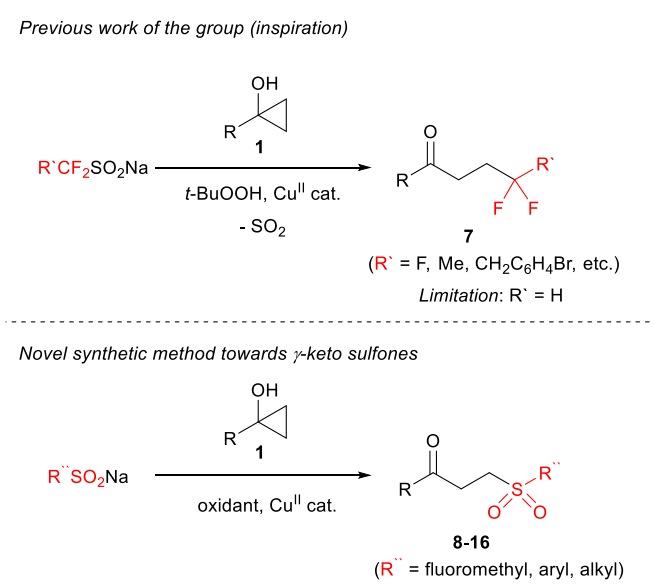
Scheme 34*. Mechanism of enantioselective epoxidation according to the Roberts group*[141a]

To conclude, a practical and efficient one-pot protocol for the synthesis of enantiomerically enriched 2-oxyranyl ketones **3** by aerobic oxidation of easily available cyclopropanols **1** has been developed. The process proceeds via the formation of prochiral peroxyketone intermediates **2**, which affords epoxides **3** enantioselectively in the presence of a poly-L-leucine catalyst and DBU as a base. The experimental protocol is operationally simple, utilising atmospheric oxygen as an eco-friendly reactant and poly-L-leucine as a "green" catalyst. The method affords epoxy ketone products in high yields and in good-to-excellent enantioselectivities. This strategy can be effectively applied as an alternative to the straightforward approach to chiral 2-oxyranyl ketones **3**, which are recognised as highly valuable synthetic intermediates.

3.2 Synthesis of γ-keto sulfones by copper-catalyzed oxidative sulfonylation of tertiary cyclopropanols (Publication II)

Our research group has previously developed protocols based on the copper catalysed oxidative cleavage of cyclopropanols leading to β-trifluoromethyl ketones and distally fluorinated ketones.[102,104]

While the introduction of a trifluoromethyl and α,α-difluoroalkyl group to the β-keto position from cyclopropane ring cleavage was successful, introducing fluoromethyl and difluoromethyl groups was not achieved efficiently, most probably due to the lower stability of fluoromethyl and difluoromethyl radicals.[142] Therefore, only trace amounts of the desired fluorinated ketones were observed, yielding fluorinated sulfones instead. This finding was confirmed by NMR, IR and X-ray analysis of the obtained sulfone products. As previously, C-S formation via ring cleavage reactions of cyclopropanols was not known, and this inspired further investigations of a practical oxidative synthesis of γ-keto sulfones **8-16** (**Scheme 35**).



***Scheme 35**. Possible pathway to γ-keto sulfones*

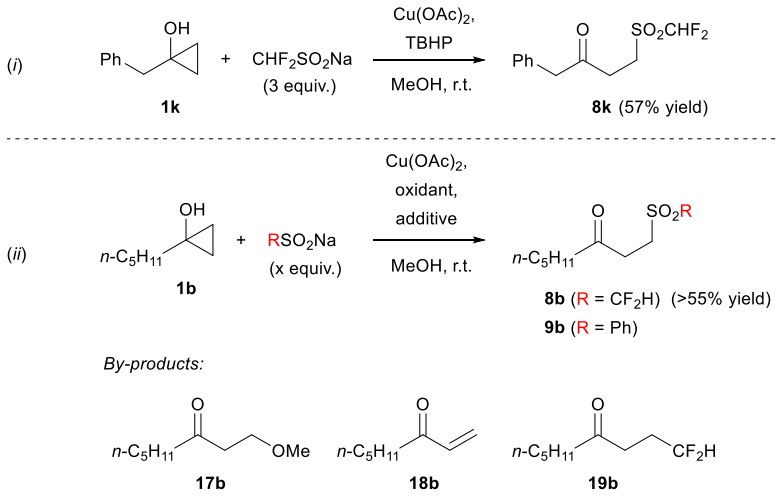
The initial result showed the formation of sulfone **8k** (57% according to NMR analysis) from cyclopropanol **1k (Table 3)**. The starting compound in the subsequent optimisation studies was the non-functionalised aliphatic amyl cyclopropanol **1b**, which was similarly transformed to the corresponding sulfone **8b** in 55% yield (NMR), together with a minor amount of methoxy ketone **17** (~10%), vinyl ketone **18** and difluoroketone **19** (35%) under the same reaction conditions (**Table 3**, entry 1). The presence of abundant amounts of by-products required the optimisation of the synthetic procedure to enhance the yield of the target sulfone product **8b** (**Table 3**).

We found, that difluoroketone **19** formation can be suppressed with the application of an $Fe(OAc)_2$ additive (20 mol%) (**Table 3**, entries 2-3). The role of the iron additive remains currently obscure; however, it could suppress a generation of difluoromethyl radicals or catalyse a sulfa-Michael addition to intermediate enone (see the mechanistic discussions below). Also, methoxy ketone (**17b**) was formed in a negligible amount, and vinyl ketone (**18b**) was still detected in 20% yield, together with the elevated yield of the main product **19b** (60%) (**Table 3**, entry 2). An increase in the reaction time to 72 hours resulted in a diminishing of the yield of vinyl ketone by-product, increasing the yield of sulfone **8b** to 77% (**Table 3**, entry 3). This result indicated the possibility that vinyl ketone acts as an intermediate according to a sulfa-Michael addition.

To extend the scope of the method to non-fluorinated sulfones, sodium benzene sulfinate ($NaSO_2Ph$) reagent was applied. With this reagent, the reaction was much faster than with fluorinated sulfinate salt, in the presence of a stoichiometric amount of copper(II) acetate (0.5 h vs. 24-72 hours), (**Table 3**, entry 4). Additionally, there was no need for an iron additive anymore and the sulfone product was produced fast and in a high (94%) yield. The increased reaction rate can be explained by the higher nucleophilicity of the sulfinate salt, causing a faster Michael-addition, even with decreased amounts of the reagent (1.5 equivalents). The target sulfone **9b** was obtained in 94% yield (NMR), with only trace amounts of by-products **17b** and **18b.** A reduction in the amount of copper(II) acetate ($Cu(OAc)_2$) to 50 mol% of Cu(II) slightly increased the

required reaction time (to 1 hour), still affording the product in a high (92%) yield (**Table 3**, entry 5). The application of 20 mol% Cu(II) salt reduced the yield of sulfone **9b** to 63% (**Table 3**, entry 6). In the absence of copper, sulfone formation did not take place (**Table 3**, entry 7).

***Table 3**. Copper-catalysed oxidative sulfonylation*



Entry	Cu catalyst [mol%]	R [equivalent]	Oxidant	Time [h]	Sulfone yield[a] [%]
1	100	CF_2H [3]	TBHP	24	55
2	100[b]	CF_2H [3]	TBHP	24	60
3	100[b]	CF_2H [3]	TBHP	72	77
4	100	Ph [1.5]	TBHP	0.5	94
5	50	Ph [1.5]	TBHP	1	92
6	20	Ph [1.5]	TBHP	1	63
7	0	Ph [1.5]	TBHP	1	0
8	100	Ph [1.5]	O_2 (air)	2	97
9	20	Ph [1.5]	O_2 (air)	3	81
10	100	Ph [1.5]	-[c]	3	60[d]

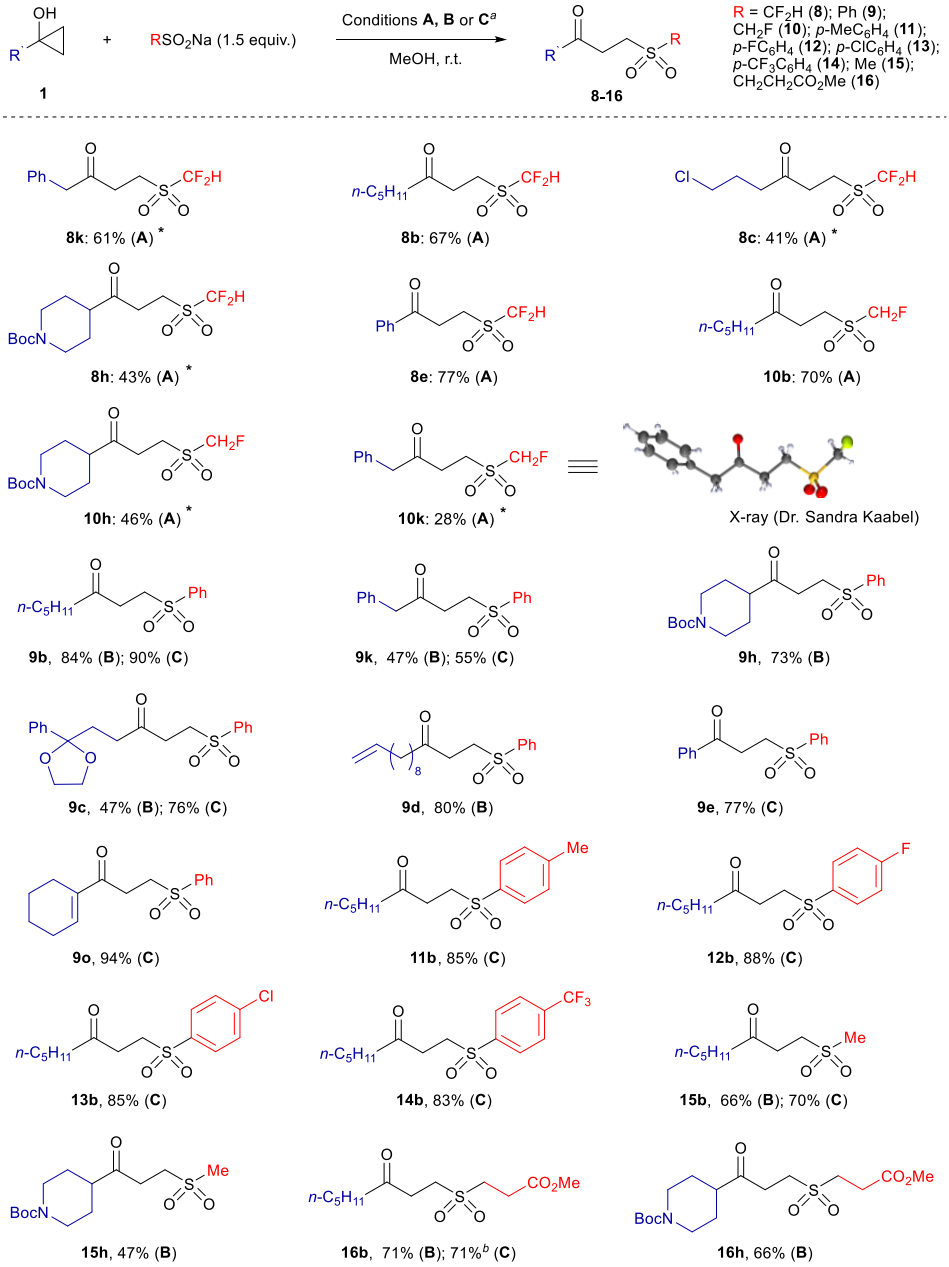
[a] Yields were determined by using ^{1}H NMR spectroscopy; [b] 20 mol% $Fe(OAc)_2$ as an additive; [c] the reaction was carried out under argon in a Schlenk tube; [d] 35% of the starting material (**1b**) remained.

It is worth mentioning, that replacing the common TBHP oxidant with air (oxygen) was successful. The reaction was carried out in an open flask with stoichiometric copper(II) acetate loadings and provided sulfone **9b** in 97% yield within 2 hours (**Table 3**, entry 8). Decreasing the amount of the copper(II) catalyst to 20%, slightly decreased the yield (81% within 3 hours; **Table 3,** entry 9).

To understand the role of the aerobic oxygen as an oxidant (or co-oxidant), we performed an experiment in a Schlenk flask under an argon atmosphere with the exclusion of air. The initial blue colour of the copper(II) species eventually turned yellow after 3 hours, presumably because of the formation of copper(I) species. An NMR analysis of the mixture indicated the presence of unreacted cyclopropanol (although 65% was

converted to sulfone **9b** due to a reduction of Cu(II) species). Given access to air, the yellowish reaction mixture changed to blue as a result of the oxidation to copper(II), together with full conversion to sulfone **9b**.

On the basis of the obtained knowledge, the scope of the transformation was investigated. In the case of fluorinated sulfinate salts, sluggish reactions were expected due to the decreased nucleophilicity of the fluorinated sulfinates. Therefore, the full conversion of the starting material required a prolonged reaction time, the use of excess (3 equiv.) sulfinate salts, as well as an iron salt additive (**Table 3**, entry 3). To explore the applicability of the method, we also used different oxidants (TBHP and air) and sulfinate salts (unsubstituted phenyl, functionalised phenyl and alkyl-substituted sulfinate salts). The obtained results are presented in **Scheme 36**.



[a]**Conditions A**: cyclopropanol **1** (0.5 mmol), sulfinate salt (3 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), $Fe(OAc)_2$ (20 mol%), TBHP (3 equiv., 70% in water, dropwise addition 20 min), r.t., 72 h; **Conditions B**: cyclopropanol **1** (1 mmol), sulfinate salt (1.5 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), TBHP (1.5 equiv., 70% in water, dropwise addition 20 min), open flask, r.t., 1 h; **Conditions C**: cyclopropanol **1** (1 mmol), sulfinate salt (1.5 equiv.), $Cu(OAc)_2 \cdot H_2O$ (1 equiv.), open flask, stirring at r.t., 2-5 h. [b] Not isolated. Yield determined by ^1H NMR spectroscopy. * Synthesised by Yulia A. Konik

***Scheme 36**. Scope of the developed oxidative sulfonylation method*

The formation of different sulfones required different reaction conditions (see experimental procedures **A** and **B** (nonaerobic), and **C** (aerobic) in Article II). With difluorinated sulfones (**8**), both groups of unfunctionalised cyclopropanols (**1b** and **1k**) and their functionalised homologues (**1c** and **1h**) afforded the expected sulfones. In the case of amyl (**1b**) and benzyl (**1k**) cyclopropanols, the isolated yields were better than the functionalised alkyl substrates (**1c** and **1h**) under the established reaction conditions (**A**) (61-67% vs. 41-43%). Phenyl cyclopropanol (**1e**) had a higher isolated yield of a sulfone (77%) than the aliphatic substrates.

Conditions (**A**) were used when performing reactions of cyclopropanols (**1b**, **1h** and **1k**) with di- and monofluorinated sulfinate salts. Oxidative sulfonylation of the functionalised cyclopropanol **1h** resulted in a diminished yield (46%). Sulfone (**10k**) was afforded in a fairly low yield (28%), although the formed crystalline compound gave the ultimate proof of a sulfone structure by X-ray analysis.

For the synthesis of sulfones (**9**, **11-16**) preparation conditions according to method **B** and **C** were applied.

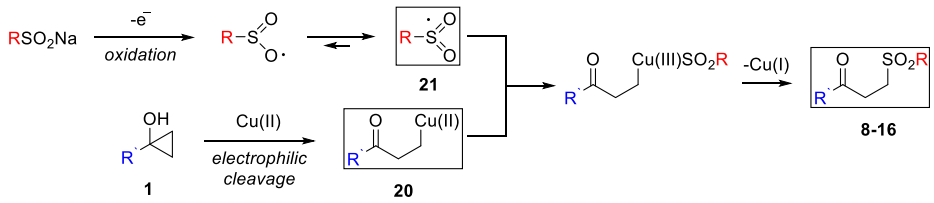
Non-functionalised phenyl sulfone derivatives (**9**) were synthesised from seven different cyclopropanols (**1b-e**, **1h**, **1k**, **1o**) in moderate to excellent yields (47-94%) with conditions **B** and **C**. It was observed that chemically less sensitive substrates afforded similar yields with both **B** and **C** conditions (**9b**: 84% (**B**) vs. 90% (**C**); **9k**: 47% (**B**) vs. 55% (**C**)), while functionalised cyclopropanol **1c** afforded sulfone with atmospheric oxygen in a remarkably better yield (**9c**: 47% (**B**) vs. 76% (**C**)).

To compare the formation of substituted phenyl sulfones (4-Me, 4-Cl, 4-F and 4-CF_3), prepared from amyl cyclopropanol (**1b**), high yields of the sulfones (**11-14**) were obtained (83-88%).

To extend the scope of the developed one-pot protocol, alkyl sulfinate salts were also found to afford alkyl sulfones (**15-16**) smoothly. The yields were, however, slightly lower (**15**: 47-70% vs. **16**: 66-71%). It is important to mention that a preparative gram-scale synthesis afforded **15b** in 76% isolated yield after recrystallisation, showing the practical usefulness of the method.

Regarding the plausible mechanism, it is important to stress that it likely involves the electrophilic copper-mediated cleavage of a cyclopropane ring to β-copper(II) ketone (**20**).[143] There are some mechanistic options to describe the following steps. First, the formation of sulfonyl radicals directly from the oxidation of sulfinate salts (**21**) could be proposed (**Scheme 37**). These radicals reacted with intermediate **20,** forming a copper(III) species and affording the corresponding sulfones (**8-16**) after the reductive elimination of the copper(I). Although the probability of the existence of that mechanism is considered to be low, the high stability of the terminal double bonds in our experiments support this mechanistic proposal, because in the opposite case it would react with rather electrophilic sulfonyl radicals and disappear.[144]

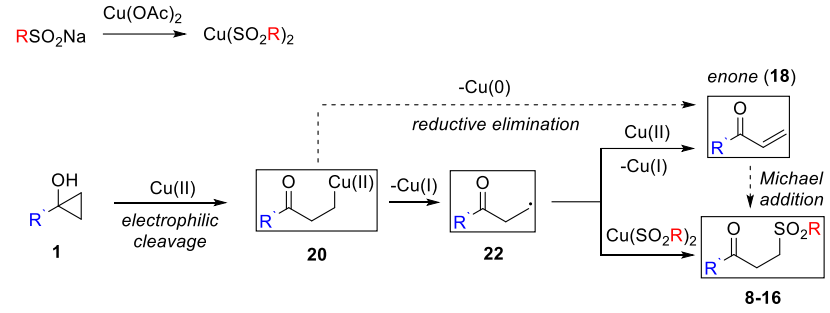
Proposed mechanism involving sulfonyl radicals



***Scheme 37**. Plausible mechanistic pathway with the participation of sulfonyl radicals*

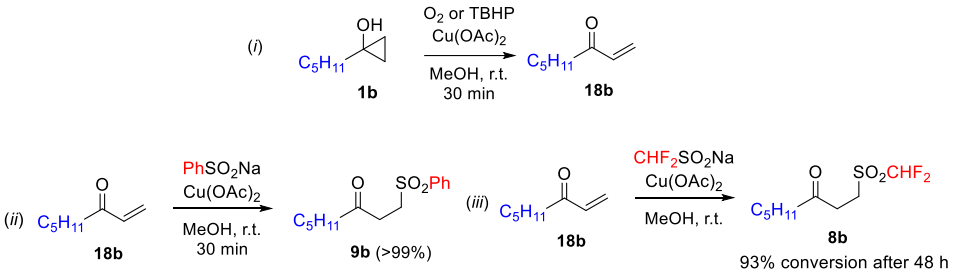
Secondly, the homolytic cleavage of the C-Cu bond in organocopper intermediate **20** can occur, producing a β-oxoalkyl radical (**22**), which may be involved in both alternative mechanisms.[145] A closer distinction between the pathways depends on the later fate of the β-keto radical species (**Scheme 38**): it may be intercepted by sulfonyl radicals from the *in situ*-generated copper sulfinate, and therefore a direct pathway to the sulfones could be achieved, or the generation of the keto sulfones can be completed *via* a sulfa-Michael addition to the enone intermediate (**18**). The formation of enone can be explained by either oxidation of the **22** intermediate in a SET process[146] or by the reductive elimination of copper(0) from the β-keto copper precursor (**20**).

Proposed mechanisms involving C-Cu homolysis



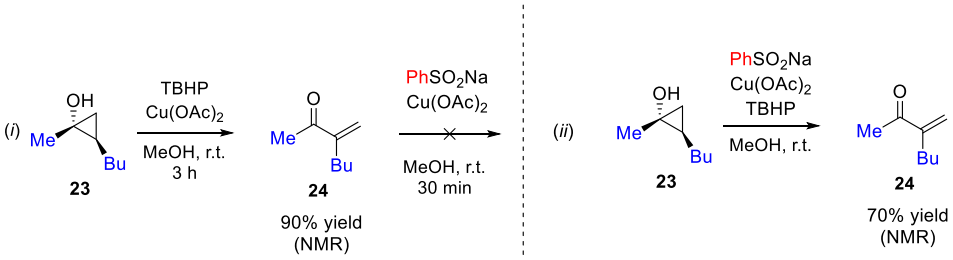
***Scheme 38**. Alternative reaction mechanisms involving C-Cu bond homolysis*

For the distinction of these two possibilities, experiments without sulfinate salts present to prevent direct sulfonylation were carried out. Thus, a solution of cyclopropanol in methanol mixed with stoichiometric copper(II)-acetate afforded vinyl ketone either in an aerobic or TBHP oxidative environment within 30 minutes in 85-95% NMR yield[147] (**Scheme 39**; (*i*)). The corresponding vinyl ketone product was isolated in 83% yield. Then the obtained vinyl ketone was allowed to react with different sulfinate salts to evaluate the individual reaction rates (**Scheme 39**; (*ii*) and (*iii*)). According to our observations, the phenyl sulfinate salt participated in a fast sulfa-Michael addition (30 min), whereas less nucleophilic fluorinated salts reacted more slowly (93% conversion in 48 hours). However, the successful Michael reactions from *in situ* vinyl ketone provided an increased probability to the mechanism regarding enone formation and a subsequent Michael reaction.



***Scheme 39**. Mechanism proving experiments (presence of vinyl ketone)*

The disubstituted cyclopropanol (**23**) was converted to α-methylene ketone (**24**) under the previously applied oxidative conditions (**Scheme 40**; (*i*)). The transformation proceeded with 90% yield (NMR) and afforded mainly the C^1-C^3 cleavage product. As expected, due to the reduced Michael reactivity of the formed enone **24**, no subsequent sulfone formation was observed. In accordance with the previous results, the one-pot operational setup stopped after the electrophilic cleavage of the disubstituted cyclopropanol had occurred, giving only traces of sulfone (**Scheme 40**; (*ii*)).

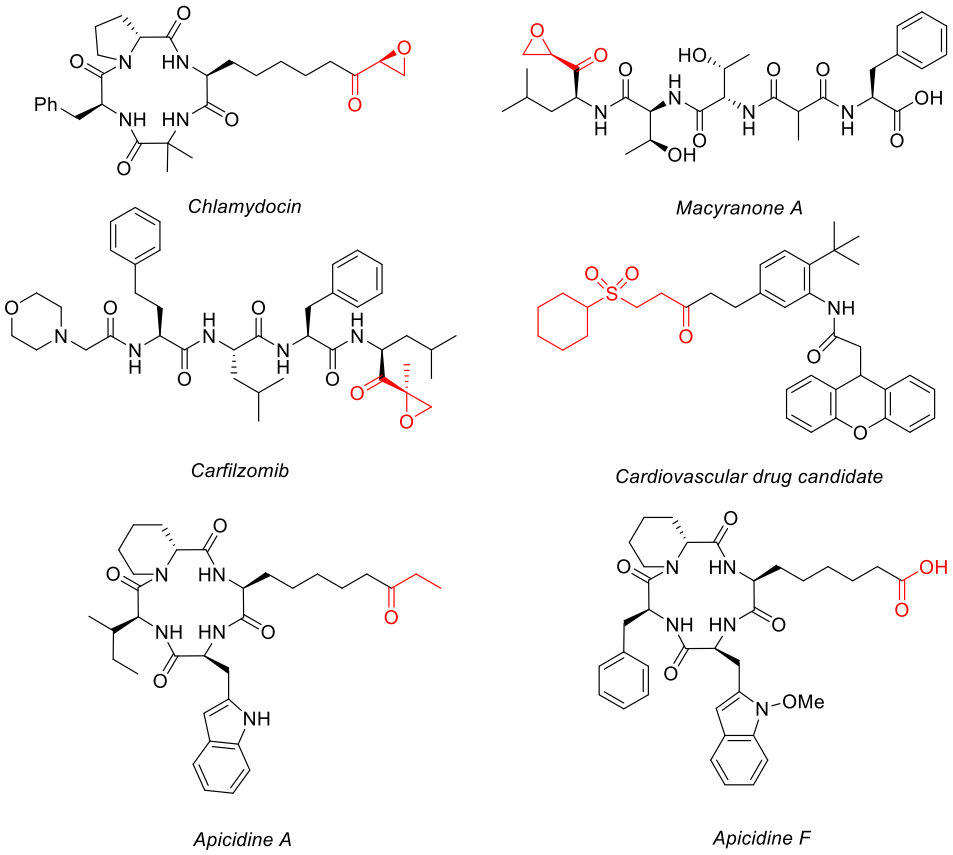


***Scheme 40**. Mechanism proving experiments with disubstituted cyclopropanol*

To conclude, we have developed a one-pot protocol for the synthesis of γ-keto sulfones from easily available cyclopropanols. The most probable mechanistic pathway is an oxidative cleavage affording α,β-unsaturated ketone as an intermediate, which undergoes a sulfa-Michael addition to afford γ-keto sulfones. The mechanism-proving experiments with disubstituted cyclopropanols support this observation, with the additional relevance of regioselectivity. The developed approach is a useful alternative to the existing methods for the synthesis of γ-keto sulfones. Furthermore, the methodology can be expanded for the preparation of different classes of β-functionalised carbonyl compounds via in situ Michael additions.

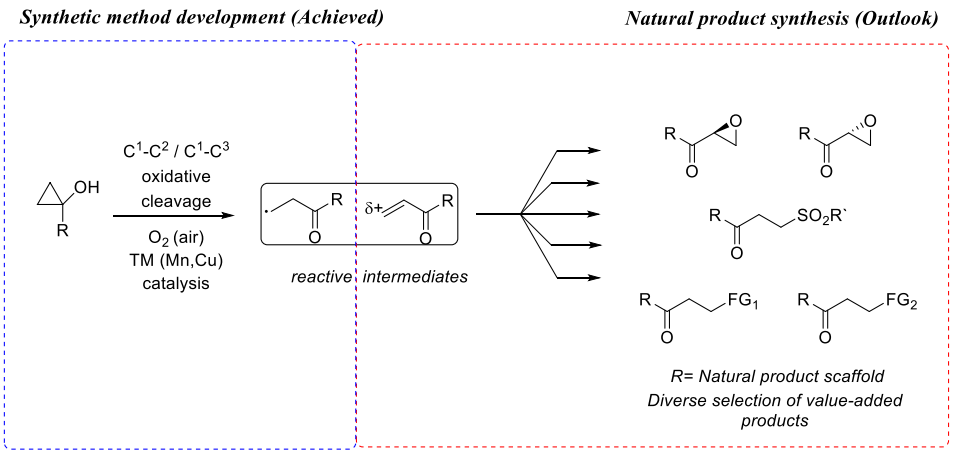
3.3 Divergent access to histone deacetylase inhibitory cyclopeptides *via* a late-stage cyclopropane ring cleavage strategy. Short synthesis of Chlamydocin (Publication III)

The successful development of the synthetic procedures presented in Chapters **3.1** and **3.2** led us to evaluate their application capability in total synthesis. As the chiral epoxy ketone motif is present in numerous bioactive natural products as well as γ-keto sulfone unit as a carbonyl bioisosteric pharmacophore warhead, it was decided to select an attractive drug target as a complex molecule. **Scheme 41** shows some possible bioactive targets.[148, 32c] After initial evaluation, we targeted the synthesis of Chlamydocin and related histone deacetylase inhibitory cyclopeptides. This natural product was isolated from a fungal strain (*Diheterospora chlamydosporia)*[129a]. Several contributions were devoted to the synthesis of Chlamydocin and related cyclopeptides with a different zinc binding bioactive motif.[132-136] However access to them was hampered by functional group incompatibilities, long sequences with low yielding transformations or not having a universal synthetic approach. We realised that these different pharmacophoric warheads could be synthesised from a common, cyclopropanol containing precursor.



***Scheme 41**. Functional groups of interest in bioactive compounds, which can be accessed from cyclopropanol in a pluripotent fashion*

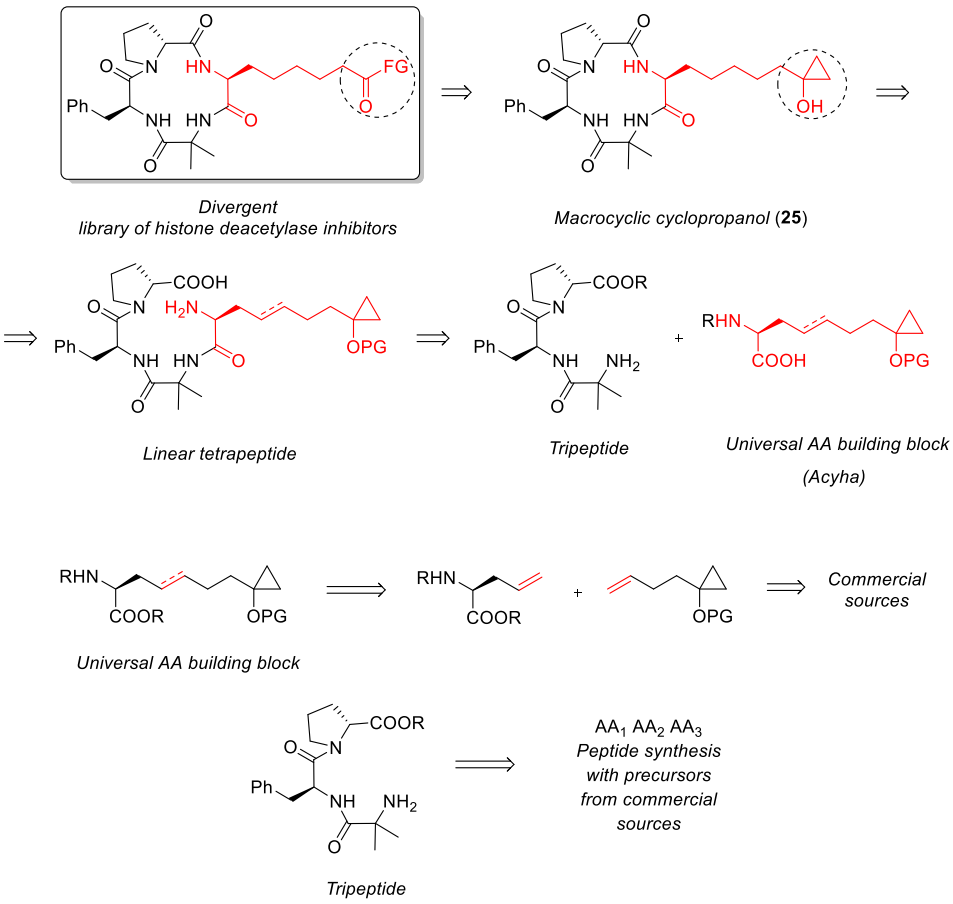
This might be carried out by a diversification possibility as a consequence of cyclopropane ring cleavage reactions. In the copper-catalysed oxidative pathway a Michael-acceptor enone is formed, which can react with a number of Michael-donors, yielding various β-functionalised carbonyl compounds, thus opening up opportunities for diversity-oriented synthesis (**Scheme 42**).



***Scheme 42**. Cyclopropanols as versatile C_3-syntons for the diversity-oriented synthesis of beta-functionalised ketones*

Additionally, the continuously increasing popularity of diversity-oriented synthesis strategies offers the persistent challenge of developing novel synthetic pathways using pluripotent functional groups.

To conclude, we selected the total synthesis of HDAc inhibitory cyclopeptides as the main synthesis targets to validate the pluripotency of cyclopropanol and develop a universal approach to these bioactive compounds. Our approach is summarised in **Scheme 43**.



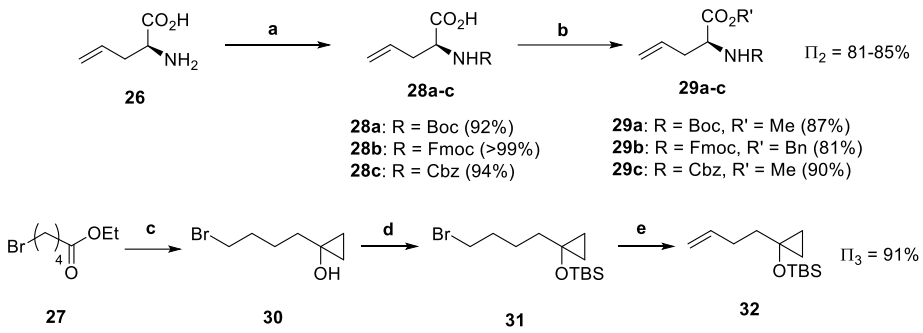
***Scheme 43**. Retrosynthetic strategy for the diversity-oriented synthesis of HDAC inhibitory cyclopeptides*

The macrocyclic cyclopropanol (**25**) was to be assembled through a macrolactamisation step between the *D*-proline C-terminus and N-terminus of the universal amino acid building block, since it is the optimal site of the ring closure.[136b] Before macrocyclisation, the required termini had to be liberated from their linear tetrapeptide precursor. The tetrapeptide is constructed by an amide-coupling protocol between a tripeptide and a non-proteinogenic amino acid building block containing a pluripotent functional group. The synthesis of tripeptide had to be realised by using known peptide-coupling methods from commercial amino acids. The universal building block ***AA*** (2-amino-7-(1-hydroxycyclopropyl)heptanoic acid: Acyha) can be prepared *via* a C-C bond formation between an amino acid precursor and an alkene with masked cyclopropanol functionality by using the metathesis approach. The participating coupling partners for the metathesis are readily available from commercial sources (**26** and **27**).

The synthesis sequence started with Boc-protection at the N-terminus of *S*-allyl glycine (**26**),[149] followed by the protection of the C-terminus through esterification with methyl iodide.[150] This two-step sequence afforded an 80% overall yield for **29a**. Various protecting groups (e.g. Cbz and Fmoc) were also installed on the N-terminus of the *S*-allyl

glycine in order to increase the applicability of different synthesis techniques, including solid-phase synthesis.

Similarly, ethyl 5-bromovalerate (**27**) was cyclopropanated by the Kulinkovich protocol, affording cyclopropanol (**30**) in a quantitative yield. However, the immediate protection of the hydroxyl group in bromine-containing cyclopropanol **30** was necessary due to its quite fast decomposition, presumably caused by traces of generated HBr. Thus, the introduction of the TBS-protecting group afforded stable silyl protected cyclopropanol (**31**). HBr was eliminated using a strong base affording the alkene coupling partner bearing a protected cyclopropanol function (**32**). The overall yield of **32** was 91% (**Scheme 44**).



Reagents and conditions: for **29a**, a) Boc_2O, $NaHCO_3$, MeOH, sonification; b) K_2CO_3, MeI, acetone; for **29b**, a) FmocOSu, K_2CO_3, dioxane/H_2O; b) BnBr, $NaHCO_3$, DMF; for **4c**, a) CbzCl, $NaHCO_3$, H_2O; b) K_2CO_3, MeI, acetone; for **6**: c) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O; d) TBSCl, imidazole, THF; e) *t*-BuOK, THF

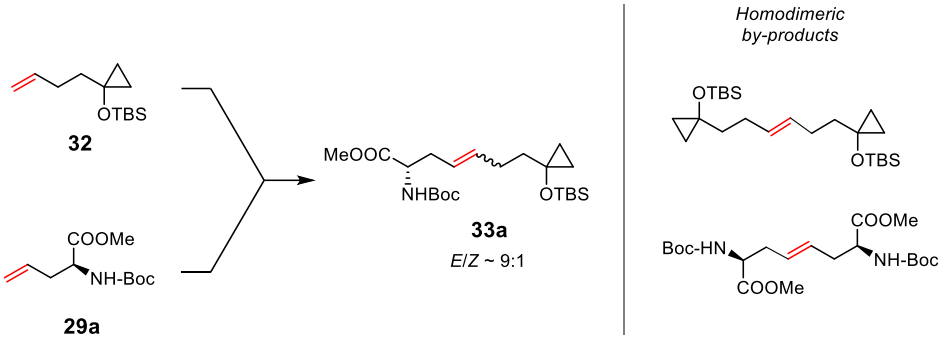
***Scheme 44**. Synthesis of cross-metathesis coupling partners*

The cross-metathesis approach has been widely applied in a synthesis similar to Acyha, protected amino acid building blocks.[151-154] However, this cross-coupling required optimisation, because the coupling partners might afford non-selective self-metathesis products (belonging to Type I, according to the Grubbs classification).[155]

At the initial runs, when 3 equiv. of **32** was used in the presence of 5 mol% Grubbs II (**G-II**) catalyst, unsatisfactory yields (31%) were attained (**Table 4**, entry 1) due to the low conversion of the starting materials and homodimerisation processes. Increasing the amount of **32** to 5 equiv. to suppress the homodimerisation only slightly improved the yield of the target product **33** (**Table 4**, entry 2). It was supposed that the observed deactivation of the **G-II** catalyst occurred due to a phosphine release.[156] To overcome this drawback, CuI (10 mol%) was added as a phosphine scavenger, thus suppressing the decomposition pathway.[157] However, only a slight increase in yield (40%) was achieved (entry 3). In order to prove the assumption of catalyst deactivation, the catalyst loading was increased to 10%. Doing so increased the yield, and a nearly full conversion of the starting material **29a** was achieved (**Table 4**, entry 4). When **G-II** was replaced by a more stable Hoveyda-Grubbs II catalyst (**HG-II)** (5 mol%) and the static argon atmosphere was changed to a dynamic argon flow to flush away the forming ethylene, full conversion in a significantly shorter time with a 50% yield of the desired product was obtained (**Table 4**, entry 5). Using a 5-fold excess of the inexpensive cyclopropane compound **32** made it possible to increase the yield up to 67% in the presence of 3 mol% of the catalyst (**Table 4**, entry 6).[155] DCM being replaced by toluene resulted in shortened reaction times and in

slightly better yields (69%; **Table 4**, entry 7). Finally, heating the reaction mixture at 50 °C provided the required cross-coupled product **33** in an acceptable 75% yield just after 1 h reaction, with only 1 mol% of **HG-II** (**Table 4**, entry 8). Due to the following hydrogenation step, the ratio of (E/Z)-isomers was not important.

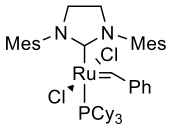
***Table 4**. Optimisation of the cross-metathesis step*



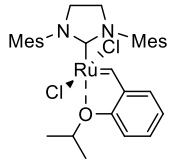
Entry	32 [equiv.]	Solvent	Cat. loading [%]	Time [h]	Yield [%]
1	3	DCM	5 (**G-II**)	11	31
2	5	DCM	5 (**G-II**)	30	32
3	3[a]	DCM	5 (**G-II**)	24	40
4	3	DCM	10 (**G-II**)	3	49
5	3[b]	DCM	5 (**HG-II**)	2	50
6	5	DCM	3 (**HG-II**)	2	67
7	5	Toluene	3 (**HG-II**)	1	69
8	5[c]	Toluene	1 (**HG-II**)	1	75

[a] CuI (10 mol%) was used as an additive; [b] Reactions with HG-II were performed under dynamic argon flow; [c] At 50 °C.

Grubbs 2nd generation catalyst **(G-II)**

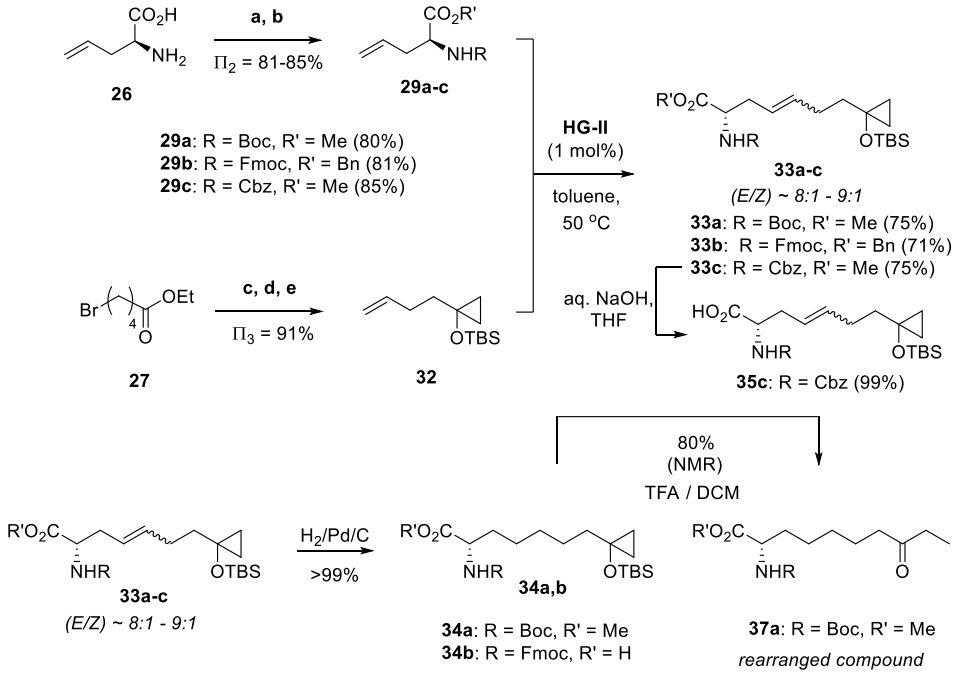


Hoveyda-Grubbs 2nd generation catalyst **(HG-II)**



The metathesis-coupled building block (**33**) can either be incorporated into the peptide scaffold, or a reduction can be carried out before to prepare the saturated building block **34**. In our synthetic scheme, the direct coupling of Cbz-protected acid **35c** obtained from basic hydrolysis of unsaturated ester **33c** was allowed to react with tripeptide **36**. We had encountered incompatibilities in the orthogonality of the protecting groups (Boc vs. TBS). When using the model building block **34a,** the TBS

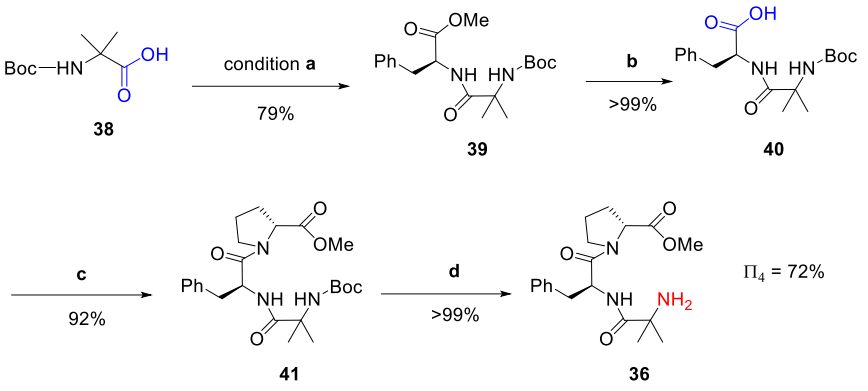
acid-labile group did not tolerate the Boc removal conditions and resulted in ethyl ketone **37a** from the cyclopropanol rearrangement. The final reaction sequence for the Acyha synthesis is shown in **Scheme 45**.



Reagents and conditions: for **29a**, a) Boc_2O, $NaHCO_3$, MeOH, sonification; b) K_2CO_3, MeI, acetone; for **29b**, a) FmocOSu, K_2CO_3, dioxane/H_2O; b) BnBr, $NaHCO_3$, DMF; for **29c**, a) CbzCl, $NaHCO_3$, H_2O; b) K_2CO_3, MeI, acetone; for **32**: c) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O; d) TBSCl, imidazole, THF; e) *t*-BuOK, THF. **HG-II** = Hoveyda-Grubbs catalyst, 2nd generation.

***Scheme 45**. Synthesis of the universal building block – 2-amino-7-(1-hydroxycyclopropyl)heptanoic acid (Acyha)*

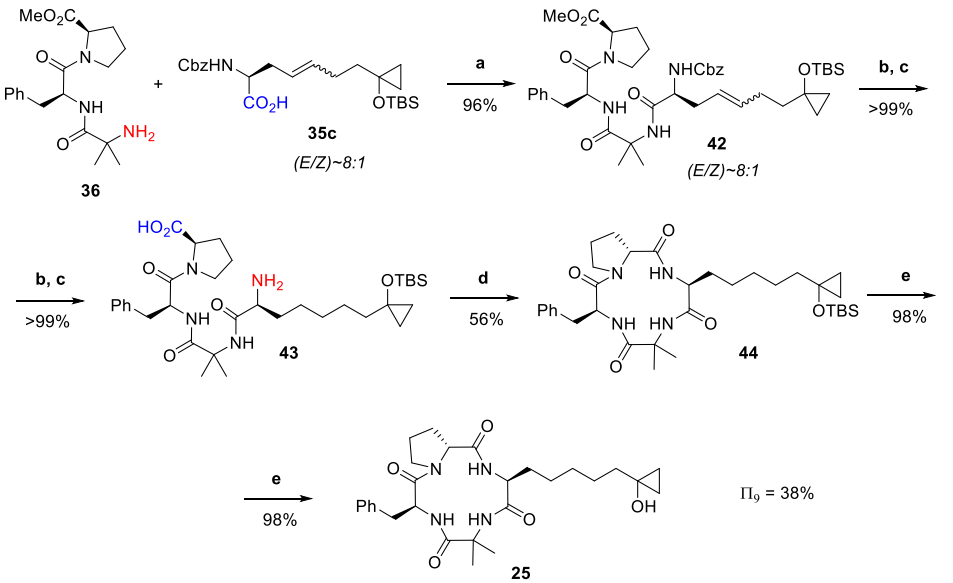
The tripeptide synthesis was based on the literature precedents from Kazmaier[136h] and Baldwin[136e] starting with commercially available Boc-aminoisobutyric acid (**38**). (**Scheme 46**).



Reagents and conditions: **a**) ClCOO^{i}Bu, NEM, then (*S*)-Phe-OMe hydrochloric salt in THF; **b**) 1M aq.NaOH in THF; **c**) (*R*)-Pro-OMe hydrochloric salt, TEA,HOBT,DCC in THF; **d**) 4M HCl in dioxane, DCM

***Scheme 46**. Synthesis of tripeptide **36** for further peptide coupling*

The linear tetrapeptide **42** was synthesised via a TBTU-mediated peptide coupling reaction in excellent yield (96%). The following two steps aimed to liberate both the C- and N-termini in the tetrapeptide. The carboxylic acid motif was liberated via alkaline hydrolysis, whilst the N-terminal Cbz protecting group was removed according to a simultaneous flow mode hydrogenation protocol, together with a double bond reduction, resulting in precursor **43**. After slight optimisation, it was found that HATU-mediated macrocyclisation[132d] is the most efficient approach, while the pyridine nitrogen of HATU assists in preforming the required entropically disfavoured cyclisation conformation,[158] yielding the protected macrocyclic tetrapeptide **44** in affordable yield (56%). The subsequent removal of silyl protection from the cyclopeptide provided macrocyclic pluripotent cyclopropanol **25** (**Scheme 47**).

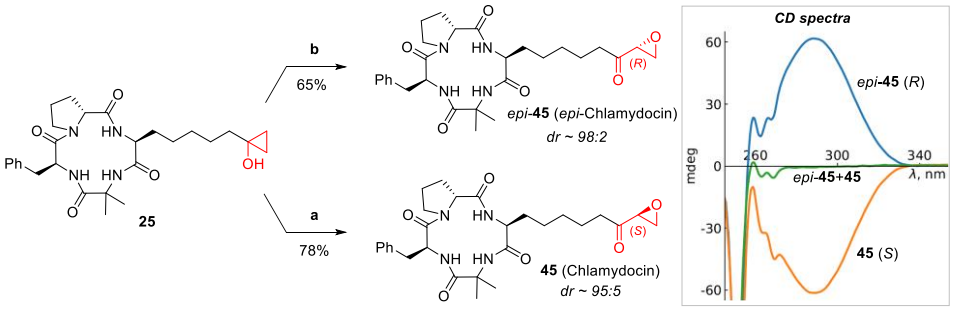


Reagents and conditions: a) TBTU, HOBT, Et_3N in CH_2Cl_2; b) NaOH in THF/H_2O; c) 10% Pd/C, H_2 in MeOH, H-Cube® (60 °C, 60 bar); d) HATU, DIPEA in DMF; e) 1 M TBAF in THF

Scheme 47**. Synthesis of macrocyclic cyclopropanol **25

Then the aerobic oxidation protocol (see Chapter 3.1) was applied to synthesise Chlamydocin (**45**) and its R-epoxide epimer (epi-**45**). As the epoxide motif in the natural product **45** has S-configuration, poly-D-leucine (PDL) was used in the epoxidation step of the oxidised cyclopropanol to afford 65-78% yield. The overall yield of total synthesis of Chlamydocin (**45**) and its epimer over 10 steps (the longest linear sequence from **26**) was 26%. Excellent diastereoselectivities, dr 95:5 – 98:2, were obtained in the PDL/PLL-mediated asymmetric epoxidation step. The absolute configuration of the synthesised cyclopeptide diastereomers was proved by CD spectroscopic measurements (measured by Nele Konrad, TalTech). The source of the CD signal derived from the (*S*)-configuration of the chiral centre in the epoxide motif, showing a negative Cotton effect with a maximum at ~290 nm for the (*S*)-stereoisomer. Accordingly, a positive absorption band was seen for the epimer. In addition, comparing the optical rotation ($[\alpha]_D$ = −140) of the samples with that value from the literature ($[\alpha]_D$ = −147.5)[129,136]. **Scheme 48** also demonstrated full accordance with the precedents.

It can be concluded that our synthesis protocol compared to that of Schmidt (17% overall yield over 18 steps; previous highest yield synthesis from *R,R*-tartaric acid)[136b] offers the preparation of the anticancer natural product Chlamydocin in the highest yield (26% overall yield) and demonstrates outstanding stereoselectivity.



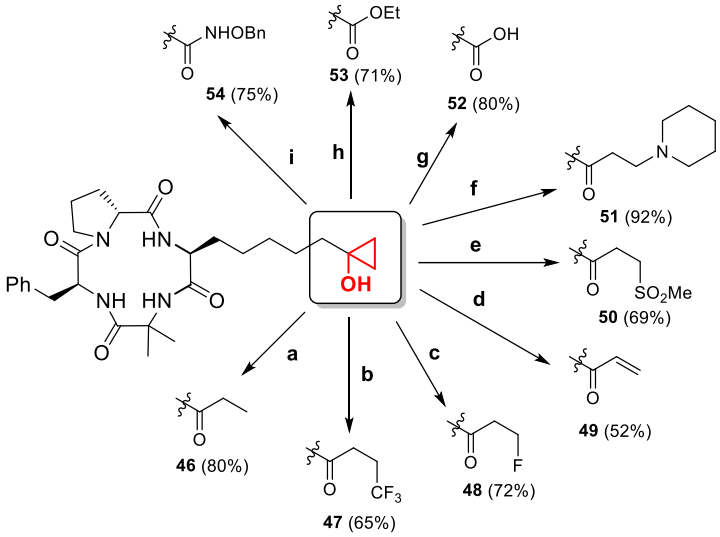
Reagents and conditions: a) Air, 0.5 mol% $Mn(acac)_3$ in THF, 0 °C, 2 h, then poly-D-leucine/SiO_2, DBU, -25 °C, 48 h; b) Air, 0.5 mol% $Mn(acac)_3$ in THF, 0 °C, 2 h, then poly-L-leucine/SiO_2, DBU, -25 °C, 48 h.

***Scheme 48**. Stereodivergent synthesis of Chlamydocin and its epimer*

Based on the achieved stereochemical diversity, a series of chlamydocin analogues were generated by exploiting the pluripotency of the cyclopropanol function from the common precursor **25**.

The supposed pluripotent intermediate **25** underwent facile rearrangement to the corresponding carbonyl compounds in the presence of an acid catalyst. Even, the direct transformation of the TBS-protected cyclopropanol **44** to Aoda-containing cyclopeptide **46** was obtained in 80% yield by treatment with TFA in DCM. Considering the importance of fluorinated compounds in medicinal chemistry,[159] including ^{18}F PET imaging,[160] late-stage trifluoromethylation[102-104] and fluorination[97], fluorinated analogues **47** and **48** were successfully synthesised. A number of functionalised carbonyl compounds were prepared through the copper-catalysed aerobic oxidation of the cyclopropanol moiety, e.g. vinyl ketone **49**, γ-ketosulfone **50** and β-amino ketone **51**. The successful synthesis of aza-Michael adduct **51** is an extension of the preparation of sulfa-Michael adducts (Chapter **3.2**) by exploiting the pluripotency of the formed enone intermediate.

A side chain of Asu in compound **52** was installed by the fast and high-yielding oxidation of cyclopropanol **25** with bis(trifluoroacetoxy)iodobenzene (PIFA) in glacial acetic acid.[107] Bioactive Asu derivatives[132] were also prepared. The oxidation of **25** with PIFA in ethanol afforded the corresponding ethyl ester **53**. The formation of amides was realized *via* the generation of mixed anhydrides from cyclopropanols in the aprotic media.[161] Thus, the oxidation of cyclopropanol **25** with $PhI(O_2CAr)_2$ [Ar = 2,4,6-trichlorophenyl] in CH_2Cl_2 generated a mixed anhydride, which was activated for the subsequent nucleophilic attack. The latter produced benzyl-protected hydroxamic acid **54** in 75% yield in reaction with $BnONH_2$. Analogue **54** is the immediate precursor of the free hydroxamic acid, known as a strong HDAC inhibitor (**Scheme 49**).[132]



Reagents and conditions: a) TFA, CH_2Cl_2, 24 h; b) Togni reagent, 10 mol% $[Cu(CH_3CN)_4]BF_4$, 20 min; c) Selectfluor, 20 mol% AgF, C_6H_6/H_2O, reflux, 4 h; d) Air, $Cu(OAc)_2$, MeOH, 3 h; e) Air, $Cu(OAc)_2$, $MeSO_2Na$, MeOH, 3 h; f) Air, $Cu(OAc)_2$, piperidine, MeOH, 45 min; g) PIFA, acetic acid, 30 min; h) PIFA, ethanol, 30 min; i) $PhI(O_2CAr)_2$ [Ar = 2,4,6-trichlorophenyl], CH_2Cl_2, 2 h, then NH_2OBn (10 equiv.), 10 h. All of the reactions were carried out at room temperature unless noted otherwise

***Scheme 49**. Divergent preparation of Chlamydocin analogues by late-stage cyclopropane ring cleavage*

In conclusion, the first use of the cyclopropanol group as a robust pluripotent intermediate for diversity-oriented synthesis was demonstrated. Stereochemical and functional diversity on multiple levels was achieved. The total synthesis of chlamydocin, its (*R*)-epoxide epimer, and several chlamydocin analogues verified the efficiency of the approach to access a number of different functional groups containing HDAC inhibitory peptides. Due to the broad spectrum of chemical transformations of cyclopropanol chemistry, further advances in the late stage diversification from the single cyclopropanol precursor can be expected, and these will be suitable for the generation of bioactive molecular libraries in general and HDAC inhibitory peptides in particular, facilitating drug discovery programmes and providing greater hope for solving medical-societal problems.

Conclusions

The successful development of biomimetic, transition metal-catalysed, environmentally friendly, oxidative ring cleavage methodologies of tertiary cyclopropanols was achieved. The synthetic application of the mentioned ring cleavage methods was demonstrated in the total synthesis of bioactive scaffolds, including HDAc inhibitory cyclopeptide products, obtained in step-economic manner, with good yields, and chemo- and regioselectivity. Our synthetic approach to the targeted analogues followed the concept of diversity-oriented synthesis through the pluripotency of the cyclopropanol functional group.

The specific results:

- It was shown that atmospheric oxygen can be used as an efficient oxidant to perform ring cleavage of cyclopropanols facilitated by transition metal (Mn, Cu) catalysis.
    - A method for the synthesis of chiral α,β-epoxy ketones in high yield (58-84%) and enantioselectivity (80-97% ee), under mild conditions with exceptional tolerance for a number of functional groups was developed.
    - A method for the synthesis of γ-keto sulfones (27-94%) via the intermediate formation of enones was elaborated. The method can be used for the preparation of enones and expanded to aza-Michael adducts.
- A general strategy for the total synthesis of HDAc inhibitory cyclopeptides and their analogues was developed, characterised by mild reaction conditions and perfect stereoselectivity for the formation of AOE derivatives. Chlamydocin was synthesised in 10 steps in 26% overall yield, the best outcome reported to date.
- The developed approach enabled the diversity-oriented synthesis of a wide variety of bioactive cyclopeptide analogues, proving the cyclopropanol functional group to be a pluripotent structural motif.

References

[1](a) *Green Chemistry*; Lancaster, M. **2002**, Cambridge, The Royal Society of Chemistry; (b) *Green Chemistry: theory and practice*; Anastas, P.T; Warner, J.C. **1998**, Oxford, Oxford University Press.

[2] *Modern Oxidation Methods*; Bäckvall, J.-E. **2010**, Weinheim, Wiley.

[3] Hone, C.A.; Kappe, C.O. *Top. Curr. Chem*. **2019**, *377*, 2-45.

[4] *Green Oxidation in Organic Synthesis*; Jiao, N.; Stahl, S.S. (Ed.); **2019**, Hoboken, NJ, Wiley.

[5] *Cyclopropanes in Organic Synthesis*; Kulinkovich, O.G. **2015**, Hoboken, NJ, Wiley.

[6] Hone, C.A; Roberge, D.M; Kappe, C.O. *ChemSusChem* **2016**, *9*, 1-11.

[7] Caron, S; Dugger, R.W; Ruggeri, S.G; Ragan, J.A; Ripin, D.H.B. *Chem.Rev.* **2006**, *106*, 2943-2989.

[8] Osterberg, P.M; Niemeier, J.K; Welch, C.J; Hawkins, J.M; Martinelli, J.R; Johnson, T.E; Root, T.W; Stahl, S.S. *Org. Process Res. Dev.* **2015**, *19*, 1537-1543.

[9] Elvira, K.S; Solvas, X.C; Wootton, R.C.R; deMello A.J. *Nat. Chem.* **2013**, *5*, 905-915.

[10] Gemoets, H.P.L; Su, Y; Shang, M; Hessel, V; Luque, R; Noël, T. *Chem. Soc. Rev*. **2016**, *45*, 83-117.

[11] Streckx, H; Morel, B; Maes, B.U.W. *Angew. Chem. Int. Ed.* **2019**, *58*, 7946-7970.

[12] Parmeggiani, C; Cardona, F. *Green Chem.* **2012**, *14*, 547-564.

[13] (a) Bell, A.T. *Science*, **2003**, *299*, 1688-1691; (b) Schlögl, R; Hamid, S.B.A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1628-1637; (c) Polshettiwar, W; Varma, R.S. *Green Chem*. **2010**, *12*, 743-754.

[14] (a) Dominguez de Villota, E; García Carmona, M.T; Rubio, J.J; Ruiz de Andrés, S. *Br. J. Anaesth*. **1981**, *53*, 1325-1328; (b) Kendrew, J.C; Bodo, G; Dintzis, H.M; Parrish, R.G; Wyckoff, H. *Nature*, **1958**, *181*, 662-666.

[15] Meunier, B; de Visser, S.P; Shaik, S. *Chem.Rev.* **2004**, *104*, 3947-3980.

[16] McCall, K.A; Huang, C; Fierke, C.A; *J. Nutr.* **2000**, *130*, 1437-1446.

[17] Festa, R.A; Thiele, D.J. *Curr. Biol.* **2011**, *21*, 877-883.

[18] Dismukes, G.C. *Chem. Rev.* **1996**, *96*, 2909-2926.

[19] McCann, S.D; Stahl, S.S. *Acc. Chem. Res.* **2015**, *48*, 1756-1766.

[20] Bugg, T.D.H. *Tetrahedron*, **2003**, *59*, 7075-7101.

[21] Edmondson, D.E; Mattevi, A; Binda, C; Li, M; Hubálek, F. *Curr. Med. Chem.* **2004**, *11*, 1983-1993.

[22] Weschler, C.J; Hoffman, B.M; Basolo, F.J. *J. Am. Chem. Soc.* **1975**, *97*, 5278-5280.

[23] (a) Petsi, M; Zografos, A.L. *Synthesis*, **2018**, *50*, 4715-4745; (b) Meng, S-S; Lin, L-R; Luo, X; Lv, H-J; Zhao, J-L; Chan, A.S.C. *Green Chem*. **2019**, *21*, 6187-6193.

[24] Klinman, J.P. *Chem. Rev.* **1996**, *96*, 2541-2562.

[25] Vaughan, O.P.H; Kyriakou, G; Macleod, N; Tikhov, M; Lambert, R.M. *J. Catal.* **2005**, *236*, 401-404.

[26] Irie, R; Noda, K; Ito, Y; Katsuki, T. *Tetrahedron*, **1990**, *32*, 1055-1058.

[27] Zhang, W; Loebach, J.L; Wilson, S.R; Jacobsen, E.N. *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

[28] Monnier, J.R. *Appl. Catal. A-Gen.* **2001**, *221*, 73-91.

[29] Mukaiyama, T; Yamada, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17-35.

[30] Yamada, T; Ikeno, T; Ohtsuka, Y; Kezuka, S; Sato, M; Iwakura, I. *Sci. Technol. Adv. Mater.* **2006**, 7, 184-196.

[31] Bougauchi, M; Watanabe, S; Arai, T; Sasai, H; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329-2330.
[32] (a) Pineschi, M. *Eur. J. Org. Chem*. **2006**, 4979-4988. (b) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359-2383. (c) Gorzynski Smith, J. *Synthesis* **1984**, 629-656. (d) *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed.; **2006**, Weinheim, Wiley.
[33] (a) Meng, L.; Mohan, R.; Kwok, B. H. B.; Elofsson, M.; Sin, N.; Crews, C. M. *Proc. Natl. Acad. Sci*. **1999**, *96*, 10403-10408. (b) Demo, S. D.; Kirk, C. J.; Aujay, M. A.; Buchholz, T. J.; Dajee, M.; Ho, M. N.; Jiang, J.; Laidig, G. J.; Lewis, E. R.; Parlati, F.; Shenk, K. D.; Smyth, M. S.; Sun, C. M.; Vallone, M. K.; Woo, T. M.; Molineaux, C. J.; Bennett, M. K. *Cancer Res*. **2007**, *67*, 6383-6391. (c) Keller, L.; Plaza, A.; Dubiella, C.; Groll, M.; Kaiser, M.; Müller, R. *J. Am. Chem. Soc*. **2015**, *137*, 8121-8130. (d) Tsunematsu, Y.; Nishimura, S.; Hattori, A.; Oishi, S.; Fujii, N.; Kakeya, H. *Org. Lett*. **2015**, *17*, 258-261. (e) Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem*. **2009**, 371-377.
[34] Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett*. **1976**, *17*, 1831-1834.
[35] Weitz, E; Scheffer, A. *Ber.*, **1921**, *54*, 2327-2344.
[36] Porter, M. J.; Skidmore, J. *Org. React*. **2009**, *74*, 425-672.
[37] (a) Lygo, B; Gardiner, S.D; McLeod, M.C; To, D.C.M. *Org. Biomol. Chem.* **2007**, *5*, 2283-2290; (b) Lu, X; Liu, Y; Sun, B; Cindric, B; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134-8135; (c) Wang, X; Reisinger, C; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070-6071.
[38] (a) Juliá, S; Masana, J; Vega, J.C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929-931; (b) Juliá, S; Guixer, J; Masana, J; Rocas, J; Colonna, S; Annuziata, R; Molinari, H; *J. Chem. Soc. Perkin Trans. 1*, **1982**, 1317-1324.
[39] Marsman, B; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312-2314.
[40] (a) Lauret, C; Roberts, S.M. *Aldrichimica Acta*, **2002**, *35*, 47-51; (b) Geller, T; Roberts, S.M. *J. Chem. Soc. Perkin Trans. 1* **1999**, 1397-1398.
[41] Porter, M.J; Skidmore, *Chem. Commun*. **2000**, 1215-1225.
[42] Lygo, B; Wainwright, P.G. *Tetrahedron Lett*. **1998**, *32*, 1599-1602.
[43] (a) Corey, E.J; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287-1290; (b) Arai, S; Tsuge, H; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 7563-7566.
[44] (a) Reisinger, C; Wang, X; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 8112-8115; (b) Lifchits, O; Mahlau, M; Reisinger, C.M; Lee, A; Farés, C; Polyak, I; Gopakumar, G; Thiel, W; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677-6693.
[45] Enders, D; Zhu, J; Raabe, G. *Angew. Chem. Int. Ed.* **1996**, *35*, 1725-1728.
[46] Kirihara, M; Ichinose, M; Takizawa, S; Momose, T. *Chem. Commun.* **1998**, 1691-1692.
[47] Morisson, V; Barnier, J.-P; Blanco, L. *Tetrahedron Lett.* **1999**, *40*, 4045-4046.
[48] Barnier, J.-P; Morisson V; Blanco, L. *Synth. Commun.* **2001**, *31*, 349-357.
[49] Kulinkovich, O.G; Astashko, D.A; Tyvorskii, V.I; Ilyina, N.A. *Synthesis*, **2001**, 1453-1455.
[50] Tyvorskii, V.I; Astashko, D.A; Kulinkovich, O.G. *Tetrahedron*, **2004**, *60*, 1473-1479.
[51] (a) Shaaban, S; Liang, S; Liua N.-W; Manolikakes, G. *Org. Biomol.Chem*., **2017**, *15*, 1947-1955; (b) Liu, N.-W; Liang S; Manolikakes, G. *Synthesis,* **2016**, *48*, 1939-1973; (c) Feng, M; Tang, B; Liang S.H; Jiang, X. *Curr. Top. Med. Chem.*, **2016**, *16*, 1200-1216; (d) Drabowicz, J; Kielbasinski, P; Zajac A; Wach-Panfilow, P. *Comprehensive Organic Synthesis*, ed. Knochel P; Molander, G.A. Elsevier: Amsterdam, 2nd Ed., **2014**, Vol. 6, 131-174; (e) Markitanov, Y. M; Timoshenko V.M; Shermolovich, Y.G. *J. Sulfur Chem*., **2014**, *35*, 188-236; (f) Meadows, D.C; Gervay-Hague, J. *Med. Res. Rev*., **2006**, *26*, 793-814.

[52] (a) Meanwell, N.A. *J. Med. Chem.* **2011**, *54*, 2529-2591; (b) Patani, G.A; LaVoie, E.J. *Chem. Rev.* **1996,** *96*, 3147-3176; (c) Konduru, N.K; Dey, S; Sajid, M; Owais, M; Ahmed, N. *Eur. J. Med. Chem.* **2013**, *59*, 23-30; (d) Curti, C; Laget, M; Ortiz Carle, A; Gellis, A; Vanelle; P. *Eur. J. Med. Chem*. **2007**, *42*, 880-884.
[53] (a) Patai, S; Rappoport, Z; Stirling, C.J.M. *The Chemistry of Sulphones and Sulfoxides*, **1988**, Wiley, New York; (b) Julia, M; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833-4836; (c) Taylor, R.J.K; Casy, G. *Org. React.* **2004**, *62*, 359-425.
[54] (a) Pinnick, H.W; Reynolds, M.A. *J. Org. Chem.* **1979**, *44*, 160-161; (b) Sreedhar, B; Reddy, M.A; Reddy, P.S. *Synlett*, **2008**, 1949-1952; (c) Jin, Z; Xu, J; Yang, S; Song, B.-A; Chi, Y.R. *Angew. Chem. Int. Ed.* **2013**, *52*, 12354-12358.
[55] (a) Khatik, G.L; Kumar, R; Chakraborti, A.K. *Org. Lett.* **2006**, *8*, 2433-2436; (b) Rana, N.K; Selvakumar, S; Singh, V.K. *J. Org. Chem.* **2010**, *75*, 2089-2091; (c) Enders, D; Lüttgen, K; Narine, A.A. *Synthesis*, **2007**, 959-980; (d) Yadav, J.S; Reddy, B.V.S; Baishya, G; *J. Org. Chem.* **2003**, *68*, 7098-7100.
[56] (a) Voutyritsa, E; Triandafillidi, I; Kokotos, C.G. *Synthesis*, **2017**, 917-924; (b) Jegelka, M; Plietker, B; *Chem. Eur. J.* **2011**, *17*, 10417-10430; (c) Kirihara, M; Itou, A; Noguchi, T; Yamamoto, J. *Synlett*, **2010**, 1557.
[57] Bhunia, A; Yetra, S.R; Bhojgude, S.S; Biju, A.T. *Org. Lett.* **2012**, *14*, 2830-2833.
[58] Vellakaran, M; Andappan, M.M.S; Nagaiah, K; Nanubolu, J.B. *Eur. J. Org. Chem.* **2016**, 3575-3583.
[59] Fang, G; Liu, J; Shang, W; Liu, Q; Bi, X. *Chem. – Asian J.* **2016**, *11*, 3334.
[60] Jana, N.K; Verkade, J.G. *Org. Lett.* **2003**, *5*, 3787-3790.
[61] Lutz, M; Wenzler, M; Likthotvorik, I. *Synthesis*, **2018**, *50*, 2231-2234.
[62] Gruffin, R.J; Henderson, A; Curtin, N.J; Echalier, A; Endicott, J.A; Hardcastle, I.R; Newell, D.R; Noble, M.E.M; Wang, L.-Z; Golding, B.T. *J. Am. Chem. Soc.* **2006**, *128*, 6012-6013.
[63] (a) Breslow, R.J. *J. Am. Chem. Soc.* **1957**, *79*, 1762-1763; (b) Paul, M; Sudkaow, P; Wessels, A; Schlörer, N.E; Neudörfl, J.-M; Berkessel, A. *Angew. Chem. Int. Ed.* **2018**, 57, 8310-8315.
[64] Heravi, M.M; Hajiabbasi, P. *Mol. Divers.* **2014**, *18*, 411-439.
[65] Katsuki, T; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, 102, 5974-5976.
[66] Cha, J.K; Kulinkovich, O.G. *Org. React.* 2012, 77, 1-159.
[67] Liu, Q; You, B; Xie, G; Wang, X. *Org. Biomol. Chem.* **2019**, DOI: 10.1039/C9OB02197C.
[68] Iskryk, M; Barysevich, M; Ošeka, M; Adamson, J; Kananovich, D.G. *Synthesis*, **2019**, *51*, 1935-1948.
[69] (a) Kulinkovich, O.G. *Chem. Rev.* **2003**, *103*, 2597-2632; (b) Gibson, D.H; De Puy, C.H; *Chem. Rev.* **1974**, *74*, 605-623.
[70] Imamoto, T; Kamiya, Y; Hatajima, T; Takahashi, H. *Tetrahedron Lett*. **1989**, *30*, 5149-5152.
[71] Simmons, H.E; Smith, R.D. *J. Am. Chem. Soc.* **1958**, 80, 5323-5324.
[72] Kulinkovich, O.G; Sviridov, S.V; Vasilevskii, D.A. *Zh. Org. Khim*. **1989**, *25*, 2244-2245.
[73] Kulinkovich, O.G; Sviridov, S.V; Vasilevski, D.A. *Synthesis*, **1991**, 234.
[74] (a) Corey, E.J; Rao, S.A; Noe, M.C. *J. Am. Chem. Soc.* **1994**, *116*, 9345-9346; (b) Konik, Y.A; Kananovich, D. G; Kulinkovich, O.G. *Tetrahedron* **2013**, *69*, 6673-6678; (c) Kulinkovich, O.G; Kananovich, D.G; Lopp, M; Snieckus, V. *Adv. Synth. Catal.* **2014**, *356*, 3615-3626.
[75] (a) Chaplinski, V; de Meijere, A. *Angew. Chem. Int. Ed.* **1996**, 35, 413-414; (b) Bertus, P; Szymoniak, J. *Chem. Commun.* **2001**, 1792-1793; (c) Lee, J; Kim, H; Cha, J.K. *J. Am. Chem. Soc.* **1996**, *118*, 4198-4199.

[76] (a) Fukuzawa, S.; Furuya, H.; Tsuchimoto, T. *Tetrahedron,* **1996**, *52*, 1953-1960; (b) Sato, T; Watanabe, M; Murayama, E. *Tetrahedron Lett*. **1986**, *27*, 1621-1624.
[77] (a) Murai, S; Aya, T; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354-4356; (b) Lechevallier, A; Huet, F; Conia, J.M. *Tetrahedron* **1983**, *39*, 3317-3327.
[78] de Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809-826.
[79] Allen, F.H; Kennard, O; Taylor, R. *Acc. Chem. Res*. **1983**, *16*, 146-153.
[80] Gauss, J; Cremer, D; Stanton, J.F. *J. Phys. Chem. A* **2000**, *104*, 1319-1324.
[81] (a) Cremer, D; Gauss, J; *J. Am. Chem. Soc.* **1986**, *108*, 7467-7477; (b) Exner, K; von Ragué Schleyer, P. *J. Phys. Chem. A* **2001**, *105*, 3407-3416.
[82] Carion, R; Champagne, B; Monaco, G; Zanasi, R; Pelloni, S; Lazzeretti, P. *J. Chem. Theory Comput.* **2010**, *6*, 2002-2018.
[83] *The chemistry of the cyclopropane group*; Liu, H.-U; Walsh, C.T. (**1987**) (eds Patai, S; Rappoport; Z.) Wiley, New York.
[84] De Puy, C. H. *Acc. Chem. Res.* **1968**, 1, 33-41;
[85] (a) Conia, J.M; Robson, M.J; *Angew. Chem. Int. Ed.* **1975**, *14*, 473-485; (b) Neureiter, N. P. *J. Org. Chem.* **1959**, *24*, 2044-2046.
[86] Nikolaev, A; Orellana, A. *Synthesis*, **2016**, *48*, 1741-1768.
[87] Mills, L.R; Rousseaux, S.A.L. *Eur. J. Org. Chem.* **2019**, 8-26.
[88] Barysevich, M.V; Kazlova, V.V; Kukel, A.G; Liubina, A.I; Hurski, A.L; Zhabinskii, V.N; Khripach, V.A. *Chem. Commun.* **2018**, *54*, 2800-2803.
[89] De Puy, C. H; Dappen, G. M; Hausser, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 3156-3157.
[90] Schaafsma, S.E; Molenaar, E.J.F; Steinberg, H; De Boer, Th.J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1301-1312.
[91] (a) Iwasawa, N; Funahashi, M; Narasaka, K. *Chem. Lett.* **1994**, 1697-1700; (b) Martinez, A. M; Cushmac, G. E; Roček, J. *J. Am. Chem. Soc.* **1975**, *97*, 6502-6510.
[92] Sherry, B; Abeles, R. H. *Biochemistry* **1985**, *24*, 2594-2605.
[93] (a) Sun, U. J; Lee, J; Cha, J. K. *Tetrahedron Lett*. **1997**, *38*, 5233-5236; (b) Shirai, M; Okamoto, S; Sato, F. *Tetrahedron Lett*. **1999**, *40*, 5331-5332.
[94] Liu, Y; Wang, Q.-L; Chen, Z; Zhou, C.-S; Xiong, B.-Q; Zhang, P.-L; Yang C.-A; Zhou, Q. *Beilstein J. Org. Chem*. **2019**, *15*, 256–278.
[95] Zhang, Y.-H; Zhang, W.-W; Zhang, Z.-Y; Zhao, K; Loh, T.-P. *Org. Lett.* **2019**, 21, 5101-5105.
[96] (a) Davis, D.C; Haskins, C.W; Dai, M. *Synlett*, **2017**, *28*, 913-918; (b) Wang, L; Ding, Q; Li, X; Peng, Y. *Asian J. Org. Chem*. **2019**, *8*, 385-390.
[97] Ishida, N; Okumura, S; Nakanishi, Y; Murakami, M. *Chem. Lett*. **2015**, *44*, 821-823.
[98] Ye, Z; Gettys, K.E; Shen, X; Dai, M. *Org. Lett*. **2015**, 17, 6074-6077.
[99] Ye, Z; Dai, M. *Org. Lett.* **2015**, *17*, 2190-2193.
[100] Feng, Y.-S; Shu, Y.-J; Cao, P; Xu, T; Xu, H.-J. *Org. Biomol. Chem.* **2017**, *15*, 3590-3593.
[101] Ye, Z; Cai, X; Li, J; Dai, M. *ACS Catal*. **2018**, *8*, 5907–5914.
[102] Kananovich, D.G; Konik, Y.A; Zubrytski, D.M; Järving, I; Lopp, M. *Chem. Commun*. **2015**, *51*, 8349-8352.
[103] Li, Y; Ye, Z; Bellmann, T.M; Chi, T; Dai, M. *Org. Lett.* **2015**, *17*, 2186-2189.
[104] Konik, Y.A; Kudrjashova, M; Konrad, N; Kaabel, S; Järving, I; Lopp, M; Kananovich, D.G. *Org. Biomol. Chem.* **2017**, *15*, 4635-4643.
[105] Prakash, G.K.S; Krishnamurti, R; Olah, G.A. *J. Am. Chem. Soc.* **1989**, *111*, 393-395.
[106] Rubottom, G. M; Marrero, R; Krueger, D. S; Schreiner, J. L. *Tetrahedron Lett*. **1977**, *18*, 4013.

[107] (a) Kirihara, M; Yokoyama, S; Kakuda, H; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 6907-6910; (b) Kirihara, M; Yokoyama, S; Kakuda, H; Momose, T. *Tetrahedron*, **1998**, *54*, 13943-13954.
[108] De Puy, C. H; Schnack, L. G; Hausser, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 3343-3346.
[109] Salaün, J. *Chem. Rev.* **1983**, *83*, 619-632.
[110] Mills, L.R; Arbelaez, L.M.B; Rousseaux, S.A.L. *J. Am. Chem. Soc.* **2017**, *139*, 11357-11360.
[111] Ebner, C; Carreira, E.M. *Chem. Rev.* **2017**, *117*, 11651-11679.
[112] Haym, I; Brimble, M.A. *Org. Biomol. Chem*. **2012**, *10*, 7649-7665.
[113] Cai, X; Liang, W; Dai, M. *Tetrahedron*, **2019**, *75*, 193-208.
[114] Astashko, D.A; Tyvorskii, I.V. *Tetrahedron Lett.* **2011**, *52*, 4792-4794.
[115] Piers, E; Friesen, R.W. *J. Org. Chem.* **1986**, *51*, 3405-3406.
[116] Keaton, K.A; Philips, A.J. *Org. Lett.* **2007**, *14*, 2717-2719.
[117] Rao, N.N; Parida, B.B; Cha, J.K. *Org. Lett.* **2014**, *16*, 6208-6211.
[118] Hurski, A.L; Kulinkovich, O.G. *Tetrahedron Lett*. **2010**, *51*, 3497-3500.
[119] (a) Ma, K; Yin, X; Dai, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 15209-15212; (b) Tan, Q; Yang, Z; Jiang, D; Cheng, Y; Yang, J; Xi, S; Zhang, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 6420-6424.
[120] Galloway, W.R.J.D; Bender, A: Welch, M; Spring, D.R. *Chem. Commun*. 2009, 2446-2462.
[121] Burke, M.D; Schreiber, S.L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.
[122] Galloway, W.R.J.D; Isidro-Llobet, A; Spring, D.R. *Nat. Commun.* **2010**, *1*, 1-13.
[123] Schreiber, S.L. *Nature*, **2009,** *457*, 153-154.
[124] (a) Vinogradov, A.A; Yin, Y; Suga, H. *J. Am. Chem. Soc*. **2019**, *141*, 4167-4181; (b) Henninot, A; Collins, J.C; Nuss, J.M. *J. Med. Chem*. **2018**, *61*, 1382-1414.
[125] (a) Räder, A.F.B; Weinmüller, M; Reichart, F; Schumacher-Klinger, A; Merzbach, S; Gilon, C; Hoffman, A; Kessler, H. *Angew. Chem. Int. Ed.* **2018**, *57*, 14414-14438; (b) Biron, E; Chatterjee, J; Ovadia, O; Langenegger, D; Brueggen, J; Hoyer, D; Schmid, H; Jelinek, R; Gilon, C; Hoffman, A; Kessler, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2595-2599.
[126] (a) Bolden, J.E; Peart, M.J; Johnstone, R.W. *Nat. Rev. Drug Discov.* **2006**, *5*, 769-784; (b) Falkenberg, K.J; Johnstone, R.W. *Nat. Rev. Drug Discov.* **2014**, *13*, 673-691.
[127] Newkirk, T.L; Bowers, A.A; Williams, R.M. *Nat. Prod. Rep.* **2009**, *26*, 1293-1320.
[128] (a) Mann, B.S; Johnson, J.R; Cohen, M.H; Justice, R; Pazdur, R. *Oncologist* **2007**, *12*, 1247-1252; (b) Eckschlager, T; Plch, J; Stiborova, M; Hrabeta, J. *Int. J. Mol. Sci.* **2017**, *18*, 1414-1438.
[129] (a) Closse, A; Huguenin, R. *Helv. Chim. Acta* **1974**, *53*, 533-545; (b) Shute, R.E; Dunlap, B; Rich, D.H. *J. Med. Chem.* **1987**, *30*, 71-78; (c) Kijima, M; Yoshida, M; Suguta, K; Horinouchi, S; Beppu, T. *J. Biol. Chem.* **1993**, *268*, 22429-22435; (d) Umehara, K; Nahahara, K; Kiyota, S; Iwami, M; Okamoto, M; Tanaka, H; Kohsaka, M; Aoki, H; Imanaka, H. *J. Antibiot.* **1983**, *36*, 478-483; (e) Meinke, P.T; Liberator, P. *Curr. Med. Chem.* **2001**, *8*, 211-235.
[130] (a) Miller, T.A; Witter, D.J; Belvedere, S. *J. Med. Chem*. **2003**, *46*, 5097-5116; (b) Luan, Y; Li, J; Bernatchez, J.A; Li, R. *J. Med. Chem.* **2019**, *62*, 3171-3183; (c) Banerjee, S; Adhikari, N; Amin, S.A; Jha, T. *Eur. J. Med. Chem.* **2019**, *164*, 214-240; c) Hai, Y; Christianson, D.W. *Nat. Chem. Biol.* **2016**, *12*, 741-747.
[131] (a) Bieliauskas, A.V; Pflum, M.K.H. *Chem. Soc. Rev.* **2008**, *37*, 1402-1413; (b) Porter, N.J; Christianson, D.W. *ACS Chem. Biol.* **2017**, *12*, 2281-2286; (c) Olsen, C.A; Montero, A; Leman, L.J; Ghadiri, M.R. *ACS Med. Chem. Lett.* **2012**, *3*, 749-753.

[132] (a) Kitir, B; Maolanon, A.R; Ohm, R.G; Colaco, A.R; Fristrup, P; Madsen, A.S; Olsen, C.A. *Biochemistry* **2017**, *56*, 5134-5146; (b) Wang, S; Li, X; Wei, Y; Xiu, Z; Nishino, N. *ChemMedChem*, **2014**, *9*, 627-637; (c) Traoré, M; Mietton, F; Maubon, D; Peuchmaur, M; Hilário, F.F; de Freitas, R.P; Bougdour, A; Curt, A; Maynadier, M; Vial, H; Pelloux, H; Hakimi, M.-A; Wong, Y.S. *J. Org. Chem.* **2013**, *78*, 3655-3675; (d) Islam, S; Bhuiyan, M.P.I; Islam, N; Nsiama, T.K; Oishi, N; Kato, T; Nishino, N; Ito, A; Yoshida, M. *Amino Acids*, **2012**, *42*, 2103-2110; (e) Bhuiyan, M.P; Kato, T; Okauchi, T; Nishino, N; Maeda, S; Nishino, T.G; Yoshida, M. *Bioorg. Med. Chem.* **2006**, *14*, 3438-3846; (f) Nishino, N; Jose, B; Shinta, R; Kato, T; Komatsu, Y; Yoshida, M. *Bioorg. Med. Chem.* **2004**, *12*, 5777-5784.

[133] (a) Pahari, A.K; Mukherjee, J.P; Chattopadhyay, S.K. *Tetrahedron* **2014**, *70*, 7185-7191; (b) Montero, A; Beierle, J.M; Olsen, C.A; Ghadiri, M.R. *J. Am. Chem. Soc.* **2009**, *131*, 3033-3041; (c) Bajgrowicz, J.A; El Hallaoui, A; Jacquier, R; Pigiere, C; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833-1843.

[134] (a) Mahindra, A; Millard, C.J; Black, I; Archibald, L.J; Schwabe, J.W.R; Jamieson, A.G. *Org. Lett.* **2019**, *21*, 3178-3182; (b) Chattopadhyay, S.K; Sil, S; Mukherjee, J.P. *Beilstein J. Org. Chem.* **2017**, *13*, 2153-2156; (c) Liu, T; Kapustin, G; Etzkorn, F.A. *J. Med. Chem*. **2007**, *50*, 2003-2006; (d) Kahnberg, P; Lucke, A.J; Glenn, M.P; Boyle, G.M; Tyndall, J.D.A; Parsons, P.G; Fairlie, D.P. *J. Med. Chem*. **2006**, *49*, 7611-7622; (e) Wernic, D; DiMaio, J; Adams, J. *J. Org. Chem.* **1989**, *54*, 4224-4228.

[135] Baldwin, J.E; Adlington, R.M; Godfrey, C.R.A; Patel. V.K. *J. Chem. Soc. Chem. Commun.* **1991**, 1277-1279.

[136] (a) Schmidt, U; Lieberknecht, A; Griesser, H; Bartkowiak, F. *Angew. Chem. Int. Ed*. **1984**, *23*, 318-320; (b) Schmidt, U; Lieberknecht, A; Griesser, H; Utz, R; Beuttler, T; Bartkowiak, F. *Synthesis* **1986**, 361-366; (c) Taunton, J; Hassig, C.A; Schreiber, S.L. *Science* **1996**, *272*, 408-411; (d) Kawai, M; Gardner, J.H; Rich, D.H. *Tetrahedron Lett*. **1986**, *17*, 1877-1880; (e) Baldwin, J.E; Adlington, R.M; Godfrey, C.R.A; Patel, V.K. *Tetrahedron* **1993**, *49*, 7837-7856; (f) Servatius, P; Kazmaier, U. *J. Org. Chem.* **2018**, *83*, 11341-11349; (g) Servatius, P; Kazmaier, U. *Org. Biomol. Chem.* **2018**, *16*, 3464-3472; (h) Quirin, C; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 371-377.

[137] (a) Smeets, N.B.H; van der Weide, P.L.J; Meuldijk, J; Vekemans, J.A.J.M; Hulshof, L.A. *Org. Process Res. Dev.* **2005**, 9, 757-762; (b) Baars, S; Drauz, K.-H; Krimmer, H.-P; Roberts, S.M; Sander, J; Skidmore, J; Zanardi, G. *Org. Process Res. Dev.* **2003**, 7, 509-513.

[138] Bentley, P.A; Kroutil, W; Littlechild, J.A; Roberts, S.M. *Chirality* **1997**, *9*, 198-202.

[139] Kulinkovich, O. *Eur. J. Org. Chem.* **2004**, 4517-4529.

[140] (a) Kelly, D.R; Caroff, E; Flood R.W; Heal, W; Roberts, S.M. *Chem. Commun*. **2004**, 2016-2017; (b) Fernandes, R. A. *Tetrahedron: Asymmetry* **2008**, *19*, 15-18.

[141] (a) Kelly, D.R; Roberts, S.M. *Chem. Commun*. **2004**, 2018-2020; (b) Kelly, D.R; Roberts, S.M. *Biopolymers* **2006**, *84*, 74-89; (c) Berkessel, A; Koch, B; Toniolo, C; Rainaldi, M; Broxterman, Q.B; Kaptein, B. *Biopolymers* **2006**, *84*, 90-96; (d) Weyer, A; Díaz, D; Nierth, A; Schlörer, N.E; Berkessel, A. *ChemCatChem* **2012**, *4*, 337–340; (e) Bérubé, C; Barbeau, X; Lagüe, P; Voyer, N. *Chem. Commun*. **2017**, *53*, 5099-5102.

[142] (a) Ni, C; Hu, J. *Chem. Soc. Rev.* **2016**, *45*, 5441-5454; (b) Liang, T; Neumann, C. N; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264.

[143] Ryu, I; Matsumoto, K; Kameyama, Y; Ando, M; Kusumoto, N; Ogawa, A; Kambe, M; Murai, S; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 12330-12339.

[144] Lan, X.-W; Wang, N.-X; Bai, C.-B; Zhang, W; Xing, Y; Wen, J.-L; Wang, Y.-J; Li, Y.-H. *Sci. Rep.* **2015**, 5, 18391-18398.
[145] *Modern organocopper chemistry*; Krause, N. (ed), **2002**, Weinheim, Wiley.
[146] Kochi, J.K. *J. Am. Chem. Soc.* **1963**, *85*, 1958-1968.
[147] (a) Li, L.-Z; Xiao, B; Guo, Q.-X; Xue, S. *Tetrahedron*, **2006**, *62*, 7762-7771; (b) Hasegawa, E; Tateyama, M; Nagumo, R; Tayama, E; Iwamoto, H. *Beilstein J. Org. Chem.* **2013**, *9*, 1397-1406.
[148] Kim, K.B; Crews, C.M. *Nat. Prod. Rep.* **2013**, *30*, 600-604.
[149] Einhorn, J; Einhorn, C; Luche, J.L. *Synlett*, **1991**, 37-38.
[150] Mangold, S.L; Grubbs, R.H. *Chem. Sci*. **2015**, *6*, 4561-4569.
[151] Gibson, S. E; Gibson, V.C; Keen, S.P. Chem. Commun. **1997**, *17*, 1107-1108.
[152] Wang, Z.J; Spiccia, N.D; Jackson, W.R; Robinson, A.J. *J. Pept. Sci.* **2013**, *19*, 470-476.
[153] Chattopadhyay, S.K; Sil, S; Mukherjee, J.P. *Beilstein J. Org. Chem*. **2017**, *13*, 2153-2156.
[154] Salih, N; Adams, H; Jackson, R.F.W. *J. Org. Chem*. **2016**, *81*, 8386-8393.
[155] Chatterjee, A.K; Choi, T.L; Sanders, D.P; Grubbs. R.H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
[156] Crabtree, R.H. *Chem. Rev.* **2015**, *115*, 127-150.
[157] (a) Roy, S; Spilling, C.D. *Org. Lett.* **2010**, *12*, 5326-5329; (b) Voigtritter, K; Ghorai, S; Lipshutz, B.H. *J. Org. Chem.* **2011**, *76***,** 4697-4702.
[158] (a) Carpino, L.A. *J.Am. Chem. Soc.* **1993**, *115*, 4397-4398; (b) Loiseau, N; Cavelier, F; Noel, J.-P; Gomis, J.-M. *J. Peptide Sci.* **2002**, *8*, 335-346.
[159] (a) Yerien, D.E; Bonesi, S; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398-8427; (b) Prakash Reddy, V. *Organofluorine Compounds in Biology and Medicine* Elsevier, Amsterdam, **2015**. (c) Purser, S; Moore, P.R; Swallow, S; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330.
[160] (a) Lee, E; Kamlet, A.S; Powers, D.C; Neumann, C.N; Boursalian, G.B; Furuya, T; Choi, D.C; Hooker, J.M; Ritter, T. *Science* **2011**, *334*, 639-642; (b) Campbell, M.G; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474-480; (c) Neumann, C.N; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3216-3221; (d) Tago, T; Toyohara, J. *Molecules*, **2018**, *23*, 300-326.
[161] (a) Zubrytski, D.M; Kananovich, D.G; Kulinkovich, O.G. *Tetrahedron*, **2014**, 70, 2944-2950; (b) Zubrytski, D.M; Kananovich, D.G; Matiushenkov, E.A. *Russ. J. Org. Chem.* **2017**, *53*, 813-823.

Acknowledgements

I would like to express my gratitude to everyone who contributed to the completion of this doctoral thesis, as it could not have been written without them.

First of all, I would like to thank Professor Margus Lopp, who has given me the chance to complete a PhD project in Estonia and did his very best to help me fight off my homesickness, contributing to my maturation in every aspect of life. I would like to thank Dr. Dzmitry Kananovich, who has guided me persistently through the maze of synthetic organic chemistry. I would like to thank all of my co-workers for all their help and for creating a friendly atmosphere, which facilitated the research and aided my integration into an initially novel society. I would also like to thank my family and friends for their patience and unconditional support.

Finally, I would like to express my gratitude to those organisations who have contributed financially to the completion of this PhD project. This work has been partially supported by the ASTRA "TUT Institutional Development Program for 2016-2022" Graduate School of Functional Materials and Technologies (2014-2020.4.01.16-0032). Furthermore, I would like to acknowledge the TTÜ Grant B58 and IUT Grant 19-32 from the Tallinn University of Technology and Estonian Ministry of Education and Research. Finally, I would like to acknowledge the COST action CA15106 "C-H Activation in Organic Synthesis" (CHAOS) for support in presenting my results in international conferences and meetings.

REPUBLIC OF ESTONIA
MINISTRY OF EDUCATION
AND RESEARCH

Abstract

Oxidative ring-cleavage reactions of cyclopropanols and their application for the synthesis of bioactive cyclopeptides

The continuously emerging demand for environmentally benign chemical transformations, along with applicability in industrial processes, in accordance with the principles of modern, efficient synthetic methods, have strongly affected contemporary research in the field of synthetic organic chemistry. In addition, growing societal concerns, as a vast driving force, require immediate application of recently improved and elaborated novel methodologies.

Previously, oxidative transformations were developed without regard to the mentioned criteria, leading to harmful environmental impacts, low selectivity profiles and inefficient application potentials. The successful utilisation of the most abundant, inexpensive aerobic oxygen has opened up several research approaches for optimal use, although fine-tuning the reaction conditions, especially through bio-inspired catalytic pathways, has remained a challenge. Catalytic, aerobic oxidations were envisioned as attractive alternatives for the preparation of a number of value-added products, such as chiral α,β-epoxy ketones, γ-keto sulfones and further β-Michael adducts, as their previously elaborated synthetic pathways were less efficient. The oxidative cyclopropane ring cleavage synthetic methodologies offer this favourable replacement through chemo- and regioselectivity performed under mild and properly designed conditions, demonstrating operational simplicity and exemplary functional group tolerance. Due to these beneficial features, they are considered to be ideal candidates for pluripotent functional groups applied in the late stage, while meeting the principles of diversity-oriented synthesis in the total synthesis of bioactive compounds, drug candidates and targets, with a view to the long-term goal of a healthy society through the facilitation of drug discovery programmes.

The present thesis focuses on the synthetic development of environmentally benign, bio-inspired, transition metal-catalysed, aerobic oxidative cyclopropane ring cleavage methodologies and their late-stage application in the total synthesis of bioactive cyclopeptide targets, thus meeting the requirements of the diversity-oriented synthesis paradigm.

The first chapter presents the results of the manganese-catalysed aerobic oxidative cleavage protocol for the enantioselective synthesis of α,β-epoxy ketones, which is a relevant pharmacophore motif in several natural products, *inter alia* histone deacetylase inhibitory cyclopeptides.

The second chapter describes an aerobic, copper-catalysed methodology to access the carbonyl bioisoster γ-keto sulfone moiety and a universal precursor for β-Michael adducts.

The third chapter provides a summary of the application of the recently developed aerobic oxidative cleavage methodologies described in the thesis, in combination with previous methods in the total synthesis of biologically relevant histone deacetylase inhibitory cyclopeptides in a diversity-oriented manner.

Finally, concluding remarks and outlooks for future directions/expansion of the investigation, as well as long-term goals in relation to society, are presented.

Lühikokkuvõte

Tsüklopropanoolide oksüdeerivad tsükliavamisreaktsioonid ja nende rakendus bioaktiivsete tsüklopeptiidide sünteesil

Käesolev uurimistöö sünteetilise orgaanilise keemia vallas on tugevalt mõjutatud kaasaja orgaanilisele keemiale esitatavatest uutest nõuetest. Keemilised muundumised peavad jälgima keskonnasõbralikke põhimõtteid ning peavad olema praktikas efektiivsed. Lisaks sellele peab olema arvestatud ühiskonna probleeme, mille lahendusi ootab ühiskond ja nendest johtuvaid kasvavaid sotsiaalsed nõudeid.

Käesolev töö panustab uute oksüdatsioonimeetodite arendamisse. Seni tuntud oksüdatsioonimeetodid on tihti madala selektiivsusega ja tööstuslikes rakendustes ebaefektiivsed, seetõttu ka keskkonnale kahjulikud. Töös kasutatakse oksüdeerijana kõige rikkalikumalt esinevat ja odavat õhuhapnikku, mis avab mitu uut uurimissuunda, eriti bioinspireeritud katalüütiliste sünteesiradade kaudu. Saadud tulemused näitavad vajalike edasiste uuringute suunda. Katalüütilisi aeroobseid oksüdatsioone kasutati väärtuslike bioaktiivsete molekulide sünteesiks (enantiomeersed α,β-epoksüketoonid, γ-keto sulfoonid ja β-Michaeli aduktid). Leidsime, et tsüklopropanoolide oksüdeerivad tsükliavamisreaktsioonid pakuvad efektiivset asendust tuntud meetoditele kasutuse lihtsuse ja kemo- ning regioselektiivsuse tõttu. Väljaarendatud meetodid demonstreerivad sünteesiskeemide lihtsust ja, mis sünteesikeemia jaoks oluline, reaktsioonitingimuste vastuvõetavust erinevate funktsionaalsete rühmade jaoks. Tänu neile kasulikele omadustele on tsüklopropanoolid ideaalsed pluripotentsed funktsionaalsed rühmad, mis võimaldavad rakendada divergentse sünteesi põhimõtteid erinevate ravimite kandidaatide sünteesil. See lähenemisviis toetab kindlasti ravimite avastamise uuringuid ja selle kaudu ka ühiskonna ootusi.

Käesolev doktoritöö keskendub keskkonnasõbralikele, bioinspireeritud, siirdemetall-katalüüsitud, aeroobsetele oksüdaatiivsetele tsüklopropanoolide tsükliavamisreaktsiooni meetoditele ja nende divergentse sünteesi põhimõtete rakendamisele bioaktiivsete tsüklopeptiidide totaalsünteesis.

Esimese peatüki tulemuste põhjal tehakse järeldus, et mangaankatalüüsitud aeroobsel oksüdatiivsel tsükliavamisreaktsioonil saab sünteesida enantiomeerseid α,β-epoksüketoone, mis esinevad struktuurfragmentidena mitmetes looduslikes ainetes, sealhulgas histooni deatsetülaasi inhibeerivates tsüklopeptiidides.

Teises peatükis kirjeldatakse vasega katalüüsitavat aeroobset oksüdatsiooni γ-ketosulfoonrühma, mis on karbonüülrühma bioisosteer, ja β-Michaeli liitumisproduktide universaalse eelkäija saamiseks.

Kolmas peatükk annab kokkuvõtte aeroobse oksüdatiivse tsükloavamisreaktsiooni meetodi rakendamisest bioloogiliselt oluliste histooni deatsetülaasi inhibeerivate tsüklopeptiidide sünteesil divergentsel viisil.

Lõpuks esitatakse arendatud meetodite perspektiiv ja uurimise edasised võimalikud suunad.

Appendix

Publication I

G.Z. Elek, V. Borovkov, M. Lopp, D.G. Kananovich. "Enantioselective One-Pot Synthesis of α,β-Epoxy Ketones via Aerobic Oxidation of Cyclopropanols". *Org. Lett.* **2017**, *19*, 3544-3547.

Organic LETTERS

Letter

pubs.acs.org/OrgLett

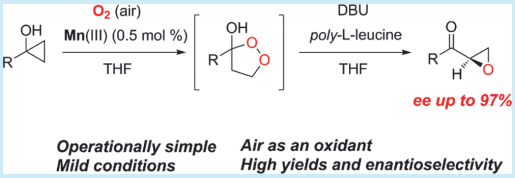
Enantioselective One-Pot Synthesis of α,β-Epoxy Ketones via Aerobic Oxidation of Cyclopropanols

Gábor Zoltán Elek, Victor Borovkov, Margus Lopp, and Dzmitry G. Kananovich*

Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia

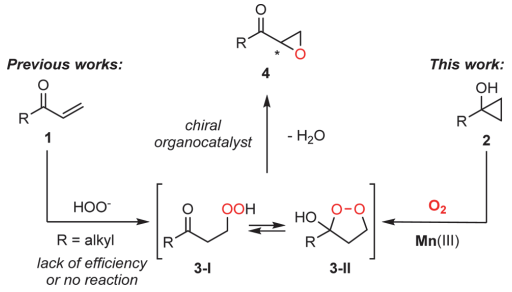
Supporting Information

ABSTRACT: An efficient, mild, and environmentally benign method was developed for the asymmetric synthesis of 2-oxyranyl ketones from easily available tertiary cyclopropanols. The one-pot protocol includes the aerobic oxidation of cyclopropanol derivatives catalyzed by Mn(III) complexes followed by the poly-L-leucine-assisted stereoselective elimination of water from the intermediate peroxides with DBU to afford the corresponding epoxy ketones in high yields and good-to-excellent enantioselectivities (up to 97%).



Enantiomerically enriched α,β-epoxy ketones are highly valuable starting materials for the production of numerous chiral compounds (e.g., pharmaceuticals, agrochemicals, fragrances, etc.).[1] Moreover, the epoxy ketone structural motif is responsible for the high bioactivity of several natural products.[2] Since the initial report by Wynberg in 1976,[3] the majority of methods to obtain enantiomerically enriched epoxy ketones are based on the epoxidation of α,β-unsaturated ketones by using the Weitz−Scheffer reaction and its modifications.[4] Despite extensive studies in this field, the developed methods are mostly limited to the reactive aromatic chalcone-type ketones, while the epoxidation of other enone substrates remained an arduous task due to long reaction times, low conversions, and poor enantioselectivities.[5] These shortcomings arise from the insufficient reactivity of the enone double bond toward the addition of hydroperoxide anion. For this reason, alkyl vinyl ketones **1** continue to be a challenging family of substrates for this type of epoxidation (Scheme 1).[5a,c]

Scheme 1. Alternative Methodology for the Preparation of Chiral 2-Oxyranyl Ketones 4 from Tertiary Cyclopropanols 2 via β-Peroxyketone Intermediates 3



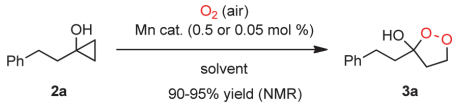
Due to growing interest to the cyclopropanol chemistry,[6,7] we envisioned filling the existing gap by using easily available cyclopropanols **2** as starting compounds[8] for the synthesis of chiral epoxy ketones **4**. Tertiary cyclopropanols **2** are readily oxidized under the aerobic conditions by using transition-metal catalysts[9] to afford β-peroxyketones **3-I**, which are in equilibrium with 1,2-dioxolane form **3-II**. We assumed that the peroxides **3** can be further stereoselectively transformed into chiral 2-oxyranyl ketones **4** by means of asymmetric organocatalytic methods. Here, we report a general approach for the synthesis of chiral 2-oxyranyl ketones **4** by using the aerobic oxidation of tertiary cyclopropanols **2** to peroxyketone intermediates **3** followed by stereoselective elimination of water.

To achieve this goal, the following major steps must be implemented: (1) development of the effective aerobic oxidation protocol yielding β-peroxyketones **3**; (2) finding the conditions and organocatalyst suitable for the enantioselective conversion of **3** into **4**; and (3) combination of these two processes into the one-pot procedure. The first oxidation step was studied on a model compound 1-(2-phenylethyl)-cyclopropanol (**2a**) (Scheme 2). Among different transition-metal complexes used to catalyze the aerobic oxidation of cyclopropanols,[9] manganese salts were found to be the most effective, affording high yields of β-peroxyketones.[9d,e,g] Shortcomings of the previously used procedure[9d] were the use of benzene as a solvent and molecular oxygen as an oxidant. We found that the aerobic oxidation of cyclopropanol **2a** can be easily achieved in less toxic solvents by simple stirring of a solution of **2a** and a manganese catalyst under air in open flask, affording peroxide **3a** in high yield (up to 95% according to NMR analysis). The best results were achieved in environmentally benign dimethyl carbonate (DMC),[10] THF, and 2-

Received: May 18, 2017
Published: June 13, 2017

DOI: 10.1021/acs.orglett.7b01519
Org. Lett. 2017, 19, 3544−3547

Scheme 2. Aerobic Oxidation of Cyclopropanol 2a[a]



solvents: dimethyl carbonate (DMC), THF, MeTHF
Mn catalysts: $Mn(OAc)_2$, $Mn(acac)_3$, MnCl(OEP)[b]

[a]Reaction conditions: **2a** (0.5 mmol) and Mn catalyst were dissolved in 0.5 mL of a solvent and stirred under air (open vial) until full conversion of starting material (TLC monitoring). [b]OEP = 2,3,7,8,12,13,17,18-octaethylporphyrin.

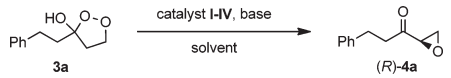
methyltetrahydrofuran (MeTHF) with 0.5 mol % of manganese acetate and acetylacetonate catalysts (see Table S1, entries 2, 3, and 6–8). The latter was especially effective, allowing the rate of aerobic oxidation to increase and affording the full conversion of starting material within 3 h even at 0.05 mol % loading. The formation of minor amounts of identified byproducts can be further suppressed by performing the oxidation at 0 °C (see Table S1, entry 11).

It has been demonstrated that metalloporphyrins that are easily soluble in many organic solvents may also be effectively used as oxidation catalysts.[11] In our hands, 0.5 mol % of MnCl(OEP) catalyst (OEP = 2,3,7,8,12,13,17,18-octaethylporphyrin) afforded peroxide **3a** in nearly quantitative yield in dimethyl carbonate as a solvent (see Table S1, entry 12). However, oxidation proceeded considerably slower compared with the other manganese salts, presumably as a result of additional steric hindrance caused by the porphyrin ligand. Other potential oxygen carriers like iron and cobalt porphyrin complexes were inefficient in catalyzing the aerobic oxidation of **2a**.

The main task of the current study was to perform the enantioselective transformation of peroxide **3a** into epoxy ketone **4a**. To find the suitable conditions, several well-known organocatalysts were first tested. Our initial attempts with cinchona-alkaloid-derived primary amine **I** (as TFA salt),[5a,12] thiourea **II**, and squaramide **III** failed to afford the desired epoxy ketone **4a** (Table 1, entry 1). However, commercially available poly-L-leucine (PLL on silica gel, catalyst **IV**)[13] in the presence of 1 equiv of DBU as a base resulted in the fast and quantitative conversion of peroxide **3a** into epoxy ketone **4a** with 86% ee (Table 1, entry 2). Although application of PLL for the asymmetric epoxidation of chalcones was commenced by Juliá and Colonna in the early 1980s[14] and the initial protocol was improved in the following intensive studies,[5c,15] we report here for the first time the enantioselective transformation of prochiral aliphatic peroxyketones using PLL catalyst. The composition of PLL used in our experiments was analyzed by MALDI MS.[16] Both catalysts (commercially purchased and prepared in our laboratory by polymerization of L-leucine *N*-carboxyanhydride with 1,3-diaminopropane initiator)[17] had a number-average degree of polymerization (DP_n) of about 17–18 and average molecular weight close to 2000–2100 (see the Supporting Information). These catalysts were used in the following screening of suitable reaction condition to transform peroxide **3a** into epoxy ketone **4a** (Table 1).

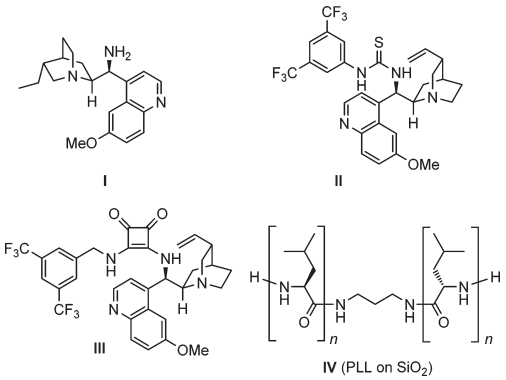
Starting from **3a**, in the presence of 7.5 mol % of PLL the reaction was completed within 1 h and 2-oxyranyl ketone **4a** was obtained in 86% ee at 20 °C (Table 1, entry 2). Lowering

Table 1. Asymmetric Transformation of Peroxide 3a into 2-Oxyranyl Ketone 4a[a]



entry	cat. (mol %)	solvent	base	temp (°C)	time (h)	ee[b] (%)
1	I–III (20%)	DMC		20	50	[c]
2	IV (7.5%)[d]	THF	DBU	20	1	86
3	IV (2.5%)	THF	DBU	20	1	34
4	IV (7.5%)	MeTHF	DBU	20	1	88
5	IV (7.5%)	toluene	DBU	20	1	74
6	IV (7.5%)	DME	DBU	20	1	68
7	IV (7.5%)	MTBE	DBU	20	1	64
8	IV (7.5%)	CH_2Cl_2	DBU	20	1	58
9	IV (7.5%)	DMC	DBU	20	1	48
10	IV (7.5%)	dioxane	DBU	20	1	32
11	IV (7.5%)	CH_3CN	DBU	20	1	16
12	IV (7.5%)	THF	DIPEA	20	12	70
13	IV (7.5%)	THF	TMP[e]	20	12	78
14	IV (7.5%)	THF	DBU	40	1	66
15	**IV (7.5%)**	**THF**	**DBU**	**−25**	**24**[f]	**94**

[a]Yield of 2-oxyranyl ketone **4a** for all reactions was considered as quantitative according to NMR. [b]Enantiomeric excess was determined by HPLC analysis using an AD-H column. [c]No epoxide **4a** formed. [d]Calculated according to average molecular weight of PLL polymer. [e]TMP = 2,2,6,6-tetramethylpiperidine. [f]The reaction mixture was stirred in a freezer at −25 °C for 24 h.



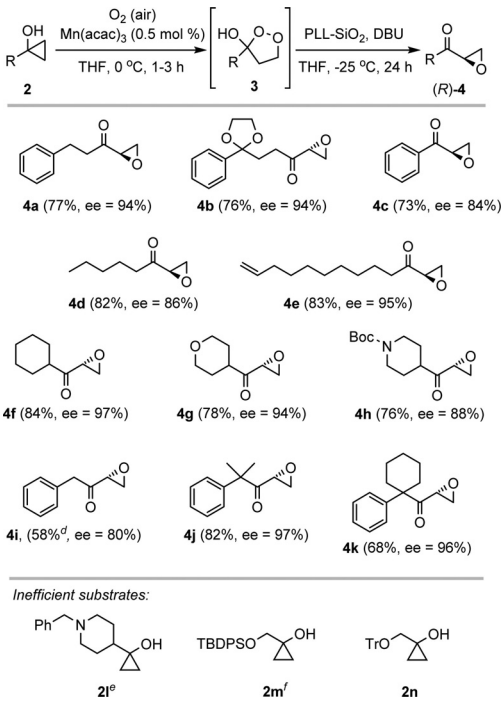
the amount of catalyst inevitably leads to a drastic decrease of the enantioselectivity (Table 1, entry 3). In addition, the used solvent strongly affects the enantiomeric purity of the product (Table 1, entries 4–11) with the highest ee values achieved in THF and MeTHF (86% and 88% ee, respectively).[18] Weaker bases than DBU also reduced the reaction rate and enantioselectivity of the product (Table 1, entries 12 and 13). Temperature is another important factor in the stereoselective epoxide formation: the ee of product **4a** dropped from 86% to 66% when the temperature was raised from 20 to 40 °C (Table 1, entry 2 vs 14). Lowering the temperature to −25 °C led to a noticeable improvement of the selectivity: **4a** was obtained with high 94% ee (Table 1, entry 15).

On the basis of the results of optimization studies, an operationally simple one-pot protocol for the conversion of cyclopropanols **2** into enantiomerically enriched 2-oxyranyl ketones **4** was attained under the following conditions: aerobic

DOI: 10.1021/acs.orglett.7b01519
Org. Lett. 2017, 19, 3544–3547

oxidation at 0 °C; THF as a solvent; 0.5 mol % of $Mn(acac)_3$ as an oxidation catalyst. The subsequent epoxide formation by using silica gel supported PLL and DBU at −25 °C. The products, epoxy ketones **4**, are isolated after filtration of the catalyst and evaporation of the solvent followed by purification with flash silica gel chromatography. Using these conditions at a 1.5 mmol scale, the isolated yield of epoxy ketone **4a** from cyclopropanol **2a** was 77% and the ee was 94% (Scheme 3).

Scheme 3. Asymmetric Synthesis of (*R*)-2-Oxyranyl Ketones 4 by Aerobic Oxidation of Tertiary Cyclopropanols 2[a,b]



[a]Typical reaction conditions: cyclopropanol **2** (1.5 mmol), THF (1.5 mL), $Mn(acac)_3$ (0.5 mol %); then PLL (240 mg) on SiO_2, DBU (1.5 mmol). [b]Isolated yields; enantiomeric excess was determined by HPLC analysis using an AD-H column. [c]Using 2 mol % of $Mn(acac)_3$. [d]Yield after quenching of the reaction mixture with 1 M AcOH. [e]No reaction. [f]TBDMS = *tert*-butyldimethylsilyl.

The following examples of oxidation of different functionalized tertiary cyclopropanols **2** to epoxy ketone **4** demonstrate a wide scope of this method (Scheme 3). The reaction proceeds smoothly and affords the corresponding epoxy ketones **4** in good isolated yields (68−84%) and in high enantioselectivities (84−97% ee), giving primary and secondary alkyl- (**4d**, **4f**), phenyl- (**4c**), and alkenyl-substituted (**4e**) epoxy ketones. Even the functionalized compounds bearing 1,3-dioxolane **4b**, tetrahydropyranyl **4g**, and Boc-protected piperidine **4h** moieties were obtained flawlessly.

To test some mechanistic aspects of the aerobic oxidation, a piperidine derivative **2l** was also tested in this reaction. As expected, the reaction did not occur due to the inactivation of manganese catalyst with the amino function of substrate. We also observed the inhibition of aerobic oxidation of **2a** by MnCl(OEP) catalyst in the presence of pyridine and *N*-methylimidazole. A commonly accepted mechanism of the aerobic oxidation of cyclopropanols implies the single-electron transfer (SET) from a cyclopropanol substrate yielding the oxoalkyl radical, which is rapidly intercepted by molecular oxygen.[9] Strong coordination of amino ligands to the manganese catalytic center prevents a weaker binder, such as cyclopropanol, to interact with the metal ion, hence making the SET process less probable.

A one-pot protocol for cyclopropanols **2n** and **2m** failed: the first aerobic oxidation step proceeded smoothly (within 3 h), but the subsequent epoxide forming step was very slow and resulted in the tar formation for compound **2m**. The preparation of benzyl-substituted epoxy ketone **4i** under standard conditions was problematic because of decomposition caused by enolization in the presence of DBU. This process was suppressed by addition of acetic acid at −25 °C after the completion of epoxidation, giving 58% isolated yield of **4i**. The nonenolizable benzyl ketones **4j** and **4k** were obtained in good yields and excellent enantioselectivities (96−97% ee).

To define the stereochemistry of products **4**, the value of optical rotation of **4c** and **4i** (see the Supporting Information) was compared with the literature data for the corresponding *R*-[19] and *S*-isomers,[20] thus confirming the *R*-configuration of compounds obtained. The same stereoconfiguration is expected from the model of Kelly and Roberts.[15a−c,21] The α-helical structure of PLL catalyst and *N*-terminal amino groups are essential for the supramolecular binding of prochiral substrate **3** to provide an oxy-anion hole for the hydrogen bonding of peroxyenolate intermediates, thus favoring a *re* transition state leading to the *R*-enantiomer.

In conclusion, we have developed a practical and efficient one-pot approach for the synthesis of enantiomerically enriched 2-oxyranyl ketones **4** by aerobic oxidation of easily available cyclopropanols **2** via intermediate formation of peroxyketone intermediates **3**, followed by enantioselective epoxide formation in the presence of poly-L-leucine catalyst and DBU. The experimental protocol is operationally simple, utilizing atmospheric oxygen as an eco-friendly reactant and poly-L-leucine as a "green" catalyst. The method affords high yields and good-to-excellent enantiomeric purity of the epoxy ketone products. This strategy can be effectively applied as a straightforward approach to chiral 2-oxyranyl ketones **4**, which are highly demanded synthetic intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01519.

Experimental details and characterization data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dzmitry.kananovich@ttu.ee.

ORCID

Dzmitry G. Kananovich: 0000-0002-2664-4491

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.7b01519
Org. Lett. 2017, 19, 3544−3547

■ ACKNOWLEDGMENTS

Funding from the European Union's Seventh Framework Program for research, technological development and demonstration (Grant No. 621364 (TUTIC-Green)), from the Centre of Excellence in Molecular Cell Engineering (Grant No. 2014-2020.4.01.15-0013), from the Estonian Ministry of Education and Research (Grant No. IUT 19-32) and from Tallinn University of Technology (TTÜ, Grant No. B58) is gratefully acknowledged. We thank Dr. Ivar Järving (Tallinn University of Technology, TTÜ) for help with HRMS measurements and Dr. Karin Valmsen (TTÜ) for MALDI-TOF analysis. Dr. Alexander-Mati Müürisepp (TTÜ) is acknowledged for measuring IR spectra.

■ REFERENCES

(1) Reviews: (a) Pineschi, M. *Eur. J. Org. Chem.* **2006**, *2006*, 4979. (b) Lauret, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2359. (c) Gorzynski Smith, J. *Synthesis* **1984**, *1984*, 629. (d) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.

(2) (a) Meng, L.; Mohan, R.; Kwok, B. H. B.; Elofsson, M.; Sin, N.; Crews, C. M. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 10403. (b) Demo, S. D.; Kirk, C. J.; Aujay, M. A.; Buchholz, T. J.; Dajee, M.; Ho, M. N.; Jiang, J.; Laidig, G. J.; Lewis, E. R.; Parlati, F.; Shenk, K. D.; Smyth, M. S.; Sun, C. M.; Vallone, M. K.; Woo, T. M.; Molineaux, C. J.; Bennett, M. K. *Cancer Res.* **2007**, *67*, 6383. (c) Keller, L.; Plaza, A.; Dubiella, C.; Groll, M.; Kaiser, M.; Müller, R. *J. Am. Chem. Soc.* **2015**, *137*, 8121. (d) Tsunematsu, Y.; Nishimura, S.; Hattori, A.; Oishi, S.; Fujii, N.; Kakeya, H. *Org. Lett.* **2015**, *17*, 258. (e) Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, *2009*, 371.

(3) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, *17*, 1831.

(4) Reviews: (a) Porter, M. J.; Skidmore, J. *Org. React.* **2009**, *74*, 426. (b) Reisinger, C. *Epoxidations and Hydroperoxidations of α,β-Unsaturated Ketones*; Springer-Verlag: Berlin, 2012. (c) Pellissier, H.; Lattanzi, A.; Dalpozzo, R. *Asymmetric Synthesis of Three-Membered Rings*; Wiley-VCH: Weinheim, 2017. (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.

(5) (a) Lifchits, O.; Mahlau, M.; Reisinger, C. M.; Lee, A.; Farès, C.; Polyak, I.; Gopakumar, G.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2013**, *135*, 6677. (b) Lygo, B.; Gardiner, S. D.; McLeod, M. C.; To, D. C. M. *Org. Biomol. Chem.* **2007**, *5*, 2283. (c) Lauret, C.; Roberts, S. M. *Aldrichimica Acta* **2002**, *35*, 47.

(6) Recent reviews: (a) Nikolaev, A.; Orellana, A. *Synthesis* **2016**, *48*, 1741. (b) Haym, I.; Brimble, M. A. *Org. Biomol. Chem.* **2012**, *10*, 7649.

(7) Recent examples of synthetic applications of cyclopropanols: (a) Feng, Y.-S.; Shu, Y.-J.; Cao, P.; Xu, T.; Xu, H.-J. *Org. Biomol. Chem.* **2017**, *15*, 3590. (b) Zhou, X.; Yu, S.; Kong, L.; Li, X. *ACS Catal.* **2016**, *6*, 647. (c) Davis, D. C.; Walker, K. L.; Hu, C.; Zare, R. N.; Waymouth, R. M.; Dai, M. *J. Am. Chem. Soc.* **2016**, *138*, 10693. (d) Tumma, N.; Gyanchander, E.; Cha, J. K. *J. Org. Chem.* **2017**, *82*, 4379. (e) Lu, S.-C.; Li, H.-S.; Xu, S.; Duan, G.-Y. *Org. Biomol. Chem.* **2017**, *15*, 324. (f) Davis, D. C.; Haskins, C. W.; Dai, M. *Synlett* **2017**, *28*, 913. (g) Zhang, H.; Wu, G.; Yi, H.; Sun, T.; Wang, B.; Zhang, Y.; Dong, G.; Wang, J. *Angew. Chem., Int. Ed.* **2017**, *56*, 3945. (h) Zhou, X.; Qi, Z.; Yu, S.; Kong, L.; Li, Y.; Tian, W.-F.; Li, X. *Adv. Synth. Catal.* **2017**, *359*, 1620. (i) Konik, Y. A.; Kudrjashova, M.; Konrad, N.; Kaabel, S.; Jarving, I.; Lopp, M.; Kananovich, D. G. *Org. Biomol. Chem.* **2017**, *15*, 4635.

(8) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1.

(9) (a) Kirihara, M.; Takizawa, S.; Momose, T. *Chem. Commun.* **1998**, *16*, 1691. (b) Morisson, V.; Barnier, J.-P.; Blanco, L. *Tetrahedron Lett.* **1999**, *40*, 4045. (c) Barnier, J.-P.; Morisson, V.; Blanco, L. *Synth. Commun.* **2001**, *31*, 349. (d) Kulinkovich, O. G.; Astashko, D. A.; Tyvorskii, V. I.; Ilyina, N. A. *Synthesis* **2001**, *2001*, 1453. (e) Tyvorskii, V. I.; Astashko, D. A.; Kulinkovich, O. G. *Tetrahedron* **2004**, *60*, 1473. (f) Kirihara, M.; Kakuda, H.; Ichinose, M.; Ochiai, Y.; Takizawa, S.; Mokuya, A.; Okubo, K.; Hatano, A.; Shiro, M. *Tetrahedron* **2005**, *61*, 4831. (g) Astashko, D. A.; Tyvorskii, V. I. *Tetrahedron Lett.* **2011**, *52*, 4792. (h) Tyagi, S.; Cook, C. D.; DiDonato, D. A.; Key, J. A.; McKillican, B. P.; Eberle, W. J.; Carlin, T. J.; Hunt, D. A.; Marshall, S. J.; Bow, N. L. *J. Org. Chem.* **2015**, *80*, 11941. (i) Han, W.-B.; Li, S.-G.; Lu, X.-W.; Wu, Y. *Eur. J. Org. Chem.* **2014**, *2014*, 3841.

(10) (a) Tundo, P.; Selva, M. *Acc. Chem. Res.* **2002**, *35*, 706. (b) Tundo, P.; Aricò, F.; Rosamilia, A. E.; Grego, S.; Rossi, L. Dimethyl Carbonate: Green Solvent and Ambident Reagent. In *Green Chemical Reactions*; Tundo, P., Esposito, V., Eds.; Springer: Dordrecht, 2008; pp 213−232.

(11) Recent reviews: (a) Barona-Castaño, J.; Carmona-Vargas, C.; Brocksom, T.; de Oliveira, K. *Molecules* **2016**, *21*, 310. (b) Lu, H.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899. (c) Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011**, *40*, 1950. (d) Che, C.-M.; Huang, J.-S. *Chem. Commun.* **2009**, 3996.

(12) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134.

(13) (a) Geller, T.; M. Roberts, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1397. (b) Dhanda, A.; Drauz, K.-H.; Geller, T.; Roberts, S. M. *Chirality* **2000**, *12*, 313.

(14) (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (b) Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317.

(15) Reviews: (a) Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006**, *84*, 74. (b) Berkessel, A.; Koch, B.; Toniolo, C.; Rainaldi, M.; Broxterman, Q. B.; Kaptein, B. *Biopolymers* **2006**, *84*, 90. (c) Carrea, G.; Colonna, S.; Kelly, D. R.; Lazcano, A.; Ottolina, G.; Roberts, S. M. *Trends Biotechnol.* **2005**, *23*, 507. (d) Porter, M. J.; Roberts, S. M.; Skidmore, J. *Bioorg. Med. Chem.* **1999**, *7*, 2145.

(16) Bentley, P. A.; Kroutil, W.; Littlechild, J. A.; Roberts, S. M. *Chirality* **1997**, *9*, 198.

(17) Baars, S.; Drauz, K.-H.; Krimmer, H.-P.; Roberts, S. M.; Sander, J.; Skidmore, J.; Zanardi, G. *Org. Process Res. Dev.* **2003**, *7*, 509.

(18) THF is known as a preferred solvent for Juliá−Colonna epoxidation with the PLL catalyst: Kelly, D. R.; Bui, T. T. T.; Caroff, E.; Drake, A. F.; Roberts, S. M. *Tetrahedron Lett.* **2004**, *45*, 3885.

(19) Kelly, D. R.; Caroff, E.; Flood, R. W.; Heal, W.; Roberts, S. M. *Chem. Commun.* **2004**, 2016.

(20) Fernandes, R. A. *Tetrahedron: Asymmetry* **2008**, *19*, 15.

(21) Kelly, D. R.; Roberts, S. M. *Chem. Commun.* **2004**, 2018.

DOI: 10.1021/acs.orglett.7b01519
Org. Lett. 2017, 19, 3544−3547

Publication II

Y.A. Konik, **G.Z. Elek**, S. Kaabel, I. Järving, M. Lopp, D.G. Kananovich. “Synthesis of γ-keto sulfones by copper-catalyzed oxidative sulfonylation of tertiary cyclopropanols”. *Org. Biomol. Chem.* **2017**, *15*, 8334-8340.

Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 8334

Synthesis of γ-keto sulfones by copper-catalyzed oxidative sulfonylation of tertiary cyclopropanols†

Yulia A. Konik,[a] Gábor Zoltán Elek,[b] Sandra Kaabel,[b] Ivar Järving,[b] Margus Lopp[b] and Dzmitry G. Kananovich*[b]

Received 2nd July 2017,
Accepted 12th September 2017

DOI: 10.1039/c7ob01605k

rsc.li/obc

Tertiary cyclopropanols undergo ring-opening oxidative sulfonylation to afford γ-keto sulfones when reacting with sulfinate salts in the presence of a copper(II) acetate catalyst and an oxidant (*tert*-butyl hydroperoxide or atmospheric oxygen). Various fluoroalkyl, aryl and alkyl sulfinate salts are successfully employed as sulfonylation reagents, affording the corresponding sulfones in up to 94% yields. The experimental protocol is mild and tolerates a number of functionalities in the cyclopropanol substrate. The reaction proceeds *via* a one-pot oxidation–Michael addition mechanism and can serve as a useful addition to the existing methods for the preparation of γ-keto sulfones based on the sulfa-Michael reaction.

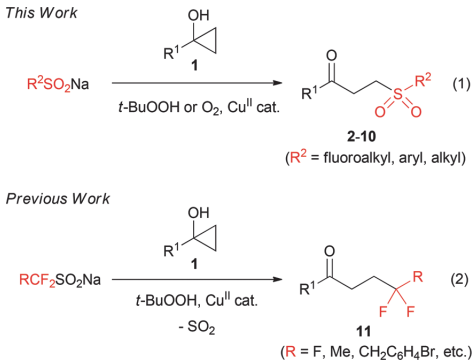
Introduction

The synthesis of sulfones attracts considerable attention because numerous valuable compounds, such as pharmaceuticals and agrochemicals, contain the sulfonyl group as a key structural motif.[1] In addition, sulfones are well-known intermediates for the construction of C–C bonds,[2] for example in Julia olefination[2b] and Ramberg–Bäcklund[2c] reactions.

γ-Keto sulfones are traditionally prepared from α,β-enones *via* the Michael addition of sulfinate anions,[3] or thiols[4] and the subsequent oxidation[5] of intermediate thio-substituted ketones. Alternative approaches have been reported in recent years, such as the N-heterocyclic carbene-catalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones,[6] along with the palladium[7] and silver-catalyzed[8] transformation of allylic alcohols *via* the *in situ* formation of an α,β-enone intermediate.[7]

As a contribution to further development in the field, we report in the current paper the synthesis of γ-keto sulfones **2–10** *via* the oxidative sulfonylation of tertiary cyclopropanols (**1**) with sulfinate salts (Scheme 1, eqn (1)) in the presence of copper(II) acetate.

Cyclopropanols **1** are synthetically useful compounds due to the facile cleavage of their strained cyclopropane ring under mild conditions. The regioselective ring opening of cyclopropanols adjacent to the alcohol group carbon–carbon bonds is assisted by transition metals *via* single- or two-electron redox processes[9] and results in β-functionalized carbonyl compounds.[10] In these transformations, cyclopropanols act as synthetic equivalents of homoenolate anions, thus providing a "polarity inverted" alternative to Michael addition reactions. This alternative route to β-functionalized ketones is especially beneficial when the corresponding addition reaction to the enone double bond fails to afford the desired product.[10a,11] Easy access to diversely functionalized cyclopropanols by the Kulinkovich cyclopropanation of carboxylic esters[12] further increases the attractiveness of these strained compounds as precursors of β-functionalized ketones.



Scheme 1 Synthesis of γ-keto sulfones **2–10** (eqn (1)) and distally fluorinated ketones **11** (eqn (2)) from cyclopropanols **1** and sulfinate salts.

[a]*Department of Organic Chemistry, Belarusian State University, Leningradskaya 14, 220050 Minsk, Belarus*
[b]*Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia. E-mail: dzmitry.kananovich@ttu.ee*

† Electronic supplementary information (ESI) available: Experimental details and spectral data. CCDC 1533651. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob01605k

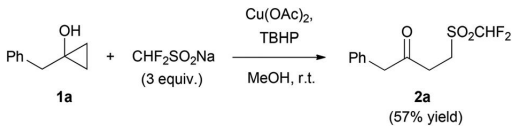
Results and discussion

We reported recently that tertiary cyclopropanols **1** when reacting with fluorinated sulfinate salts in the presence of copper(II) acetate catalyst (20–100 mol%) and *tert*-butyl hydroperoxide (TBHP, 3 equiv.) result in distally fluorinated ketones **11** (Scheme 1, eqn (2)).[11,13] In this transformation, fluorinated sulfinate salts serve as a precursor of reactive fluoroalkyl copper species, presumably *via* the intermediate formation of fluoroalkyl radicals. Good yields of the corresponding fluorinated ketones **11** were attained with sodium triflinate (Langlois reagent) and α,α-difluoroalkylsulfinates. On the other hand, the use of sodium fluoromethylsulfinate (CFH_2SO_2Na) and difluoromethylsulfinate (CHF_2SO_2Na) was not so successful, affording the corresponding fluorinated ketones in low yields, likely due to the lower stability of the corresponding fluoromethyl and difluoromethyl radicals.[14] Instead, the reaction of CHF_2SO_2Na (3 equiv.) with benzyl cyclopropanol **1a** (R^1 = $PhCH_2$) in methanol, together with $Cu(OAc)_2$ (1 equiv.) and TBHP (3 equiv.), resulted in the formation of difluoromethyl sulfone **2a** as a major product in nearly 57% yield (by ^{1}H NMR) (Scheme 2).

Pure crystalline fluorinated sulfone **2a** was isolated from the reaction mixture by precipitation with hexane from the solution in chloroform or diethyl ether. The structure of sulfone **2a** was confirmed by NMR, exhibiting signals of the CHF_2 moiety at δ = 6.16 ppm (t, J_{HF} = 52.9 Hz) in ^{1}H NMR and at δ = −122.9 ppm (d, J_{HF} = 52.9 Hz) in ^{19}F NMR spectra. The IR spectrum of **2a** revealed two characteristics for sulfone strong bands at 1345 and 1160 cm^{-1}.

Similarly, amyl cyclopropanol **1b** afforded the corresponding difluoromethyl sulfone **2b** in nearly 55% yield (by ^{1}H NMR) under the same reaction conditions, along with methoxy ketone **13b** (10%) and difluoro ketone **11b** (35%) by-products (Table 1, entry 1). Although the formation of **11b** could be suppressed by introducing 20 mol% of $Fe(OAc)_2$ as an additive in addition to copper(II) acetate (entry 2), it resulted in only a slight increase in the yield of the target sulfone **2b** (up to 60%) due to the formation of vinyl ketone **12b** as an additional by-product in about 20% yield. Nevertheless, the latter can be further converted into the target sulfone product **2b** with prolonged reaction time (72 h) *via* the sulfa-Michael reaction, thus allowing us to achieve an acceptable 77% yield of **2b** (entry 3).

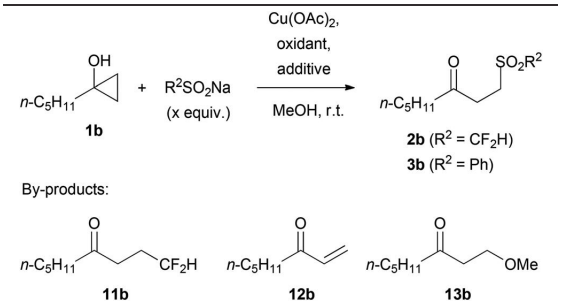
In order to expand the scope of the method, the sulfonylation reaction of amyl cyclopropanol (**1b**) with sodium benzenesulfinate ($PhSO_2Na$) was further explored (Table 1, entries 4–10).



1a **2a** (57% yield)

Scheme 2 Formation of difluoromethyl sulfone **2a** from cyclopropanol **1a**.

Table 1 Optimization experiments for the copper-catalyzed oxidative sulfonylation of cyclopropanol **1b**



1b **2b** (R^2 = CF_2H) **3b** (R^2 = Ph) **11b** **12b** **13b**

Entry	Cu cat. (mol%)	R^2 (*x* eq.)	Oxidant	Time	Yield of sulfone[a] (%)
1	100	CF_2H (3 eq.)	TBHP	24 h	55
2	100[b]	CF_2H (3 eq.)	TBHP	24 h	60
3	100[b]	CF_2H (3 eq.)	TBHP	72 h	77
4	100	Ph (1.5 eq.)	TBHP	0.5 h	94
5	50	Ph (1.5 eq.)	TBHP	1 h	92
6	20	Ph (1.5 eq.)	TBHP	1 h	63
7	0	Ph (1.5 eq.)	TBHP	1 h	0
8	100	Ph (1.5 eq.)	O_2	2 h	97
9	20	Ph (1.5 eq.)	O_2	3 h	81
10	100	Ph (1.5 eq.)	—[c]	3 h	60[d]

[a] Yields were determined by using ^{1}H NMR spectroscopy. [b] 20 mol% $Fe(OAc)_2$ as an additive. [c] The reaction was carried out under argon in a Schlenk tube. [d] 35% of the starting material (**1b**) remained.

To our delight, in contrast to the slowly reacting fluorinated methanesulfinate salt, $PhSO_2Na$ reacted faster and achieved completion within 30 min (entry 4) affording phenyl sulfone **3b** in a high 94% yield. This remarkable difference of this reaction was a possibility to reduce the amount of the Cu catalyst and to avoid the use of an iron salt additive. Thus, in the presence of only 1 equiv. of $Cu(OAc)_2$, without an additional Fe co-catalyst, the yield of sulfone product **3b** remained high until 50 mol% of Cu catalyst loadings (Table 1, entries 4 and 5). However, further reduction of the catalyst amount led to diminished yields, and in the absence of a copper catalyst, no sulfone product was formed (Table 1, entries 6 and 7). It was also possible to reduce the amounts of $PhSO_2Na$ and TBHP oxidant: a high yield of sulfone **3b** was achieved with only 1.5 equiv. of both $PhSO_2Na$ and TBHP (Table 1, entries 4 and 5). Moreover, the reaction with $PhSO_2Na$ also proceeds well with atmospheric oxygen, the most favorable industrial oxidizer. Although the reaction was slower compared to that with TBHP (Table 1, entry 8), the stirring of the reaction mixture in an open flask afforded an acceptable yield of sulfone **3b** even with 20 mol% of $Cu(OAc)_2$ catalyst (Table 1, entry 9). To confirm the role of atmospheric oxygen as an oxidant, an experiment with no air access (in a Schlenk tube under an argon atmosphere) was performed (entry 10). We observed that the reaction mixture turned yellow after 3 h (due to the reduction of Cu(II) into Cu(I) species) and

the reaction stopped. NMR analysis revealed the incomplete transformation of cyclopropanol **1b**: only 65% of the substrate was consumed and transformed into sulfone **3b** due to oxidation with Cu(II) species. After exposing the content of the reaction vessel to air, the oxidation of Cu(I) into Cu(II) species took place, along with the full conversion of the starting material **1b** into sulfone **3b**.

With the established reaction conditions, a number of cyclopropanols **1a–h**, along with fluoromethyl-, alkyl- and arylsulfinate salts, were used for the preparation of γ-keto sulfones **2–10** (Scheme 3). Difluoro- and fluoromethyl sulfones **2** and **4** were prepared from the corresponding sulfinate salts (3 equiv.) and TBHP as an oxidant (3 equiv.) in the presence of $Cu(OAc)_2$ (1 equiv.) and iron acetate additive (20 mol%; conditions A). Besides the abovementioned alkyl cyclopropanols **1a** and **1b**, functionalized cyclopropanols **1c** and **1d** smoothly reacted with sulfinate salt CHF_2SO_2Na to afford the corresponding sulfones **2c** and **2d** (Scheme 3). After 72 h reaction time, the latter were isolated in 41% and 43% yields respectively as crystalline solids by simple precipitation with hexane from the chloroform solution of the crude reaction mixtures. Phenyl cyclopropanol **1e** was more reactive than aliphatic substrates, affording the corresponding difluoromethyl sulfone **2e** in a noticeably higher yield. The same transformation performed with cyclopropanols **1a**, **1b** and **1d** and sodium monofluoromethylsulfinate (CFH_2SO_2Na) yielded the corresponding monofluoromethyl sulfones **4**. In this case, only the reaction of benzyl cyclopropanol **1a** with CFH_2SO_2Na was inefficient, yielding the corresponding sulfone **4a** in a low 28% yield (37% yield found by NMR of the crude reaction mixture).[15] X-ray analysis of the crystals of compound **4a** provided final proof of the sulfone structure (Scheme 3).‡

The preparative transformations with $PhSO_2Na$ and several cyclopropanol substrates (**1a**, **1b**, and **1f**) were performed in a 1 mmol scale using TBHP (conditions B) and atmospheric oxygen (conditions C) as an oxidizer, in the presence of 1 equiv. of $Cu(OAc)_2$. As a rule, both procedures B and C afforded similar yields of the corresponding sulfone products. Thus, with the model substrate **1b**, sulfone **3b** was isolated in 84 and 90% yields correspondingly (Scheme 3). Similar yields (47% and 55%) of phenyl sulfone **3a** were also attained in the case of benzyl cyclopropanol **1a**. The use of atmospheric oxygen was noticeably beneficial only for the preparation of compound **3f** (76% *vs.* 47% yield with TBHP).

Further examples of functionalized aliphatic and aromatic sulfones **3**, **5–10** have been prepared and isolated in 47–94% yields following the same experimental protocol (Scheme 3). A number of substituted benzenesulfinates (*p*-Me, F, Cl, CF_3) in reaction with cyclopropanol **1b** afforded the corresponding aryl sulfone products **5–8** in nearly the same yields as parent $PhSO_2Na$. Alkylsulfinate salts (sodium methylsulfinate and sodium 1-methyl 3-sulfinopropanoate) smoothly afforded solid alkyl sulfones **9** and **10**, which were isolated in 47–71% yields by simple filtration after the evaporation of the solvent used for extraction (see the ESI†). In a gram-scale experiment, 76% yield of pure sulfone **9b** was attained after recrystallization from hexane. It is worth noting that in the case of unsaturated compounds **3g** and **3h**, terminal and conjugated double bonds in the products remained intact, and no sulfonylation of olefin moieties occurred.[16]

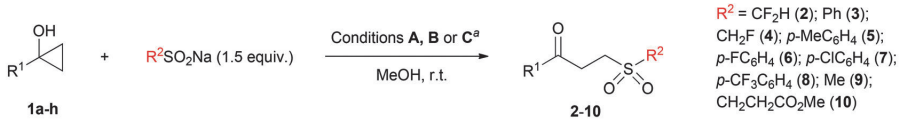
Discussing the possible mechanisms of the sulfonylation reaction, three possibilities could be considered (Scheme 4). All the mechanistical pathways begin with the ring cleavage of cyclopropane with electrophilic Cu(II) species producing β-copper(II) ketone **A**.[17] However, the further fate of these reactive species could be different. The first mechanism implies the generation of sulfonyl radicals by the oxidation of the sulfinate salt.[16] Copper(III) intermediate **B** is produced by the reaction of sulfonyl radicals with β-copper(II) ketone **A**, and the reductive elimination of Cu(I) affords sulfone products **2–10**.[16e] Since sulfonyl radicals are prone to attack unsaturated bonds[16] and alkenes are used to capture these species,[16e] the smooth production of unsaturated sulfones **3g** and **3h** (Scheme 3) indicates that the involvement of free sulfonyl radicals is improbable.

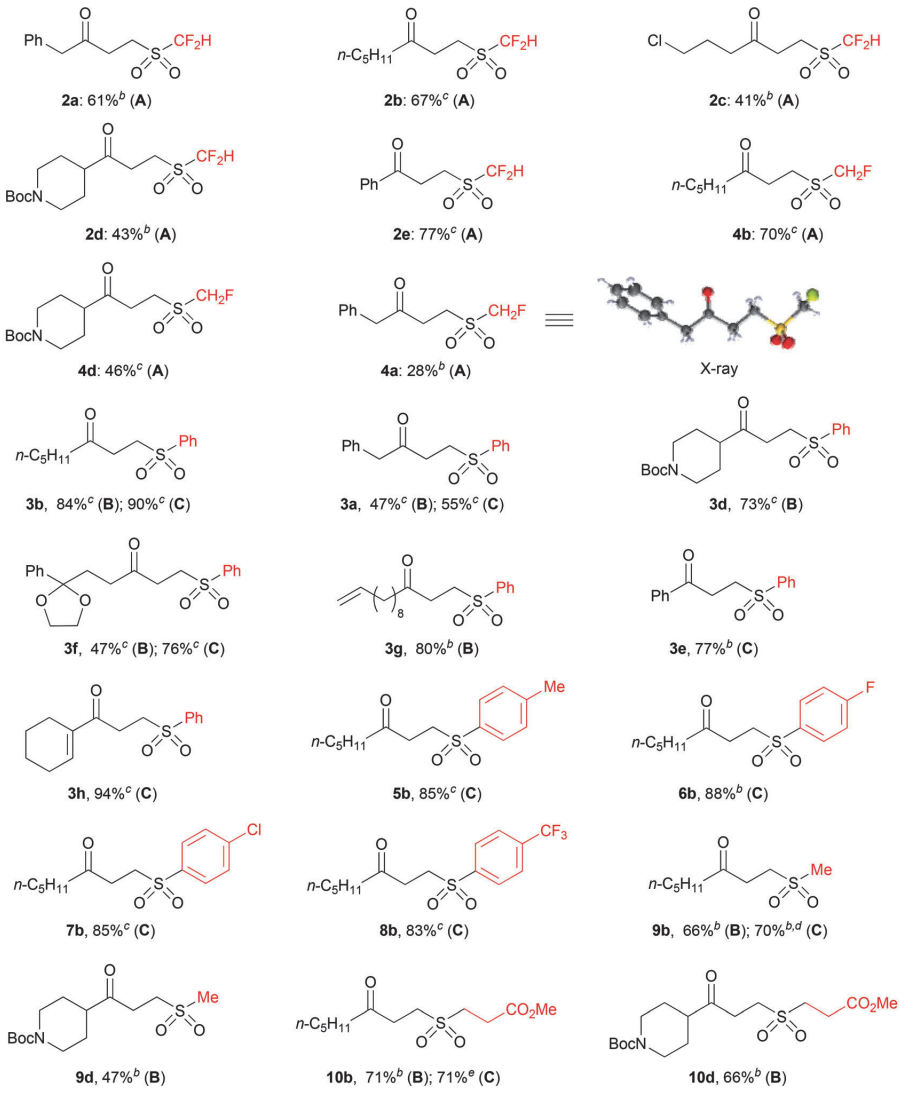
The second possibility (mechanism II) implies the homolysis[17,18] of the Cu^{II}–carbon bond in intermediate **A** to produce oxoalkyl radical **C**, which could intercept the sulfonyl radical from the copper(II) sulfinate, generated *in situ*. Finally, the third mechanism suggests the intermediate formation of α,β-enone **12** from organocopper compound **A** *via* the elimination of copper(0)[17b] or *via* homolysis and oxidation of oxoalkyl radical **C**.[19] The subsequent sulfa-Michael reaction affords sulfones **2–10**.

To distinguish between these two alternative mechanisms, a number of control experiments have been performed (Scheme 4). First of all, we found that cyclopropanol **1b** was smoothly oxidized to enone **12b** when reacted with both TBHP and atmospheric oxygen in the presence of $Cu(OAc)_2$ (eqn (1)).[20] Furthermore, enone **12b** quickly reacts with $PhSO_2Na$ under standard reaction conditions, to afford sulfone **3b** (eqn (2)). The same addition reaction with less nucleophilic CHF_2SO_2Na was significantly slower and 93% conversion of the starting material was achieved after 48 h reaction time (eqn (3)). Since enone **12b** was indeed detected as an intermediate in the sulfonylation reaction of **1b** with CHF_2SO_2Na (see above), these results strongly support the operation of the one-pot oxidation–Michael addition mechanism.

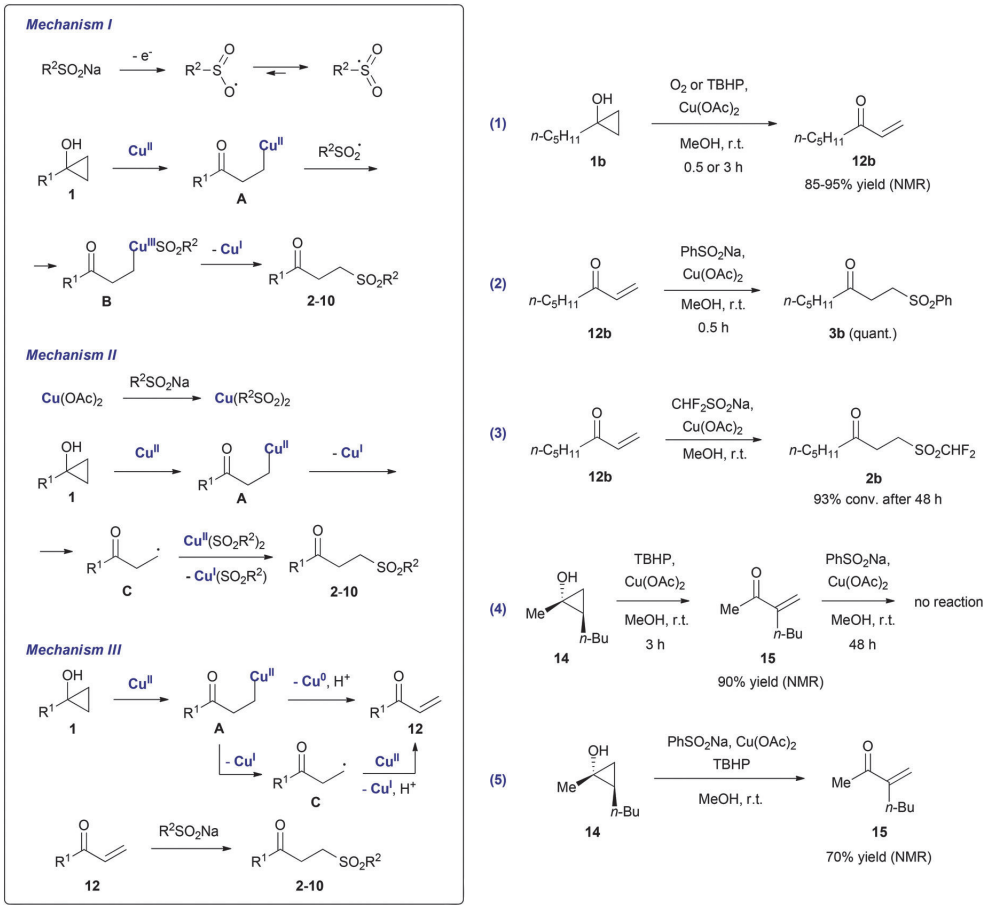
Experiments performed with disubstituted cyclopropanol **14** provide further evidence for the formation of enone intermediates (Scheme 4, eqn (4) and (5)). Cyclopropanol **14** affords α-methylene ketone **15** when oxidized with TBHP in the presence of $Cu(OAc)_2$.[21] On the other hand, we found that ketone **15** is inert towards the subsequent addition of

‡Crystal data for **4a**: $C_{11}H_{13}FO_3S$, M_r = 244.27 g mol^{-1}, monoclinic, $P2_1/c$ (no. 14), a = 15.2903(14) Å, b = 5.0921(4) Å, c = 16.0912(14) Å, β = 115.067(11)°, V = 1134.85(19) Å^3, Z = 4, Cu-Kα radiation (λ = 1.54184 Å) at T = 123.0 K, μ(CuKα) = 2.600 mm^{-1}, D_{calc} = 1.430 g cm^{-3}, 9604 reflections measured (6.382° ≤ 2Θ ≤ 134.804°) of which 2005 unique (R_{int} = 0.0878, R_{sigma} = 0.0529), final R_1 [$F^2 > 2\sigma(F^2)$] = 0.0562, wR_2 (all data) = 0.1565. The crystallographic data is deposited with the Cambridge Crystallographic Data Centre (CCDC 1533651†).





Scheme 3 Preparation of sulfones **2–10** *via* the ring-opening sulfonylation of cyclopropanols **1**. [a] Conditions **A**: cyclopropanol **1** (0.5 mmol), sulfinate salt (3 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), $Fe(OAc)_2$ (20 mol%), TBHP (3 equiv., 70% in water, dropwise addition for 20 min), r.t., 72 h; conditions **B**: cyclopropanol **1** (1 mmol), sulfinate salt (1.5 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), TBHP (1.5 equiv., 70% in water, dropwise addition for 20 min), open flask, r.t., 1 h; conditions **C**: cyclopropanol **1** (1 mmol), sulfinate salt (1.5 equiv.), $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), open flask, stirring at r.t., 2–5 h. [b] Yield of the solid product, isolated by filtration after the evaporation of the solvent used for extraction and hexane washing or obtained by precipitation from chloroform with hexane (see the ESI†). [c] Yield of the isolated product after column chromatography on silica gel. [d] Starting from 1 g of cyclopropanol **1b**, sulfone **9b** was obtained in 76% yield after recrystallization from hexane (see the ESI†). [e] Not isolated. Yield determined by ^{1}H NMR spectroscopy.



Scheme 4 Plausible mechanisms of the sulfonylation reaction and control experiments.

$PhSO_2Na$ (eqn (4)). In accordance with these observations, we found that when cyclopropanol **14** was subjected to the standard reaction conditions (eqn (5)), unsaturated ketone **15** was formed as the major product (~70% yield as per NMR), with only trace amounts of sulfone products detected.

Conclusions

In the present work, we demonstrated that cyclopropanols can serve as suitable and easily available starting materials for the preparation of γ-keto sulfones. The reaction proceeds under mild conditions and demonstrates good functional group tolerance. The possibility of using atmospheric oxygen as an oxidant adds a green dimension to the method. Taking into account the importance of the sulfone group as a pharmacophore fragment and bioisoster of the carbonyl group[22] the developed approach is a useful addition to the existing methods for the preparation of γ-keto sulfones based on sulfa-Michael reactions. The reaction proceeds *via* the one-pot oxidation–Michael addition mechanism, which can be expanded for the preparation of other classes of β-functionalized carbonyl compounds under mild reaction conditions *via* the *in situ* generation of enone intermediates[23] from cyclopropanols as easily available starting materials.

Experimental

Experimental details and spectral data for new compounds are given in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Funding from the European Union's Seventh Framework Program for research, technological development and demonstration Grant No. 621364 (TUTIC-Green), from the Centre of Excellence in Molecular Cell Engineering Grant No. 2014–2020.4.01.15-0013, from the Estonian Ministry of Education and Research Grant IUT19-32 and from Tallinn University of Technology Grant No B58 is gratefully acknowledged. Y. K. is grateful to the Dora Plus program for the financial support of a short research stay at the Tallinn University of Technology. S. K. and I. J. are grateful for the support from research Grants IUT19-9 and PUT692. We are thankful to the reviewers for helpful discussions regarding the reaction mechanism.

Notes and references

1 Recent reviews: (*a*) S. Shaaban, S. Liang, N.-W. Liua and G. Manolikakes, *Org. Biomol. Chem.*, 2017, **15**, 1947; (*b*) N.-W. Liu, S. Liang and G. Manolikakes, *Synthesis*, 2016, 1939; (*c*) M. Feng, B. Tang, S. H. Liang and X. Jiang, *Curr. Top. Med. Chem.*, 2016, **16**, 1200; (*d*) J. Drabowicz, P. Kielbasinski, A. Zajac and P. Wach-Panfilow, in *Comprehensive Organic Synthesis*, ed. P. Knochel and G. A. Molander, Elsevier, Amsterdam, 2nd edn, 2014, vol. 6, pp. 131–174; (*e*) Y. M. Markitanov, V. M. Timoshenko and Y. G. Shermolovich, *J. Sulfur Chem.*, 2014, **35**, 188; (*f*) D. C. Meadows and J. Gervay-Hague, *Med. Res. Rev.*, 2006, **26**, 793.

2 (*a*) S. Patai, Z. Rappoport and C. J. M. Stirling, *The Chemistry of Sulphones and Sulphoxides*, Wiley, New York, 1988; (*b*) M. Julia and J.-M. Paris, *Tetrahedron Lett.*, 1973, **14**, 4833; (*c*) R. J. K. Taylor and G. Casy, *Org. React.*, 2004, **62**, 359.

3 For examples, see: (*a*) H. W. Pinnick and M. A. Reynolds, *J. Org. Chem.*, 1979, **44**, 160; (*b*) G.-P. Lu, C. Cai, F. Chen, R.-L. Ye and B.-J. Zhou, *ACS Sustainable Chem. Eng.*, 2016, **4**, 1804; (*c*) M. Fernandez, U. Uria, L. Orbe, J. L. Vicario, E. Reyes and L. Carrillo, *J. Org. Chem.*, 2014, **79**, 441; (*d*) Y. Yang, L. Tang, S. Zhang, X. Guo, Z. Zha and Z. Wang, *Green Chem.*, 2014, **16**, 4106; (*e*) Z. Jin, J. Xu, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2013, **52**, 12354; (*f*) B. Sreedhar, M. A. Reddy and P. S. Reddy, *Synlett*, 2008, 1949; (*g*) A. Brandt, A. Wojtasiewicz, M. Śnieżek and M. Mąkosza, *Tetrahedron*, 2010, **66**, 3378; (*h*) P. Ciuffreda, S. Casati, L. Alessandrini, G. Terraneo and E. Santaniello, *Steroids*, 2003, **68**, 733; (*i*) P. Bonete and C. Nájera, *Tetrahedron*, 1995, **51**, 2763; (*j*) S. De Lombaert and L. Ghosez, *Tetrahedron Lett.*, 1984, **25**, 3475; (*k*) J. Otera, T. Mandai, M. Shiba, T. Saito, K. Shimohata, K. Takamori and Y. Kawasaki, *Organometallics*, 1983, **2**, 332; (*l*) W. Keim, J. Herwig and G. Pelzer, *J. Org. Chem.*, 1997, **62**, 422.

4 (*a*) G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2433; (*b*) N. K. Rana, S. Selvakumar and V. K. Singh, *J. Org. Chem.*, 2010, **75**, 2089; (*c*) D. Enders, K. Lüttgen and A. A. Narine, *Synthesis*, 2007, 959; (*d*) J. S. Yadav, B. V. S. Reddy and G. Baishya, *J. Org. Chem.*, 2003, **68**, 7098.

5 (*a*) E. Voutyritsa, I. Triandafillidi and C. G. Kokotos, *Synthesis*, 2017, 917; (*b*) M. Jegelka and B. Plietker, *Chem. – Eur. J.*, 2011, **17**, 10417; (*c*) N. K. Jana and J. G. Verkade, *Org. Lett.*, 2003, **5**, 3787; (*d*) M. Kirihara, A. Itou, T. Noguchi and J. Yamamoto, *Synlett*, 2010, 1557; (*e*) A. Shaabani, P. Mirzaei, S. Naderi and D. G. Lee, *Tetrahedron*, 2004, **60**, 11415.

6 A. Bhunia, S. R. Yetra, S. S. Bhojgude and A. T. Biju, *Org. Lett.*, 2012, **14**, 2830.

7 M. Vellakkaran, M. M. S. Andappan, K. Nagaiah and J. B. Nanubolu, *Eur. J. Org. Chem.*, 2016, 3575.

8 G. Fang, J. Liu, W. Shang, Q. Liu and X. Bi, *Chem. – Asian J.*, 2016, **11**, 3334.

9 Recent reviews: (*a*) A. Nikolaev and A. Orellana, *Synthesis*, 2016, 1741; (*b*) I. Haym and M. A. Brimble, *Org. Biomol. Chem.*, 2012, **10**, 7649; (*c*) O. Kulinkovich, *Eur. J. Org. Chem.*, 2004, 4517; (*d*) O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597.

10 Recent examples: (*a*) G. Z. Elek, V. Borovkov, M. Lopp and D. G. Kananovich, *Org. Lett.*, 2017, **19**, 3544; (*b*) Y.-S. Feng, Y.-J. Shu, P. Cao, T. Xu and H.-J. Xu, *Org. Biomol. Chem.*, 2017, **15**, 3590; (*c*) N. Tumma, E. Gyanchander and J. K. Cha, *J. Org. Chem.*, 2017, **82**, 4379; (*d*) S.-C. Lu, H.-S. Li, S. Xu and G.-Y. Duan, *Org. Biomol. Chem.*, 2017, **15**, 324; (*e*) D. C. Davis, C. W. Haskins and M. Dai, *Synlett*, 2017, 913; (*f*) H. Zhang, G. Wu, H. Yi, T. Sun, B. Wang, Y. Zhang, G. Dong and J. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3945; (*g*) X. Zhou, Z. Qi, S. Yu, L. Kong, Y. Li, W.-F. Tian and X. Li, *Adv. Synth. Catal.*, 2017, **359**, 1620; (*h*) X. Zhou, S. Yu, L. Kong and X. Li, *ACS Catal.*, 2016, **6**, 647; (*i*) D. C. Davis, K. L. Walker, C. Hu, R. N. Zare, R. M. Waymouth and M. Dai, *J. Am. Chem. Soc.*, 2016, **138**, 10693; (*j*) M.-H. Shen, X.-L. Lu and H.-D. Xu, *RSC Adv.*, 2015, **5**, 98757; (*k*) S. Wang, L.-N. Guo, H. Wang and X.-H. Duan, *Org. Lett.*, 2015, **17**, 4798; (*l*) R. V. N. S. Murali, N. N. Rao and J. K. Cha, *Org. Lett.*, 2015, **17**, 3854.

11 (*a*) D. G. Kananovich, Y. A. Konik, D. M. Zubrytski, I. Järving and M. Lopp, *Chem. Commun.*, 2015, **51**, 8349; (*b*) Y. Li, Z. Ye, T. M. Bellman, T. Chi and M. Dai, *Org. Lett.*, 2015, **17**, 2186; (*c*) X.-P. He, Y.-J. Shu, J.-J. Dai, W.-M. Zhang, Y.-S. Feng and H.-J. Xu, *Org. Biomol. Chem.*, 2015, **13**, 7159; (*d*) Z. Ye, K. E. Gettys, X. Shen and M. Dai, *Org. Lett.*, 2015, **17**, 6074.

12 J. K. Cha and O. G. Kulinkovich, *Org. React.*, 2012, **77**, 1.

13 Y. A. Konik, M. Kudrjashova, N. Konrad, S. Kaabel, I. Jarving, M. Lopp and D. G. Kananovich, *Org. Biomol. Chem.*, 2017, **15**, 4635.

14 (*a*) C. Ni and J. Hu, *Chem. Soc. Rev.*, 2016, **45**, 5441; (*b*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214.

15 Significant amount of benzaldehyde was detected in the crude reaction mixture.

16 Examples of radical sulfonylation reactions of unsaturated compounds: (*a*) Y. Jiang and T.-P. Loh, *Chem. Sci.*, 2014, **5**, 4939; (*b*) W. Wei, J. Li, D. Yang, J. Wen, Y. Jiao, J. You and H. Wang, *Org. Biomol. Chem.*, 2014, **12**, 1861; (*c*) M.-H. Huang, Y.-L. Zhu, W.-J. Hao, A.-F. Wang, D.-C. Wang, F. Liu, P. Wei, S.-J. Tu and B. Jiang, *Adv. Synth. Catal.*, 2017, **359**, 2229; (*d*) A. U. Meyer, K. Straková, T. Slanina and B. König, *Chem. – Eur. J.*, 2016, **22**, 8694; (*e*) X.-W. Lan, N.-X. Wang, C.-B. Bai, W. Zhang, Y. Xing, J.-L. Wen, Y.-J. Wang and Y.-H. Li, *Sci. Rep.*, 2015, **5**, 18391, DOI: 10.1038/srep1839.

17 (*a*) I. Ryu, M. Ando, A. Ogawa, S. Murai and N. Sonoda, *J. Am. Chem. Soc.*, 1983, **105**, 7192; (*b*) I. Ryu, K. Matsumoto, Y. Kameyama, M. Ando, N. Kusumoto, A. Ogawa, N. Kambe, S. Murai and N. Sonoda, *J. Am. Chem. Soc.*, 1993, **115**, 12330; (*c*) E. Hasegawa, K. Nemoto, R. Nagumo, E. Tayama and H. Iwamoto, *J. Org. Chem.*, 2016, **81**, 2692.

18 J. T. B. H. Jastrzebski and G. van Koten, in *Modern Organocopper Chemistry*, ed. N. Krause, Wiley-VCH, Weinheim, 2002, pp. 1–44.

19 J. K. Kochi, *J. Am. Chem. Soc.*, 1963, **85**, 1958.

20 Formation of enones by copper-catalyzed oxidation of cyclopropanols: (*a*) L.-Z. Li, B. Xiao, Q.-X. Guo and S. Xue, *Tetrahedron*, 2006, **62**, 7762; (*b*) E. Hasegawa, M. Tateyama, R. Nagumo, E. Tayama and H. Iwamoto, *Beilstein J. Org. Chem.*, 2013, **9**, 1397.

21 Regioselective ring-opening at the least substituted C1–C3 bond of the cyclopropane **14** supports electrophilic attack of Cu(II) and formation of β-copper(II) ketone **A** as the initial step,[17] since an alternative radical pathway would result in scissoring of the C1–C2 bond. See for example: W.-B. Han, S.-G. Li, X.-W. Lu and Y. Wu, *Eur. J. Org. Chem.*, 2014, 3841.

22 (*a*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (*b*) G. A. Patani and E. J. LaVoie, *Chem. Rev.*, 1996, **96**, 3147; (*c*) N. K. Konduru, S. Dey, M. Sajid, M. Owais and N. Ahmed, *Eur. J. Med. Chem.*, 2013, **59**, 23; (*d*) C. Curti, M. Laget, A. Ortiz Carle, A. Gellis and P. Vanelle, *Eur. J. Med. Chem.*, 2007, **42**, 880.

23 X. Jie, Y. Shang, X. Zhang and W. Su, *J. Am. Chem. Soc.*, 2016, **138**, 5623.

Publication III

G.Z. Elek, K. Koppel, D.M. Zubrytski, N. Konrad, I. Järving, M. Lopp, D.G. Kananovich. "Divergent Access to Histone Deacetylase Inhibitory Cyclopeptides via Late-Stage Cyclopropane Ring Cleavage Strategy. Short Synthesis of Chlamydocin". *Org.Lett*. **2019**, *21*, 8473-8478.

OL | Organic Letters

Cite This: Org. Lett. 2019, 21, 8473−8478

Letter

pubs.acs.org/OrgLett

Divergent Access to Histone Deacetylase Inhibitory Cyclopeptides via a Late-Stage Cyclopropane Ring Cleavage Strategy. Short Synthesis of Chlamydocin

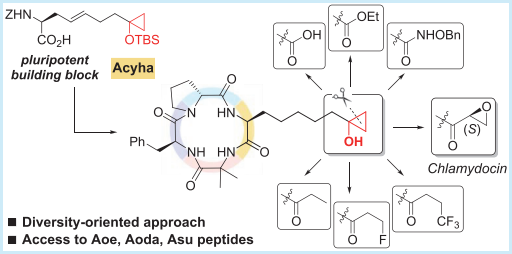
Gábor Zoltán Elek,[†] Kaur Koppel,[†] Dzmitry M. Zubrytski,[‡] Nele Konrad,[†] Ivar Järving,[†] Margus Lopp,[†] and Dzmitry G. Kananovich*[,†]

[†]Tallinn University of Technology, School of Science, Department of Chemistry and Biotechnology, Akadeemia tee 15, 12618 Tallinn, Estonia

[‡]Belarusian State University, Department of Organic Chemistry, Leningradskaya 14, 220050 Minsk, Belarus

Supporting Information

ABSTRACT: A unified step-economical strategy for accessing histone deacetylase inhibitory peptides is proposed, based on the late-stage installation of multiple zinc-binding functionalities via the cleavage of the strained cyclopropane ring in the common pluripotent cyclopropanol precursor. The efficacy of the proposed diversity-oriented approach has been validated by short stereoselective synthesis of natural product chlamydocin, containing a challenging-to-install fragment of (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) and a range of its analogues, derivatives of 2-amino-8-oxodecanoic and 2-aminosuberic acids.



Histone deacetylase (HDAC) enzymes serve as epigenetic gene expression mediators via the regulation of deacetylation/acetylation of histone proteins within eukaryotic cells.[1] Dysfunction of HDAC enzymes is associated with numerous severe physiological processes like cancer, neurodegeneration, and metabolic disorders,[2] thus making them a validated target for therapeutic intervention. Several naturally occurring cyclopeptides with extremely high inhibitory activity against zinc-dependent HDAC enzymes are known.[3] Their structural organization is archetypal and includes a cyclic cap that is responsible for interaction with the peripheral binding site of the enzyme, a hydrophobic spacer, and a zinc-binding group (ZBG) to capture a zinc ion in the catalytic pocket (Figure 1).[1,3] The spacer with ZBG is approximately isosteric with acetylated lysine, suggesting that it mimics an acetylated histone protein.[3] Several natural cyclopeptides [chlamydocin (**1**),[4a] HC-toxin,[4b] trapoxins,[4c] WF-3161,[4d] etc.] contain the epoxy ketone function as a zinc-binding motif in the side chain of (2*S*,9*S*)-2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe). Zinc-binding ethyl ketone and carboxylate functions are present in apicidines,[4e] in their 2-amino-8-oxodecanoic (Aoda) and 2-aminosuberic acid (Asu) structural units, respectively (Figure 1). The structural principles of such peptides have been translated into HDAC inhibitory drugs approved by the Food and Drug Administration for cancer treatment (e.g., Vorinostat, Belinostat, and Romidepsin).[5] Due to the significance of HDAC inhibitors as therapeutic agents, the clarification of the HDAC enzyme function and design of more selective inhibitors, especially on the level of isoforms, has attracted a great deal of attention.[6] It has been shown that the inhibitory potential and selectivity profile of the peptide HDAC inhibitors can be further diversified by the modification of ZBG or the amino acid sequence.[1,6]

A number of methods have been reported for the synthesis of Aoda[7] and Asu[8] building blocks, compatible with peptide synthesis under the standard Boc/Fmoc/Cbz protocols. In contrast, a vulnerable epoxide functionality, along with an additional chiral center, requires advanced synthetic planning for the Aoe-containing peptides. For example, the first total synthesis of chlamydocin and trapoxin B was implemented by Schmidt[9] and later by Schreiber[10] via multistep sequences from (*R*,*R*)-tartaric acid-derived precursors. The Rich group utilized epoxidation of the corresponding racemic allylic alcohol under Sharpless conditions,[11] while Baldwin exploited free radical homologation of 2-amino-5-iodopentanoic acid.[12] More recently, the Kazmaier group reported the synthesis of several Aoe-containing cyclopeptides via chelate enolate Claisen rearrangement.[13]

Despite these creative contributions, synthesis of similar targets via the distinct multistep protocols from the diverse building blocks hampers access to the realm of HDAC inhibitory peptides. Therefore, the development of a step-economical and general synthetic strategy is highly desired for the preparation of the corresponding molecular libraries.[1,6] Due to the interest of our group in cyclopropanol chemistry,

Received: September 18, 2019
Published: October 9, 2019

DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

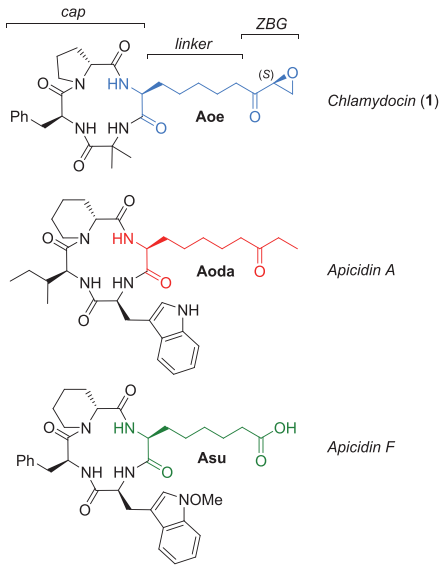


Figure 1. Examples of natural HDAC inhibitors with different zinc-binding groups (ZBGs) in the side chain.

we noticed that all the required zinc-binding motifs [ethyl ketone, carboxylate, and even (*S*)-epoxy ketone] can be straightforwardly generated from the same cyclopropanol moiety, thus offering the required general approach (Figure 2). Cyclopropanols are easily available[14] and versatile synthetic intermediates,[15] with continuously emerging new applications in the synthesis of natural products.[16] The internal ring strain

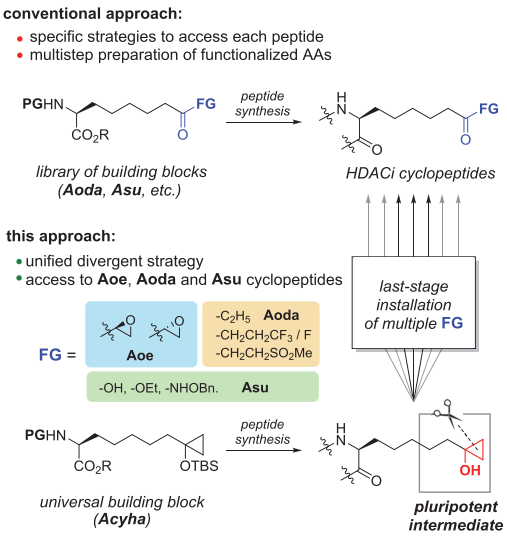


Figure 2. Conventional and proposed strategies for accessing HDAC inhibitory peptides.

of the cyclopropane and the presence of an electron-donating hydroxyl group facilitate ring opening with a range of electrophilic and radical species.[15] These reactions typically occur under mild conditions well tolerated by other functionalities, which makes the cyclopropanol motif suitable for late-stage cleavage. Herein, we demonstrate for the first time the utilization of the cyclopropanol unit as an efficient pluripotent group for diversity-oriented synthesis, which is validated by a concise divergent synthesis of natural product chlamydocin **1** (Figure 1), and a set of its known analogues[1,6] with histone deacetylase inhibitory activity.

Implementation of our approach requires a single universal building block, 2-amino-7-(1-hydroxycyclopropyl)heptanoic acid (Acyha). A carbon skeleton of the latter was assembled by cross-metathesis of two readily available alkene partners, protected (*S*)-allyl glycine **4** and alkene **6** with a masked cyclopropanol functionality (Scheme 1).

Both **4** and **6** can be accessed from commercial starting materials via a short high-yield reaction sequence. The N-terminus of (*S*)-allyl glycine (**3**) was masked with a range of protective groups (Boc, Cbz, and Fmoc) followed by the esterification of the C-terminus to provide amino acid coupling partners **4a**–**c**. TBS-protected cyclopropanol **6** was easily prepared in multigram quantities in three steps and 90% overall yield from ethyl 5-bromovalerate (**5**) via the consequent Kulinkovich cyclopropanation, silylation, and HBr elimination steps.

Because the metathesis of alkene partners **4** and **6** is of type I,[17] its statistical nature and the fast inactivation of the Grubb's catalyst afforded rather low yields of cross-coupling product **7a** in the initial runs. After optimization (see the Supporting Information), we were able to increase the yield of target product **7a** to 75% by using only 1 mol % of the second generation of the Hoveyda–Grubbs catalyst and a 5-fold excess of readily available alkene **6**. Under optimal conditions, cross-coupled products **7a**–**c**, decorated with orthogonal protecting groups at the N- and C-termini, were smoothly prepared in 71–75% yields. The reduction of the double bond and debenzylation of the C-terminus (for Fmoc analogue **7b**) by hydrogenation afforded protected Acyha derivatives **8a** and **8b** in quantitative yields with an intact cyclopropane moiety. It should be noted that the TBS-protected cyclopropanol unit cannot tolerate strong acids, as was evidenced by the fast transformation of **8a** into the corresponding Aoda derivative **9a** under typical Boc removal conditions (TFA/CH_2Cl_2), even prior to the removal of the Boc group itself (see the Supporting Information).

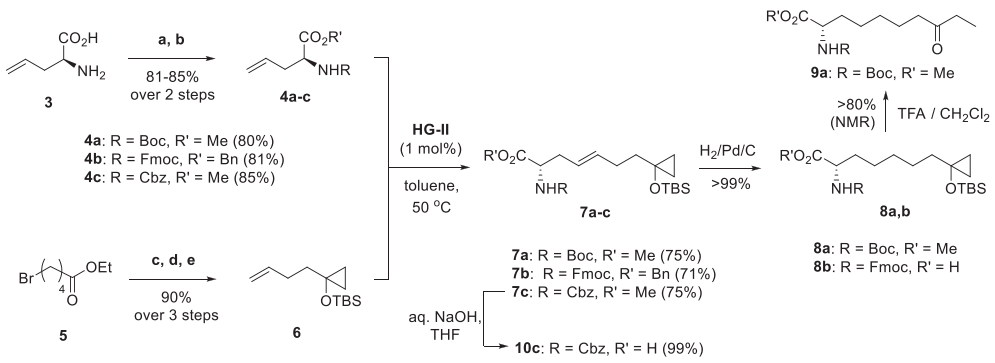
Considering the protecting group compatibility issues, Cbz-carboxylic acid **10c** was selected for the total synthesis of chlamydocin (Scheme 2).

Extensive studies of the synthesis of chlamydocin[9,11−13] and its Aoda/Asu analogues[6c−h] led us to select this macrocycle as the first target to validate our approach. The most efficient strategy for the closure of its macrocyclic ring involved macrolactamization at the C-terminus of D-proline.[9b] Therefore, Aib-Phe-D-Pro-OMe tripeptide **11** was prepared from the corresponding amino acids in 73% total yield over four steps by using standard peptide coupling protocols (see the Supporting Information).[12,13c]

Next, the TBTU-mediated peptide coupling of **11** with Acyha derivative **10c** afforded tetrapeptide **12** in 96% yield. The hydrogenation of the double bond in the latter was conveniently performed in flow mode with the simultaneous

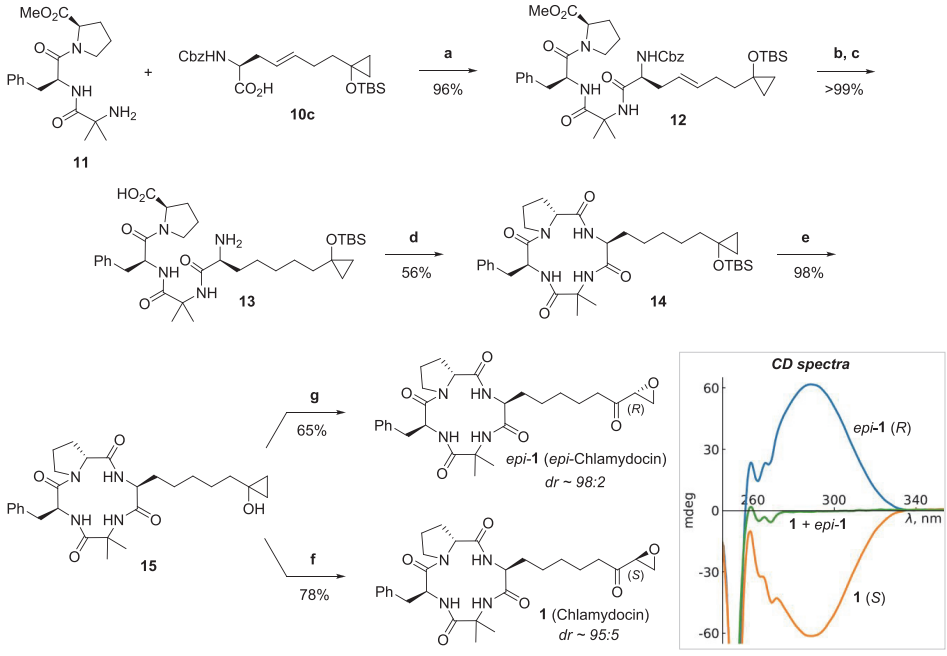
DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

Scheme 1. Synthesis of Protected 2-Amino-7-(1-hydroxycyclopropyl)heptanoic Acid (Acyha) Derivatives[a]



[a]Reagents and conditions for **4a**: (a) Boc_2O, $NaHCO_3$, MeOH, sonification; (b) K_2CO_3, MeI, acetone. Reagents and conditions for **4b**: (a) FmocOSu, K_2CO_3, dioxane/H_2O; (b) BnBr, $NaHCO_3$, DMF. Reagents and conditions for **4c**: (a) CbzCl, $NaHCO_3$, H_2O; (b) K_2CO_3, MeI, acetone. Reagents and conditions for **6**: (c) EtMgBr, Ti(O*i*-Pr)$_4$, Et_2O; (d) TBSCl, imidazole, THF; (e) *t*-BuOK, THF. **HG-II** = Hoveyda−Grubbs catalyst, second generation.

Scheme 2. Stereodivergent Synthesis of Chlamydocin (1) and Its Epimer *epi*-1[a]



[a]Reagents and conditions: (a) TBTU, HOBT, Et_3N in CH_2Cl_2; (b) NaOH in THF/H_2O; (c) 10% Pd/C, H_2 in MeOH, H-Cube (60 °C, 60 bar); (d) HATU, DIEA in DMF; (e) 1 M TBAF in THF; (f) air, 0.5 mol % Mn(acac)$_3$ in THF, 0 °C, 2 h, then poly-D-leucine/SiO_2, DBU, −25 °C, 48 h; (g) air, 0.5 mol % Mn(acac)$_3$ in THF, 0 °C, 2 h, then poly-L-leucine/SiO_2, DBU, −25 °C, 48 h.

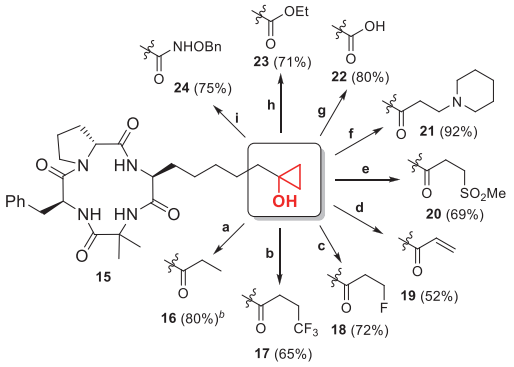
removal of the Cbz group, yielding tetrapeptide **13** in quantitative yield after the hydrolytic release of free carboxylate at the D-proline terminus. HATU-enabled macrocyclization afforded macrocyclic tetrapeptide **14** in 56% yield. Finally, the removal of the TBS group in **14** produced the key intermediate **15** with an unmasked cyclopropanol functionality. The latter was transformed into the corresponding (*S*)-epoxy ketone.[18] The aerobic oxidation of **15** catalyzed by 0.5 mol % Mn(acac)$_3$ followed by treatment with DBU in the presence of silica-supported poly-D-leucine afforded chlamydocin **1** in 78% yield. The same transformation performed with poly-L-leucine as a chiral mediator led to the corresponding (*R*)-epoxide epimer

DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

epi-**1**, thus demonstrating stereochemical divergence. Both transformations yielded the corresponding macrocycles as almost pure (*S*)- and (*R*)-diastereoisomers, according to the chiral HPLC analysis [dr >95:5 (see the Supporting Information)]. The measured specific rotation for synthetic **1** ($[\alpha]_D = -140°$) was close to the reported for the natural sample ($[\alpha]_D = -147.5°$).[4a] The (*S*)-configuration of the chiral center in the epoxide moiety of **1** was proven by CD spectroscopy (Scheme 2), showing a negative Cotton effect with a maximum at ∼290 nm for (*S*)-stereoisomer **1**, and an accordingly positive absorption band for its (*R*)-counterpart *epi*-**1**, in full accord with the literature data.[9,11]

Following our method, the natural product chlamydocin was prepared in an affordable 26% overall yield over 10 steps [counted as the longest linear sequence from **3** (see Scheme S1)]. Even more important is the fact that our approach creates a shortcut to a series of chlamydocin analogues by exploiting the pluripotency of the cyclopropanol function in common precursor **15**, as demonstrated by a series of successful cyclopropane cleavage reactions (Scheme 3).

Scheme 3. Divergent Preparation of Aoda- and Asu-Containing Chlamydocin Analogues by Late-Stage Ring Cleavage of the Common Cyclopropane Precursor 15[a]



[a]Reagents and conditions: (a) TFA, CH_2Cl_2, 24 h; (b) Togni reagent, 10 mol % $[Cu(CH_3CN)_4]BF_4$, 20 min; (c) SelectFluor, 20 mol % AgF, C_6H_6/H_2O, reflux, 4 h; (d) air, $Cu(OAc)_2$, MeOH, 3 h; (e) air, $Cu(OAc)_2$, $MeSO_2Na$, MeOH, 3 h; (f) air, $Cu(OAc)_2$, piperidine, MeOH, 45 min; (g) PIFA, acetic acid, 30 min; (h) PIFA, ethanol, 30 min; (i) $PhI(O_2CAr)_2$ (Ar = 2,4,6-trichlorophenyl), CH_2Cl_2, 2 h, then NH_2OBn (10 equiv), 10 h. All reactions were carried out at rt unless noted otherwise. TFA = trifluoroacetic acid, and PIFA = iodosobenzene bis(trifluoroacetate). [b]Compound **16** was prepared directly from TBS-protected cyclopropanol **14**.

Cyclopropanols undergo facile rearrangement to the corresponding carbonyl compounds in the presence of acid or base catalysts.[15c] Therefore, the transformation of TBS-protected cyclopropanol **14** to Aoda-containing cyclopeptide[6c,e] **16** was achieved in 80% yield by treatment with TFA in CH_2Cl_2. In view of the importance of fluorinated compounds in medicinal chemistry,[19] including ^{18}F PET imaging,[20] late-stage trifluoromethylation[21] and fluorination[22] were successfully performed to afford fluorinated Aoda analogues **17** and **18**. A number of functionalized ketones have been prepared via the copper-catalyzed aerobic oxidation of the cyclopropanol moiety,[23] e.g., vinyl ketone **19**, γ-ketosulfone **20**, and β-amino ketone **21**.[24] A side chain of 2-aminosuberic acid (Asu) in compound **22** was installed by the fast and high-yield oxidation of cyclopropanol **15** with bis(trifluoroacetoxy)iodobenzene (PIFA) in acetic acid.[25] Known bioactive Asu derivatives[6,8] have also been prepared. Oxidation of **15** with PIFA in ethanol afforded the corresponding ethyl ester[6c] **23**. We also developed a one-pot protocol for the synthesis of amides (see Scheme S2) via intermediate generation of mixed anhydrides from cyclopropanols in aprotic media.[25d] Thus, oxidation of cyclopropanol **15** with $PhI(O_2CAr)_2$ (Ar = 2,4,6-trichlorophenyl) in CH_2Cl_2 followed by addition of $BnONH_2$ produced benzyl-protected hydroxamic acid **24** in 75% yield. Compound **24** is the immediate precursor of the corresponding free hydroxamic acid,[6d] known as a strong HDAC inhibitor.[6,8]

In conclusion, here we demonstrate the first use of a cyclopropanol functionality as a powerful pluripotent intermediate for diversity-oriented synthesis, on both stereochemical and functional diversity levels. The expedient synthesis of the natural product chlamydocin, its (*R*)-epoxide epimer, and several chlamydocin analogues has verified the efficacy of our approach for accessing Aoe-, Aoda-, and Asu-containing HDAC inhibitory peptides, including their ZBG-modified congeners. Due to the broad spectrum of chemical transformations provided by the rapidly evolving field of cyclopropanol chemistry,[15,16] further advances in the last-stage diversification from the single cyclopropanol precursor can be expected, which are suitable for the generation of bioactive molecular libraries in general and HDAC inhibitory peptides in particular.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03305.

Experimental procedures and characterization data for new compounds and copies of NMR spectra, HPLC chromatograms, and CD spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dzmitry.kananovich@taltech.ee.

ORCID

Margus Lopp: 0000-0002-8041-2595

Dzmitry G. Kananovich: 0000-0002-2664-4491

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding from the Centre of Excellence in Molecular Cell Engineering (Grant 2014-2020.4.01.15-0013), the Estonian Ministry of Education and Research (Grant IUT19-32), and TalTech (Grant B58) is gratefully acknowledged. Support from COST Action CA15106 "C−H Activation in Organic Synthesis" (CHAOS) is gratefully acknowledged. This work has been partially supported by ASTRA "TUT Institutional Development Program for 2016-2022" Graduate School of Functional Materials and Technologies (2014-2020.4.01.16-

DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

0032). The work previously appeared as a preprint (doi 10.26434/chemrxiv.8858078.v1).

REFERENCES

(1) (a) Luan, Y.; Li, J.; Bernatchez, J. A.; Li, R. *J. Med. Chem.* **2019**, *62*, 3171. (b) Banerjee, S.; Adhikari, N.; Amin, S. A.; Jha, T. *Eur. J. Med. Chem.* **2019**, *164*, 214. (c) Hai, Y.; Christianson, D. W. *Nat. Chem. Biol.* **2016**, *12*, 741. (d) Falkenberg, K. J.; Johnstone, R. W. *Nat. Rev. Drug Discovery* **2014**, *13*, 673. (e) Bieliauskas, A. V.; Pflum, M. K. H. *Chem. Soc. Rev.* **2008**, *37*, 1402. (f) Miller, T. A.; Witter, D. J.; Belvedere, S. *J. Med. Chem.* **2003**, *46*, 5097. (g) Bolden, J. E.; Peart, M. J.; Johnstone, R. W. *Nat. Rev. Drug Discovery* **2006**, *5*, 769.

(2) (a) Minucci, S.; Pelicci, P. G. *Nat. Rev. Cancer* **2006**, *6*, 38. (b) Xu, W. S.; Parmigiani, R. B.; Marks, P. A. *Oncogene* **2007**, *26*, 5541. (c) Acharya, M. R.; Sparreboom, A.; Venitz, J.; Figg, W. D. *Mol. Pharmacol.* **2005**, *68*, 917. (d) Johnstone, R. W. *Nat. Rev. Drug Discovery* **2002**, *1*, 287. (e) Steffan, J. S.; Bodai, L.; Pallos, J.; Poelman, M.; McCampbell, A.; Apostol, B. L.; Kazantsev, A.; Schmidt, E.; Zhu, Y.-Z.; Greenwald, M.; Kurokawa, R.; Housman, D. E.; Jackson, G. R.; Marsh, J. L.; Thompson, L. M. *Nature* **2001**, *413*, 739. (f) Feng, D.; Liu, T.; Sun, Z.; Bugge, A.; Mullican, S. E.; Alenghat, T. E.; Liu, X. S.; Lazar, M. A. *Science* **2011**, *331*, 1315.

(3) Newkirk, T. L.; Bowers, A. A.; Williams, R. M. *Nat. Prod. Rep.* **2009**, *26*, 1293.

(4) (a) Closse, A.; Huguenin, R. *Helv. Chim. Acta* **1974**, *57*, 533. (b) Shute, R. E.; Dunlap, B.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 71. (c) Kijima, M.; Yoshida, M.; Suguta, K.; Horinouchi, S.; Beppu, T. *J. Biol. Chem.* **1993**, *268*, 22429. (d) Umehara, K.; Nakahara, K.; Kiyoto, S.; Iwami, M.; Okamoto, M.; Tanaka, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1983**, *36*, 478. (e) Meinke, P. T.; Liberator, P. *Curr. Med. Chem.* **2001**, *8*, 211.

(5) (a) Mann, B. S.; Johnson, J. R.; Cohen, M. H.; Justice, R.; Pazdur, R. *Oncologist* **2007**, *12*, 1247. (b) Eckschlager, T.; Plch, J.; Stiborova, M.; Hrabeta, J. *Int. J. Mol. Sci.* **2017**, *18*, 1414.

(6) (a) Porter, N. J.; Christianson, D. W. *ACS Chem. Biol.* **2017**, *12*, 2281. (b) Olsen, C. A.; Montero, A.; Leman, L. J.; Ghadiri, M. R. *ACS Med. Chem. Lett.* **2012**, *3*, 749. (c) Kitir, B.; Maolanon, A. R.; Ohm, R. G.; Colaco, A. R.; Fristrup, P.; Madsen, A. S.; Olsen, C. A. *Biochemistry* **2017**, *56*, 5134. (d) Wang, S.; Li, X.; Wei, Y.; Xiu, Z.; Nishino, N. *ChemMedChem* **2014**, *9*, 627. (e) Traore, M.; Mietton, F.; Maubon, D.; Peuchmaur, M.; Francisco Hilario, F.; Pereira de Freitas, R.; Bougdour, A.; Curt, A.; Maynadier, M.; Vial, H.; Pelloux, H.; Hakimi, M.-A.; Wong, Y.-S. *J. Org. Chem.* **2013**, *78*, 3655. (f) Islam, S.; Bhuiyan, M. P. I.; Islam, N.; Nsiama, T. K.; Oishi, N.; Kato, T.; Nishino, N.; Ito, A.; Yoshida, M. *Amino Acids* **2012**, *42*, 2103. (g) Bhuiyan, M. P.; Kato, T.; Okauchi, T.; Nishino, N.; Maeda, S.; Nishino, T. G.; Yoshida, M. *Bioorg. Med. Chem.* **2006**, *14*, 3438. (h) Nishino, N.; Jose, B.; Shinta, R.; Kato, T.; Komatsu, Y.; Yoshida, M. *Bioorg. Med. Chem.* **2004**, *12*, 5777.

(7) (a) Pahari, A. K.; Mukherjee, J. P.; Chattopadhyay, S. K. *Tetrahedron* **2014**, *70*, 7185. (b) Montero, A.; Beierle, J. M.; Olsen, C. A.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2009**, *131*, 3033. (c) Bajgrowicz, J. A.; El Hallaoui, A.; Jacquier, R.; Pigiere, C.; Viallefont, P. *Tetrahedron* **1985**, *41*, 1833.

(8) (a) Mahindra, A.; Millard, C. J.; Black, I.; Archibald, L. J.; Schwabe, J. W. R.; Jamieson, A. G. *Org. Lett.* **2019**, *21*, 3178. (b) Chattopadhyay, S. K.; Sil, S.; Mukherjee, J. P. *Beilstein J. Org. Chem.* **2017**, *13*, 2153. (c) Liu, T.; Kapustin, G.; Etzkorn, F. A. *J. Med. Chem.* **2007**, *50*, 2003. (d) Kahnberg, P.; Lucke, A. J.; Glenn, M. P.; Boyle, G. M.; Tyndall, J. D. A.; Parsons, P. G.; Fairlie, D. P. *J. Med. Chem.* **2006**, *49*, 7611. (e) Wernic, D.; DiMaio, J.; Adams, J. *J. Org. Chem.* **1989**, *54*, 4224.

(9) (a) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Bartkowiak, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 318. (b) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Beuttler, T.; Bartkowiak, F. *Synthesis* **1986**, *1986*, 361.

(10) Taunton, J.; Hassig, C. A.; Schreiber, S. L. *Science* **1996**, *272*, 408.

(11) Kawai, M.; Gardner, J. H.; Rich, D. H. *Tetrahedron Lett.* **1986**, *27*, 1877.

(12) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Patel, V. K. *Tetrahedron* **1993**, *49*, 7837.

(13) (a) Servatius, P.; Kazmaier, U. *J. Org. Chem.* **2018**, *83*, 11341. (b) Servatius, P.; Kazmaier, U. *Org. Biomol. Chem.* **2018**, *16*, 3464. (c) Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, *2009*, 371.

(14) Synthesis of cyclopropanols from esters: (a) Cha, J. K.; Kulinkovich, O. G. *Org. React.* **2012**, *77*, 1. Synthesis from cyclopropane precursors: (b) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516. (c) Cheng, K.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 2346. (d) Montesinos-Magraner, M.; Costantini, M.; Ramirez-Contreras, R.; Muratore, M. E.; Johansson, M. J.; Mendoza, A. *Angew. Chem., Int. Ed.* **2019**, *58*, 5930. (e) Yu, Z.; Mendoza, A. *ACS Catal.* **2019**, *9*, 7870. (f) Parra, A.; Amenos, L.; Guisan-Ceinos, M.; Lopez, A.; Garcia Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833. (g) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (h) Simaan, M.; Marek, I. *Angew. Chem., Int. Ed.* **2018**, *57*, 1543. (i) Harris, M. R.; Wisniewska, H. M.; Jiao, W.; Wang, X.; Bradow, J. N. *Org. Lett.* **2018**, *20*, 2867. (j) Benoit, G.; Charette, A. B. *J. Am. Chem. Soc.* **2017**, *139*, 1364.

(15) Reviews: (a) Mills, L. R.; Rousseaux, S. A. *Eur. J. Org. Chem.* **2019**, *2019*, 8. (b) Nikolaev, A.; Orellana, A. *Synthesis* **2016**, *48*, 1741. (c) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (d) Liu, Y.; Wang, Q.-L.; Chen, Z.; Zhou, C.-S.; Xiong, B.-Q.; Zhang, P.-L.; Yang, C.-A.; Zhou, Q. *Beilstein J. Org. Chem.* **2019**, *15*, 256.

(16) Reviews: (a) Cai, X.; Liang, W.; Dai, M. J. *Tetrahedron* **2019**, *75*, 193. (b) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651. (c) Kulinkovich, O. G. *Cyclopropanes in Organic Synthesis*; Wiley: Hoboken, NJ, 2015. (d) Haym, I.; Brimble, M. A. *Org. Biomol. Chem.* **2012**, *10*, 7649. Recent examples: (e) Tan, Q.; Yang, Z.; Jiang, D.; Cheng, Y.; Yang, J.; Xi, S.; Zhang, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 6420. (f) Ma, K.; Yin, X.; Dai, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 15209.

(17) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(18) Elek, G. Z.; Borovkov, V.; Lopp, M.; Kananovich, D. G. *Org. Lett.* **2017**, *19*, 3544.

(19) (a) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398. (b) Prakash Reddy, V. *Organofluorine Compounds in Biology and Medicine*; Elsevier: Amsterdam, 2015. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(20) (a) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639. (b) Campbell, M. G.; Ritter, T. *Org. Process Res. Dev.* **2014**, *18*, 474. (c) Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3216. (d) Tago, T.; Toyohara, J. *Molecules* **2018**, *23*, 300.

(21) (a) Konik, Y. A.; Kudrjashova, M.; Konrad, N.; Kaabel, S.; Järving, I.; Lopp, M.; Kananovich, D. G. *Org. Biomol. Chem.* **2017**, *15*, 4635. (b) Kananovich, D. G.; Konik, Y. A.; Zubrytski, D. M.; Järving, I.; Lopp, M. *Chem. Commun.* **2015**, *51*, 8349. (c) Li, Y.; Ye, Z.; Bellman, T. M.; Chi, T.; Dai, M. *Org. Lett.* **2015**, *17*, 2186. (d) He, X.-P.; Shu, Y.-H.; Dai, J.-J.; Zhang, W.-M.; Feng, Y.-S.; Xu, H.-J. *Org. Biomol. Chem.* **2015**, *13*, 7159. (e) Ye, Z.; Gettys, K. E.; Shen, X.; Dai, M. *Org. Lett.* **2015**, *17*, 6074.

(22) (a) Ren, S.; Feng, C.; Loh, T.-P. *Org. Biomol. Chem.* **2015**, *13*, 5105. (b) Zhao, H.; Fan, X.; Yu, J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490. (c) Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T. *Chem. - Eur. J.* **2015**, *21*, 8060. (d) Ishida, N.; Okumura, S.; Nakanishi, Y.; Murakami, M. *Chem. Lett.* **2015**, *44*, 821. (e) Deng, Y.; Kauser, N. I.; Islam, S. M.; Mohr, J. T. *Eur. J. Org. Chem.* **2017**, *2017*, 5872.

(23) Konik, Y. A.; Elek, G. Z.; Kaabel, S.; Järving, I.; Lopp, M.; Kananovich, D. G. *Org. Biomol. Chem.* **2017**, *15*, 8334.

(24) For the alternative β-amination protocols, see: (a) Ye, Z.; Dai, M. *Org. Lett.* **2015**, *17*, 2190. (b) Shen, M.-H.; Lu, X.-L.; Xu, H.-D. *RSC Adv.* **2015**, *5*, 98757.

DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

(25) (a) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron Lett.* **1995**, *36*, 6907. (b) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron* **1998**, *54*, 13943. (c) Kananovich, D. G.; Zubrytski, D. M.; Kulinkovich, O. G. *Synlett* **2010**, *2010*, 1043−1046. (d) Zubrytski, D. M.; Kananovich, D. G.; Kulinkovich, O. G. *Tetrahedron* **2014**, *70*, 2944. (e) Zubrytski, D. M.; Kananovich, D. G.; Matiushenkov, E. A. *Russ. J. Org. Chem.* **2017**, *53*, 813.

DOI: 10.1021/acs.orglett.9b03305
Org. Lett. 2019, 21, 8473−8478

Curriculum vitae

Personal data

Name:	Gábor Zoltán Elek
Date of birth:	13.11.1991
Place of birth:	Szeged, Hungary
Citizenship:	Hungarian

Contact data

E-mail:	elek.gabor.zoltan@gmail.com

Education

2016–2020	Tallinn University of Technology – PhD
2014–2016	Budapest University of Technology and Economics – MSC (cum laude)
2010–2014	Budapest University of Technology and Economics – BSC
2006–2010	Deák Ferenc Bilingual High school – High School

Language competence

Hungarian	Native
English	Fluent
Estonian	Intermediate
German	Intermediate
Russian	Beginner
Swedish	Beginner
Norwegian	Beginner

Professional employment

2016–2020	TalTech, Department of Chemistry and Biotechnology, junior researcher

Supervised theses

2017–2018	Kaur Koppel, BSc thesis, defended at TalTech
2019–2019	Pauline Vailhé, MSc thesis, defended at University of Montpellier, France

Teaching experience

Autumn 2019	Organic Chemistry laboratory practice
2016–2020	Seminars: Stereochemistry and Chemical Reaction Mechanisms

Elulookirjeldus

Isikuandmed

Nimi:	Gábor Zoltán Elek
Sünniaeg:	13.11.1991
Sünnikoht:	Szeged, Ungari
Kodakondsus:	Ungari

Kontaktandmed

E-post:	elek.gabor.zoltan@gmail.com

Hariduskäik

2016–2020	Tallinna Tehnikaülikool – PhD
2014–2016	Budapesti Tehnikaülikool – MSC (cum laude)
2010–2014	Budapesti Tehnikaülikool – BSC
2006–2010	Deák Ferenc Kakskeelne Gümnaasium – Keskharidus

Keelteoskus

Ungari keel	Emakeel
Inglise keel	Kõrgtase
Eesti keel	Kesktase
Saksa keel	Kesktase
Vene keel	Algtase
Rootsi keel	Algtase
Norra keel	Algtase

Teenistuskäik

2016–2020	TalTech, Keemia ja biotehnoloogia instituut, nooremteadur

Juhendatud lõputööd

2017–2018	Kaur Koppel, bakalauereusetöö, kaitstud TalTech-is
2019–2019	Pauline Vailhé, magistritöö, kaitstud Montpellier Ülikoolis, Prantsusmaal

Õpetamiskogemus

Sügis 2019	Orgaanilise keemia laboripraktikum
2016–2020	Seminarid: Stereokeemia, Keemiliste Reaktsioonide Mehhanismid